KCE REPORT 248S

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

WHAT ARE THE RECOMMENDED CLINICAL ASSESSMENT AND SCREENING TESTS DURING PREGNANCY?

APPENDIX





KCE REPORT 248S
GOOD CLINICAL PRACTICE

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APPENDIX

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2015 www.kce.fgov.be

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Acknowledgements:	Endnote: Nicolas Fairon (KCE) Synthesis: Karin Rondia (KCE), Gudrun Briat (KCE) Chapter on diabetes: Pamela Gironi (Erasme), Paul Ramaekers (UZ Antwerpen), Katrien Benhalima (UZ Leuven), Chantal Mathieu (UZ Leuven) Chapter on hypothyroidism: Yves Jacquemin (UA), Rodrigo Moreno-Reyes (ULB) Chapter on vitamin D deficiency: Yves Jacquemin (UA) Chapter on CMV: Walter Foulon (UZ Brussel), Yves Jacquemin (UA) Chapter on Toxoplasmosis: Walter Foulon (UZ Brussel), Yves Jacquemin (UA) Chapter on risk factors: Françoise Mambourg (KCE)

	OHRI Chapters: Becky Skidmore for Conducting literature search; Raymond Daniel for acquisition of articles, Misty Pratt and Katrina Sullivan for screening, formatting, data extraction, risk of bias assessment; Rafat Islam for screening, and help with GRADE; Dianna Wolfe for screening, data extraction, risk of bias assessment; Mona Hersi for screening, and formatting; and Brian Younho Hong for screening.
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Publication date:	7 July 2015 (2nd edition; 1st edition: 30 June 2015)
Domain:	Good Clinical Practice (GCP)
MeSH:	Prenatal care; Prenatal diagnosis; Pregnancy
NLM Classification:	WQ175
Language:	English
Format:	Adobe® PDF™ (A4)
Legal depot:	D/2015/10.273/59

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How to refer to this document?

Gyselaers W, Jonckheer P, Ahmadzai N, Ansari MT, Carville S, Dworzynski K, Gaudet L, Glen J, Jones K, Miller P, Tetzlaff J M, Alexander S, Allegaert K, Beeckman K, Ceysens G, Christiane Y, De Ronne N, de Thysebaert B, Dekker N, Denys A, Eeckeleers P, Hernandez A, Mathieu E, Seuntjens L, Verleye L, Stordeur S. What are the recommended clinical assessment and screening tests during pregnancy? – Appendix. Good Clinical Practice (GCP) Brussels: Belgian Health Care Knowledge Centre (KCE). 2015. KCE Reports 248S. D/2015/10.273/59.

This document is available on the website of the Belgian Health Care Knowledge Centre.

TABLE OF CONTENTS

LIST OF FIGURES **7**
LIST OF TABLES **12**
1. COMPOSITION OF EXPERTS AND STAKEHOLDERS GROUPS **24**
1.1. COMPOSITION OF THE GUIDELINE DEVELOPMENT GROUP 24
1.2. COMPOSITION OF THE STAKEHOLDERS GROUP 25
1.3. COMPOSITION OF THE KCE EXPERT TEAM 25
1.4. EXTERNAL RESEARCHERS INVOLVED IN THE GUIDELINE DEVELOPMENT 26
2. TOPICS PROPOSED BY THE GDG **27**
3. RISK FACTORS THAT MAY IMPLY ADDITIONAL CARE **29**
4. PATHWAYS FOR SCREENING OF CMV, TOXOPLASMOSIS AND GESTATIONAL DIABETES **32**
4.1. CYTOMEGALOVIRUS 32
4.2. TOXOPLASMOSIS 33
4.3. GESTATIONAL DIABETES 34
5. P.I.C.O. FOR FULL SEARCH QUESTIONS **37**
5.1. CYTOMEGALOVIRUS 37
5.2. TOXOPLASMOSIS 39
5.3. CHLAMYDIA TRACHOMATIS 41
5.4. GROUP B STREPTOCOCCUS 42
5.5. GESTATIONAL DIABETES 43
5.6. HYPOTHYROIDISM 45
5.7. VITAMIN D DEFICIENCY 47
5.8. RISK OF PRETERM BIRTH 48
5.9. RISK OF PREECLAMPSIA 51
5.10. SURVEILLANCE OF PREGNANCIES THAT PASSED THEIR DUE DATE 52
6. SEARCH STRATEGIES **54**
6.1. SEARCH STRATEGY FOR GUIDELINES 54

6.2. SEARCH STRATEGIES FOR OTHER PUBLICATIONS (SYSTEMATIC REVIEWS, META-ANALYSES, INDIVIDUAL STUDIES) FOR FULL SEARCH QUESTIONS 55
6.2.1. Cytomegalovirus 55
6.2.2. Toxoplasmosis 60
6.2.3. Chlamydia trachomatis 64
6.2.4. Group B streptococcus 69
6.2.5. Gestational diabetes 73
6.2.6. Hypothyroidism 78
6.2.7. Vitamin D deficiency 110
6.2.8. Risk of preterm birth 128
6.2.9. Risk of preeclampsia 179
6.2.10. Pregnancies that passed their due date 200
7. STUDY SELECTION 221
7.1. STUDY SELECTION FOR FULL SEARCH QUESTIONS 221
7.1.1. Cytomegalovirus 221
7.1.2. Toxoplasmosis 222
7.1.3. Chlamydia trachomatis 223
7.1.4. Group B streptococcus 224
7.1.5. Gestational diabetes 225
7.1.6. Hypothyroidism 227
7.1.7. Vitamin D deficiency 229
7.1.8. Risk of preeclampsia 233
7.1.9. Pregnancies that passed their due date 234
8. QUALITY APPRAISAL 235
8.1. QUALITY APPRAISAL TOOLS 235
8.1.1. Guidelines 235
8.1.2. Systematic reviews 236
8.1.3. RCTs 238
8.1.4. Observational studies 240
8.1.5. Diagnostic accuracy studies 241

8.2. QUALITY APPRAISAL OF GUIDELINES 244
8.3. QUALITY APPRAISAL FOR FULL SEARCH QUESTIONS 245
8.3.1. Cytomegalovirus 245
8.3.2. Toxoplasmosis 247
8.3.3. Chlamydia trachomatis 251
8.3.4. Group B streptococcus 252
8.3.5. Gestational diabetes 259
8.3.6. Hypothyroidism 268
8.3.7. Vitamin D deficiency 278
8.3.8. Risk of preterm birth 296
8.3.9. Risk of preeclampsia 308
8.3.10. Pregnancies that passed their due date 308
9. EVIDENCE TABLES 315
9.1. CYTOMEGALOVIRUS 315
9.2. TOXOPLASMOSIS 317
9.2.1. Screening for toxoplamosis 317
9.2.2. Lifestyle advice for toxoplasmosis 325
9.3. CHLAMYDIA TRACHOMATIS 329
9.4. GROUP B STREPTOCOCCUS 333
9.5. GESTATIONAL DIABETES 358
9.5.1. Universal screening vs. selected screening of gestational diabetes 358
9.5.2. Early risk-factor vs. late non-risk factor screening.of gestational diabetes 362
9.5.3. Different screening tests comparison.for gestational diabetes 367
9.5.4. Diagnostic accuracy 370
9.6. HYPOTHYROIDISM 377
9.6.1. Screening for hypothyroidism in asymptomatic pregnancies 377
9.6.2. Therapy for subclinical hypothyroidism during pregnancy 381
9.7. VITAMIN D DEFICIENCY 389
9.7.1. Vitamin D supplementation during pregnancy 389

9.8. RISK OF PRETERM BIRTH 417
9.8.1. Screening for preterm birth risk 417
9.8.2. Progesterone 419
9.8.3. Cerclage 435
9.8.4. Reduced physical activity 443
9.9. PREGNANCIES THAT PASSED THEIR DUE DATE 446
10. SUMMARY OF FINDINGS TABLES AND GRADE PROFILES 461
10.1. CYTOMEGALOVIRUS 461
10.1.1. Lifestyle advice for CMV infection 461
10.2. TOXOPLASMOSIS 462
10.2.1. Screening for toxoplasmosis infection 462
10.2.2. Lifestyle advice for toxoplamosis infection 466
10.3. CHLAMYDIA TRACHOMATIS 468
10.4. GROUP B STREPTOCOCCUS 470
10.5. GESTATIONAL DIABETES 472
10.5.1. Universal screening vs. selected screening 472
10.5.2. Early risk-factor vs. late non-risk factor screening.of gestational diabetes 474
10.5.3. Different screening tests comparison.for gestational diabetes 476
10.5.4. Diagnostic accuracy 479
10.6. HYPOTHYROISDISM 481
10.6.1. Screening for hypothyroidism 481
10.6.2. Therapy for subclinical hypothyroidism 484
10.7. VITAMIN D DEFICIENCY 487
10.7.1. Vitamin D supplementation vs. no vitamin D supplementation 487
10.7.2. Vitamin D + calcium vs. no vitamin D/calcium supplementation 491
10.8. RISK OF PRETERM BIRTH 492
10.8.1. Screening by repeat digital vaginal exam versus no screening 492
10.8.2. Progesterone vs no progesterone to prevent preterm birth 493
10.8.3. Cerclage vs no cerclage to prevent preterm birth 495

10.9. PREGNANCIES THAT PASSED THEIR DUE DATE 498
11. FOREST PLOTS 504
11.1. CMV 504
11.2. TOXOPLASMOSIS 504
11.2.1. Mandatory monthly screening (1992-1995) versus recommended screening (1987-1991) in France[121] 504
11.2.2. After (1984 - 1990) versus prior (1966) implementation of screening plus treatment[53] 505
11.2.3. Prenatal screening and treatment (1976 – 1987) vs. untreated during pregnancy (1966 – 1975)[54] 506
11.2.4. Countries with prenatal screening plus treatment policies (1996 – 2000) vs. countries with neonatal screening programmes (1992 – 2000)[23] 507
11.2.5. Lifestyle for toxoplasmosis 508
11.3. CHLAMYDIA TRACHOMATIS 508
11.3.1. Routine screening vs. no routine screening for chlamydia trachomatis 508
11.3.2. Universal screening vs. screening at the discretion of attending medical staff for chlamydia trachomatis 509
11.4. GROUP B STREPTOCOCCUS 510
11.4.1. Universal screening vs. no screening for GBS 510
11.4.2. Universal screening vs. risk based prophylaxis for GBS 511
11.4.3. Universal screening vs. risk based prophylaxis (matched groups without risk factors) 512
11.4.4. Late (35 – 37 weeks) universal screening vs. early (26 – 28 weeks) universal screening 512
11.5. GESTATIONAL DIABETES 512
11.5.1. Routine screening vs. selective screening for gestational diabetes 512
11.5.2. Early screening vs. late screening for gestational diabetes 514
11.5.3. Comparisons of different thresholds for the 75g OGTT for screening for gestational diabetes 516
11.5.4. Comparisons of different combinations of GCT and OGTT for screening for gestational diabetes 517
11.6. HYPOTHYROIDISM 520
11.6.1. Therapy for subclinical hypothyroidism 520

11.7. VITAMIN D DEFICIENCY 524
11.7.1. Vitamin D supplementation versus no vitamin D supplementation 524
11.8. RISK OF PRETERM BIRTH 527
11.8.1. Progesterone vs no progesterone 527
11.8.2. Cerclage vs no cerclage 531
11.9. PREGNANCIES THAT PASSED THEIR DUE DATE 533
12. EXCLUDED STUDIES 542
13. EXAMPLE OF LIME SURVEY 543
14. SUMMARY OF UPDATING PROCESS OF 2004 RECOMMENDATIONS 545
14.1. NUMBER OF APPOINTEMENTS 545
14.2. BMI 547
14.3. BLOOD PRESSURE 551
14.4. PROTEINURIA 553
14.5. FUNDAL HEIGHT MEASUREMENT 556
14.6. FOETAL POSITION 558
14.7. FOETAL MOVEMENTS COUNTING 560
14.8. FOETAL HEART AUSCULTATION 562
14.9. ULTRASOUND SCAN DURING THE FIRST TRIMESTER 564
14.10. ULTRASOUND SCAN AFTER THE FIRST TRIMESTER 567
14.11. ANAEMIA 572
14.12. PLATELETS AND LEUKOCYTES COUNT 574
14.13. BLOOD GROUP, RHESUS AND ATYPICAL RED CELL ANTIBODIES 576
14.14. HAEMOGLOBIN DISORDERS 579
14.15. HEPATITIS B 581
14.16. HEPATITIS C 583
14.17. HIV 586
14.18. RUBELLA 588
14.19. SYPHILIS 590
14.20. HERPES SIMPLEX 592

14.21. VARICELLA 594
14.22. ASYMPTOMATIC BACTERIAL VAGINOSIS 596
14.23. ASYMPTOMATIC BACTERIURIA 598
15. EXTERNAL REVIEW 600
15.1. EVALUATION OF THE RECOMMENDATIONS 600
16. CATEGORIES OF EVIDENCE LEVELS AND GRADE OF RECOMMENDATIONS 605
16.1. KCE 2004 CLASSIFICATION 605
16.2. NICE 2008 CLASSIFICATION 606
16.3. EAC 2014 CLASSIFICATION 607
■ **REFERENCES 609**

LIST OF FIGURES

Figure 1 – Pathway of screening for CMV 32
Figure 2 – Pathway of screening for toxoplasmosis 33
Figure 3 – Classical screening strategy for gestational diabetes in Belgium 34
Figure 4 – Screening strategy for gestational diabetes proposed by the Dutch-speaking region of Belgium 35
Figure 5 – Screening strategy for gestational diabetes proposed by the French-speaking gynaecologists of Belgium in 2011 36
Figure 6 – PRISMA flowchart: screening for CMV 221
Figure 7 – PRISMA flowchart: screening for toxoplasmosis 222
Figure 8 – PRISMA flowchart: screening for chlamydia trachomatis 223
Figure 9 – PRISMA flowchart: screening for group B streptoccocus 224
Figure 10 – PRISMA flowchart: screening for gestational diabetes 225
Figure 11 – PRISMA flowchart: screening for gestational diabetes – diagnostic accuracy studies 226
Figure 12 – PRISMA flowchart: screening for hypothyroidism 227
Figure 13 – PRISMA flowchart: hypothyroidism therapy in pregnant women with subclinical hypothyroidism 228
Figure 14 – PRISMA flowchart: screening for vitamin D deficiency 229
Figure 15 – PRISMA flowchart: vitamin D supplementation during pregnancy 230

Figure 16 – PRISMA flowchart: screening for risk of preterm birth by transvaginal ultrasound, and digital exam in exclusively or predominantly low risk pregnant women 231
Figure 17 – PRISMA flowchart: progesterone, cervical cerclage and reduced activities in exclusively or predominantly low risk pregnant women with short cervix 232
Figure 18 – PRISMA flow chart: screening for risk of preeclampsia 233
Figure 19 – PRISMA flow chart: surveillance of prolonged pregnancies 234
Figure 20 – Lifestyle advice for CMV: Forest plot for maternal seroconversion 504
Figure 21 – Screening for toxoplasmosis infection: Forest plot for infections in newborn 504
Figure 22 – Screening for toxoplasmosis infection: Forest plot for clinical signs at 3 years 505
Figure 23 – Sreening for toxoplasmosis infection: Forest plot for incidence of primary infection during pregnancy 505
Figure 24 – Screening for toxoplasmosis infection: Forest plot for incidence of congenital infection 506
Figure 25 – Screening for toxoplasmosis infection: Forest plot for incidence of symptomatic congenital infection 506
Figure 26 – Screening for toxoplasmosis infection: Forest plot for serious neurological sequelae or death .. 507
Figure 27. Lifestyle for toxoplasmosis: Forest plot for seroconversion rate 508
Figure 28 – Screening for chlamydia: Forest plot for preterm labour 508
Figure 29 – Screening for chlamydia: Forest plot for maternal febrile morbidity 509
Figure 30 – Screening for chlamydia: Forest plot for intra- and/or post-partum antibiotic treatment 509
Figure 31 – Screening for chlamydia: Forest plot for maternal febrile morbidity 509
Figure 32 – Screening for chlamydia: Forest plot for neonatal febrile morbidity 509
Figure 33 – Screening for GBS: Forest plot for early onset Group B neonatal sepsis 510
Figure 34 – Screening for GBS: Forest plot for mortality due to GBS sepsis 510
Figure 35 – Screening for GBS: Forest plot for early onset Group B neonatal sepsis 511
Figure 36 – Screening for GBS: Forest plot for early onset Group B neonatal sepsis – unadjusted / adjusted results 511
Figure 37 – Screening for GBS: Forest plot for mortality due to GBS sepsis 511
Figure 38 – Screening for GBS: Forest plot for positive GBS culture based neonatal screen 512
Figure 39 – Screening for GBS: Forest plot for positive blood and group B streptococci culture results in newborns 512

Figure 40 – Screening for gestational diabetes: Forest plot for macrosomia in two step 50g GCT 100g OGTT 512
Figure 41 – Screening for gestational diabetes: Forest plot for macrosomia with one step 75g OGTT..... 513
Figure 42 – Screening for gestational diabetes: Forest plot for large for gestational age with one step 75g OGTT ≥ 8.0mmol/L 513
Figure 43 – Screening for gestational diabetes: Forest plot for large for gestational age with one step 75g OGTT ≥ 10mmol/L 513
Figure 44 – Screening for gestational diabetes: Forest plot for respiratory distress with one step 75g OGTT 513
Figure 45 – Screening for gestational diabetes: Forest plot for hypoglycaemia with one step 75g OGTT 514
Figure 46 – Screening for gestational diabetes: Forest plot for birth weight ≥4000g with two-step 50g GCT 100g OGTT 514
Figure 47 – Screening for gestational diabetes: Forest plot for macrosomia with GCT undefined threshold . 514
Figure 48 – Screening for gestational diabetes: Forest plot for macrosomia with two-step 50g GCT 100g OGTT 514
Figure 49 – Screening for gestational diabetes: Forest plot for malformations with GCT undefined threshold 515
Figure 50 – Screening for gestational diabetes: Forest plot for malformations with two-step 50g GCT 100g OGTT 515
Figure 51 – Screening for gestational diabetes: Forest plot for fetal mortality with two-step 50g GCT 100g OGTT 515
Figure 52 – Screening for gestational diabetes: Forest plot for perinatal mortality with GCT undefined threshold 515
Figure 53 – Screening for gestational diabetes: Forest plot for respiratory distress syndrome with two-step 50g GCT 100g OGTT 516
Figure 54 – Screening for gestational diabetes: Forest plot for diabetes on follow-up with defined threshold 516
Figure 55 – Screening for gestational diabetes: Forest plot for preeclampsia with GCT undefined threshold 516
Figure 56 – Screening for gestational diabetes: Forest plot for large for gestational age: 8.9 vs 10.0mmol/L 516
Figure 57 – Screening for gestational diabetes: Forest plot for large for gestational age: 8.9 vs 12.2mmol/L 517
Figure 58 – Screening for gestational diabetes: Forest plot for large for gestational age: 10.0 vs 12.2mmol/L 517

Figure 59 – Screening for gestational diabetes: Forest plot for hypoglycaemia with one-step vs two-step 50g GCT 75g OGTT 517
Figure 60 – Screening for gestational diabetes: Forest plot for hypoglycaemia with one-step 75g vs two-step 50g 100 OGTT 517
Figure 61 – Screening for gestational diabetes: Forest plot for hypoglycaemia with two-step 50g GCT with 75g vs 100g OGTT 518
Figure 62 – Screening for gestational diabetes: Forest plot for preeclampsia with one-step vs two-step 50g GCT 75g OGTT 518
Figure 63 – Screening for gestational diabetes: Forest plot for preeclampsia with two-step 50g GCT with 75g vs 100g OGTT 518
Figure 64 – Screening for gestational diabetes: Coupled sensitivity / specificity plot with 50g GCT and 140mg/dl threshold (not in at-risk groups) 518
Figure 65 – Screening for gestational diabetes: Coupled sensitivity / specificity plot with 50g GCT and 130mg/dl threshold (at-risk group) 518
Figure 66 – Screening for gestational diabetes: Coupled sensitivity / specificity plot with 50g GCT and 135mg/dl threshold (at-risk group) 519
Figure 67 – Screening for gestational diabetes: Coupled sensitivity / specificity plot with 50g GCT and 140mg/dl threshold (at-risk groups) 519
Figure 68 – Screening for gestational diabetes: Coupled sensitivity / specificity plot with 50g GCT and threshold range of 130-139mg/dl (at-risk group) 519
Figure 69 – Screening for gestational diabetes: Coupled sensitivity / specificity plot with 50g GCT and threshold range of 140-149mg/dl (at-risk group) 519
Figure 70 – Levothyroxine versus no treatment: Forest plot for miscarriage 520
Figure 71 – Levothyroxine versus no treatment: Forest plot for preterm birth < 37 weeks 521
Figure 72 – Levothyroxine versus no treatment: Forest plot for very preterm Birth (<34 weeks) 521
Figure 73 – Levothyroxine versus no treatment: Forest plot for preeclampsia 522
Figure 74 – Levothyroxine versus no treatment: Forest plot for gestational Hypertension 522
Figure 75 – Levothyroxine versus no treatment: Forest plot for NICU admission 523
Figure 76 – Levothyroxine versus no treatment: Forest plot for low birth weight <2500 grams 523
Figure 77 – Third trimester vitamin D vs. no vitamin D supplementation: Forest plot for gestational age at delivery (weeks) 524

Figure 78 – Third trimester vitamin D vs. no vitamin D supplementation: Forest plot for low birth weight (various definitions) 524
Figure 79 – Third trimester vitamin D vs. no vitamin D supplementation: Forest plot for birth weight <2500 grams 525
Figure 80 – Third trimester vitamin D vs. no vitamin D supplementation: Forest plot for birth length in centimetres 525
Figure 81 – Third trimester vitamin D vs. no vitamin D supplementation: Forest plot for head circumference (cm) at birth 526
Figure 82 – Third trimester vitamin D vs. no vitamin D supplementation: Forest plot for neonatal death 526
Figure 83 – Progesterone vs. no active intervention: Forest plot for perinatal mortality 527
Figure 84 – Progesterone vs. no active intervention: Forest plot for neonatal death 527
Figure 85 – Progesterone vs. no active intervention: Forest plot for still birth/fetal death 528
Figure 86 – Progesterone vs. no active intervention: Forest plot for abortion <20 weeks 528
Figure 87 – Progesterone vs. no active intervention: Forest plot for seizure 528
Figure 88 – Progesterone vs. no active intervention: Forest plot for neonatal survival free of morbidities 529
Figure 89 – Progesterone vs. no active intervention: Forest plot for major adverse neonatal outcomes (mortality and 4 common morbidities: intraventricular haemorrhage, necrotizing enterocolitis, respiratory distress syndrome, periventricular leukomalacia) 529
Figure 90 – Progesterone vs. no active intervention: Forest plot for PTB <37 weeks 530
Figure 91 – Progesterone vs. no active intervention: Forest plot for PTB <34 weeks 530
Figure 92 – Progesterone vs. no active intervention: Forest plot for PTB <28 weeks 531
Figure 93 – Cerclage (+ modified bed rest +/- progesterone) vs. bed rest (+/- progesterone): Forest plot for total major maternal adverse event 531
Figure 94 – Cerclage vs no cerclage: Forest plot for PTB <37 weeks gestation 532
Figure 95 – Cerclage vs. no cerclage: Forest plot for PTB <34 weeks gestation 532
Figure 96 – Cerclage vs. no cerclage: Forest plot for PTB <28 weeks gestation 533
Figure 97 – Various surveillance interventions for prolonged pregnancy: Forest plot for neonatal death 533
Figure 98 – Various surveillance interventions for prolonged pregnancy: Forest plot for perinatal death 534
Figure 99 – Various surveillance interventions for prolonged pregnancy: Forest plot for still birth 534
Figure 100 – Various surveillance interventions for prolonged pregnancy: Forest plot for NICU admission 535

Figure 101 – Various surveillance interventions for prolonged pregnancy: Forest plot for Apgar score (various cut offs) 535
Figure 102 – Routine scan versus indicated scan for prolonged pregnancy: Forest plot for hypoxic ischemic encephalopathy grades 2 and 3 536
Figure 103 – Routine scan versus indicated scan for prolonged pregnancy: Forest plot for cerebral palsy 536
Figure 104 – [Test 1:(CTG+fetal movement)] +/- Test 2: partial BP if non reactive test 1 versus: [Test 1:(CTG+fetal movement) +Test2: AFV]+/- Test 2: partial BP if non reactive test 1 for prolonged pregnancy: Forest plot for meconium aspiration syndrome 537
Figure 105 – Routine scan versus indicated scan for prolonged pregnancy: Forest plot for neonatal convulsion 537
Figure 106 – Routine scan versus indicated scan for prolonged pregnancy: Forest plot for cerebral haemorrhage 538
Figure 107 – Routine scan versus indicated scan for prolonged pregnancy: Forest plot for cerebral damage 538
Figure 108 – Various surveillance interventions for prolonged pregnancy: Forest plot for instrumental delivery 539
Figure 109 – CTG+ AFI versus CTG+AFD for prolonged pregnancy: Forest plot for C-section due to fetal distress 539
Figure 110 – BP2 versus CTG+AFD for prolonged pregnancy: Forest plot for C-section due to fetal distress 540
Figure 111 – Various surveillance interventions for prolonged pregnancy: Forest plot for C-section for reasons other than fetal distress or lack of progression of labor 540
Figure 112 – Various interventions versus CTG+AFD for prolonged pregnancy: Forest plot for C-section due to failure to progress or ante partum distress 541

LIST OF TABLES

Table 1 – List of proposed topics by the GDG to be included in the guideline 27
Table 2 – Comparison of risk factors 29
Table 3 – PICO framework CMV infection 37
Table 4 – PICO framework toxoplasmosis infection 39
Table 5 – PICO framework chlamydia trachomatis infection 41
Table 6 – PICO Framework group B streptococcus infection 42
Table 7 – PICO framework gestational diabetes 43

Table 8 – PICO framework hypothyroidism 45
Table 9 – PICO framework vitamin D deficiency 47
Table 10 – PICO framework preterm birth risk 48
Table 11 – PICO framework preeclampsia risk 51
Table 12 – PICO framework surveillance of pregnancies 52
Table 13 – Search results - Guidelines on antenatal care 54
Table 14 – Search strategies: Benefits-harms of screening and lifestyle advice for CMV infection during pregnancy 55
Table 15 – Search strategies: Benefits-harms of screening and advice for toxoplasmosis infection during pregnancy 60
Table 16 – Search strategies: Benefits-harms of screening for chlamydia trachomatis infection during pregnancy 64
Table 17 – Search strategies: Benefits-harms of screening for GBS infection during pregnancy 69
Table 18 – Search strategies: Benefits-harms of different stategies of screening for gestational diabetes 73
Table 19 – Search strategies: Benefits-harms of screening for hypothyroidism during pregnancy (SRs) 78
Table 20 – Search strategies: Benefits-harms of screening for hypothyroidism during pregnancy (Primary studies) 82
Table 21 – Second search strategies: Benefits-harms of screening for hypothyroidism during euthyroid pregnancies (Primary studies) 88
Table 22 – Search strategies: Benefits-harms of therapy for subclinical hypothyroidism during pregnancy (SRs) 94
Table 23 –Search strategies: Benefits-harms of therapy for subclinical hypothyroidism during pregnancy (Primary- RCTs) 97
Table 24 – Second search strategies: Benefits-harms of therapy for subclinical hypothyroidism during euthyroid pregnancy (Primary- RCTs) 100
Table 25 – Search strategies: Benefits-harms of therapy for subclinical hypothyroidism during pregnancy (Primary- Observational) 104
Table 26 – Second search strategies: Benefits-harms of therapy for subclinical hypothyroidism during euthyroid pregnancy (Primary- Observational) 107
Table 27 – Search strategies: Benefits-harms of screening for vitamin D deficiency during pregnancy (SRs) 110

Table 28 – Search strategies: Benefits-harms of screening for vitamin D deficiency during pregnancy (Primary studies) 114
Table 29 – Search strategies: Benefits-harms of vitamin D supplementation during pregnancy (SRs) 119
Table 30 – Search strategies: Benefits-harms of vitamin D supplementation during pregnancy (Primary-RCTs) 122
Table 31 – Search strategies: Benefits-harms of vitamin D supplementation during pregnancy (Primary-Observational) 125
Table 32 – Search strategies: Benefits-harms of transvaginal ultrasound for cervical length, funneling, or both, and/or digital vaginal exam in exclusively or predominantly low risk pregnant women (SRs) 128
Table 33 – Search strategies: Benefits-harms of transvaginal ultrasound for cervical length, funneling, or both in exclusively or predominantly low risk pregnant women (Primary RCTs/CCTs) 133
Table 34 – Search strategies: Benefits-harms of transvaginal ultrasound for cervical length, funneling, or both in exclusively or predominantly low risk pregnant women (Primary observational studies) 138
Table 35 – Search strategies: Benefits-harms of digital vaginal exam with or without transvaginal exam in exclusively or predomninantly low risk pregnant women (Primary RCTs and CCTs) 141
Table 36 – Search strategies: Benefits-harms of digital vaginal exam with or without transvaginal ultrasound in exclusively or predomninantly low risk pregnant women (Primary observational studies) 145
Table 37 – Search strategies: Benefits-harms of progesterone, cervical cerclage and reduced physical activity and in asymptomatic pregnant women with short cervix (SRs) 150
Table 38 – Search strategies: Benefits-harms of progesterone in asymptomatic pregnant women with short cervix (Primary RCTs) 157
Table 39 – Search strategies: Benefits-harms of cerclage in asymptomatic pregnant women with short cervix (Primary RCTs) 164
Table 40 – Search strategies: Benefits-harms of bed rest in asymptomatic pregnant women with short cervix (Primary RCTs) 168
Table 41 – Search strategies: Benefits-harms of progesterone, cerlcage and bed rest in asymptomatic pregnant women with short cervix (Primary observational evidence) 172
Table 42 – Search strategies: Benefits-harms of screening for preeclampsia risk with additional tests compared with usual routine assessment based on history and physical exam (SRs) 179
Table 43 – Search strategies: Benefits-harms of screening for preeclampsia risk with additional tests compared with usual routine assessment based on history and physical exam (Primary RCTs) 185

Table 44 – Search strategies: Benefits-harms of screening for preeclampsia risk with additional tests compared with usual routine assessment based on history and physical exam (Primary observational evidene excluding “dipstick” intervention) 191

Table 45 – Search strategies: Benefits-harms of screening for preeclampsia risk with additional tests compared with usual routine assessment based on history and physical exam (Primary observational evidence for dipstick intervention only) 196

Table 46 – Search strategies: Benefits-harms of different monitoring strategies by CTG, ultrasound, and combination of these tests with or without other tests in asymptomatic pregnant women remaining undelivered after ~40 weeks gestation (SRs) 200

Table 47 – Search strategies: Benefits-harms of monitoring strategies by CTG in asymptomatic pregnant women remaining undelivered after ~40 weeks gestation (Primary RCTs) 205

Table 48 – Search strategies: Benefits-harms of monitoring strategies by ultrasound examination of amniotic fluid index, volume and depth in asymptomatic pregnant women remaining undelivered after ~40 weeks gestation (Primary RCTs) 209

Table 49 – Search strategies: Benefits-harms of monitoring strategies by combination of CTG and ultrasound examination of amniotic fluid index, volume and depth in asymptomatic pregnant women remaining undelivered after ~40 weeks gestation (Primary RCTs) 212

Table 50 – Search strategies: Benefits-harms of monitoring strategies by CTG, ultrasound examination of amniotic fluid index, volume and depth, and combination of these tests in asymptomatic pregnant women remaining undelivered after ~40 weeks gestation (Primary observational body of evidence) 217

Table 51 – AGREE II instrument 235

Table 52 – AMSTAR checklist 236

Table 53 – Modified AMSTAR checklist 237

Table 54 – Cochrane Collaboration’s tool for assessing risk of bias 238

Table 55 – Quality appraisal for cohort studies – tool used by the NCGC 240

Table 56 – Quality appraisal for cohort studies – tool used by the OHRI 241

Table 57 – The QUADAS tool 241

Table 58 – AGREE scores of identified guidelines 244

Table 59 – Lifestyle advice for CMV: Quality appraisal of the one selected primary observational study (ADLER 2004[5]) 245

Table 60 – Screening for toxoplasmosis: Quality appraisal of selected primary studies (Cohort studies) – screening vs. no screening 247

Table 61 – Lifestyle advice for toxoplasmosis: Quality appraisal of selected systematic review - (prenatal education) vs. no specific advice 249
Table 62 – Lifestyle advice for toxoplasmosis: Quality appraisal of selected primary studies (Cohort studies) – routine advice vs, no specific advice 250
Table 63 – Screening for chlamydia: Quality appraisal of selected primary studies (Cohort studies) 251
Table 64 – Screening for GBS: Quality appraisal of selected primary studies (Cohort studies) – screening vs. no screen / risk based prophylaxis for GBS (part 1) 252
Table 65 – Screening for chlamydia: Quality appraisal of selected primary studies (Cohort studies) – screenong vs. no screen / risk based prophylaxis for GBS (part 2) 254
Table 66 – Screening for chlamydia: Quality appraisal of selected primary studies (cohort studies) – screening vs. no screen / risk based prophylaxis for GBS (part 3) 256
Table 67 – Screening for chlamydia: Quality appraisal of selected primary studies (Cohort studies) – late vs. early screening for GBS 257
Table 68 – Screening for gestational diabetes: Quality appraisal of selected primary studies (RCTs) – universal vs. selected screening 259
Table 69 – Screening for gestational diabetes: Quality appraisal of selected primary studies (Cohort studies) – universal vs. selected screening 260
Table 70 – Screening for gestational diabetes: Quality appraisal of selected primary studies (Cohort studies) – early vs. late screening 262
Table 71 – Screening for gestational diabetes: Quality appraisal of selected primary studies (Cohort studies) – different thresholds for tests used 263
Table 72 – Screening for gestational diabetes: Quality appraisal of selected primary studies (RCTs) – different test combinations used 264
Table 73 – Diagnostic accuracy for gestational diabetes: Quality appraisal of the included studies 265
Table 74 – Screening for hypothyroidism: Quality appraisal of selected primary studies (RCTs) 268
Table 75 – Therapy for subclinical hypothyroidism during pregnancy: Quality appraisal of the selected systematic review 270
Table 76 – Therapy for subclinical hypothyroidism during pregnancy: Quality appraisal of the selected primary studies (RCTs) 271
Table 77 – Therapy for subclinical hypothyroidism during pregnancy: Quality appraisal for RCTs included in the Reid et al. 2013 SR 275
Table 78 – Therapy for subclinical hypothyroidism during pregnancy: Quality appraisal of the selected studies (Observational study) 277

Table 79 – Vitamin D supplementation: Quality appraisal of the selected SR (De-Regil et al., 2012[58]) 278
Table 80 – Vitamin D supplementation: Quality appraisal of selected primary studies (RCTs) 280
Table 81 – Vitamin D supplementation: Quality appraisal of selected primary studies (Observational studies) 291
Table 82 – Progesterone therapy to prevent preterm birth in asymptomatic women with short cervix but no additional risk factors for preterm birth: Quality appraisal of selected primary studies (RCTs) 296
Table 83 – Cerclage versus no cerclage to prevent preterm birth in asymptomatic women with short cervix but no additional risk factors for preterm birth: Quality appraisal of selected primary studies (RCTs) 305
Table 84 – Reduced physical activity vs. no activity restriction to prevent preterm birth in asymptomatic women with short cervix but no additional risk factors for preterm birth: Quality appraisal of selected primary studies (Observational study) - 308
Table 85 – Surveillance of pregnancies that passed their due date: Quality appraisal of selected primary studies (RCTs) 308
Table 86 – Surveillance of pregnancies that passed their due date: Quality appraisal of selected primary studies (Observational studies) 313
Table 87 – Lifestyle advice for CMV: Evidence table of RCT (ADLER 2004) 315
Table 88 – Screening for toxoplasmosis: Evidence table of observational study (Aspöck & Pollak, 1992) 317
Table 89 – Screening for toxoplasmosis: Evidence table of observational study (Cortina-Borja et al., 2010) 318
Table 90 – Screening for toxoplasmosis: Evidence table of observational study (Hengst 1992) 320
Table 91 – Screening for toxoplasmosis: Evidence table of observational study (Henri et al.,1992) 321
Table 92 – Screening for toxoplasmosis: Evidence table of observational study (Ricci et al., 2003) 322
Table 93 – Screening for toxoplasmosis: Evidence table of observational study (Wallon et al., 2013) 323
Table 94 – Lifestyle advice for toxoplasmosis: Evidence table of systematic review (Di Mario et al., 2013) .. 325
Table 95 – Lifestyle for toxoplasmosis: Evidence table of observational study (Breugelmans et al., 2004 & Foulon et al., 1988) 327
Table 96 – Lifestyle for toxoplasmosis: Evidence table of observational study (Pawlowski et al., 2001) 328
Table 97 – Screening for chlamydia: Evidence table of observational study (Beal, 1992) 329
Table 98 – Screening for chlamydia: Evidence table of observational study (Quinlivan, Petersen & Gurrin, 1998) 331
Table 99 – Screening for GBS: Evidence table of observational study (Abdelmaaboud & Mohammed, 2011) 333

Table 100 – Screening for GBS: Evidence table of observational study (Angstetra, Ferguson & Giles, 2007) 334
Table 101 – Screening for GBS: Evidence table of observational study (Brozanski et al., 2000) 336
Table 102 – Screening for GBS: Evidence table of observational study (Davis et al., 2001) 337
Table 103 – Screening for GBS: Evidence table of observational study (Gilson et al., 2000) 338
Table 104 – Screening for GBS: Evidence table of observational study (Hafner et al., 1998) 340
Table 105 – Screening for GBS: Evidence table of observational study (Horvath et al., 2013) 341
Table 106 – Screening for GBS: Evidence table of observational study (Jeffery & Moses Lahra, 1998) 342
Table 107 – Screening for GBS: Evidence table of observational study (Lijoi et al., 2007) 343
Table 108 – Screening for GBS: Evidence table of observational study (Lin et al., 2011) 344
Table 109 – Screening for GBS: Evidence table of observational study (Locksmith et al., 1999) 345
Table 110 – Screening for GBS: Evidence table of observational study (Main & Slage, 2000) 347
Table 111 – Screening for GBS: Evidence table of observational study (Puopolo et al., 2005 and groups from an earlier study from the same research group (that is referenced in the study Chen et al., 2001) 349
Table 112 – Screening for GBS: Evidence table of observational study (Reisner et al., 2000) 350
Table 113 – Screening for GBS: Evidence table of observational study (Renner et al., 2006) 351
Table 114 – Screening for GBS: Evidence table of observational study (Schrag et al., 2013, Centre for Disease Control and Prevention, 2009, Schrag et al., 2002, Schrag et al., 2002a, and Schrag et al., 2000) 352
Table 115 – Screening for GBS: Evidence table of observational study (Share et al., 2001) 354
Table 116 – Screening for GBS: Evidence table of observational study (Vergani et al., 2002) 355
Table 117 – Screening for GBS: Evidence table of observational study (Voluménie et al., 2001) 356
Table 118 – Screening for gestational diabetes: Evidence table (Bebbington et al., 1999) 358
Table 119 – Screening for gestational diabetes: Evidence table (Davis et al., 2013) 359
Table 120 – Screening for gestational diabetes: Evidence table (Dietrich et al., 1987) 361
Table 121 – Screening for gestational diabetes: Evidence table (Dong 1993) 362
Table 122 – Screening for gestational diabetes: Evidence table (Jovanovic 1985) 364
Table 123 – Screening for gestational diabetes: Evidence table (Lapolla et al., 1995) 365
Table 124 – Screening for gestational diabetes: Evidence table (Lindqvist et al., 2014) 367
Table 125 – Screening for gestational diabetes: Evidence table (Meltzer et al., 2010) 368
Table 126 – Diagnostic accuracy for gestational diabetes tests: Evidence table (Ayach et al., 2006) 370

Table 127 – Diagnostic accuracy for gestational diabetes tests: Evidence table (Espinosa de los Monteros et al., 1999) 371
Table 128 – Diagnostic accuracy for gestational diabetes tests: Evidence table (Perucchini et al., 1999) 373
Table 129 – Diagnostic accuracy for gestational diabetes tests: Evidence table (Thitadilok et al., 1995) 374
Table 130 – Diagnostic accuracy for gestational diabetes tests: Evidence table (Weerakiet et al., 2006) 375
Table 131 – Screening for hypothyroidism: Evidence table (Lazarus, 2012) 377
Table 132 – Screening for hypothyroidism: Evidence table (Negro et al., 2010) 379
Table 133 – Therapy for subclinical hypothyroidism: Evidence table for the selected systematic review (Reid et al., 2013) 381
Table 134 – Therapy for subclinical hypothyroidism: Evidence table of RCTs (Mao et al., 2013) 382
Table 135 – Therapy for subclinical hypothyroidism: Evidence table of RCTs (Jain et al., 2013) 383
Table 136 – Therapy for subclinical hypothyroidism: Evidence table of RCTs (Kim et al., 2011) 384
Table 137 – Therapy for subclinical hypothyroidism: Evidence table of RCTs (Negro et al., 2005) 385
Table 138 – Therapy for subclinical hypothyroidism: Evidence table of one RCT excluded from Reid et al., 2013 (Negro et al., 2010) 386
Table 139 – Therapy for subclinical hypothyroidism: Evidence table of observational study (Wang et al., 2012) 388
Table 140 – Vitamin D supplementation: Evidence table of systematic review (De-Regil et al., 2012) 389
Table 141 – Vitamin D supplementation: Evidence table of RCTs (Asemi et al., 2013) 391
Table 142 – Vitamin D supplementation: Evidence table of RCTs (Brooke et al., 1980) 392
Table 143 – Vitamin D supplementation: Evidence table of RCTs (Delvin et al., 1986) 394
Table 144 – Vitamin D supplementation: Evidence table of RCTs (Diogenes et al., 2013 and Companions) 395
Table 145 – Vitamin D supplementation: Evidence table of RCTs (Grant et al., 2014) 396
Table 146 – Vitamin D supplementation: Evidence table of RCTs (Mallet et al., 1986) 397
Table 147 – Vitamin D supplementation: Evidence table of RCTs (Marya et al., 1988) 398
Table 148 – Vitamin D supplementation: Evidence table of RCTs (Marya et al., 1987) 399
Table 149 – Vitamin D supplementation: Evidence table of RCTs (Roth et al., 2012) 400
Table 150 – Vitamin D supplementation: Evidence table of RCTs (Yu et al., 2009) 402
Table 151 – Vitamin D supplementation: Evidence table of observational study (Althaus et al.) 404
Table 152 – Vitamin D supplementation: Evidence table of observational study (Cremers et al., 2011) 405

Table 153 – Vitamin D supplementation: Evidence table of observational study (Erkkola et al.2009) 406
Table 154 – Vitamin D supplementation: Evidence table of observational study (Goldring et al., 2013)..... 407
Table 155 – Vitamin D supplementation: Evidence table of observational study (Haugen et al., 2009)..... 408
Table 156 – Vitamin D supplementation: Evidence table of observational study (Jacobsen et al., 2013)..... 409
Table 157 – Vitamin D supplementation: Evidence table of observational study (Kalra et al., 2012)..... 410
Table 158 – Vitamin D supplementation: Evidence table of observational study (Marjamaki et al., 2010, Companion[79])..... 412
Table 159 – Vitamin D supplementation: Evidence table of observational study (Marya et al., 1981) 413
Table 160 – Vitamin D supplementation: Evidence table of observational study (Maslova et al., 2013)..... 414
Table 161 – Vitamin D supplementation: Evidence table of observational study (Rochati et al., 2010)..... 415
Table 162 – Preterm birth risk: Evidence table of systematic reviews regarding the diagnosis of pathology or effect of Intervention (Alexander et al., 2010)..... 417
Table 163 – Descriptive summary assessment of eight RCTs included of progesterone versus no progesterone in prevention of preterm birth..... 419
Table 164 – Progesterone in prevention of preterm birth risk: Evidence table of RCTs (Bimbashi et al., 2013)..... 420
Table 165 – Progesterone in prevention of preterm birth risk: Evidence table of RCTs (Brenner and Hendricks, 1962)..... 421
Table 166 – Progesterone in prevention of preterm birth risk: Evidence table of RCTs (DeFranco et al., 2007)..... 422
Table 167 – Progesterone in prevention of preterm birth risk: Evidence table of RCTs (Fonseca et al., 2007)[89] 423
Table 168 – Progesterone in prevention of preterm birth risk: Evidence table of RCTs (Grobman et al., 2012)..... 426
Table 169 – Progesterone in prevention of preterm birth risk: Evidence table of RCTs (Hassan et al., 2011)..... 429
Table 170 – Progesterone in prevention of preterm birth risk: Evidence table of RCTs (Moghtadaei et al., 2008) 432
Table 171 – Progesterone in prevention of preterm birth risk: Evidence table of RCTs (van Os et al., 2014) 433
Table 172 – Descriptive summary of four studies included for cerclage vs no cerclage highlighting heterogeneity among the studies in preterm risk..... 435
Table 173 – Cerclage in prevention of preterm birth risk: Evidence table of RCTs (Berghella et al., 2004)... 435

Table 174 – Cerclage in prevention of preterm birth risk: Evidence table of observational study (Hassan et al., 2001) 438
Table 175 – Cerclage in prevention of preterm birth risk: Evidence table of observational study (Sakai et al., 2006) 439
Table 176 – Cerclage in prevention of preterm birth risk: Evidence table of observational study (Skupski et al., 2014) 441
Table 177 – Reduced activity to prevent preterm birth risk: Evidence table of observational study (Grobman et al., 2013) 443
Table 178 – Descriptive summary of the six studies included for surveillance of prolonged pregnancies..... 446
Table 179 – Surveillance in prolonged pregnancies: Evidence table of RCTs (Alfirevic et al., 1997)..... 449
Table 180 – Surveillance in prolonged pregnancies: Evidence table of RCTs (Alfirevic et al., 1995)..... 451
Table 181 – Surveillance in prolonged pregnancies: Evidence table of RCTs (Oral et al., 1999) 453
Table 182 – Surveillance in prolonged pregnancy : Evidence table of observational study routine ultrasound (Lindqvist PG et al. (2014) [100]) 454
Table 183 – Surveillance in prolonged pregnancies: Evidence table of observational study (Eden, R.D., 1981) 456
Table 184 – Surveillance in prolonged pregnancies: Evidence table of observational study. (El-Damarawy et al., 1993) 459
Table 185 - Summary of findings and GRADE profile: advice vs. no advice for CMV infection..... 461
Table 186 – Summary of findings and GRADE profile: mandatory monthly (after 1992-1995) vs. recommended screening (prior 1987-1991) for toxoplasmosis 462
Table 187 – Summary of findings and GRADE profile: after (1984 - 1990) vs. prior (1966) to implementation of toxoplasmosis screening plus treatment..... 463
Table 188 – Summary of findings and GRADE profile: prenatal toxoplasmosis screening and treatment (1976 – 1987) vs. untreated during pregnancy (1966 – 1975) 464
Table 189 – Summary of findings and GRADE profile: countries with prenatal toxoplasmosis screening plus treatment policies (1996 – 2000) vs. countries with neonatal screening programmes (1992 – 2000)..... 464
Table 190 – GRADE profile: prenatal education programme (second phase 1983 – 1990, third phase 1991 – 2001) vs. no specific education programme 1979 – 1982)..... 466
Table 191 – Summary of findings and GRADE profile: universal screening versus no screening for chlamydia trachomatis..... 468

Table 192 – Summary of findings and GRADE profile: universal screening vs. medical staff discretion screening for chlamydia trachomatis 469
Table 193 Summary of findings and GRADE profile: universal GBS screening vs. no screening 470
Table 194 – Summary of findings and GRADE profile: universal late (35-37 weeks gestation) vs. universal early (26-28 week) gestation screening for GBS 471
Table 195 – Summary of findings and GRADE profile: universal versus selected screening for gestational diabetes 472
Table 196 – Summary of findings and GRADE profile: early versus late screening for gestational diabetes 474
Table 197 – Summary of findings and GRADE profile: comparisons of different combinations of glucose challenge and glucose tolerance tests when screening for gestational diabetes 476
Table 198 – Summary of findings and GRADE profile: comparisons of different thresholds for the 75g OGTT when screening for gestational diabetes 477
Table 199 – Summary of findings and GRADE profile: comparisons of different combinations of glucose challenge and glucose tolerance tests when screening for gestational diabetes 478
Table 200 – Summary of findings and clinical evidence profile for studies investigating 50g glucose challenge test (at listed thresholds) compared to the reference standard of 100g oral glucose tolerance test (non-risk population) 479
Table 201 – Summary of findings and clinical evidence profile for studies investigating 50g glucose challenge test (at listed thresholds) compared to the reference standard of 100g oral glucose tolerance test (at-risk populations) 479
Table 202 – Summary of findings and GRADE profile: universal screening versus no screening for hypothyroidism in asymptomatic pregnancies 481
Table 203 – Summary of findings and GRADE profile: universal versus targeted TSH screening in TPO-antibody positive pregnant women 482
Table 204 – Summary of findings and GRADE profile: universal screening for TPO-antibody positive hypothyroidism (i.e. raised TSH) versus screening in only high risk pregnancies 483
Table 205 – Summary of findings and GRADE profile: levothyroxine versus no treatment for subclinical hypothyroidism 484
Table 206 – Summary of findings and GRADE profile: selenomethionine versus no treatment for subclinical hypothyroidiism 486
Table 207 – Summary of findings and GRADE profile GRADE vitamin D supplementation (RCTs) vs no supplementation 487

Table 208 – Summary of findings and GRADE profile: vitamin D vs. no vitamin D supplementation (observational studies): type 1 diabetes mellitus 490
Table 209 – Summary of findings and GRADE profile: vitamin D plus calcium vs. no treatment 491
Table 210 – Summary of findings and GRADE profile: repeated digital exam 492
Table 211 – Summary of findings and GRADE profile: progesterone versus no active intervention 493
Table 212 – Summary of findings and GRADE profile: cerclage vs no cerclage 495
Table 213 – Summary of findings and GRADE profile: reduced activity to prevent preterm birth and its sequelae in asymptomatic women with short cervix but no additional risk factors for preterm birth 497
Table 214 – Summary of findings and GRADE profile: surveillance of postterm pregnancies: neonatal death 498
Table 215 – KCE categories of evidence level and grade of recommendation (2004) 605
Table 216 – NICE categories of evidence level and grade of recommendation (2008) 606
Table 217 – EAC categories of evidence level and grade of recommendation (2014) 607

1. COMPOSITION OF EXPERTS AND STAKEHOLDERS GROUPS

1.1. Composition of the Guideline Development Group

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1.2. Composition of the Stakeholders Group

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1.3. Composition of the KCE expert team

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1.4. External researchers involved in the guideline development

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Laura M. Gaudet (OHRI)	Clinical expert
Jennifer Marie Tetzlaff (OHRI)	Research Associate

2. TOPICS PROPOSED BY THE GDG

Table 1 – List of proposed topics by the GDG to be included in the guideline

NUMBER OF CONSULTATION & CLINCAL EXAMINATION
1. Consultation: More for primipare?
2. Hypertension: History taking? Which measurement and when? Home monitoring?
3. Depression/psychosocial disorders: For every pregnant women? How?
CLINICAL BIOLOGY
4. Diabetes: For every pregnant women? Which threshold?
5. Thyroïde disorders: Screening?
6. Proteinuria: Which testing (stick vs urine/creat ratio)?
7. Blood group: To be determined 2 times?
INFECTIONS
8. CMV: Screening still useful? Safety of acyclovir? Systematic neonatal screening?
9. Asymptomatic bacteriuria: Management?
10. Hepatitis: All kind or HepBSAg alone?
11. Toxoplasmosis: Still useful given the lower incidence?
12. Vaccination (boostrix, influenza) : Which, when?
13. Immunoglobin (varicella-zoster)?
14. Nutritional advise?(listeriose)
TECHNICAL EXAMINATION
15. Ultrasound: • sense and nonsense of 3rd trimester scan • sense and nonsense of very early scan (< 10 weeks) • systematic measurement of cervical length
16. Follow up of pregnancy which have exceeded the normal term: CTG, amniotic fluid measurement

17. Echo-doppler: role in hypertension?
18. Aneuploidy and genetic disorders
SPECIFIC CONDITIONS
19. Use of nutritional supplementation
20. Anti-D prophylaxis in women rhesus D negative (1 of 2 injections?)
21. Risk of preeclempsia
22. Risk of preterm birth: history taking? BMI? Cervical length measurement?
23. Factors for a risk stratification: definition

3. RISK FACTORS THAT MAY IMPLY ADDITIONAL CARE

Table 2 – Comparison of risk factors

KCE 2004 guideline (FR/NL)	NICE 2008 guideline	Australian 2014 guideline	KCE 2015 guideline
1. General information			
Age < 16 ou > 40 / Leeftijd < 16 of > 40	Age 40 years or older	Adolescent-teenager or > 40 years	Age < 18 years or > 40 years
Début des soins à proximité du terme / Late prenatale zorg			Late antenatal care: 1st antenatal consultation after 20 weeks
Risques au travail / Occupation hazards	Occupational hazards		
Milieu défavorisé, vulnérabilité sociale / suboptimale socio-economische omstandigheden	Women who are particularly vulnerable (e.g. women 18 years or younger) or who lack social support	• Psychosocial issues/ mental health problems • Developmental delay or other disabilities • Vulnerability or lack of social support	Lack of social support, domestic violence, psycho-social vulnerability
Utilisation de médicaments / Geneesmiddelen gebruik	Medicines	On medication	Use of medicines
		Immunization	Immunization status (lack of vaccination again hepatitis B, rubella and/or lack of history of rubella, varicella, toxoplasmosis, CMV)
2. Lifestyle factors			
Drogues / Druggebruik	Drug use such as heroin, cocaine (including crack cocaine) and ecstasy	Use of recreational drugs such as heroin, cocaine (including crack cocaine), ecstasy and cannabis	Drug use
Consommation d'alcool / Alcohol	Higher risk of developing complications if alcohol	History of alcohol misuse	Alcohol consumption
			Active and/or passive smoking
Tatouages et piercings / Tattoos en piercings			

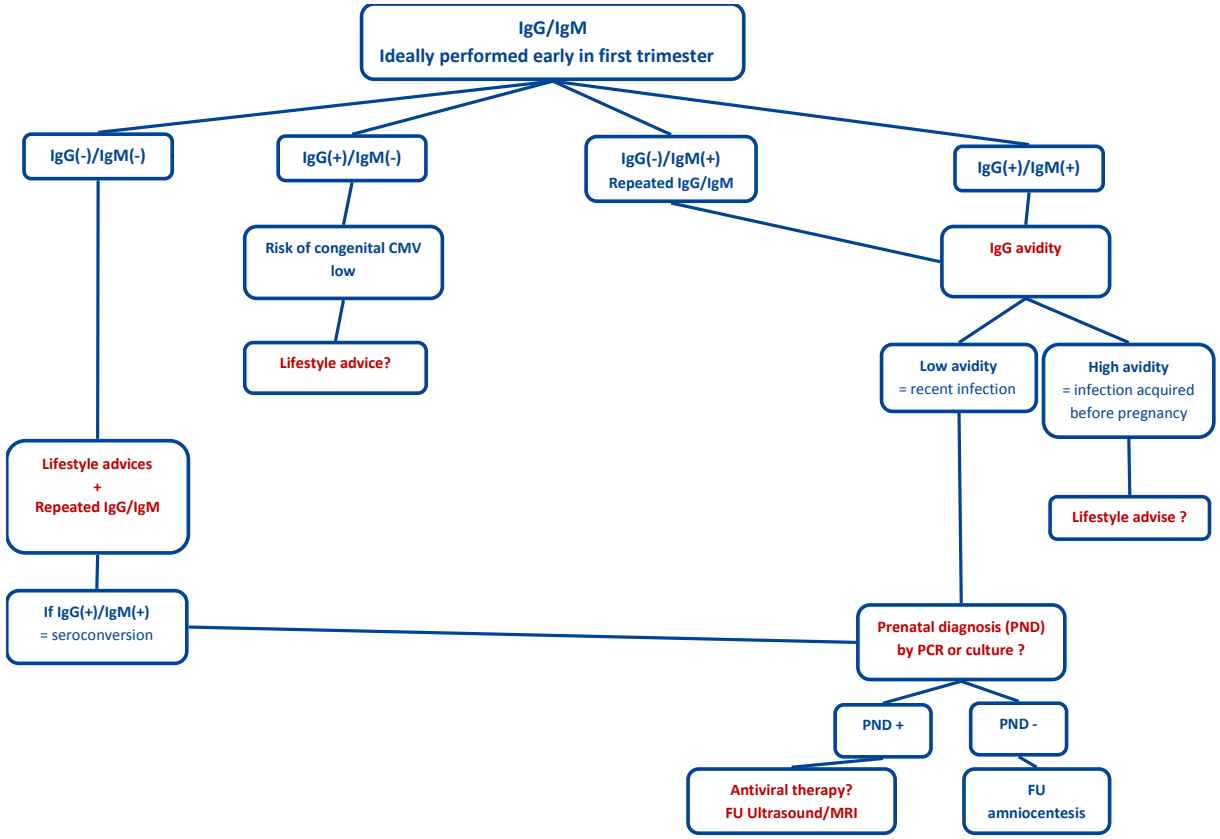
Comportement à risques pour des affections sexuellement transmissibles			**Sexual behaviours that may impact the pregnancy**
3. Familial history			
Facteurs de risque familiaux et génétiques / Familiale en genetische risicofactoren	Family history of genetic disorder		Familial diseases or genetic disorders
4. Personal history			
Toutes pathologies préexistantes qui peuvent avoir une répercussion sur la grossesse / Elke andere voorafbestaande pathologie die van belang kan zijn tijdens de zwangerschap	Existing conditions: • cardiac disease, including hypertension • renal disease • hepatic disease • endocrine disorders or diabetes • psychiatric disorders (on medication) • haematological disorders, including sickle cell or thalassaemia, thromboembolic disease, autoimmune diseases such as antiphospholipid syndrome • epilepsy requiring anticonvulsant drugs • malignant disease • severe asthma • HIV or hepatitis B virus (HBV) infected • cystic fibrosis • autoimmune disorders • obesity (body mass index, BMI, 35 kg/m² or more at first contact) or underweight (BMI less than 18 kg/m² at first contact)	Existing other conditions: • cardiovascular disease (e.g. hypertension, rheumatic heart disease) • other conditions (e.g. kidney disease, diabetes; thyroid, haematological or autoimmune disorders; epilepsy, malignancy; severe asthma; HIV, hepatitis B or hepatitis C infection) • psychiatric disorders • obesity or underweight	All pre-existing pathologies or surgical interventions that can have an impact on the pregnancy, including: • diabetes, • endocrine disorders, • auto-immune disorders, • cardiac disease, • renal disease, • hepatic disease
Diabète / Diabetes	Diabetes	Diabetes	See above
Maladies auto-immunes / Auto-immuunziekten	Endocrine disorder		See above
5. Gynaecological history			
Pathologie utérine (anomalie congénitale, chirurgie de l'utérus, cytologie anormale du col),	Uterine surgery including caesarean section, myomectomy or cone biopsy	Uterine surgery (e.g. caesarean section, myomectomy or cone biopsy)	• Uterine pathology (congenital anomaly, abnormal cervix cytology)

césarienne / Baarmoederpathologie (anatomische afwijkingen, chirurgische ingrepen, afwijkende cytologie), voorgeschiedenis van besnijdenis			• Uterine surgery (e.g. caesarean section, myomectomy or cone biopsy)
Excision / Voorgeschiedenis van besnijdenis		Female genital mutilation	Genital mutilation
6. Clinical exam			
Tension artérielle / Bloeddruk			
Protéinurie (bandelette) / Urineonderzoek (dipstick): proteïnurie		Test for proteinuria	
7. Experiences in previous pregnancies			
Fausses couches répétées / Herhaald miskraam	Recurrent miscarriage (three or more consecutive pregnancy losses) or a mid-trimester loss	Recurrent miscarriage	Three or more documented miscarriages
Prééclampsie (syndrome HELLP) / Pre-eclampsie (HELLP)	Severe pre-eclampsia, HELLP syndrome or eclampsia	Pre-eclampsia or eclampsia	Pregnancy induced hypertension and pre-eclampsia (HELL syndrome)
Groupes sanguins antagonists, immunization rhésus / Rhesus-iso-immunisatie en bloedgroepantagonisme	Rhesus isoimmunisation or other significant blood group antibodies	Rhesus isoimmunisation or other significant blood group antibodies	Rhesus isoimmunisation or other significant blood group antibodies
	A stillbirth or neonatal death	Pre-term birth, stillbirth or neonatal death	Preterm birth
Grande multiparité / Grande multipariteit	Grand multiparity (parity four or more)	Four or more previous births	Grand multiparity (parity four or more)
Morbidité périnatale grave / Ernstige perinatale morbiditeit	A baby with a congenital anomaly (structural or chromosomal)	Baby with a congenital abnormality (structural or chromosomal)	Severe perinatal morbidity (congenital or acquired)
	Antenatal or postpartum haemorrhage on two occasions	Antenatal or postpartum haemorrhage	
	Puerperal psychosis	Puerperal psychosis	
	• a small-for-gestational-age (SGA) infant (less than fifth centile) • a large-for-gestational-age (LGA) infant (greater than 95th centile) • a baby weighing less than 2500 g or more than 4500 g	Small or large-for-gestational-age baby	

4. PATHWAYS FOR SCREENING OF CMV, TOXOPLASMOSIS AND GESTATIONAL DIABETES

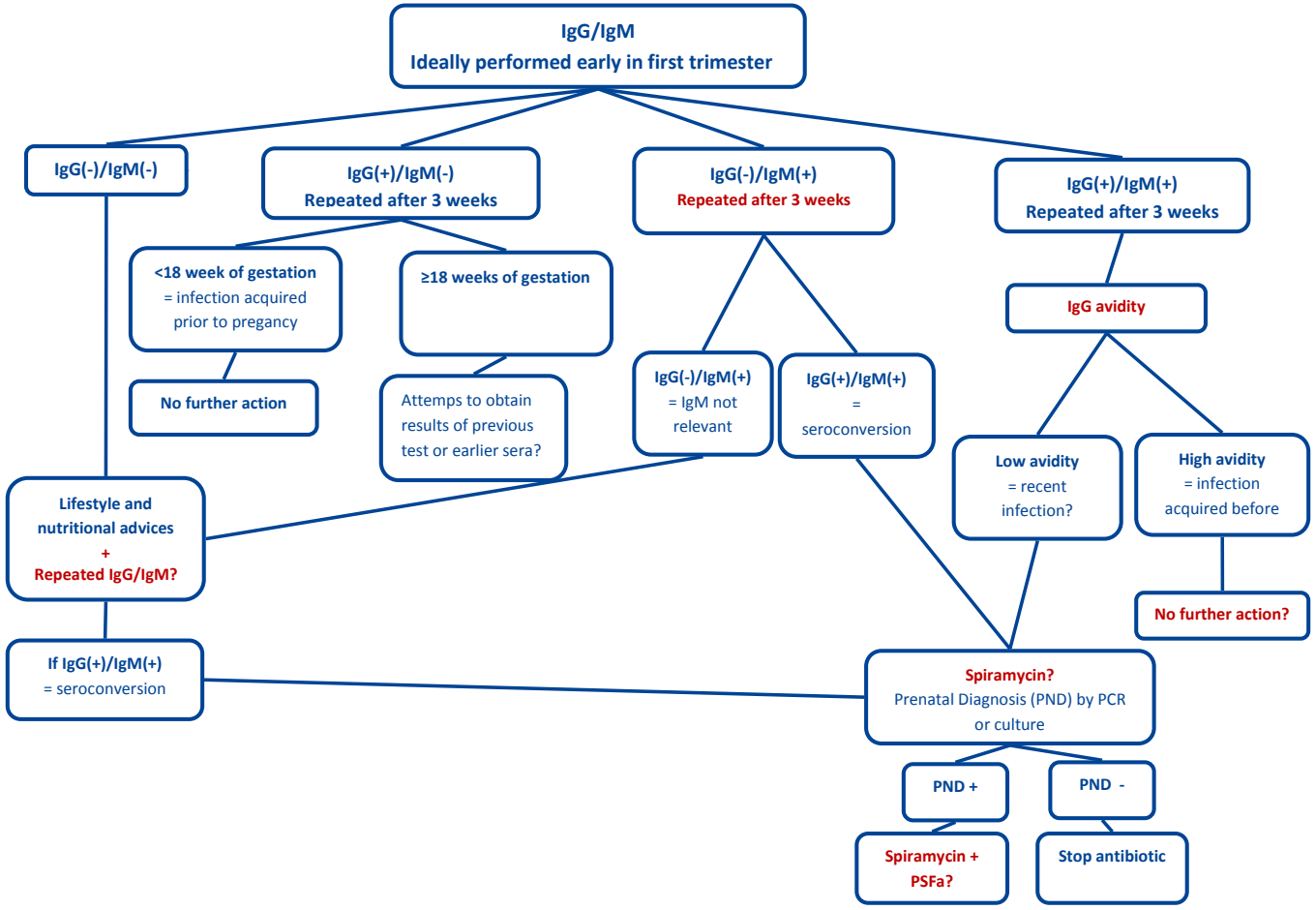
4.1. Cytomegalovirus

Figure 1 – Pathway of screening for CMV



4.2. Toxoplasmosis

Figure 2 – Pathway of screening for toxoplasmosis



4.3. Gestational diabetes

Figure 3 – Classical screening strategy for gestational diabetes in Belgium

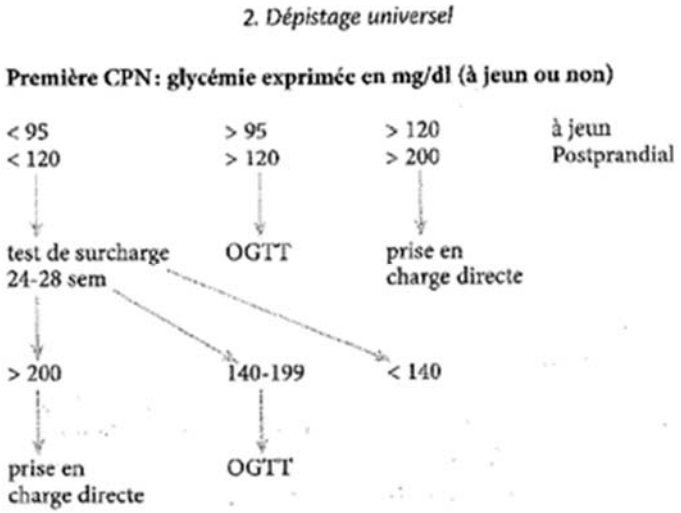


Figure 4 – Screening strategy for gestational diabetes proposed by the Dutch-speaking region of Belgium

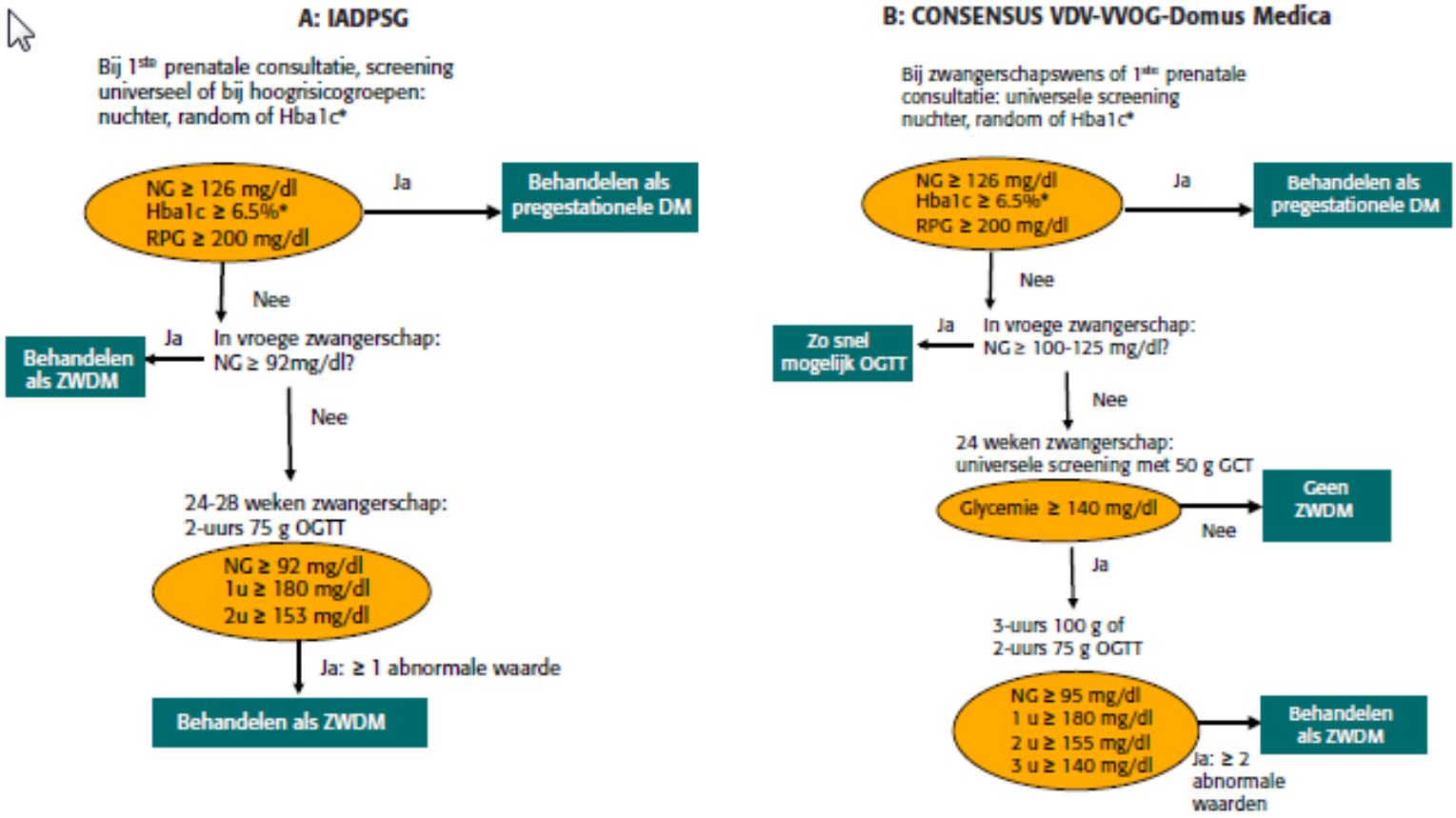
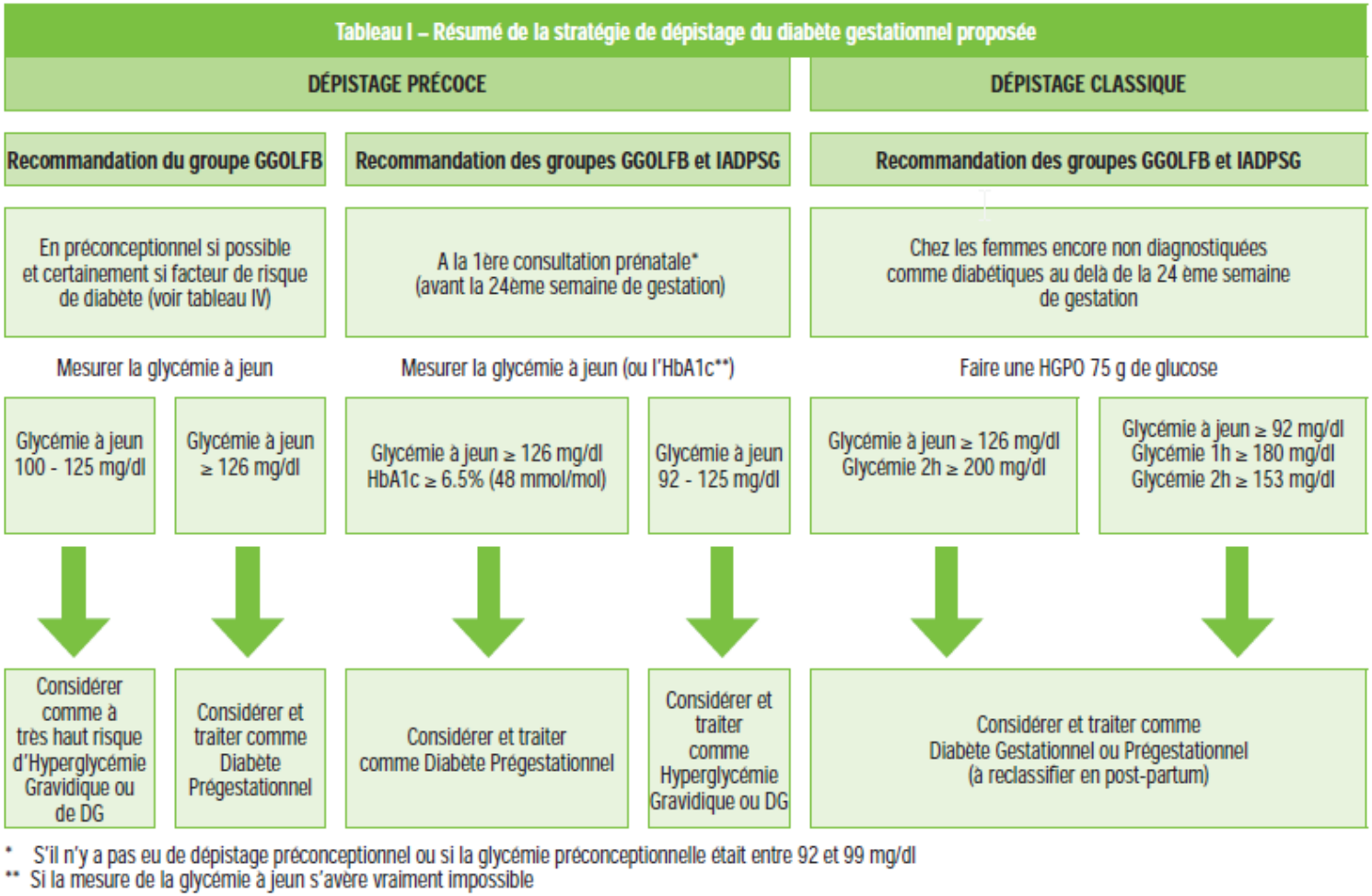


Figure 5 – Screening strategy for gestational diabetes proposed by the French-speaking gynaecologists of Belgium in 2011



* S'il n'y a pas eu de dépistage préconceptionnel ou si la glycémie préconceptionnelle était entre 92 et 99 mg/dl
** Si la mesure de la glycémie à jeun s'avère vraiment impossible

5. P.I.C.O. FOR FULL SEARCH QUESTIONS

5.1. Cytomegalovirus

Table 3 – PICO framework CMV infection

Domain	Description
Research question 1a	***What are the benefits and harms of CMV screening in all healthy pregnant women, compared with no routine screening?***
Population	Included: Healthy pregnant women Excluded: Previously diagnosed with CMV infection
Intervention	Serological screening tests for CMV (see Appendix 4) • IgG antibodies (Dye Test, Elisa, IFI); IgM antibodies (ISAgA = immuno-sorbent agglutination assay) Diagnosis procedures • IgG avidity • PCR or culture in amniotic fluid or cord blood for prenatal diagnostic Treatment by antiviral Treatment by Immunoglobulin *Lifestyle advise (for all pregnant women, independently of the CMV status): nutritional advises (for negative test): regularly wash the hands, especially after contact with saliva or urine of small children (e.g. after changing diapers), avoid kisses on the mouth or cheek, do not share food, drinks, or eating utensils used by young children, do not put a child's pacifier in the mouth, do not share a toothbrush with a young child, clean toys, countertops, and other surfaces that come into contact with children's urine or saliva.*
Comparator	No screening test
Outcomes	**Miscarriage or stillbirth** Fetal and neonatal morbidity: low birth weight, splenomegaly, hepatomegaly, jaundice, thrombocytopenia, pneumonia, microcephaly, **neurological damage**: **visual impairment** (cataract, chorioretinitis), **neurosensory deafness** Children morbidity: **permanent neurological damage** (hearing or visual impairment), impaired motor and sensory development, learning difficulties **Psychological impact of testing** (parental anxiety due to false positive results and uncertainties related to prognosis of children with an antenatal diagnosis) **Termination** **Fetal adverse events of treatment: unanticipated adverse events,** neutropenia, renal toxicity **Maternal adverse events of treatment**

Domain	Description
	Most important outcomes • **Miscarriage or stillbirth** • **Neurological damage** • **Termination**
Confounding factors	Pregnancy periods for the efficacy of treatment, time lag between seroconversion and antiviral treatment, socio-economic status (education level), prematurity, perinatal complications or infections, alcohol for the neurological outcomes, professional occupation and number of children in the household for the efficacy of advices
Research question 1b	***What are the benefits and harms of lifestyle advices to prevent infection with cytomegalovirus during pregnancy?***
Population	Included: Healthy pregnant women with or without negative CMV serology
Intervention	Lifestyle advices: regularly wash your hands, especially after contact with saliva or urine of small children (e.g. after changing diapers), avoid kisses on the mouth or cheek, do not share food, drinks, or eating utensils used by young children, do not put a child's pacifier in your mouth, do not share a toothbrush with a young child, clean toys, countertops, and other surfaces that come into contact with children's urine or saliva.
Comparator	No specific lifestyle advice
Outcomes	**Miscarriage or stillbirth** Fetal and neonatal morbidity: low birth weight, splenomegaly, hepatomegaly, jaundice, thrombocytopenia, pneumonia, microcephaly, **neurological damage**: **visual impairment** (cataract, chorioretinitis), **neurosensory deafness** Children morbidity: **permanent neurological damage** (hearing or visual impairment), impaired motor and sensory development, learning difficulties **Termination** **Psychological impact of lifestyle advice (fear for infection, hampered relationship with other children)** **Most important outcomes (idem than question 1a)**
Confounding factors	Professional occupation (contact with young children), number of small children in the household, socioeconomic status (education level), prematurity, perinatal complications or infections, alcohol for the neurological outcomes

5.2. Toxoplasmosis

Table 4 – PICO framework toxoplasmosis infection

Domain	Description
Research question 2a	***What are the benefits and harms of toxoplasmosis screening in all healthy pregnant women, compared with no routine screening? (This implicitly requires that the test results should guide subsequent management of toxoplasmosis seroconversion)?***
Population	Included: Healthy pregnant women Excluded: Previously diagnosed with toxoplasmosis infection
Intervention	Serological screening tests for toxoplasmosis (see Appendix 4) • IgG antibodies (Dye Test, Elisa, IFI); IgM antibodies (ISAgA = immuno-sorbent agglutination assay) Diagnosis procedures • IgG avidity enzyme-linked (ELISA) • IgA, IgE/PCR or culture in amniotic fluid for prenatal diagnostic Treatment by spiramycin (macrolide) or roxithromycine Treatment by pyrimethamine + sulfadiazine + folinic acid (PSFa) if PCR+ *Nutritional advices (for negative test): washing hands before handling food, washing fruits and vegetables before eating, thoroughly cooking raw meat and ready-prepared chilled meals, wearing gloves and washing hands after handling soil and gardening, avoiding cat faeces in cat litter or in soil.*
Comparator	No screening test
Outcomes	**Miscarriage or stillbirth** Fetal morbidity: intracranial abnormalities, microcephaly, **neurological lesions, chorioretinitis**, eye damage from inflammation of the retina or other parts of the eye, seizure, prematurity, low birth weight, enlarged liver and spleen, diarrhea or vomiting, feeding problems, jaundice, skin rash (tiny red spots or bruising) at birth Children morbidity: **permanent neurological damage** (visual impairment), seizure that required anticonvulsant treatment **Psychological impact of testing** (parental anxiety due to false positive results and uncertainties related to prognosis of children with an antenatal diagnosis) Psychological impact of lifestyle advices (quality of life, fear for infection) **Fœtal adverse events of treatment: e.g.unanticipated adverse events, haemotoxicity.** **Maternal adverse events of treatment**: nausea, loss of appetite, diarrhea, mild hepatotoxicity, arthralgia, platelet drop severe, anemia, **reversible leucopenia**, mild urticaria, erythematous pruriginous skin rash. **Most important outcomes** • **Miscarriage or stillbirth** • **Neurological damage**

	• **Chorioretinis**
Confounding factors	Pregnancy periods (low risk of congenital infection early in the pregnancy but more severe outcome), labo performing the PCR, time lag between seroconversion and antibiotic treatment, socio-economic status (education level), prematurity, perinatal complications or infections, alcohol for the neurological outcomes.
Research question 2b	***What are the benefits and harms of lifestyle advices to prevent infection with toxoplasmosis during pregnancy?***
Population	Included: Healthy pregnant women Excluded: Previously diagnosed with toxoplasmosis infection
Intervention	Lifestyles and nutritional advices: washing hands before handling food, washing fruits and vegetables before eating, thoroughly cooking raw meat and ready-prepared chilled meals, wearing gloves and washing hands after handling soil and gardening, avoiding cat faeces in cat litter or in soil.
Comparator	No lifestyles and nutritional advices
Outcomes	Mother seroconversion and congenital infection **Miscarriage or stillbirth** Fetal morbidity: intracranial abnormalities, microcephaly, **neurological lesions**, **chorioretinitis**, eye damage from inflammation of the retina or other parts of the eye, seizure, prematurity, low birth weight, enlarged liver and spleen, diarrhea or vomiting, feeding problems, jaundice, skin rash (tiny red spots or bruising) at birth Children morbidity: **permanent neurological damage** (visual impairment), seizure that required anticonvulsant treatment **Adverse events of the lifestyles and nutritional advices** (quality of life, anxiety, nutritional restriction) **Most important outcomes (idem than question 2a)**
Confounding factors	Socio-economic status (education level), prematurity, perinatal complications or infections, alcohol for the neurological outcomes

5.3. Chlamydia trachomatis

Table 5 – PICO framework chlamydia trachomatis infection

Domain	Description
Research question 3	***What are the benefits and harms of chlamydia screening in all healthy pregnant women, compared with no routine screening or targeted tests in women with risk factors? (This implicitly requires that the test results should guide subsequent management of chlamydia infection)***
Population	Included: asymptomatic pregnant women
Intervention	Universal screening tests for chlamydia: In urine or endocervical samples: • Cell culture Antigen detection tests: EIA (enzyme immunoassay) or DFA (direct fluorescent antibody test) • Nucleic acid amplification test: LCR (ligase chain reaction) or PCR (polymerase chain reaction) • Nucleic acid hybridisation test: DNA probe) • Gram staining or Pap smear Treatment • Azithromycin, erythromycin, amoxycillin
Comparator	No screening tests or targeted tests in women with risk factors (see below)
Outcomes	**Stillbirth and perinatal mortality** Obstetrical complications: IUGR and low birth weight, PROM (rupture of membrane), **preterm birth** Infant morbidity: sepsis, **conjunctivitis**, otitis, URI, pneumonia, diarrhea Maternal morbidity: antepartum hemorrhage, **pelvic inflammatory disease** (PID) **Maternal adverse effect** of screening and treatment **Most important outcomes**: • **Preterm birth** • **Conjunctivitis** • **Pelvis inflammatory disease (PID)**
Confounding factors	Socio-economic status, smoking status for preterm birth
Risk factors: already diagnosed with chlamydia trachomatis infection or other sexually transmissible infections; age <25y; behavioural risk (e.g.multiple partners, no stable relationship); living in a big city (urban v. rural)	

5.4. Group B streptococcus

Table 6 – PICO Framework group B streptococcus infection

Domain	Description
Research question 4	***What are the benefits and harms of group B streptococcus screening in all healthy pregnant women, compared with*** ***a. GBS prophylaxis without a particular protocol (no screening or non-specified ad hoc intrapartum antibiotic use)?*** ***b. risk factor based prophylaxis?***
Population	Asymptomatic healthy pregnant women at 35-37 weeks
Intervention	Screening tests for GBS, • Rectal and vaginal swab specimens at 35-37 weeks of pregnancy • Rapid intrapartum testing (HTA 2009) Treatment • Penicillin IV (or IM) • Cefazolin or clindamycin if penicillin allergy
Comparator	No screening tests Direct treatment of at risk women (specifics listed at end of protocol – risk factors)
Outcomes	**Stillbirth and perinatal mortality** Neonatal morbidity: • Early onset GBS neonatal disease (EOD): <7 days **neonatal sepsis**, pneumonia, meningitis • Late onset disease (LOD): 7 days-3 months sepsis, meningitis, urinary tract infection due to GBS or other bacterial organisms, osteoarthritis, respiratory disease, cellulitis. Maternal morbidity: caesarian; chorioamnionitis, sepsis in the peri/postpartum period, urinary tract infection in the peri/postpartum period with any bacteria **Maternal adverse effects** associated to screening or treatment **Most important outcomes**: • **Neonatal sepsis** • **Stillbirth-neonatal death** • **Adverse events (e.g. candida infection,allergic reaction to antibiotics)**
Risk factors: previously baby infected with GBS; GBS found in the urine at any time during this pregnancy; start labour <37 weeks gestation; rupture of membranes at term & labour will last > 18H; unexplained, mild fever during labour.	
Note: At risk women would be treated regardless of screening in both intervention and comparator groups. Intervention = systematic screening of everyone + treatment of at risk women. Comparator = No screening + treatment of at risk women.	

5.5. Gestational diabetes

Table 7 – PICO framework gestational diabetes

Domain	Description
Research question 5a	***Which screening strategies are more accurate and effective to screen healthy pregnant women for gestational diabetes?*** • ***At which threshold?*** • ***At which gestational age (<24 weeks, 24-30 weeks, 30 weeks or more)?*** • ***In all women (universal) or in women at risk?***
Population	Included: Healthy pregnant women, with or without risk factors for diabetes Excluded: Women with pre-existing diabetes mellitus; women already diagnosed with gestational diabetes.
Intervention	Diabetes tests according to different screening strategies (see Appendix 4) for the three strategies promoted in Belgium) **Screening tests used <24 weeks:** Fasting plasma glucose: 120 mg/dl (OK if <95 mg/dl) *and/or* HbA1c test: 6.5% *and/or* Random plasma glucose: 200 mg/dl **If known risk factors:** 50g glucose challenge test & glycemia after 1H if risk factors (O' Sullivan test): 140 mg/dl 75g glucose challenge test & glycemia after 2H if risk factors (WHO): 140 mg/dl **Screening tests used ≥24 weeks in first or second steps (see strategies below):** 50g glucose challenge test & glycemia after 1h: 140 mg/dl 75g glucose challenge test & glycemia after 1&2h: 2 abnormal values among 95 mg/dl at time 0; 180 mg/dl after 1h, 155 mg/dl after 2h. 100g glucose challenge test & glycemia after 1,2&3h: 2 abnormal values among 95 mg/dl at time 0; 180 mg/dl after 1h, 155 mg/dl after 2h and 140 mg/dl after 3h.
Comparator	Another of the three screening strategies described in (Appendix 3), another glycaemia threshold for O'Sullivan test (130mg vs. 140mg)
Outcomes	Gestational diabetes (as defined by the study) Mode of birth (normal vaginal birth, operative vaginal birth, caesarean section) Adverse events associated with test (nausea, vomiting) **Maternal type 2 diabetes** Hypertensive disorders and preeclampsia **Perinatal mortality (miscarriage / still birth / neonatal death)** **Large-for-gestational age / macrosomia** (birth weight greater than or equal to 90th percentile, or greater than 4500g)

Domain	Description
	Respiratory distress syndrome, hyperbilirubinemia, hypocalcemia, polycythemia, hypertrophic cardiomyopathy Neonatal hypoglycaemia Birth injury (e.g. brachial plexus injury). **Most important outcomes:** • **Fetal and neonatal morbidity** • **Stillbirth-neonatal death** • **Long term type 2 diabetes** • The adverse events of the glucose challenge, as acute discomfort, nausea… has to be taken into account.
Risk factors: previous history of gestational diabetes or glucose intolerance; family history of diabetes or ethnicity; advanced maternal age (>35 y); obesity (BMI before pregnancy ≥25 or 30); maternal birth weight >4.1 or < 2.7 kg; previous macrosomia (> 4 or 4.5 kg), previous unexplained stillbirth, unexplained preterm birth, pre-eclampsia, repeated miscarriage; previous neonatal hypoglycemia, hypocalcemia, or hyperbilirubinemia; repeated glycosuria in pregnancy; polyhydramnios; suspected macrosomia; polycystic ovary syndrome; corticoid treatment; gestational HTA.	
Note: Also interested in diagnostic accuracy outcomes if no diagnostic RCT's are identified – with focus on both sensitivity and specificity (i.e. neither missing cases nor providing treatment to those falsely classified as having the condition)	
Research question 5b	***What is the diagnostic accuracy of the 50g glucose challenge test?*** • ***At which threshold?*** • ***At which gestational age (<24 weeks, 24-30 weeks, 30 weeks or more)?*** • ***In all women (universal) or in women at risk?***
Population	Healthy pregnant women, with or without risk factor of diabetes Exclusions: Women with pre-existing diabetes mellitus; Women already diagnosed with gestational diabetes.
Index test	Two-step method according to different thresholds for the initial 50g glucose challenge test (GCT) ▪ **50g glucose challenge test & glycaemia after 1H with threshold 130mg/dl** followed by 100g oral glucose tolerance test & glycaemia after 1,2&3h: 2 abnormal values among 95 mg/dl at time 0; 180 mg/dl after 1h, 155 mg/dl after 2h and 140 mg/dl after 3h ▪ **50g glucose challenge test & glycaemia after 1H with threshold 135 mg/dl** followed by 100g oral glucose tolerance test & glycaemia after 1,2&3h: 2 abnormal values among 95 mg/dl at time 0; 180 mg/dl after 1h, 155 mg/dl after 2h and 140 mg/dl after 3h ▪ **50g glucose challenge test & glycaemia after 1H with threshold 140 mg/dl** followed by 100g oral glucose tolerance test & glycaemia after 1,2&3h: 2 abnormal values among 95 mg/dl at time 0; 180 mg/dl after 1h, 155 mg/dl after 2h and 140 mg/dl after 3h
Reference standard	One-step method (no initial GCT): 100g oral glucose tolerance test (OGTT) & glycaemia after 1,2&3h: 2 abnormal values among 95 mg/dl at time 0; 180 mg/dl after 1h, 155 mg/dl after 2h and 140 mg/dl after 3h
Outcomes	**Diagnostic accuracy** with focus on both sensitivity and specificity (i.e. neither missing cases nor providing treatment to those falsely classified as having the condition)

Domain	Description
Review strategy	Stratify by: Time of testing: Early (<24 weeks) vs. late (≥24 weeks) Testing strategy: Universal (all pregnant women) vs. selected (based on risk factors for gestational diabetes)
Risk factors: previous history of gestational diabetes or glucose intolerance; family history of diabetes or ethnicity; advanced maternal age (>35 y); obesity (BMI before pregnancy ≥25 or 30); maternal birth weight >4.1 or < 2.7 kg; previous macrosomia (> 4 or 4.5 kg), previous unexplained stillbirth, unexplained preterm birth, pre-eclampsia, repeated miscarriage; previous neonatal hypoglycemia, hypocalcemia, or hyperbilirubinemia; repeated glycosuria in pregnancy; polyhydramnios; suspected macrosomia; polycystic ovary syndrome; corticoid treatment; gestational HTA.	

5.6. Hypothyroidism

Table 8 – PICO framework hypothyroidism

Domain	Description
Research question 6a	***What are the benefits and harms of routine screening for hypothyroidism in asymptomatic pregnant women compared with no routine screening (or targeted screening of clinically at risk women)? (This implicitly requires that test results should guide subsequent management of hypothyroidism)***
Population	Included: Healthy pregnant women, asymptomatic for hypothyroidisms Excluded: pregnant women with clinical or overt hypothyroidism
Intervention	Screening of hypothyroidism: TSH ± FT4
Comparator	No testing (or targeted TSH testing in a subset of women clinically judged at very high risk of hypothyroidism)
Outcomes	Maternal death Maternal morbidity: respiratory and cardiovascular clinical events, **gestational hypertension and preeclampsia**, symptomatic hypothyroidism, post-partum depression **Maternal total major/serious adverse events** **Neonatal/infant death, still birth, miscarriage** **Neonatal/infant morbidity: prematurity, IUGR, low birth weight,** NICU admission, craniosynostosis, premature closure of the epiphyses in children and adult height, **Neuro-cognitive-psychological-behavioural development: (motor-sensory deficits, IQ, attention deficit, and mood disorders)** **Infant/childhood total major/serious adverse events** **Most important outcomes** • **Still birth, miscarriage** • **Neurological impairement**

	• **Maternal and infant adverse events**
Confounding factors	Pregnancy periods, labo performing the test, time lag between seroconversion and antibiotic for the test Socio-economic status (education level), prematurity, perinatal complication or infection, alcohol for decreased neuropsychological development.
Risk factors: history of previous thyroid dysfunction, goitre, positive thyroid antibodies, cervical irradiation, or thyroid surgery; age>30; family history of thyroid disease; diabetes type 1 or any other autoimmune disease; history of repeated abortions, prematurity, or infertility; morbid obesity; treatment with lithium, amiodarone, or recent administration of iodinated contrast; living in an area with moderate to severe deficiency of iodine.	
Research question 6b	***Compared with no or lower pharmacological doses, what are the benefits and harms of levothyroxine or selenomethionine treatment of pregnant women with subclinical hypothyroidism? Do treatment effects vary with their risk status (i.e. low versus high risk for hypothyroidism)?***
Population	Included: Pregnant women with subclinical hypothyroidism (with* or without risk factors) Excluded: Pregnant women with clinical or overt hypothyroidism
Intervention	Treatment started early: • Levothyroxine • Selenomethionine
Comparator	Placebo/No treatment/lower doses of the intervention drug/alternative treatment (e.g. levothyroxine versus selenomethionine)
Outcomes	Maternal death Maternal morbidity: respiratory and cardiovascular clinical events, **gestational hypertension and preeclampsia**, symptomatic hypothyroidism, post-partum depression **Maternal total major/serious adverse events** **Neonatal/infant death, still birth, miscarriage** **Neonatal/infant morbidity: prematurity, IUGR, Low birth weight,** NICU admission, craniosynostosis, premature closure of the epiphyses in children and adult height, **Neuro-cognitive-psychological-behavioural development: (motor-sensory deficits, IQ, attention deficit, and mood disorders)** **Infant/childhood total major/serious adverse events** **Most important outcomes** • **Still birth, miscarriage** • **Neurological impairement** • **Maternal and infant adverse events**
Confounding factors	Socio-economic status (education level), prematurity, perinatal complication or infection, alcohol for decreased neuropsychological development.
Risk factors: history of previous thyroid dysfunction, goitre, positive thyroid antibodies, cervical irradiation, or thyroid surgery; age>30; family history of thyroid disease; diabetes type 1 or any other autoimmune disease; history of repeated abortions, prematurity, or infertility; morbid obesity; treatment with lithium, amiodarone, or recent administration of iodinated contrast; living in an area with moderate to severe deficiency of iodine.	

5.7. Vitamin D deficiency

Table 9 – PICO framework vitamin D deficiency

Domain	Description
Research question 7a	***What are the benefits and harms of routine vitamin D deficiency screening of all healthy pregnant women compared with no routine screening (or targeted screening of clinically at risk women)? (This implicitly requires that test results should guide subsequent management of vitamin D deficiency)***
Population	Included: Healthy Pregnant women, with* or without risk factors for vitamin D deficiency Excluded: pregnancies associated with specific co-morbidities or risks (e.g. gestational hypertension, high risk for preterm birth, etc.)
Intervention	Serum 25(OH)D
Comparator	No testing (or targeted testing in a subgroup of women)
Outcomes	Maternal death Maternal morbidity: gestational hypertension and preeclampsia; gestational diabetes mellitus,hypercalcemia and kidney stones **Maternal total major/serious adverse events** Neonatal/infant death, still birth, miscarriage Fetal/infant morbidity: prematurity, **IUGR, low birth weight**, birth length, head circumference, NICU admission, Apgar score Long-term morbidity later in life: asthma, schizophrenia, type 1 DM, multiple sclerosis and cancer **Infant/childhood total major/serious adverse events** **Most important outcomes** • **IUGR and low birth weigth** • **Maternal and infant adverse events**
Confounding factors	Smoking, maternal age, low maternal BMI, maternal diseases (but the guideline focus on healthy women), alcohol and ethnicity for IUGR Individual metabolism, maternal BMI, maternal diseases (but focus on healthy pregnant women), seasonal influence for the absorption-concentration of vitamin D
Possible risk factors of vitamin D deficiency: women of South Asian, African, Caribbean or Middle Eastern family origin; women who have limited exposure to sunlight, such as women who are predominantly housebound, or usually remain covered when outdoors; women who eat a diet particularly low in vitamin D, such as women who consume no oily fish, eggs, meat, vitamin D-fortified margarine or breakfast cereal; women with a pre-pregnancy BMI>30 kg/m2.	
Research question 7b	***Compared with no or lower dose supplementation, what are the benefits and harms of vitamin D supplementation during pregnancy? Do treatment effects vary by patient risk (i.e. low versus high risk for vitamin D deficiency) or baseline vitamin D levels (i.e. established baseline hypovitaminosis D versus unclear or normal baseline vitamin D levels)?***
Population	Included: Pregnant women (healthy, with or without risk factors* and/or documented hypovitaminosis D)

	Excluded: Pregnancies associated with specific co-morbidities or risks (e.g. gestational hypertension, high risk for preterm birth, etc.)
Intervention	Nutritional supplement on vitamin D
Comparator	Placebo/no supplement/lower doses of vitamin D
Outcomes	Idem than question 7a
Confounding factors	Smoking, maternal age, low maternal BMI, maternal diseases (but the guideline focus on healthy women), alcohol and ethnicity for IUGR
Possible risk factors of vitamin D deficiency: women of South Asian, African, Caribbean or Middle Eastern family origin; women who have limited exposure to sunlight, such as women who are predominantly housebound, or usually remain covered when outdoors; women who eat a diet particularly low in vitamin D, such as women who consume no oily fish, eggs, meat, vitamin D-fortified margarine or breakfast cereal; women with a pre-pregnancy BMI>30 kg/m2.	

5.8. Risk of preterm birth

Table 10 – PICO framework preterm birth risk

Domain	Description
Research question 8a	***In pregnant women judged to be exclusively at low risk for preterm birth based on history, physical exam, or both, what are the comparative benefits and harms of mid-to-third trimester transvaginal ultrasound for cervical length, funnelling, or both, and/or digital vaginal exam in routine patient management?***
Population	Asymptomatic pregnant women judged on presentation (i.e. history and/or exam before cervical assessment) to be at low risk for preterm birth (common presenting risk factors include women with history of preterm birth, surgery to the cervix; multiple gestation, uterine malformation, and polyhydramnios -- studies exclusively or majorly in populations with one or more of these risk factors should be excluded; also exclude studies when study population risk for preterm birth is unclear or mixed).
Intervention	Screening for risk of preterm birth, one test alone or in combination (at mid-to-third trimester): • **Transvaginal ultrasound** (cervical length and funnelling) (consider Cochrane review of Berghella 2013) • **Digital exam** (or Bishop score) • **Transvaliginal ultrasound and digital exam** Subsequent management should be guided by the results of aforementioned tests (exclude fFN and Actim Partus because not in use in Belgium for low risk women)
Comparator	No routine screening for risk of preterm birth or an alternative screening test?
Outcomes	**Perinatal mortality/survival (miscarriage, still birth, and/or neonatal death)** **Neurological development at age 18-24 mo** Neonatal survival without morbidities : IVH, cerebral palsy, periventricular leukomalacia, bronchopulmonary dysplasia, necrotizing enterocolitis, retinopathy, patent ductus arterious **Serious maternal adverse events** Maternal mortality

Domain	Description
	Preterm birth (< 28 weeks, < 34 weeks, <37 weeks) **Most important outcomes** • **Perinatal survival** • **Neurological damage** • **Maternal and infant adverse events** • **Date of birth**
Counfounding factors	Pregnancy period, IVF and smoking
Research question 8b	***In pregnant women judged to be predominantly at low risk for preterm birth based on history, physical exam, or both, what are the comparative benefits and harms of mid-to-third trimester transvaginal ultrasound for cervical length, funnelling, or both and/or digital vaginal exam in routine patient management?***
Population	Asymptomatic pregnant women judged on presentation to be a mix (i.e. high, low, and/or inconclusive) risk population studies when it is clear (on history and/or exam before cervical assessment) that >50% are low risk.
Intervention	Screening for risk of preterm birth, one test alone or in combination (at mid-to-third trimester): • **Transvaginal ultrasound** (cervical length and funnelling) (consider Cochrane review of Berghella 2013) • **Digital exam** (or Bishop score) • **Transvaliginal ultrasound and digital exam** Subsequent management should be guided by the results of aforementioned tests (exclude fFN and Actim Partus because not in use in Belgium for low risk women)
Comparator	No routine screening for risk of preterm birth or an alternative screening test?
Outcomes	Idem than question 8a
Counfounding factors	Pregnancy period, IVF and smoking
Research question 8c	***Compared with each other or no active intervention (i.e. expectant management), what is the comparative benefits and harms of progesterone therapy, cerclage, and/or reduced physical activity (e.g. bed rest) to prevent preterm birth and its sequelae in asymptomatic women with short cervix but no additional risk factors for preterm birth (i.e. exclusively low risk populations as judged on history and physical exam before cervical assessment)?***
Population	Asymptomatic pregnant women with short cervix and no other risk factors for preterm birth (exclude women with history of preterm birth, surgery to the cervix; multiple gestation, uterine malformation, and polyhydramnios). In other words, exclusively low risk populations as judged on history and physical exam before cervical assessment
Intervention	Management • Progesterone • Reduced physical activities, bed rest • Cervical cerclage

Domain	Description
	Various combinations of above
Comparator	No active intervention or one or more of the alternative intervention(s) above
Outcomes	Idem than question 8a
Counfounding factors	Pregnancy period, IVF and smoking
Research question 8d	***Compared with each other or no active intervention (i.e. expectant management), what is the comparative benefits and harms of progesterone therapy, cerclage, and/or reduced physical activity (e.g. bed rest) to prevent preterm birth and its sequelae in asymptomatic pregnant populations with short cervix who are predominantly at low risk (as judged on history and physical exam before cervical assessment) for preterm birth?***
Population	Studies in asymptomatic pregnant women with short cervix who are predominantly (>50%) low risk as judged on history and physical exam before cervical assessment
Intervention	Management • Progesterone • Reduced physical activities, bed rest • Cervical cerclage Various combinations of above
Comparator	No active intervention or one or more of the alternative intervention(s) above
Outcomes	Idem than question 8a
Counfounding factors	Pregnancy period, IVF and smoking

5.9. Risk of preeclampsia

Table 11 – PICO framework preeclampsia risk

Domain	Description
Research question 9	***What are the benefits and harms of screening of asymptomatic healthy pregnant women for preeclampsia risk with additional tests compared with usual routine assessment based on history and physical exam?***
Population	Asymptomatic healthy pregnant women Include –studies in pregnancies with no preeclampsia risk; women with general risk/mixed risk Exclude – studies in which women were exclusively or predominantly (>50%) with one or more preeclampsia risk
Intervention	Imaging or biological screening for risk of preeclampsia, one test alone or in combination, in addition to history taking and clinical examination such as: • Dipstick for proteinuria • Pulsatility index of the uterine arteries measured during an Doppler ultrasound scan • Biomarkers: o Pregnancy-associated plasma protein-A (PAPP-A). o placental growth factor (PIGF) in combination with soluble fms-like tyrosine kinase-1 (sFlt-1) • Fetal DNA and RNA in maternal plasma (may be helpful in the prediction of preeclampsia as they are markers of the trophoblast apoptosis). • Combination of any of the above tests?
Comparator	No further risk assessment beyond history and physical exam
Outcomes	Maternal morbidity: **preeclampsia,** pulmonary edema, cerebral hemorrhage, hepatic failure, renal failure, seizures (eclampsia), disseminated intravascular coagulation (primarily with abruption) Maternal mortality Obstetrical complications (preterm birth, **growth restriction**, abruption placenta) Perinatal mortality: stillbirth + neonatal mortality Neonatal morbidity outcomes: admission to a neonatal intensive care unit, low birth weight Patient satisfaction Patient's planning for adverse consequences even death **Most important outcomes** • **Preeclampsia**
Counfounding factors	Socio-economic statis/education (only in the USA and developing countries where there is no universal health care); gestational age at entry (substantial difference in gestational age at testing); substantial differences in risk factors; smoking status

Risk factors for pre-eclampsia:

1. pre-existing hypertension (or treatment of hypertension) or pregnancy induced hypertension within the first 12 weeks of gestation (Diastolic >80 mmHg)
2. women with metabolic syndrome and diabetes
3. conception through assisted reproductive techniques
4. obese women (BMI >35 kg/m^2)
5. women with positive family history of preeclampsia
6. multiple pregnancy
7. age over 40 years
8. low age (below 18- 20)
9. pregnancy interval of more than 10 years
10. pre-existing renal disease, and
11. clotting disorders (factor V Leiden mutation, homozygous MTHFR mutation, hyperhomocysteinemia, presence of antiphospholipid antibodies or established diagnosis of systematic lupus erythematosus , and the combination of multiple thrombophilias)

5.10. Surveillance of pregnancies that passed their due date

Table 12 – PICO framework surveillance of pregnancies

Domain	Description
Research question 10	***In low risk (for adverse consequences of post-datism) asymptomatic pregnant women who remain undelivered past 40 weeks of gestation, compared with each other or no intervention/routine clinical follow up, what are benefits and harms of:*** • ***Nonstress test cardiotocography (CTG)?*** • ***Ultrasound estimation of amniotic pool depth/volume/index?*** • ***Combination of the two test above with or without other tests/assessments (i.e. full or modified biophysical profile)?***
Population	Healthy Women pregnant beyond 40 weeks of gestation who are not particularly of advance maternal age or obese, or have personal or maternal history of post-date pregnancy.
Intervention	Monitoring by one test alone or in combination • Nonstress test cardiotocography (CTG) • Ultrasound estimation of amniotic pool depth/volume/index • Combination of the two test above with or without other tests/assessments (i.e. full or modified biophysical profile)? Management should be guided by results of these tests (e.g. induction of labour when positive test results)
Comparator	Management guided by: • No testing (routine follow-up) • Alternative test/testing strategy • same test/testing strategy but a different management threshold
Outcomes	**Perinatal mortality/survival (miscarriage, still birth, and/or neonatal death)** **Obstetrical complications** (e.g. non progressive labor, instrumental delivery, caesarian section, analgesia used, **maternal lesions** as perineal trauma, prolonged labour, chorioamnionitis, postpartum hemorrhage, and endomyometritis)

Domain	Description
	Admission to neonatal intensive care unit, meconium aspiration syndrome, shoulder dystocia, and Apgar score **Neurodevelopment development impairment at childhood follow-up** Maternal anxiety **Most important outcomes** • **Perinatal mortality** • **Neurological development impairement** • **Admission in NICU** • **Maternal lesions**
Confounding factors	Ethnicity, genetic, parity

6. SEARCH STRATEGIES

6.1. Search strategy for guidelines

The search strategy for guidelines was performed in October 2013 and focuses on guidelines published after 2004. Several search engines were used.

Table 13 – Search results - Guidelines on antenatal care

Date	October 2013	
Search engine	**Search term**	**Number of hits**
GIN guideline resource http://www.g-i-n.net	Antenatal care	4
National Guideline Clearinghouse (NGC) from UK http://www.guideline.gov/	Antenatal	60
New Zealand Guidelines Group (NZGG) http://www.nzgg.org.nz/	Pregnancy	3
National Institute for Health and Care Excellence (NICE) guidelines from US http://www.nice.org.uk/	Antenatal care; Pregnancy	9
Scottish Intercollegiate Guidelines Network (SIGN) http://www.sign.ac.uk/	Obstetrics & gynaecology	0
Society of Obstetricians and Gynaecologists of Canada (SOGC) http://sogc.org/clinical-practice-guidelines/	Antenatal, Pregnancy	18
Royal College of Obstetricians and Gynaecologists (RCOG) from UK https://www.rcog.org.uk	Pregnancy	21
Australian clinical practice guidelines - National Health and Medical Research Council (NHMRC) http://www.nhmrc.gov.au/	Women's health	3
Haute Autorité de Santé (HAS) from France http://www.has-sante.fr/portail/jcms/c_1101438/fr/tableau-des-recommandations-de-bonne-pratique		1
Institute for Clinical Systems Improvement (ICSI) from US http://www.icsi.org/index.asp	Women's health	1

After removal of duplicate guidelines, 95 guidelines were selected based on title and abstract. Of these, 91 guidelines were excluded for the following reasons:

- 89 guidelines were excluded because they focused only on a specific question
- 2 general guidelines were excluded because of unclear or insufficient methodology

6.2. Search strategies for other publications (systematic reviews, meta-analyses, individual studies) for full search questions

6.2.1. Cytomegalovirus

Table 14 – Search strategies: Benefits-harms of screening and lifestyle advice for CMV infection during pregnancy

Database	Medline (Ovid)	
Date	20-05-2014	
Search strategy		
1	cytomegalovirus/	17354
2	exp cytomegalovirus infections/	21356
3	cytomegal*.ti,ab.	35085
4	cmv.ti,ab.	19969
5	(hhv5 or hhv 5).ti,ab.	23
6	(herpesvirus 5 or herpes virus 5).ti,ab.	95
7	(saliva* adj2 gland* adj2 virus*).ti,ab.	162
8	(inclusion* adj2 disease*).ti,ab.	1157
9	(saliva* adj2 gland* adj2 disease*).ti,ab.	534
10	or/1-9	47314
11	letter/	840786
12	editorial/	355994
13	news/	161749
14	exp historical article/	320669
15	anecdotes as topic/	4543
16	comment/	584772
17	case report/	1680216
18	(letter or comment*).ti.	96495
19	or/11-18	3340446
20	randomized controlled trial/ or random*.ti,ab.	811192
21	19 not 20	3322922
22	animals/ not humans/	3847854
23	exp animals, laboratory/	724095
24	exp animal experimentation/	6314
25	exp models, animal/	414688
26	exp rodentia/	2663804
27	(rat or rats or mouse or mice).ti.	1109813
28	or/21-27	7767001
29	exp pregnancy/	709531
30	pregnant women/	5523
31	prenatal care/	20175

32	exp prenatal diagnosis/	59878
33	exp pregnancy complications/	336806
34	perinatal care/	2778
35	(antenatal* or ante-natal* or prenatal* or pre-natal* or perinatal* or peri-natal* or pregnan* or antepartum or ante-partum or peripartum or peri-partum).ti,ab.	455715
36	or/29-35	857548
37	randomized controlled trial.pt.	373788
38	controlled clinical trial.pt.	88373
39	randomi#ed.ab.	351557
40	placebo.ab.	153950
41	drug therapy.fs.	1698549
42	randomly.ab.	212697
43	trial.ab.	304929
44	groups.ab.	1354210
45	or/37-44	3345377
46	clinical trials as topic.sh.	169943
47	trial.ti.	126393
48	or/37-40,42,46-47	924060
49	epidemiologic studies/	5959
50	exp case control studies/	658793
51	exp cohort studies/	1347396
52	cross-sectional studies/	174978
53	case control.ti,ab.	77893
54	(cohort adj (study or studies or analys*)).ti,ab.	90767
55	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.	147438
56	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.	782852
57	or/49-56	1969975
58	meta-analysis/	47989
59	meta-analysis as topic/	13752
60	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.	64910
61	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.	84734
62	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.	25622
63	(search strategy or search criteria or systematic search or study selection or data extraction).ab.	27340
64	(search* adj4 literature).ab.	27772
65	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.	91595
66	cochrane.jw.	10749
67	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.	1376
68	or/58-67	211973
69	48 or 57 or 68	2799899

	70	mass screening/	81513
	71	screen*.ti.	116382
	72	70 or 71	156839
	73	10 and 36 and 69	675
	74	10 and 36 and 72	124
	75	73 or 74	765
	76	75 not 28	702
Note			
Database		**Embase (Ovid)**	
Date		20-05-2014	
Search strategy			
	1	cytomegal*.ti,ab.	38655
	2	cmv.ti,ab.	26878
	3	(hhv5 or hhv 5).ti,ab.	31
	4	(herpesvirus 5 or herpes virus 5).ti,ab.	88
	5	(saliva* adj2 gland* adj2 virus*).ti,ab.	132
	6	(inclusion* adj2 disease*).ti,ab.	1314
	7	(saliva* adj2 gland* adj2 disease*).ti,ab.	543
	8	exp cytomegalovirus/	29152
	9	exp cytomegalovirus infection/	23873
	10	or/1-9	64413
	11	letter.pt. or letter/	838297
	12	note.pt.	554436
	13	editorial.pt.	444065
	14	case report/ or case study/	1891947
	15	(letter or comment*).ti.	146333
	16	or/11-15	3580563
	17	randomized controlled trial/ or random*.ti,ab.	949031
	18	16 not 17	3552801
	19	animal/ not human/	1179709
	20	nonhuman/	4293765
	21	exp animal experiment/	1668497
	22	exp experimental animal/	399210
	23	animal model/	752719
	24	exp rodent/	2666161
	25	(rat or rats or mouse or mice).ti.	1155192
	26	or/18-25	9457910
	27	exp pregnancy/	546617
	28	pregnant woman/	32179
	29	prenatal diagnosis/	45652

30	prenatal screening/	5586
31	prenatal care/	26068
32	exp pregnancy complication/	103216
33	perinatal care/	8793
34	(antenatal* or ante-natal* or prenatal* or pre-natal* or perinatal* or peri-natal* or pregnan* or antepartum or ante-partum or peripartum or peri-partum).ti,ab.	521340
35	or/27-34	793412
36	random*.ti,ab.	867049
37	factorial*.ti,ab.	22599
38	(crossover* or cross over*).ti,ab.	67944
39	((doubl* or singl*) adj blind*).ti,ab.	152135
40	(assign* or allocat* or volunteer* or placebo*).ti,ab.	638477
41	crossover procedure/	38825
42	double blind procedure/	113073
43	single blind procedure/	18225
44	randomized controlled trial/	341422
45	or/36-44	1386094
46	clinical study/	56039
47	exp case control study/	84544
48	family study/	10357
49	longitudinal study/	66207
50	retrospective study/	343202
51	prospective study/	249423
52	cross-sectional study/	112824
53	cohort analysis/	166518
54	follow-up/	793912
55	cohort*.ti,ab.	392271
56	54 and 55	80124
57	case control.ti,ab.	90786
58	(cohort adj (study or studies or analys*)).ti,ab.	115382
59	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.	182120
60	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.	1020951
61	or/46-53,56-60	1668832
62	systematic review/	74385
63	meta-analysis/	78612
64	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.	81268
65	((systematic or evidence) adj3 (review* or overview*)).ti,ab.	95816
66	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.	29030
67	(search strategy or search criteria or systematic search or study selection or data extraction).ab.	30007
68	(search* adj4 literature).ab.	33798

69	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.	104868
70	cochrane.jw.	11325
71	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.	2079
72	or/62-71	269650
73	45 or 61 or 72	2979087
74	mass screening/	44652
75	screen*.ti.	140053
76	or/74-75	165335
77	10 and 35 and 73	703
78	10 and 35 and 76	138
79	77 or 78	812
80	79 not 26	685

Note

Database	**The Cochrane library (Wiley)**	
Date	20-05-2014	
Search strategy		
#1	(antenatal* or ante-natal* or prenatal* or pre-natal* or perinatal* or peri-natal* or pregnan* or antepartum or ante-partum or peripartum or peri-partum):ti,ab,kw	26615
#2	(cytomegal* or cmv):ti,ab,kw	1370
#3	(HHV5 or HHV 5 or herpesvirus 5 or herpes virus 5):ti,ab	290
#4	(saliva* near/2 gland* near/2 virus*):ti,ab	0
#5	(inclusion* near/2 disease*):ti,ab	41
#6	(saliva* near/2 gland* near/2 disease*):ti,ab	7
#7	1-#6	1684
#8	#1 and #7	42
Note		

6.2.2. Toxoplasmosis

Table 15 – Search strategies: Benefits-harms of screening and advice for toxoplasmosis infection during pregnancy

Database	Medline (Ovid)	
Date	20-05-2014	
Search strategy		
1	exp toxoplasmosis/	16588
2	toxoplasma/	10203
3	(toxoplasmosis or toxoplasma).ti,ab.	21160
4	1 or 2 or 3	23945
5	letter/	840786
6	editorial/	355994
7	news/	161749
8	exp historical article/	320669
9	anecdotes as topic/	4543
10	comment/	584772
11	case report/	1680216
12	(letter or comment*).ti.	96495
13	or/5-12	3340446
14	randomized controlled trial/ or random*.ti,ab.	811192
15	13 not 14	3322922
16	animals/ not humans/	3847854
17	exp animals, laboratory/	724095
18	exp animal experimentation/	6314
19	exp models, animal/	414688
20	exp rodentia/	2663804
21	(rat or rats or mouse or mice).ti.	1109813
22	or/15-21	7767001
23	4 not 22	12897
24	exp pregnancy/	709531
25	pregnant women/	5523
26	prenatal care/	20175
27	exp prenatal diagnosis/	59878
28	exp pregnancy complications/	336806
29	perinatal care/	2778
30	(antenatal* or ante-natal* or prenatal* or pre-natal* or perinatal* or peri-natal* or pregnan* or antepartum or ante-partum or peripartum or peri-partum).ti,ab.	455715
31	or/24-30	857548
32	23 and 31	2884
33	randomized controlled trial.pt.	373788

34	controlled clinical trial.pt.	88373
35	randomi#ed.ab.	351557
36	placebo.ab.	153950
37	drug therapy.fs.	1698549
38	randomly.ab.	212697
39	trial.ab.	304929
40	groups.ab.	1354210
41	or/33-40	3345377
42	clinical trials as topic.sh.	169943
43	trial.ti.	126393
44	or/33-36,38,42-43	924060
45	epidemiologic studies/	5959
46	exp case control studies/	658793
47	exp cohort studies/	1347396
48	cross-sectional studies/	174978
49	case control.ti,ab.	77893
50	(cohort adj (study or studies or analys*)).ti,ab.	90767
51	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.	147438
52	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.	782852
53	or/45-52	1969975
54	meta-analysis/	47989
55	meta-analysis as topic/	13752
56	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.	64910
57	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.	84734
58	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.	25622
59	(search strategy or search criteria or systematic search or study selection or data extraction).ab.	27340
60	(search* adj4 literature).ab.	27772
61	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.	91595
62	cochrane.jw.	10749
63	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.	1376
64	or/54-63	211973
65	44 or 53 or 64	2799899
66	32 and 65	603
67	mass screening/	81513
68	screen*.ti.	116382
69	67 or 68	156839
70	32 and 69	227
71	70 not 66	150

	72 66 or 70	753
Note		
Database	**Embase (Ovid)**	
Date	20-05-2014	
Search strategy		
	1 congenital toxoplasmosis/	2106
	2 toxoplasmosis/	16612
	3 exp toxoplasma/	13421
	4 (toxoplasmosis or toxoplasma).ti,ab.	21827
	5 or/1-4	27591
	6 letter.pt. or letter/	838297
	7 note.pt.	554436
	8 editorial.pt.	444065
	9 case report/ or case study/	1891947
	10 (letter or comment*).ti.	146333
	11 or/6-10	3580563
	12 randomized controlled trial/ or random*.ti,ab.	949031
	13 11 not 12	3552801
	14 animal/ not human/	1179709
	15 nonhuman/	4293765
	16 exp animal experiment/	1668497
	17 exp experimental animal/	399210
	18 animal model/	752719
	19 exp rodent/	2666161
	20 (rat or rats or mouse or mice).ti.	1155192
	21 or/13-20	9457910
	22 5 not 21	13096
	23 exp pregnancy/	546617
	24 pregnant woman/	32179
	25 prenatal diagnosis/	45652
	26 prenatal screening/	5586
	27 prenatal care/	26068
	28 exp pregnancy complication/	103216
	29 perinatal care/	8793
	30 (antenatal* or ante-natal* or prenatal* or pre-natal* or perinatal* or peri-natal* or pregnan* or antepartum or ante-partum or peripartum or peri-partum).ti,ab.	521340
	31 or/23-30	793412
	32 22 and 31	2956
	33 random*.ti,ab.	867049
	34 factorial*.ti,ab.	22599

35	(crossover* or cross over*).ti,ab.	67944
36	((doubl* or singl*) adj blind*).ti,ab.	152135
37	(assign* or allocat* or volunteer* or placebo*).ti,ab.	638477
38	crossover procedure/	38825
39	double blind procedure/	113073
40	single blind procedure/	18225
41	randomized controlled trial/	341422
42	or/33-41	1386094
43	clinical study/	56039
44	exp case control study/	84544
45	family study/	10357
46	longitudinal study/	66207
47	retrospective study/	343202
48	prospective study/	249423
49	cross-sectional study/	112824
50	cohort analysis/	166518
51	follow-up/	793912
52	cohort*.ti,ab.	392271
53	51 and 52	80124
54	case control.ti,ab.	90786
55	(cohort adj (study or studies or analys*)).ti,ab.	115382
56	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.	182120
57	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.	1020951
58	or/43-50,53-57	1668832
59	systematic review/	74385
60	meta-analysis/	78612
61	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.	81268
62	((systematic or evidence) adj3 (review* or overview*)).ti,ab.	95816
63	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.	29030
64	(search strategy or search criteria or systematic search or study selection or data extraction).ab.	30007
65	(search* adj4 literature).ab.	33798
66	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.	104868
67	cochrane.jw.	11325
68	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.	2079
69	or/59-68	269650
70	42 or 58 or 69	2979087
71	32 and 70	516
72	mass screening/	44652
73	screen*.ti.	140053

74	or/72-73	165335
75	32 and 74	213
76	75 not 71	150
77	71 or 75	666

Note	
Database	**The Cochrane Library (Wiley)**
Date	20-05-2014
Search strategy	

#1	(toxoplasmosis or toxoplasma):ti,ab,kw	155
#2	(antenatal* or ante-natal* or prenatal* or pre-natal* or perinatal* or peri-natal* or pregnan* or antepartum or ante-partum or peripartum or peri-partum):ti,ab,kw	26615
#3	#1 and #2	20

Note	

6.2.3. *Chlamydia trachomatis*

Table 16 – Search strategies: Benefits-harms of screening for chlamydia trachomatis infection during pregnancy

Database	**Medline (OVID)**	
Date	29-07-2014	
Search strategy		
1	exp chlamydia/	12757
2	exp chlamydia infections/	17611
3	chlam#di*.ti,ab.	22996
4	trachoma*.ti,ab.	14557
5	or/1-4	29603
6	letter/	850327
7	editorial/	362043
8	news/	163787
9	exp historical article/	323755
10	anecdotes as topic/	4574
11	comment/	594648
12	case report/	1693562
13	(letter or comment*).ti.	97923
14	or/6-13	3376362
15	randomized controlled trial/ or random*.ti,ab.	828104

16	14 not 15	3358584
17	animals/ not humans/	3881775
18	exp animals, laboratory/	732705
19	exp animal experimentation/	6412
20	exp models, animal/	421268
21	exp rodentia/	2691792
22	(rat or rats or mouse or mice).ti.	1120531
23	or/16-22	7846730
24	exp pregnancy/	715741
25	pregnant women/	5588
26	prenatal care/	20405
27	exp prenatal diagnosis/	60324
28	exp pregnancy complications/	339910
29	perinatal care/	2838
30	(antenatal* or ante-natal* or prenatal* or pre-natal* or perinatal* or peri-natal* or pregnan* or antepartum or ante-partum or peripartum or peri-partum).ti,ab.	462031
31	or/24-30	866952
32	randomized controlled trial.pt.	379829
33	controlled clinical trial.pt.	88924
34	randomi#ed.ab.	360003
35	placebo.ab.	156509
36	drug therapy.fs.	1720200
37	randomly.ab.	217404
38	trial.ab.	312355
39	groups.ab.	1379484
40	or/32-39	3399257
41	clinical trials as topic.sh.	171237
42	trial.ti.	129448
43	or/32-35,37,41-42	940525
44	epidemiologic studies/	6013
45	exp case control studies/	673359
46	exp cohort studies/	1371137
47	cross-sectional studies/	179918
48	case control.ti,ab.	79871
49	(cohort adj (study or studies or analys*)).ti,ab.	94224

	50	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.	150945
	51	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.	803405
	52	or/44-51	2011364
	53	meta-analysis/	50050
	54	meta-analysis as topic/	13913
	55	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.	68008
	56	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.	88390
	57	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.	26346
	58	(search strategy or search criteria or systematic search or study selection or data extraction).ab.	28100
	59	(search* adj4 literature).ab.	28866
	60	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.	95839
	61	cochrane.jw.	11035
	62	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.	1436
	63	or/53-62	220045
	64	43 or 52 or 63	2857942
	65	mass screening/	82453
	66	screen*.ti.	118566
	67	65 or 66	159455
	68	5 and 31 and 64	932
	69	5 and 31 and 67	337
	70	68 or 69	1159
	71	70 not 23	1088
Database		**Embase (OVID)**	
Date		29-07-2014	
Search strategy			
	1	exp chlamydia/	19632
	2	exp chlamydiasis/	17743
	3	chlam#di*.ti,ab.	26298
	4	trachoma*.ti,ab.	15876
	5	or/1-4	36522
	6	letter.pt. or letter/	846693
	7	note.pt.	563063

8	editorial.pt.	449219
9	case report/ or case study/	1909812
10	(letter or comment*).ti.	147876
11	or/6-10	3618086
12	randomized controlled trial/ or random*.ti,ab.	969233
13	11 not 12	3589953
14	animal/ not human/	1184528
15	nonhuman/	4342047
16	exp animal experiment/	1686321
17	exp experimental animal/	407638
18	animal model/	765218
19	exp rodent/	2696376
20	(rat or rats or mouse or mice).ti.	1165627
21	or/13-20	9557054
22	exp pregnancy/	552087
23	pregnant woman/	33561
24	prenatal diagnosis/	46078
25	prenatal screening/	5701
26	prenatal care/	26455
27	exp pregnancy complication/	104300
28	perinatal care/	9762
29	(antenatal* or ante-natal* or prenatal* or pre-natal* or perinatal* or peri-natal* or pregnan* or antepartum or ante-partum or peripartum or peri-partum).ti,ab.	528923
30	or/22-29	802794
31	random*.ti,ab.	886659
32	factorial*.ti,ab.	23031
33	(crossover* or cross over*).ti,ab.	69054
34	((doubl$ or singl$) adj blind$).ti,ab.	154737
35	(assign* or allocat* or volunteer* or placebo*).ti,ab.	650178
36	crossover procedure/	39607
37	double blind procedure/	114525
38	single blind procedure/	18590
39	randomized controlled trial/	346373
40	or/31-39	1413242
41	clinical study/	58085

42	exp case control study/	86890
43	family study/	10432
44	longitudinal study/	68149
45	retrospective study/	353194
46	prospective study/	256813
47	cross-sectional study/	118033
48	cohort analysis/	173236
49	follow-up/	817480
50	cohort*.ti,ab.	407650
51	49 and 50	83760
52	case control.ti,ab.	92984
53	(cohort adj (study or studies or analys*)).ti,ab.	119978
54	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.	186544
55	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.	1051652
56	or/41-48,51-55	1715797
57	systematic review/	77531
58	meta-analysis/	81072
59	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.	84712
60	((systematic or evidence) adj3 (review* or overview*)).ti,ab.	99494
61	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.	29661
62	(search strategy or search criteria or systematic search or study selection or data extraction).ab.	30745
63	(search* adj4 literature).ab.	35040
64	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.	108743
65	cochrane.jw.	11405
66	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.	2189
67	or/57-66	277774
68	40 or 56 or 67	3051079
69	mass screening/	44996
70	screen*.ti.	142638
71	or/69-70	168124
72	5 and 30 and 68	951
73	5 and 30 and 71	323
74	72 or 73	1177

	75	74 not 21	1066
Database		**The Cochrane Libarary (Wiley)**	
Date		29-07-2014	
Search strategy			
	#1	chlamydi* or chlamidi* or trachoma*:ti,ab,kw	1391
	#2	(antenatal* or ante-natal* or prenatal* pre-natal* or perinatal* or peri-natal* or pregnan*):ti,ab	17634
	#3	#1 and #2	145

6.2.4. Group B streptococcus

Table 17 – Search strategies: Benefits-harms of screening for GBS infection during pregnancy

Database		**Medline (OVID)**	
Date		12 August 2014	
Search strategy			
	1	streptococcus agalactiae/	6572
	2	(streptococcus adj (agalactiae or mastitidis or nocardi)).ti,ab.	2265
	3	GBS.ti,ab.	5101
	4	(strep* adj2 b).ti,ab.	7133
	5	or/1-4	12729
	6	letter/	852506
	7	editorial/	363365
	8	news/	164387
	9	exp historical article/	325601
	10	anecdotes as topic/	4585
	11	comment/	597237
	12	case report/	1701850
	13	(letter or comment*).ti.	98362
	14	or/6-13	3391294
	15	randomized controlled trial/ or random*.ti,ab.	838736
	16	14 not 15	3373410
	17	animals/ not humans/	3902412
	18	exp animals, laboratory/	735998
	19	exp animal experimentation/	6453
	20	exp models, animal/	424507
	21	exp rodentia/	2706824
	22	(rat or rats or mouse or mice).ti.	1126940
	23	or/16-22	7886635

24	exp pregnancy/	720424
25	pregnant women/	5621
26	prenatal care/	20592
27	exp prenatal diagnosis/	60663
28	exp pregnancy complications/	342541
29	perinatal care/	2868
30	(antenatal* or ante-natal* or prenatal* or pre-natal* or perinatal* or peri-natal* or pregnan* or antepartum or ante-partum or peripartum or peri-partum).ti,ab.	465851
31	or/24-30	872842
32	randomized controlled trial.pt.	385620
33	controlled clinical trial.pt.	89658
34	randomi#ed.ab.	366343
35	placebo.ab.	158580
36	drug therapy.fs.	1732585
37	randomly.ab.	220129
38	trial.ab.	317617
39	groups.ab.	1393154
40	or/32-39	3428648
41	clinical trials as topic.sh.	171994
42	trial.ti.	131902
43	or/32-35,37,41-42	951651
44	epidemiologic studies/	6059
45	exp case control studies/	682344
46	exp cohort studies/	1387786
47	cross-sectional studies/	183039
48	case control.ti,ab.	80945
49	(cohort adj (study or studies or analys*)).ti,ab.	96192
50	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.	152960
51	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.	816500
52	or/44-51	2036776
53	meta-analysis/	50912
54	meta-analysis as topic/	13987
55	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.	69212
56	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.	89997
57	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.	26877
58	(search strategy or search criteria or systematic search or study selection or data extraction).ab.	28814
59	(search* adj4 literature).ab.	29345
60	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.	97859
61	cochrane.jw.	11340
62	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.	1446
63	or/53-62	223538

64	43 or 52 or 63	2892785
65	mass screening/	83063
66	screen*.ti,ab.	479679
67	65 or 66	160634
68	5 and 31 and 64	829
69	5 and 31 and 67	308
70	or/68-69	1246
71	70 not 23	1150

Database	Embase (OVID)
Date	12 August 2014

Search strategy

1	streptococcus agalactiae/	9189
2	(streptococcus adj (agalactiae or mastitidis or nocardi)).ti,ab.	2499
3	GBS.ti,ab.	6444
4	(strep* adj2 b).ti,ab.	7707
5	or/1-4	15860
6	letter.pt. or letter/	847979
7	note.pt.	564650
8	editorial.pt.	450157
9	case report/ or case study/	1912691
10	(letter or comment*).ti.	148146
11	or/6-10	3624319
12	randomized controlled trial/ or random*.ti,ab.	972733
13	11 not 12	3596120
14	animal/ not human/	1185678
15	nonhuman/	4351218
16	exp animal experiment/	1689714
17	exp experimental animal/	409209
18	animal model/	767587
19	exp rodent/	2701995
20	(rat or rats or mouse or mice).ti.	1167593
21	or/13-20	9575236
22	exp pregnancy/	552834
23	pregnant woman/	33782
24	prenatal diagnosis/	46119
25	prenatal screening/	5713
26	prenatal care/	26515
27	exp pregnancy complication/	104465
28	perinatal care/	9775

29	(antenatal* or ante-natal* or prenatal* or pre-natal* or perinatal* or peri-natal* or pregnan* or antepartum or ante-partum or peripartum or peri-partum).ti,ab.	530057
30	or/22-29	804179
31	random*.ti,ab.	890028
32	factorial*.ti,ab.	23115
33	(crossover* or cross over*).ti,ab.	69264
34	((doubl$ or singl$) adj blind$).ti,ab.	155198
35	(assign* or allocat* or volunteer* or placebo*).ti,ab.	652414
36	crossover procedure/	39769
37	double blind procedure/	114758
38	single blind procedure/	18650
39	randomized controlled trial/	347300
40	or/31-39	1418211
41	clinical study/	58540
42	exp case control study/	87289
43	family study/	10446
44	longitudinal study/	68492
45	retrospective study/	354901
46	prospective study/	258065
47	cross-sectional study/	119080
48	cohort analysis/	174386
49	follow-up/	821937
50	cohort*.ti,ab.	410614
51	49 and 50	84576
52	case control.ti,ab.	93388
53	(cohort adj (study or studies or analys*)).ti,ab.	120779
54	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.	187296
55	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.	1057032
56	or/41-48,51-55	1724129
57	systematic review/	78129
58	meta-analysis/	81521
59	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.	85352
60	((systematic or evidence) adj3 (review* or overview*)).ti,ab.	100162
61	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.	29747
62	(search strategy or search criteria or systematic search or study selection or data extraction).ab.	30850
63	(search* adj4 literature).ab.	35271
64	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.	109450
65	cochrane.jw.	11405
66	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.	2202
67	or/57-66	279255
68	40 or 56 or 67	3064052

69	mass screening/	45062
70	screen*.ti,ab.	593094
71	or/69-70	609812
72	5 and 30 and 68	705
73	5 and 30 and 71	741
74	72 or 73	1220
75	74 not 21	1004

Database	**The Cochrane Library (Wiley)**	
Date	28 July 2014	
Search strategy		
#1	(streptococcus near (agalactiae or mastitidis or nocardi)):ti,ab,kw	133
#2	(strep* near/2 b):ti,ab	224
#3	GBS:ti,ab	137
#4	{or #1-#3}	361
#5	(antenatal* or ante-natal* or prenatal* or pre-natal* or perinatal* or peri-natal* or pregnan* or antepartum or ante-partum or peripartum or peri-partum):ti,ab,kw	26757
#6	#4 and #5	113

6.2.5. Gestational diabetes

Table 18 – Search strategies: Benefits-harms of different stategies of screening for gestational diabetes

Database	**Medline (OVID)**	
Date	30-07-2014	
Search strategy		
1	(HbA1c or HbA or GHb or HbAIC or A1C or HbA1).ti,ab.	30058
2	((glycosylated or glycated or glycoslated) adj3 (haemoglobin or hemoglobin)).ti,ab.	12163
3	*hemoglobin a, glycosylated/	6060
4	((blood or random or tolerance or plasma or fast*) adj3 (glucose or sugar*)).ti,ab.	117139
5	(RBS or RBG or OGTT).ti,ab.	6957
6	*glucose tolerance test/	4835
7	*blood glucose/	38208
8	or/1-7	156723
9	*diabetes, gestational/	4692
10	(diabet* adj3 (gestation* or pregnan*)).ti.	7800
11	(diabet* adj2 gestation*).ab.	6913
12	or/9-11	11424
13	8 and 12	3862
14	screen*.ti.	118639

15	*mass screening/	42947
16	*prenatal diagnosis/	19214
17	or/14-16	147559
18	12 and 17	793
19	randomized controlled trial.pt.	379924
20	controlled clinical trial.pt.	88928
21	randomi#ed.ab.	360227
22	placebo.ab.	156570
23	drug therapy.fs.	1720529
24	randomly.ab.	217529
25	trial.ab.	312561
26	groups.ab.	1380111
27	or/19-26	3400475
28	clinical trials as topic.sh.	171252
29	trial.ti.	129546
30	or/19-22,24,28-29	940915
31	letter/	850653
32	editorial/	362248
33	news/	163908
34	exp historical article/	323832
35	anecdotes as topic/	4574
36	comment/	594984
37	case report/	1693789
38	(letter or comment*).ti.	97981
39	or/31-38	3377404
40	randomized controlled trial/ or random*.ti,ab.	828529
41	39 not 40	3359624
42	animals/ not humans/	3882117
43	exp animals, laboratory/	732764
44	exp animal experimentation/	6415
45	exp models, animal/	421345
46	exp rodentia/	2691999
47	(rat or rats or mouse or mice).ti.	1120797
48	or/41-47	7848377
49	epidemiologic studies/	6016
50	exp case control studies/	673543
51	exp cohort studies/	1371457
52	cross-sectional studies/	180042
53	case control.ti,ab.	79922
54	(cohort adj (study or studies or analys*)).ti,ab.	94341
55	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.	151053

	56	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.	804067
	57	or/49-56	2012354
	58	meta-analysis/	50068
	59	meta-analysis as topic/	13914
	60	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.	68064
	61	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.	88489
	62	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.	26362
	63	(search strategy or search criteria or systematic search or study selection or data extraction).ab.	28113
	64	(search* adj4 literature).ab.	28893
	65	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.	95924
	66	cochrane.jw.	11035
	67	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.	1437
	68	or/58-67	220233
	69	30 or 57 or 68	2859361
	70	13 and 69	1708
	71	18 or 70	2299
	72	71 not 48	2145
	73	limit 72 to (dutch or english or french or german)	2017
Database		**Embase (OVID)**	
Date		30-07-2014	
Search strategy			
	1	*hemoglobin A1c/	5023
	2	*oral glucose tolerance test/	1191
	3	*glucose tolerance test/	4222
	4	*glucose blood level/	25900
	5	(HbA1c or HbA or GHb or HbAIC or A1C or HbA1).ti,ab.	48079
	6	((blood or random or tolerance or plasma or fast*) adj3 (glucose or sugar*)).ti,ab.	148968
	7	(RBS or RBG or OGTT).ti,ab.	10620
	8	((glycosylated or glycated or glycoslated) adj3 (haemoglobin or hemoglobin)).ti,ab.	14994
	9	or/1-8	197605
	10	(diabet* adj3 (gestation* or pregnan*)).ti.	9852
	11	(diabet* adj2 gestation*).ab.	10006
	12	*pregnancy diabetes mellitus/	10548
	13	or/10-12	16991
	14	9 and 13	5521
	15	screen*.ti.	142638
	16	*mass screening/	19525

17	*prenatal screening/	1996
18	*prenatal diagnosis/	22240
19	or/15-18	170303
20	13 and 19	972
21	random*.ti,ab.	886659
22	factorial*.ti,ab.	23031
23	(crossover* or cross over*).ti,ab.	69054
24	((doubl$ or singl$) adj blind$).ti,ab.	154737
25	(assign* or allocat* or volunteer* or placebo*).ti,ab.	650178
26	crossover procedure/	39607
27	double blind procedure/	114525
28	single blind procedure/	18590
29	randomized controlled trial/	346373
30	or/21-29	1413242
31	letter.pt. or letter/	846693
32	note.pt.	563063
33	editorial.pt.	449219
34	case report/ or case study/	1909812
35	(letter or comment*).ti.	147876
36	or/31-35	3618086
37	randomized controlled trial/ or random*.ti,ab.	969233
38	36 not 37	3589953
39	animal/ not human/	1184528
40	nonhuman/	4342047
41	exp animal experiment/	1686321
42	exp experimental animal/	407638
43	animal model/	765218
44	exp rodent/	2696376
45	(rat or rats or mouse or mice).ti.	1165627
46	or/38-45	9557054
47	clinical study/	58085
48	exp case control study/	86890
49	family study/	10432
50	longitudinal study/	68149
51	retrospective study/	353194
52	prospective study/	256813
53	cross-sectional study/	118033
54	cohort analysis/	173236
55	follow-up/	817480
56	cohort*.ti,ab.	407650
57	55 and 56	83760
58	case control.ti,ab.	92984

	59	(cohort adj (study or studies or analys*)).ti,ab.	119978
	60	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.	186544
	61	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.	1051652
	62	or/47-54,57-61	1715797
	63	systematic review/	77531
	64	meta-analysis/	81072
	65	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.	84712
	66	((systematic or evidence) adj3 (review* or overview*)).ti,ab.	99494
	67	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.	29661
	68	(search strategy or search criteria or systematic search or study selection or data extraction).ab.	30745
	69	(search* adj4 literature).ab.	35040
	70	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.	108743
	71	cochrane.jw.	11405
	72	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.	2189
	73	or/63-72	277774
	74	30 or 62 or 73	3051079
	75	14 and 74	2107
	76	20 or 75	2829
	77	76 not 46	2635
	78	limit 77 to (dutch or english or french or german)	2469
Database		**The Cochrane Library (Wiley)**	
Date		30-07-2014	
Search strategy			
	#1	(hba1c or hba or ghb or hbaic or a1c or hba1):ti,ab	5361
	#2	((glycosylated or glycated or glycoslated) near/3 (haemoglobin or hemoglobin)):ti,ab	2066
	#3	((blood or random or tolerance or plasma or fast*) near/3 (glucose or sugar*)):ti,ab	13333
	#4	(rbs or rbg or ogtt):ti,ab	656
	#5	[mh ^"hemoglobin a, glycosylated"]	3669
	#6	[mh ^"glucose tolerance test"]	1589
	#7	[mh ^"blood glucose"]	11213
	#8	{or #1-#7}	20771
	#9	[mh ^"diabetes, gestational"]	317
	#10	(diabet* near/3 (gestation* or pregnan*)):ti	467
	#11	(diabet* near/2 gestation*):ab	394
	#12	{or #9-#11}	612
	#13	#8 and #12	361
	#14	screen*:ti	6478
	#15	[mh ^"mass screening"]	4206

#16	[mh ^"prenatal diagnosis"]	338
#17	2-#16	7851
#18	#12 and #17	64
#19	#13 or #18	385

6.2.6. Hypothyroidism

Table 19 – Search strategies: Benefits-harms of screening for hypothyroidism during pregnancy (SRs)

Database	Medline (OVID) & Embase
Date	28-04-2014
Search strategy	1 exp Pregnancy/ or exp Pregnancy Complications/ (1316130) 2 Pregnant Women/ (37186) 3 exp Pregnancy Trimesters/ (577418) 4 pregnan*.tw. (786246) 5 Prenatal Care/ or exp Prenatal Diagnosis/ (178597) 6 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (306050) 7 or/1-6 (1649609) 8 Diagnostic Tests, Routine/ (66837) 9 ((routine* or mass or standard* or universal*) adj3 test*).tw. (97653) 10 exp Mass Screening/ (251280) 11 (screen* or detect*).tw. (4247410) 12 (early adj3 (diagnos* or identif* or recogni*)).tw. (225770) 13 or/8-12 (4607654) 14 7 and 13 (201636) 15 exp Thyroid Function Tests/ (30101) 16 ((thyroid* or thyroxin* or thyrotropin* or thyrotrophin* or TSH or thyronin* or triiodothyronin* or tri-iodothyronin*) adj3 (assess* or calculat* or measur* or determin* or evaluat* or examin* or identif* or test* or screen*)).tw. (45205) 17 (basal adj2 metaboli*).tw. (7384) 18 exp Thyroid Diseases/pc (4280) 19 exp Thyroid Diseases/di (55092) 20 or/15-19 (118335) 21 7 and 20 (8185) 22 exp Thyroid Diseases/ (279520) 23 (thyroid* adj2 (disease* or disorder* or dysfunction*)).tw. (36765) 24 Thyroid Gland/me, pp (12950) 25 exp Thyroxine/bl (18345) 26 exp Thyrotropin/bl (14857) 27 ((thyroid* or thyroxin* or thyrotropin* or thyrotrophin* or TSH or thyronin* or triiodothyronin* or tri-iodothyronin*) adj3 (blood or serum)).tw. (27862)

28 (hypothyroid* or hypo-thyroid*).tw. (57620)
29 goiter*.tw. (25576)
30 ((grave* or Basedow*) adj2 disease*).tw. (22851)
31 or/22-30 (325467)
32 14 and 31 (3220)
33 21 or 32 (9672)
34 exp Animals/ not (exp Animals/ and Humans/) (7873321)
35 33 not 34 (8785)
36 (comment or editorial or interview or letter or news).pt. (2771551)
37 35 not 36 (8443)
38 limit 37 to systematic reviews [Limit not valid in Embase; records were retained] (4459)
39 meta analysis.pt. (47108)
40 exp meta-analysis as topic/ (26465)
41 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw. (145473)
42 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (176792)
43 exp Technology assessment, biomedical/ (20505)
44 (cochrane or health technology assessment or evidence report).jw. (24555)
45 or/39-44 (334474)
46 37 and 45 (107)
47 38 or 46 (4472)
48 limit 47 to yr="2011-current" (1074)
49 48 use prmz (39)
50 exp pregnancy/ (1252244)
51 exp pregnancy disorder/ (395634)
52 pregnant woman/ (37186)
53 pregnan*.tw. (786246)
54 exp prenatal care/ or prenatal diagnosis/ (154836)
55 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (306050)
56 or/50-55 (1732632)
57 exp diagnostic test/ (678170)
58 ((routine* or mass or standard* or universal*) adj3 test*).tw. (97653)
59 mass screening/ (125653)
60 (screen* or detect*).tw. (4247410)
61 (early adj3 (diagnos* or identif* or recogni*)).tw. (225770)
62 or/57-61 (5079660)
63 56 and 62 (233704)
64 thyroid function test/ (23711)

65 ((thyroid* or thyroxin* or thyrotropin* or thyrotrophin* or TSH or thyronin* or triiodothyronin* or tri-iodothyronin*) adj3 (assess* or calculat* or measur* or determin* or evaluat* or examin* or identif* or test* or screen*)).tw. (45205)
66 free thyroxine index/ (3959)
67 (basal adj2 metaboli*).tw. (7384)
68 exp thyroid disease/di, pc [Diagnosis, Prevention] (58745)
69 or/64-68 (115351)
70 56 and 69 (8654)
71 exp thyroid disease/ (279520)
72 (thyroid* adj2 (disease* or disorder* or dysfunction*)).tw. (36765)
73 exp thyroxine blood level/ (9728)
74 thyrotropin blood level/ (8980)
75 ((thyroid* or thyroxin* or thyrotropin* or thyrotrophin* or TSH or thyronin* or triiodothyronin* or tri-iodothyronin*) adj3 (blood or serum)).tw. (27862)
76 (hypothyroid* or hypo-thyroid*).tw. (57620)
77 goiter*.tw. (25576)
78 ((grave* or Basedow*) adj2 disease*).tw. (22851)
79 or/71-78 (313354)
80 63 and 79 (4456)
81 70 or 80 (10388)
82 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (36234989)
83 exp humans/ or exp human experimentation/ or exp human experiment/ (27963237)
84 82 not 83 (8273323)
85 81 not 84 (9589)
86 (letter or editorial).pt. (2464663)
87 85 not 86 (9224)
88 limit 87 to "reviews (maximizes specificity)" (79)
89 meta-analysis/ (124963)
90 "systematic review"/ (73413)
91 "meta analysis (topic)"/ (12792)
92 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw. (145473)
93 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (176792)
94 biomedical technology assessment/ (19404)
95 (cochrane or health technology assessment or evidence report).jw. (24555)
96 or/89-95 (367230)
97 87 and 96 (153)
98 88 or 97 (163)
99 limit 98 to yr="2011-current" (75)
100 99 use emez (51)
101 49 or 100 (90)

	102 remove duplicates from 101 (75) [UNIQUE HITS] 103 102 use prmz (38) [MEDLINE UNIQUE HITS] 104 102 use emez (37) [EMBASE UNIQUE HITS]
Note	
Database	**The Cochrane library**
Date	02-05-2014
Search strategy	ID Search Hits #1 [mh Pregnancy] 5764 #2 [mh "Pregnancy Complications"] 7732 #3 [mh "Pregnant Women"] 95 #4 [mh "Pregnancy Trimesters"] 1459 #5 pregnan*:ti,ab,kw 25022 #6 [mh "Prenatal Care"] or [mh "Prenatal Diagnosis"] 1935 #7 (prenatal* or antenatal* or (ante next natal*) or antepartum or (ante next partum) or perinatal* or (peri next natal*) or peripartum or (peri next partum)):ti,ab,kw 6004 #8 {or #1-#7} 27209 #9 [mh "Diagnostic Tests, Routine"] 309 #10 ((routine* or mass or standard* or universal*) near/3 test*):ti,ab,kw 3550 #11 [mh "Mass Screening"] 4940 #12 (screen* or detect*):ti,ab,kw 53436 #13 (early near/3 (diagnos* or identif* or recogni*)):ti,ab,kw 2064 #14 {or #9-#13} 57549 #15 #8 and #14 2751 #16 [mh "Thyroid Function Tests"] 566 #17 ((thyroid* or thyroxin* or thyrotropin* or thyrotrophin* or TSH or thyronin* or triiodothyronin* or tri-iodothyronin*) near/3 (assess* or calculat* or function* or measur* or determin* or evaluat* or examin* or identif* or measur* or test* or screen*)):ti,ab,kw 1200 #18 (basal near/2 metaboli*):ti,ab,kw 501 #19 [mh "Thyroid Diseases"/di,pc] 252 #20 {or #16-#19} 1834 #21 #8 and #20 88 #22 [mh "Thyroid Diseases"] 1627 #23 (thyroid* near/2 (disease* or disorder* or dysfunction*)):ti,ab,kw 464 #24 [mh "Thyroid Gland"/me,pp] 142 #25 [mh Thyroxine/bl] or [mh Thyrotropin/bl] 870 #26 ((thyroid* or thyroxin* or thyrotropin* or thyrotrophin* or TSH or thyronin* or triiodothyronin* or tri-iodothyronin*) near/3 (blood or serum)):ti,ab,kw 718 #27 (hypothyroid* or (hypo next thyroid*)):ti,ab,kw 718 #28 goiter*:ti,ab,kw 358 #29 ((grave* or Basedow*) near/2 disease*):ti,ab,kw 386 #30 3-#29 2892

	#31 #15 and #30 25 #32 #21 or #31 Publication Date from 2011 to 2014 19 DSR – 3 DARE - 2 CENTRAL – 12 (did not download – review search only) NHS EED – 1 (did not download – review search only)
Note	

Table 20 – Search strategies: Benefits-harms of screening for hypothyroidism during pregnancy (Primary studies)

Database	Medline (Ovid) & Embase
Date	06-05-2014
Search strategy	1 exp Pregnancy/ or exp Pregnancy Complications/ (1406129) 2 Pregnant Women/ (44462) 3 exp Pregnancy Trimesters/ (663687) 4 pregnan*.tw. (862575) 5 Prenatal Care/ or exp Prenatal Diagnosis/ (185103) 6 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (320943) 7 or/1-6 (1763400) 8 Diagnostic Tests, Routine/ (68590) 9 ((routine* or mass or standard* or universal*) adj3 test*).tw. (103436) 10 exp Mass Screening/ (255714) 11 (screen* or detect*).tw. (4406873) 12 (early adj3 (diagnos* or identif* or recogni*)).tw. (244661) 13 or/8-12 (4790911) 14 7 and 13 (210219) 15 exp Thyroid Function Tests/ (30671) 16 ((thyroid* or thyroxin* or thyrotropin* or thyrotrophin* or TSH or thyronin* or triiodothyronin* or tri-iodothyronin*) adj3 (assess* or calculat* or measur* or determin* or evaluat* or examin* or identif* or test* or screen*)).tw. (51075) 17 (basal adj2 metaboli*).tw. (9399) 18 exp Thyroid Diseases/pc (4282) 19 exp Thyroid Diseases/di (55167) 20 or/15-19 (126292) 21 7 and 20 (8698) 22 exp Thyroid Diseases/ (312627) 23 (thyroid* adj2 (disease* or disorder* or dysfunction*)).tw. (39795) 24 Thyroid Gland/me, pp (12953) 25 exp Thyroxine/bl (18349) 26 exp Thyrotropin/bl (14860) 27 ((thyroid* or thyroxin* or thyrotropin* or thyrotrophin* or TSH or thyronin* or triiodothyronin* or tri-iodothyronin*) adj3 (blood or serum)).tw. (31336)

28	(hypothyroid* or hypo-thyroid*).tw. (64881)
29	goiter*.tw. (28998)
30	((grave* or Basedow*) adj2 disease*).tw. (24851)
31	or/22-30 (361855)
32	14 and 31 (3359)
33	21 or 32 (10280)
34	exp Animals/ not (exp Animals/ and Humans/) (8674498)
35	33 not 34 (9269)
36	(comment or editorial or interview or letter or news).pt. (2786857)
37	35 not 36 (8927)
38	(controlled clinical trial or randomized controlled trial).pt. (455001)
39	clinical trials as topic.sh. (169504)
40	(randomi#ed or randomly or RCT$1 or placebo*).tw. (1410952)
41	((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (294678)
42	trial.ti. (289768)
43	or/38-42 (1814632)
44	37 and 43 (289)
45	controlled clinical trial.pt. (88214)
46	Controlled Clinical Trial/ or Controlled Clinical Trials as Topic/ (480327)
47	(control* adj2 trial*).tw. (319976)
48	(nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (73010)
49	(nRCT or nRCTs or non-RCT$1).tw. (638)
50	(control* adj3 ("before and after" or "before after")).tw. (6002)
51	time series.tw. (33611)
52	(pre- adj3 post-).tw. (109186)
53	(pretest adj3 posttest).tw. (6214)
54	(control* adj2 stud$3).tw. (343432)
55	Control Groups/ (73288)
56	(control$ adj2 group$1).tw. (746059)
57	or/45-56 (1844010)
58	37 and 57 (553)
59	exp Cohort Studies/ (1503599)
60	cohort$1.tw. (663754)
61	Retrospective Studies/ (828724)
62	(longitudinal or prospective or retrospective).tw. (1702897)
63	((followup or follow-up) adj (study or studies)).tw. (88724)
64	Observational study.pt. (1963)
65	(observation$2 adj (study or studies)).tw. (109230)
66	((population or population-based) adj (study or studies or analys#s)).tw. (25947)
67	((multidimensional or multi-dimensional) adj (study or studies)).tw. (186)
68	Comparative Study.pt. (1672336)

69 ((comparative or comparison) adj (study or studies)).tw. (184863)
70 exp Case-Control Studies/ (737634)
71 ((case-control* or case-based or case-comparison) adj (study or studies)).tw. (140936)
72 or/59-71 (4898149)
73 37 and 72 (1575)
74 44 or 58 or 73 (1974)
75 74 use prmz (1150)
76 exp pregnancy/ (1339001)
77 exp pregnancy disorder/ (451267)
78 pregnant woman/ (44462)
79 pregnan*.tw. (862575)
80 exp prenatal care/ or prenatal diagnosis/ (161813)
81 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (320943)
82 or/76-81 (1868416)
83 exp diagnostic test/ (752484)
84 ((routine* or mass or standard* or universal*) adj3 test*).tw. (103436)
85 mass screening/ (128989)
86 (screen* or detect*).tw. (4406873)
87 (early adj3 (diagnos* or identif* or recogni*)).tw. (244661)
88 or/83-87 (5326184)
89 82 and 88 (247762)
90 thyroid function test/ (24272)
91 ((thyroid* or thyroxin* or thyrotropin* or thyrotrophin* or TSH or thyronin* or triiodothyronin* or tri-iodothyronin*) adj3 (assess* or calculat* or measur* or determin* or evaluat* or examin* or identif* or test* or screen*)).tw. (51075)
92 free thyroxine index/ (4382)
93 (basal adj2 metaboli*).tw. (9399)
94 exp thyroid disease/di, pc [Diagnosis, Prevention] (58820)
95 or/90-94 (123522)
96 82 and 95 (9258)
97 exp thyroid disease/ (312627)
98 (thyroid* adj2 (disease* or disorder* or dysfunction*)).tw. (39795)
99 exp thyroxine blood level/ (10793)
100 thyrotropin blood level/ (9469)
101 ((thyroid* or thyroxin* or thyrotropin* or thyrotrophin* or TSH or thyronin* or triiodothyronin* or tri-iodothyronin*) adj3 (blood or serum)).tw. (31336)
102 (hypothyroid* or hypo-thyroid*).tw. (64881)
103 goiter*.tw. (28998)
104 ((grave* or Basedow*) adj2 disease*).tw. (24851)
105 or/97-104 (350105)
106 89 and 105 (4704)
107 96 or 106 (11145)
108 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (37232147)

109	exp humans/ or exp human experimentation/ or exp human experiment/ (28265279)
110	108 not 109 (8968510)
111	107 not 110 (10266)
112	(letter or editorial).pt. (2479446)
113	111 not 112 (9901)
114	randomized controlled trial/ or controlled clinical trial/ (931510)
115	exp "clinical trial (topic)"/ (101233)
116	(randomi#ed or randomly or RCT$1 or placebo*).tw. (1410952)
117	((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (294678)
118	trial.ti. (289768)
119	or/114-118 (1945278)
120	113 and 119 (378)
121	controlled clinical trial/ (472831)
122	"controlled clinical trial (topic)"/ (2776)
123	(control* adj2 trial*).tw. (319976)
124	(nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (73010)
125	(nRCT or nRCTs or non-RCT$1).tw. (638)
126	(control* adj3 ("before and after" or "before after")).tw. (6002)
127	time series analysis/ (13843)
128	time series.tw. (33611)
129	pretest posttest control group design/ (201)
130	(pre- adj3 post-).tw. (109186)
131	(pretest adj3 posttest).tw. (6214)
132	controlled study/ (4309705)
133	(control* adj2 stud$3).tw. (343432)
134	control group/ (73288)
135	(control$ adj2 group$1).tw. (746059)
136	or/121-135 (5485130)
137	113 and 136 (1265)
138	cohort analysis/ (329675)
139	cohort$1.tw. (663754)
140	retrospective study/ (828724)
141	longitudinal study/ (151443)
142	prospective study/ (612040)
143	(longitudinal or prospective or retrospective).tw. (1702897)
144	follow up/ (814338)
145	((followup or follow-up) adj (study or studies)).tw. (88724)
146	observational study/ (56474)
147	(observation$2 adj (study or studies)).tw. (109230)
148	population research/ (68303)
149	((population or population-based) adj (study or studies or analys#s)).tw. (25947)

	150 ((multidimensional or multi-dimensional) adj (study or studies)).tw. (186) 151 exp comparative study/ (2685881) 152 ((comparative or comparison) adj (study or studies)).tw. (184863) 153 exp case control study/ (737634) 154 ((case-control* or case-based or case-comparison) adj (study or studies)).tw. (140936) 155 or/138-154 (6125033) 156 113 and 155 (2092) 157 120 or 137 or 156 (2927) 158 157 use emczd (1936) 159 75 or 158 (3086) 160 remove duplicates from 159 (2374) [TOTAL UNIQUE HITS] 161 160 use prmz (1138) [MEDLINE UNIQUE HITS] 162 160 use emczd (1236) [EMBASE UNIQUE HITS]
Note	
Database	**The Cochrane library**
Date	04-05-2014
Search strategy	ID Search Hits #1 [mh Pregnancy] 5764 #2 [mh "Pregnancy Complications"] 7732 #3 [mh "Pregnant Women"] 95 #4 [mh "Pregnancy Trimesters"] 1459 #5 pregnan*:ti,ab,kw 25022 #6 [mh "Prenatal Care"] or [mh "Prenatal Diagnosis"] 1935 #7 (prenatal* or antenatal* or (ante next natal*) or antepartum or (ante next partum) or perinatal* or (peri next natal*) or peripartum or (peri next partum)):ti,ab,kw 6004 #8 {or #1-#7} 27209 #9 [mh "Diagnostic Tests, Routine"] 309 #10 ((routine* or mass or standard* or universal*) near/3 test*):ti,ab,kw 3550 #11 [mh "Mass Screening"] 4940 #12 (screen* or detect*):ti,ab,kw 53436 #13 (early near/3 (diagnos* or identif* or recogni*)):ti,ab,kw 2064 #14 {or #9-#13} 57549 #15 #8 and #14 2751 #16 [mh "Thyroid Function Tests"] 566 #17 ((thyroid* or thyroxin* or thyrotropin* or thyrotrophin* or TSH or thyronin* or triiodothyronin* or tri-iodothyronin*) near/3 (assess* or calculat* or function* or measur* or determin* or evaluat* or examin* or identif* or measur* or test* or screen*)):ti,ab,kw 1200 #18 (basal near/2 metaboli*):ti,ab,kw 501 #19 [mh "Thyroid Diseases"/di,pc] 252 #20 {or #16-#19} 1834 #21 #8 and #20 88 #22 [mh "Thyroid Diseases"] 1627

	#23 (thyroid* near/2 (disease* or disorder* or dysfunction*)):ti,ab,kw 464 #24 [mh "Thyroid Gland"/me,pp] 142 #25 [mh Thyroxine/bl] or [mh Thyrotropin/bl] 870 #26 ((thyroid* or thyroxin* or thyrotropin* or thyrotrophin* or TSH or thyronin* or triiodothyronin* or tri-iodothyronin*) near/3 (blood or serum)):ti,ab,kw 718 #27 (hypothyroid* or (hypo next thyroid*)):ti,ab,kw 718 #28 goiter*:ti,ab,kw 358 #29 ((grave* or Basedow*) near/2 disease*):ti,ab,kw 386 #30 3-#29 2892 #31 #15 and #30 25 #32 #21 or #31 93 DSR – 8 (did not download; search for primary studies only) DARE – 2 (did not download; search for primary studies only) CENTRAL – 78 (Primary studies) NHS EED – 5 (did not download; search for primary studies only)
Note	Searches for primary studies were conducted across OVID MEDLINE, OVID Embase, and the Cochrane Library on May 4, 2014. A second search for euthyroid pregnancies (a term overlooked in the original search) only was subsequently performed on July 20, 2014. The followings search strategies belong to the second search:

Table 21 – Second search strategies: Benefits-harms of screening for hypothyroidism during euthyroid pregnancies (Primary studies)

Database	Medline (OVID)
Date	20- 07- 2014
Search strategy	1 exp Pregnancy/ or exp Pregnancy Complications/ (749057) 2 Pregnant Women/ (5577) 3 exp Pregnancy Trimesters/ (32732) 4 pregnan*.tw. (372204) 5 Prenatal Care/ or exp Prenatal Diagnosis/ (79357) 6 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (143859) 7 or/1-6 (864882) 8 Diagnostic Tests, Routine/ (7042) 9 ((routine* or mass or standard* or universal*) adj3 test*).tw. (44354) 10 exp Mass Screening/ (101054) 11 (screen* or detect*).tw. (2005433) 12 (early adj3 (diagnos* or identif* or recogni*)).tw. (101481) 13 or/8-12 (2146531) 14 7 and 13 (98168) 15 exp Thyroid Function Tests/ (18715) 16 ((thyroid* or thyroxin* or thyrotropin* or thyrotrophin* or TSH or thyronin* or triiodothyronin* or tri-iodothyronin*) adj3 (assess* or calculat* or measur* or determin* or evaluat* or examin* or identif* or test* or screen*)).tw. (21263) 17 (basal adj2 metaboli*).tw. (3654) 18 exp Thyroid Diseases/pc (2232) 19 exp Thyroid Diseases/di (22353) 20 or/15-19 (56475) 21 7 and 20 (4209) 22 exp Thyroid Diseases/ (119877) 23 (thyroid* adj2 (disease* or disorder* or dysfunction*)).tw. (16952) 24 Thyroid Gland/me, pp (13048) 25 exp Thyroxine/bl (18479) 26 exp Thyrotropin/bl (14989) 27 ((thyroid* or thyroxin* or thyrotropin* or thyrotrophin* or TSH or thyronin* or triiodothyronin* or tri-iodothyronin*) adj3 (blood or serum)).tw. (13770) 28 (hypothyroid* or hypo-thyroid*).tw. (26943) 29 goiter*.tw. (12379) 30 ((grave* or Basedow*) adj2 disease*).tw. (10953) 31 or/22-30 (153684) 32 14 and 31 (1461) 33 21 or 32 (4885) 34 exp Animals/ not (exp Animals/ and Humans/) (3968668) 35 33 not 34 (4333) 36 (comment or editorial or interview or letter or news).pt. (1523465)

37	35 not 36 (4147)
38	(controlled clinical trial or randomized controlled trial).pt. (462939)
39	clinical trials as topic.sh. (171051)
40	(randomi#ed or randomly or RCT$1 or placebo*).tw. (630927)
41	((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (131169)
42	trial.ti. (128892)
43	or/38-42 (952763)
44	37 and 43 (157)
45	controlled clinical trial.pt. (88847)
46	Controlled Clinical Trial/ or Controlled Clinical Trials as Topic/ (93809)
47	(control* adj2 trial*).tw. (147609)
48	(nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (34331)
49	(nRCT or nRCTs or non-RCT$1).tw. (287)
50	(control* adj3 ("before and after" or "before after")).tw. (2712)
51	time series.tw. (16211)
52	(pre- adj3 post-).tw. (43493)
53	(pretest adj3 posttest).tw. (3020)
54	(control* adj2 stud$3).tw. (156435)
55	Control Groups/ (1468)
56	(control$ adj2 group$1).tw. (322316)
57	or/45-56 (733639)
58	37 and 57 (244)
59	exp Cohort Studies/ (1367586)
60	cohort$1.tw. (285551)
61	Retrospective Studies/ (498368)
62	(longitudinal or prospective or retrospective).tw. (746519)
63	((followup or follow-up) adj (study or studies)).tw. (38545)
64	Observational study.pt. (3446)
65	(observation$2 adj (study or studies)).tw. (47457)
66	((population or population-based) adj (study or studies or analys#s)).tw. (11662)
67	((multidimensional or multi-dimensional) adj (study or studies)).tw. (79)
68	Comparative Study.pt. (1686600)
69	((comparative or comparison) adj (study or studies)).tw. (80506)
70	exp Case-Control Studies/ (671042)
71	((case-control* or case-based or case-comparison) adj (study or studies)).tw. (66923)
72	or/59-71 (3315306)
73	37 and 72 (1014)
74	44 or 58 or 73 (1181)
75	euthyroid*.tw. (9823)
76	14 and 75 (171)
77	76 not (34 or 36) (158)

	78 77 and (43 or 57 or 72) (63) 79 78 not 74 (2) [2 UNIQUE EUTHYROID RECORDS]

Note: This strategy is for only "euthyroid" records. Searches for primary studies were conducted across OVID MEDLINE, OVID Embase, and the Cochrane Library on May 4, 2014. A second search for euthyroid pregnancies (a term overlooked in the original search) only was subsequently performed on July 20, 2014.

Database	Embase
Date	20- 07- 2014
Search strategy	1 exp pregnancy/ (637562) 2 exp pregnancy disorder/ (457396) 3 pregnant woman/ (40653) 4 pregnan*.tw. (503127) 5 exp prenatal care/ or prenatal diagnosis/ (112855) 6 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (182898) 7 or/1-6 (1050478) 8 exp diagnostic test/ (755581) 9 ((routine* or mass or standard* or universal*) adj3 test*).tw. (61329) 10 mass screening/ (48172) 11 (screen* or detect*).tw. (2482966) 12 (early adj3 (diagnos* or identif* or recogni*)).tw. (148620) 13 or/8-12 (3281615) 14 7 and 13 (156522) 15 thyroid function test/ (12366) 16 ((thyroid* or thyroxin* or thyrotropin* or thyrotrophin* or TSH or thyronin* or triiodothyronin* or tri-iodothyronin*) adj3 (assess* or calculat* or measur* or determin* or evaluat* or examin* or identif* or test* or screen*)).tw. (30460) 17 free thyroxine index/ (4528) 18 (basal adj2 metaboli*).tw. (5882) 19 exp thyroid disease/di, pc [Diagnosis, Prevention] (35045) 20 or/15-19 (73502) 21 7 and 20 (5465) 22 exp thyroid disease/ (195972) 23 (thyroid* adj2 (disease* or disorder* or dysfunction*)).tw. (23437) 24 exp thyroxine blood level/ (11026) 25 thyrotropin blood level/ (9688) 26 ((thyroid* or thyroxin* or thyrotropin* or thyrotrophin* or TSH or thyronin* or triiodothyronin* or tri-iodothyronin*) adj3 (blood or serum)).tw. (17852) 27 (hypothyroid* or hypo-thyroid*).tw. (38812) 28 goiter*.tw. (16829) 29 ((grave* or Basedow*) adj2 disease*).tw. (14135) 30 or/22-29 (216021) 31 14 and 30 (3514) 32 21 or 31 (6836)

33	exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (20694820)
34	exp humans/ or exp human experimentation/ or exp human experiment/ (15120514)
35	33 not 34 (5575318)
36	32 not 35 (6379)
37	(letter or editorial).pt. (1303356)
38	36 not 37 (6148)
39	randomized controlled trial/ or controlled clinical trial/ (482581)
40	exp "clinical trial (topic)"/ (110231)
41	(randomi#ed or randomly or RCT$1 or placebo*).tw. (814665)
42	((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (168700)
43	trial.ti. (169049)
44	or/39-43 (1154563)
45	38 and 44 (267)
46	controlled clinical trial/ (386148)
47	"controlled clinical trial (topic)"/ (3029)
48	(control* adj2 trial*).tw. (182703)
49	(nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (40406)
50	(nRCT or nRCTs or non-RCT$1).tw. (390)
51	(control* adj3 ("before and after" or "before after")).tw. (3413)
52	time series analysis/ (14201)
53	time series.tw. (18293)
54	pretest posttest control group design/ (203)
55	(pre- adj3 post-).tw. (69607)
56	(pretest adj3 posttest).tw. (3340)
57	controlled study/ (4376533)
58	(control* adj2 stud$3).tw. (195134)
59	control group/ (75345)
60	(control$ adj2 group$1).tw. (440565)
61	or/46-60 (4850703)
62	38 and 61 (1079)
63	cohort analysis/ (172855)
64	cohort$1.tw. (407164)
65	retrospective study/ (353385)
66	longitudinal study/ (68820)
67	prospective study/ (257416)
68	(longitudinal or prospective or retrospective).tw. (1006236)
69	follow up/ (840871)
70	((followup or follow-up) adj (study or studies)).tw. (51520)
71	observational study/ (58283)
72	(observation$2 adj (study or studies)).tw. (66632)
73	population research/ (69495)

	74 ((population or population-based) adj (study or studies or analys#s)).tw. (14849) 75 ((multidimensional or multi-dimensional) adj (study or studies)).tw. (109) 76 exp comparative study/ (1024239) 77 ((comparative or comparison) adj (study or studies)).tw. (106964) 78 exp case control study/ (86736) 79 ((case-control* or case-based or case-comparison) adj (study or studies)).tw. (78157) 80 or/63-79 (3192086) 81 38 and 80 (1286) 82 45 or 62 or 81 (1999) 83 euthyroidism/ (3160) 84 euthyroid*.tw. (13885) 85 (83 or 84) and 14 (366) 86 85 not (35 or 37) (344) 87 86 and (44 or 61 or 80) (138) 88 87 not 82 (2) [2 UNIQUE EUTHYROID RECORDS] *Note: Same 2 records (1 conference version) as retrieved through MEDLINE*

Note: This strategy is for only "euthyroid" records. Searches for primary studies were conducted across OVID MEDLINE, OVID Embase, and the Cochrane Library on May 4, 2014. A second search for euthyroid pregnancies (a term overlooked in the original search) only was subsequently performed on July 20, 2014.

