KCE REPORT 228S

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

PREVENTION OF PRETERM BIRTH IN WOMEN AT RISK: SELECTED TOPICS

APPENDIX





KCE REPORT 228S
GOOD CLINICAL PRACTICE

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

PREVENTION OF PRETERM BIRTH IN WOMEN AT RISK: SELECTED TOPICS

APPENDIX

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COLOPHON

Title:	prevention of preterm birth in women at risk: selected topics – Appendix
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Layout:	Ine Verhulst
Disclaimer:	• **The external experts were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.** • **Subsequently, a (final) version was submitted to the validators. The validation of the report results from a consensus or a voting process between the validators. The validators did not co-author the scientific report and did not necessarily all three agree with its content.** • **Finally, this report has been approved by common assent by the Executive Board.** • **Only the KCE is responsible for errors or omissions that could persist. The policy recommendations are also under the full responsibility of the KCE.**
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1. COMPOSITION OF THE GUIDELINE DEVELOPMENT GROUP

1.1. Composition of the Guideline Development Group

Clinicians	Field of expertise, affiliations
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1.2. Composition of the KCE expert team

KCE member	Specific role
Kristel De Gauquier	Program Director
Dominique Paulus	Project Coordinator
Leen Verleye	Principal Investigator
Dominique Roberfroid	Investigator

1.3. External researchers involved in the guideline development

Ottawa Health Care Research Institute - name	Specific role
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Ms. Chantelle Garritty	Senior Research Manager
Dr. Mohammed T. Ansari MD, MSc, MPhil	Associate Investigator and Senior Methodologist
Ms. Kaviata Singh MPH, BSc Pharm	Senior Research Associate
Dr. Laura Gaudet MSc, MD, FRCSC	Clinical expert
Dr. Mark Walker MSc, MD, FRCSC	Clinical expert
Dr. Nadera Ahmadzai MD, MPH, MSc	Research Associate
Dr. Brian Hutton	Statistician
Ms. Rebecca Skidmore	Information Specialist
Mr. Raymond Daniel	Librarian Assistant

2. SCOPING

Table 1 – Overview possible research topics and selection by stakeholders

	EE1	EE2	EE3	EE4	EE5	EE6	EE7
Identification patients at risk / indications to start secondary/tertiary prevention							
fetal fibronectin testing				x		x	x
transvaginal cervical sonography (cervical length)		x	x		x	x	x
(repeated) vaginal digital examination		x					
assessment of the frequency of uterine conracions by ambulatory uterine monitoring	x						
Actim partus test (phosphorylated insuline-like growth factor binding protein 1 in cervical secretions)				x			x
Clinical diagnosis of PPROM: sterile speculum examination and patient history							
diagnosis of PPROM by nitrazine test (alkaline pH of cervicavaginal discharge)						x	
diagnosis of PPROM by by microscopic ferning							
diagnosis of PPROM by absorbent pad (AmnioSense)							
diagnosis of PPROM: Diamine/oxidase radio-immunoassay							
diagnosis of PPROM: IGFBP-1 (Actim Prom™)							
diagnosis of PPROM: placental alpha microglobulin-1 (Amnisure®)					x		
cervical score and bishop score							
fatigue, work related stress, cervix changes	x						
other 2:							
other 3:							
Strategies for secondary prevention (in patients at risk)							
screening & treatment periodontal diseasse							
cervical cerclage		x				x	x

	EE1	EE2	EE3	EE4	EE5	EE6	EE7
cervical pessary					x		x
progestogens			x	x		x	x
preconceptional interventions such as control of diabetes, hypertension, asthma,…							
interconceptional antimicrobial treatment in women with a previous early preterm birth							
antiplatelet drugs/low dose aspirin for secondary prevention of indicated preterm births				x			
bed rest, limited work and reduced sexual activity / relaxation therapy			x				
omega-3 polyunsaturated fatty acids supplements	x						
more intensive prenatal care in women at increased risk	x						
antibiotic treatment of bacterial vaginosis in women with a previous preterm birth							x
vitamine C/E supplements							
vaginal progesterone		x	x			x	
cox inhibitors							
screening & treatment of asymptomatic bacteriuria							x
hospitalisation versus ambulatory strategies					x		
Zinc supplementation							
Magnesium supplementation	x						
other 2:							
other 3:							
Strategies for teriary prevention of (adverse outcomes associated with) preterm birth / treatment of preterm labour							
(antenal corticosteroids)							
antibiotic treatment of all women with threatened preterm labour (to prevent neonatal infection with group B streptococcus)				x			

	EE1	EE2	EE3	EE4	EE5	EE6	EE7
tocolysis: choice of tocolytic agents			x			x	x
tocolysis: duration of treatment		x	x			x	x
tocolysis: maintenance therapy progestogens			x		x	x	x
tocolysis: maintenance therapy nifedipine			x				x
(mode) of delivery							x
Magnesium sulphate	x	x	x	x	x		
rest, surveillance, logistic support	x						
other 2:							
other 3:							