Database	**The Cochrane library (CENTRAL)**
Date	20- 07- 2014
Search strategy	#1 [mh Pregnancy] 5773 #2 [mh "Pregnancy Complications"] 7745 #3 [mh "Pregnant Women"] 95 #4 [mh "Pregnancy Trimesters"] 1462 #5 pregnan*:ti,ab,kw 25155 #6 [mh "Prenatal Care"] or [mh "Prenatal Diagnosis"] 1937 #7 (prenatal* or antenatal* or (ante next natal*) or antepartum or (ante next partum) or perinatal* or (peri next natal*) or peripartum or (peri next partum)):ti,ab,kw 6037 #8 {or #1-#7} 27351 #9 [mh "Diagnostic Tests, Routine"] 309 #10 ((routine* or mass or standard* or universal*) near/3 test*):ti,ab,kw 3583 #11 [mh "Mass Screening"] 4946 #12 (screen* or detect*):ti,ab,kw 53847 #13 (early near/3 (diagnos* or identif* or recogni*)):ti,ab,kw 2081 #14 {or #9-#13} 57991 #15 #8 and #14 2757 #16 [mh "Thyroid Function Tests"] 566 #17 ((thyroid* or thyroxin* or thyrotropin* or thyrotrophin* or TSH or thyronin* or triiodothyronin* or tri-iodothyronin*) near/3 (assess* or calculat* or function* or measur* or determin* or evaluat* or examin* or identif* or measur* or test* or screen*)):ti,ab,kw 1206

#18	(basal near/2 metaboli*):ti,ab,kw	504
#19	[mh "Thyroid Diseases"/di,pc]	252
#20	{or #16-#19}	1844
#21	#8 and #20	90
#22	[mh "Thyroid Diseases"]	1627
#23	(thyroid* near/2 (disease* or disorder* or dysfunction*)):ti,ab,kw	468
#24	[mh "Thyroid Gland"/me,pp]	142
#25	[mh Thyroxine/bl] or [mh Thyrotropin/bl]	871
#26	((thyroid* or thyroxin* or thyrotropin* or thyrotrophin* or TSH or thyronin* or triiodothyronin* or tri-iodothyronin*) near/3 (blood or serum)):ti,ab,kw	724
#27	(hypothyroid* or (hypo next thyroid*)):ti,ab,kw	728
#28	goiter*:ti,ab,kw	361
#29	((grave* or Basedow*) near/2 disease*):ti,ab,kw	389
#30	3-#29	2914
#31	#15 and #30	25
#32	#21 or #31	95
#33	euthyroid*:ti,ab,kw	429
#34	#15 and #33	3
#35	#34 not #32	0 [NO UNIQUE EUTHYROID RECORDS]

Note: This strategy is for only “euthyroid” records. Searches for primary studies were conducted across OVID MEDLINE, OVID Embase, and the Cochrane Library on May 4, 2014. A second search for euthyroid pregnancies (a term overlooked in the original search) only was subsequently performed on July 20, 2014. Strategies are attached.

Table 22 – Search strategies: Benefits-harms of therapy for subclinical hypothyroidism during pregnancy (SRs)

Database	Medline (OVID) & Embase
Date	19- 05- 2014
Search strategy	1 exp Pregnancy/ or exp Pregnancy Complications/ (1319855) 2 Pregnant Women/ (37696) 3 exp Pregnancy Trimesters/ (579119) 4 pregnan*.tw. (789824) 5 Prenatal Care/ (46230) 6 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (307673) 7 or/1-6 (1636642) 8 exp Thyroxine/ (84675) 9 (Berlthyrox or Dexnon or Eferox or Elthyrone or Eltroxin* or Euthyrox or Eutirox or "L-T4" or "L-thyrox" or "L-Thyroxin" or "L-Thyroxine" or "Levo-T" or "Levo Thyroxine" or Levothroid or Levothyrox or Levothyroid or Levothyroxin* or Levoxine or Levoxyl or Levothyrox or Novothyral or Novothyrox or Oroxine).tw. (12366) 10 (Soloxine or Synthroid or Synthrox or "T4 Thyroid Hormone" or Tetraiodothyronine or Thevier or Thyratabs or Thyrax or Thyreoideum or Thyroxin* or Thyroxinal or Tiroidine or "Tiroxina Leo" or Unithroid).tw. (51376) 11 ("BRN 2228515" or CCRIS 6739 or "EINECS 200-101-1" or "HSDB 3108" or "NSC 36397" or "UNII-Q51BO43MG4").tw. (0) 12 Selenomethionine/ (3294) 13 (Selenomethionine or "L-Selenomethioninum" or "Selenium-L-methionine" or "Seleno-L-methionine" or "SelenoSource AF 2000" or "UNII-964MRK2PEL").tw. (4264) 14 Hypothyroidism/dt (11087) 15 or/8-14 (112694) 16 7 and 15 (9750) 17 exp Animals/ not (exp Animals/ and Humans/) (7895901) 18 16 not 17 (7131) 19 (comment or editorial or interview or letter or news).pt. (2783436) 20 18 not 19 (6863) 21 limit 20 to systematic reviews [Limit not valid in Embase; records were retained] (3628) 22 meta analysis.pt. (47845) 23 exp meta-analysis as topic/ (26882) 24 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw. (147512) 25 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (178753) 26 exp Technology assessment, biomedical/ (20526) 27 (cochrane or health technology assessment or evidence report).jw. (24695) 28 or/22-27 (338154) 29 20 and 28 (72) 30 21 or 29 (3635) 31 limit 30 to yr="2011-current" (800)

32 31 use prmz (20)
33 exp pregnancy/ (1255732)
34 exp pregnancy disorder/ (397167)
35 pregnant woman/ (37696)
36 pregnan*.tw. (789824)
37 exp prenatal care/ (124934)
38 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (307673)
39 or/33-38 (1736335)
40 levothyroxine/ (43819)
41 (Berlthyrox or Dexnon or Eferox or Elthyrone or Eltroxin* or Euthyrox or Eutirox or "L-T4" or "L-thyrox" or "L-Thyroxin" or "L-Thyroxine" or "Levo-T" or "Levo thyroxine" or Levothroid or Levothyroid or Levothyrox or Levothyroxin* or Levoxine or Levoxyl or Levothyrox or Novothyral or Novothyrox or Oroxine).tw. (12366)
42 (Soloxine or Synthroid or Synthrox or "T4 Thyroid Hormone" or Tetraiodothyronine or Thevier or Thyratabs or Thyrax or Thyreoideum or Thyroxin* or Thyroxinal or Tiroidine or "Tiroxina Leo" or Unithroid).tw. (51376)
43 ("BRN 2228515" or CCRIS 6739 or "EINECS 200-101-1" or "HSDB 3108" or "NSC 36397" or "UNII-Q51BO43MG4").tw. (0)
44 selenomethionine/ (3294)
45 (Selenomethionine or "L-Selenomethioninum" or "Selenium-L-methionine" or "Seleno-L-methionine" or "SelenoSource AF 2000" or "UNII-964MRK2PEL").tw. (4264)
46 hypothyroidism/dt (11087)
47 subclinical hypothyroidism/dt (138)
48 or/40-47 (86905)
49 39 and 48 (8264)
50 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (36382875)
51 exp humans/ or exp human experimentation/ or exp human experiment/ (28087060)
52 50 not 51 (8297386)
53 49 not 52 (6262)
54 (letter or editorial).pt. (2474642)
55 53 not 54 (6039)
56 meta-analysis/ (126457)
57 "systematic review"/ (74385)
58 "meta analysis (topic)"/ (13141)
59 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw. (147512)
60 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (178753)
61 biomedical technology assessment/ (19425)
62 (cochrane or health technology assessment or evidence report).jw. (24695)
63 or/56-62 (371094)
64 55 and 63 (86)
65 limit 64 to yr="2011-current" (38)

	66 65 use emez (27) 67 32 or 66 (47) 68 remove duplicates from 67 (36) [TOTAL UNIQUE RECORDS] 69 68 use prmz (18) [UNIQUE MEDLINE RECORDS] 70 68 use emez (18) [UNIQUE EMBASE HITS]
Note	
Database	**The Cochrane library**
Date	19- 05- 2014
Search strategy	ID Search Hits #1 [mh Pregnancy] 5764 #2 [mh "Pregnancy Complications"] 7732 #3 [mh "Pregnant Women"] 95 #4 [mh "Pregnancy Trimesters"] 1459 #5 pregnan*:ti,ab,kw 25023 #6 [mh "Prenatal Care"] 1054 #7 (prenatal* or antenatal* or (ante next natal*) or antepartum or (ante next partum) or perinatal* or (peri next natal*) or peripartum or (peri next partum)):ti,ab,kw 6004 #8 {or #1-#7} 27205 #9 [mh Thyroxine] 958 #10 (Berlthyrox or Dexnon or Eferox or Elthyrone or Eltroxin* or Euthyrox or Eutirox or "L-T4" or "L-thyrox" or "L-Thyroxin" or "L-Thyroxine" or "Levo-T" or "Levo Thyroxine" or Levothroid or Levothyroid or Levothyrox or Levothyroxin* or Levoxine or Levoxyl or Levothyrox or Novothyral or Novothyrox or Oroxine):ti,ab,kw 424 #11 (Soloxine or Synthroid or Synthrox or "T4 Thyroid Hormone" or Tetraiodothyronine or Thevier or Thyratabs or Thyrax or Thyreoideum or Thyroxin* or Thyroxinal or Tiroidine or "Tiroxina Leo" or Unithroid):ti,ab,kw 1341 #12 ("BRN 2228515" or CCRIS 6739 or "EINECS 200-101-1" or "HSDB 3108" or "NSC 36397" or "UNII-Q51BO43MG4"):ti,ab,kw 0 #13 [mh Selenomethionine] 48 #14 (Selenomethionine or "L-Selenomethioninum" or "Selenium-L-methionine" or "Seleno-L-methionine" or "SelenoSource AF 2000" or "UNII-964MRK2PEL"):ti,ab,kw 91 #15 [mh Hypothyroidism/dt] 169 #16 {or #9-#15} 1624 #17 #8 and #16 Publication Date from 2011 to 2014 17 DSR – 1 DARE – 3 CENTRAL – 12 [did not download – SR search only] NHS EED – 1 [did not download – SR search only]
Note	

Table 23 –Search strategies: Benefits-harms of therapy for subclinical hypothyroidism during pregnancy (Primary- RCTs)

Database	Medline (OVID) & Embase
Date	28- 05- 2014
Search strategy	1 exp Pregnancy/ or exp Pregnancy Complications/ (1320731) 2 Pregnant Women/ (37799) 3 exp Pregnancy Trimesters/ (579575) 4 pregnan*.tw. (790743) 5 Prenatal Care/ (46268) 6 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (308069) 7 or/1-6 (1638071) 8 exp Thyroxine/ (84729) 9 (Berlthyrox or Dexnon or Eferox or Elthyrone or Eltroxin* or Euthyrox or Eutirox or "L-T4" or "L-thyrox" or "L-Thyroxin" or "L-Thyroxine" or "Levo-T" or "Levo Thyroxine" or Levothroid or Levothyrox or Levothyroid or Levothyroxin* or Levoxine or Levoxyl or Levothyrox or Novothyral or Novothyrox or Oroxine).tw. (12380) 10 (Soloxine or Synthroid or Synthrox or "T4 Thyroid Hormone" or Tetraiodothyronine or Thevier or Thyratabs or Thyrax or Thyreoideum or Thyroxin* or Thyroxinal or Tiroidine or "Tiroxina Leo" or Unithroid).tw. (51416) 11 ("BRN 2228515" or CCRIS 6739 or "EINECS 200-101-1" or "HSDB 3108" or "NSC 36397" or "UNII-Q51BO43MG4").tw. (0) 12 Selenomethionine/ (3297) 13 (Selenomethionine or "L-Selenomethioninum" or "Selenium-L-methionine" or "Seleno-L-methionine" or "SelenoSource AF 2000" or "UNII-964MRK2PEL").tw. (4269) 14 Hypothyroidism/dt (11100) 15 or/8-14 (112786) 16 7 and 15 (9761) 17 exp Animals/ not (exp Animals/ and Humans/) (7901717) 18 16 not 17 (7142) 19 (comment or editorial or interview or letter or news).pt. (2788368) 20 18 not 19 (6874) 21 (controlled clinical trial or randomized controlled trial).pt. (457202) 22 clinical trials as topic.sh. (169939) 23 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1401637) 24 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (285646) 25 trial.ti. (282817) 26 or/21-25 (1794902) 27 20 and 26 (243) 28 (control* adj2 trial*).tw. (319365) 29 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (72449) 30 (nRCT or nRCTs or non-RCT$1).tw. (641) 31 (control* adj3 ("before and after" or "before after")).tw. (5825) 32 time series.tw. (33538)

33 (pre- adj3 post-).tw. (107560)
34 (pretest adj3 posttest).tw. (6176)
35 (control* adj2 stud$3).tw. (339555)
36 Control Groups/ (61572)
37 (control$ adj2 group$1).tw. (725901)
38 or/28-37 (1468016)
39 20 and 38 (423)
40 27 or 39 (556)
41 limit 40 to yr="2013-current" (67)
42 41 use prmz (32)
43 exp pregnancy/ (1256544)
44 exp pregnancy disorder/ (397641)
45 pregnant woman/ (37799)
46 pregnan*.tw. (790743)
47 exp prenatal care/ (125046)
48 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (308069)
49 or/43-48 (1737915)
50 levothyroxine/ (43847)
51 (Berlthyrox or Dexnon or Eferox or Elthyrone or Eltroxin* or Euthyrox or Eutirox or "L-T4" or "L-thyrox" or "L-Thyroxin" or "L-Thyroxine" or "Levo-T" or "Levo thyroxine" or Levothroid or Levothyroid or Levothyrox or Levothyroxin* or Levoxine or Levoxyl or Levothyrox or Novothyral or Novothyrox or Oroxine).tw. (12380)
52 (Soloxine or Synthroid or Synthrox or "T4 Thyroid Hormone" or Tetraiodothyronine or Thevier or Thyratabs or Thyrax or Thyreoideum or Thyroxin* or Thyroxinal or Tiroidine or "Tiroxina Leo" or Unithroid).tw. (51416)
53 ("BRN 2228515" or CCRIS 6739 or "EINECS 200-101-1" or "HSDB 3108" or "NSC 36397" or "UNII-Q51BO43MG4").tw. (0)
54 selenomethionine/ (3297)
55 (Selenomethionine or "L-Selenomethioninum" or "Selenium-L-methionine" or "Seleno-L-methionine" or "SelenoSource AF 2000" or "UNII-964MRK2PEL").tw. (4269)
56 hypothyroidism/dt (11100)
57 subclinical hypothyroidism/dt (138)
58 or/50-57 (86979)
59 49 and 58 (8275)
60 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (36421917)
61 exp humans/ or exp human experimentation/ or exp human experiment/ (28119382)
62 60 not 61 (8304106)
63 59 not 62 (6273)
64 (letter or editorial).pt. (2479024)
65 63 not 64 (6050)
66 randomized controlled trial/ or controlled clinical trial/ (932585)
67 exp "clinical trial (topic)"/ (103588)
68 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1401637)
69 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (285646)
70 trial.ti. (282817)

	71 or/66-70 (1926692) 72 65 and 71 (303) 73 (control* adj2 trial*).tw. (319365) 74 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (72449) 75 (nRCT or nRCTs or non-RCT$1).tw. (641) 76 (control* adj3 ("before and after" or "before after")).tw. (5825) 77 time series analysis/ (13856) 78 time series.tw. (33538) 79 pretest posttest control group design/ (202) 80 (pre- adj3 post-).tw. (107560) 81 (pretest adj3 posttest).tw. (6176) 82 controlled study/ (4319125) 83 (control* adj2 stud$3).tw. (339555) 84 control group/ (61572) 85 (control$ adj2 group$1).tw. (725901) 86 or/73-85 (5375280) 87 65 and 86 (801) 88 72 or 87 (925) 89 limit 88 to yr="2013-current" (120) 90 89 use emez (90) 91 42 or 90 (122) 92 remove duplicates from 91 (106) 93 92 use prmz (30) 94 92 use emez (76)
Note	
Database	**The Cochrane library**
Date	29- 05- 2014
Search strategy	ID Search Hits #1 [mh Pregnancy] 5764 #2 [mh "Pregnancy Complications"] 7732 #3 [mh "Pregnant Women"] 95 #4 [mh "Pregnancy Trimesters"] 1459 #5 pregnan*:ti,ab,kw 25024 #6 [mh "Prenatal Care"] 1054 #7 (prenatal* or antenatal* or (ante next natal*) or antepartum or (ante next partum) or perinatal* or (peri next natal*) or peripartum or (peri next partum)):ti,ab,kw 6004 #8 {or #1-#7} 27206 #9 [mh Thyroxine] 958

#10 (Berlthyrox or Dexnon or Eferox or Elthyrone or Eltroxin* or Euthyrox or Eutirox or "L-T4" or "L-thyrox" or "L-Thyroxin" or "L-Thyroxine" or "Levo-T" or "Levo Thyroxine" or Levothroid or Levothyroid or Levothyrox or Levothyroxin* or Levoxine or Levoxyl or Levothyrox or Novothyral or Novothyrox or Oroxine):ti,ab,kw 424
#11 (Soloxine or Synthroid or Synthrox or "T4 Thyroid Hormone" or Tetraiodothyronine or Thevier or Thyratabs or Thyrax or Thyreoideum or Thyroxin* or Thyroxinal or Tiroidine or "Tiroxina Leo" or Unithroid):ti,ab,kw 1341
#12 ("BRN 2228515" or CCRIS 6739 or "EINECS 200-101-1" or "HSDB 3108" or "NSC 36397" or "UNII-Q51BO43MG4"):ti,ab,kw 0
#13 [mh Selenomethionine] 48
#14 (Selenomethionine or "L-Selenomethioninum" or "Selenium-L-methionine" or "Seleno-L-methionine" or "SelenoSource AF 2000" or "UNII-964MRK2PEL"):ti,ab,kw 91
#15 [mh Hypothyroidism/dt] 169
#16 {or #9-#15} 1624
#17 #8 and #16 Publication Date from 2013 to 2014 6

DSR – 1 (did not download – RCT search only)
DARE – 1 (did not download – RCT search only)
CENTRAL – 3
NHS EED – 1 (did not download – RCT search only)

Note

Searches for primary studies were conducted across OVID MEDLINE, OVID Embase, and the Cochrane Library on May 28th and 29th, 2014. A second search for euthyroid pregnancies (a term overlooked in the original search) only was subsequently performed on July 24th, 2014. The following search strategies belong to the second search for RCTs:

Table 24 – Second search strategies: Benefits-harms of therapy for subclinical hypothyroidism during euthyroid pregnancy (Primary- RCTs)

Database	Medline (OVID) & Embase
Date	24- 07- 2014
Search strategy	1 exp Pregnancy/ or exp Pregnancy Complications/ (1331843) 2 Pregnant Women/ (39050) 3 exp Pregnancy Trimesters/ (584435) 4 pregnan*.tw. (800428) 5 Prenatal Care/ (46834) 6 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (312423) 7 or/1-6 (1654128) 8 exp Thyroxine/ (85240) 9 (Berlthyrox or Dexnon or Eferox or Elthyrone or Eltroxin* or Euthyrox or Eutirox or "L-T4" or "L-thyrox" or "L-Thyroxin" or "L-Thyroxine" or "Levo-T" or "Levo Thyroxine" or Levothroid or Levothyrox or Levothyroid or Levothyroxin* or Levoxine or Levoxyl or Levothyrox or Novothyral or Novothyrox or Oroxine).tw. (12511) 10 (Soloxine or Synthroid or Synthrox or "T4 Thyroid Hormone" or Tetraiodothyronine or Thevier or Thyratabs or Thyrax or Thyreoideum or Thyroxin* or Thyroxinal or Tiroidine or "Tiroxina Leo" or Unithroid).tw. (51755)

11 ("BRN 2228515" or CCRIS 6739 or "EINECS 200-101-1" or "HSDB 3108" or "NSC 36397" or "UNII-Q51BO43MG4").tw. (0)
12 Selenomethionine/ (3314)
13 (Selenomethionine or "L-Selenomethioninum" or "Selenium-L-methionine" or "Seleno-L-methionine" or "SelenoSource AF 2000" or "UNII-964MRK2PEL").tw. (4295)
14 Hypothyroidism/dt (11214)
15 or/8-14 (113555)
16 7 and 15 (9848)
17 exp Animals/ not (exp Animals/ and Humans/) (7958583)
18 16 not 17 (7216)
19 (comment or editorial or interview or letter or news).pt. (2817230)
20 18 not 19 (6946)
21 (controlled clinical trial or randomized controlled trial).pt. (463432)
22 clinical trials as topic.sh. (171159)
23 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1427880)
24 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (289498)
25 trial.ti. (288978)
26 or/21-25 (1825255)
27 20 and 26 (249)
28 (control* adj2 trial*).tw. (327148)
29 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (73813)
30 (nRCT or nRCTs or non-RCT$1).tw. (677)
31 (control* adj3 ("before and after" or "before after")).tw. (5925)
32 time series.tw. (34166)
33 (pre- adj3 post-).tw. (110559)
34 (pretest adj3 posttest).tw. (6296)
35 (control* adj2 stud$3).tw. (345438)
36 Control Groups/ (63964)
37 (control$ adj2 group$1).tw. (738609)
38 or/28-37 (1495876)
39 20 and 38 (427)
40 27 or 39 (564)
41 limit 40 to yr="2013-current" (73)
42 euthyroid*.tw. (20461)
43 7 and 42 (1577)
44 43 not (17 or 19) (1383)
45 44 and (26 or 38) (166)
46 limit 45 to yr="2013-current" (35)
47 46 not 41 (16)
48 47 use prmz (8)
49 exp pregnancy/ (1267003)
50 exp pregnancy disorder/ (402206)

51 pregnant woman/ (39050)
52 pregnan*.tw. (800428)
53 exp prenatal care/ (126396)
54 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (312423)
55 or/49-54 (1755175)
56 levothyroxine/ (44196)
57 (Berlthyrox or Dexnon or Eferox or Elthyrone or Eltroxin* or Euthyrox or Eutirox or "L-T4" or "L-thyrox" or "L-Thyroxin" or "L-Thyroxine" or "Levo-T" or "Levo thyroxine" or Levothroid or Levothyroid or Levothyrox or Levothyroxin* or Levoxine or Levoxyl or Levothyrox or Novothyral or Novothyrox or Oroxine).tw. (12511)
58 (Soloxine or Synthroid or Synthrox or "T4 Thyroid Hormone" or Tetraiodothyronine or Thevier or Thyratabs or Thyrax or Thyreoideum or Thyroxin* or Thyroxinal or Tiroidine or "Tiroxina Leo" or Unithroid).tw. (51755)
59 ("BRN 2228515" or CCRIS 6739 or "EINECS 200-101-1" or "HSDB 3108" or "NSC 36397" or "UNII-Q51BO43MG4").tw. (0)
60 selenomethionine/ (3314)
61 (Selenomethionine or "L-Selenomethioninum" or "Selenium-L-methionine" or "Seleno-L-methionine" or "SelenoSource AF 2000" or "UNII-964MRK2PEL").tw. (4295)
62 hypothyroidism/dt (11214)
63 subclinical hypothyroidism/dt (145)
64 or/56-63 (87627)
65 55 and 64 (8362)
66 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (36797001)
67 exp humans/ or exp human experimentation/ or exp human experiment/ (28434648)
68 66 not 67 (8363925)
69 65 not 68 (6351)
70 (letter or editorial).pt. (2502989)
71 69 not 70 (6125)
72 randomized controlled trial/ or controlled clinical trial/ (943244)
73 exp "clinical trial (topic)"/ (110075)
74 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1427880)
75 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (289498)
76 trial.ti. (288978)
77 or/72-76 (1960945)
78 71 and 77 (310)
79 (control* adj2 trial*).tw. (327148)
80 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (73813)
81 (nRCT or nRCTs or non-RCT$1).tw. (677)
82 (control* adj3 ("before and after" or "before after")).tw. (5925)
83 time series analysis/ (14100)
84 time series.tw. (34166)
85 pretest posttest control group design/ (203)
86 (pre- adj3 post-).tw. (110559)
87 (pretest adj3 posttest).tw. (6296)
88 controlled study/ (4367154)

	89 (control* adj2 stud$3).tw. (345438) 90 control group/ (63964) 91 (control$ adj2 group$1).tw. (738609) 92 or/79-91 (5444919) 93 71 and 92 (811) 94 78 or 93 (937) 95 limit 94 to yr="2013-current" (130) 96 euthyroidism/ (2611) 97 euthyroid*.tw. (20461) 98 (96 or 97) and 55 (1688) 99 98 not (68 or 70) (1483) 100 99 and (77 or 92) (295) 101 limit 100 to yr="2013-current" (51) 102 101 not 95 (26) 103 102 use emez (18) 104 48 or 103 (26) 105 remove duplicates from 104 (20) [TOTAL UNIQUE HITS] 106 105 use prmz (7) [MEDLINE UNIQUE HITS] 107 105 use emez (13) [EMBASE UNIQUE HITS]
Note: Overlap with previous searches was removed.	
Database	**The Cochrane library**
Date	24- 07- 2014
Search strategy	ID Search Hits ID Search Hits #1 [mh Pregnancy] 5773 #2 [mh "Pregnancy Complications"] 7745 #3 [mh "Pregnant Women"] 95 #4 [mh "Pregnancy Trimesters"] 1462 #5 pregnan*:ti,ab,kw 25155 #6 [mh "Prenatal Care"] 1056 #7 (prenatal* or antenatal* or (ante next natal*) or antepartum or (ante next partum) or perinatal* or (peri next natal*) or peripartum or (peri next partum)):ti,ab,kw 6038 #8 {or #1-#7} 27347 #9 [mh Thyroxine] 959 #10 (Berlthyrox or Dexnon or Eferox or Elthyrone or Eltroxin* or Euthyrox or Eutirox or "L-T4" or "L-thyrox" or "L-Thyroxin" or "L-Thyroxine" or "Levo-T" or "Levo Thyroxine" or Levothroid or Levothyroid or Levothyrox or Levothyroxin* or Levoxine or Levoxyl or Levothyrox or Novothyral or Novothyrox or Oroxine):ti,ab,kw 428 #11 (Soloxine or Synthroid or Synthrox or "T4 Thyroid Hormone" or Tetraiodothyronine or Thevier or Thyratabs or Thyrax or Thyreoideum or Thyroxin* or Thyroxinal or Tiroidine or "Tiroxina Leo" or Unithroid):ti,ab,kw 1347

	#12 ("BRN 2228515" or CCRIS 6739 or "EINECS 200-101-1" or "HSDB 3108" or "NSC 36397" or "UNII-Q51BO43MG4"):ti,ab,kw 0 #13 [mh Selenomethionine] 48 #14 (Selenomethionine or "L-Selenomethioninum" or "Selenium-L-methionine" or "Seleno-L-methionine" or "SelenoSource AF 2000" or "UNII-964MRK2PEL"):ti,ab,kw 92 #15 [mh Hypothyroidism/dt] 169 #16 {or #9-#15} 1632 #17 #8 and #16 18 #18 euthyroid*:ti,ab,kw 429 #19 #8 and #18 12 #20 #19 not #17 Publication Year from 2013 to 2014 0
Note: Overlap with previous searches was removed.	

Table 25 – Search strategies: Benefits-harms of therapy for subclinical hypothyroidism during pregnancy (Primary- Observational)

Database	Medline (OVID) & Embase
Date	29- 05- 2014
Search strategy	1 exp Pregnancy/ or exp Pregnancy Complications/ (1321195) 2 Pregnant Women/ (37800) 3 exp Pregnancy Trimesters/ (579596) 4 pregnan*.tw. (790952) 5 Prenatal Care/ (46284) 6 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (308164) 7 or/1-6 (1638509) 8 exp Thyroxine/ (84740) 9 (Berlthyrox or Dexnon or Eferox or Elthyrone or Eltroxin* or Euthyrox or Eutirox or "L-T4" or "L-thyrox" or "L-Thyroxin" or "L-Thyroxine" or "Levo-T" or "Levo Thyroxine" or Levothroid or Levothyrox or Levothyroid or Levothyroxin* or Levoxine or Levoxyl or Levothyrox or Novothyral or Novothyrox or Oroxine).tw. (12382) 10 (Soloxine or Synthroid or Synthrox or "T4 Thyroid Hormone" or Tetraiodothyronine or Thevier or Thyratabs or Thyrax or Thyreoideum or Thyroxin* or Thyroxinal or Tiroidine or "Tiroxina Leo" or Unithroid).tw. (51421) 11 ("BRN 2228515" or CCRIS 6739 or "EINECS 200-101-1" or "HSDB 3108" or "NSC 36397" or "UNII-Q51BO43MG4").tw. (0) 12 Selenomethionine/ (3297) 13 (Selenomethionine or "L-Selenomethioninum" or "Selenium-L-methionine" or "Seleno-L-methionine" or "SelenoSource AF 2000" or "UNII-964MRK2PEL").tw. (4269) 14 Hypothyroidism/dt (11103) 15 or/8-14 (112799) 16 7 and 15 (9763) 17 exp Animals/ not (exp Animals/ and Humans/) (7903665) 18 16 not 17 (7144) 19 (comment or editorial or interview or letter or news).pt. (2789327) 20 18 not 19 (6875)

21 exp Cohort Studies/ (1516297)
22 cohort$1.tw. (671276)
23 Retrospective Studies/ (834901)
24 (longitudinal or prospective or retrospective).tw. (1693780)
25 ((followup or follow-up) adj (study or studies)).tw. (82033)
26 Observational study.pt. (2468)
27 (observation$2 adj (study or studies)).tw. (110446)
28 ((population or population-based) adj (study or studies or analys#s)).tw. (25284)
29 ((multidimensional or multi-dimensional) adj (study or studies)).tw. (169)
30 Comparative Study.pt. (1676988)
31 ((comparative or comparison) adj (study or studies)).tw. (168703)
32 exp Case-Control Studies/ (744586)
33 ((case-control* or case-based or case-comparison) adj (study or studies)).tw. (142008)
34 or/21-33 (4881360)
35 20 and 34 (1232)
36 limit 35 to yr="2011-current" (298)
37 36 use prmz (127)
38 exp pregnancy/ (1256980)
39 exp pregnancy disorder/ (397641)
40 pregnant woman/ (37800)
41 pregnan*.tw. (790952)
42 exp prenatal care/ (125062)
43 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (308164)
44 or/38-43 (1738331)
45 levothyroxine/ (43857)
46 (Berlthyrox or Dexnon or Eferox or Elthyrone or Eltroxin* or Euthyrox or Eutirox or "L-T4" or "L-thyrox" or "L-Thyroxin" or "L-Thyroxine" or "Levo-T" or "Levo thyroxine" or Levothroid or Levothyroid or Levothyrox or Levothyroxin* or Levoxine or Levoxyl or Levothyrox or Novothyral or Novothyrox or Oroxine).tw. (12382)
47 (Soloxine or Synthroid or Synthrox or "T4 Thyroid Hormone" or Tetraiodothyronine or Thevier or Thyratabs or Thyrax or Thyreoideum or Thyroxin* or Thyroxinal or Tiroidine or "Tiroxina Leo" or Unithroid).tw. (51421)
48 ("BRN 2228515" or CCRIS 6739 or "EINECS 200-101-1" or "HSDB 3108" or "NSC 36397" or "UNII-Q51BO43MG4").tw. (0)
49 selenomethionine/ (3297)
50 (Selenomethionine or "L-Selenomethioninum" or "Selenium-L-methionine" or "Seleno-L-methionine" or "SelenoSource AF 2000" or "UNII-964MRK2PEL").tw. (4269)
51 hypothyroidism/dt (11103)
52 subclinical hypothyroidism/dt (138)
53 or/45-52 (86991)
54 44 and 53 (8277)
55 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (36434116)
56 exp humans/ or exp human experimentation/ or exp human experiment/ (28129985)
57 55 not 56 (8305702)

58	54 not 57 (6275)
59	(letter or editorial).pt. (2479652)
60	58 not 59 (6051)
61	cohort analysis/ (333466)
62	cohort$1.tw. (671276)
63	retrospective study/ (834901)
64	longitudinal study/ (152140)
65	prospective study/ (615984)
66	(longitudinal or prospective or retrospective).tw. (1693780)
67	follow up/ (796362)
68	((followup or follow-up) adj (study or studies)).tw. (82033)
69	observational study/ (57953)
70	(observation$2 adj (study or studies)).tw. (110446)
71	population research/ (67418)
72	((population or population-based) adj (study or studies or analys#s)).tw. (25284)
73	((multidimensional or multi-dimensional) adj (study or studies)).tw. (169)
74	exp comparative study/ (2630765)
75	((comparative or comparison) adj (study or studies)).tw. (168703)
76	exp case control study/ (744586)
77	((case-control* or case-based or case-comparison) adj (study or studies)).tw. (142008)
78	or/61-77 (6040590)
79	60 and 78 (1389)
80	limit 79 to yr="2011-current" (374)
81	80 use emez (255)
82	37 or 81 (382)
83	remove duplicates from 82 (305) [TOTAL UNIQUE RECORDS]
84	83 use prmz (124) [UNIQUE MEDLINE RECORDS]
85	83 use emez (181) [UNIQUE EMBASE RECORDS]

Note

Searches for primary studies were conducted across OVID MEDLINE, OVID Embase, and the Cochrane Library on May 29th 2014. A second search for euthyroid pregnancies (a term overlooked in the original search) only was subsequently performed on July 24th, 2014. The followings search strategy belong to the second search for observational studies:

Table 26 – Second search strategies: Benefits-harms of therapy for subclinical hypothyroidism during euthyroid pregnancy (Primary- Observational)

Database	Medline (OVID) & Embase
Date	24- 07- 2014
Search strategy	1 exp Pregnancy/ or exp Pregnancy Complications/ (1331843) 2 Pregnant Women/ (39050) 3 exp Pregnancy Trimesters/ (584435) 4 pregnan*.tw. (800428) 5 Prenatal Care/ (46834) 6 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (312423) 7 or/1-6 (1654128) 8 exp Thyroxine/ (85240) 9 (Berlthyrox or Dexnon or Eferox or Elthyrone or Eltroxin* or Euthyrox or Eutirox or "L-T4" or "L-thyrox" or "L-Thyroxin" or "L-Thyroxine" or "Levo-T" or "Levo Thyroxine" or Levothroid or Levothyrox or Levothyroid or Levothyroxin* or Levoxine or Levoxyl or Levothyrox or Novothyral or Novothyrox or Oroxine).tw. (12511) 10 (Soloxine or Synthroid or Synthrox or "T4 Thyroid Hormone" or Tetraiodothyronine or Thevier or Thyratabs or Thyrax or Thyreoideum or Thyroxin* or Thyroxinal or Tiroidine or "Tiroxina Leo" or Unithroid).tw. (51755) 11 ("BRN 2228515" or CCRIS 6739 or "EINECS 200-101-1" or "HSDB 3108" or "NSC 36397" or "UNII-Q51BO43MG4").tw. (0) 12 Selenomethionine/ (3314) 13 (Selenomethionine or "L-Selenomethioninum" or "Selenium-L-methionine" or "Seleno-L-methionine" or "SelenoSource AF 2000" or "UNII-964MRK2PEL").tw. (4295) 14 Hypothyroidism/dt (11214) 15 or/8-14 (113555) 16 7 and 15 (9848) 17 exp Animals/ not (exp Animals/ and Humans/) (7958583) 18 16 not 17 (7216) 19 (comment or editorial or interview or letter or news).pt. (2817230) 20 18 not 19 (6946) 21 exp Cohort Studies/ (1541997) 22 cohort$1.tw. (691738) 23 Retrospective Studies/ (851424) 24 (longitudinal or prospective or retrospective).tw. (1729745) 25 ((followup or follow-up) adj (study or studies)).tw. (82937) 26 Observational study.pt. (3623) 27 (observation$2 adj (study or studies)).tw. (114009) 28 ((population or population-based) adj (study or studies or analys#s)).tw. (25704) 29 ((multidimensional or multi-dimensional) adj (study or studies)).tw. (172) 30 Comparative Study.pt. (1687501) 31 ((comparative or comparison) adj (study or studies)).tw. (170639) 32 exp Case-Control Studies/ (758877) 33 ((case-control* or case-based or case-comparison) adj (study or studies)).tw. (144850)

34 or/21-33 (4957000)
35 20 and 34 (1253)
36 limit 35 to yr="2011-current" (318)
37 euthyroid*.tw. (20461)
38 7 and 37 (1577)
39 38 not (17 or 19) (1383)
40 39 and 34 (361)
41 limit 40 to yr="2011-current" (113)
42 41 not 36 (45)
43 42 use prmz (21)
44 exp pregnancy/ (1267003)
45 exp pregnancy disorder/ (402206)
46 pregnant woman/ (39050)
47 pregnan*.tw. (800428)
48 exp prenatal care/ (126396)
49 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (312423)
50 or/44-49 (1755175)
51 levothyroxine/ (44196)
52 (Berlthyrox or Dexnon or Eferox or Elthyrone or Eltroxin* or Euthyrox or Eutirox or "L-T4" or "L-thyrox" or "L-Thyroxin" or "L-Thyroxine" or "Levo-T" or "Levo thyroxine" or Levothroid or Levothyroid or Levothyrox or Levothyroxin* or Levoxine or Levoxyl or Levothyrox or Novothyral or Novothyrox or Oroxine).tw. (12511)
53 (Soloxine or Synthroid or Synthrox or "T4 Thyroid Hormone" or Tetraiodothyronine or Thevier or Thyratabs or Thyrax or Thyreoideum or Thyroxin* or Thyroxinal or Tiroidine or "Tiroxina Leo" or Unithroid).tw. (51755)
54 ("BRN 2228515" or CCRIS 6739 or "EINECS 200-101-1" or "HSDB 3108" or "NSC 36397" or "UNII-Q51BO43MG4").tw. (0)
55 selenomethionine/ (3314)
56 (Selenomethionine or "L-Selenomethioninum" or "Selenium-L-methionine" or "Seleno-L-methionine" or "SelenoSource AF 2000" or "UNII-964MRK2PEL").tw. (4295)
57 hypothyroidism/dt (11214)
58 subclinical hypothyroidism/dt (145)
59 or/51-58 (87627)
60 50 and 59 (8362)
61 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (36797001)
62 exp humans/ or exp human experimentation/ or exp human experiment/ (28434648)
63 61 not 62 (8363925)
64 60 not 63 (6351)
65 (letter or editorial).pt. (2502989)
66 64 not 65 (6125)
67 cohort analysis/ (342579)
68 cohort$1.tw. (691738)
69 retrospective study/ (851424)
70 longitudinal study/ (155624)
71 prospective study/ (627222)

	72 (longitudinal or prospective or retrospective).tw. (1729745)
	73 follow up/ (815304)
	74 ((followup or follow-up) adj (study or studies)).tw. (82937)
	75 observational study/ (61789)
	76 (observation$2 adj (study or studies)).tw. (114009)
	77 population research/ (68245)
	78 ((population or population-based) adj (study or studies or analys#s)).tw. (25704)
	79 ((multidimensional or multi-dimensional) adj (study or studies)).tw. (172)
	80 exp comparative study/ (2648784)
	81 ((comparative or comparison) adj (study or studies)).tw. (170639)
	82 exp case control study/ (758877)
	83 ((case-control* or case-based or case-comparison) adj (study or studies)).tw. (144850)
	84 or/67-83 (6131946)
	85 66 and 84 (1414)
	86 limit 85 to yr="2011-current" (398)
	87 euthyroidism/ (2611)
	88 euthyroid*.tw. (20461)
	89 (87 or 88) and 50 (1688)
	90 89 not (63 or 65) (1483)
	91 90 and 84 (420)
	92 limit 91 to yr="2011-current" (137)
	93 92 not 86 (62)
	94 93 use emez (41)
	95 43 or 94 (62)
	96 remove duplicates from 95 (42) [UNIQUE RECORDS]
	97 96 use prmz (20) [UNIQUE MEDLINE RECORDS]
	98 96 use emez (22) [UNIQUE EMBASE RECORDS]
Note	

6.2.7. Vitamin D deficiency

Table 27 – Search strategies: Benefits-harms of screening for vitamin D deficiency during pregnancy (SRs)

Database	Medline (OVID) & Embase
Date	01-01-2011 to 24-04-2014
Search strategy	1 exp Pregnancy/ or exp Pregnancy Complications/ (1315752) 2 Pregnant Women/ (37082) 3 exp Pregnancy Trimesters/ (577073) 4 pregnan*.tw. (785807) 5 Prenatal Care/ (46009) 6 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (305875) 7 or/1-6 (1630476) 8 exp Vitamin D Deficiency/di, pc (5516) 9 exp Vitamin D/bl (10922)a 10 ((vitamin D$1 or D vitamin$1 or "25-hydroxyvitamin D" or "hydroxyvitamin D" or "hydroxyvitamins D" or calciferol* or cholecalciferol* or calciol* or hydroxycholecalciferol* or calcifediol* or calcidiol* or calderol* or dedrogyl* or hidroferol* or dihydroxycholecalciferol* or di-hydroxycholecalciferol* or "dihydroxyvitamin D" or "dihydroxyvitamins D" or "di-hydroxyvitamin D" or "di-hydroxyvitamins D" or calcitriol* or "25(OH)D" or "25-OHCC" or "25-OHD3" or "25-HCC" or ergocalciferol*) adj3 (blood* or serum* or test*)).tw. (17147) 11 7 and (8 or 9 or 10) (1918) 12 Diagnostic Tests, Routine/ (66796) 13 ((routine* or mass or standard* or universal*) adj3 test*).tw. (97573) 14 exp Mass Screening/ (251140) 15 (screen* or detect*).tw. (4244322) 16 (early adj3 (diagnos* or identif* or recogni*)).tw. (225570) 17 or/12-16 (4604322) 18 7 and 17 (197701) 19 exp Vitamin D Deficiency/ (34610) 20 (vitamin D$1 adj3 (defici* or lack* or insuffici*)).tw. (20854) 21 (ricket* or rachitis or osteomalacia*).tw. (34608) 22 exp Vitamin D/ (129246) 23 1406-16-2.rn. (33632) 24 (vitamin D$1 or D vitamin$1 or "25-hydroxyvitamin D" or "hydroxyvitamin D" or "hydroxyvitamins D" or cholecalciferol* or calciol* or hydroxycholecalciferol* or calciferol* or calcifediol* or calcidiol* or calderol* or dedrogyl* or hidroferol* or dihydroxycholecalciferol* or di-hydroxycholecalciferol* or "dihydroxyvitamin D" or "dihydroxyvitamins D" or "di-hydroxyvitamin D" or "di-hydroxyvitamins D" or calcitriol* or "25(OH)D" or "25-OHCC" or "25-OHD3" or "25-HCC" or ergocalciferol*).tw. (109825) 25 or/19-24 (187735) 26 18 and 25 (750) 27 11 or 26 (2468) 28 exp Animals/ not (exp Animals/ and Humans/) (7870616) 29 27 not 28 (2163)

30 (comment or editorial or interview or letter or news).pt. (2770335)
31 29 not 30 (2085)
32 limit 31 to systematic reviews [Limit not valid in Embase; records were retained] (1103)
33 meta analysis.pt. (47108)
34 exp meta-analysis as topic/ (26398)
35 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw. (145242)
36 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (176560)
37 exp Technology assessment, biomedical/ (20503)
38 (cochrane or health technology assessment or evidence report).jw. (24555)
39 or/33-38 (334055)
40 31 and 39 (75)
41 32 or 40 (1111)
42 limit 41 to yr="2011-current" (610)
43 42 use prmz (37)
44 exp pregnancy/ (1251899)
45 exp pregnancy disorder/ (395377)
46 pregnant woman/ (37082)
47 pregnan*.tw. (785807)
48 exp prenatal care/ (124439)
49 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (305875)
50 or/44-49 (1729605)
51 vitamin D deficiency/di, pc (3363)
52 ((vitamin D$1 or D vitamin$1 or "25-hydroxyvitamin D" or "hydroxyvitamin D" or "hydroxyvitamins D" or calciferol* or cholecalciferol* or calciol* or hydroxycholecalciferol* or calcifediol* or calcidiol* or calderol* or dedrogyl* or hidroferol* or dihydroxycholecalciferol* or di-hydroxycholecalciferol* or "dihydroxyvitamin D" or "dihydroxyvitamins D" or "di-hydroxyvitamin D" or "di-hydroxyvitamins D" or calcitriol* or "25(OH)D" or "25-OHCC" or "25-OHD3" or "25-HCC" or ergocalciferol*) adj3 (blood* or serum* or test*)).tw. (17147)
53 50 and (51 or 52) (1456)
54 exp diagnostic test/ (677715)
55 ((routine* or mass or standard* or universal*) adj3 test*).tw. (97573)
56 mass screening/ (125638)
57 (screen* or detect*).tw. (4244322)
58 (early adj3 (diagnos* or identif* or recogni*)).tw. (225570)
59 or/54-58 (5076022)
60 50 and 59 (233196)
61 vitamin D deficiency/ (23962)
62 (vitamin D$1 adj3 (defici* or lack* or insuffici*)).tw. (20854)
63 exp rickets/ (19257)
64 (ricket* or rachitis or osteomalacia*).tw. (34608)

	65 exp vitamin D/ (129246) 66 1406-16-2.rn. (33632) 67 (vitamin D$1 or D vitamin$1 or "25-hydroxyvitamin D" or "hydroxyvitamin D" or "hydroxyvitamins D" or calciferol* or cholecalciferol* or calciol* or hydroxycholecalciferol* or calcifediol* or calcidiol* or calderol* or dedrogyl* or hidroferol* or dihydroxycholecalciferol* or di-hydroxycholecalciferol* or "dihydroxyvitamin D" or "dihydroxyvitamins D" or "di-hydroxyvitamin D" or "di-hydroxyvitamins D" or calcitriol* or "25(OH)D" or "25-OHCC" or "25-OHD3" or "25-HCC" or ergocalciferol*).tw. (109825) 68 or/61-67 (188946) 69 60 and 68 (994) 70 53 or 69 (2256) 71 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (36219419) 72 exp humans/ or exp human experimentation/ or exp human experiment/ (27950900) 73 71 not 72 (8270090) 74 70 not 73 (2093) 75 (letter or editorial).pt. (2463549) 76 74 not 75 (2039) 77 meta-analysis/ (124814) 78 "systematic review"/ (73257) 79 "meta analysis (topic)"/ (12725) 80 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw. (145242) 81 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (176560) 82 biomedical technology assessment/ (19402) 83 (cochrane or health technology assessment or evidence report).jw. (24555) 84 or/77-83 (366787) 85 76 and 84 (87) 86 limit 85 to yr="2011-current" (67) 87 86 use emez (47) 88 43 or 87 (84) 89 remove duplicates from 88 (66) [UNIQUE RECORDS] 90 89 use prmz (34) [UNIQUE MEDLINE RECORDS] 91 89 use emez (32) [UNIQUE EMBASE RECORDS]
Note	
Database	**The Cochrane Library**
Date	25-04-2014
Search strategy	ID Search Hits #1 [mh Pregnancy] 5739 #2 [mh "Pregnancy Complications"] 7679 #3 [mh "Pregnant Women"] 94

#4 [mh "Pregnancy Trimesters"] 1454
#5 pregnan*:ti,ab,kw 24760
#6 [mh "Prenatal Care"] 1049
#7 (prenatal* or antenatal* or (ante next natal*) or antepartum or (ante next partum) or perinatal* or (peri next natal*) or peripartum or (peri next partum)):ti,ab,kw 5933
#8 {or #1-#7} 26918
#9 [mh "Vitamin D Deficiency/di, pc"] 0
#10 [mh "Vitamin D/bl"] 0
#11 (((vitamin next D*) or (D next vitamin*) or "25-hydroxyvitamin D" or "hydroxyvitamin D" or "hydroxyvitamins D" or calciferol* or cholecalciferol* or calciol* or hydroxycholecalciferol* or calcifediol* or calcidiol* or calderol* or dedrogyl* or hidroferol* or dihydroxycholecalciferol* or (di next hydroxycholecalciferol*) or "dihydroxyvitamin D" or "dihydroxyvitamins D" or (di next "hydroxyvitamin D") or "di-hydroxyvitamins D" or calcitriol* or "25(OH)D" or "25-OHCC" or "25-OHD3" or "25-HCC" or ergocalciferol*) near/3 (blood* or serum* or test*)):ti,ab,kw 2179
#12 #8 and (#9 or #10 or #11) 105
#13 [mh "Diagnostic Tests, Routine"] 305
#14 ((routine* or mass or standard* or universal*) near/3 test*):ti,ab,kw 3515
#15 [mh "Mass Screening"] 4874
#16 (screen* or detect*):ti,ab,kw 52773
#17 (early near/3 (diagnos* or identif* or recogni*)):ti,ab,kw 2027
#18 {or #13-#17} 56838
#19 #8 and #18 2719
#20 [mh "Vitamin D Deficiency"] 464
#21 ("vitamin D" near/3 (defici* or lack* or insuffici*)):ti,ab,kw 624
#22 (ricket* or rachitis or osteomalacia*):ti,ab,kw 204
#23 [mh "Vitamin D"] 2306
#24 ("vitamin D" or "Vitamin D3" or (D next vitamin*) or "25-hydroxyvitamin D" or "hydroxyvitamin D" or "hydroxyvitamins D" or cholecalciferol* or calciol* or hydroxycholecalciferol* or calcifediol* or calcidiol* or calderol* or dedrogyl* or hidroferol* or dihydroxycholecalciferol* or (di next hydroxycholecalciferol*) or "dihydroxyvitamin D" or "dihydroxyvitamins D" or (di next "hydroxyvitamin D") or "di-hydroxyvitamins D" or calcitriol*):ti,ab,kw 4274
#25 {or #20-#24} 4408
#26 #19 and #25 6
#27 #12 or #26 109
#28 #26 or #27 Publication Date from 2011 to 2014 40

DSR – 4
DARE – 1
CENTRAL – 35 (did not download – searching for reviews only)

Note

Table 28 – Search strategies: Benefits-harms of screening for vitamin D deficiency during pregnancy (Primary studies)

Database	Medline (OVID) & Embase
Date	02-05-2014
Search strategy	1 exp Pregnancy/ or exp Pregnancy Complications/ (1406129) 2 Pregnant Women/ (44462) 3 exp Pregnancy Trimesters/ (663687) 4 pregnan*.tw. (862575) 5 Prenatal Care/ (47408) 6 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (320943) 7 or/1-6 (1743817) 8 exp Vitamin D Deficiency/di, pc (5532) 9 exp Vitamin D/bl (10947) 10 ((vitamin D$1 or D vitamin$1 or "25-hydroxyvitamin D" or "hydroxyvitamin D" or "hydroxyvitamins D" or calciferol* or cholecalciferol* or calciol* or hydroxycholecalciferol* or calcifediol* or calcidiol* or calderol* or dedrogyl* or hidroferol* or dihydroxycholecalciferol* or di-hydroxycholecalciferol* or "dihydroxyvitamin D" or "dihydroxyvitamins D" or "di-hydroxyvitamin D" or "di-hydroxyvitamins D" or calcitriol* or "25(OH)D" or "25-OHCC" or "25-OHD3" or "25-HCC" or ergocalciferol*) adj3 (blood* or serum* or test*)).tw. (17588) 11 7 and (8 or 9 or 10) (1941) 12 Diagnostic Tests, Routine/ (68590) 13 ((routine* or mass or standard* or universal*) adj3 test*).tw. (103436) 14 exp Mass Screening/ (255714) 15 (screen* or detect*).tw. (4406873) 16 (early adj3 (diagnos* or identif* or recogni*)).tw. (244661) 17 or/12-16 (4790911) 18 7 and 17 (206260) 19 exp Vitamin D Deficiency/ (35094) 20 (vitamin D$1 adj3 (defici* or lack* or insuffici*)).tw. (21706) 21 (ricket* or rachitis or osteomalacia*).tw. (41142) 22 exp Vitamin D/ (137045) 23 1406-16-2.rn. (35893) 24 (vitamin D$1 or D vitamin$1 or "25-hydroxyvitamin D" or "hydroxyvitamin D" or "hydroxyvitamins D" or cholecalciferol* or calciol* or hydroxycholecalciferol* or calciferol* or calcifediol* or calcidiol* or calderol* or dedrogyl* or hidroferol* or dihydroxycholecalciferol* or di-hydroxycholecalciferol* or "dihydroxyvitamin D" or "dihydroxyvitamins D" or "di-hydroxyvitamin D" or "di-hydroxyvitamins D" or calcitriol* or "25(OH)D" or "25-OHCC" or "25-OHD3" or "25-HCC" or ergocalciferol*).tw. (116332) 25 or/19-24 (201859) 26 18 and 25 (784) 27 11 or 26 (2523) 28 exp Animals/ not (exp Animals/ and Humans/) (8674498) 29 27 not 28 (2200) 30 (comment or editorial or interview or letter or news).pt. (2786857) 31 29 not 30 (2121)

32	(controlled clinical trial or randomized controlled trial).pt. (455001)
33	clinical trials as topic.sh. (169504)
34	(randomi#ed or randomly or RCT$1 or placebo*).tw. (1410952)
35	((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (294678)
36	trial.ti. (289768)
37	or/32-36 (1814632)
38	31 and 37 (228)
39	controlled clinical trial.pt. (88214)
40	Controlled Clinical Trial/ or Controlled Clinical Trials as Topic/ (480327)
41	(control* adj2 trial*).tw. (319976)
42	(nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (73010)
43	(nRCT or nRCTs or non-RCT$1).tw. (638)
44	(control* adj3 ("before and after" or "before after")).tw. (6002)
45	time series.tw. (33611)
46	(pre- adj3 post-).tw. (109186)
47	(pretest adj3 posttest).tw. (6214)
48	(control* adj2 stud$3).tw. (343432)
49	Control Groups/ (73288)
50	(control$ adj2 group$1).tw. (746059)
51	or/39-50 (1844010)
52	31 and 51 (258)
53	exp Cohort Studies/ (1503599)
54	cohort$1.tw. (663754)
55	Retrospective Studies/ (828724)
56	(longitudinal or prospective or retrospective).tw. (1702897)
57	((followup or follow-up) adj (study or studies)).tw. (88724)
58	Observational study.pt. (1963)
59	(observation$2 adj (study or studies)).tw. (109230)
60	((population or population-based) adj (study or studies or analys#s)).tw. (25947)
61	((multidimensional or multi-dimensional) adj (study or studies)).tw. (186)
62	Comparative Study.pt. (1672336)
63	((comparative or comparison) adj (study or studies)).tw. (184863)
64	exp Case-Control Studies/ (737634)
65	((case-control* or case-based or case-comparison) adj (study or studies)).tw. (140936)
66	or/53-65 (4898149)
67	31 and 66 (672)
68	38 or 52 or 67 (856)
69	68 use prmz (440)
70	exp pregnancy/ (1339001)
71	exp pregnancy disorder/ (451267)
72	pregnant woman/ (44462)

73 pregnan*.tw. (862575)
74 exp prenatal care/ (131460)
75 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (320943)
76 or/70-75 (1866094)
77 vitamin D deficiency/di, pc (3377)
78 ((vitamin D$1 or D vitamin$1 or "25-hydroxyvitamin D" or "hydroxyvitamin D" or "hydroxyvitamins D" or calciferol* or cholecalciferol* or calciol* or hydroxycholecalciferol* or calcifediol* or calcidiol* or calderol* or dedrogyl* or hidroferol* or dihydroxycholecalciferol* or di-hydroxycholecalciferol* or "dihydroxyvitamin D" or "dihydroxyvitamins D" or "di-hydroxyvitamin D" or "di-hydroxyvitamins D" or calcitriol* or "25(OH)D" or "25-OHCC" or "25-OHD3" or "25-HCC" or ergocalciferol*) adj3 (blood* or serum* or test*)).tw. (17588)
79 76 and (77 or 78) (1485)
80 exp diagnostic test/ (752484)
81 ((routine* or mass or standard* or universal*) adj3 test*).tw. (103436)
82 mass screening/ (128989)
83 (screen* or detect*).tw. (4406873)
84 (early adj3 (diagnos* or identif* or recogni*)).tw. (244661)
85 or/80-84 (5326184)
86 76 and 85 (247371)
87 vitamin D deficiency/ (24444)
88 (vitamin D$1 adj3 (defici* or lack* or insuffici*)).tw. (21706)
89 exp rickets/ (22498)
90 (ricket* or rachitis or osteomalacia*).tw. (41142)
91 exp vitamin D/ (137045)
92 1406-16-2.rn. (35893)
93 (vitamin D$1 or D vitamin$1 or "25-hydroxyvitamin D" or "hydroxyvitamin D" or "hydroxyvitamins D" or calciferol* or cholecalciferol* or calciol* or hydroxycholecalciferol* or calcifediol* or calcidiol* or calderol* or dedrogyl* or hidroferol* or dihydroxycholecalciferol* or di-hydroxycholecalciferol* or "dihydroxyvitamin D" or "dihydroxyvitamins D" or "di-hydroxyvitamin D" or "di-hydroxyvitamins D" or calcitriol* or "25(OH)D" or "25-OHCC" or "25-OHD3" or "25-HCC" or ergocalciferol*).tw. (116332)
94 or/87-93 (203580)
95 86 and 94 (1053)
96 79 or 95 (2342)
97 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (37232147)
98 exp humans/ or exp human experimentation/ or exp human experiment/ (28265279)
99 97 not 98 (8968510)
100 96 not 99 (2162)
101 (letter or editorial).pt. (2479446)
102 100 not 101 (2107)
103 randomized controlled trial/ or controlled clinical trial/ (931510)
104 exp "clinical trial (topic)"/ (101233)
105 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1410952)
106 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (294678)
107 trial.ti. (289768)
108 or/103-107 (1945278)

109	102 and 108 (252)
110	controlled clinical trial/ (472831)
111	"controlled clinical trial (topic)"/ (2776)
112	(control* adj2 trial*).tw. (319976)
113	(nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (73010)
114	(nRCT or nRCTs or non-RCT$1).tw. (638)
115	(control* adj3 ("before and after" or "before after")).tw. (6002)
116	time series analysis/ (13843)
117	time series.tw. (33611)
118	pretest posttest control group design/ (201)
119	(pre- adj3 post-).tw. (109186)
120	(pretest adj3 posttest).tw. (6214)
121	controlled study/ (4309705)
122	(control* adj2 stud$3).tw. (343432)
123	control group/ (73288)
124	(control$ adj2 group$1).tw. (746059)
125	or/110-124 (5485130)
126	102 and 125 (444)
127	cohort analysis/ (329675)
128	cohort$1.tw. (663754)
129	retrospective study/ (828724)
130	longitudinal study/ (151443)
131	prospective study/ (612040)
132	(longitudinal or prospective or retrospective).tw. (1702897)
133	follow up/ (814338)
134	((followup or follow-up) adj (study or studies)).tw. (88724)
135	observational study/ (56474)
136	(observation$2 adj (study or studies)).tw. (109230)
137	population research/ (68303)
138	((population or population-based) adj (study or studies or analys#s)).tw. (25947)
139	((multidimensional or multi-dimensional) adj (study or studies)).tw. (186)
140	exp comparative study/ (2685881)
141	((comparative or comparison) adj (study or studies)).tw. (184863)
142	exp case control study/ (737634)
143	((case-control* or case-based or case-comparison) adj (study or studies)).tw. (140936)
144	or/127-143 (6125033)
145	102 and 144 (698)
146	109 or 126 or 145 (989)
147	146 use emczd (685)
148	69 or 147 (1125)
149	remove duplicates from 148 (878) [TOTAL UNIQUE HITS]

	150 149 use prmz (415) [MEDLINE UNIQUE HITS] 151 149 use emczd (463) [EMBASE UNIQUE HITS]
Note	
Database	**The Cochrane library**
Date	04-05-2014
Search strategy	ID Search Hits #1 [mh Pregnancy] 5764 #2 [mh "Pregnancy Complications"] 7732 #3 [mh "Pregnant Women"] 95 #4 [mh "Pregnancy Trimesters"] 1459 #5 pregnan*:ti,ab,kw 25022 #6 [mh "Prenatal Care"] 1054 #7 (prenatal* or antenatal* or (ante next natal*) or antepartum or (ante next partum) or perinatal* or (peri next natal*) or peripartum or (peri next partum)):ti,ab,kw 6004 #8 {or #1-#7} 27204 #9 [mh "Vitamin D Deficiency/di, pc"] 0 #10 [mh "Vitamin D/bl"] 0 #11 (((vitamin next D*) or (D next vitamin*) or "25-hydroxyvitamin D" or "hydroxyvitamin D" or "hydroxyvitamins D" or calciferol* or cholecalciferol* or calciol* or hydroxycholecalciferol* or calcifediol* or calcidiol* or calderol* or dedrogyl* or hidroferol* or dihydroxycholecalciferol* or (di next hydroxycholecalciferol*) or "dihydroxyvitamin D" or "dihydroxyvitamins D" or (di next "hydroxyvitamin D") or "di-hydroxyvitamins D" or calcitriol* or "25(OH)D" or "25-OHCC" or "25-OHD3" or "25-HCC" or ergocalciferol*) near/3 (blood* or serum* or test*)):ti,ab,kw 2213 #12 #8 and (#9 or #10 or #11) 107 #13 [mh "Diagnostic Tests, Routine"] 309 #14 ((routine* or mass or standard* or universal*) near/3 test*):ti,ab,kw 3550 #15 [mh "Mass Screening"] 4940 #16 (screen* or detect*):ti,ab,kw 53436 #17 (early near/3 (diagnos* or identif* or recogni*)):ti,ab,kw 2064 #18 {or #13-#17} 57549 #19 #8 and #18 2751 #20 [mh "Vitamin D Deficiency"] 466 #21 ("vitamin D" near/3 (defici* or lack* or insuffici*)):ti,ab,kw 643 #22 (ricket* or rachitis or osteomalacia*):ti,ab,kw 206 #23 [mh "Vitamin D"] 2320 #24 ("vitamin D" or "Vitamin D3" or (D next vitamin*) or "25-hydroxyvitamin D" or "hydroxyvitamin D" or "hydroxyvitamins D" or cholecalciferol* or calciol* or hydroxycholecalciferol* or calcifediol* or calcidiol* or calderol* or dedrogyl* or hidroferol* or dihydroxycholecalciferol* or (di next hydroxycholecalciferol*) or "dihydroxyvitamin D" or "dihydroxyvitamins D" or (di next "hydroxyvitamin D") or "di-hydroxyvitamins D" or calcitriol*):ti,ab,kw 4355 #25 {or #20-#24} 4489 #26 #19 and #25 6

	#27	#12 or #26	111
	#28	#26 or #27	111
	DSR – 5 (did not download – search for primary studies only) DARE – 1 (did not download – search for primary studies only) CENTRAL – 105 (primary studies)		
Note			

Table 29 – Search strategies: Benefits-harms of vitamin D supplementation during pregnancy (SRs)

Database	Medline (OVID) & Embase
Date	12-05-2014
Search strategy	1 exp Pregnancy/ or exp Pregnancy Complications/ (1318123) 2 Pregnant Women/ (37306) 3 exp Pregnancy Trimesters/ (577903) 4 pregnan*.tw. (787995) 5 Prenatal Care/ (46126) 6 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (306865) 7 or/1-6 (1633971) 8 exp Vitamin D/ and exp Dietary Supplements/ (6817) 9 exp Cholecalciferol/ and exp Dietary Supplements/ (1384) 10 exp Ergocalciferols/ and exp Dietary Supplements/ (371) 11 ((vitamin D$1 or D vitamin$1 or "25-hydroxyvitamin D" or "hydroxyvitamin D" or "hydroxyvitamins D" or calciferol* or cholecalciferol* or calciol* or hydroxycholecalciferol* or calcifediol* or calcidiol* or calderol* or dedrogyl* or hidroferol* or dihydroxycholecalciferol* or di-hydroxycholecalciferol* or "dihydroxyvitamin D" or "dihydroxyvitamins D" or "di-hydroxyvitamin D" or "di-hydroxyvitamins D" or calcitriol* or "25(OH)D" or "25-OHCC" or "25-OHD3" or "25-HCC" or ergocalciferol*) adj5 (supplement* or neutraceutical* or nutraceutical* or nutriceutical* or fortifi*)).tw. (14557) 12 (vitamin D$1 or D vitamin$1 or "25-hydroxyvitamin D" or "hydroxyvitamin D" or "hydroxyvitamins D" or calciferol* or cholecalciferol* or calciol* or hydroxycholecalciferol* or calcifediol* or calcidiol* or calderol* or dedrogyl* or hidroferol* or dihydroxycholecalciferol* or di-hydroxycholecalciferol* or "dihydroxyvitamin D" or "dihydroxyvitamins D" or "di-hydroxyvitamin D" or "di-hydroxyvitamins D" or calcitriol* or "25(OH)D" or "25-OHCC" or "25-OHD3" or "25-HCC" or ergocalciferol*).tw. and exp Dietary Supplements/ (5161) 13 or/8-12 (19179) 14 7 and 13 (1596) 15 exp Animals/ not (exp Animals/ and Humans/) (7887368) 16 14 not 15 (1524) 17 (comment or editorial or interview or letter or news).pt. (2778265) 18 16 not 17 (1463) 19 limit 18 to systematic reviews [Limit not valid in Embase; records were retained] (981) 20 meta analysis.pt. (47690) 21 exp meta-analysis as topic/ (26635)

22 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw. (146423)
23 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (177811)
24 exp Technology assessment, biomedical/ (20522)
25 (cochrane or health technology assessment or evidence report).jw. (24681)
26 or/20-25 (336282)
27 18 and 26 (98)
28 19 or 27 (992)
29 28 use prmz (59)
30 exp pregnancy/ (1254102)
31 exp pregnancy disorder/ (396118)
32 pregnant woman/ (37306)
33 pregnan*.tw. (787995)
34 exp prenatal care/ (124659)
35 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (306865)
36 or/30-35 (1733331)
37 exp Vitamin D/ and diet supplementation/ (4388)
38 ((vitamin D$1 or D vitamin$1 or "25-hydroxyvitamin D" or "hydroxyvitamin D" or "hydroxyvitamins D" or calciferol* or cholecalciferol* or calciol* or hydroxycholecalciferol* or calcifediol* or calcidiol* or calderol* or dedrogyl* or hidroferol* or dihydroxycholecalciferol* or di-hydroxycholecalciferol* or "dihydroxyvitamin D" or "dihydroxyvitamins D" or "di-hydroxyvitamin D" or "di-hydroxyvitamins D" or calcitriol* or "25(OH)D" or "25-OHCC" or "25-OHD3" or "25-HCC" or ergocalciferol*) adj5 (supplement* or neutraceutical* or nutraceutical* or nutriceutical* or fortifi*)).tw. (14557)
39 (vitamin D$1 or D vitamin$1 or "25-hydroxyvitamin D" or "hydroxyvitamin D" or "hydroxyvitamins D" or calciferol* or cholecalciferol* or calciol* or hydroxycholecalciferol* or calcifediol* or calcidiol* or calderol* or dedrogyl* or hidroferol* or dihydroxycholecalciferol* or di-hydroxycholecalciferol* or "dihydroxyvitamin D" or "dihydroxyvitamins D" or "di-hydroxyvitamin D" or "di-hydroxyvitamins D" or calcitriol* or "25(OH)D" or "25-OHCC" or "25-OHD3" or "25-HCC" or ergocalciferol*).tw. and diet supplementation/ (2634)
40 or/37-39 (17924)
41 36 and 40 (1601)
42 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (36314806)
43 exp humans/ or exp human experimentation/ or exp human experiment/ (28029083)
44 42 not 43 (8287294)
45 41 not 44 (1536)
46 (letter or editorial).pt. (2470071)
47 45 not 46 (1496)
48 meta-analysis/ (125741)
49 "systematic review"/ (73750)
50 "meta analysis (topic)"/ (12906)
51 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw. (146423)

	52 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (177811) 53 biomedical technology assessment/ (19421) 54 (cochrane or health technology assessment or evidence report).jw. (24681) 55 or/48-54 (369107) 56 47 and 55 (115) 57 56 use emez (86) 58 29 or 57 (145) 59 limit 58 to yr="2011-current" (94) 60 remove duplicates from 59 (72) [TOTAL UNIQUE HITS] 61 60 use prmz (35) [MEDLINE UNIQUE HITS] 62 60 use emez (37) [EMBASE UNIQUE HITS]
Note	
Database	**The Cochrane library**
Date	10-05-2014
Search strategy	ID Search Hits #1 [mh Pregnancy] 5764 #2 [mh "Pregnancy Complications"] 7732 #3 [mh "Pregnant Women"] 95 #4 [mh "Pregnancy Trimesters"] 1459 #5 pregnan*:ti,ab,kw 25022 #6 [mh "Prenatal Care"] 1054 #7 (prenatal* or antenatal* or (ante next natal*) or antepartum or (ante next partum) or perinatal* or (peri next natal*) or peripartum or (peri next partum)):ti,ab,kw 6004 #8 {or #1-#7} 27204 #9 [mh "Vitamin D"] and [mh "Dietary Supplements"] 485 #10 [mh Cholecalciferol] and [mh "Dietary Supplements"] 203 #11 [mh Ergocalciferols] and [mh "Dietary Supplements"] 35 #12 (("vitamin D" or "Vitamin D3" or (D next vitamin*) or "25-hydroxyvitamin D" or "hydroxyvitamin D" or "hydroxyvitamins D" or calciferol* or cholecalciferol* or calciol* or hydroxycholecalciferol* or calcifediol* or calcidiol* or calderol* or dedrogyl* or hidroferol* or dihydroxycholecalciferol* or (di next hydroxycholecalciferol*) or "dihydroxyvitamin D" or "dihydroxyvitamins D" or (di next hydroxyvitamin D) or "di-hydroxyvitamins D" or calcitriol* or "25(OH)D" or "25-OHCC" or "25-OHD3" or "25-HCC" or ergocalciferol*) near/5 (supplement* or neutraceutical* or nutraceutical* or nutriceutical* or fortifi*)):ti,ab,kw 1259 #13 ("vitamin D" or "Vitamin D3" or (D next vitamin*) or "25-hydroxyvitamin D" or "hydroxyvitamin D" or "hydroxyvitamins D" or calciferol* or cholecalciferol* or calciol* or hydroxycholecalciferol* or calcifediol* or calcidiol* or calderol* or dedrogyl* or hidroferol* or dihydroxycholecalciferol* or (di next hydroxycholecalciferol*) or "dihydroxyvitamin D" or "dihydroxyvitamins D" or (di next hydroxyvitamin D) or "di-hydroxyvitamins D" or calcitriol* or "25(OH)D" or "25-OHCC" or "25-OHD3" or "25-HCC" or ergocalciferol*):ti,ab,kw and [mh "Dietary Supplements"] 535 #14 #9 or #10 or #11 or #12 or #13 1399

	#15 #8 and #14 Publication Date from 2011 to 2014, in Cochrane Reviews (Reviews and Protocols), Other Reviews and Technology Assessments 4 DSR - 2 DARE - 1 HTA - 1
Note	

Table 30 – Search strategies: Benefits-harms of vitamin D supplementation during pregnancy (Primary-RCTs)

Database	Medline (OVID) & Embase
Date	24-05- 2014
Search strategy	1 exp Pregnancy/ or exp Pregnancy Complications/ (1320731) 2 Pregnant Women/ (37799) 3 exp Pregnancy Trimesters/ (579575) 4 pregnan*.tw. (790620) 5 Prenatal Care/ (46268) 6 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (308010) 7 or/1-6 (1637916) 8 exp Vitamin D/ and exp Dietary Supplements/ (6864) 9 exp Cholecalciferol/ and exp Dietary Supplements/ (1395) 10 exp Ergocalciferols/ and exp Dietary Supplements/ (375) 11 ((vitamin D$1 or D vitamin$1 or "25-hydroxyvitamin D" or "hydroxyvitamin D" or "hydroxyvitamins D" or calciferol* or cholecalciferol* or calciol* or hydroxycholecalciferol* or calcifediol* or calcidiol* or calderol* or dedrogyl* or hidroferol* or dihydroxycholecalciferol* or di-hydroxycholecalciferol* or "dihydroxyvitamin D" or "dihydroxyvitamins D" or "di-hydroxyvitamin D" or "di-hydroxyvitamins D" or calcitriol* or "25(OH)D" or "25-OHCC" or "25-OHD3" or "25-HCC" or ergocalciferol*) adj5 (supplement* or neutraceutical* or nutraceutical* or nutriceutical* or fortifi*)).tw. (14727) 12 (vitamin D$1 or D vitamin$1 or "25-hydroxyvitamin D" or "hydroxyvitamin D" or "hydroxyvitamins D" or calciferol* or cholecalciferol* or calciol* or hydroxycholecalciferol* or calcifediol* or calcidiol* or calderol* or dedrogyl* or hidroferol* or dihydroxycholecalciferol* or di-hydroxycholecalciferol* or "dihydroxyvitamin D" or "dihydroxyvitamins D" or "di-hydroxyvitamin D" or "di-hydroxyvitamins D" or calcitriol* or "25(OH)D" or "25-OHCC" or "25-OHD3" or "25-HCC" or ergocalciferol*).tw. and exp Dietary Supplements/ (5193) 13 or/8-12 (19377) 14 7 and 13 (1607) 15 exp Animals/ not (exp Animals/ and Humans/) (7901717) 16 14 not 15 (1535) 17 (comment or editorial or interview or letter or news).pt. (2787731) 18 16 not 17 (1474) 19 (controlled clinical trial or randomized controlled trial).pt. (457201) 20 clinical trials as topic.sh. (169939) 21 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1401317) 22 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (285600)

23 trial.ti. (282746)
24 or/19-23 (1794557)
25 18 and 24 (309)
26 (201108* or 201109* or 201110* or 201111* or 201112* or 2012* or 2013* or 2014*).ed. (2739950)
27 25 and 26 (69)
28 27 use prmz (69)
29 exp pregnancy/ (1256544)
30 exp pregnancy disorder/ (397641)
31 pregnant woman/ (37799)
32 pregnan*.tw. (790620)
33 exp prenatal care/ (125046)
34 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (308010)
35 or/29-34 (1737760)
36 exp Vitamin D/ and diet supplementation/ (4420)
37 ((vitamin D$1 or D vitamin$1 or "25-hydroxyvitamin D" or "hydroxyvitamin D" or "hydroxyvitamins D" or calciferol* or cholecalciferol* or calciol* or hydroxycholecalciferol* or calcifediol* or calcidiol* or calderol* or dedrogyl* or hidroferol* or dihydroxycholecalciferol* or di-hydroxycholecalciferol* or "dihydroxyvitamin D" or "dihydroxyvitamins D" or "di-hydroxyvitamin D" or "di-hydroxyvitamins D" or calcitriol* or "25(OH)D" or "25-OHCC" or "25-OHD3" or "25-HCC" or ergocalciferol*) adj5 (supplement* or neutraceutical* or nutraceutical* or nutriceutical* or fortifi*)).tw. (14727)
38 (vitamin D$1 or D vitamin$1 or "25-hydroxyvitamin D" or "hydroxyvitamin D" or "hydroxyvitamins D" or calciferol* or cholecalciferol* or calciol* or hydroxycholecalciferol* or calcifediol* or calcidiol* or calderol* or dedrogyl* or hidroferol* or dihydroxycholecalciferol* or di-hydroxycholecalciferol* or "dihydroxyvitamin D" or "dihydroxyvitamins D" or "di-hydroxyvitamin D" or "di-hydroxyvitamins D" or calcitriol* or "25(OH)D" or "25-OHCC" or "25-OHD3" or "25-HCC" or ergocalciferol*).tw. and diet supplementation/ (2651)
39 or/36-38 (18117)
40 35 and 39 (1613)
41 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (36421917)
42 exp humans/ or exp human experimentation/ or exp human experiment/ (28119382)
43 41 not 42 (8304106)
44 40 not 43 (1548)
45 (letter or editorial).pt. (2478539)
46 44 not 45 (1508)
47 randomized controlled trial/ or controlled clinical trial/ (932584)
48 exp "clinical trial (topic)"/ (103588)
49 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1401317)
50 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (285600)
51 trial.ti. (282746)
52 or/47-51 (1926347)
53 46 and 52 (351)
54 (2011* or 2012* or 2013* or 2014*).em. (7842614)
55 53 and 54 (237)
56 55 use emez (176)

	57 28 or 56 (245) 58 remove duplicates from 57 (191) [TOTAL UNIQUE RECORDS] 59 58 use prmz (64) [UNIQUE MEDLINE RECORDS] 60 58 use emez (127) [UNIQUE EMBASE RECORDS]
Note	
Database	**The Cochrane library**
Date	24-05 -2014
Search strategy	ID Search Hits #1 [mh Pregnancy] 5764 #2 [mh "Pregnancy Complications"] 7732 #3 [mh "Pregnant Women"] 95 #4 [mh "Pregnancy Trimesters"] 1459 #5 pregnan*:ti,ab,kw 25024 #6 [mh "Prenatal Care"] 1054 #7 (prenatal* or antenatal* or (ante next natal*) or antepartum or (ante next partum) or perinatal* or (peri next natal*) or peripartum or (peri next partum)):ti,ab,kw 6004 #8 {or #1-#7} 27206 #9 [mh "Vitamin D"] and [mh "Dietary Supplements"] 485 #10 [mh Cholecalciferol] and [mh "Dietary Supplements"] 203 #11 [mh Ergocalciferols] and [mh "Dietary Supplements"] 35 #12 (("vitamin D" or "Vitamin D3" or (D next vitamin*) or "25-hydroxyvitamin D" or "hydroxyvitamin D" or "hydroxyvitamins D" or calciferol* or cholecalciferol* or calciol* or hydroxycholecalciferol* or calcifediol* or calcidiol* or calderol* or dedrogyl* or hidroferol* or dihydroxycholecalciferol* or (di next hydroxycholecalciferol*) or "dihydroxyvitamin D" or "dihydroxyvitamins D" or (di next hydroxyvitamin D) or "di-hydroxyvitamins D" or calcitriol* or "25(OH)D" or "25-OHCC" or "25-OHD3" or "25-HCC" or ergocalciferol*) near/5 (supplement* or neutraceutical* or nutraceutical* or nutriceutical* or fortifi*)):ti,ab,kw 1259 #13 ("vitamin D" or "Vitamin D3" or (D next vitamin*) or "25-hydroxyvitamin D" or "hydroxyvitamin D" or "hydroxyvitamins D" or calciferol* or cholecalciferol* or calciol* or hydroxycholecalciferol* or calcifediol* or calcidiol* or calderol* or dedrogyl* or hidroferol* or dihydroxycholecalciferol* or (di next hydroxycholecalciferol*) or "dihydroxyvitamin D" or "dihydroxyvitamins D" or (di next hydroxyvitamin D) or "di-hydroxyvitamins D" or calcitriol* or "25(OH)D" or "25-OHCC" or "25-OHD3" or "25-HCC" or ergocalciferol*):ti,ab,kw and [mh "Dietary Supplements"] 535 #14 #9 or #10 or #11 or #12 or #13 1399 #15 #8 and #14 Publication Date from 2011 to 2014 35 DSR – 2 (did not download; primary study search only) DARE – 1 (did not download; primary study search only) CENTRAL – 31 HTA - 1 (did not download; primary study search only)
Note	

Table 31 – Search strategies: Benefits-harms of vitamin D supplementation during pregnancy (Primary-Observational)

Database	Medline (OVID) & Embase
Date	27- 05- 2014
Search strategy	1 exp Pregnancy/ or exp Pregnancy Complications/ (1320731) 2 Pregnant Women/ (37799) 3 exp Pregnancy Trimesters/ (579575) 4 pregnan*.tw. (790743) 5 Prenatal Care/ (46268) 6 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (308069) 7 or/1-6 (1638071) 8 exp Vitamin D/ and exp Dietary Supplements/ (6864) 9 exp Cholecalciferol/ and exp Dietary Supplements/ (1395) 10 exp Ergocalciferols/ and exp Dietary Supplements/ (375) 11 ((vitamin D$1 or D vitamin$1 or "25-hydroxyvitamin D" or "hydroxyvitamin D" or "hydroxyvitamins D" or calciferol* or cholecalciferol* or calciol* or hydroxycholecalciferol* or calcifediol* or calcidiol* or calderol* or dedrogyl* or hidroferol* or dihydroxycholecalciferol* or di-hydroxycholecalciferol* or "dihydroxyvitamin D" or "dihydroxyvitamins D" or "di-hydroxyvitamin D" or "di-hydroxyvitamins D" or calcitriol* or "25(OH)D" or "25-OHCC" or "25-OHD3" or "25-HCC" or ergocalciferol*) adj5 (supplement* or neutraceutical* or nutraceutical* or nutriceutical* or fortifi*)).tw. (14736) 12 (vitamin D$1 or D vitamin$1 or "25-hydroxyvitamin D" or "hydroxyvitamin D" or "hydroxyvitamins D" or calciferol* or cholecalciferol* or calciol* or hydroxycholecalciferol* or calcifediol* or calcidiol* or calderol* or dedrogyl* or hidroferol* or dihydroxycholecalciferol* or di-hydroxycholecalciferol* or "dihydroxyvitamin D" or "dihydroxyvitamins D" or "di-hydroxyvitamin D" or "di-hydroxyvitamins D" or calcitriol* or "25(OH)D" or "25-OHCC" or "25-OHD3" or "25-HCC" or ergocalciferol*).tw. and exp Dietary Supplements/ (5193) 13 or/8-12 (19386) 14 7 and 13 (1608) 15 exp Animals/ not (exp Animals/ and Humans/) (7901717) 16 14 not 15 (1536) 17 (comment or editorial or interview or letter or news).pt. (2788368) 18 16 not 17 (1475) 19 controlled clinical trial.pt. (88369) 20 Controlled Clinical Trial/ or Controlled Clinical Trials as Topic/ (480705) 21 (control* adj2 trial*).tw. (319365) 22 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (72449) 23 (nRCT or nRCTs or non-RCT$1).tw. (641) 24 (control* adj3 ("before and after" or "before after")).tw. (5825) 25 time series.tw. (33538) 26 (pre- adj3 post-).tw. (107560) 27 (pretest adj3 posttest).tw. (6176) 28 (control* adj2 stud$3).tw. (339555) 29 Control Groups/ (61572) 30 (control$ adj2 group$1).tw. (725901)

31 or/19-30 (1817199)
32 18 and 31 (262)
33 exp Cohort Studies/ (1514576)
34 cohort$1.tw. (671011)
35 Retrospective Studies/ (834132)
36 (longitudinal or prospective or retrospective).tw. (1693121)
37 ((followup or follow-up) adj (study or studies)).tw. (82009)
38 Observational study.pt. (2347)
39 (observation$2 adj (study or studies)).tw. (110385)
40 ((population or population-based) adj (study or studies or analys#s)).tw. (25277)
41 ((multidimensional or multi-dimensional) adj (study or studies)).tw. (169)
42 Comparative Study.pt. (1676233)
43 ((comparative or comparison) adj (study or studies)).tw. (168659)
44 exp Case-Control Studies/ (743543)
45 ((case-control* or case-based or case-comparison) adj (study or studies)).tw. (141950)
46 or/33-45 (4878902)
47 18 and 46 (408)
48 32 or 47 (559)
49 limit 48 to yr="2000-current" (510)
50 49 use prmz (201)
51 exp pregnancy/ (1256544)
52 exp pregnancy disorder/ (397641)
53 pregnant woman/ (37799)
54 pregnan*.tw. (790743)
55 exp prenatal care/ (125046)
56 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (308069)
57 or/51-56 (1737915)
58 exp Vitamin D/ and diet supplementation/ (4420)
59 ((vitamin D$1 or D vitamin$1 or "25-hydroxyvitamin D" or "hydroxyvitamin D" or "hydroxyvitamins D" or calciferol* or cholecalciferol* or calciol* or hydroxycholecalciferol* or calcifediol* or calcidiol* or calderol* or dedrogyl* or hidroferol* or dihydroxycholecalciferol* or di-hydroxycholecalciferol* or "dihydroxyvitamin D" or "dihydroxyvitamins D" or "di-hydroxyvitamin D" or "di-hydroxyvitamins D" or calcitriol* or "25(OH)D" or "25-OHCC" or "25-OHD3" or "25-HCC" or ergocalciferol*) adj5 (supplement* or neutraceutical* or nutraceutical* or nutriceutical* or fortifi*)).tw. (14736)
60 (vitamin D$1 or D vitamin$1 or "25-hydroxyvitamin D" or "hydroxyvitamin D" or "hydroxyvitamins D" or calciferol* or cholecalciferol* or calciol* or hydroxycholecalciferol* or calcifediol* or calcidiol* or calderol* or dedrogyl* or hidroferol* or dihydroxycholecalciferol* or di-hydroxycholecalciferol* or "dihydroxyvitamin D" or "dihydroxyvitamins D" or "di-hydroxyvitamin D" or "di-hydroxyvitamins D" or calcitriol* or "25(OH)D" or "25-OHCC" or "25-OHD3" or "25-HCC" or ergocalciferol*).tw. and diet supplementation/ (2651)
61 or/58-60 (18126)
62 57 and 61 (1614)
63 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (36421917)
64 exp humans/ or exp human experimentation/ or exp human experiment/ (28119382)
65 63 not 64 (8304106)

66 62 not 65 (1549)
67 (letter or editorial).pt. (2479024)
68 66 not 67 (1509)
69 controlled clinical trial/ (473129)
70 "controlled clinical trial (topic)"/ (2852)
71 (control* adj2 trial*).tw. (319365)
72 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (72449)
73 (nRCT or nRCTs or non-RCT$1).tw. (641)
74 (control* adj3 ("before and after" or "before after")).tw. (5825)
75 time series analysis/ (13856)
76 time series.tw. (33538)
77 pretest posttest control group design/ (202)
78 (pre- adj3 post-).tw. (107560)
79 (pretest adj3 posttest).tw. (6176)
80 controlled study/ (4319125)
81 (control* adj2 stud$3).tw. (339555)
82 control group/ (61572)
83 (control$ adj2 group$1).tw. (725901)
84 or/69-83 (5468105)
85 68 and 84 (370)
86 cohort analysis/ (333191)
87 cohort$1.tw. (671011)
88 retrospective study/ (834132)
89 longitudinal study/ (152021)
90 prospective study/ (615528)
91 (longitudinal or prospective or retrospective).tw. (1693121)
92 follow up/ (796362)
93 ((followup or follow-up) adj (study or studies)).tw. (82009)
94 observational study/ (57832)
95 (observation$2 adj (study or studies)).tw. (110385)
96 population research/ (67418)
97 ((population or population-based) adj (study or studies or analys#s)).tw. (25277)
98 ((multidimensional or multi-dimensional) adj (study or studies)).tw. (169)
99 exp comparative study/ (2630010)
100 ((comparative or comparison) adj (study or studies)).tw. (168659)
101 exp case control study/ (743543)
102 ((case-control* or case-based or case-comparison) adj (study or studies)).tw. (141950)
103 or/86-102 (6038313)
104 68 and 103 (469)
105 85 or 104 (658)
106 limit 105 to yr="2000-current" (585)

	107 106 use emez (421) 108 50 or 107 (622) 109 remove duplicates from 108 (477) [TOTAL UNIQUE RECORDS] 110 109 use prmz (192) [MEDLINE UNIQUE RECORDS] 111 109 use emez (285) [EMBASE UNIQUE RECORDS]
Note	

6.2.8. Risk of preterm birth

Table 32 – Search strategies: Benefits-harms of transvaginal ultrasound for cervical length, funneling, or both, and/or digital vaginal exam in exclusively or predominantly low risk pregnant women (SRs)

Database	Medline (OVID) & Embase
Date	17-06-2014
Search strategy	1 exp Pregnancy/ or exp Pregnancy Complications/ (1325050) 2 Pregnant Women/ (38208) 3 exp Pregnancy Trimesters/ (581418) 4 pregnan*.tw. (794409) 5 Prenatal Care/ (46503) 6 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (309719) 7 or/1-6 (1644240) 8 ((healthy or asymptomatic* or symptomless* or low risk* or lowrisk* or no risk* or norisk* or normal* or routine or standard or uncomplicated or safe or without complication* or without risk*) adj3 (female* or patient* or maternal* or mother* or pregnan* or wom#n)).tw. (658788) 9 7 and 8 (98691) 10 Diagnostic Tests, Routine/ (67549) 11 ((routine* or mass or standard* or universal*) adj3 test*).tw. (99058) 12 exp Mass Screening/ (254045) 13 (screen* or detect*).tw. (4301975) 14 (early adj3 (identif* or recogni*)).tw. (69809) 15 or/10-14 (4553343) 16 7 and 15 (190915) 17 Cervical Length Measurement/ (1068) 18 ((cervix* or cervical* or endocervical* or endo-cervical*) adj3 (length* or measur*)).tw. (5940) 19 Cervix Uteri/us (891) 20 Vagina/us (687) 21 ((cervical* or cervix* or vagina* or transvaginal* or trans-vaginal*) adj3 (ultrason* or ultra-son* or ultrasound* or ultra-sound* or sonograph* or endoson* or endo-son* or endosound* or endo-sound* or scan*)).tw. (20589) 22 (TV ultrason* or TV ultra-son* or TV ultrasound* or TV ultra-sound* or TVU or TVUS or "TVU CL").tw. (640) 23 Uterine Cervical Incompetence/us (159)

24 exp Obstetric Labor, Premature/us (358)
25 ((digital* or cervical* or cervix or vaginal* or funnel*) adj3 (assess* or exam*)).tw. (27489)
26 (Bishop* adj score*).tw. (1939)
27 or/17-26 (52585)
28 (9 or 16) and 27 (4483)
29 exp Obstetric Labor, Premature/ (46316)
30 ((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw. (73173)
31 (PTL or sPTL or PTB or sPTB or PTD or sPTD).tw. (12073)
32 Uterine Contraction/ (13768)
33 ((uterus* or uterine) adj3 contraction*).tw. (8387)
34 Cervical Ripening/ (2567)
35 ((cervical or cervix*) adj3 (dilat* or ripen*)).tw. (9077)
36 exp Labor Onset/ (4484)
37 (preterm* or pre-term* or prematur* or pre-matur*).tw. (313354)
38 or/32-36 (29804)
39 37 and 38 (4885)
40 or/29-31,39 (96397)
41 28 and 40 (1168)
42 exp Animals/ not (exp Animals/ and Humans/) (7922193)
43 41 not 42 (1159)
44 (comment or editorial or interview or letter or news).pt. (2800393)
45 43 not 44 (1149)
46 limit 45 to systematic reviews [Limit not valid in Embase; records were retained] (679)
47 meta analysis.pt. (48765)
48 exp meta-analysis as topic/ (27502)
49 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw. (150160)
50 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (181457)
51 exp Technology assessment, biomedical/ (20552)
52 (cochrane or health technology assessment or evidence report).jw. (24875)
53 or/47-52 (342994)
54 45 and 53 (63)
55 46 or 54 (685)
56 limit 55 to yr="2011-current" (285)
57 56 use prmz (19)
58 exp pregnancy/ (1260614)
59 exp pregnancy disorder/ (399339)
60 pregnant woman/ (38208)
61 pregnan*.tw. (794409)

62 exp prenatal care/ (125541)
63 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (309719)
64 or/58-63 (1744507)
65 ((healthy or asymptomatic* or symptomless* or low risk* or lowrisk* or no risk* or norisk* or normal* or routine or standard or uncomplicated or safe or without complication* or without risk*) adj3 (female* or patient* or maternal* or mother* or pregnan* or wom#n)).tw. (658788)
66 64 and 65 (100309)
67 exp diagnostic test/ (684776)
68 ((routine* or mass or standard* or universal*) adj3 test*).tw. (99058)
69 mass screening/ (126662)
70 (screen* or detect*).tw. (4301975)
71 (early adj3 (identif* or recogni*)).tw. (69809)
72 or/67-71 (5032370)
73 64 and 72 (226672)
74 transvaginal echography/ or cervical length measurement/ (12862)
75 ((cervix* or cervical* or endocervical* or endo-cervical*) adj3 (length* or measur*)).tw. (5940)
76 ((cervical* or cervix* or vagina* or transvaginal* or trans-vaginal*) adj3 (ultrason* or ultra-son* or ultrasound* or ultra-sound* or sonograph* or endoson* or endo-son* or endosound* or endo-sound* or scan*)).tw. (20589)
77 (TV ultrason* or TV ultra-son* or TV ultrasound* or TV ultra-sound* or TVU or TVUS or "TVU CL").tw. (640)
78 ((digital* or cervical* or cervix or vaginal* or funnel*) adj3 (assess* or exam*)).tw. (27489)
79 (Bishop* adj score*).tw. (1939)
80 or/74-79 (57351)
81 (66 or 73) and 80 (5621)
82 premature labor/ (40196)
83 ((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw. (73173)
84 (PTL or sPTL or PTB or sPTB or PTD or sPTD).tw. (12073)
85 uterus contraction/ (6799)
86 ((uterus* or uterine) adj3 contraction*).tw. (8387)
87 uterine cervix ripening/ (1796)
88 ((cervical or cervix*) adj3 (dilat* or ripen*)).tw. (9077)
89 labor onset/ (2043)
90 (preterm* or pre-term* or prematur* or pre-matur*).tw. (313354)
91 or/85-89 (23032)
92 90 and 91 (4224)
93 or/82-84,92 (94601)
94 81 and 93 (1255)
95 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (36562118)
96 exp humans/ or exp human experimentation/ or exp human experiment/ (28237645)
97 95 not 96 (8326044)
98 94 not 97 (1247)
99 (editorial or letter).pt. (2488988)
100 98 not 99 (1238)

	101 meta-analysis/ (128310) 102 "systematic review"/ (75693) 103 "meta analysis (topic)"/ (13690) 104 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw. (150160) 105 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (181457) 106 biomedical technology assessment/ (19450) 107 (cochrane or health technology assessment or evidence report).jw. (24875) 108 or/101-107 (376148) 109 100 and 108 (80) 110 limit 109 to yr="2011-current" (40) 111 110 use emez (28) 112 57 or 111 (47) 113 remove duplicates from 112 (33) [TOTAL UNIQUE RECORDS] 114 113 use prmz (17) [MEDLINE UNIQUE RECORDS] 115 113 use emez (16) [EMBASE UNIQUE RECORDS]
Note	
Database	**The Cochrane library**
Date	18-06-2014
Search strategy	ID Search Hits #1 [mh Pregnancy] or [mh "Pregnancy Complications"] 11072 #2 [mh "Pregnant Women"] 95 #3 [mh "Pregnancy Trimesters"] 1461 #4 pregnan*:ti,ab,kw 25068 #5 [mh "Prenatal Care"] 1056 #6 (prenatal* or antenatal* or (ante next natal*) or antepartum or (ante next partum) or perinatal* or (peri next natal*) or peripartum or (peri next partum)):ti,ab,kw 6013 #7 {or #1-#6} 27254 #8 ((healthy or asymptomatic* or symptomless* or (low next risk*) or lowrisk* or (no next risk*) or norisk* or normal* or routine or standard or uncomplicated or safe or (without next complication*) or (without next risk*)) near/3 (female* or patient* or maternal* or mother* or pregnan* or woman* or women*)):ti,ab,kw 28776 #9 #7 and #8 2569 #10 [mh "Diagnostic Tests, Routine"] 309 #11 ((routine* or mass or standard* or universal*) near/3 test*) 5837 #12 [mh "Mass Screening"] 4943 #13 screen* or detect*:ti,ab,kw 61665 #14 (early near/3 (identif* or recogni*)):ti,ab,kw 649

#15 {or #10-#14} 65806
#16 #7 and #15 3239
#17 [mh "Cervical Length Measurement"] 31
#18 ((cervix* or cervical* or endocervical* or endo-cervical*) near/3 (length* or measur*)):ti,ab,kw 318
#19 [mh "Cervix Uteri"/us] 53
#20 [mh Vagina/us] 49
#21 ((cervical* or cervix* or vagina* or transvaginal* or (trans next vaginal*)) near/3 (ultrason* or (ultra next son*) or ultrasound* or (ultra next sound*) or sonograph* or endoson* or (endo next son*) or endosound* or (endo next sound*) or scan*)):ti,ab,kw 773
#22 TV next (ultrason* or (ultra next son*) or ultrasound* or (ultra next sound*)):ti,ab,kw 2
#23 [mh "Uterine Cervical Incompetence"/us] 14
#24 [mh "Obstetric Labor, Premature"/us] 17
#25 ((digital* or cervical* or cervix or vaginal* or funnel*) near/3 (assess* or exam*)):ti,ab,kw 1089
#26 Bishop* adj score*:ti,ab,kw 1
#27 {or #17-#26} 2047
#28 (#9 or #16) and #27 178
#29 [mh "Obstetric Labor, Premature"] 1106
#30 ((labor* or labour* or birth* or deliver*) near/3 (preterm* or (pre next term*) or prematur* or (pre next matur*))):ti,ab,kw 2950
#31 (PTL or sPTL or PTB or sPTB or PTD or sPTD):ti,ab,kw 134
#32 [mh "Uterine Contraction"] 340
#33 ((uterus* or uterine) near/3 contraction*):ti,ab,kw 686
#34 [mh "Cervical Ripening"] 278
#35 ((cervical or cervix*) near/3 (dilat* or ripen*)):ti,ab,kw 1537
#36 [mh "Labor Onset"] 503
#37 (preterm* or (pre next term*) or prematur* or (pre next matur*)):ti,ab,kw 13325
#38 {or #32-#36} 2399
#39 #37 and #38 275
#40 #29 or #30 or #31 or #39 3077
#41 #28 and #40 Publication Year from 2011 to 2014 32

DSR – 6 (*Reviews*)
DARE – 4 (*Reviews*)
CENTRAL – 20
NHS EED – 2

Table 33 – Search strategies: Benefits-harms of transvaginal ultrasound for cervical length, funneling, or both in exclusively or predominantly low risk pregnant women (Primary RCTs/CCTs)

Database	Medline (OVID) & Embase
Date	16-10-2014
Search strategy	1 exp Pregnancy/ or exp Pregnancy Complications/ (1448601) 2 Pregnant Women/ (47870) 3 exp Pregnancy Trimesters/ (677499) 4 pregnan*.tw. (894821) 5 Prenatal Care/ (49221) 6 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (335039) 7 or/1-6 (1800371) 8 ((healthy or asymptomatic* or symptomless* or low risk* or lowrisk* or no risk* or norisk* or normal* or routine or standard or uncomplicated or safe or without complication* or without risk*) adj3 (female* or patient* or maternal* or mother* or pregnan* or wom#n)).tw. (724435) 9 7 and 8 (112278) 10 Diagnostic Tests, Routine/ (70771) 11 ((routine* or mass or standard* or universal*) adj3 test*).tw. (108512) 12 exp Mass Screening/ (266698) 13 (screen* or detect*).tw. (4607008) 14 (early adj3 (identif* or recogni*)).tw. (76502) 15 or/10-14 (4876983) 16 7 and 15 (204687) 17 Cervical Length Measurement/ (1185) 18 ((cervix* or cervical* or endocervical* or endo-cervical*) adj3 (length* or measur*)).tw. (6409) 19 Cervix Uteri/us (926) 20 Vagina/us (715) 21 ((cervical* or cervix* or vagina* or transvaginal* or trans-vaginal*) adj3 (ultrason* or ultra-son* or ultrasound* or ultra-sound* or sonograph* or endoson* or endo-son* or endosound* or endo-sound* or scan*)).tw. (21222) 22 (TV ultrason* or TV ultra-son* or TV ultrasound* or TV ultra-sound* or TVU or TVUS or "TVU CL").tw. (668) 23 Uterine Cervical Incompetence/us (160) 24 exp Obstetric Labor, Premature/us (376) 25 or/17-24 (26669) 26 (9 or 16) and 25 (3654) 27 exp Obstetric Labor, Premature/ (50075) 28 ((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw. (80299) 29 (PTL or sPTL or PTB or sPTB or PTD or sPTD).tw. (12847) 30 Uterine Contraction/ (16536) 31 ((uterus* or uterine) adj3 contraction*).tw. (10356) 32 Cervical Ripening/ (2652) 33 ((cervical or cervix*) adj3 (dilat* or ripen*)).tw. (10171) 34 exp Labor Onset/ (5140)

35 (preterm* or pre-term* or prematur* or pre-matur*).tw. (347395)
36 or/30-34 (34587)
37 35 and 36 (5452)
38 or/27-29,37 (104874)
39 26 and 38 (1061)
40 exp Animals/ not (exp Animals/ and Humans/) (8896253)
41 39 not 40 (1054)
42 (comment or editorial or interview or letter or news).pt. (2895997)
43 41 not 42 (1044)
44 (controlled clinical trial or randomized controlled trial).pt. (482894)
45 clinical trials as topic.sh. (175847)
46 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1495485)
47 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (307674)
48 trial.ti. (310502)
49 or/44-48 (1915812)
50 43 and 49 (148)
51 controlled clinical trial.pt. (90496)
52 Controlled Clinical Trial/ or Controlled Clinical Trials as Topic/ (486631)
53 (control* adj2 trial*).tw. (345537)
54 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (77399)
55 (nRCT or nRCTs or non-RCT$1).tw. (727)
56 (control* adj3 ("before and after" or "before after")).tw. (6348)
57 time series.tw. (35994)
58 (pre- adj3 post-).tw. (117768)
59 (pretest adj3 posttest).tw. (6561)
60 (control* adj2 stud$3).tw. (363132)
61 Control Groups/ (80206)
62 (control$ adj2 group$1).tw. (786465)
63 or/51-62 (1937955)
64 43 and 63 (144)
65 50 or 64 (207)
66 64 use prmz (63)
67 exp pregnancy/ (1377959)
68 exp pregnancy disorder/ (462982)
69 pregnant woman/ (47870)
70 pregnan*.tw. (894821)
71 exp prenatal care/ (135286)
72 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (335039)
73 or/67-72 (1924671)
74 ((healthy or asymptomatic* or symptomless* or low risk* or lowrisk* or no risk* or norisk* or normal* or routine or standard or uncomplicated or safe or without complication* or without risk*) adj3 (female* or patient* or maternal* or mother* or pregnan* or wom#n)).tw. (724435)

75 73 and 74 (114247)
76 exp diagnostic test/ (772773)
77 ((routine* or mass or standard* or universal*) adj3 test*).tw. (108512)
78 mass screening/ (134097)
79 (screen* or detect*).tw. (4607008)
80 (early adj3 (identif* or recogni*)).tw. (76502)
81 or/76-80 (5427887)
82 73 and 81 (246776)
83 transvaginal echography/ or cervical length measurement/ (13301)
84 ((cervix* or cervical* or endocervical* or endo-cervical*) adj3 (length* or measur*)).tw. (6409)
85 ((cervical* or cervix* or vagina* or transvaginal* or trans-vaginal*) adj3 (ultrason* or ultra-son* or ultrasound* or ultra-sound* or sonograph* or endoson* or endo-son* or endosound* or endo-sound* or scan*)).tw. (21222)
86 (TV ultrason* or TV ultra-son* or TV ultrasound* or TV ultra-sound* or TVU or TVUS or "TVU CL").tw. (668)
87 or/83-86 (31604)
88 (75 or 82) and 87 (4664)
89 premature labor/ (43216)
90 ((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw. (80299)
91 (PTL or sPTL or PTB or sPTB or PTD or sPTD).tw. (12847)
92 uterus contraction/ (9453)
93 ((uterus* or uterine) adj3 contraction*).tw. (10356)
94 uterine cervix ripening/ (1844)
95 ((cervical or cervix*) adj3 (dilat* or ripen*)).tw. (10171)
96 labor onset/ (2586)
97 (preterm* or pre-term* or prematur* or pre-matur*).tw. (347395)
98 or/92-96 (27671)
99 97 and 98 (4777)
100 or/89-91,99 (102872)
101 88 and 100 (1135)
102 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (38532520)
103 exp humans/ or exp human experimentation/ or exp human experiment/ (29345167)
104 102 not 103 (9189023)
105 101 not 104 (1129)
106 (editorial or letter).pt. (2565336)
107 105 not 106 (1120)
108 randomized controlled trial/ or controlled clinical trial/ (971577)
109 exp "clinical trial (topic)"/ (118814)
110 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1495485)
111 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (307674)
112 trial.ti. (310502)
113 or/108-112 (2055248)
114 107 and 113 (180)

	115 controlled clinical trial/ (478490) 116 "controlled clinical trial (topic)"/ (3298) 117 (control* adj2 trial*).tw. (345537) 118 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (77399) 119 (nRCT or nRCTs or non-RCT$1).tw. (727) 120 (control* adj3 ("before and after" or "before after")).tw. (6348) 121 time series analysis/ (14546) 122 time series.tw. (35994) 123 pretest posttest control group design/ (208) 124 (pre- adj3 post-).tw. (117768) 125 (pretest adj3 posttest).tw. (6561) 126 controlled study/ (4439999) 127 (control* adj2 stud$3).tw. (363132) 128 control group/ (80206) 129 (control$ adj2 group$1).tw. (786465) 130 or/115-129 (5689719) 131 107 and 130 (261) 132 114 or 131 (323) 133 132 use emczd (242) 134 66 or 133 (305) 135 limit 134 to yr="2012-current" (111) 136 remove duplicates from 135 (93) [TOTAL UNIQUE HITS] 137 136 use prmz (21) [MEDLINE UNIQUE HITS] 138 136 use emczd (72) [EMBASE UNIQUE HITS]
Note	
Database	**The Cochrane library**
Date	16-10-2014
Search strategy	ID Search Hits #1 [mh Pregnancy] or [mh "Pregnancy Complications"] 11137 #2 [mh "Pregnant Women"] 96 #3 [mh "Pregnancy Trimesters"] 1469 #4 pregnan*:ti,ab,kw 25440 #5 [mh "Prenatal Care"] 1061 #6 (prenatal* or antenatal* or (ante next natal*) or antepartum or (ante next partum) or perinatal* or (peri next natal*) or peripartum or (peri next partum)):ti,ab,kw 6110 #7 {or #1-#6} 27655 #8 ((healthy or asymptomatic* or symptomless* or (low next risk*) or lowrisk* or (no next risk*) or norisk* or normal* or routine or standard or uncomplicated or safe or (without next complication*) or (without next risk*)) near/3 (female* or patient* or maternal* or mother* or pregnan* or woman* or women*)):ti,ab,kw 29166 #9 #7 and #8 2608 #10 [mh "Diagnostic Tests, Routine"] 311

#11 ((routine* or mass or standard* or universal*) near/3 test*) 5918
#12 [mh "Mass Screening"] 4996
#13 screen* or detect*:ti,ab,kw 62828
#14 (early near/3 (identif* or recogni*)):ti,ab,kw 668
#15 {or #10-#14} 67033
#16 #7 and #15 3291
#17 [mh "Cervical Length Measurement"] 31
#18 ((cervix* or cervical* or endocervical* or endo-cervical*) near/3 (length* or measur*)):ti,ab,kw 326
#19 [mh "Cervix Uteri"/us] 53
#20 [mh Vagina/us] 49
#21 ((cervical* or cervix* or vagina* or transvaginal* or (trans next vaginal*)) near/3 (ultrason* or (ultra next son*) or ultrasound* or (ultra next sound*) or sonograph* or endoson* or (endo next son*) or endosound* or (endo next sound*) or scan*)):ti,ab,kw 794
#22 TV next (ultrason* or (ultra next son*) or ultrasound* or (ultra next sound*)):ti,ab,kw 2
#23 [mh "Uterine Cervical Incompetence"/us] 14
#24 [mh "Obstetric Labor, Premature"/us] 17
#25 {or #17-#24} 1058
#26 (#9 or #16) and #25 125
#27 [mh "Obstetric Labor, Premature"] 1112
#28 ((labor* or labour* or birth* or deliver*) near/3 (preterm* or (pre next term*) or prematur* or (pre next matur*))):ti,ab,kw 3012
#29 (PTL or sPTL or PTB or sPTB or PTD or sPTD):ti,ab,kw 143
#30 [mh "Uterine Contraction"] 340
#31 ((uterus* or uterine) near/3 contraction*):ti,ab,kw 701
#32 [mh "Cervical Ripening"] 280
#33 ((cervical or cervix*) near/3 (dilat* or ripen*)):ti,ab,kw 1550
#34 [mh "Labor Onset"] 505
#35 (preterm* or (pre next term*) or prematur* or (pre next matur*)):ti,ab,kw 13585
#36 {or #30-#34} 2426
#37 #35 and #36 277
#38 #27 or #28 or #29 or #37 3143
#39 #26 and #38 Publication Year from 2012 to 2014 24

DSR – 4 (*did not download – RCT search only*)
DARE – 3 (*did not download – RCT search only*)
CENTRAL – 16
NHS EED – 1 (*did not download – RCT search only*)

Table 34 – Search strategies: Benefits-harms of transvaginal ultrasound for cervical length, funneling, or both in exclusively or predominantly low risk pregnant women (Primary observational studies)

Database	Medline (OVID) & Embase
Date	16-08-2014
Search strategy	1 exp Pregnancy/ or exp Pregnancy Complications/ (1428257) 2 Pregnant Women/ (46789) 3 exp Pregnancy Trimesters/ (672474) 4 pregnan*.tw. (881640) 5 Prenatal Care/ (48481) 6 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (329344) 7 or/1-6 (1775110) 8 ((healthy or asymptomatic* or symptomless* or low risk* or lowrisk* or no risk* or norisk* or normal* or routine or standard or uncomplicated or safe or without complication* or without risk*) adj3 (female* or patient* or maternal* or mother* or pregnan* or wom#n)).tw. (713152) 9 7 and 8 (110784) 10 Diagnostic Tests, Routine/ (70050) 11 ((routine* or mass or standard* or universal*) adj3 test*).tw. (106578) 12 exp Mass Screening/ (261779) 13 (screen* or detect*).tw. (4522336) 14 (early adj3 (identif* or recogni*)).tw. (74903) 15 or/10-14 (4787950) 16 7 and 15 (201360) 17 Cervical Length Measurement/ (1154) 18 ((cervix* or cervical* or endocervical* or endo-cervical*) adj3 (length* or measur*)).tw. (6315) 19 Cervix Uteri/us (906) 20 Vagina/us (696) 21 ((cervical* or cervix* or vagina* or transvaginal* or trans-vaginal*) adj3 (ultrason* or ultra-son* or ultrasound* or ultra-sound* or sonograph* or endoson* or endo-son* or endosound* or endo-sound* or scan*)).tw. (20973) 22 (TV ultrason* or TV ultra-son* or TV ultrasound* or TV ultra-sound* or TVU or TVUS or "TVU CL").tw. (655) 23 Uterine Cervical Incompetence/us (160) 24 exp Obstetric Labor, Premature/us (363) 25 or/17-24 (26321) 26 (9 or 16) and 25 (3614) 27 exp Obstetric Labor, Premature/ (49078) 28 ((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw. (78832) 29 (PTL or sPTL or PTB or sPTB or PTD or sPTD).tw. (12512) 30 Uterine Contraction/ (16428) 31 ((uterus* or uterine) adj3 contraction*).tw. (10267) 32 Cervical Ripening/ (2621) 33 ((cervical or cervix*) adj3 (dilat* or ripen*)).tw. (10094) 34 exp Labor Onset/ (5049) 35 (preterm* or pre-term* or prematur* or pre-matur*).tw. (341316)

36 or/30-34 (34291)
37 35 and 36 (5395)
38 or/27-29,37 (102944)
39 26 and 38 (1045)
40 exp Animals/ not (exp Animals/ and Humans/) (8787626)
41 39 not 40 (1038)
42 (comment or editorial or interview or letter or news).pt. (2839289)
43 41 not 42 (1028)
44 exp Cohort Studies/ (1562789)
45 cohort$1.tw. (704482)
46 Retrospective Studies/ (863334)
47 (longitudinal or prospective or retrospective).tw. (1776045)
48 ((followup or follow-up) adj (study or studies)).tw. (90721)
49 Observational study.pt. (4108)
50 (observation$2 adj (study or studies)).tw. (116347)
51 ((population or population-based) adj (study or studies or analys#s)).tw. (26715)
52 ((multidimensional or multi-dimensional) adj (study or studies)).tw. (193)
53 Comparative Study.pt. (1698810)
54 ((comparative or comparison) adj (study or studies)).tw. (188823)
55 exp Case-Control Studies/ (769719)
56 ((case-control* or case-based or case-comparison) adj (study or studies)).tw. (146915)
57 or/44-56 (5057184)
58 43 and 57 (506)
59 58 use prmz (239)
60 exp pregnancy/ (1359787)
61 exp pregnancy disorder/ (459258)
62 pregnant woman/ (46789)
63 pregnan*.tw. (881640)
64 exp prenatal care/ (133850)
65 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (329344)
66 or/60-65 (1899446)
67 ((healthy or asymptomatic* or symptomless* or low risk* or lowrisk* or no risk* or norisk* or normal* or routine or standard or uncomplicated or safe or without complication* or without risk*) adj3 (female* or patient* or maternal* or mother* or pregnan* or wom#n)).tw. (713152)
68 66 and 67 (112735)
69 exp diagnostic test/ (766069)
70 ((routine* or mass or standard* or universal*) adj3 test*).tw. (106578)
71 mass screening/ (131338)
72 (screen* or detect*).tw. (4522336)
73 (early adj3 (identif* or recogni*)).tw. (74903)
74 or/69-73 (5334936)

75 66 and 74 (243113)
76 transvaginal echography/ or cervical length measurement/ (13138)
77 ((cervix* or cervical* or endocervical* or endo-cervical*) adj3 (length* or measur*)).tw. (6315)
78 ((cervical* or cervix* or vagina* or transvaginal* or trans-vaginal*) adj3 (ultrason* or ultra-son* or ultrasound* or ultra-sound* or sonograph* or endoson* or endo-son* or endosound* or endo-sound* or scan*)).tw. (20973)
79 (TV ultrason* or TV ultra-son* or TV ultrasound* or TV ultra-sound* or TVU or TVUS or "TVU CL").tw. (655)
80 or/76-79 (31214)
81 (68 or 75) and 80 (4611)
82 premature labor/ (42674)
83 ((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw. (78832)
84 (PTL or sPTL or PTB or sPTB or PTD or sPTD).tw. (12512)
85 uterus contraction/ (9417)
86 ((uterus* or uterine) adj3 contraction*).tw. (10267)
87 uterine cervix ripening/ (1831)
88 ((cervical or cervix*) adj3 (dilat* or ripen*)).tw. (10094)
89 labor onset/ (2555)
90 (preterm* or pre-term* or prematur* or pre-matur*).tw. (341316)
91 or/85-89 (27452)
92 90 and 91 (4732)
93 or/82-84,92 (101060)
94 81 and 93 (1120)
95 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (37963623)
96 exp humans/ or exp human experimentation/ or exp human experiment/ (28879620)
97 95 not 96 (9085649)
98 94 not 97 (1114)
99 (editorial or letter).pt. (2522851)
100 98 not 99 (1105)
101 cohort analysis/ (347802)
102 cohort$1.tw. (704482)
103 retrospective study/ (863334)
104 longitudinal study/ (158348)
105 prospective study/ (636844)
106 (longitudinal or prospective or retrospective).tw. (1776045)
107 follow up/ (849155)
108 ((followup or follow-up) adj (study or studies)).tw. (90721)
109 observational study/ (63594)
110 (observation$2 adj (study or studies)).tw. (116347)
111 population research/ (69823)
112 ((population or population-based) adj (study or studies or analys#s)).tw. (26715)
113 ((multidimensional or multi-dimensional) adj (study or studies)).tw. (193)
114 exp comparative study/ (2726779)
115 ((comparative or comparison) adj (study or studies)).tw. (188823)

	116 exp case control study/ (769719) 117 ((case-control* or case-based or case-comparison) adj (study or studies)).tw. (146915) 118 or/101-117 (6311297) 119 100 and 118 (567) 120 119 use emczd (348) 121 59 or 120 (587) [TOTAL UNIQUE RECORDS] 122 121 use prmz (239) [MEDLINE UNIQUE RECORDS] 123 121 use emczd (348) [EMBASE UNIQUE RECORDS]
Note	Observational studies

Table 35 – Search strategies: Benefits-harms of digital vaginal exam with or without transvaginal exam in exclusively or predomninantly low risk pregnant women (Primary RCTs and CCTs)

Database	Medline (OVID) & Embase
Date	16-08-2014
Search strategy	1 exp Pregnancy/ or exp Pregnancy Complications/ (1427808) 2 Pregnant Women/ (46710) 3 exp Pregnancy Trimesters/ (672043) 4 pregnan*.tw. (881235) 5 Prenatal Care/ (48459) 6 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (329133) 7 or/1-6 (1774530) 8 ((healthy or asymptomatic* or symptomless* or low risk* or lowrisk* or no risk* or norisk* or normal* or routine or standard or uncomplicated or safe or without complication* or without risk*) adj3 (female* or patient* or maternal* or mother* or pregnan* or wom#n)).tw. (712944) 9 7 and 8 (110703) 10 Diagnostic Tests, Routine/ (70028) 11 ((routine* or mass or standard* or universal*) adj3 test*).tw. (106545) 12 exp Mass Screening/ (261748) 13 (screen* or detect*).tw. (4521206) 14 (early adj3 (identif* or recogni*)).tw. (74867) 15 or/10-14 (4786746) 16 7 and 15 (201236) 17 ((digital* or cervical* or cervix or vaginal* or funnel*) adj3 (assess* or exam*)).tw. (29665) 18 (Bishop* adj score*).tw. (2008) 19 or/17-18 (31418) 20 (9 or 16) and 19 (1539) 21 exp Obstetric Labor, Premature/ (49013) 22 ((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw. (78750) 23 (PTL or sPTL or PTB or sPTB or PTD or sPTD).tw. (12493) 24 Uterine Contraction/ (16424) 25 ((uterus* or uterine) adj3 contraction*).tw. (10263)

26	Cervical Ripening/ (2620)
27	((cervical or cervix*) adj3 (dilat* or ripen*)).tw. (10089)
28	exp Labor Onset/ (5042)
29	(preterm* or pre-term* or prematur* or pre-matur*).tw. (341130)
30	or/24-28 (34275)
31	29 and 30 (5392)
32	or/21-23,31 (102857)
33	20 and 32 (466)
34	exp Animals/ not (exp Animals/ and Humans/) (8786867)
35	33 not 34 (462)
36	(comment or editorial or interview or letter or news).pt. (2838892)
37	35 not 36 (461)
38	(controlled clinical trial or randomized controlled trial).pt. (470286)
39	clinical trials as topic.sh. (171983)
40	(randomi#ed or randomly or RCT$1 or placebo*).tw. (1462188)
41	((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (302794)
42	trial.ti. (302026)
43	or/38-42 (1874263)
44	37 and 43 (62)
45	controlled clinical trial.pt. (89643)
46	Controlled Clinical Trial/ or Controlled Clinical Trials as Topic/ (484127)
47	(control* adj2 trial*).tw. (335519)
48	(nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (75674)
49	(nRCT or nRCTs or non-RCT$1).tw. (692)
50	(control* adj3 ("before and after" or "before after")).tw. (6186)
51	time series.tw. (34820)
52	(pre- adj3 post-).tw. (114580)
53	(pretest adj3 posttest).tw. (6423)
54	(control* adj2 stud$3).tw. (355501)
55	Control Groups/ (78016)
56	(control$ adj2 group$1).tw. (771243)
57	or/45-56 (1901496)
58	37 and 57 (60)
59	exp Cohort Studies/ (1562640)
60	cohort$1.tw. (703992)
61	Retrospective Studies/ (863196)
62	(longitudinal or prospective or retrospective).tw. (1775275)
63	((followup or follow-up) adj (study or studies)).tw. (90696)
64	Observational study.pt. (4108)
65	(observation$2 adj (study or studies)).tw. (116244)
66	((population or population-based) adj (study or studies or analys#s)).tw. (26708)
67	((multidimensional or multi-dimensional) adj (study or studies)).tw. (193)

68 Comparative Study.pt. (1698810)
69 ((comparative or comparison) adj (study or studies)).tw. (188783)
70 exp Case-Control Studies/ (769671)
71 ((case-control* or case-based or case-comparison) adj (study or studies)).tw. (146857)
72 or/59-71 (5055916)
73 37 and 72 (196)
74 44 or 58 (86) [RCTS/CCTS]
75 74 use prmz (37) [MEDLINE RCTS/CCTS]
76 exp pregnancy/ (1359356)
77 exp pregnancy disorder/ (458888)
78 pregnant woman/ (46710)
79 pregnan*.tw. (881235)
80 exp prenatal care/ (133791)
81 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (329133)
82 or/76-81 (1898797)
83 ((healthy or asymptomatic* or symptomless* or low risk* or lowrisk* or no risk* or norisk* or normal* or routine or standard or uncomplicated or safe or without complication* or without risk*) adj3 (female* or patient* or maternal* or mother* or pregnan* or wom#n)).tw. (712944)
84 82 and 83 (112652)
85 exp diagnostic test/ (765726)
86 ((routine* or mass or standard* or universal*) adj3 test*).tw. (106545)
87 mass screening/ (131336)
88 (screen* or detect*).tw. (4521206)
89 (early adj3 (identif* or recogni*)).tw. (74867)
90 or/85-89 (5333471)
91 82 and 90 (242954)
92 ((digital* or cervical* or cervix or vaginal* or funnel*) adj3 (assess* or exam*)).tw. (29665)
93 (Bishop* adj score*).tw. (2008)
94 or/92-93 (31418)
95 (84 or 91) and 94 (1763)
96 premature labor/ (42609)
97 ((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw. (78750)
98 (PTL or sPTL or PTB or sPTB or PTD or sPTD).tw. (12493)
99 uterus contraction/ (9413)
100 ((uterus* or uterine) adj3 contraction*).tw. (10263)
101 uterine cervix ripening/ (1830)
102 ((cervical or cervix*) adj3 (dilat* or ripen*)).tw. (10089)
103 labor onset/ (2548)
104 (preterm* or pre-term* or prematur* or pre-matur*).tw. (341130)
105 or/99-103 (27436)
106 104 and 105 (4729)

107	or/96-98,106 (100973)
108	95 and 107 (509)
109	exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (37958195)
110	exp humans/ or exp human experimentation/ or exp human experiment/ (28875169)
111	109 not 110 (9084672)
112	108 not 111 (505)
113	(editorial or letter).pt. (2522541)
114	112 not 113 (505)
115	randomized controlled trial/ or controlled clinical trial/ (954745)
116	exp "clinical trial (topic)"/ (112973)
117	(randomi#ed or randomly or RCT$1 or placebo*).tw. (1462188)
118	((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (302794)
119	trial.ti. (302026)
120	or/115-119 (2012154)
121	114 and 120 (81)
122	controlled clinical trial/ (476240)
123	"controlled clinical trial (topic)"/ (3117)
124	(control* adj2 trial*).tw. (335519)
125	(nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (75674)
126	(nRCT or nRCTs or non-RCT$1).tw. (692)
127	(control* adj3 ("before and after" or "before after")).tw. (6186)
128	time series analysis/ (14304)
129	time series.tw. (34820)
130	pretest posttest control group design/ (205)
131	(pre- adj3 post-).tw. (114580)
132	(pretest adj3 posttest).tw. (6423)
133	controlled study/ (4397746)
134	(control* adj2 stud$3).tw. (355501)
135	control group/ (78016)
136	(control$ adj2 group$1).tw. (771243)
137	or/122-136 (5618080)
138	114 and 137 (118)
139	cohort analysis/ (347653)
140	cohort$1.tw. (703992)
141	retrospective study/ (863196)
142	longitudinal study/ (158306)
143	prospective study/ (636707)
144	(longitudinal or prospective or retrospective).tw. (1775275)
145	follow up/ (848604)
146	((followup or follow-up) adj (study or studies)).tw. (90696)
147	observational study/ (63494)
148	(observation$2 adj (study or studies)).tw. (116244)

	149 population research/ (69811) 150 ((population or population-based) adj (study or studies or analys#s)).tw. (26708) 151 ((multidimensional or multi-dimensional) adj (study or studies)).tw. (193) 152 exp comparative study/ (2726554) 153 ((comparative or comparison) adj (study or studies)).tw. (188783) 154 exp case control study/ (769671) 155 ((case-control* or case-based or case-comparison) adj (study or studies)).tw. (146857) 156 or/139-155 (6309540) 157 114 and 156 (230) 158 121 or 138 (144) [RCTS/CCTS] 159 158 use emczd (107) [MEDLINE RCTS/CCTS] 160 75 or 159 (144) 161 limit 160 to yr="2009-current" (52) 162 remove duplicates from 161 (41) [TOTAL UNIQUE HITS] 163 162 use prmz (10) [MEDLINE UNIQUE HITS] 164 162 use emczd (31) [EMBASE UNIQUE HITS]
Note	

Table 36 – Search strategies: Benefits-harms of digital vaginal exam with or without transvaginal ultrasound in exclusively or predomninantly low risk pregnant women (Primary observational studies)

Database	Medline (OVID) & Embase
Date	16-08-2014
Search strategy	1 exp Pregnancy/ or exp Pregnancy Complications/ (1428257) 2 Pregnant Women/ (46789) 3 exp Pregnancy Trimesters/ (672474) 4 pregnan*.tw. (881640) 5 Prenatal Care/ (48481) 6 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (329344) 7 or/1-6 (1775110) 8 ((healthy or asymptomatic* or symptomless* or low risk* or lowrisk* or no risk* or norisk* or normal* or routine or standard or uncomplicated or safe or without complication* or without risk*) adj3 (female* or patient* or maternal* or mother* or pregnan* or wom#n)).tw. (713152) 9 7 and 8 (110784) 10 Diagnostic Tests, Routine/ (70050) 11 ((routine* or mass or standard* or universal*) adj3 test*).tw. (106578) 12 exp Mass Screening/ (261779) 13 (screen* or detect*).tw. (4522336) 14 (early adj3 (identif* or recogni*)).tw. (74903) 15 or/10-14 (4787950) 16 7 and 15 (201360) 17 ((digital* or cervical* or cervix or vaginal* or funnel*) adj3 (assess* or exam*)).tw. (29673)

18	(Bishop* adj score*).tw. (2008)
19	or/17-18 (31426)
20	(9 or 16) and 19 (1541)
21	exp Obstetric Labor, Premature/ (49078)
22	((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw. (78832)
23	(PTL or sPTL or PTB or sPTB or PTD or sPTD).tw. (12512)
24	Uterine Contraction/ (16428)
25	((uterus* or uterine) adj3 contraction*).tw. (10267)
26	Cervical Ripening/ (2621)
27	((cervical or cervix*) adj3 (dilat* or ripen*)).tw. (10094)
28	exp Labor Onset/ (5049)
29	(preterm* or pre-term* or prematur* or pre-matur*).tw. (341316)
30	or/24-28 (34291)
31	29 and 30 (5395)
32	or/21-23,31 (102944)
33	20 and 32 (468)
34	exp Animals/ not (exp Animals/ and Humans/) (8787626)
35	33 not 34 (464)
36	(comment or editorial or interview or letter or news).pt. (2839289)
37	35 not 36 (463)
38	(controlled clinical trial or randomized controlled trial).pt. (470286)
39	clinical trials as topic.sh. (171983)
40	(randomi#ed or randomly or RCT$1 or placebo*).tw. (1462909)
41	((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (302907)
42	trial.ti. (302141)
43	or/38-42 (1875007)
44	37 and 43 (62)
45	controlled clinical trial.pt. (89643)
46	Controlled Clinical Trial/ or Controlled Clinical Trials as Topic/ (484149)
47	(control* adj2 trial*).tw. (335687)
48	(nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (75693)
49	(nRCT or nRCTs or non-RCT$1).tw. (692)
50	(control* adj3 ("before and after" or "before after")).tw. (6189)
51	time series.tw. (34871)
52	(pre- adj3 post-).tw. (114654)
53	(pretest adj3 posttest).tw. (6424)
54	(control* adj2 stud$3).tw. (355631)
55	Control Groups/ (78043)
56	(control$ adj2 group$1).tw. (771422)
57	or/45-56 (1902066)
58	37 and 57 (60)
59	exp Cohort Studies/ (1562789)

60 cohort$1.tw. (704482)
61 Retrospective Studies/ (863334)
62 (longitudinal or prospective or retrospective).tw. (1776045)
63 ((followup or follow-up) adj (study or studies)).tw. (90721)
64 Observational study.pt. (4108)
65 (observation$2 adj (study or studies)).tw. (116347)
66 ((population or population-based) adj (study or studies or analys#s)).tw. (26715)
67 ((multidimensional or multi-dimensional) adj (study or studies)).tw. (193)
68 Comparative Study.pt. (1698810)
69 ((comparative or comparison) adj (study or studies)).tw. (188823)
70 exp Case-Control Studies/ (769719)
71 ((case-control* or case-based or case-comparison) adj (study or studies)).tw. (146915)
72 or/59-71 (5057184)
73 37 and 72 (197)
74 44 or 58 (86)
75 74 use prmz (37)
76 exp pregnancy/ (1359787)
77 exp pregnancy disorder/ (459258)
78 pregnant woman/ (46789)
79 pregnan*.tw. (881640)
80 exp prenatal care/ (133850)
81 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (329344)
82 or/76-81 (1899446)
83 ((healthy or asymptomatic* or symptomless* or low risk* or lowrisk* or no risk* or norisk* or normal* or routine or standard or uncomplicated or safe or without complication* or without risk*) adj3 (female* or patient* or maternal* or mother* or pregnan* or wom#n)).tw. (713152)
84 82 and 83 (112735)
85 exp diagnostic test/ (766069)
86 ((routine* or mass or standard* or universal*) adj3 test*).tw. (106578)
87 mass screening/ (131338)
88 (screen* or detect*).tw. (4522336)
89 (early adj3 (identif* or recogni*)).tw. (74903)
90 or/85-89 (5334936)
91 82 and 90 (243113)
92 ((digital* or cervical* or cervix or vaginal* or funnel*) adj3 (assess* or exam*)).tw. (29673)
93 (Bishop* adj score*).tw. (2008)
94 or/92-93 (31426)
95 (84 or 91) and 94 (1766)
96 premature labor/ (42674)
97 ((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw. (78832)
98 (PTL or sPTL or PTB or sPTB or PTD or sPTD).tw. (12512)

99 uterus contraction/ (9417)
100 ((uterus* or uterine) adj3 contraction*).tw. (10267)
101 uterine cervix ripening/ (1831)
102 ((cervical or cervix*) adj3 (dilat* or ripen*)).tw. (10094)
103 labor onset/ (2555)
104 (preterm* or pre-term* or prematur* or pre-matur*).tw. (341316)
105 or/99-103 (27452)
106 104 and 105 (4732)
107 or/96-98,106 (101060)
108 95 and 107 (512)
109 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (37963623)
110 exp humans/ or exp human experimentation/ or exp human experiment/ (28879620)
111 109 not 110 (9085649)
112 108 not 111 (508)
113 (editorial or letter).pt. (2522851)
114 112 not 113 (508)
115 randomized controlled trial/ or controlled clinical trial/ (954880)
116 exp "clinical trial (topic)"/ (113144)
117 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1462909)
118 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (302907)
119 trial.ti. (302141)
120 or/115-119 (2013026)
121 114 and 120 (81)
122 controlled clinical trial/ (476254)
123 "controlled clinical trial (topic)"/ (3125)
124 (control* adj2 trial*).tw. (335687)
125 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (75693)
126 (nRCT or nRCTs or non-RCT$1).tw. (692)
127 (control* adj3 ("before and after" or "before after")).tw. (6189)
128 time series analysis/ (14323)
129 time series.tw. (34871)
130 pretest posttest control group design/ (205)
131 (pre- adj3 post-).tw. (114654)
132 (pretest adj3 posttest).tw. (6424)
133 controlled study/ (4398747)
134 (control* adj2 stud$3).tw. (355631)
135 control group/ (78043)
136 (control$ adj2 group$1).tw. (771422)
137 or/122-136 (5619500)
138 114 and 137 (118)
139 cohort analysis/ (347802)
140 cohort$1.tw. (704482)

141	retrospective study/ (863334)
142	longitudinal study/ (158348)
143	prospective study/ (636844)
144	(longitudinal or prospective or retrospective).tw. (1776045)
145	follow up/ (849155)
146	((followup or follow-up) adj (study or studies)).tw. (90721)
147	observational study/ (63594)
148	(observation$2 adj (study or studies)).tw. (116347)
149	population research/ (69823)
150	((population or population-based) adj (study or studies or analys#s)).tw. (26715)
151	((multidimensional or multi-dimensional) adj (study or studies)).tw. (193)
152	exp comparative study/ (2726779)
153	((comparative or comparison) adj (study or studies)).tw. (188823)
154	exp case control study/ (769719)
155	((case-control* or case-based or case-comparison) adj (study or studies)).tw. (146915)
156	or/139-155 (6311297)
157	114 and 156 (232)
158	121 or 138 (144)
159	158 use emczd (107)
160	75 or 159 (144)
161	limit 160 to yr="2009-current" (52)
162	remove duplicates from 161 (41)
163	162 use prmz (1)
164	162 use emczd (40)
165	73 use prmz (98) [MEDLINE OBSERVATIONAL STUDIES]
166	157 use emczd (138) [EMBASE OBSERVATIONAL STUDIES]
167	165 or 166 (236)
168	remove duplicates from 167 (169) [TOTAL UNIQUE HITS]
169	168 use prmz (97) [MEDLINE UNIQUE HITS]
170	168 use emczd (72) [EMBASE UNIQUE HITS]

Note

Table 37 – Search strategies: Benefits-harms of progesterone, cervical cerclage and reduced physical activity and in asymptomatic pregnant women with short cervix (SRs)

Database	Medline (OVID) & Embase
Date	01-09-2014
Search strategy	1 exp Pregnancy/ or exp Pregnancy Complications/ (1340644) 2 Pregnant Women/ (39737) 3 exp Pregnancy Trimesters/ (587144) 4 pregnan*.tw. (807561) 5 Prenatal Care/ (47209) 6 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (315452) 7 or/1-6 (1666041) 8 ((healthy or asymptomatic* or symptomless* or low risk* or lowrisk* or no risk* or norisk* or normal* or routine or standard or uncomplicated or safe or without complication* or without risk*) adj3 (female* or patient* or maternal* or mother* or pregnan* or wom#n)).tw. (672435) 9 7 and 8 (100700) 10 Uterine Cervical Incompetence/ (2380) 11 ((cervix* or cervical*) adj3 (incompeten* or insufficien* or short* or weak*)).tw,kw. (4645) 12 7 and (10 or 11) (4367) 13 9 or 12 (104556) 14 Cerclage, Cervical/ (1860) 15 cerclage*.tw,kw. (5105) 16 ((cervix* or cervical*) adj3 (stitch* or sutur*)).tw,kw. (503) 17 (McDonald adj3 (stitch* or sutur*)).tw,kw. (38) 18 (Shirodkar adj3 (stitch* or sutur*)).tw,kw. (51) 19 tracheloplast*.tw,kw. (7) 20 or/14-19 (5833) 21 13 and 20 (1875) 22 exp Progesterone/ (134175) 23 (progesterone* or pregnenedione*).tw,kw. (143655) 24 57-83-0.rn. (66031) 25 Progestins/ (30045) 26 (progestin* or progestogen* or progestagen* or progestational* or gestagen*).tw,kw. (40503) 27 (Hydroxyprogesteron* or 17-alpha-Hydroxyprogesteron* or 17-Hydroxyprogesteron* or BRN 2062088 or EINECS 200-699-4 or HSDB 3343 or Hidroxiprogesteron* or Idrossiprogesteron* or NSC 15468 or Oxiprogesteronum or Prodix or Prodox or Proluton or Setaderm or UNII-21807M87J2).tw,kw. (8483) 28 68-96-2.rn. (5939) 29 (Agolutin or Bio-luton or CCRIS 533 or Corlutin or Corlutina or Corluvite or Corporin or Corpus luteum hormone* or Crinone or Cyclogest or EINECS 200-350-6 or Endometrin or Flavolutan or Fologenon).tw,kw. (833) 30 (Gesterol or Gestone or Gestormone or Gestron or Glanducorpin or Gynlutin or Gynoluton or Gynolutone or HSDB 3389 or Hormoflaveine or Hormoluton).tw,kw. (124)

31 (Lingusorbs or Lipo-Lutin or Lucorteum or Luteal hormone* or Luteinique or Luteocrin normale or Luteodyn or Luteogan or Luteohormone or Luteol or Luteopur or Luteosan or Luteostab or Luteovis or Lutex or Lutidon or Lutin or Lutociclina or Lutocyclin or Lutocylin or Lutoform or Lutogyl or Lutren or Lutromone).tw,kw. (154)
32 (Membrettes or Methylpregnone or NSC 64377 or NSC 9704 or NSC-9704 or Nalutron or Percutacrine Luteinique or Piaponon or Primolut or Prochieve or Progekan or Progestasert or Progesterol or Progesterona or Progesteronum or Progestone or Progestosol or Progestron or Progestronol or Projestaject or Prolets or Prolidon or Proluton or Prolutone or Prometrium or Protormone or Syngesterone or Syngestrets or Synovex or Syntolutan or UNII-4G7DS2Q64Y or Utrogestan).tw,kw. (1825)
33 Dydrogesterone/ (1821)
34 ("6-Dehydro-9 beta-10 alpha-progesterone" or "10alpha-Isopregnenone" or CCRIS 9069 or Dydrogesteron* or Didrogesterone or Dehydrogesterone or Diphaston or Duphaston or Duvaron or EINECS 205-806-8).tw,kw. (1211)
35 (Gestatron or Gynorest or HSDB 3321 or Hydrogesterone or Hydrogestrone or Isopregnenone or NSC 92336 or Prodel or Retro-6-dehydroprogesterone or Retrone or Terolut or UNII-90I02KLE8K).tw,kw. (19)
36 152-62-5.rn. (1363)
37 17-Hydroxyprogesterone capro*.tw,kw. (117)
38 (17 alpha-hydroxyprogesterone capro* or 17-alpha-hydroxy-progesterone capro* or hydroxyprogesterone capro* or hydroxyprogesterone hexanoate).tw,kw. (805)
39 (17OHP or Delalutin or Makena or Neolutin or oxyprogesterone caproate or Prolutin or Proluton).tw,kw. (799)
40 Medroxyprogesterone Acetate.tw,kw. (9980)
41 (AI3-60127 or Amen or Aragest or BRN 2066112 or CCRIS 371 or Clinofem or Clinovir or Curretab or Cycrin or Cykrina or DMPA or (Depo* adj Medroxyprogesterone Acetate) or Depo-Provera or DP150 or Depcorlutin or Depo-Clinovir or Depo-Map).tw,kw. (5141)
42 (Depo-Prodasone or Depo-Progevera or Depo-Promone or Depo-Provera or Depo-Ralovera or Depo-progestin or Depo-subQ provera or Depocon or Deporone or Dugan or EINECS 200-757-9 or Farlutal or Farlutin or Gestapuran or Hysron or Indivina or Lutopolar or Lutoral).tw,kw. (2953)
43 (MPA GYM or MPA Hexal or MPA-Noury or MPA-beta or Med-Pro or Medrosterona or Medroxyprogesterone 17-acetate or Mepastat or Meprate or Methylacetoxyprogesterone or Metigestrona or NSC 21171 or NSC-26386 or Nadigest or Nidaxin or Oragest or Medroxyacetate progesterone or Medroxyprogesterone 17-Acetate).tw,kw. (97)
44 (Perlutex or Prodasone or Progestalfa or Progeston or Progevera or Promone-E or Provera or Proverone or Ralovera or Repromap or Repromix or Sirprogen or Sumiferm or Supprestral or Suprestral or U 8839 or UNII-C2QI4IOI2G or Veramix or Veraplex).tw,kw. (3837)
45 71-58-9.rn. (13521)
46 Allylestrenol/ (346)
47 (Allylestrenol* or Allyloestrenol* or Alilestrenol* or BRN 3148038 or CCRIS 9068 or EINECS 207-082-9 or Gestanin or Gestanol or Gestanon or Gestanyn or NSC 37723 or Orageston or Organon or Turinal or UNII-I47VB5DZ8O).tw,kw. (7096)
48 432-60-0.rn. (236)
49 Chlormadinone Acetate/ (3471)
50 (Ay 13390-6 or Bovisynchron or C-Quens or CCRIS 129 or Chlormadinon* or Cero or Chlordion or Clordion or EINECS 206-118-0 or Fertiletten or Gestafortin or HSDB 3591 or ICI 39575 or Lormin or Lutestral or Luteran or Lutinyl or Lutoral or Matrol or Menstridyl or Minipill or Neo-Eunomin or NSC 92338 or NSC-92338 or Normenon or RS 1280 or Retex or STG 155 or Skedule or Synchrosyn or Traslan or UNII-0SY050L61N or Verton).tw,kw. (2052)
51 302-22-7.rn. (2051)
52 or/22-51 (254866)
53 13 and 52 (5014)

54 Bed Rest/ (9389)
55 bedrest*.tw. (1782)
56 (rest* adj5 bed).tw. (10290)
57 (confin* adj5 bed).tw. (1167)
58 (rest* adj2 (antenatal* or ante natal* or antepartum or ante partum or prenatal* or pregnanc*)).tw. (2209)
59 ((confin* or limit* or reduc* or restrict*) adj5 activit*).tw. (286368)
60 "ABR/AR".tw. (2)
61 or/54-60 (305041)
62 13 and 61 (1303)
63 21 or 53 or 62 (7855)
64 exp Animals/ not (exp Animals/ and Humans/) (8001129)
65 63 not 64 (6951)
66 (comment or editorial or interview or letter or news).pt. (2833089)
67 65 not 66 (6882)
68 limit 67 to systematic reviews [Limit not valid in Embase; records were retained] (3668)
69 meta analysis.pt. (51142)
70 exp meta-analysis as topic/ (28940)
71 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw. (157132)
72 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (189289)
73 exp Technology assessment, biomedical/ (20660)
74 (cochrane or health technology assessment or evidence report).jw. (25443)
75 or/69-74 (356525)
76 67 and 75 (171)
77 68 or 76 (3686)
78 limit 77 to yr="2011-current" (993)
79 78 use prmz (40)
80 exp pregnancy/ (1275254)
81 exp pregnancy disorder/ (404533)
82 pregnant woman/ (39737)
83 pregnan*.tw. (807561)
84 exp prenatal care/ (127132)
85 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (315452)
86 or/80-85 (1767605)
87 ((healthy or asymptomatic* or symptomless* or low risk* or lowrisk* or no risk* or norisk* or normal* or routine or standard or uncomplicated or safe or without complication* or without risk*) adj3 (female* or patient* or maternal* or mother* or pregnan* or wom#n)).tw. (672435)
88 86 and 87 (102345)
89 uterine cervix incompetence/ (1214)
90 ((cervix* or cervical*) adj3 (incompeten* or insufficien* or short* or weak*)).tw,kw. (4645)

91 86 and (89 or 90) (4074)
92 88 or 91 (105910)
93 uterine cervix cerclage/ (1860)
94 cerclage*.tw,kw. (5105)
95 ((cervix* or cervical*) adj3 (stitch* or sutur*)).tw,kw. (503)
96 (McDonald adj3 (stitch* or sutur*)).tw,kw. (38)
97 (Shirodkar adj3 (stitch* or sutur*)).tw,kw. (51)
98 tracheloplast*.tw,kw. (7)
99 or/93-98 (5833)
100 92 and 99 (1686)
101 progesterone/ (122740)
102 (progesterone* or pregnenedione*).tw,kw. (143655)
103 57-83-0.rn. (66031)
104 exp gestagen/ (135742)
105 (progestin* or progestogen* or progestagen* or progestational* or gestagen*).tw,kw. (40503)
106 (Hydroxyprogesteron* or 17-alpha-Hydroxyprogesteron* or 17-Hydroxyprogesteron* or BRN 2062088 or EINECS 200-699-4 or HSDB 3343 or Hidroxiprogesteron* or Idrossiprogesteron* or NSC 15468 or Oxiprogesteronum or Prodix or Prodox or Proluton or Setaderm or UNII-21807M87J2).tw,kw. (8483)
107 68-96-2.rn. (5939)
108 (Agolutin or Bio-luton or CCRIS 533 or Corlutin or Corlutina or Corluvite or Corporin or Corpus luteum hormone* or Crinone or Cyclogest or EINECS 200-350-6 or Endometrin or Flavolutan or Fologenon).tw,kw. (833)
109 (Gesterol or Gestone or Gestormone or Gestron or Glanducorpin or Gynlutin or Gynoluton or Gynolutone or HSDB 3389 or Hormoflaveine or Hormoluton).tw,kw. (124)
110 (Lingusorbs or Lipo-Lutin or Lucorteum or Luteal hormone* or Luteinique or Luteocrin normale or Luteodyn or Luteogan or Luteohormone or Luteol or Luteopur or Luteosan or Luteostab or Luteovis or Lutex or Lutidon or Lutin or Lutociclina or Lutocyclin or Lutocylin or Lutoform or Lutogyl or Lutren or Lutromone).tw,kw. (154)
111 (Membrettes or Methylpregnone or NSC 64377 or NSC 9704 or NSC-9704 or Nalutron or Percutacrine Luteinique or Piaponon or Primolut or Prochieve or Progekan or Progestasert or Progesterol or Progesterona or Progesteronum or Progestone or Progestosol or Progestron or Progestronol or Projestaject or Prolets or Prolidon or Proluton or Prolutone or Prometrium or Protormone or Syngesterone or Syngestrets or Synovex or Syntolutan or UNII-4G7DS2Q64Y or Utrogestan).tw,kw. (1825)
112 ("6-Dehydro-9 beta-10 alpha-progesterone" or "10alpha-Isopregnenone" or CCRIS 9069 or Dydrogesteron* or Didrogesterone or Dehydrogesterone or Diphaston or Duphaston or Duvaron or EINECS 205-806-8).tw,kw. (1211)
113 (Gestatron or Gynorest or HSDB 3321 or Hydrogesterone or Hydrogestrone or Isopregnenone or NSC 92336 or Prodel or Retro-6-dehydroprogesterone or Retrone or Terolut or UNII-90I02KLE8K).tw,kw. (19)
114 152-62-5.rn. (1363)
115 17-Hydroxyprogesterone capro*.tw,kw. (117)
116 (17 alpha-hydroxyprogesterone capro* or 17-alpha-hydroxy-progesterone capro* or hydroxyprogesterone capro* or hydroxyprogesterone hexanoate).tw,kw. (805)
117 (17OHP or Delalutin or Makena or Neolutin or oxyprogesterone caproate or Prolutin or Proluton).tw,kw. (799)
118 Medroxyprogesterone Acetate.tw,kw. (9980)

119 (AI3-60127 or Amen or Aragest or BRN 2066112 or CCRIS 371 or Clinofem or Clinovir or Curretab or Cycrin or Cykrina or DMPA or (Depo* adj Medroxyprogesterone Acetate) or Depo-Provera or DP150 or Depcorlutin or Depo-Clinovir or Depo-Map).tw,kw. (5141)
120 (Depo-Prodasone or Depo-Progevera or Depo-Promone or Depo-Provera or Depo-Ralovera or Depo-progestin or Depo-subQ provera or Depocon or Deporone or Dugan or EINECS 200-757-9 or Farlutal or Farlutin or Gestapuran or Hysron or Indivina or Lutopolar or Lutoral).tw,kw. (2953)
121 (MPA GYM or MPA Hexal or MPA-Noury or MPA-beta or Med-Pro or Medrosterona or Medroxyprogesterone 17-acetate or Mepastat or Meprate or Methylacetoxyprogesterone or Metigestrona or NSC 21171 or NSC-26386 or Nadigest or Nidaxin or Oragest or Medroxyacetate progesterone or Medroxyprogesterone 17-Acetate).tw,kw. (97)
122 (Perlutex or Prodasone or Progestalfa or Progeston or Progevera or Promone-E or Provera or Proverone or Ralovera or Repromap or Repromix or Sirprogen or Sumiferm or Supprestral or Suprestral or U 8839 or UNII-C2QI4IOI2G or Veramix or Veraplex).tw,kw. (3837)
123 71-58-9.rn. (13521)
124 (Allylestrenol* or Allyloestrenol* or Alilestrenol* or BRN 3148038 or CCRIS 9068 or EINECS 207-082-9 or Gestanin or Gestanol or Gestanon or Gestanyn or NSC 37723 or Orageston or Organon or Turinal or UNII-I47VB5DZ8O).tw,kw. (7096)
125 432-60-0.rn. (236)
126 (Ay 13390-6 or Bovisynchron or C-Quens or CCRIS 129 or Chlormadinon* or Cero or Chlordion or Clordion or EINECS 206-118-0 or Fertiletten or Gestafortin or HSDB 3591 or ICI 39575 or Lormin or Lutestral or Luteran or Lutinyl or Lutoral or Matrol or Menstridyl or Minipill or Neo-Eunomin or NSC 92338 or NSC-92338 or Normenon or RS 1280 or Retex or STG 155 or Skedule or Synchrosyn or Traslan or UNII-0SY050L61N or Verton).tw,kw. (2052)
127 302-22-7.rn. (2051)
128 or/101-127 (276379)
129 92 and 128 (5250)
130 bed rest/ (9389)
131 bedrest*.tw. (1782)
132 (rest* adj5 bed).tw. (10290)
133 (confin* adj5 bed).tw. (1167)
134 (rest* adj2 (antenatal* or ante natal* or antepartum or ante partum or prenatal* or pregnanc*)).tw. (2209)
135 ((confin* or limit* or reduc* or restrict*) adj5 activit*).tw. (286368)
136 "ABR/AR".tw. (2)
137 or/130-136 (305041)
138 92 and 137 (1317)
139 100 or 129 or 138 (7906)
140 meta-analysis/ or "systematic review"/ or "meta analysis (topic)"/ or biomedical technology assessment/ (211918)
141 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw. (157132)
142 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (189289)
143 (health technology assessment or health technology assessment reports or health technology assessment winchester england).jn. (1832)
144 (evidence report technology assessment or evidence report technology assessment summary).jn. (442)
145 "cochrane database of systematic reviews".jn. (15072)
146 ("cochrane database of systematic reviews" or "cochrane database of systematic reviews online").jn. (21944)
147 or/140-146 (389879)

	148 139 and 147 (208) 149 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (37057646) 150 exp humans/ or exp human experimentation/ or exp human experiment/ (28653096) 151 149 not 150 (8406125) 152 148 not 151 (208) 153 (editorial or letter).pt. (2515875) 154 152 not 153 (206) 155 154 use emez (135) 156 limit 155 to yr="2011-current" (60) 157 79 or 156 (100) 158 remove duplicates from 157 (72) [TOTAL UNIQUE RECORDS] 159 158 use prmz (34) [MEDLINE UNIQUE RECORDS] 160 158 use emez (38) [EMBASE UNIQUE RECORDS]
Note	
Database	**The Cochrane library**
Date	01-09-2014
Search strategy	ID Search Hits #1 [mh Pregnancy] or [mh "Pregnancy Complications"] 11132 #2 [mh "Pregnant Women"] 96 #3 [mh "Pregnancy Trimesters"] 1469 #4 pregnan*:ti,ab,kw 25357 #5 [mh "Prenatal Care"] 1059 #6 (prenatal* or antenatal* or (ante next natal*) or antepartum or (ante next partum) or perinatal* or (peri next natal*) or peripartum or (peri next partum)):ti,ab,kw 6080 #7 {or #1-#6} 27565 #8 ((healthy or asymptomatic* or symptomless* or (low next risk*) or lowrisk* or (no next risk*) or norisk* or normal* or routine or standard or uncomplicated or safe or (without next complication*) or (without next risk*)) near/3 (female* or patient* or maternal* or mother* or pregnan* or woman* or women*)):ti,ab,kw 29073 #9 #7 and #8 2599 #10 [mh "Uterine Cervical Incompetence"] 58 #11 ((cervix* or cervical*) near/3 (incompeten* or insufficien* or short* or weak*)):ti,ab,kw 185 #12 #7 and (#10 or #11) 143 #13 #9 or #12 2723 #14 [mh "Cerclage, Cervical"] 54 #15 cerclage*:ti,ab,kw 151 #16 (McDonald near/4 (stitch* or sutur*)):ti,ab,kw 2 #17 (Shirodkar near/4 (stitch* or sutur*)):ti,ab,kw 2 #18 tracheloplast*:ti,ab,kw 0 #19 2-#18 151 #20 #13 and #19 70

#21 [mh Progesterone] 2333
#22 (progesterone* or pregnenedione*):ti,ab,kw 4271
#23 [mh Progestins] 397
#24 (progestin* or progestogen* or progestagen* or progestational* or gestagen*):ti,ab,kw 2128
#25 (Hydroxyprogesteron* or 17-alpha-Hydroxyprogesteron* or 17-Hydroxyprogesteron* or "BRN 2062088" or "EINECS 200-699-4" or "HSDB 3343" or Hidroxiprogesteron* or Idrossiprogesteron* or "NSC 15468" or Oxiprogesteronum or Prodix or Prodox or Proluton or Setaderm or "UNII-21807M87J2"):ti,ab,kw 265
#26 (Agolutin or "Bio-luton" or "CCRIS 533" or Corlutin or Corlutina or Corluvite or Corporin or ("Corpus luteum" next hormone*) or Crinone or Cyclogest or "EINECS 200-350-6" or Endometrin or Flavolutan or Fologenon):ti,ab,kw 54
#27 (Gesterol or Gestone or Gestormone or Gestron or Glanducorpin or Gynlutin or Gynoluton or Gynolutone or "HSDB 3389" or Hormoflaveine or Hormoluton):ti,ab,kw 1
#28 (Lingusorbs or "Lipo-Lutin" or Lucorteum or (Luteal next hormone*) or Luteinique or "Luteocrin normale" or Luteodyn or Luteogan or Luteohormone or Luteol or Luteopur or Luteosan or Luteostab or Luteovis or Lutex or Lutidon or Lutin or Lutociclina or Lutocyclin or Lutocylin or Lutoform or Lutogyl or Lutren or Lutromone):ti,ab,kw 3
#29 (Membrettes or Methylpregnone or "NSC 64377" or "NSC 9704" or "NSC-9704" or Nalutron or (Percutacrine next Luteinique) or Piaponon or Primolut or Prochieve or Progekan or Progestasert or Progesterol or Progesterona or Progesteronum or Progestone or Progestosol or Progestron or Progestronol or Projestaject or Prolets or Prolidon or Proluton or Prolutone or Prometrium or Protormone or Syngesterone or Syngestrets or Synovex or Syntolutan or "UNII-4G7DS2Q64Y" or Utrogestan):ti,ab,kw 49
#30 [mh Dydrogesterone] 120
#31 ("6-Dehydro-9 beta-10 alpha-progesterone" or "10alpha-Isopregnenone" or "CCRIS 9069" or Dydrogesteron* or Didrogesterone or Dehydrogesterone or Diphaston or Duphaston or Duvaron or "EINECS 205-806-8"):ti,ab,kw 184
#32 (Gestatron or Gynorest or "HSDB 3321" or Hydrogesterone or Hydrogestrone or Isopregnenone or "NSC 92336" or Prodel or Retro-6-dehydroprogesterone or Retrone or Terolut or "UNII-90I02KLE8K"):ti,ab,kw 1
#33 (17 next Hydroxyprogesterone next capro*):ti,ab,kw 9
#34 ("17 alpha-hydroxyprogesterone" next capro*) or ("17-alpha-hydroxy-progesterone" next capro*) or (hydroxyprogesterone next capro*) or "hydroxyprogesterone hexanoate":ti,ab,kw 111
#35 (17OHP or Delalutin or Makena or Neolutin or "oxyprogesterone caproate" or Prolutin or Proluton):ti,ab,kw 18
#36 "Medroxyprogesterone Acetate":ti,ab,kw 1434
#37 ("AI3-60127" or Amen or Aragest or "BRN 2066112" or "CCRIS 371" or Clinofem or Clinovir or Curretab or Cycrin or Cykrina or DMPA or (Depo* next "Medroxyprogesterone Acetate") or "Depo-Provera" or DP150 or Depcorlutin or "Depo-Clinovir" or "Depo-Map"):ti,ab,kw 178
#38 ("Depo-Prodasone" or "Depo-Progevera" or "Depo-Promone" or "Depo-Provera" or "Depo-Ralovera" or "Depo-progestin" or "Depo-subQ provera" or Depocon or Deporone or Dugan or "EINECS 200-757-9" or Farlutal or Farlutin or Gestapuran or Hysron or Indivina or Lutopolar or Lutoral):ti,ab,kw 42
#39 ("MPA GYM" or "MPA Hexal" or "MPA-Noury" or "MPA-beta" or "Med-Pro" or Medrosterona or "Medroxyprogesterone 17-acetate" or Mepastat or Meprate or Methylacetoxyprogesterone or Metigestrona or "NSC 21171" or "NSC-26386" or Nadigest or Nidaxin or Oragest or "Medroxyacetate progesterone" or "Medroxyprogesterone 17-Acetate"):ti,ab,kw 19
#40 (Perlutex or Prodasone or Progestalfa or Progeston or Progevera or "Promone-E" or Provera or Proverone or Ralovera or Repromap or Repromix or Sirprogen or Sumiferm or Supprestral or Suprestral or "U 8839" or "UNII-C2QI4IOI2G" or Veramix or Veraplex):ti,ab,kw 75
#41 [mh Allylestrenol] 10
#42 (Allylestrenol* or Allyloestrenol* or Alilestrenol* or "BRN 3148038" or "CCRIS 9068" or "EINECS 207-082-9" or Gestanin or Gestanol or Gestanon or Gestanyn or "NSC 37723" or Orageston or Organon or Turinal or "UNII-I47VB5DZ8O"):ti,ab,kw 112

	#43 [mh "Chlormadinone Acetate"] 81 #44 ("Ay 13390-6" or Bovisynchron or "C-Quens" or "CCRIS 129" or Chlormadinon* or Cero or Chlordion or Clordion or "EINECS 206-118-0" or Fertiletten or Gestafortin or "HSDB 3591" or "ICI 39575" or Lormin or Lutestral or Luteran or Lutinyl or Lutoral or Matrol or Menstridyl or Minipill or Neo-Eunomin or "NSC 92338" or "NSC-92338" or Normenon or "RS 1280" or Retex or "STG 155" or Skedule or Synchrosyn or Traslan or "UNII-0SY050L61N" or Verton):ti,ab,kw 120 #45 {or #21-#44} 7187 #46 #13 and #45 177 #47 [mh "Bed Rest"] 390 #48 bedrest*:ti,ab,kw 93 #49 (rest* near/5 bed):ti,ab,kw 846 #50 (confin* near/5 bed):ti,ab,kw 48 #51 (rest* near/2 (antenatal* or (ante next natal*) or antepartum or "ante partum" or prenatal* or pregnanc*)):ti,ab,kw 81 #52 ((confin* or limit* or reduc* or restrict*) near/5 activit*):ti,ab,kw 4407 #53 "ABR/AR":ti,ab,kw 0 #54 4-#53 5339 #55 #13 and #54 50 #56 #20 or #46 or #55 Publication Year from 2011 to 2014, in Cochrane Reviews (Reviews and Protocols), Other Reviews and Technology Assessments 19 DSR – 15 DARE – 4 HTA - 0
Note	

Table 38 – Search strategies: Benefits-harms of progesterone in asymptomatic pregnant women with short cervix (Primary RCTs)

Database	Medline (OVID) & Embase
Date	17-09-2014
Search strategy	1 exp Pregnancy/ or exp Pregnancy Complications/ (1347093) 2 Pregnant Women/ (40049) 3 exp Pregnancy Trimesters/ (588827) 4 pregnan*.tw. (811808) 5 Prenatal Care/ (47377) 6 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (316945) 7 or/1-6 (1674064) 8 ((healthy or asymptomatic* or symptomless* or low risk* or lowrisk* or no risk* or norisk* or normal* or routine or standard or uncomplicated or safe or without complication* or without risk*) adj3 (female* or patient* or maternal* or mother* or pregnan* or wom#n)).tw. (675930) 9 7 and 8 (101160) 10 Uterine Cervical Incompetence/ (2387) 11 ((cervix* or cervical*) adj3 (incompeten* or insufficien* or short* or weak*)).tw,kw. (4686) 12 7 and (10 or 11) (4398) 13 9 or 12 (105045)

14 exp Progesterone/ (134427)
15 (progesterone* or pregnenedione*).tw,kw. (144118)
16 57-83-0.rn. (66139)
17 Progestins/ (30116)
18 (progestin* or progestogen* or progestagen* or progestational* or gestagen*).tw,kw. (40574)
19 (Hydroxyprogesteron* or 17-alpha-Hydroxyprogesteron* or 17-Hydroxyprogesteron* or BRN 2062088 or EINECS 200-699-4 or HSDB 3343 or Hidroxiprogesteron* or Idrossiprogesteron* or NSC 15468 or Oxiprogesteronum or Prodix or Prodox or Proluton or Setaderm or UNII-21807M87J2).tw,kw. (8497)
20 68-96-2.rn. (5948)
21 (Agolutin or Bio-luton or CCRIS 533 or Corlutin or Corlutina or Corluvite or Corporin or Corpus luteum hormone* or Crinone or Cyclogest or EINECS 200-350-6 or Endometrin or Flavolutan or Fologenon).tw,kw. (838)
22 (Gesterol or Gestone or Gestormone or Gestron or Glanducorpin or Gynlutin or Gynoluton or Gynolutone or HSDB 3389 or Hormoflaveine or Hormoluton).tw,kw. (124)
23 (Lingusorbs or Lipo-Lutin or Lucorteum or Luteal hormone* or Luteinique or Luteocrin normale or Luteodyn or Luteogan or Luteohormone or Luteol or Luteopur or Luteosan or Luteostab or Luteovis or Lutex or Lutidon or Lutin or Lutociclina or Lutocyclin or Lutocylin or Lutoform or Lutogyl or Lutren or Lutromone).tw,kw. (155)
24 (Membrettes or Methylpregnone or NSC 64377 or NSC 9704 or NSC-9704 or Nalutron or Percutacrine Luteinique or Piaponon or Primolut or Prochieve or Progekan or Progestasert or Progesterol or Progesterona or Progesteronum or Progestone or Progestosol or Progestron or Progestronol or Projestaject or Prolets or Prolidon or Proluton or Prolutone or Prometrium or Protormone or Syngesterone or Syngestrets or Synovex or Syntolutan or UNII-4G7DS2Q64Y or Utrogestan).tw,kw. (1826)
25 Dydrogesterone/ (1822)
26 ("6-Dehydro-9 beta-10 alpha-progesterone" or "10alpha-Isopregnenone" or CCRIS 9069 or Dydrogesteron* or Didrogesterone or Dehydrogesterone or Diphaston or Duphaston or Duvaron or EINECS 205-806-8).tw,kw. (1213)
27 (Gestatron or Gynorest or HSDB 3321 or Hydrogesterone or Hydrogestrone or Isopregnenone or NSC 92336 or Prodel or Retro-6-dehydroprogesterone or Retrone or Terolut or UNII-90I02KLE8K).tw,kw. (19)
28 152-62-5.rn. (1364)
29 17-Hydroxyprogesterone capro*.tw,kw. (117)
30 (17 alpha-hydroxyprogesterone capro* or 17-alpha-hydroxy-progesterone capro* or hydroxyprogesterone capro* or hydroxyprogesterone hexanoate).tw,kw. (808)
31 (17OHP or Delalutin or Makena or Neolutin or oxyprogesterone caproate or Prolutin or Proluton).tw,kw. (800)
32 Medroxyprogesterone Acetate.tw,kw. (9999)
33 (AI3-60127 or Amen or Aragest or BRN 2066112 or CCRIS 371 or Clinofem or Clinovir or Curretab or Cycrin or Cykrina or DMPA or (Depo* adj Medroxyprogesterone Acetate) or Depo-Provera or DP150 or Depcorlutin or Depo-Clinovir or Depo-Map).tw,kw. (5157)
34 (Depo-Prodasone or Depo-Progevera or Depo-Promone or Depo-Provera or Depo-Ralovera or Depo-progestin or Depo-subQ provera or Depocon or Deporone or Dugan or EINECS 200-757-9 or Farlutal or Farlutin or Gestapuran or Hysron or Indivina or Lutopolar or Lutoral).tw,kw. (2959)
35 (MPA GYM or MPA Hexal or MPA-Noury or MPA-beta or Med-Pro or Medrosterona or Medroxyprogesterone 17-acetate or Mepastat or Meprate or Methylacetoxyprogesterone or Metigestrona or NSC 21171 or NSC-26386 or Nadigest or Nidaxin or Oragest or Medroxyacetate progesterone or Medroxyprogesterone 17-Acetate).tw,kw. (98)
36 (Perlutex or Prodasone or Progestalfa or Progeston or Progevera or Promone-E or Provera or Proverone or Ralovera or Repromap or Repromix or Sirprogen or Sumiferm or Supprestral or Suprestral or U 8839 or UNII-C2QI4IOI2G or Veramix or Veraplex).tw,kw. (3845)
37 71-58-9.rn. (13543)

38 Allylestrenol/ (346)
39 (Allylestrenol* or Allyloestrenol* or Alilestrenol* or BRN 3148038 or CCRIS 9068 or EINECS 207-082-9 or Gestanin or Gestanol or Gestanon or Gestanyn or NSC 37723 or Orageston or Organon or Turinal or UNII-I47VB5DZ8O).tw,kw. (7100)
40 432-60-0.rn. (236)
41 Chlormadinone Acetate/ (3473)
42 (Ay 13390-6 or Bovisynchron or C-Quens or CCRIS 129 or Chlormadinon* or Cero or Chlordion or Clordion or EINECS 206-118-0 or Fertiletten or Gestafortin or HSDB 3591 or ICI 39575 or Lormin or Lutestral or Luteran or Lutinyl or Lutoral or Matrol or Menstridyl or Minipill or Neo-Eunomin or NSC 92338 or NSC-92338 or Normenon or RS 1280 or Retex or STG 155 or Skedule or Synchrosyn or Traslan or UNII-0SY050L61N or Verton).tw,kw. (2053)
43 302-22-7.rn. (2053)
44 or/14-43 (255521)
45 13 and 44 (5031)
46 (controlled clinical trial or randomized controlled trial).pt. (473266)
47 clinical trials as topic.sh. (173008)
48 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1456820)
49 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (294260)
50 trial.ti. (296203)
51 or/46-50 (1859343)
52 45 and 51 (494)
53 exp Animals/ not (exp Animals/ and Humans/) (8021168)
54 52 not 53 (468)
55 (comment or editorial or interview or letter or news).pt. (2846125)
56 54 not 55 (467)
57 56 use prmz (218)
58 exp pregnancy/ (1280125)
59 exp pregnancy disorder/ (405956)
60 pregnant woman/ (40049)
61 pregnan*.tw. (811808)
62 exp prenatal care/ (127520)
63 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (316945)
64 or/58-63 (1775262)
65 ((healthy or asymptomatic* or symptomless* or low risk* or lowrisk* or no risk* or norisk* or normal* or routine or standard or uncomplicated or safe or without complication* or without risk*) adj3 (female* or patient* or maternal* or mother* or pregnan* or wom#n)).tw. (675930)
66 64 and 65 (102812)
67 uterine cervix incompetence/ (1218)
68 ((cervix* or cervical*) adj3 (incompeten* or insufficien* or short* or weak*)).tw,kw. (4686)
69 64 and (67 or 68) (4097)
70 66 or 69 (106398)
71 progesterone/ (122972)
72 (progesterone* or pregnenedione*).tw,kw. (144118)