3. SEARCH STRATEGIES

3.1.1. Fetal fibronectin test and Actim Partus test

Database	MEDLINE and EMBASE
Data	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Embase<1980 to 2013 Week 23>
Search Strategy	1 exp Obstetric Labor, Premature/ (42756) 2 ((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw,kw. (69438) 3 (PTL or sPTL or PTB or sPTB or PTD or sPTD).tw,kw. (11046) 4 (predict* adj2 delivery).tw,kw. (1393) 5 Uterine Contraction/ (13946) 6 ((uterus* or uterine) adj3 contraction*).tw,kw. (8399) 7 Cervical Ripening/ (2398) 8 ((cervical or cervix*) adj3 (dilat* or ripen*)).tw,kw. (8993) 9 exp Labor Onset/ (4122) 10 (preterm* or pre-term* or prematur* or pre-matur*).tw,kw. (302946) 11 (5 or 6 or 7 or 8 or 9) and 10 (4734) 12 or/1-4,11 (92142) 13 Fibronectins/ (52883) 14 ((fetal or foetal) adjfibronectin*).mp. (984) 15 fFN.mp. (464) 16 TLiIQ*.mp. (2) 17 Quikcheck*.mp. (2) 18 EINECS 289-149-2.tw,kw. (0) 19 ((opsonic adj3 glycoprotein*) or LETS Protein* or cold-insoluble globulin* or (alpha adj3 binding glycoprotein*)).tw,kw. (431) 20 fibronectins.rn. (20587) 21 "Insulin-Like Growth Factor Binding Protein 1"/ (5135) 22 ("Insulin-Like Growth Factor Binding Protein 1" or "IGF-Binding Protein 1").tw,kw. (2795) 23 (IGFBP-1 or phIGFBP-1 or pIGFBP-1).tw,kw. (5080) 24 Actim* partus.mp. (12) 25 or/13-24 (60998) 26 12 and 25 (1233) 27 exp Animals/ not (exp Animals/ and Humans/) (7906230) 28 26 not 27 (1217)

29	limit 28 to yr="2008-current" (420)
30	29 use prmz (129)
31	premature labor/ (37282)
32	((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw,kw. (69438)
33	(PTL or sPTL or PTB or sPTB or PTD or sPTD).tw,kw. (11046)
34	(predict* adj2 delivery).tw,kw. (1393)
35	uterus contraction/ (7040)
36	((uterus* or uterine) adj3 contraction*).tw,kw. (8399)
37	uterine cervix ripening/ (1660)
38	((cervical or cervix*) adj3 (dilat* or ripen*)).tw,kw. (8993)
39	Labor Onset/ (1793)
40	(preterm* or pre-term* or prematur* or pre-matur*).tw,kw. (302946)
41	(35 or 36 or 37 or 38 or 39) and 40 (4082)
42	or/31-34,41 (90546)
43	fibronectin/ (52883)
44	((fetal or foetal) adjfibronectin*).mp. (984)
45	fFN.mp. (464)
46	TLiIQ*.mp. (2)
47	Quikcheck*.mp. (2)
48	EINECS 289-149-2.tw,kw. (0)
49	((opsonic adj3 glycoprotein*) or LETS Protein* or cold-insoluble globulin* or (alpha adj3 binding glycoprotein*)).tw,kw. (431)
50	98725-78-1.rn. (0)
51	"somatomedin binding protein 1"/ (3002)
52	("Insulin-Like Growth Factor Binding Protein 1" or "IGF-Binding Protein 1").tw,kw. (2795)
53	(IGFBP-1 or phIGFBP-1 or pIGFBP-1).tw,kw. (5080)
54	Actim* partus.mp. (12)
55	or/43-54 (60454)
56	42 and 55 (1224)
57	exp animals/ (35380104)
58	exp animal experimentation/ (1596558)
59	exp models animal/ (1105876)
60	exp animal experiment/ (1596558)
61	nonhuman/ (4069604)
62	exp vertebrate/ (34475122)
63	or/57-62 (36540117)
64	exp humans/ (27543462)
65	exp human experimentation/ (324778)

	66 exp human experiment/ (312971) 67 or/64-66 (27545499) 68 63 not 67 (8996170) 69 56 not 68 (1207) 70 limit 69 to yr="2008-current" (414) 71 70 use emez (291) 72 30 or 71 (420) 73 remove duplicates from 72 (301) 74 73 use prmz (123) MEDLINE UNIQUE HITS 75 73 use emez (178) EMBASE UNIQUE HITS
Note	

Database	**Cochrane Library (Wiley Interface), including CDSR, DARE, Central, HTA, and NHS EED**
Database	Date run: 11/06/13 02:46:52.552 Description: 2013 Jun 10 - Post PRESS
Search Strategy	#1 [mh "Obstetric Labor, Premature"] 984 #2 ((labor* or labour* or birth* or deliver*) near/4 (preterm* or pre-term* or prematur* or pre-matur*)):ti,ab,kw 2843 #3 (PTL or sPTL or PTB or sPTB or PTD or sPTD):ti,ab,kw 97 #4 (predict* near/3 delivery):ti,ab,kw 41 #5 [mh "Uterine Contraction"] 333 #6 ((uterus* or uterine) near/4 contraction*):ti,ab,kw 649 #7 [mh "Cervical Ripening"] 258 #8 ((cervical or cervix*) near/4 (dilat* or ripen*)):ti,ab,kw 1452 #9 [mh "Labor Onset"] 463 #10 (preterm* or pre-term* or prematur* or pre-matur*):ti,ab,kw 11797 #11 (#5 or #6 or #7 or #8 or #9) and #10 257 #12 #1 or #2 or #3 or #4 or #11 2968 #13 [mhFibronectins] 131 #14 ((fetal or foetal) next fibronectin*):ti,ab,kw 62 #15 fFN:ti,ab,kw 19

	#16 TLiIQ*:ti,ab,kw 0 #17 Quikcheck*:ti,ab,kw 0 #18 "EINECS 289-149-2":ti,ab,kw 0 #19 ((opsonic near/4 glycoprotein*) or (LETS next Protein*) or ("cold-insoluble" next globulin*) or (alpha near/4 (binding next glycoprotein*))):ti,ab,kw 2 #20 [mh "Insulin-Like Growth Factor Binding Protein 1"] 161 #21 ("Insulin-Like Growth Factor Binding Protein 1" or "IGF-Binding Protein 1"):ti,ab,kw 192 #22 ("IGFBP-1" or "phIGFBP-1" or "pIGFBP-1"):ti,ab,kw 174 #23 Actim* next partus:ti,ab,kw 2 #24 {or #13-#23} 394 #25 #12 and #24 from 2008 to 2013 20 DSR – 1 DARE – 2 CENTRAL – 11 HTA – 5 NHS EED - 1
Note	

3.1.1.1. Actim partus test: de novo search (2005-2007)

Data base	**MEDLINE and EMBASE**
Date	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Embase <1980 to 2013 Week 29>
Search Strategy	1 exp Obstetric Labor, Premature/ (43481) 2 ((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw,kw. (70898) 3 (PTL or sPTL or PTB or sPTB or PTD or sPTD).tw,kw. (11453) 4 (predict* adj2 delivery).tw,kw. (1424) 5 Uterine Contraction/ (14071) 6 ((uterus* or uterine) adj3 contraction*).tw,kw. (8486) 7 Cervical Ripening/ (2429)

8	((cervical or cervix*) adj3 (dilat* or ripen*)).tw,kw. (9076)
9	exp Labor Onset/ (4188)
10	(preterm* or pre-term* or prematur* or pre-matur*).tw,kw. (309186)
11	(5 or 6 or 7 or 8 or 9) and 10 (4797)
12	or/1-4,11 (94095)
13	"Insulin-Like Growth Factor Binding Protein 1"/ (5220)
14	("Insulin-Like Growth Factor Binding Protein 1" or "IGF-Binding Protein 1").tw,kw. (2842)
15	(IGFBP-1 or phIGFBP-1 or pIGFBP-1).tw,kw. (5165)
16	Actim* partus.mp. (12)
17	or/13-16 (7875)
18	12 and 17 (178)
19	exp Animals/ not (exp Animals/ and Humans/) (8036266)
20	18 not 19 (176)
21	20 use prmz (69)
22	premature labor/ (37687)
23	((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw,kw. (70898)
24	(PTL or sPTL or PTB or sPTB or PTD or sPTD).tw,kw. (11453)
25	(predict* adj2 delivery).tw,kw. (1424)
26	uterus contraction/ (7092)
27	((uterus* or uterine) adj3 contraction*).tw,kw. (8486)
28	uterine cervix ripening/ (1679)
29	((cervical or cervix*) adj3 (dilat* or ripen*)).tw,kw. (9076)
30	Labor Onset/ (1819)
31	(preterm* or pre-term* or prematur* or pre-matur*).tw,kw. (309186)
32	(26 or 27 or 28 or 29 or 30) and 31 (4131)
33	or/22-25,32 (92427)
34	"somatomedin binding protein 1"/ (3023)
35	("Insulin-Like Growth Factor Binding Protein 1" or "IGF-Binding Protein 1").tw,kw. (2842)
36	(IGFBP-1 or phIGFBP-1 or pIGFBP-1).tw,kw. (5165)
37	Actim* partus.mp. (12)
38	or/34-37 (7302)
39	33 and 38 (167)

	40 exp animals/ (36003347)
	41 exp animal experimentation/ (1606226)
	42 exp models animal/ (1129984)
	43 exp animal experiment/ (1606226)
	44 nonhuman/ (4094241)
	45 exp vertebrate/ (35076707)
	46 or/40-45 (37168430)
	47 exp humans/ (28036666)
	48 exp human experimentation/ (326659)
	49 exp human experiment/ (314444)
	50 or/47-49 (28038707)
	51 46 not 50 (9131279)
	52 39 not 51 (165)
	53 52 use emez (107)
	54 21 or 53 (176)
	55 remove duplicates from 54 (109) UNIQUE REFERENCES
	56 55 use prmz (64) MEDLINE UNIQUE REFERENCES
	57 55 use emez (45) EMBASE UNIQUE REFERENCES
Note	

Database	**Cochrane Library (Wiley Interface), including CDSR, DARE, Central, HTA, and NHS EED**
Date	Date Run: 24/07/13 02:00:28.354 Description: 2013 Jul 23
Search Strategy	#1 [mh "Obstetric Labor, Premature"] 991 #2 ((labor* or labour* or birth* or deliver*) near/4 (preterm* or pre-term* or prematur* or pre-matur*)):ti,ab,kw 2858 #3 (PTL or sPTL or PTB or sPTB or PTD or sPTD):ti,ab,kw 98 #4 (predict* near/3 delivery):ti,ab,kw 41 #5 [mh "Uterine Contraction"] 334 #6 ((uterus* or uterine) near/4 contraction*):ti,ab,kw 650 #7 [mh "Cervical Ripening"] 258

	#8 ((cervical or cervix*) near/4 (dilat* or ripen*)):ti,ab,kw 1455 #9 [mh "Labor Onset"] 463 #10 (preterm* or pre-term* or prematur* or pre-matur*):ti,ab,kw 11857 #11 (#5 or #6 or #7 or #8 or #9) and #10 258 #12 #1 or #2 or #3 or #4 or #11 2984 #13 [mh "Insulin-Like Growth Factor Binding Protein 1"] 162 #14 ("Insulin-Like Growth Factor Binding Protein 1" or "IGF-Binding Protein 1"):ti,ab,kw 193 #15 ("IGFBP-1" or "phIGFBP-1" or "pIGFBP-1"):ti,ab,kw 174 #16 Actim* next partus:ti,ab,kw 2 #17 {or #13-#16} 238 #18 #12 and #17 4 CENTRAL - 2 records HTA - 2 records
Note	

3.1.2. Transvaginal ultrasound

Database	**MEDLINE and EMBASE**
Date	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Embase <1980 to 2013 Week 24>
Search Strategy	1 exp Obstetric Labor, Premature/ (42805) 2 ((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw,kw. (69512) 3 (PTL or sPTL or PTB or sPTB or PTD or sPTD).tw,kw. (11061) 4 (predict* adj2 delivery).tw,kw. (1394) 5 Uterine Contraction/ (13948) 6 ((uterus* or uterine) adj3 contraction*).tw,kw. (8400) 7 Cervical Ripening/ (2400) 8 ((cervical* or cervix*) adj3 (dilat* or ripen*)).tw,kw. (8996) 9 exp Labor Onset/ (4124) 10 (preterm* or pre-term or prematur* or pre-matur*).tw,kw. (302773) 11 (5 or 6 or 7 or 8 or 9) and 10 (4737)