73 57-83-0.rn. (66139)
74 exp gestagen/ (135975)
75 (progestin* or progestogen* or progestagen* or progestational* or gestagen*).tw,kw. (40574)
76 (Hydroxyprogesteron* or 17-alpha-Hydroxyprogesteron* or 17-Hydroxyprogesteron* or BRN 2062088 or EINECS 200-699-4 or HSDB 3343 or Hidroxiprogesteron* or Idrossiprogesteron* or NSC 15468 or Oxiprogesteronum or Prodix or Prodox or Proluton or Setaderm or UNII-21807M87J2).tw,kw. (8497)
77 68-96-2.rn. (5948)
78 (Agolutin or Bio-luton or CCRIS 533 or Corlutin or Corlutina or Corluvite or Corporin or Corpus luteum hormone* or Crinone or Cyclogest or EINECS 200-350-6 or Endometrin or Flavolutan or Fologenon).tw,kw. (838)
79 (Gesterol or Gestone or Gestormone or Gestron or Glanducorpin or Gynlutin or Gynoluton or Gynolutone or HSDB 3389 or Hormoflaveine or Hormoluton).tw,kw. (124)
80 (Lingusorbs or Lipo-Lutin or Lucorteum or Luteal hormone* or Luteinique or Luteocrin normale or Luteodyn or Luteogan or Luteohormone or Luteol or Luteopur or Luteosan or Luteostab or Luteovis or Lutex or Lutidon or Lutin or Lutociclina or Lutocyclin or Lutocylin or Lutoform or Lutogyl or Lutren or Lutromone).tw,kw. (155)
81 (Membrettes or Methylpregnone or NSC 64377 or NSC 9704 or NSC-9704 or Nalutron or Percutacrine Luteinique or Piaponon or Primolut or Prochieve or Progekan or Progestasert or Progesterol or Progesterona or Progesteronum or Progestone or Progestosol or Progestron or Progestronol or Projestaject or Prolets or Prolidon or Proluton or Prolutone or Prometrium or Protormone or Syngesterone or Syngestrets or Synovex or Syntolutan or UNII-4G7DS2Q64Y or Utrogestan).tw,kw. (1826)
82 ("6-Dehydro-9 beta-10 alpha-progesterone" or "10alpha-Isopregnenone" or CCRIS 9069 or Dydrogesteron* or Didrogesterone or Dehydrogesterone or Diphaston or Duphaston or Duvaron or EINECS 205-806-8).tw,kw. (1213)
83 (Gestatron or Gynorest or HSDB 3321 or Hydrogesterone or Hydrogestrone or Isopregnenone or NSC 92336 or Prodel or Retro-6-dehydroprogesterone or Retrone or Terolut or UNII-90I02KLE8K).tw,kw. (19)
84 152-62-5.rn. (1364)
85 17-Hydroxyprogesterone capro*.tw,kw. (117)
86 (17 alpha-hydroxyprogesterone capro* or 17-alpha-hydroxy-progesterone capro* or hydroxyprogesterone capro* or hydroxyprogesterone hexanoate).tw,kw. (808)
87 (17OHP or Delalutin or Makena or Neolutin or oxyprogesterone caproate or Prolutin or Proluton).tw,kw. (800)
88 Medroxyprogesterone Acetate.tw,kw. (9999)
89 (AI3-60127 or Amen or Aragest or BRN 2066112 or CCRIS 371 or Clinofem or Clinovir or Curretab or Cycrin or Cykrina or DMPA or (Depo* adj Medroxyprogesterone Acetate) or Depo-Provera or DP150 or Depcorlutin or Depo-Clinovir or Depo-Map).tw,kw. (5157)
90 (Depo-Prodasone or Depo-Progevera or Depo-Promone or Depo-Provera or Depo-Ralovera or Depo-progestin or Depo-subQ provera or Depocon or Deporone or Dugan or EINECS 200-757-9 or Farlutal or Farlutin or Gestapuran or Hysron or Indivina or Lutopolar or Lutoral).tw,kw. (2959)
91 (MPA GYM or MPA Hexal or MPA-Noury or MPA-beta or Med-Pro or Medrosterona or Medroxyprogesterone 17-acetate or Mepastat or Meprate or Methylacetoxyprogesterone or Metigestrona or NSC 21171 or NSC-26386 or Nadigest or Nidaxin or Oragest or Medroxyacetate progesterone or Medroxyprogesterone 17-Acetate).tw,kw. (98)
92 (Perlutex or Prodasone or Progestalfa or Progeston or Progevera or Promone-E or Provera or Proverone or Ralovera or Repromap or Repromix or Sirprogen or Sumiferm or Supprestral or Suprestral or U 8839 or UNII-C2QI4IOI2G or Veramix or Veraplex).tw,kw. (3845)
93 71-58-9.rn. (13543)
94 (Allylestrenol* or Allyloestrenol* or Alilestrenol* or BRN 3148038 or CCRIS 9068 or EINECS 207-082-9 or Gestanin or Gestanol or Gestanon or Gestanyn or NSC 37723 or Orageston or Organon or Turinal or UNII-I47VB5DZ8O).tw,kw. (7100)
95 432-60-0.rn. (236)

	96 (Ay 13390-6 or Bovisynchron or C-Quens or CCRIS 129 or Chlormadinon* or Cero or Chlordion or Clordion or EINECS 206-118-0 or Fertiletten or Gestafortin or HSDB 3591 or ICI 39575 or Lormin or Lutestral or Luteran or Lutinyl or Lutoral or Matrol or Menstridyl or Minipill or Neo-Eunomin or NSC 92338 or NSC-92338 or Normenon or RS 1280 or Retex or STG 155 or Skedule or Synchrosyn or Traslan or UNII-0SY050L61N or Verton).tw,kw. (2053) 97 302-22-7.rn. (2053) 98 or/71-97 (277051) 99 70 and 98 (5268) 100 randomized controlled trial/ or controlled clinical trial/ (957312) 101 exp "clinical trial (topic)"/ (116087) 102 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1456820) 103 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (294260) 104 trial.ti. (296203) 105 or/100-104 (1998527) 106 99 and 105 (619) 107 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (37190527) 108 exp humans/ or exp human experimentation/ or exp human experiment/ (28766294) 109 107 not 108 (8425819) 110 106 not 109 (590) 111 (editorial or letter).pt. (2525212) 112 110 not 111 (588) 113 112 use emez (394) 114 57 or 113 (612) 115 limit 114 to yr="2013-current" (101) 116 remove duplicates from 115 (80) [TOTAL RECORDS] 117 116 use prmz (25) [UNIQUE MEDLINE RECORDS] 118 116 use emez (55) [UNIQUE EMBASE RECORDS]
Note	
Database	**The Cochrane Library**
Date	17-09-2014
Search strategy	ID Search Hits #1 [mh Pregnancy] or [mh "Pregnancy Complications"] 11132 #2 [mh "Pregnant Women"] 96 #3 [mh "Pregnancy Trimesters"] 1469 #4 pregnan*:ti,ab,kw 25359 #5 [mh "Prenatal Care"] 1059 #6 (prenatal* or antenatal* or (ante next natal*) or antepartum or (ante next partum) or perinatal* or (peri next natal*) or peripartum or (peri next partum)):ti,ab,kw 6081 #7 {or #1-#6} 27567

#8 ((healthy or asymptomatic* or symptomless* or (low next risk*) or lowrisk* or (no next risk*) or norisk* or normal* or routine or standard or uncomplicated or safe or (without next complication*) or (without next risk*)) near/3 (female* or patient* or maternal* or mother* or pregnan* or woman* or women*)):ti,ab,kw 29074
#9 #7 and #8 2599
#10 [mh "Uterine Cervical Incompetence"] 58
#11 ((cervix* or cervical*) near/3 (incompeten* or insufficien* or short* or weak*)):ti,ab,kw 185
#12 #7 and (#10 or #11) 143
#13 #9 or #12 2723
#14 [mh "Cerclage, Cervical"] 54
#15 cerclage*:ti,ab,kw 151
#16 (McDonald near/4 (stitch* or sutur*)):ti,ab,kw 2
#17 (Shirodkar near/4 (stitch* or sutur*)):ti,ab,kw 2
#18 tracheloplast*:ti,ab,kw 0
#19 2-#18 151
#20 #13 and #19 70
#21 [mh Progesterone] 2333
#22 (progesterone* or pregnenedione*):ti,ab,kw 4272
#23 [mh Progestins] 397
#24 (progestin* or progestogen* or progestagen* or progestational* or gestagen*):ti,ab,kw 2128
#25 (Hydroxyprogesteron* or 17-alpha-Hydroxyprogesteron* or 17-Hydroxyprogesteron* or "BRN 2062088" or "EINECS 200-699-4" or "HSDB 3343" or Hidroxiprogesteron* or Idrossiprogesteron* or "NSC 15468" or Oxiprogesteronum or Prodix or Prodox or Proluton or Setaderm or "UNII-21807M87J2"):ti,ab,kw 265
#26 (Agolutin or "Bio-luton" or "CCRIS 533" or Corlutin or Corlutina or Corluvite or Corporin or ("Corpus luteum" next hormone*) or Crinone or Cyclogest or "EINECS 200-350-6" or Endometrin or Flavolutan or Fologenon):ti,ab,kw 54
#27 (Gesterol or Gestone or Gestormone or Gestron or Glanducorpin or Gynlutin or Gynoluton or Gynolutone or "HSDB 3389" or Hormoflaveine or Hormoluton):ti,ab,kw 1
#28 (Lingusorbs or "Lipo-Lutin" or Lucorteum or (Luteal next hormone*) or Luteinique or "Luteocrin normale" or Luteodyn or Luteogan or Luteohormone or Luteol or Luteopur or Luteosan or Luteostab or Luteovis or Lutex or Lutidon or Lutin or Lutociclina or Lutocyclin or Lutocylin or Lutoform or Lutogyl or Lutren or Lutromone):ti,ab,kw 3
#29 (Membrettes or Methylpregnone or "NSC 64377" or "NSC 9704" or "NSC-9704" or Nalutron or (Percutacrine next Luteinique) or Piaponon or Primolut or Prochieve or Progekan or Progestasert or Progesterol or Progesterona or Progesteronum or Progestone or Progestosol or Progestron or Progestronol or Projestaject or Prolets or Prolidon or Proluton or Prolutone or Prometrium or Protormone or Syngesterone or Syngestrets or Synovex or Syntolutan or "UNII-4G7DS2Q64Y" or Utrogestan):ti,ab,kw 49
#30 [mh Dydrogesterone] 120
#31 ("6-Dehydro-9 beta-10 alpha-progesterone" or "10alpha-Isopregnenone" or "CCRIS 9069" or Dydrogesteron* or Didrogesterone or Dehydrogesterone or Diphaston or Duphaston or Duvaron or "EINECS 205-806-8"):ti,ab,kw 184
#32 (Gestatron or Gynorest or "HSDB 3321" or Hydrogesterone or Hydrogestrone or Isopregnenone or "NSC 92336" or Prodel or Retro-6-dehydroprogesterone or Retrone or Terolut or "UNII-90I02KLE8K"):ti,ab,kw 1
#33 (17 next Hydroxyprogesterone next capro*):ti,ab,kw 9
#34 ("17 alpha-hydroxyprogesterone" next capro*) or ("17-alpha-hydroxy-progesterone" next capro*) or (hydroxyprogesterone next capro*) or "hydroxyprogesterone hexanoate":ti,ab,kw 111
#35 (17OHP or Delalutin or Makena or Neolutin or "oxyprogesterone caproate" or Prolutin or Proluton):ti,ab,kw 18

#36 "Medroxyprogesterone Acetate":ti,ab,kw 1434
#37 ("AI3-60127" or Amen or Aragest or "BRN 2066112" or "CCRIS 371" or Clinofem or Clinovir or Curretab or Cycrin or Cykrina or DMPA or (Depo* next "Medroxyprogesterone Acetate") or "Depo-Provera" or DP150 or Depcorlutin or "Depo-Clinovir" or "Depo-Map"):ti,ab,kw 178
#38 ("Depo-Prodasone" or "Depo-Progevera" or "Depo-Promone" or "Depo-Provera" or "Depo-Ralovera" or "Depo-progestin" or "Depo-subQ provera" or Depocon or Deporone or Dugan or "EINECS 200-757-9" or Farlutal or Farlutin or Gestapuran or Hysron or Indivina or Lutopolar or Lutoral):ti,ab,kw 42
#39 ("MPA GYM" or "MPA Hexal" or "MPA-Noury" or "MPA-beta" or "Med-Pro" or Medrosterona or "Medroxyprogesterone 17-acetate" or Mepastat or Meprate or Methylacetoxyprogesterone or Metigestrona or "NSC 21171" or "NSC-26386" or Nadigest or Nidaxin or Oragest or "Medroxyacetate progesterone" or "Medroxyprogesterone 17-Acetate"):ti,ab,kw 19
#40 (Perlutex or Prodasone or Progestalfa or Progeston or Progevera or "Promone-E" or Provera or Proverone or Ralovera or Repromap or Repromix or Sirprogen or Sumiferm or Supprestral or Suprestral or "U 8839" or "UNII-C2QI4IOI2G" or Veramix or Veraplex):ti,ab,kw 75
#41 [mh Allylestrenol] 10
#42 (Allylestrenol* or Allyloestrenol* or Alilestrenol* or "BRN 3148038" or "CCRIS 9068" or "EINECS 207-082-9" or Gestanin or Gestanol or Gestanon or Gestanyn or "NSC 37723" or Orageston or Organon or Turinal or "UNII-I47VB5DZ8O"):ti,ab,kw 112
#43 [mh "Chlormadinone Acetate"] 81
#44 ("Ay 13390-6" or Bovisynchron or "C-Quens" or "CCRIS 129" or Chlormadinon* or Cero or Chlordion or Clordion or "EINECS 206-118-0" or Fertiletten or Gestafortin or "HSDB 3591" or "ICI 39575" or Lormin or Lutestral or Luteran or Lutinyl or Lutoral or Matrol or Menstridyl or Minipill or Neo-Eunomin or "NSC 92338" or "NSC-92338" or Normenon or "RS 1280" or Retex or "STG 155" or Skedule or Synchrosyn or Traslan or "UNII-0SY050L61N" or Verton):ti,ab,kw 120
#45 {or #21-#44} 7188
#46 #13 and #45 178
#47 [mh "Bed Rest"] 390
#48 bedrest*:ti,ab,kw 93
#49 (rest* near/5 bed):ti,ab,kw 846
#50 (confin* near/5 bed):ti,ab,kw 48
#51 (rest* near/2 (antenatal* or (ante next natal*) or antepartum or "ante partum" or prenatal* or pregnanc*)):ti,ab,kw 81
#52 ((confin* or limit* or reduc* or restrict*) near/5 activit*):ti,ab,kw 4409
#53 "ABR/AR":ti,ab,kw 0
#54 #4-#53 5341
#55 #13 and #54 50
#56 #46 Publication Year from 2013 to 2014 16
DSR – 7 – *did not download; primary study search only*
DARE – 1– *did not download; primary study search only*
CENTRAL - 8

Note

Table 39 – Search strategies: Benefits-harms of cerclage in asymptomatic pregnant women with short cervix (Primary RCTs)

Database	Medline (OVID) & Embase
Date	17-09-2014
Search strategy	1 exp Pregnancy/ or exp Pregnancy Complications/ (1347093) 2 Pregnant Women/ (40049) 3 exp Pregnancy Trimesters/ (588827) 4 pregnan*.tw. (811808) 5 Prenatal Care/ (47377) 6 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (316945) 7 or/1-6 (1674064) 8 ((healthy or asymptomatic* or symptomless* or low risk* or lowrisk* or no risk* or norisk* or normal* or routine or standard or uncomplicated or safe or without complication* or without risk*) adj3 (female* or patient* or maternal* or mother* or pregnan* or wom#n)).tw. (675930) 9 7 and 8 (101160) 10 Uterine Cervical Incompetence/ (2387) 11 ((cervix* or cervical*) adj3 (incompeten* or insufficien* or short* or weak*)).tw,kw. (4686) 12 7 and (10 or 11) (4398) 13 9 or 12 (105045) 14 Cerclage, Cervical/ (1871) 15 cerclage*.tw,kw. (5133) 16 ((cervix* or cervical*) adj3 (stitch* or sutur*)).tw,kw. (506) 17 (McDonald adj3 (stitch* or sutur*)).tw,kw. (38) 18 (Shirodkar adj3 (stitch* or sutur*)).tw,kw. (51) 19 tracheloplast*.tw,kw. (7) 20 or/14-19 (5866) 21 13 and 20 (1884) 22 (controlled clinical trial or randomized controlled trial).pt. (473266) 23 clinical trials as topic.sh. (173008) 24 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1456820) 25 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (294260) 26 trial.ti. (296203) 27 or/22-26 (1859343) 28 21 and 27 (241) 29 exp Animals/ not (exp Animals/ and Humans/) (8021168) 30 28 not 29 (241) 31 (comment or editorial or interview or letter or news).pt. (2846125) 32 30 not 31 (234) 33 32 use prmz (113) 34 exp pregnancy/ (1280125) 35 exp pregnancy disorder/ (405956) 36 pregnant woman/ (40049) 37 pregnan*.tw. (811808)

38 exp prenatal care/ (127520)
39 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (316945)
40 or/34-39 (1775262)
41 ((healthy or asymptomatic* or symptomless* or low risk* or lowrisk* or no risk* or norisk* or normal* or routine or standard or uncomplicated or safe or without complication* or without risk*) adj3 (female* or patient* or maternal* or mother* or pregnan* or wom#n)).tw. (675930)
42 40 and 41 (102812)
43 uterine cervix incompetence/ (1218)
44 ((cervix* or cervical*) adj3 (incompeten* or insufficien* or short* or weak*)).tw,kw. (4686)
45 40 and (43 or 44) (4097)
46 42 or 45 (106398)
47 uterine cervix cerclage/ (1871)
48 cerclage*.tw,kw. (5133)
49 ((cervix* or cervical*) adj3 (stitch* or sutur*)).tw,kw. (506)
50 (McDonald adj3 (stitch* or sutur*)).tw,kw. (38)
51 (Shirodkar adj3 (stitch* or sutur*)).tw,kw. (51)
52 tracheloplast*.tw,kw. (7)
53 or/47-52 (5866)
54 46 and 53 (1693)
55 randomized controlled trial/ or controlled clinical trial/ (957312)
56 exp "clinical trial (topic)"/ (116087)
57 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1456820)
58 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (294260)
59 trial.ti. (296203)
60 or/55-59 (1998527)
61 54 and 60 (262)
62 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (37190527)
63 exp humans/ or exp human experimentation/ or exp human experiment/ (28766294)
64 62 not 63 (8425819)
65 61 not 64 (262)
66 (editorial or letter).pt. (2525212)
67 65 not 66 (259)
68 67 use emez (164)
69 33 or 68 (277)
70 limit 69 to yr="2011-current" (95)
71 remove duplicates from 70 (69) [TOTAL RECORDS]
72 71 use prmz (29) [UNIQUE MEDLINE RECORDS]
73 71 use emez (40) [UNIQUE EMBASE RECORDS]

Note

Database	The Cochrane library
Date	17-09-2014
Search strategy	ID Search Hits #1 [mh Pregnancy] or [mh "Pregnancy Complications"] 11132 #2 [mh "Pregnant Women"] 96 #3 [mh "Pregnancy Trimesters"] 1469 #4 pregnan*:ti,ab,kw 25359 #5 [mh "Prenatal Care"] 1059 #6 (prenatal* or antenatal* or (ante next natal*) or antepartum or (ante next partum) or perinatal* or (peri next natal*) or peripartum or (peri next partum)):ti,ab,kw 6081 #7 {or #1-#6} 27567 #8 ((healthy or asymptomatic* or symptomless* or (low next risk*) or lowrisk* or (no next risk*) or norisk* or normal* or routine or standard or uncomplicated or safe or (without next complication*) or (without next risk*)) near/3 (female* or patient* or maternal* or mother* or pregnan* or woman* or women*)):ti,ab,kw 29074 #9 #7 and #8 2599 #10 [mh "Uterine Cervical Incompetence"] 58 #11 ((cervix* or cervical*) near/3 (incompeten* or insufficien* or short* or weak*)):ti,ab,kw 185 #12 #7 and (#10 or #11) 143 #13 #9 or #12 2723 #14 [mh "Cerclage, Cervical"] 54 #15 cerclage*:ti,ab,kw 151 #16 (McDonald near/4 (stitch* or sutur*)):ti,ab,kw 2 #17 (Shirodkar near/4 (stitch* or sutur*)):ti,ab,kw 2 #18 tracheloplast*:ti,ab,kw 0 #19 2-#18 151 #20 #13 and #19 70 #21 [mh Progesterone] 2333 #22 (progesterone* or pregnenedione*):ti,ab,kw 4272 #23 [mh Progestins] 397 #24 (progestin* or progestogen* or progestagen* or progestational* or gestagen*):ti,ab,kw 2128 #25 (Hydroxyprogesteron* or 17-alpha-Hydroxyprogesteron* or 17-Hydroxyprogesteron* or "BRN 2062088" or "EINECS 200-699-4" or "HSDB 3343" or Hidroxiprogesteron* or Idrossiprogesteron* or "NSC 15468" or Oxiprogesteronum or Prodix or Prodox or Proluton or Setaderm or "UNII-21807M87J2"):ti,ab,kw 265 #26 (Agolutin or "Bio-luton" or "CCRIS 533" or Corlutin or Corlutina or Corluvite or Corporin or ("Corpus luteum" next hormone*) or Crinone or Cyclogest or "EINECS 200-350-6" or Endometrin or Flavolutan or Fologenon):ti,ab,kw 54 #27 (Gesterol or Gestone or Gestormone or Gestron or Glanducorpin or Gynlutin or Gynoluton or Gynolutone or "HSDB 3389" or Hormoflaveine or Hormoluton):ti,ab,kw 1 #28 (Lingusorbs or "Lipo-Lutin" or Lucorteum or (Luteal next hormone*) or Luteinique or "Luteocrin normale" or Luteodyn or Luteogan or Luteohormone or Luteol or Luteopur or Luteosan or Luteostab or Luteovis or Lutex or Lutidon or Lutin or Lutociclina or Lutocyclin or Lutocylin or Lutoform or Lutogyl or Lutren or Lutromone):ti,ab,kw 3

#29 (Membrettes or Methylpregnone or "NSC 64377" or "NSC 9704" or "NSC-9704" or Nalutron or (Percutacrine next Luteinique) or Piaponon or Primolut or Prochieve or Progekan or Progestasert or Progesterol or Progesterona or Progesteronum or Progestone or Progestosol or Progestron or Progestronol or Projestaject or Prolets or Prolidon or Proluton or Prolutone or Prometrium or Protormone or Syngesterone or Syngestrets or Synovex or Syntolutan or "UNII-4G7DS2Q64Y" or Utrogestan):ti,ab,kw 49
#30 [mh Dydrogesterone] 120
#31 ("6-Dehydro-9 beta-10 alpha-progesterone" or "10alpha-Isopregnenone" or "CCRIS 9069" or Dydrogesteron* or Didrogesterone or Dehydrogesterone or Diphaston or Duphaston or Duvaron or "EINECS 205-806-8"):ti,ab,kw 184
#32 (Gestatron or Gynorest or "HSDB 3321" or Hydrogesterone or Hydrogestrone or Isopregnenone or "NSC 92336" or Prodel or Retro-6-dehydroprogesterone or Retrone or Terolut or "UNII-90I02KLE8K"):ti,ab,kw 1
#33 (17 next Hydroxyprogesterone next capro*):ti,ab,kw 9
#34 ("17 alpha-hydroxyprogesterone" next capro*) or ("17-alpha-hydroxy-progesterone" next capro*) or (hydroxyprogesterone next capro*) or "hydroxyprogesterone hexanoate":ti,ab,kw 111
#35 (17OHP or Delalutin or Makena or Neolutin or "oxyprogesterone caproate" or Prolutin or Proluton):ti,ab,kw 18
#36 "Medroxyprogesterone Acetate":ti,ab,kw 1434
#37 ("AI3-60127" or Amen or Aragest or "BRN 2066112" or "CCRIS 371" or Clinofem or Clinovir or Curretab or Cycrin or Cykrina or DMPA or (Depo* next "Medroxyprogesterone Acetate") or "Depo-Provera" or DP150 or Depcorlutin or "Depo-Clinovir" or "Depo-Map"):ti,ab,kw 178
#38 ("Depo-Prodasone" or "Depo-Progevera" or "Depo-Promone" or "Depo-Provera" or "Depo-Ralovera" or "Depo-progestin" or "Depo-subQ provera" or Depocon or Deporone or Dugan or "EINECS 200-757-9" or Farlutal or Farlutin or Gestapuran or Hysron or Indivina or Lutopolar or Lutoral):ti,ab,kw 42
#39 ("MPA GYM" or "MPA Hexal" or "MPA-Noury" or "MPA-beta" or "Med-Pro" or Medrosterona or "Medroxyprogesterone 17-acetate" or Mepastat or Meprate or Methylacetoxyprogesterone or Metigestrona or "NSC 21171" or "NSC-26386" or Nadigest or Nidaxin or Oragest or "Medroxyacetate progesterone" or "Medroxyprogesterone 17-Acetate"):ti,ab,kw 19
#40 (Perlutex or Prodasone or Progestalfa or Progeston or Progevera or "Promone-E" or Provera or Proverone or Ralovera or Repromap or Repromix or Sirprogen or Sumiferm or Supprestral or Suprestral or "U 8839" or "UNII-C2QI4IOI2G" or Veramix or Veraplex):ti,ab,kw 75
#41 [mh Allylestrenol] 10
#42 (Allylestrenol* or Allyloestrenol* or Alilestrenol* or "BRN 3148038" or "CCRIS 9068" or "EINECS 207-082-9" or Gestanin or Gestanol or Gestanon or Gestanyn or "NSC 37723" or Orageston or Organon or Turinal or "UNII-I47VB5DZ8O"):ti,ab,kw 112
#43 [mh "Chlormadinone Acetate"] 81
#44 ("Ay 13390-6" or Bovisynchron or "C-Quens" or "CCRIS 129" or Chlormadinon* or Cero or Chlordion or Clordion or "EINECS 206-118-0" or Fertiletten or Gestafortin or "HSDB 3591" or "ICI 39575" or Lormin or Lutestral or Luteran or Lutinyl or Lutoral or Matrol or Menstridyl or Minipill or Neo-Eunomin or "NSC 92338" or "NSC-92338" or Normenon or "RS 1280" or Retex or "STG 155" or Skedule or Synchrosyn or Traslan or "UNII-0SY050L61N" or Verton):ti,ab,kw 120
#45 {or #21-#44} 7188
#46 #13 and #45 178
#47 [mh "Bed Rest"] 390
#48 bedrest*:ti,ab,kw 93
#49 (rest* near/5 bed):ti,ab,kw 846
#50 (confin* near/5 bed):ti,ab,kw 48
#51 (rest* near/2 (antenatal* or (ante next natal*) or antepartum or "ante partum" or prenatal* or pregnanc*)):ti,ab,kw 81
#52 ((confin* or limit* or reduc* or restrict*) near/5 activit*):ti,ab,kw 4409

	#53 "ABR/AR":ti,ab,kw 0 #54 4-#53 5341 #55 #13 and #54 50 #56 #20 Publication Year from 2011 to 2014 21 DSR – 4 – *did not download; primary study search only* DARE – 3 – *did not download; primary study search only* CENTRAL – 14
Note	

Table 40 – Search strategies: Benefits-harms of bed rest in asymptomatic pregnant women with short cervix (Primary RCTs)

Database	Medline (OVID) & Embase
Date	17-09-2014
Search strategy	1 exp Pregnancy/ or exp Pregnancy Complications/ (1347093) 2 Pregnant Women/ (40049) 3 exp Pregnancy Trimesters/ (588827) 4 pregnan*.tw. (811808) 5 Prenatal Care/ (47377) 6 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (316945) 7 or/1-6 (1674064) 8 ((healthy or asymptomatic* or symptomless* or low risk* or lowrisk* or no risk* or norisk* or normal* or routine or standard or uncomplicated or safe or without complication* or without risk*) adj3 (female* or patient* or maternal* or mother* or pregnan* or wom#n)).tw. (675930) 9 7 and 8 (101160) 10 Uterine Cervical Incompetence/ (2387) 11 ((cervix* or cervical*) adj3 (incompeten* or insufficien* or short* or weak*)).tw,kw. (4686) 12 7 and (10 or 11) (4398) 13 9 or 12 (105045) 14 Bed Rest/ (9418) 15 bedrest*.tw. (1785) 16 (rest* adj5 bed).tw. (10342) 17 (confin* adj5 bed).tw. (1172) 18 (rest* adj2 (antenatal* or ante natal* or antepartum or ante partum or prenatal* or pregnanc*)).tw. (2215) 19 ((confin* or limit* or reduc* or restrict*) adj5 activit*).tw. (287686) 20 "ABR/AR".tw. (2) 21 or/14-20 (306430) 22 13 and 21 (1309) 23 (controlled clinical trial or randomized controlled trial).pt. (473266) 24 clinical trials as topic.sh. (173008) 25 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1456820) 26 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (294260) 27 trial.ti. (296203)

28 or/23-27 (1859343)
29 22 and 28 (120)
30 exp Animals/ not (exp Animals/ and Humans/) (8021168)
31 29 not 30 (108)
32 (comment or editorial or interview or letter or news).pt. (2846125)
33 31 not 32 (108)
34 33 use prmz (56)
35 exp pregnancy/ (1280125)
36 exp pregnancy disorder/ (405956)
37 pregnant woman/ (40049)
38 pregnan*.tw. (811808)
39 exp prenatal care/ (127520)
40 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (316945)
41 or/35-40 (1775262)
42 ((healthy or asymptomatic* or symptomless* or low risk* or lowrisk* or no risk* or norisk* or normal* or routine or standard or uncomplicated or safe or without complication* or without risk*) adj3 (female* or patient* or maternal* or mother* or pregnan* or wom#n)).tw. (675930)
43 41 and 42 (102812)
44 uterine cervix incompetence/ (1218)
45 ((cervix* or cervical*) adj3 (incompeten* or insufficien* or short* or weak*)).tw,kw. (4686)
46 41 and (44 or 45) (4097)
47 43 or 46 (106398)
48 bed rest/ (9418)
49 bedrest*.tw. (1785)
50 (rest* adj5 bed).tw. (10342)
51 (confin* adj5 bed).tw. (1172)
52 (rest* adj2 (antenatal* or ante natal* or antepartum or ante partum or prenatal* or pregnanc*)).tw. (2215)
53 ((confin* or limit* or reduc* or restrict*) adj5 activit*).tw. (287686)
54 "ABR/AR".tw. (2)
55 or/48-54 (306430)
56 47 and 55 (1323)
57 randomized controlled trial/ or controlled clinical trial/ (957312)
58 exp "clinical trial (topic)"/ (116087)
59 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1456820)
60 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (294260)
61 trial.ti. (296203)
62 or/57-61 (1998527)
63 56 and 62 (136)
64 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (37190527)
65 exp humans/ or exp human experimentation/ or exp human experiment/ (28766294)
66 64 not 65 (8425819)

	67 63 not 66 (124) 68 (editorial or letter).pt. (2525212) 69 67 not 68 (124) 70 69 use emez (71) 71 34 or 70 (127) 72 limit 71 to yr="2003-current" (69) 73 remove duplicates from 72 (51) [TOTAL RECORDS] 74 73 use prmz (26) [UNIQUE MEDLINE RECORDS 75 73 use emez (25) [UNIQUE EMBASE RECORDS]
Note	
Database	**The Cochrane library**
Date	17-09-2014
Search strategy	ID Search Hits #1 [mh Pregnancy] or [mh "Pregnancy Complications"] 11132 #2 [mh "Pregnant Women"] 96 #3 [mh "Pregnancy Trimesters"] 1469 #4 pregnan*:ti,ab,kw 25359 #5 [mh "Prenatal Care"] 1059 #6 (prenatal* or antenatal* or (ante next natal*) or antepartum or (ante next partum) or perinatal* or (peri next natal*) or peripartum or (peri next partum)):ti,ab,kw 6081 #7 {or #1-#6} 27567 #8 ((healthy or asymptomatic* or symptomless* or (low next risk*) or lowrisk* or (no next risk*) or norisk* or normal* or routine or standard or uncomplicated or safe or (without next complication*) or (without next risk*)) near/3 (female* or patient* or maternal* or mother* or pregnan* or woman* or women*)):ti,ab,kw 29074 #9 #7 and #8 2599 #10 [mh "Uterine Cervical Incompetence"] 58 #11 ((cervix* or cervical*) near/3 (incompeten* or insufficien* or short* or weak*)):ti,ab,kw 185 #12 #7 and (#10 or #11) 143 #13 #9 or #12 2723 #14 [mh "Cerclage, Cervical"] 54 #15 cerclage*:ti,ab,kw 151 #16 (McDonald near/4 (stitch* or sutur*)):ti,ab,kw 2 #17 (Shirodkar near/4 (stitch* or sutur*)):ti,ab,kw 2 #18 tracheloplast*:ti,ab,kw 0 #19 2-#18 151 #20 #13 and #19 70 #21 [mh Progesterone] 2333 #22 (progesterone* or pregnenedione*):ti,ab,kw 4272 #23 [mh Progestins] 397

#24 (progestin* or progestogen* or progestagen* or progestational* or gestagen*):ti,ab,kw 2128
#25 (Hydroxyprogesteron* or 17-alpha-Hydroxyprogesteron* or 17-Hydroxyprogesteron* or "BRN 2062088" or "EINECS 200-699-4" or "HSDB 3343" or Hidroxiprogesteron* or Idrossiprogesteron* or "NSC 15468" or Oxiprogesteronum or Prodix or Prodox or Proluton or Setaderm or "UNII-21807M87J2"):ti,ab,kw 265
#26 (Agolutin or "Bio-luton" or "CCRIS 533" or Corlutin or Corlutina or Corluvite or Corporin or ("Corpus luteum" next hormone*) or Crinone or Cyclogest or "EINECS 200-350-6" or Endometrin or Flavolutan or Fologenon):ti,ab,kw 54
#27 (Gesterol or Gestone or Gestormone or Gestron or Glanducorpin or Gynlutin or Gynoluton or Gynolutone or "HSDB 3389" or Hormoflaveine or Hormoluton):ti,ab,kw 1
#28 (Lingusorbs or "Lipo-Lutin" or Lucorteum or (Luteal next hormone*) or Luteinique or "Luteocrin normale" or Luteodyn or Luteogan or Luteohormone or Luteol or Luteopur or Luteosan or Luteostab or Luteovis or Lutex or Lutidon or Lutin or Lutociclina or Lutocyclin or Lutocylin or Lutoform or Lutogyl or Lutren or Lutromone):ti,ab,kw 3
#29 (Membrettes or Methylpregnone or "NSC 64377" or "NSC 9704" or "NSC-9704" or Nalutron or (Percutacrine next Luteinique) or Piaponon or Primolut or Prochieve or Progekan or Progestasert or Progesterol or Progesterona or Progesteronum or Progestone or Progestosol or Progestron or Progestronol or Projestaject or Prolets or Prolidon or Proluton or Prolutone or Prometrium or Protormone or Syngesterone or Syngestrets or Synovex or Syntolutan or "UNII-4G7DS2Q64Y" or Utrogestan):ti,ab,kw 49
#30 [mh Dydrogesterone] 120
#31 ("6-Dehydro-9 beta-10 alpha-progesterone" or "10alpha-Isopregnenone" or "CCRIS 9069" or Dydrogesteron* or Didrogesterone or Dehydrogesterone or Diphaston or Duphaston or Duvaron or "EINECS 205-806-8"):ti,ab,kw 184
#32 (Gestatron or Gynorest or "HSDB 3321" or Hydrogesterone or Hydrogestrone or Isopregnenone or "NSC 92336" or Prodel or Retro-6-dehydroprogesterone or Retrone or Terolut or "UNII-90I02KLE8K"):ti,ab,kw 1
#33 (17 next Hydroxyprogesterone next capro*):ti,ab,kw 9
#34 ("17 alpha-hydroxyprogesterone" next capro*) or ("17-alpha-hydroxy-progesterone" next capro*) or (hydroxyprogesterone next capro*) or "hydroxyprogesterone hexanoate":ti,ab,kw 111
#35 (17OHP or Delalutin or Makena or Neolutin or "oxyprogesterone caproate" or Prolutin or Proluton):ti,ab,kw 18
#36 "Medroxyprogesterone Acetate":ti,ab,kw 1434
#37 ("AI3-60127" or Amen or Aragest or "BRN 2066112" or "CCRIS 371" or Clinofem or Clinovir or Curretab or Cycrin or Cykrina or DMPA or (Depo* next "Medroxyprogesterone Acetate") or "Depo-Provera" or DP150 or Depcorlutin or "Depo-Clinovir" or "Depo-Map"):ti,ab,kw 178
#38 ("Depo-Prodasone" or "Depo-Progevera" or "Depo-Promone" or "Depo-Provera" or "Depo-Ralovera" or "Depo-progestin" or "Depo-subQ provera" or Depocon or Deporone or Dugan or "EINECS 200-757-9" or Farlutal or Farlutin or Gestapuran or Hysron or Indivina or Lutopolar or Lutoral):ti,ab,kw 42
#39 ("MPA GYM" or "MPA Hexal" or "MPA-Noury" or "MPA-beta" or "Med-Pro" or Medrosterona or "Medroxyprogesterone 17-acetate" or Mepastat or Meprate or Methylacetoxyprogesterone or Metigestrona or "NSC 21171" or "NSC-26386" or Nadigest or Nidaxin or Oragest or "Medroxyacetate progesterone" or "Medroxyprogesterone 17-Acetate"):ti,ab,kw 19
#40 (Perlutex or Prodasone or Progestalfa or Progeston or Progevera or "Promone-E" or Provera or Proverone or Ralovera or Repromap or Repromix or Sirprogen or Sumiferm or Supprestral or Suprestral or "U 8839" or "UNII-C2QI4IOI2G" or Veramix or Veraplex):ti,ab,kw 75
#41 [mh Allylestrenol] 10
#42 (Allylestrenol* or Allyloestrenol* or Alilestrenol* or "BRN 3148038" or "CCRIS 9068" or "EINECS 207-082-9" or Gestanin or Gestanol or Gestanon or Gestanyn or "NSC 37723" or Orageston or Organon or Turinal or "UNII-I47VB5DZ8O"):ti,ab,kw 112
#43 [mh "Chlormadinone Acetate"] 81

	#44 ("Ay 13390-6" or Bovisynchron or "C-Quens" or "CCRIS 129" or Chlormadinon* or Cero or Chlordion or Clordion or "EINECS 206-118-0" or Fertiletten or Gestafortin or "HSDB 3591" or "ICI 39575" or Lormin or Lutestral or Luteran or Lutinyl or Lutoral or Matrol or Menstridyl or Minipill or Neo-Eunomin or "NSC 92338" or "NSC-92338" or Normenon or "RS 1280" or Retex or "STG 155" or Skedule or Synchrosyn or Traslan or "UNII-0SY050L61N" or Verton):ti,ab,kw 120 #45 {or #21-#44} 7188 #46 #13 and #45 178 #47 [mh "Bed Rest"] 390 #48 bedrest*:ti,ab,kw 93 #49 (rest* near/5 bed):ti,ab,kw 846 #50 (confin* near/5 bed):ti,ab,kw 48 #51 (rest* near/2 (antenatal* or (ante next natal*) or antepartum or "ante partum" or prenatal* or pregnanc*)):ti,ab,kw 81 #52 ((confin* or limit* or reduc* or restrict*) near/5 activit*):ti,ab,kw 4409 #53 "ABR/AR":ti,ab,kw 0 #54 4-#53 5341 #55 #13 and #54 50 #56 #55 Publication Year from 2003 to 2014 28 DSR – 11 – *did not download; primary study search only* DARE – 1 – *did not download; primary study search only* CENTRAL - 16
Note	

Table 41 – Search strategies: Benefits-harms of progesterone, cerlcage and bed rest in asymptomatic pregnant women with short cervix (Primary observational evidence)

Database	Medline (OVID) & Embase
Date	17-09-2014
Search strategy	1 exp Pregnancy/ or exp Pregnancy Complications/ (1347093) 2 Pregnant Women/ (40049) 3 exp Pregnancy Trimesters/ (588827) 4 pregnan*.tw. (811808) 5 Prenatal Care/ (47377) 6 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (316945) 7 or/1-6 (1674064) 8 ((healthy or asymptomatic* or symptomless* or low risk* or lowrisk* or no risk* or norisk* or normal* or routine or standard or uncomplicated or safe or without complication* or without risk*) adj3 (female* or patient* or maternal* or mother* or pregnan* or wom#n)).tw. (675930) 9 7 and 8 (101160) 10 Uterine Cervical Incompetence/ (2387) 11 ((cervix* or cervical*) adj3 (incompeten* or insufficien* or short* or weak*)).tw,kw. (4686) 12 7 and (10 or 11) (4398) 13 9 or 12 (105045)

14 Cerclage, Cervical/ (1871)
15 cerclage*.tw,kw. (5133)
16 ((cervix* or cervical*) adj3 (stitch* or sutur*)).tw,kw. (506)
17 (McDonald adj3 (stitch* or sutur*)).tw,kw. (38)
18 (Shirodkar adj3 (stitch* or sutur*)).tw,kw. (51)
19 tracheloplast*.tw,kw. (7)
20 or/14-19 (5866)
21 13 and 20 (1884)
22 exp Progesterone/ (134427)
23 (progesterone* or pregnenedione*).tw,kw. (144118)
24 57-83-0.rn. (66139)
25 Progestins/ (30116)
26 (progestin* or progestogen* or progestagen* or progestational* or gestagen*).tw,kw. (40574)
27 (Hydroxyprogesteron* or 17-alpha-Hydroxyprogesteron* or 17-Hydroxyprogesteron* or BRN 2062088 or EINECS 200-699-4 or HSDB 3343 or Hidroxiprogesteron* or Idrossiprogesteron* or NSC 15468 or Oxiprogesteronum or Prodix or Prodox or Proluton or Setaderm or UNII-21807M87J2).tw,kw. (8497)
28 68-96-2.rn. (5948)
29 (Agolutin or Bio-luton or CCRIS 533 or Corlutin or Corlutina or Corluvite or Corporin or Corpus luteum hormone* or Crinone or Cyclogest or EINECS 200-350-6 or Endometrin or Flavolutan or Fologenon).tw,kw. (838)
30 (Gesterol or Gestone or Gestormone or Gestron or Glanducorpin or Gynlutin or Gynoluton or Gynolutone or HSDB 3389 or Hormoflaveine or Hormoluton).tw,kw. (124)
31 (Lingusorbs or Lipo-Lutin or Lucorteum or Luteal hormone* or Luteinique or Luteocrin normale or Luteodyn or Luteogan or Luteohormone or Luteol or Luteopur or Luteosan or Luteostab or Luteovis or Lutex or Lutidon or Lutin or Lutociclina or Lutocyclin or Lutocylin or Lutoform or Lutogyl or Lutren or Lutromone).tw,kw. (155)
32 (Membrettes or Methylpregnone or NSC 64377 or NSC 9704 or NSC-9704 or Nalutron or Percutacrine Luteinique or Piaponon or Primolut or Prochieve or Progekan or Progestasert or Progesterol or Progesterona or Progesteronum or Progestone or Progestosol or Progestron or Progestronol or Projestaject or Prolets or Prolidon or Proluton or Prolutone or Prometrium or Protormone or Syngesterone or Syngestrets or Synovex or Syntolutan or UNII-4G7DS2Q64Y or Utrogestan).tw,kw. (1826)
33 Dydrogesterone/ (1822)
34 ("6-Dehydro-9 beta-10 alpha-progesterone" or "10alpha-Isopregnenone" or CCRIS 9069 or Dydrogesteron* or Didrogesterone or Dehydrogesterone or Diphaston or Duphaston or Duvaron or EINECS 205-806-8).tw,kw. (1213)
35 (Gestatron or Gynorest or HSDB 3321 or Hydrogesterone or Hydrogestrone or Isopregnenone or NSC 92336 or Prodel or Retro-6-dehydroprogesterone or Retrone or Terolut or UNII-90I02KLE8K).tw,kw. (19)
36 152-62-5.rn. (1364)
37 17-Hydroxyprogesterone capro*.tw,kw. (117)
38 (17 alpha-hydroxyprogesterone capro* or 17-alpha-hydroxy-progesterone capro* or hydroxyprogesterone capro* or hydroxyprogesterone hexanoate).tw,kw. (808)
39 (17OHP or Delalutin or Makena or Neolutin or oxyprogesterone caproate or Prolutin or Proluton).tw,kw. (800)
40 Medroxyprogesterone Acetate.tw,kw. (9999)
41 (AI3-60127 or Amen or Aragest or BRN 2066112 or CCRIS 371 or Clinofem or Clinovir or Curretab or Cycrin or Cykrina or DMPA or (Depo* adj Medroxyprogesterone Acetate) or Depo-Provera or DP150 or Depcorlutin or Depo-Clinovir or Depo-Map).tw,kw. (5157)

42 (Depo-Prodasone or Depo-Progevera or Depo-Promone or Depo-Provera or Depo-Ralovera or Depo-progestin or Depo-subQ provera or Depocon or Deporone or Dugan or EINECS 200-757-9 or Farlutal or Farlutin or Gestapuran or Hysron or Indivina or Lutopolar or Lutoral).tw,kw. (2959)
43 (MPA GYM or MPA Hexal or MPA-Noury or MPA-beta or Med-Pro or Medrosterona or Medroxyprogesterone 17-acetate or Mepastat or Meprate or Methylacetoxyprogesterone or Metigestrona or NSC 21171 or NSC-26386 or Nadigest or Nidaxin or Oragest or Medroxyacetate progesterone or Medroxyprogesterone 17-Acetate).tw,kw. (98)
44 (Perlutex or Prodasone or Progestalfa or Progeston or Progevera or Promone-E or Provera or Proverone or Ralovera or Repromap or Repromix or Sirprogen or Sumiferm or Supprestral or Suprestral or U 8839 or UNII-C2QI4IOI2G or Veramix or Veraplex).tw,kw. (3845)
45 71-58-9.rn. (13543)
46 Allylestrenol/ (346)
47 (Allylestrenol* or Allyloestrenol* or Alilestrenol* or BRN 3148038 or CCRIS 9068 or EINECS 207-082-9 or Gestanin or Gestanol or Gestanon or Gestanyn or NSC 37723 or Orageston or Organon or Turinal or UNII-I47VB5DZ8O).tw,kw. (7100)
48 432-60-0.rn. (236)
49 Chlormadinone Acetate/ (3473)
50 (Ay 13390-6 or Bovisynchron or C-Quens or CCRIS 129 or Chlormadinon* or Cero or Chlordion or Clordion or EINECS 206-118-0 or Fertiletten or Gestafortin or HSDB 3591 or ICI 39575 or Lormin or Lutestral or Luteran or Lutinyl or Lutoral or Matrol or Menstridyl or Minipill or Neo-Eunomin or NSC 92338 or NSC-92338 or Normenon or RS 1280 or Retex or STG 155 or Skedule or Synchrosyn or Traslan or UNII-0SY050L61N or Verton).tw,kw. (2053)
51 302-22-7.rn. (2053)
52 or/22-51 (255521)
53 13 and 52 (5031)
54 Bed Rest/ (9418)
55 bedrest*.tw. (1785)
56 (rest* adj5 bed).tw. (10342)
57 (confin* adj5 bed).tw. (1172)
58 (rest* adj2 (antenatal* or ante natal* or antepartum or ante partum or prenatal* or pregnanc*)).tw. (2215)
59 ((confin* or limit* or reduc* or restrict*) adj5 activit*).tw. (287686)
60 "ABR/AR".tw. (2)
61 or/54-60 (306430)
62 13 and 61 (1309)
63 21 or 53 or 62 (7884)
64 exp Animals/ not (exp Animals/ and Humans/) (8021168)
65 63 not 64 (6977)
66 (comment or editorial or interview or letter or news).pt. (2846125)
67 65 not 66 (6907)
68 (control* adj2 trial*).tw. (335917)
69 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (75356)
70 (nRCT or nRCTs or non-RCT$1).tw. (710)
71 (control* adj3 ("before and after" or "before after")).tw. (6026)
72 time series.tw. (34997)
73 (pre- adj3 post-).tw. (113420)
74 (pretest adj3 posttest).tw. (6398)

75 (control* adj2 stud$3).tw. (351940)
76 Control Groups/ (66412)
77 (control$ adj2 group$1).tw. (752960)
78 exp Cohort Studies/ (1574773)
79 cohort$1.tw. (712124)
80 Retrospective Studies/ (870256)
81 (longitudinal or prospective or retrospective).tw. (1769406)
82 ((followup or follow-up) adj (study or studies)).tw. (84044)
83 Observational study.pt. (4707)
84 (observation$2 adj (study or studies)).tw. (117866)
85 ((population or population-based) adj (study or studies or analys#s)).tw. (26119)
86 ((multidimensional or multi-dimensional) adj (study or studies)).tw. (178)
87 Comparative Study.pt. (1703985)
88 ((comparative or comparison) adj (study or studies)).tw. (172996)
89 exp Case-Control Studies/ (776653)
90 ((case-control* or case-based or case-comparison) adj (study or studies)).tw. (147863)
91 or/68-90 (6072895)
92 67 and 91 (2260)
93 limit 92 to yr="1999-current" (1513)
94 93 use prmz (672)
95 exp pregnancy/ (1280125)
96 exp pregnancy disorder/ (405956)
97 pregnant woman/ (40049)
98 pregnan*.tw. (811808)
99 exp prenatal care/ (127520)
100 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (316945)
101 or/95-100 (1775262)
102 ((healthy or asymptomatic* or symptomless* or low risk* or lowrisk* or no risk* or norisk* or normal* or routine or standard or uncomplicated or safe or without complication* or without risk*) adj3 (female* or patient* or maternal* or mother* or pregnan* or wom#n)).tw. (675930)
103 101 and 102 (102812)
104 uterine cervix incompetence/ (1218)
105 ((cervix* or cervical*) adj3 (incompeten* or insufficien* or short* or weak*)).tw,kw. (4686)
106 101 and (104 or 105) (4097)
107 103 or 106 (106398)
108 uterine cervix cerclage/ (1871)
109 cerclage*.tw,kw. (5133)
110 ((cervix* or cervical*) adj3 (stitch* or sutur*)).tw,kw. (506)
111 (McDonald adj3 (stitch* or sutur*)).tw,kw. (38)
112 (Shirodkar adj3 (stitch* or sutur*)).tw,kw. (51)
113 tracheloplast*.tw,kw. (7)

114 or/108-113 (5866)
115 107 and 114 (1693)
116 progesterone/ (122972)
117 (progesterone* or pregnenedione*).tw,kw. (144118)
118 57-83-0.rn. (66139)
119 exp gestagen/ (135975)
120 (progestin* or progestogen* or progestagen* or progestational* or gestagen*).tw,kw. (40574)
121 (Hydroxyprogesteron* or 17-alpha-Hydroxyprogesteron* or 17-Hydroxyprogesteron* or BRN 2062088 or EINECS 200-699-4 or HSDB 3343 or Hidroxiprogesteron* or Idrossiprogesteron* or NSC 15468 or Oxiprogesteronum or Prodix or Prodox or Proluton or Setaderm or UNII-21807M87J2).tw,kw. (8497)
122 68-96-2.rn. (5948)
123 (Agolutin or Bio-luton or CCRIS 533 or Corlutin or Corlutina or Corluvite or Corporin or Corpus luteum hormone* or Crinone or Cyclogest or EINECS 200-350-6 or Endometrin or Flavolutan or Fologenon).tw,kw. (838)
124 (Gesterol or Gestone or Gestormone or Gestron or Glanducorpin or Gynlutin or Gynoluton or Gynolutone or HSDB 3389 or Hormoflaveine or Hormoluton).tw,kw. (124)
125 (Lingusorbs or Lipo-Lutin or Lucorteum or Luteal hormone* or Luteinique or Luteocrin normale or Luteodyn or Luteogan or Luteohormone or Luteol or Luteopur or Luteosan or Luteostab or Luteovis or Lutex or Lutidon or Lutin or Lutociclina or Lutocyclin or Lutocylin or Lutoform or Lutogyl or Lutren or Lutromone).tw,kw. (155)
126 (Membrettes or Methylpregnone or NSC 64377 or NSC 9704 or NSC-9704 or Nalutron or Percutacrine Luteinique or Piaponon or Primolut or Prochieve or Progekan or Progestasert or Progesterol or Progesterona or Progesteronum or Progestone or Progestosol or Progestron or Progestronol or Projestaject or Prolets or Prolidon or Proluton or Prolutone or Prometrium or Protormone or Syngesterone or Syngestrets or Synovex or Syntolutan or UNII-4G7DS2Q64Y or Utrogestan).tw,kw. (1826)
127 ("6-Dehydro-9 beta-10 alpha-progesterone" or "10alpha-Isopregnenone" or CCRIS 9069 or Dydrogesteron* or Didrogesterone or Dehydrogesterone or Diphaston or Duphaston or Duvaron or EINECS 205-806-8).tw,kw. (1213)
128 (Gestatron or Gynorest or HSDB 3321 or Hydrogesterone or Hydrogestrone or Isopregnenone or NSC 92336 or Prodel or Retro-6-dehydroprogesterone or Retrone or Terolut or UNII-90I02KLE8K).tw,kw. (19)
129 152-62-5.rn. (1364)
130 17-Hydroxyprogesterone capro*.tw,kw. (117)
131 (17 alpha-hydroxyprogesterone capro* or 17-alpha-hydroxy-progesterone capro* or hydroxyprogesterone capro* or hydroxyprogesterone hexanoate).tw,kw. (808)
132 (17OHP or Delalutin or Makena or Neolutin or oxyprogesterone caproate or Prolutin or Proluton).tw,kw. (800)
133 Medroxyprogesterone Acetate.tw,kw. (9999)
134 (AI3-60127 or Amen or Aragest or BRN 2066112 or CCRIS 371 or Clinofem or Clinovir or Curretab or Cycrin or Cykrina or DMPA or (Depo* adj Medroxyprogesterone Acetate) or Depo-Provera or DP150 or Depcorlutin or Depo-Clinovir or Depo-Map).tw,kw. (5157)
135 (Depo-Prodasone or Depo-Progevera or Depo-Promone or Depo-Provera or Depo-Ralovera or Depo-progestin or Depo-subQ provera or Depocon or Deporone or Dugan or EINECS 200-757-9 or Farlutal or Farlutin or Gestapuran or Hysron or Indivina or Lutopolar or Lutoral).tw,kw. (2959)
136 (MPA GYM or MPA Hexal or MPA-Noury or MPA-beta or Med-Pro or Medrosterona or Medroxyprogesterone 17-acetate or Mepastat or Meprate or Methylacetoxyprogesterone or Metigestrona or NSC 21171 or NSC-26386 or Nadigest or Nidaxin or Oragest or Medroxyacetate progesterone or Medroxyprogesterone 17-Acetate).tw,kw. (98)
137 (Perlutex or Prodasone or Progestalfa or Progeston or Progevera or Promone-E or Provera or Proverone or Ralovera or Repromap or Repromix or Sirprogen or Sumiferm or Supprestral or Suprestral or U 8839 or UNII-C2QI4IOI2G or Veramix or Veraplex).tw,kw. (3845)

138 71-58-9.rn. (13543)
139 (Allylestrenol* or Allyloestrenol* or Alilestrenol* or BRN 3148038 or CCRIS 9068 or EINECS 207-082-9 or Gestanin or Gestanol or Gestanon or Gestanyn or NSC 37723 or Orageston or Organon or Turinal or UNII-I47VB5DZ8O).tw,kw. (7100)
140 432-60-0.rn. (236)
141 (Ay 13390-6 or Bovisynchron or C-Quens or CCRIS 129 or Chlormadinon* or Cero or Chlordion or Clordion or EINECS 206-118-0 or Fertiletten or Gestafortin or HSDB 3591 or ICI 39575 or Lormin or Lutestral or Luteran or Lutinyl or Lutoral or Matrol or Menstridyl or Minipill or Neo-Eunomin or NSC 92338 or NSC-92338 or Normenon or RS 1280 or Retex or STG 155 or Skedule or Synchrosyn or Traslan or UNII-0SY050L61N or Verton).tw,kw. (2053)
142 302-22-7.rn. (2053)
143 or/116-142 (277051)
144 107 and 143 (5268)
145 bed rest/ (9418)
146 bedrest*.tw. (1785)
147 (rest* adj5 bed).tw. (10342)
148 (confin* adj5 bed).tw. (1172)
149 (rest* adj2 (antenatal* or ante natal* or antepartum or ante partum or prenatal* or pregnanc*)).tw. (2215)
150 ((confin* or limit* or reduc* or restrict*) adj5 activit*).tw. (287686)
151 "ABR/AR".tw. (2)
152 or/145-151 (306430)
153 107 and 152 (1323)
154 115 or 144 or 153 (7933)
155 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (37190527)
156 exp humans/ or exp human experimentation/ or exp human experiment/ (28766294)
157 155 not 156 (8425819)
158 154 not 157 (7068)
159 (editorial or letter).pt. (2525212)
160 158 not 159 (7024)
161 (control* adj2 trial*).tw. (335917)
162 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (75356)
163 (nRCT or nRCTs or non-RCT$1).tw. (710)
164 (control* adj3 ("before and after" or "before after")).tw. (6026)
165 time series analysis/ (14323)
166 time series.tw. (34997)
167 pretest posttest control group design/ (206)
168 (pre- adj3 post-).tw. (113420)
169 (pretest adj3 posttest).tw. (6398)
170 controlled study/ (4410990)
171 (control* adj2 stud$3).tw. (351940)
172 control group/ (66412)
173 (control$ adj2 group$1).tw. (752960)
174 cohort analysis/ (351534)

175	cohort$1.tw. (712124)
176	retrospective study/ (870256)
177	longitudinal study/ (158850)
178	prospective study/ (640803)
179	(longitudinal or prospective or retrospective).tw. (1769406)
180	follow up/ (832325)
181	((followup or follow-up) adj (study or studies)).tw. (84044)
182	observational study/ (65288)
183	(observation$2 adj (study or studies)).tw. (117866)
184	population research/ (68938)
185	((population or population-based) adj (study or studies or analys#s)).tw. (26119)
186	((multidimensional or multi-dimensional) adj (study or studies)).tw. (178)
187	exp comparative study/ (2672805)
188	((comparative or comparison) adj (study or studies)).tw. (172996)
189	exp case control study/ (776653)
190	((case-control* or case-based or case-comparison) adj (study or studies)).tw. (147863)
191	or/161-190 (10505959)
192	160 and 191 (3020)
193	limit 192 to yr="1999-current" (2101)
194	193 use emez (1501)
195	94 or 194 (2173)
196	remove duplicates from 195 (1633) [TOTAL UNIQUE RECORDS]
197	196 use prmz (635) [UNIQUE MEDLINE RECORDS]
198	196 use emez (998) [UNIQUE EMBASE RECORDS]

Note

6.2.9. Risk of preeclampsia

Table 42 – Search strategies: Benefits-harms of screening for preeclampsia risk with additional tests compared with usual routine assessment based on history and physical exam (SRs)

Database	Medline (OVID) & Embase
Date	20-10-2014
Search strategy	1 exp pregnancy/ or exp Pregnancy Complications/ (1359684) 2 Pregnant Women/ (40716) 3 exp Pregnancy Trimesters/ (591738) 4 pregnan*.tw. (819805) 5 Prenatal Care/ or exp Prenatal Diagnosis/ (184097) 6 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (320738) 7 or/1-6 (1708600) 8 ((healthy or asymptomatic* or symptomless* or low risk* or lowrisk* or no risk* or norisk* or normal* or routine or standard or uncomplicated or safe or without complication* or without risk*) adj3 (female* or patient* or maternal* or mother* or pregnan* or wom#n)).tw. (682720) 9 7 and 8 (102330) 10 Diagnostic Tests, Routine/ (69128) 11 ((routine* or mass or standard* or universal*) adj3 test*).tw. (102915) 12 exp Mass Screening/ (262732) 13 (screen* or detect*).tw. (4455980) 14 (early adj3 (identif* or recogni*)).tw. (73061) 15 or/10-14 (4715871) 16 7 and 15 (201234) 17 Pre-Eclampsia/ (61876) 18 (pre-eclamp* or preeclamp*).tw. (49850) 19 tox?emi*.tw. (9928) 20 "eclampsia 1".tw. (58) 21 (EPH adj2 (gestos* or complex*)).tw. (985) 22 ((edema or oedema) adj proteinuria-hypertension adj2 (gestos* or complex*)).tw. (70) 23 or/17-22 (77267) 24 (9 or 16) and 23 (21060) 25 Pre-Eclampsia/bl, di, pc, ur, us (8810) 26 exp Proteinuria/di, ur (12236) 27 ((protein* or albumin* or microalbumin* or micro-albumin*) adj3 (urine or urinary)).tw. (43835) 28 Creatinine/ur (12407) 29 (creatinine adj3 (urine or urinary or ratio*)).tw. (29052) 30 Urinalysis/ (69177) 31 urinalys*.tw. (14828) 32 (dipstick* or dip stick*).tw. (5858) 33 Reagent Strips/ (5470)

34 ((timed or 24 hour or 24h or "24 h" or daily) adj2 (urine or urinary)).tw. (30573)
35 exp Ultrasonography, Doppler/ (84112)
36 (Doppler adj2 (flowmetry or ultrasound* or ultrason*)).tw. (56067)
37 Uterine Artery/us (280)
38 ((Doppler or ultrasound* or ultrason*) adj3 uterine arter*).tw. (1781)
39 Pulsatile Flow/ (14113)
40 (pulsatil* adj3 (flow or index* or indices*)).tw. (17631)
41 exp Biological Markers/ (796624)
42 biomarker*.tw. (257356)
43 ((biologic* or biochemical or chemical or clinical or serum) adj1 marker*).tw. (64486)
44 exp Pregnancy Proteins/bl, ur (10321)
45 (placenta* adj2 protein*).tw. (3158)
46 Pregnancy-Associated Plasma Protein-A/ (3249)
47 ("Pregnancy Associated" and alpha and "Plasma Protein").tw. (378)
48 ("PAPP-A" or PAPPA or "PAPP-alpha").tw. (3105)
49 (IGFBP-4 and (Metalloproteinase or Protease or Proteinase)).tw. (351)
50 Vascular Endothelial Growth Factor Receptor-1/ (8811)
51 vasculotropin receptor 1.tw. (0)
52 (FIT1 or "FIT-1" or "sFlt-1" or "VEGFR-1").tw. (8121)
53 ("VEGF Receptor" adj2 FLT*).tw. (436)
54 "fms-Like Tyrosine Kinase".tw. (3602)
55 "Proto-Oncogene Protein flt".tw. (0)
56 (placenta* adj growth factor).tw. (3552)
57 PIGF.tw. (547)
58 exp DNA/bl (14691)
59 exp RNA/bl (15834)
60 ((DNA or RNA or cfDNA or cffDNA or ccffDNA or cfRNA or cffRNA or ccffRNA or deoxyribonucleic acid$1 or deoxy-ribonucleic acid$1 or ribonucleic acid$1 or ribo-nucleic acid$1) adj5 (blood or plasma or serum)).tw. (78397)
61 or/25-60 (1383839)
62 24 and 61 (7465)
63 exp Animals/ not (exp Animals/ and Humans/) (8102966)
64 62 not 63 (7281)
65 (comment or editorial or interview or letter or news).pt. (2885807)
66 64 not 65 (7216)
67 limit 66 to systematic reviews [Limit not valid in Embase; records were retained] (2655)
68 meta analysis.pt. (53744)
69 exp meta-analysis as topic/ (30163)
70 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw. (162595)
71 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (195439)

72 exp Technology assessment, biomedical/ (20944)
73 (cochrane or health technology assessment or evidence report).jw. (26081)
74 or/68-73 (367677)
75 66 and 74 (126)
76 67 or 75 (2670)
77 limit 76 to yr="2011-current" (1232)
78 77 use prmz (44)
79 exp pregnancy/ (1292198)
80 exp pregnancy disorder/ (407904)
81 pregnant woman/ (40716)
82 pregnan*.tw. (819805)
83 exp prenatal care/ or prenatal diagnosis/ (159561)
84 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (320738)
85 or/79-84 (1793449)
86 ((healthy or asymptomatic* or symptomless* or low risk* or lowrisk* or no risk* or norisk* or normal* or routine or standard or uncomplicated or safe or without complication* or without risk*) adj3 (female* or patient* or maternal* or mother* or pregnan* or wom#n)).tw. (682720)
87 85 and 86 (103749)
88 exp diagnostic test/ (699869)
89 ((routine* or mass or standard* or universal*) adj3 test*).tw. (102915)
90 mass screening/ (130897)
91 (screen* or detect*).tw. (4455980)
92 (early adj3 (diagnos* or identif* or recogni*)).tw. (239047)
93 or/88-92 (5318495)
94 85 and 93 (243993)
95 preeclampsia/ (61876)
96 (pre-eclamp* or preeclamp*).tw. (49850)
97 tox?emi*.tw. (9928)
98 "eclampsia 1".tw. (58)
99 (EPH adj2 (gestos* or complex*)).tw. (985)
100 ((edema or oedema) adj proteinuria-hypertension adj2 (gestos* or complex*)).tw. (70)
101 or/95-100 (77267)
102 (87 or 94) and 101 (23253)
103 Pre-Eclampsia/di, pc (8444)
104 exp Proteinuria/di (8093)
105 ((protein* or albumin* or microalbumin* or micro-albumin*) adj3 (urine or urinary)).tw. (43835)
106 creatinine urine level/ (6390)
107 (creatinine adj3 (urine or urinary or ratio*)).tw. (29052)
108 exp Urinalysis/ (75048)
109 urinalys*.tw. (14828)
110 (dipstick* or dip stick*).tw. (5858)

111 test strip/ (2525)
112 ((timed or 24 hour or 24h or "24 h" or daily) adj2 (urine or urinary)).tw. (30573)
113 Doppler flowmetry/ (26476)
114 (Doppler adj2 (flowmetry or ultrasound* or ultrason*)).tw. (56067)
115 ((Doppler or ultrasound* or ultrason*) adj3 uterine arter*).tw. (1781)
116 pulsatile flow/ (14113)
117 (pulsatil* adj3 (flow or index* or indices*)).tw. (17631)
118 biological marker/ (303706)
119 (biomarker* or bioindicator*).tw. (260940)
120 ((biologic* or biochemical or chemical or clinical or serum) adj1 (indicator* or marker*)).tw. (76075)
121 placenta protein/ (1682)
122 (placenta* adj2 protein*).tw. (3158)
123 pregnancy associated plasma protein A/ (3249)
124 ("Pregnancy Associated" and alpha and "Plasma Protein").tw. (378)
125 ("PAPP-A" or PAPPA or "PAPP-alpha").tw. (3105)
126 (IGFBP-4 and (Metalloproteinase or Protease or Proteinase)).tw. (351)
127 vasculotropin receptor 1/ (5914)
128 "vasculotropin receptor 1".tw. (0)
129 (FIT1 or "FIT-1" or "sFlt-1" or "VEGFR-1").tw. (8121)
130 ("VEGF Receptor" adj2 FLT*).tw. (436)
131 "fms-Like Tyrosine Kinase".tw. (3602)
132 "Proto-Oncogene Protein flt".tw. (0)
133 (placenta* adj growth factor).tw. (3552)
134 PIGF.tw. (547)
135 exp DNA/ and maternal plasma/ (658)
136 exp RNA/ and maternal plasma/ (244)
137 ((DNA or RNA or cfDNA or cffDNA or ccffDNA or cfRNA or cffRNA or ccffRNA or deoxyribonucleic acid$1 or deoxy-ribonucleic acid$1 or ribonucleic acid$1 or ribo-nucleic acid$1) adj5 (blood or plasma or serum)).tw. (78397)
138 or/103-137 (860857)
139 102 and 138 (6763)
140 meta-analysis/ or "systematic review"/ or "meta analysis (topic)"/ or biomedical technology assessment/ (218269)
141 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw. (162595)
142 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (195439)
143 (health technology assessment or health technology assessment reports or health technology assessment winchester england).jn. (1865)
144 (evidence report technology assessment or evidence report technology assessment summary).jn. (443)
145 "cochrane database of systematic reviews".jn. (15498)
146 ("cochrane database of systematic reviews" or "cochrane database of systematic reviews online").jn. (22370)
147 or/140-146 (401137)
148 139 and 147 (172)

	149 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (37583663) 150 exp humans/ or exp human experimentation/ or exp human experiment/ (29082374) 151 149 not 150 (8502888) 152 148 not 151 (172) 153 (editorial or letter).pt. (2554888) 154 152 not 153 (169) 155 limit 154 to yr="2011-current" (78) 156 155 use emez (46) 157 78 or 156 (90) 158 remove duplicates from 157 (65) 159 158 use prmz (38) 160 158 use emez (27)
Note	
Database	**The Cochrane library**
Date	20-10-2014
Search strategy	ID Search Hits #1 [mh Pregnancy] or [mh "Pregnancy Complications"] 11137 #2 [mh "Pregnant Women"] 96 #3 [mh "Pregnancy Trimesters"] 1469 #4 pregnan*:ti,ab,kw 25440 #5 [mh "Prenatal Care"] or [mh "Prenatal Diagnosis"] 1948 #6 (prenatal* or antenatal* or (ante next natal*) or antepartum or (ante next partum) or perinatal* or (peri next natal*) or peripartum or (peri next partum)):ti,ab,kw 6110 #7 {or #1-#6} 27660 #8 ((healthy or asymptomatic* or symptomless* or (low next risk*) or lowrisk* or (no next risk*) or norisk* or normal* or routine or standard or uncomplicated or safe or (without next complication*) or (without next risk*)) near/3 (female* or patient* or maternal* or mother* or pregnan* or wom?n)):ti,ab,kw 29144 #9 #7 and #8 2599 #10 [mh "Diagnostic Tests, Routine"] 311 #11 ((routine* or mass or standard* or universal*) near/3 test*):ti,ab,kw 3634 #12 [mh "Mass Screening"] 4996 #13 (screen* or detect*):ti,ab,kw 54650 #14 (early near/3 (identif* or recogni*)):ti,ab,kw 668 #15 {or #10-#14} 58047 #16 #7 and #15 2734 #17 [mh Pre-Eclampsia] 613 #18 ((pre next eclamp*) or preeclamp*):ti,ab,kw 1213 #19 tox*emi*:ti,ab,kw 93 #20 "eclampsia 1":ti,ab,kw 3

#21	(EPH near/2 (gestos* or complex*)):ti,ab,kw	12
#22	(edema or oedema) next ("proteinuria-hypertension" near/2 (gestos* or complex*)):ti,ab,kw	0
#23	{or #17-#22}	1278
#24	(#9 or #16) and #23	281
#25	[mh Pre-Eclampsia/bl,di,pc,ur,us]	334
#26	[mh Proteinuria/di,ur]	344
#27	(protein* or albumin* or microalbumin* or (micro next albumin*)) near/3 (urine or urinary):ti,ab,kw	2192
#28	[mh Creatinine/ur]	864
#29	creatinine near/3 (urine or urinary or ratio*):ti,ab,kw	1646
#30	[mh Urinalysis]	214
#31	urinalys*:ti,ab,kw	1385
#32	dipstick* or (dip next stick*):ti,ab,kw	223
#33	[mh "Reagent Strips"]	92
#34	((timed or (24 next hour*) or 24h or "24 h" or daily) near/2 (urine or urinary)):ti,ab,kw	2571
#35	[mh "Ultrasonography, Doppler"]	2518
#36	(Doppler near/2 (flowmetry or ultrasound* or ultrason*)):ti,ab,kw	3343
#37	[mh "Uterine Artery"/us]	13
#38	(Doppler or ultrasound* or ultraso*) near/3 (uterine next arter*) .tw.	3
#39	[mh "Pulsatile Flow"]	460
#40	pulsatil* near/3 (flow or index* or indices*):ti,ab,kw	893
#41	[mh "Biological Markers"]	14828
#42	(biologic* or biochemical or chemical or clinical or serum) next (indicator* or marker*):ti,ab,kw	10472
#43	biomarker* or bioindicator*:ti,ab,kw	5281
#44	[mh "Pregnancy Proteins"/bl,ur]	234
#45	(placenta* near/2 protein*):ti,ab,kw	40
#46	[mh "Pregnancy-Associated Plasma Protein-A"]	19
#47	"Pregnancy Associated" and alpha and "Plasma Protein":ti,ab,kw	8
#48	"PAPP-A" or PAPPA or "PAPP-alpha":ti,ab,kw	99
#49	"IGFBP-4" and (Metalloproteinase or Protease or Proteinase):ti,ab,kw	2
#50	[mh "Vascular Endothelial Growth Factor Receptor-1"]	33
#51	"vasculotropin receptor 1":ti,ab,kw	23
#52	FIT1 or "FIT-1" or "sFlt-1" or "VEGFR-1":ti,ab,kw	46
#53	"VEGF Receptor" near/2 FLT*:ti,ab,kw	1
#54	"fms-Like Tyrosine Kinase":ti,ab,kw	40
#55	"Proto-Oncogene Protein flt":ti,ab,kw	0
#56	placenta* next "growth factor":ti,ab,kw	52
#57	PIGF:ti,ab,kw	4
#58	[mh DNA/bl]	474
#59	[mh RNA/bl]	1320
#60	(DNA or RNA or cfDNA or cffDNA or ccffDNA or cfRNA or cffRNA or ccffRNA or (deoxyribonucleic next acid*) or ("deoxy-ribonucleic" next acid*) or (ribonucleic next acid) or ("ribo-nucleic" next acid)) near/5 (blood or plasma or serum):ti,ab,kw	2147
#61	{or #25-#60}	34530

	#62 #24 and #61 Publication Year from 2011 to 2014	41
	DSR - 9 DARE - 2 CENTRAL – 28 (*did not download – review search only*) HTA – 1 NHS EED – 1 (*did not download – review search only*	
Note		

Table 43 – Search strategies: Benefits-harms of screening for preeclampsia risk with additional tests compared with usual routine assessment based on history and physical exam (Primary RCTs)

Database	Medline (OVID) & Embase
Date	03-11-2014
Search strategy	1 exp pregnancy/ or exp Pregnancy Complications/ (1450408) 2 Pregnant Women/ (48024) 3 exp Pregnancy Trimesters/ (678488) 4 pregnan*.tw. (896460) 5 Prenatal Care/ or exp Prenatal Diagnosis/ (190658) 6 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (335708) 7 or/1-6 (1822978) 8 ((healthy or asymptomatic* or symptomless* or low risk* or lowrisk* or no risk* or norisk* or normal* or routine or standard or uncomplicated or safe or without complication* or without risk*) adj3 (female* or patient* or maternal* or mother* or pregnan* or wom#n)).tw. (726851) 9 7 and 8 (112786) 10 Diagnostic Tests, Routine/ (70939) 11 ((routine* or mass or standard* or universal*) adj3 test*).tw. (108899) 12 exp Mass Screening/ (267375) 13 (screen* or detect*).tw. (4619800) 14 (early adj3 (identif* or recogni*)).tw. (76836) 15 or/10-14 (4890599) 16 7 and 15 (209098) 17 Pre-Eclampsia/ (63707) 18 (pre-eclamp* or preeclamp*).tw. (52000) 19 tox?emi*.tw. (16257) 20 "eclampsia 1".tw. (69) 21 (EPH adj2 (gestos* or complex*)).tw. (1093) 22 ((edema or oedema) adj proteinuria-hypertension adj2 (gestos* or complex*)).tw. (75) 23 or/17-22 (85078) 24 (9 or 16) and 23 (23050) 25 Pre-Eclampsia/bl, di, pc, ur, us (8818)

26 exp Proteinuria/di, ur (12242)
27 ((protein* or albumin* or microalbumin* or micro-albumin*) adj3 (urine or urinary)).tw. (46009)
28 Creatinine/ur (12418)
29 (creatinine adj3 (urine or urinary or ratio*)).tw. (30320)
30 Urinalysis/ (72667)
31 urinalys*.tw. (15655)
32 (dipstick* or dip stick*).tw. (5919)
33 Reagent Strips/ (5668)
34 ((timed or 24 hour or 24h or "24 h" or daily) adj2 (urine or urinary)).tw. (32451)
35 exp Ultrasonography, Doppler/ (85023)
36 (Doppler adj2 (flowmetry or ultrasound* or ultrason*)).tw. (57178)
37 Uterine Artery/us (282)
38 ((Doppler or ultrasound* or ultrason*) adj3 uterine arter*).tw. (1786)
39 Pulsatile Flow/ (14418)
40 (pulsatil* adj3 (flow or index* or indices*)).tw. (18145)
41 exp Biological Markers/ (799241)
42 (biomarker* or bioindicator*).tw. (262687)
43 ((biologic* or biochemical or chemical or clinical or serum) adj1 (indicator* or marker*)).tw. (76997)
44 exp Pregnancy Proteins/bl, ur (10332)
45 (placenta* adj2 protein*).tw. (3309)
46 Pregnancy-Associated Plasma Protein-A/ (3257)
47 ("Pregnancy Associated" and alpha and "Plasma Protein").tw. (381)
48 ("PAPP-A" or PAPPA or "PAPP-alpha").tw. (3119)
49 (IGFBP-4 and (Metalloproteinase or Protease or Proteinase)).tw. (351)
50 Vascular Endothelial Growth Factor Receptor-1/ (8828)
51 vasculotropin receptor 1.tw. (0)
52 (FIT1 or "FIT-1" or "sFlt-1" or "VEGFR-1").tw. (8133)
53 ("VEGF Receptor" adj2 FLT*).tw. (437)
54 "fms-Like Tyrosine Kinase".tw. (3605)
55 "Proto-Oncogene Protein flt".tw. (0)
56 (placenta* adj growth factor).tw. (3561)
57 PIGF.tw. (549)
58 exp DNA/bl (14729)
59 exp RNA/bl (15863)
60 ((DNA or RNA or cfDNA or cffDNA or ccffDNA or cfRNA or cffRNA or ccffRNA or deoxyribonucleic acid$1 or deoxy-ribonucleic acid$1 or ribonucleic acid$1 or ribo-nucleic acid$1) adj5 (blood or plasma or serum)).tw. (79740)
61 or/25-60 (1412988)
62 24 and 61 (7531)
63 exp Animals/ not (exp Animals/ and Humans/) (8906348)
64 62 not 63 (7337)
65 (comment or editorial or interview or letter or news).pt. (2900270)
66 64 not 65 (7272)

67 (controlled clinical trial or randomized controlled trial).pt. (483747)
68 clinical trials as topic.sh. (175982)
69 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1501053)
70 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (308452)
71 trial.ti. (311658)
72 or/67-71 (1922016)
73 66 and 72 (341)
74 73 use prmz (242)
75 exp pregnancy/ (1379679)
76 exp pregnancy disorder/ (463728)
77 pregnant woman/ (48024)
78 pregnan*.tw. (896460)
79 exp prenatal care/ or prenatal diagnosis/ (166599)
80 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (335708)
81 or/75-80 (1929830)
82 ((healthy or asymptomatic* or symptomless* or low risk* or lowrisk* or no risk* or norisk* or normal* or routine or standard or uncomplicated or safe or without complication* or without risk*) adj3 (female* or patient* or maternal* or mother* or pregnan* or wom#n)).tw. (726851)
83 81 and 82 (114500)
84 exp diagnostic test/ (774669)
85 ((routine* or mass or standard* or universal*) adj3 test*).tw. (108899)
86 mass screening/ (134342)
87 (screen* or detect*).tw. (4619800)
88 (early adj3 (diagnos* or identif* or recogni*)).tw. (258350)
89 or/84-88 (5570061)
90 81 and 89 (258188)
91 preeclampsia/ (63707)
92 (pre-eclamp* or preeclamp*).tw. (52000)
93 tox?emi*.tw. (16257)
94 "eclampsia 1".tw. (69)
95 (EPH adj2 (gestos* or complex*)).tw. (1093)
96 ((edema or oedema) adj proteinuria-hypertension adj2 (gestos* or complex*)).tw. (75)
97 or/91-96 (85078)
98 (83 or 90) and 97 (25476)
99 Pre-Eclampsia/di, pc (8453)
100 exp Proteinuria/di (8097)
101 ((protein* or albumin* or microalbumin* or micro-albumin*) adj3 (urine or urinary)).tw. (46009)
102 creatinine urine level/ (6914)
103 (creatinine adj3 (urine or urinary or ratio*)).tw. (30320)
104 exp Urinalysis/ (79244)
105 urinalys*.tw. (15655)

106 (dipstick* or dip stick*).tw. (5919)
107 test strip/ (2722)
108 ((timed or 24 hour or 24h or "24 h" or daily) adj2 (urine or urinary)).tw. (32451)
109 Doppler flowmetry/ (27290)
110 (Doppler adj2 (flowmetry or ultrasound* or ultrason*)).tw. (57178)
111 ((Doppler or ultrasound* or ultrason*) adj3 uterine arter*).tw. (1786)
112 pulsatile flow/ (14418)
113 (pulsatil* adj3 (flow or index* or indices*)).tw. (18145)
114 biological marker/ (305415)
115 (biomarker* or bioindicator*).tw. (262687)
116 ((biologic* or biochemical or chemical or clinical or serum) adj1 (indicator* or marker*)).tw. (76997)
117 placenta protein/ (2041)
118 (placenta* adj2 protein*).tw. (3309)
119 pregnancy associated plasma protein A/ (3257)
120 ("Pregnancy Associated" and alpha and "Plasma Protein").tw. (381)
121 ("PAPP-A" or PAPPA or "PAPP-alpha").tw. (3119)
122 (IGFBP-4 and (Metalloproteinase or Protease or Proteinase)).tw. (351)
123 vasculotropin receptor 1/ (5927)
124 "vasculotropin receptor 1".tw. (0)
125 (FIT1 or "FIT-1" or "sFlt-1" or "VEGFR-1").tw. (8133)
126 ("VEGF Receptor" adj2 FLT*).tw. (437)
127 "fms-Like Tyrosine Kinase".tw. (3605)
128 "Proto-Oncogene Protein flt".tw. (0)
129 (placenta* adj growth factor).tw. (3561)
130 PIGF.tw. (549)
131 exp DNA/ and maternal plasma/ (661)
132 exp RNA/ and maternal plasma/ (244)
133 ((DNA or RNA or cfDNA or cffDNA or ccffDNA or cfRNA or cffRNA or ccffRNA or deoxyribonucleic acid$1 or deoxy-ribonucleic acid$1 or ribonucleic acid$1 or ribo-nucleic acid$1) adj5 (blood or plasma or serum)).tw. (79740)
134 or/99-133 (877469)
135 98 and 134 (6850)
136 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (38606163)
137 exp humans/ or exp human experimentation/ or exp human experiment/ (29409297)
138 136 not 137 (9198536)
139 135 not 138 (6680)
140 (editorial or letter).pt. (2568489)
141 139 not 140 (6610)
142 randomized controlled trial/ or controlled clinical trial/ (973470)
143 exp "clinical trial (topic)"/ (120175)
144 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1501053)
145 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (308452)
146 trial.ti. (311658)

	147 or/142-146 (2062339) 148 141 and 147 (510) 149 148 use emczd (311) 150 74 or 149 (553) 151 remove duplicates from 150 (418) [TOTAL UNIQUE RECORDS] 152 151 use prmz (214) [UNIQUE MEDLINE RECORDS] 153 151 use emczd (204) [UNIQUE EMBASE RECORDS]
Note	
Database	**The Cochrane library (CENTRAL)**
Date	03-11-2014
Search strategy	ID Search Hits #1 [mh Pregnancy] or [mh "Pregnancy Complications"] 11185 #2 [mh "Pregnant Women"] 97 #3 [mh "Pregnancy Trimesters"] 1473 #4 pregnan*:ti,ab,kw 26181 #5 [mh "Prenatal Care"] or [mh "Prenatal Diagnosis"] 1956 #6 (prenatal* or antenatal* or (ante next natal*) or antepartum or (ante next partum) or perinatal* or (peri next natal*) or peripartum or (peri next partum)):ti,ab,kw 6356 #7 {or #1-#6} 28475 #8 ((healthy or asymptomatic* or symptomless* or (low next risk*) or lowrisk* or (no next risk*) or norisk* or normal* or routine or standard or uncomplicated or safe or (without next complication*) or (without next risk*)) near/3 (female* or patient* or maternal* or mother* or pregnan* or wom?n)):ti,ab,kw 29677 #9 #7 and #8 2685 #10 [mh "Diagnostic Tests, Routine"] 318 #11 ((routine* or mass or standard* or universal*) near/3 test*):ti,ab,kw 3710 #12 [mh "Mass Screening"] 5042 #13 (screen* or detect*):ti,ab,kw 56255 #14 (early near/3 (identif* or recogni*)):ti,ab,kw 712 #15 {or #10-#14} 59736 #16 #7 and #15 2866 #17 [mh Pre-Eclampsia] 614 #18 ((pre next eclamp*) or preeclamp*):ti,ab,kw 1251 #19 tox*emi*:ti,ab,kw 93 #20 "eclampsia 1":ti,ab,kw 3 #21 (EPH near/2 (gestos* or complex*)):ti,ab,kw 12 #22 (edema or oedema) next ("proteinuria-hypertension" near/2 (gestos* or complex*)):ti,ab,kw 0 #23 {or #17-#22} 1316 #24 (#9 or #16) and #23 291 #25 [mh Pre-Eclampsia/bl,di,pc,ur,us] 334 #26 [mh Proteinuria/di,ur] 344

#27 (protein* or albumin* or microalbumin* or (micro next albumin*)) near/3 (urine or urinary):ti,ab,kw 2236
#28 [mh Creatinine/ur] 864
#29 creatinine near/3 (urine or urinary or ratio*):ti,ab,kw 1698
#30 [mh Urinalysis] 215
#31 urinalys*:ti,ab,kw 1430
#32 dipstick* or (dip next stick*):ti,ab,kw 227
#33 [mh "Reagent Strips"] 92
#34 ((timed or (24 next hour*) or 24h or "24 h" or daily) near/2 (urine or urinary)):ti,ab,kw 2595
#35 [mh "Ultrasonography, Doppler"] 2520
#36 (Doppler near/2 (flowmetry or ultrasound* or ultrason*)):ti,ab,kw 3370
#37 [mh "Uterine Artery"/us] 13
#38 (Doppler or ultrasound* or ultraso*) near/3 (uterine next arter*) .tw. 3
#39 [mh "Pulsatile Flow"] 461
#40 pulsatil* near/3 (flow or index* or indices*):ti,ab,kw 900
#41 [mh "Biological Markers"] 14893
#42 (biologic* or biochemical or chemical or clinical or serum) next (indicator* or marker*):ti,ab,kw 10742
#43 biomarker* or bioindicator*:ti,ab,kw 5565
#44 [mh "Pregnancy Proteins"/bl,ur] 234
#45 (placenta* near/2 protein*):ti,ab,kw 40
#46 [mh "Pregnancy-Associated Plasma Protein-A"] 20
#47 "Pregnancy Associated" and alpha and "Plasma Protein":ti,ab,kw 8
#48 "PAPP-A" or PAPPA or "PAPP-alpha":ti,ab,kw 105
#49 "IGFBP-4" and (Metalloproteinase or Protease or Proteinase):ti,ab,kw 2
#50 [mh "Vascular Endothelial Growth Factor Receptor-1"] 33
#51 "vasculotropin receptor 1":ti,ab,kw 25
#52 FIT1 or "FIT-1" or "sFlt-1" or "VEGFR-1":ti,ab,kw 49
#53 "VEGF Receptor" near/2 FLT*:ti,ab,kw 1
#54 "fms-Like Tyrosine Kinase":ti,ab,kw 41
#55 "Proto-Oncogene Protein flt":ti,ab,kw 0
#56 placenta* next "growth factor":ti,ab,kw 54
#57 PIGF:ti,ab,kw 4
#58 [mh DNA/bl] 477
#59 [mh RNA/bl] 1321
#60 (DNA or RNA or cfDNA or cffDNA or ccffDNA or cfRNA or cffRNA or ccffRNA or (deoxyribonucleic next acid*) or ("deoxy-ribonucleic" next acid*) or (ribonucleic next acid) or ("ribo-nucleic" next acid)) near/5 (blood or plasma or serum):ti,ab,kw 2178
#61 {or #25-#60} 35096
#62 #24 and #61 159

DSR – 19 (*did not download; RCT search only*)
DARE – 5 (*did not download; RCT search only*)
CENTRAL – 132
HTA – 1 (*did not download; RCT search only*)
NHS EED – 2 (*did not download; RCT search only*)

Table 44 – Search strategies: Benefits-harms of screening for preeclampsia risk with additional tests compared with usual routine assessment based on history and physical exam (Primary observational evidene excluding "dipstick" intervention)

Database	Medline (OVID) & Embase
Date	06-11-2014
Search strategy	1 exp pregnancy/ or exp Pregnancy Complications/ (1451811) 2 Pregnant Women/ (48085) 3 exp Pregnancy Trimesters/ (678712) 4 pregnan*.tw. (897216) 5 Prenatal Care/ or exp Prenatal Diagnosis/ (190811) 6 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (335996) 7 or/1-6 (1824595) 8 ((healthy or asymptomatic* or symptomless* or low risk* or lowrisk* or no risk* or norisk* or normal* or routine or standard or uncomplicated or safe or without complication* or without risk*) adj3 (female* or patient* or maternal* or mother* or pregnan* or wom#n)).tw. (727709) 9 7 and 8 (112843) 10 Diagnostic Tests, Routine/ (70999) 11 ((routine* or mass or standard* or universal*) adj3 test*).tw. (108986) 12 exp Mass Screening/ (267694) 13 (screen* or detect*).tw. (4625133) 14 (early adj3 (identif* or recogni*)).tw. (76995) 15 or/10-14 (4896254) 16 7 and 15 (209270) 17 Pre-Eclampsia/ (63777) 18 (pre-eclamp* or preeclamp*).tw. (52064) 19 tox?emi*.tw. (16260) 20 "eclampsia 1".tw. (69) 21 (EPH adj2 (gestos* or complex*)).tw. (1093) 22 ((edema or oedema) adj proteinuria-hypertension adj2 (gestos* or complex*)).tw. (75) 23 or/17-22 (85155) 24 (9 or 16) and 23 (23063) 25 Pre-Eclampsia/bl, di, pc, us (8385) 26 exp Ultrasonography, Doppler/ (85214) 27 (Doppler adj2 (flowmetry or ultrasound* or ultrason*)).tw. (57267) 28 Uterine Artery/us (285) 29 ((Doppler or ultrasound* or ultrason*) adj3 uterine arter*).tw. (1787) 30 Pulsatile Flow/ (14442) 31 (pulsatil* adj3 (flow or index* or indices*)).tw. (18158) 32 exp Biological Markers/ (801138) 33 (biomarker* or bioindicator*).tw. (263432) 34 ((biologic* or biochemical or chemical or clinical or serum) adj1 (indicator* or marker*)).tw. (77072) 35 exp Pregnancy Proteins/bl, ur (10341)

36 (placenta* adj2 protein*).tw. (3312)
37 Pregnancy-Associated Plasma Protein-A/ (3259)
38 ("Pregnancy Associated" and alpha and "Plasma Protein").tw. (380)
39 ("PAPP-A" or PAPPA or "PAPP-alpha").tw. (3122)
40 (IGFBP-4 and (Metalloproteinase or Protease or Proteinase)).tw. (351)
41 Vascular Endothelial Growth Factor Receptor-1/ (8848)
42 vasculotropin receptor 1.tw. (0)
43 (FIT1 or "FIT-1" or "sFlt-1" or "VEGFR-1").tw. (8145)
44 ("VEGF Receptor" adj2 FLT*).tw. (438)
45 "fms-Like Tyrosine Kinase".tw. (3621)
46 "Proto-Oncogene Protein flt".tw. (0)
47 (placenta* adj growth factor).tw. (3565)
48 PIGF.tw. (549)
49 exp DNA/bl (14754)
50 exp RNA/bl (15911)
51 ((DNA or RNA or cfDNA or cffDNA or ccffDNA or cfRNA or cffRNA or ccffRNA or deoxyribonucleic acid$1 or deoxy-ribonucleic acid$1 or ribonucleic acid$1 or ribo-nucleic acid$1) adj5 (blood or plasma or serum)).tw. (79821)
52 or/25-51 (1247739)
53 24 and 52 (6788)
54 exp Animals/ not (exp Animals/ and Humans/) (8916219)
55 53 not 54 (6637)
56 (comment or editorial or interview or letter or news).pt. (2909972)
57 55 not 56 (6578)
58 controlled clinical trial.pt. (90638)
59 Controlled Clinical Trial/ or Controlled Clinical Trials as Topic/ (487383)
60 (control* adj2 trial*).tw. (347848)
61 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (77812)
62 (nRCT or nRCTs or non-RCT$1).tw. (743)
63 (control* adj3 ("before and after" or "before after")).tw. (6383)
64 time series.tw. (36175)
65 (pre- adj3 post-).tw. (118574)
66 (pretest adj3 posttest).tw. (6607)
67 (control* adj2 stud$3).tw. (364889)
68 Control Groups/ (81366)
69 (control$ adj2 group$1).tw. (790890)
70 or/58-69 (1947290)
71 57 and 70 (1381)
72 exp Cohort Studies/ (1617170)
73 cohort$1.tw. (736867)
74 Retrospective Studies/ (890211)
75 (longitudinal or prospective or retrospective).tw. (1832379)
76 ((followup or follow-up) adj (study or studies)).tw. (92330)

77 Observational study.pt. (6075)
78 (observation$2 adj (study or studies)).tw. (121553)
79 ((population or population-based) adj (study or studies or analys#s)).tw. (27368)
80 ((multidimensional or multi-dimensional) adj (study or studies)).tw. (195)
81 Comparative Study.pt. (1729844)
82 ((comparative or comparison) adj (study or studies)).tw. (191679)
83 exp Case-Control Studies/ (798688)
84 ((case-control* or case-based or case-comparison) adj (study or studies)).tw. (151837)
85 or/72-84 (5194236)
86 57 and 85 (2822)
87 71 or 86 (3256)
88 87 use prmz (2350)
89 exp pregnancy/ (1380996)
90 exp pregnancy disorder/ (463936)
91 pregnant woman/ (48085)
92 pregnan*.tw. (897216)
93 exp prenatal care/ or prenatal diagnosis/ (166715)
94 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (335996)
95 or/89-94 (1931464)
96 ((healthy or asymptomatic* or symptomless* or low risk* or lowrisk* or no risk* or norisk* or normal* or routine or standard or uncomplicated or safe or without complication* or without risk*) adj3 (female* or patient* or maternal* or mother* or pregnan* or wom#n)).tw. (727709)
97 95 and 96 (114557)
98 exp diagnostic test/ (775055)
99 ((routine* or mass or standard* or universal*) adj3 test*).tw. (108986)
100 mass screening/ (134505)
101 (screen* or detect*).tw. (4625133)
102 (early adj3 (diagnos* or identif* or recogni*)).tw. (258705)
103 or/98-102 (5576046)
104 95 and 103 (258387)
105 preeclampsia/ (63777)
106 (pre-eclamp* or preeclamp*).tw. (52064)
107 tox?emi*.tw. (16260)
108 "eclampsia 1".tw. (69)
109 (EPH adj2 (gestos* or complex*)).tw. (1093)
110 ((edema or oedema) adj proteinuria-hypertension adj2 (gestos* or complex*)).tw. (75)
111 or/105-110 (85155)
112 (97 or 104) and 111 (25491)
113 Pre-Eclampsia/di, pc (8460)
114 Doppler flowmetry/ (27305)
115 (Doppler adj2 (flowmetry or ultrasound* or ultrason*)).tw. (57267)

116 ((Doppler or ultrasound* or ultrason*) adj3 uterine arter*).tw. (1787)
117 pulsatile flow/ (14442)
118 (pulsatil* adj3 (flow or index* or indices*)).tw. (18158)
119 biological marker/ (306229)
120 (biomarker* or bioindicator*).tw. (263432)
121 ((biologic* or biochemical or chemical or clinical or serum) adj1 (indicator* or marker*)).tw. (77072)
122 placenta protein/ (2042)
123 (placenta* adj2 protein*).tw. (3312)
124 pregnancy associated plasma protein A/ (3259)
125 ("Pregnancy Associated" and alpha and "Plasma Protein").tw. (380)
126 ("PAPP-A" or PAPPA or "PAPP-alpha").tw. (3122)
127 (IGFBP-4 and (Metalloproteinase or Protease or Proteinase)).tw. (351)
128 vasculotropin receptor 1/ (5934)
129 "vasculotropin receptor 1".tw. (0)
130 (FIT1 or "FIT-1" or "sFlt-1" or "VEGFR-1").tw. (8145)
131 ("VEGF Receptor" adj2 FLT*).tw. (438)
132 "fms-Like Tyrosine Kinase".tw. (3621)
133 "Proto-Oncogene Protein flt".tw. (0)
134 (placenta* adj growth factor).tw. (3565)
135 PIGF.tw. (549)
136 exp DNA/ and maternal plasma/ (661)
137 exp RNA/ and maternal plasma/ (244)
138 ((DNA or RNA or cfDNA or cffDNA or ccffDNA or cfRNA or cffRNA or ccffRNA or deoxyribonucleic acid$1 or deoxy-ribonucleic acid$1 or ribonucleic acid$1 or ribo-nucleic acid$1) adj5 (blood or plasma or serum)).tw. (79821)
139 or/113-138 (712257)
140 112 and 139 (6152)
141 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (38672021)
142 exp humans/ or exp human experimentation/ or exp human experiment/ (29465596)
143 141 not 142 (9208096)
144 140 not 143 (6016)
145 (editorial or letter).pt. (2577136)
146 144 not 145 (5952)
147 controlled clinical trial/ (479181)
148 "controlled clinical trial (topic)"/ (3358)
149 (control* adj2 trial*).tw. (347848)
150 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (77812)
151 (nRCT or nRCTs or non-RCT$1).tw. (743)
152 (control* adj3 ("before and after" or "before after")).tw. (6383)
153 time series analysis/ (14610)
154 time series.tw. (36175)
155 pretest posttest control group design/ (211)
156 (pre- adj3 post-).tw. (118574)

	157 (pretest adj3 posttest).tw. (6607) 158 controlled study/ (4451440) 159 (control* adj2 stud$3).tw. (364889) 160 control group/ (81366) 161 (control$ adj2 group$1).tw. (790890) 162 or/147-161 (5708566) 163 146 and 162 (2162) 164 cohort analysis/ (363126) 165 cohort$1.tw. (736867) 166 retrospective study/ (890211) 167 longitudinal study/ (165516) 168 prospective study/ (656679) 169 (longitudinal or prospective or retrospective).tw. (1832379) 170 follow up/ (872299) 171 ((followup or follow-up) adj (study or studies)).tw. (92330) 172 observational study/ (68607) 173 (observation$2 adj (study or studies)).tw. (121553) 174 population research/ (70694) 175 ((population or population-based) adj (study or studies or analys#s)).tw. (27368) 176 ((multidimensional or multi-dimensional) adj (study or studies)).tw. (195) 177 exp comparative study/ (2767647) 178 ((comparative or comparison) adj (study or studies)).tw. (191679) 179 exp case control study/ (798688) 180 ((case-control* or case-based or case-comparison) adj (study or studies)).tw. (151837) 181 or/164-180 (6464859) 182 146 and 181 (2480) 183 163 or 182 (3512) 184 183 use emczd (2093) 185 88 or 184 (4443) 186 remove duplicates from 185 (3319) [TOTAL UNIQUE HITS] 187 186 use prmz (2166) [MEDLINE UNIQUE HITS] 188 186 use emczd (1153) [EMBASE UNIQUE HITS]
Note	Observational studies

Table 45 – Search strategies: Benefits-harms of screening for preeclampsia risk with additional tests compared with usual routine assessment based on history and physical exam (Primary observational evidence for dipstick intervention only)

Database	Medline (OVID) & Embase
Date	07-11-2014
Search strategy	1 exp pregnancy/ or exp Pregnancy Complications/ (1362098) 2 Pregnant Women/ (40782) 3 exp Pregnancy Trimesters/ (592195) 4 pregnan*.tw. (821291) 5 Prenatal Care/ or exp Prenatal Diagnosis/ (184366) 6 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (321338) 7 or/1-6 (1711519) 8 ((healthy or asymptomatic* or symptomless* or low risk* or lowrisk* or no risk* or norisk* or normal* or routine or standard or uncomplicated or safe or without complication* or without risk*) adj3 (female* or patient* or maternal* or mother* or pregnan* or wom#n)).tw. (684243) 9 7 and 8 (102471) 10 Diagnostic Tests, Routine/ (69224) 11 ((routine* or mass or standard* or universal*) adj3 test*).tw. (103143) 12 exp Mass Screening/ (263328) 13 (screen* or detect*).tw. (4466866) 14 (early adj3 (identif* or recogni*)).tw. (73332) 15 or/10-14 (4727355) 16 7 and 15 (201619) 17 Pre-Eclampsia/ (61969) 18 (pre-eclamp* or preeclamp*).tw. (49946) 19 tox?emi*.tw. (9932) 20 "eclampsia 1".tw. (58) 21 (EPH adj2 (gestos* or complex*)).tw. (985) 22 ((edema or oedema) adj proteinuria-hypertension adj2 (gestos* or complex*)).tw. (70) 23 or/17-22 (77383) 24 (9 or 16) and 23 (21089) 25 Pre-Eclampsia/di, ur (6601) 26 exp Proteinuria/di, ur (12255) 27 ((protein* or albumin* or microalbumin* or micro-albumin*) adj3 (urine or urinary)).tw. (43947) 28 Creatinine/ur (12427) 29 (creatinine adj3 (urine or urinary or ratio*)).tw. (29120) 30 Urinalysis/ (69310) 31 urinalys*.tw. (14862) 32 (dipstick* or dip stick*).tw. (5876) 33 Reagent Strips/ (5480) 34 ((timed or 24 hour or 24h or "24 h" or daily) adj2 (urine or urinary)).tw. (30618) 35 or/25-34 (182606) 36 24 and 35 (2876)

37	exp Animals/ not (exp Animals/ and Humans/) (8119075)
38	36 not 37 (2824)
39	(comment or editorial or interview or letter or news).pt. (2898246)
40	38 not 39 (2783)
41	controlled clinical trial.pt. (90638)
42	Controlled Clinical Trial/ or Controlled Clinical Trials as Topic/ (486838)
43	(control* adj2 trial*).tw. (343616)
44	(nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (76746)
45	(nRCT or nRCTs or non-RCT$1).tw. (739)
46	(control* adj3 ("before and after" or "before after")).tw. (6173)
47	time series.tw. (35767)
48	(pre- adj3 post-).tw. (115599)
49	(pretest adj3 posttest).tw. (6527)
50	(control* adj2 stud$3).tw. (358026)
51	Control Groups/ (67507)
52	(control$ adj2 group$1).tw. (764671)
53	or/41-52 (1906508)
54	40 and 53 (556)
55	exp Cohort Studies/ (1615905)
56	cohort$1.tw. (732374)
57	Retrospective Studies/ (887873)
58	(longitudinal or prospective or retrospective).tw. (1803011)
59	((followup or follow-up) adj (study or studies)).tw. (85069)
60	Observational study.pt. (6075)
61	(observation$2 adj (study or studies)).tw. (120862)
62	((population or population-based) adj (study or studies or analys#s)).tw. (26513)
63	((multidimensional or multi-dimensional) adj (study or studies)).tw. (178)
64	Comparative Study.pt. (1729844)
65	((comparative or comparison) adj (study or studies)).tw. (174592)
66	exp Case-Control Studies/ (798321)
67	((case-control* or case-based or case-comparison) adj (study or studies)).tw. (151259)
68	or/55-67 (5136028)
69	40 and 68 (1045)
70	54 or 69 (1269)
71	70 use prmz (728)
72	exp pregnancy/ (1294479)
73	exp pregnancy disorder/ (408248)
74	pregnant woman/ (40782)
75	pregnan*.tw. (821291)
76	exp prenatal care/ or prenatal diagnosis/ (159757)
77	(prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (321338)

78 or/72-77 (1796389)
79 ((healthy or asymptomatic* or symptomless* or low risk* or lowrisk* or no risk* or norisk* or normal* or routine or standard or uncomplicated or safe or without complication* or without risk*) adj3 (female* or patient* or maternal* or mother* or pregnan* or wom#n)).tw. (684243)
80 78 and 79 (103893)
81 exp diagnostic test/ (700595)
82 ((routine* or mass or standard* or universal*) adj3 test*).tw. (103143)
83 mass screening/ (131250)
84 (screen* or detect*).tw. (4466866)
85 (early adj3 (diagnos* or identif* or recogni*)).tw. (239754)
86 or/81-85 (5330687)
87 78 and 86 (244411)
88 preeclampsia/ (61969)
89 (pre-eclamp* or preeclamp*).tw. (49946)
90 tox?emi*.tw. (9932)
91 "eclampsia 1".tw. (58)
92 (EPH adj2 (gestos* or complex*)).tw. (985)
93 ((edema or oedema) adj proteinuria-hypertension adj2 (gestos* or complex*)).tw. (70)
94 or/88-93 (77383)
95 (80 or 87) and 94 (23284)
96 Pre-Eclampsia/di (6040)
97 exp Proteinuria/di (8104)
98 ((protein* or albumin* or microalbumin* or micro-albumin*) adj3 (urine or urinary)).tw. (43947)
99 creatinine urine level/ (6397)
100 (creatinine adj3 (urine or urinary or ratio*)).tw. (29120)
101 exp Urinalysis/ (75184)
102 urinalys*.tw. (14862)
103 (dipstick* or dip stick*).tw. (5876)
104 test strip/ (2529)
105 ((timed or 24 hour or 24h or "24 h" or daily) adj2 (urine or urinary)).tw. (30618)
106 or/96-105 (178432)
107 95 and 106 (3126)
108 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (37682201)
109 exp humans/ or exp human experimentation/ or exp human experiment/ (29166549)
110 108 not 109 (8517252)
111 107 not 110 (3079)
112 (editorial or letter).pt. (2565336)
113 111 not 112 (3031)
114 controlled clinical trial/ (478674)
115 "controlled clinical trial (topic)"/ (3313)
116 (control* adj2 trial*).tw. (343616)
117 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (76746)

118	(nRCT or nRCTs or non-RCT$1).tw. (739)
119	(control* adj3 ("before and after" or "before after")).tw. (6173)
120	time series analysis/ (14477)
121	time series.tw. (35767)
122	pretest posttest control group design/ (210)
123	(pre- adj3 post-).tw. (115599)
124	(pretest adj3 posttest).tw. (6527)
125	controlled study/ (4437916)
126	(control* adj2 stud$3).tw. (358026)
127	control group/ (67507)
128	(control$ adj2 group$1).tw. (764671)
129	or/114-128 (5657998)
130	113 and 129 (1040)
131	cohort analysis/ (361861)
132	cohort$1.tw. (732374)
133	retrospective study/ (887873)
134	longitudinal study/ (164463)
135	prospective study/ (654391)
136	(longitudinal or prospective or retrospective).tw. (1803011)
137	follow up/ (841198)
138	((followup or follow-up) adj (study or studies)).tw. (85069)
139	observational study/ (67922)
140	(observation$2 adj (study or studies)).tw. (120862)
141	population research/ (69327)
142	((population or population-based) adj (study or studies or analys#s)).tw. (26513)
143	((multidimensional or multi-dimensional) adj (study or studies)).tw. (178)
144	exp comparative study/ (2703834)
145	((comparative or comparison) adj (study or studies)).tw. (174592)
146	exp case control study/ (798321)
147	((case-control* or case-based or case-comparison) adj (study or studies)).tw. (151259)
148	or/131-147 (6329510)
149	113 and 148 (1208)
150	130 or 149 (1722)
151	150 use emez (1047)
152	71 or 151 (1775)
153	limit 152 to yr="2004-current" (1076)
154	remove duplicates from 153 (843) [TOTAL UNIQUE HITS]
155	154 use prmz (405) [MEDLINE UNIQUE HITS]
156	154 use emez (438) [EMBASE UNIQUE HITS]

Note

6.2.10. Pregnancies that passed their due date

Table 46 – Search strategies: Benefits-harms of different monitoring strategies by CTG, ultrasound, and combination of these tests with or without other tests in asymptomatic pregnant women remaining undelivered after ~40 weeks gestation (SRs)

Database	Medline (OVID) & Embase
Date	16-06-2014
Search strategy	1 exp Pregnancy/ or exp Pregnancy Complications/ (1325050) 2 Pregnant Women/ (38208) 3 exp Pregnancy Trimesters/ (581418) 4 pregnan*.tw. (794316) 5 Prenatal Care/ or exp Prenatal Diagnosis/ (179929) 6 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (309667) 7 or/1-6 (1662769) 8 Oligohydramnios/pc (40) 9 (oligohydramnios adj5 prevent*).tw. (45) 10 8 or 9 (77) 11 7 and 10 (70) 12 Pregnancy, Prolonged/ (4556) 13 ((prolonged or postterm or postdate* or post-term or post-date* or past due or overdue or beyond term or 41 week$1 or 42 week$1 or 43 week$1) adj5 (pregnan* or gestation*)).tw. (11392) 14 12 or 13 (13461) 15 (biophysical profile* or BPP).tw. (2424) 16 ((f?etal$2 or f?etus$2 or maternal*) adj3 (kick or kicks or kicked or kicking)).tw. (39) 17 Fetal Movement/ (3942) 18 ((f?etal$2 or f?etus$2) adj3 (activit* or move* or tone or breathing)).tw. (11298) 19 exp Fetal Monitoring/ (16148) 20 ((f?etal$2 or f?etus$2) adj3 (assess* or monitor* or surveillance*)).tw. (17961) 21 Heart Rate, Fetal/ (11288) 22 FHR.tw. (3440) 23 ((f?etal$2 or f?etus$2) adj3 (heart rate* or heart beat* or heartbeat*)).tw. (12589) 24 Cardiotocography/ (4387) 25 (cardiotocogra* or cardio tocogra* or CTG).tw. (9490) 26 Palpation/ (17626) 27 palpat*.tw. (24903) 28 ((intermittent or periodic*) adj3 auscultat*).tw. (195) 29 exp Ultrasonography/ and Amniotic Fluid/ (2735) 30 (amnio* adj fluid* adj3 (ultrason* or ultrasound* or echograph* or ectograph* or sonograph*)).tw. (538) 31 (amnio* adj fluid* adj3 (analy* or assess* or calculat* or estimat* or evaluat* or measur*)).tw. (4223) 32 (AFV adj3 (analy* or assess* or calculat* or estimat* or evaluat* or measur*)).tw. (70) 33 (amnio* adj (fluid* or pool*) adj3 (depth$1 or index* or level$1 or volume$1)).tw. (5590)

34 Amniotic Fluid/an [Analysis] (7727)
35 Oligohydramnios/ (4439)
36 oligohydramnio*.tw. (4581)
37 ((nonstress or non-stress) adj2 test*).tw. (1695)
38 (NST or NSTs).tw. (3251)
39 (contraction$1 adj2 stress test*).tw. (401)
40 (CST or CSTs).tw. (5134)
41 or/15-40 (119038)
42 14 and 41 (2297)
43 11 or 42 (2366)
44 exp Animals/ not (exp Animals/ and Humans/) (7922193)
45 43 not 44 (2323)
46 (comment or editorial or interview or letter or news).pt. (2800030)
47 45 not 46 (2300)
48 limit 47 to systematic reviews [Limit not valid in Embase; records were retained] (1233)
49 meta analysis.pt. (48765)
50 exp meta-analysis as topic/ (27502)
51 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw. (150114)
52 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (181414)
53 exp Technology assessment, biomedical/ (20552)
54 (cochrane or health technology assessment or evidence report).jw. (24875)
55 or/49-54 (342920)
56 47 and 55 (46)
57 48 or 56 (1244)
58 limit 57 to yr="2011-2014" (191)
59 58 use prmz (8)
60 exp pregnancy/ (1260614)
61 exp pregnancy disorder/ (399339)
62 pregnant woman/ (38208)
63 pregnan*.tw. (794316)
64 exp prenatal care/ (125541)
65 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (309667)
66 or/60-65 (1744387)
67 oligohydramnios/pc [Prevention] (40)
68 (oligohydramnios adj5 prevent*).tw. (45)
69 67 or 68 (77)
70 66 and 69 (74)
71 prolonged pregnancy/ (4556)

72 ((prolonged or postterm or postdate* or post-term or post-date* or past due or overdue or beyond term or 41 week$1 or 42 week$1 or 43 week$1) adj5 (pregnan* or gestation*)).tw. (11392)
73 71 or 72 (13461)
74 fetal biophysical profile/ (137)
75 (biophysical profile* or BPP).tw. (2424)
76 ((f?etal$2 or f?etus$2 or maternal*) adj3 (kick or kicks or kicked or kicking)).tw. (39)
77 fetus movement/ (2433)
78 ((f?etal$2 or f?etus$2) adj3 (activit* or move* or tone or breathing)).tw. (11298)
79 fetus monitoring/ (8428)
80 ((f?etal$2 or f?etus$2) adj3 (assess* or monitor* or surveillance*)).tw. (17961)
81 fetus heart rate/ (7069)
82 FHR.tw. (3440)
83 ((f?etal$2 or f?etus$2) adj3 (heart rate* or heart beat* or heartbeat*)).tw. (12589)
84 exp fetus echography/ (16044)
85 cardiotocography/ (4387)
86 (cardiotocogra* or cardio tocogra* or CTG).tw. (9490)
87 palpation/ (17626)
88 palpat*.tw. (24903)
89 ((intermittent or periodic*) adj3 auscultat*).tw. (195)
90 exp echography/ and exp amnion fluid/ (1611)
91 (amnio* adj fluid* adj3 (ultrason* or ultrasound* or echograph* or ectograph* or sonograph*)).tw. (538)
92 (amnio* adj fluid* adj3 (analy* or assess* or calculat* or estimat* or evaluat* or measur*)).tw. (4223)
93 (AFV adj3 (analy* or assess* or calculat* or estimat* or evaluat* or measur*)).tw. (70)
94 (amnio* adj (fluid* or pool*) adj3 (depth$1 or index* or level$1 or volume$1)).tw. (5590)
95 exp amnion fluid/an [Drug Analysis] (2392)
96 Oligohydramnios/ (4439)
97 oligohydramnio*.tw. (4581)
98 fetus heart rate/ (7069)
99 ((nonstress or non-stress) adj2 test*).tw. (1695)
100 (NST or NSTs).tw. (3251)
101 (contraction$1 adj2 stress test*).tw. (401)
102 (CST or CSTs).tw. (5134)
103 ((prolonged or postterm or post-date* or postdate* or post-term or past due or overdue or beyond term or 41 week$1 or 42 week$1) adj5 (pregnan* or gestation*)).tw. (11037)
104 or/74-103 (132911)
105 73 and 104 (11311)
106 70 or 105 (11384)
107 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (36562118)
108 exp humans/ or exp human experimentation/ or exp human experiment/ (28237645)
109 107 not 108 (8326044)
110 106 not 109 (10700)
111 (editorial or letter).pt. (2488688)

	112 110 not 111 (10595) 113 meta-analysis/ (128310) 114 "systematic review"/ (75693) 115 "meta analysis (topic)"/ (13690) 116 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw. (150114) 117 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (181414) 118 biomedical technology assessment/ (19450) 119 (cochrane or health technology assessment or evidence report).jw. (24875) 120 or/113-119 (376074) 121 112 and 120 (143) 122 limit 121 to yr="2011-current" (47) 123 122 use emez (27) 124 59 or 123 (35) 125 remove duplicates from 124 (30) [TOTAL UNIQUE RECORDS] 126 125 use prmz (8) [MEDLINE UNIQUE RECORDS] 127 125 use emez (22) [EMBASE UNIQUE RECORDS]
Note	
Database	**The Cochrane library**
Date	16-06-2014
Search strategy	ID Search Hits #1 [mh Pregnancy] or [mh "Pregnancy Complications"] 11072 #2 [mh "Pregnant Women"] 95 #3 [mh "Pregnancy Trimesters"] 1461 #4 pregnan*:ti,ab,kw 25068 #5 [mh "Prenatal Care"] or [mh "Prenatal Diagnosis"] 1937 #6 (prenatal* or antenatal* or (ante next natal*) or antepartum or (ante next partum) or perinatal* or (peri next natal*) or peripartum or (peri next partum)):ti,ab,kw 6013 #7 {or #1-#6} 27259 #8 [mh Oligohydramnios/pc] 7 #9 Oligohydramnios near/3 prevent*:ti,ab,kw 8 #10 #8 or #9 12 #11 #7 and #10 12 #12 [mh "Pregnancy, Prolonged"] 113 #13 ((prolonged or postterm or postdate* or (post next term) or (post next date*) or "past due" or overdue or "beyond term" or "41 weeks" or "42 weeks" or "43 weeks") near/5 (pregnan* or gestation*)):ti,ab,kw 475 #14 #12 or #13 475 #15 (biophysical next profile*) or BPP:ti,ab,kw 94

	#16 ((fetal* or foetal* or fetus* or foetus* or maternal*) near/3 (kick or kicks or kicked or kicking)):ti,ab,kw 3 #17 [mh "Fetal Movement"] 62 #18 ((fetal* or foetal* or fetus* or foetus*) near/3 (activit* or move* or tone or breathing)):ti,ab,kw 191 #19 [mh "Fetal Monitoring"] 356 #20 ((fetal* of foetal* or fetus* or foetus*) near/3 (assess* or monitor* or surveillance*)):ti,ab,kw 62 #21 [mh "Heart Rate, Fetal"] 317 #22 FHR:ti,ab,kw 113 #23 ((fetal* or foetal* or fetus* or foetus*) near/3 ((heart next rate*) or (heart next beat*) or heartbeat*)):ti,ab,kw 768 #24 [mh cardiotocography] 133 #25 (cardiotocogra* or (cardio next tocogra*) or CTG):ti,ab,kw 502 #26 [mh Palpation] 344 #27 palpat*:ti,ab,kw 818 #28 (intermittent or periodic*) near/3 auscultat*:ti,ab,kw 25 #29 [mh Ultrasonography] and [mh "Amniotic Fluid"] 19 #30 (amnio* next fluid* near/3 (ultrason* or ultrasound* or echograph* or ectograph* or sonograph*)):ti,ab,kw 10 #31 (amnio* next fluid* near/3 (analy* or assess* or calculat* or estimat* or evaluat* or measur*)):ti,ab,kw 61 #32 (AFV near/3 (analy* or assess* or calculat* or estimat* or evaluat* or measur*)):ti,ab,kw 5 #33 (amnio* next (fluid* or pool*) near/3 (depth* or index* or level* or volume*)):ti,ab,kw 117 #34 [mh "Amniotic Fluid"/an] 195 #35 [mh Oligohydramnios] 44 #36 oligohydramnio*:ti,ab,kw 99 #37 (nonstress or "non-stress") near/2 test*:ti,ab,kw 93 #38 (NST or NSTs):ti,ab,kw 89 #39 contraction* near/2 (stress next test*):ti,ab,kw 16 #40 CST or CSTs:ti,ab,kw 183 #41 {or #15-#40} 2841 #42 #14 and #41 111 #43 #11 or #42 Publication Year from 2011 to 2014 23 *DSR – 4 records* *DARE – 1 record* *CENTRAL – 18 records (did not download – review search only)*
Note	

Table 47 – Search strategies: Benefits-harms of monitoring strategies by CTG in asymptomatic pregnant women remaining undelivered after ~40 weeks gestation (Primary RCTs)

Database	Medline (OVID) & Embase
Date	12/13-08-2014
Search strategy	1 exp Pregnancy/ or exp Pregnancy Complications/ (1338169) 2 Pregnant Women/ (39401) 3 exp Pregnancy Trimesters/ (585883) 4 pregnan*.tw. (805367) 5 Prenatal Care/ or exp Prenatal Diagnosis/ (181747) 6 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (314473) 7 or/1-6 (1681367) 8 Oligohydramnios/pc (43) 9 (oligohydramnios adj5 prevent*).tw. (46) 10 8 or 9 (81) 11 7 and 10 (74) 12 Pregnancy, Prolonged/ (4593) 13 ((prolonged or postterm or postdate* or post-term or post-date* or past due or overdue or beyond term or 41 week$1 or 42 week$1 or 43 week$1) adj5 (pregnan* or gestation*)).tw. (11562) 14 12 or 13 (13643) 15 exp Fetal Monitoring/ (16272) 16 ((f?etal$2 or f?etus$2) adj3 (assess* or monitor* or surveillance*)).tw. (18199) 17 Heart Rate, Fetal/ (11428) 18 FHR.tw. (3486) 19 ((f?etal$2 or f?etus$2) adj3 (heart rate* or heart beat* or heartbeat*)).tw. (12727) 20 Cardiotocography/ (4481) 21 (cardiotocogra* or cardio tocogra* or CTG).tw. (9662) 22 Palpation/ (17908) 23 palpat*.tw. (25270) 24 ((intermittent or periodic*) adj3 auscultat*).tw. (200) 25 Oligohydramnios/ (4509) 26 oligohydramnio*.tw. (4647) 27 ((nonstress or non-stress) adj2 test*).tw. (1706) 28 (NST or NSTs).tw. (3292) 29 (contraction$1 adj2 stress test*).tw. (401) 30 (CST or CSTs).tw. (5261) 31 or/15-30 (96359) 32 14 and 31 (1793) 33 11 or 32 (1866) 34 (controlled clinical trial or randomized controlled trial).pt. (470028) 35 clinical trials as topic.sh. (171898)

36 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1442306)
37 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (292168)
38 trial.ti. (292584)
39 or/34-38 (1842231)
40 33 and 39 (235)
41 controlled clinical trial.pt. (89633)
42 Controlled Clinical Trial/ or Controlled Clinical Trials as Topic/ (483704)
43 (control* adj2 trial*).tw. (331686)
44 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (74640)
45 (nRCT or nRCTs or non-RCT$1).tw. (689)
46 (control* adj3 ("before and after" or "before after")).tw. (5976)
47 time series.tw. (34421)
48 (pre- adj3 post-).tw. (111834)
49 (pretest adj3 posttest).tw. (6353)
50 (control* adj2 stud$3).tw. (348866)
51 Control Groups/ (64917)
52 (control$ adj2 group$1).tw. (745638)
53 or/41-52 (1862137)
54 33 and 53 (269)
55 40 or 54 (367)
56 exp Animals/ not (exp Animals/ and Humans/) (7989829)
57 55 not 56 (363)
58 (comment or editorial or interview or letter or news).pt. (2826406)
59 57 not 58 (363)
60 59 use prmz (158)
61 exp pregnancy/ (1272942)
62 exp pregnancy disorder/ (403363)
63 pregnant woman/ (39401)
64 pregnan*.tw. (805367)
65 exp prenatal care/ (126836)
66 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (314473)
67 or/61-66 (1763818)
68 oligohydramnios/pc [Prevention] (43)
69 (oligohydramnios adj5 prevent*).tw. (46)
70 68 or 69 (81)
71 67 and 70 (78)
72 prolonged pregnancy/ (4593)
73 ((prolonged or postterm or postdate* or post-term or post-date* or past due or overdue or beyond term or 41 week$1 or 42 week$1 or 43 week$1) adj5 (pregnan* or gestation*)).tw. (11562)
74 72 or 73 (13643)
75 fetus monitoring/ (8488)
76 ((f?etal$2 or f?etus$2) adj3 (assess* or monitor* or surveillance*)).tw. (18199)

77 fetus heart rate/ (7165)
78 FHR.tw. (3486)
79 ((f?etal$2 or f?etus$2) adj3 (heart rate* or heart beat* or heartbeat*)).tw. (12727)
80 exp fetus echography/ (16265)
81 cardiotocography/ (4481)
82 (cardiotocogra* or cardio tocogra* or CTG).tw. (9662)
83 palpation/ (17908)
84 palpat*.tw. (25270)
85 ((intermittent or periodic*) adj3 auscultat*).tw. (200)
86 Oligohydramnios/ (4509)
87 oligohydramnio*.tw. (4647)
88 fetus heart rate/ (7165)
89 ((nonstress or non-stress) adj2 test*).tw. (1706)
90 (NST or NSTs).tw. (3292)
91 (contraction$1 adj2 stress test*).tw. (401)
92 (CST or CSTs).tw. (5261)
93 or/75-92 (106467)
94 74 and 93 (1810)
95 71 or 94 (1887)
96 randomized controlled trial/ or controlled clinical trial/ (951355)
97 exp "clinical trial (topic)"/ (112362)
98 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1442306)
99 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (292168)
100 trial.ti. (292584)
101 or/96-100 (1979326)
102 95 and 101 (260)
103 controlled clinical trial/ (475832)
104 "controlled clinical trial (topic)"/ (3101)
105 (control* adj2 trial*).tw. (331686)
106 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (74640)
107 (nRCT or nRCTs or non-RCT$1).tw. (689)
108 (control* adj3 ("before and after" or "before after")).tw. (5976)
109 time series analysis/ (14189)
110 time series.tw. (34421)
111 pretest posttest control group design/ (205)
112 (pre- adj3 post-).tw. (111834)
113 (pretest adj3 posttest).tw. (6353)
114 controlled study/ (4384206)
115 (control* adj2 stud$3).tw. (348866)
116 control group/ (64917)
117 (control$ adj2 group$1).tw. (745638)

	118 or/103-117 (5568731) 119 95 and 118 (453) 120 102 or 119 (537) 121 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (36980943) 122 exp humans/ or exp human experimentation/ or exp human experiment/ (28588462) 123 121 not 122 (8394056) 124 120 not 123 (528) 125 (editorial or letter).pt. (2510236) 126 124 not 125 (528) 127 126 use emez (382) 128 60 or 127 (540) 129 limit 128 to yr="2012-current" (72) 130 remove duplicates from 129 (60) [TOTAL UNIQUE RECORDS] 131 130 use prmz (13) [UNIQUE MEDLINE RECORDS] 132 130 use emez (47) [UNIQUE EMBASE RECORDS]
Note	
Database	**The Cochrane library**
Date	12-08-2014
Search strategy	ID Search Hits #1 [mh Pregnancy] or [mh "Pregnancy Complications"] 11112 #2 [mh "Pregnant Women"] 95 #3 [mh "Pregnancy Trimesters"] 1465 #4 pregnan*:ti,ab,kw 25258 #5 [mh "Prenatal Care"] or [mh "Prenatal Diagnosis"] 1943 #6 (prenatal* or antenatal* or (ante next natal*) or antepartum or (ante next partum) or perinatal* or (peri next natal*) or peripartum or (peri next partum)):ti,ab,kw 6062 #7 {or #1-#6} 27469 #8 [mh Oligohydramnios/pc] 7 #9 Oligohydramnios near/3 prevent*:ti,ab,kw 9 #10 #8 or #9 13 #11 #7 and #10 13 #12 [mh "Pregnancy, Prolonged"] 113 #13 ((prolonged or postterm or postdate* or (post next term) or (post next date*) or "past due" or overdue or "beyond term" or "41 weeks" or "42 weeks" or "43 weeks") near/5 (pregnan* or gestation*)):ti,ab,kw 481 #14 #12 or #13 481 #15 [mh "Fetal Monitoring"] 357 #16 ((fetal* of foetal* or fetus* or foetus*) near/3 (assess* or monitor* or surveillance*)):ti,ab,kw 66 #17 [mh "Heart Rate, Fetal"] 317 #18 FHR:ti,ab,kw 113 #19 ((fetal* or foetal* or fetus* or foetus*) near/3 ((heart next rate*) or (heart next beat*) or heartbeat*)):ti,ab,kw 774

	#20 [mh cardiotocography] 133 #21 (cardiotocogra* or (cardio next tocogra*) or CTG):ti,ab,kw 516 #22 [mh Palpation] 345 #23 palpat*:ti,ab,kw 825 #24 (intermittent or periodic*) near/3 auscultat*:ti,ab,kw 25 #25 [mh Oligohydramnios] 45 #26 oligohydramnio*:ti,ab,kw 102 #27 (nonstress or "non-stress") near/2 test*:ti,ab,kw 93 #28 (NST or NSTs):ti,ab,kw 89 #29 contraction* near/2 (stress next test*):ti,ab,kw 16 #30 CST or CSTs:ti,ab,kw 186 #31 {or #15-#30} 2538 #32 #14 and #31 100 #33 #11 or #32 Publication Year from 2012 to 2014 19 DSR – 4 *did not download – primary study search* DARE - 1 *did not download – primary study search* CENTRAL - 14
Note	

Table 48 – Search strategies: Benefits-harms of monitoring strategies by ultrasound examination of amniotic fluid index, volume and depth in asymptomatic pregnant women remaining undelivered after ~40 weeks gestation (Primary RCTs)

Database	Medline (OVID) & Embase
Date	12/13- 08- 2014
Search strategy	1 exp Pregnancy/ or exp Pregnancy Complications/ (1338169) 2 Pregnant Women/ (39401) 3 exp Pregnancy Trimesters/ (585883) 4 pregnan*.tw. (805418) 5 Prenatal Care/ or exp Prenatal Diagnosis/ (181747) 6 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (314492) 7 or/1-6 (1681425) 8 Oligohydramnios/pc (43) 9 (oligohydramnios adj5 prevent*).tw. (46) 10 8 or 9 (81) 11 7 and 10 (74) 12 Pregnancy, Prolonged/ (4593) 13 ((prolonged or postterm or postdate* or post-term or post-date* or past due or overdue or beyond term or 41 week$1 or 42 week$1 or 43 week$1) adj5 (pregnan* or gestation*)).tw. (11563) 14 12 or 13 (13644) 15 exp Ultrasonography/ and Amniotic Fluid/ (2766)

16	(amnio* adj fluid* adj3 (ultrason* or ultrasound* or echograph* or ectograph* or sonograph*)).tw. (545)
17	(amnio* adj fluid* adj3 (analy* or assess* or calculat* or estimat* or evaluat* or measur*)).tw. (4264)
18	(AFV adj3 (analy* or assess* or calculat* or estimat* or evaluat* or measur*)).tw. (70)
19	(amnio* adj (fluid* or pool*) adj3 (depth$1 or index* or level$1 or volume$1)).tw. (5656)
20	Amniotic Fluid/an [Analysis] (7748)
21	Oligohydramnios/ (4509)
22	oligohydramnio*.tw. (4647)
23	or/15-22 (22240)
24	14 and 23 (954)
25	11 or 24 (1027)
26	(controlled clinical trial or randomized controlled trial).pt. (470028)
27	clinical trials as topic.sh. (171898)
28	(randomi#ed or randomly or RCT$1 or placebo*).tw. (1442444)
29	((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (292178)
30	trial.ti. (292612)
31	or/26-30 (1842381)
32	25 and 31 (108)
33	controlled clinical trial.pt. (89633)
34	Controlled Clinical Trial/ or Controlled Clinical Trials as Topic/ (483704)
35	(control* adj2 trial*).tw. (331727)
36	(nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (74646)
37	(nRCT or nRCTs or non-RCT$1).tw. (690)
38	(control* adj3 ("before and after" or "before after")).tw. (5976)
39	time series.tw. (34424)
40	(pre- adj3 post-).tw. (111858)
41	(pretest adj3 posttest).tw. (6354)
42	(control* adj2 stud$3).tw. (348890)
43	Control Groups/ (64917)
44	(control$ adj2 group$1).tw. (745721)
45	or/33-44 (1862300)
46	25 and 45 (123)
47	32 or 46 (170)
48	exp Animals/ not (exp Animals/ and Humans/) (7989829)
49	47 not 48 (166)
50	(comment or editorial or interview or letter or news).pt. (2826730)
51	49 not 50 (166)
52	51 use prmz (68)
53	exp pregnancy/ (1272942)
54	exp pregnancy disorder/ (403363)
55	pregnant woman/ (39401)
56	pregnan*.tw. (805418)
57	exp prenatal care/ (126836)

58 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (314492)
59 or/53-58 (1763876)
60 oligohydramnios/pc [Prevention] (43)
61 (oligohydramnios adj5 prevent*).tw. (46)
62 60 or 61 (81)
63 59 and 62 (78)
64 prolonged pregnancy/ (4593)
65 ((prolonged or postterm or postdate* or post-term or post-date* or past due or overdue or beyond term or 41 week$1 or 42 week$1 or 43 week$1) adj5 (pregnan* or gestation*)).tw. (11563)
66 64 or 65 (13644)
67 exp echography/ and exp amnion fluid/ (1636)
68 (amnio* adj fluid* adj3 (ultrason* or ultrasound* or echograph* or ectograph* or sonograph*)).tw. (545)
69 (amnio* adj fluid* adj3 (analy* or assess* or calculat* or estimat* or evaluat* or measur*)).tw. (4264)
70 (AFV adj3 (analy* or assess* or calculat* or estimat* or evaluat* or measur*)).tw. (70)
71 (amnio* adj (fluid* or pool*) adj3 (depth$1 or index* or level$1 or volume$1)).tw. (5656)
72 exp amnion fluid/an [Drug Analysis] (2392)
73 Oligohydramnios/ (4509)
74 oligohydramnio*.tw. (4647)
75 or/67-74 (17387)
76 66 and 75 (817)
77 63 or 76 (894)
78 randomized controlled trial/ or controlled clinical trial/ (951355)
79 exp "clinical trial (topic)"/ (112362)
80 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1442444)
81 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (292178)
82 trial.ti. (292612)
83 or/78-82 (1979476)
84 77 and 83 (121)
85 controlled clinical trial/ (475832)
86 "controlled clinical trial (topic)"/ (3101)
87 (control* adj2 trial*).tw. (331727)
88 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (74646)
89 (nRCT or nRCTs or non-RCT$1).tw. (690)
90 (control* adj3 ("before and after" or "before after")).tw. (5976)
91 time series analysis/ (14189)
92 time series.tw. (34424)
93 pretest posttest control group design/ (205)
94 (pre- adj3 post-).tw. (111858)
95 (pretest adj3 posttest).tw. (6354)
96 controlled study/ (4384206)
97 (control* adj2 stud$3).tw. (348890)

	98 control group/ (64917) 99 (control$ adj2 group$1).tw. (745721) 100 or/85-99 (5568894) 101 77 and 100 (192) 102 84 or 101 (233) 103 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (36980943) 104 exp humans/ or exp human experimentation/ or exp human experiment/ (28588462) 105 103 not 104 (8394056) 106 102 not 105 (225) 107 (editorial or letter).pt. (2510483) 108 106 not 107 (225) 109 108 use emez (161) 110 52 or 109 (229) 111 limit 110 to yr="1980-current" (226) 112 remove duplicates from 111 (176) [TOTAL UNIQUE RECORDS] 113 112 use prmz (65) [MEDLINE UNIQUE RECORDS] 114 112 use emez (111) [EMBASE UNIQUE RECORDS]

Table 49 – Search strategies: Benefits-harms of monitoring strategies by combination of CTG and ultrasound examination of amniotic fluid index, volume and depth in asymptomatic pregnant women remaining undelivered after ~40 weeks gestation (Primary RCTs)

Database	Medline (OVID) & Embase
Date	12/13- 08- 2014
Search strategy	1 exp Pregnancy/ or exp Pregnancy Complications/ (1338169) 2 Pregnant Women/ (39401) 3 exp Pregnancy Trimesters/ (585883) 4 pregnan*.tw. (805418) 5 Prenatal Care/ or exp Prenatal Diagnosis/ (181747) 6 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (314492) 7 or/1-6 (1681425) 8 Oligohydramnios/pc (43) 9 (oligohydramnios adj5 prevent*).tw. (46) 10 8 or 9 (81) 11 7 and 10 (74) 12 Pregnancy, Prolonged/ (4593) 13 ((prolonged or postterm or postdate* or post-term or post-date* or past due or overdue or beyond term or 41 week$1 or 42 week$1 or 43 week$1) adj5 (pregnan* or gestation*)).tw. (11563) 14 12 or 13 (13644) 15 exp Fetal Monitoring/ (16272) 16 ((f?etal$2 or f?etus$2) adj3 (assess* or monitor* or surveillance*)).tw. (18199) 17 Heart Rate, Fetal/ (11428)

18	FHR.tw. (3486)
19	((f?etal$2 or f?etus$2) adj3 (heart rate* or heart beat* or heartbeat*)).tw. (12727)
20	Cardiotocography/ (4481)
21	(cardiotocogra* or cardio tocogra* or CTG).tw. (9662)
22	Palpation/ (17908)
23	palpat*.tw. (25271)
24	((intermittent or periodic*) adj3 auscultat*).tw. (200)
25	((nonstress or non-stress) adj2 test*).tw. (1706)
26	(NST or NSTs).tw. (3292)
27	(contraction$1 adj2 stress test*).tw. (401)
28	(CST or CSTs).tw. (5262)
29	or/15-28 (90744)
30	exp Ultrasonography/ and Amniotic Fluid/ (2766)
31	(amnio* adj fluid* adj3 (ultrason* or ultrasound* or echograph* or ectograph* or sonograph*)).tw. (545)
32	(amnio* adj fluid* adj3 (analy* or assess* or calculat* or estimat* or evaluat* or measur*)).tw. (4264)
33	(AFV adj3 (analy* or assess* or calculat* or estimat* or evaluat* or measur*)).tw. (70)
34	(amnio* adj (fluid* or pool*) adj3 (depth$1 or index* or level$1 or volume$1)).tw. (5656)
35	Amniotic Fluid/an [Analysis] (7748)
36	Oligohydramnios/ (4509)
37	oligohydramnio*.tw. (4647)
38	or/30-37 (22240)
39	29 and 38 (2374)
40	14 and 39 (290)
41	11 or 40 (364)
42	(controlled clinical trial or randomized controlled trial).pt. (470028)
43	clinical trials as topic.sh. (171898)
44	(randomi#ed or randomly or RCT$1 or placebo*).tw. (1442444)
45	((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (292178)
46	trial.ti. (292612)
47	or/42-46 (1842381)
48	41 and 47 (74)
49	controlled clinical trial.pt. (89633)
50	Controlled Clinical Trial/ or Controlled Clinical Trials as Topic/ (483704)
51	(control* adj2 trial*).tw. (331727)
52	(nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (74646)
53	(nRCT or nRCTs or non-RCT$1).tw. (690)
54	(control* adj3 ("before and after" or "before after")).tw. (5976)
55	time series.tw. (34424)
56	(pre- adj3 post-).tw. (111858)
57	(pretest adj3 posttest).tw. (6354)
58	(control* adj2 stud$3).tw. (348890)

59 Control Groups/ (64917)
60 (control$ adj2 group$1).tw. (745721)
61 or/49-60 (1862300)
62 41 and 61 (65)
63 48 or 62 (97)
64 exp Animals/ not (exp Animals/ and Humans/) (7989829)
65 63 not 64 (93)
66 (comment or editorial or interview or letter or news).pt. (2826730)
67 65 not 66 (93)
68 67 use prmz (39)
69 exp pregnancy/ (1272942)
70 exp pregnancy disorder/ (403363)
71 pregnant woman/ (39401)
72 pregnan*.tw. (805418)
73 exp prenatal care/ (126836)
74 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (314492)
75 or/69-74 (1763876)
76 oligohydramnios/pc [Prevention] (43)
77 (oligohydramnios adj5 prevent*).tw. (46)
78 76 or 77 (81)
79 75 and 78 (78)
80 prolonged pregnancy/ (4593)
81 ((prolonged or postterm or postdate* or post-term or post-date* or past due or overdue or beyond term or 41 week$1 or 42 week$1 or 43 week$1) adj5 (pregnan* or gestation*)).tw. (11563)
82 80 or 81 (13644)
83 fetus monitoring/ (8488)
84 ((f?etal$2 or f?etus$2) adj3 (assess* or monitor* or surveillance*)).tw. (18199)
85 fetus heart rate/ (7165)
86 FHR.tw. (3486)
87 ((f?etal$2 or f?etus$2) adj3 (heart rate* or heart beat* or heartbeat*)).tw. (12727)
88 exp fetus echography/ (16265)
89 cardiotocography/ (4481)
90 (cardiotocogra* or cardio tocogra* or CTG).tw. (9662)
91 palpation/ (17908)
92 palpat*.tw. (25271)
93 ((intermittent or periodic*) adj3 auscultat*).tw. (200)
94 fetus heart rate/ (7165)
95 ((nonstress or non-stress) adj2 test*).tw. (1706)
96 (NST or NSTs).tw. (3292)
97 (contraction$1 adj2 stress test*).tw. (401)
98 (CST or CSTs).tw. (5262)
99 or/83-98 (101265)

100	exp echography/ and exp amnion fluid/ (1636)
101	(amnio* adj fluid* adj3 (ultrason* or ultrasound* or echograph* or ectograph* or sonograph*)).tw. (545)
102	(amnio* adj fluid* adj3 (analy* or assess* or calculat* or estimat* or evaluat* or measur*)).tw. (4264)
103	(AFV adj3 (analy* or assess* or calculat* or estimat* or evaluat* or measur*)).tw. (70)
104	(amnio* adj (fluid* or pool*) adj3 (depth$1 or index* or level$1 or volume$1)).tw. (5656)
105	exp amnion fluid/an [Drug Analysis] (2392)
106	Oligohydramnios/ (4509)
107	oligohydramnio*.tw. (4647)
108	or/100-107 (17387)
109	99 and 108 (3042)
110	82 and 109 (292)
111	79 or 110 (370)
112	randomized controlled trial/ or controlled clinical trial/ (951355)
113	exp "clinical trial (topic)"/ (112362)
114	(randomi#ed or randomly or RCT$1 or placebo*).tw. (1442444)
115	((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (292178)
116	trial.ti. (292612)
117	or/112-116 (1979476)
118	111 and 117 (83)
119	controlled clinical trial/ (475832)
120	"controlled clinical trial (topic)"/ (3101)
121	(control* adj2 trial*).tw. (331727)
122	(nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (74646)
123	(nRCT or nRCTs or non-RCT$1).tw. (690)
124	(control* adj3 ("before and after" or "before after")).tw. (5976)
125	time series analysis/ (14189)
126	time series.tw. (34424)
127	pretest posttest control group design/ (205)
128	(pre- adj3 post-).tw. (111858)
129	(pretest adj3 posttest).tw. (6354)
130	controlled study/ (4384206)
131	(control* adj2 stud$3).tw. (348890)
132	control group/ (64917)
133	(control$ adj2 group$1).tw. (745721)
134	or/119-133 (5568894)
135	111 and 134 (96)
136	118 or 135 (124)
137	exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (36980943)
138	exp humans/ or exp human experimentation/ or exp human experiment/ (28588462)
139	137 not 138 (8394056)
140	136 not 139 (119)

	141 (editorial or letter).pt. (2510483) 142 140 not 141 (119) 143 142 use emez (82) 144 68 or 143 (121) 145 limit 144 to yr="1980-current" (120) 146 remove duplicates from 145 (95) [TOTAL UNIQUE RECORDS] 147 146 use prmz (37) [MEDLINE UNIQUE RECORDS] 148 146 use emez (58) [EMBASE UNIQUE RECORDS]
Database	**The Cochrane library**
Date	13- 08- 2014
Search strategy	ID Search Hits #1 [mh Pregnancy] or [mh "Pregnancy Complications"] 11112 #2 [mh "Pregnant Women"] 95 #3 [mh "Pregnancy Trimesters"] 1465 #4 pregnan*:ti,ab,kw 25259 #5 [mh "Prenatal Care"] or [mh "Prenatal Diagnosis"] 1943 #6 (prenatal* or antenatal* or (ante next natal*) or antepartum or (ante next partum) or perinatal* or (peri next natal*) or peripartum or (peri next partum)):ti,ab,kw 6062 #7 {or #1-#6} 27470 #8 [mh Oligohydramnios/pc] 7 #9 Oligohydramnios near/3 prevent*:ti,ab,kw 9 #10 #8 or #9 13 #11 #7 and #10 13 #12 [mh "Pregnancy, Prolonged"] 113 #13 ((prolonged or postterm or postdate* or (post next term) or (post next date*) or "past due" or overdue or "beyond term" or "41 weeks" or "42 weeks" or "43 weeks") near/5 (pregnan* or gestation*)):ti,ab,kw 481 #14 #12 or #13 481 #15 [mh "Fetal Monitoring"] 357 #16 ((fetal* of foetal* or fetus* or foetus*) near/3 (assess* or monitor* or surveillance*)):ti,ab,kw 66 #17 [mh "Heart Rate, Fetal"] 317 #18 FHR:ti,ab,kw 113 #19 ((fetal* or foetal* or fetus* or foetus*) near/3 ((heart next rate*) or (heart next beat*) or heartbeat*)):ti,ab,kw 774 #20 [mh cardiotocography] 133 #21 (cardiotocogra* or (cardio next tocogra*) or CTG):ti,ab,kw 516 #22 [mh Palpation] 345 #23 palpat*:ti,ab,kw 825 #24 (intermittent or periodic*) near/3 auscultat*:ti,ab,kw 25 #25 (nonstress or "non-stress") near/2 test*:ti,ab,kw 93 #26 (NST or NSTs):ti,ab,kw 89 #27 contraction* near/2 (stress next test*):ti,ab,kw 16 #28 CST or CSTs:ti,ab,kw 186

#29	{or #15-#28}	2469	
#30	[mh Ultrasonography] and [mh "Amniotic Fluid"]	20	
#31	(amnio* next fluid* near/3 (ultrason* or ultrasound* or echograph* or ectograph* or sonograph*)):ti,ab,kw	10	
#32	(amnio* next fluid* near/3 (analy* or assess* or calculat* or estimat* or evaluat* or measur*)):ti,ab,kw	62	
#33	(AFV near/3 (analy* or assess* or calculat* or estimat* or evaluat* or measur*)):ti,ab,kw	5	
#34	(amnio* next (fluid* or pool*) near/3 (depth* or index* or level* or volume*)):ti,ab,kw	118	
#35	[mh "Amniotic Fluid"/an]	197	
#36	[mh Oligohydramnios]	45	
#37	oligohydramnio*:ti,ab,kw	102	
#38	{or #30-#37}	349	
#39	#29 and #38	76	
#40	#14 and #39	26	
#41	#11 or #40 Publication Year from 1980 to 2014	38	

DSR – 5 *did not download – primary study search*
DARE – 1 *did not download – primary study search*
CENTRAL – 32

Table 50 – Search strategies: Benefits-harms of monitoring strategies by CTG, ultrasound examination of amniotic fluid index, volume and depth, and combination of these tests in asymptomatic pregnant women remaining undelivered after ~40 weeks gestation (Primary observational body of evidence)

Database	Medline (OVID) & Embase
Date	20- 08- 2014
Search strategy	1 exp Pregnancy/ or exp Pregnancy Complications/ (1428424) 2 Pregnant Women/ (46841) 3 exp Pregnancy Trimesters/ (672625) 4 pregnan*.tw. (882075) 5 Prenatal Care/ or exp Prenatal Diagnosis/ (188300) 6 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (329534) 7 or/1-6 (1795575) 8 Oligohydramnios/pc (43) 9 (oligohydramnios adj5 prevent*).tw. (46) 10 8 or 9 (81) 11 7 and 10 (74) 12 Pregnancy, Prolonged/ (5502) 13 ((prolonged or postterm or postdate* or post-term or post-date* or past due or overdue or beyond term or 41 week$1 or 42 week$1 or 43 week$1) adj5 (pregnan* or gestation*)).tw. (12693) 14 12 or 13 (15062) 15 exp Fetal Monitoring/ (17420) 16 ((f?etal$2 or f?etus$2) adj3 (assess* or monitor* or surveillance*)).tw. (19271) 17 Heart Rate, Fetal/ (12701)

18	FHR.tw. (3706)
19	((f?etal$2 or f?etus$2) adj3 (heart rate* or heart beat* or heartbeat*)).tw. (13786)
20	Cardiotocography/ (5107)
21	(cardiotocogra* or cardio tocogra* or CTG).tw. (9929)
22	Palpation/ (19804)
23	palpat*.tw. (28580)
24	((intermittent or periodic*) adj3 auscultat*).tw. (204)
25	exp Ultrasonography/ and Amniotic Fluid/ (2862)
26	(amnio* adj fluid* adj3 (ultrason* or ultrasound* or echograph* or ectograph* or sonograph*)).tw. (559)
27	(amnio* adj fluid* adj3 (analy* or assess* or calculat* or estimat* or evaluat* or measur*)).tw. (4801)
28	(AFV adj3 (analy* or assess* or calculat* or estimat* or evaluat* or measur*)).tw. (72)
29	(amnio* adj (fluid* or pool*) adj3 (depth$1 or index* or level$1 or volume$1)).tw. (6082)
30	Amniotic Fluid/an [Analysis] (7748)
31	Oligohydramnios/ (4615)
32	oligohydramnio*.tw. (4745)
33	((nonstress or non-stress) adj2 test*).tw. (1722)
34	(NST or NSTs).tw. (3350)
35	(contraction$1 adj2 stress test*).tw. (418)
36	(CST or CSTs).tw. (5367)
37	or/15-36 (118190)
38	14 and 37 (2319)
39	11 or 38 (2392)
40	exp Cohort Studies/ (1563011)
41	cohort$1.tw. (705229)
42	Retrospective Studies/ (863730)
43	(longitudinal or prospective or retrospective).tw. (1777465)
44	((followup or follow-up) adj (study or studies)).tw. (90753)
45	Observational study.pt. (4109)
46	(observation$2 adj (study or studies)).tw. (116477)
47	((population or population-based) adj (study or studies or analys#s)).tw. (26735)
48	((multidimensional or multi-dimensional) adj (study or studies)).tw. (193)
49	Comparative Study.pt. (1698814)
50	((comparative or comparison) adj (study or studies)).tw. (188910)
51	exp Case-Control Studies/ (769835)
52	((case-control* or case-based or case-comparison) adj (study or studies)).tw. (147046)
53	or/40-52 (5059508)
54	39 and 53 (693)
55	exp Animals/ not (exp Animals/ and Humans/) (8788879)
56	54 not 55 (692)
57	(comment or editorial or interview or letter or news).pt. (2840602)
58	56 not 57 (689)
59	58 use prmz (388)

60 exp pregnancy/ (1359938)
61 exp pregnancy disorder/ (459423)
62 pregnant woman/ (46841)
63 pregnan*.tw. (882075)
64 exp prenatal care/ (133901)
65 (prenatal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum).tw. (329534)
66 or/60-65 (1900081)
67 oligohydramnios/pc [Prevention] (43)
68 (oligohydramnios adj5 prevent*).tw. (46)
69 67 or 68 (81)
70 66 and 69 (78)
71 prolonged pregnancy/ (5502)
72 ((prolonged or postterm or postdate* or post-term or post-date* or past due or overdue or beyond term or 41 week$1 or 42 week$1 or 43 week$1) adj5 (pregnan* or gestation*)).tw. (12693)
73 71 or 72 (15062)
74 fetus monitoring/ (9636)
75 ((f?etal$2 or f?etus$2) adj3 (assess* or monitor* or surveillance*)).tw. (19271)
76 fetus heart rate/ (8438)
77 FHR.tw. (3706)
78 ((f?etal$2 or f?etus$2) adj3 (heart rate* or heart beat* or heartbeat*)).tw. (13786)
79 exp fetus echography/ (16330)
80 cardiotocography/ (5107)
81 (cardiotocogra* or cardio tocogra* or CTG).tw. (9929)
82 palpation/ (19804)
83 palpat*.tw. (28580)
84 ((intermittent or periodic*) adj3 auscultat*).tw. (204)
85 exp echography/ and exp amnion fluid/ (1734)
86 (amnio* adj fluid* adj3 (ultrason* or ultrasound* or echograph* or ectograph* or sonograph*)).tw. (559)
87 (amnio* adj fluid* adj3 (analy* or assess* or calculat* or estimat* or evaluat* or measur*)).tw. (4801)
88 (AFV adj3 (analy* or assess* or calculat* or estimat* or evaluat* or measur*)).tw. (72)
89 (amnio* adj (fluid* or pool*) adj3 (depth$1 or index* or level$1 or volume$1)).tw. (6082)
90 exp amnion fluid/an [Drug Analysis] (2392)
91 Oligohydramnios/ (4615)
92 oligohydramnio*.tw. (4745)
93 fetus heart rate/ (8438)
94 ((nonstress or non-stress) adj2 test*).tw. (1722)
95 (NST or NSTs).tw. (3350)
96 (contraction$1 adj2 stress test*).tw. (418)
97 (CST or CSTs).tw. (5367)
98 or/74-97 (123241)
99 73 and 98 (2203)

100	70 or 99 (2280)
101	cohort analysis/ (348024)
102	cohort$1.tw. (705229)
103	retrospective study/ (863730)
104	longitudinal study/ (158413)
105	prospective study/ (637105)
106	(longitudinal or prospective or retrospective).tw. (1777465)
107	follow up/ (849715)
108	((followup or follow-up) adj (study or studies)).tw. (90753)
109	observational study/ (63693)
110	(observation$2 adj (study or studies)).tw. (116477)
111	population research/ (69859)
112	((population or population-based) adj (study or studies or analys#s)).tw. (26735)
113	((multidimensional or multi-dimensional) adj (study or studies)).tw. (193)
114	exp comparative study/ (2727259)
115	((comparative or comparison) adj (study or studies)).tw. (188910)
116	exp case control study/ (769835)
117	((case-control* or case-based or case-comparison) adj (study or studies)).tw. (147046)
118	or/101-117 (6314386)
119	100 and 118 (789)
120	exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (37971943)
121	exp humans/ or exp human experimentation/ or exp human experiment/ (28886242)
122	120 not 121 (9087347)
123	119 not 122 (788)
124	(editorial or letter).pt. (2524041)
125	123 not 124 (787)
126	125 use emczd (449)
127	59 or 126 (837)
128	remove duplicates from 127 (600) [TOTAL UNIQUE REFS]
129	128 use prmz (383) [MEDLINE UNIQUE HITS]
130	128 use emczd (217) EMBASE UNIQUE HITS]

7. STUDY SELECTION

7.1. Study selection for full search questions

7.1.1. Cytomegalovirus

On May 2014 a search was performed in MEDLINE (including PreMedline), Embase and CENTRAL to identify systematic reviews, RCTs and observational studies evaluating the benefits and harms of CMV screening and advice during pregnancy.

We identified a total of 1428 records (MEDLINE=702, EMBASE=685, Cochrane Library=42). After de-duplicating, 1023 records were screened on title and abstract. A total of 92 records were screened on full text.

7.1.1.1. Benefits-harms of universal screening for CMV during pregnancy

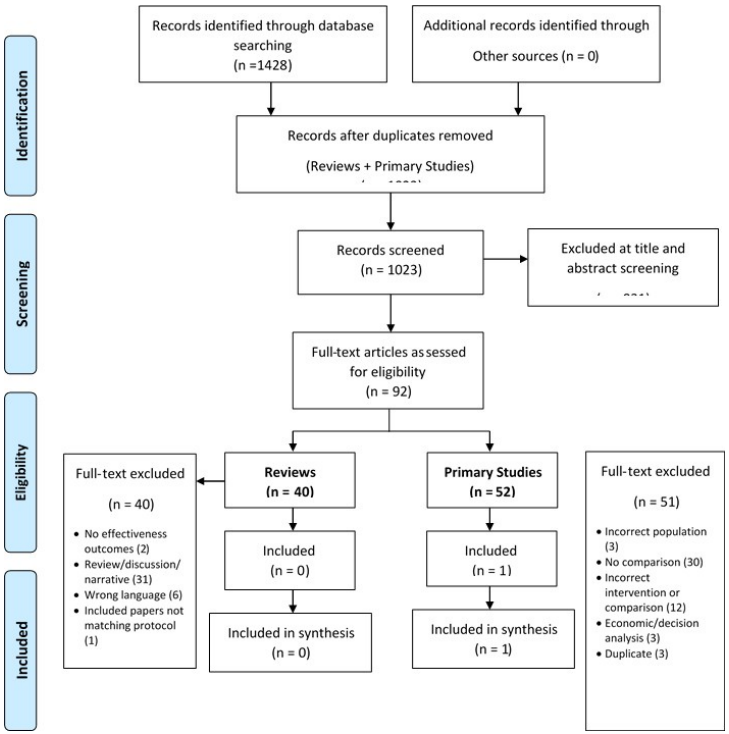
Among the 92 records screened on full text, no systematic reviews, randomized controlled trials or observational studies were identified that investigated the effects of screening vs. no screening for CMV infection.

7.1.1.2. Benefits-harms of lifestyle advice regarding CMV during pregnancy

Among the 92 records screened on full text, no systematic review investigated the effectiveness of advice on cytomegalovirus (including educational programmes) compared to general advice (not including specific systematic details on cytomegalovirus). One cluster randomised controlled trial was identified.[5]

This study investigated advice in combination with adherence measures (home visits) compared to no advice (nor any adherence measures).

Figure 6 – PRISMA flowchart: screening for CMV



7.1.2. Toxoplasmosis

On May 2014 a search was performed in MEDLINE (including PreMedline), Embase and CENTRAL to identify systematic reviews, RCTs and observational studies evaluating the benefits and harms of toxoplasmosis screening and advice during pregnancy.

We identified a total of 2516 records (MEDLINE=753, EMBASE=666, Cochrane Library=20). After de-duplicating, 1147 were screened on title and abstract. A total of 123 records were screened on full text.

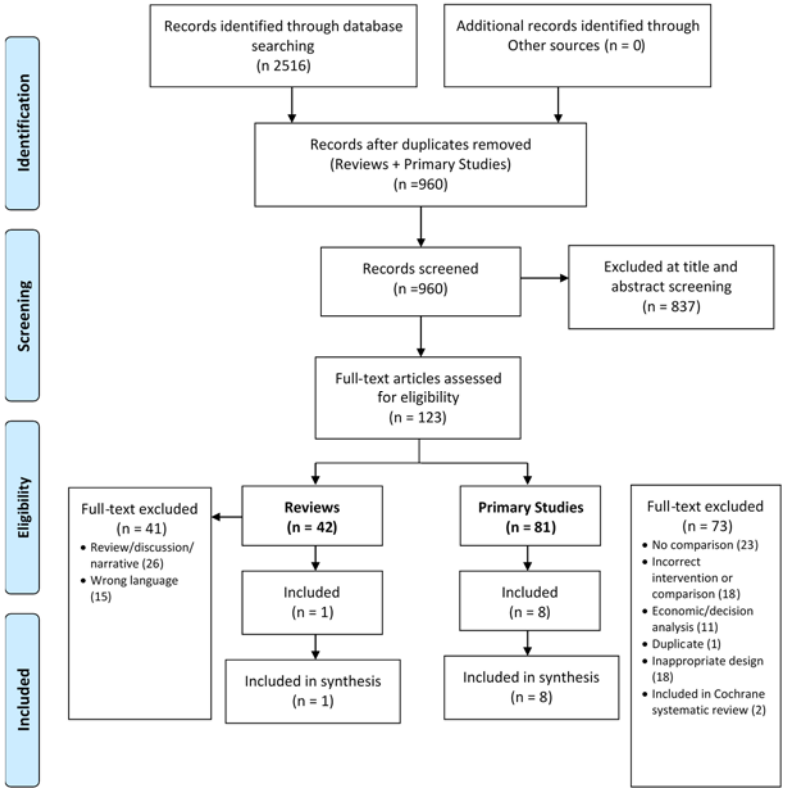
7.1.2.1. Benefits-harms of universal screening for toxoplasmosis during pregnancy

Among the 123 records screened on full text, no systematic review were identified that investigated the effects of screening vs. no screening for toxoplasmosis infection. No randomized controlled trials were identified and six observational studies were included.[6-11]

7.1.2.2. Benefits-harms of lifestyle advice regarding toxoplasmosis during pregnancy

Among the 123 records screened on full text, one systematic review from the Cochrane collaboration[12] as well as two observational studies (pre-post design) were identified.that investigated the benefits and harms of advice on toxoplasmosis (including educational programmes) compared to general advice (not including specific systematic details on toxoplasmosis).

Figure 7 – PRISMA flowchart: screening for toxoplasmosis

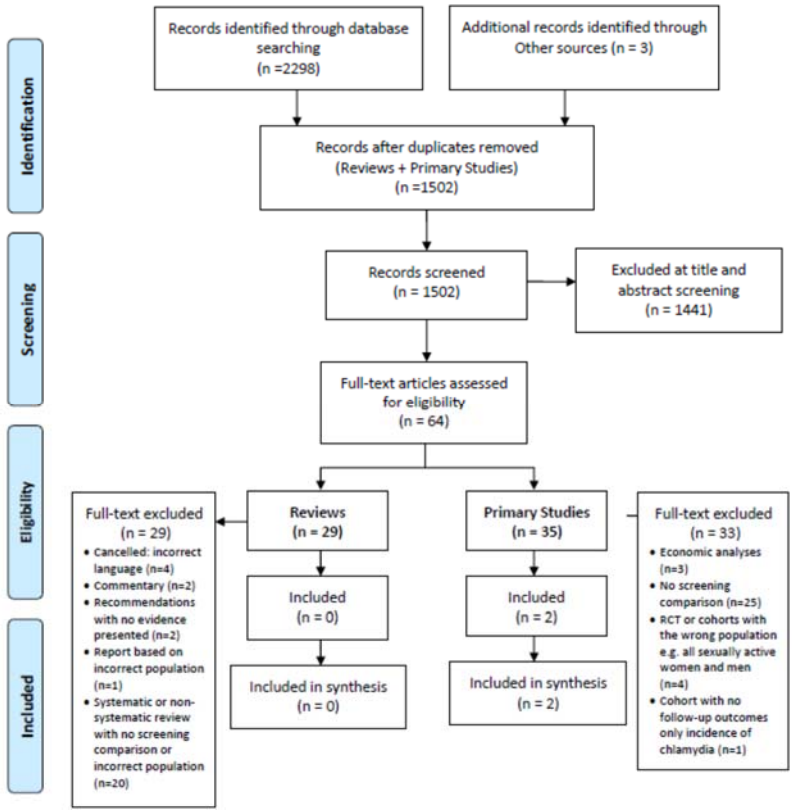


7.1.3. Chlamydia trachomatis

On July 2014 a search was performed in MEDLINE (including PreMedline), Embase and CENTRAL to identify systematic reviews, RCTs and observational studies evaluating the benefits and harms of Chlamydia trachomatis screening during pregnancy.

We identified a total of 2298 records (MEDLINE=1088, EMBASE=1066, Cochrane Library=145). After de-duplicating, 1502 records formed the first screening set. A total of 64 records were screened on full text. No systematic reviews or randomized controlled trials that investigated the effects of universal screening vs. no screening or risk based testing for chlamydia trachomatis were retrieved in the search. Two observational studies have been found.[13]

Figure 8 – PRISMA flowchart: screening for chlamydia trachomatis

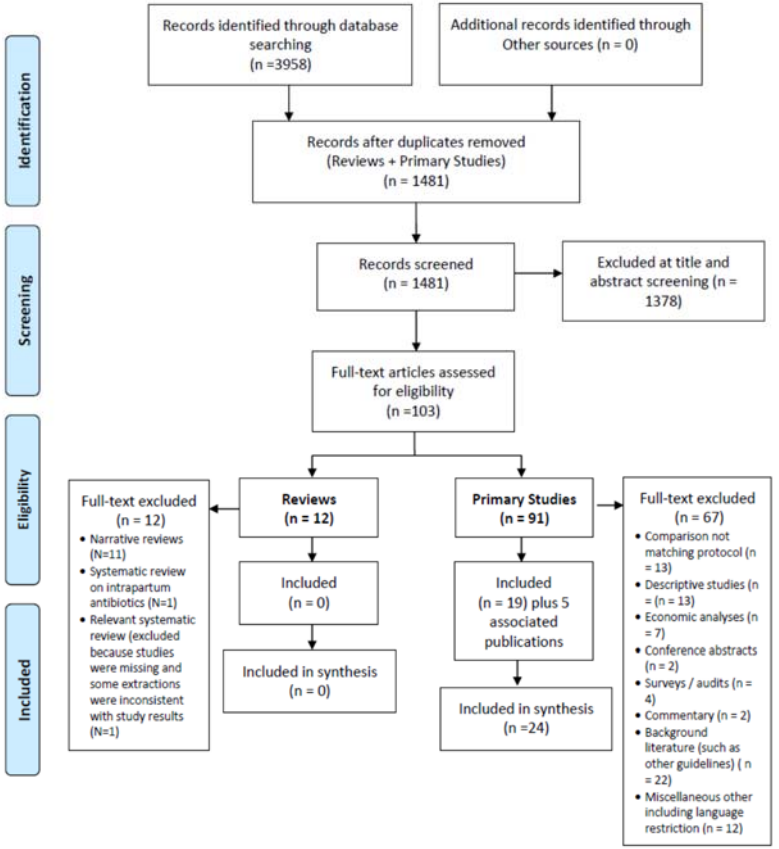


7.1.4. Group B streptococcus

On August 2014 a search was performed in MEDLINE (including PreMedline), Embase and CENTRAL to identify systematic reviews, RCTs and observational studies evaluating the benefits and harms of GBS screening during pregnancy. We identified a total of 3958 records (MEDLINE=1150, EMBASE=1004, Cochrane Library=113). After de-duplicating, 1481 records formed the first screening set. A total of 103 records were screened on full text.

One systematic review was identified (Taminato et al., 2011)[14] that investigated the best screening strategy for GBS in pregnant women. There were a number of studies missing from this systematic review and some errors in the data that were entered into the analysis. It also included studies with universal screening protocols at 26-28 weeks. Therefore rather than updating this review, we carried out a new review and excluded the systematic review by Taminato et al. (2011). No RCTs were retrieved and 19 observational studies[2, 15-31] were found.

Figure 9 – PRISMA flowchart: screening for group B streptoccocus



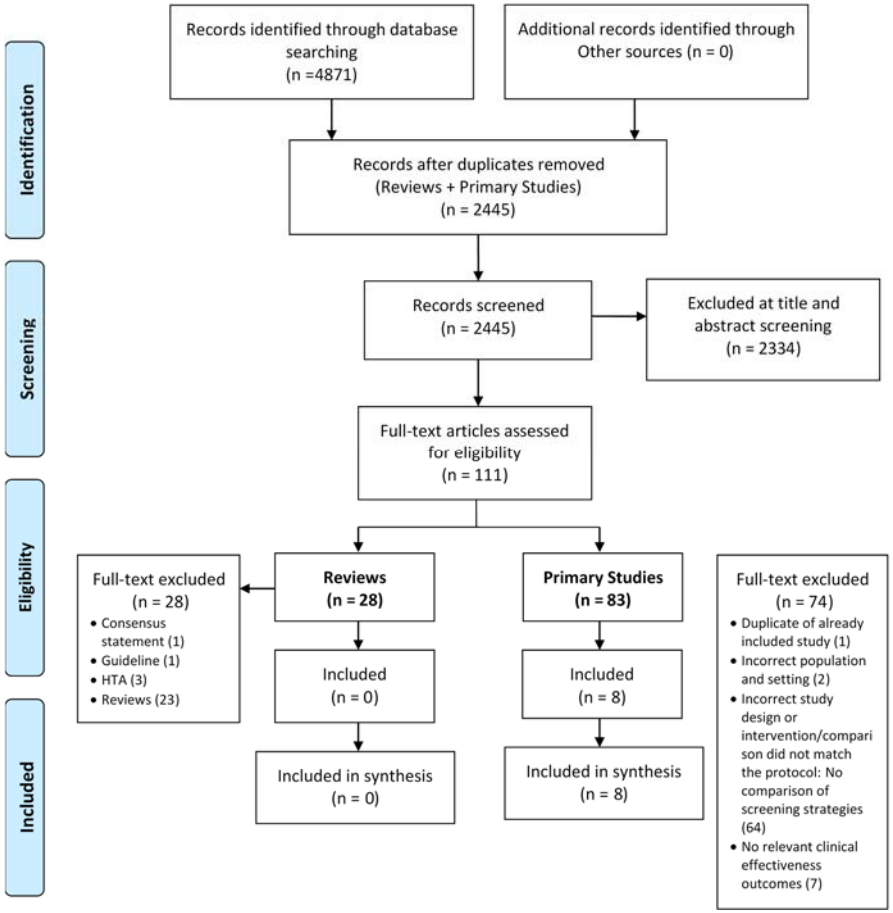
7.1.5. Gestational diabetes

On July 2014 a search was performed in MEDLINE (including PreMedline), Embase and CENTRAL to identify systematic reviews, RCTs and observational studies evaluating the benefits and harms of different screening of gestational diabetes. A single search strategy was performed for both questions (see Appendix 6). A total of 4871 records were identified (MEDLINE=2017, EMBASE=2469, Cochrane Library=385), and after de-duplicating, 2445 records formed the first screening set.

7.1.5.1. Benefit-harms of different strategies of screening for gestation diabetes

A total of 111 records were screened on full text. One Cochrane Review was found which seemed to match inclusion criteria but was finally excluded.[32] Two RCTs and 6 observational studies met the eligibility criteria.

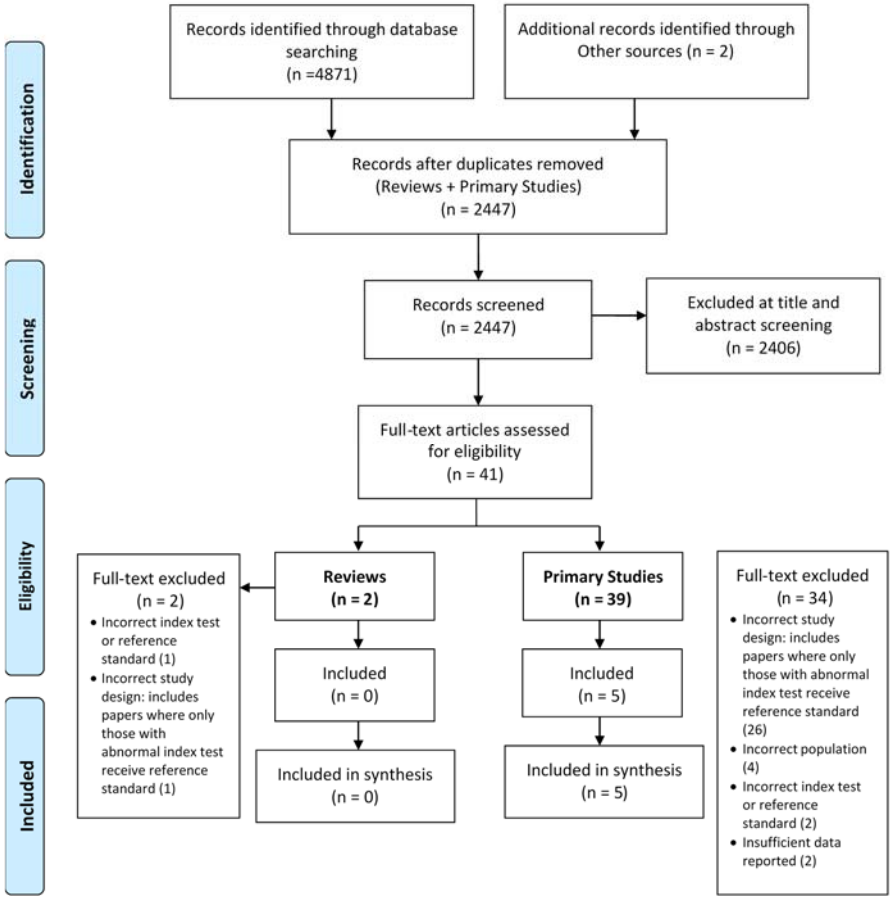
Figure 10 – PRISMA flowchart: screening for gestational diabetes



7.1.5.2. Diagnostic accuracy of the 50g glucose challenge test as a screening strategy for gestational diabetes

A total of 41 records were screened on full text. No systematic reviwew was found on this question but five cohort studies were retrieved looking at the diagnostic accuracy of the 50g GCT compared with a reference standard of 100g OGTT.