12 or/1-4,11 (92241)
13 exp Obstetric Labor, Premature/us [Ultrasonography] (336)
14 Cervix Uteri/us [Ultrasonography] (857)
15 Vagina/us [Ultrasonography] (664)
16 ((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*)).tw,kw. (18101)
17 (TV ultrason* or TV ultra-son* or TV ultrasound* or TV ultra-sound* or TVU or TVUS).tw,kw. (557)
18 or/13-17 (18855)
19 Endosonography/ (25162)
20 ((endoscop* or endo-scop*) adj3 (echo* or ultrason* or ultra-son* or ultrasound* or ultra-sound*)).tw,kw. (18496)
21 (echotomograph* or echograph*).tw,kw. (21391)
22 Ultrasonography/ (279746)
23 exp Ultrasonography, Prenatal/ (38347)
24 ((prenatal* or pre-natal* or antenatal* or ante-natal* or antepartum* or ante-partum*) adj3 (ultrason* or ultra-son* or ultrasound* or ultra-sound* or sonograph* or endoson* or endo-son* or endosound* or endo-sound*)).tw,kw. (12782)
25 or/19-24 (357526)
26 Cervix uteri/ (37417)
27 Vagina/ (46615)
28 (cervix* or cervical* or vagina* or transvaginal* or trans-vaginal*).tw,kw. (545301)
29 or/26-28 (564369)
30 25 and 29 (15880)
31 18 or 30 (28652)
32 12 and 31 (2266)
33 exp Animals/ not (exp Animals/ and Humans/) (7909058)
34 32 not 33 (2257)
35 limit 34 to yr="2008-current" (909)
36 35 use prmz (387)
37 premature labor/ (37331)
38 ((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw,kw. (69512)
39 (PTL or sPTL or PTB or sPTB or PTD or sPTD).tw,kw. (11061)
40 (predict* adj2 delivery).tw,kw. (1394)
41 uterus contraction/ (7042)
42 ((uterus* or uterine) adj3 contraction*).tw,kw. (8400)
43 uterine cervix ripening/ (1662)
44 ((cervical* or cervix*) adj3 (dilat* or ripen*)).tw,kw. (8996)
45 labor onset/ (1795)

46 (preterm* or pre-term or prematur* or pre-matur*).tw,kw. (302773)
47 (41 or 42 or 43 or 44 or 45) and 46 (4085)
48 or/37-40,47 (90645)
49 exp transvaginal echography/ (11132)
50 ((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*)).tw,kw. (18101)
51 (TV ultrason* or TV ultra-son* or TV ultrasound* or TV ultra-sound* or TVU or TVUS).tw,kw. (557)
52 or/49-51 (23347)
53 endoscopic echography/ (16718)
54 ((endoscop* or endo-scop*) adj3 (echo* or ultrason* or ultra-son* or ultrasound* or ultra-sound*)).tw,kw. (18496)
55 (echotomograph* or echograph*).tw,kw. (21391)
56 echography/ (279746)
57 exp fetus echography/ (14140)
58 ((prenatal* or pre-natal* or antenatal* or ante-natal* or antepartum* or ante-partum*) adj3 (ultrason* or ultra-son* or ultrasound* or ultra-sound* or sonograph* or endoson* or endo-son* or endosound* or endo-sound*)).tw,kw. (12782)
59 or/53-58 (331875)
60 Cervix uteri/ (37417)
61 Vagina/ (46615)
62 (cervix* or cervical* or vagina* or transvaginal* or trans-vaginal*).tw,kw. (545301)
63 or/60-62 (564369)
64 59 and 63 (13178)
65 52 or 64 (31878)
66 48 and 65 (2315)
67 exp animals/ (35401329)
68 exp animal experimentation/ (1598052)
69 exp models animal/ (1107058)
70 exp animal experiment/ (1598052)
71 nonhuman/ (4073457)
72 exp vertebrate/ (34496068)
73 or/67-72 (36562262)
74 exp humans/ (27561859)
75 exp human experimentation/ (325030)
76 exp human experiment/ (313223)
77 or/74-76 (27563896)
78 73 not 77 (8999918)
79 66 not 78 (2307)
80 limit 79 to yr="2008-current" (1054)

	81 80 use emez (834) 82 36 or 81 (1221) 83 remove duplicates from 82 (906) 84 83 use prmz (351) MEDLINE UNIQUE HITS 85 83 use emez (555) EMBASE UNIQUE HITS
Note	

Database	**Cochrane Library (Wiley Interface), including CDSR, DARE, Central, HTA, and NHS EED**
Date	Date Run: 11/06/13 03:00:08.715 Description: 2013 Jun 10 - Post PRESS
Search Strategy	#1 [mh "Obstetric Labor, Premature"] 984 #2 ((labor* or labour* or birth* or deliver*) near/4 (preterm* or pre-term* or prematur* or pre-matur*)):ti,ab,kw 2843 #3 (PTL or sPTL or PTB or sPTB or PTD or sPTD):ti,ab,kw 97 #4 (predict* near/3 delivery):ti,ab,kw 41 #5 [mh "Uterine Contraction"] 333 #6 ((uterus* or uterine) near/4 contraction*):ti,ab,kw 649 #7 [mh "Cervical Ripening"] 258 #8 ((cervical or cervix*) near/4 (dilat* or ripen*)):ti,ab,kw 1452 #9 [mh "Labor Onset"] 463 #10 (preterm* or pre-term* or prematur* or pre-matur*):ti,ab,kw 11797 #11 (#5 or #6 or #7 or #8 or #9) and #10 257 #12 #1 or #2 or #3 or #4 or #11 2968 #13 [mh "Obstetric Labor, Premature"/us] 14 #14 [mh "Cervix Uteri"/us] 47 #15 [mh Vagina/us] 45 #16 ((cervical* or cervix* or vagina* or transvaginal* or trans-vaginal*) near/4 (ultrason* or ultra-son* or ultrasound* or ultra-sound* or sonograph* or endoson* or endo-son* or endosound* or endo-sound*)):ti,ab,kw 672 #17 ((TV next ultrason*) or (TV next ultra-son*) or (TV next ultrasound*) or (TV next ultra-sound*) or TVU or TVUS):ti,ab,kw 14 #18 {or #13-#17} 689 #19 [mh Endosonography] 298