Figure 11 – PRISMA flowchart: screening for gestational diabetes – diagnostic accuracy studies



7.1.6. Hypothyroidism

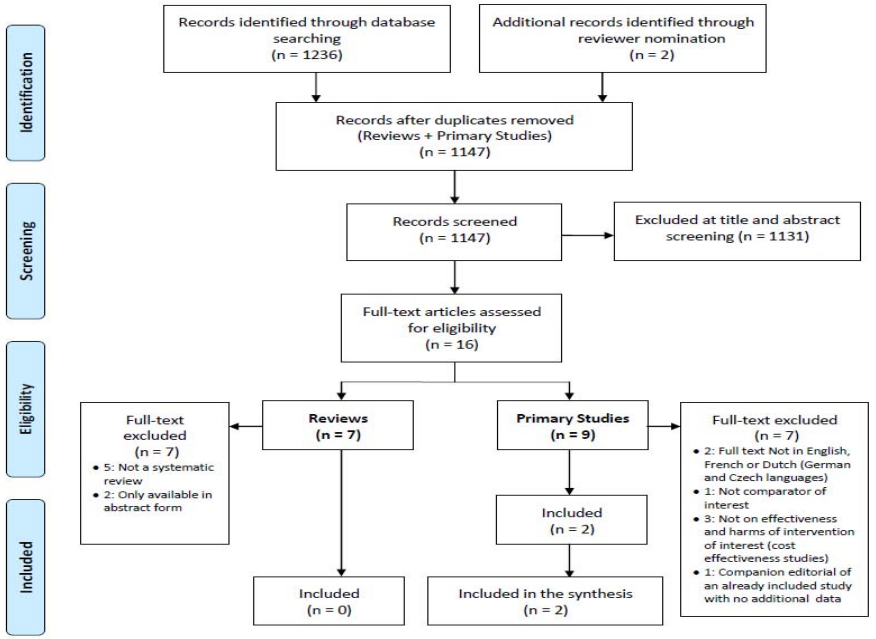
On April-May 2014 a search was performed in MEDLINE (including PreMedline), Embase and CENTRAL to identify systematic reviews, RCTs and observational studies evaluating the benefits and harms of hypothyroidism screening during pregnancy. On July 2014, a second search was performed in the same databases to identify systematic reviews, RCTs and observational studies evaluating the benefits and harms of hypothyroidism screening for **subclinical hypothyroidism during euthyroid pregnancy**

On May, a search was performed in MEDLINE (including PreMedline), Embase and CENTRAL to identify systematic reviews, RCTs and observational studies evaluating the benefits and harms of hypothyroidism therapy during pregnancy. On July 2014, a second search was performed in the same databases to identify systematic reviews, RCTs and observational studies evaluating the benefits and harms of hypothyroidism therapy for **subclinical hypothyroidism during euthyroid pregnancy.**

7.1.6.1. Benefit-harms of routine screening for hypothyroidism in asymptomatic pregnancies

We identified a total of 1236 records (MEDLINE=805, EMBASE=378, Cochrane Library=51, and reviewer nominated= 2) of which 91 were removed after de-duplicating. A total of 1147 were screened on title and abstract and 16 records on full text. Two large randomised controlled trials[33, 34] met the eligibility criteria and were included in the synthesis to answer this question:

Figure 12 – PRISMA flowchart: screening for hypothyroidism

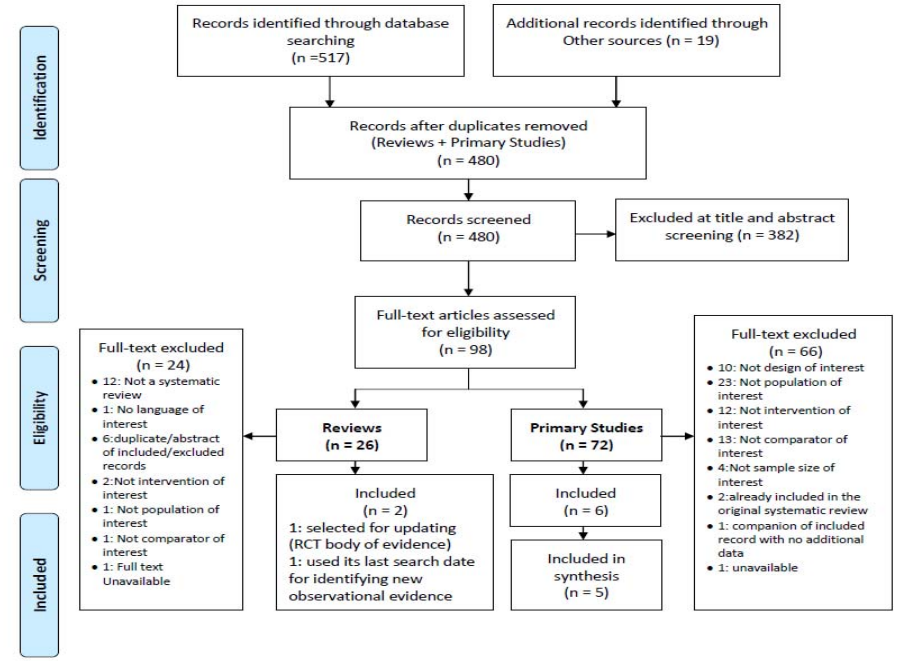


For screening systematic reviews, a total of 80 bibliographic records were identified (MEDLINE=38, EMBASE=37, Cochrane Library=5), and after de-duplicating, 74 records formed the full screening set. Of these 67 records excluded based on Level 1 (title and abstract) screening. Of the 7 records passed to Level 2 (full-text) screening, all were excluded for reasons stated in the above diagram. Then we decided to do a de novo synthesis and searched for primary studies from 1994-onwards (from 20 years ago to present). For de novo synthesis of primary studies, we identified a total of 1160 bibliographic records (MEDLINE=769, EMBASE=343, Cochrane Library=46, and reviewer nominated=2), and after de-duplicating, 1073 records formed the full screening set. Of these 1064 was excluded based on Level 1 screening, and 9 records were screened at Level 2 (full-text). Two of the records met the eligibility criteria, and 7 were excluded for various reasons stated in the above diagram.

7.1.6.2. Benefits-harms of hypothyroidism therapy in Pregnant Women with Subclinical Hypothyroidism

We identified a total of 536 records (MEDLINE=199, EMBASE=309, Cochrane Library=7, and reviewer nominated= 21) of which 56 were removed after de-duplicating. A total of 480 were screened on title and abstract, and 98 records on full text. A total of 8 records met the eligibility criteria and 6 records were included in the synthesis to answer this question.

Figure 13 – PRISMA flowchart: hypothyroidism therapy in pregnant women with subclinical hypothyroidism



For screening systematic reviews, a total of 47 bibliographic records were identified (MEDLINE=18, EMBASE=18, Cochrane Library=4, tagged in question 2b as relevant for question 2c=7), and after de-duplicating, 40 records formed the full screening set. Of these 14 records excluded based on Level 1 (title and abstract) screening. Of the 26 records passed to Level 2 (full-text) screening, 24 were excluded for various reasons stated in the above diagram. We used 1 SR to update for RCT body of evidence, and the other SR last search date was used to identify new primary studies for de novo synthesis. For de novo synthesis of primary studies, we identified a total of 4-89 bibliographic records (MEDLINE=181, EMBASE=291, Cochrane Library=3, reviewer nominated=14), and after de-duplicating, 440 records formed the full screening set. Of these 368 was excluded based on Level 1 screening, and 72 records were screened at Level 2 (full-text). 67 of the records were excluded for various reasons stated in the above diagram.

7.1.7. Vitamin D deficiency

On April-May 2014 a search was performed in MEDLINE (including PreMedline), Embase and CENTRAL to identify systematic reviews, RCTs and observational studies evaluating the benefits and harms of vitamin D deficiency screening during pregnancy.

On May 2014 a search was performed in MEDLINE (including PreMedline), Embase and CENTRAL to identify systematic reviews, RCTs and observational studies evaluating the benefits and harms of vitamin D supplementation during pregnancy.

7.1.7.1. Benefits-harms of screening for vtamin D Deficiency during pregnancy

A total of 1054 records were identified (MEDLINE=449, EMBASE=495, Cochrane Library=110), and after de-duplicating, 981 records formed the first screening set. A total of 15 records were screened on full text. None of these records met the eligibility criteria.

Figure 14 – PRISMA flowchart: screening for vitamin D deficiency

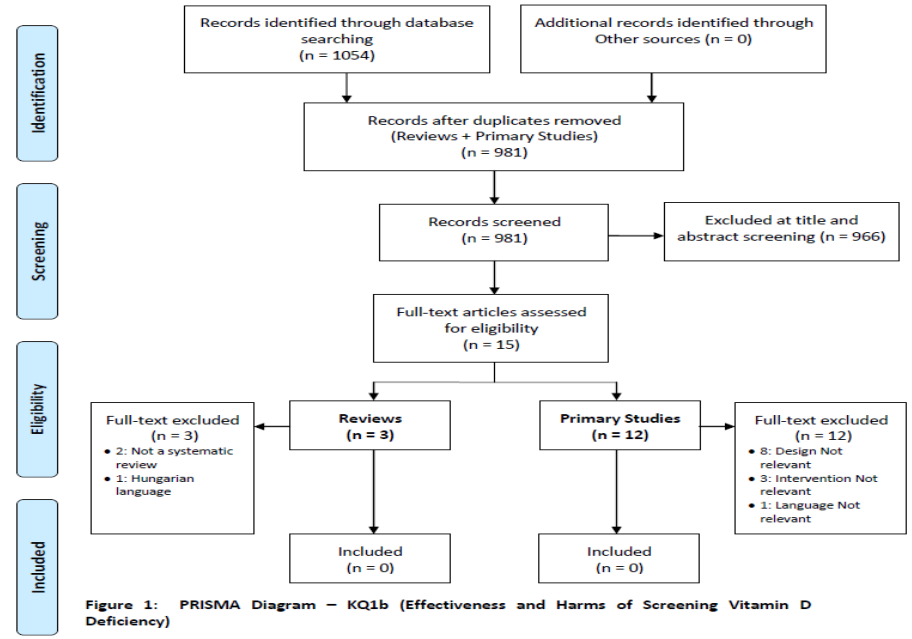


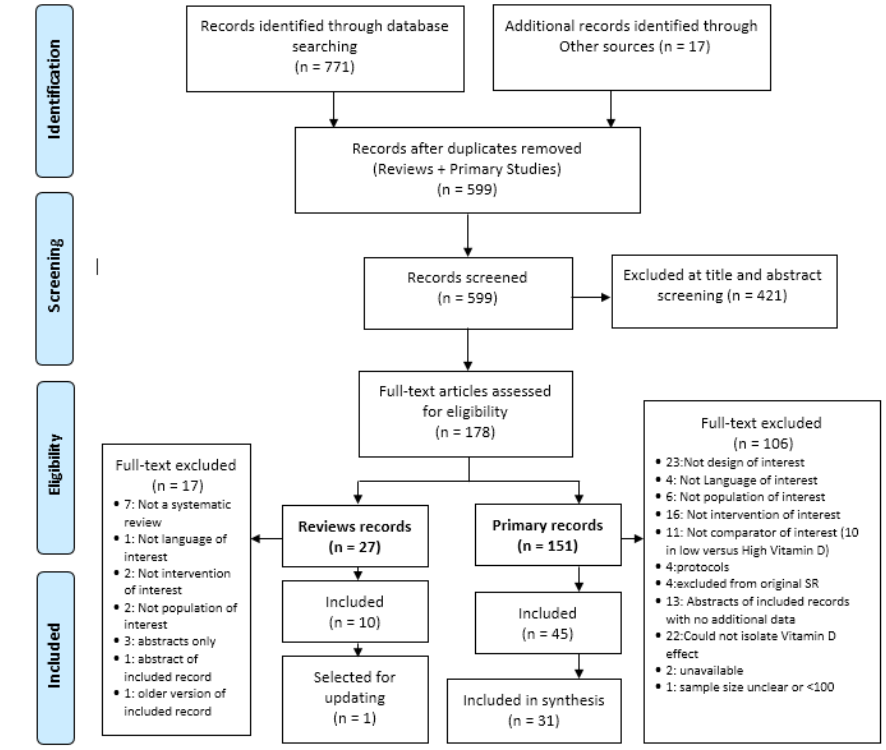
Figure 1: PRISMA Diagram – KQ1b (Effectiveness and Harms of Screening Vitamin D Deficiency)

For screening systematic reviews, a total of 71 bibliographic records were identified (MEDLINE=34, EMBASE=32, Cochrane Library=5), and after de-duplicating, 66 records formed the full screening set. Of these 63 records excluded based on Level 1 (title and abstract) screening. Of the 3 records passed to Level 2 (full-text) screening, all were excluded for various reasons stated in the above diagram. Then we decided to do a de novo synthesis and searched for primary studies without any date restriction. For de novo synthesis of primary studies, we identified a total of 983 bibliographic records (MEDLINE=415, EMBASE=463, Cochrane Library=105), and after de-duplicating, 915 records formed the full screening set. Of these 912 was excluded based on Level 1 screening, and 12 records were screened at Level 2 (full-text). None of the records met the eligibility criteria and were excluded for various reasons stated in the above diagram.

7.1.7.2. Benefits-harms of Vitamin D Supplementation during Pregnancy

A total of 788 records were identified (MEDLINE=291, EMBASE=449, Cochrane Library=31, and reviewer nominated= 17), and after de-duplicating, 599 records formed the first screening set. A total of 178 full texts were screened on full text, and 55 records met the eligibility criteria. Finally, 32 records were included in the synthesis to answer this question (Figure 15).

Figure 15 – PRISMA flowchart: vitamin D supplementation during pregnancy



For screening systematic reviews, a total of 72 bibliographic records were identified (MEDLINE=35, EMBASE=37), and after de-duplicating the same 72 records formed the full screening set. Of these 45records excluded based on Level 1 (title and abstract) screening. Of the 27 records passed to Level 2 (full-text) screening, 17 were excluded for various reasons stated in the above diagram. Of the 10 included reviews 1 was selected for updating for RCT body of evidence, and the primary studies included in 1 review were added n the database for primary studies). For observational studies we decided to conduct a de novo synthesis of primary observational studies, we identified a total of 716 bibliographic records (MEDLINE=256, EMBASE=412, Cochrane Library=31, reviewer nominated=17), and after de-duplicating, 527 records formed the full screening set. Of these 376 was excluded based on Level 1 screening, and 151 records were screened at Level 2 (full-text). 45 records met the eligibility criteria and the rest were excluded for various reasons stated in the above diagram. Of these 31 records (21 studies) were included in the synthesis because 14 records did not report outcome data.

7.1.7.3. *Risk of preterm birth*

On June 2014 a search was performed in MEDLINE (including PreMedline), Embase and CENTRAL to identify systematic reviews, RCTs and observational studies evaluating the benefits and harms of ultrasound and digital vaginal exam for risk of preterm birth screening in low-risk women.

On September 2014 a search was performed in MEDLINE (including PreMedline), Embase and CENTRAL to identify systematic reviews, RCTs and observational studies evaluating the benefits and harms of specific interventions (progesterone, cervical cerclage and reduced physical activity) for risk of preterm birth in low-risk women.

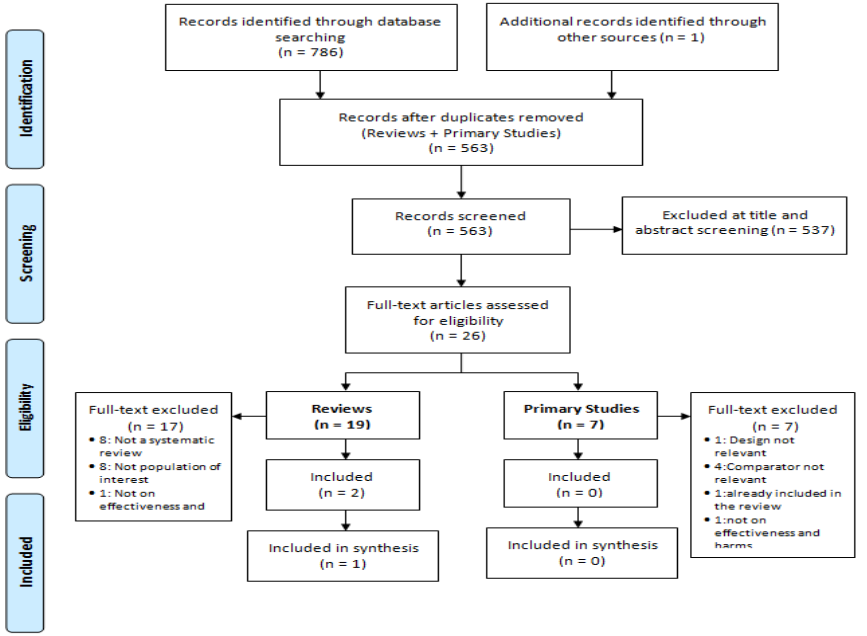
7.1.7.4. *Benefits-harms of transvaginal ultrasound and/or digital vaginal exam for risk of preterm birth screening in exclusively or predominantly low risk pregnant women*

A total of 787 records were identified (MEDLINE=378, EMBASE=382, Cochrane Library=26, and reviewer nominated=1), and after de-duplicating, 563 records formed the first screening set. A total of 26 records were screened on full text full. One record (systematic review by Alexander et al.) was included in the synthesis to answer this question. No primary evidence was identified.

We did not identify any systematic review or primary study to assess the comparative benefits and harms of transvaginal ultrasound for cervical length, funnelling or both in exclusively or predominantly low risk pregnant women.

We found one relevant systematic review of moderate quality that investigated outcomes of repeat digital exam throughout pregnancy and included two low and unclear risk of bias randomised controlled trials (total N analysed =6070) in women likely to be predominantly at low risk for preterm birth; no evidence was found addressing TVU exam or a combination of both TVU and digital exam.[35]

Figure 16 – PRISMA flowchart: screening for risk of preterm birth by transvaginal ultrasound, and digital exam in exclusively or predominantly low risk pregnant women



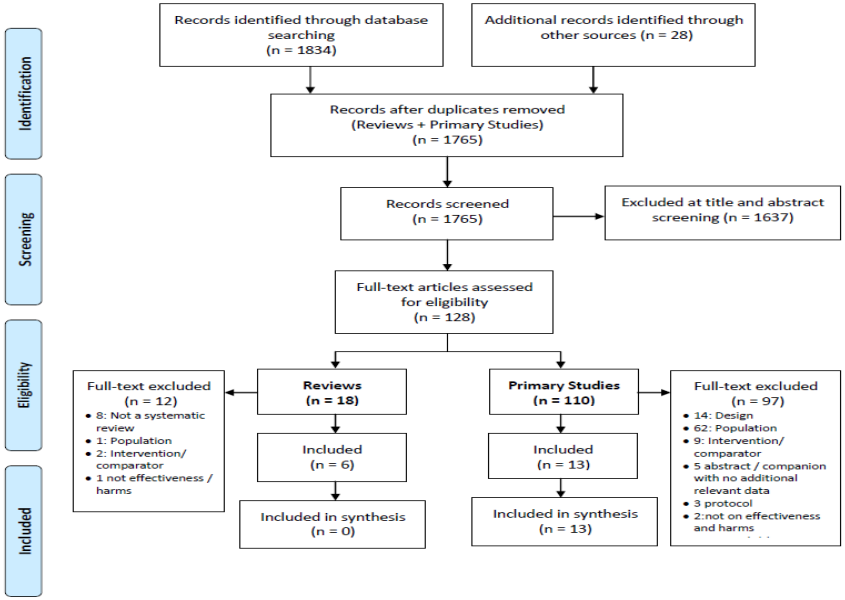
For screening systematic reviews, a total of 44 bibliographic records were identified (MEDLINE=17, Embase=16, Cochrane Library=10, reviewer nominated= 1), and after de-duplicating, 38 records formed the full screening set. Of the 19 records passed to Level 2 (full-text) screening, 17 were excluded for various reasons stated in the above diagram. 2 reviews were identified for updating for RCT body of evidence, of which one did not have any evidence on the population of interest. For observational body of evidence, we had to conduct de novo synthesis. For de novo synthesis we searched for primary observational studies from inception to present. For synthesis of primary studies, we identified a total of 743 bibliographic records (MEDLINE= 361, Embase= 366, and Cochrane= 16) and after de-duplicating, 525 records formed the full screening set. Of these 477 were excluded based on Level 1 screening, and 7 records were screened at Level 2 (full-text). Of these none passed level two and were excluded for various reasons stated in the diagram.

7.1.7.5. Benefits-harms of progesterone, cervical cerclage and reduced physical activity for risk of preterm birth in asymptomatic pregnant women with short cervix

A total of 1862 records were identified (MEDLINE=715, EMBASE=1100, Cochrane Library=19, and reviewer nominated=28), and after de-duplicating, 722 records formed the first screening set. A total of 128 records were screened on full text.

No systematic review was identified for updating. For de novo synthesis, a total of 13 studies were identified of which nine were RCTs and 4 observational cohort studies. Eight studies (all RCT design) evaluated benefits and harms of progesterone versus no active treatment, four studies (1 RCT and 3 observational) assessed benefits and harms of cerclage versus no cerclage, and one cohort study compared reduced physical activity versus no activity restriction in the population of interest.

Figure 17 – PRISMA flowchart: progesterone, cervical cerclage and reduced activities in exclusively or predominantly low risk pregnant women with short cervix



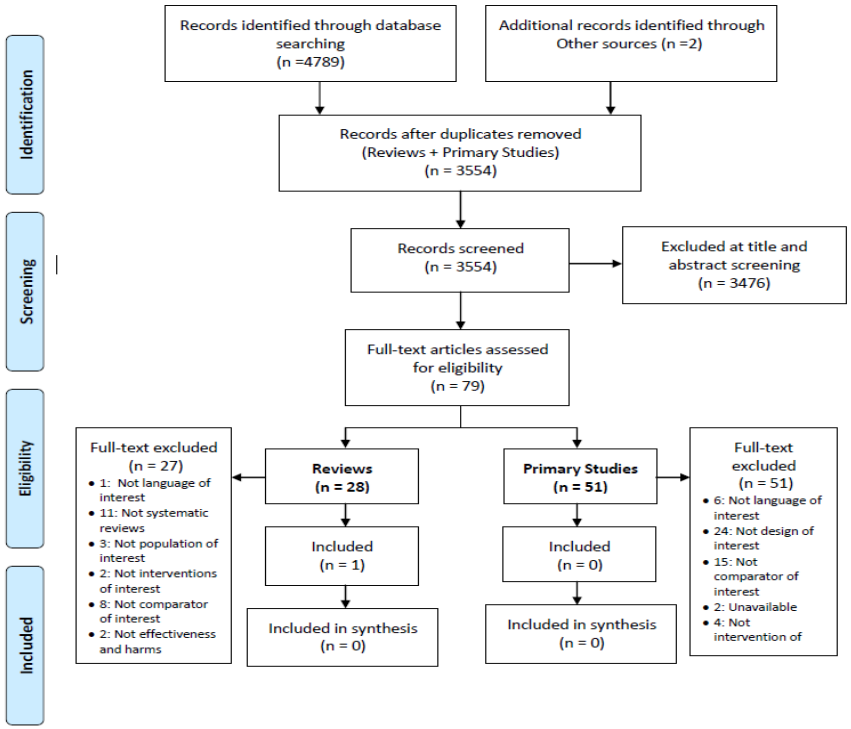
For screening systematic reviews, a total of =92 bibliographic records were identified (MEDLINE=34, EMBASE=38, Cochrane Library=19, reviewer nominated=1), and after de-duplicating, 78 records formed the full screening set. Of these 60 records excluded based on Level 1 (title and abstract) screening. Of the 18 records passed to Level 2 (full-text) screening, 12 were excluded for various reasons stated in the above diagram. No reviews were identified for updating. Of the 6 records, the last search date of 3 reviews were used for identifying new primary RCTs and the selected studies in these and in the remaining reviews were screened for eligibility for de novo synthesis for RCT body of evidence. For observational body of evidence, we had to search for primary studies from 15 years onwards for conducting de novo synthesis. For synthesis of primary studies, we identified a total of 1770 bibliographic records (MEDLINE=681, EMBASE=1062, reviewer nominated=27), and after de-duplicating, 1687 records formed the full screening set. Of these 1577 was excluded based on Level 1 screening, and 110 records were screened at Level 2 (full-text). Of these 13 passed level two and 97 were excluded for various reasons stated in the diagram.

7.1.8. Risk of preeclampsia

On October-November 2014 a search was performed in MEDLINE (including PreMedline), Embase and CENTRAL to identify systematic reviews, RCTs and observational studies evaluating the benefits and harms of screening for preeclampsia risk with additional tests compared with usual routine assessment in low-risk women.

A total of 4791 records were identified (MEDLINE=2813, EMBASE=1832, Cochrane Library=144, and reviewer nominated=2), and after de-duplicating, 3554 records formed the full screening set. A total of 79 full texts were screened and one systematic review by Stampalija et al., 2010[36] met the eligibility criteria. The high quality review had not identified any primary studies on the intervention of interest that it covered (pulsatility index). No systematic reviews of other relevant interventions were identified and no primary evidence was identified. As such, this question remained unanswered.

Figure 18 – PRISMA flow chart: screening for risk of preeclampsia



For screening systematic reviews, a total of 79 bibliographic records were identified (MEDLINE=38, EMBASE=27, Cochrane Library=12, reviewer nominated= 2), and after de-duplicating, all 76 records formed the full screening set. Of these 49 records excluded based on Level 1 (title and abstract) screening. Of the 28 records passed to Level 2 (full-text) screening, 27 were excluded for various reasons stated in the above diagram. 1 review was identified that had broader scope and had not identified any primary study on the intervention of interest. We did not identify any primary study to update this review for the intervention of interest. For de novo synthesis we searched for primary studies with no date restriction for observational and for RCTs for all interventions of interest; however, we restricted the observational evidence for one of the interventions, dipstick, to 2004 onwards based on KCE consultation. For de novo synthesis of primary studies, we identified a total of 4712 bibliographic records (MEDLINE=2775, EMBASE=1805, Cochrane Library=132), and after de-duplicating, 3478 records formed the full screening set. Of these 3427 was excluded based on Level 1 screening, and 51 records were screened at Level 2 (full-text). All of the 51 records were excluded for various reasons stated in the diagram.

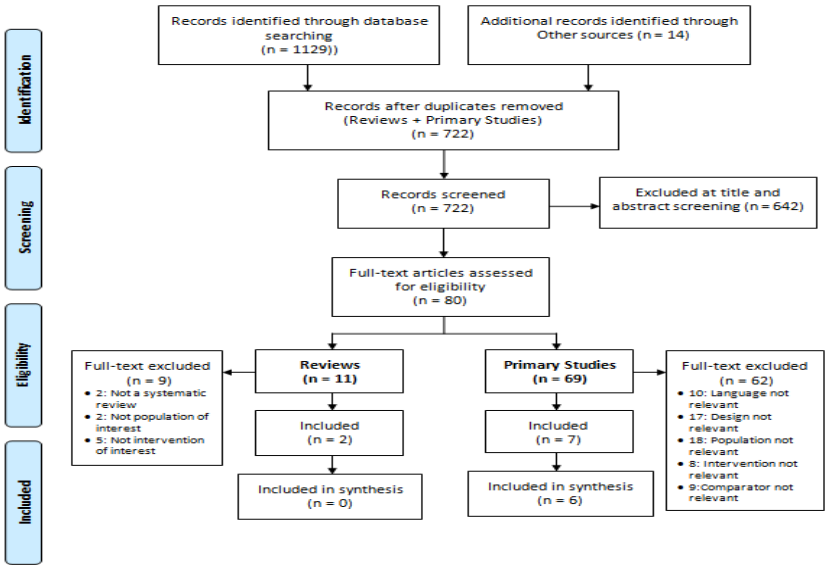
7.1.9. Pregnancies that passed their due date

On June-August 2014 a search was performed in MEDLINE (including PreMedline), Embase and CENTRAL to identify systematic reviews, RCTs and observational studies evaluating the benefits and harms of different monitoring strategies by CTG, ultrasound, and combination of these tests with or without other tests in asymptomatic pregnant women remaining undelivered after ~40 weeks gestation.

A total of 1143 records were identified (MEDLINE=516, EMBASE=502, Cochrane Library=109, and reviewer nominated=14), and after de-duplicating, 722 records formed the full screening set. A total of 80 records were screened on full text, and nine records met the eligibility criteria (see) and six records were included in the synthesis to answer this question.

No systematic review was identified for updating. For de novo synthesis, a total of seven unique primary studies were identified of which one [5] did not provide outcome data, so six studies were ultimately included in the synthesis. Of these three were RCTs [6-8] two were cohort studies (one prospective [9] and one retrospective [10]) and one prospective study where it was unclear whether participants were 'allocated' to their intervention or not [11] was treated as a prospective comparative cohort in the synthesis.

Figure 19 – PRISMA flow chart: surveillance of prolonged pregnancies



For screening systematic reviews, a total of ~~36~~ bibliographic records were identified (MEDLINE=8, EMBASE=22, Cochrane Library=4, reviewer nominated= 2), and after de-duplicating, 34 records formed the full screening set. Of these 23 records excluded based on Level 1 (title and abstract) screening. Of the 11 records passed to Level 2 (full-text) screening, 9 were excluded for various reasons stated in the above diagram. No review was identified for updating but one review's last search date was used for identifying primary RCTs onwards, and selected included primary studies of 2 reviews were screened for eligibility. For de novo synthesis we also searched for primary studies with no date restriction for observational studies, and for RCTs: 2012- onwards for first intervention, and 1980s- onwards for second and third intervention of interest. For de novo synthesis of primary studies, we identified a total of 1105 bibliographic records (MEDLINE=508, EMBASE=480, Cochrane Library=105, reviewer nominated=12), and after de-duplicating, 688 records formed the full screening set. Of these 619 was excluded based on Level 1 screening, and 69 records were screened at Level 2 (full-text). Of these 62 were excluded for various reasons stated in the diagram, and 6 records were included in the-synthesis.

8. QUALITY APPRAISAL

8.1. Quality appraisal tools

8.1.1. Guidelines

The AGREE II evaluation score was used to critically appraise guidelines retrieved (Table 51).

Table 51 – AGREE II instrument

Critical appraisal of clinical practice guidelines - AGREE II
Domain 1. Scope and Purpose
1. The overall objective(s) of the guideline is (are) specifically described.
2. The health question(s) covered by the guideline is (are) specifically described.
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.
Domain 2. Stakeholder Involvement
4. The guideline development group includes individuals from all the relevant professional groups.
5. The views and preferences of the target population (patients, public, etc.) have been sought.
6. The target users of the guideline are clearly defined.
Domain 3. Rigour of Development
7. Systematic methods were used to search for evidence.
8. The criteria for selecting the evidence are clearly described.
9. The strengths and limitations of the body of evidence are clearly described.
10. The methods for formulating the recommendations are clearly described.
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.
12. There is an explicit link between the recommendations and the supporting evidence.
13. The guideline has been externally reviewed by experts prior to its publication.
14. A procedure for updating the guideline is provided.
Domain 4. Clarity of Presentation
15. The recommendations are specific and unambiguous.
16. The different options for management of the condition or health issue are clearly presented.
17. Key recommendations are easily identifiable.
Domain 5. Applicability
18. The guideline describes facilitators and barriers to its application.

Critical appraisal of clinical practice guidelines - AGREE II
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.
20. The potential resource implications of applying the recommendations have been considered.
21. The guideline presents monitoring and/ or auditing criteria.
Domain 6. Editorial Independence
22. The views of the funding body have not influenced the content of the guideline.
23. Competing interests of guideline development group members have been recorded and addressed.

8.1.2. Systematic reviews

AMSTAR criteria were used to assess systematic reviews (Table 52 and 53).

Table 52 – AMSTAR checklist

Question	Answer
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	Yes/No/Can't answer/NA
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	Yes/No/Can't answer/NA
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	Yes/No/Can't answer/NA
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	Yes/No/Can't answer/NA
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	Yes/No/Can't answer/NA
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	Yes/No/Can't answer/NA

7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	Yes/No/Can't answer/NA
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	Yes/No/Can't answer/NA
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	Yes/No/Can't answer/NA
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	Yes/No/Can't answer/NA
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	Yes/No/Can't answer/NA

Table 53 – Modified AMSTAR checklist

Question	Answer
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	Yes/No/Unclear/NA
2. Was there either a: • **Duplicate** (i.e. two independent reviewers) **screening** of the literature? Or, • **Independent verification** of all/partial screened records (if partial, reliability statistics should have been reported and should be indicative of high concordance)	Yes/No/Unclear/NA
3. Was there either a: • **Duplicate** (i.e. two independent reviewer) **data extraction** from studies? Or, • **Independent verification** of all/partial extracted data (if partial, reliability statistics should have been reported and should be indicative of high accuracy)	Yes/No/Unclear/NA
4. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated.	Yes/No/Unclear/NA
5. Was a list of studies (included) provided?	Yes/No/Unclear/NA

A list of included studies should be provided.	
6. Were the characteristics of the included studies provided?	Yes/No/Unclear/NA
7. Was the scientific quality of the included studies assessed and documented? And was it adequate based on judgement (e.g. standard tool was used or important biasing domains were answered)?	Yes/No/Unclear/NA
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in evidence synthesis.	Yes/No/Unclear/NA
9. Were the methods used to combine the findings of studies appropriate?	Yes/No/Unclear/NA
The overall judgement will be made consensually by two reviewers taking into account the importance of the modified AMSTAR across all of the responses across all questions. Final categorization will be: High quality Moderate quality Low quality	

8.1.3. RCTs

To assess risk of bias of randomised controlled trials, the Cochrane Collaboration's tool was used (Table 54).

Table 54 – Cochrane Collaboration's tool for assessing risk of bias

Domain	Support for judgement	Review authors' judgement
Selection bias		
Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment
Performance bias		
Blinding of participants and personnel Assessments should be made for each main outcome (or class of outcomes)	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study

Domain	Support for judgement	Review authors' judgement
Detection bias		
Blinding of outcome assessment Assessments should be made for each main outcome (or class of outcomes)	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Detection bias due to knowledge of the allocated interventions by outcome assessors
Attrition bias		
Incomplete outcome data Assessments should be made for each main outcome (or class of outcomes)	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any reinclusions in analyses performed by the review authors	Attrition bias due to amount, nature or handling of incomplete outcome data
Reporting bias		
Selective reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found	Reporting bias due to selective outcome reporting
Other bias		
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool If particular questions/entries were prespecified in the review's protocol, responses should be provided for each question/entry	Bias due to problems not covered elsewhere in the table

To conduct the quality appraisal of comparative cohort studies, the following two tools was used (Table 55 & 62).

8.1.4. Observational studies

Only comparative cohort studies should be selected. Two tools were used to perform the quality appraisal for this kind of studies (Table 55 and 56).

Table 55 – Quality appraisal for cohort studies – tool used by the NCGC

Domains	Options	Ref 1	Ref 2	Ref 3	Ref 4	Ref 5
Domain 1: Selection bias						
• Can selection bias sufficiently be excluded?	Yes/No/Insufficient info to assess					
• Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis?	Yes/No/Insufficient info to assess					
Domain 2: Detection bias						
• Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups?	Yes/No/Insufficient info to assess					
• Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups?	Yes/No/Insufficient info to assess					
• Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis?	Yes/No/Insufficient info to assess					
• Is the assessment of outcome made blind to exposure status?	Yes/No/Insufficient info to assess					

Domains	Options	Ref 1	Ref 2	Ref 3	Ref 4	Ref 5
If no to question 6, does this have an impact on the assessment of the outcome?	Yes/No/ Not possible in this type of exposure /Insufficient info to assess					
• Is the follow-up sufficiently long to measure all relevant outcomes?	Yes/No/Insufficient info to assess					
Domain 3: Attrition bias						
• Can selective loss-to-follow-up be sufficiently excluded?	Yes/No/Insufficient info to assess					

Table 56 – Quality appraisal for cohort studies – tool used by the OHRI

Domain	Support for judgment	Review authors' judgment
Selection bias		
Information bias		
Confounding		
Overall assessment		
Applicability concern		

8.1.5. Diagnostic accuracy studies

The quality assessment tool used for the quality assessment of diagnostic accuracy studies was QUADAS Tool. (Table 57)

Table 57 – The QUADAS tool

Domain 1: Patient selection	
A. Risk of bias	
• **Was a consecutive or random sample of patients enrolled?**	Yes/No/Unclear
• **Was a case-control design avoided?**	Yes/No/Unclear
• **Did the study avoid inappropriate exclusions?**	Yes/No/Unclear
Could the selection of patients have introduced bias?	RISK: LOW/HIGH/UNCLEAR

B. Concerns regarding applicability	
Is there concern that the included patients do not match the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 2: Index test(s) *(if more than 1 index test was used, please complete for each test)*	
A. Risk of bias	
• **Were the index test results interpreted without knowledge of the results of the reference standard?**	Yes/No/Unclear
• **If a threshold was used, was it pre-specified?**	Yes/No/Unclear
Could the conduct or interpretation of the index test have introduced bias?	RISK: LOW/HIGH/UNCLEAR
B. Concerns regarding applicability	
Is there concern that the index test, its conduct, or interpretation differ from the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 3: Reference standard	
A. Risk of bias	
• **Is the reference standard likely to correctly classify the target condition?**	Yes/No/Unclear
• **Were the reference standard results interpreted without knowledge of the results of the index test?**	Yes/No/Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	RISK: LOW/HIGH/UNCLEAR
B. Concerns regarding applicability	
Is there concern that the target condition as defined by the reference standard does not match the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 4: Flow and timing	
A. Risk of bias	
• **Was there an appropriate interval between index test(s) and reference standard?**	Yes/No/Unclear
• **Did all patients receive a reference standard?**	Yes/No/Unclear
• **Did patients receive the same reference standard?**	Yes/No/Unclear
• **Were all patients included in the analysis?**	Yes/No/Unclear
Could the patient flow have introduced bias?	RISK: LOW/HIGH/UNCLEAR

Item	Label	Yes	No	Unclear	Not applicable
1.	Was the spectrum of patients representative of the patients who will receive the test in practice?				
2.	Were selection criteria clearly described?				
3.	Is the reference standard likely to correctly classify the target condition?				
4.	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?				
5.	Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?				
6.	Did patients receive the same reference standard regardless of the index test result?				
7.	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?				
8.	Was the execution of the index test described in sufficient detail to permit replication of the test?				
9.	Was the execution of the reference standard described in sufficient detail to permit its replication?				
10.	Were the index test results interpreted without knowledge of the results of the reference standard?				
11.	Were the reference standard results interpreted without knowledge of the results of the index test?				
12.	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?				
13.	Were uninterpretable/ intermediate test results reported?				
14.	Were withdrawals from the study explained?				

8.2. Quality appraisal of guidelines

The screening of the **guidelines** was performed on title and abstract by a group of two researchers (PJ and FM) based on the P.I.C.O. in- and exclusion criteria. This evaluation was done in two steps. First, only the rigour of development that includes 7 different criteria was assessed. If the global assessment of this dimension was too low (score ≤ 3 for each criterion), the evaluation process stopped and the guideline was excluded. Second, a good assessment of the dimension 'rigour of development' led to assess the other dimensions of the guideline. The final appraisal was formulated after a comprehensive evaluation of the guideline (Table 58).

Table 58 – AGREE scores of identified guidelines

Critical appraisal of clinical practice guidelines - AGREE II	Australian 2014	Nice 2008
Domain 1. Scope and Purpose		
1. The overall objective(s) of the guideline is (are) specifically described.	6,5	7,0
2. The health question(s) covered by the guideline is (are) specifically described.	5,5	5,5
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	5,5	7,0
Domain 2. Stakeholder Involvement		
4. The guideline development group includes individuals from all the relevant professional groups.	4,0	6,0
5. The views and preferences of the target population (patients, public, etc.) have been sought.	6,0	4,5
6. The target users of the guideline are clearly defined.	7,0	7,0
Domain 3. Rigour of Development		
7. Systematic methods were used to search for evidence.	5,0	7,0
8. The criteria for selecting the evidence are clearly described.	5,0	6,0
9. The strengths and limitations of the body of evidence are clearly described.	5,0	6,0
10. The methods for formulating the recommendations are clearly described.	5,5	4,5
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	5,0	6,0
12. There is an explicit link between the recommendations and the supporting evidence.	5,0	6,5
13. The guideline has been externally reviewed by experts prior to its publication.	5,0	6,5
14. A procedure for updating the guideline is provided.	6,5	5,5
Domain 4. Clarity of Presentation		
15. The recommendations are specific and unambiguous.	4,5	6,5
16. The different options for management of the condition or health issue are clearly presented.	5,5	6,5
17. Key recommendations are easily identifiable.	6,5	6,0
Domain 5. Applicability		
18. The guideline describes facilitators and barriers to its application.	6,5	5,0

Critical appraisal of clinical practice guidelines - AGREE II	Australian 2014	Nice 2008
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	6,5	6,5
20. The potential resource implications of applying the recommendations have been considered.	4,0	5,5
21. The guideline presents monitoring and/ or auditing criteria.	6,0	3,0
Domain 6. Editorial Independence		
22. The views of the funding body have not influenced the content of the guideline.	5,5	5,5
23. Competing interests of guideline development group members have been recorded and addressed.	7,0	6,5
Final appraisal		
Overal quality	5,0	6,0

8.3. Quality appraisal for full search questions

8.3.1. Cytomegalovirus

Table 59 – Lifestyle advice for CMV: Quality appraisal of the one selected primary observational study (ADLER 2004[5])

Domain	Support for judgement	Review authors' judgement
Selection bias		
Random sequence generation	Randomisation of child care centres (cluster randomisation) was done with the use of SAS. To achieve approximately equal sample sizes per group, the assignment of each centre was randomised annually. This randomisation was weighted on the basis of enrolment in the previous year.	High risk of selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence
Allocation concealment	Allocation concealment not reported.	High risk of selection bias (biased allocation to interventions) due to inadequate information provided of concealment of allocations prior to assignment.
Performance bias		
Blinding of participants and personnel Assessments should be made for each main outcome (or class of outcomes)	Blinding of participants and personnel unclear. Control group received basic information on CMV and the reasons for the study. Women in the intervention group(s) also had adherence measured every three months (additional motivation to education/advice alone).	High risk of performance bias due to knowledge of the allocated interventions by participants and personnel during the study

Domain	Support for judgement	Review authors' judgement
Detection bias		
Blinding of outcome assessment Assessments should be made for each main outcome (or class of outcomes)	Blinding of outcome assessors unclear.	High risk of detection bias due to possible knowledge of the allocated interventions by outcome assessors
Attrition bias		
Incomplete outcome data Assessments should be made for each main outcome (or class of outcomes)	Appropriate exclusions were made.	No risk of attrition bias due to amount, nature or handling of incomplete outcome data
Reporting bias		
Selective reporting	Pre-specified intervention groups were terminated within one year the initiation of the study due to interim data analysis. For the remaining two years, new enrolments were assigned to intervention group two only. And intervention group one participants were reassigned to intervention group two. However, data is reported for both intervention groups, therefore for this review seroconversion rates for intervention groups one and two were combined.	High risk of reporting bias due to selective outcome reporting
Other bias		
Other sources of bias	Despite making conclusions based on connections between pregnancy status at enrolment, data is not presented on pregnancy status in respect to intervention group allocation. Therefore data in this review must be considered indirect as it was not possible to exclude non-pregnant women from the analysis.	Indirectness due to incomplete reporting of pre-specified sub-groups.

8.3.2. Toxoplasmosis

Table 60 – Screening for toxoplasmosis: Quality appraisal of selected primary studies (Cohort studies) – screening vs. no screening

Domains	Aspöck & Pollak (1992)[8]	Cortina-Borja et al., (2010)[24]	Hengst (1992)[54]	Henri (1992)[55]	Ricci et al., (2003)[97]	Wallon et al., 2013[122]
Domain 1: Selection bias						
• Can selection bias sufficiently be excluded?*	No, no description of the 'before' group provided	No, selection bias is somewhat controlled by enrolment of all women at specific sites, but it is a bit unclear whether they are representative regions.	No, since it is a history comparison and from this publication it is impossible to know.	No, since in the first part the screening programme was incomplete which may mean that only 'at risk' women were screened.	No, since no screening was conducted in one group at the same hospital and during the same time period, it is most likely the case that this was a 'low risk' group.	Yes – since all samples from one reference laboratory were used it is relatively unbiased from that perspective
• Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis?*	No description of confounders provided in the methods or results, or considered in the analysis. They are alluded to in the discussion section.	Yes, the most important confounder, gestational age at seroconversion is considered. However, this is the only factor used as a counfounder.	No possible confounders described or considered in the analysis.	No, no baseline characteristics are provided.	No, gestational age is considered in one group only.	Yes – gestational age is considered. However, apart from this only overall age is given, but no other baseline characteristics are described.
Domain 2: Detection bias						
• Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups?*	No, it is unclear which type of information or assessment was provided prior to screening implementation.	Yes, screening programmes are described for each country.	Insufficient info to assess. In the 'before' group screening is provided with no treatment, but not further details are given.	Insufficient info to assess. Labels such as 'incomplete' and 'non-systematic' are used without a clear description.	Yes, the screening and assessment processes are clearly described.	No – screening is recommended but it is unclear what percentage of women were screened before 1992
• Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups?*	Yes, the method of assessment is described.	Yes, outcomes are and method of assessment described.	Yes, the methods of assessment are described.	Yes, the outcomes are mainly self-explanatory.	Yes, the outcome are clearly defined.	Yes – definitions and protocols are provided in a supplementary document

Domains	Aspöck & Pollak (1992)[8]	Cortina-Borja et al., (2010)[24]	Hengst (1992)[54]	Henri (1992)[55]	Ricci et al., (2003)[97]	Wallon et al., 2013[122]
• Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis?*	No, possible changes in prevalence rate were not taken into consideration.	Insufficient information to assess. Difficult to know how different prevalence rates in the different countries may impact on results.	Insufficient information, since it is unclear without the description of the 'before' sample and prevalence rates change over time.	Insufficient information, since the description of the groups is quite sparse.	Insufficient information to assess because selection is not very clearly described.	Insufficient info to assess
• Is the assessment of outcome made blind to exposure status?*	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Yes – screening was carried out prior to any prenatal investigation and is therefore blind to the pregnancy outcome.
If no to question 6, does this have an impact on the assessment of the outcome?**	No the outcomes are objective and therefore would not be influenced by blinding.	No the outcomes are objective and therefore would not be influenced by blinding.	No the outcomes are objective and therefore would not be influenced by blinding.	No the outcomes are objective and therefore would not be influenced by blinding.	No the outcomes are objective and therefore would not be influenced by blinding.	No the outcomes are objective and therefore would not be influenced by blinding.
• Is the follow-up sufficiently long to measure all relevant outcomes?*	No, only infection rates reported, unclear how many were symptomatic	Yes, the median follow-up was 4 years.	Only newborns in the 'before' sample seemed to have been followed up.	A one year follow-up may be sufficient for some, but not all outcomes.	A one year follow-up may be sufficient for some, but not all outcomes.	Yes – 3 year follow-up
Domain 3: Attrition bias						
• Can selective loss-to-follow-up be sufficiently excluded?*	Insufficient info to assess.	No, statistical analyses were carried out to investigate whether loss to follow-up may have influenced the results.	Insufficient information to assess.	Insufficient information to assess.	There was a considerable loss to follow-up in the prenatal screening group but not in the neonatal group.	No – numbers are only provided for the whole group rather than divided by recommended vs. Mandatory groups

** Options: Yes/No/Insufficient info to assess*
*** Options: Yes/No/ Not possible in this type of exposure /Insufficient info to assess*

Table 61 – Lifestyle advice for toxoplasmosis: Quality appraisal of selected systematic review - (prenatal education) vs. no specific advice

Systematic review	A priori study design	Duplicate study selection and data extraction	Comprehensive literature search	Publication status not used as inclusion	List of in- and excluded studies provided	Characteristics of included studies provided	Study quality assessed and documented	Quality assessment used in conclusions	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated	Global evaluation
Di Mario et al., (2013)[28]	Yes, Cochrane reviews are based on a published protocol	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes, it was appropriate not to pool results	No, but only two studies identified, lack of available evidence is discussed. It cannot be ruled out that lack of evidence indicates studies without reported intervention differences were not published.	Yes	Good quality systematic review.

Table 62 – Lifestyle advice for toxoplasmosis: Quality appraisal of selected primary studies (Cohort studies) – routine advice vs, no specific advice

Domains	Breugelmans et al., (2004)[15]	Pawlowski et al., (2001)[87]
Domain 1: Selection bias		
• Can selection bias sufficiently be excluded?*	No, it is unclear how systematic participants were selected in each time period.	Insufficient info to assess, because it is a bit unclear how the sample prior to the intervention was selected.
• Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis?*	No, confounding factors were not described or considered.	No, only a few of the baseline characteristics of the groups are described and none considered in the analysis.
Domain 2: Detection bias		
• Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups?*	No – even in the pre-intervention period, advice must have been given, but that was not described.	No – exposure in the pre-intervention period is not described (i.e. the type of general advice provided).
• Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups?*	Yes, the outcomes are clear.	No, a 'standardised questionnaire' was used. However, it is subjectively rated and the scale does not seem to be validated.
• Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis?*	No, differences of prevalence during the study time are not taken into consideration (i.e. it is assumed rates have not changed over time).	No, differences of prevalence during the study time are not taken into consideration (i.e. it is assumed rates have not changed over time).
• Is the assessment of outcome made blind to exposure status?*	Insufficient information to assess since, most likely, different people would be involved in the training and the testing.	Insufficient information to assess since, most likely different people would be involved in the training and the testing.
If no to question 6, does this have an impact on the assessment of the outcome?**	No the outcome is objective and therefore it should not be affected by blinding.	Yes, since the outcome measure is subjective knowledge of the intervention may introduce bias.
• Is the follow-up sufficiently long to measure all relevant outcomes?*	Yes, for the one outcome that is reported (seroconversion rate) the follow-up is appropriate.	Insufficient to assess since changes in behaviour may take a while.
Domain 3: Attrition bias		
• Can selective loss-to-follow-up be sufficiently excluded?*	Insufficient info to assess.	Insufficient info to assess.

** Options: Yes/No/Insufficient info to assess*
*** Options: Yes/No/ Not possible in this type of exposure /Insufficient info to assess*

8.3.3. *Chlamydia trachomatis*

Table 63 – Screening for chlamydia: Quality appraisal of selected primary studies (Cohort studies)

Domain	Beal (1992)[37]	Quinlivan (1998)[13]
Domain 1: Selection bias		
Can selection bias sufficiently be excluded?*	No this before-and-after design relied on retrospective analyses of medical charts and therefore it is hard to exclude selection bias.	Yes, this is a prospective cohort design where selection bias has been minimised.
Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis?*	No, while the paper identifies that no other screening/medical protocol changes were instituted between the two different time periods, there may have been other factors influencing the results. Authors state that there were no significant differences between groups at baseline for age, pregnancy history and race but no raw data is provided and no other confounding factors are accounted for in the study design or analysis.	No, apart from age which is controlled through the specific population of interest, other possible confounders are not accounted for in the study design or analysis. There is also the possibility that allocation to groups may have been based on a particular unknown factor associated with GP referral decision or location of the pregnant women's' residence.
Domain 2: Detection bias		
Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups?*	Yes, the two screening protocols (none vs. universal) are clear. Although they do not clearly describe the specific test they use for screening.	No, while the universal protocol is clear (although 8 people still did not receive screening in this group and there is no explanation as to why), the comparison protocol is completely unclear. It is based on the discretion of the attending medical staff and we have no knowledge if this is based on a risk-assessment of the pregnant women or based on the skills or interests of the person attending on any particular day.
Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups?*	Yes, outcomes and method of assessment are clearly described.	Yes, outcomes and method of assessment are clearly described.
Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis?*	No, due to the retrospective nature of chart review it is not clear whether some of the women may have already been feverish or on antibiotics at enrolment.	Not applicable
Is the assessment of outcome made blind to exposure status?*	Unclear.	Unclear.
If no to question 6, does this have an impact on the assessment of the outcome?**	No the outcome is objective and therefore would not be influenced by blinding.	No the outcome is objective and therefore would not be influenced by blinding.

Domain	Beal (1992)[37]	Quinlivan (1998)[13]
Is the follow-up sufficiently long to measure all relevant outcomes?*	No, it is unclear how long the follow-up time was.	No, it is unclear how long the follow-up time was.
Domain 3: Attrition bias		
Can selective loss-to-follow-up be sufficiently excluded?*	No, insufficient information is given on why there are different totals given for different outcomes.	No, insufficient information is provided to assess attrition bias.

** Options: Yes/No/Insufficient info to assess*
*** Options: Yes/No/ Not possible in this type of exposure / Insufficient info to assess*

8.3.4. Group B streptococcus

Table 64 – Screening for GBS: Quality appraisal of selected primary studies (Cohort studies) – screening vs. no screen / risk based prophylaxis for GBS (part 1)

Domains	Abdelmaaboud (2011)[15]	Angstetra (2007)[16]	Brozanski (2000)[17]	Gilson (2000)[19]	Hafner (1998)[20]	Horvath (2013)[21]
Domain 1: Selection bias						
• Can selection bias sufficiently be excluded?*	No, it is a retrospective study design and therefore it is hard to exclude selection bias.	No, even though part of the data were collected prospectively, a historic comparison was made.	No, this is a retrospective study and it therefore depends on how records are kept and how complete the record keeping is.	No, this is a retrospective study design which means that it may be compromised by bad record keeping and other factors.	No, it is a bit unclear whether data were collected prospective or retrospetively.	No, prospective cohort with an historic control.
• Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis?*	No, possible confounders are described but not accounted for in the study design or analysis	No, only a limited number of characteristics are described and none are controlled for in the analysis	No, characteristics are only described by GBS status rather than in groups.	No, characteristics are described, but the analysis does not account for any group differences.	No, characteristics were not described.	No, characteristics were not described by study group.

Domains	Abdelmaaboud (2011)[15]	Angstetra (2007)[16]	Brozanski (2000)[17]	Gilson (2000)[19]	Hafner (1998)[20]	Horvath (2013)[21]
Domain 2: Detection bias						
• Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups?*	Yes, methods are clearly described.	No, the historical control protocol is not very clearly described, but the method of assessment was similar.	Yes, according to published ACOG and CDC guidelines.	No, clinical practice in the control group is not very clearly defined.	Yes, methods are clearly described.	No, the protocol used for the historic sample is not very clearly described.
• Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups?*	Yes, outcome and method of assessment are clearly described.	Yes, the outcome was clearly defined.	No, not a very detailed description.	No, three different groups of outcomes are described in the methods, but only an overall outcome is reported. It is a bit unclear why a differentiation was made and how it may have affected the results.	No, methods of assessment were not described in detail..	Yes, the outcome is clearly described.
• Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis?*	Not applicable.	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
• Is the assessment of outcome made blind to exposure status?*	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
If no to question 6, does this have an impact on the assessment of the outcome?**	No the outcome is objective and therefore would not be influenced by blinding.	No the outcome is objective and therefore would not be influenced by blinding.	No the outcome is objective and therefore would not be influenced by blinding.	No the outcome is objective and therefore would not be influenced by blinding.	No the outcome is objective and therefore would not be influenced by blinding.	No the outcome is objective and therefore would not be influenced by blinding.
• Is the follow-up sufficiently long to measure all relevant outcomes?*	Yes, early-onset GBS can be assessed in a 7 day period.	Yes, early-onset GBS can be assessed in a 7 day period.	No, follow-up in records was only 48 hours rather than a week.	Yes, early-onset GBS can be assessed in a 7 day period.	No. the follow-up time is unclear.	No, it is unclear how long the follow-up time was.

Domains	Abdelmaaboud (2011)[15]	Angstetra (2007)[16]	Brozanski (2000)[17]	Gilson (2000)[19]	Hafner (1998)[20]	Horvath (2013)[21]
Domain 3: Attrition bias						
• Can selective loss-to-follow-up be sufficiently excluded?*	Insufficient info to assess	Insufficient info to assess	Insufficient info to assess	Insufficient info to assess	Insufficient info to assess	Insufficient info to assess

** Options: Yes/No/Insufficient info to assess*
*** Options: Yes/No/ Not possible in this type of exposure /Insufficient info to assess*

Table 65 – Screening for chlamydia: Quality appraisal of selected primary studies (Cohort studies) – screenong vs. no screen / risk based prophylaxis for GBS (part 2)

Domains	Jeffrey (1998)[38]	Lin (2011)[23]	Locksmith (1999)[24]	Main (2000)[25]	Puopolo (2005)[26] and Chen (2001)[39]	Reisner (2000)[27]
Domain 1: Selection bias						
• Can selection bias sufficiently be excluded?*	No, but data were collected prospectively.	No, data were retrospectively reviewed and it is therefore possible that there are biases due to data collection	No, this is a retrospective study with all the biases that are inherent in this design.	Yes, the majority of these cohorts are collected prospectively.	No, this is a retrospective sample.	Yes, this is a prospective study including all women who deliver in the centre.
• Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis?*	No, neither was there a detailed description of the two cohorts nor were any adjustments made in the analysis.	No, neither clearly desribed nor adjusted in the analysis.	No, a good description of the groups is provided, but no adjustements are made in the analysis.	No, the three groups are clearly described but no adjustements are made for differences in the analysis of the outcome.	No, baseline characteristics were not provided.	No, only a limited number of characteristics were described and none adjusted in the analysis.
Domain 2: Detection bias						
• Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups?*	Yes, exposure to intervention strategies is clearly described.	Yes, the exposure is clearly described.	Yes, this is clearly described.	Yes, procedure of exposure is clearly describe.	Yes, exposure is clearly defined.	Yes, exposure is clearly defined.

• Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups?*	No, even though a description is provided it is later a bit unclear whether to select the blood positive or total incidence the incidence outcome.	Yes, the outcome was clearly defined	Yes, the outcome is clearly defined.	Yes, the outcome is clearly defined	No, even though the outcome is clearly described there seems to be a mismatch between the study results described between the two studies.	Yes,, the outcome is defined.
• Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis?*	Not applicable.	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
• Is the assessment of outcome made blind to exposure status?*	Not applicable.	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
If no to question 6, does this have an impact on the assessment of the outcome?**	No the outcome is objective and therefore would not be influenced by blinding.	No the outcome is objective and therefore would not be influenced by blinding.	No the outcome is objective and therefore would not be influenced by blinding.	No the outcome is objective and therefore would not be influenced by blinding.	No the outcome is objective and therefore would not be influenced by blinding.	No the outcome is objective and therefore would not be influenced by blinding.
• Is the follow-up sufficiently long to measure all relevant outcomes?*	Yes, early-onset GBS can be assessed in a 7 day period.	No, there is a diagram which only describes a 48 hour period. 7 days would be more appropriate.	Yes, early-onset GBS can be assessed in a 7 day period.	Yes, early-onset GBS can be assessed in a 7 day period.	Yes, early-onset GBS can be assessed in a 7 day period.	Insufficient information to assess.
Domain 3: Attrition bias						
• Can selective loss-to-follow-up be sufficiently excluded?*	Insufficient info to assess.	Insufficient info to assess.	Insufficient info to assess.	Insufficient info to assess.	Insufficient info to assess.	Insufficient info to assess.

** Options: Yes/No/Insufficient info to assess*
*** Options: Yes/No/ Not possible in this type of exposure /Insufficient info to assess*

Table 66 – Screening for chlamydia: Quality appraisal of selected primary studies (cohort studies) – screening vs. no screen / risk based prophylaxis for GBS (part 3)

Domains	Renner (2006)[28]	Schrag (2013)[29] and associated references[3, 40, 41]	Share (2001)[42]	Vergani (2002)[30]	Voluménie (1998)[31]
Domain 1: Selection bias					
• Can selection bias sufficiently be excluded?*	No, this is a retrospective study	No, data were collected retrospecitve.	No, this study was conducted using retrospective case reviews.	No, it is a retrospective case review study	No, this was a study with prospective data collection for the screening protocol compared to a historic control.
• Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis?*	No, confounders are neither described nor accounted for in the analysis.	Yes, they are described and accounted for	No, the group characteristics are clearly described but no adjustements were made in the analysis.	No, only a limited number of maternal characteristics are provided and they are not accounted for in the analysis.	No, the groups are neither clearly described nor are attempts made to adjust for possible confounders in their analysis
Domain 2: Detection bias					
• Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups?*	Yes, exposure is clearly defined.	Yes, exposure is defined by protocol.	Yes, exposure is clearly defined.	Yes, exposure is clearly defined.	Yes, exposure is clearly defined.
• Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups?*	Yes, the method of assessment is described.	Yes, outcomes are clearly defined	No, outcome assessment was not described.	Yes, the outcomes is clearly defined and methods of assessment are the same in the three groups.	Yes, the method of assessment is described.
• Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis?*	Not applicable.	Not applicable	Not applicable	Not applicable	Not applicable
• Is the assessment of outcome made blind to exposure status?*	Not applicable.	Not applicable	Not applicable	Not applicable	Not applicable

Domains	Renner (2006)[28]	Schrag (2013)[29] and associated references[3, 40, 41]	Share (2001)[42]	Vergani (2002)[30]	Voluménie (1998)[31]
If no to question 6, does this have an impact on the assessment of the outcome?**	No the outcome is objective and therefore would not be influenced by blinding.	No the outcome is objective and therefore would not be influenced by blinding.	No the outcome is objective and therefore would not be influenced by blinding.	No the outcomes are objective and therefore would not be influenced by blinding.	No the outcome is objective and therefore would not be influenced by blinding.
• Is the follow-up sufficiently long to measure all relevant outcomes?*	Yes, early-onset GBS can be assessed in a 7 day period.	Yes, early-onset GBS can be assessed in a 7 day period.	Insufficient info do assess.	Yes, early-onset GBS can be assessed in a 7 day period.	Yes, early-onset GBS can be assessed in a 7 day period.
Domain 3: Attrition bias					
• Can selective loss-to-follow-up be sufficiently excluded?*	Insufficient info to assess.	Insufficient info do assess.	Insufficient info do assess.	Insufficient info do assess.	Insufficient info do assess.

** Options: Yes/No/Insufficient info to assess*
*** Options: Yes/No/ Not possible in this type of exposure /Insufficient info to assess*

Table 67 – Screening for chlamydia: Quality appraisal of selected primary studies (Cohort studies) – late vs. early screening for GBS

Domains	Davis (2001)[18]	Lijoi (2007)[2]
Domain 1: Selection bias		
• Can selection bias sufficiently be excluded?*	No, this is a retrospective study.	No, even though it is a prospective study data are concurrently selected (therefore there are likely reasons why some were screened and others not)
• Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis?*	No, the groups are not very clearly described with regards to baseline characteristics. No adjustments were made in the analysis.	No, even though attempts were made to match the groups by excluding women with risk factors there are other variables that may have influenced the outcomes which are not considered in their analysis.
Domain 2: Detection bias		
• Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups?*	Yes, exposure and methods are sufficiently described.	No, it is unclear why some women were screened and others not.
• Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups?*	No, there are several different categories of GBS infection and even though they are described it is unclear wether they are symptomatic or not.	No, it is unclear whether or not the culture positive newborns were symptomatic or not (numbers seemed to be a lot higher than in other studies).

Domains	Davis (2001)[18]	Lijoi (2007)[2]
• Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis?*	Not applicable	Not applicable
• Is the assessment of outcome made blind to exposure status?*	Not applicable	Not applicable
If no to question 6, does this have an impact on the assessment of the outcome?**	No the outcomes are objective and therefore would not be influenced by blinding.	No the outcome is objective and therefore would not be influenced by blinding.
• Is the follow-up sufficiently long to measure all relevant outcomes?*	No, follow-up is not very clearly described.	No, follow-up is not very clearly described.
Domain 3: Attrition bias		
• Can selective loss-to-follow-up be sufficiently excluded?*	Insufficient info to assess.	Insufficient info to assess.

** Options: Yes/No/Insufficient info to assess*
*** Options: Yes/No/ Not possible in this type of exposure /Insufficient info to assess*

8.3.5. Gestational diabetes

Table 68 – Screening for gestational diabetes: Quality appraisal of selected primary studies (RCTs) – universal vs. selected screening

Bebbington 1999[43]		
Domain	**Support for judgement**	**Review authors' judgement**
Selection bias		
• **Random sequence generation**	Authors state "random allocation" with no further details.	High risk of selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence. There is insufficient detail to allow an assessment of whether the "random allocation" would produce comparable groups.
• **Allocation concealment**	Allocation concealment not reported.	High risk of selection bias (biased allocation to interventions) due to inadequate information provided concerning concealment of allocations prior to assignment.
Performance bias		
• **Blinding of participants and personnel** • **Assessments should be made for each main outcome (or class of outcomes)**	Blinding of participants and personnel unclear as no information provided.	There may be some risk of performance bias due to knowledge of the allocated interventions by participants and personnel during the study; however the outcome of interest is objective so risk is minimal.
Detection bias		
• **Blinding of outcome assessment** • **Assessments should be made for each main outcome (or class of outcomes)**	Authors state "blinded assessors collected outcomes postpartum".	Low risk of detection bias due to blinding of personnel to the allocated interventions during the study.
Attrition bias		
• **Incomplete outcome data** • **Assessments should be made for each main outcome (or class of outcomes)**	The outcome of interest, macrosomia, is only presented as percentages. This absence of raw data is problematic as calculating backwards based on allocation to groups is insufficient because attrition is reported. 18 people were lost to follow-up but no information is provided about their original allocation of baseline characteristics.	High risk of attrition bias due to incomplete reporting of outcome data.
Reporting bias		
• **Selective reporting**	No details reported.	Low risk of reporting bias due to selective outcome reporting.

Table 69 – Screening for gestational diabetes: Quality appraisal of selected primary studies (Cohort studies) – universal vs. selected screening

Domain	Davis 2013[44]	Dietrich 1987[45]	Lindqvist 2014[46]
Domain 1: Selection bias			
Can selection bias sufficiently be excluded?*	No this before-and-after design relied on retrospective analyses of medical charts and therefore it is hard to exclude selection bias.	Yes, this is a prospective study including all women seeking care from this prenatal clinic.	No this research design relied on retrospective analyses of medical charts and therefore it is hard to exclude selection bias.
Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis?*	No information is provided on possible confounders, and no information is provided on treatment for those who were diagnosed with gestational diabetes.	No controlling for confounders is provided in the analyses but selected baseline characteristics are reported and seem equivalent in each group. Authors state that the patient profiles of each group were not significantly different.	No controlling for confounders is provided in the analyses with respect to this particular comparison of screening strategies, but baseline characteristics are reported and seem equivalent in each group. Authors do not give details of treatment provided to both groups for those diagnosed with gestational diabetes.
Domain 2: Detection bias			
Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups?*	No, while the 'after' 2007 screening protocol for universal screening is clear, the pre-2007 selected screening policy is unclear whether this is also semi-universal but two weeks earlier (still after 24 weeks) or solely motivated by risk-factor screening.	Yes, a clear description is supplied for both the universal and risk-factor screening protocols.	Yes, a clear description is supplied for both the universal and risk-factor screening protocols.
Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups?*	Macrosomia and large for gestational age are clearly defined. No specific definition is provided for respiratory distress or neonatal hypoglycaemia. And congenital abnormality, stillbirth and neonatal death are only described in the text as "uncommon in all groups at both time periods" rather than reported with raw data which precludes analysis.	Infant birth weight is clearly defined. However both outcomes of interest are only reported narratively as "not significantly different" which precludes analysis of the findings being included in the current review.	The calculation used to large for gestational age is clearly defined.
Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis?*	Not applicable – outcomes are all neonatal and women were pregnant at the point of enrolment.	Not applicable – outcomes are all neonatal and women were pregnant at the point of enrolment.	Not applicable – outcomes are all neonatal and women were pregnant at the point of enrolment.

Domain	Davis 2013[44]	Dietrich 1987[45]	Lindqvist 2014[46]
Is the assessment of outcome made blind to exposure status?*	Unclear but unlikely given the retrospective nature of the study design.	Unclear but unlikely given the retrospective nature of the study design.	Unclear but unlikely given the retrospective nature of the study design.
If no to question 6, does this have an impact on the assessment of the outcome?**	No the outcome is objective and therefore would not be influenced by blinding.	No the outcome is objective and therefore would not be influenced by blinding.	No the outcome is objective and therefore would not be influenced by blinding.
Is the follow-up sufficiently long to measure all relevant outcomes?*	No, it is unclear how long the follow-up time was.	No, it is unclear how long the follow-up time was.	No, it is unclear how long the follow-up time was.
Domain 3: Attrition bias			
Can selective loss-to-follow-up be sufficiently excluded?*	No, insufficient information is given around attrition. Original sample sizes are given in the outcome reporting tables.	No, insufficient information is given around attrition	No, insufficient information is given around attrition. Raw numbers and percentages reported to not directly correlate so unreported loss-to-follow-up seems likely.

** Options: Yes/No/Insufficient info to assess*
*** Options: Yes/No/ Not possible in this type of exposure / Insufficient info to assess*

Table 70 – Screening for gestational diabetes: Quality appraisal of selected primary studies (Cohort studies) – early vs. late screening

Domain	Dong 1993[47]	Jovanovic 1985[48]	Lapolla 1995[49]
Domain 1: Selection bias			
Can selection bias sufficiently be excluded?*	No this research design relied on retrospective analyses of medical charts and therefore it is hard to exclude selection bias.	Yes, this is a prospective cohort design where selection bias has been minimised.	No, although this is a prospective cohort design, the comparison does not truly reflect risk factor screening vs. universal screening, but rather a comparison of those who have a risk factor so are screened early and those do not have a risk factor so are screened late. It is a sub-set of the protocol comparison of interest. This has been taken into account with respect to indirectness in the quality appraisal.
Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis?*	Comparable patient characteristics are not presented for each group and no controlling for confounders is provided in the analysis. Authors note that the women in the early screening group had more severe glucose intolerance in their first gestational diabetes pregnancy that the late testing women did. Therefore it is possible that the baseline characteristics in the two groups were not comparable.	Comparable patient characteristics are not presented for each group and no controlling for confounders is provided in the analysis. No information provided on treatment of those who were diagnosed with gestational diabetes.	Comparable patient characteristics are not presented for each group and no controlling for confounders is provided in the analysis. No information provided on treatment of those who were diagnosed with gestational diabetes.
Domain 2: Detection bias			
Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups?*	Yes, the two screening protocols (early vs. late) are clear. Although they do not clearly describe the specific test they use for screening (50g, 75g or 100g glucose load?).	Yes, the two screening protocols (early vs. late) are clear.	Yes, the two screening protocols (early vs. late) are clear.
Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups?*	No outcomes and method of assessment are not clearly described. And only percentages are reported.	Yes, outcomes and method of assessment are clear.	No outcomes and method of assessment are not clearly described. And only percentages are reported.

Domain	Dong 1993[47]	Jovanovic 1985[48]	Lapolla 1995[49]
Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis?*	Not applicable.	Not applicable – outcomes are all neonatal and women were pregnant at the point of enrolment.	Not applicable – outcomes are all neonatal and women were pregnant at the point of enrolment.
Is the assessment of outcome made blind to exposure status?*	Unclear but unlikely given the retrospective nature of the study design.	Unclear.	Unclear.
If no to question 6, does this have an impact on the assessment of the outcome?**	No the outcome is objective and therefore would not be influenced by blinding.	No the outcome is objective and therefore would not be influenced by blinding.	No the outcome is objective and therefore would not be influenced by blinding.
Is the follow-up sufficiently long to measure all relevant outcomes?*	No, it is unclear how long the follow-up time was.	Yes, specify two-year duration.	No, it is unclear how long the follow-up time was.
Domain 3: Attrition bias			
Can selective loss-to-follow-up be sufficiently excluded?*	No, insufficient information is given on attrition with respect to the lower numbers at follow-up.	No, insufficient information is provided to assess attrition bias.	No, insufficient information is provided to assess attrition bias.

** Options: Yes/No/Insufficient info to assess*
*** Options: Yes/No/ Not possible in this type of exposure / Insufficient info to assess*

Table 71 – Screening for gestational diabetes: Quality appraisal of selected primary studies (Cohort studies) – different thresholds for tests used

Domain	Lindqvist 2014[46]
Domain 1: Selection bias	
Can selection bias sufficiently be excluded?*	No this research design relied on retrospective analyses of medical charts and therefore it is hard to exclude selection bias.
Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis?*	No controlling for confounders is provided in the analyses with respect to this particular comparison of screening strategies, but baseline characteristics are reported and seem equivalent in each group. Authors do not give details of treatment provided to groups for those diagnosed with gestational diabetes.
Domain 2: Detection bias	
Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups?*	Yes, a clear description is supplied for each of the risk-factor screening threshold protocols.

Domain	Lindqvist 2014[46]
Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups?*	The calculation used to large for gestational age is clearly defined.
Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis?*	Not applicable – outcomes are all neonatal and women were pregnant at the point of enrolment.
Is the assessment of outcome made blind to exposure status?*	Unclear but unlikely given the retrospective nature of the study design.
If no to question 6, does this have an impact on the assessment of the outcome?**	No the outcome is objective and therefore would not be influenced by blinding.
Is the follow-up sufficiently long to measure all relevant outcomes?*	No, it is unclear how long the follow-up time was.
Domain 3: Attrition bias	
Can selective loss-to-follow-up be sufficiently excluded?*	No, insufficient information is given around attrition. Raw numbers and percentages reported to not directly correlate so unreported loss-to-follow-up seems likely.

** Options: Yes/No/Insufficient info to assess*
*** Options: Yes/No/ Not possible in this type of exposure / Insufficient info to assess*

Table 72 – Screening for gestational diabetes: Quality appraisal of selected primary studies (RCTs) – different test combinations used

Domain	Support for judgement	Review authors' judgement
Domain 1: Selection bias		
Random sequence generation	Authors state "block randomisation" used, but no further detail given.	High risk of selection bias (biased allocation to interventions) due to inadequate information supplied about generation of a randomised sequence
Allocation concealment	Authors state "opaque envelopes were prepared by research staff not involved in participant recruitment".	No risk of selection bias (biased allocation to interventions) due to adequate concealment of allocations prior to assignment
Performance bias		
Blinding of participants and personnel **Assessments should be made for each main outcome (or class of outcomes)**	Authors state "as a result of the nature of the test, both the participant and the study coordinator were not blinded".	Low risk of performance bias due to knowledge of the allocated interventions by participants and personnel during the study because outcomes are objective.
Domain 2: Detection bias		
Blinding of outcome assessment **Assessments should be made for each main outcome (or class of outcomes)**	No description of measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received.	Low risk of detection bias due to knowledge of the allocated interventions by outcome assessors because outcomes are objective.

Domain	Support for judgement	Review authors' judgement
Domain 3: Attrition bias		
Incomplete outcome data **Assessments should be made for each main outcome (or class of outcomes)**	Attrition is comparable within each group 5%, 6%, 5% respectively and for similar reasons (e.g. did not complete OGTT, incomplete cost data). Although findings for the outcome of interest are reported only as percentages and it is unclear whether these are calculated using the number randomised, number who received testing, or number analysed which respect to clinical outcomes (as the focus is on the cost analysis).	Low risk of attrition bias due to amount, nature or handling of incomplete outcome data.
Domain 4: Reporting bias		
Selective reporting	No pre-specification of clinical outcomes of interest.	Low risk of reporting bias due to selective outcome reporting

Table 73 – Diagnostic accuracy for gestational diabetes: Quality appraisal of the included studies

Domain	Kind of answers	Ayach 2006	Espinosadelos 1999	Perucchini 1999	Thitadilok 1995	Weerakiet 2006
Domain 1: Patient selection						
A. Risk of bias						
• **Was a consecutive or random sample of patients enrolled?**	Yes/No/ Unclear	Yes	Yes	Yes	Unclear	Yes
• **Was a case-control design avoided?**	Yes/No/ Unclear	Yes	Yes	Yes	Yes	Yes
• **Did the study avoid inappropriate exclusions?**	Yes/No/ Unclear	Yes	Yes	Yes	Yes	Yes
Could the selection of patients have introduced bias?	Risk: Low/High	**Low**	**Low**	**Low**	**Low**	**Low**
B. Concerns regarding applicability						
Is there concern that the included patients do not match the review question?	Concern: Low/High	**Low**	**Low**	**Low**	**Low**	**Low**

Domain	Kind of answers	Ayach 2006	Espinosadelos 1999	Perucchini 1999	Thitadilok 1995	Weerakiet 2006
Domain 2: Index test(s)						
A. Risk of bias						
• **Were the index test results interpreted without knowledge of the results of the reference standard?**	Yes/No/ Unclear	Yes	Yes	Yes	Yes	Yes
• **If a threshold was used, was it pre-specified?**	Yes/No/ Unclear	Yes	Yes	Yes	No	No
Could the conduct or interpretation of the index test have introduced bias?	Risk: Low/High	**Low**	**Low**	**Low**	**Low**	**High**
B. Concerns regarding applicability						
Is there concern that the index test, its conduct, or interpretation differ from the review question?	Concern: Low/High	**Low**	**Low**	**Low**	**High**	**Low**
Domain 3: Reference standard						
A. Risk of bias						
• **Is the reference standard likely to correctly classify the target condition?**	Yes/No/ Unclear	Yes	Yes	Yes	Yes	Yes
• **Were the reference standard results interpreted without knowledge of the results of the index test?**	Yes/No/ Unclear	Unclear	Unclear	Unclear	Unclear	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Risk: Low/High	**High**	**High**	**High**	**High**	**Low**
B. Concerns regarding applicability						
Is there concern that the target condition as defined by the reference standard does not match the review question?	Concern: Low/High	**Low**	**Low**	**Low**	**Low**	**Low**

Domain	Kind of answers	Ayach 2006	Espinosadelos 1999	Perucchini 1999	Thitadilok 1995	Weerakiet 2006
Domain 4: Flow and timing						
A. Risk of bias						
• **Was there an appropriate interval between index test(s) and reference standard?**	Yes/No/ Unclear	Unclear	Yes	Yes	Yes	Yes
• **Did all patients receive a reference standard?**	Yes/No/ Unclear	Yes	Yes	Yes	Yes	Yes
• **Did patients receive the same reference standard?**	Yes/No/ Unclear	Yes	Yes	Yes	Yes	Yes
• **Were all patients included in the analysis?**	Yes/No/ Unclear	No	Yes	Yes	Yes	Yes
Could the patient flow have introduced bias?	Risk: Low/High	**High**	**Low**	**Low**	**Low**	**Low**

8.3.6. Hypothyroidism

Table 74 – Screening for hypothyroidism: Quality appraisal of selected primary studies (RCTs)

Domain	Support for judgement	Review authors' judgement	Overall Risk of Bias
Lazarus, 2012[33]			
Selection bias			High risk for all outcomes
Random sequence generation	Computer generated block design	Low risk of Bias	
Allocation concealment	method of concealment is not described	Unclear risk of Bias	
Performance bias			
Blinding of participants and personnel Assessments should be made for each main outcome (or class of outcomes)	No blinding; outcome is likely to be influenced	High risk of Bias	
Detection bias			
Blinding of outcome assessment Assessments should be made for each main outcome (or class of outcomes)	Participants' non-blinding is likely to have influenced outcome assessment	High risk of Bias	
Attrition bias			
Incomplete outcome data Assessments should be made for each main outcome (or class of outcomes)	> 20% of women with missing outcomes data	Unclear risk of Bias	
Reporting bias			
Selective reporting	Protocol available	Low risk of Bias	
Other bias			
Other sources of bias	The impact on test positive population misclassification bias is unclear, but TSH and FT4 cut-off values were periodically adjusted. TSH was slightly higher in the screening group than in the control group but adjusted estimates did not differ for IQ	Unclear risk of Bias	

Domain	Support for judgement	Review authors' judgement	Overall Risk of Bias
Negro, 2010[34]			
Selection bias			Low risk for all outcomes
Random sequence generation	Computer generated block design	Low risk of Bias	
Allocation concealment	Sequentially numbered, opaque, sealed	Low risk of Bias	
Performance bias			
Blinding of participants and personnel Assessments should be made for each main outcome (or class of outcomes)	Risk assessment and drug treatment	Low risk of Bias	
Detection bias			
Blinding of outcome assessment Assessments should be made for each main outcome (or class of outcomes)	outcome measurement is not likely to be influenced by lack of blinding	Low risk of Bias	
Attrition bias			
Incomplete outcome data Assessments should be made for each main outcome (or class of outcomes)	Low rates and sensitivity analyses with multiple imputations	Low risk of Bias	
Reporting bias			
Selective reporting	Outcomes were prospectively defined and are reported	Low risk of Bias	
Other bias			
Other sources of bias	No serious concerns about prognostic imbalance	Low risk of Bias	

Table 75 – Therapy for subclinical hypothyroidism during pregnancy: Quality appraisal of the selected systematic review

Question	Answer
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review. To score "Yes": 1-need to refer to a protocol, ethics approval, or pre-determined/a priori published research objectives; and/ or 2- mention that a clinical equipoise existed; and/ or 3- the objective of the SR does match its eligibility criteria; and/ or 4- there is clear objective in the SR that shows the need for conducting the SR	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
2. Was there either a: • Duplicate (i.e. two independent reviewers) screening of the literature? Or, • Independent verification of all/partial screened records (if partial, reliability statistics should have been reported and should be indicative of high concordance)	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
3. Was there either a: • Duplicate (i.e. two independent reviewer) data extraction from studies? Or, • Independent verification of all/partial extracted data (if partial, reliability statistics should have been reported and should be indicative of high accuracy)	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
4. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
5. Was a list of studies (included) provided? A list of included studies should be provided.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
6. Were the characteristics of the included studies provided?	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

7. Was the scientific quality of the included studies assessed and documented? And was it adequate based on judgement (e.g. standard tool was used or important biasing domains were answered)?	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in evidence synthesis.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
9. Were the methods used to combine the findings of studies appropriate?	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
10. What is the overall judgement taking into account the importance of the modified AMSTAR across all of the responses across all questions? Note: If the answer for Questions 8 is "No", that is to say if the SR has not used a tool to assess the quality of included studies, then the overall judgment can Not rate as "High" or "Moderate" quality. Please consider the following points in overall rating: a. Publication bias (comprehensive search; for instance, at least MEDLINE should be searched) b. Inaccuracy/major concerns in data extraction and screening c. Major concerns in critical appraisal	High quality Moderate quality Low quality

Table 76 – Therapy for subclinical hypothyroidism during pregnancy: Quality appraisal of the selected primary studies (RCTs)

Domain	Support for judgement	Review authors' judgement	Overall Study Risk
Jain S., 2013[52]			
Selection bias			Overall study risk: Unclear
Random sequence generation	No information provided	Unclear	
Allocation concealment	No information provided	Unclear	
Performance bias			
Blinding of participants and personnel	No information provided for blinding of personnel; no placebo, and participants are not blinded	Unclear	

Assessments should be made for each main outcome (or class of outcomes)			
Detection bias			
Blinding of outcome assessment **Assessments should be made for each main outcome (or class of outcomes)**	No information provided; outcomes are all objective	Low	
Attrition bias			
Incomplete outcome data **Assessments should be made for each main outcome (or class of outcomes)**	100 women randomized, and data analyzed for 100 women (no loss to follow-up)	Low	
Reporting bias			
Selective reporting	No study protocol available; unclear why subgroup analyses was based on TSH and TPOAb levels for composite outcome of preterm birth or miscarriage	Unclear	
Other bias			
Other sources of bias	No information provided	Unclear	
Kim C.-H., 2011[53]			
Selection bias			Overall study risk: Unclear
Random sequence generation	Subjects were randomized by the use of a computer-generated list.	Low	
Allocation concealment	Subjects were randomized by the use of sealed envelopes - not reported that envelopes are sequentially numbered and opaque; the sequence of allocation to the two groups was provided to the investigating physicians, and randomization was performed as planned according to the randomization list order.	Unclear	
Performance bias			
Blinding of participants and personnel **Assessments should be made for each main outcome (or class of outcomes)**	No treatment in second arm and treatment were tailored based on TSH levels.	Unclear	

Detection bias			
Blinding of outcome assessment **Assessments should be made for each main outcome (or class of outcomes)**	Unclear whether personnel are blinded; all outcomes are objective	Low	
Attrition bias			
Incomplete outcome data **Assessments should be made for each main outcome (or class of outcomes)**	No patient was lost to follow-up or abandoned the study	Low	
Reporting bias			
Selective reporting	No study protocol available	Unclear	
Other bias			
Other sources of bias	Funding not reported; single-centre trial; authors state no conflicts of interest; no significant baseline differences, but no details on some of the pre-specified confounders of interest (SES, maternal alcohol use)	Unclear	
Negro R., 2005[54]			
Selection bias			Overall study risk: Unclear
Random sequence generation	A computer program was used to randomly assign the patients to one or the other group	Low	
Allocation concealment	A sealed opaque envelope was assigned to each patient and only the doctor applying the treatment knew which group each patient had been assigned to, and did not participate in any subsequent phase of the study	Low	
Performance bias			
Blinding of participants and personnel **Assessments should be made for each main outcome (or class of outcomes)**	Only the doctor applying the treatment knew which group each patient had been assigned toPlacebo was used Participants blinded; some caregivers blinded, some unblended.	Unclear	
Detection bias			

Blinding of outcome assessment **Assessments should be made for each main outcome (or class of outcomes)**	Medical doctors attended different phases of the protocol so that each was blinded to which group the patients belonged. Adequate blinding of medical personnel, and outcomes are all objective.	Low	
Attrition bias			
Incomplete outcome data **Assessments should be made for each main outcome (or class of outcomes)**	Quote: "All study patients completed the protocol" Numbers per group in the text differ from numbers per group in Figure 1. Unclear where drop-outs occurred and why	Unclear	
Reporting bias			
Selective reporting	Reference made to protocol, but could not find protocol in search.	Unclear	
Other bias			
Other sources of bias	Funding not reported; conflict of interest not reported; no baseline differences; unclear whether study is single-centre/multi-centre	Unclear	
Negro R., 2010[34]			
Selection bias			Unclear risk for all outcomes
Random sequence generation	Unclear for subgroup analysis of interest (low risk women with subclinical hypothyroid)	Unclear risk of Bias	
Allocation concealment	Sequentially numbered, opaque, sealed	Low risk of Bias	
Performance bias			
Blinding of participants and personnel **Assessments should be made for each main outcome (or class of outcomes)**	Unclear, particularly due to co-medication etc	Unclear risk of Bias	
Detection bias			
Blinding of outcome assessment **Assessments should be made for each main outcome (or class of outcomes)**	outcome measurement is not likely to be influenced by lack of blinding	Low risk of Bias	

Attrition bias		
Incomplete outcome data **Assessments should be made for each main outcome (or class of outcomes)**	Low rates and sensitivity analyses with multiple imputations	Low risk of Bias
Reporting bias		
Selective reporting	Outcomes were prospectively defined and are reported	Low risk of Bias
Other bias		
Other sources of bias	No serious concerns about prognostic imbalance	Low risk of Bias

Table 77 – Therapy for subclinical hypothyroidism during pregnancy: Quality appraisal for RCTs included in the Reid et al. 2013 SR

Domain	Support for judgement	Review authors' judgement	Overall Study Risk
Negro, 2006[55]			
Selection Bias			Unclear– all outcomes
Random sequence generation	Quote: "A computer program was used to randomly assign the TPOAb+ patients to either group A or group B."	Low	
Allocation concealment	Quote: "A sealed opaque envelope was assigned to each…patient to either group A or group B " Unclear how envelopes were assigned.	Unclear	
Performance Bias			
Blinding of participants and personnel Assessment should be made for each main outcome (or class of outcomes)	Quote: "Only the doctor treating the patient, who did not participate in any subsequent phase of the study, knew which group the patient was in." Control group received no treatment, and participants were not blinded.	Unclear– all outcomes	
Detection Bias			
Blinding of outcome assessment Assessments should be made for each main outcome (or class of outcomes)	Quote: "Medical doctors participated in different phases of the protocol, so that each was unaware of which group the patients belonged to." All outcomes were objective.	Low – all outcomes	

Domain	Support for judgement	Review authors' judgement	Overall Study Risk
Attrition Bias			
Incomplete outcome data Assessment should be made for each main outcome (or class of outcomes)	Of the 115 that were randomized to treatment/no treatment, dropouts were related to miscarriage	Low – all outcomes	
Reporting Bias			
Selective reporting	Refers to a study protocol, but not clear whether miscarriage was prespecified.	Unclear – –All outcomes	
Other Bias			
Other sources of bias	Funding not reported; author conflict of interest not reported; slight age difference between treatment and no treatment groups; single centre	Unclear	
Outcomes Assessed	gestational hypertension, preeclampsia, preterm birth, miscarriage, placental abruption, birth weight, birth length, head circumference, Apgar score		
Negro, 2007[56]			
Selection Bias			Unclear – all outcomes
Random sequence generation	Quote: "A computer program was used to randomly assign the TPOAb+ patients to either group S1 or group S0."	Low	
Allocation concealment	Quote: "A sealed opaque envelope was assigned to each patient." Unclear how envelopes were assigned.	Unclear	
Performance Bias			
Blinding of participants and personnel Assessment should be made for each main outcome (or class of outcomes)	Quote: "Only the doctor who treated the patient, who did not participate in any subsequent phase of the study, knew to which group the patient was assigned."	Unclear – all outcomes	

Domain	Support for judgement	Review authors' judgement	Overall Study Risk
	Participants in control group were given placebo, some caregivers blinded, some unblinded.		
Detection Bias			
Blinding of outcome assessment	Quote: "Different medical doctors participated in different phases of the protocol, so that each was unaware of which group to which the patients belonged." All outcomes objective	Low – all outcomes	
Attrition Bias			
Incomplete outcome data	All reasons for drop-outs provided (miscarriage and personal reasons) and numbers similar across groups	Low – all outcomes	
Reporting Bias			
Selective reporting	Study referred to a protocol; obstetrical complications and miscarriage do not appear to be prespecified	Unclear – all outcomes	
Other Bias			
Other sources of bias	Funding not reported; authors state they have nothing to disclose; no differences in baseline data between groups; single centre study	Unclear	
Outcomes Assessed	Gestational hypertension, preeclampsia, premature deliveries, miscarriage, permanent hypothyroidism, birth weight, birth length, head circumference, Apgar score		

Table 78 – Therapy for subclinical hypothyroidism during pregnancy: Quality appraisal of the selected studies (Observational study)

Domain	Support for judgement	Review authors' judgement
Wang 2012[57]		
Selection bias	Some attrition occurred: 16/756 was lost to follow up with no information provided regarding the similarity of exposed and no-exposed groups.	Unclear risk of bias
Information bias	Actual exposure assessment was not carried out; only recommended treatment stated (Exposure status was classified as yes or no and was dependent on patient consent). Categorization likely to be valid but very possible to be associated with imbalances for important confounders. Outcome assessment was done using objective definitions but timing of outcome assessment not stated. No blinding.	High risk of bias

Confounding	No baseline information provided for the treatment versus no treatment arm except the age, which was significantly different between groups. There is no suggestion that analyses were adjusted for potential confounders.	High risk of bias
Overall assessment	Pre-term birth, low birth weight, hypertension, miscarriage. (Alsoanaemia, Apgar score and post-partum haemorrhage).	High risk of bias
Applicability	For the subgroup of interest (women with subclinical hypothyroidism who received treatment of interest during early pregnancy).	High applicability

8.3.7. Vitamin D deficiency

Table 79 – Vitamin D supplementation: Quality appraisal of the selected SR (De-Regil et al., 2012[58])

Question	Answer
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review. To score "Yes": 1-need to refer to a protocol, ethics approval, or pre-determined/a priori published research objectives; and/ or 2- mention that a clinical equipoise existed; and/ or 3- the objective of the SR does match its eligibility criteria; and/ or 4- there is clear objective in the SR that shows the need for conducting the SR	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
2. Was there either a: • Duplicate (i.e. two independent reviewers) screening of the literature? Or, • Independent verification of all/partial screened records (if partial, reliability statistics should have been reported and should be indicative of high concordance)	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
3. Was there either a: • Duplicate (i.e. two independent reviewer) data extraction from studies? Or, • Independent verification of all/partial extracted data (if partial, reliability statistics should have been reported and should be indicative of high accuracy)	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
4. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
5. Was a list of studies (included) provided? A list of included studies should be provided.	☐ Yes ☐ No

	□ Can't answer □ Not applicable
6. Were the characteristics of the included studies provided?	□ Yes □ No □ Can't answer □ Not applicable
7. Was the scientific quality of the included studies assessed and documented? And was it adequate based on judgement (e.g. standard tool was used or important biasing domains were answered)?	□ Yes □ No □ Can't answer □ Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in evidence synthesis.	□ Yes □ No □ Can't answer □ Not applicable
9. Were the methods used to combine the findings of studies appropriate?	□ Yes □ No □ Can't answer □ Not applicable
10. What is the overall judgement taking into account the importance of the modified AMSTAR across all of the responses across all questions? Note: If the answer for Questions 8 is "No", that is to say if the SR has not used a tool to assess the quality of included studies, then the overall judgment can Not rate as "High" or "Moderate" quality. <u>Please consider the following points in overall rating:</u> a. Publication bias (comprehensive search; for instance, at least MEDLINE should be searched) b. Inaccuracy/major concerns in data extraction and screening c. Major concerns in critical appraisal	High quality Moderate quality Low quality

Table 80 – Vitamin D supplementation: Quality appraisal of selected primary studies (RCTs)

Domain	Support for judgement	Review authors' judgement	Overall Study Risk
Grant, 2014[59]			
Selection Bias			Unclear – gestational diabetes Low – all other outcomes
Random sequence generation	Quote: "...restricted randomization within blocks of variable size using a computer generated randomization list." CRoB: Using a computer random number generator	Low	
Allocation concealment	Quote: "The allocation sequence was concealed from research staff involved in recruitment. The study statistician randomly allocated a treatment to each participant and labelled identical study medicine bottles such that study staff and participants were unaware of the treatment status" CRoB: Sequentially numbered drug containers of identical appearance	Low	
Performance Bias			
Blinding of participants and personnel	Quote: "Bottles of study medicine were prepared by Ddrops Company...with the study medicine bottles for the 3 groups being identical in colour, shape, and volume and the study medicine identical in colour, consistency, and taste." CRoB: Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken	Low - all outcomes	
Detection Bias			
Blinding of outcome assessment	Quote: Not mentioned in the paper CRoB: Outcome isn't likely to be affected by the lack of blinding	Low – all outcomes	
Attrition Bias			
Incomplete outcome data	Quote: The outcomes we're interested in are all during pregnancy or at birth. Figure 1 shows that during this time period the loss of patients was modest across groups (n=3 for each group), and was for similar reasons (ex. moving from region) CRoB: Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups	Low – all outcomes	
Reporting Bias			

Domain	Support for judgement	Review authors' judgement	Overall Study Risk
Selective reporting	Quote: The objective was to determine the Vitamin D dose necessary to achieve serum 25(OH)D concentration ≥20 ng/mL during infancy Reviewer's assessment: Outcomes same between methods and results, I don't think they're missing any outcomes they should have reported on	Unclear – gestational diabetes (incident cases not reported separately) Low –all other outcomes	
Other Bias			
Other sources of bias	Funding: Non-profit; COI: Authors state they don't not have financial conflict of interest; Baseline balance: Baseline characteristics appear balanced; No additional bias detected	Low	
Outcomes Assessed	Maternal hypercalcemia, birth weight, fetal death, gestational age at birth, gestational diabetes (incident cases not reported separately)		
Asemi, Z, 2013[60]			
Selection bias			Unclear – all outcomes
Random sequence generation	Random assignment was performed by the use of computer-generated random numbers	Low	
Allocation concealment	A trained midwife at the maternity clinic performed the randomized allocation sequence and assigned participants to the groups	Unclear	
Performance bias			
Blinding of participants and personnel	"double-blind" trial – placebo pills contained microcrystalline cellulose and were packed in identical tablets and coded by the producer to guarantee blinding No information on who was blinded	Unclear – all outcomes	
Detection bias			
Blinding of outcome assessment	Outcomes are objective	Low – all outcomes	
Attrition bias			
Incomplete outcome data	Among individuals in the vitD group, 3 were excluded. 3 women were also excluded in the placebo group (preterm delivery, intrauterine fetal death, placental abruption, GDM and severe preeclampsia)	Low – all outcomes	
Reporting bias			
Selective reporting	Participants excluded based on key outcomes	Unclear	

Domain	Support for judgement	Review authors' judgement	Overall Study Risk
Other bias			
Other sources of bias	No significant baseline differences; single-centre trial; non-industry funding, and no conflicts of interest reported	Low	
Outcomes Assessed	Outcomes: Pre-eclampsia, Gestational diabetes, Preterm birth, Intrauterine death (all as reasons for exclusion for rest of measurements after randomization and treatment), placental abruption		
Diogenes 2013[61]			
Selection Bias			High - all outcomes
Random sequence generation	Quote: "Participants were randomly and single-blinded assigned to receive a commercially available supplement…or a placebo...Random assignment was done by a member of the research team in a 1:1 ratio within permuted blocks of size 10" RoB: Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk'.	Unclear	
Allocation concealment	Quote: Not reported on RoB: Insufficient information to permit judgement of 'Low risk' or 'High risk'.	Unclear	
Performance Bias			
Blinding of participants and personnel	Quote: "Participants were randomly and single-blinded assigned to receive a commercially available supplement…or a placebo." RoB: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding	High - all outcomes	
Detection Bias			
Blinding of outcome assessment	Quote: Not reported RoB: Insufficient information to permit judgement of 'Low risk' or 'High risk' OR No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding	Unclear - Pregnancy complications Low - Length of gestation, preterm birth	
Attrition Bias			
Incomplete outcome data	Quote: See Figure 1 – outcomes that we're interested in was assessed during gestation and upon delivery. At this time placebo group lost 37% of patients and calcium group lost 30% of patients. RoB: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups	High - all outcomes	

Domain	Support for judgement	Review authors' judgement	Overall Study Risk
Reporting Bias			
Selective reporting	Quote: No difference between methods and results. Objective was to investigate the effects of calcium plus vitamin D during pregnancy on bone mass during lactation...therefore no expectation of other outcomes relevant for this review	Low	
Other Bias			
Other sources of bias	Non-profit funding, Authors declare no COI, Baseline variables appear similar between groups, No additional sources detected	Low	
Outcomes Assessed	Pregnancy complications, Length of gestation, preterm birth		
Perumal N, 2014[62]			
Selection bias			Unclear for selective reporting
Random sequence generation	n/a	n/a	
Allocation concealment	n/a	n/a	
Performance bias			
Blinding of participants and personnel	n/a	n/a	
Detection bias			
Blinding of outcome assessment	n/a	n/a	
Attrition bias			
Incomplete outcome data	n/a	n/a	
Reporting bias			
Selective reporting	Abstract; insufficient information to permit judgement	Unclear	
Other bias			
Other sources of bias	n/a	n/a	

Domain	Support for judgement	Review authors' judgement	Overall Study Risk
Outcomes Assessed	No relevant outcomes		
Roth 2013[63]			
Selection Bias			High – hypercalcemia, hypercalciuria Low – all other outcomes
Random sequence generation	Quote: "Assignment was based on computer-generated randomization list, with 1:1 allocation, using permuted block of size 4 and 8" CRoB: Using a computer random number generator	Low	
Allocation concealment	Quote: "The allocation sequence was prepared by icddr,b personnel not otherwise involved in the study, and was concealed from investigators. Popular Pharmaceuticals Ltd. (Dhaka) prepared the supplements off-site using individual opaque glass vials labelled with unique participant identifiers based on the randomization list" CRoB: Sequentially numbered drug containers of identical appearance	Low	
Performance Bias			
Blinding of participants and personnel	Quote: "Participants and research staff (including lab personnel) were blinded to allocation" CRoB: Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.	Low – all outcomes	
Detection Bias			
Blinding of outcome assessment	Quote: "Participants and research staff (including lab personnel) were blinded to allocation" CRoB: Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.	Low – all outcomes	
Attrition Bias			
Incomplete outcome data	Quote: See Figure 1 for flowchart, see Table 4 for calcium (hypercalcaemia measurements were taken from only 130 patients (i.e. the "Analysis" section of the flowchart) CRoB: Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups OR Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups	High – hypercalcemia, hypercalciuria Low – all other outcomes	

Domain	Support for judgement	Review authors' judgement	Overall Study Risk
Reporting Bias			
Selective reporting	Quote: Trial is registered online Reviewer's assessment: The trial registration record is very different from the paper. For example, one of the focuses in the record is how vitamin D affects immunology – this isn't mentioned in the paper at all. Outcomes differed slightly between record and results, for example, protocol doesn't mention still births and neonatal death, neonatal and maternal adverse events.	High	
Other Bias			
Other sources of bias	Non-profit funding, Authors declare no COI, Baseline variables appear similar between groups, No additional sources detected	Low	
Outcomes Assessed	Maternal serious clinical adverse events; preterm birth, gestational age at birth, preeclampsia, caesarean section, birth weight (including LBW and VLBW), length, head circumference, still birth, neonatal death, neonatal serious non-fatal adverse events, maternal hypercalcemia, hypercalciuria		
Rodda CP, 2011[64]			
Selection bias			Unclear for selective reporting
Random sequence generation	n/a	n/a	
Allocation concealment	n/a	n/a	
Performance bias			
Blinding of participants and personnel	n/a	n/a	
Detection bias			
Blinding of outcome assessment	n/a	n/a	
Attrition bias			
Incomplete outcome data	n/a	n/a	
Reporting bias			
Selective reporting	Abstract: Insufficient information to permit judgement	Unclear	

Domain	Support for judgement	Review authors' judgement	Overall Study Risk
Other bias			
Other sources of bias	n/a	n/a	
Outcomes Assessed	No relevant outcomes	Unclear	
Yu, CKH, 2009[65]			
Selection bias			High – all outcomes
Random sequence generation	"Subjects were randomized within each ethnic group. Computer generated random number lists were drawn up by an independent researcher, with randomization in blocks of 15"	Low	
Allocation concealment	"The person seeing the pregnant women allocated the next available number on entry to the trial."	High	
Performance bias			
Blinding of participants and personnel	"The treatment was not blinded to the women or doctor..."	High – all outcomes	
Detection bias			
Blinding of outcome assessment	For outcomes near time of delivery, no blinding. For outcomes at 3 years; blinding, however it is possible that outcome assessors could become unblinded.	Unclear - Asthma at 3 years (this was assessed as part of observational data set) High – all other outcomes	
Attrition bias			
Incomplete outcome data	Loss to follow-up similar for each group; minimal loss to follow-up (n=1) for outcomes at delivery Greater losses at 3 years (12%), numbers different between groups and not all reasons reported	Unclear - Asthma at 3 years (assessed as part of observational data set) Low - all other outcomes	
Reporting bias			
Selective reporting	No evidence of selective reporting bias	Low	
Other bias			

Domain	Support for judgement	Review authors' judgement	Overall Study Risk
Other sources of bias	There was no significant difference in the baseline characteristics across the three treatment groups; non-profit funding; no statement of COI in primary report; authors of follow-up report state no conflict of interest.	Low	
Outcomes:	stillbirth, neonatal death, maternal adverse effects, caesarean section, asthma at 3 years, small for gestational age/birth weight, gestational age at birth, maternal hypercalcemia		
Brooke OG, 1980[66]			
Selection bias			High – all outcomes
Random sequence generation	Each patient was randomly allocated to the treatment but no additional details provided	Unclear	
Allocation concealment	Unclear: no information regarding concealment of allocation	Unclear	
Performance bias			
Blinding of participants and personnel	"the trial was double blind" (p.752); no additional information	Unclear – all outcomes	
Detection bias			
Blinding of outcome assessment	Mentions that "the code was broken and the treatment group identified" – unclear whether investigators knew of treatment when doing assessments	Unclear – all outcomes	
Attrition bias			
Incomplete outcome data	Unclear number of randomised participants. Preterm deliveries, congenital malformations, and maternal illnesses likely to affect fetal growth (such as diabetes) were eliminated from the trial. There is not complete documentation of the exclusions	High – all outcomes	
Reporting bias			
Selective reporting	Participants were excluded for adverse events, many of which are key outcomes in assessing infant growth	High	
Other bias			
Other sources of bias	Unclear whether baseline characteristics would have been similar if they had not excluded the women with adverse effects; non-profit funding; no statement regarding COIs	Unclear	
Outcomes:	Birth weight; length; head circumference, gestational age at birth, birth weight < 2500 g; small for gestational age		

Domain	Support for judgement	Review authors' judgement	Overall Study Risk
Mallet E, 1986[67]			
Selection bias			High
Random sequence generation	"A table of random numbers was used to assign women to treatment groups"	Low	
Allocation concealment	Not reported	Unclear	
Performance bias			
Blinding of participants and personnel	Not reported as blinded and one arm is "no treatment"	High – all outcomes	
Detection bias			
Blinding of outcome assessment	No blinding reported for outcomes assessment, but outcomes are objective	Low – all outcomes	
Attrition bias			
Incomplete outcome data	Unclear whether there was attrition, but numbers are uneven between groups; likely that there were losses to follow-up	Unclear – all outcomes	
Reporting bias			
Selective reporting	Have not reported any adverse effects or birth related outcomes	Unclear	
Other bias			
Other sources of bias	Limited baseline characteristics; no funding information provided; no mention of COIs	Unclear	
Outcomes:	Birth weight		
Delvin EE, 1986[68]			
Selection bias			High – all outcomes
Random sequence generation	No information reported	Unclear	
Allocation concealment	"Forty women were assigned by a blind randomization process" – method not described	Unclear	

Domain	Support for judgement	Review authors' judgement	Overall Study Risk
Performance bias			
Blinding of participants and personnel	Unblinded for participants (one group did not receive intervention)	High – all outcomes	
Detection bias			
Blinding of outcome assessment	Reported outcomes of interest are objective	Low – all outcomes	
Attrition bias			
Incomplete outcome data Assessments should be made for each main outcome (or class of outcomes)	1 subject lost in control group and 5 in vitD group; no reasons given	High – all outcomes	
Reporting bias			
Selective reporting	Insufficient information to judge	Unclear	
Other bias			
Other sources of bias	No information on funding, author COIs or baseline characteristics	Unclear	
Outcomes:	caesarean section (none; inferred from reporting of vaginal deliveries); preterm birth (none; inferred from reporting of 'term births'), gestational age at birth		
Marya RK 1987[69]			
Selection bias			High
Random sequence generation	Method of sequence generation not reported	Unclear	
Allocation concealment	Method of allocation concealment not reported	Unclear	
Performance bias			
Blinding of participants and personnel	No blinding reported and one group is not given any treatment	High	

Domain	Support for judgement	Review authors' judgement	Overall Study Risk
Detection bias			
Blinding of outcome assessment	No blinding reported; outcome is objective but unclear when testing was done (if more frequently in one group or the other)	Unclear	
Attrition bias			
Incomplete outcome data	There are only 182 in control and 188 in supplement – no description of what happened to these people	High	
Reporting bias			
Selective reporting	No reason to suggest selective outcome reporting but no protocol available.	Unclear	
Other bias			
Other sources of bias	No presentation of baseline characteristics, funding source not reported, no statement regarding conflicts of interest.	Unclear	
Outcomes assessed	Outcomes: Pre-eclampsia (toxaemia)		
Marya RK 1988[70]			
Selection bias			High – all outcomes
Random sequence generation	Method of sequence generation not reported	Unclear	
Allocation concealment	Method of allocation concealment not reported	Unclear	
Performance bias			
Blinding of participants and personnel	No blinding reported and one group is not given any treatment	High – all outcomes	
Detection bias			
Blinding of outcome assessment	No blinding reported; outcome is objective but unclear when testing was done (if more frequently in one group or the other)	Low – All Outcomes	
Attrition bias			
Incomplete outcome data	No losses reported but reasons for exclusion included pregnancy complications (which could have occurred after treatment); tables suggest that 100 contributed outcome data in each arm (100% follow-up)	Unclear	

Domain	Support for judgement	Review authors' judgement	Overall Study Risk
Reporting bias			
Selective reporting	No reason to suggest selective outcome reporting but no protocol available. Note, their conclusions and results are not congruent.	Unclear	
Other bias			
Other sources of bias	Baseline characteristics similar, funding source not reported, no statement regarding conflicts of interest.	Unclear	
Outcomes assessed	Outcomes: Birth weight, Birth length, Head circumference, low birth weight (<2.5 kg), gestational age at birth, maternal hypercalcemia		

Table 81 – Vitamin D supplementation: Quality appraisal of selected primary studies (Observational studies)

Domain	Support for judgment	Review authors' judgment
Kalra P, 2012[71]		
Selection bias	Participants in two vitamin D groups "…were randomly assigned (by use of random number tables)…" and allocation was by an open list (as per clinical trial registration record). Control group (no Vit D) was recruited concurrently; not allocated by randomization. 202 women did not return for follow-up. The 97 women who completed the study "were significantly older, had higher BMI and higher dietary Ca intake…"	High
Information bias	Assessment of exposure should be valid (it was allocated) however, the study was open-label so there is a high risk of performance bias. Assessment of outcomes should also be valid as they are objective measures and "investigators who measured anthropometry of infants and followed them were blinded to the mothers' treatment category."	High
Confounding	There appeared to be no imbalance at baseline between the groups in most major confounders but there was no adjustment in the analysis and data were not provided for most outcomes of interest.	Unclear
Overall assessment	Stillbirth; caesarean section; gestational diabetes; hypertension; birth weight; length; head circumference, infant preterm birth (most data not shown)	High
Applicability concern	Study conducted in south Asians in low-middle socioeconomic group	Serious concern
Cremers 2010,[72] Companion[73]		
Selection bias	Both Vit D and no VitD groups drawn from same communities. Women with pre-term birth excluded (N=4, not stated which group). Potential confounders are not stated per exposure group so balance is unclear. Substantial attrition at inception -- 70% of 1365 with successful blood sampling. Reasons included non-availability of blood samples, 34 week questionnaire, informed consent, home visits for data collection, and lung function tests.	Unclear

Domain	Support for judgment	Review authors' judgment
Information bias	Exposure assessed prospectively by participant questionnaire with unreported validity and reliability. Authors stated they collected data on brand, type, during and trimester of use and dosage and converted this to daily estimated intake using a standardized list of supplements used at that time in the Netherlands. No blinding to exposure. There is a risk that participants may have altered their behavior after the 34 week of pregnancy differentially between the groups so some analyses (those including 3rd trimester data) could be affected. Prospective assessment of outcome using repeated and validated measures; same assessment for both exposed and non-exposed. No blinding of outcome assessors mentioned but unlikely. Unclear if non-blinding of outcome assessors could affect outcome.	Unclear
Confounding	Confounding: Data on potential confounders collected by questionnaires at 14 and 34 weeks pregnancy and when child was 1, 2, 4-5 and 6-7. Potential confounders are not stated per exposure group so balance is unclear. All analyses were adjusted for recruitment group, maternal age at delivery, maternal education level, maternal smoking during pregnancy, maternal alcohol consumption during pregnancy, birth weight, use of multivitamins at age 2 years, environmental tobacco smoke, physical activity, at age 4-5 and 6-7 years. Adjustment for multivitamin at age 2 years may not fully control for the time-varying vitamin D intake during childhood. Important residual confounders include family history of atopy, confounding by other antennal vitamins, pregnancy diet/sunlight exposure, pets at home, and geographic residence of children.	High
Overall assessment	Pre-term birth, birth weight, lung function	High
Applicability concern	Similar to the population of interest	No concern
Maslova 2013,[74] Companion[75]		
Selection bias	Groups drawn from same communities. No obvious differential bias in selection of individuals for eligibility although certain regions had very low recruitment rates and distribution of recruitment by exposure group is not provided. Substantial missing data and reasons for this are not clear nor are they presented by exposure group. E.g. Asthma at 18 months: 101,042 enrolled; 87,045 with singleton births and first enrolled pregnancy in cohort, 45,004 with data on Vit D supplementation from food frequency questionnaire; 33,425 with data on Asthma at 18 months of age; 28,686 with data on current asthma at 7 years	High
Information bias	Same method of assessment for all exposure groups; 3 questionnaires and 2 telephone interviews at various times during pregnancy; each one asking about the month previous. Validity of questionnaire not established but authors state it is similar to another one with good established validity based on serum vitamin D levels. No blinding. Assessment of current asthma based on recall of physician diagnosis of asthma and recall of recurrent wheeze in past 12 months; Assessment of other variations of this outcome although objective (e.g. prescription records), are a proxy for the outcome and could be differentially available based on exposure status.	Unclear
Confounding	Data on potential covariates (which were age-adjusted) were provided only across total vitamin D intake groups (not specific to intake from vitamin D supplements). Quite a few variables were associated with both total vitamin D intake and intake from supplements alone including, for the latter, greater likelihood of breastfeeding >=7 months, LMP in winter months, being nulliparous, having higher education, normal BMI, being non-smokers, less exposed to second-hand smoke and more likely to exercise, use tanning beds and have a healthier diet including higher consumption of folate, n-3 fatty acids, calcium, vitamins A, C and E, selenium and zinc. Level of vitamin D supplementation also seemed to be associated with vitamin D levels from diet. Nearly all of these (and more) were controlled in analysis with the exception of Vit D in diet; likely an important confounder.	High

Domain	Support for judgment	Review authors' judgment
Overall assessment	Asthma	High
Applicability concern	Similar to the population of interest	No concern
Marjamäki, 2010[76]		
Selection bias	Selection from same population (no expected differential selection). For T1D, apparently 86.6% exposure data from those invited to participate and no missing outcome data among those with exposure data.	Low
Information bias	Risk of non-differential misclassification possible due to problems of recall but not judged to be at high risk. Risk not judged to be associated with exposure or outcome. Assessed at 1-3 months post-delivery using a questionnaire that is stated to be validated for diet (but not specifically stated to be validated for supplement use) and asking participants about supplementation throughout pregnancy. No blinding to exposure. T1D: outcome assessed using standardized criteria and only included confirmed cases. Only concern is that the frequency of visits (and hence the true timing and possibly the assessment of outcome) was modified based on ICA test results, which were not 100% associated with T1D diagnosis. No statement regarding blinding of outcome assessment.	Unclear
Confounding	Those in exposed group (Vit D supplements) were more likely to have a higher maternal education, paternal education, be having their 1st child, be non-smokers during pregnancy, have maternal BMI < 25 kg/m2, be living in one region of Finland, have had a complicated vaginal delivery, eat more fish and have higher consumption of vitamin D form diet than those in the non-exposed group (no Vit D supplements). Not all of these were controlled in the analysis (Vit D from diet, maternal BMI) and some other factors not considered (childhood exposure to Vit D)	High
Overall assessment	Type 1 diabetes	High
Applicability concern	Similar to the population of interest	No concern
Rochat, 2009[77]		
Selection bias	From same population – no expected differential selection; baseline characteristics not all balanced: significantly more women with Vit D supplementation with a birth from Dec-May and non-supplemented women with a birth from Jun-Nov; exposed group had significantly more primigravida women, younger and non-smoking mothers. Number analyzed was limited to two of five countries participating and number eligible from those two countries is not stated.	High
Information bias	No blinding to exposure/non-exposure. Assessment was based on a single question about current Vit D use, posed in the third trimester. Unclear if bias would be present; if so, likely to be non-differential. Unclear about validity of outcome assessment. They state outcome assessment for 'birth and early childhood variables' was assessed 'when the child was 2 months of age'.	Unclear
Confounding	There are significant imbalances at baseline (see comparability of groups) and for outcomes of interest, there is no adjustment for confounding	High
Overall assessment	Gestational age at birth, birth weight, caesarean section, pregnancy complications (non-specific)	High

Domain	Support for judgment	Review authors' judgment
Applicability concern	Strictly rural settings. Baseline rates of prematurity and sequelae as well as atopy are likely to be different than in urban settings	Serious concern
Haugen, 2009[78]		
Selection bias	Although it is a birth cohort in which both arms originates from the same base, there is considerable missing data and reasons for this are unclear	Unclear
Information bias	Exposure is ascertained by 3 questionnaires (at 15, 22 and 30 weeks gestation). FFQ at week 22 is a validated tool; validity at other time points not stated. Outcome data was based on birth registry using various pre-defined measures and reported by midwives (unclear if they were aware of study or Vit D status but this seems unlikely to affect results). Likely a valid measure.	Unclear
Confounding	Although adjusted for majority of the potential confounders, they did not account for socio economical status, and dietary intake of Vitamin D.	High
Overall assessment	Pre-eclampsia	High
Applicability concern	Similar to the population of interest	No concern
Erkkola, 2009[79]		
Selection bias	Selection from same population (no expected differential selection). For asthma, substantial (>50%) missing exposure or outcome data and no information on missing data per exposure group or reasons for losses to follow-up.	High
Information bias	Risk of non-differential misclassification possible due to problems of recall but not judged to be at high risk. Risk not judged to be associated with exposure or outcome. Assessed at 1-3 months post-delivery using a questionnaire that is stated to be validated for diet (but not specifically stated to be validated for supplement use) and asking participants about supplementation throughout pregnancy. No blinding to exposure. Asthma: using standard definition with some risk of problem of recall; however not likely to be associated with exposure (i.e. if present, judged to be non-differential). No statement regarding blinding of outcome assessment.	Unclear
Confounding	Those in exposed group (Vit D supplements) were more likely to have a higher maternal education, paternal education, be having their 1st child, be non-smokers during pregnancy, have maternal BMI < 25 kg/m2, be living in one region of Finland, have had a complicated vaginal delivery, eat more fish and have higher consumption of vitamin D form diet than those in the non-exposed group (no Vit D supplements). Not all of these were controlled in the analysis (Vit D from diet, maternal BMI) and some other factors not considered (childhood exposure to Vit D, household smoking during childhood)	High
Overall	Asthma	High
Applicability concern	Similar to the population of interest	No concern

Domain	Support for judgment	Review authors' judgment
Goldring, 2013;[80] Companion to RCT[65]		
Selection bias	Long-term follow-up of appropriately randomized trial with risk of bias due to lack of allocation concealment. At 3 years, approximately 12%) lost to follow-up, numbers different between groups and not all reasons reported	Unclear
Information bias	Exposure was a planned intervention however exposure status was not blinded so there is a risk of performance bias. Outcome assessment was blinded at 3 years but there is a risk of unblinding.	High
Confounding	The groups were balanced at baseline and outcome assessment was adjusted for many important confounders	Low
Overall	Asthma	High
Applicability concern	Race, and stat dose	Serious (Very serious for Stat dose of vit D)
Jacobsen 2013,[81] Companion[82]		
Selection bias	Although both arms from the same source, they are from different time periods which may result in important differences which may or may not be accounted for. No information on the balance of important covariates (i.e. similarity of groups). No information regarding missing data.	Unclear
Information bias	Assessment of exposure is in form of a 'natural experiment' and may not reflect true intake levels. Assessment of outcome (Type 1 diabetes) is based on a diabetes registry and paper suggests it should account for all diagnosed cases. Note: data are only available for all births after 1981; however, the abstract is presented as to suggest it is from 1961- 1985. Time period of non-exposed group is unclear.	High
Confounding	It is an abstract in which no information on baseline characteristics or adjustment for confounders is presented.	Unclear
Overall assessment	T1D	High
Applicability concern	No major point noted.	No concern
Baghlaf 2012[83]		
Selection bias	Insufficient data (abstract); only statement that "demographic data were similar in both groups"; no information regarding missing data.	Unclear
Information bias	Insufficient data (abstract)	Unclear
Confounding	Adjustment was done only for few confounders of interest.	High
Overall assessment	NICU admission, Apgar scores	High
Applicability concern	The women are with documented hypovitaminosis; and only in term pregnancies	Very serious concern

Domain	Support for judgment	Review authors' judgment
Marya RK, 1981[84]		
Selection bias	Method of sequence generation and allocation unclear. Unclear number of eligible women from which this set was chosen so attrition not noted.	Unclear
Information bias	Exposure was by intervention but no blinding reported; no blinding of outcome assessment reported.	Unclear
Confounding	Baseline characteristics not reported and no adjustment for confounders	High
Overall assessment	Birth weight	High
Applicability concern	South Asian race and cultural differences	Serious concern

8.3.8. Risk of preterm birth

Table 82 – Progesterone therapy to prevent preterm birth in asymptomatic women with short cervix but no additional risk factors for preterm birth: Quality appraisal of selected primary studies (RCTs)

Domain	Support for judgement	Review authors' judgement	Overall Study RoB
Bimbashi et al., 2013[85]			Unclear
Selection bias			
Random sequence generation	No information available other than "women.were randomly assigned"	Unclear	
Allocation concealment	No information available on concealment of allocation	Unclear	
Performance bias			
Blinding of participants and personnel	Un-blinded for participants and likely personnel – comparator was 'no treatment'. However it seems unlikely that lack of blinding would have influenced substantially the outcomes of interest in this paper	Unclear	
Detection bias			
Blinding of outcome assessment	Unclear if outcome assessment was blinded or not, although as no details are provided, it seems unlikely. However, outcomes of interest reported in this paper are not deemed likely to be affected by lack of blinding.	Low	

Domain	Support for judgement	Review authors' judgement	Overall Study RoB
Attrition bias			
Incomplete outcome data	No information on numbers included, numbers lost to follow-up or numbers analyzed.	Unclear	
Reporting bias			
Selective reporting	Abstract/poster presentation only. Results are not clearly reported for most outcomes. Methods section also states that secondary outcomes of interest included 'fetal or neonatal death' and major adverse outcomes before discharge from hospital but these are reported combined in the results in a rather ambiguous manner.	Unclear	
Other bias			
Other sources of bias	Funding: Not reported COI: Not reported Confounding: Not reported	Unclear	
Outcomes	Preterm birth <34 weeks; fetal or neonatal death, major adverse outcomes before discharge from hospital (RDS, IVH, NE)		
Hassan et al., 2011[86]			High
Selection bias			
Random sequence generation	Randomization was accomplished using a centralized interactive voice response (IVR) system, and was stratified according to center, risk strata (previous PTB or not) and using a permuted blocks strategy with a block size of four.	Low	
Allocation concealment	Drug kits were numbered independently from the treatment assignments in the randomization blocks, and the IVR system (upon generating treatment assignment for new subject) specified which kit number was to be dispensed to the subject.	Low	
Performance bias			
Blinding of participants and personnel	Study drug packaging, applicators and their contents were identical in appearance. Participants self -administered drugs and placebo.	Low	
Detection bias			
Blinding of outcome assessment	"All outcomes were determined and the databases was locked prior to the unsealing of the randomization code" Although not explicitly stated it is likely that outcome assessors were masked to treatment status	Low	

Domain	Support for judgement	Review authors' judgement	Overall Study RoB
Attrition bias			
Incomplete outcome data	1 lost to follow-up in treatment group; 6 lost to follow-up in placebo group.	Low	
Reporting bias			
Selective reporting	References a study protocol and trial registration record available; all pre-specified outcomes were reported in the results	Low	
Other bias			
Other sources of bias	Funding: Mixed funded in part by Columbia Laboratories Inc. Conflict of interest: stated and present for 17 authors Confounding: No baseline imbalances were noted for the following variables: BMI, history of preterm labour/delivery, age, race or previous cervical surgery. No information regarding SES, smoking status, hypertension or diabetes (although pts with uncontrolled conditions were excluded) or IVF. Multiple gestations were excluded. For full adjusted analyses of main outcomes, age, race and BMI were included in the model.	High	
Outcomes	Prenatal death (fetal and neonatal death); Preterm birth (<28, 33, 35 and 37 weeks); composite neonatal morbidity/mortality (including RDS, bronchopulmonary dysplasia, proven sepsis, NE, IVH, Grade III/IV, perventricular leukomalacia, perinatal death, fetal death and neonatal death); Neonates without co morbidities; Maternal complications – chorioamnionitis, post partum haemorrhage		
DeFranco et al., 2007[87]			High
Selection bias			
Random sequence generation	Main trial: "An SAS (SAS Institute Inc., Cary, NC, USA) procedure for variable block size was used to generate the randomization schedule stratified by study site" (Pg. 689 of main study report) This subgroup: "using a separate Randomization scheme." No details provided but assumed to be computerized as above.	Low	
Allocation concealment	No details regarding method or potential knowledge of allocation schedule "The study patients, obstetric care providers, study investigators, study coordinators and study monitors were blind to the exposure status (progesterone or placebo) of all study patients"	Unclear	
Performance bias			
Blinding of participants and personnel	Identical placebo ("identical bioadhesive delivery system, but without progesterone"), "The study patients, obstetric care providers, study investigators, study coordinators and study monitors were blind to the exposure status (progesterone or placebo) of all study patients"	Low	

Domain	Support for judgement	Review authors' judgement	Overall Study RoB
Detection bias			
Blinding of outcome assessment	"The study patients, obstetric care providers, study investigators, study coordinators and study monitors were blind to the exposure status (progesterone or placebo) of all study patients"	Low	
Attrition bias			
Incomplete outcome data	Report states that 9 subjects were recruited into the trial for this subgroup analysis and the results report 9 as the total so no losses in this subset have been assumed	Low	
Reporting bias			
Selective reporting	This report presents data for the subgroup of interest only for PTB ≤ 32 weeks. However, many other relevant outcomes were assessed in this study and not presented for this subgroup including: PTB <37 wks, <=35 wks, <=28 wks; neonatal death+death in first year; RDS, NICU admission, IVH and NE. Clinical trial registration (NCT00086177) record also lists outcomes not reported for this subgroup. Authors state that the reason for not completing this pre-planned subgroup analysis is due to low recruitment of eligible subjects.	Unclear	
Other bias			
Other sources of bias	Funding: Industry producing the active intervention and no statement of independence. Conflict of interest: Stated and present for at least two authors Confounding: No baseline data reported for women in subgroup of interest to this review	High	
Outcomes	Preterm birth ≤ 32 wks		
van Os et al., 2014[88]			Unclear
Selection bias			
Random sequence generation	"computerized randomization" (published trial protocol pg. 3)	Low	
Allocation concealment	"Once informed consent has been given, and patient data have been entered in a web based database, computerized randomization will take place" (published trial protocol pg. 3)	Low	
Performance bias			
Blinding of participants and personnel	"Identical appearing placebo" (published trial protocol pg. 3)	Low	

Domain	Support for judgement	Review authors' judgement	Overall Study RoB
	"The label codes indicating progesterone or placebo are only known in the central pharmacy...disclosed to the central office only after data on primary outcome have been collected…researchers involved in the follow-up program… will remain blinded for a longer period." For interim analysis, the epidemiologist will be given label codes A and B.(from published trial protocol Pg. 3) "Double-blinded" (from trial registry) Judgement: participants, personnel are masked to intervention group.		
Detection bias			
Blinding of outcome assessment	Outcome assessors appear to be masked to the intervention group (see excerpts from above)	Low	
Attrition bias			
Incomplete outcome data	80 women were randomized. At the time the abstract was presented, data were available for 74. There is no information on how many were missing from each group or reasons but the numbers missing are low and are not judged to be of major concern for affecting the results substantially	Unclear	
Reporting bias			
Selective reporting	Other relevant outcomes were recorded in this study (as per trial registration record and published trial protocol) but not reported in this abstract, including: perinatal death, "maternal morbidity" and childhood neurodevelopmental outcome at 24 months of age; the latter of which was possibly not yet recorded. The study protocol also states an intention to conduct a subgroup analysis (interaction assessment) between intervention and ethnicity but we do not have this information. As this is an abstract, the outcomes presented are a selection of those recorded but are those of primary interest and don't appear to be selected based on significance of results.	Unclear	
Other bias			
Other sources of bias	Funding: Non-industry Conflict of interest: Report states that authors report no conflicts of interest Confounding: No baseline data presented (abstract only)	Unclear	
Outcomes	Results reported: Preterm birth < 32, <34 and <37 weeks, composite poor neonatal outcome (death or severe morbidity) Others: please see above in assessment of potential reporting bias		

Domain	Support for judgement	Review authors' judgement	Overall Study RoB
Grobman et al., 2012[4]			Unclear
Selection bias			
Random sequence generation	Use of the simple urn method of randomization, with stratification according to clinical center, was used by the data coordinating center to create the computer-generated randomization sequence.	Low	
Allocation concealment	No details regarding method of concealment or potential knowledge of allocation schedule	Unclear	
Performance bias			
Blinding of participants and personnel	Treatment and placebo were identically appearing IM injections. "Study was double masked; neither the patient nor medical staff (including research and clinical personnel) was aware of the treatment assignment." (p.390.e3)	Low	
Detection bias			
Blinding of outcome assessment	"Study was double masked; neither the patient nor medical staff (including research and clinical personnel) was aware of the treatment assignment." (p.390.e3); Prenatal, delivery, newborn and post-partum outcomes "extracted by study personnel after delivery".	Low	
Attrition bias			
Incomplete outcome data	No participants were lost to follow-up	Low	
Reporting bias			
Selective reporting	Registration information at ClinicalTrials.gov #NCT00439374. Secondary outcomes are different from the secondary outcomes listed in the report, although the outcome data for these is provided in the report. Sub-group analyses done that were not defined a priori but the report identifies them as such.	Low	
Other bias			
Other sources of bias	Funding: Non-industry (NCRR and NICHD) Conflict of interest: Authors report no conflict of interest	Unclear	

Domain	Support for judgement	Review authors' judgement	Overall Study RoB
	Confounding: Slightly more African American participants in progesterone group (~55%) than placebo group (49%). No major imbalances for BMI, past history of PTB, maternal age (although study notes that women in progesterone group were slightly older), smoking status or substance abuse. Multiple gestations, uncontrolled hypertension and diabetes mellitus and previous cervical surgery excluded. No details on SES or IVF. Note: 18/327 in the intervention group and 33/330 in the placebo group discontinued the intervention.		
Outcomes	Fetal and neonatal death, Preterm birth <37, <35, <32, <28 weeks gestation; composite adverse infant/neonatal outcome (death, RDS, bronchopulmonary dysplasia, early-onset sepsis, NE grade II or III, IVH grade III or IV, perventricular leukomalacia, retinopathy of prematurity grade III or IV), neonate without major morbidities, infant seizures gestational hypertension or preeclampsia, gestational diabetes, cholestasis, placental abruption, chorioamnionitis		
Fonseca et al., 2007[89]			Unclear
Selection bias			
Random sequence generation	"Computer-generated random-number lists"	Low	
Allocation concealment	Numbered drug packs; central randomization	Low	
Performance bias			
Blinding of participants and personnel	"The investigators, participants, and clinicians were unaware of the treatment assignments. The general practitioners and obstetricians of the patients were also unaware of the results of cervical assessments on follow-up ultrasonography."	Low	
Detection bias			
Blinding of outcome assessment	Above and "Data on pregnancy outcomes were obtained from the hospital maternity records or the patients' general medical practitioners" "all outcomes were determined before the randomization code of the trial was broken"	Low	
Attrition bias			
Incomplete outcome data	No losses to follow-up are reported. i.e. full follow-up	Low	
Reporting bias			
Selective reporting	No trial protocol is available. There is a trial registration record but this was initiated after the trial was complete. However, important outcomes appear to be reported and there is no reason to suggest that this study is selectively reported.	Low	

Domain	Support for judgement	Review authors' judgement	Overall Study RoB
Other bias			
Other sources of bias	Funding: non-profit COI: Report states: "No potential conflict of interest relevant to this article was reported" Confounding: There are no baseline imbalances for variables reported (including BMI, history of PTB, age, twin pregnancies, Black race, smoking status) and all of these are adjusted in the analysis. No baseline data regarding SES, hypertension, diabetes, IVF or previous cervical surgery.	Unclear	
Outcomes	Fetal and neonatal death, PTB < 34 wks (including subgroup analyses); SAEs (maternal and infant); Composite: major infant AEs before discharge from hospital (IVH, RDS, retinopathy of prematurity or NE); Composite: need to special neonatal care (admission to NICU, ventilation, phototherapy, treatment for proven or suspected sepsis, or blood transfusion)		
Brenner and Hendricks (1962)[90]			Unclear
Selection bias			
Random sequence generation	"Patients were assigned totally at random into one of two groups…". No other details.	Unclear	
Allocation concealment	No information on concealment of allocation	Unclear	
Performance bias			
Blinding of participants and personnel	"Double-blind" study. Placebo is similar (same tablet base). Study is short and outcome assessed do not suggest that any possible breaking of blinding would compromise the study results	Low	
Detection bias			
Blinding of outcome assessment	Outcome assessors are blinded. "obstetric records were made entirely by the resident and the nursing staffs of the University Hospitals, most of whom were not aware that the such a study was in progress and none of whom was aware of the exact nature of the study.	Low	
Attrition bias			
Incomplete outcome data	Two hundred women randomized; 195 completed the study. Number lost per group and reasons for losses not reported but number of losses are small.	Low	
Reporting bias			
Selective reporting	No protocol or trial registration record available (old study).	Unclear	

Domain	Support for judgement	Review authors' judgement	Overall Study RoB
Other bias			
Other sources of bias	Funding: Non-profit, seemingly no vested interest COI: No statement provided regarding conflicts of interest Confounding: Few confounders are reported in this paper (although full thesis is apparently available); report states only that 'groups were highly comparable by age, by previous obstetric experience (with details in a Table) and by race (with details in text)	Unclear	
Outcomes	Fetal death, neonatal death (and perinatal death calculated), percent of birth prior to estimated date of confinement, number of infants in good condition upon leaving hospital and maternal post-partum complications.		
Moghtadaei et al. (2008)[91]			Unclear
Selection bias			
Random sequence generation	"A randomised, double-blind, placebo-controlled trial...". No other details provided	Unclear	
Allocation concealment	No details regarding method or potential knowledge of allocation schedule	Unclear	
Performance bias			
Blinding of participants and personnel	"A randomised, double-blind, placebo-controlled trial...". No other details but for the outcomes of interest, we do not deem the risk of unblinding to be likely to affect the study results substantially.	Low	
Detection bias			
Blinding of outcome assessment	No details regarding blinding of outcome assessment, but none of the outcomes are subjective	Low	
Attrition bias			
Incomplete outcome data	No reported losses but no denominator provided for outcome assessment.	Unclear	
Reporting bias			
Selective reporting	Unclear – as this is just a poster presentation I am not sure what outcomes they decided to look at a prior	Unclear	

Domain	Support for judgement	Review authors' judgement	Overall Study RoB
Other bias			
Other sources of bias	Poster/abstract presentation only Funding: Not reported COI: Not reported Confounding: Baseline characteristics not reported	Unclear	
Outcomes	Preterm birth <37 weeks, <35 weeks, <32 weeks, maternal complications (hypertension, diabetes, intrauterine growth restriction)		

Table 83 – Cerclage versus no cerclage to prevent preterm birth in asymptomatic women with short cervix but no additional risk factors for preterm birth: Quality appraisal of selected primary studies (RCTs)

Domain	Support for judgement	Review authors' judgement	Overall Study Risk
Berghella et al. (2004)[92]			High
Selection bias			
Random sequence generation	"Randomization included allocation that was accomplished by computer-generated numbers in permuted blocks of 6." (p.1313) The generator of the assignment was the principal investigator.	Low	
Allocation concealment	Concealed in sequentially numbered, opaque, sealed envelopes. The executor was the research nurse.	Low	
Performance bias			
Blinding of participants and personnel	"There was no blinding or masking because cerclage required spinal anesthesia in the operating room." Some women in bed-rest only group received rescue cerclages; there were more drop-outs in cerclage group (women who chose not to receive cerclage after being allocated to that group) and it is possible there were differences in adherence to bed-rest (fidelity of intervention) - all of which could have affected outcome.	High	

Detection bias		
Blinding of outcome assessment	No blinding of outcome assessment – As relevant outcomes were all objective, it is deemed unlikely that this would have introduced bias	Low
Attrition bias		
Incomplete outcome data	No patients lost to follow-up	Low
Reporting bias		
Selective reporting	No protocol found. Sub analyses were prespecified, but only selected sub analyses were reported and not those of interest to this review.	High
Other bias		
Other sources of bias	Funding: Unclear: Berlex Foundation may be affiliated with Bayer, (other funders: Center for Research on Women and Newborn Health, Philadelphia Perinatal Society) Conflict of interest: not reported Confounding: No data for subgroup of interest. For full group, moderate differences (non-significant) for race distribution between study groups (cerclage+bed rest vs. bed rest: white: 10 vs. 20%; black: 80 vs. 73%; hispanic: 10 vs. 7%) and parity (77 vs. 60%). No major difference at baseline in maternal age or smoking status. No details regarding SES, maternal weight, hypertension, diabetes mellitus, *in vitro* fertilization or previous history of cervical surgery.'	Unclear
Outcomes	PTB <35, <34, <32, <28, <24 weeks gestation, death, composite neonatal morbidity (any of respiratory distress syndrome, intraventricularhermorrhage (III or IV), necrotizing enterocolitis or sepsis); Neonates free of disease/neonates without adverse events (inferred based on previous)	

Domain	Support for judgement	Review authors' judgement
Skupski et al. (2014)[93]		
Selection bias	Groups come from 2 campuses of one hospital each using different a protocol (cerclage or bed rest) to manage women with a short cervix at midtrimester; groups are significantly different for several baseline factors (including prior second trimester loss, prior preterm birth, progesterone use, cervical length and gestational age at time of intervention) between the two units. Missing data is not balanced between the two groups (5/117 and 10/65 eligible) and reasons for missing data are not stated.	High
Information bias	Retrospective concurrent cohort – cerclage group data collection was prospective, while bed rest group was retrospective. No measurement of compliance/fidelity of the intervention "bed rest." Outcomes of interest are objective and ascertainment of outcome is not considered a concern.	Unclear

Confounding	Baseline characteristics such as education, socioeconomic status, weight and race were not reported. The groups differed significantly in their history of loss and preterm birth, as well as gestational age at diagnosis, and shorter cervical length at diagnosis and there is no control for confounding in the analysis.	High
Overall assessment	Outcomes: Preterm delivery <24 weeks, <28 weeks, <32 weeks, <35 weeks and <37 weeks, chorioamnionitis	High
Applicability	40% of population had history of preterm birth or second trimester loss	Serious concern
Sakai et al. (2006)[94]		
Selection bias	Cerclage was performed at physician's discretion. Populations are fairly similar based on reported baseline characteristics for patients with cervical shortening including in subgroups based cervical IL-8 levels . There were no obvious differences between groups at baseline, although a few potential confounders were not reported.	Unclear
Information bias	Information retrospectively collected. Validity of ascertainment of exposure is unclear due to unclear fidelity of bed rest (adherence); outcomes (all objective) believed to be valid.	Unclear
Confounding	No confounding variables determined. Some of interest are not reported.	Unclear
Overall assessment	PTB <34 and <37 wks gestation	Unclear
Applicability	Had a short cervix, more than half had prior pre-term births	Very Serious concern
Hassan et al. (2001)[95]		
Selection bias	Exposure status is based on physician's discretion. Groups significantly different at baseline – maternal age significantly higher in cerclage group, gestational age at ultrasonography significantly higher in no cerclage group. Previous risk also different (but not significant: history of spontaneous and voluntary abortion and history of preterm delivery all higher in cerclage group (40 vs. 20%, 56 vs. 47% and 32 vs. 16% respectively).	High
Information bias	Information collected retrospectively. It's unclear how patients were treated/managed by their individual care providers other than cerclage vs. no cerclage. Outcome assessment also collected retrospectively but no reason to suggest that there would be a substantial issue with external or internal validity in this respect.	Unclear
Confounding	The groups differed significantly in maternal age and gestational age at diagnosis and risk factors differed between groups. None of these variables were considered in the analysis.	High
Overall assessment	Outcomes: Preterm delivery <28 weeks, <32 weeks, <34 weeks, and <37 weeks. Note: chorioamnionitis, fetal death and elevated blood pressure were also reported but only for the subset of women being induced for labour and this was not reported per exposure group.	High
Applicability	A fair proportion (actual proportion unclear) of the population is high risk due to past cervical surgery, abortion, voluntary termination and preterm birth. The majority of the population is of African race.	Very Serious concern

Table 84 – Reduced physical activity vs. no activity restriction to prevent preterm birth in asymptomatic women with short cervix but no additional risk factors for preterm birth: Quality appraisal of selected primary studies (Observational study) -

Domain	Support for judgement	Review authors' judgement
Grobman et al. (2013)[96]		
Selection bias	Activity restriction guidelines were at the discretion of the attending physician; respondent bias Baseline imbalances were noted for many factors.	High
Information bias	Exposure ascertainment bias (actual physical activity was not measured and physician guidance may have varied)	High
Confounding	Women who had any activity restriction recommendations were older and more likely to be Hispanic. Very serious concerns about unmeasured confounding (because it is a post hoc subgroup analysis) and time-varying nature of adherence to activity recommendation.	High
Overall assessment	Outcomes: Preterm birth <37 weeks and <34 weeks comparing two definitions of activity restriction vs. no activity restriction	High
Applicability	77% non-white (about 50% of population was of African descent), 30% with history of miscarriage, 16% smokers	Very Serious concern

8.3.9. Risk of preeclampsia

No study selected.

8.3.10. Pregnancies that passed their due date

Table 85 – Surveillance of pregnancies that passed their due date: Quality appraisal of selected primary studies (RCTs)

Domain	Support for judgement	Review authors' judgement	Overall Study Risk
Alfirevic et al., 1997[97]			Unclear
Selection bias			
Random sequence generation	"Women were allocated to monitoring groups by sealed envelopes prepared in blocks of 100. Each block was prepared by shuffling two sets of 50 cards which were sealed in sequentially numbered opaque envelopes."	Low	
Allocation concealment	"The allocation sequence was recorded on a master list which was held separately. An envelope was opened for every woman who entered the trial. A record was kept on the day assessment unit of the name, hospital number, envelope number and allocation. Compliance with allocation was checked by comparing the record kept by midwives on the day assessment unit and the master list kept by principal investigator."	Low	
Performance bias			

Domain	Support for judgement	Review authors' judgement	Overall Study Risk
Blinding of participants and personnel	Blinding of patients: not reported. Women could request induction; therefore, if women were not blinded, the overall induction outcome and induction due to maternal request could have been biased. Blinding of personnel: Yes, blinded. "Ante partum monitoring results were recorded on the separate forms at the time of fetal assessment. Only the overall monitoring result ('test normal' or 'test abnormal') was recorded in the case notes. Details about the type of fetal monitoring, individual test results and reason for induction of labour were not disclosed in order to avoid bias in the management of labour, delivery or the neonate." Blinding of personnel in the post-natal period: not reported—likely didn't occur The blinding of post-natal personnel caring for neonates was not reported; however, it was unlikely that the level of post-natal care provided would have been greatly influenced by knowledge of the antenatal monitoring type.	Low – all outcomes	
Detection bias			
Blinding of outcome assessment	"Details about the type of fetal monitoring, individual test results and reason for induction of labour were not disclosed in order to avoid bias in the management of labour, delivery or the neonate." Post-term fetal monitoring outcome assessors: blinding not possible Labour and delivery outcome assessors: blinded Neonatal outcome assessors: blinded	Low – all outcomes	
Attrition bias			
Incomplete outcome data	"Outcome information was available for all randomised women." The outcome data reported in the table were complete and all data appeared to have been included in the analyses. There were no exclusions or losses to follow-up.	Low – all outcomes	
Reporting bias			
Selective reporting	No protocol or trial registration information found. No specific reason to suspect that outcomes were selectively reported, however method sections does not specify which outcomes were pre-specified.	Unclear	
Other bias			
Other sources of bias	Funding: not reported Conflict of interest: not reported Confounding: No baseline imbalances noted but not all variables of interest stated. Randomization and large sample size with no loss to follow-up should ensure even distribution of potential confounders between groups at analysis.	Unclear	
Outcomes	Instrumental delivery, caesarean section, perinatal mortality, admission to NICU, Apgar score, other - c-section due to fetal distress, other - c-section due to failure to progress		

Domain	Support for judgement	Review authors' judgement	Overall Study Risk
Alfirevic et al., 1995[98]			Unclear
Selection bias			
Random sequence generation	"Women were allocated to monitoring groups using sealed envelopes prepared in blocks of 50." Selection bias may have occurred due to inadequate randomization—the randomization procedure was not described.	Unclear	
Allocation concealment	"Women were allocated to monitoring groups using sealed envelopes prepared in blocks of 50. A sequentially numbered, opaque envelope was opened for every woman who entered the trial." Selection bias is unlikely to occur due to inadequate concealment of allocation before assignment.	Low	
Performance bias			
Blinding of participants and personnel	Blinding of patients: not reported—likely didn't occur Blinding of personnel: blinded. "Ante partum monitoring results were recorded on the separate forms at the time of fetal assessment. Only the overall monitoring result ('test normal' or 'test abnormal') was recorded in the case notes. Details about the type of fetal monitoring, individual test results and reason for induction of labour were not disclosed in order to avoid bias in the management of labour, delivery or infant."	Low – all outcomes	
Detection bias			
Blinding of outcome assessment	"Details about the type of fetal monitoring, individual test results, and reason for induction of labour were not disclosed in order to avoid bias in the management of labour, delivery or infant." Post-term fetal monitoring outcome assessors: blinding not possible Labour and delivery outcome assessors: blinded Neonatal outcome assessors: blinded. Apgar and NICU assessments would have been made by labour and delivery personnel, who were blinded. Perinatal death is an objective outcome, unbiased by blinding.	Low – all outcomes	
Attrition bias			
Incomplete outcome data	There was no loss to follow-up; therefore, risk of attrition bias was low.	Low – all outcomes	
Reporting bias			
Selective reporting	No protocol or trial registration record referenced. Outcomes measured in this study were compared to those measured in similar studies. No obvious major outcomes were missing from the report; methods section does not state if all outcomes were pre-specified	Unclear	

Domain	Support for judgement	Review authors' judgement	Overall Study Risk
Other bias			
Other sources of bias	Funding: not reported Conflict of interest: not reported Confounding: No apparent confounding for maternal age, height, booking weight, race, parity, smoking and timing of the first antenatal hospital visit (groups were comparable). Other potential confounders not reported. No control for confounding in the analysis.	Unclear	
Outcomes	Perinatal mortality (still birth), Apgar score, Admission to NICU, Caesarean section (and associated reasons), Other - complicated pregnancies: need for obstetricians' or neonatologists' intervention (induction, operative delivery, resuscitation or specialist neonatal care)		
Oral, 1999[99]			Unclear
Selection bias			
Random sequence generation	No information provided in the abstract of this study in English language. "Not described" as reported by Nabhan et al., Cochrane review [26]. Selection bias may or may not have occurred due to sequence generation.	Unclear	
Allocation concealment	No information provided in the abstract of this study in English language. "Not described" as reported by Nabhan et al., Cochrane review [26] Unclear if selection bias may have occurred due to lack of allocation concealment	Unclear	
Performance bias			
Blinding of participants and personnel	Not data reported in abstract. Performance bias may or may have occurred due to lack of blinding of patients and personnel.	Unclear – all outcomes	
Detection bias			
Blinding of outcome assessment	Not reported in abstract. "Not stated. Probably not done due to different technique" (as reported by Nabhan et al. [26]) Unclear if detection bias may have occurred due to lack of blinding of outcome assessors	Unclear – all outcomes	
Attrition bias			
Incomplete outcome data	Unable to assess from abstract	Unclear – all outcomes	

Domain	Support for judgement	Review authors' judgement	Overall Study Risk
Reporting bias			
Selective reporting	Unable to determine from abstract. Some outcomes may have been reported in full texts that were not reported in the abstract. Nabhan et al. [26] report risk of reporting bias to be low. The Oral paper appears in most forest plots of outcomes in Nabhan et al.	Low	
Other bias			
Other sources of bias	Unable to assess from abstract	Unclear	
Outcomes	Perinatal morality, Apgar score, admission to NICU, C-section, c-section due to fetal distress		

Table 86 – Surveillance of pregnancies that passed their due date: Quality appraisal of selected primary studies (Observational studies)

Domain	Support for judgement	Review authors' judgement
Lindqvist, 2014[100]		
Selection bias	Groups come from 2 units in one hospital, and population is significantly different for several factors (BMI, age < 25, and nullipara, SES, country of birth) at baseline between the two units. Data comes from subgroup that is undelivered past 42 weeks, the prevalence of which was different between the two units. Analysis included in review excluded women receiving intervention (at 41 weeks) but delivering from 41-42 weeks gestation.	High
Information bias	Information retrospectively collected, and outcomes are objective.	Low
Confounding	Not reported for sample remaining undelivered at 42 weeks (analysis group) For full study group there were differences between arms in terms of BMI, maternal age<25, nullipara, low disposable income, education <9 years and Nordic country of birth and marital status. All were considered in logistic regression and only those with p<0.05 were included in the final model. Groups also differed in terms of post-term pregnancies (greater in the indicated scan group vs. routine scan group) and the analysis included in this review excluded women receiving intervention (at 41 weeks) but delivering from 41-42 weeks gestation.	Unclear
Overall assessment	Severe adverse fetal outcome (composite), (including apgar 5min<4), cerebral damage (including cerebral palsy), severe asphyxia, cerebral haemorrhage/intracranial haemorrhage, Hypoxic ischemic encephalopathy grades 2 and 3, fetal death (including antenatal and postnatal deaths), caesarean delivery and instrumental delivery	High
Applicability	Large-for-gestational age babies are excluded from the analysis; also excludes data for women receiving the intervention (at 41 weeks) but delivering from 41-42 weeks gestation	Very Serious concern
El-Damarawy, 1993[101]		
Selection bias	Groups appear to be selected from the same population (one antenatal clinic in Egypt) but there are no details on either the process of selection for allocation to specific testing or any details of losses to follow-up, if this was relevant (although period for follow-up was short). There are no details regarding baseline characteristics to assess comparability of the groups.	Unclear
Information bias	Appears to be a prospective study. Exposure was well defined and outcome ascertainment also seems well defined	Low
Confounding	Unclear – no details reported regarding all important confounders	Unclear
Overall assessment	Perinatal mortality, Apgar score	Unclear
Applicability	Labelled a serious as it was conducted in a developing country; there are no further details regarding the characteristics of the women included.	Serious concern

Domain	Support for judgement	Review authors' judgement
Eden,1982[102]		
Selection bias	Groups are from different non-overlapping time periods over the course of three years; no baseline data is presented for comparability of groups. No information regarding prospective follow-up including drop-outs/losses to follow-up.	High
Information bias	Fidelity of intervention and subsequent management unclear. Assessment of outcome does not seem to have been blinded, but outcomes, with the exception of Apgar score, all seem objective.	Unclear
Confounding	No baseline data reported; no adjustment for potential confounding in the analysis. Different time-periods and selection method for study unclear.	High
Overall assessment	Perinatal mortality (including ante partum, intrapartum and neonatal death), Apgar score at 1 and 5min <7, caesarean section, meconium aspiration, other neonatal harm: need for resuscitation/intubation of neonate, perinatal morbidity (composite)	High
Applicability	Not applicable	No concern

9. EVIDENCE TABLES

9.1. Cytomegalovirus

Table 87 – Lifestyle advice for CMV: Evidence table of RCT (ADLER 2004)

Prevention of child-to-mother transmission of cytomegalovirus among pregnant women ADLER 2004[5]	
Methods	
• **Design**	Cluster randomised trial – by childcare centre to avoid control group becoming informed of intervention details. Randomised using SAS. Randomised annually, weighted on the basis of enrolment the previous year.
• **Source of funding and competing interest**	Study supported by a grant from the National Institutes of Health (USA). No declaration of interest stated.
• **Setting**	124 childcare centres in Central, Northern and East Virginia, USA from 1999 through 2001.
• **Sample size**	Total n=166
• **Duration and follow-up**	Enrolment spanned from 1999 through 2001. Women enrolled during this time had their serum collected every 3 months for 12 months or until delivery.
• **Statistical analysis**	Logistic regression used to determine the factors associated with maternal seroconversion.
Patient characteristics	
• **Eligibility criteria**	Pregnant women or women attempting pregnancy (not using contraception), with a child <36 months enrolled in one of the 124 childcare centres.
• **Exclusion criteria**	Women who were seropositive for CMV (42), and who failed to provide follow-up specimens (26).
• **Patient & disease characteristics**	Patient characteristics presented in relation to maternal seroconversion: Maternal age at enrolment (mean±SD): No seroconversion 32.7±3.9; Seroconversion 32.6±4.1 Child's age at enrolment (mean months±SD): No seroconversion 20.7±6.1; Seroconversion 16.8±8.8 Pregnant at any time during enrolment: No seroconversion 129; Seroconversion 11 Not pregnant at any time during enrolment: No seroconversion 24; Seroconversion 2 Child shedding CMV during maternal enrolment: No seroconversion 30; Seroconversion 11 Child not shedding CMV during maternal enrolment: No seroconversion 123; Seroconversion 2
Interventions	
• **Intervention group**	1. (n = 23) Orientations session where women received information about CMV and potential complications. Educational video demonstrating potential techniques to avoid acquisition of CMV, plus detailed written and oral instructions for behavioral recommendations. Protective behavior included frequent hand washing (i.e. after exposure to a child's bodily fluids, handling dirty laundry, touching the child's toys or bathing the child) and wearing protective gloves. Behavior to avoid included intimate contact with a child (ie kissing on the mouth), sleeping together, sharing towels, food and drink.

	Home visits every three months were conducted to assess adherence. Mothers estimated (self-report) the percentage of times biweekly that they performed or avoided specific behavior. Liquid soap and latex gloves were provided on each visit. Glove and soap use were monitored (gloves counted, soap weighed) as an indirect objective measure of adherence to protective behavior. Women in this intervention group knew their serological status but were unaware if their child was shedding CMV. 2. (n = 92) Women in this intervention group were treated the same as intervention group one, with the addition of knowing their child's initial CMV culture status (but not any subsequent cultures). Women were informed that if their child was not shedding at enrollment, there was a high probability that their child could begin to shed CMV at any time during the study. During the first year of the study intervention group one was terminated (interim data analysis showed that half of the children who shed CMV at any time during the study up to that point were not shedding at enrollment). All women assigned to intervention group one were reassigned to intervention group two, and all subsequent enrollment was to intervention group two).
• **Control group**	(n = 51) Basic information about CMV and the reasons for the study but no intervention. Women in this group were not told their serological status or whether their child was shedding CMV.
Results	
• **Seroconversion**	Seroconversion: women's serum collected every 3 months for 12 months or until delivery. All maternal sera were stored at -80° until the woman completed participation; seroconversion was then measured with the use of an enzyme immunoassay. Control group: 4/51 (7.8%) Combined intervention groups 1 & 2 (details below): 9/115 (7.8%) • Intervention group 1 (education, adherence and unaware of child's initial CMV status) 1/23 (4.3%) • Intervention group 2 (education, adherence and aware of child's initial CMV status) 8/92 (8.7%)
Limitations and other comments	
• **Limitations**	Allocation concealment for the women and centres and blinding of outcome assessors is unclear. Indirect population due to 15.7% not being pregnant at any point during enrolment. Due to random assignment by daycare centre rather than by person, baseline numbers of pregnant women per group were not proportionate. Only two pregnant women were assigned to the control group. And indirect outcome as seroconversion is not explicitly listed on review protocol but may be a surrogate for adverse pregnancy outcomes, or adverse maternal or newborn outcomes. Incomplete outcome reporting – only seroconversion is reported based on intervention group. All other results (i.e. self-report and objectives measures of adherence to preventative behaviours) are presented according to pregnancy status at enrolment. Numbers presented in different tables do not add up and no attrition information covering missing numbers is reported. This could also be due to the use of confusing definitions of study timeframes. For example data is presented on seroconversion based on pregnancy status 'before enrolment', adherence measures based on pregnancy status 'at enrolment' and seroconversion based on pregnancy status 'during enrolment' and separately on group allocation. Yet it is not possible to make conclusions on the effect of the intervention on pregnant women in particular due to different numbers being presented for different 'pregnancy status' timeframes. The authors offer narrative conclusions that the intervention was successful in pregnant women based on their subjective observation of womens' engagement during the initial advice session, however they go on to state that no evidence for this observation is reflected in subsequent infection rates.

9.2. Toxoplasmosis

9.2.1. Screening for toxoplamosis

Table 88 – Screening for toxoplasmosis: Evidence table of observational study (Aspöck & Pollak, 1992)

Prevention of prenatal toxoplasmosis by serological screening of pregnant women in Austria. Aspöck & Pollak, 1992[8]	
Methods	
• **Design**	Before and after study using historical data
• **Source of funding and competing interest**	Not reported
• **Setting**	Austria – after introduction of a screening programme (presumably any healthcare setting where these test are carried out)
• **Sample size**	The authors state that between 1981 and 1991 N=167,041 were screened. However, it is unclear how many women were ever screened or treated prior to this.
• **Duration and follow-up**	Not clearly described
• **Statistical analysis**	Not clearly described
Patient characteristics	
• **Eligibility criteria**	Not described in detail but presumably all pregnant women in Austria
• **Exclusion criteria**	Not described
• **Patient & disease characteristics**	Not described
Interventions	
• **Intervention group**	Every women is tested for antibodies at the beginning of her pregnancy and, in case of seronegativity again in the second and third trimester
• **Control group**	Vague historical data collected by a paediatrician called Otto Thalhammer in the 1950s and 60s
• **Screening tests (used from 1975 onwards)**	The first test (Sabin-Feldman-test or Indirect Fluorescent Antibody test) for assessment of the toxoplasmosis immune status is performed as early as possible. If the test is negative, further tests are carried out in the second and the third trimester. A low antibody titer found by the first test, in most cases was interpreted as an old (latent) infection acquired before (mostly long before) pregnancy. These cases were confirmed by a second test obtained 2-3 weeks later. Low titers were defined as 1:16, 1:64 and 1:256. If a high titer 1:1000 (or higher) is found, an immediate clarification is attempted by repeating the analysis on the first serum sample, concomitantly with a second sample obtained as soon as possible.
Results	
• **Prenatal toxoplasmosis infection**	Before screening (1950s and 1960s): 50-70 per 10,000 After screening was brought in with the prenatal care-programme: <1 per 10,000

Limitations and other comments	
• **Limitations**	This study pays no attention to methodological rigour. There is no clear description of how the historical data was derived and neither is there any clear detail of the sample of women that was screened when the programme was brought in (such as baseline characteristics and adherence to test regime). There is a vague mention of possible environmental factors contributing to lower infection rates, but no direct data is provided.

Table 89 – Screening for toxoplasmosis: Evidence table of observational study (Cortina-Borja et al., 2010)

Prenatal treatment for serious neurological sequelae of congenital toxoplasmosis: an observational prospective cohort study. Cortina-Borja et al., 2010[24] as part of the European Multicentre study on congenital toxoplasmosis (EMSCOT)	
Methods	
• **Design**	Prospective cohort study
• **Source of funding and competing interest**	European Commission with additional support provided by the UK national eye institute. Research at the Institute of Child Health and Great Ormond Street Hospital for Children NHS trust benefits from R&D funding received from the NHS Executive. The funding sources had no role in the design and writing and all authors declared that they had no financial disclosures relating to the study.
• **Setting**	14 Centres in six European countries (Prenatal screening: France, Austria and Italy; Neonatal screening: Sweden, Poland and Denmark)
• **Sample size**	Total N=293
• **Duration and follow-up**	Until at least 4 years of age
• **Statistical analysis**	All models were adjusted for gestational age. In the neonatal group maternal seroconversion was based on an adjusted midpoint between conception or in Sweden and Denmark (1992-1996) between the first prenatal booking sample and birth. All odds ratios (ORs) were modelled using WinBUGS software. The Bayesian framework was chosen because there were numerical problems caused by the low event rate and the relatively small sample size. Sensitivity analyses were used to determine the robustness of the findings to different assumptions. These included: • Underreporting of terminations (excluding data from Austria and Italy where no terminations were reported) • Outcome of terminations (extreme assuption that the terminated fetuses could have been born alive and develop normally • Certainty of Serious Neurological Sequelae or Death (SNSD) caused by toxoplasmosis • Potential error in imputed gestational age for children identified by neonatal screening
Patient characteristics	
• **Eligibility criteria**	Only foetuses with congenital toxoplasmosis were included
• **Exclusion criteria**	To avoid referral bias, only mothers or children in whom a positive screen test result preceded prenatal treatment or diagnostic investigations were included.
• **Patient & disease characteristics**	No detailed description provided.
Interventions	
• **Intervention group**	Prenatal screening regimes varied: France (prenatal monthly screening), Austria (prenatal screening and retesting at 12, 20 and 32 weeks) and Italy (prenatal monthly screening in Milan and 3 monthly retesting in Naples) Treatment regimens: Spiramycin in France and Italy, and pyrimethamine-suphonamide after 15 weeks in Austria

• **Control group**	Neonatal screening (in Sweden and Denmark(1992-1996) with IgG_R and IgM, and in Poland and Denmark (1997-2000) with IgM and IgA)
Results	
• **Overall cases of serious neurological sequelae or death (unadjusted)**	Definition of outcome: this described as a composite outcome comprising a pediatric report at any age of microcephaly, insertion of intraventricular shunt, an abnormal or suspicious neurodevelopmental examination that resulted in referral to a specialist, seizures during infancy or at an older age that required anticonvulsant treatment, severe bilateral visual impairment (visual acuity of Snellen 6/60 or less in both eyes assessed after 3 years), cerebral palsy, or death from any cause before 2 years of age including termination of pregnancy. Prenatal screening: 14/221 (6.3%) Neonatal screening: 9/72 (12.5%)
• **Overall cases of serious neurological sequelae or death (adjusted)**	Adjusted OR for prenatal treatment was 0.24 (95% Bayesian credible intervals 0.07-0.71) and the average risk difference between treated and untreated mothers was 8.7% (2.0% - 18.1%)
Limitations and other comments	
• **Limitations**	Even though the authors adjusted for many factors and carried out sensitivity analyses there are selection biases that cannot be ruled out in observational studies. Different unreported baseline characteristics in the different countries, underreporting of terminations, some outcomes may not have been due to toxoplasmosis. Relatively small sample size.

Table 90 – Screening for toxoplasmosis: Evidence table of observational study (Hengst 1992)

Screening for toxoplasmosis in pregnant women: presentation of a screening programme in the former 'East' Germany and the present status of Germany. Hengst, 1992[54]	
Methods	
• **Design**	Before and after study
• **Source of funding and competing interest**	Not stated
• **Setting**	All setting conducting screening in the DDR (former 'East' Germany)
• **Sample size**	Before N=1,697 (historical data) and after N=147,642 the initiation of a formal screening programme (after numbers are from different areas in East-Germany between 1984 and 1990)
• **Duration and follow-up**	Infected children were followed up for 9/10 years
• **Statistical analysis**	Not described
Patient characteristics	
• **Eligibility criteria**	Only limited information described in this study. However, the sample prior to screening was presumably described in a thesis from 1978 by the same author which was referenced (copy was not obtained)
• **Exclusion criteria**	None explicity described
• **Patient & disease characteristics**	Baseline characteristics are not explicitly described. However, the sample prior to screening was presumably described in a thesis from 1978 by the same author which was referenced (copy was not obtained).
Interventions	
• **Intervention group**	After 1975 a screening programme was introduced in East Germany using the Sabin-Feldman dye-test on one sample obtained in the first trimester. If the sample was sero-positive no further testing was performed. If the sample was seronegative two further examinations at 32 weeks gestation and at delivery were performed. If a seroconversion was indicated during pregnancy treatment was started. Treatment consisted of piramycin (3g/d) for 4 weeks during the first 16 weeks of gestation. After 16 weeks the schedule changed to pyrimethamine (first 50 mg, then 25 mg every day for 28 days) in combination with sufonamids (50 mg/kg/d).
• **Control group**	A prospective sample of pregnant women who were followed without treatment (presumably not screened the details of this sample are described in more detail in a thesis by the author from 1978 which is referenced).
Results	
• **Primary infections in pregnacy**	Before screening + treatment: 13/1,697 (0.8%) After screening + treatment: 775/147,642 (0.5%)
• **Congenital infection**	Before screening + treatment: 9/1,697 (0.5%) After screening + treatment: 124/109,935 (0.1%)

• **Clinical outcomes**	Details only available for 8 of the 9 children from the cohort that did not receive treatment and results of 53 cordocentesis after treatment with spiramycin was introduced in 1986. For the sample before screening + treatment it is described that there was 'one intracranical calcification, 1 hydrochephalus, 1 retarded skull-growth, 6 EEG abnormalities and 3 children developed chorioretinitis, 3 strabismus and 7 psycho-mental disturbances. Four of the 8 children had a lower level of intellectual capacity in intelligence tests than expected for their age. After treatment was introduced out of 53 cases of suspected toxoplasmosis 11 were seropositive, three had fatal hydrocephalus, one ended in spontaneous abortion and 2 pregnancies were terminated by induced abortion. 4 children had no clinical symptoms and there was one loss to follow-up.
Limitations and other comments	
• **Limitations**	No details are provided on gestational age in the 'before treatment' group and no baseline details or levels of adherence to screening or treatment are provided. It is difficult to identify where the 53 cases of cordocentesis came from. It does not contain a separate methods section.

Table 91 – Screening for toxoplasmosis: Evidence table of observational study (Henri et al.,1992)

Twenty-two years screening for toxoplasmosis in pregnancy: Liege – Belgium. Henri et al., 1992[55]	
Methods	
• **Design**	Epidemiological data from three cohorts with different screening strategies
• **Source of funding and competing interest**	Not stated
• **Setting**	Any setting where screening is provided within Liege – Belgium between from 1966 to 1987.
• **Sample size**	A total of N=27,757 pregnant women of which N=20,901 were screened. N=8,486 (which is the total number in the seroconversion results section) were seronegative and in N=251 seroconversion occurred. An overall N= 200 were followed up of which N=99 were treated during pregnancy
• **Duration and follow-up**	200 newborns were followed-up to the age of one year.
• **Statistical analysis**	Not described
Patient characteristics	
• **Eligibility criteria**	All pregnant women in Liege
• **Exclusion criteria**	None specified
• **Patient & disease characteristics**	Not described
Interventions	
• **Intervention group**	One comparison was between Policies Policy 1: Complete prenatal screening + complete prophylactic advice + systematic prenatal treatment (1982-1987) Second comparison: treatment (spiramycin and sulfadiazine-pyrimethamine) vs no treatment
• **Control group**	Policy 2: Complete prenatal screening + some prophylactic advice + nearly systematic treatment Policy 3: Incomplete prenatal screening (no prophylactic advice) non systematic treatment (1966-1975)

Results	
• **Seroconversion**	Policy 1: 48/3,859 (1.2%) Policy 2: 74/2,601 (2.8%) Policy 3: 129/2,027 (6.4%)
• **Symptomatic congenital toxoplasmosis (symptoms not described)**	Newborns from treated mothers: 3/99 (3%) Newborns from untreated mothers: 3/101 (3%)
Limitations and other comments	
• **Limitations**	This is a very short publication with limited detail. Gestational age has not been taken into consideration. The advice provided was also not described. No baseline characteristics were provided.

Table 92 – Screening for toxoplasmosis: Evidence table of observational study (Ricci et al., 2003)

Sreening and prevention of congenital toxoplasmosis: an effectiveness study in a population with high infection rates. Ricci et al., 2003[97]	
Methods	
• **Design**	Cohort study (main sample prospectively collected plus an additional sample of 19 neonates from a retrospective sample)
• **Source of funding and competing interest**	Not stated
• **Setting**	One hospital in a large urban area (1,035 bed general hospital) - Italy
• **Sample size**	Prenatal screening N=8,061 of which N=2,773 were excluded due to past infection Neonatal screening N=9,730
• **Duration and follow-up**	Neonates were followed-up for one year
• **Statistical analysis**	Chi-squared test (Fisher's exact test) for categorical variables. Multiple regression was used for clinical sequelae as dependant variables.
Patient characteristics	
• **Eligibility criteria**	All screened and unscreened women who were pregnant (in the time period from January 1996 to December 2000)
• **Exclusion criteria**	Women who were screened and who had a past infection.
• **Patient & disease characteristics**	Baseline characteristics not described.
Interventions	
• **Intervention group**	IgG and IgM screening was carried out during the first trimester with repeated monthly testing for women with no evidence of past infection. Infected women were treated with spiramycin (3g) daily before the 16th gestational week. Thereafter they received 25 mg pyrimethamine and 2 g sulfadiazine daily
• **Control group**	Neonatal tests were performed if the mother had not undergone prenatal screening; a cord blood sample was taken in the delivery room or a venous blood sample was obtained on the first day of life; ELISA, IgG, IgM and direct agglutination were assessed.

Results	
• **Incidence of congenital infections**	Prenatal screening: 16/5,288 (0.3%) Neonatal screening: 4/9,730 (0.04%)
• **Clinical symptoms**	Definition of outcome: described in the text as clinical signs of disease at 1 year Prenatal screening: 4/5,288 (0.08%) Neonatal screeing: 1/9,730 (0.01%)
• **Serious clinical sequelae after treatment**	Definition of outcome: these were described in detail in a table, but for this outcome groups of prenatal and neonatal infected children were combined to investigate the effects of treatment. The list of sequelae consisted of chorioretinitis, central nervous system calcification, central nervous system toxicity, hydrocephalus and central nervous system toxoplasmosis. This was investigated in one combined neonatal group of those exposed to foetal infection (N=163). It is stated that when the effects of therapy were adjusted for month of infection the odds ratio (OR) from lacking therapy was not associated with clinical sequelae whereas gestational month was associated with sequelae (OR 1.4, p= 0.08).
Limitations and other comments	
• **Limitations**	In the screening group amongst the group of women who were infected during pregnancy, there was a large number of pregnancies that did not reach full term and additionally a relatively large number that was lost to follow-up. Furthermore the groups are not comparable since presumably pregnant women at risk (i.e. after a scan) would be screened either way. This would mean that the baseline probability of risk would be higher in the screening group than in the comparison group.

Table 93 – Screening for toxoplasmosis: Evidence table of observational study (Wallon et al., 2013)

Congenital toxoplasmosis infection: monthly prenatal screening decreases transmission rate and improves clinical outcome at age 3 years. Wallon et al., 2013[122]	
Methods	
• **Design**	Observational cohort study (before and after mandatory monthly screening): retrospective case identification from laboratory results and prospective follow-up collection of data on pre- and postnatal treatment and clinical outcomes
• **Source of funding and competing interest**	Supported by a grant by the Hospices de Lyon. All authors submitted a form for the disclosure of potential conflicts of interest and none were reported.
• **Setting**	Various settings: case identification took place in one reference laboratory in Lyon; follow-up by paediatricians, general practitioners, ophthalmologists and laboratories.
• **Sample size**	N=2048 mother / infant pairs of whom N=424 were identified between the years 1987 - 1991 and N=1624 from 1992-1995. In 1996 PCR diagnosis and pyrimethamine and sulfadiazine antenatal treatment became available and a sample of N=1150 infected children was identified between 1996 and 2008.
• **Duration and follow-up**	Children were followed up for 3 years
• **Statistical analysis**	Logistic regression was used to assess the effects of gestational age (GA) at the time of maternal infection, and of calendar periods on the risk of congenital infection. The possibly nonlinear relationship between GA and risk was modelled using a flexible cubic regression spline approach. The results were then transformed into probabilities of congenital infection corresponding to maternal infections at different GA, and 95% confidence intervals (CIs) were estimated using the nonparametric bootstrap technique.

Patient characteristics	
• **Eligibility criteria**	All pregnant women diagnosed with acute toxoplasmosis infections at the reference laboratory of Lyon between 1987 and December 2008.
• **Exclusion criteria**	Pregnant women who were referred specifically for suspected foetal infection or had been infected prior to conception or for whom GA at maternal infection could not be estimated. Foetuses or children for whom congenital infection could neither be confirmed nor ruled out were also excluded.
• **Patient & disease characteristics**	Very limited overall statistics were reported: mean maternal age at conception was 29 years (sd 5 years range 16-48 years), no mother was known to suffer from immune deficiency.
Interventions	
• **Intervention group**	Mandatory screening and monthly retesting
• **Control group**	Recommended screening without specified frequency
• **Screening protocol (unchanged since 1987)**	Screening: Acute maternal toxoplasma infection was defined as a change from negative to positive specific immunoglobulin G (IgG) antibodies or a significant increase in IgG with concomitant high immunoglobulin M (IgM) titers. All samples were tested for Toxoplasma IgM and IgG antibodies using commercial tests, and the results classified as positive or negative according to the manufacturers' cutoffs. Antenatal diagnosis offered for infections acquired between 5 and 32 weeks of gestation, used mice inoculation with fetal blood and amniotic fluid as standard tests until December 1995, and PCR and mice inoculation of amniotic fluid after that time. Tests used for newborns: specific anti-Toxoplasma IgM were detected using an immunosorbent agglutination assay. Specific IgA antibodies were detected using an ELISA technique from 1993 to 2004 and using an immunosorbent agglutination assay thereafter.
Results	
• **Number of infected children of infected mothers**	Before 1992: 125 children of 424 mothers (29%) After 1992: 388 children of 1624 mothers (24%)
• **Risk of clinical signs at age 3 years (before and after PCR diagnosis and treatment became available in 1995)**	Before 1995: 87 children with clinical signs of 794 infected children (11%) After 1995: 46 children with clinical signs of 1150 infected children (4%)
• **Initiation of antenatal treatment**	First trimester: Median difference of 4 days earlier treatment associated with mandatory monthly mandatory screening (95%CI -8.6 to 0.6; p=0.0007) Second trimester: Median difference of 6 days earlier treatment associated with mandatory monthly mandatory screening (95%CI -9.9 to -2.1; p=0.0004) Third trimester: Median difference of 8 days earlier treatment associated with mandatory monthly mandatory screening (95%CI -12.8 to -3.2; p=0.0001)

Limitations and other comments	
• **Limitations**	It is a before and after study and many of other changes in the health and social system are not explored. Neither is a change in prevalence of toxoplasmosis during this long time period considered. The only aspect that is accounted for is gestational age. Apart from maternal age overall no other baseline measure are reported or considered in the analysis. However, all samples were identified from one reference laboratory which makes it somewhat less prone to selection bias.

9.2.2. Lifestyle advice for toxoplasmosis

Table 94 – Lifestyle advice for toxoplasmosis: Evidence table of systematic review (Di Mario et al., 2013)

Prenatal education for congenital toxoplasmosis. Di Mario et al., 2013[28]	
Methods	
• **Design**	Cochrane systematic review
• **Source of funding and competing interest**	No external sources of support were supplied and there were none known declarations of interest
• **Search date**	15th January 2012
• **Searched databases**	Cochrane Pregnancy and Childbirth Group's trials register, PubMed, Embase, CINAHL, LILACS (Latin American and Caribbean Health Science Literature) and IMEMR (Eastern Mediterranean Region Index Medicus) and reference lists of relevant papers, reviews and websites
• **Included study designs**	Randomised, quasi-randomised and cluster randomised trials
• **Number of included studies**	2
• **Statistical analysis**	Data from the two trials were not pooled because one of the two trials did not provide raw data.
Patient characteristics	
• **Eligibility criteria**	Women of reproductive age irrespective of their pregnant status irrespective of their toxoplasmosis seropositive status.
• **Exclusion criteria**	None explicitly stated
• **Patient & disease characteristics**	Carter et al., (1989): 432 pregnant women attending early prenatal classes in six centers. Wallon et al., (2006): 5023 women attending prenatal clinics who had been screened and tested seronegative for toxoplasmosis
Interventions	
• **Intervention group**	Carter et al., (1989): Training material consisted of a three-page hand-out along with a display poster and resource materials for teachers. Teachers received one hour basic training on toxoplasmosis prevention. A 10 minute presentation focused on toxoplasmosis prevention was given during the first prenatal class. The contents of the intervention focused on cats, food and personal hygiene. Wallon et al., (2006): A 20 page brochure containing four pages of information on toxoplasmosis and an audiotape containing a conversation between a physician and her patient on issues relevant to pregnancy including questions on toxoplasmosis

• **Control group**	In both studies described as 'usual care'
Results – since results were not pooled they are described here by study rather than outcome.	
• **Carter et al., (1989)[20]**	Changes is three classes of behaviour: • Pet hygiene behaviour: women in intervention classes reported to behave significantly better than the women in control classes ($p<0.05$). • Food hygience behaviour: women in the intervention classes reported to behave significantly better than the women in the control group with respect to cooking roast beef ($p<0.05$) and hamburgers ($p<0.01$). • Personal hygiene behaviour: women in the intervention classes reported to behave significantly better than women in control classes only in the subgroup of women who had professional occupations ($p<0.05$)
• **Wallon et al., (2006)[46]**	The following results were reported: • Seroconversion for toxoplasmosis detected during the study did not differ between groups – 13/2591 (0.5%) in the intervention and 4/1358 (0.3%) in the control group (p=0.35) • Consumption of undercooked meat: Prenatal education on congenital toxoplasmosis was not sifnificantly associated with the outcome 'no consumption of undercooked meat of any type (multiple regression OR 1.21 (95% CI 0.98-1.50) • Handwashing: prenatal education was not significantly associated with the outcome ' handwashing after contact with transmission factor and before meals' (multiple logistic regression OR 1.01; 95% CI 0.83, 1.22) • Baseline behaviours concerning toxoplasmosis, smoking and alcohol consumption were significantly associated with both the outcomes measured after controlling for baseline knowledge.
Limitations and other comments	
• **Limitations**	Even though the systematic review was well conducted a review can only be as good as the studies that are included. The two included RCTs both had serious limitations which would have affected risk of bias for each outcome since they were all self-reported items and therefore a subjective outcome measure. Carter et al. (1989) had unclear randomisation, unclear baseline characteristics and high levels of differential loss to follow-up (attrition bias), there was only a short follow-up time of 6 months. Furthermore, a non-validated scale was used to measure behaviour and no raw data is presented. The second trial also has very serious risk of bias impacting on all outcomes which were self-rated behaviours measured in a questionnaire (pre- and post- test design). The study was published as a poster and summarised in a review paper, but details of the statistical analysis were not described. Women in the control group were more likely to be lost to follow up than those in the intervention group, 52% and 40% respectively. Therefore there was a high risk of attrition bias.

Table 95 – Lifestyle for toxoplasmosis: Evidence table of observational study (Breugelmans et al., 2004 & Foulon et al., 1988)

Prevention of toxoplasmosis during pregnancy – an epidemiologic survey over 22 consecutive years. Breugelmans et al., 2004[15,35]	
Methods	
• **Design**	Pre-Post study design during 3 study periods.
• **Source of funding and competing interest**	Not reported
• **Setting**	Hospital setting in Belgium
• **Sample size**	Over the 23 years of data collection an overall N = 27,827 pregnant women participated in the study divided into three periods. N=2,986 before the intervention N= 8,300 after the first round of intervention and N=16,541 after the second round of intervention.
• **Duration and follow-up**	During pregnancy until birth
• **Statistical analysis**	Differences between the three groups of women were assessed by the chi-square test.
Patient characteristics	
• **Eligibility criteria**	All pregnant women attending the participating hospital.
• **Exclusion criteria**	None explicitly stated
• Patient & disease characteristics	Baseline characteristics not provided
Interventions	
• **Intervention group**	Second period (1983-1990): A written list of recommendations provided by the physician during the first prenatal consultation (not to eat raw or undercook meat, hand washing after touching meat and avoidance of contact with cat faeces or possibly contaminated items for instance during gardening). Third period (1991 – 2001): This consisted of a more rigorous campaign consisting of a leaflet with a detailed description of the disease as well as the recommendations that featured in the second phase. Around mid-gestation midwives reiterated these recommendations.
• **Control group**	First study period (1979 – 1982): No specific recommendations on how to prevent a toxoplasmosis infection were provided.
Results	
• **Seroconversion rate during pregnancy**	First study period: 1.43% Second study period: 0.53% Third study period: 0.09%
Limitations and other comments	
• **Limitations**	There are many biases associated with before-and-after studies. During the study period of 23 many changes take place in clinical practice and once knowledge about a particular infection increases and a leaflet is designed motivation of clinicians is high. No overall baseline characteristics of the population are provided and therefore it is unclear whether any changes in other variables may have caused the differences apart from the leaflets provided. National screening programmes did also come into practice during this period and became more systematic during this time. It is therefore difficult to establish how all of these factors inter-relate.

Table 96 – Lifestyle for toxoplasmosis: Evidence table of observational study (Pawlowski et al., 2001)

Impact of health education on knowledge and prevention behaviour for congenital toxoplasmosis: the experience in Poznan, Poland. Pawlowski et al., 2001[87]	
Methods	
• **Design**	Pre- post study
• **Source of funding and competing interest**	It is stated that the study was encouraged by European Research Network on Congenital Toxoplasmosis and supported by the Polish-American scientific co-operation grant (Maria Curie Sklodowska Joint Fund II).
• **Setting**	Poland – hospital setting.
• **Sample size**	A total of N= 8,267 of which two comparisons had relevant data: First study period: N=4,311 (1991-1992) Second study period: N=2,710 (1997)
• **Duration and follow-up**	Baseline data were collected at initial visit and outcome were measured 1 week after birth.
• **Statistical analysis**	Not described in a detailed separate section, but for the most part correlations are used. There were no adjustments for multiple testing and confounders.
Patient characteristics	
• **Eligibility criteria**	Pregnancy
• **Exclusion criteria**	None explicitly stated
• **Patient & disease characteristics**	Seropositivity in pregnant women 1991-1992 was 58.9% and in 1997 it was 44.0%.
Interventions	
• **Intervention group**	In 1991 an educational programme was implemented. This included various educational activities, such as training of health care professionals, printed material, mass media campaign and school education programmes
• **Control group**	The control group were studied before this material was made public.
Results	
• **Knowledge of toxoplasmosis**	First study period: 24.3% Second study period: 45.3%
• **Correct behaviour**	Only measured in the second study period: 55.2%
Limitations and other comments	
• **Limitations**	It is noteworthy that even after the entire training programme of those pregnant women who answered the survey only just over half of them reported adherence to correct behaviour. However, whether or not that is an actual improvement is impossible to know since the same measure was not obtained in the earlier study period.

9.3. Chlamydia trachomatis

Table 97 – Screening for chlamydia: Evidence table of observational study (Beal, 1992)

Chlamydia infection in a nurse-midwifery caseload. Beal, 1992[37]	
Methods	
• **Design**	Before and after retrospective chart review study. In June 1986 diagnosis and treatment of chlamydia became part of routine antepartum care.
• **Source of funding and competing interest**	Yale University School of Nursing Competitive Small Grants Programme.
• **Setting**	Inner-city tertiary-care centre nurse-midwifery service.
• **Sample size**	291 charts reviewed. No prenatal chlamydia testing control group (delivered between May 85-86), n = 139. At least one antepartal chlamydia test treatment group (delivered between July 86-87), n = 152.
• **Duration and follow-up**	Not stated other than the date periods for each treatment and comparison group.
• **Statistical analysis**	Group comparisons were made using the chi squared test.
Patient characteristics	
• **Eligibility criteria**	None stated. Presume all medical charts available for all women who delivered between May 1985 and July 1987.
• **Exclusion criteria**	None stated.
• **Patient & disease characteristics**	Group equivalency: author reports no significant differences between groups for age, gravidity, parity, haematocrit at term, weeks' gestation at registration for antenatal care, number of prenatal visits and race. No other concomitant changes had been instituted in the nurse-midwifery protocols so it was believed the design allowed for an ex post facto approach. Data on gonorrhea infection showed an incidence of 6% in the control group and 9% in the intervention group (p > 0.2).
Interventions	
• **Intervention group**	The after cohort consisted of all women who delivered between July 1986 and July 1987. From June 1986 clients were routinely screened for chlamydia at the initial and 36 week visits using cervical culture. Some women were also tested at the 30-week visit. Incidence of chlamydia in the intervention group was 30%. The medication for all subjects treated for chlamydia was a course of oral erythromycin 500mg four times a day for a week. In nurse-midwife narrative notes, 35 (88%) of the women had reported taking the prescription completely and correctly. Three women reported specifically that they discontinued due to gastrointestinal intolerance.
• **Control group**	The before cohort consisted of all those women who delivered between May 1985 and May 1986 when there was no chlamydia screening.
Results	
• **Outcome 1**	Incidence of maternal febrile morbidity. Defined as intrapartum or postpartum fever as measured by oral temperature > 100.4°F Intrapartum fever: Screening group: 6/152 (4%) No screening group: 9/138 (6.5%) *p* = 0.470 Postpartum fever:

	Screening group: 12/152 (8%) No screening group: 14/138 (10%) *p* = 0.643
• **Outcome 2**	Incidence of intrapartum or postpartum antibiotic treatment (presume maternal only although not specified). Intrapartum antibiotic treatment: Screening group: 1/152 (0.7%) No screening group: 3/138 (2%) *p* = 0.548 Postpartum antibiotic treatment: Screening group: 35/152 (23%) No screening group: 30/138 (22%) *p* = 0.903
• **Outcome 3**	Diagnosis of preterm labour. Screening group: 12/152 (8%) No screening group: 8/136 (6%) *p* = 0.997
Limitations and other comments	
• **Limitations**	While the study did take into account age, diagnoses of other sexually transmitted diseases and the setting was defined as urban, other confounding factors around behavioural risks were not taken into account. The retrospective nature of the design is also a limiting factor, as outcome data that may have related to the incidence of infection (such as number of vaginal examinations and incidence of PROMS) could have been collected. The retrospective design also relied on the completeness of chart notes. Researchers noted that quality and completeness of charts varied highly, this may have resulted from some care being provided from outside sources than the nurse-midwives in the clinic setting. Attrition reporting: Initially the author reports 139 women in the no screening control group. However in the results section fever and antibiotic data is reported for 138 women and preterm birth for 136 women. No information is given about the women missing from the analyses.

Table 98 – Screening for chlamydia: Evidence table of observational study (Quinlivan, Petersen & Gurrin, 1998)

High prevalence of chlamydia and pap-smear abnormalities in pregnant adolescents warrants routine screening. Quinlivan, Petersen & Gurrin, 1998[13]	
Methods	
• **Design**	Prospective cohort.
• **Source of funding and competing interest**	Innovative Funding for Homeless Youth Programme, Commonwealth Department of Health.
• **Setting**	Three metropolitan hospitals in Perth, Australia.
• **Sample size**	Universal screening intervention group, n = 100. Screening at medical staff discretion control group, n = 60.
• **Duration and follow-up**	One year, January 1997 to January 1998.
• **Statistical analysis**	Group comparisons were made using the chi squared test.
Patient characteristics	
• **Eligibility criteria**	All pregnant women aged ≤17 years who planned to continue with their pregnancy and intended to deliver at King Edward Memorial Hospital for Women, Joondalup Health Campus, or Osborne Park Hospital. These were the preliminary study group for the 'What Happens to Adolescent Mothers' study.
• **Exclusion criteria**	None stated.
• **Patient & disease characteristics**	Group equivalency: author reports no significant differences between groups for age and racial characteristics. Chlamydia infection was 38% in Aboriginal women and 24% in non-Aboriginal women (p=0.23), however the study lacked sufficient power to determine if this was statistically significant.
Interventions	
• **Intervention group**	Universal screening of 100 women who attended the adolescent pregnancy clinic at King Edward Memorial Hospital. This hospital had a policy to offer routine screening for endocervical chlamydial infection and Pap-smear abnormalities. Chlamydia swabs were discussed with the women and a pamphlet on cervical cancer was distributed, along with other educational material. Women were then offered the opportunity to be screened, and if they consented, testing was performed at the first or second antenatal visit. Chlamydia swabs were collected from the endocervix and enzyme immunoassay (EIA) was performed on the samples. EIA sensitivity (64-100%), specificity (89-100%). Women with positive results were evaluated, counseled, and offered treatment with erythromycin 300mg four times a day for seven days. Sexual contacts were offered treatment with doxycycline 100mg twice a day for seven days. Proof of cure testing was offered. Incidence of screening and chlamydia • 92/100 (92%) women were screened • 25/92 (27%) positive for chlamydia
• **Control group**	60 women who attended general antenatal clinics at King Edward Memorial and Osborne Park Hospitals, and Joondalup Health Campus. Chlamydia swabs were performed at the discretion of the attending medical practitioner with patient consent. Follow-up and treatment were also at the discretion of the individual attending physician. Incidence of screening and chlamydia • 11/60 (18%) women were screened (p < 0.001) • 2/11 (22%) positive for chlamydia (p = 0.78)

Results	
• **Outcome 1**	Incidence of maternal febrile morbidity. Defined as temperature > 37.8°C within 72 hours of birth which required medical review, investigation, and the prescription of antibiotics. Screening group: 11/100 (11%) No screening group: 9/60 (15%) *p* = 0.62
• **Outcome 2**	Incidence of new-born febrile morbidity. Defined as temperature > 37.8°C within 72 hours of birth which required medical review, investigation, and the prescription of antibiotics. Universal screening group: 10/100 (10%) Medical staff discretion screening group: 15/60 (25%) *p* = 0.02
Limitations and other comments	
• **Limitations**	Confounding factors: Delivery location (and therefore study group allocation) was largely determined by general practitioner referral and the suburb in which the women resided. This may have confounded results due to suburb relating to socioeconomic status, rural/urban differences, and behavioural risk. Authors do report that there was no difference between groups in the percentage of those screened who had an abnormal Pap-smear result. The universal screening group was located in a specialist adolescent pregnancy clinic which may have included different pre- and ante-natal management practices than those performed at general antenatal clinics. Outcome reporting: Data on febrile morbidity are presented only as percentages; therefore raw numbers were calculated by the reviewer. However this involved having to assume that each pregnant woman gave birth successfully on one baby. It was also assumed that initial group allocation numbers were used as the denominator (as no attrition data reported). This population (pregnant adolescents) may have already existing higher-risk factors in terms of sexual behaviour than the wider population. No data is presented on how medical staff in the control group used their clinical knowledge to determine the necessity for a chlamydia test. We cannot assume that this was based on the confirmation of high-risk behaviour. There are no reasons offered as to why medical and nursing staff failed to offer screening to the adolescents in the general antenatal clinic. It is suggested that time constraints were the major contribution. The authors imply that pregnant adolescents may not be identified as a group at particular risk by general practitioners performing shared care or obstetric staff attending general antenatal clinics where the emphasis is increasingly shifting to problems associated with the older antenatal woman. There is also no data presented on the 8% of women in the universal screening group who did not undergo a chlamydia test.

9.4. Group B streptococcus

Table 99 – Screening for GBS: Evidence table of observational study (Abdelmaaboud & Mohammed, 2011)

Universal screening vs. risk-based strategy for prevention of early-onset neonatal group B streptococcal disease. Abdelmaaboud & Mohammed, 2011[15]			
Methods			
• **Design**	Retrospective cohort		
• **Source of funding and competing interest**	Not stated		
• **Setting**	Department of Obstetrics and Gynaecology and Neonatal Intensive Care Unit (NICU), Women's Hospital, Qatar		
• **Sample size**	Between 2003 and 2009 a total of 87,260 live births were recorded (for the screening approach between 2003 and 2006 N= 48,400; and the risk based approach between 2006 and 2009 N=38,860) and from the delivery records 1268 live births were randomly sampled to estimate the difference between universal screening and risk-based strategies in the two time periods.		
• **Duration and follow-up**	Until identification of Early Onset Group B streptococcal disease (72 hours)		
• **Statistical analysis**	Described as follows, *note type of test not specified*: 'Data were represented as number and percent or mean ± SD when appropriate. A p< 0.05 was considered to be statistically significant'		
Patient characteristics			
• **Eligibility criteria**	All live births during the specified time period		
• **Exclusion criteria**	Not specifically stated		
• **Patient & disease characteristics**	Random sample characteristics (N=1268) – n (%) unless otherwise specified *p<0.01, **p<0.001		
		Screened group (N=657)	Risk-based group (N=611)
	Age (yrs), mean (sd)	24.6 (3.2)	26.3 (7.1)
	Prenatal care	598 (91)	562 (92)
	Preterm delivery**	46 (6.9)	84 (13.8)
	PROM ≥18 hrs	53 (8.1)	50 (8.4)
	Intrapartum fever	22 (*stated as 3.6, should be 3.3*)	26 (3.9)
	GBS bacteriuria*	22 (3.3)	11 (1.9)
	Previous infant with GBS disease*	3 (0.49)	1 (0.21)
Interventions			
• **Intervention group**	Maternal screening by taking rectovaginal swabs and urine culture at 35-37 weeks of gestation and for all high-risk cases at time of presentation (preterm labor, intrapartum fever of ≥38°C, clinical chorioamnionitis or GBS colonization). All screening cultures were processed at the microbiology laboratory using procedures in compliance with the CDC guidelines. During labor intrapartum antibiotic prophylaxis was given to all women screened positive for GBS in urine or rectovaginal swab and those with risk factors (2 g of ampicillin intravenously then 1 g every 6 hrs until delivery unless there was penicillin allergy in which case clindamycin 900 mg was given every 8 hrs.		
• **Control group**	Risk based screening using the same risk-factors specified in the intervention group		

Results	
• **Early onset GBS disease (EOGBS):**	Outcome description: neonates were evaluated for EOGBS according to established guidelines. A complete blood count white blood cell and its differential and blood culture were obtained if the neonate was judged at significant risk for EOGBS on the basis of a variety of clinical risk factors including maternal GBS colonisation, inadequate IAP, maternal intrapartum fever, duration of rupture of membranes, clinical diagnosis of chorioamnionitis, preterm delivery and the mother having had a previous neonate with GBS disease. Overall – 45/87260 (0.52 per 1000) *For the two approaches only 'per 1000' numbers are provided and numbers add up to more than the 45 cases that were reported (i.e. 48).* Screening approach – described as 0.53 per 1000 which would make it 26/48400 Risk based approach – described as 0.57 per 1000 which would make it 22/38860
Limitations and other comments	
• **Limitations**	It is commendable that the characteristics of a subsample are described, but unfortunately some of the details are missing (regarding tests and total numbers of EOGBS cases in each group. None of the baseline differences are taken into consideration in the analysis.

Table 100 – Screening for GBS: Evidence table of observational study (Angstetra, Ferguson & Giles, 2007)

Institution of universal screening for group B streptococcus (GBS) from a risk management protocol results in reductoin of early-onset GBS disease in a tertiary obstetric unit. Angstetra, Ferguson & Giles, 2007[16]		
Methods		
• **Design**	Prospective cohort with a historical control group	
• **Source of funding and competing interest**	Not stated.	
• **Setting**	John Hunter Hospital, Newcastle, Australia	
• **Sample size**	42,471 pregnant women (between the years 1994 and 2006) – 30,978 live births pre-screening and 8303 after the screening protocol was implemented	
• **Duration and follow-up**	7 days after delivery	
• **Statistical analysis**	Chi-squared test with Yates correction.	
Patient characteristics		
• **Eligibility criteria**	Women booked to deliver or referred to the hospital because of a complication with pregnancy.	
• **Exclusion criteria**	Data from women who delivered during the year 2003 because this was a transition period from risk-based to universal screening approach.	
• **Patient & disease characteristics**	Years 2002 and 2005 were used as examples for birth demographics (only percentages provided), stating that 'the demographics have not changed over the two epochs':	
		2002 (risk-based) / 2005 (universal screening)
	Normal vaginal birth	68.3 / 65.1

	Lower segment caesarean section	22.3	24.2
	Vacuum	5.8	6
	Forceps	2.6	3.7
	Birthweight (grams < 1500)	4.3	4.2
	1500-2499	9.1	8.4
	2500+	86.6	87.4
	Gestational age <34 wks	7.2	7.6
	34-36	7	6.8
	37+	85.8	85.6
	Length of stay (days)	3.2	3.2
	Perinatal mortality per 1000	22	22
	Neonatal death per 1000	9	8
	Stillborn per 1000	13	14
Interventions			
• **Intervention group**	Universal screening: all women are offered a rectovaginal swab for GBS detection at 34-37 weeks gestation (positive predictive value 87% and negative predictive value 96% - *as reported in the paper*). This involved self-collection of the swab which were plated directly on to Granada media plates – colorimetric differential medium for GBS incubated anaerobically for 24-48 hrs and then observed for orange-coloured colonies. Intrapartum antibiotic prophylaxis is offered to women if there has been a previous infant with invasive GBS disease, GBS bacteriuria in the current pregnancy, a positive screening culture during the current pregnancy, preterm labour of < 37 weeks gestation, whether spontaneous or induced (unless known to be GBS negative within the last two weeks), an intrapartum temperature of ≥38°C (on two occasions 2 hrs apart) regardless of GBS status and prolonged ruptured membrane of ≥ 18 hrs where GBS status is unknown. Intrapartum antibiotic treatment is not indicated if there is negative rectovaginal GBS screening culture after 34 weeks gestation in the current pregnancy regardless of duration of membrane rupture. If in a previous pregnancy a positive GBS screening culture has been found the women only receives intrapartum antibiotics if also positive in the current pregnancy. The antibiotic of choice for intrapartum GBS prophylaxis are intravenous benzylpenicillin 1.2 g initially then 600 mg i.v. four hourly until delivery or for penicillin-sensitive individuals either i.v. cehalothin 2 g initially then 1 g i.v. six hourly or i.v. clindamycin 600 mg i.v. eight hourly until delivery.		
• **Control group**	Risk-based prophylaxis: not described explicitly but presumably using the same risks as described above.		
Results			
• **Early onset neonatal sepsis (EONS): Culture positive for GBS**	Investigations of neonatal sepsis included blood culture, full blood count and C-reactive protein. Examination of CSF, urine and chest radiography is performed when the infant is stable and clinically indicated. The prospectively collected database to identify any blood or cerebrospinal fluid culture positive for GBS obtained from an infant < 7 days was obtained from the microbiology department. Screening: 0/8303 Risk-based: 26/30978 (0.84 per 1000)		

Limitations and other comments	
• **Limitations**	As in most of the other studies over time many other factors may contribute to changes in the incidence of GBS. Also in this particular study the positive predictive value of 87% is not particularly high which seems to indicate that cases would be missed after the introduction of screening. The sample sizes are so different that by chance alone it is unlikely that there would be not be any cases in the 2 years after screening was introduced. There are also mistakes in the calculation. The absolute risk reduction is described as 84% - when it should be 0.84 per 1000 which would make it 0.084%

Table 101 – Screening for GBS: Evidence table of observational study (Brozanski et al., 2000)

Effect of a screening-based prevention policy on prevalence of early-onset Group B Streptococcal sepsis. Brozanski et al., 2000[17]	
Methods	
• **Design**	Retrospective cohort
• **Source of funding and competing interest**	Not stated
• **Setting**	Magee Women's Hospital, Pittsburgh, Pennsylvania, USA
• **Sample size**	After the introduction of screening N = 28,733, before universal screening N = 31,133
• **Duration and follow-up**	Until Group B Streptococcal sepsis could be identified according to the records – 48 hours after birth
• **Statistical analysis**	Chi-squared for categorical and t-test for continuous variables
Patient characteristics	
• **Eligibility criteria**	Women who delivered between Jan 1992 and June 1995 (before screening) and October 1995 through to August 1999 after screening was introduced.
• **Exclusion criteria**	Not stated
• **Patient & disease characteristics**	Demographics only provided by colonization status rather than by screening strategy
Interventions	
• **Intervention group**	According to CDC protocol: Routine prenatal screening for GBS between 35 and 37 weeks gestation and for all women who were either known to be colonized with GBS or whose colonization status was unknown when their fever was at least 38°C, when they had rupture of membranes for at least 18 hours, when they had GBS bacteriuria, or when they had previous infants with early-onset group B streptococcal sepsis. To optimize the yield of screening cultures selective broth media testing specimens from the distal vagina and anal canal was used.
• **Control group**	Risk-based prophylaxis (not very clearly described but the American Academy of Pediatrics and American College of Obstetrics and Gynaecology guidelines are mentioned which recommended risk based chemoprophylaxis)
Results	
• **Early onset neonatal sepsis (EONS): Culture positive for GBS**	Early onset group B streptococcal sepsis was defined as positive culture of blood or CSF in neonate within 48 hours after birth. Screening: 4/28733 (0.14 per 1000) Risk-based: 36/31133 (1.16 per 1000)

Limitations and other comments	
• **Limitations**	As with many of the other before-after studies there is no consideration of other factors that may have contributed to a change in the incidence of GBS sepsis during this time period.

Table 102 – Screening for GBS: Evidence table of observational study (Davis et al., 2001)

Introduction of the new Centre for Disease Control and Prevention group B streptococcal prevention guideline at a large West Coast health maintenance organisation. Davis et al., 2001[18]	
Methods	
• **Design**	Retrospective cohort (before-and-after) study
• **Source of funding and competing interest**	Not stated
• **Setting**	Group Health Cooperative (GHC) of Puget Sound covering medical use data from 2 hospitals in western Washington State, USA
• **Sample size**	N=1337 pregnancies at baseline (i.e. prior to implementation) and N=2438 after implementation of universal screening. Additionally there were two groups, referred to as 'development' and 'introduction', but these are not included in this extraction table due to unclear guideline use during these periods.
• **Duration and follow-up**	Not explicitly stated
• **Statistical analysis**	The analysis focused mainly on the effects of the guideline protocols on the length of stay
Patient characteristics	
• **Eligibility criteria**	All women giving birth at the included two hospitals between October 1995 and December 1997
• **Exclusion criteria**	None stated
• **Patient & disease characteristics**	The following pregnancy characteristics were provided n (%) unless otherwise stated: Risk based (baseline) N=1337 — Screening N = 2438 Term: 1265 (94.6) — 2303 (94.5) Preterm (<37 wks): 72 (5.4) — 135 (5.5) Screened at least once Term: 1123 (88.8) — 2095 (91.0) Preterm: 62 (86.1) — 91 (6.4) Screening time according to guideline Term: 545 (48.5) — 1561 (74.5) Preterm: 30 (48.4) — 31 (34.1) GBS positive Term: 251 (22.4) — 492 (23.5) Preterm: 10 (16.1) — 21 (23.1) Intrapartum antibiotic use Term: 150 (12.0) — 579 (25.1) Preterm: 21 (29.2) — 72 (53.3) Intrapartum antibiotic timing

	Prophylaxis ≥ 4 hrs before delivery	53 (31.0)	345 (53.0)
	Prophylaxis ≥ 2 times before delivery	17 (9.9)	88 (13.5)
	Median duration of treatment (hrs) 1.8		4.3
Interventions			
• **Intervention group**	Screening at 35-37 weeks and intrapartum antibiotic prophylaxis to all GBS positive women regardless of risk factors		
• **Control group**	Screening at 28 weeks and intrapartum antibiotic prophylaxis only provided to GBS positive women with risk factors.		
Results			
• **Children with positive blood and GBS streptococci culture**	Screening at 35-37 wks n/per live births: 3/2425 (1.2 per 1000) Screening at 28 wks plus risk based prophylaxis n/per live births: 0/1330		
Limitations and other comments			
• **Limitations**	In addition to the limitation of disease prevalence and participant characteristics changing over time, which is not accounted in the analysis, this study had a particularly small sample size for this outcome. It is therefore possible that the result is due to chance rather than intervention.		

Table 103 – Screening for GBS: Evidence table of observational study (Gilson et al., 2000)

Prevention of Group B Streptococcus Early-Onset Neonatal Sepsis: Comparison of the Center for Disease Control and Prevention screening-based protocol to a risk-based protocol in infants greater than 37 weeks gestation. Gilson et al., 2000[19]			
Methods			
• **Design**	Retrospective cohort study		
• **Source of funding and competing interest**	In part supported by a General Clinical Research Center grant		
• **Setting**	Screened group: Prenatal care and delivery at University of New Mexico Hospital; Control group: Prenatal care obtained at outlying satellite clinics but the baby was delivered at the University of New Mexico Hospital		
• **Sample size**	Of an overall sample of 3 164 screened mother-infant pairs and 2 684 unscreened pairs a random sample of N=420 of screened women were compared to a matched sample of 407 women with unknown GBS status.		
• **Duration and follow-up**	7-10 days		
• **Statistical analysis**	Two-tailed t tests for continuous variables, Fisher's exact test for binary frequency data and Wilcoxon rank sum test for nonparametric data.		
Patient characteristics			
• **Eligibility criteria**	Screened or unscreened women giving birth at the University of New Mexico Hospital during the study period from 1/10/1994 to 30/6/1996		
• **Exclusion criteria**	None stated		
• **Patient & disease characteristics**	Random sample of screened mothers and matched controls:	GBS screened (N=420)	GBS unscreened (N=407)
	Maternal age (yr)	25 (6)	24 (6)
	Gestational age (wks)	9.2 (1.4)	39.3 (1.5)

	Parity (median, IQR)	1 (0-2)	1 (0-2)
	Infant weight (g)	3289 (512)	3336 (509)
	Rapture of Membrane (hr)	7.2 (8.8)	6.5 (8.3)
	Rapture of Membrane > 18 hr N (%)	37 (8.9)	34 (8.4)
	Chorioamnionitis N (%)	28 (6.7)	23 (5.7)
	Endometritis N(%)	11 (2.6)	15 (3.7)
	Other STDs N(%)	28 (6.7)	28 (6.9)
Interventions			
• **Intervention group**	At 35 o 37 weeks gestation both lower vaginal and rectal swabs (two swabs) were collected and combined in transport medium, inoculated and incubated in selective Todd-Hewitt broth for 16-24 hours and then subcultured onto nonselective 5% sheep blood agar. Intrapartum chemoprophylaxis was given to all GBS positive women and to term patients with the following risk factors: maternal fever (≥38°C) in labour, prolonged (≥18 hours) rupture of membranes, or a history of a prior GBS infant.		
• **Control group**	Chemoprophylaxis for women with the following risk factors: maternal fever (≥38°C) in labour, prolonged (≥18 hours) rupture of membranes, or a history of a prior GBS infant		
Results			
• **Early onset neonatal sepsis (EONS): Culture positive for GBS**	Definition of outcome: infants in whom GBS was isolated from a normally sterile central site (blood, cerebrospinal fluid, or urine from a normally sterile central site (blood cerebrospinal fluid, or urine obtained by suprapubic aspiration) within the first 7 days of life. Screened: N=0 Unscreened: N=4/407 (9.8 per 1000) (Length of stay 9.8 days (5.5))		
• **EONS: strongly suspected sepsis**	Definition of outcome: infants with a negative blood culture but in whom the paediatric staff maintained a strong clinical suspicion of sepsis and who were maintained on intravenous antibiotics for 7 to 10 days. Strongly suspected sepsis included presence of one or more of the following signs and/or symptoms: (1) pneumonia (defined as presence of respiratory distress, including a respiratory rate ≥ 60, intercostal retractions, persistent oxygen requirement, and a pediatric radiologic diagnosis of pulmonary infiltrates consistent with pneumonitis), (2) ratio of immature to total neutrophils ≥0.20, (3) neutropenia with an absolute neutrophil count ≤1.5x10^9/l, (4) persistent apnoeic and bradycardic episodes refractory to all treatment except mechanical ventilation, (5) hyperglycemia (≥120 mg/dl), or hypoglycemia (≤30 mg/dl fasting) concurrent with temperature instability and (6) thrombocytopenia (platelet count ≤100,000/mm^3) Screened: N=6 (Length of stay 7.0 days (1.7)) Unscreened: N=11 (Length of stay 7.2 days (1.5))		
• **EONS: low probability sepsis**	Definition of outcome: infants considered possibly at risk for GBS sepsis and who were observed on antibiotics for 48 to 72 hours or until culture results were known to be negative. Screened: N=6 (Length of stay 3.3 days (0.9)) Unscreened: N=9 (Length of stay 3.6 (0.7))		
Limitations and other comments			
• **Limitations**	The strength of this study is that the data was collected concomitantly and that the two groups were matched for baseline risk. However, as stated in the discussion only 48% of women who were candidates for chemoprophylaxis received antimicrobials appropriately in a timely fashion within 4 hours of delivery.		

Table 104 – Screening for GBS: Evidence table of observational study (Hafner et al., 1998)

Group B streptococci during pregnancy: a comparison of two screening and treatment protocols. Hafner et al., 1998[20]	
Methods	
• **Design**	Prospective cohort
• **Source of funding and competing interest**	Not stated
• **Setting**	Clinical obstetrics and gynaecology department at the Donau-hospital, Vienna, Austria
• **Sample size**	Universal screening N = 3952 (recruited Dec 1994 – Jan 1997), risk-factor prophylaxis N = 3700 (recruited Sep 1992 – Nov 1994)
• **Duration and follow-up**	Until status of neonatal GBS status could be ascertained
• **Statistical analysis**	Chi-squared test with Yates' correction.
Patient characteristics	
• **Eligibility criteria**	Women giving birth during the specified time period
• **Exclusion criteria**	None stated
• **Patient & disease characteristics**	The only description provided is that the 'demographic composition did not change considerably in either of the periods; > 90% of the women who deliver in the hospital are native Austrians'.
Interventions	
• **Intervention group**	Women were screened during weeks 33 through 35. Swabs were taken from the distal third of the vagina and rectum. They were cultured on sheep blood agar (aerobic) for between 24 and 48 hours and put in a thioglycollate enrichment broth. Rectal smear were cultured on Columbia nalidix acid agar. Incubation time was between 24 and 48 hours. Women with positive results for group B streptococci were given amoxicillin and clavulanic acid intravenously at intervals of 6 hours from the entry into the delivery room. Women allergic to penicillin received 600 mg clindamycin intravenously.
• **Control group**	Antibiotics were administered only if high-risk factors were present on entry to the delivery room. High-risk factors were: premature rupture of membranes before gestational week 37, rupture of membrane > 8 hours, delivery time ≥ 18 hours, maternal fever during delivery (≥37.5°C), group B streptococcal infection of a sibling in the past, or maternal diabetes mellitus.
Results	
• **Early onset neonatal sepsis (EONS)**	Neonates showing signs of inflammatory disease or elevated C-reactive protein level were transferred to the neonatology service. Swabs were taken from the throat, the umbilicus and the ears and antibiotic treatment with ampicillina at 100 mg/kg body weight and aminoglycoside at 5 mg/kg body weight was instituted. Screened: 4/3952 (1 per 1000) Risk based: 20/3700 (5.4 per 1000)
Limitations and other comments	
• **Limitations**	Characteristics of the two groups were not described in detail. The sample does not seem to be large enough and the number of culture positive cases is higher than in most other studies.

Table 105 – Screening for GBS: Evidence table of observational study (Horvath et al., 2013)

Screening pregnant women for group B streptococcus infection between 30 and 32 weeks of pregnancy in a population at high risk for premature birth. Horvath et al., 2013[21]	
Methods	
• **Design**	Prospective cohort with historic control
• **Source of funding and competing interest**	It is stated that the authors have no conflicts of interest
• **Setting**	Teaching hospital in Szombathely, Hungary
• **Sample size**	Screening sample N = 24950 (collected from Jan 1995 through Dec 2011) No screening N = 19722 (collected from Feb 1984 through Dec 1994)
• **Duration and follow-up**	Until neonatal GBS status was ascertained
• **Statistical analysis**	For categorical variables the Chi-square or the Fisher exact test was used. To test associations among multiple variables, logistic regression was performed. P-values < 0.05 were considered significant
Patient characteristics	
• **Eligibility criteria**	Women giving birth during these time periods
• **Exclusion criteria**	None specifically stated
• **Patient & disease characteristics**	It is only described that 'most were middle- to low-income and all had received some prenatal care.
Interventions	
• **Intervention group**	Physicians collected samples from the participants' distal vagina (without speculum placement) and rectum approximately between 30 and 32 weeks gestation. Swabs (Transwab for Aerobes and Anaerobes) were used for collection, and the samples were then placed in Stuart transport medium and sent to the laboratory for culture. GBS positive women and women with risk factors for the transmission of early onset GBS disease would automatically receive intrapartum antibiotic prophylaxis. Special attention was paid to women who seemed likely to undergo a premature delivery. The intravenous prophylactic regimen administered during labor was 2 g of ampicillin followed by 1 g of ampicillin every 4 hours until delivery. Patients allergic to penicillin received erythromycin or clindamycin intravenously in equivalent dosage.
• **Control group**	It is described that the women in this group did not undergo GBS screening and received no intrapartum prophylaxis.
Results	
• **Neonatal GBS infection**	Neonatal GBS infection was considered definite if there were clinical signs of GBS disease and/or if blood, cerebrospinal fluid, urine, tracheal aspirate, or lung tissue were found positive for GBS. Screened: 63/25857 (2.4 per 1000) – neonatal sample larger than N above because of 789 twins and 59 triplets born during this time No screening: 149/19722 (7.5 per 1000)
• **Death from neonatal GBS infection**	Screened: 1/25857 (0.04 per 1000) Not screened: 29/19722 (1.5 per 1000)

Limitations and other comments	
• **Limitations**	No baseline characteristics described or accounted for in the analysis. The timeframe is so large that it cannot be ruled out that other factors apart from the screening could have contributed to these results.

Table 106 – Screening for GBS: Evidence table of observational study (Jeffery & Moses Lahra, 1998)

Eight-year outcome of universal screening and intrapartum antibiotics for maternal Group B Streptococcal carriers. Jeffery & Moses Lahra, 1998[22]	
Methods	
• **Design**	Prospective cohort study
• **Source of funding and competing interest**	The second author was funded by a scholarship (Sydney Tapping Bequest)
• **Setting**	Department of Neonatal Medicine, King George V Hospital (KGVH), Sydney
• **Sample size**	Before screening protocol implementation N=5732 in the eight year period after implementation N=36,342
• **Duration and follow-up**	48 hours after birth (data was prospectively collected over 16 months before screening and 8 years after implementation.
• **Statistical analysis**	Pre-intervention and intervention mortality rates for Early Onset Group B Streptococcal Disease (EOGBCD) were compared using the chi squared statistic and the Fisher's exact test for small numbers where appropriate. Comparison of morbidity was made using confidence intervals and relative risk ratios. A P value of p<.05 was considered statistically significant.
Patient characteristics	
• **Eligibility criteria**	All women who booked at KGVH for delivery or who were referred to KGVH because of a complication with the pregnancy or with labour.
• **Exclusion criteria**	None explicitly stated
• **Patient & disease characteristics**	Baseline characteristics not described
Interventions	
• **Intervention group**	Screening protocol: antenatal screening for all women at 28 weeks gestation or 24 weeks if known risk factors for preterm birth, by low vaginal swab, cultured onto blood agar, with identification by colony morphology, hemolysis and positive Christie-Atkins-Munch-Peterson reaction. Maternal carriers were treated with intravenous ampicillin in labor, 1 g every 6 hours until delivery, unless there was a history of penicillin allergy, when cephalosporin was used. In addition women with a routine midstream urine test positive for GBS at any antenatal visit or a history of neonate with EOGBSD and women with preterm labor with an unknown carrier status were also treated with intrapartum antibiotics. Prior to introduction of the protocol there was a 3 months in-service education programme for all staff
• **Control group**	The background rate of EOGBSD was determined prospectively over a 16-month period (Nov 1986 to Feb 1988) before the intervention. Even though not clearly described, it is implicit that this did not involve any particular screening or intervention programme, but presumably pregnant women were treated on the discretion of the attending physician.

Results	
• **EOGBSD**	Definition of outcome: EOGBSD was determined prospectively by two methods, both before and after intervention: (1) a positive culture of blood or CSF in neonate within 48 hours of birth, and (2) a positive urine streptococcal antigen test within 48 hours of birth in a neonate with clinical signs of sepsis. Screening protocol: 28/36342 (0.8 per 1000) Unscreened (before protocol implementation: 28/5732 (4.9 per 1000)
Limitations and other comments	
• **Limitations**	Even though this is a prospective study of all women in one hospital during a long time period it is hard to know whether there were possibly other factors accounting for some of the results. No confounding factors are considered and a 3 month education programme took place before implementation which in itself could have caused some improvement in outcome.

Table 107 – Screening for GBS: Evidence table of observational study (Lijoi et al., 2007)

The efficacy of 2002 CDC guidelines in preventing perinatal group B streptococcal vertical transmission: a prospective study. Lijoi et al., 2007[2]	
Methods	
• **Design**	Prospective cohort study
• **Source of funding and competing interest**	Not stated
• **Setting**	Department of obstetrics and gynaecology, University of Genoa, Italy
• **Sample size**	Screened group N = 1273; unscreened or screened <35 weeks of gestation N = 396
• **Duration and follow-up**	Until neonatal GBS status could be ascertained with follow-up of 7-10 days after birth.
• **Statistical analysis**	Chi-squared test, p-value of < 0.05 was considered significant
Patient characteristics	
• **Eligibility criteria**	Pregnant women who presented to the department to give birth
• **Exclusion criteria**	In order to obtain a homogenous population women with additional risk factors were excluded: gestational age < 37 wks, length of membrane rupture > 18 hrs, intrapartum fever (> 38°C), and previous delivery of an infant with invasive GBS disease
• **Patient & disease characteristics**	The following characteristics are described - N(%) unless otherwise specified: Screened N = 1273 — Not screened or early screen N = 396 Age median (range): 29 (16-39) — 28 (17-38) Gestational age mean (median): 39 (37) — 39 (37) First pregnancy: 766 (60.2) — 242 (61.1) Second pregnancy: 258 (20.3) — 72 (18.2) Third or more pregnancy: 249 (19.6) — 82 (20.7) Cesarean section: 341 (26.8) — 96 (24.2) Duration of intrapartum chemoprophylaxis hrs (mean (sd): 3.8 (2.3) — Not performed

Interventions	
• **Intervention group**	Specimens for GBS culture were collected and processed according to CDC 2002 guidelines; two different swabs were used to collect cultures from the lower vagina and the rectum of the mother. There different swabs were used to collect cultures from internal ear, anterior nares and pharynx of the newborn. The swabs were placed in appropriate nonnutritive transport medium and were inoculated in a selective broth medium supplemented with both gentamicin and nalidixic acid. Inoculated selective broths were incubated for 18-24 h at 35-37°C in ambient air. The broths were subcultured into a sheep blood agar plate. All organisms suggestive of GBS were inspected and identified. If GBS was not identified after incubation for 18-24 h a new incubation was performed and, after 48 h, a new inspection aimed at identifying suspect organisms. Treatment consisted of an initial dose of ampicillin (2 g intravenously) at the beginning of labor, followed by 1 g intravenously every 4 h until delivery. Women with history of ampicillin allergy received clindamycin (900 mg intravenously every 8 h until delivery).
• **Control group**	Absence of culture based screening for vaginal and rectal GBS colonization, and culture based screening performed more than 5 weeks before delivery or performed before 35 weeks' gestation.
Results	
• **Culture positive for GBS**	All newborns received in the first hour of life a culture based screening for auricular nasopharyngeal GBS colonization. A clinical follow-up of the newborns was performed at 7-10 days after birth. Screening group: 52/1286 (4.0% with 95% CI 2.8-5.0) (N more than pregnant women due to multiple births) Not screened or early screened: 13/396 (3.3 % with 95% CI 1.8-5.5) – figures were also provided for those who were not screened (9/216 – 4.2%) and those who were screened early (4/180 – 2.2%)
Limitations and other comments	
• **Limitations**	The main limitation of this study is the insufficient sample size and the large difference in group size. Furthermore the difference in group size indicates that the large majority of the service follows the guideline and maybe those who did not receive the screening would also have other factors contributing to why this was not carried out. The outcome is maybe a bit indirect since not all culture positive infants would develop sepsis and the rate of culture positive newborns in substantially larger than in those the report early onset GBS sepsis.

Table 108 – Screening for GBS: Evidence table of observational study (Lin et al., 2011)

The changing face of Early Onset Neonatal Sepsis after the implementation of a maternal Group B Streptococcus screening and intrapartum prophylaxis policy – a study in one medical center. Lin et al., 2011[23]	
Methods	
• **Design**	Retrospective chart review
• **Source of funding and competing interest**	Not described
• **Setting**	Taipei Mackay Memorial Hospital (TPMMH), Taiwan
• **Sample size**	Before policy: N= 15,209 After introduction of policy: N = 17,405
• **Duration and follow-up**	Retrospective chart review – presumably until hospital discharge (diagnosis within 72 hours after birth)

• **Statistical analysis**	GBS early onset sepsis rates were compared using the chi-squared test / Fisher's exact test for categorical variables and the independent two sample t test for continuous outcomes. Time trends during the study period with regards to GBS early onset sepsis were analysed using the Cochran-Armitage trend test.
Patient characteristics	
• **Eligibility criteria**	All live born infants delivered at TPMMH with a birth weight more than 400 g.
• **Exclusion criteria**	Not specifically described
• **Patient & disease characteristics**	Not specifically described
Interventions	
• **Intervention group**	Screening and intrapartum antibiotic prophylaxis (IAP): GBS culture screen at wk 35-37 (unless GBS bacteriuria has been examined in the pregnancy or previous neonate had severe GBS infection) with additional patient education delivered by the outpatient department nurses. IAP was given when (1) the culture was GBS positive (2) a previous neonate had severe GBS infection (regardless of the result of GBS screen in the pregnancy (3) unknown GBS screen but with a preterm birth < 37 wks, (4) unknown GBS screen with term birth but rupture of membrane over 18 hours or (4) unknown GBS screen with term birth but body temperature > 38°C in parturient period.
• **Control group**	GBS screening and IAP was not routinely performed.
Results	
• **Early onset sepsis (EOS):**	Outcome definition: A positive culture in blood drawn within 72 hours after birth. Screening policy: 20/17,405 (1.1 per 1000) Before screening policy: 22/15,209 (1.4 per 1000)
• **Time trend analysis**	The description in the results section (with Figure) states 'GBS EOS decreased dramatically from 2001 to 2007 (trend p = 0.009).
Limitations and other comments	
• **Limitations**	This is a very large scale study with data that is divided by year and incidence of GBS EOS is given in a Figure for the years 2001 to 2008. However, confounding factors are not considered in the analysis. Statistics are quite basic, especially the trend analysis is not particularly clearly described.

Table 109 – Screening for GBS: Evidence table of observational study (Locksmith et al., 1999)

Maternal and neonatal infection rates with three different protocols for prevention of group B streptococcal disease. Locksmith et al., 1999[24]	
Methods	
• **Design**	Retrospective cohort study
• **Source of funding and competing interest**	Not stated
• **Setting**	University of Florida-Shands Hospital, USA
• **Sample size**	Selective screening N=7810, American College of Obstetricians and Gynecologists (ACOG) risk factor prevention N=7917, and universal screening N = 4453
• **Duration and follow-up**	Until neonatal GBS could be ascertained and 7 days follow-up

• **Statistical analysis**	Demographics and other categorical data were analysed using the chi-squared test (with Yates' correction where needed). The risk of chance results from multiple comparisons was dealt using the Bonferroni method. Comparisons between groups were made by calculating risk ratios and 95% confidence intervals.
Patient characteristics	
• **Eligibility criteria**	Women who delivered of live infants at the hospital between August 1991 and April 1998
• **Exclusion criteria**	None explicitly stated
• **Patient & disease characteristics**	The following characteristics are described - N(%) unless otherwise specified (*p<0.05, **p<0.001):

	Selective screening N=7810	ACOG screening N=7917	Universal screening N=4453
Delivery < 37 wks**	1561 (20)	1760 (22)	1087 (24)
Risk factor present**	2082 (27)	2023 (29)	1277 (29)
Race:			
White	4452 (57)	4643 (59)	2622 (59)
African American**	3046 (39)	2797 (35)	1474 (33)
Other**	312 (4)	477 (6)	357 (8)
Parity:			
Nulliparous	2198 (28)	2575 (33)	1480 (33)
Parous	5612 (72)	5342 (67)	2972 (67)
Age:			
≤20 yrs*	2836 (36)	2769 (35)	1501 (34)
21 – 35 yrs	4634 (59)	4738 (60)	2683 (60)
≥ 36 yrs**	340 (4)	410 (5)	269 (6)

Interventions	
• **Intervention group**	The Centre for Disease Control and Prevention endorsed universal screening policy (after July 1996)
• **Control group**	1. Selective screening: Group B streptococcal cultures obtained only for women who were admitted to the hospital for management of preterm labour. Intrapartum chemoprophylaxis was offered to those who had both a recognised risk factor for early onset group B streptococcal infection and a positive culture test (August 1991 – August 1993) 2. ACOG screening: Same as protocol one but intrapartum chemoprophylaxis was offered to women whose colonisation status was unknown but who had a risk factor. Risk factors were defined as anticipated delivery before 37 weeks gestation, preterm premature rupture of membranes, duration of membrane rupture > 18 hours (prolonged rupture of membranes), maternal fever indicative of chorioamnionitis, and a previous infant with group B streptococcal infection.
Results	
• **Neonatal infection rates**	Definition of outcome: The isolation of group B streptococci from a normally sterile site (blood or cerebrospinal fluid) in an infant younger than 7 days with an additional retrospective search of the hospital's microbiology laboratory records for the time after 7 days. Rates were: Universal screening:6/4453 (1.35 per 1000)

	ACOG screening: 15/7917 (1.89 per 1000) Selective screening: 23/7810 (2.94 per 1000) Reported risk ratios compared to selective screening only: ACOG: 0.64 (95% CI 0.33 – 1.23) Universal screening: 0.45 (95% CI 0.18 – 1.12)
Limitations and other comments	
• **Limitations**	Even though they used subgroups to explore differences in way of risk factors and term delivery (not extracted separately here) they did not add this into their risk ratio analysis. Pre-term delivery rate seems quite large. Since it is a retrospective design over a long time period we cannot rule out that other factors and changes over time have contributed to these results.

Table 110 – Screening for GBS: Evidence table of observational study (Main & Slage, 2000)

Prevention of early-onset invasive neonatal group B streptococcal disease in private hospital setting: The superiority of culture-based protocols. Main & Slage, 2000[25]			
Methods			
• **Design**	Prospective cohort		
• **Source of funding and competing interest**	Not stated		
• **Setting**	A large *private* tertiary care hospital in San Francisco, USA		
• **Sample size**	Baseline – N = 6829; American College of Obstetricians and Gynecologists risk based prevention (ACOG) – N = 13,270; Centers for Disease Control and Prevention universal screening – N = 9304		
• **Duration and follow-up**	Data were collected between January 1992 and December 1998; evaluation of streptococcal infection in neonates was carried out within the first 7 days after birth.		
• **Statistical analysis**	Comparison of categorical variables was done with chi-squared analysis (with the Yates correction where appropriate). The rate of early-onset infections was calculated for each treatment strategy and presented as the incidence per 1000 births. Odds ratios were not calculated because of the 0 rates for some time periods.		
Patient characteristics			
• **Eligibility criteria**	Pregnant women who delivered babies during these time periods		
• **Exclusion criteria**	None explicitly stated		
• **Patient & disease characteristics**	The following characteristics are described - N(%) unless otherwise specified (*p<0.05, **p<0.001):		
		Baseline N=6829	ACOG screening N=13,270	Universal screening N=9304
	Delivery < 37 wks	704 (10.3)	1,289 (9.7)	951 (10.2)
	Mothers delivered	6719	12,960	9078
	Race:			
	White	2964 (44.1)	7102 (54.8)	5047 (55.6)
	Asian	3053 (45.4	5108 (40.6)	3651 (40.2)
	African American	450 (6.7)	536 (4.1)	318 (3.5)

	Other	262 (3.9)	56 (0.5)	62 (0.7)
	Parity:			
	Nulliparous	3336 (49.6)	6942 (53.6)	4843 (53.3)
	Parous	3383 (50.4)	6018 (46.4)	4235 (46.7)
	Age:			
	≤20 yrs	169 (2.5)	197 (1.5)	120 (1.3)
	21 – 35 yrs	5024 (74.8)	9555 (73.7)	6563 (72.3)
	≥ 36 yrs	1526 (22.7)	3208 (24.8)	2395 (26.4)
	Prenatal care initiation ≤14 wk	6524 (97.1)	13044 (98.3	8978 (96.5)

Interventions	
• **Intervention group**	Universal screening according to the Centers for Disease Control and Prevention protocol
• **Control group**	Risk based screening according to the American College of Obstetricians and Gynaecologists Baseline screening: A variety of less organised approaches used for Group B Streptococcal prophylaxis with an emphasis on antibiotic treatment of preterm labour and intrapartum fevers.
Results	
• **Early onset group B streptococcal**	Defined as blood or cerebrospinal fluid culture positive for group b streptococci within the first 7 days after birth. Universal screening: 0/9304 ACOG protocol: 15/13270 (1.1 per 1000) Baseline rate: 8/6829 (1.1 per 1000)
Limitations and other comments	
• **Limitations**	No account of any confounding factors, for instance it is unclear how many women had risk factors. The main observation is that compared to the similar study by Locksmith et al. (1999) above, baseline characteristics are very different. This could be due to the 'private' hospital environment that the data were collected from (maybe more affluent area). It is therefore a little difficult to say how much could be extrapolated from this data.

Table 111 – Screening for GBS: Evidence table of observational study (Puopolo et al., 2005 and groups from an earlier study from the same research group (that is referenced in the study Chen et al., 2001)

Early-onset group B streptococcal disease in the era of maternal screening. Puopolo et al., 2005[26] and No increase in rates of early-onset neonatal sepsis by non-group B Streptococcus or ampicillin-resistant organisms. Chen et al., 2001[39]	
Methods	
• **Design**	Retrospective cohort
• **Source of funding and competing interest**	National Institute of Health grant and a grant from the Children's Hospital Boston Office of Faculty Development.
• **Setting**	Brigham and Women's Hospital, Harvard Medical School Boston, USA
• **Sample size**	Baseline N = 25,934 (1990 to 1992), Risk based prophylaxis N = 34,262 (1993 – 1996) and Universal screening N = 67,260 (1997 – 2003)
• **Duration and follow-up**	Until neonatal GBS sepsis could be determined (presumably within 7 days)
• **Statistical analysis**	Time trend analysis using the Mantel-Haenszel test.
Patient characteristics	
• **Eligibility criteria**	All live births recorded during between the years 1990 and 2003 in the hospital
• **Exclusion criteria**	None explicitly stated
• **Patient & disease characteristics**	No table with demographic characteristics is provided in either the earlier or the later publication. In the earlier paper the rate of preterm birth is provided which was 8.9% in the baseline cohort and 8.7% in the risk based prophylaxis group. It is also stated that there were no significant differences in with regards to ethnicity and insurance status. The later publication describes the rates of very low birth weight (birth weight 400 – 1499 g). However, the overall low birth weight rate is only provided for the last (universal screening) cohort (1502/67260 or 2.2%). For the earlier cohorts only the rate of GBS infection in low birth cohorts was provided but not the actual rate.
Interventions	
• **Intervention group**	Universal screening according to the Centre for Disease Control and Prevention (CDC) guidelines.
• **Control group**	Risk based prophylaxis according to the American College of Obstetrics and Gynecology (ACOG) guidelines Baseline (without GBS prophylaxis)
Results	
• **Early onset sepsis (EOS):**	Definition of outcome: A complete blood count white blood cell count differential and blood culture were obtained if the infant was judged at significant risk for EOS on the basis of a variety of clinical risk factors including maternal GBS colonisation, inadequate IAP, maternal intrapartum fever, duration of rupture of membranes, clinical diagnosis of chorioamnionitis, preterm delivery, multiple gestation, sustained fetal tachycardia, and the mother having had a previous infant with GBS disease. A lumbar puncture was not performed as part of the routine evaluation for sepsis in well-appearing infants. Universal screening: 25/67260 (0.37 per 1000) Risk based prophylaxis: 90/34262 (2.6 per 1000) No GBS prophylaxis: 99/25934 (3.8 per 1000)

Limitations and other comments	
• **Limitations**	No details on baseline characteristics were provided and no multivariable analysis was carried out. The data were collected retrospectively a method which is inherently more biased than prospective designs. Over such a long time period many other chances would have occurred that may have influenced these results (such as rate of uptake of screening and other demographic or clinical factors.

Table 112 – Screening for GBS: Evidence table of observational study (Reisner et al., 2000)

Performance of a group B streptococcal prophylaxis protocol combining high-risk treatment and low-risk treatment. Reisner et al., 2000[27]	
Methods	
• **Design**	Prospective cohort study compared to a historic control group
• **Source of funding and competing interest**	Not stated
• **Setting**	Level III community hospital, Seattle, USA
• **Sample size**	Before screening protocol (no consistent GBS prophylaxis) N = 8188, Screening protocol N = 9932
• **Duration and follow-up**	Unclear but presumably until neonatal outcomes could be ascertained through microbiologic cultures.
• **Statistical analysis**	2 tailed Fisher exact test and chi-squared tests.
Patient characteristics	
• **Eligibility criteria**	All women giving birth in the hospital (prospectively collected between Feb 1994 through Jan 1997 compared to the 2 years preceding this time period)
• **Exclusion criteria**	None explicitly stated
• **Patient & disease characteristics**	Demographic characteristics were only described for the prospective sample. It is stated that the population consisted mostly of white, married, insured women. The authors write that twenty-eight percent of women were minorities, 21% were funded by public assistance, and only 3% were <19 years of age.
Interventions	
• **Intervention group**	Universal screening: High risk women were provided with intrapartum chemoprophylaxis and low-risk women were screened and if positive were treated (it is unclear at which gestational week they were screened) by using a rapid immunoconcentration assay method. After the first year of the protocol the rapid test was changed to an optical immunoassay test because of its improved performance at equivalent cost.
• **Control group**	Before 1994 women with asymptomatic preterm labour, women with prolonged rupture of membranes and carriers of group B streptococci were not consistently prophylactically treated during labour.
Results	
• **Group B neonatal sepsis: Culture positive**	Definition: It is described that neonatal outcomes were tracked through microbiologic cultures and cross-checked with the special care nursery database. All cases of neonatal sepsis were ascertained during the 36 months of the protocol. Universal screening and prophylaxis: 2/9932 (0.2 per 1000) Inconsistent prophylaxis: 9/8188 (1.1 per 1000)

Limitations and other comments	
• **Limitations**	There are two main limitations. One is the representativeness of the population and it is also unclear whether demographic characteristics differed between the earlier and later cohort. The other is that the screening method was changed after one year with the first rapid screening methods most likely having lower levels of sensitivity than the later protocol.

Table 113 – Screening for GBS: Evidence table of observational study (Renner et al., 2006)

Efficacy of a strategy to prevent neonatal early-onset group B streptococcal (GBS) sepsis. Renner et al., 2006[28]	
Methods	
• **Design**	Before and after study (retrospective)
• **Source of funding and competing interest**	Not stated
• **Setting**	University Women's Hospital Basel, Switzerland
• **Sample size**	Screening group: N=9,385 and No screening group: N=16,126
• **Duration and follow-up**	Data collected over a 12 year period
• **Statistical analysis**	Risk ratios and confidence intervals were calculated and further statistics were the chi-squared and the Fisher's exact tests (the latter when the expected cell value was less than 5).
Patient characteristics	
• **Eligibility criteria**	All live births at the hospital between 1997 and 2002 compared to a group of live births during the years 1984-1993 (but it is not explicitly stated whether these data were all live births collected at the same hospital)
• **Exclusion criteria**	None explicitly stated
• **Patient & disease characteristics**	Baseline characteristics not explicitly described
Interventions	
• **Intervention group**	Universal GBS screening at 35-37 weeks gestation (swab taken from the lower third of the vagina and processed using selective broth medium), risk factor detection and administration of intrapartum antibiotic prophylaxis (IAP) in the presence of GBS or unknown colonization plus an additional risk factor, or in case a previous child had contracted GBS sepsis. Risk factors were: Rupture of membrane > 12 hours, delivery < 37 weeks, maternal intrapartum sings of infection (≥38°C), CRP ≥20 mg/L, Leukocytosis ≥18,000/µL, or persistent fetal tachycardia.
• **Control group**	No screen and no routine intrapartum antibiotic prophylaxis
Results	
• **Early onset neonatal sepsis (EONS)**	Outcome definition: A positive blood culture with clinical symptoms appearing within 7 days postpartum. Bacterial identification was established according to the Manual of Clinical Microbiology following the NCCL Guidelines of susceptibility testing. Screening and IAP: 5/9385 (0.53 per 1000) No screening or routine IAP: 16/16126 (1 per 1000)
• **Mortality due to EONS**	Screening and IAP: 0/9385

	No screening or routine IAP: 1/16126 (0.06 per 1000)
Limitations and other comments	
• **Limitations**	It is unclear whether possibly other factors could have accounted for the group differences because confounders were considered in the analysis. The authors acknowledge that it was impossible to extract the percentage of GBS screened women and the prevalence of GBS among the study population.

Table 114 – Screening for GBS: Evidence table of observational study (Schrag et al., 2013, Centre for Disease Control and Prevention, 2009, Schrag et al., 2002, Schrag et al., 2002a, and Schrag et al., 2000)

Intrapartum antibiotic prophylaxis for the prevention of perinatal group B streptococcal disease: Experience in the United States and implications for a potential group B streptococcal vaccine. Schrag et al., 2013[3, 29, 40, 41, 103]	
Methods	
• **Design**	Population based multi-center retrospective cohort study
• **Source of funding and competing interest**	The Office of Women's Health of the US Centre for Disease Control and Prevention (CDC) and by the Antimicrobial Resistance Program and the Emerging Infections Program of the National Center for Infectious Diseases.
• **Setting**	Records of hospital births in eight geographical areas in the USA.
• **Sample size**	A stratified random sample of an overall 629,912 live births: Screened group (N=2628) ; risk based group (N=2515) from Schrag et al., (2002)[82]
• **Duration and follow-up**	Until early onset group B streptococcal infection could be identified
• **Statistical analysis**	The risk of early onset disease in the screened group relative to the risk-based group was evaluated by univariate and multivariable models in which the disease status of the infant was the dependent variable. All variables that were associated with disease at a significance level of less than 0.15 in univariate models, as well as variables identified in previous studies as risk factors for early onset disease were considered in multivariable models. The final multivariable model included main effects with a significance level of less than 0.05. All two way interactions of main effects were evaluated.
Patient characteristics	
• **Eligibility criteria**	Stratified (according to surveillance area, the year, and the birth hospital) random samples from of births from birth-registry data. Random samples were taken from 629,912 live births in 1998 and 1999 in eight geographical areas where there was active surveillance for group B streptococcal infection. At least 500 births were selected per surveillance area to allow for accurate area-specific estimates.
• **Exclusion criteria**	Surveillance area hospitals with fewer than 10 births per year.
• **Patient & disease characteristics**	Differences in baseline characteristics (percent) between screened and risk-based groups (*p<0.05; **p<0.001)

	Screened Group (N = 2628)		Risk-Based Group (N = 2515)	
Ethnic Group**				
Non-Hispanic		93.1		87.5
Hispanic	8.7			12.5
Prenatal Care**				
> 1 prenatal visit	99.4			97.1
Prenatal record in chart		97.6		92.7

Adequacy of prenatal care**		
Inadequate	11.2	19.4
Intermediate	28.7	33.9
Adequate	60.1	46.7
Preterm delivery**	7.1	14.0
Prevalence of group B streptococcal bacteriuria*	3.4	1.9
Previous infant with group B streptococcal disease*	0.5	0.2

Interventions	
• **Intervention group**	Screening approach: Women are screened for carriage of group B streptococcus between 35 and 37 weeks of gestation and intrapartum chemoprophylaxis is offered to carriers.
• **Control group**	Risk based approach: Women presenting at the time of labour with clinical risk factors for disease transmission (including fever, a prolonged interval between rupture of the membranes and delivery or preterm delivery) are offered antibiotic prophylaxis
Results	
• **Early-Onset Group B Streptococcal Disease**	Using all cases in the 629,912 sample (N=312) Univariate analysis: RR 0.48 (95% CI 0.38 to 0.61) Multivariable analysis: Adjusted RR 0.46 (95% CI 0.36 to 0.60)
• **Time trend analysis**	Schrag et al., (2013) describe in a review of the longitudinal ongoing cohort study that there was a decrease by more than 80% from 1.8 cases/1000 in the 1990s to 0.26 cases/1000 in 2010 during this time universal screening was implemented (2001). Raw data are updated on the Active Bacterial Core surveillance database (from the Centre for Disease Control and Prevention website, but were not provided in the publication (only rates per 1000).
Limitations and other comments	
• **Limitations**	This is a well conducted study which adjusted for a lot of possible confounders (such as intrapartum fever, having previously had an infant with group B streptococcal disease, medicaid payment, group B streptococcal bacteriuria, preterm delivery, prolonged interval between membrane rupture and delivery, inadequate prenatal care, black race, and maternal age < 20 years). However, as with all observational studies we cannot rule out that other factors apart from those selected may have accounted for the differences over and above those already taken into consideration.

Table 115 – Screening for GBS: Evidence table of observational study (Share et al., 2001)

Implementation of guidelines for preventing early onset group B streptococcal infection. Share et al., 2001[42]			
Methods			
• **Design**	Retrospective cohort study		
• **Source of funding and competing interest**	Not stated		
• **Setting**	University Hospitals of Cleveland, USA		
• **Sample size**	Before implementation of universal screening N = 7531; Universal screening N = 7180		
• **Duration and follow-up**	GBS infection was ascertained during the first 72 hours of life		
• **Statistical analysis**	Chi-squared analysis and Fisher's exact test.		
Patient characteristics			
• **Eligibility criteria**	Women who delivered infants at the hospital in the time period from 1995 to 1997		
• **Exclusion criteria**	None specifically stated		
• **Patient & disease characteristics**	The following characteristics are described - N(%) unless otherwise specified. Maternal demographics were only reported from a subset of the sample:		
		Baseline N=7531	Universal screening N=7180
	Maternal demographics from subsample	N = 576	N = 1135
	Race:		
	White	347 (60.2)	596 (44.7)
	Black	213 (37)	498 (53.4)
	Other	9 (1.6)	10 (1)
	Unreported	7	11
	Age:		
	≤20 yrs	169 (2.5)	120 (1.3)
Interventions			
• **Intervention group**	Intrapartum prophylaxis provided to women with risk factors and women known to be GBS colonized determined by screening culture at 35 to 37 weeks of gestation. In this group 84.7% were screened.		
• **Control group**	Before institutional implementation of the screening protocol (details of why 53.3% of women in this group were screened were not provided)		
Results			
• **GBS sepsis**	Defined using a chart review of infants less than or equal to 72 hours of age and identified to be GBS culture positive by the microbiology lab at the hospital. Universal screening: 7/7180 (0.97 per 1000) Prior to implementation: 20/7531 (2.7 per 1000)		

	For a further third time period (1998-1999) outcome data, but not demographic data: 2 years after implementation: 3/7194 (0.4 per 1000)
Limitations and other comments	
• **Limitations**	There are limited demographic details and those are also only reported for a subgroup of women. It is unclear why a third group was later added for which no demographics were collected and apart from the GBS sepsis rate no other data were reported from this additional group. Other risks of bias with regards to retrospective data collection (such as reporting biases, completeness of data etc) and univariate analyses methods (no adjustment for possible confounding factors) also apply.

Table 116 – Screening for GBS: Evidence table of observational study (Vergani et al., 2002)

Impact of different prevention strategies on neonatal group B streptococcal disease. Vergani et al., 2002[30]	
Methods	
• **Design**	Retrospective cohort study
• **Source of funding and competing interest**	Not stated
• **Setting**	San Gerardo University Hospital, Monza, Italy
• **Sample size**	Historic controls N = 8 573; Risk Factors prophylaxis N = 10,303; Universal Screening N=13,754 (at 26-28 weeks N = 7 602 and at 35-37 weeks N = 6 152)
• **Duration and follow-up**	Data were collected between 1991-1999 with a historic sample 1987-1990
• **Statistical analysis**	Chi-squared tests and Odds ratio analysis
Patient characteristics	
• **Eligibility criteria**	All maternal and neonatal charts recorded during this time period
• **Exclusion criteria**	None specifically stated
• **Patient & disease characteristics**	The following characteristics are described - N(%) unless otherwise specified (demographics described for the combined universal screening group only and not divided into the two subgroups – below only those cases screened at 35-37 weeks gestation are presented to make this group comparable to the other studies of universal screening):

	Baseline N=8573	ACOG screening N=10,303	Universal screening N=13,754
Time period	1987-1990	1991-1994	1995-1999
Clinical risk factors[a]	1397 (16.3)	1732 (16.8)	2182 (15.9)
Nulliparae	4900 (57)	6223 (60)	8114 (59)
Maternal age (years):			
<20	48 (1)	62 (1)	82 (1)
20-35	7043 982)	8356 (81)	10,728 (78)
>35	1482 (17)	1885 (18)	2943 (21)

[a] Including preterm labour at < 37 weeks, rupture of membranes >12 hours, maternal fever >37.5°C, maternal urinary infection with GBS during the index pregnancy, or previous pregnancy complicated by neonatal GBS infection.

Interventions	
• **Intervention group**	Universal screening: Along the lines of the American guidelines (such as the Centre for Disease Control and Prevention). Cultures from the distal vagina and anus were obtained with a Dacron swab plated onto a Columbia colistin-nalidixic acid agar plate and then inoculated into selective broth medium (in the subgroup we will report this was carried out at 35-37 weeks gestation). Women with positive cultures or with risk factors (see footnote in table above) received antibiotic prophylaxis.
• **Control group**	Historic control: No specific screening or antibiotic prophylaxis protocol Risk Factor prophylaxis: Women with risk factors received antibiotic prophylaxis
Results	
• **Early onset GBS morbidity – culture positive**	Definition of outcome: The presence of GBS sepsis, pneumonia during the initial 7 days of life and meningitis. GBS sepsis was defined as a positive blood culture accompanied by two or more of the following inflammatory indices: ratio of bands to total neutrophils ≥20%, white blood cell count >20,000/mL or <5000 mL, and C-reactive protein > 1.5 mg/dl. Meningitis was defined as a positive culture results of the cerebro-spinal fluid. Diagnosis of pneumonia was based on the characteristic radiologic pattern in neonates with positive blood cultures or with positive auricular or pharyngeal cultures accompanied by inflammatory indices. Cases of clinical suspicion of sepsis in the absence of positive cultures were not included in the analysis. Universal screening (35-37 wks gestation): 3/6152 (0.5 per 1000) Risk factor prophylaxis: 8/10303 (0.8 per 1000) Historic control: 8/8573 (0.9 per 1000)
• **GBS related mortality**	Universal screening (35-37 wks gestation): 0/6152 (0 per 1000) Risk factor prophylaxis: 1/10303 (0.1 per 1000) Historic control: 4/8573 (0.5 per 1000)
Limitations and other comments	
• **Limitations**	The analysis does not take into account possible confounding factors that may influence the results. Otherwise all other limitations with regards to observational studies apply.

Table 117 – Screening for GBS: Evidence table of observational study (Voluménie et al., 2001)

Neonatal group B streptococcal infection: Results of 33 months of universal maternal screening and antibioprophylaxis. Voluménie et al., 2001[31]	
Methods	
• **Design**	Retrospective cohort study with historic control group
• **Source of funding and competing interest**	Not stated
• **Setting**	One tertiary perinatal centre, Clarmart Cedex, France
• **Sample size**	Universal screening group N = 5374 (collected between 1994 – 1996) comparison with a group consisting of deliveries of years 1992 and 1993. However only rates of GBS are provided for the control group rather than the number of cases and total numbers of deliveries.
• **Duration and follow-up**	Unclear (various time-points are described in the study such as 7 and 10 day antibiotic treatment)

• **Statistical analysis**	Chi-squared analysis.
Patient characteristics	
• **Eligibility criteria**	All pregnant women attending prenatal care in the hospital.
• **Exclusion criteria**	None stated
• **Patient & disease characteristics**	Demographic or other baseline characteristics not described
Interventions	
• **Intervention group**	Universal screening: Screening was performed between 35 and 37 weeks gestation by a single vaginal swab. Vaginal specimens were collected without speculum by sweeping a sterile ryon-tipped swab in the lower third of vagina. Swabs were inoculated onto a 5% sheep blood Agar plate. The plate was then incubated at 37°C in an anaerobic atmosphere and screened for the presence of haemolytic Streptococci after 24 hours. Negative plates were further incubated a reexamined after 48 hours. The presence of group B Streptococci was confirmed by latex agglutination testing.
• **Control group**	Described as the time preceding the protocol, but it is unclear how at risk pregnant women were dealt with.
Results	
• **'Infected'**	Described as infants with clinical or biological signs of GBS infection. This rather than colonisation was used because during the study time GBS was not systematically ascertained in neonates born from non-infected mothers: Universal screening: 46/5374 (0.86% of term births) Incidence of neonatal infection in the two preceding years was 1.3% in 1992 and 1.4% in 1993
Limitations and other comments	
• **Limitations**	This study lacks a lot of detail. Demographics are not described and the numbers in the control group are unclear. The definition of outcome is also vague and does not ascertain whether the cases of 'infected' neonates actually are colonised with GBS. Hence the much higher rate of infection compared to other studies.

9.5. Gestational diabetes

9.5.1. Universal screening vs. selected screening of gestational diabetes

Table 118 – Screening for gestational diabetes: Evidence table (Bebbington et al., 1999)

A randomised controlled trial comparing routine screening vs. selected screening for gestational diabetes in a low risk population. Bebbington, Milner, Wilson and Harris, 1999[43]	
Methods	
• **Design**	Randomised controlled trial – abstract only, no full text available.
• **Source of funding and competing interest**	NR
• **Setting**	British Colombia Women's Hospital, Canada
• **Sample size**	n=2401; routine screening n=1197, selected screening n=1204
• **Duration and follow-up**	NR
• **Statistical analysis**	Group comparisons were made using the chi squared test.
Patient characteristics	
• **Eligibility criteria**	Low risk pregnancy
• **Exclusion criteria**	Any of the usual risk factors for gestational diabetes
• **Patient & disease characteristics**	NR
Interventions	
• **Intervention group**	Routine testing group (n=1197). All women received a 50g glucose screen. A 100g glucose tolerance test was carried out on those women who had a 1 hour glucose of >7.8mmol/l on 50g screening. Treatment: Women who had a positive glucose tolerance test (2 abnormal values) were referred to the Pregnancy and Diabetes Programme at BCWH for management.
• **Control group**	Selected screening (n=1204). Only tested if selected indication arose during pregnancy (no further details provided). For those that were screened the same testing strategy was used as the routine testing group. Treatment as described above.
Results	
• **Macrosomia**	Outcome description: macrosomia defined as birth weight = 4000g Routine screening group: 143/1197 (11.96%) Selected screening group: 139/1204 (11.54%) *p* = 0.796
Limitations and other comments	
• **Limitations**	This is a research abstract only; no access to any full text was discovered. There is very little data from which to make sufficient conclusions. It is especially hard to know what 'selected indicators during pregnancy' they considered to warrant screening.

	Attrition: Outcomes reported as percentages only where denominators have to be assumed to be original allocation population despite authors reporting that complete data is missing for 18 women who were lost to follow-up. Details of their original group allocation and presence or absence in final analyses are unclear.

Table 119 – Screening for gestational diabetes: Evidence table (Davis et al., 2013)

A threefold increase in gestational diabetes over two years: review of screening practices and pregnancy outcomes in Indigenous women of Cape York, Australia. Davis, Mclean, Sinha and Falhammar, 2013[44]	
Methods	
• **Design**	Retrospective before and after cohort study.
• **Source of funding and competing interest**	Clinical Practice Improvement Centre of Queensland Health, Australia
• **Setting**	All Indigenous pregnant women from Cape York who receive antenatal care mainly from outreach teams from Cairns Base Hospital and routinely delivered at Cairns Base Hospital.
• **Sample size**	Universal screening intervention group (2008), n = 134. Non-universal screening control group (2006), n = 127.
• **Duration and follow-up**	Two time periods. 1 January to 31 December 2006 and 1 January to 31 December 2008 (universal screening introduced in 2007)
• **Statistical analysis**	Group comparisons were made using the chi squared test, or Fisher's exact test if the frequency was small.
Patient characteristics	
• **Eligibility criteria**	All indigenous pregnant women from Cape York who had medical records at Cairns Base Hospital.
• **Exclusion criteria**	None stated.
• **Patient & disease characteristics**	Prevalence of diabetes in pregnancy rose from 7.1% (9/127) in 2006 to 16.4% (22/134) in 2008 (*p*=0.033). In 2006 (non-universal screening): • 7.1% (9/127) of women were not screened at all, • 54.3% (69/127) received random blood glucose only, • 7.1% (9/127) a glucose challenge test and • 31.4% (40/127) of women had an oral glucose tolerance test. In 2008 (universal screening): • 11.9% (16/134) had no screening at all, • 21.6% (29/134) were tested with a random blood glucose only, • 0.7% (1/134) with a glucose challenge test and, • 65.6% (88/134) with an oral glucose tolerance test. No other descriptive statistics are reported with respect to screening comparison.
Interventions	
• **Intervention group**	Universal testing (n=134) of all indigenous women using the 75g oral glucose tolerance test at 26-30 weeks (instead of 24-28 weeks, see below). Diagnosis threshold of 2h ≥8.0mmol/L This policy was introduced in 2007. The intervention group were all indigenous women from 2008. Treatment: no information on treatment reported.

• **Control group**	Non-universal screening (n=127) The Primary Clinical Care Manual guidelines were used to screen for gestational diabetes in Cape York in 2006. Based on similar screening protocols from other high-risk populations a random blood glucose level was undertaken at each visit and if the level was ≥5.0mmol/L, fasting blood glucose was performed. At 24 weeks, a random blood glucose was performed again, and if ≥5.0mmol/L or pregnancy 'at risk' of gestational diabetes, a 75g oral glucose challenge test was performed. An 'at risk' pregnancy included age >35 years, obese (BMI >35), previous baby >4.0kg, previous neonatal hypoglycaemic episode, unexplained recurrent miscarriage, stillbirth, neonatal death, family history of diabetes and past history of gestational diabetes. If normal, the oral glucose tolerance test was to be repeated at 32 weeks. This policy changed in 2007. The comparison group were all indigenous women from 2006. Treatment: no information on treatment reported.
Results	
• **Large for gestational age**	Outcome description: LGA defined as >90th percentile Universal screening group: 9/134 (6.7%) Non-universal screening group: 7/127 (5.5%) *p* = not reported for this comparison
• **Macrosomia**	Outcome description: macrosomia defined as >4000g Universal screening group: 8/134 (5.9%) Non-universal screening group: 2/127 (1.6%) *p* = not reported for this comparison
• **Respiratory distress**	No additional description supplied. Universal screening group: 4/134 (2.9%) Non-universal screening group: 11/127 (8.7%) *p* = not reported for this comparison
• **Neonatal hypoglycaemia**	No additional description supplied. Universal screening group: 18/134 (13.4%) Non-universal screening group: 12/127 (9.4%) *p* = not reported for this comparison
• **Congenital abnormality/ stillbirth and neonatal death**	Described narratively only in the text as "uncommon in all groups in both time periods".
Limitations and other comments	
• **Limitations**	The definition of their population pre-universal screening is slightly unclear. It does not seem to be based solely on risk-factor assessment. It is also unclear whether both the before and after groups are considered high-risk due to their focus on indigenous population. Outcome reporting: serious perinatal outcomes of congenital abnormalities, stillbirths and neonatal deaths are only described in the text with no raw data presented for analysis.

Table 120 – Screening for gestational diabetes: Evidence table (Dietrich et al., 1987)

Gestational diabetes screening in a private, Medwestern American population. Dietrich, Dolnicek and Rayburn, 1987[45]	
Methods	
• **Design**	Prospective cohort
• **Source of funding and competing interest**	None reported
• **Setting**	A private Midwestern prenatal clinic, United States of America
• **Sample size**	Groups were formed from consecutive women depending on the physicians providing care. The women in the first five physician groups underwent routine diabetes screening (n=1000). Those in the other five physician groups underwent diabetes screening selectively only in the presence of standard risk factors (n=1000).
• **Duration and follow-up**	Between October 1983 and April 1985.
• **Statistical analysis**	Group comparisons were made using the chi squared test.
Patient characteristics	
• **Eligibility criteria**	Consecutive women attending the private prenatal clinic.
• **Exclusion criteria**	None reported.
• **Patient & disease characteristics**	None of the patient characteristics differed significantly between the two groups: Maternal age (years): universal screening 25; selective screening 24 Obesity (%): universal screening 30; selective screening 28 Strong family history of diabetes (%):universal screening 15; selective screening 14
Interventions	
• **Intervention group**	Routine diabetes screening (n=1000). Testing began between 24-28 weeks gestation. Determination of a maternal serum glucose level 1 hour after ingestion of a 50g glucose challenge with a commercially prepared solution 9fasting state not required). A level of ≥50 mg/dl was considered abnormal and required definitive evaluation with a 3 hour glucose tolerance test within 1 week. The usual 100g oral glucose challenge test was used. Standard criteria for an abnormal result involved two or more elevated glucose values (fasting >105mg/dl; 1 hour >195 mg/dl; 2 hours >145mg/dl; and 3 hours >130 mg/dl). Treatment: Patients with abnormal 3 hour glucose tolerance test results were referred for diabetic dietary counseling. They were evaluated at least every 2 weeks, then weekly during the last trimester. Fasting and 2 hour post-prandial glucose values were obtained at each prenatal clinic visit.
• **Control group**	Selective screening (n=1000) based on standard risk factors. These included a maternal age >30 years, obesity (20% above ideal body weight), first-degree family history of diabetes, poor obstetric history (habitual abortions, previous anomalous infant, previous preterm delivery), previous macrosomic infant (≥4000g), or persistent glycosuria. Screening began as early as conveniently possible. Testing and treatment programmes were the same as the universal screening intervention group.
Results	
• **Infant birth weight ≥4000g**	Reported narratively: “not significantly different between the routine and select screening groups”
• **Perinatal deaths**	Reported narratively: “not significantly different between the routine and select screening groups”

Limitations and other comments	
• **Limitations**	Incomplete outcome reporting: No raw data provided and perinatal outcomes are only referred to narratively in terms of significance in the text. It is also unclear if the percentages offered in the text use the full population as the denominator or only those diagnosed with gestational diabetes.

9.5.2. Early risk-factor vs. late non-risk factor screening.of gestational diabetes

Table 121 – Screening for gestational diabetes: Evidence table (Dong 1993)

Value of early glucose tolerance testing in women who had gestational diabetes in their previous pregnancy. Dong, Beischer, Wein and Sheedy, 1993[47]	
Methods	
• **Design**	Retrospective cohort
• **Source of funding and competing interest**	Mercy Maternity Hospital Research Foundation and the Victorian Health Promotion Foundation
• **Setting**	Mercury Hospital for Women, Australia
• **Sample size**	n=1027 consecutive pregnant women with single deliveries and at risk for gestational diabetes on the basis of a previous gestational diabetes diagnosis during a past pregnancy.
• **Duration and follow-up**	February 1971 to October 1992.
• **Statistical analysis**	Group comparisons were made using the chi squared test, Fisher exact probability, McNemar test and Student *t* test as appropriate.
Patient characteristics	
• **Eligibility criteria**	Pregnant women who had gestational diabetes diagnosed in their previous pregnancy.
• **Exclusion criteria**	Women who had diabetes mellitus diagnosed at the postnatal visit or at a subsequent gestational diabetes follow-up testing prior to the subsequent pregnancy (of interest for this study) were excluded. Women with multiple pregnancies and those who delivered before 20 weeks gestation.
• **Patient & disease characteristics**	Patient characteristics only presented for those who received early screening. However it is noted by authors that the women in the early screening group had more severe glucose intolerance in their first gestational diabetes pregnancy that the late testing women did. Therefore it is possible that the baseline characteristics in the two groups were not comparable. This is concerning as there is no information detailing why the women were allocated to early or late screening (see limitations row below).

Interventions	
• **Intervention group**	Early screening (n=180): Testing before 24 weeks gestation. Hospital policy to perform a 3 hour glucose tolerance test on all pregnant women at 26-30 weeks (glucose load not defined). When earlier glucose tolerance testing is performed because of gestational diabetes in a previous pregnancy, an appointment is made at the first antenatal visit for the test to be performed at the next visit in 4-6 weeks times, in some women this is performed at a later visit but for the purpose of this study, early was defined as before 24 weeks gestation. If an early glucose tolerance test is normal then policy is to repeat the test at 30 weeks gestation. Gestational diabetes was diagnosed by the combination of a 1 hour glucose value of 9.0mmol/L or above and a 2 hour value of 7.0mmol/L or above. The condition was designated as severe when the 1 hour glucose value was 10.0mmol/L or above in addition to a 2 hour value of 7.89mmol/L or above. Treatment: Most patients with gestational diabetes received nutritional counseling regarding the importance of a modified carbohydrate diet. If they had severe gestational diabetes they were referred to a diabetes nurse educator for instruction regarding home blood glucose monitoring and were lent a blood glucose meter for the duration of their pregnancy. Insulin therapy was recommended if 2 hour post-prandial blood glucose levels were ≥6.5mmol/L on 2 or more occasions. Incidence of recurrent gestational diabetes: 49.4% (89/180)
• **Control group**	Late/usual screening (n=685): Testing only after 24 weeks gestation. Testing and treatment the same as in the early screening intervention group. Incidence of recurrent gestational diabetes: 34% (233/685).
• **Third group not included in current review**	Those who were not tested in their subsequent pregnancy (n=162). Inspection of the case notes showed that the reason for failure to test were delivery before 30 weeks gestation (12), initial attendance after 34 weeks gestation (69), failure to keep the appointment for the glucose tolerance test (65) and administrative failure i.e. glucose tolerance test not ordered (16).
Results	
• **Macrosomia**	Outcome description: macrosomia defined as birth weight ≥ 90th percentile. Early screening group: 27/180 (15%) Late/usual screening group: 124/685 (18.1%) *p* = not reported for this comparison
• **Preeclampsia**	No additional description supplied. Early screening group: 13/180 (7.2%) Late/usual screening group: 33/685 (4.8%) *p* = not reported for this comparison
• **Perinatal mortality rate**	No additional description supplied. Early screening group: 4/180 (2.2%) Late/usual screening group: 4/685 (0.6%) *p* = not reported for this comparison
• **Major malformations**	No additional description supplied. Early screening group: 5/180 (2.8%) Late/usual screening group: 21/685 (3.1%)

	p = not reported for this comparison
• **Diabetes mellitus at follow-up**	No additional description supplied. Early screening group: 24/150 (16.0%) Late/usual screening group: 2/483 (8.1%) *p* < 0.01
Limitations and other comments	
• **Limitations**	This comparison does not truly reflect risk factor screening vs. universal screening, but rather both groups represent what risk factor screening would look like and the comparison of non-risk factor screening is not present. This has been accounted for as indirectness in the quality appraisal. Outcome reporting: Outcomes reported as percentages only – denominators have to be assumed to be original allocation population, except for the diabetes mellitus at follow-up as percentages of participants followed up is presented.

Table 122 – Screening for gestational diabetes: Evidence table (Jovanovic 1985)

Screening for gestational diabetes: optimum timing and criteria for retesting. Jovanovic and Peterson, 1985[48]	
Methods	
• **Design**	Prospective cohort
• **Source of funding and competing interest**	None reported
• **Setting**	Private practice specialising in low risk pregnancies in New York City, United States of America.
• **Sample size**	n=600
• **Duration and follow-up**	Two year duration (unspecified)
• **Statistical analysis**	No statistical analysis, only raw data and percentages provided.
Patient characteristics	
• **Eligibility criteria**	Not reported
• **Exclusion criteria**	Not reported
• **Patient & disease characteristics**	Ethnicity: 80% white, 13% black, 5-6% Hispanic Age range between 20-40 year, majority (60%) were 25-29. No additional baseline characteristics described.

Interventions	
• **Intervention group**	Early screening (n=300): first 300 pregnant women were screened between 9-20 weeks gestation. 1h 50g glucose challenge test. If abnormal (≥150mg/dl) then underwent a 100g oral glucose tolerance test within two days. Blood samples were defined as abnormal if fasting >105mg/dl, 1h >195mg/dl, 2h >160mg/dl and 3h>145mg/dl. Those who did not meet the criteria for gestational diabetes were rescreened at 27-31 weeks gestation. Treatment: Not reported.
• **Control group**	Late screening (n=300): late registrants were screened for the first time (after at least 4h of fasting) between 27-31 weeks. Those women who had an abnormal glucose challenge test had a 3h glucose tolerance test performed within two days of the challenge test. Thresholds for the glucose tolerance test were the same as in the early screening intervention group. Treatment: Not reported.
Results	
• **Birth weight ≥ 4000g**	No additional description supplied. Early screening group: 32/300 (10.7%) Late factor screening group: 23/300 (7.7%) *p* = not reported for this comparison
Limitations and other comments	
• **Limitations**	Incomplete reporting: no information supplied on treatment received when gestation diabetes is diagnosed. No baseline comparability data reported.

Table 123 – Screening for gestational diabetes: Evidence table (Lapolla et al., 1995)

A screening programme for gestational diabetes in a north Mediterranean area. Lapolla et al., 1995[49]	
Methods	
• **Design**	Prospective cohort
• **Source of funding and competing interest**	None reported
• **Setting**	Family Planning Clinic's from a North Mediterranean area, Italy.
• **Sample size**	n= 490. Early risk factor screening, n=234; Late non-risk factor screening, n=256.
• **Duration and follow-up**	From 1990 to 1991.
• **Statistical analysis**	Group comparisons were made using the Student *t* test and chi squared test corrected by Yates and Fisher's exact test, as appropriate.
Patient characteristics	
• **Eligibility criteria**	All pregnant non-diabetic women receiving obstetric care at the Family Planning Clinics of the Padua district.
• **Exclusion criteria**	None reported

• **Patient & disease characteristics**	None reported with respect to our screening comparison. Only reported with respect to gestational diabetes diagnosis (see limitations row).
Interventions	
• **Intervention group**	Early risk factor screening (n=234) women with one or more risk factors for gestational diabetes including family history of diabetes mellitus, maternal macrosomia, history of diabetic tendency, maternal age ≥35 years, habitual abortions, history of toxiemia, pat or present macrosomia, unexplained stillbirths, congenital anomalies, obesity, glycosuria, past or present polyhydramnios, pyelonephritis or recurrent urinary tract infections. Women received the O'Sullivan oral glucose challenge test. The test was performed in a fasting state and a plasma glucose value of 140mg/dl was considered threshold. If positive a 3 hour 100g oral glucose tolerance test was performed and was interpreted according to Carpenter and Coustan criteria. Women at risk were tested between the 10th and 14th week of gestation and if negative repeated testing was performed at 24th to 28th weeks gestation. If still negative the test was again performed at the 32nd to 34th week gestation. Treatment: In the presence of gestational diabetes women were given a diet of 30-35kcal/kg/desirable body weight, providing sufficient calories to allow a weight gain of 9-13.6kg. Women's fasting and post-prandial plasma glucose checked twice a month. If fasting plasma glucose >5.3 and/or 1 hour post prandial plasma glucose >7.2mmol/L two or more times within a 2 week period then insulin treatment was started and checked once a week until childbirth. All women with gestational diabetes monitored their own capillary fasting and post prandial glucose levels at home using reflectometers.
• **Control group**	Late non-risk factor screening (n=256) women without risk factors. Same screening tests as above but only performed for the first time at the 24th to 28th week of gestation. No information on treatment reported.
Results	
• **Fetal mortality**	Outcome description: fetal mortality was a consequence of encephalomyelocele and hydrotorax Early risk-factor screening group: 1/234 (0.4%) Late non-risk factor screening group: 0/224 (0%) *p* = not reported for this comparison
• **Macrosomia**	No additional description supplied. Early risk-factor screening group: 35/234 (14.9%) Late non-risk factor screening group: 16/224 (7.1%) *p* < 0.01
• **Infant malformations**	Outcome description: malformations included tracheomalacia, pyloric stenosis, radius.ulna aplasia, bilateral vesicoureteral reflux, encephalomyelocele hydrothorax, severe myocardiopathy. Early risk-factor screening group: 5/234 (2.1%) Late non-risk factor screening group: 1/224 (0.4%) *p* = not reported for this comparison
• **Respiratory distress syndrome**	No additional description supplied. Early risk-factor screening group: 1/234 (0.4%) Late non-risk factor screening group: 5/224 (2.2%)

	p = not reported for this comparison
Limitations and other comments	
• **Limitations**	Baseline characteristics are presumed to not be comparable (only reported with respect to gestational diabetes diagnosis rather than our comparison of interest) as women are specifically grouped based on risk factors. Therefore this comparison does not truly reflect risk factor screening vs. universal screening, but rather both groups represent what risk factor screening would look like and the comparison of non-risk factor screening is not present. This has been accounted for as indirectness in the quality appraisal.

9.5.3. Different screening tests comparison.for gestational diabetes

Table 124 – Screening for gestational diabetes: Evidence table (Lindqvist et al., 2014)

No consensus on gestational diabetes mellitus screening regimes in Sweden: pregnancy outcomes in relation to different screening regimes 2011 to 2012, a cross-sectional study. Lindqvist, Persson, Lindkvist and Mogren[46]	
Methods	
• **Design**	Retrospective cohort
• **Source of funding and competing interest**	Umeå University and the County Council of Västerbotten.
• **Setting**	Data retrieved from the Swedish Maternal Health Care Register for 43 different Maternal Health Care Areas (MHCA) based on geographic boundaries. A consultant obstetrician and a consultant midwife are responsible for the guidelines regarding maternal and fetal surveillance and medical management within each MHCA. Local guidelines may differ between MHCA.
• **Sample size**	n=184,183 deliveries.
• **Duration and follow-up**	1 January 2011 to 31 December 2012, Sweden.
• **Statistical analysis**	Group comparisons were made using chi-squared and independent samples t-tests.
Patient characteristics	
• **Eligibility criteria**	Not reported
• **Exclusion criteria**	Not reported
• **Patient & disease characteristics**	Age, mean (range): universal screening 30 years (15-49), selective screening 8.9mmol/L 29.8 years (15-49), selective screening 10mmol/L 29.8 years (13-54), selective screening 12.2mmol/L 31.4 years (14-57). BMI, mean (range): universal screening 25.04 (13.63-55.98), selective screening 8.9mmol/L 24.99 (13.82-56.65), selective screening 10mmol/L 25.04 (13.90-62.06), selective screening 12.2mmol/L 24.11 (13.97-56.40).
Interventions	
• **Intervention group 1**	Universal screening (n=20822): 75g oral glucose tolerance test 2 hour cut-off value of 10mmol/L. Incidence of gestational diabetes 2.2% (456/20822)
• **Intervention group 2**	Selective screening (n=8634): 75g oral glucose tolerance test 2 hour cut-off value of 8.9mmol/L

	Background factors of family history of diabetes mellitus type 2, previous gestational diabetes, macrosomic infant (≥4.5kg), and B<I >30kg/m^2 were used by 81% of MHCA as indicators for oral glucose tolerance test. Other indicators were unexplained intrauterine fetal death, maternal age >35 years, and immigrant status. The most prevalent risk indicator for oral glucose tolerance test was elevated random blood glucose (8.0-9.0mmol/L) which was presented in all the MHCA using selective screening. Incidence of gestational diabetes 2.9% (252/8634)
• **Intervention group 3**	Selective screening (n=104688): 75g oral glucose tolerance test 2 hour cut-off value of 10mmol/L. Risk-factor information as described in intervention group 2. Incidence of gestational diabetes 1.4% (1494/104688)
• **Intervention group 4**	Selective screening (n=50039): 75g oral glucose tolerance test 2 hour cut-off value of 12.2mmol/L. Risk-factor information as described in intervention group 2. Incidence of gestational diabetes 0.8% (377/50039)
Results	
• **Large for gestational age**	Outcome description: calculated using Marsal's curve Universal screening (10.0mmol/L threshold): 890/20822 (4.3%) Selective screening (8.9mmol/L threshold): 382/8634 (4.4%) Selective screening (10.0mmol/L threshold): 4375/104688 (4.2%) Selective screening (12.2 mmol/L threshold): 1903/50039 (3.8%) *p* = not reported for this comparison
Limitations and other comments	
• **Limitations**	Outcome reporting: Percentages and raw numbers reported do not directly correlate. Raw numbers used to calculate the percentages based on baseline allocation population.

Table 125 – Screening for gestational diabetes: Evidence table (Meltzer et al., 2010)

Gestational diabetes mellitus screening and diagnosis: a prospective randomised controlled trial comparing costs of one-step and two-step methods. Meltzer, Snyder, Penrod, Nudi and Morin, 2010[50]	
Methods	
• **Design**	RCT cost minimisation analysis
• **Source of funding and competing interest**	Canadian Diabetes Association
• **Setting**	Royal Victoria Hospital site of the McGill University Health Center, Canada.
• **Sample size**	n=1500 subset of an original 5758. Sample size for the entire population was powered to detect a difference of 2% between study groups in the prevalence of gestational diabetes with 80% power and α=0.05 , allowing 5% attrition. Within the budget constraints for cost analyses, the initial 500 women in each group with complete cost data, who had completed the allocated test procedures, were included, as this sample was felt to be representative.
• **Duration and follow-up**	January 2001 and January 2002.

• **Statistical analysis**	Group comparisons were made using chi squared analysis.
Patient characteristics	
• **Eligibility criteria**	All pregnant women referred for gestational diabetes screening, context of universal screening at 24-28 weeks gestation, although it may be earlier in the presence of risk factors. All obstetricians were reminded of clinical practice guidelines for gestational diabetes screening, but the interpretation of the glucose test results and referral for further testing or gestational diabetes clinical care were their responsibility as usual.
• **Exclusion criteria**	Non-fasting state on arrival, significant language barrier or refused to participate.
• **Patient & disease characteristics**	No statistically significant differences were found between the study groups for all characteristics. Age, mean (SD): two-step with 100g OGTT 30.9 years (5.0), two-step with 75g OGTT 31.1 years (5.0), one-step 31.3 years (5.3). Previous gestational diabetes (%): two-step with 100g OGTT 2.4%, two-step with 75g OGTT 1.8%, one-step 1.4% Family history of gestational diabetes (%): two-step with 100g OGTT 43.2%, two-step with 75g OGTT 40.6%, one-step 43.2%
Interventions	
• **Intervention group 1**	Two-step method [50g ±100g] (n=517): 50g glucose challenge test with threshold 7.8mmol/L, then 3 hour 100g oral glucose tolerance test with threshold 8.1 mmol/L. Treatment: Initiation of insulin therapy when fasting plasma glucose exceeded 5.3mmol/: or 1 hour plasma glucose exceeded 7.8mmopl/L despite dietary therapy. Using the same glycaemic goals and a less intensive protocol, management of impaired glucose tolerance by the nutritionist also remained consistent during the study. Incidence of gestational diabetes: 18/486 (3.7%) Excluded from analysis (n=17) due to incomplete lab results and incomplete cost data.
• **Intervention group 2**	Two-step method [50g±75g] (n=518): 50g glucose challenge test with threshold 7.8mmol/L, then 2 hour 75g oral glucose tolerance test with threshold 8.9mmol/L. Treatment: as described for intervention group 1. Incidence of gestational diabetes: 18/485 (3.7%) Excluded from analysis (n=18) due to incomplete lab results and incomplete cost data.
• **Intervention group 3**	One-step method [75g] (n=516): 2 hour 75g glucose tolerance test, threshold unclear. Treatment: as described for intervention group 1. Incidence of gestational diabetes: 18/497 (3.6%) Excluded from analysis (n=16) due to incomplete lab results and incomplete cost data.
Results	
• **Preeclampsia**	No additional description supplied. Two-step method [50g ±100g] 18/500 (3.5%) Two-step method [50g ±75g] 17/500 (3.3%) One-step method [75g] 27/500 (5.4%) *p* <0.05
• **Neonatal hypoglycaemia**	No additional description supplied. Two-step method [50g ±100g] 18/500 (3.5%) Two-step method [50g ±75g] 21/500 (4.2%) One-step method [75g] 33/500 (6.5%) *p* <0.05
Limitations and other comments	
• **Limitations**	No detailed provided on block randomisation method.

	Outcome reporting: only percentages supplied so raw numbers calculated on the assumption of their reported numbers analysed although unclear if it is this or numbers who received testing.

9.5.4. Diagnostic accuracy

Table 126 – Diagnostic accuracy for gestational diabetes tests: Evidence table (Ayach et al., 2006)

Comparison between 100g glucose tolerance test and two other screening tests for gestational diabetes: combined fasting glucose with risk factors and 50g glucose tolerance test. Ayach W, Costa R A A, de Matlos Paranhos, Calderon I & Rudge M V C, 2006[104]	
Methods	
• **Design**	Prospective cohort study
• **Source of funding and competing interest**	No external source of funding
• **Setting**	University hospital, Brazil
• **Sample size**	n=341 included (460 recruited but 119 were unable to participate as they did not meet the inclusion criteria, due to miscarriage (n = 7), pseudocyesis (n = 1), premature childbirth (n = 2), fetal death (n = 2), intolerance to oral glucose (n = 3), and dropout before performing the 50-g GTT (n = 86) or 100-g GTT (n = 18).
• **Time interval between tests**	Study conducted between July, 1997 and December, 1999. Tests were performed between the 24th and 28th weeks of pregnancy but no details reported on time between index and reference tests.
• **Statistical analysis**	As described by authors: Comparison of the diagnostic efficiency between the tests was done using Student's t test. The statistical significance was set at 5% ($p < 0.05$).
Patient characteristics	
• **Eligibility criteria**	All pregnant women with no previous history of diabetes mellitus who sought prenatal care in HU-UFMS during the first half of their pregnancies were considered eligible.
• **Exclusion criteria**	Participation in the study was terminated according to the following criteria: failure to perform or finish the screening and diagnostic tests, withdrawal of consent or premature termination of the pregnancy.
• **Patient & disease characteristics**	Age ≥30 years n=54 (15.8%). BMI ≥27kg/m^2 n=49 (14.4%). White n=208 (61%). Primigravida n=148 (43.4%)
• **Prevalence of disease**	Not reported.
Interventions	
• **Index test**	The 50-g GTT screening was considered positive when the one-hour post-intake glucose level was ≥ 140 mg/dl. Performed between the 24th and 28th weeks of pregnancy.
• **Reference standard**	All the pregnant women also underwent 100-g GTT, which was considered positive when two or more values equalled or exceeded 95, 180, 155 and 140 mg/dl, under fasting conditions, at one, two and three hours after glucose intake, respectively. Performed between the 24th and 28th weeks of pregnancy.

Results	
• **Threshold 140 mg/dL**	Sensitivity: 76.9% (46.2-95) *p*=0.62, Specificity: 86.6% (82.4-90) *p* < 0.000001, PPV: 18.5 (9.3-31.4) *p*=0.0002, NPV: 98.9 (97-99.8) *p*=0.8, PLR: 5.7 (2.6-9.5) *p*=0.0002, NLR: 0.27 (0.05-2.6) *p*=0.9

		Condition		
		Positive	Negative	
Test	Positive	10	44	54
	Negative	3	284	287
		13	328	341

Limitations and other comments	
• **Limitations**	No details on timing between the index test and the reference standard and it is unclear whether reference standard results were interpreted without knowledge of the index test. 2x2 tables calculated from data presented, and using an estimated prevalence of 5% for gestational diabetes in pregnant women.

Table 127 – Diagnostic accuracy for gestational diabetes tests: Evidence table (Espinosa de los Monteros et al., 1999)

The after breakfast 50-g, 1-hour glucose challenge test in urban Mexican pregnant women: Its sensitivity and specificity evaluated by three diagnostic criteria for gestational diabetes mellitus. Espinosa de los Monteros A, Parra A, Hisalgo R & Zambrana M, 1999[105]	
Methods	
• **Design**	Retrospective cohort study
• **Source of funding and competing interest**	Source of funding and declarations of interested not stated.
• **Setting**	Third level medical institution for routine care, Mexico
• **Sample size**	n=445 included
• **Time interval between tests**	Recruitment between July 1st and December 30th 1996, GCT performed at 24-28 weeks of gestation followed by OGTT 1 week later.
• **Statistical analysis**	As described by authors: The sensitivity and specificity, the positive and negative prognostic values and the receiver operating characteristic (ROC) graphs were calculated by standard methods, using for the diagnosis of GDM the criteria of the NDDG, Carpenter & Coustan's and Sacks et al. The unpaired Student t-test was applied when appropriate. NB – data only reported for Carpenter & Coustan's criteria.
Patient characteristics	
• **Eligibility criteria**	Urban Mexican women (living in Mexico City), a high-risk population for diabetes. All pregnant women between 24 and 28 weeks of gestation.
• **Exclusion criteria**	Previous history of diabetes mellitus.

• **Patient & disease characteristics**	24.7% were nulliparous, 19.3% were <25 years of age, 42.5% had a family history of diabetes mellitus (one or both parents) and 54.8% were overweight (more than 110% of the ideal body weight for height and gestational age).
• **Prevalence of disease**	Not stated.
Interventions	
• **Index test**	50-g, 1-hour GCT performed 1 to 2 hours after their usual home breakfast (and thus the breakfast was not standardized). Followed by a 100-g 3 hour OGTT 1 week later.
• **Reference standard**	100-g 3-hour OGTT. Non-heparinized venous blood samples were obtained at 0,1,2 and 3 hours and centrifuged (3000 rpm during 30 minutes) within 30 minutes after they were obtained; the serum was separated and kept frozen at -20°C until analysed. On each sample glucose was determined in duplicate by a glucose oxidase method (GOD-PAP) using an automatic enzymatic autoanalyzer. The intra-assay coefficient of variation at two different glucose levels (<4.4 mmol/L and <10 mmol/L) were 3.5% and 2.5% respectively, and the interassay coefficient of variation was less than 4.5%
Results	
• **Threshold 130 mg/dL**	Carpenter & Coustan's – Sensitivity: 90.4% Specificity 80.9% PPV: 38.5

		Condition		
		Positive	Negative	
Test	Positive	20	81	101
	Negative	2	342	344
		22	423	445

• **Threshold 135 mg/dL**	Carpenter & Coustan's – Sensitivity: 88.5% Specificity 86.0% PPV: 45.5

		Condition		
		Positive	Negative	
Test	Positive	20	59	79
	Negative	3	363	366
		23	422	445

• **Threshold 140 mg/dL**	Carpenter & Coustan's – Sensitivity: 88.5% Specificity 87.0% PPV: 47.4

		Condition		
		Positive	Negative	
Test	Positive	19	55	74
	Negative	3	368	371
		22	423	445

Limitations and other comments	
• **Limitations**	As this is a retrospective study, it is unclear whether results of the reference standard were interpreted without knowledge of the index test results.

	2x2 tables calculated from data presented, and using an estimated prevalence of 5% for gestational diabetes in pregnant women (this may be an under-estimate given that the authors report the population is high-risk).

Table 128 – Diagnostic accuracy for gestational diabetes tests: Evidence table (Perucchini et al., 1999)

Using fasting plasma glucose concentrations to screen for gestational diabetes mellitus: prospective population based study. Perucchini D, Fischer U, Spinas GA, Huch R, Huch A & Lehmann R, 1999[106]	
Methods	
• **Design**	Prospective cohort study
• **Source of funding and competing interest**	Funded by University Hospital Zurich, No declarations of interest.
• **Setting**	Outpatient clinic in a university hospital, Switzerland.
• **Sample size**	n=520 (558 gave consent, but 38 were excluded because of vomiting after the 100g glucose intake or incomplete data).
• **Time interval between tests**	GCT between 24th and 28th gestational week, followed by a 3 hour 100g OGCT 1 week later. Over 21 months (1995-1997).
• **Statistical analysis**	As described by authors: Relations between different groups and variables analyzed with the Student's t test and the Mann-Whitney U test where appropriate; P<0.05 was considered significant. Sensitivity, specificity and predictive values were calculated using a 2x2 contingency table. Receiver operator curves were used to construct a graphic representation of the relation between sensitivity and specificity over all possible diagnostic cutoff values.
Patient characteristics	
• **Eligibility criteria**	Pregnant women with a singleton pregnancy.
• **Exclusion criteria**	Women with pre-existing diabetes and those not examined by an obstetrician before the 24th gestational week. Women who went into labour prior to the 28th week of gestation.
• **Patient & disease characteristics**	Race categorized as white (European) 63%; 328, Asian 19%;99, African 6%;31, and others 12%;62. Mean age 28.4 (SD 0.2; range 17-45) and mean BMI 23.8 (SD 0.2)
• **Prevalence of disease**	Not stated.
Interventions	
• **Index test**	Standard 1 hour, 50g GCT between the 24th and 28th gestational week, with a venous plasma blood glucose measurement 1 hour later. The women had to record the time of last food intake, although the challenge was performed irrespective of this or of the time of day. All patients were asked to return for a 3 hour diagnostic 100g OGCT within the next week.
• **Reference standard**	The OCGT was performed in the morning after a 12 hour overnight fast and 3 days of 150-200g (minimum) carbohydrate diet. Gestational diabetes was diagnosed if two or more values of the tolerance test equalled or exceeded the thresholds proposed and adopted by the 4th international workshop conference on gestational diabetes (Capenter & Coustan). Venous plasma glucose concentration was determined by a hexokinase method.

Results				
• **Threshold 140 mg/dL**	Sensitivity: 59%, Specificity: 91%			
		Condition		
		Positive	Negative	
Test	Positive	15	44	59
	Negative	11	450	461
		26	494	520
Limitations and other comments				
• **Limitations**	It is unclear whether reference standard results were interpreted without knowledge of the index test. 2x2 tables calculated from data presented, and using an estimated prevalence of 5% for gestational diabetes in pregnant women.			

Table 129 – Diagnostic accuracy for gestational diabetes tests: Evidence table (Thitadilok et al., 1995)

The screening for gestational diabetes employing 50g glucose test, Thitadilok W & Techatraisak K, 1995[107]	
Methods	
• **Design**	Prospective cohort
• **Source of funding and competing interest**	Not stated.
• **Setting**	Antenatal hospital clinic, Thailand.
• **Sample size**	n=304 included
• **Time interval between tests**	Recruitment between August – December 1993. Screening at 24-28 weeks of gestation. OGTT performed 1 week later.
• **Statistical analysis**	As described by authors: Employing a simple statistic with reference to the sensitivity, specificity and the receiver operating characteristic curve
Patient characteristics	
• **Eligibility criteria**	Pregnant women of 24-28 gestational weeks who met each of the following criteria; aged over 30, obese, familial history of diabetes mellitus, prior history of delivery of a macrosomic infant or malformed infant or stillborn infant, glycosuria detected at the antenatal clinic visit and those with hypertension.
• **Patient characteristics**	Not stated.
• **Prevalence of disease**	Not stated.
Interventions	
• **Index test(s)**	The patients were asked to drink a 200ml solution containing 50g glucose within 15 minutes without prior fasting. One hour thereafter the plasma glucose levels were determined employing the glucose oxidase test method (Hitachi 717 autoanalyser). The patients were asked to return for a 100g glucose tolerance test the following week.

• **Reference standard**	The patients were instructed to have each meal with a carbohydrate content of at least 150g for 3 days prior to the test. They fasted from midnight before the test was carried out in the morning. Drinking the 400ml solution containing 100g glucose within 15 minutes was instructed followed by determination of plasma glucose levels at 1, 2 and 3 hours respectively.
Results	
• **Threshold 130-139mg/dL**	Sensitivity 91.3%, Specificity 62.9%

		Condition		
		Positive	Negative	
Test	Positive	14	107	121
	Negative	1	182	183
		15	289	304

• **Threshold 140-149mg/dL**	Sensitivity 91.3%, Specificity 77.9%

		Condition		
		Positive	Negative	
Test	Positive	14	64	78
	Negative	1	225	226
		15	289	304

Limitations and other comments	
• **Limitations**	It is unclear whether reference standard results were interpreted without knowledge of the index test. Thresholds presented as ranges rather than specific points – indirect evidence based on deviation from review protocol. 2x2 tables calculated from data presented, and using an estimated prevalence of 5% for gestational diabetes in pregnant women (this may be an under-estimate given that the population is high-risk). 2x2 data therefore differs slightly from total GDM reported by author (n=23), attempting to calculate prevalence using author-reported GDM works out at 7.5%.

Table 130 – Diagnostic accuracy for gestational diabetes tests: Evidence table (Weerakiet et al., 2006)

Can adiponectin predict gestational diabetes? Weerakiet S, Lertnarkorn K, Panburana P, Pitakitronakorn S, Vesathada K & Wansumrith S, 2006[108]	
Methods	
• **Design**	Cross-sectional study
• **Source of funding and competing interest**	Funding from a grant from the Faculty of Medicine, Ramathibodi Hospital. Competing interests not stated.
• **Setting**	Hospital, Thailand
• **Sample size**	n=359 included. (370 enrolled, but 11 excluded due hypertension, diabetes, and asthma diagnosis and positive HBSAg and HIV infection)
• **Time interval between tests**	Recruitment between July 2004 and March 2005, Screening undertaken between 21st and 27th week gestation, OCTT done between 24th and 28th week gestation. No detailed information provided on number of women screened <24 weeks.

• **Statistical analysis**	As described by authors: The areas under the receiver-operator characteristic curves were compared between the glucose concentrations of the 50-g GCT and adiponectin concentrations. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were also determined.
Patient characteristics	
• **Eligibility criteria**	Women with singleton pregnancy who were at risk of GDM. Criteria for screening were as follows: maternal age >30 years; obesity; family history of diabetes mellitus; prior GDM; glucosuria; symptoms or signs suggestive of hyperglycemia; and history of poor obstetric outcome.
• **Exclusion criteria**	Hypertension, a known diagnosis of DM and chronic disease that required treatment. Also excluded were women who had any positive result to test for syphilis, hepatitis B virus surface antigen (HBSAg) and human immunodeficiency virus (HIV) antibody.
• **Patient & disease characteristics**	Age 31.8±6.1 years, pre-pregnancy BMI 23.2±4.3 kg/m^2, sampling-day BMI 25.6±4.6 kg.m^2.
• **Prevalence of disease**	Reported as 16.7%
Interventions	
• **Index test**	The two-step approach was performed in all women. A 1-h 50g GCT was performed between the 21st and 27th week of gestation.
• **Reference standard**	3 hour 100g OGTT was done between the 24th and 28th week of gestation. All blood samples for glucose determinations were immediately centrifuged at room temperature. Plasma was separated and determinations performed within 1 h. The blood samples for adiponectiin determination were also immediately centrifuged at 1500rev/min for 15 min at 4°C. Plasma was stored at -70°C until assayed.
Results	
• **Threshold 140 mg/dL**	Sensitivity 90%, specificity 61%, PPV 32%, NPV 97%

		Condition		
		Positive	Negative	
Test	Positive	54	117	171
	Negative	6	182	188
		60	299	359

Limitations and other comments	
• **Limitations**	2x2 table calculated from data and prevalence reported (16.7%). Population may have included women who received the 50g GCT earlier than 24 weeks (which is a separate strata of the review protocol), however no detail is provided on this population.

9.6. Hypothyroidism

9.6.1. Screening for hypothyroidism in asymptomatic pregnancies

Table 131 – Screening for hypothyroidism: Evidence table (Lazarus, 2012)

Antenatal Thyroid Screening and Childhood Cognitive Function. Lazarus, 2012[33]	
Methods	
• **Design**	Randomized Control Trial
• **Source of funding and competing interest**	Supported by the Welcome Trust and Compagnia di San Paulo, Turin. Dr. Lazarus reports receiving consulting fees from Abbott Diagnostics and lecture fees from Abbott Diagnostics and Merck (Darmstadt). No other potential conflict of interest relevant to this article was reported
• **Setting**	The women were recruited from 10 centers in the United Kingdom and 1 center in Italy; Blood samples were sent to the laboratory at the University Hospital of Wales, Cardiff, or to Ospedale Sant'Anna, Turin, Italy.
• **Sample size**	Total N randomized = 21 846 (treatment N: 10 924; control N: 10 922) (16 346 from UK, 5500 from Italy) Total N analyzed = (treatment N: 10 905; control N: 10881) (24% of women declined to have their children assessed)
• **Duration and follow-up**	Duration: Start date: Not reported; End date: Not reported Follow up: a) Treatment of Women in the intervention group: Levels of thyrotropin and free T4 were checked 6 weeks after the start of levothyroxine therapy and at 30 weeks gestation. Intervention lasted length of pregnancy, after which they were referred to their family physician to see if treatment should be continued b) Outcome #1: IQ of children for women who tested positive at 3 years of age
• **Statistical analysis**	Intent to treat
Patient characteristics	
• **Eligibility criteria**	Pregnant women to participate at their first antenatal hospital visit.
• **Exclusion criteria**	Exclusion criteria were an age of less than 18 years, a gestational age of more than 15 weeks 6 days, twin pregnancies, and known thyroid disease
• **Patient & disease characteristics**	**Baseline characteristics were only provided for women who tested positive in the screening and control group Mean Age at delivery ± SD (years): Intervention:30±5.4; Control: 31±5.3 Median gestational age at screening (IQR): Intervention: 12 weeks 3 days (11,6 - 13,6); Control: 12 weeks 3 days (11,6 - 13,5); Thyrotropin (mIU/litre) Median, IQR: United Kingdom: Intervention: 3.8 (1.5 - 4.7); Control: 3.2 (1.2 - 4.2) Turin: Intervention: 3.1 (1.3 – 4.0); Control: 2.4 (1.3 – 3.9) At baseline women who tested positive in the screening and control groups were similar with respect to baseline characteristics and socioeconomic characteristics, with the exception that thyrotropin levels were higher in the screening group than in the control group among the women in the United Kingdom.
Interventions	
• **Intervention group**	Levothyroxine (starting dose, 150 µg/day); adjustment of the dose as necessary based on of thyrotropin and free T4 at 6 weeks after the initiation, and at 30 weeks gestation.

• **Control group**	Serum samples from women in the control group, stored at −40°C, were assayed for levels of free T4 and thyrotropin after delivery.
Results	
• **Outcome 1**	*Analysis restricted to test positive patients in both groups* Childhood outcomes *Control standardised **IQ at 3 years** (as measured by Wechsler Preschool and Primary Scale of Intelligence)*: **(Control Group − Screening Group)** MD= 0.8 (95% CI, -1.1, 2.6), P = 0.40 ***IQ< 85***: MD = 2.1 (-2.6 to 6.7) P = 0.39 RR= 0.85 (95% CI, 0.60, 1.22); RD = -2.1 (95% CI, -6.7, 2.6) No differences in IQ for other cut-offs and individual assessment components
• **Outcome 2**	***Behavior****(Child Behavior Checklist T-score)* (control group – screening group) MD= 0.7 (95% CI,-1.2, 2.5) P = 0.49 ***Behavior*** *(Behavior Rating Inventory of Executive Function, preschool T-score)*: Intervention: Median (IQR) = 40 (47-55); Control: Median (IQR): 40 (47-55) MD= zero, P = 0.59
• **Outcome 3**	***Preterm birth (<37 wks)***: Intervention: 5.6%; Control: 7.9%, P = 0.20 RR= 0.71 (95% CI, 0.42, 1.20) ****RR was calculated by us.**
• **Outcome 4**	Maternal outcomes *Maternal Becks Depression Inventory*: 1 case each group Intervention: 1/390 (0.26%); Control: 1/404 (0.25%)
Limitations and other comments	
• **Limitations**	External validity: Very serious applicability concern. For detail please see *scientific evidence for question 2b* Internal validity: High risk of Bias. For detail please refer to *scientific evidence for question 2b*.

Table 132 – Screening for hypothyroidism: Evidence table (Negro et al., 2010)

Universal Screening Versus Case Finding for Detection and Treatment of Thyroid Hormonal Dysfunction During Pregnancy. Negro et al., (2010)[34]	
Methods	
• **Design**	RCT (once assigned to groups women were stratified according to risk, and all high risk women were tested no matter their assigned group)
• **Source of funding and competing interest**	First author and others have nothing to declare. One author is a consultant for Abbott Pharmaceuticals.
• **Setting**	Two ambulatory clinics of community hospitals in southern Italy. Women were recruited from the Division of Obstetrics and Gynaecology, Vito Fazzi Hospital (Lecce, Italy) and the Division of Obstetrics and Gynaecology, Casa di Cura Salus (Brindisi, Italy).
• **Sample size**	Total N randomized=4 562 (treatment N: 2280; control N: 2282) Total N analyzed= Treatment N: 2259; Control N: 2257
• **Duration and follow-up**	Recruitment Duration: Start date: March 2005; End Date: February 2008 Study Completion: December 2008 Follow up: a) Treatment of women in the intervention group: Intervention lasted the length of the pregnancy. Following testing in the first trimester, all patients with thyroid dysfunction were tested at least once during the second and third trimester. b) Obstetrical or neonatal outcomes c)
• **Statistical analysis**	Intention-to-treat basis; women lost to follow-up were assumed to have no adverse outcomes, regardless of group assignment in the main analysis.
Patient characteristics	
• **Eligibility criteria**	Spontaneously pregnant women with singletons within the first 11 wk of gestation and no history of thyroid disease
• **Exclusion criteria**	Not reported
• **Patient & disease characteristics**	Mean Age±SD (years): Control: 28.9 ± 5; Treatment: 28.7 ± 5 Previous babies (%): Control: 1619 (70.9%); Treatment: 1595 (70%) Smoking (%): Control: 120 (5.3%); Treatment: 128 (5.6%) First gynecological visit (wk): Control: 8.8 ± 1.6; Treatment: 8.8 ± 1.5 TSH first trimester (mIU/liter): Control: 1.4 ± 1.3; Treatment: 1.4 ± 1.4 fT4 first trimester (pmol/liter): Control: 11.9 ± 2.4; Treatment: 11.9 ± 2.5 TPO-Ab+ (%): Control: 186 (8.2%); Treatment: 198 (8.7%) Family history of thyroid disease (%): Control: 292 (12.8%); Treatment: 283 (12.4%) Goiter (%): Control: 20 (0.9%); Treatment: 23 (1%) Symptoms of hypo- or hyperthyroidism (%): Control: 167 (7.3%); Treatment: 179 (7.8%) Type 1 diabetes/autoimmune disease (%): Control: 22 (0.9%); Treatment: 25 (1%) Irradiation (%): Control: 2 (0.09%); Treatment: 0 Previous miscarriage/preterm deliveries (%): Control: 30 (1.3%); Treatment: 36 (1.6%)

Interventions	
• **Intervention group**	Levothyroxine with a TSH above 2.5 mIU/liter in TPO antibody-positive women and anti-thyroid medication in women with an undetectable TSH and elevated free T4. Levothyroxine was initiated and titrated during the first trimester to maintain theTSHlevel less than 2.5 mIU/liter. During the second and third trimesters, levothyroxine was titrated to keep the TSH less than 3.0 mIU/liter.
• **Control group**	Low-risk women in the case-finding group had their sera frozen at -70 °C and assayed postpartum.
Results	
• **Outcome 1**	Majority of adverse effects were in the 95% of women who were euthyroid ****RR was calculated by another reviewer, treatment vs. control was confirmed by this reviewer** Neonatal *Miscarriage*: Treatment vs. Control 92/2259 vs. 102/2257, RR= 0.90 (95% CI, 0.68, 1.19) *Perinatal/neonatal death*: Treatment vs. Control 12/2259 vs. 13/2257, RR= 0.92 (95% CI, 0.42, 2.02) *NICU admission*: Treatment vs. Control 119/2259 vs. 114/2257, RR= 1.04 (95% CI, 0.81, 1.34) *Birth weight >2500g*: Treatment vs. Control 102/2259 vs. 105/2257, RR= 0.97 (95% CI, 0.74, 1.27) *Preterm birth <37 weeks*: Treatment vs. Control 147/2259 vs. 148/2257, RR= 0.99 (95% CI, 0.80, 1.24) *Preterm birth <34 weeks*: Treatment vs. Control 42/2259 vs. 43/2257, RR= 0.98 (95% CI, 0.64, 1.49)
• **Outcome 2**	Maternal *Gestational hypertension*: Treatment vs. Control 124/2259 vs 122/2257, RR= 1.02 (95% CI, 0.80, 1.29) *Preeclampsia*: Treatment vs. Control 73/2259 vs. 84/2257, RR= 0.87 (95% CI, 0.64, 1.18) *Congestive heart failure*: zero events
• **Outcome 3**	Total (maternal and/or neonatal) adverse outcomes: Treatment vs. Control 1559/2259 vs. 1545/2257, RR= 1.01 (95% CI, 0.97, 1.05) In a subgroup analysis of low risk women, odds for adverse maternal/neonatal outcomes favored universal screening [OR= 0.43, 95% CI 0.26, 0.70)]. However, the crude relative risk for at least one adverse event 0.96 (95% CI, 0.89, 1.04)
Limitations and other comments	
• **Limitations**	External validity: Serious applicability concern. For detail please refer to *scientific evidence for question 2b.* Internal validity: Low risk of bias. For detail please refer to *scientific evidence for question 2b*.

9.6.2. Therapy for subclinical hypothyroidism during pregnancy

Table 133 – Therapy for subclinical hypothyroidism: Evidence table for the selected systematic review (Reid et al., 2013)

Interventions for clinical and subclinical hypothyroidism pre-pregnancy and during pregnancy (Review). Reid et al., 2013[51]	
Methods	
• **Design**	Systematic review
• **Source of funding and competing interest**	Internal sources (ARCH, Robinson Institute, Discipline of Obstetrics and Gynaecology, The University of Adelaide, Australia.) and external sources (National Health and Medical Council, Australia and Department of Health and Ageing, Australia.) None.
• **Search date**	March 31, 2013
• **Searched databases**	The Cochrane Pregnancy and Childbirth Group's Trials Register, Cochrane Central Register for Controlled Trials (CENTRAL); MEDLINE; EMBASE; hand searches of 30 journals and the proceedings of major conferences; weekly current awareness alerts for 44 journals and monthly BioMed Central email alerts.
• **Included study designs**	RCT or quasi-randomized trials, cluster-randomized trials and studies published as abstracts only.
• **Number of included studies**	4 (2 for the population of interest: pregnant women with subclinical hypothyroidism)
• **Statistical analysis**	Fixed effects meta-analysis was conducted where it was reasonable to assume that the studies were estimating the same underlying treatment effect that involved similar trial's population, methods and intervention, Random effects meta-analysis was conducted in case of clinical heterogeneity or substantial statistical heterogeneity. Reporting bias (e.g. selective outcome) was examined if there were 10 or more studies in the meta-analysis. Assessed ROB using the Cochrane Handbook for Systematic Reviews of Interventions.
Patient characteristics	
• **Eligibility criteria**	Population: Pregnant (either pre-pregnancy or during pregnancy) women with a diagnosis of hypothyroidism, subclinical hypothyroidism or isolated maternal hypotheroxinaemia. Intervention: RCT, Cluster-randomized trials comparing one intervention with another or with placebo and combinations of therapy could be used
• **Exclusion criteria**	Intervention: Cross-over designs.
• **Patient & disease characteristics**	Pregnant women with subclinical hypothyroidism [with euthyroid (positive for thyroid antibodies), autoimmune thyroid diseases], were compared on treatment with levothyroxine and selenomethaionine and placebo.
Interventions	
• **Intervention group**	Trial 1 (Negro et al 2006): Levothyroxine (dose: varied depending on TSH and thyroid peroxidise antibody; length: from 1st endocrinological consultation to the end of pregnancy, regimen and timing if relevant) Trial 2 (Negro et al 2007): Selenomethionine (200 microgm/day at or after 12 weeks of gestation; advised to use iodized salt)
• **Control group**	Trial 1: No treatment (including dose, length, regimen and timing if relevant) Trial 2: Placebo

Results	
• **Pre-eclampsia**	Levothyroxine versus no treatment: RR= 0.61; 95% CI (0.11, 3.48) Selenomethionine versus placebo: RR= 1.44; 95% CI (0.25, 8.38)
• **Preterm birth**	Levothyroxine versus no treatment: RR= 0.28; 95% CI (0.10, 0.80); Selenomethionine versus placebo: RR= 0.96; 95% CI (0.20, 4.61)
• **Miscarriage (1st trimester)**	Levothyroxine versus no treatment: RR= 0.25; 95% CI (0.06, 1.15); Selenomethionine versus placebo: RR= 0.85; 95% CI (0.30, 2.42)
• **Gestational hypertension**	Levothyroxine versus no treatment: 1 study; 105 participants; RR= 0.65; 95% CU (0.22, 1.92)
• **Placental abruption**	Levothyroxine versus no treatment: RR= 0.30; 95% CI (0.01, 7.29)
• **Hypothyroidism (2 months after birth and after stopping levothyroxine)**	Selenomethionine versus placebo: RR=0.77; 95% CI (0.21, 2.75)
Limitations and other comments	
• **Limitations**	External validity: Not applicable (individual updated outcomes are assessed for applicability in the result section of the report). Internal Validity: Modified AMSTAR: High quality

Table 134 – Therapy for subclinical hypothyroidism: Evidence table of RCTs (Mao et al., 2013)

Effect of selenium supplementation on thyroid function in UK pregnant women: A randomised, controlled pilot trial. Mao et al., 2013[109]	
Methods	
• **Design**	RCT
• **Source of funding and competing interest**	Not industry, COI Yes
• **Setting**	Single center, developed country
• **Sample size**	230
• **Duration and follow-up**	23 wks (12-35 wks gestation)
• **Statistical analysis**	
Patient characteristics	
• **Eligibility criteria**	Women who are 12-14 weeks pregnant with their first baby visiting the John Radcliffe Hospital for a 12-week pregnancy scan
• **Exclusion criteria**	If <18 years old, current smokers, taking any supplement containing selenium, taking thyroid medication, multiple pregnancy, abnormal ultrasound scan, chronic protein in the urine, heparin treatment, HIV, Hepatitis-B or Hepatitis-C positive, yeast intolerance (supplement contains yeast), inability or refusal to give informed consent
• **Patient & disease characteristics**	Unclear,

	Hypothyroid status: NR
Interventions	
• **Intervention group**	Selenium (Se), 60ug, started at 1st trimester (1st-12th week of pregnancy), duration of treatment unclear (followed-up at 35 weeks, but does not specify when women stopped taking selenium)
• **Control group**	Placebo
Results	
• **Oucome**	NoT reported
Limitations and other comments	
• **Limitations**	Unclear applicability

Table 135 – Therapy for subclinical hypothyroidism: Evidence table of RCTs (Jain et al., 2013)

Role of thyroid autoantibodies (anti-TPO) in adverse pregnancy outcomes. Jain et al., 2013[52]	
Methods	
• **Design**	RCT
• **Source of funding and competing interest**	Not reported
• **Setting**	Unclear
• **Sample size**	100
• **Duration and follow-up**	First trimester until delivery
• **Statistical analysis**	Chi^2
Patient characteristics	
• **Eligibility criteria**	Women with normal thyroid function and thyroid autoantibodies (anti-TPO+)
• **Exclusion criteria**	Non reported
• **Patient & disease characteristics**	Women with risk factor TPOAb+
Interventions	
• **Intervention group**	Levothyroxine, dose not reported, started at 1st trimester (1st-12th week of pregnancy) Duration of treatement: until birth
• **Control group**	No treatment
Results	
• **Preterm birth**	Levothyroxine: N=50, drop out=0, N analysed=44, N events: 5 No treatment: N=50, drop out=0, N analysed=33, N events: 13

	Chi square: 4.159, p=0.0414
• **Miscarriage**	Levothyroxine: N=50, drop out=0, N analysed=50, N events: 6 No treatment: N=50, drop out=0, N analysed=50, N events: 17 Chi square: 3.858, p=0.0495
Limitations and other comments	
• **Limitations**	Serious concern for applicability

Table 136 – Therapy for subclinical hypothyroidism: Evidence table of RCTs (Kim et al., 2011)

Effect of levothyroxine treatment on in vitro fertilization and pregnancy outcome in infertile women with subclinical hypothyroidism undergoing in vitro fertilization/intracytoplasmic sperm injection. Kim et al., 2011[53]	
Methods	
• **Design**	RCT
• **Source of funding and competing interest**	Source not reported, no competing interest
• **Setting**	Single center
• **Sample size**	64
• **Duration and follow-up**	Prior to pregnancy until miscarriage, stillbirth or live birth
• **Statistical analysis**	
Patient characteristics	
• **Eligibility criteria**	Criteria not state as "inclusion," but described as follows: "infertile patients with subclinical hypothyroidism who had undergone IVF/IDSI cycles between March 2006 and Sept. 2009" at one university-based infertility clinic in South Korea and "All subjects had regular ovulatory cycles (duration, 21-35 days). They were in good health with normal cardiac, hepatic, and renal functions and they had experienced spontaneous onset of puberty and normal sexual development."
• **Exclusion criteria**	Criteria not state as "exclusion," but described as follows: "None of the subjects had a previous medical history of subclinical and clinical hypothyroidism, and they had not taken any infertility medications (clomiphene and/or gonadotropins) within the preceding 3 months."
• **Patient & disease characteristics**	Women with risk factor Subclinical hypothyroidism
Interventions	
• **Intervention group**	Levothyroxine, 50 ug/OD, started in pre-pregnancy Duration of treatement: until before birth
• **Control group**	No treatment

Results	
• **Preterm birth <34 weeks**	Levothyroxine: N=17, drop out=0, N analysed=17, N events: 0 No treatment: N=12, drop out=0, N analysed=12, N events: 1
• **Miscarriage**	Levothyroxine: N=17, drop out=0, N analysed=17, N events: 0 No treatment: N=12, drop out=0, N analysed=12, N events: 4 p=0.021
• **Stillbirth**	Levothyroxine: N=17, drop out=0, N analysed=17, N events: 0 No treatment: N=32, drop out=0, N analysed=12, N events: 0
• **Overt hypo-thyroidsim**	Levothyroxine: N=17, drop out=0, N analysed=17, N events: 0 No treatment: N=32, drop out=0, N analysed=12, N events: 1 p=0.039
Limitations and other comments	
• **Limitations**	No concern for applicability

Table 137 – Therapy for subclinical hypothyroidism: Evidence table of RCTs (Negro et al., 2005)

Levothyroxine treatment in thyroid peroxidase antibody-positive women undergoing assisted reproduction technologies: a prospective study. Negro et al., 2005[54]	
Methods	
• **Design**	RCT
• **Source of funding and competing interest**	Not reported
• **Setting**	Single center
• **Sample size**	72
• **Duration and follow-up**	From 1 month prior to assisted reproduction technologies throughout pregnancy
• **Statistical analysis**	
Patient characteristics	
• **Eligibility criteria**	Infertile women who had to undergo a first assisted reproduction technology procedure between January 1999 and January 2003. They had to be euthyroid and TPOAb+
• **Exclusion criteria**	Women with overt thyroid dysfunction
• **Patient & disease characteristics**	Women with risk factor TPOAb+

Interventions	
• **Intervention group**	Levothyroxine, 1 mg/kg/OD, started in pre-pregnancy Duration of treatement: until birth
• **Control group**	Placebo
Results	
• **Miscarriage**	Levothyroxine: N=24, drop out=0, N analysed=24, N events: 8 Placebo: N=21, drop out=0, N analysed=21, N events: 11
Limitations and other comments	
• **Limitations**	Serious concern for applicability

Table 138 – Therapy for subclinical hypothyroidism: Evidence table of one RCT excluded from Reid et al., 2013 (Negro et al., 2010)

Universal Screening Versus Case Finding for Detection and Treatment of Thyroid Hormonal Dysfunction During Pregnancy. Negro et al., 2010[34]	
Methods	
• **Design**	RCT
• **Source of funding and competing interest**	First author and others have nothing to declare. One author is a consultant for Abbott Pharmaceuticals.
• **Setting**	Two ambulatory clinics of community hospitals in southern Italy. Women were recruited from the Division of Obstetrics and Gynaecology, Vito Fazzi Hospital (Lecce, Italy) and the Division of Obstetrics and Gynaecology, Casa di Cura Salus (Brindisi, Italy).
• **Sample size**	Total N randomized=4 562 (treatment N: 2280; control N: 2282) Total N analyzed= Treatment N: 2259; Control N: 2257 Total N low risk, hypothyroid = 77
• **Duration and follow-up**	Recruitment Duration: Start date: March 2005; End Date: February 2008 Study Completion: December 2008 Follow up: a) Treatment of women in the intervention group: Intervention lasted the length of the pregnancy. Following testing in the first trimester, all patients with thyroid dysfunction were tested at least once during the second and third trimester. b) Obstetrical or neonatal outcomes
• **Statistical analysis**	Intention-to-treat basis; women lost to follow-up were assumed to have no adverse outcomes, regardless of group assignment in the main analysis.
Patient characteristics	
• **Eligibility criteria**	Spontaneously pregnant women with singletons within the first 11 wk of gestation and no history of thyroid disease
• **Exclusion criteria**	Not reported
• **Patient & disease characteristics**	Not available for the subgroup of interest (patient characteristics for the entire study is provided in Question 2b evidence table).

Interventions	
• **Intervention group**	Levothyroxine with a TSH above 2.5 mIU/liter in TPO antibody-positive women and anti-thyroid medication in women with an undetectable TSH and elevated free T4. Levothyroxine was initiated and titrated during the first trimester to maintain theTSHlevel less than 2.5 mIU/liter. During the second and third trimesters, levothyroxine was titrated to keep the TSH less than 3.0 mIU/liter.
• **Control group**	Low-risk women in the case-finding group had their sera frozen at -70 °C and assayed postpartum.
Results	
• **Outcome 1**	Majority of adverse effects were in the 95% of women who were euthyroid ****RR was calculated by another reviewer, treatment vs. control was confirmed by this reviewer** Neonatal *Miscarriage*: Treatment vs. Control 2/43 (4.7%) vs. 7/34 (20.6%), RR 0.23 (95% CI 0.05, 1.02) *Perinatal/neonatal death*: Treatment vs. Control 0/43 (0%) vs. 0/34 (0%), *NICU admission*: Treatment vs. Control 3/43(7.3%) vs. 6/34 (22.2%), RR 0.35 (95% CI 0.08, 1.52) *Preterm birth 34-37 weeks*: Treatment vs. Control 1/43 (2.4%) vs. 2/34 (7.4%), RR 0.40 (95% CI 0.04, 4.18) *Preterm birth <34 weeks*: Treatment vs. Control 2/43 (4.9%) vs. 3/34 (11.1%), RR 0.53 (95% CI 0.09, 2.98) *Apgar score 5 min, 3 or less*: Treatment vs. Control 0/43 (0%) vs. 1/34 (3.7%), RR 0.27 (95% CI 0.01, 6.31)
• **Outcome 2**	Maternal *Gestational hypertension*: Treatment vs. Control 1/43 (2.4%) vs. 3/34 (11.1%), RR 0.26 (0.03, 2.42) *Preeclampsia*: Treatment vs. Control 2/43 (4.9%0 vs. 2/34 (7.4%), RR 0.79 (0.12, 5.33) *Gestational diabetes*: Treatment vs. Control 3/43 (7.3%) vs. 3/34 (11.1%), RR 0.79 (0.17, 3.67) *Placental abruption*: Treatment vs. Control 0/43 (0%) vs. 1/34 (3.7%), RR 0.27 (95% CI 0.01, 6.31)
Limitations and other comments	
• **Limitations**	External validity: Serious applicability concern. For detail please refer to *scientific evidence for question 2b.* Internal validity: Low risk of bias. For detail please refer to *scientific evidence for question 2b*.

Table 139 – Therapy for subclinical hypothyroidism: Evidence table of observational study (Wang et al., 2012)

Effects of maternal subclinical hypothyroidism on obstetrical outcomes during early pregnancy. Wang et al., 2012[57]	
Methods	
• **Design**	Observational Cohort Study
• **Source of funding and competing interest**	Funding and competing interests not reported
• **Setting**	10 hospitals in Shenyang, China
• **Sample size**	Total N enrolled = 756 Total N analyzed = 740; Normal TSH group N = 542; SCH group = 198 (2:over hypothyroidism) SCH Treatment N = 28; SCH Control (untreated) N=168 (only the SCH group was of interest)
• **Duration and follow-up**	2007 to 2009; women enrolled at <=12 weeks gestation and followed until delivery
• **Statistical analysis**	Categorical variables were compared using Pearson's X2 test, estimates of relative risk of thyroid disease for several variables were calculated by Mantel-Haenszel common odds ratio (OR) and t-test, p<0.05 was considered to be statistically significant
Patient characteristics	
• **Eligibility criteria**	Women aged 19 to 45yr old in early pregnancy (<=12 weeks)
• **Exclusion criteria**	NR
• **Patient & disease characteristics**	Age (yr): Normal TSH: 27.82±0.14; High TSH: 28.14±0.27 Gestational age at screening: Normal TSH: 6±0.05; High TSH: 6±0.07 Smokers: Normal TSH: 2(0.37%); High TSH: 3(1.52%) Passive smokers: Normal TSH: 94(17.34%); High TSH: 24(12.12%) Primiparity: Normal TSH: 522(96.31%); High TSH: 194(97.98%) Previous Disease: Hyperthyroidism: Normal TSH: 0; High TSH: 1(0.5%) Hypothyroidism: Normal TSH: 0; High TSH: 6(3.03%) Diabetes: Normal TSH: 7(1.29%); High TSH: 6(3.03%) "The age of women who received L-T4 treatment was higher than that of women who did not receive treatment in the SCH group (30.39±0.91 vs. 27.77±0.27 yr, p=0.009)" p.324
Interventions	
• **Intervention group**	Women with subclinical hypothyroidism were recommended to receive levo-T4 (L-T4) treatment; Dose for serum TSH level 2.5-5 mIU/l was 50 ug/day; serum TSH level 5-8 mIU/l was 75 ug/day and serum TSH>8 mIU/l was 100 ug/day. Their thyroid function was tested every 4 weeks and the drug dosage was adjusted according to their serum TSH level until delivery. Women with subclinical hypothyroidism were offered L-T4 treatment according to their consent.
• **Control group**	Women with SCH who were not treated
Results	
• **Outcome 1**	Neonatal *Spontaneous Abortion*: Treated vs. Untreated 2/28 (7.14%) vs. 26/168 (15.47%), OR 95% CI 0.462 (0.104 – 2.054); p=0.299

	Preterm Birth< 37 weeks: Treated vs. Untreated 0/28 vs. 9/168 (5.36%) *Low Birth Weight:* Treated vs. Untreated 0/28 vs. 4/168 (2.38%)
• **Outcome 2**	Maternal *Gestational Hypertension:* Treated vs. Untreated 1/28 (3.57%) vs. 2/168 (1.19%)
Limitations and other comments	
• **Limitations**	External validity: No applicability concern [For the subgroup of interest (women with subclinical hypothyroidism who received treatment of interest during early pregnancy)]. Internal validity: Refer to Risk of Bias Assessment for this study.

9.7. Vitamin D deficiency

9.7.1. Vitamin D supplementation during pregnancy

Table 140 – Vitamin D supplementation: Evidence table of systematic review (De-Regil et al., 2012)

Vitamin D supplementation for women during pregnancy (Review). De-Regil et al., 2012[58]	
Methods	
• **Design**	Systematic Review
• **Source of funding and competing interest**	Internal Funding: Micronutrients Unit, Department of Nutrition for Health and Development, World Health Organization, Switzerland; Programa de Nutricion, Escuela Graduada de Salud Publica, Universidad de Puerto Rico, Puerto Rico. External Funding: Micronutrient Initiative (MI), Canada Conflict of Interest: None
• **Search date**	October 31, 2011
• **Searched databases**	The Cochrane Pregnancy and Childbirth Group's Trials Register, CENTRAL, MEDLINE and EMBASE; hand searches of 30 journals and the proceedings of major conferences; weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.
• **Included study designs**	RCT and Quasi-RCT (randomisation at either individual or cluster level)
• **Number of included studies**	6 studies (9 references)
• **Statistical analysis**	Random effects meta-analysis, with reporting bias (ex. publication bias) if there are 10 or more studies, assessed ROB using the Cochrane handbook
Patient characteristics	
• **Eligibility criteria**	Population: Pregnant women of any gestational or chronological age, parity (number of births) and number of foetuses.

	Intervention: Vitamin D supplementation during pregnancy irrespective of dose, duration or time of commencement of supplementation. The included trials testing vitamin D alone or in combination with other micronutrients as long as the intervention and the control group were treated similarly
• **Exclusion criteria**	Crossover trials or any other observational designs (e.g. cohort or case-control studies)
• **Patient & disease characteristics**	Pregnant women were recruited and received supplements during third trimester (after 28 weeks gestation).
Interventions	
• **Intervention group**	Vitamin D supplementation during pregnancy irrespective of dose, duration or time of commencement of supplementation (includes trials testing vitamin D alone or in combination with other micronutrients)
• **Control group**	No treatment/placebo (no vitamins or minerals); calcium (but no vitamin D); calcium + other vitamins and minerals (but no vitamin D).
Results	
• **Maternal Primary**	1) **Pre-eclampsia** Vitamin D + Calcium vs. no treatment/placebo: RR= 0.67; 95% CI (0.33, 1.35) 2) **Gestational diabetes** No studies reported on this outcome
• **Infant Primary**	1) **Preterm birth** No studies reported on this outcome 2) **Low birth weight** Vitamin D vs. no treatment/placebo: RR 0.48; 95% CI (0.23, 1.01)
• **Maternal Secondary**	1) **Caesarean section** No studies reported on this outcome 2) **Gestational hypertension** No studies reported on this outcome 3) **Side effects** Vitamin D vs. no treatment/placebo: Nephritic syndrome: RR 0.17; 95% CI (0.01, 4.06) 4) **Maternal death** No studies reported on this outcome
• **Infant Secondary**	1) **Birth length** Vitamin D vs. no treatment/placebo: MD 0.97 cm; 95% CI (-0.41, 2.34 cm) 2) **Head circumference at birth** Vitamin D vs. no treatment/placebo: MD 0.43 cm; 95% CI (0.06, 0.79 cm) 3) **Birth weight** Vitamin D vs. no treatment/placebo: MD 39.55 g; 95% CI (-240.68, 319.78 g) 4) **Admission to intensive care unit during neonatal period**

	No studies reported on this outcome **5) Stillbirth** Vitamin D vs. no treatment/placebo: RR 0.17; 95% CI (0.01, 4.06) **6) Neonatal death (within 28 days)** Vitamin D vs. no treatment/placebo: RR 0.17; 95% CI (0.01, 4.06) **7) Apgar score less than 7 at 5 minutes** No studies reported on this outcome **8) Neonatal infection** No studies reported on this outcome **9) Very preterm birth (less than 34 weeks)** No studies reported on this outcome
Limitations and other comments	
• **Limitations**	External Validity: Not applicable (individual updated outcomes are assessed for applicability in the result section of the report). Internal Validity: Modified AMSTAR: High quality

Table 141 – Vitamin D supplementation: Evidence table of RCTs (Asemi et al., 2013)

Vitamin D supplementation affects serum high-sensitivity C-reactive protein, insulin resistance, and biomarkers of oxidative stress in pregnant women. Asemi et al., 2013	
Methods	
• **Design**	RCT
• **Source of funding and competing interest**	Not industry source, no conflict of interest
• **Setting**	Unclear, developing country
• **Sample size**	54
• **Duration and follow-up**	25 until 34 wks gestation
• **Statistical analysis**	
Patient characteristics	
• **Eligibility criteria**	Pregnant women, primigravida, aged 18-40 y old with a singleton pregnancy at 25 wk of gestation who attended maternity clinics affiliated with Kashan University of Medical Sciences, Kashan, Iran
• **Exclusion criteria**	Preeclampsia, hypertension, GDM, intrauterine fetal death, or those with a history of rheumatoid arthritis, hepatic or renal failure, metabolic bone disease and malabsorption or thyroid, parathyroid or adrenal diseases; smokers and those taking medication
• **Patient & disease characteristics**	Iranian women, primagravida aged 18-40 yrs with singleton pregnancy; with limited physical activity and sun exposure than others

	Healthy with risk factor (Low for many but not exclusively population with low serum [vit D])
Interventions	
• **Intervention group**	Oral vit D3 (cholecalciferol), 400 IU/d, 25 until 34 wks gestation + Folic acid: 400 ug/d from beginning of pregnancy; Ferrous sulphate: 60 mg/d from 2nd trimester
• **Control group**	Placebo (once daily) + Folic acid: 400 ug/d from beginning of pregnancy; Ferrous sulphate: 60 mg/d from 2nd trimester
Results	
• **Still birth/fetal death**	Intervention: N=27, drop out=0, N analysed=27, N events: 1 Placebo: N=27, drop out=0, N analysed=27, N events: 0
• **Preterm birth <34weeks**	Intervention: N=27, drop out=0, N analysed=27, N events: 1 Placebo: N=27, drop out=0, N analysed=27, N events: 1
• **Gestational diabetes**	Intervention: N=27, drop out=0, N analysed=27 N events: 0 Placebo: N=27, drop out=0, N analysed=27, N events: 1
• **Preeclampsia**	Intervention: N=27, drop out=0, N analysed=27 N events: 0 Placebo: N=27, drop out=0, N analysed=27, N events: 1
• **Placenta abruption**	Intervention: N=27, drop out=0, N analysed=27, N events: 1 Placebo: N=27, drop out=0, N analysed=27, N events: 0
Limitations and other comments	
• **Limitations**	Serious concern for applicability (Ethnicity)

Table 142 – Vitamin D supplementation: Evidence table of RCTs (Brooke et al., 1980)

Vitamin D supplements in pregnant Asian women: effects on calcium status and fetal growth. Brooke et al., 1980[66] and Companions[110, 111]	
Methods	
• **Design**	RCT
• **Source of funding and competing interest**	Source not industry, Confict of interest not reported
• **Setting**	Single center
• **Sample size**	Not reported
• **Duration and follow-up**	28-32 wks gestation until day 6 postpartum
• **Statistical analysis**	
Patient characteristics	
• **Eligibility criteria**	First generation Asian immigrants to Britain

• **Exclusion criteria**	Preterm deliveries, congenital malformations, and maternal illnesses likely to affect fetal growth (such as diabetes); these could be excluded after randomization and treatment.
• **Patient & disease characteristics**	First generation Asian women living in UK originating chiefly from the Indian subcontinent. Mostly Indian; others from Pakistan, Bangladesh, Sri Lanka, Mauritius, and east Africa. Healthy with risk factor (Not limited to Vit D deficient population but seems that most were Vit D deficient)
Interventions	
• **Intervention group**	Oral Vit D2 (calciferol), 1000IU/d, 28-32 wks gestation until delivery
• **Control group**	Placebo (once daily)
Results	
• **Gestational age at birth**	Intervention: N=unclear, drop out=unclear, N analysed=59, Median: 39.1 week, SD: 0.2 Placebo: N=unclear, drop out=unclear, N analysed=67, Median: 39.3 week, SD: 0.2
• **Birth weight (continuous)**	Intervention: N=unclear, drop out=unclear, N analysed=59, Median: 3157 grams, SD: 468.5 Placebo: N=unclear, drop out=unclear, N analysed=67, Median: 3034 grams, SD: 469.3.
• **Birth length (Crown-heel length)**	Intervention: N=unclear, drop out=unclear, N analysed=59, Median: 49.7 cm, SD: 2.3 Placebo: N=unclear, drop out=unclear, N analysed=67, Median: 49.5 cm, SD: 3.27
• **Birth weight < 2500 g**	Intervention: N=unclear, drop out=unclear, N analysed=59, N events: 7 Placebo: N=unclear, drop out=unclear, N analysed=69, N events: 15
• **Preterm birth other (small for gestational age - less than 10th percentile weight, Gairdner standards (reference 18 in study)**	Intervention: N=unclear, drop out=unclear, N analysed=59, N events: 9 Placebo: N=unclear, drop out=unclear, N analysed=67, N events: 19
• **Head circumference (Occipitofrontal)**	Intervention: N=unclear, drop out=unclear, N analysed=59, Median: 34.5 cm, SD: 0.76 Placebo: N=unclear, drop out=unclear, N analysed=67, Median: 34.3 cm, SD: 1.63
Limitations and other comments	
• **Limitations**	Serious concern for applicability (Race)

Table 143 – Vitamin D supplementation: Evidence table of RCTs (Delvin et al., 1986)

Vitamin D supplementation during pregnancy: effect on neonatal calcium homeostasis. Delvin et al., 1986[68]	
Methods	
• **Design**	RCT
• **Source of funding and competing interest**	Not reported
• **Setting**	Single center
• **Sample size**	40
• **Duration and follow-up**	3rd month of pregnancy until day 4 postpartum
• **Statistical analysis**	
Patient characteristics	
• **Eligibility criteria**	Women presenting for compulsory 3rd month gestation visit; all recruited in Dec (all June births) in France
• **Exclusion criteria**	NR
• **Patient & disease characteristics**	Women at one centre in Lyon France due to give birth in June Healthy with unclear risk factor (vitD levels NR)
Interventions	
• **Intervention group**	Oral vit D3 (cholecalciferol), 1000 IU/d, Last trimester of pregnancy
• **Control group**	No intervention
Results	
• **Preterm birth (Inferred from term births - not further defined)**	Intervention: N=20, drop out=5, Unclear 15 or 20, N events: 0 No intervention: N=20, drop out=1, Unclear 19 or 20, N events: 0
• **Gestational age at birth calculated from last menses.**	No group-specific data provided
• **Caesarian section**	Intervention N=20, drop out=5, Unclear 15 or 20, N events: 0 No intervention: N=20, drop out=1, Unclear 19 or 20, N events: 0
Limitations and other comments	
• **Limitations**	No serious concern for applicability

Table 144 – Vitamin D supplementation: Evidence table of RCTs (Diogenes et al., 2013 and Companions)

Effect of calcium plus vitamin D supplementation during pregnancy in Brazilian adolescent mothers: a randomized, placebo-controlled trial. Diogenes et al., 2013[61] and Companion[112]	
Methods	
• **Design**	RCT
• **Source of funding and competing interest**	Not industry source, no conflict of interest
• **Setting**	Single center, developing country
• **Sample size**	84
• **Duration and follow-up**	23-29 wks gestation until 20 wks postpartum
• **Statistical analysis**	
Patient characteristics	
• **Eligibility criteria**	Between 13 and 19 years of age, pregnant for the first time, carrying a single fetus, between 23 and 29 wk of gestation, and intending to exclusively or predominantly breastfeed.
• **Exclusion criteria**	Individuals with chronic health problems, pregnancy complications, smokers, users of nutritional supplements besides iron plus folate supplements provided during standard prenatal care, and mothers who decided not to breastfeed
• **Patient & disease characteristics**	Adolescent women who habitually consumed low-calcium diets and who received prenatal care at the Maternidade Escola, Universidade Federal do Rio de Janeiro Special population: Brazilian adolescent mothers with low calcium diets, without specific risk factor for Vit D deficiency (Mixed deficient and not deficient)
Interventions	
• **Intervention group**	Oral vit D3 (cholecalciferol), 200 IU/d + Ca 600mg/d + Prenatal iron supplement daily (no other details provided); 26 wks gestation until delivery
• **Control group**	Placebo (once daily) + + Prenatal iron supplement daily (no other details provided)
Results	
• **Pregnancy complication resulting in deop out**	Intervention: N=43, drop out=unclear, N analysed=unclear, N events: 0 Placebo: N=41, drop out=unclear, N analysed=unclear, N events: 2
• **Preterm birth (not defined)**	Intervention: N=43, drop out=unclear, N analysed=unclear, N events: 0 Placebo: N=41, drop out=unclear, N analysed=unclear, N events: 0
• **Gestational age at birth**	No group-specific data provided
Limitations and other comments	
• **Limitations**	Serious concern for applicability (Adolescents with low calcium diet)

Table 145 – Vitamin D supplementation: Evidence table of RCTs (Grant et al., 2014)

Vitamin D during pregnancy and infancy and infant serum 25-hydroxyvitamin D concentration. Grant et al., 2014[59]	
Methods	
• **Design**	RCT
• **Source of funding and competing interest**	Not industry source, no conflict of interest
• **Setting**	Single center
• **Sample size**	260
• **Duration and follow-up**	26-30 mo. gestation until 6 mo. postpartum
• **Statistical analysis**	
Patient characteristics	
• **Eligibility criteria**	Estimated gestation was 26 to 30 wks, singleton pregnancy; recruited from one primary care maternity clinic in Aukland NZ (lat. 26oS)
• **Exclusion criteria**	Women taking vitamin D supplementation >200 IU per day, those with a history of renal stones or hypercalcemia, or any serious pregnancy complications at enrolment.
• **Patient & disease characteristics**	Healthy women recruited in Aukland NZ Without specific risk factor for Vit D deficiency (Mixed deficient and not deficient)
Interventions	
• **Intervention group**	Group 1: Oral vit D3 (cholecalciferol), 2000 IU/d (infants were subsequently given 800 IU/d), started 3rd trimester Group 2: Oral vit D lower dose, 1000IU/d (infants were subsequently given 400IU/d), started 3rd trimester
• **Control group**	Placebo (once daily)
Results	
• **Still birth/fetal death**	Group 1: N=86, drop out=5, N analysed=81 N events: 0 Group 2: N=87, drop out=3, N analysed=84, N events: 0 Placebo: N=87, drop out=2, N analysed=85, N events: 1
• **Preterm birth (gestational age at birth)**	Group 1: N=86, drop out=5, N analysed=81 N events: NA, Median: 40 weeks, lower (25%) quartile: 39, upper (75%) quartile: 40 Group 2: N=87, drop out=3, N analysed=84, N events: NA, Median: 40 weeks, lower (25%) quartile: 39, upper (75%) quartile: 40 Placebo: N=87, drop out=2, N analysed=85, N events: NA, Median: 39 weeks, lower (25%) quartile: 38, upper (75%) quartile: 40
• **Hypercalcemia & kidney stones**	Group 1: N=86, drop out=5, N analysed= unclear (226 total across the group), N events: 0 Group 2: N=87, drop out=3, N analysed= unclear (226 total across the group), N events: 0 Placebo: N=87, drop out=2, N analysed=unclear (226 total across the group), N events: 0
• **Birth weight**	Group 1: N=86, drop out=5, N analysed=81 N events: NA, Median: 3540 grams, lower (25%) quartile: 3230, upper (75%) quartile: 3900 Group 2: N=87, drop out=4, N analysed=83, N events: NA, Median: 3480 grams, lower (25%) quartile: 3140, upper (75%) quartile: 3870

	Placebo: N=87, drop out=2, N analysed=85, N events: NA, Median: 3465 grams, lower (25%) quartile: 3161, upper (75%) quartile: 3780
Limitations and other comments	
• **Limitations**	Serious concern for applicability (Race)

Table 146 – Vitamin D supplementation: Evidence table of RCTs (Mallet et al., 1986)

Vitamin D supplementation in pregnancy: a controlled trial of two methods. Mallet et al., 1986[67]	
Methods	
• **Design**	RCT
• **Source of funding and competing interest**	Not reported
• **Setting**	Single center
• **Sample size**	Unclear (numbers are uneven between groups, suggesting these are analyzed numbers as opposed to randomized numbers)
• **Duration and follow-up**	3rd trimester of pregnancy until delivery
• **Statistical analysis**	
Patient characteristics	
• **Eligibility criteria**	White pregnant women and their infants born at term during February and March in an industrial region in Northwest France
• **Exclusion criteria**	NR
• **Patient & disease characteristics**	White pregnant women with infants born at term during February and March (winter mo) in France Healthy women with unclear risk factor - selected based on February or March term birth (vit D levels NR)
Interventions	
• **Intervention group**	Group 1: Oral vit D (type not reported), 1000 IU/d, for last 3 mo of pregnancy Group 2: Oral vit D, 200,000IU/single dose at 7th mo. gestation
• **Control group**	No intervention
Results	
• **Birth weight (continuous)**	Group 1: N=unclear, drop out=unclear, N analysed=48, Median: 3280 grams, SD: 86 Group 2: N=unclear, drop out=unclear, N analysed=27, Median: 3210 grams, SD: 90 No intervention: N=unclear, drop out=unclear, N analysed=29, Median: 3460 grams, SD: 70
Limitations and other comments	
• **Limitations**	No serious concern for applicability (Very serious for Stat dose of Vit D)

Table 147 – Vitamin D supplementation: Evidence table of RCTs (Marya et al., 1988)

Effect of vitamin D supplementation during pregnancy on foetal growth. Marya et al., 1988[70]	
Methods	
• **Design**	RCT
• **Source of funding and competing interest**	Not reported
• **Setting**	Single center, developing
• **Sample size**	200
• **Duration and follow-up**	28 wks gestation to term or delivery
• **Statistical analysis**	
Patient characteristics	
• **Eligibility criteria**	Women aged 20-35 years, attending the antenatal clinical of Medical College Hospital (Rohtak, India)
• **Exclusion criteria**	'patients with such complications as preeclampsia, antepartum haemorrhage, or premature delivery or with twin pregnancies
• **Patient & disease characteristics**	Women in India aged 20-35 years Healthy with unclear risk factor (vitD levels NR)
Interventions	
• **Intervention group**	Oral vit D3 (cholecalciferol), 600,000 IU (2 single doses; 1 in 7th and 1 in 8th month of pregnancy)
• **Control group**	No intervention
Results	
• **Birth weight (continuous)**	Intervention: N=100, drop out=unclear, N analysed=100, Median: 2990 grams, SD: 360 No intervention: N=100, drop out=unclear, N analysed=100, Median: 2800 grams, SD: 370
• **Birth length (Crown to heel; using standard methods (reference 12 therein)**	Intervention: N=100, drop out=unclear, N analysed=100, Median: 50.06 cm, SD: 1.79 No intervention: N=100, drop out=unclear, N analysed=100, Median: 48.'(cm, SD: 2.04
• **Head circumference**	Intervention: N=100, drop out=unclear, N analysed=100, Median: 33.99 cm, SD: 1.02 No intervention: N=100, drop out=unclear, N analysed=100, Median: 33.41 cm, SD: 1.11
• **Birth weight < 2500 g**	Intervention: N=100, drop out=unclear, N analysed=100, N events: 4 No intervention: N=100, drop out=unclear, N analysed=100, N events: 19
• **Gestational age**	Intervention: N=100, drop out=unclear, N analysed=100, Median: 38.65 weeks, SD: 1.77 No intervention: N=100, drop out=unclear, N analysed=100, Median: 38.86 weeks, SD: 1.69
• **Hypercalcemia & kidney stones**	Intervention: N=100, drop out=unclear, N analysed=100, N events: 0 No intervention: N=100, dop out=unclear, N analysed=100, N events: 0
Limitations and other comments	
• **Limitations**	Very serious concern of applicability (Race and exclusion of women who developed preeclampsia, antepartum haemorrhage, pre-term delivery and twin pregnancies)

Table 148 – Vitamin D supplementation: Evidence table of RCTs (Marya et al., 1987)

Effect of calcium and vitamin D supplementation on toxaemia of pregnancy. Marya et al., 1987[69]	
Methods	
• **Design**	RCT
• **Source of funding and competing interest**	Not reported
• **Setting**	Single center, developing
• **Sample size**	400
• **Duration and follow-up**	20-24 wks gestation to 36 wks or term, according to Cochrane review
• **Statistical analysis**	
Patient characteristics	
• **Eligibility criteria**	Women aged 20-35 years, attending the antenatal clinical of Medical College Hospital (Rohtak, India)
• **Exclusion criteria**	NR
• **Patient & disease characteristics**	Women in India aged 20-35 years Healthy with unclear risk factor (vitD levels NR)
Interventions	
• **Intervention group**	Oral vit D (type not reported), 1200 IU/d + Ca, 375 mg/d, 20-24 wks gestation until delivery
• **Control group**	No intervention
Results	
• **Preeclampsia ("toxaemia": SBP >140 mmHg and/or SBP > 90 mmHg with urinary proteins > 3000 mg/24 h")**	Intervention: N=200, drop out=unclear, N analysed=200, N events: 12 Placebo: N=200, drop out=unclear, N analysed=200, N events: 18
Limitations and other comments	
• **Limitations**	Serious concern of applicability (Race)

Table 149 – Vitamin D supplementation: Evidence table of RCTs (Roth et al., 2012)

Randomized placebo-controlled trial of high-dose prenatal third-trimester vitamin D3 supplementation in Bangladesh: The AViDD trial. Roth et al., 2013[12]	
Methods	
• **Design**	RCT
• **Source of funding and competing interest**	Not industry source, no conflict of interest
• **Setting**	Single center, developind country
• **Sample size**	160
• **Duration and follow-up**	26 to <30 wks gestation until 1 yr postpartum
• **Statistical analysis**	
Patient characteristics	
• **Eligibility criteria**	Aged 18 to <35 years; gestational age of 26 to <30 wks, estimated based on the first day of the last menstrual period; current residence in Dhaka at a fixed address; planned to deliver at the Shimantik maternity centre, and to stay in Dhaka throughout the pregnancy and for at least one month past the date of delivery
• **Exclusion criteria**	Use of any dietary supplement containing more than 400IU/day (10mcg/day) of vitamin D within the month prior to enrolment, or refusal to stop taking supplemental vitD at any dose after enrolment; current use of anti-convulsing or anti-mycobacterial (tuberculosis) medications, severe anaemia (Hb <70g/L); systolic BP >=140 mmHg or DPB >=90 mmHg; positive urine dipstick for proteinuria or glycosuria; complicated medical or obstetric history; or, reported prior history of delivery of an infant with a major congenital anomaly, birth asphyxia, or perinatal death.
• **Patient & disease characteristics**	Healthy women living in Dhaka, Bangladesh With risk factor (mixed deficient and not deficient)
Interventions	
• **Intervention group**	Oral vit D3 (cholecalciferol), 35,000 IU/week + Iron: 66 mg/d Folic acid: 350 mcg/d, 26 to <30 wks gestation until delivery
• **Control group**	Placebo (once daily) + Iron: 66 mg/d Folic acid: 350 mcg/d
Results	
• **Still birth/fetal death**	Intervention: N=80, drop out=7, N analysed=73, N events: 1 Placebo: N=80, drop out=6, N analysed=74, N events: 1
• **Neonatal death**	Intervention: N=80, drop out=7, N analysed=73 N events: 1 Placebo: N=80, drop out=6, N analysed=74, N events: 3
• **Preterm birth (34-<37weeks)**	Intervention: N=80, drop out=9, N analysed=71 N events: 7 Placebo: N=80, drop out=6, N analysed=74, N events: 13
• **Gestational age at birth**	Intervention: N=80, drop out=7, N analysed=73, Median 38.2 weeks, SD: 2.1
• **Preeclampsia**	Intervention: N=80, drop out=7, N analysed=73, N events: 0 Placebo: N=80, drop out=6, N analysed=74, N events: 1

• **Hypercalcemia, hypercalciuria & kidney stones (Confirmed hypercalcemia, defined as adj-Ca>2.60 mmol/L on two separate consecutive blood specimens)**	Intervention: N=80, drop out=7, N analysed=80, N events: 0 Placebo: N=80, drop out=6, N analysed=74, N events: 0
• **Hypercalcemia, hypercalciuria & kidney stones (Transient hypercalciuria: one urine ca:cr > 1.0 mmol/mmol)**	Intervention: N=80, drop out=7, N analysed=80, N events: 4 Placebo: N=80, drop out=6, N analysed=74, N events: 3
• **Hypercalcemia, hypercalciuria & kidney stones (Hypercalciuria: Urine ca:cr - two consecutive ca:cr > 1.0 mmol/mmol ; or ca:cr > 1.0 mmol/mm)**	Intervention: N=80, drop out=7, N analysed=80, N events: 1 Placebo: N=80, drop out=6, N analysed=74, N events: 0
• **Individual major adverse events (Gastroenteritis)**	Intervention: N=80, drop out=7, N analysed=73 N events: 1
• **Individual major adverse events (Preterm delivery with rupture of membranes)**	Intervention: N=80, drop out=7, N analysed=73 N events: 1
• **Maternal serious adverse events (Not specifically defined but included 1 of each of the following: pre-eclampsia, injury (burn), premature delivery with rupture of membranes and gastroenteritis)**	Intervention: N=80, drop out=7, N analysed=73, N events: 2 Placebo: N=80, drop out=6, N analysed=74, N events: 0
• **Caesarian section**	Intervention: N=80, drop out=7, N analysed=73, N events: 44 Placebo: N=80, drop out=6, N analysed=74, N events: 44
• **Infant serious adverse events**	Intervention: N=80, drop out=7, N analysed=73, N events: 6 Placebo: N=80, drop out=6, N analysed=74, N events: 7
• **Head circumference (Average of paired repeated measures)**	Intervention: N=80, drop out=7 (+6 missing data), N analysed=67, Median: 32.9 cm, SD: 1.8 Placebo: N=80, drop out=6 (+9 missing data), N analysed=65, Median: 33.0 cm, SD : 1, 5
• **Birth length (Average of paired repeated measures)**	Intervention: N=80, drop out=12, N analysed=68, Median: 48.2 cm, SD: 2.5 Placebo: N=80, drop out=11, N analysed=69, Median: 48.0 cm, SD: 2.9
• **Low birth weight**	Intervention: N=80, drop out=7, N analysed=63, N events: 2 Placebo: N=80, drop out=8, N analysed=74, N events: 1
• **Very low birth weight**	Intervention: N=80, drop out=7, N analysed=63, N events: 1 Placebo: N=80, drop out=8, N analysed=74, N events: 1

• **Birth weight (Average of paired repeated measures using digital scale)**	Intervention: N=80, drop out=8, N analysed=72, Median 2802 grams, SD: 543 Placebo: N=80, drop out=8, N analysed=72, Median 2788 grams, SD: 378
Limitations and other comments	
• **Limitations**	Serious concern for applicability (Race and extensive exclusion criteria)

Table 150 – Vitamin D supplementation: Evidence table of RCTs (Yu et al., 2009)

Vitamin D deficiency and supplementation during pregnancy. Yu et al., 2009[65] and Prenatal vitamin d supplementation and child respiratory health: a randomised controlled trial. Goldring et al.[80]	
Methods	
• **Design**	RCT
• **Source of funding and competing interest**	Not industry source, Confict of interest not reported for initial report (up to delivery); authors of follow-up declare that they have no competing interests
• **Setting**	Single center
• **Sample size**	180
• **Duration and follow-up**	27 wks gestation until child aged 3 yrs.
• **Statistical analysis**	
Patient characteristics	
• **Eligibility criteria**	Women attending the routine glucose challenge at 27 wks at the antenatal clinic at St. Mary's Hospital, UK from one of the following ethnic populations: Indian Asian, Middle Eastern, Black and Caucasian, who could speak English or who had a health advocate who could interpret.
• **Exclusion criteria**	Pre-existing sarcoidosis, osteomalacia, renal dysfunction and tuberculosis. Further exclusions for 3 year follow-up: severe congenital or developmental abnormalities likely to significantly affect respiratory health or lung function (e.g. congenital thoracic dystrophy)
• **Patient & disease characteristics**	Healthy women in UK of 4 specific races: Indian Asian, Middle Eastern, Black and Caucasian Without risk factor (not limited to Vit D deficient population but seems that most were Vit D deficient)
Interventions	
• **Intervention group**	Group 1: Oral vit D2 (cholecalciferol), 200,000 IU single dose, 27 wks gestation until delivery Group 2: Oral Vit D (ergocalciferol), 800 IU/d
• **Control group**	No intervention
Results	
• **Still birth/fetal death (Unexplained stillbirth at 41 wks)**	Group 1: N=60, drop out=0, N analysed=60, N events: 0 Group 2: N=60, drop out=0, N analysed=60, N events: 0 No intervention: N=60, drop out=1, N analysed=59, N events: 1

• **Neonatal death (one neonatal death at day 2 as a result of meconium aspiration)**	Group 1: N=60, drop out=0, N analysed=60, N events: 0 Group 2: N=60, drop out=0, N analysed=60, N events: 0 No intervention: N=60, drop out=1, N analysed=59, N events: 1
• **Neonatal and child death (one death aged 16 hours from meconium aspiration and one child with congenital abnormalities died post-operatively aged 17 mo)**	Group 1: N=60, drop out=0, N analysed=60, N events: 0 Group 2: N=60, drop out=0, N analysed=60, N events: 0 No intervention: N=60, drop out=1, N analysed=59, N events: 2
• **Birth weight (Small for gestational age: birth weight < 10th percentile after adjustments for gestation at delivery, infant sex, maternal ethnicity, parity, height and weight (reference #25 provided therein)**	Group 1: N=60, drop out=0, N analysed=60, N events: NR 13% Group 2: N=60, drop out=0, N analysed=60, N events: NR 15% No intervention: N=60, drop out=1, N analysed=59, NR 17%
• **Birth weight (continuous)**	Group 1: N=60, drop out=8, N analysed=52, Median: 3290 grams, SD: 467 Group 2: N=60, drop out=4, N analysed=56, Median: 3321 grams, SD: 525 No intervention: N=60, drop out=10, N analysed=50, Median: 3268 grams, SD: 585
• **Gestational age at birth**	Group 1: N=60, drop out=8, N analysed=52, Median: 40 weeks, SD: 1 Group 2: N=60, drop out=4, N analysed=56, Median: 39 weeks, SD: 2 No intervention: N=60, drop out=10, N analysed=59, Median: 40 weeks, SD: 1
• **Hypercalcemia**	Group 1: N=60, drop out=2 for delivery data, N analysed=60, N events: 0 Group 2: N=60, drop out=5 for delivery data, N analysed=60, N events: 0 No intervention: N=60, drop out=4 for delivery data, N analysed=59, N events: 0
• **Maternam nephritic syndrome**	Group 1: N=60, drop out=0, N analysed=60, N events: 0 Group 2: N=60, drop out=0, N analysed=60, N events: 0 No intervention: N=60, drop out=1, N analysed=59, N events: 1
Limitations and other comments	
• **Limitations**	Serious concern for applicability (serious for Race and very serious for Stat dose of Vit D)

Table 151 – Vitamin D supplementation: Evidence table of observational study (Althaus et al.)