	#20 ((endoscop* or endo-scop*) near/4 (echo* or ultrason* or ultra-son* or ultrasound* or ultra-sound*)):ti,ab,kw 217 #21 (echotomograph* or echograph*):ti,ab,kw 708 #22 [mh ^Ultrasonography] 790 #23 [mh "Ultrasonography, Prenatal"] 438 #24 ((prenatal* or pre-natal* or antenatal* or ante-natal* or antepartum* or ante-partum*) near/4 (ultrason* or ultra-son* or ultrasound* or ultra-sound* or sonograph* or endoson* or endo-son* or endosound* or endo-sound*)):ti,ab,kw 454 #25 {or #19-#24} 2324 #26 [mh "Cervix uteri"] 907 #27 [mh Vagina] 958 #28 (cervix* or cervical* or vagina* or transvaginal* or trans-vaginal*):ti,ab,kw 14082 #29 1-#28 14082 #30 #25 and #29 249 #31 #18 or #30 772 #32 #12 and #31 from 2008 to 2013 44 DSR – 8 DARE – 9 CENTRAL - 23 HTA – 1 NHS EED - 3
Note	

Database	**MEDLINE and EMBASE**
Date	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Embase<1980 to 2013 Week 30>
Search Strategy	1 exp Obstetric Labor, Premature/ (43741) 2 ((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw,kw. (71346) 3 (PTL or sPTL or PTB or sPTB or PTD or sPTD).tw,kw. (11508) 4 (predict* adj2 delivery).tw,kw. (1434) 5 Uterine Contraction/ (14120) 6 ((uterus* or uterine) adj3 contraction*).tw,kw. (8520) 7 Cervical Ripening/ (2442)

8 ((cervical* or cervix*) adj3 (dilat* or ripen*)).tw,kw. (9105)
9 exp Labor Onset/ (4216)
10 (preterm* or pre-term or prematur* or pre-matur*).tw,kw. (309976)
11 (5 or 6 or 7 or 8 or 9) and 10 (4835)
12 or/1-4,11 (94598)
13 exp Obstetric Labor, Premature/us [Ultrasonography] (341)
14 Cervix Uteri/us [Ultrasonography] (872)
15 Vagina/us [Ultrasonography] (671)
16 ((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*)).tw,kw. (18404)
17 (TV ultrason* or TV ultra-son* or TV ultrasound* or TV ultra-sound* or TVU or TVUS).tw,kw. (574)
18 or/13-17 (19176)
19 Endosonography/ (26052)
20 ((endoscop* or endo-scop*) adj3 (echo* or ultrason* or ultra-son* or ultrasound* or ultra-sound*)).tw,kw. (19000)
21 (echotomograph* or echograph*).tw,kw. (21523)
22 Ultrasonography/ (285082)
23 exp Ultrasonography, Prenatal/ (39313)
24 ((prenatal* or pre-natal* or antenatal* or ante-natal* or antepartum* or ante-partum*) adj3 (ultrason* or ultra-son* or ultrasound* or ultra-sound* or sonograph* or endoson* or endo-son* or endosound* or endo-sound*)).tw,kw. (12984)
25 or/19-24 (364311)
26 Cervix uteri/ (37971)
27 Vagina/ (47397)
28 (cervix* or cervical* or vagina* or transvaginal* or trans-vaginal*).tw,kw. (555085)
29 or/26-28 (574299)
30 25 and 29 (16210)
31 18 or 30 (29168)
32 12 and 31 (2332)
33 exp Animals/ not (exp Animals/ and Humans/) (8047559)
34 32 not 33 (2321)
35 limit 34 to yr="2005-2007" (356)
36 35 use prmz (160)
37 premature labor/ (37928)
38 ((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw,kw. (71346)
39 (PTL or sPTL or PTB or sPTB or PTD or sPTD).tw,kw. (11508)
40 (predict* adj2 delivery).tw,kw. (1434)
41 uterus contraction/ (7140)

42 ((uterus* or uterine) adj3 contraction*).tw,kw. (8520)
43 uterine cervix ripening/ (1692)
44 ((cervical* or cervix*) adj3 (dilat* or ripen*)).tw,kw. (9105)
45 labor onset/ (1845)
46 (preterm* or pre-term or prematur* or pre-matur*).tw,kw. (309976)
47 (41 or 42 or 43 or 44 or 45) and 46 (4168)
48 or/37-40,47 (92923)
49 exptransvaginal echography/ (11299)
50 ((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*)).tw,kw. (18404)
51 (TV ultrason* or TV ultra-son* or TV ultrasound* or TV ultra-sound* or TVU or TVUS).tw,kw. (574)
52 or/49-51 (23729)
53 endoscopic echography/ (17450)
54 ((endoscop* or endo-scop*) adj3 (echo* or ultrason* or ultra-son* or ultrasound* or ultra-sound*)).tw,kw. (19000)
55 (echotomograph* or echograph*).tw,kw. (21523)
56 echography/ (285082)
57 exp fetus echography/ (14786)
58 ((prenatal* or pre-natal* or antenatal* or ante-natal* or antepartum* or ante-partum*) adj3 (ultrason* or ultra-son* or ultrasound* or ultra-sound* or sonograph* or endoson* or endo-son* or endosound* or endo-sound*)).tw,kw. (12984)
59 or/53-58 (338289)
60 Cervix uteri/ (37971)
61 Vagina/ (47397)
62 (cervix* or cervical* or vagina* or transvaginal* or trans-vaginal*).tw,kw. (555085)
63 or/60-62 (574299)
64 59 and 63 (13468)
65 52 or 64 (32431)
66 48 and 65 (2385)
67 exp animals/ (36091653)
68 exp animal experimentation/ (1607821)
69 exp models animal/ (1131571)
70 exp animal experiment/ (1607821)
71 nonhuman/ (4098479)
72 exp vertebrate/ (35163037)
73 or/67-72 (37257882)
74 exp humans/ (28113679)
75 exp human experimentation/ (326951)
76 exp human experiment/ (314732)