Vitamin D supplementation and neonatal outcomes in term pregnancies. Althaus et al.	
Methods	
• **Design**	Observational cohort
• **Source of funding and competing interest**	Not reported (NR)
• **Setting**	Unclear
• **Sample size**	Those who delivered at term - no other details
• **Duration and follow-up**	NR
• **Statistical analysis**	
Patient characteristics	
• **Eligibility criteria**	Those who delivered at term - no other details
• **Exclusion criteria**	NR
• **Patient & disease characteristics**	Those who delivered at term - no other details Documented hypovitaminosis
Interventions	
• **Intervention group**	Intervention: vit D (type not reported), dose: 50 000 IU, 1/week
• **Control group**	No intervention
Results	
• **NICU admission**	Duration of observation: NR Intervention: drop out=NR, N analysed=NR, N events: NR Comparator: drop out=NR, N analysed=189, N events: NR
• **Apgar score (please note timing in definition) <7 at five minutes**	Duration of observation: NR Intervention: drop out=NR, N analysed=NR, N events: NR
Limitations and other comments	
• **Limitations**	Very serious concern for applicability (Documented hypovitaminosis D and only term deliveries)

Table 152 – Vitamin D supplementation: Evidence table of observational study (Cremers et al., 2011)

Maternal and child's vitamin D supplement use and vitamin D level in relation to childhood lung function: the KOALA Birth Cohort Study. Cremers ert al., 2011[72]	
Methods	
• **Design**	Observational cohort
• **Source of funding and competing interest**	Not industry source, No confict of interest
• **Setting**	Multicenter
• **Sample size**	2834 in KOALA birth cohort; 436 eligible for study cohort KOALA= Child, parents and health: lifestyle and genetic constitution (acronym uses Dutch words
• **Duration and follow-up**	~7 years (Participants enrolled between 14-18 weeks gestation; data collected up to child at 6-7 years of age)
• **Statistical analysis**	
Patient characteristics	
• **Eligibility criteria**	Healthy pregnant women (from another study on pregnancy-related pelvic girdle pain among women in the Netherlands and from other sources specifically targeted to recruit a sample of anthroposophic participants) who had availability of biosamples, availability of questionnaire data at 34 weeks pregnancy, and written informed consent)
• **Exclusion criteria**	Birth at less than 37 weeks of pregnancy and congenital abnormalities related to immunity (such as Down's syndrome)
• **Patient & disease characteristics**	Healthy pregnant women from the Netherlands with a conventional lifestyle and pregnant women with an alternative lifestyle with regard to child-rearing practices, diet (organic, vegetarian), vaccination programs and/or use of antibiotics Healthy without specific risk factor for Vit D deficiency BMI in prepregnancy: KOALA birth cohort: 23.6 (4.0); Study cohort: 23.8 (3.7) Not limited to Vit D deficient population but average was below 50 nmol/L
Interventions	
• **Intervention group**	Group 1: Vit D (type not reported), dose >=10 ug, Daily dose (frequency of dosing not reported) Group 2: Oral Vit D, <10 ug, Daily dose (frequency of dosing not reported) Duration of treatment: Assessed at 34 wks, and multivitamin use classified by duration and period of use throughout pregnancy
• **Control group**	No intervention
Results	
• **Lung function (Children's lung function at age 6-7 years: Forced expiratory volume in 1 second)**	Duration of observation: Mean 6-7 years of age Intervention: drop out=923, N analysed=221, N events: NA Comparator 1: drop out=923, N analysed=38, N events: NA Comparator 2: drop out=923, N analysed=177, N events: NA
• **Lung function (Children's lung function: Forced vital capacity z-score)**	Duration of observation: Mean 6-7 years of age Intervention: drop out=923, N analysed=221, N events: NA Comparator 1: drop out=923, N analysed=38, N events: NA Comparator 2: drop out=923, N analysed=177, N events: NA
Limitations and other comments	
• **Limitations**	See quality appraisal

Table 153 – Vitamin D supplementation: Evidence table of observational study (Erkkola et al.2009)

Maternal vitamin D intake during pregnancy is inversely associated with asthma and allergic rhinitis in 5-year-old children. Erkkola et al., 2009[79]	
Methods	
• **Design**	Observational cohort
• **Source of funding and competing interest**	Not industry source, No confict of interest
• **Setting**	Multicenter
• **Sample size**	4193 invited; 2145 eligible at 5 years (with maternal dietary data and follow-up at 5 years); 1825 who agreed to participate in this study
• **Duration and follow-up**	5 years
• **Statistical analysis**	
Patient characteristics	
• **Eligibility criteria**	Families with an infant born between 20 October 1997 and 31 December 2002 carrying increased genetic risk for Type 1 diabetes (defined as high risk genotype: HLA-DQB1*02/*0302 or moderate risk genotype HLA-DQB1*0302/x, where x = other than *02, *0301 or *0602) recruited after delivery in the Turku, Tampere and Oulu University hospitals (Finland)
• **Exclusion criteria**	Infants with congenital anomalies or severe systemic disease are excluded, as are families in which both parents do not understand Finnish, Swedish or English
• **Patient & disease characteristics**	Mothers/families of children with increased genetic risk of type 1 diabetes who was born between 20 October 1997 and 30 September 2001 in 3 hospitals in Finland. Special population (families of infants carrying increased genetic risk for Type 1 diabetes) without specific risk factor for Vit D deficiency
Interventions	
• **Intervention group**	Intervention: Oral vit D (mixed sources, type not reported), mean dose (SD): 1.3 (2.6) ug
• **Control group**	No intervention
Results	
• **Asthma (Persistent asthma: diagnosed by a physician, with the child having had either wheezing or asthma medication during the previous 12 months)**	Duration of observation: 5 years Intervention: drop out=NR, N analysed=534, N events: NR (93 total arms) Comparator: drop out=NR, N analysed=1135, N events: NR (93 total arms)
Limitations and other comments	
• **Limitations**	See quality appraisal

Table 154 – Vitamin D supplementation: Evidence table of observational study (Goldring et al., 2013)

Prenatal vitamin d supplementation and child respiratory health: a randomised controlled trial. Goldring et al., 2013[80]	
Methods	
• **Design**	Observational study (RCT but this had been moved to observational due to the long-term follow-up)
• **Source of funding and competing interest**	Not industry source, Conflict of interest Not reported for initial report (up to delivery); authors of follow-up report declare that they have no competing interests
• **Setting**	Single,
• **Sample size**	180
• **Duration and follow-up**	~3 years, 3 months (27 weeks gestation until child at age 3)
• **Statistical analysis**	
Patient characteristics	
• **Eligibility criteria**	Women attending the routine glucose challenge at 27 weeks at the antenatal clinic at St. Mary's Hospital, UK from one of the following ethnic populations: Indian Asia, Middle Eastern, Black and Caucasian who could speak English or who had a health advocate who could interpret.
• **Exclusion criteria**	Pre-existing sarcoidosis, osteomalacia, renal dysfunction and tuberculosis; further exclusions for 3 year follow-up: severe congenital or developmental abnormalities likely to significantly affect respiratory health or lung function (e.g. congenital thoracic dystrophy)
• **Patient & disease characteristics**	Mixed races - chosen based on race Healthy with risk factor Not limited to Vit D deficient population but baseline median was below 50 nmol/L (26 nmol/L)
Interventions	
• **Intervention group**	Intervention: Oral vit D2 (calciferol), 200 000 IU, single dose Oral Vit D (ergocalciferol), 800 IU, Once daily, ~12 weeks (from 27 weeks gestation to term)
• **Control group**	No intervention
Results	
• **Asthma (Wheeze ever' in past 3 years - defined by the International Study of Asthma and Allergies in Childhood (ISAAC))**	Duration of observation: Birth to 3 years Intervention: N=60, drop out=8, N analysed=52, N events: 15 Comparator 1: N=60, drop out=4, N analysed=56, N events: 11 Comparator 2: : N=60, drop out=10, N analysed=50, N events: 14
• **Asthma (Any bronchodilator use)**	Duration of observation: Birth to 3 years Intervention: N=60, drop out=8, N analysed=52, N events: 14 Comparator 1: N=60, drop out=4, N analysed=56, N events: 10 Comparator 2: N=60, drop out=11, N analysed=49, N events: 4
Limitations and other comments	
• **Limitations**	Serious concern for applicability (Race) and very serious for Stat dose of Vit D

Table 155 – Vitamin D supplementation: Evidence table of observational study (Haugen et al., 2009)

Vitamin D supplementation and reduced risk of preeclampsia in nulliparous women. Haugen et al., 2009[78]	
Methods	
• **Design**	Observational cohort
• **Source of funding and competing interest**	Not industry source, No confict of interest
• **Setting**	Multicenter
• **Sample size**	23 423
• **Duration and follow-up**	Week 15 through to delivery
• **Statistical analysis**	
Patient characteristics	
• **Eligibility criteria**	Pregnant women part of the Norwegian Mother and Child Cohort Study with singleton birth and data from both Q1 and Q2 (one analysis was limited to those with Q3 data as well) and with a registered food intake between 4500 kJ and 20,000 kJ
• **Exclusion criteria**	NR
• **Patient & disease characteristics**	Pregnant women in Norway Healthy without specific risk factor for Vit D deficiency BMI in prepregnancy: < 20: 3113 (13%); 20-24: 12,906 (55%); 25-29: 4653 (20%); >=30: 1988 (9%); missing data: 763 (3%)
Interventions	
• **Intervention group**	Intervention: Oral vit D (type not reported), dose not reported Oral vit D another dose (in case more than one comparator with different doses) +/- others, 20 ug
• **Control group**	No intervention Vit D another dose (in case more than one comparator with different doses) +/- others, dose 10.0-14.9 ug Not reported only that this group is supplements without vitamin D Vit D another dose (in case more than one comparator with different doses) +/- others, dose 5.0-9.9 ug Vit D another dose (in case more than one comparator with different doses) +/- others, dose< 5.0 ug
Results	
• **Preeclampsia (As registered in the Medical Birth Registry of Norway)**	Duration of observation: Unclear but at least 15 weeks gestation until delivery Intervention: drop out=NR, N analysed=18695, N events: 958 Comparator 1: drop out=NR, N analysed=2930, N events: 175 Comparator 2: drop out=NR, N analysed=1798, N events: 13
• **Preeclampsia**	Duration of observation: Unclear but at least 15 weeks gestation until delivery Group 1: drop out=NR, N analysed=2924, N events: 138 Comparator 1: drop out=NR, N analysed=1541, N events: 69 Comparator 2: drop out=NR, N analysed=2465, N events: 107

	Comparator 3: drop out=NR, N analysed=5374, N events: 311 Comparator 4: drop out=NR, N analysed=6291, N events: 333 Comparator 5: drop out=NR, N analysed=4728, N events: 309
Limitations and other comments	
• **Limitations**	See quality appraisal

Table 156 – Vitamin D supplementation: Evidence table of observational study (Jacobsen et al., 2013)

Influence of early exposure to vitamin D for later development of type 1 diabetes - the d-tect study. Annals of Nutrition and Metabolism. Jacobsen, et al., 2013[81]	
Methods	
• **Design**	Observational cohort
• **Source of funding and competing interest**	Not reported (NR)
• **Setting**	Unclear
• **Sample size**	NR
• **Duration and follow-up**	NR
• **Statistical analysis**	
Patient characteristics	
• **Eligibility criteria**	NR
• **Exclusion criteria**	NR
• **Patient & disease characteristics**	All people registered in the Danish childhood Diabetes Registry - all patients born since 1981. Healthy without specific risk factor for Vit D deficiency
Interventions	
• **Intervention group**	Intervention: Oral vit D (type not reported), dose not reported
• **Control group**	No intervention
Results	
• **Type 1 diabetes mellitus**	Duration of observation: NR Intervention: drop out=NR, N analysed=NR, N events: NR Comparator: drop out=NR, N analysed=NR, N events: NR
Limitations and other comments	
• **Limitations**	See quality appraisal

Table 157 – Vitamin D supplementation: Evidence table of observational study (Kalra et al., 2012)

Effect of vitamin D supplementation during pregnancy on neonatal mineral homeostasis and anthropometry of the newborn and infant. Kalra et al., 2012[71]	
Methods	
• **Design**	Observational study (Mixed: two Vit D groups randomized; no vit D group concurrent, as such it was considered as observational study)
• **Source of funding and competing interest**	Notindustry source, No conflict of interest
• **Setting**	Single, developing country
• **Sample size**	299 randomized to one of two treatment arms; 43 served as controls (recruited in 3rd trimester and receiving 'usual' care)
• **Duration and follow-up**	12-15 months (12-24 wks gestation to 9 months post-partum)
• **Statistical analysis**	
Patient characteristics	
• **Eligibility criteria**	Pregnant women who attended the antenatal clinic in Queen Mary Hospital, India between 12 and 24 weeks gestation
• **Exclusion criteria**	Subjects already on Ca or vitamin D, anticonvulsants, antitubercular treatment or had any medical condition that affected Ca and vitamin D metabolism (including renal and hepatic disease)
• Patient & disease characteristics	Indian women Healthy with risk factor BMI at trial entry: (total sample with outcome data): 23.5 (3.6); total who did not return for follow-up: 22.4 (3.4) Not limited to Vit D deficient population but baseline median was below 50 nmol/L (31 nmol/L)
Interventions	
• **Intervention group**	Intervention: Oral Vit D3 (cholecalciferol) 3000 ug, 2 single doses; 1 at induction (12-24 weeks) and 1 at 28 weeks + Ca (1 g calcium carbonate), once daily Vit D lower dose (+/- others), 1500 ug, single dose at 12-24 weeks gestation + Ca, 1 g calcium carbonate, once daily
• **Control group**	Ca, 1g calcium carbonate,
Results	
• **Caesarean section**	Duration of observation: at delivery Intervantion: drop out=unclear, N analysed=49, N events: NR Comparator 1: drop out=unclear, N analysed=48, N events: NR Comparator 2: drop out=unclear, N analysed=43, N events: NR
• **Gestational hypertension**	Duration of observation: 12-15 months (12-24 wks gestation to 9 months post-partum) Intervention: drop out=unclear, N analysed=49, N events: NR Comparator 1: drop out=unclear, N analysed=48, N events: NR

	Comparator 2: drop out=unclear, N analysed=43, N events: NR
• **Still birth/fetal death**	Duration of observation: 12-15 months (12-24 wks gestation to 9 months post-partum) Intervention: drop out=unclear, N analysed=49, N events: NR Comparator 1: drop out=unclear, N analysed=48, N events: NR Comparator 2: drop out=unclear, N analysed=43, N events: NR
• **Pregnancy-related complications (composite endpoint but not pre-specified).**	Duration of observation: 12-15 months (12-24 wks gestation to 9 months post-partum) Intervention: drop out=unclear, N analysed=49, N events: NR Comparator 1: drop out=unclear, N analysed=48, N events: NR Comparator 2: drop out=unclear, N analysed=43, N events: NR
• **Gestational diabetes (Pregnancy-related complications (composite endpoint but not pre-specified))**	Duration of observation: 12-15 months (12-24 wks gestation to 9 months post-partum) Intervention: drop out=unclear, N analysed=49, N events: NR Comparator 1: drop out=unclear, N analysed=48, N events: NR Comparator 2: drop out=unclear, N analysed=43, N events: NR
• **Birth weight (continuous outcome)**	Duration of observation: at delivery Intervention 1: drop out=unclear, N analysed=35, Mean: 3.03 Kg, SD: 3.85 Comparator 1: drop out=unclear, N analysed=36, Mean: 3.08 Kg, SD: 4.06 Comparator 2: drop out=unclear, N analysed=38, Mean: 2.77 Kg, SD: 3.99
• **Head circumference**	Duration of observation: at delivery Intervention 1: drop out=unclear, N analysed=35, Mean: 34.4 cm, SD: 0.6 Comparator 1: drop out=unclear, N analysed=36, Mean: 34.5 cm, SD: 0.9 Comparator 2: drop out=unclear, N analysed=38, Mean: 33.6 cm, SD: 0.8
• **Birth length**	Duration of observation: at delivery Intervention 1: drop out=unclear, N analysed=35, Mean: 50.1 cm, SD: 0.9 Comparator 1: drop out=unclear, N analysed=36, Mean: 50.3 cm, SD: 0.9 Comparator 2: drop out=unclear, N analysed=38, Mean: 49.4 cm, SD: 2.4
• **Gestational age**	Duration of observation: at delivery Intervention 1: drop out=unclear, N analysed=35, Mean: NR Comparator 1: drop out=unclear, N analysed=36, Mean: NR Comparator 2: drop out=unclear, N analysed=38, Mean: NR
Limitations and other comments	
• **Limitations**	Serious concern for applicability (South Asian race and low-middle income socioeconomic group)

Table 158 – Vitamin D supplementation: Evidence table of observational study (Marjamaki et al., 2010, Companion[79])

Maternal intake of vitamin D during pregnancy and risk of advanced beta cell autoimmunity and type 1 diabetes in offspring. Marjamaki et al., 2010,[76] Companion[79]	
Methods	
• **Design**	Observational cohort
• **Source of funding and competing interest**	Not industry source, No confict of interest
• **Setting**	Multicenter
• **Sample size**	4297 invited; 3723 with maternal dietary intake data
• **Duration and follow-up**	Mean 4.3 years (range: 0.2 - 8.9 years).
• **Statistical analysis**	
Patient characteristics	
• **Eligibility criteria**	Families with an infant born between 20 October 1997 and 31 December 2002 carrying increased genetic risk for Type 1 diabetes (defined as high risk genotype: HLA-DQB1*02/*0302 or moderate risk genotype HLA-DQB1*0302/x, where x = other than *02, *0301 or *0602) recruited after delivery in the Turku, Tampere and Oulu University hospitals (Finland)
• **Exclusion criteria**	Infants with congenital anomalies or severe systemic disease are excluded, as are families in which both parents do not understand Finnish, Swedish or English
• **Patient & disease characteristics**	Mothers/families of children with increased genetic risk of type 1 diabetes who were born between 20 October 1997 and 31 December 2002 in 3 hospitals in Finland Special population (families of infants carrying increased genetic risk for Type 1 diabetes) without specific risk factor for Vit D deficiency
Interventions	
• **Intervention group**	Intervention: Oral vit D (mixed sources, type not reported), mean dose (SD): 1.3 (2.6) ug
• **Control group**	No intervention
Results	
• **Type 1 diabetes mellitus**	Duration of observation: Mean 4.3 (range: 0.2-8.9) Intervention: N=unclear, drop out=NR, N analysed=1117, N events: NR (55 total arms) Comparator: N=unclear, drop out=NR, N analysed=2606, N events: NR (55 total arms)
Limitations and other comments	
• **Limitations**	See quality appraisal

Table 159 – Vitamin D supplementation: Evidence table of observational study (Marya et al., 1981)

Effects of vitamin D supplementation in pregnancy. Marya et al., 1981[84]	
Methods	
• **Design**	Non-randomized experimental (for comparisons of interest)
• **Source of funding and competing interest**	Not reported
• **Setting**	Single, developing country
• **Sample size**	Unclear: "120 pregnant women investigated at labour"
• **Duration and follow-up**	~3 months (3rd trimester of pregnancy until delivery)
• **Statistical analysis**	
Patient characteristics	
• **Eligibility criteria**	NR
• **Exclusion criteria**	Patients with complications such as preeclampsia, antepartum haemorrhage, or twins Healthy with risk factor
• **Patient & disease characteristics**	Unclear
Interventions	
• **Intervention group**	Intervention: Oral Vit D2 (calciferol), 600 000 IU, 2 single doses; 1 in 7th and 1 in 8th month of pregnancy Oral Vit D lower dose (+/- others), 1200 IU, once daily + Ca, 375 , once daily, Higher dose given in 7th and 8th month of pregnancy; lower dose given in third trimester daily until delivery
• **Control group**	No intervention
Results	
• **Birth weight (continuous)**	Duration of observation: NR Intervention: drop out=unclear, N analysed=20, Median: 3.14 grams, SD: 0.45 Comparato 1: drop out=unclear, N analysed=25, Median: 2.89 grams, SD: 0.32 Comparator 2: drop out=unclear, N analysed=75, Median: 2.73 grams, SD: 0.36:
Limitations and other comments	
• **Limitations**	Serious concern for applicability (South Asian race and cultural differences)

Table 160 – Vitamin D supplementation: Evidence table of observational study (Maslova et al., 2013)

Vitamin D intake in mid-pregnancy and child allergic disease - a prospective study in 44,825 Danish mother-child pairs. Maslova et al., 2013[74]	
Methods	
• **Design**	Observational cohort
• **Source of funding and competing interest**	Not industry source, No confict of interest
• **Setting**	Multicenter
• **Sample size**	101, 045 in full cohort; 87, 056 with singletons/first enrolled pregnancy in cohort with 45004 with Vit D supplement data
• **Duration and follow-up**	~ 7 years (Enrolled during first antenatal visit, week 6-10 and followed up to child at age 7 years
• **Statistical analysis**	
Patient characteristics	
• **Eligibility criteria**	Women were eligible for enrolment if they could speak Danish and planned to carry to term; this analysis was limited to those carrying singletons, first enrolled pregnancies in the cohort and those with Vit D supplement exposure information from the food frequency questionnaire administered at 25 weeks gestation
• **Exclusion criteria**	Women who reported Vit D intake resulting in unrealistic energy intake estimates (set to <2500kJ/day or > 25,000 kJ/day
• **Patient & disease characteristics**	Danish pregnant women Healthy without specific risk factor for Vit D deficiency BMI in prepregnancy: Approximately 4% BMI <=18.5; 68% 18.6-24.9; 20% 25-29.9; 8% >=30 Mixed deficient and not deficient in vitamin D
Interventions	
• **Intervention group**	Intervention: Oral vit D (mix - mostly Vit D 3 but some Vit D 2), dose Quintile 5 (IU not reported) - median 15.0 ug/day, Daily dose (frequency of dosing not reported) Other (mix - mostly Vit D 3 but some Vit D 2), dose: Quintile 4 (IU not reported) - median 10.0 ug/day, Daily dose (frequency of dosing not reported)
• **Control group**	Other (mix - mostly Vit D 3 but some Vit D 2), dose: Quintile 4 (IU not reported) - median 7.1 ug/day, Daily dose (frequency of dosing not reported Other (mix - mostly Vit D 3 but some Vit D 2), dose: Quintile 4 (IU not reported) - median 5.0 ug/day, Daily dose (frequency of dosing not reported Other (mix - mostly Vit D 3 but some Vit D 2), dose: Quintile 4 (IU not reported) - median 0.0 ug/day, Daily dose (frequency of dosing not reported
Results	
• **Asthma (Ever prescribed asthma cases)**	Duration of observation: 7 years (birth to 7 years of age) Intervention: drop out=NR, N analysed=2062, N events: 671 Comparator 1: drop out=NR, N analysed=11860, N events: 3842

	Comparator 2: drop out=NR, N analysed=1589, N events: 440 Comparator 3: drop out=NR, N analysed=8872, N events: 2736 Comparator 4: drop out=NR, N analysed=4374, N events: 1216
• **Asthma (Current asthma at age 7)**	Duration of observation: 7 years (birth to 7 years of age) Intervention: drop out=NR, N analysed=2058, N events: 86 Comparator 1: drop out=NR, N analysed=11828, N events: 481 Comparator 2: drop out=NR, N analysed=1589, N events: 49 Comparator 3: drop out=NR, N analysed=8849, N events: 348 Comparator 4: drop out=NR, N analysed=4362, N events: 158
• **Asthma (Ever Asthma up to 18 months of age - self-reported doctor asthma diagnosis)**	Duration of observation: 7 years (birth to 7 years of age) Intervention: drop out=NR, N analysed=2387, N events: 417 Comparator 1: drop out=NR, N analysed=14064, N events: 2443 Comparator 2: drop out=NR, N analysed=1761, N events: 266 Comparator 3: drop out=NR, N analysed=101472, N events: 1675 Comparator 4: drop out=NR, N analysed=5071, N events: 835
Limitations and other comments	
• **Limitations**	See quality appraisal

Table 161 – Vitamin D supplementation: Evidence table of observational study (Rochati et al., 2010)

Maternal vitamin D intake during pregnancy increases gene expression of ILT3 and ILT4 in cord blood. Rochat et al., 2010[77]	
Methods	
• **Design**	Observational cohort
• **Source of funding and competing interest**	Not industry source, No confict of interest
• **Setting**	Multicenter
• **Sample size**	1133
• **Duration and follow-up**	Third trimester until 2 months postpartum
• **Statistical analysis**	
Patient characteristics	
• **Eligibility criteria**	Pregnant women who lived or worked on family-run farms where any kind of livestock was kept were assigned to the farm group; reference group was composed of women from the same rural areas not living or working on a farm

• **Exclusion criteria**	Living on farms without livestock, maternal age below 18 years, twin pregnancies, home births, premature deliveries, genetic disease in the offspring, absent telephone connection, insufficient knowledge of the country's language, intention to move away from the study area and commuting to a metropolitan area.
• **Patient & disease characteristics**	Pregnant women from rural areas of Austria, Finland, France, Germany and Switzerland; data only from women from France and Finland Healthy without specific risk factor for Vit D deficiency
Interventions	
• **Intervention group**	Intervention: Oral vit D (type not reported), dose (not reported)
• **Control group**	No intervention
Results	
• **Gestational age**	Duration of observation: NA Intervention: drop out=NR, N analysed=79, Mean: 40 weeks, SD: 1.2 Comparator: drop out=NR, N analysed=270, Mean: 40 weeks, SD: 1.09
• **Birth weight (continuous outcome)**	Duration of observation: NA Intervention: drop out=NR, N analysed=79, Mean: 3720 grams, SD: 523 Comparator: drop out=NR, N analysed=270, Mean: 3543 grams, SD: 449
• **Caesarean Section**	Duration of observation: NA Intervention: drop out=NR, N analysed=79, N events: 7 Comparator: drop out=NR, N analysed=270,
• **Pregnancy complications (no further information provided)**	Duration of observation: NA Intervention: drop out=NR, N analysed=79, N events: 7 Comparator: drop out=NR, N analysed=270,
Limitations and other comments	
• **Limitations**	Serious concern for applicability (Strictly rural settings. Baseline rates of prematurity and sequelae as well as atopy are likely to be different than in urban settings)

9.8. Risk of preterm birth

9.8.1. Screening for preterm birth risk

Table 162 – Preterm birth risk: Evidence table of systematic reviews regarding the diagnosis of pathology or effect of Intervention (Alexander et al., 2010)

Repeat digital cervical assessment in pregnancy for identifying women at risk of preterm labour (Review). Alexander S., et al. 2010(Alexander, 2010 #42)	
Methods	
• **Design**	Systematic Review and Meta-analysis
• **Source of funding and competing interest**	Sources of Funding: Université Libre de Bruxelles (ULB) - School of Public Health, Belgium Conflict of Interest: Sophie Alexander was co-author of the Buekens 1994 included study. Trial assessment and data extraction for this trial was carried out independently by two members of the review team who were not involved in the study.
• **Search date**	September 2009
• **Searched databases**	Quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL); weekly searches of MEDLINE; handsearches of 30 journals and the proceedings of major conferences; weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts; In addition, we searched CENTRAL (*The Cochrane Library* 2009, Issue 3) using the search strategy listed in Appendix 1
• **Included study designs**	RCTs comparing repeat digital cervical assessment with internal examination limited to clinical indication or no internal examination; Quasi-RCTs
• **Number of included studies**	2
• **Statistical analysis**	Used fixed-effect inverse variance meta analysis for combining data where trials are examining the same intervention, and judged the trials' populations and methods sufficiently similar. Where there was suspected clinical or methodological heterogeneity between studies sufficient to suggest that treatment effects differed between trials, used random-effects meta analysis; assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions;* publication bias not assessed
Patient characteristics	
• **Eligibility criteria**	All pregnant women with repeat digital cervical assessment all through pregnancy
• **Exclusion criteria**	Have not included studies where repeat cervical assessment is only a component of complex interventions targeted at decreasing preterm birth
• **Patient & disease characteristics**	Buekens (1994): All women booked for prenatal care in seven European countries (Belgium, Denmark, Hungary, Ireland, Italy, Portugal, Spain). Mortensen (1987): Review has only included women in group III of this study – women with no complications during pregnancy delivering in the county of Skaraborg in 1982
Interventions	
• **Intervention group**	Pregnant women evaluated with digital cervical examination at every prenatal visit (Buekens) or at weeks 24, 28 and 32 weeks (Moretensen)

• **Control group**	No cervical screening (except where medically indicated)
Results	
Preterm Birth <37 weeks	Systematic digital cervical examination vs. no examination unless medically indicated OR = 1.05; 95% CI [0.85, 1.31]
Preterm Birth <34 weeks	Systematic digital cervical examination vs. no examination unless medically indicated OR = 0.93 95% CI [0.65, 1.34]
Low Birthweight	Systematic digital cervical examination vs. no examination unless medically indicated OR = 0.85 95% CI [0.69, 1.04]
Very Low Birthweight	Systematic digital cervical examination vs. no examination unless medically indicated OR = 0.81 95% CI [0.53, 1.24]
Stillbirth	Systematic digital cervical examination vs. no examination unless medically indicated OR = 1.09 95% CI [0.61, 19.5]
Neonatal Death	Systematic digital cervical examination vs. no examination unless medically indicated OR = 1.47 95% CI [0.76, 2.84]
NICU Admission	Systematic digital cervical examination vs. no examination unless medically indicated OR = 1.09 95% CI [0.93, 1.27]
IUGR	Systematic digital cervical examination vs. no examination unless medically indicated OR: Not estimable
Respiratory Distress Syndrome	Systematic digital cervical examination vs. no examination unless medically indicated OR: Not estimable
Limitations and other comments	
• **Limitations**	Internal Validity: See RoB for included studies External Validity: Moderate applicability

9.8.2. Progesterone

Table 163 – Descriptive summary assessment of eight RCTs included of progesterone versus no progesterone in prevention of preterm birth

S#	Author, Year of publication	Intervention vs. comparator	Cervical length	Applicability concern	Risk of Bias	Population risk status
1	Bimbashi, 2013[85]	Vaginal progesterone (dose and frequency not reported; from 24- 34 wks GA) vs. no active intervention	<30mm	Unclear (limited information to assess applicability)	Unclear	Unclear
2	Brenner, 1962[90]	Oral progesterone, medroxyprotesterone acetate, (20mg QID from 36 and 38 wks GA to delivery) vs. placebo	Unclear	Very serious (not exclusively low risk, enrolled and treated late in pregnancy (from a 36 wks gestation at the earliest); no consideration of cervical length; primarily non-white (~92%)	Unclear	Predominantly low
3	Defranco, 2007[87][7]	Bioadhesive-vaginal progesterone (90mg/day from 18 and 22 wks +6 days GA to 37wks GA/delivery/PROM) vs. placebo	<25mm	Unclear (unclear if women had other risk factors in addition to short cervix)	High risk	Unclear
4	Fonseca, 2007[89]	Vaginal progesterone (200mg/day, from 24-33 wks+6 days GA) vs. placebo	<15	Serious (not exclusively low risk population)	Unclear	Predominantly low (low for subgroup for PTB< 34 weeks)
5	Grobman, 2012[4]	17-alpha-hydroxyprotesterone caporate (1ml= 250mg/wk from 16 and 23 wks+6 days of GA to 36 wks +6 days GA or delivery (whichever occurred first) vs. placebo	<30mm (<15;15-30;<10;10-20; 20-30)	Serious (One-third of the women had previous miscarriage <19 weeks and approximately half were of black race)	Unclear Unclear	Predominantly low
6	Hassan, 2011[86]	Vaginal progesterone (90mg/day) vs. Placebo (vaginal gel once/day)from between 20 wks and 23 wks 6 days GA to 36 wks 6 days/rupture of membranes/delivery (whichever occurred first)	10-20mm	Serious (a subset of the population has a history of preterm birth and cervical surgery)	High risk	Predominantly low (low for subgroup for PTB< 33 weeks)
7	Moghtadaei, 2008[91]	17 alpha-hydroxyprogestrone caproate (250mg/wk from 16-20 wk GA to 34 wk GA) vs. placebo	Normal cervix	Very serious (study conducted in developing country. Unclear if exclusively low risk population as women are aged >=35 years)	Unclear	Unclear
8	van Os, 2014[88]	Vaginal progesterone (200mg/day from 18-34 wk GA or delivery) vs. placebo	<30mm	No	Unclear	Low

Table 164 – Progesterone in prevention of preterm birth risk: Evidence table of RCTs (Bimbashi et al., 2013)

Progesterone for prevention of preterm birth. Bimbashi et al., 2013[85]	
Methods	
• **Design**	Randomized controlled trial.
• **Source of funding and competing interest**	Funding source not reported; No statement regarding declaration of interest
• **Setting**	Setting not reported (authors are from one university hospital in Albania)
• **Sample size**	Number of patients needed: NR Number of patients included: NR
• **Duration and follow-up**	Start and end dates of the study: NR Inclusion and follow-up periods: From between 20 and 24 wks gestation; endpoint of follow-up unclear. At least to hospital discharge.
• **Statistical analysis**	Not stated
Patient characteristics	
• **Eligibility criteria**	Women with a singleton pregnancy with a cervical length <30 mm at two independent measurements between 20 and 24 wks gestation.
• **Exclusion criteria**	NR
• **Patient & disease characteristics**	Women with a singleton pregnancy with a cervical length <30 mm at two independent measurements between 20 and 24 wks gestation. No other details. Baseline characteristics and risk of confounding unclear as no baseline characteristics are presented.
Interventions	
• **Intervention group**	***Group 1:*** Progesterone (vaginal progesterone tablets) from 24 to 34 wks gestation Details: No other details provided
• **Control group**	***Group 2:*** No additional treatment from 24-34 wks gestation
Results	
• **Preterm birth**	*Preterm birth ≤ 34 wks (spontaneous) (Progesterone vs. no treatment)* 9.2% vs. 17.2% (group sizes not reported)
• **Neonatal harms**	*Major adverse outcomes before discharge from hospital – neonatal morbidity and mortality (Progesterone vs. no treatment)* Unclear: “The study also found a 33% decrease in neonatal morbidity and mortality”
Limitations and other comments	
• Limitations	External validity/applicability: Unclear (This is an abstract/poster and has limited information to rate applicability) Internal validity: Unclear risk of bias (This is an abstract/poster and has limited information to rate risk of bias; no details regarding most major domains)

Table 165 – Progesterone in prevention of preterm birth risk: Evidence table of RCTs (Brenner and Hendricks, 1962)

Effect of medroxyprogesterone acetate upon the duration and characteristics of human gestation and labour. Brenner and Hendricks, 1962[90]	
Methods	
• **Design**	Randomized double-blind controlled trial.
• **Source of funding and competing interest**	Public research funds and charity foundation (National Institutes of Health United States Public Health Service and Josiah Macy Jr., Foundation program); No statement regarding declaration of interest
• **Setting**	Antepartum clinic of University Hospitals of Cleveland (USA); unclear if urban or rural; unclear if single or multicentre
• **Sample size**	Number of patients needed: NR Number of patients randomized: 200 Number of patients included: 195
• **Duration and follow-up**	Start and end dates of the study: June-Dec. 1959 Inclusion and follow-up periods: From between 36-38 weeks gestation until delivery
• **Statistical analysis**	Not stated
Patient characteristics	
• **Eligibility criteria**	Women between 36 and 38 weeks gestation, apparently accurate menstrual history and willingness to participate
• **Exclusion criteria**	Not reported
• **Patient & disease characteristics**	Women between 36 and 38 weeks gestation enrolled in the ante partum clinic of University Hospitals of Cleveland (Ohio, USA); Approx. 71% with no history of PTB; no details on previous cervical surgery, uterine anomalies, polyhydramnios. Primarily non-white (~92%), no consideration of cervical length. Few confounders reported in this paper (although full thesis apparently available); report states only that 'groups were highly comparable by age, by previous obstetric experience (with details in a Table) and by race (with details in text)'
Interventions	
• **Intervention group**	***Group 1:*** Progesterone (Oral medroxyprogesterone acetate tablet) [4x20 mg tablets/day] from between 36 to 38 weeks gestation until delivery Additional monitoring/treatment for all study groups: Followed-up at weekly intervals
• **Control group**	***Group 2:*** Placebo (tablet base) [4 tablets/day] from between 36 to 38 weeks gestation until delivery Additional monitoring/treatment for all study groups: As described above.
Results	
• **Offspring death**	*Intrauterine death (Progesterone vs. Placebo)* 1/98 vs. 0/97 *Neonatal death at delivery (Progesterone vs. Placebo)* 0/98 vs. 1/97
• **Neonatal survival without morbidities**	*'Infants described as being in good condition when they left the hospital'(Progesterone vs. Placebo)* 97/98 vs. 96/97
• **Maternal harms/complications**	*Post-partum complications* "Post-partum complications were highly comparable in the two groups"

Limitations and other comments	
• **Limitations**	External validity/applicability: Very serious concern (not exclusively low risk, enrolled and treated late in pregnancy (from a 36 weeks gestation at the earliest); no consideration of cervical length; primarily non-white (~92%)) Internal validity: Unclear risk of bias (due to unclear method of randomization, concealment of allocation, risk of selective outcome reporting (no protocol or registration; this is an old study), no statement regarding COI and very little data with respect to potential confounders)

Table 166 – Progesterone in prevention of preterm birth risk: Evidence table of RCTs (DeFranco et al., 2007)

Vaginal progesterone is associated with a decrease in risk for early preterm birth and improved neonatal outcome in women with a short cervix: a secondary analysis from a randomized, double-blind, placebo-controlled trial. DeFranco et al., 2007[87]	
Methods	
• **Design**	Randomized controlled trial.
• **Source of funding and competing interest**	Healthcare industry (Columbia Laboratories, Inc); Report states declarations of interest (One author is a consultant and has received honoraria from Cook Biotech, Inc and another is an employee of Columbia Laboratories, Inc.)
• **Setting**	Multicentre trial (patients from 17 USA centres – group of relevance to this review; full study is 53 international centres) 17 USA medical centres, unclear if mix of urban/rural or all urban
• **Sample size**	Number of patients needed: NR for our subgroup of interest Number of patients included: 9
• **Duration and follow-up**	Start and end dates of the study: April 2004 (first recruitment) to January 2007 (last delivery) Inclusion and follow-up periods: From between 18 and 22 weeks 6 days gestation; endpoint of follow-up unclear. At least to delivery/loss but as long as 11 months post-partum in at least one case.
• **Statistical analysis**	ITT
Patient characteristics	
• **Eligibility criteria**	Between 18 and 45 years of age with an estimated gestational age between 16 weeks 0 days and 22 weeks 6 days and a short cervix (<=25 mm); able to understand English or a common local language; provide written informed consent; demonstrate understanding of the purpose of the study; and agree to adhere to the study protocol
• **Exclusion criteria**	Previous spontaneous PTB in a singleton gestation in the immediate preceding pregnancy and 1) a history of adverse reaction to progesterone or any component of the formulation; (2) progesterone treatment within 4 weeks before enrolment; (3) treatment for a seizure disorder, a psychiatric illness or chronic hypertension at the time of enrolment; (4) a history of acute or chronic congestive heart failure, renal failure, uncontrolled diabetes mellitus, an active liver disorder, HIV infection with a CD4 count of < 350 cells/mm3 and requiring multiple antiviral agents; (5) placenta previa; (6) a history or suspicion of breast or genital tract malignancy; (7) a history or suspicion of thromboembolic disease; (8) a Mullerian duct anomaly; (9) enrollment in another investigational study within 1 month of screening for the present study; (10) a major fetal anomaly diagnosed by ultrasound or a known chromosomal disorder; (11) multifetal gestation 12) a cervical cerclage or planned cervical cerclage placement during the current pregnancy; (13) preterm labour, preterm premature rupture of membranes, clinical chorioamnionitis or vaginal bleeding; (14) a history of previous preterm delivery without spontaneous preterm labour (indicated preterm delivery); (15) unwillingness or inability to comply with study procedures as explained by the clinical trial personnel.

• **Patient & disease characteristics**	Women with short cervix (≤25 mm), no history of PTB in immediately previous singleton pregnancy and current singleton gestation at one of 17 USA sites Baseline characteristics and risk of confounding unclear as no baseline characteristics are presented for women in the subgroup of interest to this review.
Interventions	
• **Intervention group**	***Group 1:*** Progesterone [90 mg/day] from 18-22 weeks 6 days gestation to delivery/37 week's gestation/PROM. Details: polycarbophil-based bioadhesive vaginal gel that contains 8% (wt/wt) progesterone administered by a prefilled, single-use, disposable plastic applicator - Prochieve 8%/Cinon 8% by Columbia Laboratories, Inc. (Livingston, NJ) Additional monitoring/treatment for all study groups: Monitoring/tests: TVU cervical measurement at 28 weeks gestation. Management: If a patient developed spontaneous preterm labor during the study period, she was treated and kept in the study until delivery, in the absence of preterm rupture of membranes. The treatment protocol for spontaneous preterm labor was instituted at the discretion of the treating physician. It may have included hospitalization, hydration, bed rest, tocolysis and/or steroids. The study drug was to be continued during treatment for preterm labor. If the patient developed preterm rupture of membranes during the study period, the study drug was discontinued
• **Control group**	***Group 2:*** Placebo [once/day] from 18-22 weeks 6 days gestation to delivery/37 weeks gestation/PROM. Details: identical bioadhesive delivery system to active treatment group, but without progesterone - Replans by Columbia Laboratories, Inc. (Livingston, NJ, USA)Additional monitoring/treatment for all study groups: As described above.
Results	
• **Preterm birth**	*Preterm birth ≤ 32 weeks (Progesterone vs. placebo)* 0/4 vs. 2/5
Limitations and other comments	
• **Limitations**	External validity/applicability: Unclear (Risk factors unclear for women selected solely on basis of short cervix) Internal validity: High risk of bias (due to funding source, involvement of funder and conflicts of interest of authors)

Table 167 – Progesterone in prevention of preterm birth risk: Evidence table of RCTs (Fonseca et al., 2007)[89]

Progesterone and the risk of preterm birth among women with a short cervix. Fonseca et al., 2007 [10]	
Methods	
• **Design**	Randomized controlled trial.
• **Source of funding and competing interest**	Non-profit research funds (Fetal Medicine Foundation, London [Charity No. 1037116]); Report states that "No potential conflict of interest relevant to this article was reported"
• **Setting**	Multicentre study (8 sites); Brazil (1), Chile (1), Greece (1), UK (5 around London); Hospitals (mix maternity, university, general); likely mostly urban.
• **Sample size**	Number of patients needed: 250 Number of patients included: 250
• **Duration and follow-up**	Start and end dates of the study: Sept. 2003 – May 2006 Inclusion and follow-up periods: From between 20-25 weeks gestation; unclear end of follow-up but at least until discharge from hospital

• **Statistical analysis**	ITT For most main outcomes, both crude and adjusted relative risks (95% CIs) presented. Logistic regression analyses were clustered on maternal identifiers to account for no independence between twin pairs and adjusted for maternal age, body-mass index, smoking status, race, history of preterm birth, and cervical length at the time of randomization
Patient characteristics	
• **Eligibility criteria**	Women with singleton or twin pregnancies who were undergoing routine ultrasonography at 20 to 25 weeks of gestation, who agreed to transvaginal ultrasonographic measurement of cervical length and who had a cervical length of ≤15 mm
• **Exclusion criteria**	Major fetal abnormalities, painful regular uterine contractions, a history of ruptured membranes or a cervical cerclage
• **Patient & disease characteristics**	Asymptomatic pregnant women with singleton or twin pregnancy with a cervical length ≤15 mm at routine mid-trimester screening. Approx. 12% with previous PTB and approximately 9.6% with twin pregnancy. No information on previous cervical surgery, uterine malformations or polyhydramnios. Race: Approx. 38% White; 55% Black; 7% other; Age: median (IQR): 29 (24-34) years There are no baseline imbalances for variables reported (including BMI, history of PTB, age, twin pregnancies, black race, smoking status) and all of these are adjusted in the analysis. No data regarding socioeconomic status, hypertension, diabetes, in vitro fertilization
Interventions	
• **Intervention group**	***Group 1:*** Progesterone (vaginal progesterone tablets) [200 mg/day] from 24 to 33 weeks 6 days gestation Details: vaginal capsules of micronized progesterone (Utrogetan, Besins International Belgium) Additional monitoring/education/treatment for all study groups: Monitoring/tests: ultrasound visits every 2 weeks for fetal growth and cervical measurement to 34 weeks gestation. Education/instruction: women were instructed to avoid sexual intercourse.
• **Control group**	***Group 2:*** Placebo [once/day] from 24 to 33 weeks 6 days gestation Details: 'identical-appearing capsules' containing safflower oil (Medicaps) Additional monitoring/treatment for all study groups: As described above.
Results	
• **Offspring death**	*Fetal death (Progesterone vs. Placebo)* 1/125 vs. 1/125; p-value = 0.98 *Neonatal death (Progesterone vs. Placebo)* 2/125 vs. 7/125; Unadjusted RR: 0.29; 95% CI: 0.06, 1.42; p-value = 0.13; Adjusted RR: 0.34; 95% CI: 0.06, 1.81; p-value = 0.22
• **Preterm birth**	*Spontaneous delivery at <34 weeks (Progesterone vs. Placebo)* 24/125 vs. 43/125; Unadjusted RR: 0.56; 95% CI: 0.36, 0.86; p-value = 0.007; Adjusted RR: 0.56; 95% CI: 0.32, 0.91; p-value = 0.02 (Note: any delivery <34 weeks, including spontaneous + medically indicated, also reported) *Subgroup data for spontaneous delivery at <34 weeks (data is estimated from forest plot):* *Subgroup: asymptomatic pregnant women with singleton or twin pregnancy with a cervical length <12 mm at routine midtrimester screening (Progesterone vs. Placebo)* Unadjusted RR: 0.60; 95% CI: 0.40, 1.00 *Subgroup: asymptomatic pregnant women with singleton or twin pregnancy with a cervical length 12 -15 mm at routine midtrimester screening(Progesterone vs. Placebo)*

Unadjusted RR: 0.80; 95% CI: 0.45. just over 1.00

Subgroup: asymptomatic pregnant women with singleton or twin pregnancy with a cervical length ≤15 mm at routine midtrimester screening and age >=35 years(Progesterone vs. Placebo)

Unadjusted RR: 0.65; 95% CI: 0.30, just over 1.00

Subgroup: asymptomatic pregnant women with singleton or twin pregnancy with a cervical length ≤15 mm at routine midtrimester screening and age <35 years(Progesterone vs. Placebo)

Unadjusted RR: 0.65; 95% CI: 0.40, 1.00

Subgroup: asymptomatic pregnant women with singleton or twin pregnancy with a cervical length ≤15 mm at routine midtrimester screening and BMI >=30.0(Progesterone vs. Placebo)

Unadjusted RR:0.80 ; 95% CI: 0.30, 2.00

Subgroup: asymptomatic pregnant women with singleton or twin pregnancy with a cervical length ≤15 mm at routine midtrimester screening and BMI >=20-29.9(Progesterone vs. Placebo)

Unadjusted RR: 0.65 ; 95% CI: 0.40, 1.00

Subgroup: asymptomatic pregnant women with singleton or twin pregnancy with a cervical length ≤15 mm at routine midtrimester screening and BMI <20.0*(Progesterone vs. Placebo)*

Unadjusted RR: 0.45 ; 95% CI: 0.09, 1.90

Subgroup: asymptomatic white pregnant women with singleton or twin pregnancy with a cervical length ≤15 mm at routine midtrimester screening(Progesterone vs. Placebo)

Unadjusted RR: 0.40; 95% CI: 0.30, 1.50

Subgroup: asymptomatic black pregnant women with singleton or twin pregnancy with a cervical length ≤15 mm at routine midtrimester screening(Progesterone vs. Placebo)

Unadjusted RR: 0.70 ; 95% CI: 0.30, 1.90

Subgroup: asymptomatic parous pregnant women with no history of PTB, a singleton or twin pregnancy and a cervical length ≤15 mm at routine midtrimester screening(Progesterone vs. Placebo)

Unadjusted RR: 0.75; 95% CI: 0.30, 2.00

Subgroup: asymptomatic nulliparous pregnant women with a singleton or twin pregnancy and a cervical length ≤15 mm at routine midtrimester screening(Progesterone vs. Placebo)

Unadjusted RR: 0.55; 95% CI: 0.30, 1.00

Subgroup: asymptomatic nulliparous pregnant women or parous with no history of PTB prior to 34 weeks gestation with a singleton or twin pregnancy and a cervical length ≤15 mm at routine midtrimester screening(Progesterone vs. Placebo)

20/112 vs. 34/109; Unadjusted RR: 0.57; 95% CI: 0.35, 0.93; p-value = 0.03

Subgroup: asymptomatic pregnant women with a singleton pregnancy and a cervical length ≤15 mm at routine midtrimester screening(Progesterone vs. Placebo)

20/114 vs. 36/112; Unadjusted RR: 0.54; 95% CI: 0.34, 0.88; p-value = 0.02

• **Neonatal harms**	*Major adverse outcomes before discharge from the hospital (intraventricular hemorrhage, respiratory distress syndrome, retinopathy of prematurity or necrotizing enterocolitis) (Progesterone vs. Placebo)* 11/125 vs. 19/125; Unadjusted RR: 0.59; 95% CI: 0.26, 1.25; p-value = 0.17; Adjusted RR: 0.57; 95% CI: 0.23, 1.31; p-value = 0.19
• **Maternal harms/complications**	*'Important adverse events' (not further defined) (Progesterone vs. Placebo)* Report states: "There were no important adverse events or side effects in either group."
Limitations and other comments	
• **Limitations**	External validity/applicability: Serious concern (Not exclusively low-risk population) Internal validity: Unclear risk of Bias (all domains were rated as low risk of bias with the exception of 'other' as some potential confounders were not reported or accounted for)

Table 168 – Progesterone in prevention of preterm birth risk: Evidence table of RCTs (Grobman et al., 2012)

17 alpha-hydroxyprogesteronecaproate to prevent prematurity in nulliparas with cervical length less than 30 mm (Grobman et al., 2012)[4]	
Methods	
• **Design**	Randomized controlled trial.
• **Source of funding and competing interest**	Non-industry (National Center for Research Resources and National Institute of Child Health and Human Development). Report states there are no declarations of interest.
• **Setting**	Multicenter (14 centres of the Maternal-Fetal Medicine Units Network of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, United States; urban)
• **Sample size**	Number of patients needed: 1000 Number of patients randomized: 657 (study stopped) Number of patients included: 657
• **Duration and follow-up**	Start and end dates of the study: April 2007-May 2011 Inclusion and follow-up periods: From between 16 weeks 0 days and 22 weeks 3 days gestation to hospital discharge.
• **Statistical analysis**	ITT analysis for all major outcomes; Unadjusted risk estimates 18/327 in the intervention group and 33/330 in the placebo group discontinued the intervention.
Patient characteristics	
• **Eligibility criteria**	Nulliparous (no prior pregnancy that progressed 19 weeks 6 days) with a viable singleton gestation and had a cervical length <30 mm between 16 weeks 0 days and 22 weeks 3 days and who, after giving informed consent and receiving a "compliance" injection of placebo, returned for randomization (conducted between 16 weeks 3 days and 22 weeks 6 days).

• **Exclusion criteria**	Women with selective fetal reduction to a singleton gestation; had sonographic evidence of an additional fetal pole/embryo at 12 weeks of gestation; had received progestogen treatment >14 weeks 6 days; had experienced vaginal bleeding heavier than spotting 15 weeks 6 days; had amniotic membranes prolapsing beyond the external os; had premature rupture of membranes; had a known major fetal anomaly or aneuploidy; had a current or planned cervical cerclage; had a known müllerian abnormality; had a contraindication to IM injections; had maternal medical conditions that increase the probability of preterm delivery (eg, hypertension, diabetes requiringmedication); had prior cervical surgery (ie, cold knife conization, laser vaporization, or loop electrosurgical excision procedure); or were planned to have an indicated preterm delivery. From registration record: participation in another study that influences age at delivery, participation in this trial for previous pregnancy, prenatal care or delivery planned outside relevant center; DES exposure,
• **Patient & disease characteristics**	Nulliparous women with singleton gestation and cervical length <30mm recruited between 16 weeks 0 days and 22 weeks 3 days gestation. Age (for those included in analysis; n=657): Mean (SD) - Progesterone: 22.8 (5.3); Placebo: 21.6 (4.4) Race (for those included in analysis; n=657): 23.2 and 22.4% of Progesterone and Placebo groups were non-Hispanic white; 54.7 and 48.8% were non-Hispanic black; 5.8 and 11.5% were Hispanic white; 0.6 and 0% were Hispanic black; 1.2 and 0.9% were Asian; and 14.4 and 16.4% were of another race. Other: Included ~30% women that had miscarried previously prior to 19 weeks 6 days gestation Slightly more African American participants in progesterone group (~55%) than placebo group (49%). No major imbalances for BMI, past history of PTB, maternal age (although study notes that women in progesterone group were slightly older), smoking status or substance abuse. Multiple gestations, uncontrolled hypertension and diabetes mellitus and previous cervical surgery excluded. No details on socioeconomic status or in vitro fertilization.
Interventions	
• **Intervention group**	***Group 1:*** Progesterone (intramuscular injections) [250mg/week] from 16 weeks 3 days and 23 weeks 6 days gestation to 36 weeks 6 days gestation or delivery, whichever occurred first. Details: 1 ml intramuscular injections of 17-alpha-hydroxyprogesterone caproate (17-OHP) in castor oil with benzyl benzoate and benzyl alcohol as preservatives Additional monitoring for all study groups: At weekly visits, patients in both groups were asked whether they had consulted a physician for preterm labour symptoms, had undergone any medical procedures, or had been given any corticosteroids or tocolytic medications since their last visit. Participants were also queried about any activity restrictions that had been prescribed by their health provider.
• **Control group**	***Group 2:*** Placebo (intramuscular injections) [weekly] from 16 weeks 3 days and 23 weeks 6 days gestation to 36 weeks 6 days gestation or delivery, whichever occurred first. Details: 1 ml castor oil intramuscular injections - identical to progesterone without the active ingredient Additional monitoring for all study groups: As described above.
Results	
• **Offspring death**	*Fetal death (Progesterone vs. Placebo)* 4/327 vs. 1/330; RR: 4.04; 95% CI: 0.45, 35.92 *Neonatal death (Progesterone vs. Placebo)* 6/327 vs. 8/330; RR: 0.76; 95% CI: 0.27, 2.16 Perinatal mortality *(Progesterone vs. Placebo)* 10/327 vs. 9/330

• **Preterm birth**	*Preterm birth <37 weeks (spontaneous preterm birth) (Progesterone vs. Placebo)* 54/327 vs. 55/330; RR: 0.99; 95% CI: 0.70, 1.40 *Fetal loss/abortion <20 weeks (Progesterone vs. Placebo)* 1/327 vs. 0/330 *Delivery <35 weeks (Progesterone vs. Placebo)* 44/327 vs. 53/330; RR: 0.84; 95% CI: 0.58, 1.21 *Delivery <32 weeks (Progesterone vs. Placebo)* 28/327 vs. 32/330; RR: 0.88; 95% CI: 0.54, 1.43 *Preterm birth <28 weeks (Progesterone vs. Placebo)* 15/327 vs. 22/330; RR: 0.69; 95% CI: 0.36, 1.30 *Preterm birth <34 weeks for cervical length <30 mm (Progesterone vs. Placebo)* 41/327 vs. 48/330 *Subgroup data for 'preterm birth <34 weeks combined spontaneous, medically indicated, and fetal loss/abortion <20 weeks':* *Subgroup: Cervical length <10mm (Progesterone vs. Placebo)* 5/9 vs. 6/16; RR: 1.48; 95% CI: 0.63, 3.51 *Subgroup:Cervicallength 10-20mm (Progesterone vs. Placebo)* 11/50 vs. 12/40; RR: 0.73; 95% CI: 0.36, 1.48 *Subgroup: Cervical length >20mm (Progesterone vs. Placebo)* 25/268 vs.30/274; RR: 0.85; 95% CI: 0.52, 1.41 *Subgroup:Cervicallength<15mm (Progesterone vs. Placebo)* 9/25 vs.13/31; RR: 0.86; 95% CI: 0.44, 1.67 *Subgroup:Cervical length ≥15mm (Progesterone vs. Placebo)* 32/302 vs.35/299; RR: 0.91; 95% CI: 0.58, 1.42
• **Neonatal harms**	*'Composite of serious adverse fetal or neonatal outcomes (ie, respiratory distress syndrome, bronchopulmonary dysplasia, early-onset sepsis, grade II or III necrotizing enterocolitis, grade III or IV intraventricular hemorrhage, periventricular leukomalacia, grade II or IV retinopathy of prematurity, or fetal or neonatal death) (Progesterone vs. Placebo)* 23/327 vs. 30/330; RR: 0.77; 95% CI: 0.46, 1.30 *Seizure (Progesterone vs. Placebo)* 1/320 vs. 2/322; RR: 0.50; 95% CI: 0.05, 5.52
• **Neonatal survival without morbidities**	*Inverse of 'composite of serious adverse fetal or neonatal outcomes' (defined above); Inferred (not specifically reported) (Progesterone vs. Placebo)* 304/327 vs. 300/330

Limitations and other comments	
• **Limitations**	External validity/applicability: Serious concern (One-third of the women had previous miscarriage <19 weeks and approximately half were of black race) Internal validity: Unclear risk of bias (unclear reporting of allocation concealment and a few potential confounders were not reported or accounted for)

Table 169 – Progesterone in prevention of preterm birth risk: Evidence table of RCTs (Hassan et al., 2011)

Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial. Hassan et al., 2011[86]	
Methods	
• **Design**	Randomized, double-blind, placebo-controlled trial
• **Source of funding and competing interest**	Both public research funds (Intramural Program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development/National Institutes of Health) and healthcare industry (Columbia Laboratories, Inc); Report states declarations of interest ('Author-investigators...conducted this study with the support of grants awarded by Columbia Laboratories, Inc. for the specific purpose of conducting this trial. The terms and conditions for the awarding of the grants were consistent with those which are customary for this type of industry-sponsored trial and all payments were independent of the outcome of the trial. In addition, J.K.B. and J.O.'B. have also received consulting fees and travel expenses related to Preterm Birth Advisory Committee meetings related to the project. J.O.'B. is an inventor on a patent for the use of progesterone in the prevention of preterm birth. J.A.P. received remuneration as a statistical consultant to Columbia Laboratories, Inc. G.W.C. is an employee of Columbia Laboratories, Inc.')
• **Setting**	Multicentre (44 sites, 10 countries: Belarus, Czech Republic, Chile, India, Israel, Italy, Russian Federation, South Africa, United States, Ukraine). Healthcare setting(s) not specifically reported.
• **Sample size**	Number of patients needed: 450 Number of patients randomized: 465 Number of patients included: 458
• **Duration and follow-up**	Start and end dates of the study (recruitment and follow-up): Mar. 2008 – Nov. 2010 Inclusion and follow-up periods: From between 19 wks 0 days and 23 wks 6 days gestation; endpoint of follow-up unclear but at least until discharge from hospital (trial registration record)
• **Statistical analysis**	ITT, Per protocol, and treated patient analysis presented for all major outcomes. Definitions of each are provided in the report. Serious AEs presented in trial registration record based on all treated patients. Most analyses were unadjusted Adjusted analyses noted, where relevant, below. Adjusted 1: pooled study site and risk strata Adjusted 2: pooled study site, risk strata, treatment group, gestational age at first dose, maternal age, cervical length, BMI and race Note: All data presented below are based on ITT data and unadjusted relative risks (RR), unless otherwise specified.

Patient characteristics	
• **Eligibility criteria**	1) singleton gestation; 2) gestational age between 19 + 0 and 23 + 6 weeks; 3) transvaginal sonographic cervical length between 10 and 20 mm; and 4) asymptomatic, i.e. without signs or symptoms of preterm labour; others (speaks English or common local language, signed informed consent, is deemed capable (by investigator) of consent and adherence.
• **Exclusion criteria**	1) planned cerclage; 2) acute cervical dilation, insufficiency/bulging of membranes beyond external os; 3) allergic reaction to progesterone; 4) current or recent progesterone treatment within the previous 4 weeks; 5) chronic medical conditions that would interfere with study participation or evaluation of the treatment (e.g. seizures, psychiatric disorders, uncontrolled chronic hypertension, congestive heart failure, chronic renal failure, uncontrolled diabetes mellitus with end-organ dysfunction, active thrombophlebitis or a thromboembolic disorder, history of hormone-associated thrombophlebitis or thromboembolic disorders, active liver dysfunction or disease, known or suspected malignancy of the breast or genital organs); 6) major fetal anomaly or known chromosomal abnormality; 7) uterine anatomic malformation (e.g. bicornuate uterus, septate uterus); 8) vaginal bleeding; or 9) known or suspected clinical chorioamnionitis. Others from registration record: preterm rupture of membranes, known or suspected amnionitis, or signs or symptoms of preterm labour at the time of enrolment, complete placenta previa; HIV positive with CD4 count of <350 cells/mm3 and is receiving more than one medication to prevent the transfer of AIDS to fetus; participation in another investigational study within previous month.
• **Patient & disease characteristics**	Asymptomatic women with singleton pregnancies and a cervix length from 10-20 mm recruited between 19+0 and 23+6 weeks of gestation from 10 countries (March 2008 - November 2010) Age (for those included in analysis; n=458): Progesterone group: 18-44 years; Placebo group: 18-41 years (Mean [SD]: 26.5 [5.8] and 26.2 [5.1]) Race (for those included in analysis; n=458): 32 and 30% of those on progesterone and placebo were African-American; 32 and 33% were Asian; 31% in both groups were Caucasian; and 4 and 5% were of another race. Other (for those included in analysis; n=458): 16% had a history of previous preterm birth between 20 and 35 weeks of gestation; approximately 10% had history of cervical surgery; uterine malformations, and multiple gestations excluded; polyhydramnios not stated. No baseline imbalances were noted for BMI, history of preterm labour/delivery, age, race or previous cervical surgery. No information regarding SES, smoking status, hypertension or diabetes (although pts with uncontrolled conditions were excluded) or IVF. For full adjusted analyses of main outcomes, age, race and BMI were included in the model.
Interventions	
• **Intervention group**	***Group 1:*** Progesterone (vaginal gel) [90 mg/day] from 20 -23 wks 6 days gestation to 36 wks 6 days/rupture of membranes/delivery (whichever occurred first) *Details:* Vaginal progesterone gel (Prochieve 8%, also known as Crinone 8%) *Additional monitoring/treatment for all study groups:* *Monitoring/tests*: Study participants were instructed to return to the study centre every 2 weeks to assess adverse events, use of concomitant medications, and compliance. It is assumed that other tests (e.g. ultrasound) were done to determine whether emergency cerclage was warranted, but this is unclear. *Interventions:* Patients who developed preterm labor during the study were treated according to the standard practice of the participating institutions (e.g. admission to the hospital, bed rest, intravenous fluids, tocolytic therapy, steroid administration, if clinically indicated). *Management (other):* Administration of the study drug was to be continued during treatment for preterm labor, until delivery (in the absence of preterm rupture of membranes). Emergency cerclage was allowed if the following criteria were met: 1) 21–26 weeks' gestational age; 2) cervical dilation >2 cm; 3) membranes visible; 4) intact membranes; and 5) absence of uterine contractions, clinical chorioamnionitis and significant vaginal bleeding.

• **Control group**	***Group 2:*** Placebo (vaginal gel) [once/day] from 20-23 wks 6 days gestation to 36 wks 6 days/rupture of membranes/delivery (whichever occurred first) *Details:* Placebo vaginal gel (Columbia laboratories, Inc.) identical in appearance to the progesterone gel *Additional monitoring/treatment/follow-up for all study groups:* As described above
Results	
• **Offspring - death**	*Perinatal mortality (fetal death or neonatal death) (Progesterone vs. Placebo)* 8/235 vs. 11/223; RR: 0.69; 95% CI: 0.28, 1.68; p-value = 0.413 *Neonatal death - delivery to day 28 (Progesterone vs. Placebo)* 3/235 vs. 5/223; RR: 0.57; 95% CI: 0.14, 2.35; p-value = 0.431 *Fetal death (Progesterone vs. Placebo)* 5/235 vs. 6/223; RR: 0.79; 95% CI: 0.25, 2.57; p-value = 0.700
• **Preterm birth**	*Preterm birth < 28 weeks (Progesterone vs. Placebo)* 12/235 vs. 23/223; RR: 0.50; 95% CI: 0.25, 0.97; p-value = 0.036 *Preterm birth < 33 weeks (Progesterone vs. Placebo)* 21/235 vs. 36/223; unadjusted RR: 0.55; 95% CI:0.33, 0.92; p-value = 0.020; NNT (95% CI): 14 (8, 87) Adjusted analysis 1 RR: 0.54; 95% CI:0.33, 0.89; p-value = 0.01 Adjusted analysis 2 RR: 0.52; 95% CI:0.31, 0.91; p-value = 0.02 Subgroup analysis also presented for this outcome (limited to women with no previous history of PTB) 15/197 vs. 29/189; RR: 0.50; 95% CI:0.27, 0.90; p-value = 0.02 *Preterm birth < 35 weeks (Progesterone vs. Placebo)* 34/235 vs. 52/223; RR: 0.62; 95% CI:0.42, 0.92; p-value = 0.016 *Preterm birth < 37 weeks (Progesterone vs. Placebo)* 71/235 vs. 76/223; RR: 0.89; 95% CI:0.68, 1.16; p-value = 0.376
• **Neonatal harms**	*"Composite perinatal mortality/morbidity: any of respiratory distress syndrome (RDS), bronchopulmonary dysplasia, Grade III or IV intraventricular haemorrhage, periventricular leukomalacia, proven sepsis, necrotizing enterocolitis and perinatal mortality" (Progesterone vs. Placebo)* 18/194 vs. 28/193; PP analysis: RR: 0.61; 95% CI:0.35, 1.08; P-value from ITT sample adjusted analysis 1 = 0.054
• **Neonatal survival without morbidities**	*Infants without respiratory distress syndrome (RDS), bronchopulmonary dysplasia, Grade III or IV intraventricular haemorrhage, periventricular leukomalacia, proven sepsis, necrotizing enterocolitis and perinatal mortality (Calculated based on reporting of Infants with any morbidity/mortality; ITT set) (Progesterone vs. Placebo)* 217/235 vs. 193/223
• **Maternal and neonatal SAEs**	*Composite of total SAEs (assumed to be maternal and infant combined) (Progesterone vs. Placebo)* 97/235 vs. 98/224

Limitations and other comments	
• **Limitations**	External validity/applicability: Serious concern (a subset of the population has a history of preterm birth and cervical surgery) Internal validity: High risk of bias (due to 'other risks' - funding source with no statement of independence from funders, conflict of interest present for many authors)

Table 170 – Progesterone in prevention of preterm birth risk: Evidence table of RCTs (Moghtadaei et al., 2008)

Progesterone for prevention of preterm birth and improvement in pregnancy outcomes among primiparae of advanced maternal age. Moghtadaei et al., 2008 [91]	
Methods	
• **Design**	Randomized controlled trial.
• **Source of funding and competing interest**	Not reported.
• **Setting**	Not specifically reported (authors from one institution in Iran)
• **Sample size**	Number of patients needed: NR Number of patients randomized: 260 Number of patients included: 260
• **Duration and follow-up**	Start and end dates of the study: NR Inclusion and follow-up periods: From between 16-20 weeks gestation to delivery
• **Statistical analysis**	Analysis type NR Unadjusted risk estimates
Patient characteristics	
• **Eligibility criteria**	Primiparous women ≥ 35 years of age.
• **Exclusion criteria**	Not reported.
• **Patient & disease characteristics**	Primiparous women ≥ 35 years of age. No details available on baseline characteristics (poster/abstract presentation)
Interventions	
• **Intervention group**	***Group 1:*** Progesterone (intramuscular injections) [250mg/week] from 16–20 weeks gestation to 34 weeks. Details: Intramuscular injections of 17 alpha-hydroxyprogestronecaproate (17p). Additional monitoring/treatment for all study groups: No additional management reported.
• **Control group**	***Group 2:*** Placebo (intramuscular injections) [weekly] from 16–20 weeks gestation to 34 weeks. Details: Intramuscular injections of matching placebo. Additional monitoring/treatment for all study groups: As described above.
Results	
• **Preterm birth**	*Preterm birth <37 weeks (Progesterone vs. Placebo)* 35/130 vs. 47/130 (denominator not reported; denominator assuming equal number of participants per arm is used); RR: 0.60; 95% CI: NR.

	Preterm birth <35 weeks (Progesterone vs. Placebo) 14/130 vs. 27/130 (denominator not reported; denominator assuming equal number of participants per arm is used); RR: 0.67; 95% CI: NR. *Preterm birth <32 weeks (Progesterone vs. Placebo)* 8/130 vs. 16/130; (denominator not reported; denominator assuming equal number of participants per arm is used); RR: 0.58; 95% CI: NR.
Limitations and other comments	
• **Limitations**	External validity/applicability: Very serious concern (developing country, unclear if exclusively low risk population as women are aged ≥35 years) Internal validity: Unclear risk of bias (due to unclear method of randomization, concealment of allocation, risk of selective outcome reporting, no statement regarding COI and baseline characteristics not reported)

Table 171 – Progesterone in prevention of preterm birth risk: Evidence table of RCTs (van Os et al., 2014)

Preventing preterm birth with progesterone (the Triple P Treat Study): a randomized controlled trial. van Os et al., 2014[88]	
Methods	
• **Design**	Randomized controlled trial.
• **Source of funding and competing interest**	Non-industry (ZonMW, The Netherlands Organization for Health Research and Development). Report states there are 'no declarations of interest'.
• **Setting**	Multicenter (approximately 200 clinics, including university, teaching and non-teaching hospitals, ultrasound centres and midwifery practices in the Netherlands; unclear but likely mix of urban and rural)
• **Sample size**	Number of patients needed: 1920 Number of patients randomized: 80 (study stopped after enrollment of 80 women) Number of patients included: 74
• **Duration and follow-up**	Start and end dates of the study: Between 2009 and 2013 Inclusion and follow-up periods: From 18-20 weeks gestation (after 2 cervical measurements) to (ultimately for full trial) child age 24 months
• **Statistical analysis**	ITT analysis for all major outcomes Unadjusted RR
Patient characteristics	
• **Eligibility criteria**	Women at low risk for preterm birth ≥18 years; singleton healthy pregnancy; cervical length shorter than 30 mm at 18-22 weeks:2 measurements, 2 weeks apart
• **Exclusion criteria**	Major fetal abnormalities, history of ruptured membranes, cervical or abdominal cerclage in situ, previous PTB <34 weeks, <18 years age, symptoms of preterm labour (painful regular uterine contractions, ruptured membranes)
• **Patient & disease characteristics**	Women at low risk for PTB based on history of PTB with short cervical length ≤ 30 mm and singleton gestation between 18 and 22 weeks in the Netherlands.Considered 'low' risk women as they are not to have a history of PTB but no information on previous cervical surgery. Thus either low or predominantly low.

	No details available on baseline characteristics.
Interventions	
• **Intervention group**	***Group 1:*** Progesterone (vaginal capsules) [200mg/day] from 18 to 34 weeks gestation or delivery Details: Vaginal capsules of micronized progesterone (Utrogetan, Besins International Belgium) Additional monitoring/treatment for all study groups: No additional management reported.
• **Control group**	***Group 2:*** Placebo (vaginal capsules) [once/day] from 18 to 34 weeks gestation or delivery. Details: Identical-appearing capsules (Medicaps) Additional monitoring/treatment for all study groups: As described above.
Results	
• **Preterm birth**	*Preterm birth ≤34 weeks (Progesterone vs. Placebo)* 3/39 vs. 4/35; RR: 0.64; 95% CI: 0.15, 2.60 *Preterm birth ≤37 weeks (Progesterone vs. Placebo)* 6/39 vs. 5/35; RR: 1.02; 95% CI: 0.34, 3.03 *Preterm birth <32 weeks (Progesterone vs. Placebo)* 1/39 vs. 3/35; RR: 0.28; 95% CI: 0.03, 2.60
• **Neonatal harms**	*'Composite adverse neonatal outcome defined as severe Respiratory Distress Syndrome (RDS), Bronchopulmonary Dysplasia (BPD), IntracerebralHaemorrhage> grade II, NecrotiizngEnterocolitis (NEC) > stage 1, proven sepsis and death before discharge from the nursery' (according to abstract; protocol also mentions that this includes Periventricular Leucomalacia> grade 1) (Progesterone vs. Placebo)* 2/39 vs. 3/35; RR: 0.55; 95% CI: 0.10, 3.10
• **Neonatal survival without morbidities**	*Inverse of 'composite adverse neonatal outcomes' (defined above); Inferred (not specifically reported) (Progesterone vs. Placebo)* 37/39 vs. 32/35
Limitations and other comments	
• **Limitations**	External validity/applicability: No concern Internal validity: Unclear risk of bias (due to unclear reporting of the number of missing participants, selected reporting of outcomes in the abstract, and lack of baseline data (abstract only))

9.8.3. Cerclage

Table 172 – Descriptive summary of four studies included for cerclage vs no cerclage highlighting heterogeneity among the studies in preterm risk

S #	Author, Year of publication, Design	Intervention vs. comparator	Common management	Cervical length	Applicability	Risk of Bias	Population risk
1	Berghella, 2004[92] (subgroup data), RCT	Bed rest+ cerclage vs. Bed rest	Bed rest in both groups started at home with bathroom privileges. Monitoring/tests: ultrasound examination until 28 to 30 weeks of gestation. Education/counselling: Education/counselling about preterm labour. Treatment/management: Betamethasone for fetal lung maturity was offered after 24 weeks of gestation for overt preterm labor or preterm premature rupture of membranes.	<25mm	serious	High risk	Low
4	Hassan,2001,[95] observational	Cerclage vs. no active treatment	The patient's physician managed the pregnancy at his or her discretion - unclear what this involved.	≤15mm	very serious	High risk	**Unclear** (mix population)
3	Sakai, 2006,[94] observational	Bed rest + cerclage vs. Bed rest	The majority of patients in both groups were on in-hospital bed rest. When uterine contractions were observed, ritodrine hydrochloride was given by continuous intravenous drip. When clinical evidence of chorioamnionitis was observed, the pregnancy was terminated.	≤15mm	serious	Unclear	Predominantly low (30% with previous PTB)
2	Skupski, 2014[93], observational	Cerclage + modified bed rest +/- progesterone (49% of women in this arm) vs. Bed rest +/- progesterone (26% of women in this arm)	Tocolysis and other management decisions were left in the hands of the attending physician.	≤15mm	serious	High risk	Predominantly low (40% with history of PTB or loss)

Table 173 – Cerclage in prevention of preterm birth risk: Evidence table of RCTs (Berghella et al., 2004)

Cerclage for prevention of preterm birth in women with a short cervix found on transvaginal ultrasound examination: a randomized trial. Berghella et al., 2004[92]	
Methods	
• **Design**	Randomized controlled trial
• **Source of funding and competing interest**	Public research funds (Center for Research on Women and Newborn Health (CROWN) Foundation, and the Philadelphia Perinatal Society) and unclear funding source (Berlex Foundation; possibly subsidiary of Bayer); No statement regarding declaration of interest.
• **Setting**	Multicentre (2 sites: United States – Thomas Jefferson University Hospital and the University of Pennsylvania Hospital), urban

• **Sample size**	Number of patients needed = 30 in each group (60) Number of patients randomized = 61 Number of patients included = 61; 10 in low-risk subgroup
• **Duration and follow-up**	Start and end Dates of study: Thomas Jefferson University Hospital: February 1998-June 2003; University of Pennsylvania Hospital: February 2002 until June 2003 Inclusion and follow-up periods: Unclear for low-risk subgroup - women identified incidentally on routine transabdominal anatomy ultrasound scanning. For high risk group from between 14 wks 0 days and 23 wks 6 days; endpoint of follow-up not stated.
• **Statistical analysis**	ITT, unadjusted; numerous planned subgroup analyses Report reads: "Pre-specified sub-analyses of different risk group populations were performed, with awareness of their limitations, with the only purpose of hypothesis-generation for future studies."
Patient characteristics	
• **Eligibility criteria**	Main study includes mostly asymptomatic women at high risk for preterm birth with a cervical length < 25 mm. A small subset (of relevance to this review) were non-screened low-risk women who were identified incidentally, on routine transabdominal anatomy ultrasound scanning, to have a short cervix.
• **Exclusion criteria**	Prophylactic cerclage that was placed based on historic high-risk criteria, major fetal anomaly, triplets or higher order gestations. Criteria after screening had begun included previous inclusion in another trial, current drug abuse, and regular contractions that led to preterm labour after identification of abnormal cervix by ultrasound scanning.
• **Patient & disease characteristics**	Asymptomatic pregnant women with low risk for PTB, singleton pregnancies and cervix length < 25mm identified at Thomas Jefferson University Hospital between February 1998 and June 2003, and at the University of Pennsylvania Hospital from February 2002 until June 2003. Age: No data for sub-group. For full study group: Mean (SD): Cerclage+bed rest group: 27.8 (6.4); best rest group: 29.9 (6.9) Race: Not reported for low-risk subgroup. Overall, ~77% of the women were black; ~15% white and 8% hispanic; minor differences between groups. Other: The 10 women in this subgroup (16% of women randomized) were low risk singleton pregnancies - no further details No group-specific baseline data for subgroup of interest. For full group, moderate differences (non-significant) in race distribution between study groups (cerclage+bed rest vs. bed rest: white: 10 vs. 20%; black: 80 vs. 73%; hispanic: 10 vs. 7%) and parity (77 vs. 60%). No major difference at baseline in maternal age or smoking status. No details regarding SES, maternal weight, hypertension, diabetes mellitus, *in vitro* fertilization, or previous history of cervical surgery.
Interventions	
• **Intervention/exposure group**	***Group 1***: Cerclage (McDonald cerclage) + bed rest; from between 14 wks and 23 wks 6 days gestation; endpoint of bed rest or removal of suture not stated. *Details:* *Bed rest:* Started at home with bathroom privileges *Cerclage:* McDonald cerclage within 3 days of randomization; Mersilene (5 mm) was the preferred suture. *Additional management specific to this group:* None stated *Additional monitoring/treatment/follow-up for all study groups:*

	Monitoring/tests: ultrasound examination until 28 to 30 weeks of gestation. *Education/counseling:* Education/counseling about preterm labour. *Treatment/management:* Betamethasone for fetal lung maturity was offered after 24 weeks of gestation for overt preterm labor or preterm premature rupture of membranes. Treating obstetricians discouraged from using rescue cerclage but were allowed to offer rescue cerclage if a cervical dilatation of ≥1 cm was detected on digital examination. Antibiotics, tocolytics and other interventions were left to the discretion of the obstetrician.
• **Control group**	***Group 2:*** Bed rest from between 14 wks and 23 wks 6 days gestation; endpoint not stated. *Details:* Bed rest as described above. *Additional management specific to this group:* None stated *Additional monitoring/treatment/follow-up for all study groups:* As described above
Results	
• **Offspring - death**	*Neonatal death* (Cerclage + bed rest vs. bed rest) Data for subgroup of women at low risk not reported separately - report states that "subanalyses of all outcomes for women with…no risk factors..did not show statistical differences between cerclage and no cerclage groups."
• **Preterm birth**	*Preterm birth <35 weeks, < 34 weeks, <32 weeks, < 28 weeks and < 24 weeks gestation (independent outcomes assessed in full group)* (Cerclage + bed rest vs. bed rest) Data for subgroup of women at low risk not reported separately - report states that "subanalyses of all outcomes for women with…no risk factors..did not show statistical differences between cerclage and no cerclage groups."
• **Neonatal harms**	*Composite neonatal harms: composite morbidity (any of respiratory distress syndrome, intraventricularhermorrhage (III or IV), necrotizing enterocolitis or sepsis)* (Cerclage + bed rest vs. bed rest) Data for subgroup of women at low risk not reported separately – report states that “subanalyses of all outcomes for women with…no risk factors..did not show statistical differences between cerclage and no cerclage groups.”
• **Neonatal survival without morbidities**	*Calculated (not specifically reported) - Inverse of study-defined composite outcome: 'composite morbidity (any of respiratory distress sydrome, intraventricularhermorrhage (III or IV), necrotizing enterocolitis or sepsis)* (Cerclage + bed rest vs. bed rest) Data for subgroup of women at low risk not reported separately – report states that “subanalyses of all outcomes for women with…no risk factors did not show statistical differences between cerclage and no cerclage groups.”
Limitations and other comments	
• **Limitations**	External validity/applicability: Serious concern (the majority of the full study population is black; baseline data not reported for subgroup of interest) Internal validity: High risk of bias (no blinding; some women in bed-rest only group received rescue cerclages; there were more drop-outs in cerclage group (women who chose not to receive cerclage after being allocated to that group); and the similarity of adherence to bed-rest within groups is unclear)

Table 174 – Cerclage in prevention of preterm birth risk: Evidence table of observational study (Hassan et al., 2001)

Does cervical cerclage prevent preterm delivery in patients with a short cervix? Hassan et al., 2001[95]	
Methods	
• **Design**	Retrospective comparative cohort study
• **Source of funding and competing interest**	No funding source stated; No statement regarding declaration of interest
• **Setting**	Number of centers and setting not reported. Authors from United States and Israel.
• **Sample size**	Number of patients needed: NR Number of patients eligible: 85 Number of patients analyzed (# with outcome data): 70
• **Duration and follow-up**	Start and end dates of the study: April 1994-Sept. 1999 Inclusion and follow-up periods: From between 14-24 wks gestation; end of follow-up is not reported (possibly at delivery)
• **Statistical analysis**	Chi-square
Patient characteristics	
• **Eligibility criteria**	Women with singleton gestations with a cervical length ≤15 mm by transvaginal ultrasonography at 14 to 24 weeks gestation.
• **Exclusion criteria**	Patients with multiple gestation, fetal congenital anomalies, elective cerclage placement, or unavailable obstetric outcome.
• **Patient & disease characteristics**	Women with singleton gestations who underwent transvaginal ultrasonography at 14 to 24 weeks gestation between April 1994 and September 1999 with a cervical length ≤ 15 mm. Age (Range, for those included in analysis, n=70): cerclage group: 15-45; no cerclage group: 14-41. Note: statistically higher mean age in in cerclage group Race (for those included in analysis, n=70): African-American: cerclage group: 72%; no cerclage group: 73% Other (for those included in analysis, n=70): Data for total population is reported for previous cervical surgery (cerclage: 8%; no cerclage: 8.9%); history of spontaneous abortion or preterm delivery: cerclage: 40% and 32%; no cerclage: 20 and 16%, respectively. Independent of variables unclear - if all were independent, > 50% of population would be at risk for preterm birth Statistically significant differences at baseline in maternal age (higher in cerclage group) and gestational age at ultrasonographic measurement (higher in no cerclage group). Non-significant but apparent (>5%) differences between groups in history of both spontaneous and voluntary abortion and premature delivery - all higher in the cerclage group. No differences in baseline BMI, gestations (all singleton), race, previous cervical surgery. No details on socioeconomic status, smoking/drug/alcohol use, hypertension, diabetes mellitus, *in vitro* fertilization.
Interventions	
• **Intervention group**	***Group 1:*** Cervical cerclage (McDonald) from between 14 and 24 weeks gestation; timing of removal of suture not stated. *Details:* No additional details *Additional management specific to this group:* None stated. *Additional monitoring/treatment/follow-up for all study groups*: The patient's physician managed the pregnancy at his or her discretion - unclear what this entailed.
• **Control group**	***Group 2:*** No active treatment (observation only) from between 14 and 24 weeks gestation. *Additional management specific to this group:* None stated. *Additional monitoring/treatment/follow-up for all study groups:* as above

Results	
• **Preterm Birth**	*Preterm birth <37 weeks (cerclage vs. no active treatment)* 19/25 vs. 30/45, p-value for chi-square = 0.4 *Preterm birth <34 weeks (cerclage vs. no active treatment)* 17/25 vs. 24/45, p-value for chi-square = 0.2 *Preterm birth <32 weeks (cerclage vs. no active treatment)* 14/25 vs. 19/45, p-value = 0.3 *Preterm birth <28 weeks (cerclage vs. no active treatment)* 10/25 vs. 17/45, p-value = 0.9
• **Maternal and neonatal harms**	This study reports intrauterine death and chorioamnionitis but the reporting of results is limited to those who had induction of labour and it was not reported per exposure group.
Limitations and other comments	
• **Limitations**	External validity/applicability: Very serious concern (Majority of population is of African race, and a large proportion of the population is high risk for preterm birth) Internal validity: High risk of bias (Exposure status is based on physician's discretion. Groups significantly different at baseline and important variables were not considered in the analysis.)

Table 175 – Cerclage in prevention of preterm birth risk: Evidence table of observational study (Sakai et al., 2006)

Evaluation of effectiveness of prophylactic cerclage of a short cervix according to interleukin-8 in cervical mucus. Sakai et al., 2006[94]	
Methods	
• **Design**	Retrospective comparative cohort study
• **Source of funding and competing interest**	Not industry (Japanese Ministry of Education, Science and Culture Grants-in-Aid for Scientific Research (Nos. 13470347 and 16591648) and 21st Century COE Program); No statement regarding declaration of interest.
• **Setting**	Multicentre (Gynacology Department of 4 hospitals in Toyama, Japan); assumed to be urban
• **Sample size**	Number of patients needed: NR Number of patients included: 248 eligible; 2 excluded after ultrasound examination (246 included)
• **Duration and follow-up**	Start and end dates of the study: April 1998 and March 2003 Inclusion and follow-up periods: From between 20-24 wks gestation to delivery
• **Statistical analysis**	ITT for subgroups of preterm birth <37 weeks and preterm birth <34 weeks. NR for preterm birth <37 weeks (entire population), unadjusted analyses
Patient characteristics	
• **Eligibility criteria**	Singleton pregnancy, short cervix (<=25 mm), managed by the gynecology department of 4 hospital in Toyama, Japan

• **Exclusion criteria**	Fetal distress after prenatal checkup including uterine cervical length determination, past history of repeated miscarriage in the second trimester and elective cerclage in the first trimester of current pregnancy.
• **Patient & disease characteristics**	Women with singleton pregnancy and cervical length <= 25 mm managed by the gynecology department of 4 hospital in Toyama, Japan; recruited between April 1998 to March 2003. Patient characteristics: All singleton pregnancies, approximately 30% with previous PTB; no information on previous cervical surgery, uterine malformations or polyhydramnios. Age: Mean (SD): Cerclage group + bed rest = 28.5 (3.3); Bed rest = 29.1 (2.8) Week of admission: Mean (SD): Cerclage+bed rest: 23.5 (2.9); No cerclage+bed rest: 23.7 (2.2) No major baseline imbalances noted for maternal weight (reported as <50 kg before pregnancy), previous PTB, maternal age, gestations (all singleton), smoking status. No details regarding socioeconomic status, race, hypertension, diabetes melitus, in vitro fertilization or previous cervical surgery
Interventions	
• **Intervention/exposure group**	***Group 1:*** Cerclage (McDonald or original Shirodkar cerclage) + bed rest from between 20 and 24 wks gestation to 36 wks gestation; timing of removal of suture not stated. *Details:* *Cerclage:* McDonald or original Shirodkar suture with a single stitch of mersilene tape under spinal anesthesia by a designated obstetrician at each center with relevant surgical expertise extending over at least 5 years performed cervical cerclage. *Bed rest:* majority in-hospital - not further defined; *Additional management specific to this group:* None stated *Additional monitoring/treatment/follow-up for all study groups:* When uterine contractions were observed, ritodrine hydrochloride was given by continuous intravenous drip. When clinical evidence of chorioamnionitis was observed, the pregnancy was terminated.
• **Control group**	***Group 2:*** Bed rest from between 20 and 24 wks gestation to 36 wks gestation *Details:* Bed rest as described above; unclear if some were out of hospital and, if so, duration *Additional management specific to this group:* None stated *-Additional monitoring/treatment/follow-up for all study groups:* As described above
Results	
• **Preterm Birth**	*Preterm birth < 37 weeks (cerclage vs. control)* 74/165 vs. 45/81 *Subgroup analyses* *Preterm birth < 37 weeks (cerclage vs.control in high cervical mucus IL-8 subgroup)* 32/41 vs. 20/37; unadjusted p-value = 0.0255 P value for % undelivered patients as per Kaplan Myer analysis 0.0253 *Preterm birth < 37 weeks (cerclage vs. control in normal cervical muscus IL-8 subgroups)* 41/124 vs. 24/44; unadjusted p-value = 0.0122 P value for % undelivered patients as per Kaplan Myer analysis 0.0124 *Preterm birth < 34 weeks (cerclage vs.control in normal cervical muscus IL-8 subgroups)* 5/124 vs. 6/44; unadjusted p-value = 0.0271

	P value for % undelivered patients as per Kaplan Myer analysis 0.0124
Limitations and other comments	
• **Limitations**	External validity/applicability: Serious concern (short cervix, prior preterm birth in approx 30% of patients Internal validity: Unclear risk of bias (populations are fairly similar based on reported baseline characteristics, although a few potential confounders were not reported. Information is retrospectively collected and validity of ascertainment of exposure (i.e. fidelity of intervention) is unclear).

Table 176 – Cerclage in prevention of preterm birth risk: Evidence table of observational study (Skupski et al., 2014)

Extremely short cervix in the second trimester: bed rest or modified Shirodkar cerclage? Skupski et al., 2014[93]	
Methods	
• **Design**	Retrospective comparative cohort study
• **Source of funding and competing interest**	Funding: not reported; No statement regarding declaration of interest.
• **Setting**	Multicentre (2 United States Hospitals/medical centres in urban New York)
• **Sample size**	Number of patients needed: To detect a 7-day difference = 1028 total; To detect a 14-day difference = 258 patients total; To detect a 21-day difference = 116 total Number of patients included: 189 eligible with short cervix and meeting exposure eligibility criteria; 167 contributed data
• **Duration and follow-up**	Start and end dates of the study: January 1, 2000, to December 31, 2010 Inclusion and follow-up periods: From between 13 wks 0 days and 25 wks 6 days gestation to delivery. The timing of 'enrolment' (initial cervical measurement or cerclage placement) was significantly earlier in the cerclage group compared to the bed-rest group.
• **Statistical analysis**	Chi-square analysis
Patient characteristics	
• **Eligibility criteria**	Singleton gestation between 13+0 and 25+6, endovaginal ultrasound cervical length ≤15 mm, at two institutions each using a different treatment method over the same period dates of inclusion January 1, 2000, to December 31, 2010.
• **Exclusion criteria**	Electronic medical record delivery information unavailable (i.e., latency cannot be calculated), and initial cervical length unavailable; placement of a McDonald cerclage; and delivery within 48 hours of the discovery of short cervix.
• **Patient & disease characteristics**	Pregnant women with CL <=15 mm and singleton pregnancies at two institutions each using a different treatment method over the same period, 2000-2010. Gestational age: At initial cervical length or cerclage placement (days) - measures of central tendency and dispersion not defined: cerclage group - 146 (138-156); control group - 157 (143-165) Age of patient: Measure of central tendency and dispersion not defined: Cerclage group: 31.1 (5.4); Control group: 31.6 (6.5) Other: 40% of population had prior preterm birth or second trimester loss, portion of population also taking progesterone for prevention of PTB The cerclage group was had significantly more previous PTB and 2nd trimester losses, greater use of progesterone for prevention of PTB, and shorter cervical length and earlier gestational age at enrolment. No differences between groups in maternal age, gestations (all singleton). No data regarding socioeconomic status, maternal weight, race, smoking or substance abuse, hypertension, diabetes mellitus, *in vitro* fertilization, or previous cervical surgery

Interventions	
• **Intervention/exposure group**	***Group 1***: Cerclage [from between 13 wks and 25 wks 6 days to 36 wks gestation] + modified bed rest [for 2 weeks post cervical cerclage surgery] + pelvic rest [for duration of pregnancy] +/- progesterone (~49% in this arm) [weekly intramuscular injections - dose and duration NR] *Details:* *Cerclage*: Summary: modified Shirodkar cerclage, performed by two experienced providers, always placed as high on the cervix as possible. Technique included spinal anesthesia, main surgery (detailed description in report) and spinal anaesthesia for removal at 36 wks gestation *Bed rest and pelvic rest:* pelvic rest for duration of pregnancy and modified bed rest for 2 weeks (defined as mostly resting in sitting or lying down position with ambulation only for the bathroom, to get a drink or snack, or to stretch the legs with no walking more than one city block") - patients were to resume normal physical activities for the duration of pregnancy if asymptomatic and no problems. *Progesterone:* Some participants (49% in this arm) received weekly intramuscular injections of 17-OH progesterone caproate if they had a history of PTB *Additional management specific to this group:* *Monitoring/tests:* Sterile speculum examination was used to assess membrane exposure - was performed routinely for this group. Endovaginal ultrasound was performed monthly after cerclage *Treatment:* perioperative management with 1-3 days intravenous azithromycin and ampicillin for 14-24 hours before cerclage and continuing for 12-24 hours after; indomethacin 50 mg orally immediately preoperatively and 48-72 hours of indomethacin (25 mg every 6 hours) postoperatively. *Additional monitoring/treatment/follow-up for all study groups:* Tocolysis and other management decisions at the discretion of the attending physician
• **Control group**	***Group 2:*** Bed rest [duration NR] +/- progesterone (26% in this arm) [either weekly intramuscular injections (dose and duration NR) or vaginal progesterone (frequency, dose and duration NR). *Details:* *Bed rest:* in the hospital (22/55), at home 30/55) or both (3/55). No further details provided. *Progesterone:* Some participants (26% in this arm) received either weekly intramuscular injections of 17-OH progesterone caproate if they had a history of PTB and/or vaginal progesterone therapy. *Additional management specific to this group:* *Monitoring/tests:* Endovaginal ultrasound was performed frequently in patients receiving bed rest; however, decision was left to the attending physician. *Additional monitoring/treatment/follow-up for all study groups:* As described above.
Results	
• **Preterm Birth**	*Preterm birth < 37 weeks (cercalge vs.control)* 34/112 vs. 29/55; p-value for chi-square test = 0.0066 *Preterm birth < 35 weeks (cerclage vs. control)* 21/112 vs. 25/55; p-value for chi-square test = 0.0004 *Preterm birth < 32 weeks (cerclage vs.control)* 16/112 vs. 20/55; p-value for chi-square test = 0.0023 *Preterm birth < 28 weeks (cerclage vs. control)*

	11/112 vs. 13/55; p-value for chi-square test = 0.03 *Preterm birth < 24 weeks (cerclage vs. control)* 9/112 vs. 5/55; p-value for chi-square test = 0.78
• **Specific serious maternal harms**	*Chorioamnionitis (cerclage vs. control)* "1 patient had chorioamnionitis 2 days after cerclage placement." Unclear if this is the extent of cases.
Limitations and other comments	
• **Limitations**	External validity/applicability: Serious concern (40% of population had history of PTB or second trimester loss) Internal validity: High risk of bias due to selection and confounding bias (groups are significantly different for several baseline factors (including prior second trimester loss, prior preterm birth, progesterone use, cervical length and gestational age at time of intervention) and there is no control for confounding in the analysis. Missing data is not balanced between the two groups and reasons for missing data are not stated.)

9.8.4. Reduced physical activity

Table 177 – Reduced activity to prevent preterm birth risk: Evidence table of observational study (Grobman et al., 2013)

Activity restriction among women with a short cervix. Grobman et al., 2013[96]	
Methods	
• **Design**	Prospective comparative cohort study; authors specify it is a secondary analysis of a randomized trial.
• **Source of funding and competing interest**	Not industry (grants from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) (HD21410, UL1 RR024153, UL1 TR000005; HD27869, HD27915, HD27917, HD34116, HD34208, 5UL1RR025764, HD36801, HD40500, HD40512, HD40544, M01 RR00080, UL1 RR024989 (NCRR), HD40545, HD40560, HD40485, HD53097, HD53118)); Report states there are no declarations of interest
• **Setting**	Multicentre (14 urban sites: United States - Maternal-Fetal Medicine Units Network of the Eunice Kennedy Shriver National Institute of Child Health and Human Development)
• **Sample size**	Number of patients needed: 1000 total (for main trial) Number of patients eligible: 657 (randomized in main trial); Number of patients included: 646 (secondary analysis)
• **Duration and follow-up**	Start and end dates of the study: April 2007- May 2011 (from RCT report); Inclusion and follow-up: From between 16 weeks 0 days and 22 weeks 3 days gestation to hospital discharge
• **Statistical analysis**	Type of analysis NR; analyses were both adjusted and unadjusted Adjusted for: treatment group, maternal age, black race, public insurance, estimated age at cervical length measurement, cervical length, cervical funnelling, intra-amniotic debris and any activity restriction Multivariable analyses were performed with multiple logistic regression with odds ratios (ORs) and 95% confidence intervals (CIs) reported

Patient characteristics	
• **Eligibility criteria**	Asymptomatic, nulliparous women with a viable singleton gestation and had a CL < 30 mm between 16 weeks 0 days and 22 weeks 3 days and who, after giving informed consent and receiving a "compliance" injection of placebo, returned for randomization for the main trial.. A woman was defined as nulliparous if she had no prior pregnancy that progressed 19 weeks 6 days. For the secondary analysis, women had to have responded to questionnaires regarding activity restriction
• **Exclusion criteria**	Women with selective fetal reduction to a singleton gestation; had sonographic evidence of an additional fetal pole/embryo at 12 weeks of gestation; had received progesterone treatment 14 weeks 6 days; had experienced vaginal bleeding heavier than spotting 15 weeks 6 days; had amniotic membranes prolapsing beyond the external os; had premature rupture of membranes; had a known major fetal anomaly or aneuploidy; had a current or planned cervical cerclage; had a known müllerian abnormality; had a contraindication to IM injections; had maternal medical conditions that increase the probability of preterm delivery (eg, hypertension, diabetes requiring medication); had prior cervical surgery (ie, cold knife conization, laser vaporization, or loop electrosurgical excision procedure); or were planned to have an indicated preterm delivery. From registration record: participation in another study that influences age at delivery, participation in this trial for previous pregnancy, prenatal care or delivery planned outside relevant center; DES exposure
• **Patient & disease characteristics**	Asymptomatic nulliparous women with singleton gestations and a cervical length < 30 mm between 16 weeks 0 days and 22 weeks 3 days from one of 14 centers of the Maternal-Fetal Medicine Units Network of the Eunice Kennedy Shriver NICHHD between April 2007 and May 2011. Age (for those included in analysis, n=646): Median (IQR): Activity Restriction group: 21.0 (20.0, 25.5); No Activity Restriction Group: 20.0 (19.0, 23,0); significantly different between groups Race (for those included in analysis, n=646): % in Activity Restriction group vs. no activity restriction group: Non-Hispanic white: 25.0 vs.21.8%; Hispanic white: 3.6 vs. 11.7%; Black: 55.6 vs.50.0%; Asian: 1.2 vs. 1.0%; Other: 14.7% vs. 15.5%; Note: significant difference between groups Other (for those included in analysis, n=646): Included ~30% women who had miscarried previously prior to 19 weeks 6 days gestation Baseline imbalances were noted for age (activity restricted group older than non-restricted group), race (more Hispanic in no restriction group) and other variables including gestational age, cervical length and funnelling and intra-amniotic debris at enrolment (higher GA, shorter CL and more funneling and intra-amniotic debris in restricted group) and private insurance (more common in activity restricted group). Report did not present data on maternal weight, history of PTB, smoking status, hypertension, diabetes mellitus, *in vitro* fertilization or previous cervical surgery.
Interventions	
• **Intervention/exposure group**	***Group 1:*** Reduced activity +/- progesterone (~50% on 250 mg weekly intramuscular injections of progesterone) from between 16 wks 3 days and 23 wks 6 days gestation to 36 wks 6 days gestation (progesterone) or delivery *Details:* *Reduced activity:* Definition 1: Any activity restriction: pelvic rest (no sexual activity) restriction, reduction of work activity, or reduction of non-work activity. Definition 2: Reduction of work activity or reduction of non-work activity (without regard for pelvic rest) *Progesterone:* 1 ml intramuscular injections of 17-alpha-hydroxyprogesterone caproate (17-OHP) in castor oil with benzyl benzoate and benzyl alcohol as preservatives *Additional management specific to this group:* None

	Additional monitoring/treatment/follow-up for all study groups: weekly visits where patients were asked whether they had consulted a physician for preterm labour symptoms, had undergone any medical procedures, or had been given any corticosteroids or tocolytic medications since their last visit.
• **Control group**	***Group 2:*** No reduced activity +/- progesterone (~50% on 250 mg weekly intramuscular injections of progesterone) from between 16 wks 3 days and 23 wks 6 days gestation to 36 wks 6 days gestation or delivery *Details:* *Progesterone:* 1 ml intramuscular injections of 17-OHP in castor oil with benzyl benzoate and benzyl alcohol as preservatives *Additional management specific to this group:* None *Additional monitoring/treatment/follow-up for all study groups:* As described above
Results	
• **Preterm Birth**	*Preterm birth < 37 weeks* *reduced activity (definition 1) +/- progesterone vs. no reduced activity +/- progesterone* 93/252 vs. 67/394; OR_{crude}: 2.91; 95% CI: 2.0, 4.21, p-value= <0.001; $OR_{adjusted}$: 2.37; 95% CI: 1.60, 3.53, p-value= <0.001 *reduced activity (definition 2) +/- progesterone vs. no reduced activity +/- progesterone* $OR_{adjusted}$: 2.44; 95% CI: 1.63, 3.65, p-value= NR *Preterm birth < 34 weeks* *reduced activity (definition 1) +/- progesterone vs. no reduced activity +/- progesterone* $OR_{adjusted}$: 2.28; 95% CI: 1.36, 3.80; p-value= NR *reduced activity (definition 2) +/- progesterone vs. no reduced activity +/- progesterone* $OR_{adjusted}$: 2.70; 95% CI: 1.62, 4.52, p-value= NR
Limitations and other comments	
• **Limitations**	External validity: Very serious concern (over half of the population is African-American in this subanalysis. In the main study, 1/3 of the population had previous miscarriage <19 weeks.) Internal Validity: High risk of bias (allocation was at the discretion of the attending physician. Baseline imbalances were noted for many important factors and although some were adjusted for in the analysis, many, including history of PTB were not accounted for or reported.)

9.9. Pregnancies that passed their due date

Table 178 – Descriptive summary of the six studies included for surveillance of prolonged pregnancies

Outcome Categories	A priori outcomes in protocol	First strategy tests											Second strategy tests										
		CTG	NST	fm	BP1	mBP2	mBP	pBP	AFV	AFD	AFI	uabf	f	CTG	NST	fm	BP1	mBP2	mBP	pBP	AFV	AFD	AFI	uabf	f
Fetal/infant /childhood	**Various studies**	**Intervention**												**Comparator**										
Neonatal death		No difference (GRADE: quality of evidence very low)																							
	Eden 1982	√		√				√						√		√				√	√				
	Lindqvist 2014 (R vs.I)										√[1]	√	√[1]											√	√[2]
Perinatal death		No difference (GRADE: quality of evidence very low)																							
	Alfirevic 1995					√								√								√			
	Alfirevic 1997	√									√			√								√			
	Eden 1982	√		√				√						√		√				√	√				
	El-Damarawy 1993					√									√										
	El-Damarawy 1993					√									√						√				
	Lindqvist 2014 (I vs.R)										√	√	√[2]										√[1]	√	√[1]
	Oral 1999	√									√			√								√			
Still birth		No difference (GRADE: quality of evidence very low)																							
	Eden 1982.	√		√				√						√		√				√	√				
	Lindqvist 2014 (R vs.I)										√[1]	√	√[1]											√	√[2]
NICU admission		**May be superior favouring comparator for Eden 1982** (GRADE: quality of evidence **low**)																							

	No difference (GRADE: quality of evidence very low)																					
	Alfirevic 1995					√							√					√				
	Alfirevic 1997	√							√				√					√				
	Eden 1982	√		√			√						√		√		√	√				
	Oral 1999	√							√				√					√				
Apgar score (various <7 or <4 or NR cut-offs at 1-5 minutes)	No difference (GRADE: quality of evidence very low)																					
	Alfirevic 1995					√							√					√				
	Alfirevic 1997	√							√				√					√				
	Eden 1982	√		√			√						√		√		√	√				
	El-Damarawy 1993					√							√									
	El-Damarawy 1993					√							√				√					
	El-Damarawy 1993		√										√				√					
	Lindqvist 2014 (R vs.I)							√[1]	√	√[1]										√	√[2]	
	Oral 1999	√							√				√					√				
Meconium aspiration syndrome	No difference (GRADE: quality of evidence very low)																					
	Eden 1982	√		√			√						√		√		√	√				
Hypoxic ischemic encephalopathy grades 2 and 3	No difference (GRADE: quality of evidence very low)																					
	Lindqvist 2014 (R vs.I)							√[1]	√	√[1]										√	√[2]	
Cerebral palsy	No difference (GRADE: quality of evidence very low)																					
	Lindqvist 2014 (R vs.I)							√[1]	√	√[1]										√	√[2]	
Neonatal convulsion	No difference (GRADE: quality of evidence very low)																					
	Lindqvist 2014							√[1]	√	√[1]										√	√[2]	

	(R vs.I)		
cerebral haemorrhage/intra cranial haemorrhage	No difference (GRADE: quality of evidence very low)		
	Lindqvist 2014 (R vs.I)	√[1] √ √[1]	√ √[2]
Cerebral damage (includes HIE23, cerebral palsy and cerebral haemorrhage)	No difference (GRADE: quality of evidence very low)		
	Lindqvist 2014 (I vs.R)	√ √[2]	√[1] √ √[1]
Maternal	**Various studies**	**Intervention**	**Comparator**
Instrumental delivery	No difference (GRADE: quality of evidence **Low** to very low)		
	Alfirevic 1997	√ √	√ √
	Lindqvist 2014 (I vs.R)	√ √[2]	√[1] √ √[1]
C-Section due to fetal distress (not clearly defined, but most likely fetal distress during labour)	No difference (GRADE: quality of evidence very low)		
	Alfirevic 1995	√	√ √
	Alfirevic 1997	√ √	√ √
	Oral 1999	√ √	√ √
C-Section (for reasons other than fetal distress or lack of progression of labour)	No difference (GRADE: quality of evidence Very low)		
	Alfirevic 1995	√	√ √
	Alfirevic 1997	√ √	√ √
	Eden 1982	√ √ √	√ √ √ √
	Lindqvist 2014 (I vs.R)	√ √[2]	√[1] √ √[1]
	Oral 1999	√ √	√ √
C-section due to failure to progress or ante partum distress	No difference (GRADE: quality of evidence **Low**)		
	Alfirevic 1995	√	√ √
	Alfirevic 1997	√ √	√ √

Table 179 – Surveillance in prolonged pregnancies: Evidence table of RCTs (Alfirevic et al., 1997)

A randomised comparison between amniotic fluid index and maximum pool depth in the monitoring of post-term pregnancy. Alfirevic et al., 1997 [97]	
Methods	
• **Design**	Randomized controlled trial
• **Source of funding and competing interest**	Source of funding not reported; No statement regarding declaration of interest
• **Setting**	Single centre study - Liverpool Maternity Hospital (urban), United Kingdom
• **Sample size**	Number of patients needed (by reported sample size calculation): 500 Number of patients included: 500 No losses to follow-up
• **Duration and follow-up**	Start and end dates of the study (recruitment): July 1994-July 1995 Inclusion and follow-up periods: From ~41 wks 3 days gestation to post-delivery (unclear how long infants were followed for outcome of perinatal death)
• **Statistical analysis**	Intention to treat. No missing data.
Patient characteristics	
• **Eligibility criteria**	Women with uncomplicated singleton pregnancies reaching 41 weeks of gestation.
• **Exclusion criteria**	Hypertension 140/95 mmHg or greater, significant proteinuria (greater than one plus on urine dipstick), history of antepartum haemorrhage, poor obstetric history, or prior ultrasound features suggesting suspected intrauterine growth retardation.
• **Patient & disease characteristics**	Women with singleton, uncomplicated pregnancies with gestational age greater than or equal to 41 weeks at one centre in Liverpool, UK. Gestational age at randomization was approximately 41 wks 3 days. The groups were comparable for all reported baseline variables including maternal age (mean 28 years), parity (~50% nulliparous) and gestational age at enrolment (above). This report did not present baseline data regarding maternal BMI, history of post-term pregnancy, race, socioeconomic status, number of visits to healthcare provide or substance abuse. Other: Previous Caesarean section: AFI + CTG: 7; MPD + CTG: 13; OR = 0.52 (0.2–1.33); p = 0.25
Interventions	
• **Intervention group**	***Intervention group 1:*** CTG + AFI; both every 3 days from 41 wks 3 days to spontaneous delivery/induction/c-section; up to 43 wk required induction if relevant. Details of intervention(s): CTG: The Oxford Sonicaid 8000 fetal monitor was used to analyse antenatal fetal heart rate pattern. AFI: Ultrasound measurement of the amniotic fluid volume as described by Moore and Cayle (reference provided in report) Management protocol: Normal results: follow up was arranged three days later.

	Abnormal result: If abnormal amniotic fluid volume (< 7.3 cm, rationale provided in report) or abnormal CTG (Oxford Sonicaid 8000 fetal monitor's criteria for normality were not met after 40 minutes), labour was induced. Other indication for intervention: Indication for induction: normal fetal monitoring but no spontaneous labour by 43 wks of gestation; any complication listed as an exclusion criterion (e.g. htn, significant proteinuria, antepartum hemorrhage or complication); specific maternal request for induction.
• **Control group**	***Intervention group 2:*** CTG + AFD; both every 3 days from 41 wks 3 days to spontaneous delivery/induction/c-section; up to 43 wk required induction if relevant. Details of intervention(s): CTG: The Oxford Sonicaid 8000 fetal monitor was used to analyse antenatal fetal heart rate pattern. AFD: Maximum pool depth - no further description of method Management protocol: Management protocol as above except abnormal amniotic fluid measurement for AFD was defined as maximum pool depth < 1.8 cm.
Results	
• **Offspring - death**	Perinatal death 0/250 vs. 0/250
• **Neonatal harms**	C-section due to fetal stress 20/250 vs. 10/250; OR = 2.08 (0.95–4.55); p = 0.0901 Apgar score <7 at 5 minutes 5/250 vs. 5/250; OR = 1 (0.28–3.50); p = 1 Admission to neonatal intensive care unit 4/250 vs. 4/250; OR = 1 (0.24–4.05); p = 1
• **Maternal harms**	Instrumental delivery 47/250 vs. 47/250; OR = 1 (0.63–1.56); p = 1 Caesarian section 47/250 vs. 33/250; OR = 1.52 (0.93–2.47); p = 0.1128 C-section due to failure to progress in labour 25/250 vs. 21/250; OR = 1.21 (0.65–2.22); p = 0.6425
Limitations and other comments	
• **Limitations**	External validity: No serious concerns. Findings limited to healthy women, with single fetus low-risk pregnancies, >40 weeks of gestation. Internal validity: Unclear risk of bias due to unclear risk of selective outcome reporting (no protocol available) and other bias (funding and COI not reported)

Table 180 – Surveillance in prolonged pregnancies: Evidence table of RCTs (Alfirevic et al., 1995)

A randomised controlled trial of simple compared with complex antenatal fetal monitoring after 42 weeks of gestation. Alfirevic et al., 1995[98]	
Methods	
• **Design**	Randomized controlled trial
• **Source of funding and competing interest**	Source of funding not reported; No statement regarding declaration of interest
• **Setting**	Single centre study - Liverpool Maternity Hospital (urban), United Kingdom
• **Sample size**	Number of participants needed (by reported sample size calculation): 100 Number of participants included: 145 (MPD + CTG = 73; mBP = 72) No losses to follow-up
• **Duration and follow-up**	Start and end dates of the study (recruitment): Jan. - Dec. 1993 Inclusion and follow-up periods: From 42 wks gestation until post-delivery (endpoint of follow-up not stated)
• **Statistical analysis**	Intention to treat. Approach to missing data not described but no missing data for our outcomes of interest.
Patient characteristics	
• **Eligibility criteria**	Women with uncomplicated singleton pregnancies reaching 42 weeks of gestation by certain menstrual age by LMP or with ultrasound dating prior to 20 weeks.
• **Exclusion criteria**	Hypertension 140/95 mmHg or greater, significant proteinuria (greater than one plus on urine dipstick), history of antepartum haemorrhage, poor obstetric history, or prior ultrasound features suggesting suspected intrauterine growth retardation.
• **Patient & disease characteristics**	Women with uncomplicated singleton pregnancies reaching 41 weeks gestation (study started at 42 weeks gestation) at one maternity hospital in Liverpool, U.K. Report states that groups were comparable for maternal age (median approx 28/29 years), height (no data), booking weight (no data), race (no data), parity (~,33-40% nulliparous), smoking (no data) and timing of the first antenatal hospital visit (94% by 20 weeks). No details on other potential confounders including SES, history of pre-term birth, number of healthcare visits.
Interventions	
• **Intervention group**	***Intervention group 1:*** mBP 2 (modified biophysical profile 2) including computerized CTG + AFI + US monitoring of fetal tone, breathing and movement - 2/wk from 42 wks gestation until spontaneous delivery/induction/c-section; up to 43 wk required induction if relevant. Details of intervention(s): Modified version of the biophysical profile described by Manning (reference provided in paper). CTG: Oxford Sonicaid 8000 fetal monitor – authors call this CTG (but state it is not standard CTG) but there is no mention of use of contraction testing; the test scored 0 (abnormal) or was 2 (normal). AFI: performed using Aloka 630-SSD ultrasound US: Fetal tone, breathing movements and gross body movements were monitored for up to 60 min to account for prolonged physiological resting phase in post-term pregnancies and scored as described by Manning et al. (1980). Performed using Aloka 630-SSD ultrasound Total maximum score for all five components of the test was 10.

	Management protocol: Normal result: mBP 2 score >6 and normal AFI – schedule visit in 72 hours. Abnormal result: A score <= 6 on mBP 2 or abnormal amniotic fluid volume (AFI <= 3rd centile) - indication for induction. Other indication for intervention: Induction if any complication developed which was listed as an exclusion criterion (e.g. htn, significant proteinuria, antenatal hemorrhage), due to specific maternal request for induction or reaching 43 wks gestation
• **Control group**	***Intervention group 2:*** 'simple' CTG + AFD 2/wk from 42 wks gestation until spontaneous delivery/induction/c-section; up to 43 wk where induction was indicated. Details of intervention(s): CTG: 'simple CTG' - no further description of method. AFD: maximum pool depth by US: performed using Aloka 630-SSD ultrasound Management protocol: Normal: if both CTG and AFD were normal, follow-up was arranged 72 hours later; if normal results and spontaneous delivery did not occur by 43 wks gestation, labour was induced. Abnormal: abnormal CTG (nonreactive CTG - defined as less than two accelerations (15 beats per minute (bpm) lasting at least 15 s) in 40 min; short term variability <= 5 bpm with decelerations) led to admission to hospital and induction of labour within 24 h. Other indicated intervention: Labour was also induced for reasons above. Timing of antenatal fetal monitoring sessions was the same in both groups (i.e., at randomisation and then twice weekly until 43 weeks). Ultrasound monitoring in both arms of the trial was performed using same equipment by the same person in order to avoid inter-observer variability.
Results	
• **Offspring - death**	Perinatal death: mBP vs. CTG + MPD: 1/72 vs. 0/73 (1 stillbirth)
• **Neonatal harms**	Apgar score <7 at 5 minutes: mBP vs. CTG + MPD: 1/72 vs. 0/73 Admission to neonatal intensive care unit: 0/72 vs. 2/73
• **Maternal harms**	Caesarean section: mBP vs. CTG + MPD: 13/72 vs. 7/73; OR (99% CI)= 2.1 (0.6–7.6); p = 0.22 C-section due to antepartum distress: 0/72 vs. 2/73 C-section due to fetal stress: 8/72 vs. 6/73; OR (99% CI) = 1.4 (0.3–6.0); p = 0.54 Other – composite - complicated pregnancies; defined as those requiring obstetrical or neonatal intervention (i.e., induction, operative delivery, resuscitation or specialist neonatal care): 54/72 vs. 44/73 – OR (99% CI) presented for 'uncomplicated pregnancies'
Limitations and other comments	
• **Limitations**	External validity: No serious concern. Findings limited to healthy women, with single fetus low-risk pregnancies, >40 weeks of gestation. Internal validity: Unclear risk of bias due to lack of information for assessment of selection bias, selective outcome reporting and other bias (no statement regarding funding, COI or some confounders).

Table 181 – Surveillance in prolonged pregnancies: Evidence table of RCTs (Oral et al., 1999)

A comparison between two different ultrasonographic methods for assessing amniotic fluid volume in postterm pregnancies [Turkish]. Oral et al., 1999[99]	
Methods	
• **Design**	Randomized controlled trial
• **Source of funding and competing interest**	Source of funding not reported; No statement regarding declaration of interest
• **Setting**	Not reported
• **Sample size**	Sample size needed: Not reported Eligible: Not reported Included: 101 (AFI: 48; MPD: 53) Analyzed: Not reported
• **Duration and follow-up**	Start and end dates of the study: NR Inclusion and follow-up periods: NR
• **Statistical analysis**	Not reported
Patient characteristics	
• **Eligibility criteria**	Women with singleton, uncomplicated pregnancies with gestational age >290 days
• **Exclusion criteria**	Not reported
• **Patient & disease characteristics**	Women with singleton, uncomplicated pregnancies with gestational age >290 days; no details regarding baseline characteristics/potential confounding.
Interventions	
• **Intervention group**	**Intervention group 1:** CTG+AFI [frequency and timing of testing NR] Details of intervention(s) CTG: computerized cardiotocography AFI: a four-quadrant technique was used to obtain amniotic fluid index measurement Management protocol: NR
• **Control group**	Intervention Group 2: CTG+AFD [frequency and timing of testing NR] Details of intervention(s) CT: computerized cardiotocography AFD: maximum pool depth Management protocol: NR

Results	
• **Offspring - death**	Perinatal death—data obtained from SR by Nabhan 0/48 vs. 0/53; RR = 0.0 (0.0–0.0)
• **Neonatal harms**	Admission to NICU (AFI vs. MPD)—data obtained from SR by Nabhan 1/48 vs. 1/53; RR = 1.10 (95% CI = 0.07–17.17) Apgar score <7 at 5 minutes—data obtained from SR by Nabhan 1/48 vs. 1/53; RR = 1.10 (0.07–17.17)
• **Maternal harms**	Caesarean section —data obtained from SR by Nabhan 9/48 vs. 7/53; RR = 1.42 (0.57–3.52) Caesarean for fetal distress—data obtained from SR by Nabhan 4/48 vs. 3/53; RR = 1.47 (0.35–6.25)
Limitations and other comments	
• **Limitations**	External validity: Serious concern due to unclear risk status of the women. Internal validity: Unclear as this is only available as an English abstract (the remaining information comes from an existing SR (Nahban et al.[113]). Most information for RoB assessment is not available.

Table 182 – Surveillance in prolonged pregnancy : Evidence table of observational study routine ultrasound (Lindqvist PG et al. (2014) [100])

Routine ultrasound examination at 41 weeks of gestation and risk of post-term severe adverse fetal outcome: a retrospective evaluation of two units, within the same hospital, with different guidelines, Lindqvist PG et al. 2014[100]	
Methods	
• **Design**	Retrospective comparative cohort study
• **Source of funding and competing interest**	Non-industry: Clintec, Karolinska Institute, Stockholm and SLL Stockholm county Council; Report states there are no declaration of interests
• **Setting**	Two antenatal units at one urban UniversityHospital (KarolinskaUniversityHospital), Stockholm, Sweden
• **Sample size**	Number of patients needed: NR Number of patients included: 71,040 Number included in analysis for this review (those remaining undelivered past 42 weeks): 4094
• **Duration and follow-up**	Start and end dates of the study: based on all deliveries from Jan 2002-Dec 2009 Inclusion and follow-up periods: From 18-20 weeks gestation until 1 year after delivery.
• **Statistical analysis**	ORs and 95% CI were used and logistic regression was used to adjust for possible confounders with a p<0.1. Backward and forward regression for final model, including only variables with p<0.05. No interactions were found.

Patient characteristics	
• **Eligibility criteria**	All pregnancies delivered above 32 weeks of gestation without chromosome aberrations or major malformations during an 8-year period (Jan 2002 - Dec 2009); only pregnancies that were appropriate-for-gestational age (AGA) or small-for-gestational age (SGA) were included.
• **Exclusion criteria**	Pregnancies with large-for-gestational age babies
• **Patient & disease characteristics**	Women delivering over 32 weeks gestation with AGA or SGA babies. Women recruited 18-20 weeks gestation. Extracted analysis limited to those who remained undelivered past 42 weeks gestation. Baseline characteristics not reported separately for subgroup of interest (those remaining undelivered at 42 weeks). For full study group, statistical imbalances at baseline included (BMI, maternal age, nullipara, marital status, SES [disposable income, education] country of birth, gestational age at delivery, newborn weight). Marital age, parity, BMI, disposable income, marital status and country of birth were considered in the analysis and those with p<0.05 were included in final model. No information regarding personal or familial history of post-term pregnancy, race, number of visits to healthcare provider or substance abuse.
Interventions	
• **Intervention group**	***Intervention group 1:*** Indicated screening [as clinically indicated] in third trimester by ultrasound examination with fetometry (measured for biparietal diameter, abdominal diameter, femur length, estimated fetal weight) Management protocol*:* **Normal or no test**: No intervention **Abnormal**: For abnormal fetometry (Intrauterine-estimated SGA (eSGA) ≤-22% fetal weight deviation), women with eSGA were examined by umbilical artery blood flow measurements. If this was normal: management is not stated but likely conservative management; however women with eSGA were not scheduled to continue into 42 weeks of gestation. If this was abnormal (absence of blood flow velocity throughout diastole or reversed diastolic) and flow was classified as BFC III, this was regarded as an indication for cesarean delivery. BFC II (umbilical artery pulsative index (PI) +3 SD) was regarded as indication for induction. BFC I (PI≥+2 SD) was regarded as a relative indication for induction. Women Cervical ripening status together with obstetric history (earlier vaginal delivery or cesarean) could affect the mode of delivery at the discretion of the clinician on duty.
• **Control group**	***Intervention group 2:*** routine screening with AFI + ultrasound examination of fetometry at 41 weeks gestation Details of intervention AFI: Defined as the sum of the deepest pocket of amniotic fluid in all quandrants Fetometry: biparietal diameter, abdominal diameter, femur length, estimated fetal weight. Estimated and expected FW assessed using Swedish reference algorithms (reference provided in paper) Management protocol: Normal: No planned intervention Abnormal: If oligohydramnios (AFI < 50 mm) in the postdate period, this was usually considered an indication for induction. If eSGA (fetuses estimate at ≤-22% fetal weight deviation), women with eSGA were examined by umbilical artery blood flow measurements and subsequent management proceeded as above.
Results	
• **Offspring - death**	Fetal death: Indicated vs. routine scan: 9/2650 vs. 3/1444; ORadjusted = 1.6 (0.4-6.1) Antenatal Death: 7/2650 vs. 0/1444 Postnatal death: 2/2650vs. 3/1444

• **Neonatal harms**	**Indicated vs. routine scan** Risk of severe adverse fetal outcome (Total/major harms): 41/2650 vs. 14/1444 , OR = 1.6 (0.9 – 3.0) Apgar 5min <4: 1/2650 vs. 4/1444 Severe Asphyxia (general): 29/2650 vs. 12/1444; ORadjusted = 1.1 (0.6 – 2.1) Hypoxic ischaemic encephalopathy grades 2 and 3: 2/2650 vs. 0/1444
• **Infant neurological development**	**Indicated vs. routine scan** Cerebral damage (composite:HIE23, cerebral palsy and cerebral haemorrhage): 5/2650 vs. 3/1444; ORadjusted(95% CI) = 0.9 (0.2-3.8) Seizure/neonatal convulsions: 3/2650 vs. 3/1444 Cerebral palsy: 3/2650 vs. 0/1444 Cerebral haemorrhage/intracranial haemorrhage: 1/2650 vs. 3/1444.
• **Maternal harms/complications**	**Indicated vs. routine scan** Cesarean delivery: 656/2650 vs. 344/1444; , ORadjusted (95% CI) = 1.1 (0.9-1.3) Instrumental delivery: 408/2650 vs. 229/1444, ORadjusted (95% CI) = 1.0 (0.9-1.2)
Limitations and other comments	
• **Limitations**	External validity/applicability: very serious concern (Exclusion of large-for-gestational age babies and excludes data for women having the intervention but delivering from 41-42 weeks gestation) Internal applicability: High risk of bias (due to the exclusion from relevant analysis of women receiving the intervention at 41 weeks who delivered between 41-42 weeks).

Table 183 – Surveillance in prolonged pregnancies: Evidence table of observational study (Eden, R.D., 1981)

Comparison of antepartum testing schemes for the management of the postdate pregnancy. Eden, R.D., 1981[102]	
Methods	
• **Design**	Prospective comparative cohort study
• **Source of funding and competing interest**	Non-industry (Ariel Kaare Rosholt Weathers-Lowin Medical Research Foundation); No statement regarding declaration of interest
• **Setting**	Single centre study (private and clinic practices of physician at Cedars-Sinai Medical Center in Los Angeles, United States); Urban
• **Sample size**	Number of patients needed: NR Number of patients included: 583
• **Duration and follow-up**	Start and end dates of the study: Scheme 1: Nov 1978 – Aug 1979; Scheme 2: Sept 1979 – Dec 1980; Scheme 3: Jan 1981 – Aug 1981 Inclusion and follow-up periods: From 42 weeks gestation. Endpoint of follow-up unclear.
• **Statistical analysis**	Chi-square; no details on drop-outs/losses to follow-up

Patient characteristics	
• **Eligibility criteria**	Women at >=42 weeks gestation who had prenatal care for at least 20 weeks of gestation
• **Exclusion criteria**	NR
• **Patient & disease characteristics**	Women at >=42 weeks gestation; no baseline data reported.
Interventions	
• **Intervention group**	***Scheme 1 (noted as Group 3 in our files and is not relevant to this review):*** NST (1/week) from 42 wks gestation in all participants + Biophysical profile (results of the latter not known to physicians and did not guide management (1/week) from 42 weeks gestation in all participants +/- indicated CST (based on NST results) Details of interventions The NST was performed according to the technique outlined by Martin and Schifrin. Management protocol: Normal: f the NST was reactive, the patient returned in 1 week for retesting. Abnormal: If the NST was nonreactive (accelerations were not seen within 40 minutes from the onset of testing with addition of palpation or glucose beverage), a CST was performed. Note: In both cases patients received real-time ultrasound scanning and FHR decelerations were noted during the NST (those lasting at least 30 seconds with a decrease of at least 15 bpm) but results of both of these tests had no bearing on the management of the patient (and the results of the former were not made available to the attending physicians). In participants undergoing CST, if CST was positive (classified according to the criteria of Schifrin (reference provided in report)), labour was induced; if CST was negative; the patient was asked to return for NST in 1 week; if CST was suspicious/equivocal, patient was asked to return in 24 hours. The results of the NST and CST were used for patient management without consideration of FHR decelerations ***Scheme 2 (Noted as Group 1 in our extraction files)****:* CTG+fetal movement [2/wk] from 42 wks gestation in all participants +/- partial BP* if non-reactive Test 1 Description of intervention(s) CTG/NST (all participants): as above. Note, authors refer to this as NST but also refer to monitoring uterine contractions. Partial BP (as indicated based on NST): included analysis of fetal breathing movements, fetal movements, and amniotic fluid volume; also a general survey of intrauterine contents, fetal presentation and position, biparietal diameter and FHR. Management protocol: Normal: If the NST was reactive, the patient returned semiweekly for testing without routine real-time ultrasound scanning. Abnormal: If the NST was non-reactive (accelerations were not seen within 40 minutes from the onset of testing with addition of palpation or glucose beverage), patients underwent BPP by ultrasound (see next). FHR decelerations during the NST had no bearing on patient management and did not serve as an indication for real-time ultrasound scanning. For participants undergoing BPP: • Normal: If fetal breathing movements were present, the patient returned to semi-weekly NST with indicated BPP by ultrasound. • Abnormal: If fetal breathing movements were absent but amniotic fluid volume and fetal movements were normal, the patient was similarly rescheduled for nonstress testing. If normal amniotic fluid volume and fetal movements were not observed, the patient was transferred to the labor room for induction of labour.
• **Control group**	***Scheme 3 (Noted as Group 2 in our data extraction files)***:[Test 1: CTG [2/wk] + Test 2: AFV [1/wk]] from 42 wks gestation +/- Test 3: partial BP if non-reactive test 1.

	CTG/NST: as above AFV: no further details on method Partial BP: Real-time ultrasound scanning for analysis of fetal breathing movements, fetal movements (unclear if further assessment of amniotic fluid volume at this time) Management protocol: Normal: If reactive NST, participant returned for semi-weekly NST/ultrasound and weekly AFV determination. Abnormal: If amniotic fluid volume was decreased (not defined), labour was induced If the NST was non-reactive (accelerations were not seen within 40 minutes from the onset of testing with addition of palpation or glucose beverage), patients underwent BPP by ultrasound. If FHR decelerations (lasting at least 30 seconds with a decrease of at least 15 bpm from baseline) were noted during the NST (regardless of FHR reactivity), real time ultrasound for BPP was performed and labour was induced. In participants undergoing mBP if non-reactive NST and normal AFV and fetal breathing and fetal movements present, participant was rescheduled for semi-weekly NST. If normal fetal breathing movements and fetal movements were not observed in the presence of normal amniotic fluid volume and a nonreactive NST, the patient was transferred to the labour room for induction of labour.
Results	
• **Offspring - Death**	*Mortality Rate:* 12.8 vs. 5.0 vs. 0 (corrected) *Perinatal Deaths:* 2/78 vs. 4/398 vs. 0/109 *Antepartum death:* 0/78 vs. 2/398 vs. 0/109 *Intrapartum death* 2/78 vs. 0/398 vs. 0/109 *Neonatal death:* 0/78 vs. 2/398 vs. 0/109
• **Neonatal harms**	**Scheme 1 vs. Scheme 2 vs. Scheme 3** *Apgar 1min <7:* 15.4 vs. 13.1 vs. 7.3 (%) *Apgar 5min <7:* 10.3 vs. 2.3 vs. 0 (%), p<0.05 between schemes 1 and 2 *Meconium Aspiration:* 6.4 vs. 1.3 vs. 0 (%), p<0.05 between schemes 1 and 2 *Requiring resuscitation/intubation:* 12.8 vs. 10.1 vs. 0 (%) *Total perinatal morbidity (any of the following: fetal distress requiring intervention, 5 min Apgar score <7, neonatal resuscitation, postmaturity syndrome or meconium aspiration, major congenital anomaly or perinatal death):* 25.6 vs. 14.3 vs. 5.5 (%)
• **Maternal Harms/complications**	**Scheme 1 vs. Scheme 2 vs. Scheme 3** *Caesarean delivery:* 11.5 vs. 29.9 vs. 29.4 (%)
Limitations and other comments	
• **Limitations**	External validity/applicability: No concern Internal applicability: High risk of bias due to high risk of selection bias and bias due to confounding (groups are from different non-overlapping time periods over the course of three years; no baseline data is presented)

Table 184 – Surveillance in prolonged pregnancies: Evidence table of observational study. (El-Damarawy et al., 1993)

Antepartum fetal surveillance in post-date pregnancy. El-Damarawy et al., 1993[101]	
Methods	
• **Design**	Unclear: Prospective comparative cohort or non-randomized experimental
• **Source of funding and competing interest**	No statement regarding funding; No statement regarding declaration of interest
• **Setting**	Single-centre study at Antenatal clinic of Shatby Maternity Hospital, Alexandria, Egypt; urban
• **Sample size**	Number of patients needed: Not reported Number of patients included: 45
• **Duration and follow-up**	Start and end dates of the study: Not reported Inclusion and follow-up periods: From > 42 completed wks gestation (end of follow-up not reported but near time of delivery)
• **Statistical analysis**	Not reported
Patient characteristics	
• **Eligibility criteria**	Pregnant women with documented post-datism (>42 completed weeks)
• **Exclusion criteria**	None reported
• **Patient & disease characteristics**	Unclear - no specific documented eligibility criteria or baseline characteristics. No details on potential confounding variables. Mean gestational age at admission for full group: range 42-45 wks (Mean - Group 1: 43 wks; Group 2: 42 wks 3 days; Group 3: 42 wks 3.5 days)
Interventions	
• **Intervention group**	***Intervention/exposure group 1:*** BP2 [2/wk] from >42 completed wks gestation to abnormal test or spontaneous delivery Details of intervention BP2: Fluid volume, fetal movement, fetal tone + fetal breathing + NST/heart rate – total max score = 10 *Management protocol:* Normal: No planned intervention Abnormal: Participants with score <=6 (repeated twice within 24 hours) were prepared for induction or caesarean. ***Intervention/exposure group 2:*** NST (2/wk) from >42 completed wks gestation to abnormal test or spontaneous delivery. Details of intervention NST: No further details Management protocol: Normal: No planned intervention Abnormal: Participants with two successive non-reactive NST were prepared for induction or caesarean

• **Control group**	Intervention/exposure group 3: AFV and NST (frequency unclear but likely 2/wk) from >42 completed wks gestation to abnormal test or spontaneous delivery. Abnormal test results (AFV with largest pocket < 1 cm in two perpendicular planes) were prepared for induction or caesarean
Results	
• **Offspring - death**	Perinatal mortality: Report states that there was no case of perinatal mortality (Pg. 148).
• **Neonatal harms**	Apgar score < 7 (measured at 1 and 5 minutes): 2/15 vs. 1/15 vs. 2/15
Limitations and other comments	
• **Limitations**	External validity: Serious concern (developing country and no details of baseline characteristics) Internal validity: Unclear risk of bias due to unclear risk of selection bias and confounding bias

10. SUMMARY OF FINDINGS TABLES AND GRADE PROFILES

10.1. Cytomegalovirus

10.1.1. Lifestyle advice for CMV infection

Table 185 - Summary of findings and GRADE profile: advice vs. no advice for CMV infection

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects** *Time frame is patients enrolled from 1999 through 2001*	
							No advice	**Education and adherence**		**Risk with no advice**	**Risk difference with education and adherence** (95% CI)
Maternal seroconversion (assessed with: enzyme immunoassay)											
166 (1 study)	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2,3] due to risk of bias, indirectness, imprecision	4/51 (7.8%)	9/115 (7.8%)	**RR 1** (0.32 to 3.09)	**Moderate** **78 per 1000**	**0 fewer per 1000** (from 53 fewer to 163 more)

[1] *Rating due to high risk of selection, performance and detection bias.*
[2] *The study population included both pregnant women or women 'attempting pregnancy'. 15.7% of the study participants were not pregnant at any time during enrolment. Therefore this population differs slightly from the review protocol and has therefore been downgraded for population indirectness. Seroconversion is a surrogate measure for maternal and newborn adverse outcomes and therefore an indirect outcome.*
[3] *The confidence interval of the effect crosses both default MIDs.*

10.2. Toxoplasmosis

10.2.1. Screening for toxoplasmosis infection

Table 186 – Summary of findings and GRADE profile: mandatory monthly (after 1992-1995) vs. recommended screening (prior 1987-1991) for toxoplasmosis

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With recommended screening (before)	With Mandatory monthly (after)		Risk with recommended screening (before)	Risk difference with Mandatory monthly (after) (95% CI)
Clinical signs at 3 year follow-up unadjusted (CRITICAL OUTCOME)											
1,944 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⊖⊖⊖ **VERY LOW**[1] due to risk of bias	87/794 (11%)	46/1150 (4%)	**OR 0.37** (0.26 to 0.53)	**110 per 1000**	**66 fewer per 1000** (from 48 fewer to 79 fewer)
Clinical signs at 3 years - Adjusted for gestational age at seroconversion) (CRITICAL OUTCOME)											
1,944 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, imprecision	87/794 (11%)	46/1150 (4%)	**OR 0.59** (0.4 to 0.87)	**110 per 1000**	**42 fewer per 1000** (from 13 fewer to 63 fewer)
Infection rate in newborns (IMPORTANT OUTCOME)											
2,048 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⊖⊖⊖ **VERY LOW**[1] due to risk of bias	125/424 (29.5%)	388/1624 (23.9%)	**RR 0.81** (0.68 to 0.96)	**295 per 1000**	**56 fewer per 1000** (from 12 fewer to 94 fewer)

1 Baseline characteristics are described only for the total number of participants rather than divided by group. Only gestational age is considered as a confounding factor in the analysis and other factors such as increased knowledge and advice are not included.
2 The confidence interval crosses the default MID of 0.75 and therefore after adjusting for gestational age the confidence interval ranges from a benefit favouring screening to no noticeable effect associated with it lowering our confidence in this result.

Table 187 – Summary of findings and GRADE profile: after (1984 - 1990) vs. prior (1966) to implementation of toxoplasmosis screening plus treatment

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							Before	**After**		Risk (before)	Risk difference with screening and treatment (after) (95% CI)
Incidence of congenital infection (IMPORTANT OUTCOME)											
111,632 (1 study)	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊖⊖⊖ **VERY LOW**[1] due to risk of bias	9/1,697 (0.53%)	124/109,935 (0.11%)	**RR 0.21** (0.11 to 0.42)	**5 per 1000**	**4 fewer per 1000** (from 3 fewer to 5 fewer)
Incidence of primary infection during pregnancy (IMPORTANT OUTCOME)											
149339 (1 study)	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, imprecision	13/1,697 (0.77%)	775/147,642 (0.52%)	**RR 0.69** (0.84 to 1.18)	**8 per 1000**	**2 fewer per 1000** (from 1 fewer to 1 more)

1 This study compares historical data published in a German thesis in 1978 to a much larger sample of pregnant women after screening was introduced. No confounding variables were considered and baseline characteristics were not described.
2 The confidence interval of the effect crosses the default MID and therefore ranges from an effect favouring screening to no clear benefit of screening.

Table 188 – Summary of findings and GRADE profile: prenatal toxoplasmosis screening and treatment (1976 – 1987) vs. untreated during pregnancy (1966 – 1975)

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects** *Time frame is patients enrolled from May 1999 to December 2004*	
							With untreated (Newborns with congenital toxoplasmosis)	With Screened and prenatal treated		Risk with untreated (Newborns with congenital toxoplasmosis)	Risk difference with Screened and prenatal treated (95% CI)
Symptomatic congenital toxoplasmosis – newborns (CRITICAL OUTCOME)											
200 (1 study)	very serious[1]	no serious inconsistency	no serious indirectness[2]	very serious[2]	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, imprecision	3/101 (3%)	3/99 (3%)	**RR 1.02** (0.21 to 4.93)	**30 per 1000**	**1 more per 1000** (from 23 fewer to 117 more)

1 The description of the methods lacks detail and the groups of pregnant women at different time points are not described. Results are not adjusted for any confounding factors.
2 The confidence interval of the effect crosses both default MID, i.e. ranging from appreciable benefit of prenatal screening to appreciable benefit of neonatal screening.

Table 189 – Summary of findings and GRADE profile: countries with prenatal toxoplasmosis screening plus treatment policies (1996 – 2000) vs. countries with neonatal screening programmes (1992 – 2000)

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Neonatal screening	With Countries with prenatal screening plus treatment		Risk with Neonatal screening	Risk difference with Countries with prenatal screening plus treatment (95% CI)
Serious neurological sequelae or death (newborns) – Unadjusted (CRITICAL OUTCOME)											
293 (1 study)	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, imprecision	9/72 (12.5%)	14/221 (6.3%)	**OR 0.51** (0.23 to 1.13)	**125 per 1000**	**57 fewer per 1000** (from 93 fewer to 14 more)

Serious neurological sequelae or death (newborns)- Adjusted or gestational age at seroconversion (CRITICAL OUTCOME)											
293 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, imprecision	9/72 (12.5%)	14/221 (6.3%)	**OR 0.24** (0.07 to 0.78)	**125 per 1000**	**92 fewer per 1000** (from 25 fewer to 115 fewer)

1 The data were based on very few events and the adjusted results are based on estimates of gestational age. However, a number of sensitivity analyses were carried out which makes this study methodologically stronger. A further strength is the concurrent comparison that is made across countries with different policies.
2 The confidence interval of the overall effect crosses the default MID and therefore ranges from and effect favouring screening to no appreciable benefit of screening.

Narrative evidence

Pre- post implementation of a screening programme in Austria[8]
Incidence of prenatal toxoplasmosis infection

One study reported a rate of 50-70 per 10,000 before screening (1950s and 1960s based on historical data) and a rate of less than 1 per 10,000 after screening was introduced with the prenatal care-programme in Austria. This evidence was reported only vaguely, particularly the historic comparison group and therefore should be considered very low quality.

Prenatal vs. neonatal screening in Italy[97]
Transmission rates and symptomatic congenital toxoplasmosis

One study reported lower transmission rates in the neonatal screening group (4/9730 or 0.04%) compared to prenatally screened newborns (16/5288 or 0.3%). Data was collected concurrently in one hospital. When all infected newborns were combined with an additional sample of 19 neonates who were exposed to toxoplasmosis during pregnancy (altogether N = 163) 12 were clinically affected. Neonates of women who had not been treated were more likely to be affected than treated neonates, but after adjustment for trimester of infection no significant association remained. Due to study limitation and imprecision of reported results this evidence is of very low quality.

10.2.2. Lifestyle advice for toxoplamosis infection

Table 190 – GRADE profile: prenatal education programme (second phase 1983 – 1990, third phase 1991 – 2001) vs. no specific education programme 1979 – 1982)

Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Control	With Prenatal education for toxoplasmosis		Risk with Control	Risk difference with Prenatal education for toxoplasmosis (95% CI)
Seroconversion rate - Second phase - leaflet (IMPORTANT OUTCOME)											
5008 (1 study)	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2,3] due to risk of bias, indirectness	20/1403 (1.4%)	19/3605 (0.53%)	**RR 0.37** (0.20 to 0.69)	**14 per 1000**	**9 fewer per 1000** (from 4 fewer to 11 fewer)
Seroconversion rate - Third phase - leaflet and classes (IMPORTANT OUTCOME)											
9895 (1 study)	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2,3] due to risk of bias, indirectness, large effect	20/1403 (1.4%)	8/8492 (0.09%)	**RR 0.07** (0.03 to 0.15)	**14 per 1000**	**13 fewer per 1000** (from 12 fewer to 14 fewer)

[1] Baseline characteristics of the groups are not described neither are any factors adjusted in the analysis of the data. Authors assume that seroprevalence has not changed during this time period which seems to be unlikely considering the trends in seroprevalence in other countries.
[2] Seroprevalence is a surrogate outcome for seroconversion and newborn adverse outcomes.
[3] Even though it is a large effect study bias and indirectness make it difficult to interpret.

Narrative evidence

Cochrane review on prenatal education for congenital toxoplasmosis[28]

Conclusions based on knowledge and behaviour outcomes

Even though this systematic review is well conducted results are based on two low quality randomised controlled trials which could not be pooled (see evidence extraction tables in Appendix 3.2). The authors of the review conclude that this evidence does not adequately evaluate the effectiveness of prenatal education.

Health education for congenital toxoplasmosis from Poland[87]

Knowledge and behaviour

- This observational study compares to phases of a health education programme to a historic sample before implementation. Not all outcomes could be compared between groups. knowledge of toxoplasmosis increased when more information was provided from 24.3% to 45.3% from phase 1 (no particular toxoplasmosis information) to phase three (intensive health education activities) of the study. Correct behaviour was only reported in 1496/2710 (55.2%) of women in the third phase of the programme. However, only 352 women (24%) had read the material and correct behaviour was reported to be higher in women who had not read the material (62.8%) than those who had (54.1%). Due to the study limitations and imprecision of results the evidence is of very low quality.

10.3. Chlamydia trachomatis

Table 191 – Summary of findings and GRADE profile: universal screening versus no screening for chlamydia trachomatis

Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							Without universal screening	With universal screening		Risk with no screening	Risk difference with universal screening (95% CI)
Preterm labour (CRITICAL OUTCOME)											
288 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	undetected	⨁⊖⊖⊖ VERY LOW[1,3] due to risk of bias, imprecision	8/136 (5.9%)	12/152 (7.9%)	**RR 1.34** (0.57 to 3.18)	**59 per 1000**	**20 more per 1000** (from 25 fewer to 129 more)
Maternal febrile morbidity (NOT IMPORTANT OUTCOME)											
290 (1 study)	serious[1]	no serious inconsistency	serious[3]	very serious[2]	undetected	⨁⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	23/138 (16.7%)	18/152 (11.8%)	**RR 0.71** (0.4 to 1.26)	**167 per 1000**	**48 fewer per 1000** (from 100 fewer to 43 more)
Maternal antibiotic treatment (NOT IMPORTANT OUTCOME)											
290 (1 study)	serious[1]	no serious inconsistency	serious[3]	very serious[2]	undetected	⨁⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	33/138 (23.9%)	36/152 (23.7%)	**RR 0.99** (0.66 to 1.5)	**239 per 1000**	**2 fewer per 1000** (from 81 fewer to 119 more)

[1] Outcomes were downgraded due to the retrospective nature of the study design and insufficient control of possible confounders.
[2] Outcomes were downgraded by one increment if the upper or lower 95% CI crossed the lower minimally important difference lines (MID) or the upper or lower 95% CI crossed the upper MID. Outcomes were downgraded by two increments if the upper CI simultaneously crossed the upper MID and the lower CI crossed the lower MID. Default MIDs were set at RRs of 0.75 and 1.25 for dichotomous outcomes.
[3]Downgraded due to outcome indirectness: Not an outcome listed on the protocol. May not be directly attributable to chlamydia infection.

Table 192 – Summary of findings and GRADE profile: universal screening vs. medical staff discretion screening for chlamydia trachomatis

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With staff discretion screening	**With universal screening**		**Risk with staff discretion screening**	**Risk difference with universal screening** (95% CI)
Maternal febrile morbidity (NOT IMPORTANT OUTCOME)											
160 (1 study)	serious[1]	no serious inconsistency	serious[2]	very serious[3]	undetected	⨁⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	9/60 (15%)	11/100 (11%)	**RR 0.73** (0.32 to 1.67)	**150 per 1000**	**41 fewer per 1000** (from 102 fewer to 100 more)
Neonatal febrile morbidity (NOT IMPORTANT OUTCOME)											
160 (1 study)	serious[1]	no serious inconsistency	serious[2]	serious[3]	undetected	⨁⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	33/138 (23.9%)	10/100 (10%)	**RR 0.4** (0.19 to 0.83)	**250 per 1000**	**150 fewer per 1000** (from 43 fewer to 203 fewer)

[1] Outcomes were downgraded due to the insufficient control for confounders and the unclear protocols used for the comparison group.
[2] Downgraded due to outcome indirectness: Not an outcome listed on the protocol. May not be directly attributable to chlamydia infection.
[3] Outcomes were downgraded by one increment if the upper or lower 95% CI crossed the lower minimally important difference lines (MID) or the upper or lower 95% CI crossed the upper MID. Outcomes were downgraded by two increments if the upper CI simultaneously crossed the upper MID and the lower CI crossed the lower MID. Default MIDs were set at RRs of 0.75 and 1.25 for dichotomous outcomes.

10.4. Group B streptococcus

Table 193 Summary of findings and GRADE profile: universal GBS screening vs. no screening

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)[(a)]	**Anticipated absolute effects**	
							Without screening	With universal screening		Risk with no screening	Risk difference with universal screening (95% CI)
Early onset GBS neonatal sepsis (CRITICAL OUTCOME)											
320772 (11 studies)	very serious[1]	serious[2]	no serious indirectness	no serious imprecision	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, inconsistency	386/124338 (0.31%)	159/196434 (0.08%)	**RR 0.32** (0.24 to 0.43)	**3 per 1000**	**2 fewer per 1000** (from 2 fewer to 2 fewer)
Mortality due to GBS sepsis (CRITICAL OUTCOME)											
40236 (2 studies)	very serious[3]	no serious inconsistency	no serious indirectness	serious[4]	undetected	⨁⊖⊖⊖ **VERY LOW**[3,4] due to risk of bias, imprecision	5/24699 (0.02%)	0/15537 (0%)	**Peto OR 0.18** (0.03 to 1.10)	**0.2 per 1000**	**0 fewer per 1000** (from 0 fewer to 0 more)

(a) Data were not pooled and therefore the median relative risk is reported here. When there were 0 events the Peto OR rather than RR is reported because it is more robust in these cases.

[1] The majority of the evidence comes from retrospective studies where groups are unadjusted for any baseline differences.

[2] Even though there is considerable inconsistency in effect size of the study results, there is consistency about the direction of effect.

[3] Both studies use unadjusted retrospective study designs.

[4] Due to a low event rate the confidence intervals are large and range from benefit associated with universal screening to no benefit.

Table 194 – Summary of findings and GRADE profile: universal late (35-37 weeks gestation) vs. universal early (26-28 week) gestation screening for GBS

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**
							With early universal screening	With late universal screening		Risk with early screening	Risk difference later universal (95% CI)
Positive blood and group B streptococci culture results in newborns (CRITICAL OUTCOME)											
3755 (1 study)	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	undetected	⨁⨀⨀⨀ **VERY LOW**[1,2,3] due to risk of bias, indirectness, imprecision	0/1330 (0%)	3/2425 (0.12%)	**OR 4.71** (0.44 to 50.19)	**0 per 1000**	**1.2 more per 1000** (from more to 0 more)

[1] *The outcome was reported in a study with an unadjusted retrospective study design.*
[2] *It is unclear whether or not newborns with positive GBS blood culture meant that they were symptomatic.*
[3] *The confidence interval around the effect is very large and ranges from benefit to harm associated with universal screening.*

10.5. Gestational diabetes

10.5.1. Universal screening vs. selected screening

Table 195 – Summary of findings and GRADE profile: universal versus selected screening for gestational diabetes

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects (moderate)**	
							With selected screening	**With universal screening**		**Risk with selected screening**	**Risk difference with universal screening** (95% CI)
Macrosomia (IMPORTANT OUTCOME) – Two-step 50g GCT 100g OGTT											
2401 (1 study)	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, imprecision	139/1204 (11.5%)	143/1197 (11.9%)	**RR 1.03** (0.83 to 1.29)	**115 per 1000**	**3 more per 1000** (from 20 fewer to 33 more)
Macrosomia (IMPORTANT OUTCOME) – One-step 75g OGTT											
261 (1 study)	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⨁⊖⊖⊖ **VERY LOW**[2,3] due to risk of bias, imprecision	2/127 (1.6%)	8/134 (6%)	**RR 3.79** (0.82 to 17.51)	**16 per 1000**	**45 more per 1000** (from 3 fewer to 264 more)
Large for gestational age (IMPORTANT OUTCOME) – One-step 75g OGTT ≥8.0mmol/L											
261 (1 study)	very serious[3]	no serious inconsistency	no serious indirectness	very serious[6]	undetected	⨁⊖⊖⊖ **VERY LOW**[3,6] due to risk of bias, imprecision	7/127 (5.5%)	9/134 (6.7%)	**RR 1.22** (0.47 to 3.17)	**55 per 1000**	**12 more per 1000** (from 29 fewer to 119 more)
Large for gestational age (IMPORTANT OUTCOME) – One-step 75g OGTT ≥10.0mmol/L											
125510 (1 study)	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⊖⊖⊖ **VERY LOW**[3] due to risk of bias	4375/104688 (4.2%)	890/20822 (4.3%)	**RR 1.02** (0.95 to 1.1)	**42 per 1000**	**1 more per 1000** (from 2 fewer to 4 more)

Respiratory distress (IMPORTANT OUTCOME) – One-step 75g OGTT											
261 (1 study)	very serious[3]	no serious inconsistency	no serious indirectness	serious[7]	undetected	⨁⊖⊖⊖ **VERY LOW**[3,7] due to risk of bias, imprecision	11/127 (8.7%)	4/134 (3%)	**RR 0.34** (0.11 to 1.05)	**87 per 1000**	**57 fewer per 1000** (from 77 fewer to 4 more)
Hypoglycaemia (IMPORTANT OUTCOME) – One-step 75g OGTT											
261 (1 study)	very serious[3]	no serious inconsistency	no serious indirectness	very serious[6]	undetected	⨁⊖⊖⊖ **VERY LOW**[3,6] due to risk of bias, imprecision	12/127 (9.4%)	18/134 (13.4%)	**RR 1.42** (0.71 to 2.83)	**95 per 1000**	**40 more per 1000** (from 28 fewer to 174 more)

[1] Randomisation not described in sufficient detail and incomplete outcome and attrition reporting.
[2] The confidence intervals are large and range from no harm associated with universal screening to harm.
[3] Unadjusted retrospective study design.
[4] Results are reported only for those who were diagnosed with gestational diabetes and do not represent the full populations who underwent each screening strategy.
[5] Due to a low event rate the confidence interval is large and ranges from benefit associated with universal screening to harm.
[6] The confidence intervals are very large and range from benefit associated with universal screening to harm.
[7] The confidence intervals are large and range from benefit associated with universal screening to no benefit.

Narrative evidence

One before and after retrospective cohort[44] and one prospective cohort[45] report results narratively instead of providing raw data with which to make an analysis. In addition to the findings covered in Davis 2013[44] also reported narratively that congenital abnormality, stillbirth and neonatal death were "uncommon in all groups in both time periods". The only outcomes reported by Dietrich 1987[45] were both infant birth weight ≥4000g and perinatal deaths were "not significantly different between the routine and select screening groups".

10.5.2. Early risk-factor vs. late non-risk factor screening.of gestational diabetes

Table 196 – Summary of findings and GRADE profile: early versus late screening for gestational diabetes

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects (moderate)**	
							With selected screening	**With universal screening**		**Risk with selected screening**	**Risk difference with universal screening** (95% CI)
Birth weight ≥4000g (IMPORTANT OUTCOME) – Two-step 50g GCT 100g OGTT											
600 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, imprecision	23/300 (7.7%)	32/300 (10.7%)	**RR 1.39** (0.83 to 2.32)	**77 per 1000**	**30 more per 1000** (from 13 fewer to 102 more)
Macrosomia (IMPORTANT OUTCOME) – GTT undefined threshold											
865 (1 study)	very serious[3]	no serious inconsistency	serious[5]	serious[4]	undetected	⊕⊖⊖⊖ **VERY LOW**[3,4] due to risk of bias, indirectness, imprecision	124/685 (18.1%)	27/180 (15%)	**RR 0.83** (0.57 to 1.21)	**181 per 1000**	**31 fewer per 1000** (from 78 fewer to 38 more)
Macrosomia (IMPORTANT OUTCOME) –Two-step 50g GCT 100g OGTT											
458 (1 study)	serious[1]	no serious inconsistency	serious[5]	serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2,5] due to risk of bias, indirectness, imprecision	16/224 (7.1%)	35/234 (15%)	**RR 2.09** (1.19 to 3.67)	**71 per 1000**	**77 more per 1000** (from 13 more to 190 more)
Malformations (IMPORTANT OUTCOME) – GTT undefined threshold											
865 (1 study)	very serious[3]	no serious inconsistency	serious[5]	very serious[6]	undetected	⊕⊖⊖⊖ **VERY LOW**[3,6] due to risk of bias, indirectness, imprecision	21/685 (3.1%)	5/180 (2.8%)	**RR 0.91** (0.35 to 2.37)	**31 per 1000**	**3 fewer per 1000** (from 20 fewer to 42 more)

Malformations (IMPORTANT OUTCOME) – Two-step 50g GCT 100g OGTT											
458 (1 study)	serious[1]	no serious inconsistency	serious[5]	very serious[7]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,5,7] due to risk of bias, indirectness, imprecision	1/224 (0.45%)	5/234 (2.1%)	**RR 4.79** (0.56 to 40.65)	**5 per 1000**	**19 more per 1000** (from 2 fewer to 198 more)
Fetal mortality (IMPORTANT OUTCOME) – Two-step 50g GCT 100g OGTT											
458 (1 study)	serious[1]	no serious inconsistency	serious[5]	very serious[7]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,5,7] due to risk of bias, indirectness, imprecision	0/224 (0%)	1/234 (0.43%)	**OR 7.08** (0.14 to 357.14)	**0 per 1000**	**0 more per 1000** (from 10 fewer to 20 more)[8]
Perinatal mortality (IMPORTANT OUTCOME) – GTT undefined threshold											
865 (1 study)	very serious[3]	no serious inconsistency	serious[5]	serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[2,3] due to risk of bias, indirectness, imprecision	4/685 (0.58%)	4/180 (2.2%)	**RR 3.81** (0.96 to 15.07)	**6 per 1000**	**17 more per 1000** (from 0 fewer to 84 more)
Respiratory distress syndrome (IMPORTANT OUTCOME) – Two-step 50g GCT 100g OGTT											
458 (1 study)	serious[1]	no serious inconsistency	serious[5]	very serious[7]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,5,7] due to risk of bias, indirectness, imprecision	5/224 (2.2%)	1/234 (0.43%)	**RR 0.19** (0.02 to 1.63)	**22 per 1000**	**18 fewer per 1000** (from 22 fewer to 14 more)
Diabetes on follow-up (IMPORTANT OUTCOME) – GTT undefined threshold											
633 (1 study)	very serious[3]	no serious inconsistency	serious[5]	no serious imprecision	undetected	⊕⊖⊖⊖ **VERY LOW**[3] bias, indirectness, imprecision	2/483 (0.41%)	24/150 (16%)	**RR 38.64** (9.24 to 161.6)	**4 per 1000**	**151 more per 1000** (from 33 more to 642 more)
Respiratory distress syndrome (IMPORTANT OUTCOME) – Two-step 50g GCT 100g OGTT											
Preeclampsia (NON-IMPORTANT OUTCOME) – GTT undefined threshold											
865 (1 study)	very serious[3]	no serious inconsistency	Serious[4]	serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[2,3,4] due to risk of bias, indirectness, imprecision	33/685 (4.8%)	13/180 (7.2%)	**RR 1.5** (0.81 to 2.79)	**48 per 1000**	**24 more per 1000** (from 9 fewer to 86 more)

[1] *Prospective design but no controlling for confounders and no baseline characteristics of importance are reported.*
[2] *The confidence interval for the effect is large ranging from no harm to harm associated with early screening.*
[3] *Unadjusted retrospective design*
[4] *The confidence interval for the effect is large ranging from benefit to no benefit associated with early screening.*
[5] *Downgraded for indirectness of populations used in the intervention and comparisons groups.*
[6] *The low event rate the confidence interval for the effect is very large and ranges from benefit to harm associated with early screening.*
[7] *Due to the low event rate the confidence interval for the effect is very large and ranges from benefit to harm associated with early screening.*
[8] *Absolute risk difference entered manually from RevMan calculations due to single study with rare events. When there were 0 events the Peto OR rather than RR is reported because it is more robust in these cases.*

10.5.3. Different screening tests comparison.for gestational diabetes

Table 197 – Summary of findings and GRADE profile: comparisons of different combinations of glucose challenge and glucose tolerance tests when screening for gestational diabetes

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects (moderate)**	
							With selected screening	**With universal screening**		**Risk with selected screening**	**Risk difference with universal screening** (95% CI)
Preeclampsia (NON-IMPORTANT OUTCOME) – One-step vs. two step 75g OGTT											
1000 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⨁⨁⨀⨀ **LOW**[1,2] due to risk of bias, imprecision	18/500 (3.6%)	27/500 (5.4%)	**RR 1.5** (0.84 to 2.69)	**36 per 1000**	**18 more per 1000** (from 6 fewer to 61 more)
Preeclampsia (NON-IMPORTANT OUTCOME) – One-step 75g vs. two step 100g OGTT											
1000 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⨁⨁⨀⨀ **LOW**[1,2] due to risk of bias, imprecision	17/500 (3.4%)	27/500 (5.4%)	**RR 1.59** (0.88 to 2.88)	**34 per 1000**	**20 more per 1000** (from 4 fewer to 64 more)
Preeclampsia (NON-IMPORTANT OUTCOME) – Two step: 75g vs. 100g OGTT											
1000 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	undetected	⨁⨀⨀⨀ **VERY LOW**[1,3] due to risk of bias, imprecision	17/500 (3.4%)	18/500 (3.6%)	**RR 1.06** (0.55 to 2.03)	**34 per 1000**	**2 more per 1000** (from 15 fewer to 35 more)

[1] *Unclear random sequence generation: no detail provided on their method of block randomisation.*
[2] *The confidence interval for the effect is large ranging from no harm to harm associated with the one-step screening method.*
[3] *The confidence interval for the effect is very large ranging from benefit to harm associated with the lower glucose load for the tolerance test.*

Table 198 – Summary of findings and GRADE profile: comparisons of different thresholds for the 75g OGTT when screening for gestational diabetes

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects (moderate)**	
							With selected screening	**With universal screening**		**Risk with selected screening**	**Risk difference with universal screening** (95% CI)
Large for gestational age (IMPORTANT OUTCOME) – 8.9 vs. 10.0 mmol/L											
113322 (1 study)	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⊖⊖⊖ **VERY LOW**[1] due to risk of bias	4375/104688 (4.2%)	382/8634 (4.4%)	**RR 1.06** (0.96 to 1.17)	**42 per 1000**	**3 more per 1000** (from 2 fewer to 7 more)
Large for gestational age (IMPORTANT OUTCOME) – 8.9 vs. 12.2 mmol/L											
58673 (1 study)	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, imprecision	1903/50039 (3.8%)	382/8634 (4.4%)	**RR 1.16** (1.04 to 1.3)	**38 per 1000**	**6 more per 1000** (from 2 more to 11 more)
Large for gestational age (IMPORTANT OUTCOME) – 10.0 vs. 12.2 mmol/L											
154727 (1 study)	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⊖⊖⊖ **VERY LOW**[1] due to risk of bias	1903/50039 (3.8%)	4375/104688 (4.2%)	**RR 1.1** (1.04 to 1.16)	**38 per 1000**	**4 more per 1000** (from 2 more to 6 more)

[1] *Unadjusted retrospective design*
[2] *The confidence interval for the effect ranges from no harm to harm associated with the lower threshold*

Table 199 – Summary of findings and GRADE profile: comparisons of different combinations of glucose challenge and glucose tolerance tests when screening for gestational diabetes

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects (moderate)**	
							With selected screening	**With universal screening**		**Risk with selected screening**	**Risk difference with universal screening** (95% CI)
Neonatal hypoglycaemia (IMPORTANT OUTCOME) – One-step vs. two step 75g OGTT											
1000 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⨁⨁⨀⨀ **LOW**[1,2] due to risk of bias, imprecision	21/500 (4.2%)	33/500 (6.6%)	**RR 1.57** (0.92 to 2.68)	**42 per 1000**	**24 more per 1000** (from 3 fewer to 71 more)
Neonatal hypoglycaemia (IMPORTANT OUTCOME) – One-step 75g vs. two step 100g OGTT											
1000 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⨁⨁⨀⨀ **LOW**[1,2] due to risk of bias, imprecision	18/500 (3.6%)	33/500 (6.6%)	**RR 1.83** (1.05 to 3.21)	**36 per 1000**	**30 more per 1000** (from 2 more to 80 more)
Neonatal hypoglycaemia (IMPORTANT OUTCOME) – Two step: 75g vs. 100g OGTT											
1000 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	undetected	⨁⨀⨀⨀ **VERY LOW**[1,3] due to risk of bias, imprecision	18/500 (3.6%)	21/500 (4.2%)	**RR 1.17** (0.63 to 2.16)	**36 per 1000**	**6 more per 1000** (from 13 fewer to 42 more)

[1] *Unclear random sequence generation: no detail provided on their method of block randomisation.*
[2] *The confidence interval for the effect is large ranging from no harm to harm associated with the one-step screening method.*
[3] *The confidence interval for the effect is very large ranging from benefit to harm associated with the lower glucose load for the tolerance test.*

10.5.4. Diagnostic accuracy

Table 200 – Summary of findings and clinical evidence profile for studies investigating 50g glucose challenge test (at listed thresholds) compared to the reference standard of 100g oral glucose tolerance test (non-risk population)

Study characteristics			Quality Assessment					Summary of findings		Quality
No. of studies	**Design**	**n**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	
140mg/dl threshold (non-risk population)										
2	Prospective diagnostic cohort studies	861	serious risk of bias[1]	no serious inconsistency	no serious indirectness	very serious imprecision[2]	None	77% (46-95) and 58% (37-77)	87% (82-90) and 91% (88-93)	VERY LOW

[1] Risk of bias was assessed using the QUADAS-II checklist. The majority of the evidence is from a study at high risk of bias due to unclear details around the interpretation of the reference standard.
[2] Due to too few studies providing information for each threshold it was not possible to conduct a diagnostic meta-analysis. Hence the judgement of precision was based on the variation in confidence intervals around the RevMan 5 plots.

Table 201 – Summary of findings and clinical evidence profile for studies investigating 50g glucose challenge test (at listed thresholds) compared to the reference standard of 100g oral glucose tolerance test (at-risk populations)

Study characteristics			Quality Assessment					Summary of findings		Quality
No. of studies	**Design**	**n**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	
130mg/dl threshold (at-risk population)										
1	Retrospective diagnostic cohort study	445	serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious imprecision[5]	None	91% (71-99)	81% (77-84)	LOW
135mg/dl threshold (at-risk population)										
1	Retrospective diagnostic cohort study	445	serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious imprecision[5]	None	87% (66-97)	86% (82-89)	LOW

140mg/dl threshold (at risk population)										
2	Cross-sectional and retrospective diagnostic cohort studies	804	serious risk of bias[2]	serious inconsistency[3]	no serious indirectness	very serious imprecision[5]	None	87% (66-97) and 90% (79-96)	87% (83-90) and 61% (55-66)	VERY LOW
130-139mg/dl threshold range (at risk population)										
1	Prospective diagnostic cohort study	304	very serious risk of bias[2]	no serious inconsistency	serious indirectness[4]	serious imprecision[5]	None	93% (68-100)	63% (57-69)	VERY LOW
140-149mg/dl threshold range (at risk population)										
1	Prospective diagnostic cohort study	304	very serious risk of bias[3]	no serious inconsistency	serious indirectness[4]	serious imprecision[5]	None	93% (68-100)	78% (73-83)	VERY LOW

[1] Risk of bias was assessed using the QUADAS-II checklist. The majority of the evidence is from studies at high risk of bias due to unclear details around the interpretation of the reference standard.
[2] Risk of bias was assessed using the QUADAS-II checklist. The majority of the evidence is from studies at high risk of bias due to the index test not using pre-specified thresholds and unclear details around the interpretation of the reference standard.
[3] Wide variation in point estimates and lack of overlap of confidence intervals. This inconsistency may be attributed to different criteria for what is considered 'high-risk' population in the different countries (Thailand and Mexico) and different prevalence rates used for calculations.
[4] The evidence is from a single study with serious indirectness due to the use of threshold ranges rather than specified mg/dl thresholds. The higher range includes levels outside of the review protocol.
[5] Due to too few studies providing information for each threshold it was not possible to conduct a diagnostic meta-analysis. Hence the judgement of precision was based on the variation in confidence intervals around the RevMan 5 plots.

10.6. Hypothyroisdism

10.6.1. Screening for hypothyroidism

Table 202 – Summary of findings and GRADE profile: universal screening versus no screening for hypothyroidism in asymptomatic pregnancies

Quality assessment						Summary of Findings		
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Summary of Findings** (MD= mean difference; RR= relative risk; ARD= absolute risk difference)	**Overall quality of evidence***	**Importance**
*Control standardised **IQ at 3 years** (as measured by Wechsler Preschool and Primary Scale of Intelligence)*								
794 (1 randomised trial) 3 years	very serious	no serious inconsistency	very serious indirectness	no serious imprecision	undetected	MD= -0.8 (95% CI, -2.6, 1.1) **IQ <85**, RR= 0.85 (95% CI, 0.60, 1.22); ARD= 21 fewer per 1000 (from 56 fewer to 31 more)	⨁⊖⊖⊖ **VERY LOW**	
***Behaviour** (Child Behavior Checklist T-score)*								
794 (1 randomised trial) 3 years	very serious	no serious inconsistency	very serious indirectness	no serious imprecision	undetected	MD= -0.7 (95% CI, -2.5, 1.2)	⨁⊖⊖⊖ **VERY LOW**	
Preterm birth<37 weeks								
794 (1 randomised trial) 3 years	very serious	no serious inconsistency	very serious indirectness	very serious imprecision	undetected	RR= 0.71 (95% CI, 0.42, 1.20); ARD= 23 fewer per 1000 (from 45 fewer to 16 more)	⨁⊖⊖⊖ **VERY LOW**	
***Maternal depression** (Becks Depression Inventor)*								
794 (1 randomised trial) 3 years	very serious	no serious inconsistency	very serious indirectness	very serious imprecision	undetected	1 case in each group	⨁⊖⊖⊖ **VERY LOW**	

** Outcomes were downgraded because of very serious concerns about risk of bias (Unclear reporting of the method of allocation concealment, high risk of performance and detection bias due to non-blinding, unclear risk of attrition bias due to 20% missing data, and unclear risk of other biases); indirectness (some diagnosis of hypothyroidism was based on FT4 alone; late treatment initiation by the end of first trimester; 3-year time point may not be a good proxy for any of the long-term neuro-cognitive-behavioural disabilities); and very serious imprecision for the outcome of preterm birth*

Table 203 – Summary of findings and GRADE profile: universal versus targeted TSH screening in TPO-antibody positive pregnant women

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects** *Time frame is patients enrolled from May 1999 to December 2004*	
							With universal screening	**With** targeted screening		**Risk difference with** universal screening **(95% CI)**	**Risk** with targeted screening**)**
Outcome Perinatal death											
4516 (1 study)	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision[2]	undetected	⊕⊕⊕⊖ **MODERATE**[1,2] due to indirectness	12/2259 (0.53%)	13/2257 (0.58%)	**RR 0.92** (0.42 to 2.02)	**0 fewer per 1000** (from 3 fewer to 6 more)	**6 per 1000**
Outcome Birth weight < 2500 grams											
4516 (1 study)	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision[2]	undetected	⊕⊕⊕⊖ **MODERATE**[1,2] due to indirectness	102/2259 (4.5%)	105/2257 (4.7%)	**RR 0.97** (0.74 to 1.27)	**1 fewer per 1000** (from 12 fewer to 13 more)	**47 per 1000**
Outcome Preterm birth <37 weeks											
4516 (1 study)	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision[2]	undetected	⊕⊕⊕⊖ **MODERATE**[1,2] due to indirectness	12/2259 (0.53%)	13/2257 (0.58%)	**RR 0.92** (0.42 to 2.02)	**0 fewer per 1000** (from 3 fewer to 6 more)	**6 per 1000**
Outcome 6 Preterm birth <34 weeks											
4516 (1 study)	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision[2]	undetected	⊕⊕⊕⊖ **MODERATE**[1,2] due to indirectness	42/2259 (1.9%)	43/2257 (1.9%)	**RR 0.98** (0.64 to 1.49)	**0 fewer per 1000** (from 7 fewer to 9 more)	**19 per 1000**
Outcome 7 Gestational hypertension											
4516 (1 study)	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision[2]	undetected	⊕⊕⊕⊖ **MODERATE**[1,2] due to indirectness	124/2259 (5.5%)	122/2257 (5.4%)	**RR 1.02** (0.8 to 1.29)	**1 more per 1000** (from 11 fewer to 16 more)	**54 per 1000**

Outcome 8 Pre-eclampsia											
4516 (1 study)	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision[2]	undetected	⊕⊕⊕⊖ **MODERATE**[1,2] due to indirectness	73/2259 (3.2%)	84/2257 (3.7%)	**RR 0.87** (0.64 to 1.18)	**5 fewer per 1000** (from 13 fewer to 7 more)	**37 per 1000**
Outcome 10 Total major maternal and neonatal adverse events (all pregnancies)											
4516 (1 study)	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	undetected	⊕⊕⊕⊖ **MODERATE**[1] due to indirectness	1559/2259 (69%)	1545/2257 (68.5%)	**RR 1.01** (0.97 to 1.05)	**7 more per 1000** (from 21 fewer to 34 more)	**685 per 1000**

[1] Some concerns about late treatment initiation, i.e., by the end of first trimester; perinatal outcomes only; 13% of women in the Universal screening arm and 3% in the treatment arm had first trimester TSH >2.5 but were not classified as hypothyroid because they were TPO-Ab negative (i.e. false negatives similarly distributed and managed across both randomised treatment arms); 0.4% of patients were hyperthyroid of which 11 were treated
[2] Wide CIs for relative estimate but much narrower for absolute difference

Table 204 – Summary of findings and GRADE profile: universal screening for TPO-antibody positive hypothyroidism (i.e. raised TSH) versus screening in only high risk pregnancies

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects** ***Time frame is patients enrolled from May 1999 to December 2004***	
							With universal screening	**With** targeted screening		**Risk with** universal screening	**Risk difference with** targeted screening **(95% CI)**
Outcome 1 Miscarriage											
4516 (1 study)	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision[2]	undetected	⊕⊕⊕⊖ **MODERATE**[1,2] due to indirectness	92/2259 (4.1%)	102/2257 (4.5%)	**RR 0.90** (0.68 to 1.19)	**5 fewer per 1000** (from 14 fewer to 9 more)	**45 per 1000**
Outcome 3 NICU admission											
4516 (1 study)	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision[2]	undetected	⊕⊕⊕⊖ **MODERATE**[1,2] due to indirectness	119/2259 (5.3%)	114/2257 (5.1%)	**RR 1.04** (0.81 to 1.34)	**2 more per 1000** (from 10 fewer to 17 more)	**51 per 1000**

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects** *Time frame is patients enrolled from May 1999 to December 2004*	
							With universal screening	**With** targeted screening		**Risk with** universal screening	**Risk difference with** targeted screening**(95% CI)**
Outcome 9 Congestive heart failure											
4516 (1 study)	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision[2]	undetected	⊕⊕⊕⊖ **MODERATE**[1,2] due to indirectness	0/2259 (0%)	0/2257 (0%)	**Not estimable**	-	See comment

10.6.2. Therapy for subclinical hypothyroidism

Table 205 – Summary of findings and GRADE profile: levothyroxine versus no treatment for subclinical hypothyroidism

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With No treatment	**With Levothyroxine**		**Risk with No treatment**	**Risk difference with Levothyroxine** (95% CI)
Preterm Birth< 37 weeks											
288 (4 studies)	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	undetected	⊕⊕⊖⊖ **LOW**[1,2]	29/129 (22.5%)	10/159 (6.3%)	**RR 0.29** (0.15 to 0.56)	**170 per 1000**	**121 fewer per 1000** (from 75 fewer to 145 fewer)
Very Preterm birth (<34 weeks)											
106 (2 studies)	no serious risk of bias	no serious inconsistency	serious[3]	very serious[2,4]	undetected	⊕⊖⊖⊖ **VERY LOW**[2,3,1]	4/46 (8.7%)	2/60 (3.3%)	**RR 0.43** (0.1 to 1.91)	**87 per 1000**	**50 fewer per 1000** (from 78 fewer to 79 more)

Pre-eclampsia												
182 (2 studies)	no serious risk of bias	no serious inconsistency	serious[5]	very serious[2,6]	undetected	⊕⊖⊖⊖ **VERY LOW**[2,3,1]	5/84 (6%)	4/98 (4.1%)	**RR 0.68** (0.19 2.47)	to	**Study population**	
											60 per 1000	**19 fewer per 1000** (from 48 fewer to 87 more)
											87 per 1000	**63 fewer per 1000 (from 82 fewer to 371 more)**
Gestational Hypertension												
182 (2 studies)	no serious risk of bias	no serious inconsistency	serious[5]	very serious[2,6]	undetected	⊕⊖⊖⊖ **VERY LOW**[2,3,3]	10/84 (11.9%)	6/98 (6.1%)	**RR 0.53** (0.2 to 1.38)		**119 per 1000**	**56 fewer per 1000** (from 95 fewer to 45 more)
Low birth weight < 2500g												
77 (1 study)	Serious[7]	no serious inconsistency	serious[3]	very serious[2]		⊕⊖⊖⊖ **VERY LOW**[2,4,5]	30/34 (88.2%)	40/43 (93%)	**RR 1.05** (0.91 1.22)	to	**Study population**	
											882 per 1000	**44 more per 1000** (from 79 fewer to 194 more)
Miscarriage												
366 (5 studies)	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	undetected	⊕⊕⊖⊖ **LOW**[1,2]	47/175 (26.9%)	18/191 (9.4%)	**RR 0.41** (0.26 0.66)	to	**330 per 1000**	**195 fewer per 1000** (from 112 fewer to 244 fewer)
NICU admission												
77 (1 study)	no serious risk of bias	no serious inconsistency	serious[3]	very serious[2,4]	undetected	⊕⊖⊖⊖ **VERY LOW**[1, 2,3]	6/34 (17.6%)	3/43 (7%)	**RR 0.35** (0.08 1.52)	to	**Study population**	
											176 per 1000	**115 fewer per 1000** (from 162 fewer to 92 more)

[1] *Majority of evidence comes from studies with euthyroid women who were TPO antibody positive*
[2] *fewer events, OIS not met*
[3] *>50% of the population are subclinical hypothyroid pregnant women exclusively with TPO-Ab positive status*
[4] *Wide CI including appreciable benefit and harm*
[5] *> 50% of the population is from a study in euthyroid pregnant women with TPO antibody positive status*
[6] *Wide CI including appreciable benefit and harm*
[7] *the assessment of low risk was blinded but undertaken post randomization which leaves some concerns about unmeasured and residual confounding*
[3] *fewer events, OIS not met*

Table 206 – Summary of findings and GRADE profile: selenomethionine versus no treatment for subclinical hypothyroidiism

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects** ***Time frame is patients enrolled from May 1999 to December 2004***	
							With Selenomethionine	**With** placebo		**Risk with** Selenomethionine	Risk difference with placeboonly**(95% CI)**
Preterm birth											
151 (1 study)	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2]	3/77 (3.9%)	3/74 (4.1%)	**RR 0.96** (0.2 to 4.61)	**2 fewer per 1000** (from 32 fewer to 146 more)	**41 per 1000**
Pre-eclampsia											
151 (1 study)	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2]	3/77 (3.9%)	2/74 (2.7%)	**RR 1.44** (0.25 to 8.38)	**12 more per 1000** (from 20 fewer to 199 more)	**27 per 1000**
Miscarriage											
169 (1 study)	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2]	6/85 (7.1%)	7/84 (8.3%)	**RR 0.85** (0.3 to 2.42)	**12 fewer per 1000** (from 58 fewer to 118 more)	**83 per 1000**
Hypothyroidism (after 2 months of birth and stopping Levothyroxine)											
151 (1 study)	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2]	4/77 (5.2%)	5/74 (6.8%)	**RR 0.77** (0.21 to 2.75)	**16 fewer per 1000** (from 53 fewer to 118 more)	**68 per 1000**

[1] *Evidence comes from euthyroid women with thyroid peroxidase antibodies.*
[2] *Fewer events; Wide CI*

10.7. Vitamin D deficiency

10.7.1. Vitamin D supplementation vs. no vitamin D supplementation

Table 207 – Summary of findings and GRADE profile GRADE vitamin D supplementation (RCTs) vs no supplementation

Quality assessment									Summary of Findings		
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%) With No vitamin D	Study event rates (%) With Vitamin D	Relative effect (95% CI)	Anticipated absolute effects Risk with No vitamin D	Anticipated absolute effects Risk difference with Vitamin D (95% CI)
Birth weight <2500 grams											
328 (2 studies)	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2]	34/169 (20.1%)	11/159 (6.9%)	**RR 0.36 (0.14 to 0.91)**	**201 per 1000**	**129 fewer per 1000 (from 18 fewer to 173 fewer)**
Mean birth weight (Caucasian subgroup) (Better indicated by higher values)											
77 (1 study)	very serious[1]	no serious inconsistency	no serious indirectness	serious imprecision[3]	undetected	⨁⊖⊖⊖ **VERY LOW**	29	48	-	The mean birth weight (Caucasian subgroup) in the control groups was **3460 grams**	The mean birth weight (Caucasian subgroup) in the intervention groups was **180 lower (215.23 to 144.77 lower)**
Neonatal death											
266 (2 studies)	Serious [4]	no serious inconsistency	Serious[5]	very serious[6]	undetected	⨁⊖⊖⊖ **VERY LOW**	4/133 (3%)	1/133 (0.75%)	RR 0.33 (0.05 to 2.09)	30 per 1000	20 fewer per 1000 (from 29 fewer to 33 more)
Total major maternal adverse events											
147 (1 study)	no serious risk of bias	no serious inconsistency	serious [1]	very serious[2]	undetected	⨁⊖⊖⊖ **VERY LOW**[12]	2/74 (2.7%)	2/73 (2.7%)	RR 1.01 (0.15 to 7.01)	27 per 1000	0 more per 1000 (from 23 fewer to 162 more)
Total major neonatal adverse events											
147 (1 study)	no serious risk of bias	no serious inconsistency	serious [7]	very serious[6]	undetected	⨁⊖⊖⊖ **VERY LOW**[2,1]	7/74 (9.5%)	6/73 (8.2%)	RR 0.87 (0.31 to 2.46)	95 per 1000	12 fewer per 1000 (from 65 fewer to 138 more)

Gestational age at delivery (weeks) (Better indicated by higher values)											
579 (4 studies)	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2,8]	291	288	-	The mean gestational age at delivery (weeks) in the control groups was **39 weeks**	The mean gestational age at delivery (weeks) in the intervention groups was **0.41 lower** **(0.79 to 0.04 lower)**
Vitamin Ds and doses across studies: D2 or D3 as 800 IU daily; 1000 IU daily; 600,000 IU STAT×2; 35, 000 IU weekly											
Preterm birth between 34-37 weeks of gestation											
145 (1 study)	no serious risk of bias	no serious inconsistency	serious[2]	very serious[5]	undetected	⨁⊖⊖⊖ **VERY LOW**[2,5] due to indirectness, imprecision	13/74 (17.6%)	7/71 (9.9%)	RR 0.56 (0.24 to 1.33)	176 per 1000	77 fewer per 1000 (from 134 fewer to 58 more)
Vitamin Ds and doses across studies: D3 35, 000 IU weekly.											
Caesarean Section											
147 (2 studies)	no serious risk of bias	no serious inconsistency	serious[2]	very serious[6]	undetected	⨁⊖⊖⊖ **VERY LOW**[2,6]	44/74 (59.5%)	44/73 (60.3%)	RR 1.01 (0.78 to 1.32)	595 per 1000	6 more per 1000 (from 131 fewer to 190 more)
Vitamin Ds and doses across studies: D3 1,000 IU daily; 35,000 IU weekly.											
Birth Length (cm) (Better indicated by lower values)											
463 (3 studies)	serious[1]	serious[9]	serious[2]	serious[3]	undetected	⨁⊖⊖⊖ **VERY LOW**[2,3,1,9]	236	227		The mean birth length (cm) in the control groups was 48.45	The mean birth length (cm) in the intervention groups was 0.72 higher (0.33 lower to 7.76 higher)
Vitamin Ds and doses across studies: D2 or D3 1,000 IU daily; 35,000 weekly; 600,000 IU STAT ×2.											

Head circumference at birth (Better indicated by higher values)											
458 (3 studies)	Serious [4]	no serious inconsistency	serious [2]	no serious	undetected	⨁⨁⊖⊖ **LOW**[2,4]	232	226	-	The mean head circumference at birth in the control groups was 33.4 cm	The mean head circumference at birth in the intervention groups was 0.28 higher (0.11 lower to 0.67 higher)
Hypercalcemia											
800 (4 studies)	very serious[1]	no serious inconsistency	very serious[2]	Serious[10]	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2,10]	0/400 (0%)	0/400 (0%)	-	Not estimable	

Vitamin Ds and doses across studies: D2 or D3 800 IU/daily; 2,000 IU/daily; 35,000 IU/weekly; 600,000 IU STAT×2;

[1] *High risk of bias studies*
[2] *Studies in non-Caucasian populations*
[3] *OIS criterion not fulfilled*
[4] *Mix of high and low risk of bias studies*
[5] *Studies in non-Caucasian populations*
[6] *Wide CI includes appreciable benefit and harm*
[7] *Studies in non-Caucasian populations*
[8] *Wide CI suggesting divergent potential conclusions*
[9] *Unexplained inconsistency*
[10] *Small sample size and wide CI*

Table 208 – Summary of findings and GRADE profile: vitamin D vs. no vitamin D supplementation (observational studies): type 1 diabetes mellitus

Quality assessment							Summary of Findings		
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Findings
							No vitamin D	With Vitamin D	
Type I Diabetes Mellitus in Offspring									
NR and 3273 (2 studies)	very serious[1]	very serious[2]	no serious indirectness	no serious imprecision	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2]	-	-	Not pooled. Conflicting findings, with HR ranging from 0.76 (95%CI 0.69-0.85) to 1.09 (95%CI 0.99-1.2)
Vitamin Ds and doses across studies: Type not reported and mixed Mean 1.3 ug (SD 2.6) in one study.									
Asthma (assessed with: various definitions and metrics)									
31101 (4 studies)	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⊖⊖⊖ **VERY LOW**[1]	-	-	**Not pooled** **Consistent finding of no difference between treatment and control group**
Vitamin Ds and doses across studies: Unclear, D2 and D3 mixed and D2 alone Mean 1.3 ug (SD 2.6) in one study; median 15.0 ug/day,>=10 ug; 800 IU/daily									
Preeclampsia									
23423 (1 study)	Serious[3]	Serious[4]	no serious indirectness	no serious imprecision	undetected	⨁⊖⊖⊖ **VERY LOW**[3,4]	-	-	Inconsistent findings across multiple vitamin D analyses in a single study OR range= 0.58 to 1.15
Vitamin Ds and doses across studies: NR for general 'Supplements with Vit D group' - for other analysis, divided into 6 categories (0, <5, 5-9.9, 10-14.9, 15-20, >20 ug);									
NICU admission									
290 (1 study)	very serious[1]	no serious inconsistency	very serious[5]	Serious[5]	undetected	⨁⊖⊖⊖ **VERY LOW**[1,5,6]	-	-	**Not estimable Crude OR = 0.34 (95% CI 0.16, 0.74)**	See comment	-
APGAR score									
290 (1 study)	very serious[1]	no serious inconsistency	very serious[5]	Serious[7]	undetected	⨁⊖⊖⊖ **VERY LOW**[1,5,7]	-	-	**No differences between vitamin D and no vitamin D supplementation (narratively reported results, precision unknown)**	See comment	-
Vitamin Ds and doses across studies D 50,000 IU/week.									

[1] *High risk of bias studies*
[2] *Unexplained inconsistency*
[3] *Observational study at unclear risk of bias because of concerns about unmeasured confounding (e.g. diet and sun exposure)*
[4] *Multiple inconsistent analyses within study*
[5] *Pregnancies with documented vitamin D deficiency and only term deliveries*
[6] *Small sample size with significant but fragile results*
[7] *Small sample size study, confidence interval not reported*

10.7.2. Vitamin D + calcium vs. no vitamin D/calcium supplementation

Table 209 – Summary of findings and GRADE profile: vitamin D plus calcium vs. no treatment

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With No vitamin D + Calcium	**With Vitamin D + Calcium**		**Risk with No vitamin D + Calcium**	**Risk difference with Vitamin D + Calcium** (95% CI)
Preeclampsia											
400 (1 study)	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	undetected	⨁⨀⨀⨀ **VERY LOW**[1,2,3]	18/200 (9%)	12/200 (6%)	RR 0.67 (0.33 to 1.35)	90 per 1000	30 fewer per 1000 (from 60 fewer to 32 more)

[1] *High risk of bias study*
[2] *Non-Caucasian study population*
[3] *Wide confidence interval and small sample size*

10.8. Risk of preterm birth

10.8.1. Screening by repeat digital vaginal exam versus no screening

Table 210 – Summary of findings and GRADE profile: repeated digital exam

Quality assessment							Summary of Findings				
N (studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall LoE**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With No examination (unless medically indicated)	**With Systematic digital cervical examination**		**Risk with No examination (unless medically indicated)**	**Risk difference with Systematic digital cervical examination** (95% CI)
Birth<37 weeks											
6070 (2 studies)	no serious RoB	no serious inconsistency	no serious indirectness	serious[1]	undetected	⨁⨁⨁⨀ **MODERATE**[1]	170/2968 (5.7%)	181/3102 (5.8%)	**RR 1.05** (0.86 to 1.28)	**57 per 1000**	**3 more per 1000** (from 8 fewer to 16 more)
Birth <34 weeks											
5041 (1 study)	no serious RoB	no serious inconsistency	no serious indirectness	serious[1]	undetected	⨁⨁⨁⨀ **MODERATE**[1]	61/2520 (2.4%)	57/2521 (2.3%)	**RR 0.93** (0.65 to 1.33)	**24 per 1000**	**2 fewer per 1000** (from 8 fewer to 8 more)
Low birth weight (<2500g)											
5371 (1 study)	no serious RoB	no serious inconsistency	no serious indirectness	serious[1]	undetected	⨁⨁⨁⨀ **MODERATE**[1] due to imprecision	206/2683 (7.7%)	177/2688 (6.6%)	**RR 0.86** (0.71 to 1.04)	**77 per 1000**	**11 fewer per 1000** (from 22 fewer to 3 more)
Very low birth weight (<1500g)											
5371 (1 study)	no serious RoB	no serious inconsistency	no serious indirectness	serious[1]	undetected	⨁⨁⨁⨀ **MODERATE**[1]	48/2683 (1.8%)	39/2688 (1.5%)	**RR 0.81** (0.53 to 1.23)	**18 per 1000**	**3 fewer per 1000** (from 8 fewer to 4 more)
Still birth											
5490 (1 study)	no serious RoB	no serious inconsistency	no serious indirectness	serious[1]	undetected	⨁⨁⨁⨀ **MODERATE**[1]	22/2746 (0.8%)	24/2744 (0.87%)	**RR 1.09** (0.61 to 1.94)	**8 per 1000**	**1 more per 1000** (from 3 fewer to 8 more)

Neonatal death											
5444 (1 study)	no serious RoB	no serious inconsistency	no serious indirectness	serious[1]	undetected	⨁⨁⨁⨀ **MODERATE**[1]	15/2724 (0.55%)	22/2720 (0.81%)	**RR 1.47** (0.76 to 2.83)	**6 per 1000**	**3 more per 1000** (from 1 fewer to 10 more)
NICU admission											
5329 (1 study)	no serious RoB	no serious inconsistency	no serious indirectness	serious[1]	undetected	⨁⨁⨁⨀ **MODERATE**[1]	338/2670 (12.7%)	362/2659 (13.6%)	**RR 1.08** (0.94 to 1.23)	**127 per 1000**	**10 more per 1000** (from 8 fewer to 29 more)

[1] *CI includes clinical decision threshold.*

10.8.2. Progesterone vs no progesterone to prevent preterm birth

Table 211 – Summary of findings and GRADE profile: progesterone versus no active intervention

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With No active intervention	**With Progesterone (any mode of administration)**		**Risk with No active intervention**	**Risk difference with Progesterone (any mode of administration)** (95% CI)
Perinatal mortality											
1115 (2 studies)	serious[1]	no serious inconsistency	serious[2]	very serious[3]	undetected	⨁⨀⨀⨀ **VERY LOW**[1,2,3]	20/553 (3.6%)	18/562 (3.2%)	**RR 0.88** (0.47 to 1.65)	**38 per 1000**	**5 fewer per 1000** (from 20 fewer to 25 more)
Neonatal death											
1560 (4 studies)	no serious risk of bias[4]	no serious inconsistency	serious[2]	serious[3]	undetected	⨁⨀⨀⨀ **LOW**[1,2,3]	21/775 (2.7%)	11/785 (1.4%)	**OR 0.52** (0.26 to 1.05)	**16 per 1000**	**8 fewer per 1000** (from 12 fewer to 1 more)
Neonatal survival free of morbidities											
1384 (4 studies)	no serious risk of bias[4]	no serious inconsistency	serious[2]	no serious imprecision	undetected	⨁⨁⨀⨀ **MODERATE**[1,2]	621/685 (90.7%)	655/699 (93.7%)	**RR 1.02** (0.98 to 1.06)	**910 per 1000**	**18 more per 1000** (from 18 fewer to 55 more)

Total major adverse neonatal outcomes											
1368 (4 studies)	serious[1]	no serious inconsistency	serious[5]	serious[6]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2,3]	80/683 (11.7%)	54/685 (7.9%)	**RR 0.67** (0.48 to 0.93)	**118 per 1000**	**39 fewer per 1000** (from 8 fewer to 61 fewer)
Birth <34 weeks											
981 (3 studies)	no serious risk of bias	no serious inconsistency	serious[2]	serious[6]	undetected	⊕⊖⊖⊖ **LOW**[1,2]	95/490 (19.4%)	68/491 (13.8%)	RR 0.71 (0.52 to 0.96)	145 per 1000	42 fewer per 1000 (from 6 fewer to 70 fewer)
Still Birth											
1560 (4 studies)	serious[1]	no serious inconsistency	serious[5]	very serious[3]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,5,3]	8/775 (1%)	11/785 (1.4%)	**OR 1.34** (0.54 to 3.31)	**6 per 1000**	**2 more per 1000** (from 3 fewer to 14 more)
Abortion											
657 (1 study)	no serious risk of bias	no serious inconsistency	serious[7]	very serious[8]	undetected	⊕⊖⊖⊖ **VERY LOW**[7,8]	0/330 (0%)	1/327 (0.31%)	**OR 7.46** (0.15 to 375.83)	Not estimated because zero event in one arm	
Seizures											
642 (1 study)	no serious risk of bias	no serious inconsistency	serious[9]	very serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[9,2]	2/322 (0.62%)	1/320 (0.31%)	**RR 0.52** (0.05 to 4.97)	**6 per 1000**	**3 fewer per 1000** (from 6 fewer to 25 more)
Total major maternal adverse events											
0 (1 study) N=250	no serious risk of bias	no serious inconsistency	serious[10]	serious[11]	undetected	⊕⊕⊖⊖ **LOW**[10,11]	Qualitative results only -- no difference				
Birth <37 weeks											
1449 (4 studies)	serious[1]	no serious inconsistency	serious[5]	serious[3]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,5,3]	183/718 (25.5%)	166/731 (22.7%)	**RR 0.88** (0.74 to 1.05)	**254 per 1000**	**30 fewer per 1000** (from 66 fewer to 13 more)
Birth <34 weeks											
981 (3 studies)	no serious risk of bias	no serious inconsistency	serious[2]	serious[12]	undetected	⊕⊖⊖⊖ **LOW**[2,12]	95/490 (19.4%)	68/491 (13.8%)	RR 0.71 (0.52 to 0.96)	145 per 1000	42 fewer per 1000 (from 6 fewer to 70 fewer)
Birth <28 weeks											
1115 (2 studies)	serious[1]	no serious inconsistency	serious[2]	serious[6]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2,6]	45/553 (8.1%)	27/562 (4.8%)	RR 0.59 (0.37 to 0.94)	85 per 1000	35 fewer per 1000 (from 5 fewer to 54 fewer)

[1] *Studies at unclear to high risk of bias*
[2] *Body of evidence mostly from studies judged as seriously indirect (because of concerns about race, developing country setting in which the study was conducted, maternal age and/or presence of important risk factor(s) for preterm birth for a substantial proportion of the population)*
[3] *Wide CI, includes both appreciable benefit and harm*
[4] *Only one study contributing <30% of weight at high risk*
[5] *Body of evidence not exclusively in pregnancies at low risk for PTB (a mix of very serious and serious applicability concerns)*
[6] *Fragile estimates -- OIS criterion not met*
[7] *One-third of the women had previous miscarriage <19 weeks and approximately half were of black race*
[8] *Wide CI and few total events*
[9] *One-third of the women had previous miscarriage <19 weeks and approximately half were of black race*
[10] *Single study in which not all included women were at low risk for preterm birth*
[11] *Single small study*
[12] *OIS criterion not met and upper confidence interval approach no difference*

10.8.3. Cerclage vs no cerclage to prevent preterm birth

Table 212 – Summary of findings and GRADE profile: cerclage vs no cerclage

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With No cerclage (with or without co-interventions)	**With Cerclage (with or without co-interventions)**		**Risk with No cerclage (with or without co-interventions)**	**Risk difference with Cerclage (with or without co-interventions)** (95% CI)
Neonatal death											
10 (1 study)	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2,3]	qualitative report of no significant difference				
Major neonatal adverse events											
10 (1 study)	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2,3]	qualitative report of no significant difference				
Total major maternal adverse events											
167 (1 study)	very serious[4]	no serious inconsistency	Serious[5]	very serious[6]	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2,3]	0/55 (0%)	3/112 (2.7%)	**OR 4.52** (0.40 to 50.99)	Not estimated because zero event in one arm	

Birth < 37 Weeks											
483 (3 studies)	very serious[7]	Serious[8]	serious[2,5]	very serious[6]	undetected	⨁⊖⊖⊖ **VERY LOW**[5,6,7,8]	104/181 (57.5%)	127/302 (42.1%)	**RR 0.82** (0.57 to 1.18)	**556 per 1000**	**100 fewer per 1000** (from 239 fewer to 100 more)
Birth < 34 Weeks											
235 (2 studies)	very serious[7]	very serious[8]	very serious[9]	very serious[6]	undetected	⨁⊖⊖⊖ **VERY LOW**[7,8,9,6]	30/86 (34.9%)	22/149 (14.8%)	**RR 0.67** (0.15 to 3.03)	**349 per 1000**	**115 fewer per 1000** (from 297 fewer to 708 more)
Birth < 28 Weeks											
237 (2 studies)	very serious[10]	Serious[8]	Serious[5]	very serious[6]	undetected	⨁⊖⊖⊖ **VERY LOW**[10,8,5,6]	30/100 (30%)	21/137 (15.3%)	**RR 0.68** (0.27 to 1.71)	**300 per 1000**	**96 fewer per 1000** (from 219 fewer to 213 more)

[1] RCT with no blinding of participants or personnel - concerns regarding differential fidelity of and adherence to interventions.
[2] RCT with majority population of African descent
[3] RCT subgroup in 10 patients with non-reporting quantitative data
[4] Single study at high risk of bias due to selection bias and confounding reporting unadjusted data.
[5] Not exclusively in low risk pregnancies
[6] Wide CI and OIS criterion not met.
[7] Observational studies with unclear-high risk of bias not reporting adjusted estimates
[8] I-squared > 50%
[3] Studies in populations not exclusively at low risk for preterm birth and the larger study included a substantial proportion of non-Caucasian ethnicity
[10] Both studies at high risk of bias reporting unadjusted data -- selection bias and confounding by indication
Reduced activity to prevent preterm birth

Table 213 – Summary of findings and GRADE profile: reduced activity to prevent preterm birth and its sequelae in asymptomatic women with short cervix but no additional risk factors for preterm birth

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With No reduced activity +/- progesterone (~50% on progesterone)	**With Reduced activity +/- progesterone (~50% on progesterone)**		**Risk with No reduced activity +/- progesterone (~50% on progesterone)**	**Risk difference with Reduced activity +/- progesterone (~50% on progesterone)** (95% CI)
PTB< 37 Weeks											
646 (1 study)	very serious[1]	no serious inconsistency	very serious[2]	serious[3]	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2,3,4]	67/394 (17%)	93/252 (36.9%)	**OR 2.37** (1.6 to 3.53)	**170 per 1000**	**157 more per 1000** (from 77 more to 250 more)
PTB< 34 Weeks											
646 (1 study)	very serious[1]	no serious inconsistency	very serious[2]	serious[3]	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2,3]	n/N not reported	n/N not reported	**OR 2.28** (1.36 to 3.8)	Not estimated because n/N was not reported.	

[1] High risk of bias because of very serious concerns about unmeasured confounding (because it is a post hoc subgroup analysis), time-varying nature of adherence to activity recommendation, exposure ascertainment bias (actual physical activity was not measured), and respondent bias.
[2] 77% non-white with 50% of patients of African descent, 30% with history of miscarriage, 16% smokers
[3] Small total sample size
[4] Although adjusted OR >2.0, we do not feel comfortable in upgrading the evidence here because of our concerns for risk of bias (see footnote 1)

10.9. Pregnancies that passed their due date

Table 214 – Summary of findings and GRADE profile: surveillance of postterm pregnancies: neonatal death

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated effects**	**absolute**
							Comparator arm	**Intervention arm**		**Risk Comparator arm**	**Risk difference Intervention arm** (95% CI)
Neonatal death for the following intervention/comparator (observational evidence): • **[Test 1: (CTG+ fetal movement) +/- Test 2: partial BP* if non-reactive Test 1] versus {[Test 1: (CTG+ fetal movement) + Test 2: AFV] +/- Test 3: partial BP* if non-reactive Test 1} (Eden 1982)** • **{[Routine (fetometry+ AFI) at 41 week +/- umbilical artery blood flow measurements if AFI normal but abnormal fetometry] versus [indicated scan (fetometry)] +/- umbilical artery blood flow measurements if abnormal fetometry} (Lindqvist, 2014)**										
Total participants (4601); (2 studies)	very serious[1]	NA (not pooled because of clinical diversity)	no to very serious for Lindqvist et al. 2014[2]	very serious [4]	undetected	Very Low	2/2650 (0.08%) for Lindqvist et al. 2014	3/1444(0.21%) Lindqvist et al. 2014	Imprecise estimates of effects. (Absolute risk difference demonstrated by Lindqvist et al. 2014 = 1 more per 1000; from 0 fewer to 12 more; RR= 2.75, 95% CI=0.46, 16.46)		
Perinatal death for the following intervention/comparator (observational evidence): • **Modified BP2 versus CTG+ AFD (Alfirevic 1995)** • **CTG+ AFI versus CTG+ AFD (Alfirevic 1997)** • **[Test 1: (CTG+ fetal movement) +/- Test 2: partial BP* if non-reactive Test 1] versus {[Test 1: (CTG+ fetal movement) + Test 2: AFV] +/- Test 3: partial BP* if non-reactive Test 1} (Eden 1982)** • **BP2 versus NST (El-Damarawy, 1993)** • **BP2 versus AFV+NST (El-Damarawy, 1993)** • **{[indicated scan (fetometry)] +/- umbilical artery blood flow measurements if abnormal fetometry] versus [Routines scan (fetometry+ AFI) at 41 week +/- umbilical artery blood flow measurements if AFI normal but abnormal fetometry]} (Lindqvist, 2014)** • **AFI+CTG versus AFD+CTG (Oral 1999)**										
Total participants (5377); (6 studies)	no to very Serious (for Lindqvist)[1]	NA (not pooled because of clinical diversity)	no to Very serious (for Lindqvist et al, 2014)[2]	serious for Lindqvist et al, 2014) to very serious[5]	undetected	Very Low	3/1444(0.21%) for Lindqvist et al, 2014	9/2650(0.34%) for Lindqvist et al, 2014	Imprecise estimates of effects. (Absolute risk difference demonstrated by Lindqvist et al. 2014 = 2 more per 1000; from 1 fewer to 10 more; OR 1.6 ,95% CI 0.4 to 6.1)		

Still birth for the following intervention/comparator (observational evidence): • **[Test 1: (CTG+ fetal movement) +/- Test 2: partial BP* if non-reactive Test 1] versus {[Test 1: (CTG+ fetal movement) + Test 2: AFV] +/- Test 3: partial BP* if non-reactive Test 1} (Eden 1982)** • **{[Routine (fetometry+ AFI) at 41 week +/- umbilical artery blood flow measurements if AFI normal but abnormal fetometry] versus [indicated scan (fetometry)] +/- umbilical artery blood flow measurements if abnormal fetometry} (Lindqvist, 2014)**									
Total participants (4601); (2 studies)	very serious[1]	NA (not pooled because of clinical diversity)	no to very serious (for Lindqvist et al, 2014)[2]	serious[3] (for Lindqvist et al, 2014) to Very serious [4]	undetected	Very Low	7/2650(0.26%) for Lindqvist et al, 2014	0/1444(0. %) for Lindqvist et al, 2014		Imprecise estimates of effects. (Absolute risk difference demonstrated by Lindqvist et al. 2014 = 2 fewer 1000; from 3 fewer to 3 more; RR 0.12,95% CI 0.01 to 2.14)
NICU admission (RCTs) for the following intervention/comparators: • **CTG+ AFI versus CTG+ AFD (Alfirevic 1997)** • **Modified BP2 versus CTG+ AFD (Alfirevic 1995)** • **AFI+CTG versus AFD+CTG (Oral 1999)**										
Total participants 746 ; (3 studies)	no	NA (not pooled because of clinical diversity)	serious[6]	very serious imprecision[7]	undetected	Very low	Inconclusive and imprecise estimates of effects (0)			
NICU admission (Observational evidence) for intervention **[Test 1: (CTG+ fetal movement) +/- Test 2: partial BP* if non-reactive Test 1]** versus comparator **{[Test 1: (CTG+ fetal movement) + Test 2: AFV] +/- Test 3: partial BP* if non-reactive Test 1} (Eden 1982)**										
Total participants 507 (1 study)	very serious[8]	NA (not pooled because only a single study)	no	serious[9]	undetected	Very Low	0/109 (0%)	40/398 (10.1%)	RR 22.33 (1.38 to 360.26)	Absolute risk not estimable (zero events with comparator strategy). **Findings significantly favour the comparator strategy**
Apgar score (various <7 or <4 or NR cut-offs at 1-5 minutes) for various following intervention/comparators (RCTs): • **CTG+ AFI versus CTG+ AFD (Alfirevic 1997)** • **Modified BP2 versus CTG+ AFD (Alfirevic 1995)** • **AFI+CTG versus AFD+CTG (Oral 1999)**										
Total participants (746); (3 studies)	no	NA (not pooled because of clinical diversity)	no	very serious [10]	undetected	Low	See: Apgar score for individual intervention and comparator tests and their corresponding effect estimates, all yielding inconclusive findings.			

Apgar score (various <7 or <4 or NR cut-offs at 1-5 minutes) for various following intervention/comparators (observational evidence): • **[Test 1: (CTG+ fetal movement) +/- Test 2: partial BP* if non-reactive Test 1] versus {[Test 1: (CTG+ fetal movement) + Test 2: AFV] +/- Test 3: partial BP* if non-reactive Test 1} (Eden 1982)** • **BP2 versus NST (El-Damarawy, 1993)** • **BP2 versus AFV+NST (El-Damarawy, 1993)** • **NST versus AFV+NST (El-Damarawy, 1993)** • **[Routine (fetometry+ AFI) at 41 week + Umbilical artery blood flow measurements if AFI normal but abnormal fetometry] versus {[indicated scan fetometry] +/- umbilical artery blood flow measurements if abnormal fetometry} (Lindqvist, 2014)**									
Total participants (4631); (3 studies)	very serious [11]	NA (not pooled because of clinical diversity)	no	very serious imprecision[10]	undetected	Very low	See: *Apgar score* for individual intervention and comparator tests and their corresponding effect estimates, all yielding inconclusive findings.			
Hypoxic ischemic encephalopathy grades 2 and 3 for the following intervention/comparator (observational evidence): • **{[Routine (fetometry+ AFI) at 41 week +/- umbilical artery blood flow measurements if AFI normal but abnormal fetometry] versus [indicated scan (fetometry)] +/- umbilical artery blood flow measurements if abnormal fetometry} (Lindqvist, 2014)**										
Total participants (4094); (1 study)	very serious[1]	NA (not pooled because of clinical diversity)	very serious [2]	very serious [3]	undetected	Very Low	2/2650 (0.07%)	0/1444(0.%)	RR 0.37 (0.02 to 7.64)	Not estimable because 0 event in the intervention arm.
Cerebral palsy for the following intervention/comparator (observational evidence) • **{[Routine (fetometry+ AFI) at 41 week +/- umbilical artery blood flow measurements if AFI normal but abnormal fetometry] versus [indicated scan (fetometry)] +/- umbilical artery blood flow measurements if abnormal fetometry} (Lindqvist, 2014)**										
Total participants (4094); (1 study)	very serious[1]	NA (not pooled because of clinical diversity)	very serious [2]	very serious [3]	undetected	Very Low	3/2650 (0.11%)	0/1444 (0.%)	RR 0.26 (0.01 to 5.07)	Not estimable because 0 event in the intervention arm.
Meconium aspiration syndrome for the following intervention/comparator (observational evidence): • **[Test 1: (CTG+ fetal movement) +/- Test 2: partial BP* if non-reactive Test 1] versus {[Test 1: (CTG+ fetal movement) + Test 2: AFV] +/- Test 3: partial BP* if non-reactive Test 1} (Eden 1982))**										
Total participants (507); (1 study)	very serious[8]	NA (not pooled because of clinical diversity)	No	very serious [3]	undetected	Very Low	0/109(0. %)	5/398(1.25%)	RR 3.03 (0.17 to 54.42	Not estimable because 0 event in the control arm.
Neonatal convulsion for the following intervention/comparator (observational evidence): • **{[Routine (fetometry+ AFI) at 41 week +/- umbilical artery blood flow measurements if AFI normal but abnormal fetometry] versus [indicated scan (fetometry)] +/- umbilical artery blood flow measurements if abnormal fetometry} (Lindqvist, 2014)**										
Total participants (4094); (1 study)	very serious[1]	NA (not pooled because of clinical diversity)	very serious[2]	serious [3]	undetected	Very Low	3/1444(0.21%)	3/2650(0. 11%)	RR 0.54 (0. 11 to 2.70)	1 fewer per 1000 (from 2 fewer to 4 more)

Cerebral haemorrhage/intracranial haemorrhage for the following intervention/comparator (observational evidence): • **{[Routine (fetometry+ AFI) at 41 week +/- umbilical artery blood flow measurements if AFI normal but abnormal fetometry] versus [indicated scan (fetometry)] +/- umbilical artery blood flow measurements if abnormal fetometry} (Lindqvist, 2014)**											
Total participants (4094); (1 study)	very serious[1]	NA (not pooled because of clinical diversity)	very serious[2]	very serious [3]	undetected	Very Low	3/1444(0.21%)	1/2650(0. 04%)	RR 5.51 (0. 57 to 52.88)	-	2 more per 1000 (from 0 fewer to 20 more)
Cerebral damage includes HIE23, cerebral palsy, and cerebral haemorrhage for the following intervention/comparator (observational evidence): • **{[Routine (fetometry+ AFI) at 41 week +/- umbilical artery blood flow measurements if AFI normal but abnormal fetometry] versus [indicated scan (fetometry)] +/- umbilical artery blood flow measurements if abnormal fetometry} (Lindqvist, 2014)**											
Total participants (4094); (1 study)	very serious[1]	NA (not pooled because of clinical diversity)	very serious[2]	serious [3]	undetected	Very Low	3/1444 (0.21%)	5/2650(0.19%)	OR 0.9 (0. 2 to 3.8)	2 per 1000	0 fewer per 1000 (from 2 fewer to 6 more)
Instrumental delivery for the following intervention/comparator (RCT): • **CTG+ AFI versus CTG+ AFD (Alfirevic 1997)**											
Total participants (500); (1 study)	no	NA (not pooled because of clinical diversity)	no	very serious [1]	undetected	Low	47/250 (18.8%)	47/250 (18.8%)	RR 1(0.69 to 1.44)	188 per 1000	0 fewer per 1000 (from 58 fewer to 83 more)
Instrumental delivery for the following intervention/comparator (observational evidence): • **{[indicated scan fetometry] +/- umbilical artery blood flow measurements if abnormal fetometry} versus [Routine (fetometry+ AFI) at 41 week + Umbilical artery blood flow measurements if AFI normal but abnormal fetometry] (Lindqvist, 2014)**											
Total participants (4094); (1 study)	very serious[2]	NA (not pooled because of clinical diversity)	serious[3]	no	undetected	Very low	229/1444 (15.9%)	408/2650 (15.4%)	OR 1 (0.9 to 1.2)	159 per 1000	0 fewer per 1000 (from 14 fewer to 26 more)
										See for individual intervention and comparator tests and their corresponding effect estimates, all yielding inconclusive findings.	
C-Section due to fetal distress (not clearly defined, but most likely fetal distress during labour) for various following intervention/comparators (RCTs): • **CTG+ AFI versus CTG+ AFD (Alfirevic 1997)** • **Modified BP2 versus CTG+ AFD (Alfirevic 1995)** • **AFI+CTG versus AFD+CTG (Oral 1999)**											
Total participants (746); (3 studies)	no	NA (not pooled because of clinical diversity)	no to serious [6] (for Oral 1999)	very serious [3]	undetected	Very low	13/303 (4.3) for Oral 1999 and Alfirevic 1997	24/298 (8.1) for Oral 1999 and Alfirevic 1997	RR 1.88 (0.97 to 3.62) for Oral 1999 and Alfirevic 1997	43 per 1000 for Oral 1999 and Alfirevic 1997	38 more per 1000 (from 1 fewer to 112 more) for Oral 1999 and Alfirevic 1997
										See for individual intervention and comparator tests and their corresponding effect estimates, all yielding inconclusive findings.	

C-Section (reason not reported) for various following intervention/comparators (RCTs): • **CTG+ AFI versus CTG+ AFD (Alfirevic 1997)** • **Modified BP2 versus CTG+ AFD (Alfirevic 1995)** • **AFI+CTG versus AFD+CTG (Oral 1999)**											
Total participants (746); (3 studies)	no	NA (not pooled because of clinical diversity)	no to serious [6] (for Oral 1999)	very serious [3]	undetected	Very low	See for individual intervention and comparator tests and their corresponding effect estimates, all yielding inconclusive findings.				
C-Section (reason not reported) for various following intervention/comparators (observational evidence): • **{[indicated scan fetometry] +/- umbilical artery blood flow measurements if abnormal fetometry} versus [Routine (fetometry+ AFI) at 41 week + Umbilical artery blood flow measurements if AFI normal but abnormal fetometry] (Lindqvist, 2014)** • **[Test 1: (CTG+ fetal movement) +/- Test 2: partial BP* if non-reactive Test 1] versus {[Test 1: (CTG+ fetal movement) + Test 2: AFV] +/- Test 3: partial BP* if non-reactive Test 1} (Eden 1982)**										
Total participants (4601); (2 studies)	very serious [1]	NA (not pooled because of clinical diversity)	no to Very serious[2]	serious[3]	undetected	Very low	344/1444 (23.8%) 119/398 (29.9%)	656/2650 (24.8%) 32/109 (29.4%)	OR= 1.1 (0.9 to 1.3) RR= 1.02 (0.73, 1.41)	18 more per 1000 (from 19 fewer to 51 more) 6 more per 1000 (from 79 fewer to 120 more)	
C-Section (ante partum distress) for the following intervention/comparators (RCT): • **CTG+ AFI versus CTG+ AFD (Alfirevic 1997)**											
Total participants (645); (2 study)	no	NA (not pooled because of clinical diversity)	no	very serious [3]	undetected	Low	2/73 (2.73%) for Alfirevic 1995 21/250 (8.4%) for Alfirevic 1997	0/72 (0.%) for Alfirevic 1995 25/250 (10%) for Alfirevic 1997	RR 0.20 (0.01 to 4.15) RR 1.19 (0.68 to 2.07)	Not estimable for Alfirevic 1995 84 per 1000 for Alfirevic 1997	Not estimable for Alfirevic 1995 because zero event in the intervention arm. 16 more per 1000 (from 27 fewer to 90 more) for Alfirevic 1997.

[1] High risk of selection bias/confounding due to the exclusion from relevant analysis of women receiving the intervention at 41 weeks who delivered between 41-42 weeks (Lindqvist et al.). High risk of selection bias and bias due to confounding (groups are from different non-overlapping time periods over the course of three years; no baseline data is presented) (Eden et al.)

[2]Exclusion of large-for-gestational age babies; excludes data for women having the intervention but delivering from 41-42 weeks gestation

[3]Wide CI; OIS not met

[4]Sparse events with/without small sample size,

[5]Wide CI

[6] Women's risk status is unknown in one of the studies

[7] OIS not met; Wide CI; and absolute risk reduction very wide.

[8] High risk of selection bias and bias due to confounding (groups are from different non-overlapping time periods over the course of three years; no baseline data is presented)

[9] OIS not met and imprecise magnitude of effect

[10]OIS criteria not met and absolute risk reduction very imprecise

[11]Observational studies at high risk of bias reporting crude estimates

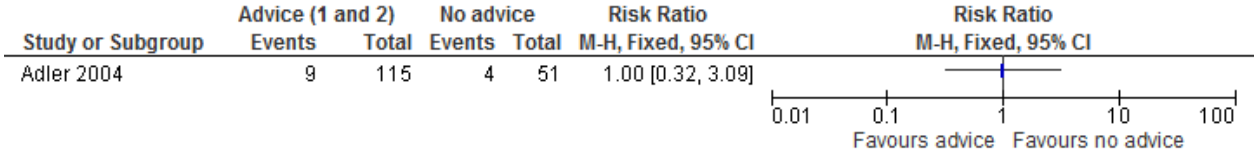
** (real time ultrasound for fetal breathing movement, fetal movement and AFV)*

Abbreviations: AFI= amniotic fluid index; AFV= amniotic fluid volume; AFD= amniotic fluid depth; BP=biophysical profile; BP2= Biophysical profile 2 (here: Fluid volume, fetal movement, fetal tone + fetal breathing + NST/heart rate – total max score = 10); CTG= Cardiotocography; pBP=partial biophysical profile (here: ultrasound assessment of fetal breathing movements, fetal movements, and amniotic fluid volume); uabf=umbilical artery blood flow measurement

11. FOREST PLOTS

11.1. CMV

Figure 20 – Lifestyle advice for CMV: Forest plot for maternal seroconversion



11.2. Toxoplasmosis

11.2.1. Mandatory monthly screening (1992-1995) versus recommended screening (1987-1991) in France[121]

Figure 21 – Screening for toxoplasmosis infection: Forest plot for infections in newborn

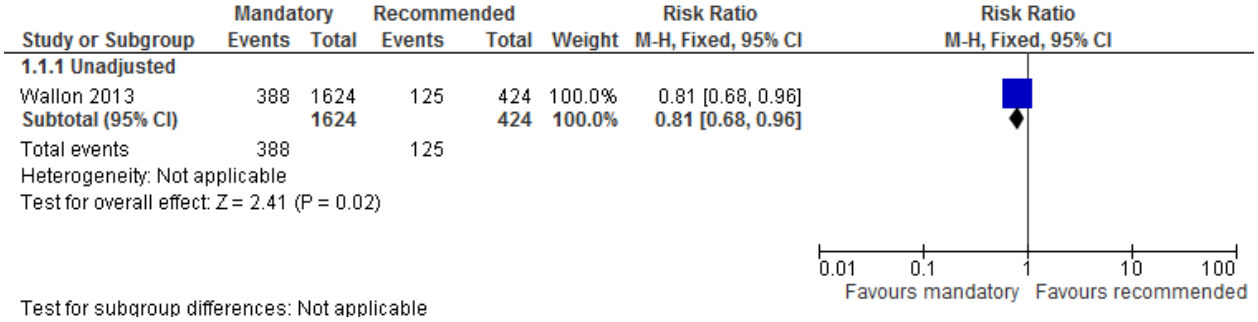
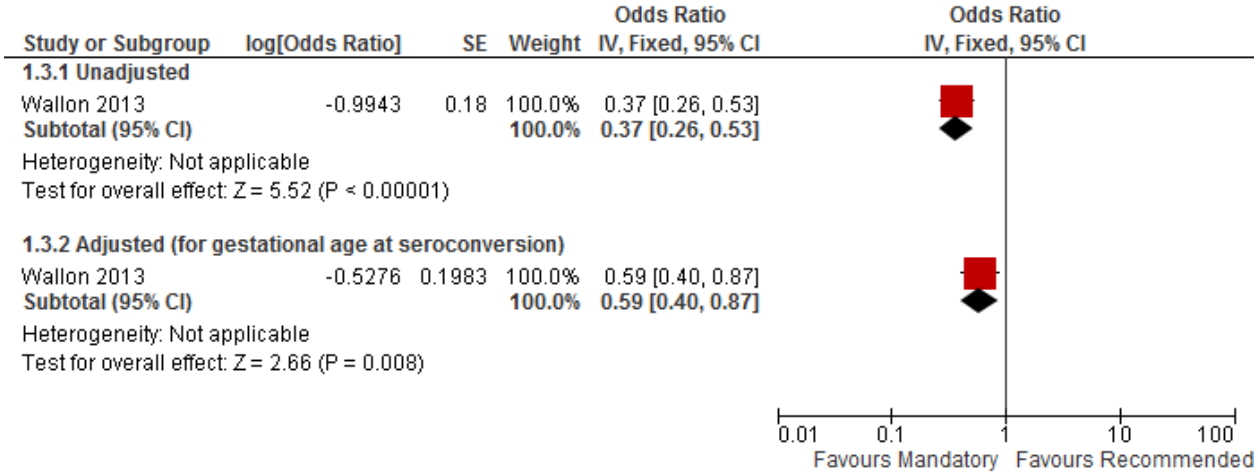


Figure 22 – Screening for toxoplasmosis infection: Forest plot for clinical signs at 3 years



11.2.2. After (1984 - 1990) versus prior (1966) implementation of screening plus treatment[53]

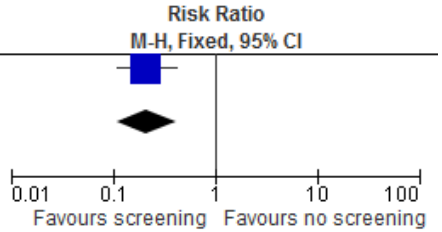
Figure 23 – Sreening for toxoplasmosis infection: Forest plot for incidence of primary infection during pregnancy



Figure 24 – Screening for toxoplasmosis infection: Forest plot for incidence of congenital infection

Study or Subgroup	After Events	After Total	Before Events	Before Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hengst 1992	124	109935	9	1697	100.0%	0.21 [0.11, 0.42]
Total (95% CI)		**109935**		**1697**	**100.0%**	**0.21 [0.11, 0.42]**
Total events	124		9			

Heterogeneity: Not applicable
Test for overall effect: Z = 4.50 (P < 0.00001)

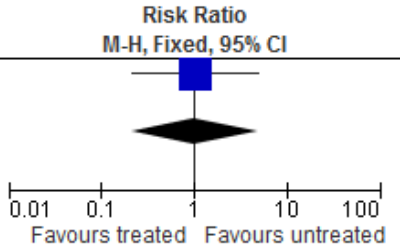


11.2.3. Prenatal screening and treatment (1976 – 1987) vs. untreated during pregnancy (1966 – 1975)[54]

Figure 25 – Screening for toxoplasmosis infection: Forest plot for incidence of symptomatic congenital infection

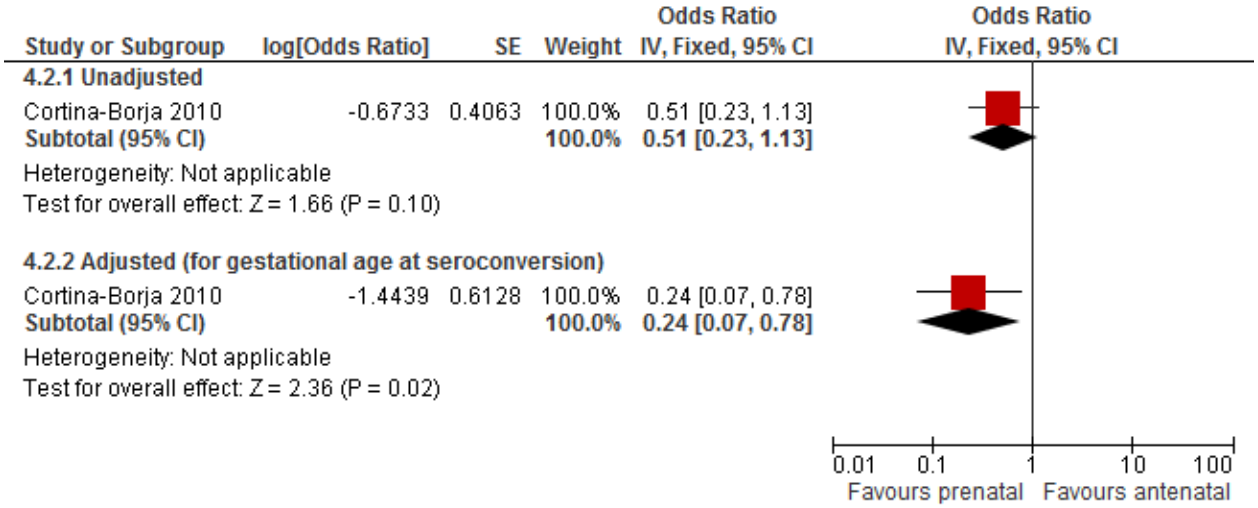
Study or Subgroup	Treated Events	Treated Total	Untreated Events	Untreated Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Henri 1992	3	99	3	101	100.0%	1.02 [0.21, 4.93]
Total (95% CI)		**99**		**101**	**100.0%**	**1.02 [0.21, 4.93]**
Total events	3		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.02 (P = 0.98)



11.2.4. Countries with prenatal screening plus treatment policies (1996 – 2000) vs. countries with neonatal screening programmes (1992 – 2000)[23]

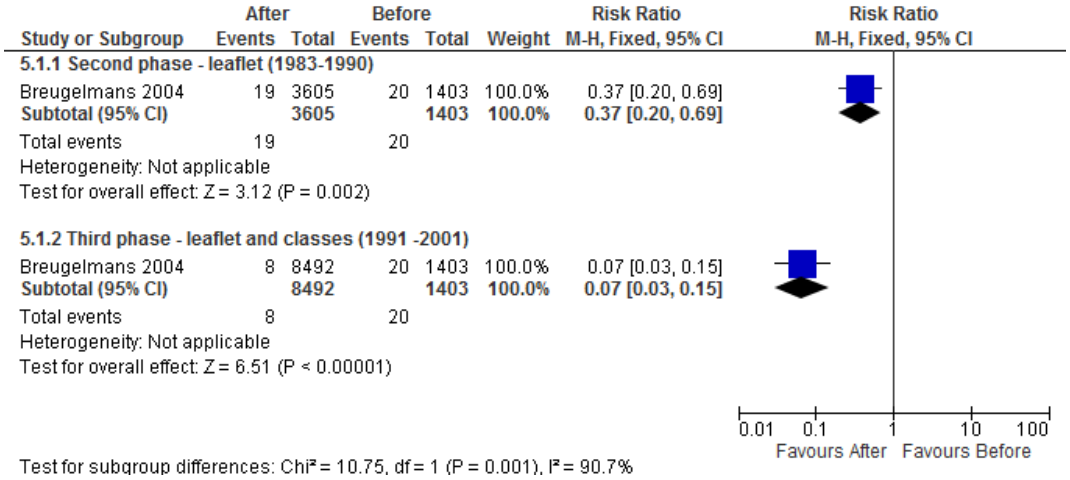
Figure 26 – Screening for toxoplasmosis infection: Forest plot for serious neurological sequelae or death



11.2.5. Lifestyle for toxoplasmosis

Figure 27. Lifestyle for toxoplasmosis: Forest plot for seroconversion rate

Routine advice (educational training) vs. no specific advice on toxoplasmosis[15]



11.3. Chlamydia trachomatis

11.3.1. Routine screening vs. no routine screening for chlamydia trachomatis

Figure 28 – Screening for chlamydia: Forest plot for preterm labour

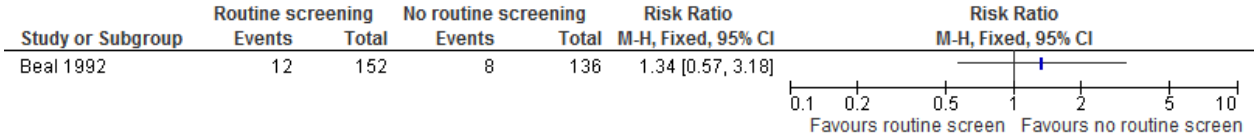


Figure 29 – Screening for chlamydia: Forest plot for maternal febrile morbidity

Study or Subgroup	Routine screening Events	Total	No routine screening Events	Total	Risk Ratio M-H, Fixed, 95% CI
Beal 1992	18	152	23	138	0.71 [0.40, 1.26]

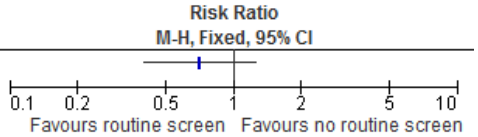
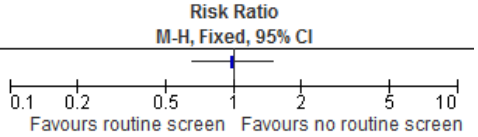


Figure 30 – Screening for chlamydia: Forest plot for intra- and/or post-partum antibiotic treatment

Study or Subgroup	Routine screening Events	Total	No routine screening Events	Total	Risk Ratio M-H, Fixed, 95% CI
Beal 1992	36	152	33	138	0.99 [0.66, 1.50]



11.3.2. Universal screening vs. screening at the discretion of attending medical staff for chlamydia trachomatis

Figure 31 – Screening for chlamydia: Forest plot for maternal febrile morbidity

Study or Subgroup	Universal screening Events	Total	Dr discretion screening Events	Total	Risk Ratio M-H, Fixed, 95% CI
Quinlivan 1998	11	100	9	60	0.73 [0.32, 1.67]

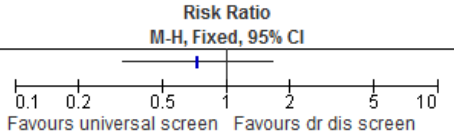
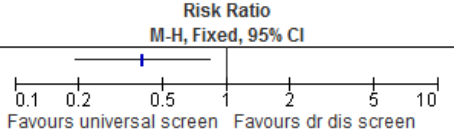


Figure 32 – Screening for chlamydia: Forest plot for neonatal febrile morbidity

Study or Subgroup	Universal screening Events	Total	Dr discretion screening Events	Total	Risk Ratio M-H, Fixed, 95% CI
Quinlivan 1998	10	100	15	60	0.40 [0.19, 0.83]



11.4. Group B streptococcus

11.4.1. Universal screening vs. no screening for GBS

Figure 33 – Screening for GBS: Forest plot for early onset Group B neonatal sepsis

Study or Subgroup	Universal Sreening Events	Total	No screening Events	Total	Risk Ratio M-H, Fixed, 95% CI	Year
Jeffrey 1998	28	36342	28	5732	0.16 [0.09, 0.27]	1998
Locksmith 1999	6	4453	23	7810	0.46 [0.19, 1.12]	1999
Gilson 2000	0	3164	4	2684	0.09 [0.01, 1.75]	2000
Reisner 2000	2	9932	9	8188	0.18 [0.04, 0.85]	2000
Main 2000	0	9304	8	6829	0.04 [0.00, 0.75]	2000
Share 2001	7	7180	20	7531	0.37 [0.16, 0.87]	2001
Vergani 2002	3	6152	8	8573	0.52 [0.14, 1.97]	2002
Puopolo 2005	25	67260	99	25934	0.10 [0.06, 0.15]	2005
Renner 2006	5	9385	16	16126	0.54 [0.20, 1.47]	2006
Lin 2011	20	17405	22	15209	0.79 [0.43, 1.45]	2011
Horvath 2013	63	25857	149	19722	0.32 [0.24, 0.43]	2013

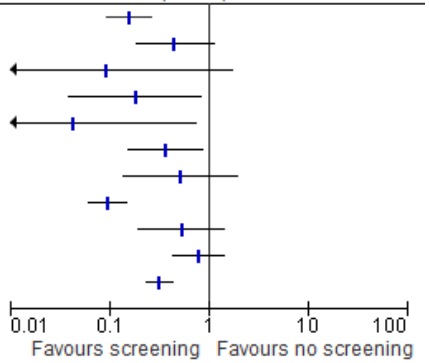
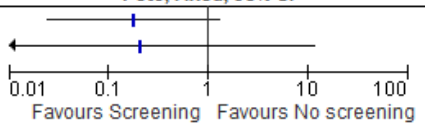


Figure 34 – Screening for GBS: Forest plot for mortality due to GBS sepsis

Study or Subgroup	Universal Sreening Events	Total	No screening Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI	Year
Vergani 2002	0	6152	4	8573	0.18 [0.02, 1.31]	2002
Renner 2006	0	9385	1	16126	0.21 [0.00, 11.97]	2006



11.4.2. Universal screening vs. risk based prophylaxis for GBS

Figure 35 – Screening for GBS: Forest plot for early onset Group B neonatal sepsis

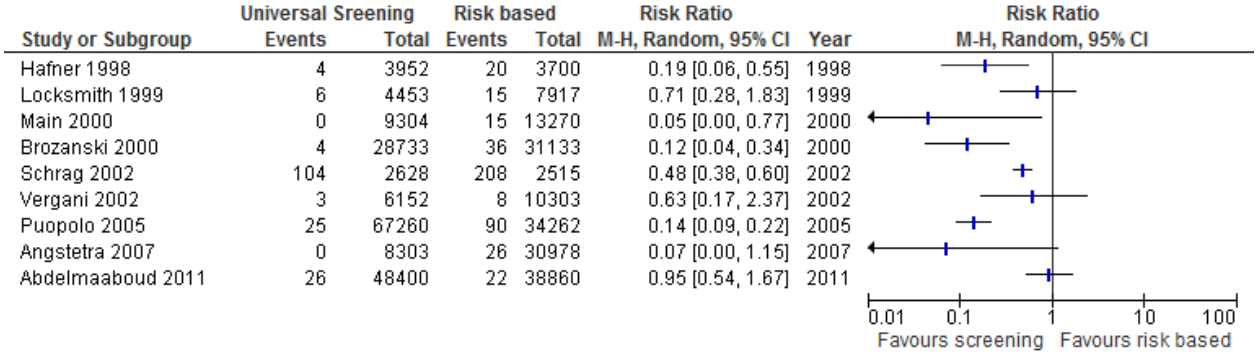


Figure 36 – Screening for GBS: Forest plot for early onset Group B neonatal sepsis – unadjusted / adjusted results

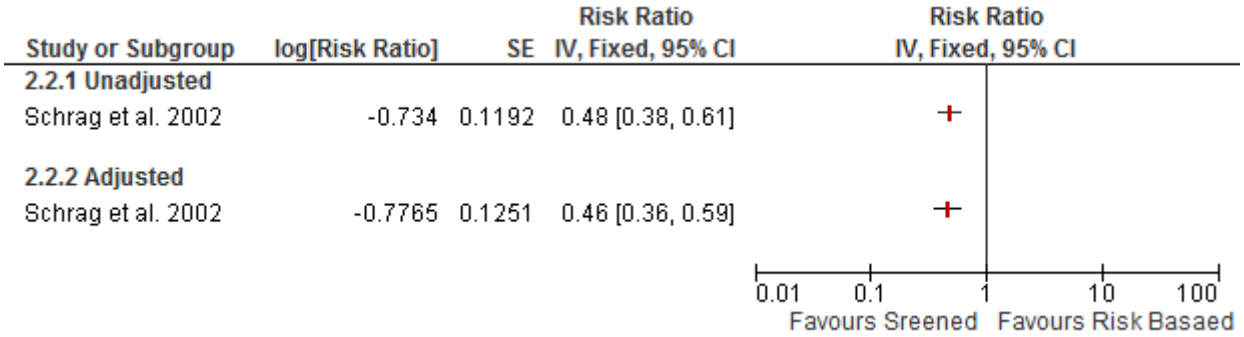
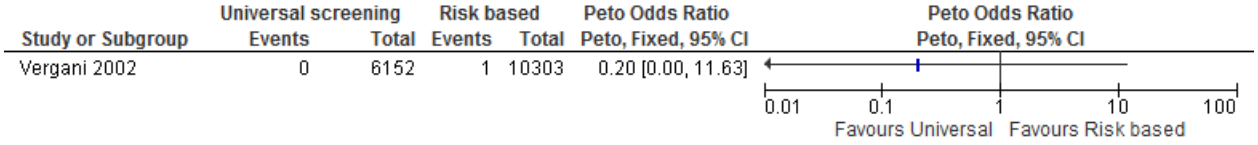
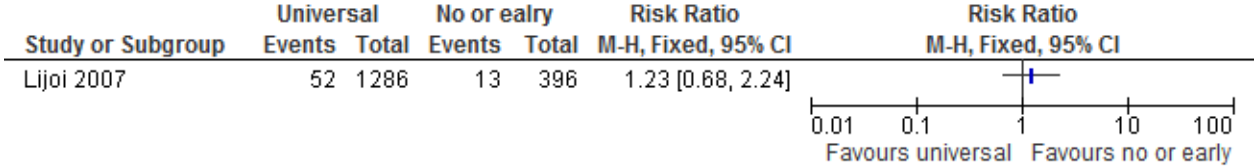


Figure 37 – Screening for GBS: Forest plot for mortality due to GBS sepsis



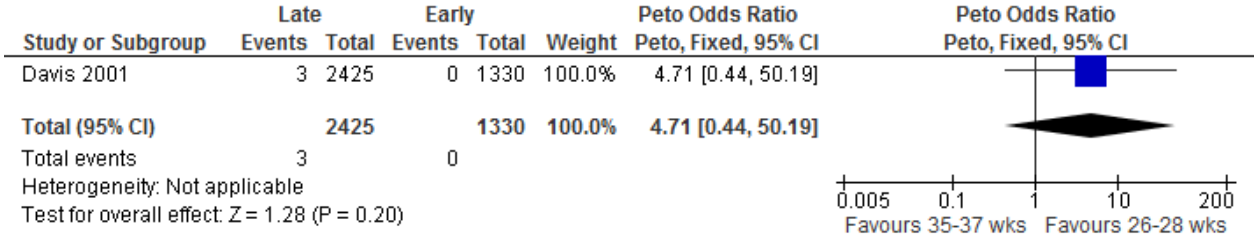
11.4.3. Universal screening vs. risk based prophylaxis (matched groups without risk factors)

Figure 38 – Screening for GBS: Forest plot for positive GBS culture based neonatal screen



11.4.4. Late (35 – 37 weeks) universal screening vs. early (26 – 28 weeks) universal screening

Figure 39 – Screening for GBS: Forest plot for positive blood and group B streptococci culture results in newborns



11.5. Gestational diabetes

11.5.1. Routine screening vs. selective screening for gestational diabetes

Figure 40 – Screening for gestational diabetes: Forest plot for macrosomia in two step 50g GCT 100g OGTT

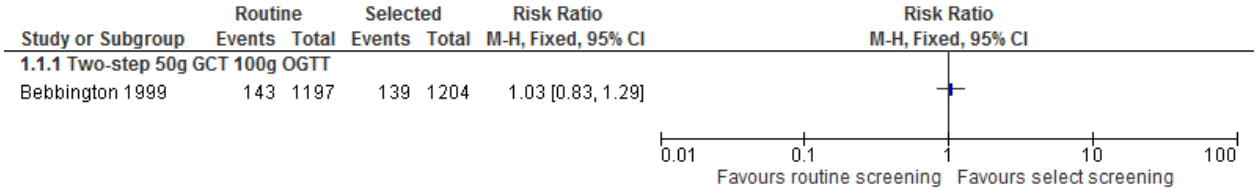


Figure 41 – Screening for gestational diabetes: Forest plot for macrosomia with one step 75g OGTT

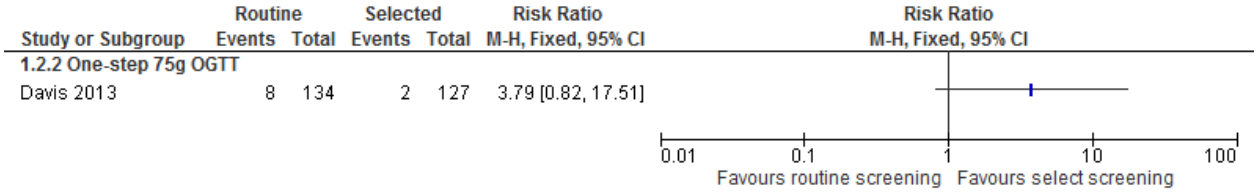


Figure 42 – Screening for gestational diabetes: Forest plot for large for gestational age with one step 75g OGTT ≥ 8.0mmol/L

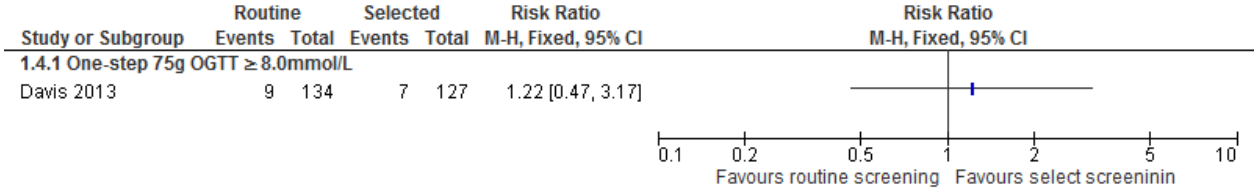


Figure 43 – Screening for gestational diabetes: Forest plot for large for gestational age with one step 75g OGTT ≥ 10mmol/L

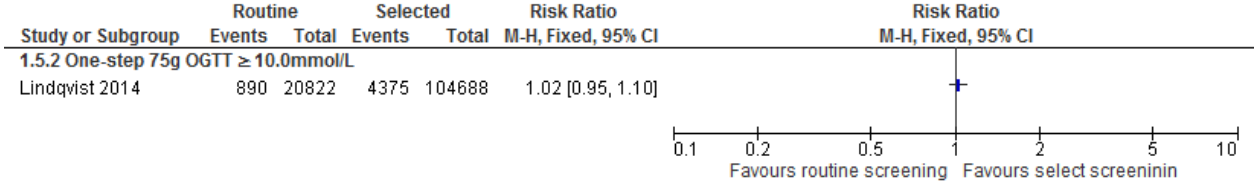


Figure 44 – Screening for gestational diabetes: Forest plot for respiratory distress with one step 75g OGTT

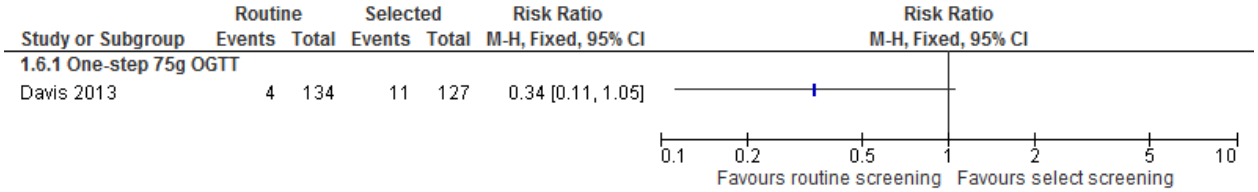
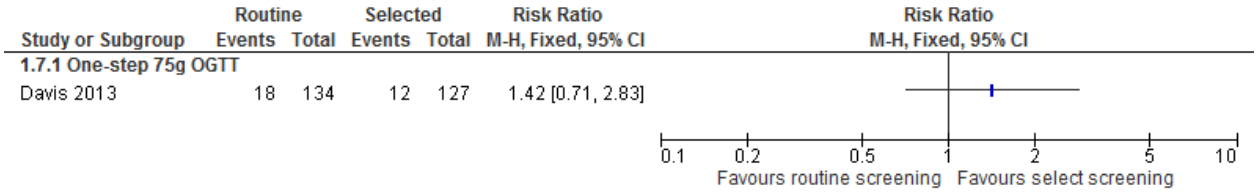


Figure 45 – Screening for gestational diabetes: Forest plot for hypoglycaemia with one step 75g OGTT



11.5.2. Early screening vs. late screening for gestational diabetes

Figure 46 – Screening for gestational diabetes: Forest plot for birth weight ≥4000g with two-step 50g GCT 100g OGTT

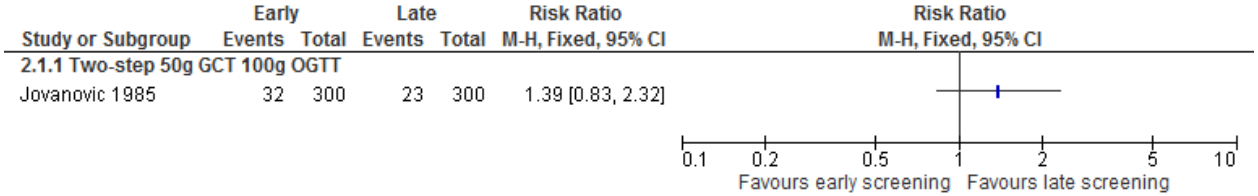


Figure 47 – Screening for gestational diabetes: Forest plot for macrosomia with GCT undefined threshold

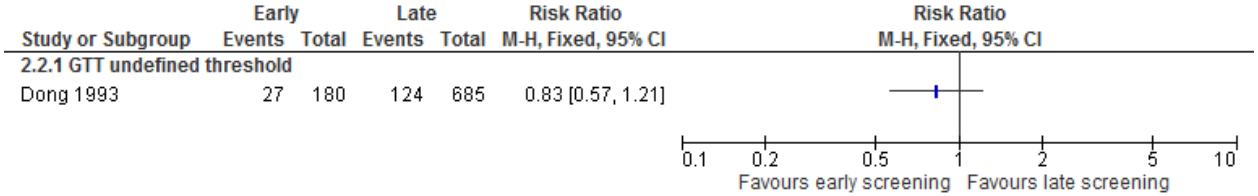


Figure 48 – Screening for gestational diabetes: Forest plot for macrosomia with two-step 50g GCT 100g OGTT

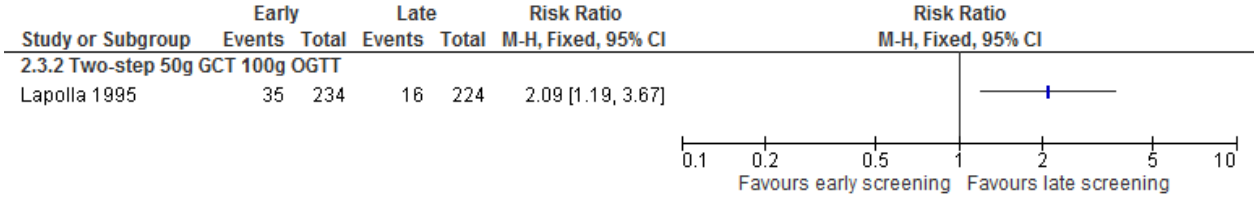


Figure 49 – Screening for gestational diabetes: Forest plot for malformations with GCT undefined threshold

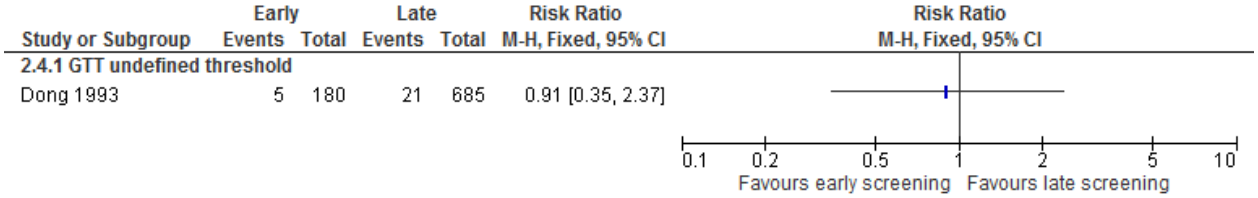


Figure 50 – Screening for gestational diabetes: Forest plot for malformations with two-step 50g GCT 100g OGTT

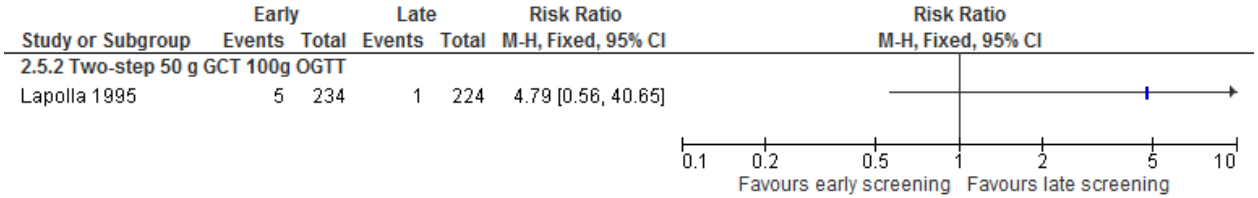


Figure 51 – Screening for gestational diabetes: Forest plot for fetal mortality with two-step 50g GCT 100g OGTT

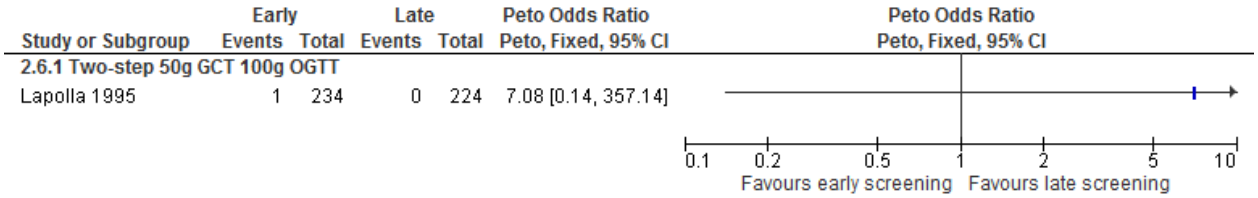


Figure 52 – Screening for gestational diabetes: Forest plot for perinatal mortality with GCT undefined threshold

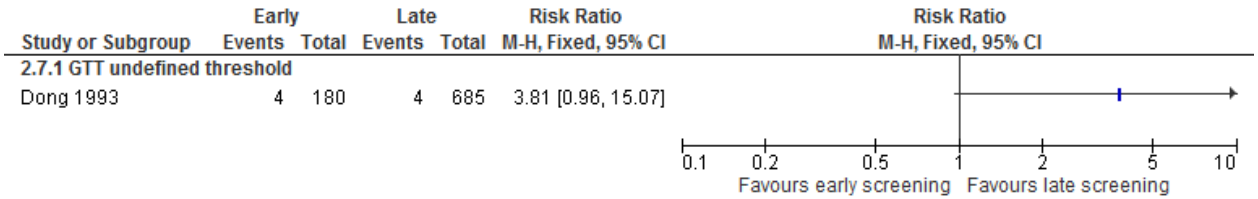


Figure 53 – Screening for gestational diabetes: Forest plot for respiratory distress syndrome with two-step 50g GCT 100g OGTT

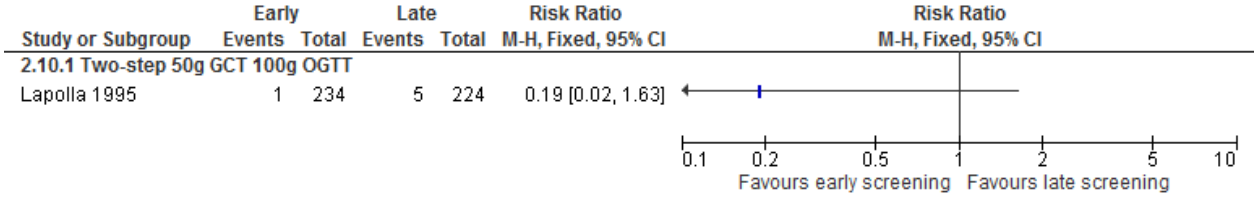


Figure 54 – Screening for gestational diabetes: Forest plot for diabetes on follow-up with defined threshold

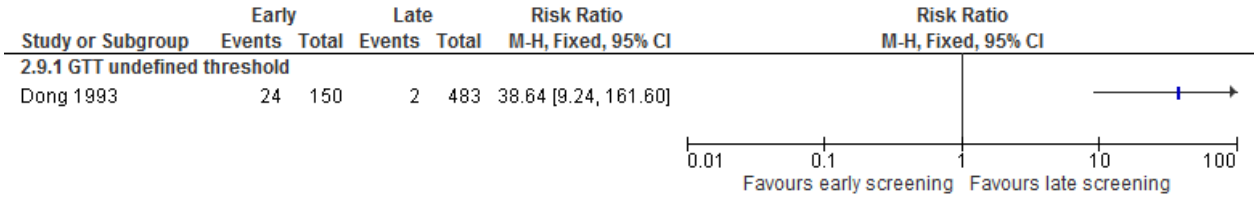
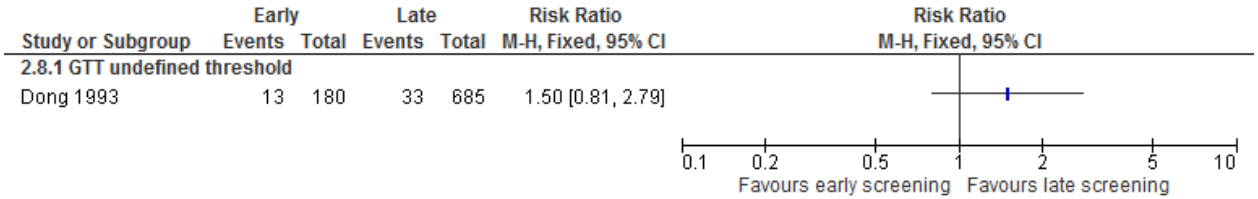


Figure 55 – Screening for gestational diabetes: Forest plot for preeclampsia with GCT undefined threshold



11.5.3. Comparisons of different thresholds for the 75g OGTT for screening for gestational diabetes

Figure 56 – Screening for gestational diabetes: Forest plot for large for gestational age: 8.9 vs 10.0mmol/L

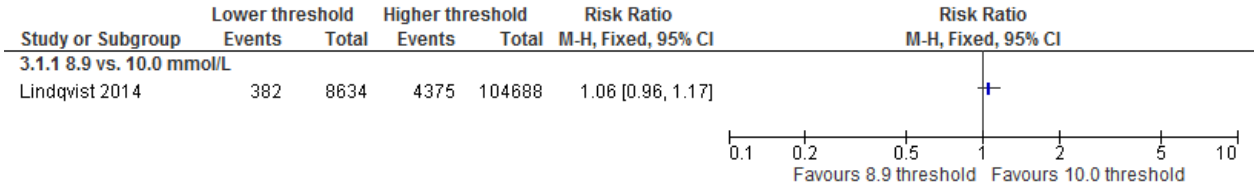


Figure 57 – Screening for gestational diabetes: Forest plot for large for gestational age: 8.9 vs 12.2mmol/L

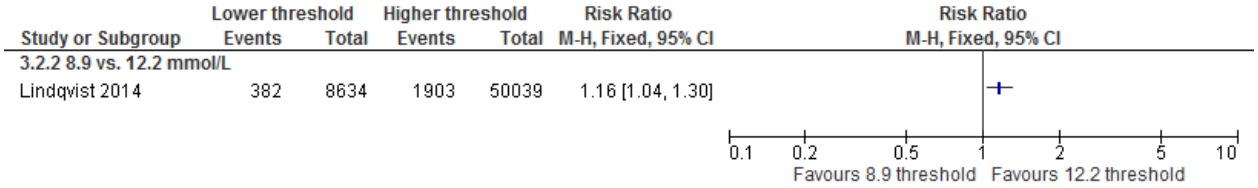
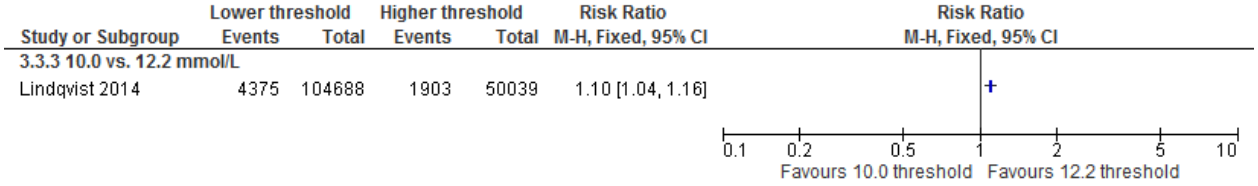


Figure 58 – Screening for gestational diabetes: Forest plot for large for gestational age: 10.0 vs 12.2mmol/L



11.5.4. Comparisons of different combinations of GCT and OGTT for screening for gestational diabetes

Figure 59 – Screening for gestational diabetes: Forest plot for hypoglycaemia with one-step vs two-step 50g GCT 75g OGTT

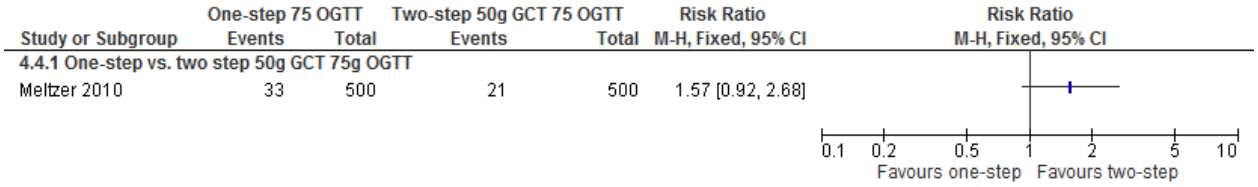


Figure 60 – Screening for gestational diabetes: Forest plot for hypoglycaemia with one-step 75g vs two-step 50g 100 OGTT

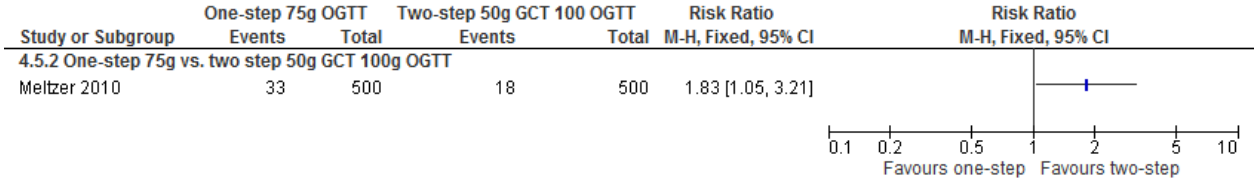


Figure 61 – Screening for gestational diabetes: Forest plot for hypoglycaemia with two-step 50g GCT with 75g vs 100g OGTT

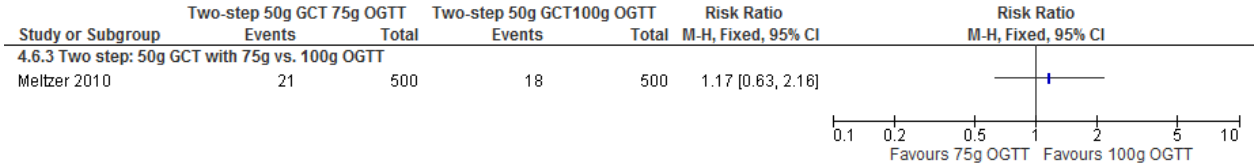


Figure 62 – Screening for gestational diabetes: Forest plot for preeclampsia with one-step vs two-step 50g GCT 75g OGTT

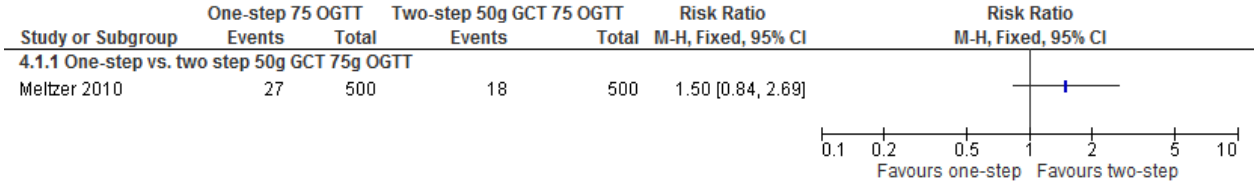


Figure 63 – Screening for gestational diabetes: Forest plot for preeclampsia with two-step 50g GCT with 75g vs 100g OGTT

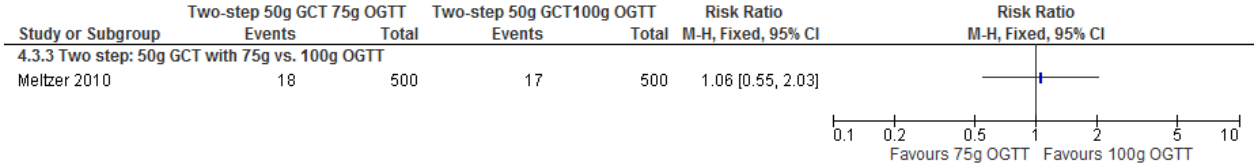


Figure 64 – Screening for gestational diabetes: Coupled sensitivity / specificity plot with 50g GCT and 140mg/dl threshold (not in at-risk groups)

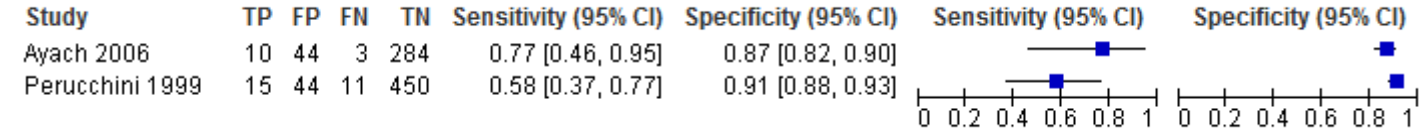


Figure 65 – Screening for gestational diabetes: Coupled sensitivity / specificity plot with 50g GCT and 130mg/dl threshold (at-risk group)

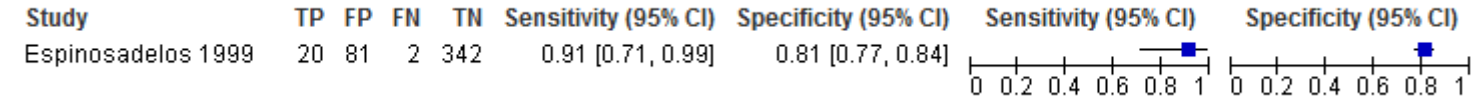


Figure 66 – Screening for gestational diabetes: Coupled sensitivity / specificity plot with 50g GCT and 135mg/dl threshold (at-risk group)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Espinosadelos 1999	20	59	3	363	0.87 [0.66, 0.97]	0.86 [0.82, 0.89]

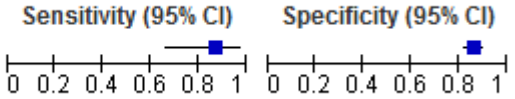


Figure 67 – Screening for gestational diabetes: Coupled sensitivity / specificity plot with 50g GCT and 140mg/dl threshold (at-risk groups)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Espinosadelos 1999	20	55	3	368	0.87 [0.66, 0.97]	0.87 [0.83, 0.90]
Weerakiet 2006	54	117	6	182	0.90 [0.79, 0.96]	0.61 [0.55, 0.66]

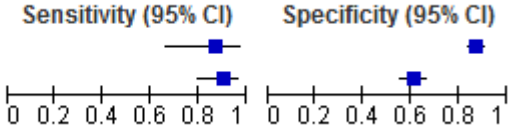


Figure 68 – Screening for gestational diabetes: Coupled sensitivity / specificity plot with 50g GCT and threshold range of 130-139mg/dl (at-risk group)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Thitadilok 1995	14	107	1	182	0.93 [0.68, 1.00]	0.63 [0.57, 0.69]

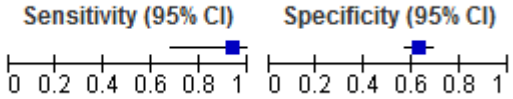
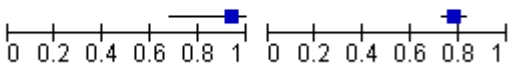


Figure 69 – Screening for gestational diabetes: Coupled sensitivity / specificity plot with 50g GCT and threshold range of 140-149mg/dl (at-risk group)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Thitadilok 1995	14	64	1	225	0.93 [0.68, 1.00]	0.78 [0.73, 0.83]



11.6. Hypothyroidism

11.6.1. Therapy for subclinical hypothyroidism

Figure 70 – Levothyroxine versus no treatment: Forest plot for miscarriage

	Levothyroxine		No treatment			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	Year
Negro 2005	8	24	11	21	46.0%	0.64 [0.32, 1.28]	2005
Negro 2006	2	57	8	58	9.9%	0.25 [0.06, 1.15]	2006
Negro 2010	2	43	7	34	9.9%	0.23 [0.05, 1.02]	2010
Kim 2011	0	17	4	12	2.8%	0.08 [0.00, 1.36]	2011
Jain 2013	6	50	17	50	31.4%	0.35 [0.15, 0.82]	2013
Total (95% CI)		**191**		**175**	**100.0%**	**0.41 [0.26, 0.66]**	
Total events	18		47				

Heterogeneity: Tau² = 0.00; Chi² = 3.91, df = 4 (P = 0.42); I² = 0%

Test for overall effect: Z = 3.68 (P = 0.0002)

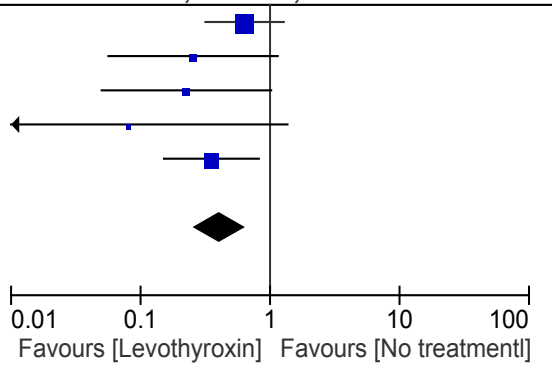


Figure 71 – Levothyroxine versus no treatment: Forest plot for preterm birth < 37 weeks

Study or Subgroup	Levothyroxine Events	Total	No treatment Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Negro 2006	4	55	13	50	38.4%	0.28 [0.10, 0.80]	2006
Negro 2010	1	43	2	34	7.7%	0.40 [0.04, 4.18]	2010
Kim 2011	0	17	1	12	4.4%	0.24 [0.01, 5.45]	2011
Jain 2013	5	44	13	33	49.5%	0.29 [0.11, 0.73]	2013
Total (95% CI)		**159**		**129**	**100.0%**	**0.29 [0.15, 0.56]**	
Total events	10		29				

Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 3 (P = 0.99); I² = 0%

Test for overall effect: Z = 3.72 (P = 0.0002)

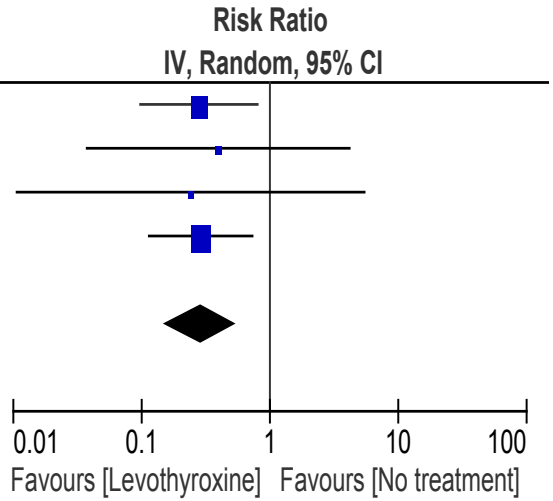


Figure 72 – Levothyroxine versus no treatment: Forest plot for very preterm Birth (<34 weeks)

Study or Subgroup	Levothyroxiine Events	Total	No treatment Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Negro 2010	2	43	3	34	65.8%	0.53 [0.09, 2.98]	2010
Kim 2011	0	17	1	12	34.2%	0.24 [0.01, 5.45]	2011
Total (95% CI)		**60**		**46**	**100.0%**	**0.43 [0.10, 1.91]**	
Total events	2		4				

Heterogeneity: Chi² = 0.19, df = 1 (P = 0.67); I² = 0%

Test for overall effect: Z = 1.11 (P = 0.27)

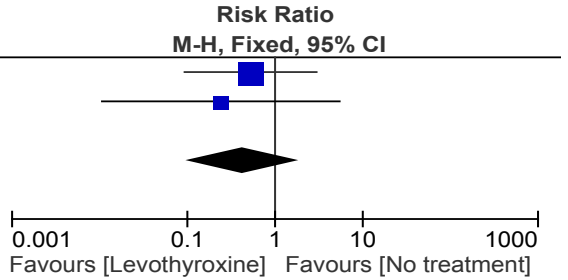


Figure 73 – Levothyroxine versus no treatment: Forest plot for preeclampsia

Study or Subgroup	Levothyroxine Events	Total	No treatment Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Negro 2006	2	55	3	50	58.5%	0.61 [0.11, 3.48]	2006
Negro 2010	2	43	2	34	41.5%	0.79 [0.12, 5.33]	2010
Total (95% CI)		**98**		**84**	**100.0%**	**0.68 [0.19, 2.47]**	
Total events	4		5				

Heterogeneity: Chi² = 0.04, df = 1 (P = 0.84); I² = 0%
Test for overall effect: Z = 0.58 (P = 0.56)

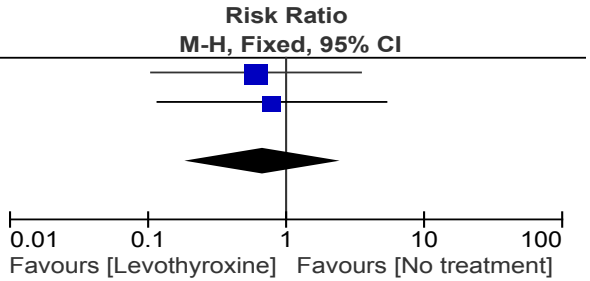


Figure 74 – Levothyroxine versus no treatment: Forest plot for gestational Hypertension

Study or Subgroup	Experimental Events	Total	No treatment Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Negro 2006	5	55	7	50	68.6%	0.65 [0.22, 1.92]	2006
Negro 2010	1	43	3	34	31.4%	0.26 [0.03, 2.42]	2010
Total (95% CI)		**98**		**84**	**100.0%**	**0.53 [0.20, 1.38]**	
Total events	6		10				

Heterogeneity: Chi² = 0.52, df = 1 (P = 0.47); I² = 0%
Test for overall effect: Z = 1.30 (P = 0.19)

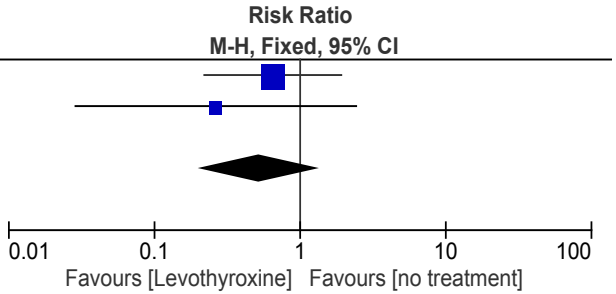


Figure 75 – Levothyroxine versus no treatment: Forest plot for NICU admission

Study or Subgroup	Levothyroxine Events	Total	No treatment Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Negro 2010	3	43	6	34	100.0%	0.35 [0.08, 1.52]	2010
Total (95% CI)		**43**		**34**	**100.0%**	**0.35 [0.08, 1.52]**	
Total events	3		6				

Heterogeneity: Not applicable
Test for overall effect: Z = 1.40 (P = 0.16)

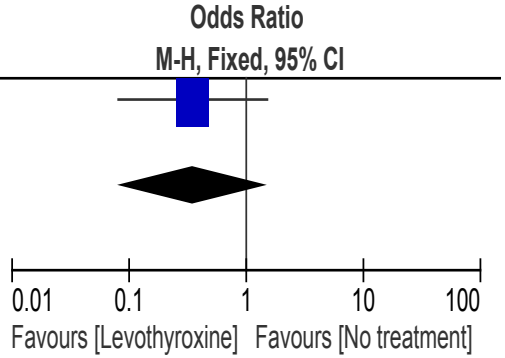
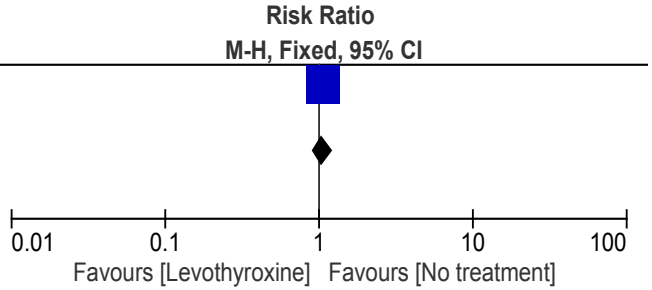


Figure 76 – Levothyroxine versus no treatment: Forest plot for low birth weight <2500 grams

Study or Subgroup	Levothyroxine Events	Total	No treatment Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Negro 2010	40	43	30	34	100.0%	1.05 [0.91, 1.22]	2010
Total (95% CI)		**43**		**34**	**100.0%**	**1.05 [0.91, 1.22]**	
Total events	40		30				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.70 (P = 0.48)



11.7. Vitamin D deficiency

11.7.1. Vitamin D supplementation versus no vitamin D supplementation

Figure 77 – Third trimester vitamin D vs. no vitamin D supplementation: Forest plot for gestational age at delivery (weeks)

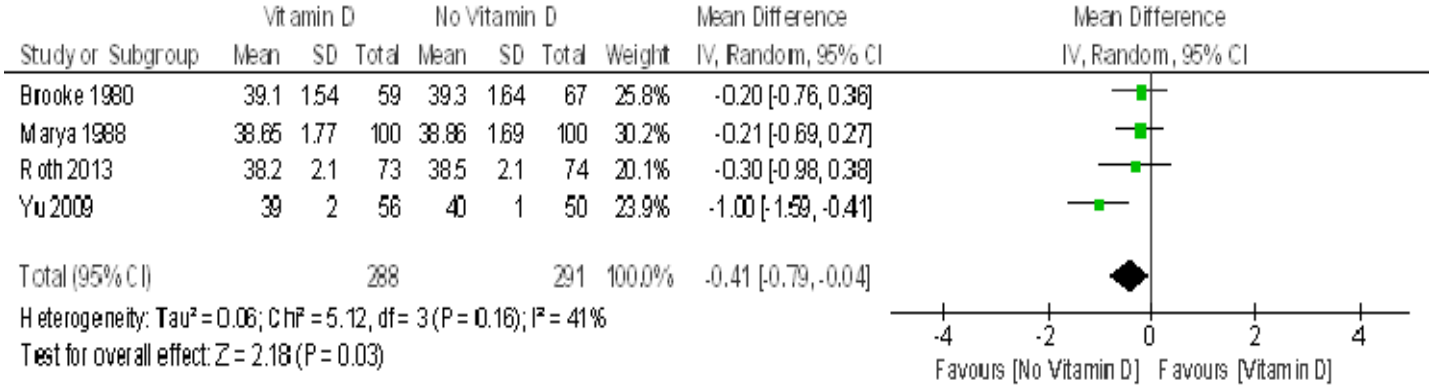


Figure 78 – Third trimester vitamin D vs. no vitamin D supplementation: Forest plot for low birth weight (various definitions)

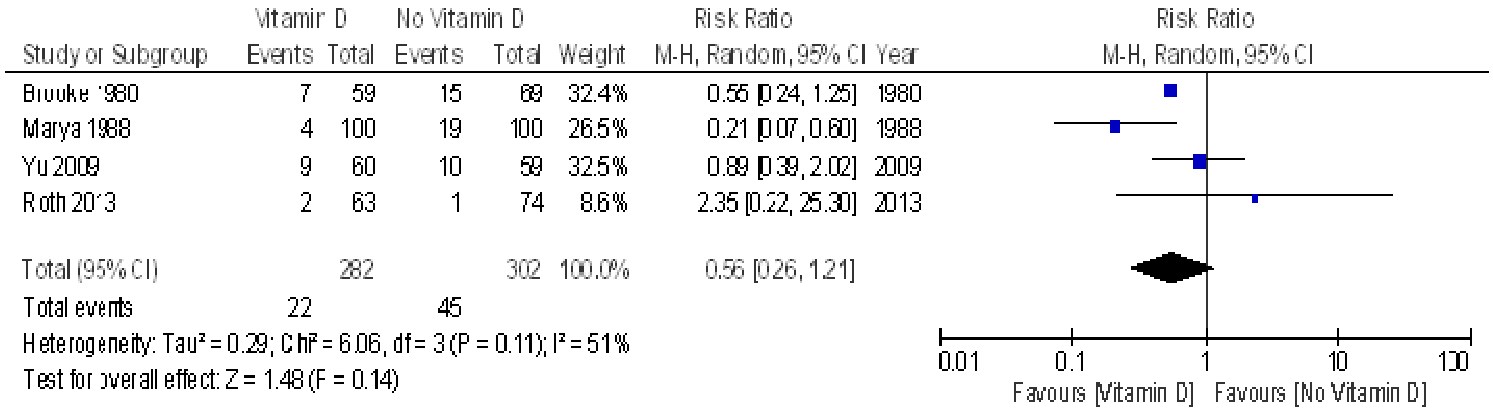


Figure 79 – Third trimester vitamin D vs. no vitamin D supplementation: Forest plot for birth weight <2500 grams

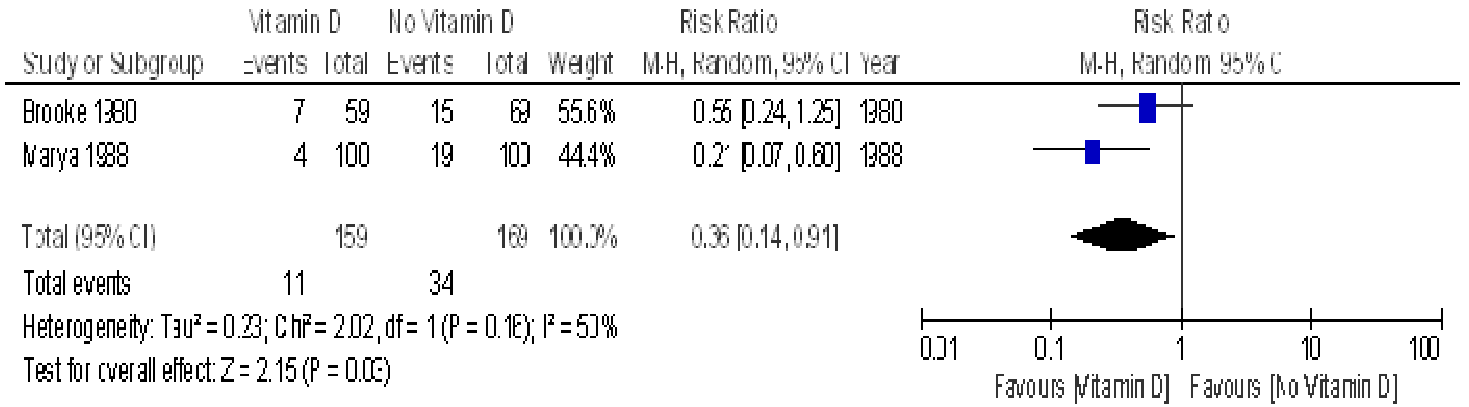


Figure 80 – Third trimester vitamin D vs. no vitamin D supplementation: Forest plot for birth length in centimetres

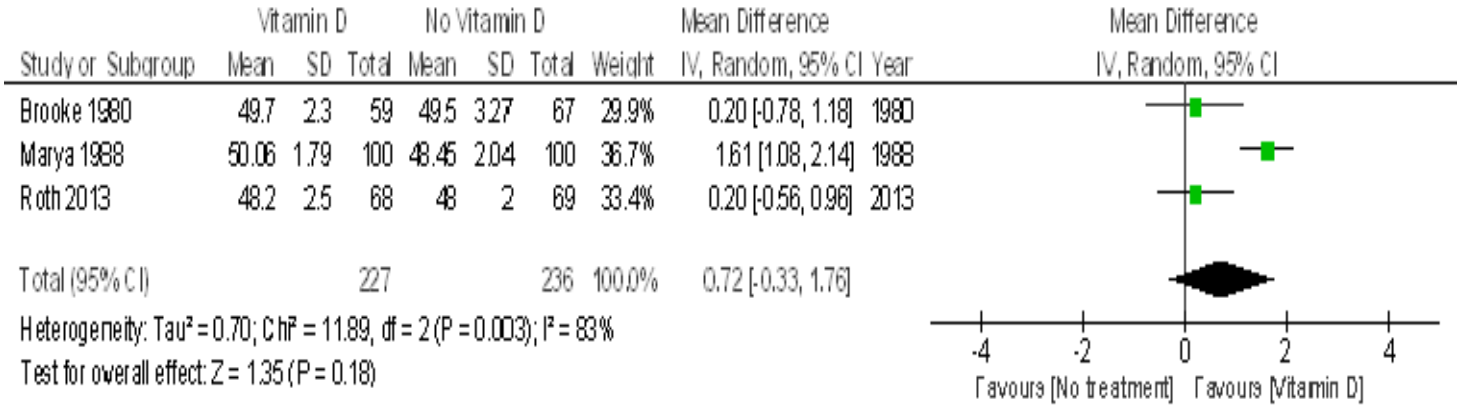


Figure 81 – Third trimester vitamin D vs. no vitamin D supplementation: Forest plot for head circumference (cm) at birth

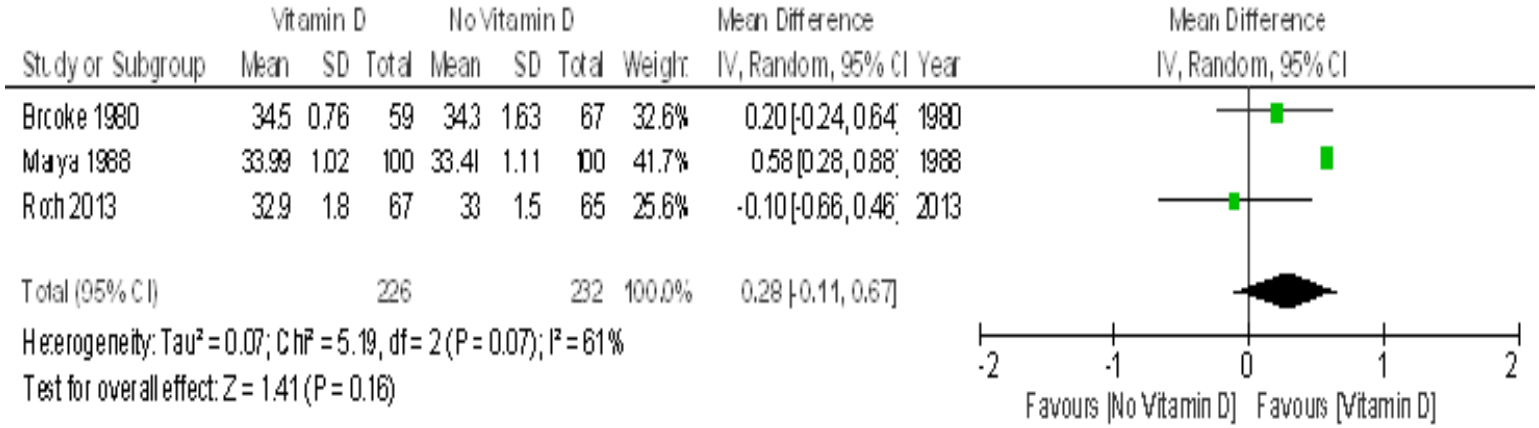
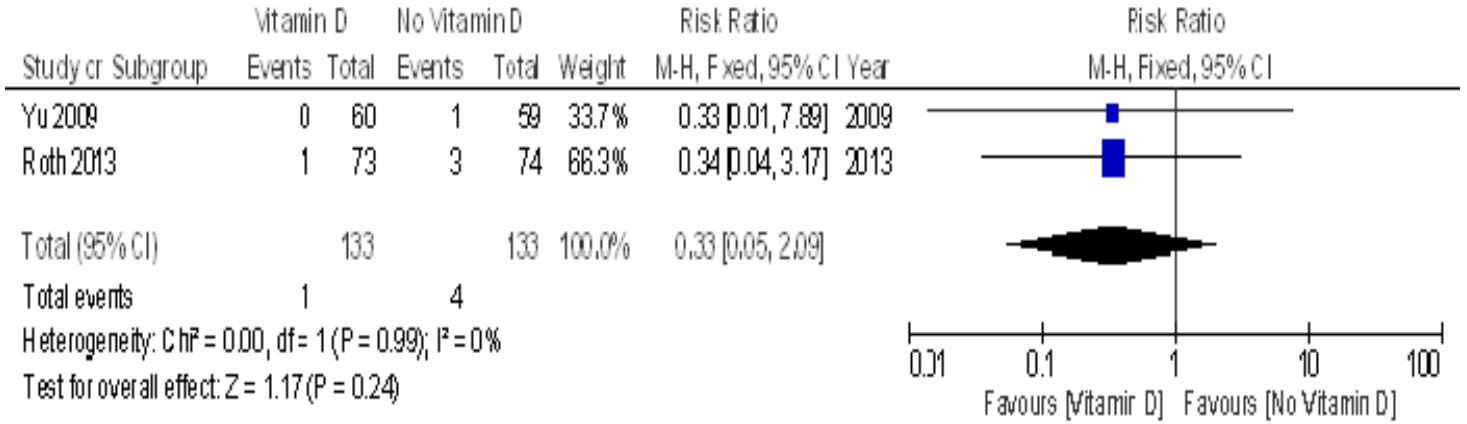


Figure 82 – Third trimester vitamin D vs. no vitamin D supplementation: Forest plot for neonatal death



11.8. Risk of preterm birth

11.8.1. Progesterone vs no progesterone

Figure 83 – Progesterone vs. no active intervention: Forest plot for perinatal mortality

Study or Subgroup	[Progesterone] Events	Total	[No active treatment] Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Hassan, 2011 (Vaginal 90mg/day)	8	235	11	223	55.8%	0.69 [0.28, 1.68]	2011
Grobman, 2012 (IM 250mg/wk)	10	327	9	330	44.2%	1.12 [0.46, 2.72]	2012
Total (95% CI)		**562**		**553**	**100.0%**	**0.88 [0.47, 1.65]**	
Total events	18		20				

Heterogeneity: Chi² = 0.57, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 0.40 (P = 0.69)

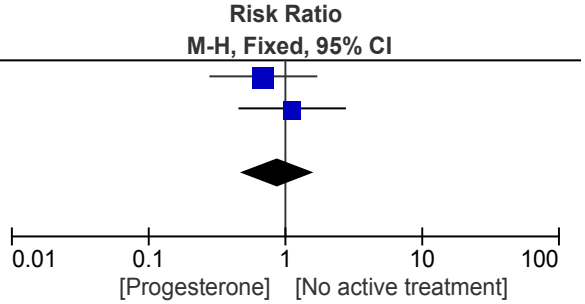


Figure 84 – Progesterone vs. no active intervention: Forest plot for neonatal death

Study or Subgroup	[Progesterone] Events	Total	[No active treatment] Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Year
Brenner 1962 (Oral, 20mg QID)	0	98	1	97	3.2%	0.13 [0.00, 6.75]	1962
Fonseca, 2007(Vaginal 200mg/day)	2	125	7	125	27.8%	0.32 [0.08, 1.20]	2007
Hassan, 2011 (Vaginal 90mg/day)	3	235	5	223	25.1%	0.57 [0.14, 2.31]	2011
Grobman, 2012 (IM 250mg/wk)	6	327	8	330	43.8%	0.75 [0.26, 2.17]	2012
Total (95% CI)		**785**		**775**	**100.0%**	**0.52 [0.26, 1.05]**	
Total events	11		21				

Heterogeneity: Chi² = 1.48, df = 3 (P = 0.69); I² = 0%
Test for overall effect: Z = 1.81 (P = 0.07)

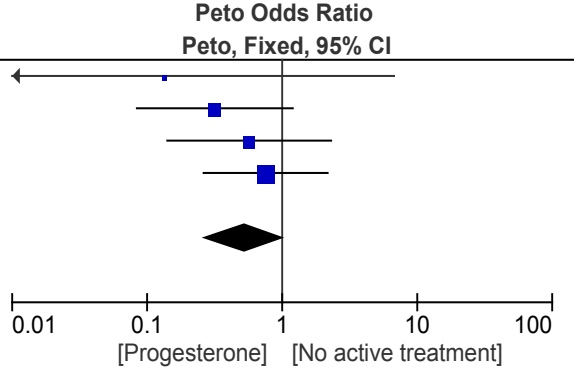


Figure 85 – Progesterone vs. no active intervention: Forest plot for still birth/fetal death

Study or Subgroup	[Progesterone] Events	Total	[No active treatment] Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Year
Brenner 1962 (Oral, 20mg QID)	1	98	0	97	5.3%	7.31 [0.15, 368.62]	1962
Fonseca, 2007(Vaginal 200mg/day)	1	125	1	125	10.6%	1.00 [0.06, 16.08]	2007
Hassan, 2011 (Vaginal 90mg/day)	5	235	6	223	57.5%	0.79 [0.24, 2.60]	2011
Grobman, 2012 (IM 250mg/wk)	4	327	1	330	26.6%	3.38 [0.58, 19.59]	2012
Total (95% CI)		**785**		**775**	**100.0%**	**1.34 [0.54, 3.31]**	
Total events	11		8				

Heterogeneity: Chi² = 2.58, df = 3 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.63 (P = 0.53)

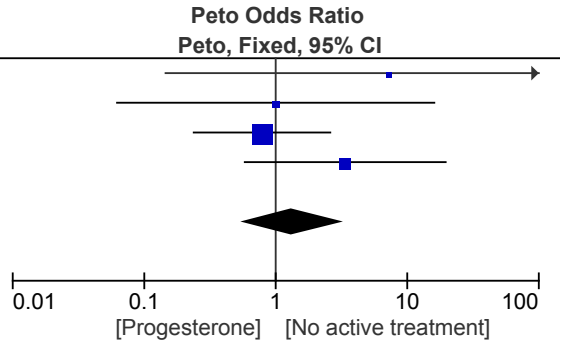


Figure 86 – Progesterone vs. no active intervention: Forest plot for abortion <20 weeks

Study or Subgroup	[Progesterone] Events	Total	[No active treatment] Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Year
Grobman, 2012 (IM 250mg/wk)	1	327	0	330	100.0%	7.46 [0.15, 375.83]	2012
Total (95% CI)		**327**		**330**	**100.0%**	**7.46 [0.15, 375.83]**	
Total events	1		0				

Heterogeneity: Not applicable
Test for overall effect: Z = 1.00 (P = 0.32)

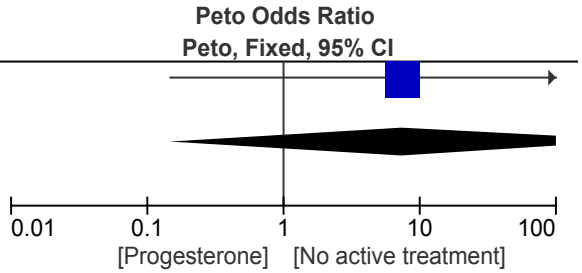


Figure 87 – Progesterone vs. no active intervention: Forest plot for seizure

Study or Subgroup	[Progesterone] Events	Total	[No active treatment] Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Year
Grobman, 2012 (IM 250mg/wk)	1	320	2	322	100.0%	0.52 [0.05, 4.97]	2012
Total (95% CI)		**320**		**322**	**100.0%**	**0.52 [0.05, 4.97]**	
Total events	1		2				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.57 (P = 0.57)

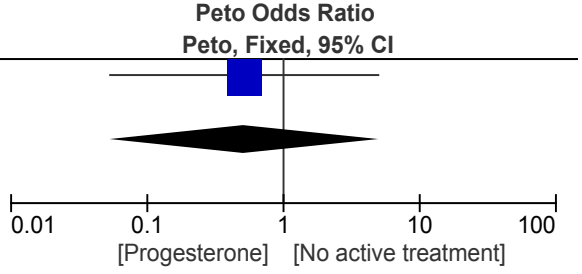


Figure 88 – Progesterone vs. no active intervention: Forest plot for neonatal survival free of morbidities

Study or Subgroup	[Progesterone] Events	Total	[No active treatment] Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Brenner 1962 (Oral, 20mg QID)	97	98	96	97	40.0%	1.00 [0.97, 1.03]	1962
Hassan, 2011 (Vaginal 90mg/day)	217	235	193	223	21.7%	1.07 [1.00, 1.14]	2011
Grobman, 2012 (IM 250mg/wk)	304	327	300	330	30.2%	1.02 [0.98, 1.07]	2012
van Os, 2014 (Vaginal 200mg/day)	37	39	32	35	8.2%	1.04 [0.92, 1.18]	2014
Total (95% CI)		**699**		**685**	**100.0%**	**1.02 [0.98, 1.06]**	
Total events	655		621				

Heterogeneity: Tau² = 0.00; Chi² = 6.39, df = 3 (P = 0.09); I² = 53%
Test for overall effect: Z = 1.20 (P = 0.23)

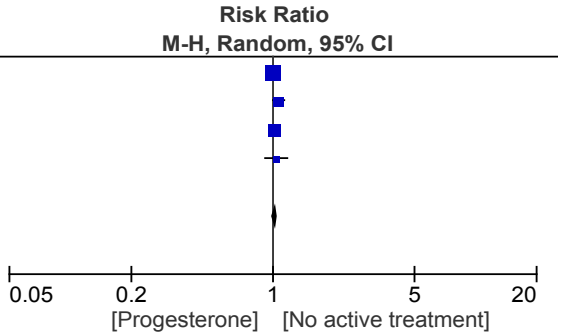


Figure 89 – Progesterone vs. no active intervention: Forest plot for major adverse neonatal outcomes (mortality and 4 common morbidities: intraventricular haemorrhage, necrotizing enterocolitis, respiratory distress syndrome, periventricular leukomalacia)

Study or Subgroup	[Progesterone] Events	Total	[No active treatment] Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Fonseca, 2007(Vaginal 200mg/day)	11	125	19	125	22.0%	0.58 [0.29, 1.17]	2007
Hassan, 2011 (Vaginal 90mg/day)	18	194	28	193	34.7%	0.64 [0.37, 1.12]	2011
Grobman, 2012 (IM 250mg/wk)	23	327	30	330	39.7%	0.77 [0.46, 1.30]	2012
van Os, 2014 (Vaginal 200mg/day)	2	39	3	35	3.6%	0.60 [0.11, 3.37]	2014
Total (95% CI)		**685**		**683**	**100.0%**	**0.67 [0.48, 0.93]**	
Total events	54		80				

Heterogeneity: Tau² = 0.00; Chi² = 0.50, df = 3 (P = 0.92); I² = 0%
Test for overall effect: Z = 2.36 (P = 0.02)

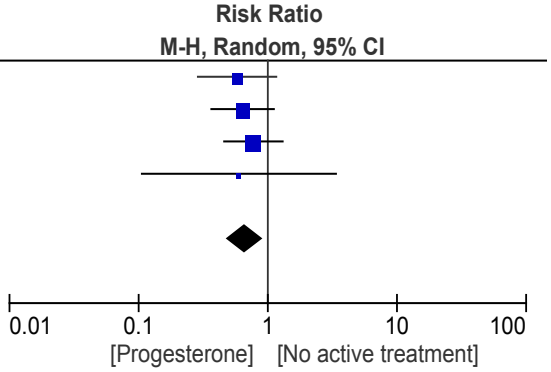


Figure 90 – Progesterone vs. no active intervention: Forest plot for PTB <37 weeks

Study or Subgroup	[Progesterone] Events	Total	[No active treatment] Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Moghtadaei, 2008 (IM 250mg/wk)	35	130	47	130	24.4%	0.74 [0.52, 1.07]	2008
Hassan, 2011 (Vaginal 90mg/day)	71	235	76	223	45.4%	0.89 [0.68, 1.16]	2011
Grobman, 2012 (IM 250mg/wk)	54	327	55	330	27.5%	0.99 [0.70, 1.40]	2012
van Os, 2014 (Vaginal 200mg/day)	6	39	5	35	2.7%	1.08 [0.36, 3.22]	2014
Total (95% CI)		**731**		**718**	**100.0%**	**0.88 [0.74, 1.05]**	
Total events	166		183				

Heterogeneity: Tau² = 0.00; Chi² = 1.41, df = 3 (P = 0.70); I² = 0%
Test for overall effect: Z = 1.39 (P = 0.17)

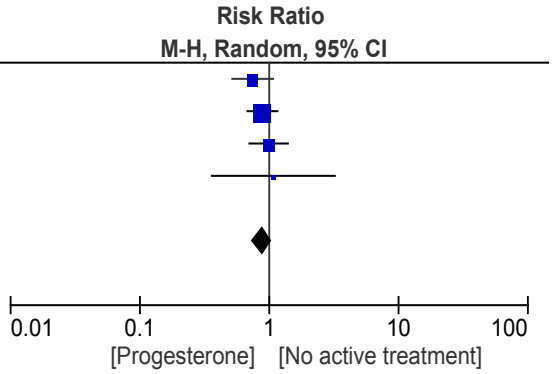


Figure 91 – Progesterone vs. no active intervention: Forest plot for PTB <34 weeks

Study or Subgroup	[Progesterone] Events	Total	[No active treatment] Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Fonseca, 2007(Vaginal 200mg/day)	24	125	43	125	43.1%	0.56 [0.36, 0.86]	2007
Grobman, 2012 (IM 250mg/wk)	41	327	48	330	52.4%	0.86 [0.58, 1.27]	2012
van Os, 2014 (Vaginal 200mg/day)	3	39	4	35	4.4%	0.67 [0.16, 2.80]	2014
Total (95% CI)		**491**		**490**	**100.0%**	**0.71 [0.52, 0.96]**	
Total events	68		95				

Heterogeneity: Tau² = 0.01; Chi² = 2.16, df = 2 (P = 0.34); I² = 7%
Test for overall effect: Z = 2.25 (P = 0.02)

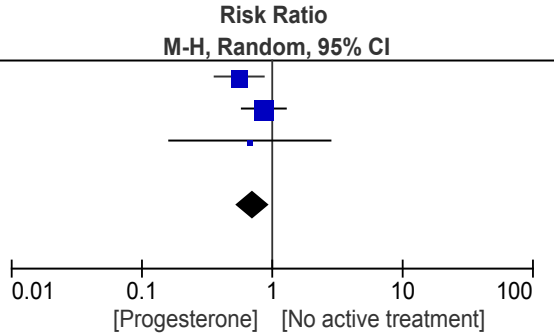
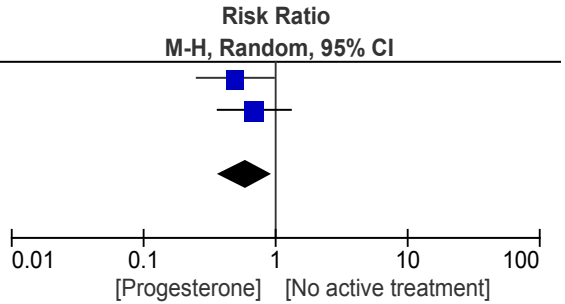


Figure 92 – Progesterone vs. no active intervention: Forest plot for PTB <28 weeks

Study or Subgroup	[Progesterone] Events	Total	[No active treatment] Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Hassan, 2011 (Vaginal 90mg/day)	12	235	23	223	47.3%	0.50 [0.25, 0.97]	2011
Grobman, 2012 (IM 250mg/wk)	15	327	22	330	52.7%	0.69 [0.36, 1.30]	2012
Total (95% CI)		**562**		**553**	**100.0%**	**0.59 [0.37, 0.94]**	
Total events	27		45				

Heterogeneity: Tau² = 0.00; Chi² = 0.48, df = 1 (P = 0.49); I² = 0%
Test for overall effect: Z = 2.24 (P = 0.03)



11.8.2. Cerclage vs no cerclage

Figure 93 – Cerclage (+ modified bed rest +/- progesterone) vs. bed rest (+/- progesterone): Forest plot for total major maternal adverse event

Study or Subgroup	Cerclage Events	Total	No cerclage Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Skupski 2014 (cerlage+mBR+/-P vs. BR+/-P)	3	112	0	55	100.0%	4.52 [0.40, 50.99]
Total (95% CI)		**112**		**55**	**100.0%**	**4.52 [0.40, 50.99]**
Total events	3		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.22 (P = 0.22)

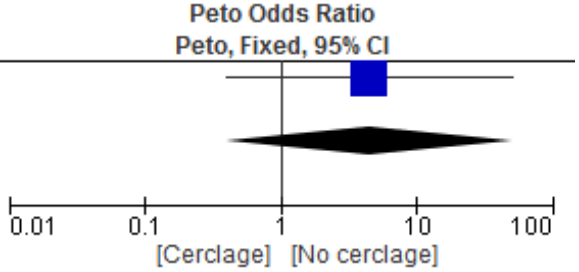


Figure 94 – Cerclage vs no cerclage: Forest plot for PTB <37 weeks gestation

Study or Subgroup	Cerclage Events	Cerclage Total	No cerclage Events	No cerclage Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Skupski 2014 (cerlage+mBR+/-P vs. BR+/-P)	34	112	29	55	30.0%	0.58 [0.40, 0.84]	
Hassan 2001 (Cerclage vs. no active treatment)	19	25	30	45	33.9%	1.14 [0.84, 1.54]	
Sakai 2006 (BR+cerclage vs. BR)	74	165	45	81	36.1%	0.81 [0.62, 1.04]	
Total (95% CI)		**302**		**181**	**100.0%**	**0.82 [0.57, 1.18]**	
Total events	127		104				

Heterogeneity: Tau² = 0.08; Chi² = 8.38, df = 2 (P = 0.02); I² = 76%
Test for overall effect: Z = 1.07 (P = 0.29)

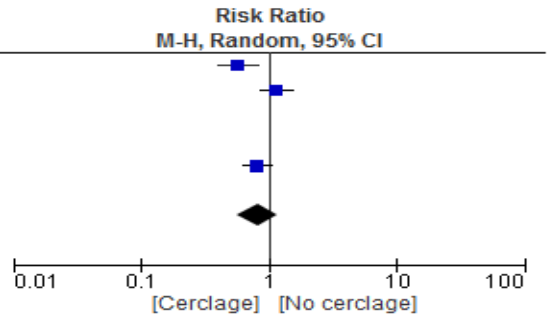


Figure 95 – Cerclage vs. no cerclage: Forest plot for PTB <34 weeks gestation

Study or Subgroup	Cerclage Events	Cerclage Total	No cerclage Events	No cerclage Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Sakai 2006 (BR+cerclage vs. BR)	5	124	6	44	43.8%	0.30 [0.09, 0.92]	
Hassan 2001 (Cerclage vs. no active treatment)	17	25	24	45	56.2%	1.27 [0.87, 1.87]	
Total (95% CI)		**149**		**89**	**100.0%**	**0.67 [0.15, 3.03]**	
Total events	22		30				

Heterogeneity: Tau² = 1.01; Chi² = 6.40, df = 1 (P = 0.01); I² = 84%
Test for overall effect: Z = 0.52 (P = 0.61)

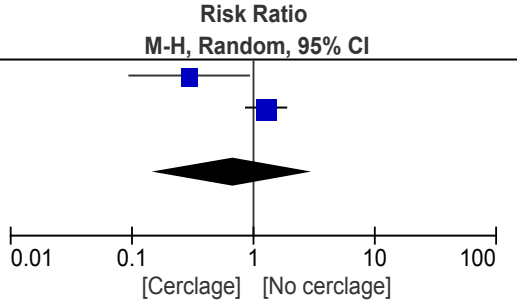
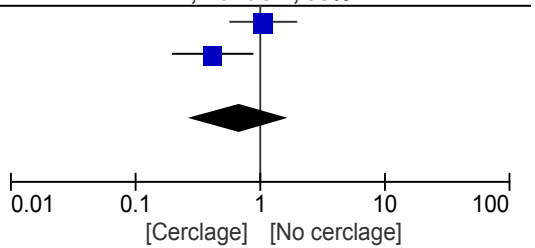


Figure 96 – Cerclage vs. no cerclage: Forest plot for PTB <28 weeks gestation

Study or Subgroup	Cerclage Events	Cerclage Total	No cerclage Events	No cerclage Total	Weight	Risk Ratio M-H, Random, 95% CI
Hassan 2001 (Cerclage vs. no active treatment)	10	25	17	45	52.5%	1.06 [0.58, 1.95]
Skupski 2014 (cerlage+mBR+/-P vs. BR+/-P)	11	112	13	55	47.5%	0.42 [0.20, 0.87]
Total (95% CI)		**137**		**100**	**100.0%**	**0.68 [0.27, 1.71]**
Total events	21		30			

Heterogeneity: Tau² = 0.33; Chi² = 3.76, df = 1 (P = 0.05); I² = 73%
Test for overall effect: Z = 0.82 (P = 0.41)



11.9. Pregnancies that passed their due date

Figure 97 – Various surveillance interventions for prolonged pregnancy: Forest plot for neonatal death

[Test 1: (CTG+ fetal movement) +/- Test 2: partial BP* if non-reactive Test 1] vs. {[Test 1: (CTG+ fetal movement) + Test 2: AFV] +/- Test 3: partial BP* if non-reactive Test 1}

Routine scan (fetometry + AFI at 41 week) +/- uabf if abnormal fetometry or AFI vs. Indicated scan (fetometry) +/- uabf if abnormal fetometry

*real time ultrasound for fetal breathing movement, fetal movement and AFV

Color code:

Blue frame: Observational evidence

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Eden 1982	2	398	0	109	25.8%	1.38 [0.07, 28.50]
Lindqvist 2014	3	1444	2	2650	74.2%	2.75 [0.46, 16.46]
Total (95% CI)		**1842**		**2759**		
Total events	5		2			

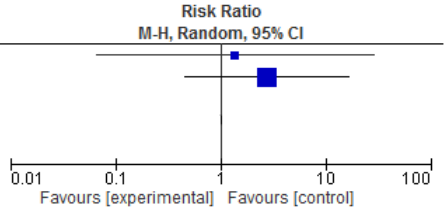
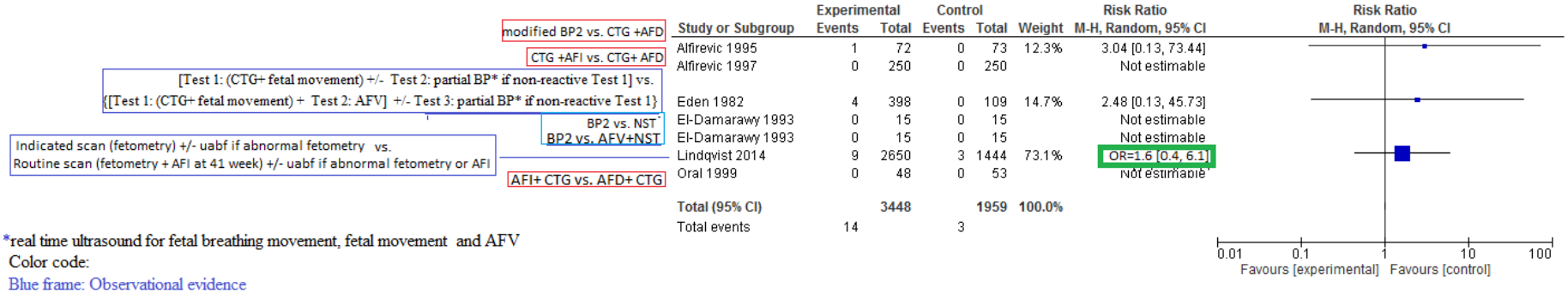


Figure 98 – Various surveillance interventions for prolonged pregnancy: Forest plot for perinatal death



*real time ultrasound for fetal breathing movement, fetal movement and AFV

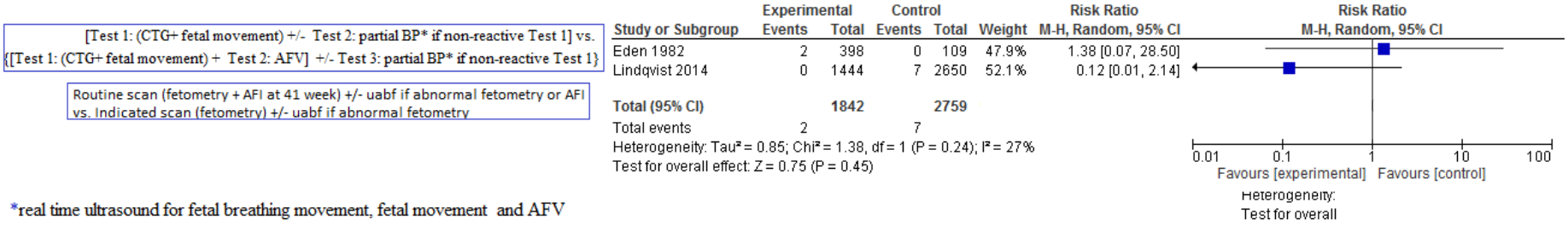
Color code:

Blue frame: Observational evidence

Red frame: RCT evidence

Green frame: Adjusted OR from observational study

Figure 99 – Various surveillance interventions for prolonged pregnancy: Forest plot for still birth



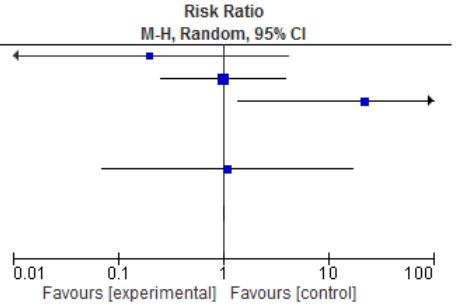
*real time ultrasound for fetal breathing movement, fetal movement and AFV

Color code:

Blue frame: Observational evidence

Figure 100 – Various surveillance interventions for prolonged pregnancy: Forest plot for NICU admission

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
modified BP2 vs. CTG +AFD						
CTG +AFI vs. CTG+ AFD						
[Test 1: (CTG+ fetal movement) +/- Test 2: partial BP* if non-reactive Test 1] vs. {[Test 1: (CTG+ fetal movement) + Test 2: AFV] +/- Test 3: partial BP* if non-reactive Test 1}						
Alfirevic 1995	0	72	2	73	20.5%	0.20 [0.01, 4.15]
Alfirevic 1997	4	250	4	250	34.6%	1.00 [0.25, 3.95]
Eden 1982	40	398	0	109	22.3%	22.33 [1.38, 360.26]
resucitation/incubation requirement; we considered it as proxy for NICU						
AFI+ CTG vs. AFD+ CTG						
Oral 1999	1	48	1	53	22.6%	1.10 [0.07, 17.17]
Total (95% CI)		**768**		**485**		
Total events	45		7			



*real time ultrasound for fetal breathing movement, fetal movement and AFV

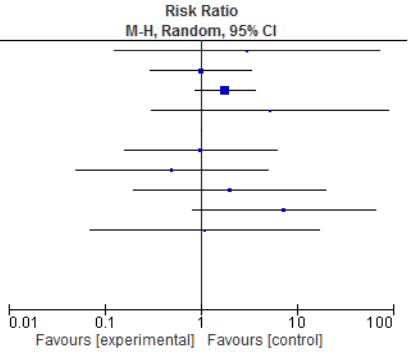
Color code:

Blue frame: Observational evidence

Red frame: RCT evidence

Figure 101 – Various surveillance interventions for prolonged pregnancy: Forest plot for Apgar score (various cut offs)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
modified BP2 vs. CTG +AFD						
Apgar<7 at 5 minutes						
Alfirevic 1995	1	72	0	73	1.7%	3.04 [0.13, 73.44]
CTG +AFI vs. CTG+ AFD						
Apgar<7 at 5 minutes						
Alfirevic 1997	5	250	5	250	11.4%	1.00 [0.29, 3.41]
[Test 1: (CTG+ fetal movement) +/- Test 2: partial BP* if non-reactive Test 1] vs. {[Test 1: (CTG+ fetal movement) + Test 2: AFV] +/- Test 3: partial BP* if non-reactive Test 1}						
Apgar at 5 minutes						
Eden 1982	52	398	8	109	33.6%	1.78 [0.87, 3.63]
Apgar<7 at 1 minute						
Eden 1982	9	398	0	109	2.1%	5.24 [0.31, 89.29]
BP2 vs. NST						
BP2 vs. AFV+NST						
NST vs. AFV+NST						
Apgar<7						
El-Damarawy 1993	2	15	2	15	5.1%	1.00 [0.16, 6.20]
El-Damarawy 1993	1	15	2	15	3.3%	0.50 [0.05, 4.94]
El-Damarawy 1993	2	15	1	15	3.3%	2.00 [0.20, 19.78]
Routine scan (fetometry + AFI at 41 week) +/- uabf if abnormal fetometry or AFI vs. Indicated scan (fetometry) +/- uabf if abnormal fetometry						
Apgar<4 at 5 minutes						
Lindqvist 2014	4	1444	1	2650	3.6%	7.34 [0.82, 65.62]
AFI+ CTG vs. AFD+ CTG						
Apgar<7 at 5 minutes						
Oral 1999	1	48	1	53	2.3%	1.10 [0.07, 17.17]
Total (95% CI)		**3053**		**3398**		
Total events	129		28			



*real time ultrasound for fetal breathing movement, fetal movement and AFV

Color code:

Blue frame: Observational evidence

Red frame: RCT evidence

Figure 102 – Routine scan versus indicated scan for prolonged pregnancy: Forest plot for hypoxic ischemic encephalopathy grades 2 and 3

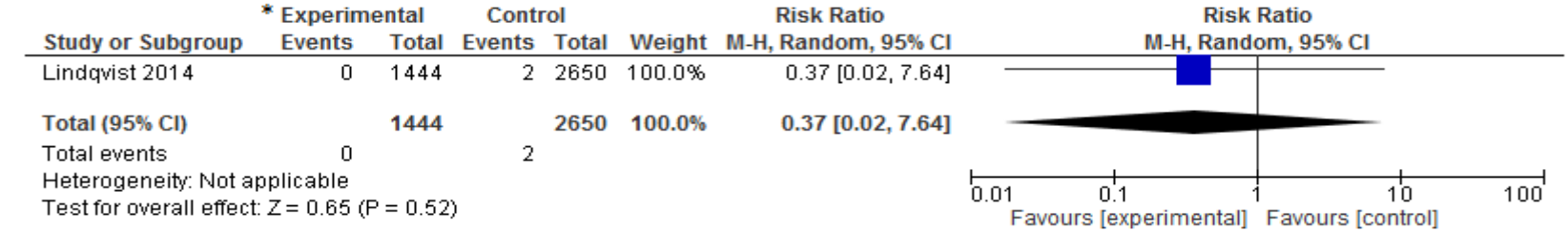


Figure 103 – Routine scan versus indicated scan for prolonged pregnancy: Forest plot for cerebral palsy

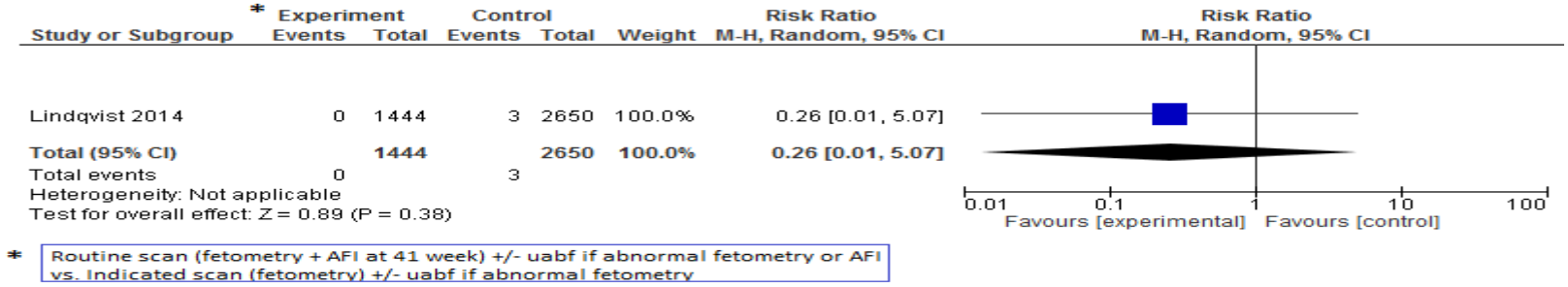
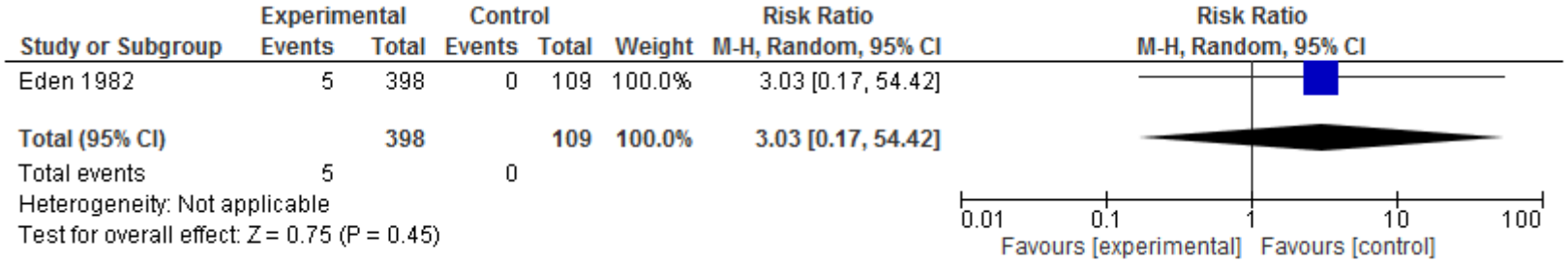


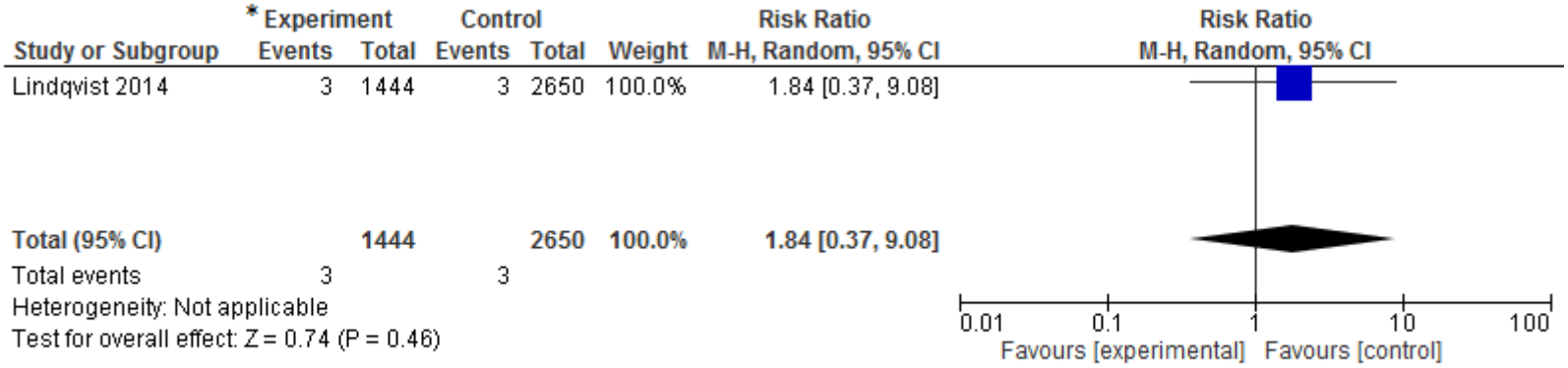
Figure 104 – [Test 1:(CTG+fetal movement)] +/- Test 2: partial BP if non reactive test 1 versus: [Test 1:(CTG+fetal movement) +Test2: AFV]+/- Test 2: partial BP if non reactive test 1 for prolonged pregnancy: Forest plot for meconium aspiration syndrome



[Test 1: (CTG+ fetal movement) +/- Test 2: partial BP* if non-reactive Test 1] vs.
{[Test 1: (CTG+ fetal movement) + Test 2: AFV] +/- Test 3: partial BP* if non-reactive Test 1}

*real time ultrasound for fetal breathing movement, fetal movement and AFV

Figure 105 – Routine scan versus indicated scan for prolonged pregnancy: Forest plot for neonatal convulsion



* Routine scan (fetometry + AFI at 41 week) +/- uabf if abnormal fetometry or AFI vs. Indicated scan (fetometry) +/- uabf if abnormal fetometry

Figure 106 – Routine scan versus indicated scan for prolonged pregnancy: Forest plot for cerebral haemorrhage

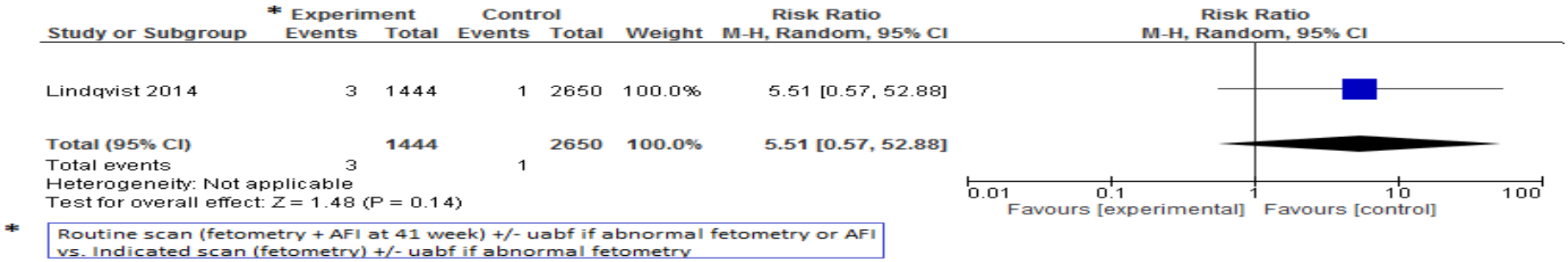


Figure 107 – Routine scan versus indicated scan for prolonged pregnancy: Forest plot for cerebral damage

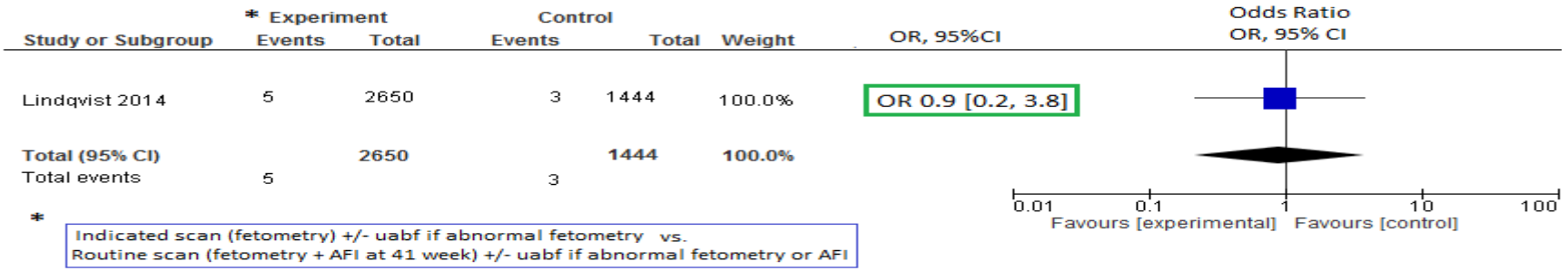


Figure 108 – Various surveillance interventions for prolonged pregnancy: Forest plot for instrumental delivery

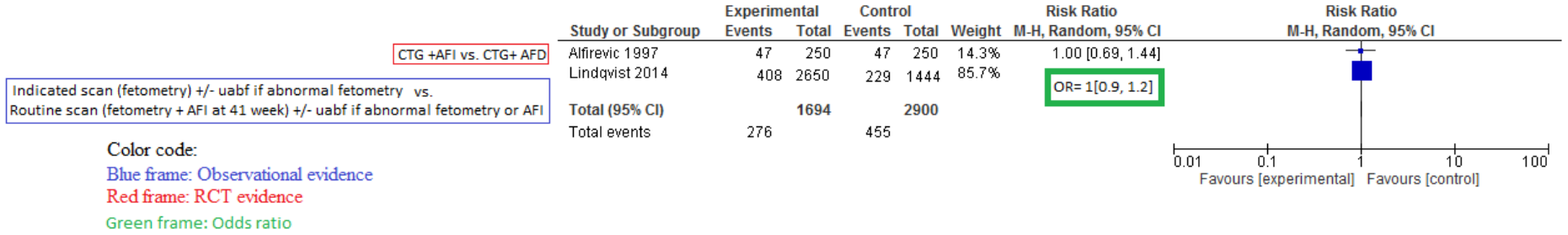


Figure 109 – CTG+ AFI versus CTG+AFD for prolonged pregnancy: Forest plot for C-section due to fetal distress

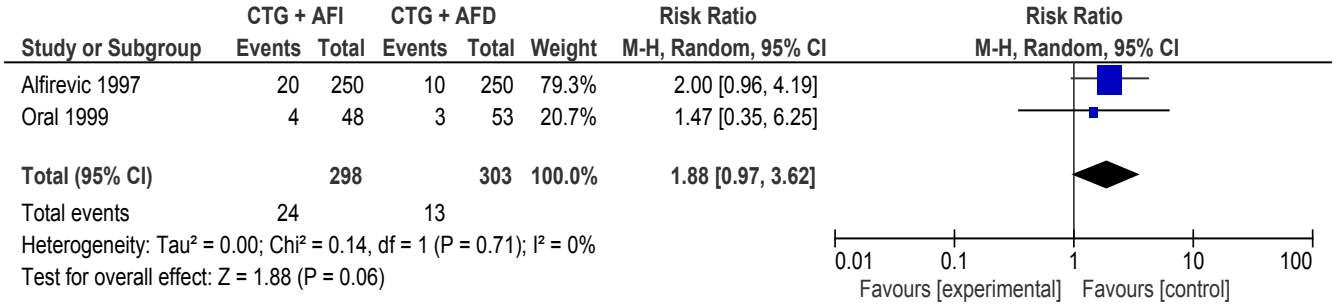


Figure 110 – BP2 versus CTG+AFD for prolonged pregnancy: Forest plot for C-section due to fetal distress

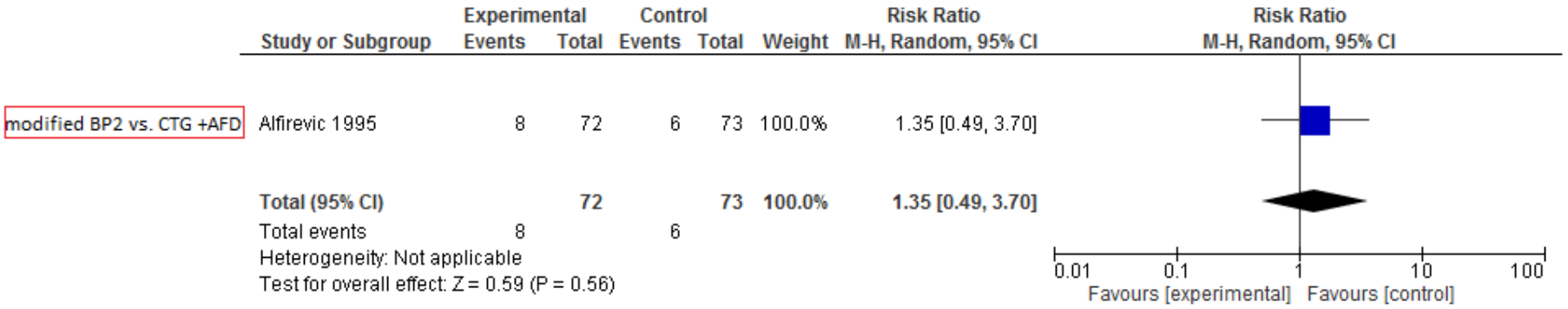


Figure 111 – Various surveillance interventions for prolonged pregnancy: Forest plot for C-section for reasons other than fetal distress or lack of progression of labor

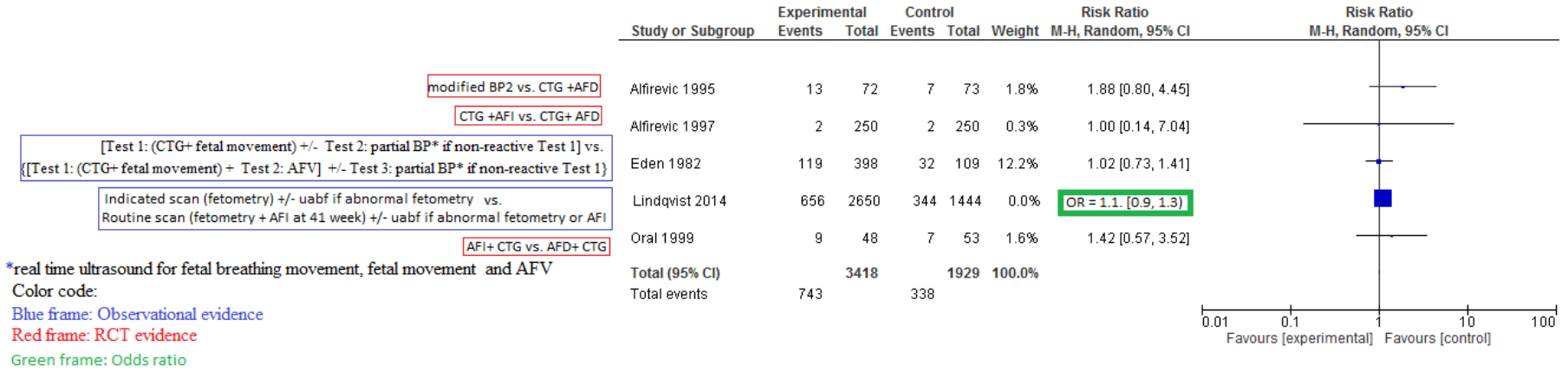
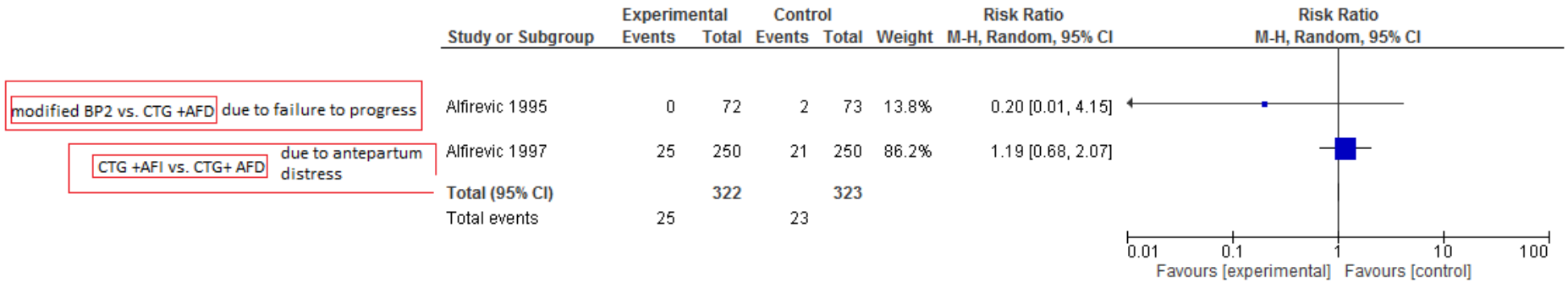


Figure 112 – Various interventions versus CTG+AFD for prolonged pregnancy: Forest plot for C-section due to failure to progress or ante partum distress



12. EXCLUDED STUDIES

Available on request.

13. EXAMPLE OF LIME SURVEY

Hepatitis B

* *9 S4Q1*

En 2004, le KCE formulait la recommandation suivante (Grade A: Recommendation directly based on level 1 evidence): "La détection de l'hépatite B avant ou au commencement de la grossesse est recommandée afin de permettre un traitement efficace du nouveau-né d'une mère contaminée."

En 2014, le guideline australien recommandait (Grade A: Body of evidence can be trusted to guide practice): "Routinely offer and recommend hepatitis B virus testing at the first antenatal visit as effective postnatal intervention can reduce the risk of mother-to-child transmission."

Il ressort de la littérature utilisée par le guideline australien que:

- Screening of all pregnant women for hepatitis B is recommended in the United Kingdom (NICE 2008) and the United States (Mast et al 2005; Lin & Vickery 2009; USPSTF 2009). The Australian Immunisation Handbook, while making recommendations on vaccination rather than screening, notes that routine antenatal screening for hepatitis B (ATAGI 2009): "is essential for preventing babies from becoming carriers of hepatitis B; and enables appropriate follow-up and management of the woman, identification of the immune status of other household members, and protection of those who are susceptible".
- Screening of all women is supported by the findings of observational studies into selective screening:
  - screening using risk factors to identify 'high-risk' women for HbsAg would miss about half of all pregnant women with HbsAg infection (Summers et al. 1987);
  - of women offered examination for hepatitis B at 18 weeks pregnancy (n=4,098), one third of women at risk of hepatitis B were not identified by selective screening (Jensen et al. 2003); and
  - universal screening resulted in an estimated detection of 50 additional pregnant women carrying hepatitis B each year who would not have been detected through selective screening (Cowan et al. 2006).
- A recent systematic review (Lin & Vickery 2009) found no new evidence on the benefits or harms of testing for hepatitis B infection in pregnant women.