	77 or/74-76 (28115723) 78 73 not 77 (9143717) 79 66 not 78 (2376) 80 limit 79 to yr="2005-2007" (351) 81 80 use emez (228) 82 36 or 81 (388) 83 remove duplicates from 82 (240) 84 83 use prmz (22) MEDLINE UNIQUE HITS 85 83 use emez (218)Embase UNIQUE HITS
Note	

Database	**Cochrane Library (Wiley Interface), including CDSR, DARE, Central, HTA, and NHS EED**
Date	Date Run: 29/07/13 23:38:10.123 Description: 2013 Jul 29 - Post PRESS
Search Strategy	#1 [mh "Obstetric Labor, Premature"] 991 #2 ((labor* or labour* or birth* or deliver*) near/4 (preterm* or pre-term* or prematur* or pre-matur*)):ti,ab,kw 2859 #3 (PTL or sPTL or PTB or sPTB or PTD or sPTD):ti,ab,kw 98 #4 (predict* near/3 delivery):ti,ab,kw 41 #5 [mh "Uterine Contraction"] 334 #6 ((uterus* or uterine) near/4 contraction*):ti,ab,kw 650 #7 [mh "Cervical Ripening"] 258 #8 ((cervical or cervix*) near/4 (dilat* or ripen*)):ti,ab,kw 1455 #9 [mh "Labor Onset"] 463 #10 (preterm* or pre-term* or prematur* or pre-matur*):ti,ab,kw 11858 #11 (#5 or #6 or #7 or #8 or #9) and #10 258 #12 #1 or #2 or #3 or #4 or #11 2985 #13 [mh "Obstetric Labor, Premature"/us] 14 #14 [mh "Cervix Uteri"/us] 48 #15 [mh Vagina/us] 45 #16 ((cervical* or cervix* or vagina* or transvaginal* or trans-vaginal*) near/4 (ultrason* or ultra-son* or ultrasound* or ultra-sound* or sonograph* or endoson* or endo-son* or endosound* or endo-sound*)):ti,ab,kw 674 #17 ((TV next ultrason*) or (TV next ultra-son*) or (TV next

	ultrasound*) or (TV next ultra-sound*) or TVU or TVUS):ti,ab,kw 14 #18 {or #13-#17} 692 #19 [mhEndosonography] 299 #20 ((endoscop* or endo-scop*) near/4 (echo* or ultrason* or ultra-son* or ultrasound* or ultra-sound*)):ti,ab,kw 236 #21 (echotomograph* or echograph*):ti,ab,kw 712 #22 [mh ^Ultrasonography] 791 #23 [mh "Ultrasonography, Prenatal"] 439 #24 ((prenatal* or pre-natal* or antenatal* or ante-natal* or antepartum* or ante-partum*) near/4 (ultrason* or ultra-son* or ultrasound* or ultra-sound* or sonograph* or endoson* or endo-son* or endosound* or endo-sound*)):ti,ab,kw 454 #25 {or #19-#24} 2340 #26 [mh "Cervix uteri"] 908 #27 [mh Vagina] 960 #28 (cervix* or cervical* or vagina* or transvaginal* or trans-vaginal*):ti,ab,kw 14155 #29 #1-#28 14155 #30 #25 and #29 250 #31 #18 or #30 775 #32 #12 and #31 from 2005 to 2007 15 DARE – 1 CENTRAL - 14
Note	

3.1.3. Secondary prevention: progestagens

3.1.3.1. Oral or vaginal progesterone - SRs

Database	MEDLINE and EMBASE
Date	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Embase <1980 to 2013 Week 24>
Search Strategy	1 exp Obstetric Labor, Premature/ (42805) 2 ((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw,kw. (69512) 3 (PTL or sPTL or PTB or sPTB or PTD or sPTD).tw,kw. (11061) 4 Uterine Contraction/ (13948) 5 ((uterus* or uterine) adj3 contraction*).tw,kw. (8400) 6 Cervical Ripening/ (2400) 7 ((cervical* or cervix*) adj3 (dilat* or ripen*)).tw,kw. (8996) 8 exp Labor Onset/ (4124) 9 (preterm* or pre-term* or prematur* or pre-matur*).tw,kw. (303203) 10 (4 or 5 or 6 or 7 or 8) and 9 (4737) 11 or/1-3,10 (91466) 12 *Pregnancy, High-Risk/ (3453) 13 *Pregnancy Complications/ (74725) 14 Uterine Cervical Incompetence/ (2371) 15 ((cervix* or cervical* or endocervical* or endo-cervical*) adj3 (incompeten* or insufficien* or short* or weak*)).tw,kw. (4296) 16 Cervical Length Measurement/ (772) 17 ((cervix* or cervical* or endocervical* or endo-cervical*) adj3 (length* or measur*)).tw,kw. (5533) 18 Cervix Uteri/ah [Anatomy & Histology] (739) 19 exp Abortion, Spontaneous/ (52016) 20 miscarr*.tw,kw. (20125) 21 (abort* adj3 (spontaneous* or habitual* or frequen* or recurr* or tubal)).tw,kw. (24109) 22 exp fetal death/ (50984) 23 ((foetal or fetal or fetus* or foetus* or prenatal* or pre-natal* or perinatal* or peri-natal*) adj3 (death* or loss*)).tw,kw. (32285) 24 Stillbirth/ (9917) 25 (stillbirth* or still-birth* or stillborn* or still-born*).tw,kw. (22014)