Depuis 1999, la Belgique procède à la vaccination systématique des nourrissons et des pré-adolescents (11-12 ans) contre l'hépatite B.

Le KCE propose en conséquence de garder la recommandation KCE 2004, mais en y ajoutant la prise en compte du statut immunitaire: "Un examen sérologique de détection des anticorps contre l'hépatite B est recommandé à toutes les femmes dont le statut immunitaire n'est pas connu, afin de pouvoir identifier les femmes non immunisées face à l'hépatite B, les sensibiliser à ce problème et permettre un traitement efficace du nouveau-né d'une mère contaminée."

Dans quelle mesure êtes-vous d'accord avec cette proposition ?

Veuillez sélectionner une réponse ci-dessous

- ○ Je ne suis pas du tout d'accord
- ○ Je ne suis plutôt pas d'accord
- ○ Je suis plutôt d'accord
- ○ Je suis tout à fait d'accord

Hepatitis B

* *10 S4Q1a* Veuillez justifier et formuler éventuellement une proposition.

11 S4Q1b

Jugez-vous que cette recommandation doit être 'forte' ou 'faible' ?

Veuillez sélectionner une réponse ci-dessous

- ○ Recommandation forte
- ○ Recommandation faible
- ◉ Sans réponse

Recommandation forte, lorsque les effets bénéfiques de l'intervention l'emportent très certainement sur les risques (*l'intervention est à mettre en pratique*) ou les effets indésirables de l'intervention l'emportent très certainement sur les bénéfices attendus (*l'intervention est à éviter*).

Recommandation faible, lorsque les effets bénéfiques de l'intervention l'emportent probablement sur les risques (*l'intervention est probablement à mettre en pratique*) ou les effets indésirables de l'intervention l'emportent probablement sur les bénéfices attendus (*l'intervention est probablement à éviter*)

12 S4Q1c Commentez votre réponse si vous le souhaitez

14. SUMMARY OF UPDATING PROCESS OF 2004 RECOMMENDATIONS

The process is presented below separately for each 24 clinical questions. Two questions are presented in the same title: blood group and rhesus, with atypical red cell antibodies.

14.1. Number of appointements

Antenatal visits:

What is the **optimal number of antenatal visits** to be scheduled considering adverse maternal or perinatal outcomes and women's preference?

a. For a woman's first pregnancy without complications?
b. For subsequent uncomplicated pregnancies?

KCE 2004 recommendation (Grade B : Recommendation directly based on level 2 evidence or issued from a guideline based on level 1 evidence)

- Pour une femme qui est primipare en cas d'absence de complication, un programme de 10 rendez-vous devrait être proposé. Pour une femme multipare en cas d'absence de complication, un programme de 7 rendez-vous devrait être proposé.
- Voor een primipara zonder complicaties is een programma van 10 raadplegingen aan te bevelen. Voor een multipara zonder complicaties is een programma van 7 raadplegingen aan te bevelen.

Literature quoted by EAC 2014 guideline (1 level 1 & 3 level IV studies)

- The NICE guidelines cited two systematic reviews that included the same randomised controlled trials (RCTs) (n=57 418) (Villar and Khan-Neelofur 2003; Carroli et al. 2001) and concluded that it is likely that antenatal care for women without risk or complications can be provided with fewer visits (between 4 and 9 visits) than traditionally offered (13-14 visits).
- A Cochrane review (Dowswell et al. 2010), which included studies in high-, middle- and low-income countries, found no strong evidence of differences in the number of preterm births or low birth weight babies between groups receiving a reduced number of antenatal visits (8 visits in high-income countries and fewer than 5 visits in low-income countries) compared with standard care (13-14 visits). However, there was some evidence that in low- and middle-income countries perinatal mortality may be increased with reduced visits. The number of inductions of labour and births by caesarean section were similar in women receiving reduced visits compared with standard care.
- Evidence concerning women's preferences about the number of antenatal visits suggests that: for some women, the gap between visits was perceived as too long when the number of visits was lower than that traditionally offered (Dowswell et al. 2010); women who were satisfied with a reduced number of antenatal visits were more likely to have a caregiver who both listened and encouraged them to ask questions than women who were not satisfied with reduced schedules (Clemet et al 1996); and women who were over 35 years of age, had previous pregnancies, were less educated or had more than two children preferred fewer appointments, whereas women who were less than 25 years of age, single or had a prior adverse pregnancy history indicated a preference for more appointments than the standard schedule (Hildingsson et al. 2002).

EAC 2014 recommendation (Grade B : Body of evidence can be trusted to guide practice in most situations)

- Determine the schedule of antenatal visits based on the individual woman's needs. For a woman's first pregnancy without complications, a schedule of ten visits should be adequate. For subsequent uncomplicated pregnancies, a schedule of seven visits should be adequate.

KCE proposition to the GDG: To keep the 2004 recommendation, without modification of content.

Results of the GDG Lime survey at the beginning of June 2014 (11 respondents)

- Totally agree: 7; somewhat agree:4; rather not agree:0; not agree at all: 0
- Strong recommendation: 6; weak recommendation: 5

GDG comments in the Lime survey at the beginning of June 2014: None

GDG comments during the GDG meeting 16/06/2014

- This recommendation concerns only low risk women
- Emergency encounter is obviously not taken into account
- **Conclusion: recommendation KCE 2004 unchanged**

KCE proposition of 2015 recommendation (Strong recommendation)

- Offer to pregnant women who do not present with complications that they take part in a programme with either 10 appointments if this is their first pregnancy or 7 appointments if they have already given birth.

GDG comments by e-mail during February 2015:

- 'Ne présentant pas de facteur de risque' conviendrait mieux il me semble car on propose le programme en début de grossesse. Ensuite on l'adapte en fonction de l'apparition de complications; zwangere vrouwen zonder risicoprofiel ipv zonder complicaties
- Ik zou specifieren: 10 of 7 raadplegingen inclusief echografieën

KCE 2015 recommendation before stakeholders meeting (Strong recommendation)

- Offer to pregnant women without risk factors a programme with either 10 appointments if this is their first pregnancy or 7 appointments if they have already given birth.

Results of the stakeholders Lime survey in March 2015 (6 respondents):

- Completely agree: 2; somewhat agree: 3; non applicable: 1
- Attention qu'il y a à l'étude dans plusieurs maternités l'organisation de consultations prénatale en pyramide inversée. Qui consiste à déterminer la majorité des risques à la première consultation et qui en l'absence de risques diminuerait les consultations prénatales à 3.

Stakeholders comments during the stakeholders meeting 25/03/2014: None

KCE 2015 recommendation: Strong recommendation, Level of evidence A (*Level of evidence from Australian 2014 guideline: A=One or more level I studies with a low risk of bias or several level II studies with low risk of bias)*

[KCE 2004]

- Offer to pregnant women without risk factors a program with either 10 appointments if this is their first pregnancy or 7 appointments if they have already given birth.
- Stel aan zwangere vrouwen zonder risicofactoren een programma voor van 10 afspraken als ze voor het eerst zwanger zijn en van 7 afspraken bij vrouwen die reeds eerder bevallen zijn.
- Proposez aux femmes enceintes ne présentant pas de facteurs de risque un programme de 10 rendez-vous si elles sont primipares et de 7 rendez-vous si elles sont multipares.

14.2. BMI

BMI

Should **weight and BMI** be regularly monitored in all Belgian low-risk pregnant women?

KCE 2004 recommendation BMI 1 (Grade B: Recommendation directly based on level 2 evidence or issued from a guideline based on level 1 evidence)

- Il est recommandé de peser la patiente et de calculer son BMI avant la grossesse ou à la 1e consultation. Un BMI <18 ou >35 est considéré comme un facteur de risque.
- Het is aan te bevelen om de vrouw te wegen en haar BMI te berekenen voor de zwangerschap of tijdens de eerste raadpleging in de zwangerschap. Een BMI <18 of >35 wordt als een risicofactor beschouwd.

KCE 2004 recommendation BMI 2 (Good practice point : Recommendation from the experts group or/and the validators)

- Il est recommandé de suivre l'évolution pondérale de la femme enceinte à chaque consultation.
- Het evalueren van de gewichtsevolutie van de zwangere vrouw is aan te bevelen tijdens elke raadpleging.

Literature quoted by EAC 2014 guideline

- Routinely measuring women's height and weight and calculating BMI at an early antenatal contact is recommended in the United Kingdom (NICE 2008; CMACE & RCOG 2010), the United States (IOM 2009) and Canada (AOM 2010; SOGC 2010). Additional advice on monitoring weight gain during pregnancy, in particular for women who are underweight, overweight or obese is also given in the Canadian and United States guidelines.
- Recent evidence on the risks associated with low or high BMI during pregnancy continues to support the routine measurement of women's weight and height and calculation of BMI at the first antenatal contact. This allows identification of women who require additional care during pregnancy.
- While pre-pregnancy BMI is independently associated with pregnancy outcomes, the amount of weight gained during pregnancy is also a contributing factor (Nohr et al. 2008; Viswanathan et al. 2008). The amount of weight gained during pregnancy varies and studies suggest that many women do not gain the amount recommended. In a large cohort study in the United States (n=94,696) (DeVader et al. 2007), 17.8% of women gained less than the recommended amount of weight over the pregnancy, 39.4% gained the recommended amount and 42.8% gained more than recommended. Similar results were found in a Canadian cohort study (n=5,377) (Crane et al 2009), with 17.1% of women gaining less than the recommended amount, 30.6% gaining the recommended amount and 52.3% gaining more weight than recommended. The US Institute of Medicine (IOM) provides guidance on weight gain in pregnancy based on pre-pregnancy BMI. When pre-pregnancy BMI is not known, a weight gain of 0.5–2 kg weight gain in the first trimester may be assumed (IOM 2009).

EAC 2014 recommendation BMI 1 (Grade B: Body of evidence can be trusted to guide practice in most situations)

- Measure women's weight and height at the first antenatal visit and calculate their BMI.

EAC 2014 Practice point BMI 1

- Repeated weighing during pregnancy should be confined to circumstances that are likely to influence clinical management.

EAC 2014 recommendation BMI 2 (Grade B: Body of evidence can be trusted to guide practice in most situations)

- Give women advice about appropriate weight gain during pregnancy in relation to their BMI.

EAC 2014 Practice point BMI 2

- Taking a respectful, positive and supportive approach and providing information about healthy eating and physical activity in an appropriate format may assist discussion of weight management.

KCE proposition to the GDG: To keep the 2004 recommendation 1 and 2, without modification of content.

Results of the GDG Lime survey at the beginning of October 2014 (11 respondents)

- Totally agree: 8; somewhat agree: 2; rather not agree: 1; not agree at all: 0
- Recommendation BMI 1: Strong 10 ; Weak: 0
- Recommendation BMI 2: Strong 8; Weak: 2

GDG comments in the Lime survey at the beginning of October 2014

- Ik ben akkoord met aanbeveling 1; Ik ben niet akkoord met aanbeveling 2, ttz ik zou het repetitief wegen van vrouwen enkel aanbevelen in situaties waarbij de BMI reeds een risicofactor aangeeft en ik zou ABSOLUUT recommendation 2 en practice point 2 toevoegen!
- Faut-il discuter aussi du bien fondé d'offrir des recommandations de prise de poids adaptée au poids de départ (cf IOM)
- Eventueel enkel aan te bevelen bij de eerste consultatie routinematig. Indien de BMI te hoog of te laag is, vaker controleren! Zie ook eerste evidentie, nergens evidentie dat het routinematig elk consult hoeft te gebeuren...
- Naast cijfers en info over aanvaardbare evolutie tijdens en in de loop vd zwangerschap is aandacht voor voeding, beweging en sedentair gedrag belangrijk.De gewichtsevolutie voor en tijdens de zwangerschap heeft gevolgen voor het kind tijdens en ook na de zwangerschap.
- Niet enkel startgewicht, maar ook de gewichtsevolutie, zijn geassocieerd met uikomst van de zwangerschap.
- Het adviseren van gezonde voedings- en levensstijl in de zwangerschap in relatie tot de BMI van de vrouw zou ik ook mee opnemen in een nationale richtlijn!

GDG comments during the GDG meeting 08/10/2014

- **The recommendation BMI 1** (measurement of women's weight and height at the first antenatal visit and calculation of their BMI) **is fully accepted.**
- **The recommendation BMI 2** (repeated weighing at each encounter) **is discussed.**

  Arguments pro:

  - Mother's weight measurement can diagnose a trend to excess or lack of weight gain that can be due to inappropriate diet habits but also other causes such as oedema.
  - Mother's weight evolution has a demonstrated relationship with foetal and neonatal outcomes (see Australian references).
  - In case of bad weight evolution, improvement is possible with educational support, mainly if the mother has a too high weight gain (see Glinoer publication).
  - It is a cheap examination.
  - It is usual in practice.

  Arguments contra:

  - The mother risks to feel guilty if she gains too much weight despite it is not always due to eating behaviour.
  - Some mothers can be stressed if the weight is measured at each encounter.
  - The utility of a measurement at each consultation is not demonstrated.
  - The Australian guideline confines repeated weighing during pregnancy to circumstances that are likely to influence clinical management.
- The GDG acknowledges the benefit of following the mother weight during pregnancy but the terms at each consultation is judged overwhelming. A regular measurement would be enough.
- An information has to be provided to women concerning their weight gain expected. The Australian recommendation 2 should be included in the Belgian guideline.
- **Conclusion: to keep the KCE 2004 recommendations 1 and 2 with minor changes and to add the Australian recommendation BMI 2: Give women advice about appropriate weight gain during pregnancy in relation to their BMI.**

KCE proposition of 2015 recommendation

Recommendation BMI 1 (Strong recommendation)

- Offer to weigh each pregnant woman and calculate her BMI starting from the 1st consultation (and/or at a preconception consultation).

Recommendation BMI 2 (Strong recommendation)

- Offer to regularly monitor each pregnant woman's weight change.

Recommendation BMI 3 (Strong recommendation)

- Advise each pregnant woman on the appropriate weight gain in relation to her BMI.

GDG comments by e-mail during February 2015:

Recommendation BMI 2

- Enkel bij BMI te hoog of te lag en indien gewicht niet toeneemt tijdens de zwangerschap?
- 'regelmatig' = te vaag

Recommendation BMI 3

- ik zou in het Engels gestational weight gain toevoegen, in het NL is dit mogelijks wat veel >>>> KCE Answer: Australian recommendation

KCE 2015 recommendation before stakeholders meeting

Recommendation BMI 1 (Strong recommendation)

- Offer to weigh each pregnant woman and calculate her BMI starting from the 1st consultation (and/or at a preconception consultation).

Recommendation BMI 2 (Strong recommendation)

- Offer to regularly monitor each pregnant woman's weight change.

Recommendation BMI 3 (Strong recommendation)

- Advise each pregnant woman on the appropriate weight gain in relation to her BMI.

Results of the stakeholders Lime survey in March 2015 (6 respondents):

- **Recommendation BMI 1:** Completely agree: 4; somewhat agree: 1; non applicable: 1
- **Recommendation BMI 2:** Completely agree: 5; non applicable: 1
- **Recommendation BMI 3:** Completely agree: 4; somewhat agree: 1; non applicable: 1

Stakeholders comments during the stakeholders meeting 25/03/2014: None

KCE 2015 recommendation: Strong recommendation, Level of evidence B (*Level of evidence from Australian 2014 guideline: B=One or two level II studies with a low risk of bias or systematic review/several level III studies with a low risk of bias)*

[KCE 2004]

- Offer to weigh each pregnant woman and calculate her BMI starting from the 1st consultation (and/or at a preconception consultation).
- Stel aan elke zwangere vrouw voor haar te wegen en haar BMI te berekenen vanaf de 1ste consultatie (en/of tijdens een consultatie voorafgaand aan de conceptie).
- Proposez à chaque femme enceinte de la peser et de calculer son BMI dès la 1è consultation (et/ou lors d'une consultation préconceptionnelle).

KCE 2015 recommendation: Strong recommendation, Level of evidence NA(PP) (*Level of evidence from Australian 2014 guideline:* PP=practice point)

[KCE 2004]

- Offer to regularly monitor each pregnant woman's weight change.
- Volg het gewicht van elke zwangere regelmatig op.
- Proposez à chaque femme enceinte de suivre régulièrement son évolution pondérale.

KCE 2015 recommendation: Strong recommendation, Level of evidence A (*Level of evidence from Australian 2014 guideline: A=One or more level I studies with a low risk of bias or several level II studies with low risk of bias)*

[KCE 2015, based on Australian 2014 guideline]

- Advise each pregnant woman on the appropriate weight gain in relation to her BMI.
- Informeer elke zwangere vrouw over de gewichtstoename die gepast is voor haar BMI.
- Conseillez chaque femme enceinte sur la prise de poids qui est appropriée à son BMI.

14.3. Blood pressure

Blood pressure

Should **blood pressure** be regularly monitored in all Belgian low-risk pregnant women?

KCE 2004 recommendation (Grade C: Recommendation directly based on level 3 evidence or issued from a guideline based on level 1 or 2 evidence)

- Il est recommandé de mesurer la pression artérielle à chaque consultation au cours de la grossesse, et lors de la consultation prénatale. Une pression artérielle diastolique de plus de 90 mmHg est considérée comme un facteur de risque.
- Het is aan te bevelen om de bloeddruk gestandaardiseerd te meten voor de zwangerschap en tijdens elke raadpleging in de zwangerschap. Een diastolische bloeddruk van > 90 mmHg wordt als een risicofactor beschouwd.

Literature quoted by EAC 2014 guideline

- **Hypertensive disorders during pregnancy include (Lowe et al 2008):**
  - *Chronic hypertension* — blood pressure ≥140 mmHg systolic and/or ≥90 mm diastolic confirmed before pregnancy or before 20 completed weeks pregnancy, without a known cause (*essential hypertension*), associated with a secondary cause such as existing kidney disease (*secondary hypertension*) or associated with measurement in a healthcare setting (*white coat hypertension*);
  - *Gestational hypertension* — new onset hypertension (defined as a blood pressure ≥140 mmHg systolic and/or ≥90 mm diastolic) after 20 weeks pregnancy without any maternal or fetal features of pre-eclampsia, followed by return of blood pressure to normal within 3 months after the birth;
  - *Pre-eclampsia* — a multi-system disorder characterised by hypertension and involvement of one or more other organ systems and/or the fetus, with raised blood pressure after 20 weeks pregnancy commonly the first manifestation and proteinuria a common additional feature (although not required to make a clinical diagnosis); and
  - *Superimposed pre-eclampsia* — development of one or more of the systemic features of preeclampsia after 20 weeks pregnancy in a woman with chronic hypertension.
- Routine measurement of women's blood pressure at the first antenatal visit and throughout pregnancy is recommended in the United Kingdom (NICE 2008; 2010) and Canada (SOGC 2008). This advice reflects the importance of predicting the risk of pre-eclampsia to allow monitoring and preventive treatment. After 20 weeks, high blood pressure and/or proteinuria may indicate pre-eclampsia.
- Studies investigating the accuracy of blood pressure measurement and other screening tests in predicting pre-eclampsia report conflicting results. Recent studies include:
  - a systematic review (n=60 599) (Cnossen et al. 2008), which found that, while mean arterial pressure is a better predictor of pre-eclampsia than systolic or diastolic blood pressure or an increase of blood pressure in the first or second trimester, its use is not supported as the sole diagnostic tool;
  - prospective studies, which also suggest the use of a combination of factors — for example maternal history, uterine artery Doppler imaging, blood pressure at 11–13 weeks, body mass index — to predict pre-eclampsia (Onwudiwe et al. 2008; Poon et al. 2008; 2009; Nijdam et al. 2010).
- Overall there was great heterogeneity between individual studies with regard to population, gestation, definitions of pre-eclampsia, method of performing tests, test thresholds, frequency of testing, intervals between the test and outcome, and reference standards.

EAC 2014 recommendation blood pressure 1 (Grade B: Body of evidence can be trusted to guide practice in most situations)

- Measure blood pressure at a woman's first antenatal visit to identify existing high blood pressure.

EAC 2014 recommendation blood pressure 2 (Consensus-based recommendation)

- Routinely measure blood pressure to identify new onset hypertension.

KCE proposition to the GDG: To keep the 2004 recommendation, without modification of content.

Results of the GDG Lime survey at the beginning of October 2014 (11 respondents)

- Totally agree: 9; somewhat agree: 2; rather not agree: 0; not agree at all: 0
- Strong recommendation: 10; weak recommendation: 1

GDG comments in the Lime survey at the beginning of October 2014

- Ik ben niet zeker dat dit de grens 90 mm is, is dit niet gewijzigd naar 80?

GDG comments during the GDG meeting 08/10/2014

- The KCE 2004 recommendation quoted a diastolic blood pressure >90 mmHg as threshold instead of ≥90 mm. It will be corrected in the 2014 recommendation.
- The French version of the KCE 2004 recommendation contains a mistake: « prenatale » should mean « preconceptionnelle ».
- The GDG fully agrees that the blood pressure should be assessed at each antenatal consultation.
- **Conclusion: to keep the KCE 2004 recommendations with minor change.**

KCE proposition of 2015 recommendation (Strong recommendation)

- Offer to measure each pregnant woman's blood pressure at every visit during pregnancy, and during the preconception consultation. A diastolic blood pressure ≥ 90 mmHg is considered **as a risk factor for preeclampsia.**

GDG comments by e-mail during February 2015:

- **KCE question: Can we add preeclampsia to specify the risk factor?** Majority of yes; perhaps, but the risks are not limited to preeclampsia only ?; pourquoi ne pas dire "facteur de risque de complication"?; Yes or 'eg preeclampsia' when there are others is eclampsia correct in dutch not pre-eclampsie?; "Hypertensieve complicaties" lijkt me correcter en vollediger dan "preeclampsie"
- Pourquoi si la recommandation est forte, ne pas être plus directif: mesurez la tenion p.e.?

KCE 2015 recommendation before stakeholders meeting (Strong recommendation)

- Offer to measure each pregnant woman's blood pressure at every visit during pregnancy, and during the preconception consultation. A diastolic blood pressure ≥ 90 mmHg is considered **as a risk factor for complications such as pre-eclampsia.**

Results of the stakeholders Lime survey in March 2015 (6 respondents):

- Completely agree: 4; somewhat agree: 1; non applicable: 1

Stakeholders comments during the stakeholders meeting 25/03/2014: None

KCE 2015 recommendation: Strong recommendation, Level of evidence NA *(Level of evidence from Australian 2014 guideline =B only for blood pressure measurement at the first antenatal visit and consensus-based for the measurement afterwards)*

[KCE 2004]

- Offer to measure each pregnant woman's blood pressure at every visit during pregnancy, and during the preconception consultation. A diastolic blood pressure ≥ 90 mmHg is considered as a risk factor for complications such as pre-eclampsia.
- Stel aan elke zwangere vrouw voor haar bloeddruk te meten tijdens elke consultatie tijdens de zwangerschap, en tijdens de consultatie voorafgaand aan de conceptie. Een diastolische bloeddruk ≥ 90 mmHg wordt beschouwd als een risicofactor voor complicaties, bijvoorbeeld pre-clampsie
- Proposez à chaque femme enceinte de mesurer sa pression artérielle lors de chaque consultation au cours de la grossesse, et lors de la consultation préconceptionnelle. Une pression artérielle diastolique ≥ 90 mmHg est considérée comme un facteur de risque de complications telles que la prééclampsie.

14.4. Proteinuria

Proteinuria

Should **proteinuria** be detected in all Belgian low-risk pregnant women?

KCE 2004 recommendation (Grade C: Recommendation directly based on level 3 evidence or issued from a guideline based on level 1 or 2 evidence)

- Il est recommandé, à chaque consultation et toujours en combinaison avec une mesure de la tension artérielle, de rechercher la protéinurie au moyen de bandelettes réactives (dipstick). L'interprétation de la protéinurie doit toutefois tenir compte de la sensibilité limitée du dipstick.
- Het is aanvaardbaar om, tijdens elke raadpleging en steeds in combinatie met het meten van de bloeddruk, de urine te testen op proteïnurie aan de hand van een dipstick. Bij de interpretatie van de testresultaten dient echter rekening gehouden te worden met de beperkte accuraatheid van de test.

Literature quoted by EAC 2014 guideline

- **Aim of the test :**
  - Detection of proteinuria in the first trimester does not predict pre-eclampsia but may lead to identification and treatment of kidney disease or urinary tract infection. After 20 weeks pregnancy, proteinuria is associated with pre-eclampsia.
  - Testing for proteinuria in pregnancy in combination with blood pressure measurement at each antenatal visit is recommended in the United Kingdom (NICE 2008). However, routine screening for proteinuria is not recommended in the United States (USPSTF 1996; ACOG 2002) or Canada (CTFPHE 1996).
- **Accuracy of tests for detecting proteinuria**:
  - The 24-hour urine collection test is considered 'the gold standard' for testing for proteinuria in women during pregnancy, although it is often inconvenient for pregnant women to undertake a 24-hour urine collection. The test is frequently used as a reference point when evaluating the accuracy of other tests such as urine dipstick visual check, urine automated analyser, 2-hour and 12-hour tests, spot protein:creatinine ratio or microalbumin:creatinine ratio (Risberg et al. 2004; Price et al. 2005; Waugh et al 2005; Schubert et al. 2006; Rizk et al. 2007; Abebe et al. 2008; Côté et al. 2008a; Dwyer et al. 2008; Kyle et al. 2008; Gangaram et al. 2009a; 2009b).
  - One study has questioned the accuracy of the 24-hour urine test (Côté et al 2008b).
- **Studies evaluating other test types have found that:**
  - Numerous high and low evidence level studies confirm the correlation of protein-creatinine ratio testing against the 'gold standard' 24-hour urine collection, for point of care testing (Haas et al. 2003; Wikstrom et al. 2006; Zadehmodarres et al. 2006; Aggarwal et al. 2008; Chen et al. 2008; Poon et al. 2008a; Al et al. 2009; Soni et al. 2009; Nasrin et al. 2010; Sethuram et al. 2011; Morris et al. 2011; Morris 2012; Tun et al. 2012).
  - Protein:creatinine ratio — is a better screening test than automated dipstick urinalysis to detect significant proteinuria (Risberg et al. 2004; Dwyer et al. 2008), may be useful to rule out clinically significant proteinuria (Waugh et al. 2004; Price et al. 2005; Côté et al. 2008a; Meads et al 2008; Gangaram et al. 2009a) and has the advantage of results being available immediately (Kyle et al. 2008).
  - Dipstick testing — is inaccurate in predicting significant proteinuria (Waugh et al 2004; Gangaram et al. 2005) and has a high incidence of false positives (Davey & MacGillivray 1988; Phelan et al. 2004).
  - 2-hour and 12-hour collections — correlate with 24-hour collections in quantifying proteinuria, with the 12-hour collection having higher sensitivity (89% versus 86%), specificity (93% versus 82%) and positive predictive value (84% versus 77%) and lower false positive (12% versus 18%) and false negative (11% versus 14%) rates than 2-hour collection (Abebe et al. 2008).
- **Automated analysis of dipsticks**

- Due to considerable observer errors involved in dipstick urinalysis, an RCOG Study Group recommended that automated dipstick readers be employed (Shennan & Waugh 2003). This can significantly improve false positive and false negative rates. An initial result of 1+ or greater of protein should be confirmed by a 24-hour urinary protein measurement or a protein:creatinine ratio (Rodriguez-Thompson & Lieberman 2001).

- **Repeat testing in the first trimester**
  - Repeat testing for proteinuria in the first trimester is of little or no benefit in predicting pre-eclampsia and should be confined to women with other risk factors such as existing or newly diagnosed high blood pressure and new or pre-existing kidney disease (Beunis et al 2004; Alto 2005; Sirohiwal et al 2009).

EAC 2014 recommendation 1 (Grade CBR: Recommendation formulated in the absence of quality evidence (where a systematic review of the evidence was conducted as part of the search strategy)

- Routinely offer testing for proteinuria at the first antenatal visit, regardless of stage of pregnancy.

EAC 2014 recommendation 2 (Grade C: Body of evidence provides some support for recommendation(s) but care should be taken in its application)

- (After 20 weeks) Offer testing for proteinuria if a woman has risk factors for, or clinical indications of, pre-eclampsia; in particular raised blood pressure.

EAC 2014 recommendation 3 (Grade B: Body of evidence can be trusted to guide practice in most situations)

- For point-of-care testing, use an automated analyser if available, as visual inspection of a urinary dipstick is the least accurate method to detect true proteinuria.

KCE proposition to the GDG: To keep the 2004 recommendation, without modification of content.

Results of the GDG Lime survey at the beginning of October 2014 (11 respondents)

- Totally agree: 6; somewhat agree: 4; rather not agree: 1; not agree at all: 0
- Strong recommendation: 4; weak recommendation: 6

GDG comments in the Lime survey at the beginning of October 2014

- Pourquoi uniquement la protéinurie? Quid des nitrites? Si on a une multipare normotendue qu'elle est la probabilité qu'elle devienne protéinurique ? Je propose :
  - A la 1ère CPN: bandelette urinaire combinée protéinurie+ nitrites;
  - 2 -22 sem: bandelette uniquement sur signe d'appel (mictions brûlantes, hypertension, atcd prééclampsie etc);
  - >22 sem : bandelette systématique. Et une recommendation de gestion de proteinurie une seule +.
- La recherche de protéinurie via tigette est utile en corrélation avec l'HTA au 3è trimestre; le taux de faux positifs des tigettes est très élevé ==> nécessité d'urines de 12h ou 24h en cas de positivité

  ==> Limiter au début de grossesse pour dépister un problème rénal et dépistage systématique à partir du 3è trimestre vu la corrélation étroite avec la pré-éclampsie
- Het formuleren 'het is aanvaardbaar' zou ik nuanceren.
- De accuraatheid van de test blijft twijfelachtig, maw is dit wel aan te bevelen.

GDG comments during the GDG meeting 08/10/2014

- In practice, it appears that health practitioners use dipsticks combining proteinuria, nitrite (and glucose) measurement. False positive proteinuria is frequent with dipstick in case of urinary infection. The nitrite measurement can help to make a triage between likely urinary infection or not. The GDG proposes to mention this possible combination test within the recommendation (with terms as envisageable/ aanvaardbaar).
- The GDG agrees with the schedule proposed by the Australian guideline:
- One measurement at the first antenatal consultation (for identification and treatment of kidney disease or urinary tract infection);
- No systematic measurement between the first consultation and 20 weeks;

- After 20 weeks, proteinuria measurement (for preeclampsia screening).
- Contrary to the Australian recommendation, the GDG agrees to offer proteinuria testing after 20 weeks at all women and not only if a woman has risk factors for, or clinical indications of, pre-eclampsia; in particular raised blood pressure. The argument to justify this position is that dipstick is broadly used in Belgium, it is not expensive and proteinuria is sometimes the first sign of pre-eclampsia.
- The GDG underlines the problem of accuracy of proteinuria testing by dipstick but the negative predictive value of this test is high and allow a triage. The last sentence of the KCE 2004 recommendation could be amended in this sense.
- **Conclusion: to keep the KCE 2004 recommendation with minor change**
-

KCE proposition of 2015 recommendation (Weak recommendation)

- Consider to search for the presence of proteinuria during the first consultation to each pregnant woman a so as to identify kidney disease and urinary tract problems. After 20 weeks of pregnancy, consider to search for the presence of proteinuria at each visit in combination with taking blood pressure measurements in order to screen for preeclampsia. In Belgium, test strips are often able to measure several elements in addition to proteins, such as nitrites.

GDG comments by e-mail during February 2015: None concerning the content.

KCE 2015 recommendation before stakeholders meeting (Weak recommendation)

- Consider to search for the presence of proteinuria during the first consultation to each pregnant woman a so as to identify kidney disease and urinary tract problems. After 20 weeks of pregnancy, consider to search for the presence of proteinuria at each visit in combination with taking blood pressure measurements in order to screen for preeclampsia. In Belgium, test strips are often able to measure several elements in addition to proteins, such as nitrites.

Results of the stakeholders Lime survey in March 2015 (6 respondents):

- Completely agree: 4; somewhat agree: 1; non applicable: 1

Stakeholders comments during the stakeholders meeting 25/03/2014: None

KCE 2015 recommendation: Weak recommendation, Level of evidence NA (*Level of evidence from Australian 2014 guideline = Consensus-based recommendation in absence of evidence for the first part and C for the second one but slightly different from the KCE recommendation)*

[KCE 2004, amended]

- Consider to assess proteinuria in pregnant women during the first consultation so as to identify kidney disease and urinary tract problems. After 20 weeks of pregnancy, consider to search for the presence of proteinuria at each visit in combination with taking blood pressure measurements in order to screen for preeclampsia. In Belgium, test strips (dipsticks) are often able to measure several elements in addition to proteins, such as nitrites.
- Overweeg om bij zwangere vrouwen te controleren op de aanwezigheid van proteïnurie tijdens de eerste consultatie om nierziekten en aandoeningen van de urinewegen te identificeren. Na 20 weken zwangerschap kunt u tijdens elke consultatie, in combinatie met het meten van de bloeddruk, controleren op de aanwezigheid van proteïnurie om een eventuele diagnose van preeclampsie uitgebreider te documenteren. De teststroken die in België worden gebruikt, laten vaak ook toe andere elementen te meten, zoals nitrieten.
- Envisagez de rechercher la présence de protéinurie lors de la première consultation des femmes enceintes afin d'identifier les maladies rénales et affections des voies urinaires. Après 20 semaines de grossesse, vous pouvez envisager de rechercher la présence de protéinurie à chaque consultation en combinaison avec une mesure de la tension artérielle afin de dépister une pré-éclampsie. En Belgique, les tigettes combinent souvent la possibilité de mesurer plusieurs éléments en plus des protéines, comme les nitrites.

14.5. Fundal height measurement

Fundal height measurement

Should **fundal height measurement** be performed in all Belgian low-risk pregnant women?

KCE 2004 recommendation (Good practice point : Recommendation from the experts group or/and the validators)

- A chaque consultation à partir de la 24è semaine de grossesse, il est recommandé de déterminer la hauteur du fond de l'utérus en vue de pouvoir détecter la dysmaturité.
- Vanaf 24 weken zwangerschap is het aan te bevelen om tijdens elke raadpleging de fundushoogte te bepalen voor de opsporing van positieve en negatieve discongruentie.

Literature quoted by EAC 2014 guideline

- The evidence on methods of growth assessment is limited:
  - an observational study found that abdominal palpation had limited value as a screening tool for intrauterine growth restriction in low-risk pregnancies (n=6,318) (Bais et al 2004);
  - two Cochrane reviews (based on the same study) found no difference in detection of intrauterine growth restriction between repeated symphysis–fundal height measurement and abdominal palpation (Neilson 2009; Robert Peter et al 2012);
  - detection of intrauterine growth restriction has been shown to be improved by plotting fundal height measurements on fetal growth charts customised for maternal height, weight, parity and ethnic group in an observational study (Roex et al 2012).
- Although current evidence does not conclusively support either method for detecting low or high birth weight babies, monitoring growth is important (Robert Peter et al 2012). Monitoring of fetal growth in women whose pre-pregnancy BMI is high (HAPO 2010) or in the underweight category (Dawes & Grudzinskas 1991; Panaretto et al 2006) is of particular importance.
- Referral for specialist advice is required when there is a discrepancy of 3 cm between observed and expected symphysis-fundal height measurements.

EAC 2014 recommendation (Consensus-based recommendation)

- Offer women assessment of foetal growth (abdominal palpation and/or symphysis-fundal height measurement) at each antenatal visit to detect small- or large-for-gestational-age infants.

KCE proposition to the GDG: To keep the 2004 recommendation, without modification of content.

Results of the GDG Lime survey at the beginning of June 2014 (11 respondents)

- Totally agree: 7; somewhat agree: 3; rather not agree: 1; not agree at all: 0
- Strong recommendation: 6; weak recommendation: 4

Justification for rather not agree :

- A l'heure actuelle, l'échographie est plus utilisée et est plus discriminante pour ce diagnostic, à mon avis.

GDG comments in the Lime survey at the beginning of June 2014

- Depuis 33 ans je prends toujours la HU et je considère que c'est un excellent signe clinique et complément avec le PO et si c'est fait de la même manière par les différents praticiens.
- Mbv klinische fundusmeting worden slechts 27% van de IUGR-baby's gedetecteerd (ECPM congres Firenze 2014)

GDG comments during the GDG meeting 16/06/2014

- In some hospitals there is no US device in each room.
- It is better to reserve the US when there is something to search; US used just for measuring the fundus length can lead to false reassurance if parents believe that everything is checked.
- Be careful that the manual examination can miss 2/3 of cases with intra-uterine growth restriction or large for gestational age babies.
- There is no evidence that US during each visit detects more growth problems than clinical examination.
- **Conclusion: ultrasound remains a second line investigation; recommendation KCE 2004 has to be unchanged.**

KCE proposition of 2015 recommendation (Strong recommendation)

- From the 24th week of pregnancy, offer to determine the height of the uterine fundus in each pregnant woman during each visit in order to detect **dysmaturity.**

GDG comments by e-mail during February 2015

- **KCE question: Is "dysmaturity" clear enough? Or such as mentioned by EAS "small- or large-for-gestational-age infants"?** Yes; Fetal growth restriction ?; Ce n'est pas forcément une croissance anormale. Ce peut aussi être un excès ou un "manque" de liquide amniotique ; I think all care providers will understand dysmaturity, for the women themselfs, this might be difficult indeed**;** Vervangen door groeiretardatie (IUGR)**?;** Het gaat niet enkel om dysmaturiteit, maar ook om macrosomie, polyhydramnion, ,,, Ik zou de term "discongruentie" gebuiken, omdat hiermee afwijkingen in de 2 richtingen worden omschreven**;** Ja liever termen als smal FGA en LFGA ipv dysmaturiteit
- Overweeg ipv stel? Tevens weinig sterke evidentie ter onderbouwing?

KCE 2015 recommendation before stakeholders meeting (Strong recommendation)

- From the 24th week of pregnancy onwards, offer to determine the height of the uterine fundus in each pregnant woman during each visit in order to detect abnormalities such as small or large for gestational age babies or olihydramnios**.**

Results of the stakeholders Lime survey in March 2015 (6 respondents):

- Completely agree: 4; somewhat agree: 1; non applicable: 1

Stakeholders comments during the stakeholders meeting 25/03/2014: None

KCE 2015 recommendation Strong recommendation, Level of evidence NA(CBR) (*Level of evidence from Australian 2014 guideline: CBR=Consensus based recommendation because insufficient evidence to support recommendation)*

[KCE 2004]

- From the 24th week of pregnancy onwards, offer to determine the height of the uterine fundus in each pregnant woman during each visit in order to detect abnormal uterine growth.
- Stel, vanaf de 24ste week van de zwangerschap, aan elke zwangere vrouw voor de fundushoogte van de baarmoeder te bepalen tijdens elke consulatie om positieve of negatieve dyscongruentie te kunnen vaststellen.
- A partir de la 24è semaine de grossesse, proposez à chaque femme enceinte de déterminer la hauteur du fond de l'utérus lors de chaque consultation en vue de pouvoir détecter une situation anormale telle qu'un retard de croissance, une macrosomie foetale ou un oligohydramnios.

14.6. Foetal position

Foetal position

Should the **fetal position** be detected by **an abdominal palpation** (Leopold manoeuvres) in all Belgian low-risk pregnant women?

KCE 2004 recommendation 1 (Grade C : Recommendation directly based on level 3 evidence or issued from a guideline based on level 1 or 2 evidence)

- A partir de la 36è semaine ou au-delà, il est recommandé de déterminer la position fœtale (au moyen des manœuvres de Léopold). A partir de la 36è semaine, une position inadéquate peut, en effet, influencer la politique à adopter ultérieurement pour la grossesse et l'accouchement.
- Vanaf 36 weken of later, is het aan te bevelen om de foetale ligging te bepalen (met behulp van de handgrepen van Leopold). Vanaf 36 weken kan een ligging immers het verdere beleid van de zwangerschap en bevalling beïnvloeden.

KCE 2004 recommendation 2 (Good practice point : Recommendation from the experts group or/and the validators)

- Lorsqu'une anomalie positionnelle est suspectée, il est recommandé de la confirmer par examen échographique.
- Wanneer een liggingsafwijking wordt vermoed, is het aan te bevelen om dit te bevestigen met een echografisch onderzoek.

Literature quoted by EAC 2014 guideline

- Abdominal palpation is accurate in identifying presentation, especially if carried out by an experienced health professional (Webb et al 2011). In Australia, it is recommended that all health professionals providing antenatal care be experienced in palpation of the pregnant abdomen including identification of the presenting part (RANZCOG 2009).
- While the positive effects of abdominal palpation are difficult to quantify, no risks have been identified and it provides a point of engagement with the mother and baby.
- Assessment of presentation by abdominal palpation before 36 weeks is not always accurate.

EAC 2014 recommendation (Grade C : Body of evidence provides some support for recommendation(s) but care should be taken in its application)

- Assess foetal presentation by abdominal palpation at 36 weeks or later, when presentation is likely to influence the plans for the birth.

KCE proposition to the GDG: To keep the 2004 recommendations, without modification of content.

Results of the GDG Lime survey at the beginning of June 2014 (11 respondents)

- Totally agree: 10; somewhat agree: 0; rather not agree: 1; not agree at all: 0
- Strong recommendation: 6; weak recommendation: 4

Justification for rather not agree :

- L'usage de l'échographie étant généralisé, il est plus facile et plus sûr de déterminer une position fœtale par les US.

GDG comments in the Lime survey at the beginning of June 2014

- Plus le praticien pratique ses manoeuvres de Léopold, plus il est compétent pour repérer les positions précises et adopter les attitudes et conseils adaptés s'il y a lieu.
- Dit is een eenvoudige onderzoeksmethode, kan makkelijk toegepast worden.

GDG comments during the GDG meeting 16/06/2014

- The Leopold manoeuvre is well known and broadly used in Belgium.
- Palpation is important to create a contact, and communicate with the women.
- **Conclusion: recommendations KCE 2004 unchanged**

KCE proposition of 2015 recommendation (Strong recommendation)

- Starting from the 36th week or later, offer to determine the fetal position (using Leopold's maneuvers) for each pregnant woman. Starting from the 36th week, an improper position could influence the policy that will be subsequently adopted for the **pregnancy** and childbirth. When a positional anomaly is suspected, consider confirming this by ultrasound examination.

GDG comments by e-mail during February 2015:

- **KCE question: Is it really an impact on pregnancy or only on childbirth?** Oui, car le prestataire de soins va demander des examens complémentaires, proposer une version…; Ca a selon moi un impact sur la grossesse dans la mesure où programmer une tentative de version influence la grossesse et que par ailleurs, si l'on décide de réaliser une césarienne élective, on écourtera la grossesse ; When one wants to trie to turn the baby (inwendige kering) it affacts pregnancy as well but this is the only point I guess; "zwangerschaps-einde" = 2 vliegen in 1 klap ?; Ja, een stuitligging kan in de zwangerschap nog leiden tot een uitwendige kering met nadien een verder vorderende zwangerschap tot gevolg.

KCE 2015 recommendations before stakeholders meeting (Strong recommendation)

- Starting from the 36th week or later, offer to determine the fetal position (using Leopold's maneuvers) for each pregnant woman. Starting from the 36th week, an improper position could influence the policy that will be subsequently adopted for the end of pregnancy and childbirth. When a positional anomaly is suspected, consider confirming this by ultrasound examination.

Results of the stakeholders Lime survey in March 2015 (6 respondents):

- Completely agree: 4; somewhat agree: 1; non applicable: 1

Stakeholders comments during the stakeholders meeting 25/03/2014: None

KCE 2015 recommendation: Strong recommendation, Level of evidence C (*Level of evidence from Australian 2014 guideline: C=One or two level III studies with a low risk of bias or level I or II studies with a moderate risk of bias)*

[KCE 2004]

- Starting from the 36th week or later, offer to each pregnant woman to determine the fetal position (using Leopold's maneuvers). Starting from the 36th week, a malposition of the fetus can influence the management at the end of pregnancy and during childbirth. When a positional anomaly is suspected, consider confirming this by ultrasound examination.
- Stel, vanaf de 36e week of later, aan elke zwangere vrouw voor de positie van de foetus te bepalen (door middel van de handgrepen van Leopold). Vanaf de 36e week kan een onjuiste positie namelijk de beslissingen beïnvloeden die later moet worden genomen op het einde van de zwangerschap. Wanneer vermoed wordt dat de foetus in een afwijkende positie ligt, overweeg dan dit te bevestigen door een echografisch onderzoek.
- A partir de la 36è semaine ou au-delà, proposez à chaque femme enceinte de déterminer la position fœtale (au moyen des manœuvres de Léopold). A partir de la 36è semaine, une position inadéquate peut, en effet, influencer la politique à adopter ultérieurement à la fin de la grossesse et à l'accouchement. Lorsqu'une anomalie positionnelle est suspectée, envisagez de la confirmer par examen échographique.

14.7. Foetal movements counting

Foetal movements

Should a **fetal movements counting** be performed in all Belgian low-risk pregnant women?

KCE 2004 recommendation 1 (Grade A : Recommendation directly based on level 1 evidence)

- Il n'existe aucune preuve attestant que le comptage en routine chaque jour des mouvements de l'enfant (c'est-à-dire en enregistrant sur un graphique les mouvements de l'enfant, par exemple selon la méthode du comptage jusqu'à dix) permette de prévenir le décès in utéro.
- Er is geen evidence dat het routinematig dagelijks tellen van kindsbewegingen (d.i.met grafische registratie van de kindsbewegingen, vb. de 'Tel tot tien' methode) doodgeboorte voorkomt.

KCE 2004 recommendation 2 (Good practice point : Recommendation from the experts group or/and the validators)

- Néanmoins, les femmes enceintes seront informées de l'importance des mouvements de l'enfant et seront averties de la nécessité de prendre contact en cas de diminution des mouvements de l'enfant.
- Zwangere vrouwen dienen geïnformeerd te worden over het belang van kindsbewegingen en geadviseerd worden om bij verminderde kindsbewegingen contact op te nemen met hun zorgverstrekker voor verder onderzoek.

Literature quoted by EAC 2014 guideline

- Foetal movement assessment is widely used to monitor foetal wellbeing (Froen et al 2008; O'Sullivan et al 2009) and is most commonly undertaken through subjective maternal perception. Foetal movement counting is a more formal method to quantify foetal movements (Mangesi & Hofmeyr 2007). Maternal perception rather than formal foetal movement counting is recommended in Australia (ANZSA 2010) and in the United Kingdom (NICE 2008b; RCOG 2011).
- **Foetal movement counting**:
  - A systematic review (n=71,730) (Mangesi & Hofmeyr 2007) found insufficient evidence to recommend for or against foetal movement counting to prevent adverse perinatal outcomes.
  - A subsequent systematic review of single studies (Heazell & Froen 2008) concluded that at present, there is no evidence that any absolute definition of reduced foetal movements is more valuable than maternal perception of reduced foetal movements in detecting intrauterine foetal death or foetal compromise.
  - A recent RCT (n=1,076) found that maternal ability to detect clinically important changes in foetal activity seemed to be improved by foetal movement counting, with increased detection of intrauterine growth restriction and improved perinatal outcomes but not perinatal mortality (Saastad et al 2011).
- **Reporting of decreased foetal movement**:
  - Guidelines from Australia (ANZSA 2010) and the United Kingdom (RCOG 2011) recommend that women contact their health professional or maternity unit if they are concerned about a reduction in or cessation of foetal movements after 28 weeks of gestation.
  - A recent systematic review (Hofmeyr & Novikova 2012) concluded that there are insufficient data from randomised trials to guide practice regarding the management of decreased foetal movement. (Hofmeyr & Novikova 2012).

EAC 2014 recommendation (Consensus-based recommendation)

- Advise women to be aware of the normal pattern of movement for their baby and to contact their health care professional promptly if they have any concerns about decreased or absent movements.

KCE proposition to the GDG: To keep the 2004 recommendation 2, but amended as follow:

KCE 2014 recommendation before GDG meeting

- Les femmes enceintes seront informées de l'importance à accorder à la perception des mouvements de l'enfant et de la nécessité de prendre contact avec un professionnel de la santé en cas de perception d'une diminution ou de l'absence de mouvements de l'enfant.

- Zwangere vrouwen zullen worden geïnformeerd over het belang van het waarnemen van bewegingen van de baby en de noodzaak om contact op te nemen met een gezondheidsdeskundige in geval er minder of geen bewegingen van het kind meer worden waargenomen

Results of the GDG Lime survey at the beginning of June 2014 (11 respondents)

- Totally agree: 9; somewhat agree: 2; rather not agree: 0; not agree at all: 0
- Strong recommendation: 8; weak recommendation: 3

GDG comments in the Lime survey at the beginning of June 2014

- Une étude américaine présentée au congrès de Bischat il y a qq années montrait combien en comparant différent suivi de fin de grossesse pour des groupe tirés au hasard (monitoring ou doppler ou amnioscopie ou mouvements du bébé) le groupe le plus fiable sur la santé fœtale était le groupe de parents à qui on avait bien expliqué d'être attentifs aux réactions du bébé, à sa manière habituelle de bouger ou subite de ne plus bcp bouger,...
- Ik denk dat het nuttig is om in de aanbeveling ook het aantal weken zwangerschap op te nemen vanaf wanneer deze informatie nuttig is=> 28 weken (zie richtlijnen ANZSA)

GDG comments during the GDG meeting 16/06/2014

- No comments
- **Conclusion: proposition KCE 2014 accepted (slightly reformulated recommendation KCE 2004)**

KCE proposition of 2015 recommendation (Strong recommendation)

- Advise each pregnant woman to be aware about the normal pattern of movement of her baby and to contact a health care professional if she has any concerns about decreased or absent movements.

GDG comments by e-mail during February 2015:

- Wat is het belang? Eerder gelimiteerd, zeker geen indicatie om routinematig aan te bevelen… eventueel veranderen in: 'belangrijk wanneer het patroon verandert'; tweede deel wel zeker ok bij verminderde kindsbewegingen!
- Gezondheidswerker of zorgverlener? … als ze meent vast te stellen dat de baby minder of niet meer beweegt.

KCE 2015 recommendation before stakeholders meeting (Strong recommendation)

- Advise each pregnant woman to be aware about the usual pattern of movement of her baby and to contact a health care professional if she has any concerns about decreased or absent movements.

Results of the stakeholders Lime survey in March 2015 (6 respondents):

- Completely agree: 3; unsure: 2; non applicable: 1

Stakeholders comments during the stakeholders meeting 25/03/2014: None

KCE 2015 recommendation: Strong recommendation, Level of evidence NA(CBR) ***(Level of evidence from Australian 2014 guideline: CBR=Consensus based recommendation because insufficient evidence to support recommendation)***

[KCE 2004]

- Advise each pregnant woman to be aware about the usual pattern of movements of her baby and to contact a health care professional if she has any concerns about decreased or absent movements.
- Adviseer elke zwangere vrouw om aandacht te hebben voor de bewegingen van het kind en contact op te nemen met een zorgverlener als ze meent vast te stellen dat de baby minder of niet meer beweegt.
- Informez chaque femme enceinte de l'importance à accorder à la perception des mouvements de l'enfant et de la nécessité de prendre contact avec un professionnel de la santé en cas de perception d'une diminution ou de l'absence de mouvements.

14.8. Foetal heart auscultation

Foetal heart auscultation

Should a **fetal heart auscultation by Doppler** be performed in all Belgian low-risk pregnant women?

KCE 2004 recommendation (Good practice point : Recommendation from the experts group or/and the validators)

- A partir de 12 semaines de grossesse, l'utilisation du « doptone » est recommandée à chaque consultation. Cet examen permet de confirmer que le foetus est bien en vie.
- Vanaf 12 weken zwangerschap is de « doptone » aan te bevelen tijdens elke raadpleging. Dit onderzoek kan bevestigen dat de foetus in leven is.

Literature quoted by EAC 2014 guideline

- Routine auscultation of the fetal heart rate is not recommended in the United Kingdom (NICE 2008a).
- Although successful detection of a fetal heart confirms that the baby is alive, it does not guarantee that the pregnancy will continue without complications (Rowland et al. 2011) and is unlikely to provide detailed information on the fetal heart rate such as decelerations or variability (NICE 2008a).
- The sensitivity of Doppler auscultation in detecting the fetal heart is 80% at 12+1 weeks gestation and 90% after 13 weeks (Rowland et al. 2011). Attempts to auscultate the fetal heart before this time may be unsuccessful, and lead to maternal anxiety and additional investigations (e.g. ultrasound) in pregnancies that are actually uncomplicated (Rowland et al. 2011). It is unlikely that the fetal heart will be audible before 28 weeks if a Pinard stethoscope is used (Wickham 2002)
- Although there is no evidence on the psychological benefits of auscultation for the mother, it may be enjoyable, reduce anxiety and increase mother–baby attachment.

EAC 2014 recommendation (Consensus-based recommendation)

- If auscultation of the fetal heart rate is performed, a Doppler may be used from 12 weeks and a Pinard stethoscope from 28 weeks.

KCE proposition to the GDG: To keep the 2004 recommendation, without modification of content.

Results of the GDG Lime survey at the beginning of October 2014 (11 respondents)

- Totally agree: 8; somewhat agree: 3; rather not agree: 0; not agree at all: 0
- Strong recommendation: 7; weak recommendation: 3; no answer: 1

GDG comments in the Lime survey at the beginning of October 2014

- Je me demande s'il ne serait pas judicieux de remplacer la formulation «est encore en vie » par «la présence d'un rythme cardiaque fœtal (RCF)»?
- Il existe une différence importante entre les cabinets privés, les hôpitaux périphériques d'un côté et les hôpitaux universitaires qui ne disposent pas toujours d'échographes dans tous les cabinets. Dans notre pratique, en dehors des 3 US de grossesse qui sont tarifiés, à chaque consultation, on regarde le BB et on écoute le cœur à l'écho. Je ne dis pas que c'est bien mais c'est un fait établi dans la province de Liège.
- Een systematische aanbeveling tot Doptoon kan een maatregel zijn ter preventie van een systematische echografie bij elke consultatie.

GDG comments during the GDG meeting 08/10/2014

- Some GDG members wonder if we have to mention the Doppler auscultation or any test of foetal cardiac rhythm (FCR). However, the Australian guideline mention only the Doppler auscultation and later in pregnancy the Pinard stethoscope. As the Pinard stethoscope is not currently used in Belgium, only the Doppler auscultation should be quoted.
- If Doppler is not mentioned, there is a risk that ultrasound will be used instead (even if not reimbursed).
- The evidence of the usefulness of the FCR examination is poor in the Australian guideline.

- The aim of the RCF auscultation is mainly reassurance that the baby is alive. The Australian guideline quotes: Although there is no evidence on the psychological benefits of auscultation for the mother, it may be enjoyable and reduce anxiety.
- This recommendation cannot be a strong recommendation. It should be formulated with terms such as envisageable/aanvaardbaar.
- **Conclusion: to keep the KCE 2004 recommendation with minor change.**

KCE proposition of 2015 recommendation (Weak recommendation)

- Starting from 12 weeks of pregnancy, consider to measure the fetal cardiac rythm via Doppler auscultation at each visit. This exam is used to confirm that the fetus is alive

GDG comments by e-mail during February 2015: None concerning the content.

KCE 2015 recommendation before stakeholders meeting (Weak recommendation)

- Starting from 12 weeks of pregnancy, consider to measure the fetal cardiac rhythm via Doppler auscultation at each visit. This exam is used to confirm that the foetus is alive.

Results of the stakeholders Lime survey in March 2015 (6 respondents):

- Completely agree: 3; somewhat agree: 1; unsure: 1; non applicable: 1

Stakeholders comments during the stakeholders meeting 25/03/2014: None

KCE 2015 recommendation: Weak recommendation, Level of evidence NA(CBR) ***(Level of evidence from Australian 2014 guideline: CBR=Consensus based recommendation because insufficient evidence to support recommendation)***

[KCE 2004, amended]

- Starting from 12 weeks of pregnancy, consider to detect the fetal cardiac rhythm via Doppler auscultation at each visit. This exam is used to confirm that the fetus is alive.
- Overweeg om, vanaf de 12de week van de zwangerschap, de hartslag van de foetus op te sporen tijdens elke consultatie met behulp van Doppler-auscultatie. Dit onderzoek bevestigt dat de foetus in leven is.
- A partir de 12 semaines de grossesse, envisagez de mesurer le rythme cardiaque foetal par auscultation Doppler à chaque consultation. Cet examen permet de confirmer que le foetus est bien en vie.

14.9. Ultrasound scan during the first trimester

Ultrasound scan during the first trimester

Should an **early ultrasound** be performed in all Belgian low-risk pregnant women?

KCE 2004 recommendation (Grade A: Recommendation directly based on level 1 evidence)

- Une échographie précoce est recommandée afin de pouvoir déterminer l'âge gestationnel et de détecter les grossesses multiples. Une bonne connaissance de l'âge gestationnel améliore notamment les performances des examens de dépistage d'un éventuel syndrome de Down et peut diminuer le nombre d'inductions causées par des erreurs dans l'évaluation du terme.
- Een echografie vroeg in de zwangerschap voor de bepaling van de zwangerschapsduur en voor de opsporing van meerlingzwangerschappen is aan te bevelen. Een consistente schatting van de zwangerschapsduur verbetert o.a. de performantie van de screeningsonderzoeken voor het syndroom van Down en kan leiden tot een daling in het aantal inducties omwille van postdatisme (overtijd zijn).

Literature quoted by EAC 2014 guideline

Accuracy and effectiveness of ultrasound assessment for gestational age

- The NICE guidelines reviewed the diagnostic value and effectiveness of screening methods in determining gestational age. Studies identified included a Cochrane review, four RCTs and a number of observational studies. Findings were as follows.
    - Accuracy of screening tests — Evidence suggests that ultrasound is a more accurate predictor of gestational age than last menstrual period (LMP) (Okonofua 1989; Rowlands & Roysten 1993; Alexander et al. 1995; Crowther et al. 1999; Taipale 2001; Savitz et al. 2002; Olesen & Thomsen 2006). If only LMP is available the estimated date of birth should be calculated as the first day of the LMP plus 282 days (Nguyen 1999). The estimated date of birth based on LMP is subject to significant error and will be influenced by the woman's age, number of previous pregnancies, BMI and whether she smokes (Savitz et al. 2002; Morin 2005).
    - Measurements used — Crown–rump length (CRL) measurement should be used in the first trimester for estimating gestational age (Selbing 1983; Taipale 2001). CRL > 90 mm is unreliable in estimating gestational age in second trimester and head circumference (HC) measurement, which appears more reliable than the biparietal diameter (BPD) (Johnsen et al 2006), should be used instead when establishing an estimated date of birth in the second trimester.
- These findings are largely supported by subsequent lower level studies as follows.
    - A small comparative study (n=30) (Martins et al. 2008) suggested that fetal head and trunk volume (HT) could be more accurate than CRL for estimating gestational age, possibly due to flexion of the fetal head affecting CRL measurement.
    - An Australian prospective cohort study (n=396) (McLennan & Schluter 2008) found that CRL measurement predictions were superior to BPD measurement predictions.
    - A retrospective comparative study (n=165,908) (Dietz et al. 2007) found that ultrasound-based estimates of gestational age were more accurate than LMP based-estimates of gestational age.
    - A prospective cohort study (Hoffman et al. 2008) found that LMP classified more births as post term than ultrasound (4.0% vs. 0.7%), with a greater difference among young women, non-Hispanic Black and Hispanic women, women of non-optimal body weight and mothers of low birth weight babies.
    - A retrospective study (n=40,730) (Koster et al. 2008) showed that the estimation of gestational age from CRL was not consistent, with reported age for a single CRL differing by up to 10 days. This highlights the need to ensure that reference curves and standards are consistently applied.
    - A prospective cross-sectional study (n=200) (Salpou et al. 2008) concluded that significant ethnic differences between mothers were not reflected in fetal biometry at second trimester. The results support the recommendation that ultrasound in practical health care can be used to assess gestational age in various populations with little risk of error due to ethnic variation.

- A recent Cochrane review (Whitworth et al. 2010), which compared selective versus routine use of ultrasound in pregnancy, concluded that ultrasound improves the early detection of multiple pregnancies.

Timing of assessment

- The systematic review conducted to inform the development of these Guidelines identified one prospective cohort study (n=8,313) (Verberg et al. 2008) that investigated the best time to conduct gestational age assessment. The study found that the earlier the ultrasound assessment in pregnancy (preferably between 10 and 12 weeks), the more accurate the prediction of date of birth. The results indicate that after 24 weeks of pregnancy, a reliable LMP provides better estimates.
- While gestational age assessment using ultrasound is more accurate in the first trimester (Kalish et al. 2004; Caughey et al. 2008), some women may not have access to ultrasound until later in pregnancy. Gestational age has been successfully estimated in the second trimester (Johnsen et al. 2005; Oleson & Thomsen 2006). (in another place in EAC)

EAC 2014 recommendation ultrasound 1st trimester 1 (Grade B : Body of evidence can be trusted to guide practice in most situations)

- Provide information and offer pregnant women who are unsure of their conception date an ultrasound scan between 8 weeks 0 day and 13 weeks 6 days to determine gestational age, detect multiple pregnancies and accurately time foetal anomaly screening.

EAC 2014 Practice point ultrasound 1st trimester 1

- The timeframe for ultrasound assessment of gestational age overlaps with that for assessment of nuchal translucency thickness as part of screening for fetal chromosomal abnormalities (11 weeks to 13 weeks 6 days), which may enable some women to have both tests in a single scan. This should only occur if women have been provided with an explanation of both tests and have given their consent to them both.

EAC 2014 Practice point ultrasound 1st trimester 2

- Ultrasound assessment of gestational age should only be performed by a person who has had specific training.

EAC 2014 Practice point ultrasound 1st trimester 3

- Repeated ultrasound assessments should only be used when clinically indicated.

KCE proposition to the GDG: To keep the 2004 recommendation, without content modification, mainly the first part because ce second part concern topic included in another KCE report (KCE report 222 on non invasive prenatal test for trisomy 21)(Hulstaert, 2014 #678).

Results of the GDG Lime survey at the beginning of October 2014 (11 respondents)

- Totally agree: 8; somewhat agree: 3; rather not agree: 0; not agree at all: 0
- Strong recommendation: 10; weak recommendation: 1

GDG comments in the Lime survey at the beginning of October 2014

- Het lijkt me sterk aanbevolen om de EAC recommendation 1 (met practice point 1, 2 en 3) bij te voegen aangezien er hier bevindingen in staan die de betrokkenheid van de patiënt verhogen, met name practice point 1: de moeder moet op de hoogte zijn van het feit dat ze beide echo's, met name voor haar vermoedelijke bevallingsdatum en de combinatietest, in één echo kan krijgen.

GDG comments during the GDG meeting 08/10/2014

- The aim of the first ultrasound (US) is not only to assess the gestational age and detect multiple pregnancy (but also exclude extra-uterine pregnancy…); the word notably will be added to the test indications in the 2004 KCE recommendation.
- The question about a specific training needed for health professionals who perform US is complex. In Belgium, there is no officially organized specific training and certification for obstetric US at present. In the NIPT report of the KCE, an audit system was suggested to assure a quality in the nuchal translucency measurement, as results of Down screening in Belgium are currently below international standards. What would be the impact of a recommendation underlining the need of specific training if no official acknowledgement of this training exists? A policy recommendation can be considered.

- The GDG agrees with the Australian proposition to link the assessment of gestational age and the assessment of nuchal translucency thickness. The best timing for the first US, i.e. 11 weeks to 13 weeks 6 days, should be specified in the 2014 recommendation.
- **Conclusion: to keep the KCE 2004 recommendation with minor changes.**

KCE proposition of 2015 recommendation (Strong recommendation)

- Offer to perform an ultrasound, between 11 and 13 weeks 6 days, on each pregnant woman, notably to be able to determine the gestational age and to detect multiple pregnancies. Accurate knowledge of the gestational age improves, for example, the efficiency of screening tests for Down syndrome and could decrease the number of inductions due to an incorrect term assessment.

GDG comments by e-mail during February 2015:

- **KCE question: Is accurate to propose the US in this timing?** Yes; Oui, l'échographe du premier trimestre doit se faire entre 11 et 13 6/7sem ; In de periode 41+0w tem 41+6w is er een verschil in perinatale sterfte tussen zwangerschappen, gedateerd volgens laatste menstruatie, en deze gedateerd volgens echografie. Van alle technieken voor dating van een zwangerschap is de 1° trimester-echografie de meest gevoelige; Eerder ook voor prenatale scxreening!

KCE 2015 recommendation before stakeholders meeting (Strong recommendation)

- Offer to perform an ultrasound, between 11 and 13 weeks 6 days, on each pregnant woman, notably to be able to determine the gestational age and to detect multiple pregnancies. Accurate knowledge of the gestational age improves, for example, the efficiency of screening tests for Down syndrome and could decrease the number of inductions due to an incorrect term assessment..

Results of the stakeholders Lime survey in March 2015 (6 respondents):

- **Recommendation ultrasound first trimester:** Completely agree: 4; somewhat agree: 1; non applicable: 1

Stakeholders comments during the stakeholders meeting 25/03/2014: None

KCE 2015 recommendation: Strong recommendation, Level of evidence B *(Level of evidence from Australian 2014 guideline: B=One or two level II studies with a low risk of bias or systematic review/several level III studies with a low risk of bias)*

[KCE 2004, slightly amended]

- Offer to each pregnant woman to perform an ultrasound between 11 and 13 weeks 6 days, notably to be able to determine the gestational age and to detect multiple pregnancies. Accurate knowledge of the gestational age improves, for example, the efficiency of screening tests for Down syndrome and could decrease the number of inductions due to an incorrect term assessment.
- Stel aan elke zwangere vrouw voor om een echografie te verrichten tussen 11 weken en 13 weken en 6 dagen zwangerschap, meer bepaald om de zwangerschapsduur te bepalen en meerlingzwangerschappen te kunnen vaststellen. Een goede kennis van de zwangerschapsduur verbetert bijv. de resultaten van onderzoeken voor het screenen op een eventueel syndroom van Down en kan het aantal inducties verminderen veroorzaakt door fouten in de evaluatie van de zwangerschapsduur.
- Proposez à chaque femme enceinte d'effectuer une échographie entre 11 et 13 semaines 6 jours, afin de pouvoir notamment déterminer l'âge gestationnel et détecter les grossesses multiples. Une bonne connaissance de l'âge gestationnel améliore p.e. les performances des examens de dépistage d'un éventuel syndrome de Down et peut diminuer le nombre d'inductions causées par des erreurs dans l'évaluation du terme.

14.10. Ultrasound scan after the first trimester

Ultrasound scan after the first trimester

What are the benefits and harms of **other schedule of ultrasound**? (between 18 and 22 weeks? after the 24th week? at 36th week ?)

KCE 2004 recommendation ultrasound after the 1st trimester 1 (Grade A: Recommendation directly based on level 1 evidence)

- Une échographie est recommandée entre la 18ème et la 22ème semaine pour la détection d'anomalies structurelles.
- Een echografie tussen 18 en 22 weken voor de opsporing van structurele afwijkingen is aan te bevelen.

KCE 2004 recommendation ultrasound after the 1st trimester 2 (Grade A: Recommendation directly based on level 1 evidence)

- On ne dispose pas de preuves suffisantes pour recommander une échographie de routine après 24 semaines de grossesse.
- De evidence geeft geen ondersteuning aan een routine echografie na 24 weken zwangerschap.

KCE 2004 recommendation ultrasound after the 1st trimester 3 (Good practice point : Recommendation from the experts group or/and the validators)

- Une échographie peut être envisagée à 36 semaines, en cas de doute concernant la position du fœtus, vu qu'une version par manœuvres externes est envisageable en cas de présentation du siège.
- Een echografie op 36 weken kan aan te bevelen zijn bij twijfel over de foetale ligging, aangezien in het geval van een stuitligging op 36 weken een uitwendige kering dient overwogen te worden

KCE 2004 recommendation ultrasound after the 1st trimester 4 (Grade C: Recommendation directly based on level 3 evidence or issued from a guideline based on level 1 or 2 evidence)

- La plupart des placentas situés dans le bas de l'utérus et dépistés à 20 semaines ne donnant pas lieu à un placenta praevia à la naissance, on ne recommandera une échographie transabdominale à 36 semaines que si l'orifice interne du col de l'utérus est complètement recouvert (à 20 semaines). Lorsque l'échographie transabdominale n'est pas claire, une échographie transvaginale peut s'avérer utile.
- Enkel indien de placenta het os internum van de cervix geheel bedekt (op 20 weken) is een transabdominale echografie op 36 weken aan te bevelen aangezien de meeste laagliggende placenta´s die opgespoord worden op 20 weken niet leiden tot placenta praevia bij de geboorte. Een transvaginale echografie kan noodzakelijk zijn wanneer de transabdominale echografie niet duidelijk is.

Literature quoted by EAC 2014 guideline

- Routinely offering women an ultrasound during the second trimester to screen for foetal abnormalities and location of the placenta is recommended in the United Kingdom (NICE 2008), the United States (ACOG 2009) and Canada (Cargill et al. 2009) and has been previously recommended in Australia (RANZCOG 2009). Although cervical length is increasingly reported, there is insufficient evidence to recommend its routine assessment (RANZCOG 2008; 3 Centres Collaboration 2012).

Accuracy and effectiveness of ultrasound assessment of foetal development and anatomy

- **Structural abnormalities**: Ultrasound has been used in the second trimester to detect anomalies of the heart (Perri et al. 2005; Del Bianco et al. 2006; Westin et al. 2006; Fadda et al. 2009), renal tract (Cho et al. 2005) and umbilical artery (Cristina et al. 2005), neural tube defects (Norem et al. 2005) and anomalies resulting from exposure to alcohol (Kfir et al. 2009). The rate of detection of structural anomalies is generally higher in the second than in the first trimester (Saltvedt et al. 2006; Hildebrand et al. 2010).
- **Placenta praevia**: Second trimester ultrasound has effectively identified placental location (Cargill et al. 2009), overlap of the cervical os (Robinson et al. 2012), placental length (which may assist in identifying risk of having a small-for-gestational age baby) (McGinty et al. 2012) and placenta praevia (which may resolve in 11 of 18 women [61%] with a prior caesarean delivery and in 44/49 [90%] without a previous caesarean section; P = 0.012, Fisher exact test) (Lal et al. 2012).

- **Type of ultrasonography**: Accurate assessment can be performed using standard 2D ultrasonography. Assessment may be performed more rapidly using 3D ultrasonography (Benacerraf et al. 2006; Pilu et al. 2006).

Timing of ultrasound assessment of foetal development and anatomy

- Recommended timing of the ultrasound scan varies in international guidelines but is generally in the range of 18–20 weeks as:
  - sensitivity in detecting structural abnormalities increases after 18 weeks gestation (Cargill et al. 2009);
  - detection of structural abnormalities before 20 weeks gestation gives women the choice of terminating the pregnancy, where this is permitted under jurisdictional legislation.
- Ultrasound can be used to assess gestational age up to 24 weeks gestation and to detect abnormalities throughout the pregnancy.
- There is no benefit from repeated diagnostic ultrasound assessments unless clinically indicated. Repeated tests may increase costs for women, be inconvenient and have the potential to increase anxiety (e.g. through false positives). As well, access for some women is limited as this technology is not available in all settings.
- Where there is any doubt as to the presenting part, obstetric ultrasound should be used to confirm the palpation findings (at 36 weeks). Ultrasound can also exclude fetal anomaly, low-lying placenta, hyperextension of the baby's head and the presence of umbilical cord around the fetal neck (RANZCOG 2009).

EAC 2014 recommendation ultrasound after the 1st trimester 1 (Grade B : Body of evidence can be trusted to guide practice in most situations)

- Offer pregnant women ultrasound screening to assess foetal development and anatomy between 18 and 20 weeks gestation.

EAC 2014 Practice point ultrasound after the 1st trimester 1

- Timing of the ultrasound will be guided by the individual situation (e.g. for women who are obese, visualisation may improve with gestational age).

EAC 2014 Practice point ultrasound after the 1st trimester 2

- Repeated ultrasound assessment may be appropriate for specific indications but should not be used for routine monitoring.

EAC 2014 Practice point ultrasound after the 1st trimester 3

- Ultrasound assessment should only be performed by healthcare professionals with appropriate training and qualifications, within the appropriate scope (e.g. diagnostic or point of care).

EAC 2014 Practice point ultrasound after the 1st trimester 4

- Further investigations, such as ultrasound, are a consideration when there is any doubt about foetal growth. This includes ultrasound for women with a BMI ≥30 as clinical assessments of foetal growth have been shown to be less reliable in this group.

EAC 2014 ultrasound after the 1st trimester (Grade of recommendation not specified)

- Offer repeat ultrasound at 32 weeks to women whose placenta extended over the internal cervical os in the 18–20 week scan.

EAC 2014 Practice point ultrasound after the 1st trimester 5

- Suspected non-cephalic presentation should be confirmed by an ultrasound assessment. (after 36 weeks)

KCE proposition to the GDG

- To keep the 2004 recommendation ultrasound after the 1st trimester 1, without modification of content.
- To keep the 2004 recommendation ultrasound after the 1st trimester 2, without modification of content.
- To keep the 2004 recommendation ultrasound after the 1st trimester 3, without modification of content.
- To keep the 2004 recommendation ultrasound after the 1st trimester 3, without modification of content.

Results of the GDG Lime survey at the beginning of October 2014 (11 respondents)

Recommendation ultrasound after the 1st trimester 1:

- Totally agree: 9; somewhat agree: 2; rather not agree: 0; not agree at all: 0
- Strong recommendation: 9; weak recommendation: 1; no answer: 1

Recommendation ultrasound after the 1st trimester 2:

- Totally agree: 5; somewhat agree: 3; rather not agree: 3; not agree at all: 0
- Strong recommendation: 2; weak recommendation: 4; no answer: 2

Recommendation ultrasound after the 1st trimester 3:

- Totally agree: 4; somewhat agree: 5; rather not agree: 2; not agree at all: 0
- Strong recommendation: 1; weak recommendation: 5; no answer: 3

Recommendation ultrasound after the 1st trimester 4:

- Totally agree: 5 somewhat agree: 4; rather not agree: 2; not agree at all: 0
- Strong recommendation: 7; weak recommendation: 1; no answer: 1

GDG comments in the Lime survey at the beginning of October 2014

Recommendation ultrasound after the 1st trimester 1

- J'allongerai l'intervalle jusqu'à 23-24 semaines.
- J'ajouterais qu'elle doit être réalisée par un échographiste entrainé aux échographies foetales et avec un matériel performant.
- Graag de extra uitleg van EAC bijvoegen gezien er hier belangrijke info bijstaat die de patiënt moet weten.
- Waarom 22 en niet 20 weken?

Recommendation ultrasound after the 1st trimester 2

- Au Royaume Uni, où il n'y a pas d'écho de routine du 3ème trim., 30% des sièges seraient non diagnostiqués! Il y avait une référence qui montrait déjà cela dans le guideline précédent et qui disait que l'écho du 3ème trimestre était autorisé. Par ailleurs il y a une mortalité au RU sur RCIU non diagnostiqué. Au moment où le RCOG planche sur l'idée de recommander un écho du 3ème trim., ce serait triste de le perdre chez nous.
- La croissance foetale, la quantité de LA sont des paramètres qui peuvent se modifier plus tard et qui peuvent influencer l'attitude obstétricale.
- Laag geboortegewicht kan een indicatie zijn om een echo te doen in het derde trimester, hoewel ook zwakke evidentie hiervoor, rond 30 weken...
- In de Westerse landen is een miskende fetale groeiretardatie op dit ogenblik één van de voornaamste - vermijdbare - oorzaken van perinatale sterfte. Klinische parameters zijn inadequaat om dit op te sporen, maar mogelijk zijn getimede echo-onderzoeken dit wel.
- Deze bewoording lijkt me beter: «Repeated ultrasound assessment may be appropriate for specific indications but should not be used for routine monitoring».

Recommendation ultrasound after the 1st trimester 3

- Voir txt precedent
- Les versions par manœuvre externe ne sont pas enseignées à l'ULG-> peu d'obstétriciens les pratiquent. Si j'avais reçu cet enseignement, je les pratiquerais certainement->nécessité d'uniformiser plus l'enseignement.
- Zelfde zwakke aanbeveling kan voor 30 weken echo ivm laag geboortegewicht... Een foetus in stuitligging kan, eventueel met externe versie, ook vaginaal geboren worden.
- De Australische aanbeveling verwijst naar een echo na vermoeden van een abnormale ligging door abdominale palpatie, deze term lijkt me nuttig te vermelden in de KCE richtlijn want staat er nu nog niet in waardoor de kans groot is dat de 36 weken echo routinematig wordt uitgevoerd zonder eerst een palpatie, maw bijna alle

Belgische zwangeren krijgen nu standaard een echo net voor 36 weken (vaak rond 33 weken) deze is ook terugbetaald en wordt als standaard zorg aanzien maar blijkt NIET nuttig, dus graag de vermelding van palpatie als alternatief.

- Ik zou voorstellen de indicatie voor echo uit te breiden met placenta previa, en navelomstrengeling.

Recommendation ultrasound after the 1st trimester 4

- Voir les deux précédents ! Si on dit un écho par trim., on est en accord avec le remboursement INAMI, l'enseignement universitaire, et le terrain. La bataille c'est de calmer les échos mensuels pas de supprimer l'écho trimestriel.
- Zou ik samenvoegen met vorige stelling die aangeeft wanneer wel een echo op 36 weken te verantwoorden is.
- Enkel indien de placenta het os internum van de cervix geheel bedekt... zou ik verzwakken en veralgemenen tot : Bij twijfel over een placenta-insertie dichtbij of overheen het cervicaal ostium...

GDG comments during the GDG meeting 08/10/2014

Ultrasound during second trimester

- In the 2004 recommendation, the timing of the second US is between 18 and 22 weeks, instead of between 18 and 20 weeks in the Australian guideline. In some countries indeed, 20 weeks is the deadline for termination. In Belgium, we are more flexible. The GDG proposes to keep the previous KCE timing without shorten or lengthen it.
- **Conclusion: to keep the recommendation KCE 2004 ultrasound after the 1st trimester 1**

Ultrasound during third trimester

- The 2004 KCE guideline recommended to perform a US during the third trimester only in specific cases (placenta praevia and foetal misposition). The GDG does not agree with this proposition and argues to perform a universal third US.
- **Arguments pro:**
  - The detection of breech position by palpation only is not accurate (as demonstrated in UK), mainly if the pregnant women is obese.
  - The third trimester US is useful not only for detection of foetal position and placenta praevia but also for identification of IUGR and macrosomia as showed in observational studies. Unrecognized IUGR is the most frequent cause of perinatal death in Western countries.
  - The third trimester US is currently performed and is reimbursed**.**
- **Argument contra:**
  - There is a lack of direct evidence of its utility.
- **Conclusion: to change the recommendations KCE 2004 ultrasound after the 1st trimester 2,3 & 4 and to formulate a WEAK recommendation about a third trimester US, i.e. which should be formulated with terms such as envisageable/aanvaardbaar.**

KCE proposition of 2015 recommendation

Recommendation ultrasound second trimester (Strong recommendation)

- Offer to perform an ultrasound, between the 18th and the 22nd week, on each pregnant woman to detect structural abnormalities.

Recommendation ultrasound third trimester (Weak recommendation)

- During the 3rd trimester, considering performing an ultrasound so as to determine the foetal position, the existence of placenta previa, and to identify intrauterine growth retardation or macrosomia.

GDG comments by e-mail during February 2015:

- **Recommendation ultrasound second trimester:** no comment
- **Recommendation ultrasound third trimester:** Is het zinvol om iets te zeggen rond (1) de minimum kwaliteitsvereisen van een verloskundige echografie, en over (2) het gebrek aan evidentie van het nut van meer dan 3 echo's per laag-risico zwangerschap?; Deze echo is in een normale zwangerschap niet bewezen nuttig tenzij bij een groeiachterstand (maar daar is al een aanbeveling over) of bij een afwijkende ligging en daar is ook aal een aanbeveling over. Deze mag geschrapt.

KCE 2015 recommendation before stakeholders meeting

Recommendation ultrasound second trimester (Strong recommendation)

- Offer to perform an ultrasound, between the 18th and the 22nd week, on each pregnant woman to detect structural abnormalities

Recommendation ultrasound third trimester (Weak recommendation)

- During the 3rd trimester, consider performing an ultrasound so as to determine the foetal position, the existence of placenta praevia, and to identify intrauterine growth retardation or macrosomia.

Results of the stakeholders Lime survey in March 2015 (6 respondents):

- **Recommendation ultrasound second trimestre:** Completely agree: 4; somewhat agree: 1; non app.: 1
- **Recommendation ultrasound third trimester:** Completely agree: 4; somewhat agree: 1; non applicable: 1

Stakeholders comments during the stakeholders meeting 25/03/2014: None

KCE 2015 recommendation

Recommendation ultrasound second trimester: Strong recommendation, Level of evidence B *(Level of evidence from Australian 2014 guideline: B=One or two level II studies with a low risk of bias or systematic review/several level III studies with a low risk of bias)*

[KCE 2004]

- Offer to each pregnant woman to perform an ultrasound between the 18th and the 22nd week, to detect structural abnormalities.
- Stel aan elke zwangere vrouw voor een echografie te verrichten, tussen de 18de en 22ste week, om eventuele structurele afwijkingen vast te stellen.
- Proposez à chaque femme enceinte d'effectuer une échographie, entre la 18ème et la 22ème semaine, afin de détecter les anomalies structurelles.

Recommendation ultrasound third trimester: Weak recommendation, Level of evidence NA,

[KCE 2004, amended]

- During the 3rd trimester, consider performing an ultrasound so as to determine the fetal position, the existence of placenta praevia, and to assess fetal growth.
- Overweeg om tijdens het 3de trimester een echografie uit te voeren om de positie van de foetus, het bestaan van een placenta praevia of groeiafwijkingen vast te stellen.
- Au cours du 3è trimestre, envisagez d'effectuer une échographie afin de déterminer la position du fœtus, de détecter l'existence d'un placenta prævia et d'évaluer la croissance foetale.

14.11. Anaemia

Anaemia

Should **anaemia** be detected in all Belgian low-risk pregnant women?

KCE 2004 recommendation anaemia 1 (Grade C : Recommendation directly based on level 3 evidence or issued from a guideline based on level 1 or 2 evidence)

- Il est recommandé de détecter l'anémie chez les femmes enceintes au début de la grossesse.
- Het is aan te bevelen om vrouwen aan het begin van de zwangerschap te testen op anemie.

KCE 2004 recommendation anaemia 2 (Good practice point : Recommendation from the experts group or/and the validators)

- Il est pratique de déterminer également, en plus de l'hémoglobine, la ferritine et les MCV, MCH et MCHC. Un second examen au début du 3è trimestre peut s'avérer indiqué pour les soins à l'accouchement et pendant le post-partum.
- Als het Hb te laag is, is het nuttig om naast hemoglobine ook ferritine en MCVMCH-MCHC te bepalen. Een herhaling van deze onderzoeken aan het begin van het 3e trimester, kan aan te bevelen zijn voor het beleid van bevalling en postpartum.

Literature quoted by EAC 2014 guideline

- Routinely offering a full blood count early in pregnancy and at 28 weeks is recommended in the United Kingdom (NICE 2008) and in Australia (RANZCOG 2009). Initial haemoglobin concentration is usually assessed in the context of this full blood count.
- Haemoglobin concentration is not sensitive enough to be the sole means of diagnosing anaemia. Diagnostic tests include:
  - full blood count (if this has not already been conducted);
  - serum ferritin, which is the most sensitive single screening test to detect adequate iron stores (90% sensitivity at a cut-off of 30 µg/litre) (Breymann 2002); and
  - specific tests for folate and vitamin B12, if mean cell volume is high.
- No recent evidence was identified by EAC concerning the anaemia screening.

EAC 2014 recommendation anaemia (Consensus-based recommendation)

- Routinely offer testing for haemoglobin concentration to pregnant women early in pregnancy (at the first visit) and at 28 weeks gestation. (consensus-based recommendation)

EAC 2014 practice point anaemia 1

- In areas where prevalence of iron-deficiency anaemia is high consider testing ferritin at the first antenatal visit.

EAC 2014 practice point anaemia 2

- Further investigation is required for women with a low haemoglobin concentration for their gestational stage. Repeat screening at 36 weeks may also be required for women who have symptoms or risk factors for anaemia or who live in or have come from an area of high prevalence.

KCE proposition to the GDG: To keep the 2004 recommendation, without modification of content.

Results of the GDG Lime survey at the beginning of June 2014 (11 respondents)

- Totally agree: 7; somewhat agree: 4; rather not agree: 0; not agree at all: 0
- Strong recommendation: 9; weak recommendation: 2

GDG comments in the Lime survey at the beginning of June 2014

- Le mot utile de la phrase à remplacer par intéressant ; ajouter éventuellement: en cas d'anémie retrouvée à cette première détermination, ces analyses (MCH, MCV, ferritine) seront effectuées en vue d'un bilan/traitement.

- Er is een duidelijke associatie tussen anemie en zwangerschapscomplicaties, vooral prematuriteit, wat op dit ogenblik de voornaamste reden van perinatale morbiditeit is. Hiervoor screenen lijkt dus zeker uiterst zinvol.
- Dit vooral met oog op ijzerrreserve bij het kind.

GDG comments during the GDG meeting 16/06/2014

- Il est pratique is a bad wording. To be replaced by il est utileand choose it is needed in an English version; no change in Dutch.
- MCV, MCH are automatically done with haemoglobin (and for the same cost).
- Ferritin measurement implies an extra cost.
- In case of abnormal result of haemoglobin, physicians can require a ferritin measurement afterwards in the same blood sample.
- If a woman had known risk factors for anaemia, ferritin measurement is done systematically.
- The second examination is a step in the preparation for childbirth and postpartum (e.g. bad results can be a reason for refusing epidural analgesia or home birth) and a mean to reduce the postnatal anaemia.
- Un second examen au début du 3è trimestre peut s'avérer indiqué pour les soins à l'accouchement et pendant le post-partum has to be changed in indiqué en prévision de l'accouchement.
- **Conclusion: recommendation KCE 2004 kept but slightly reformulated.**

KCE proposition of 2015 recommendation

- Offer to test each pregnant woman for anaemia in early pregnancy. In addition to the haemoglobin level, it is also useful to measure the ferritin and MCV, MCH and MCHC levels. A second examination at the beginning of the 3rd trimester may be indicated ahead of childbirth.

GDG comments by e-mail during February 2015:

- Een tweede onderzoek aan het begin van het 3de trimester kan aangewezen zijn ter voorbereiding van de bevalling.
- Wetenschappelijk is het correcter de bijkomende meting van ferritine etc maar te verrichten wanneer een Hb-gehalte te laag is bevonden.

KCE 2015 recommendation before stakeholders meeting (Strong recommendation)

- Offer to test each pregnant woman for anaemia in early pregnancy. In addition to the haemoglobin level, it is also useful to measure the MCV, MCH and MCHC levels. A second examination at the beginning of the 3rd trimester may be indicated ahead of childbirth.

Results of the stakeholders Lime survey in March 2015 (6 respondents):

- Completely agree: 4; somewhat agree: 1; non applicable: 1

Stakeholders comments during the stakeholders meeting 25/03/2014: None

KCE 2015 recommendation: Strong recommendation, Level of evidence NA(CBR) ***(Level of evidence from Australian 2014 guideline: CBR= Consensus based recommendation because insufficient evidence to support recommendation)***

[KCE 2004]

- Offer to test each pregnant woman for anaemia in early pregnancy. In addition to the haemoglobin level, it is also useful to measure the MCV, MCH and MCHC levels. A second examination at the beginning of the 3rd trimester may be indicated ahead of childbirth.
- Stel aan elke zwangere vrouw voor om de eventuele aanwezigheid van anemie te testen in het begin van de zwangerschap. Het is eveneens nuttig om, naast de hemoglobine, MCV, MCH en MCHC te meten. Een tweede onderzoek aan het begin van het 3de trimester kan aangewezen zijn met het oog op de bevalling.
- Proposez à chaque femme enceinte au début de la grossesse de détecter la présence d'une anémie. Il est utile de mesurer également, en plus de l'hémoglobine, les MCV, MCH et MCHC. Un second examen au début du 3è trimestre peut s'avérer indiqué en prévision de l'accouchement.

14.12. Platelets and leukocytes count

Platelets and leukocytes count

Should **platelet and leukocyte count** be performed in all Belgian low-risk pregnant women?

KCE 2004 recommendation (Good practice point : Recommendation from the experts group or/and the validators)

- Il n'est pas démontré qu'une numération plaquettaire et leucocytaire soit utile mais elle est préconisée par certains experts et certains validateurs pour la détection d'anomalies hématologiques, telle que la thrombocytopénie.
- De bepaling van witte bloedcellen en bloedplaatjes (bij de bloedname voor het opsporen van anemie) is niet bewezen nuttig, maar wordt door sommige validatoren en experten aanzien als nuttig voor de opsporing van hematologische afwijkingen, zoals o.a. trombocytopenie.

Literature quoted by EAC 2014 guideline

- None

No EAC 2014 and no Nice 2008 recommendation on this topic.

KCE proposition to the GDG: To keep the 2004 recommendation, without modification of content.

Results of the GDG Lime survey at the beginning of June 2014 (11 respondents)

Totally agree: 4; somewhat agree: 4; rather not agree: 2; not agree at all: 1

Justification for rather not agree or not agree at all :

- Indien het geen bewezen effect of nut heeft, dient dit niet te worden aangeraden. Wanneer er bepaalde voorbeschikkende factoren zijn, kan dit eventueel, net zoals andere hemoglobinopathieën overwogen worden, maar niet in de algemene populatie...
- Gezien er hier geen wetenschappelijke evidentie is lijkt het mij nutteloos om deze bloedname te doen. Ik meen te denken dat deze gedaan wordt in het vooruitzicht van mogelijke medische ingrepen tijdens de partus (epidurale). Uiteraard is dat geen correcte medische reden om deze bloedname in de zwangerschap aan te bevelen.
- Ik ben weinig overtuigd over het nut van dit onderzoek tijdens de zwangerschap.

- Strong recommendation: 3; weak recommendation: 5

GDG comments in the Lime survey at the beginning of June 2014

- Cela permet d'avoir un taux de plaquettes de départ en comparaison avec la PS de 36w

GDG comments during the GDG meeting 16/06/2014

- It is automatically done with haemoglobin (and for the same cost)
- Some anaesthetists require this test before epidural analgesia despite it is not in recent Belgian guideline.
- 2 blood samples/ pregnancy?
- Stop after utile because the following part suggests only an expert opinion. An additional information could be that this test is systematically done in practice.
- **Conclusion: text KCE 2004 kept but sentence after utile replaced by However, in Belgium, this test is done routinely by the laborator. It is not a recommendation.**

Belgian Association for Regional Anesthesia (BARA) 2013 recommendation for laboratory tests (Grade D: expert opinion without available good scientific evidence)

In the absence of any significant medical (ASA I or II), surgical or obstetrical history, and in the absence of a history of coagulation disorder, no routine platelet count or other coagulation tests are required.

- For patients with preeclampsia or other known or suspected haemostasis disorder, a platelet count, liver function test, and coagulation screening tests are recommended.
- In case of anticipated haemorrhagic complications or suggestive history of previous allo-immunization, a blood type and screen is recommended.

KCE proposition of 2015 recommendation (No strength)

- There is no evidence that platelet and leukocyte counts is useful during pregnancy. However, in Belgium, this test is often routinely performed in the laboratory at the time of anemia detection.

GDG comments by e-mail during February 2015: None concerning the content.

No KCE 2015 recommendation proposed before stakeholders meeting but an addition of the following sentence to the recommendation on anaemia (No strength)

- There is no evidence that platelet and leukocyte counts are useful during pregnancy. However, in Belgium, this test is often routinely performed in the laboratory at the time of anaemia detection.

Results of the stakeholders Lime survey in March 2015 (6 respondents):

- Completely agree: 3; unsure: 2; non applicable: 1

Stakeholders comments during the stakeholders meeting 25/03/2014: None

KCE 2015 sentence to add to the recommendation on anemia: No strength of recommendation, Level of evidence NA

- There is no evidence that platelet and leukocyte counts are useful during pregnancy. However, in Belgium, this test is often routinely performed in the laboratory at the time of anaemia detection.
- De bepaling van witte bloedcellen en bloedplaatjes is niet bewezen nuttig tijdens zwangerschap. In België wordt deze test echter vaak routinematig uitgevoerd door het laboratorium bij een bloedname voor het opsporen van anemie.
- Il n'est pas démontré qu'une numération plaquettaire et leucocytaire soit utile pendant la grossesse. Toutefois, en Belgique, ce test est réalisé en routine par le laboratoire en même temps que la détection de l'anémie.

14.13. Blood group, rhesus and atypical red cell antibodies

Blood group, Rhesus, irregular antibodies

Should **blood group and rhesus (RhD)** be determined in all Belgian low-risk pregnant women?

Should **irregular antibodies** be detected in all Belgian low-risk pregnant women?

KCE 2004 recommendation blood group and rhesus (Grade B : Recommendation directly based on level 2 evidence or issued from a guideline based on level 1 evidence)

- S'ils sont inconnus, il est recommandé de déterminer le groupe sanguin et le rhésus (RhD), avant ou au début de la grossesse.
- Het is aan te bevelen om de bloedgroep en RhD status, indien nog niet gekend, te bepalen voor of aan het begin van de zwangerschap.

KCE 2004 recommendation irregular antibodies (Grade B : Recommendation directly based on level 2 evidence or issued from a guideline based on level 1 evidence)

- La recherche d'anticorps irréguliers est recommandée avant ou au début de la grossesse.
- De opsporing van irreguliere antistoffen is aan te bevelen voor of aan het begin van de zwangerschap.

Literature quoted by EAC 2014 guideline

- Identifying blood group and rhesus D status is important to prevent haemolytic disease of the newborn (sourced from NICE (2008) but discussion of specific topics where a practice is established is not included in the guideline.
- In the list of recommendations, EAC quotes the Nice 2008 recommendation sourced from NICE Antenatal Care. Routine Care for the Healthy Pregnant Woman (National Collaborating Centre for Women's and Children's Health. Commissioned by the National Institute for Health and Clinical Excellence. London: RCOG Press).

NICE 2008 recommendation blood group and rhesus (Grade B: Directly based on level II evidence or extrapolated recommendation from level I evidence)

- Women should be offered testing for blood group and rhesus D status in early pregnancy.

NICE 2008 recommendation irregular antibodies (Grade B: Directly based on level II evidence or extrapolated recommendation from level I evidence)

- Women should be screened for atypical red cell alloantibodies in early pregnancy and again at 28 weeks, regardless of their rhesus D status.

KCE proposition to the GDG: To keep the 2004 recommendation, without modification of content.

Results of the GDG Lime survey at the beginning of June 2014 (11 respondents)

- Totally agree: 9; somewhat agree: 2; rather not agree: 0; not agree at all: 0
- Strong recommendation: 10; weak recommendation: 1

GDG comments in the Lime survey at the beginning of June 2014

- Je supprimerais la phrase sur la détection des AC irréguliers, car non validée. Ou alors spécifier dans quels cas les rechercher.

GDG comments during the GDG meeting 16/06/2014

- AC irréguliers is not enough specific as terminology: which, how?
- This topic AC irréguliers deserves a search for new references.
- **Conclusion: first recommendation KCE 2004 unchanged; more information has to be searched before deciding to suppress or reformulate the recommendation about irregular antibodies.**

Additional information found during June-September 2014

NICE 2008 quotation:

- The main antibodies that can cause severe alloimmune anaemia in the fetus are anti-D, anti-c and anti-Kell. Of lesser importance but still with the potential to cause HDN are anti-e, -Ce, -Fya, -Jka and-Cw. Anti-Lea, -Leb, -Lua, -P, -N, -Xga and high-titre low-avidity antibodies such as anti- Kna have not been associated with HDN.

RCOG 2014 recommendation 1 (Grade D: Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+)

- All women should have their blood group and antibody status determined at booking and at 28 weeks of gestation.

RCOG 2014 recommendation 2 (Grade C: A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++)

- Non-invasive foetal genotyping using maternal blood is now possible for D, C, c, E, e and K antigens. This should be performed in the first instance for the relevant antigen when maternal red cell antibodies are present.

RCOG 2014 best practice: (Recommended best practice based on the clinical experience of the guideline development group)

- For other antigens, invasive testing (chorionic villus sampling [CVS] or amniocentesis) may be considered if fetal anaemia is a concern or if invasive testing is performed for another reason (e.g. karyotyping).

KCE proposition to the GDG be e-mail at the beginning of March 2015:

Recommendation 2 irregular antibodies :

- In 2004, the KCE guideline recommended to determine the blood group and the rhesus D but also to search for the irregular antibodies early at (or before) pregnancy. The Australian guideline did not mention it but the Nice well ("women should be screened for atypical red cell antibodies in early pregnancy and again at 28 weeks, regardless of their rhesus D status.") The Netherlands guideline also recommends to detect atypical red cell antibodies. Do you agree that we keep this recommendation:"offer each pregnant women to screen for atypical red antibodies "?

No refuse received

KCE proposition of 2015 recommendation

Recommendation 1 (Strong recommendation)

- Offer to determine each pregnant woman's blood group and rhesus (Rh) factor in early pregnancy if they are unknown.

Recommendation 2 (Strong recommendation)

- Offer each pregnant women to screen for atypical red cell antibodies.

GDG comments by e-mail during February 2015: None concerning the content.

KCE 2015 recommendation (gathering the two previous recommendations) before stakeholders meeting (Strong recommendation)

- Offer to determine in early pregnancy each pregnant woman's blood group, rhesus (Rh) factor if they are unknown and to screen for atypical red cell antibodies.

Results of the stakeholders Lime survey in March 2015 (6 respondents):

- Completely agree: 4; somewhat agree: 1; non applicable: 1

Stakeholders comments during the stakeholders meeting 25/03/2014: None

KCE 2015 recommendation: Strong recommendation, Level of evidence B *(Level of evidence from NICE 2008 guideline: B= recommendation directly based on level II evidence or extrapolated recommendation from level I evidence)*

[KCE 2004]

- Offer to determine in early pregnancy each pregnant woman's blood group and rhesus (Rh) factor if they are unknown and to screen for atypical red cell antibodies.
- Stel aan elke zwangere vrouw voor om, aan het begin van de zwangerschap (of daarvoor), haar bloedgroep en rhesusfactor (RhD) te bepalen als deze onbekend zijn en te testen voor irreguliere erytrocytenantistoffen.
- Proposez à chaque femme enceinte au début de la grossesse (ou avant) de déterminer son groupe sanguin et son rhésus (RhD) s'ils sont inconnus et proposez une recherche d'anticorps anti-erythrocytaires.

14.14. Haemoglobin disorders

Haemoglobin disorders

Should **haemoglobin disorders** be detected in all Belgian low-risk pregnant women?

KCE 2004 recommendation (Grade C : Recommendation directly based on level 3 evidence or issued from a guideline based on level 1 or 2 evidence)

- On ne dispose pas de preuves suffisantes pour recommander une détection systématique des hémoglobinopathies. Il est recommandé de pratiquer un dépistage sélectif sur base de la provenance familiale (bassin méditerranéen, ethnie à risque).
- Er is onvoldoende evidence om universele opsporing van hemoglobinopathieën te ondersteunen. Selectieve opsporing op basis van etniciteit blijft aan te bevelen.

Literature quoted by EAC 2014 guideline

- Concerning the screening of haemoglobin disorders, the RANZCOG recommends that mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH) be tested in all women (RANZCOG 2009).
- A prospective study on 439 pregnant women found that MCV had a sensitivity of 92.9% and specificity of 83.9% for thalassaemia screening (Sirichotiyakul et al. 2005). Screening using MCV and MCH will identify some but not all carriers of alpha and beta globin gene changes. It should be noted that some beta globin gene changes (e.g. sickle cell trait) result in normal red cell indices and detection relies on haemoglobin electrophoresis.
- Narrative reviews indicate screening of women at increased risk of being carriers for haemoglobin disorders can identify couples who are both carriers and have a 25% risk of having a pregnancy with a significant genetic disorder for which antenatal diagnosis is possible (Langlois et al. 2008). No studies identified harms associated with screening. One study found that being well informed about haemoglobin disorders may reduce anxiety in women who are subsequently identified as carriers (Brown et al. 2011).

EAC 2014 recommendation (Consensus-based recommendation)

- As early as possible in pregnancy, routinely provide information about haemoglobin disorders and offer screening (full blood count).

EAC 2014 practice point

- Consider offering ferritin testing and haemoglobin electrophoresis as part of initial screening to women from high-risk population groups.

KCE proposition to the GDG: To keep the conclusion in the scientific text without recommendation

Results of the GDG Lime survey at the beginning of September 2014 (10 respondents)

Totally agree: 2; somewhat agree: 5; rather not agree: 3; not agree at all: 0

GDG comments in the Lime survey the beginning of September 2014

- Negatieve aanbeveling
- Tgv een achtergronde van ethnische populatieverschuivingen en -vermenging wordt verwacht dat Hb-pathieën zullen toenemen. Gezien routinematig een Hb-bepaling wordt aanbevolen tijdens de zwangerschap, is het een kleine moeite zonder meerkost om ook MCV en MCHC mee te bepalen (cfr Australian guideline). Dit kan al een eerste screening zijn.
- Ne peut-on pas reformuler la recommandation de 2004 en la détaillant un peu plus? Proposer une électrophorèse en présence d'un facteur de risque: MCH < 27 pg et absence de carence martiale, origine à haut risque (Bassin Méditerranéen, Moyen-Orient, Afrique, Inde, Asie du Sud-Est, Chine), clinique évocatrice d'une hémoglobinopathie, partenaire originaire d'une région à haut risque.
- Je garderais la recommandation de 2004. En soulignant la nécessité d'investiguer si MCV et MCH pathologiques
- Het zou goed zijn de risico groepen te benoemen

GDG comments during the GDG meeting 10/09/2014

- Not all haemoglobin disorders are detected by a low MCV.
- Prevalence in some populations and thus in some Belgian areas is relatively high.
- Outcomes for the new-born can be severe.
- No treatment exists, the only possible proposition is termination of pregnancy.
- History taking is a time-consuming challenge (to go up until all grandfathers and grandmothers)
- Electrophoresis is not expensive
- En Belgique, il existe des recommandations de 2006 de la Société belge d'hématologie qui sugèrent de dépister la présence d'hémoglobinopathies en cas d'origine autre que l'Europe du Nord, en cas de MCV ou MCH bas ou face à une clinique évocatrice d'une anomalie de l'hémoglobine. **(http://www.redcellnet.be/quidelines/depistage_prenatal_FR.pdf)**
- **Conclusion: positive recommendation in women with increased risk according to history taking or if suspicious MCV or MCH result.**

KCE proposition of 2015 recommendation (Weak recommendation)

- Do not routinely offer each pregnant woman a hemoglobinopathy test. Offer selective screening based on the risk factors (in appendix).

GDG comments by e-mail during February 2015: None concerning the content.

KCE 2015 recommendation before stakeholders meeting (Weak recommendation)

- Do not routinely offer each pregnant woman a hemoglobinopathy test. Offer selective screening based on the risk factors (in appendix)

Results of the stakeholders Lime survey in March 2015 (6 respondents):

- Completely agree: 4; somewhat agree: 1; non applicable: 1

Stakeholders comments during the stakeholders meeting 25/03/2014: None

KCE 2015 recommendation: Weak recommendation, Level of evidence NA(CBR) (*Level of evidence from Australian 2014 guideline: CBR=Consensus based recommendation because insufficient evidence to support recommendation)*

[KCE 2004]

- Do not offer to each pregnant woman screening for haemoglobin disorders based on haemoglobin electrophoresis. Offer selective screening based on risk factors.
- Stel niet aan elke zwangere vrouw voor om te screenen naar hemoglobinopathieën door middel van elektroforese. Stel een selectieve screening voor op basis van risicofactoren (in bijlage).
- Ne proposez pas à chaque femme enceinte une détection des hémoglobinopathies par électrophorèse. Proposez de pratiquer un dépistage sélectif sur base des facteurs de risque.

14.15. Hepatitis B

Hepatitis B

Should all Belgian low-risk pregnant women be screened for **hepatitis B**?

KCE 2004 recommendation (Grade A: Recommendation directly based on level 1 evidence)

- La détection de l'hépatite B avant ou au commencement de la grossesse est recommandée afin de permettre un traitement efficace du nouveau-né d'une mère contaminée.
- De opsporing van hepatitis B is aan te bevelen voor of aan het begin van de zwangerschap om een effectieve opvolging van de pasgeborene van een besmette moeder mogelijk te maken.

Literature quoted by EAC 2014 guideline (2 level 1 & 3 level IV studies)

- Screening of all pregnant women for hepatitis B is recommended in the United Kingdom (NICE 2008) and the United States (Mast et al 2005; Lin & Vickery 2009; USPSTF 2009). The Australian Immunisation Handbook, while making recommendations on vaccination rather than screening, notes that routine antenatal screening for hepatitis B (ATAGI 2009): is essential for preventing babies from becoming carriers of hepatitis B; and enables appropriate follow-up and management of the woman, identification of the immune status of other household members, and protection of those who are susceptible.
- Screening of all women is supported by the findings of observational studies into selective screening:
    - screening using risk factors to identify 'high-risk' women for HbsAg would miss about half of all pregnant women with HbsAg infection (Summers et al. 1987);
    - of women offered examination for hepatitis B at 18 weeks pregnancy (n=4,098), one third of women at risk of hepatitis B were not identified by selective screening (Jensen et al. 2003); and
    - universal screening resulted in an estimated detection of 50 additional pregnant women carrying hepatitis B each year who would not have been detected through selective screening (Cowan et al. 2006).
- A recent systematic review (Lin & Vickery 2009) found no new evidence on the benefits or harms of testing for hepatitis B infection in pregnant women.

EAC 2014 recommendation (Grade A: Body of evidence can be trusted to guide practice)

- Routinely offer and recommend hepatitis B virus testing at the first antenatal visit as effective postnatal intervention can reduce the risk of mother-to-child transmission.

Since 1999, Belgium conducts routine vaccination of infants and of pre-teens (11-12 years old) against hepatitis B.

KCE proposition to the GDG: To keep the 2004 recommendation, but for women with unknown immun status:

- Un examen sérologique de détection des anticorps contre l'hépatite B est recommandé à toutes les femmes dont le statut immunitaire n'est pas connu, afin de pouvoir identifier les femmes non immunisées face à l'hépatite B, les sensibiliser à ce problème et permettre un traitement efficace du nouveau-né d'une mère contaminée.
- Om vrouwen die niet immuun zijn voor hepatitis B te identificeren, te sensibiliseren en een effectieve opvolging van de pasgeborene van een besmette moeder mogelijk te maken, is een serologisch onderzoek naar antistoffen voor hepatitis B aan te bevelen voor alle vrouwen, tenzij hun immuunstatuut gekend is.

Results of the GDG Lime survey at the beginning of September 2014 (10 respondents)

- Totally agree: 8; somewhat agree: 2; rather not agree: 0; not agree at all: 0
- Strong recommendation: 10; weak recommendation: 0; without answer: 0

GDG comments in the Lime survey at the beginning of September 2014

- Discussie: bij vooraf gekende immuunstatus, valt dan screening weg.

GDG comments during the GDG meeting 10/09/2014

- The GDG agrees that we have to take into account the immune status and to add this in the recommendation

- **Conclusion: recommendation KCE 2004 with one minor change**

KCE proposition of 2015 recommendation (Strong recommendation)

- For pregnant women with an unknown immune status, offer a detection of hepatitis B antibodies, as effective postnatal intervention can reduce the risk of mother-to-child transmission.

GDG comments by e-mail during February 2015: None concerning the content.

KCE 2014 recommendation before stakeholders meeting (Strong recommendation)

- For pregnant women with an unknown immune status, offer a detection of hepatitis B antibodies, as effective postnatal intervention can reduce the risk of mother-to-child transmission.

Results of the stakeholders Lime survey in March 2015 (6 respondents):

- Completely agree: 4; unsure: 1; completely disagree: 1
- 'completely disagree' I would not propose sceening with hepatitis B antibodies: first of all it has to be specifed that in this case anti-HBs are ment;secondly, routine vaccination since 1999 in Belgium does not yet justifies screening based on the assumtion that the majority of pregnant women are vaccinated (still too young those who are vaccinated). I would suggest to keep recomendation on HBsAg universal screening in pregnancy, not as proposed by anti-HBs.

Stakeholders comments during the stakeholders meeting 25/03/2014:

- Proposition to change the formulation of this recommendation from ‘hepatitis B antibodies’ to ‘HBsAg’ and to delete ‘can’ before ‘reduce’.
- **Conclusion: two minor changes proposed in the recommendation**

KCE 2014 recommendation: Strong recommendation, Level of evidence A *(Level of evidence from Australian 2014 guideline: A=One or more level I studies with a low risk of bias or several level II studies with low risk of bias)*

[KCE 2004, slightly amended]

- For pregnant women with an unknown immune status, offer a detection of HBsAg (surface antigen of the hepatitis B virus), as effective postnatal intervention reduces the risk of mother-to-child transmission.
- Stel aan zwangere vrouwen van wie de immunologische status niet gekend is, voor om te testen op de eventuele aanwezigheid van HBsAg. Dit om een doeltreffende preventie van moeder-kind transmissie toe te laten.
- Proposez, aux femmes enceintes dont le statut immunitaire n’est pas connu, une détection de l’antigène de surface du virus de l'hépatite B (Ag HBs), puisqu'il existe un traitement efficace en postnatal pour réduire le risque de transmission mère-enfant.

14.16. Hepatitis C

Hepatitis C

Should all Belgian low-risk pregnant women be screened for **hepatitis C**?

KCE 2004 recommendation (Grade C : Recommendation directly based on level 3 evidence or issued from a guideline based on level 1 or 2 evidence)

- On ne dispose pas de preuves suffisantes pour recommander la détection d'une hépatite C comme analyse de routine durant la grossesse.
- Op dit ogenblik is er onvoldoende evidence om de opsporing van hepatitis C aan te bevelen als een routine tijdens de zwangerschap.

Literature quoted by EAC 2014 guideline (3 level III-2, 1 level III-3 and 5 level IV studies)

- There is limited evidence on screening of pregnant women for hepatitis C and routine testing is advised against in the United Kingdom (NICE 2008), the United States (ACOG 2007) and Canada (CPS 2008). The Australian Department of Health and Ageing advises that routine screening of pregnant women is not a clinically justifiable or cost effective approach (DoHA 2007). Lack of effective treatment options and potential psychological harm of false positive screening results have been cited as reasons not to screen routinely (Pembrey et al. 2003; 2005).
- Some bodies recommend selective testing for hepatitis C in pregnant woman with identifiable risk factors (ACOG 2007; DoHA 2007; Hepatitis Australia 2007; CPS 2008). However, population-based cohort studies suggest that screening based on risk factors may not identify all women with hepatitis C (Hutchinson et al. 2004; Lui et al. 2009), particularly if risk factors are not present or women conceal them (Prasad et al. 2007). These studies acknowledge that screening of all women is not appropriate while an effective intervention to prevent transmission remains unavailable.

The evidence does not suggest a change to the NICE recommendation, which is consistent with DoHA recommendations for hepatitis screening and the advice of Hepatitis Australia.

EAC 2014 recommendation (Grade C: Body of evidence provides some support for recommendation(s) but care should be taken in its application)

- Do not routinely offer pregnant women hepatitis C testing.

EAC 2014 practice point 1

- **Hepatitis C testing may be offered to women with identifiable risk factors:**
  - Intravenous drug use or needle sharing
  - Tattooing or body piercing
  - Incarceration
  - Receipt of blood products or invasive procedures overseas or before 1990 in Australia
  - Country of origin has a high prevalence of hepatitis C.

EAC 2014 practice point 2

- Women who are having an invasive procedure (e.g. chorionic villus sampling, amniocentesis) should be offered screening for hepatitis C before the procedure.

In Belgium, pregnant women are not quoted in the risk groups for the screening (neither in the Belgium hepatitis C plan 2014-2019, nor in Sénat 2010: **(http://www.senate.be/www/?MIval=/publications/viewPub.html&COLL=S&LEG=5&NR=631&VOLGNR=1&LANG=fr)**

List of persons at risk :

- Les personnes ayant reçu du sang, des produits sanguins ou des organes avant la mise en place du dépistage pour le virus de l'hépatite C, ou là où le dépistage n'était pas encore fort répandu ;
- Les usagers de drogues injectables actuels ou anciens ;
- Les personnes en hémodialyse à long terme ;

- Les travailleurs des soins de santé ;
- Les personnes vivant avec le VIH ;
- Les personnes présentant des tests hépatiques anormaux ou souffrant d'une maladie hépatique ;
- Les bébés nés de mères infectées ;
- Les étrangers en provenance de pays où la prévalence est élevée (p.ex. l'Egypte)
- Les personnes ayant des relations sexuelles avec des partenaires multiples ;
- Les hommes ayant des relations sexuelles avec des hommes ;
- Les usagers de drogues non injectables ou se déclarant comme tels ;
- Les personnes qui ont eu des tatouages, piercings ou acupuncture sans utilisation de matériel personnel à usage unique.

KCE proposition to the GDG: To discuss this topic in the scientific text but not to formulate a recommendation.

Results of the GDG Lime survey at the beginning of September 2014 (10 respondents)

Totally agree: 2; somewhat agree: 5; rather not agree: 3; not agree at all: 0

GDG comments in the Lime survey at the beginning of September 2014

- Negatieve boodschap is ook een boodschap... Men kan evenuteel zeggen dat routinematig screenen niet wordt aangeraden; met in de subtekst inderdaad de risicogroepen eventueel en wanneer wel... Indien u geen aanbevelingen doet hierover, laat u een zeer grote vrijheid toe die misschien ook zijn negatieve gevolgen kan hebben. Misschien toch belangrijk om een standpunt in te nemen; indien er onvoldoende evidentie is om iets aan te raden, best af te raden, tenzij er vanuit de experten toch duidelijk een ander standpunt wordt ingenomen?
- These studies acknowledge that screening of all women is not appropriate while an effective intervention to prevent transmission remains unavailable. Wat is dan uiteindelijk het doel van evt toch screenen? Persoonlijk zou ik eerder een non-screening policy aanbevelen, tot effectieve perinatale voordelen zijn beschreven.
- La prévalence de l'hépatite C est de 2% en Belgique (ce qui n'est pas du tout négligeable) et il me paraît important de détecter les femmes infectées (on estime que 75 % des femmes infectées sont non-diagnostiquées), de protéger les partenaires sexuels, de protéger le personnel soignant, d'instaurer des mesures préventives (suivi par hépatologue), de suivre les enfants nés de femmes séropositives, d'avoir des données représentatives et de déterminer si vraiment, la voie d'accouchement n'a pas d'influence sur la transmission verticale. Par ailleurs, on finira bien par pouvoir proposer un traitement en cours de grossesse.
- Ne pas recommander le dépistage sauf chez les femmes à risque (cf EAC 2014 practice)
- Misschien is het wel een goed idee om de risicogroepen te beschrijven en hierbij aan te vullen dat bij hen screening van groter belang is.

GDG comments during the GDG meeting 10/09/2014

- According to the GDG, due to the current lack of treatment, the balance benefit-harm is not in favour of the hepatitis C screening. There is no medical justification to perform hepatitis C screening during pregnancy because the result will not change anything in the pregnancy outcomes.
- Take pregnancy as an opportunity to test the global health of women is out of scope in this guideline. It would be preferable to ask general practitioners to perform a screening in their population because men also should have access to this screening.
- One respondent of the Lime Survey is in favour of the screening and provides some arguments for this: protection of sexual partners, healthcare professionals, etc. The GDG replies that the quoted reasons are more social than medical:
- Prevalence of hepatitis C: not the same in all areas; in some hospital, prevalence is high and maybe deserves specific management. It will be considered in the scientific text added to the recommendation
- Protection of healthcare practitioners: asked by some anesthesists before any anesthesia; to be linked with the local prevalence of hepatitis C.
- New treatments are possible but not yet in use. To take this into account, the GDG proposes to add currently in the scientific text.
- Antibodies measurement is not expensive at an individual level but if we consider 120 000 pregnancy/year and if we add the follow-up of the screening, this is not cheap.
- A screening focusing only on people with high risk is not sufficient because history taking is not accurate. For example, piercings and tattoos are theoretical sources of risk but they are controlled in Belgium and the use of a same needle several times should be rare. However which person with tattoos knows if the needle was new?

KCE proposition of 2015 recommendation (Weak recommendation)

- Do not routinely offer each pregnant woman hepatitis C testing

GDG comments by e-mail during February 2015:

- Ik weet niet of deze aanbeveling wel zo "weak" is, er is in elk geval niets dat men kan doen als patiente een HepC -draagster is; weglaten

KCE 2015 recommendation before stakeholders meeting (Weak recommendation)

- Do not routinely offer each pregnant woman hepatitis C testing

Results of the stakeholders Lime survey in March 2015 (6 respondents):

- Completely agree: 2; unsure: 2; somewhat disagree: 2
- 'somewhat disagree' I would propose to add as in Australian 2014 guideline that "hepatitis C screening may be offered to women with some identifiable risk factors (IVD-users, tattoing or body piercing, incarceration, recept of blood products or invasive procedures before 1990, coutry of origin with a high prevalence of hepatitis C).

Stakeholders comments during the stakeholders meeting 25/03/2014:

- Proposition to add as additional information in the text (but not in the recommendation box) that such screening may be offered to women with some identifiable risk factors (e.g. women with a history of intravenous drug use, tattoos or body piercing, needle sharing, incarceration).
- **Conclusion: recommendation unchanged but addition in the text that this screening can be offered in women with risk factors**

KCE 2015 recommendation: Weak recommendation, Level of evidence C *(Level of evidence from Australian 2014 guideline: C=One or two level III studies with a low risk of bias or level I or II studies with a moderate risk of bias*)

[KCE 2004, amended]

- Do not routinely offer to each pregnant woman hepatitis C testing.
- Stel niet routinematig aan elke zwangere vrouw voor om een serologisch onderzoek voor hepatitis C te verrichten.
- Ne proposez pas systématiquement à chaque femme enceinte une détection de l'hépatite C.

14.17. HIV

HIV

Should all Belgian low-risk pregnant women be screened for **HIV**?

KCE 2004 recommendation (Grade A: Recommendation directly based on level 1 evidence)

- Il est recommandé de proposer un test HIV à toute femme avant ou au commencement de la grossesse après lui en avoir expliqué l'utilité.
- Het is aan te bevelen om het nut van een HIV-test met elke vrouw voor of aan het begin van de zwangerschap te bespreken en deze vervolgens ook aan te bieden.

Literature quoted by EAC 2014 guideline

- Universal screening for HIV in pregnancy is recommended in the United Kingdom (de Ruiter et al. 2008; NICE 2008; RCOG 2010), the United States (Branson et al. 2006) and Canada (SOGC 2006; CPS 2008). The Australian Department of Health and Ageing also recommends that all women be routinely offered HIV screening in the first trimester (DoHA 2006). These policies are based on the availability of accurate diagnostic tests and effectiveness of antiretroviral treatment in preventing mother-to-child transmission. They also reflect the fact that screening based on risk factors would miss a substantial proportion of women with HIV (Chou et al. 2005).
- Tests for HIV diagnosis in pregnant women include:
    - standard tests - the enzyme immunoassay and Western blot protocol is highly (>99%) sensitive and specific (Samson & King 1998; Butlerys et al 2004; Chou et al 2005; Chappel et al 2009); and
    - rapid HIV tests which have similar accuracy (Butlerys et al 2004; Chou et al 2005) and provide results within hours without requiring a return visit (Tepper et al 2009), with blood-based tests having greater sensitivity than tests using oral fluids (Pai et al 2007).
- Prospective cohort studies and meta-analyses have not found a significant association between antiretroviral treatments and intrauterine growth restriction (n=8,192) (Briand et al 2009), congenital abnormalities (n=8,576)(Townsend et al 2009), or preterm birth (n=20,426)(Kourtis et al 2007).
- Providing information and support associated with testing aims to minimise the personal and social impact of HIV infection (DoHA 2006).

Current available evidence supports the 2003 NICE recommendations for HIV screening in first trimester of pregnancy.

EAC 2014 recommendation (Grade B: Body of evidence can be trusted to guide practice in most situations)

- Routinely offer and recommend HIV testing at the first antenatal visit as effective interventions are available to reduce the risk of mother-to-child transmission.

EAC 2014 Practice point

- A system of clear referral paths ensures that pregnant women who are diagnosed with an HIV infection are managed and treated by the appropriate specialist teams.

KCE proposition to the GDG: To keep the 2004 recommendation, without modification of content.

Results of the GDG Lime survey at the beginning of September 2014 (10 respondents)

- Totally agree: 8; somewhat agree: 2; rather not agree: 0; not agree at all: 0
- Strong recommendation: 8; weak recommendation: 1; without answer: 1

GDG comments in the Lime survey at the beginning of September 2014

- La connaissance de la patiente et son suivi depuis de nombreuses années ainsi que l'anamnèse peut permettre de s'en passer
- ik denk dat het meer mag zijn dan enkel bespreken, ik denk dat testing voor HIV zou moeten aangeboden en aanbevolen, aan iedereen

GDG comments during the GDG meeting 10/09/2014

- In the 2004 recommendation, the test was proposed before or during pregnancy. However, if the test is performed before pregnancy, the risk remains that pregnant woman is infected more recently. To avoid missing recent infections, the test should be performed at the beginning of pregnancy.

- **Conclusion: recommendation KCE 2004 with one minor change**

KCE proposition of 2015 recommendation (Strong recommendation)

- Offer to each pregnant woman HIV testing at the beginning of pregnancy after having explained to her why it is useful.

GDG comments by e-mail during February 2015: None concerning the content.

KCE 2015 recommendation before stakeholders meeting (Strong recommendation)

- Offer to each pregnant woman HIV testing at the beginning of pregnancy after having explained to her why it is useful.

Results of the stakeholders Lime survey in March 2015 (6 respondents):

- Completely agree: 5; somewhat agree: 1

Stakeholders comments during the stakeholders meeting 25/03/2014: None

KCE 2015 recommendation: Strong recommendation, Level of evidence B *(Level of evidence from Australian 2014 guideline: B=One or two level II studies with a low risk of bias or systematic review/several level III studies with a low risk of bias)*

[KCE 2004, slightly amended]

- Offer to each pregnant woman HIV testing at the beginning of pregnancy after having explained to her why it is useful.
- Stel aan elke zwangere vrouw een HIV-test voor aan het begin van de zwangerschap na het nut ervan te hebben uitgelegd.
- Proposez à chaque femme enceinte un test HIV au commencement de la grossesse après lui en avoir expliqué l'utilité.

14.18. Rubella

Rubella

Should all Belgian low-risk pregnant women be screened for **rubella**?

KCE 2004 recommendation (Grade B : Recommendation directly based on level 2 evidence or issued from a guideline based on level 1 evidence)

- Un examen sérologique de détection des anticorps contre la rubéole est recommandé à toutes les femmes dont le statut immunitaire n'est pas connu, afin de pouvoir identifier les femmes non immunisées face à la rubéole, les sensibiliser à ce problème et permettre leur vaccination en période de post-partum.
- Om vrouwen die niet immuun zijn voor rubella te identificeren, te sensibiliseren en een vaccinatie in het postpartum mogelijk te maken, is een serologisch onderzoek naar antistoffen voor rubella aan te bevelen voor alle vrouwen voor of aan het begin van de zwangerschap, tenzij hun immuniteitsstatus gekend is.

Literature quoted by EAC 2014 guideline

- The NICE guidelines reviewed the evidence on rubella screening in pregnancy and found:
  - high sensitivity and specificity of tests for immunity [Roche Rubella IgM eEIA recomb: Se 99.3%, Sp 100%; Abbott IMx Rubella IgM test: Se 98.3%, Sp 93.9%; Sorin ETI-RUBIK-M reverse test: Se 100%, Sp 82.7%] (Grangeot-Keros & Enders 1997);
  - high rates of congenital infection among babies born to women with symptoms of rubella in the first 12–16 weeks of pregnancy (>80% in first 12 weeks, Miller et al. 1982; 57% to 70% from weeks 9 to 16, Grillner et al. 1983); and
  - no association between congenital infections and inadvertent rubella vaccination in pregnancy (CDC 2001).
- The lack of association between inadvertent vaccination in pregnancy and congenital rubella syndrome has been substantiated in subsequent prospective cohort studies (3 level II studies), with no cases reported (Bar-Oz et al. 2004; Hamkar et al. 2006; Badilla et al. 2007).

There was insufficient new evidence to change the NICE recommendation.

EAC 2014 recommendation 1 (Grade B: Body of evidence can be trusted to guide practice in most situations)

- Routinely offer women testing for rubella immunity at the first antenatal visit to identify women at risk of contracting rubella and enable postnatal vaccination to protect future pregnancies.

EAC 2014 recommendation 2 (Grade A: Body of evidence can be trusted to guide practice)

- Inform women who have been vaccinated against rubella before they were aware of the pregnancy that the baby is highly unlikely to have been affected by the vaccine.

EAC 2014 practice point

- Women identified as non-immune to rubella antenatally should be advised to avoid contact with people experiencing possible symptoms of rubella.

KCE proposition to the GDG: To keep the 2004 recommendation, without modification of content.

Results of the GDG Lime survey at the beginning of September 2014 (10 respondents)

- Totally agree: 9; somewhat agree: 1; rather not agree: 0; not agree at all: 0
- Strong recommendation: 9; weak recommendation: 0; without answer: 1

GDG comments in the Lime survey at the beginning of September 2014: None

GDG comments during the GDG meeting 10/09/2014

- No comment
- **Conclusion: unchanged content of the recommendation KCE 2004**

KCE proposition of 2015 recommendation (Strong recommendation)

- For pregnant women with an unknown immune status, offer a detection of antibodies against rubella, in order to identify women who are not immune to rubella, make them aware of this problem and to vaccinate them during the postpartum period

GDG comments by e-mail during February 2015:

- Long sentence… two sencentces would be better**;** supprimer "proposez"==> "chez les femmes enceintes dont le statut immunitaire n'est pas connu, il faut une détection des anticorps contre la rubéole, .."

KCE 2015 recommendation before stakeholders meeting (Strong recommendation)

- For pregnant women with an unknown immune status, offer a detection of antibodies against rubella, in order to identify women who are not immune to rubella, make them aware of this problem and to vaccinate them during the postpartum period.

Results of the stakeholders Lime survey in March 2015 (6 respondents):

- Completely agree: 4; somewhat agree: 1; somewhat disagree: 1
- 'somewhat disagree' I would propose to add that testing of IgG is ment, not IgM and that the IgG testing should be offered in the beginning of the pregnancy/first trimester.

Stakeholders comments during the stakeholders meeting 25/03/2014:

- Change "make them aware of this problem" by "advise to pregnant women to stay away from anyone who has a skin rash"
  Llimit the serological tests to IgG testing (and not including IgM)
- Specify the test should be performed at the beginning of pregnancy.
- **Conclusion: three minor changes proposed in the recommendation**

KCE 2015 recommendation: Strong recommendation, Level of evidence B *(Level of evidence from Australian 2014 guideline: B=One or two level II studies with a low risk of bias or systematic review/several level III studies with a low risk of bias)*

[KCE 2004, slightly amended]

- For pregnant women with an unknown immune status, offer at the beginning of pregnancy (or before) to test for IgG antibodies against rubella, in order to identify women who are not immune to rubella, to advise them to avoid sick people with skin rash and to vaccinate them during the postpartum period.
- Stel aan zwangere vrouwen van wie de immunologische status niet gekend is, voor om te testen op IgG antilichamen tegen rubella. Dit om de vrouwen te identificeren die niet geïmmuniseerd zijn tegen rubella, hen te adviseren om personen met huiduitslag te vermijden en eventueel een vaccinatie toe te dienen tijdens het post-partum.
- Proposez, aux femmes enceintes dont le statut immunitaire n'est pas connu, une détection des anticorps IgG contre la rubéole, au début de la grossesse (ou avant). Cette détection a pour but d'identifier les femmes non immunisées contre la rubéole, de leur conseiller d'éviter d'être en contact avec des personnes présentant une éruption cutanée et de permettre leur vaccination en période de post-partum.

14.19. Syphilis

Syphilis

Should all Belgian low-risk pregnant women be screened for **syphilis**?

KCE 2004 recommendation (Grade B : Recommendation directly based on level 2 evidence or issued from a guideline based on level 1 evidence)

- Un traitement étant favorable pour le pronostic tant de la mère que de l'enfant, il est recommandé de soumettre toutes les femmes à une analyse de détection de la syphilis, avant ou au commencement de la grossesse au moyen d'un test d'hémagglutination passive pour le sérodiagnostic de la syphilis.
- Het is aan te bevelen om alle vrouwen voor of aan het begin van de zwangerschap te testen op syfilis aan de hand van een treponemale test omdat een behandeling gunstig is voor de prognose van zowel moeder als foetus.

Literature quoted by EAC 2014 guideline (2 level II and 3 level III-2 studies confirmed the diagnostic accuracy of tests for syphilis; 2 level I studies, 1 level II study, 2 level III-2 studies and 1 level III-3 study confirmed the effectiveness of treatment for syphilis).

- Universal syphilis screening programs have been shown to significantly increase the detection of pregnant women who have syphilis compared with selective screening of women considered to be a high-risk (Cameron et al. 1997; Duthie et al. 1990; Villar & Bergsjo 1997; Hurtig et al. 1998).
- Based on convincing observational evidence, universal screening of pregnant women is recommended by the United States Preventive Services Task Force (USPST 2009; Wolff et al 2009), the World Health Organization (WHO 2004), the International Union against Sexually Transmitted Infections (IUSTI) (French et al. 2009) and the United Kingdom national guidelines on the management of syphilis (Kingston et al. 2008) as it decreases the proportion of babies with clinical symptoms of syphilis infection.
- Universal screening for syphilis has been shown to be cost-effective (Garland & Kelly 1989; Abyad 1995; Cameron et al. 1997; Connor et al. 2000; Walker 2001) even in areas of low prevalence.

The new evidence did not warrant changing the NICE recommendation.

EAC 2014 recommendation (Grade B: Body of evidence can be trusted to guide practice in most situations)

- Routinely offer and recommend syphilis testing at the first antenatal visit as treating syphilis benefits both mother and baby.

EAC 2014 practice point

- Because syphilis is a rare condition in most parts of Australia and a positive result does not necessarily mean that a woman has syphilis, expert advice regarding the care of women who test positive and their partners should be sought. Assessment/testing for other sexually transmitted infections in women with positive serology is advisable.

KCE proposition to the GDG: To keep the 2004 recommendation, without modification of content.

Results of the GDG Lime survey at the beginning of September 2014 (10 respondents)

- Totally agree: 9; somewhat agree: 1; rather not agree: 0; not agree at all: 0
- Strong recommendation: 8; weak recommendation: 1; without answer: 1

GDG comments in the Lime survey at the beginning of September 2014

- A moduler selon la connaissance « de la patiente », le suivi depuis longtemps et l'anamnèse
- Ik denk dat ook geargumenteerd mag worden dat screeningstests en behandeling van Syphilis uitermate goedkoop zijn, waardoor screening in een populatie met een lage prevalentie toch nog zinvol is.

GDG comments during the GDG meeting 10/09/2014

- Even if the prevalence is low, the screening is cheap and a treatment exists.
- **Conclusion: unchanged content of the recommendation KCE 2004**

KCE proposition of 2015 recommendation (Strong recommendation)

- As treatment is favourable for the prognosis of both the mother and child, offer each pregnant woman a syphilis test, in the beginning of pregnancy (or before) using a passive hemagglutination test for the syphilis serodiagnosis.

GDG comments by e-mail during February 2015:

- **KCE question: Do you agree we avoid to specify the test?** Yes (3 x); seems to be a policital decision, but yes; oui, on ne le précise pas non plus pour le déppistage HIV; no idea is this the best method, then why not suggesting it? it is available in BE?; Inderdaad, het type van test in recent in het ZOL gewijzigd.

KCE 2015 recommendation before stakeholders meeting (Strong recommendation)

- As treatment is favourable for the prognosis of both the mother and child, offer each pregnant woman a syphilis test, in the beginning of pregnancy (or before).

Results of the stakeholders Lime survey in March 2015 (6 respondents):

- Completely agree: 4; unsure: 1; completely disagree: 1

Stakeholders comments during the stakeholders meeting 25/03/2014:

- Treponemal IgG EIA tests have high sensitivity and specificity at all stages of syphilis (except early primary syphilis) whereas non-treponemal tests may result in false negatives, particularly in very early or late syphilis, in patients with reinfection or those who are HIV positive, and have poor positive predictive value when used alone in low prevalence populations.
- The initial test is usually a test for antibodies of treponema (eg enzyme immunoassay), which identifies women with current untreated or incompletely treated infection or previous history of treated syphilis. If the test is positive, a non-treponemal test will be performed by the laboratory to confirm diagnosis and enable a quantitative value of disease activity to guide treatment.
- The INAMI/RIZIV recommends to screen syphilis in the beginning of pregnancy with the “Treponema Pallidum Hemagglutination (TPHA)” test. (INAMI. Biologie Clinique. Prescription rationnelle. Recommandations : - le dépistage opportuniste (ou non) des maladies fréquentes ; - le suivi de la grossesse. Juin 2011).
- This precision was added in the KCE 2004 guideline (French version only), but it was proposed to erase such a precision for the KCE 2015 guideline (because of the risk of evolution in the selection of test).
- **Conclusion; to add the whole explanation on the different tests in the section ‘other considerations’.**

KCE 2015 recommendation: Strong recommendation, Level of evidence B *(Level of evidence from Australian 2014 guideline: B=One or two level II studies with a low risk of bias or systematic review/several level III studies with a low risk of bias)*

[KCE 2004]

- As treatment is favourable for the prognosis of both the mother and child, offer each pregnant woman to test for, in the beginning of pregnancy (or before).
- Stel aan elke zwangere vrouw voor om te testen op syfilis, aan het begin van de zwangerschap (of daarvoor), gezien een behandeling gunstig is voor de prognose van zowel moeder als kind.
- Un traitement étant favorable pour le pronostic tant de la mère que de l'enfant, proposez à chaque femme enceinte une détection de la syphilis, au commencement de la grossesse (ou avant).

14.20. Herpes simplex

Herpes simplex

Should all Belgian low-risk pregnant women be screened for **herpes simplex**?

KCE 2004 recommendation

- On ne dispose pas de preuves suffisantes pour recommander en routine un examen sérologique de recherche d'Herpes simplex.
- Er is geen evidence om een routine (typespecifiek) serologisch onderzoek naar herpes simplex aan te bevelen.

Topic not mentioned by EAC 2014 guideline but referral to the RCOG guideline (http://www.rcog.org.uk/files/rcog-corp/uploaded-files/GT30GenitalHerpes2007.pdf)

- One study has evaluated the use of serum screening for HSV for a hypothetical cohort of women in early pregnancy with no clinical history of HSV infection, using a decision analysis model (Cleary et al. 2005). The study compared universal serum screening and targeted screening (for women estimated to be at high risk of infection) with current care (no screening). Although both screening strategies reduced cases of neonatal transmission and caesarean section deliveries for recurrent herpes, there were very high medical resource costs. As the most recent UK surveillance data (1986–1991) demonstrated a very low incidence of neonatal herpes, it seems unlikely that such a screening programme would be cost-effective at the present time.

RCOG 2007 recommendation (Grade C: Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (Evidence level IV))

- Identifying women susceptible to acquiring genital herpes in pregnancy by means of type-specific screening for HSV antibodies in pregnancy is not currently indicated.

KCE proposition to the GDG: To discuss this topic in the scientific text but not to formulate a recommendation.

Results of the GDG Lime survey at the beginning of September 2014 (10 respondents)

Totally agree: 7; somewhat agree: 1; rather not agree: 2; not agree at all: 0

GDG comments in the Lime survey at the beginning of September 2014

- Negatieve aanbeveling is beter dan geen aanbeveling
- Pourquoi ne pas dire qu'il n'y a pas d'évidence pour recommander un dépistage de routine?
- Sommige universitaire centra in België adviseren evenwel om universeel te screenen naar VARICELLA. What about this?

GDG comments during the GDG meeting 10/09/2014

- The risk of herpes simplex is vertical transmission during delivery. A screening during pregnancy does not change the outcome of the pregnancy.
- It would be better to focus on history taking and to check before the delivery by a clinical examination if the women is infected.
- **Conclusion: to change in a negative recommendation**

KCE proposition of 2015 recommendation (Weak recommendation)

- Do not routinely offer each pregnant woman a serological test for herpes simplex.

GDG comments by e-mail during February 2015:

- Volgens mij is dit "strong"!
- Weglaten

KCE 2015 recommendation before stakeholders meeting (Weak recommendation)

- Do not routinely offer pregnant women a serological test for herpes simplex.

Results of the stakeholders Lime survey in March 2015 (6 respondents):

- Completely agree: 4; unsure: 1; non applicable: 1

Stakeholders comments during the stakeholders meeting 25/03/2014: None

KCE 2015 recommendation: Weak recommendation, Level of evidence IV (*Level of evidence from RCOG 2007: IV= evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality)*

[KCE 2004, amended]

- Do not routinely offer pregnant women a serological test for herpes simplex.
- Stel niet routinematig aan zwangere vrouwen voor om een serologisch onderzoek voor herpes simplex te verrichten.
- Ne proposez pas systématiquement aux femmes enceintes un examen sérologique de recherche de l'herpès simplex.

14.21. Varicella

Varicella

Should all Belgian low-risk pregnant women be screened for **varicella**?

KCE 2004 recommendation

- On ne dispose pas de preuves suffisantes pour recommander en routine un examen sérologique de recherche des anticorps contre la varicelle.
- Er is geen evidence om een routine serologisch onderzoek naar antistoffen voor varicella aan te bevelen.

Topic not mentioned by EAC 2014 guideline but referral to the RCOG guideline (http://www.rcog.org.uk/files/rcog-corp/uploaded-files/GT13ChickenpoxinPregnancy2007.pdf)

- Although a recent study has demonstrated that antenatal varicella screening by history and serological testing for VZIG antibody in those with a negative history followed by postpartum vaccination was cost effective (Pinot de Moira 2006), this is not currently part of a UK screening programme.

No EAC 2014, NICE 2008 or RCOG 2007 recommendation

The Belgian Superior health council (Conseil Supérieur de la Santé – Hoge Gezondheid Raad 2005) had edited in 2005 some recommendations regarding vaccination against varicella http://www.health.fgov.be/internet2Prd/groups/public/@public/@shc/documents/ie2divers/7428387_fr.pdf

http://www.health.belgium.be/internet2Prd/groups/public/@public/@shc/documents/ie2divers/7428387.pdf

- Les femmes non-immunes en âge de procréer peuvent être vaccinées moyennant une contraception d'un mois. Les femmes non-immunes qui allaitent ou non leur bébé peuvent être vaccinées après l'accouchement, avec un délai de 3 mois si elles ont reçu des immunoglobulines, par exemple, contre le facteur Rhésus.
- Contrairement aux enfants chez qui l'anamnèse est généralement fiable, environ 90% des personnes de plus de 17 ans qui pensent ne pas avoir fait la varicelle, s'avèrent posséder des anticorps. Vu que cette analyse est gratuite pour le patient et a un prix de revient dix fois moindre que le prix de deux doses de vaccins; il y a intérêt à faire une sérologie avant de procéder à la vaccination.
- Niet-immune vrouwen op vruchtbare leeftijd kunnen ingeënt worden mits contraceptie gedurende een maand. Niet-immune vrouwen, ongeacht of zij borstvoeding geven, kunnen na de bevalling ingeënt worden, met inachtname van een termijn van 3 maanden in geval zij immunoglobulinen, b.v. tegen de Rhesus-factor, ontvangen hebben.
- In tegenstelling tot kinderen, bij wie de anamnese met betrekking tot varicella meestal betrouwbaar is, blijkt dat ongeveer 90% van de personen ouder dan 17 jaar, die menen varicella niet te hebben doorgemaakt, toch antilichamen hebben. Aangezien de analyse van antistoffen gratis is voor de patiënt en tien maal minder duur is dan de prijs van twee dosissen vaccin, verdient het de voorkeur een serologische analyse uit te voeren vooraleer tot de vaccinatie over te gaan.

KCE proposition to the GDG: To keep the conclusion in the scientific text without recommendation

Results of the GDG Lime survey at the beginning of September 2014 (10 respondents)

Totally agree: 5; somewhat agree: 3; rather not agree: 2; not agree at all: 0

GDG comments in the Lime survey at the beginning of September 2014

- Negatieve aanbeveling
- Ik vind dat deze wetenschappelijke guideline het advies van de HGR op zijn minst mag milderen en in een juiste context plaatsen: er is nog altijd niet bewezen dat universele varicella-screening tijdens de zwangerschap kosteneffectief is.
- Dit is een thema dat voornamelijk preconceptioneel dient besproken te worden met de cliënt, gezien het feit dat vaccinatie enkel mogelijk is buiten de zwangerschap.
- Pour ma part, je dose systématiquement les AC, car chaque année, il y a des épidémies de varicelle et les patientes téléphonent systématiquement pour savoir si elles ont un risque ou non.

GDG comments during the GDG meeting 10/09/2014

- In Belgium, a large proportion of women are infected by varicella during childhood. In the Netherlands, it is proposed to base the screening on history taking: if the women do not know if they had varicella and if they had a recent contact with an infected person, a test is performed. History taking has been shown to be reliable in terms of positive predictive value.
- The varicella problem is not far different from the rubella: a screening is interesting for the non-protected women, to provide them some advice (such as avoiding contact with infected people) and to propose vaccination after delivery.
- **Conclusion: positive recommendation in women with no previous infection according to history taking.**

KCE proposition of 2015 recommendation (Weak recommendation)

- For pregnant women who have not had chickenpox according to their medical history, consider to carry out a serological test to search for antibodies against chicken pox."

GDG comments by e-mail during February 2015

- Weglaten

KCE 2015 recommendation before stakeholders meeting (Weak recommendation)

- For pregnant women who have not had chickenpox according to their medical history, consider to carry out a serological test to search for antibodies against chicken pox.

.

Results of the stakeholders Lime survey in March 2015 (6 respondents):

- Completely agree: 1; somewhat agree: 1; unsure: 1; somewhat disagree: 2; completely disagree: 1
- 'somewhat disagree' anamnese blijft belangrijk; algemene richtlijnen te geven; indien contact met varicella dan controle patiente
- 'somewhat disagree' I would add that also here as for determination of immunse status for rubella only IgG testing is sufficient.

Stakeholders comments during the stakeholders meeting 25/03/2014:

- Limit the serological tests to IgG testing (to define the immune status)
- Add: 'Pregnant women should stay away from anyone who has varicella or a skin rash'
- **Conclusion: two minor changes proposed in the recommendation**

KCE 2015 recommendation: Weak recommendation, Level of evidence not applicable,

[KCE 2004, amended]

- For pregnant women who have not had varicella according to their medical history, consider to perform a detection of IgG against varicella. Non-immune pregnant women should stay away from anyone who has chickenpox or a skin rash.
- Overweeg om bij zwangere vrouwen met een negatieve anamnese voor varicella in de voorgeschiedenis, een serologisch onderzoek naar IgG-antilichamen tegen varicella te verrichten. Niet-immune zwangere vrouwen vermijden best contact met personen die varicella doormaken.
- Pour les femmes enceintes qui n'ont aucun antécédent de varicelle selon l'anamnèse, envisagez d'effectuer un examen sérologique de recherche des anticorps IgG contre la varicelle. Les femmes enceintes devraient éviter d'être en contact avec des personnes présentant une varicelle ou une éruption cutanée.

14.22. Asymptomatic bacterial vaginosis

Asymptomatic bacterial vaginosis

Should all Belgian low-risk pregnant women be screened for **asymptomatic bacterial vaginosis**?

KCE 2004 recommendation (Grade A: Recommendation directly based on level 1 evidence)

- On ne dispose pas de preuves suffisantes pour recommander une détection de routine de la vaginite bactérienne asymptomatique. Les données probantes suggèrent, en effet, que la détection et le traitement de la vaginite bactérienne asymptomatique ne changent rien au risque de naissance prématurée.
- Er is onvoldoende evidence om een routine opsporing van asymptomatische bacteriële vaginosis aan te bevelen. Evidence suggereert immers dat de opsporing en behandeling van asymptomatische bacteriële vaginosis niets verandert aan het risico op preterme geboorte.

Literature quoted by EAC 2014 guideline

- Routine screening for asymptomatic bacterial vaginosis in pregnancy is not recommended in the United Kingdom (NICE 2008), the United States (USPSTF 2008) or Canada (SOGC 2008).
- The systematic review supporting the United States statement (Nygren et al 2008) found that:
  - no studies directly addressed the adverse effects of screening pregnant women who are asymptomatic for bacterial vaginosis;
  - there is no clear benefit for the general population from screening and treating asymptomatic bacterial vaginosis during pregnancy; and
  - although a subgroup of high-risk women may benefit from screening and treatment for bacterial vaginosis in pregnancy, a sizeable group would receive either no benefit or may experience harm.

EAC 2014 recommendation (Grade B: Body of evidence can be trusted to guide practice in most situations)

- Do not routinely offer pregnant women testing for bacterial vaginosis.

KCE proposition to the GDG: To discuss this topic in the scientific text but not to formulate a recommendation.

Results of the GDG Lime survey at the beginning of September 2014 (10 respondents)

Totally agree: 5; somewhat agree:; 4 rather not agree:1; not agree at all: 0

GDG comments in the Lime survey at the beginning of September 2014

- Ik zou toch een negatieve aanbeveling 'routine opsporing van asymptomatische bacteriële vaginosis wordt niet aanbevolen' doen... als iets niet wordt aangeraden, wordt het afgeraden, dus bijgevolg is dit ook een belangrijke aanbeveling, niet? Indien voordien ook niet werd gekozen om negatieve aanbevelingen te doen, kan het zijn dat heel de literatuurzoektocht tot weinig heeft geleid, indien mensen enkel op zoek gaan naar de aanbeveling en niet de toelichting lezen... het lijkt mij duidelijk dat de potentiële nadelen niet opwegen tegen de potentiële voordelen...
- D'accord évidement pour aborder ce sujet en recommandant de ne pas screener vu le peu de données probantes mais en soulignant que chez certaines femmes à haut risque (lesquelles?), le screening peut avoir de l'intérêt
- What about the high risk group (of ligt dit buiten de scope van de guideline)? **S**creening voor BV lijkt zinvol in de groep met een voorgeschiedenis van preterme geboorte (vb J Perinat Neonatal Nurs. 2012 Jul-Sep;26(3):220-9. Reducing recurrent preterm births: best evidence for transitioning to predictive and preventative strategies. Cypher RL.)
- Il y a confusion entre les termes français vaginite et anglais vaginose, la vaginose étant due à la prolifération de germes normalement présents dans le vagin (gardnerella vaginalis)
- Het gaat hier over nl zwangeren, => subgroep is dit niet: afbakenen is belangrijk

GDG comments during the GDG meeting 10/09/2014

- In French, the word vaginite was used in 2004 in the KCE recommendation but vaginose is more correct. The GDG proposes to change it.
- Given a positive result, treatment is often offered systematically despite uncertainties of efficacy and despite potential harmful effect. The balance benefit-harm is not in favour of this test.
- **Conclusion: to change in a negative recommendation.**

KCE proposition of 2015 recommendation (Weak recommendation)

- Do not routinely offer each pregnant woman testing for asymptomatic bacterial vaginosis. In fact, evidence suggests that the detection and treatment of asymptomatic bacterial vaginosis does not have any effect on the risk of premature birth.

GDG comments by e-mail during February 2015: None concerning the content.

KCE 2015 recommendation before stakeholders meeting (Weak recommendation)

- Do not routinely offer pregnant women testing for asymptomatic bacterial vaginosis. In fact, evidence suggests that the detection and treatment of asymptomatic bacterial vaginosis does not have any effect on the risk of premature birth.

Results of the stakeholders Lime survey in March 2015 (6 respondents):

- Completely agree: 5; unsure: 1
- 'completely agree' eventueel wel bij voorgeschiedenis van vroeggeboorte

Stakeholders comments during the stakeholders meeting 25/03/2014: None

KCE 2015 recommendation: Weak recommendation, Level of evidence B *(Level of evidence from Australian 2014 guideline: B=One or two level II studies with a low risk of bias or systematic review/several level III studies with a low risk of bias)*

[KCE 2004, amended]

- Do not routinely offer pregnant women to test for asymptomatic bacterial vaginosis. In fact, evidence suggests that the detection and treatment of asymptomatic bacterial vaginosis does not have any effect on the risk of premature birth.
- Stel niet routinematig aan zwangere vrouwen voor een test voor asymptomatische bacteriële vaginose uit te voeren. De gegevens van het onderzoek suggereren namelijk dat de detectie en behandeling van asymptomatische bacteriële vaginose niets verandert aan het risico op vroeggeboorte.
- Ne proposez pas à toutes les femmes enceintes d'effectuer une détection de routine de la vaginose bactérienne asymptomatique. Les données probantes suggèrent, en effet, que la détection et le traitement de la vaginose bactérienne asymptomatique ne changent rien au risque de naissance prématurée.

14.23. Asymptomatic bacteriuria

Asymptomatic bacteriuria

Should all Belgian low-risk pregnant women be screened for **asymptomatic bacteriuria**?

KCE 2004 recommendation (Grade A: Recommendation directly based on level 1 evidence)

- Un examen direct des urines provenant d'un échantillon du milieu de jet en vue du comptage des globules blancs et de la détection d'une bactériurie asymptomatique est recommandé à titre d'examen de routine durant la grossesse. Le plus souvent, il est recommandé dans la littérature d'effectuer cette culture au moment de la 1ère consultation, cependant, il n'existe pas de données probantes à ce sujet.
- Een midstream pyurie bepaling/urinecultuur voor de opsporing van asymptomatische bacteriurie is aan te bevelen als een routine-onderzoek tijdens de zwangerschap. De optimale timing voor een urinecultuur en de behandeling van asymptomatische bacteriurie is ongekend. Voorlopig wordt de eerste raadpleging voorgesteld, aangezien dit tijdstip het meest wordt gehanteerd in de beschikbare evidence.

Literature quoted by EAC 2014 guideline

- Universal screening for asymptomatic bacteriuria in pregnancy is recommended in the United Kingdom (NICE 2008), the United States (USPSTF 2004; Nicolle et al. 2005), Canada (Nicolle 1994) and Scotland (SIGN 2006), based on the effectiveness of available treatments and the reduced risk of pyelonephritis.
- Screening for asymptomatic bacteriuria has been shown to reduce the number of women per 1,000 who experience pyelonephritis from 23.2 with no screening, to 16.2 with dipstick testing and 11.2 with urine culture (Rouse et al. 1995). Both tests were found to be cost beneficial compared to no screening.
- The universal screening is supported by a Cochrane review (Smaill & Vasquez 2007) and an analysis of cost-effectiveness of screening (Rouse et al 1995).. The Cochrane review found that antibiotic treatment compared with placebo or no treatment is effective in clearing asymptomatic bacteriuria (RR 0.25; 95% CI 0.14–0.48). The incidence of pyelonephritis was reduced by 75% (RR 0.23; 95% CI 0.13–0.41) (Smaill & Vasquez 2007).
- No studies were identified concerning the harms of not screening for asymptomatic bacteriuria.
- There is no consensus in the literature about the optimal timing and screening frequency for asymptomatic bacteriuria. However, in a prospective study (n=3,254), a single urine specimen obtained between 12 and 16 weeks gestation identified 80% of women who ultimately had asymptomatic bacteriuria (Stenqvist et al. 1989).
- Although most guidelines recommend a single urine culture at the first antenatal visit, two prospective studies have concluded that urine should be cultured in each trimester of pregnancy to improve the detection rate of asymptomatic bacteriuria (McIsaac et al. 2005; Tugrul et al. 2005). There has been no prospective evaluation of repeated testing during pregnancy (Schnarr & Smaill 2008).

The evidence supports the NICE recommendation.

EAC 2014 recommendation 1 (Grade A : Body of evidence can be trusted to guide practice)

- Routinely offer and recommend testing for asymptomatic bacteriuria early in pregnancy as treatment is effective and reduces the risk of pyelonephritis.

EAC 2014 recommendation 2 (Grade A : Body of evidence can be trusted to guide practice)

- Use urine culture testing wherever possible as it is the most accurate means of detecting asymptomatic bacteriuria.

EAC 2014 Practice point

- Where access to pathology services is limited, dipstick tests may be used to exclude infection, with positive results confirmed by urine culture. Appropriate storage of dipsticks is essential to the accuracy of these tests.

KCE proposition to the GDG: To keep the 2004 recommendation, without modification of content.

Results of the GDG Lime survey at the beginning of September 2014 (10 respondents)

Totally agree: 6; somewhat agree: 4; rather not agree: 0; not agree at all: 0

Strong recommendation: 9; weak recommendation: 0; without answer: 1

GDG comments in the Lime survey at the beginning of September 2014

- Wat wil de guideline zeggen over bacteriurie en prematuriteit? Er zijn heel wat literatuurdata over een positief effect van behandelde bacteriurie op preventie van preterme partus? (vb J Perinat Neonatal Nurs. 2012 Jul-Sep;26(3):220-9.
  Reducing recurrent preterm births: best evidence for transitioning to predictive and preventative strategies. Cypher RL)
- 1. sterke aanbeveling om te screenen/ 2. minder sterke aanbeveling tijdstip/ 3. methode: niet zo duidelijk=> graag discussie

GDG comments during the GDG meeting 10/09/2014

- The timing is not clear. In the Australian guideline, the authors propose to perform the test during the first antenatal encounter but it appears this is scheduled between 12-16 weeks. It is not the timing of the first antenatal visit in Belgium. The GDG proposes to replace at the first antenatal visit by at the beginning of the second trimester.
- According to the Aus. guideline, the aim of the test is to avoid pyelonephritis (and only indirectly preterm birth). The GDG proposes to add this aim to recommendation.
- **Conclusion: recommendation KCE 2004 with two minor changes**

KCE proposition of 2015 recommendation (Strong recommendation)

- Offer each pregnant woman testing for asymptomatic bacteriuria (on a mid-stream urine sample for a white blood cell count and culture) as treatment is effective and reduces the risk of pyelonephritis. Literature based on the consensus among experts recommends performing this culture at the start of the second trimester even if there are no available evidence to support this recommendation.

GDG comments by e-mail during February 2015:

- Strong recommendation but weak evidence, so strong or weak?

KCE 2015 recommendation before stakeholders meeting (Strong recommendation)

- Offer each pregnant woman testing for asymptomatic bacteriuria (on a mid-stream urine sample for a white blood cell count and culture) as treatment is effective and reduces the risk of pyelonephritis. Literature based on the consensus among experts recommends performing this culture at the start of the second trimester even if there are no available evidence to support this recommendation.

Results of the stakeholders Lime survey in March 2015 (6 respondents):

- Completely agree: 3; somewhat agree: 2; unsure: 1
- 'somewhat agree' stick is voldoende om uit te maken of midstream nodig is

Stakeholders comments during the stakeholders meeting 25/03/2014: None

KCE 2015 recommendation: Strong recommendation, Level of evidence A *(Level of evidence from Australian 2014 guideline: A=One or more level I studies with a low risk of bias or several level II studies with low risk of bias)*

[KCE 2004, amended]

- Offer each pregnant woman testing for asymptomatic bacteriuria (on a mid-stream urine sample for a white blood cell count and culture) as treatment is effective and reduces the risk of pyelonephritis. Consensus among experts recommends performing this culture at the start of the second trimester.
- Stel aan elke zwangere vrouw om asymptomatische bacteriurie op te sporen (leucocyturie en kweek op midstream urinestaal) aangezien de behandeling effectief is en het risico op pyelonefritis vermindert. Expert consensus raadt aan dit onderzoek aan het begin van het tweede trimester uit te voeren.
- Proposez à chaque femme enceinte de détecter la présence d'une bactériurie asymptomatique (par un examen direct et une culture d'urines obtenues à mi-jet) puisqu'il existe un traitement efficace pouvant réduire le risque de pyélonéphrite. Un consensus d'experts recommande d'effectuer cette détection au début du deuxième trimestre.

15. EXTERNAL REVIEW

15.1. Evaluation of the recommendations

The recommendations prepared by the guideline development group were circulated to relevant representatives of professional associations and other clinical experts not involved in the GDG (see Appendix 1), invited to act as external reviewers of the draft guideline. All expert referees made declarations of interest.

Overall, 14 stakeholders were involved in the evaluation of the clinical recommendations. All invited panellists received the scientific reports for all research questions and were asked to score each recommendation on a 5-point Likert scale indicating their level of agreement with the recommendation, with a score of '1' indicating 'completely disagree', '2' 'somewhat disagree', '3' 'unsure', '4' 'somewhat agree', and '5' 'completely agree' (the panellists were also able to answer 'not applicable' if they were not familiar with the underlying evidence). If panellists disagreed with the recommendation (score '1' or '2'), they were asked to provide an explanation supported by appropriate evidence. Scientific arguments reported by these experts were used to adapt the formulation or the strength of the clinical recommendations. This was discussed during a stakeholder meeting on March 25th, 2015. Their comments were taken into account as showed below in the minutes of the meeting. Again, no formal consensus method was used.

KCE study 2013-10 (GCP) Guideline for antenatal care

Stakeholder meeting

25 March 2015

Presents

Experts GDG: Sophie Alexander, Karel Allegaert, Katrien Beeckman, Gilles Ceysens, Yolande Christiane, Nicole Dekker, Alexandra Denys, Wilfried Gyselaers.

Stakeholders: Michele Bertrand, Isabelle Callens, Walter Foulon, Ann Loccufier, Elizaveta Padalko, Berlinde Tillie, Ruth Verbrugge

KCE: Pascale Jonckheer, Karin Rondia, Sabine Stordeur, Leen Verleye.

Minutes of the meeting

1. Agenda
2. General presentation of participants
3. KCE 2015 guideline: Background and methods; scope (baseline care for low risk women). Because additional care are needed for women with moderate or high risk factors, these are not covered by this guideline.
4. In- and exclusion criteria: This guideline **includes** recommendations on baseline clinical care for all healthy pregnant women but **does not include** information on the additional care that some women will require due to specific risk factors or pre-existing conditions. Although the guideline addresses screening for many of the complications of pregnancy, it **does not include** information on the investigation and appropriate management of these complications (for example, the management of pre-eclampsia, fetal anomalies and multiple pregnancies). In addition, this guideline **does not provide** advices about general lifestyle and nutrition of pregnant women (except for CMV and toxoplasmosis), nor about procedures or care that are not specifically related to pregnancy (e.g. breast examination for cancer screening).

5. First round of questions:
   One expert suggests to add further exclusion criteria: this guideline will not cover the follow-up of long term health status or severe maternal morbidity (e.g. diabetes, varicose veins, renal failure, heart failure occurring during the pregnancy and that have to be followed up after the delivery)
6. Lime survey: discussion of recommendations that obtained at least one score indicating a 'disagreement' (score 1 or 2)
   a. CMV:
      - CMV infection during pregnancy is a frequent problem in Belgium (0.15% to 2% of pregnant women go through a primo-infection during pregnancy) that can lead to severe neurological complications and mental disability;
      - To take a decision about the management of the pregnant woman, we need clear results (positive or negative) after the first screening step (IgG and IgM measurements in the maternal serum) ; however, in a large proportion of cases, results are not so clear and remain in a 'grey zone'; further amniocentesis is required to confirm the fetal transmission, and this procedure also induces risks, possibly leading to complications and termination of pregnancy → cascade of additional procedures that have high psychological, ethical and economical consequences. .
      - A French study (Picone O. et al. A 2-year study on cytomegalovirus infection during pregnancy in a French hospital. BJOG. 2009 May;116(6):818-23.) showed that if clear information on CMV infection during pregnancy is given, patients frequently agree to screening. The rate of seroconversion after information, observed in this study, is low after counselling.
      - CMV screening requires informed consent. Caregivers should be aware of the undesirable situation that these prenatal tests may be performed routinely, in the sense that the possible consequences are not considered before testing.
      - A lot of conflictual reactions raised during the meeting indicating that in routine practice, a change in screening practices will be really difficult to implement. A lot of health care practitioners are convinced that such a screening is essential at least during the first trimester of the pregnancy. Some of them propose to repeat this procedure each month.

      Conclusion:

      - **More data need to be collected in a registry in order to increase the evidence; in the meantime, there is insufficient evidence to support routine screening of all pregnant women. One screening in the beginning of pregnancy can be considered to encourage women to follow preventive advices.**

      Recommendation remains unchanged. A recommendation on the need of data collection will be added.

   b. Toxoplasmosis:
      - As for CMV, a lot of health care practitioners are convinced that the toxoplasmosis screening is essential and they perform it not only during the first trimester of the pregnancy but repeatedly. They argue that treatment appears to be more efficient if it is started earlier. However, the literature review does not even support the first screening nor the positive effects of treatment and the GDG has proposed to keep this first screening mainly for encouraging negative women to follow the preventive advices.

      Conclusion:

      - **Recommendation about routine screening: same formulation (without change)**

- **Primary preventive measures: Because of the efficacy of counselling, it was decided to change the strength of the recommendations from weak recommendation → strong recommendation**

c. Hepatitis C:
- It was asked to add as additional information (but not in the recommendation box) that such screening may be offered to women with some identifiable risk factors (e.g. women with a history of intravenous drug use, tattoos or body piercing, needle sharing, incarceration)

Conclusion:
- **Recommendation unchanged but addition in the text that this screening can be offered in women with risk factors**

d. Varicella:
- Recommendation: 'For pregnant women who have not had chickenpox according to their medical history, consider to carry out a serological test to search for antibodies against chicken pox'. It was advised to limit the serological tests to **IgG testing** (to define the immune status)
- It was advised to add: 'Pregnant women should **stay away from anyone who has chickenpox or a skin rash'**

Conclusion:
- **Two minor changes will be performed in the recommendation**

e. Rubella:
- It was advised to change "make them aware of this problem" by "advise to pregnant women to **stay away from anyone who has a skin rash**"
- 'For pregnant women with an unknown immune status, offer a detection of antibodies against rubella …' It was advised to limit the serological tests to **IgG testing** (and not including IgM)
- Is was asked to specify the test should be performed **at the beginning of pregnancy.**

Conclusion:
- **Three minor changes will be performed in the recommendation**

f. Hepatitis B:
- Recommendation: 'For pregnant women with an unknown immune status, offer a detection of hepatitis B antibodies as effective postnatal intervention can reduce the risk of mother-to-child transmission'. It was advised to change the formulation of this recommendation from 'hepatitis B antibodies' to '**HBsAg**' and to **delete 'can'** (keep only 'reduce').

Conclusion:
- **Two minor changes will be performed in the recommendation**

g. Chlamydiae:
    - It was advised to add in the text that a screening test has to be offered to women who are at increased risk. However, the current text already indicates 'it can be considered to test for chlamydia in pregnant women who are at increased risk, such as pregnant women younger than 25 years old or women with a history of sexually transmitted disease'.

Conclusion
- **Recommendation unchanged but addition in the text that this screening can be offered in women with risk factors**

h. Vitamin D deficiency:
- One stakeholders highlighted during the survey that vitamin D deficiency is dramatically frequent during pregnancy (100% of pregnant women). This comment leads to two questions: the accuracy of the selected threshold and the utility to perform a test which will be positive in almost everybody.

Conclusion
- **Both recommendations are accepted without change**

i. Syphilis:
- Treponemal IgG EIA tests have high sensitivity and specificity at all stages of syphilis (except early primary syphilis) whereas non-treponemal tests may result in false negatives, particularly in very early or late syphilis, in patients with reinfection or those who are HIV positive, and have poor positive predictive value when used alone in low prevalence populations.
- The initial test is usually a test for antibodies of treponema (eg enzyme immunoassay), which identifies women with current untreated or incompletely treated infection or previous history of treated syphilis. If the test is positive, a non-treponemal test will be performed by the laboratory to confirm diagnosis and enable a quantitative value of disease activity to guide treatment.
- The INAMI/RIZIV recommends to screen syphilis in the beginning of pregnancy with the "Treponema Pallidum Hemagglutination (TPHA)" test. (INAMI. Biologie Clinique. Prescription rationnelle. Recommandations : - le dépistage opportuniste (ou non) des maladies fréquentes ; - le suivi de la grossesse. Juin 2011).
- This precision was added in the KCE 2004 guideline (French version only), but it was proposed to erase such a precision for the KCE 2015 guideline (because of the risk of evolution in the selection of test).

Conclusion
- **It was advised to add the whole explanation on the different tests in the section 'other considerations'.**

j. Post-term:
- Prefer to use 'pregnancies that passed their due date' (> 40w)'

k. Hypothyroidism:
- No discussion

l. Preterm birth:
   - No discussion

m. Pre-eclampsia:
   - No discussion

n. Diabetes:
   - No score <3 obtained but comments sent by K. Benhalima (see ppt)
   - Concerning the results published by Duran A. et al. 'Introduction of IADPSG criteria for the screening and diagnosis of gestational diabetes mellitus results in improved pregnancy outcomes at a lower cost in a large cohort of pregnant women: the St. Carlos Gestational Diabetes Study': this is a Spanish cohort study showing reduced rates of adverse pregnancy outcomes and cost-effectiveness of the IADPSG approach vs the previous 2-step screening strategy with the Carpenter and Coustan criteria. However, since the publication of this paper, comments were published in reaction to this study addressing methodological questions and questions relating to cost-effectiveness of this approach.

Conclusion: No definitive answer can be given for the moment to be included in a guideline.

7. Barriers and facilitators
   a. Antenatal care is a particularly emotional topic; pregnant women need very often to be reassured and prefer to multiply screening tests rather than to avoid them; the incertitude is often badly experienced by parents-to-be.
   b. It would be useful to produce a user friendly leaflet with **questions** addressed to health care professionals (HCPs) and by pregnant women – it is essential that the scientific messages are translated in comprehensible messages for women and HCPs (first line).
   c. The implementation should be facilitated if the guideline is used or referred on many Belgian websites consulted by pregnant women (e.g. ONE, Kind & Gezin, gezondzwangerworden.be, Domus Medica, SSMG, EBMPracticeNet…).
   d. It is also essential to highlight which changes were introduced by this update in comparison with the previous guideline.
   e. A search function in the pdf would be helpful.

16. CATEGORIES OF EVIDENCE LEVELS AND GRADE OF RECOMMENDATIONS

16.1. KCE 2004 classification

Table 215 – KCE categories of evidence level and grade of recommendation (2004)

Level of evidence	Source
1a	Systematic review and meta-analysis of randomised controlled trials (RCT)
1b	At least, 1 randomised controlled trial (RCT)
2a	At least, 1 non randomised controlled trial (NRCT)
2b	At least, 1 well-designed quasi-experimental trial
3	Well-designed non-experimental descriptive studies, such as comparative studies, correlation studies or case studies
4	Expert committee reports or opinions and/or clinical experience of respected authorities
Grade of recommendation	Included evidence
A	Recommendation directly based on level 1 evidence
B	Recommendation directly based on level 2 evidence or issued from a guideline based on level 1 evidence
C	Recommendation directly based on level 3 evidence or issued from a guideline based on level 1 or 2 evidence
D	Recommendation directly based on level 4 evidence or issued from a guideline based on level 1, 2 or 3 evidence
D-D-GPP (good practice point)	Recommendation from the experts group or/and the validators

16.2. NICE 2008 classification

Table 216 – NICE categories of evidence level and grade of recommendation (2008)

Level of evidence	Definition
1a	Systematic review and meta-analysis of randomised controlled trials (RCT)
1b	At least, one randomised controlled trial
2a	At least, one well-designed controlled study without randomisation
2b	At least, one other type of well-designed quasi-experimental study
3	Well-designed non-experimental descriptive studies, such as comparative studies, correlation studies or case studies
4	Expert committee reports or opinions and/or clinical experience of respected authorities
Grade	**Definition**
A	Directly based on level I evidence
B	Directly based on level II evidence or extrapolated recommendation from level I evidence
C	Directly based on level III evidence or extrapolated recommendation from either level I or II evidence
D	Directly based on level IV evidence or extrapolated recommendation from either level I, II or III evidence
Good practice point (GPP)	The view of the Guideline Development Group
NICE Technology Appraisal	Technology Appraisal Recommendation taken from a NICE Technology Appraisal

16.3. EAC 2014 classification

Table 217 – EAC categories of evidence level and grade of recommendation (2014)

Level of evidence	Intervention	Diagnostic accuracy	Prognosis	Aetiology	Screening intervention
I	Systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation	A prospective cohort study	A prospective cohort study	A prospective cohort study
III-1	Pseudorandomised trial	A study of test accuracy with an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation	All or none	All or none	Pseudorandomised trial (ie alternate allocation or some other method)
III-2	A comparative study with concurrent controls: • Non-randomised experimental trial • Cohort study • Case-control study • Interrupted time series with control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors among persons in a single arm of a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: • Non-randomised experimental trial • Cohort study • Case-control study
III-3	A comparative study without concurrent controls: • Historical control study	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: • Historical control study

	• Two or more single arm study • Interrupted time series without parallel control				• Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of persons at different stage of disease	A cross-sectional study or case series	Case series

Grade	Definition
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in application
D	Body of evidence is weak and recommendation must be applied with caution
CBR	Recommendation formulated in the absence of quality evidence (where a systematic review of the evidence was conducted as part of the search strategy)
PP	Area is beyond the scope of the systematic literature review and advice was developed by the EAC and/or the Working Group for Aboriginal and Torres Strait Islander Women's Antenatal Care

Source: Adapted from NHMRC (2009) Levels of Evidence and Grades for Recommendations for Developers of Guidelines and NHMRC (2011) Procedures and Requirements for Meeting the 2011 NHMRC Standard for Clinical Practice Guidelines.

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