26 or/11-25 (287945)
27 exp Progesterone/ (131802)
28 (progesterone* or pregnenedione*).tw,kw. (139632)
29 57-83-0.rn. (117703)
30 Progestins/ (29346)
31 (progestin* or progestogen* or progestagen* or progestational* or gestagen*).tw,kw. (40285)
32 (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. (8371)
33 68-96-2.rn. (5833)
34 (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. (781)
35 (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)
36 (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. (147)
37 (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. (1782)
Dydrogesterone/ (1774)
39 ("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. (1188)
40 (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)
41 152-62-5.rn. (1728)
42 17-Hydroxyprogesterone capro*.tw,kw. (145)
43 (17 alpha-hydroxyprogesterone capro* or 17-alpha-hydroxy-progesterone capro* or hydroxyprogesterone capro* or hydroxyprogesterone hexanoate).tw,kw. (751)
44 (17OHP or Delalutin or Makena or Neolutin or oxyprogesterone caproate or Prolutin or Proluton).tw,kw. (767)
45 Medroxyprogesterone Acetate.tw,kw. (9828)
46 (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. (4903)
47 (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. (2872)
48 (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. (84)
49 (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. (3759)
50 71-58-9.rn. (17597)
51 Allylestrenol/ (365)
52 (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. (7056)
53 432-60-0.rn. (365)
54 Chlormadinone Acetate/ (3528)

55 (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. (2084)
56 302-22-7.rn. (3514)
57 or/27-56 (249615)
58 26 and 57 (8455)
59 limit 58 to systematic reviews [Limit not valid in Embase; records were retained] (4392)
60 meta analysis.pt. (42869)
61 exp meta-analysis as topic/ (21016)
62 (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,kw. (129533)
63 (systematic review* or systematic overview* or technology assessment* or HTA or HTAs).tw,kw. (110608)
64 exp Technology assessment, biomedical/ (20583)
65 health technology assessment winchester england.jn. (1250)
66 (evidence report technology assessment or evidence report technology assessment summary).jn. (400)
67 "cochrane database of systematic reviews".jn. (13249)
68 or/60-67 (251373)
69 58 and 68 (214)
70 59 or 69 (4412)
71 exp Animals/ not (exp Animals/ and Humans/) (7909058)
72 70 not 71 (3689)
73 limit 72 to yr="2008-current" (1543)
74 73 use prmz (74)
75 premature labor/ (37331)
76 ((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw,kw. (69512)
77 (PTL or sPTL or PTB or sPTB or PTD or sPTD).tw,kw. (11061)
78 uterus contraction/ (7042)
79 ((uterus* or uterine) adj3 contraction*).tw,kw. (8400)
80 uterine cervix ripening/ (1662)
81 ((cervical* or cervix*) adj3 (dilat* or ripen*)).tw,kw. (8996)
82 labor onset/ (1795)
83 (preterm* or pre-term* or prematur* or pre-matur*).tw,kw. (303203)
84 (78 or 79 or 80 or 81 or 82) and 83 (4085)
85 or/75-77,84 (89866)
86 *high risk pregnancy/ (3453)
87 *pregnancy complication/ (100001)

88 uterine cervix incompetence/ (1243)
89 ((cervix* or cervical* or endocervical* or endo-cervical*) adj3 (incompeten* or insufficien* or short* or weak*)).tw,kw. (4296)
90 cervical length measurement/ (772)
91 ((cervix* or cervical* or endocervical* or endo-cervical*) adj3 (length* or measur*)).tw,kw. (5533)
92 spontaneous abortion/ (37537)
93 miscarr*.tw,kw. (20125)
94 (abort* adj3 (spontaneous* or habitual* or frequen* or recurr* or tubal)).tw,kw. (24109)
95 exp fetus death/ (27522)
96 ((foetal or fetal or fetus* or foetus* or prenatal* or pre-natal* or perinatal* or peri-natal*) adj3 (death* or loss*)).tw,kw. (32285)
97 (stillbirth* or still-birth* or stillborn* or still-born*).tw,kw. (22014)
98 or/85-97 (287603)
99 progesterone/ (120570)
100 (progesterone* or pregnenedione*).tw,kw. (139632)
101 57-83-0.rn. (117703)
102 exp gestagen/ (133641)
103 (progestin* or progestogen* or progestagen* or progestational* or gestagen*).tw,kw. (40285)
104 (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. (8371)
105 68-96-2.rn. (5833)
106 (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. (781)
107 (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)
108 (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. (147)
109 (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. (1782)
110 ("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. (1188)
111 (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)
112 152-62-5.rn. (1728)

113 17-Hydroxyprogesterone capro*.tw,kw. (145)
114 (17 alpha-hydroxyprogesterone capro* or 17-alpha-hydroxy-progesterone capro* or hydroxyprogesterone capro* or hydroxyprogesterone hexanoate).tw,kw. (751)
115 (17OHP or Delalutin or Makena or Neolutin or oxyprogesterone caproate or Prolutin or Proluton).tw,kw. (767)
116 Medroxyprogesterone Acetate.tw,kw. (9828)
117 (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. (4903)
118 (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. (2872)
119 (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. (84)
120 (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. (3759)
121 71-58-9.rn. (17597)
122 (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. (7056)
123 432-60-0.rn. (365)
124 (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. (2084)
125 302-22-7.rn. (3514)
126 or/99-125 (272112)
127 98 and 126 (7862)
128 meta-analysis/ or "systematic review"/ or "meta analysis (topic)"/ or biomedical technology assessment/ (176034)
129 (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. (127897)
130 (systematic review* or systematic overview* or technology assessment* or HTA or HTAs).tw. (108942)
131 (data synthes* or data extraction* or data abstraction*).tw. (27341)
132 (health technology assessment or health technology assessment reports or health technology assessment winchester england).jn. (1987)
133 (evidence report technology assessment or evidence report technology assessment summary).jn. (400)
134 ("cochrane database of systematic reviews" or "cochrane database of systematic reviews online").jn. (21215)

	135 or/128-134 (300590) 136 127 and 135 (294) 137 exp animals/ (35401329) 138 exp animal experimentation/ (1598052) 139 exp models animal/ (1107058) 140 exp animal experiment/ (1598052) 141 nonhuman/ (4073457) 142 exp vertebrate/ (34496068) 143 or/137-142 (36562262) 144 exp humans/ (27561859) 145 exp human experimentation/ (325030) 146 exp human experiment/ (313223) 147 or/144-146 (27563896) 148 143 not 147 (8999918) 149 136 not 148 (294) 150 limit 149 to yr="2008-current" (161) 151 150 use emez (107) 152 74 or 151 (181) 153 remove duplicates from 152 (138) 154 153 use prmz (65) MEDLINE UNIQUE HITS 155 153 use emez (73) EMBASE UNIQUE HITS
Note	

Database	**Cochrane Library (Wiley Interface), including CDSR, DARE, Central, HTA, and NHS EED**
Date	Date Run: 12/06/13 03:14:19.321 Description: 2013 Jun 11 - Post PRESS
Search Strategy	#1 [mh "Obstetric Labor, Premature"] 984 #2 ((labor* or labour* or birth* or deliver*) near/4 (preterm* or pre-term* or prematur* or pre-matur*)):ti,ab,kw 2843 #3 (PTL or sPTL or PTB or sPTB or PTD or sPTD):ti,ab,kw 97 #4 [mh "Uterine Contraction"] 333 #5 ((uterus* or uterine) near/4 contraction*):ti,ab,kw 649 #6 [mh "Cervical Ripening"] 258 #7 ((cervical or cervix*) near/4 (dilat* or ripen*)):ti,ab,kw 1452 #8 [mh "Labor Onset"] 463 #9 (preterm* or pre-term* or prematur* or pre-matur*):ti,ab,kw 11797

#10 (#4 or #5 or #6 or #7 or #8) and #9 257
#11 #1 or #2 or #3 or #10 2943
#12 [mh "Pregnancy, High-Risk"] 178
#13 [mh "Pregnancy Complications"] 6985
#14 [mh "Uterine Cervical Incompetence"] 50
#15 ((cervix* or cervical*) near/4 (incompeten* or insufficien* or short* or weak*)):ti,ab,kw 191
#16 [mh "Cervical Length Measurement"] 19
#17 ((cervix* or cervical* or endocervical* or endo-cervical*) near/3 (length* or measur*)):ti,ab,kw 263
#18 [mh "Cervix Uteri"/ah] 19
#19 [mh "Abortion, Spontaneous"] 609
#20 miscarr*:ti,ab,kw 561
#21 (abort* near/4 (spontaneous* or habitual* or frequen* or recurr* or tubal)):ti,ab,kw 703
#22 [mh "fetal death"] 202
#23 ((foetal or fetal or fetus* or foetus* or prenatal* or pre-natal* or perinatal* or peri-natal*) near/4 (death* or loss*)):ti,ab,kw 607
#24 [mh Stillbirth] 40
#25 (stillbirth* or (still next birth*) or stillborn* or (still next born*)):ti,ab,kw 212
#26 2-#25 9589
#27 [mh Progesterone] 2228
#28 (progesterone* or pregnenedione*):ti,ab,kw 3806
#29 [mh Progestins] 361
#30 (progestin* or progestogen* or progestagen* or progestational* or gestagen*):ti,ab,kw 1969
#31 (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 243
#32 (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 49
#33 (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
#34 (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 2
#35 (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 45

#36 [mh Dydrogesterone] 117
#37 ("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 174
#38 (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
#39 (17 next Hydroxyprogesterone next capro*):ti,ab,kw 9
#40 ("17 alpha-hydroxyprogesterone" next capro*) or ("17-alpha-hydroxy-progesterone" next capro*) or (hydroxyprogesterone next capro*) or "hydroxyprogesterone hexanoate":ti,ab,kw 99
#41 (17OHP or Delalutin or Makena or Neolutin or "oxyprogesterone caproate" or Prolutin or Proluton):ti,ab,kw 16
#42 "Medroxyprogesterone Acetate":ti,ab,kw 1355
#43 ("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 164
#44 ("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 40
#45 ("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 22
#46 (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 73
#47 [mh Allylestrenol] 10
#48 (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 104
#49 [mh "Chlormadinone Acetate"] 80
#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):ti,ab,kw 112
#51 {or #27-#50} 6534
#52 #26 and #51 from 2008 to 2013 108
DSR - 16
DARE - 8
CENTRAL - 79
HTA – 2

	NHS EED - 3
Note	

3.1.3.2. Oral or vaginal progesterone - RCTs

Database	**MEDLINE and EMBASE**
Date	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Embase<1980 to 2013 Week 36> **Limits:**Human; 2012-present; RCT filter
Search Strategy	1 exp Obstetric Labor, Premature/ 44402 2 ((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw,kw. 72552 3 (PTL or sPTL or PTB or sPTB or PTD or sPTD).tw,kw. 11713 4 Uterine Contraction/ 14198 5 ((uterus* or uterine) adj3 contraction*).tw,kw. 8600 6 Cervical Ripening/2500 7 ((cervical* or cervix*) adj3 (dilat* or ripen*)).tw,kw. 9244 8 exp Labor Onset/ 4323 9 (preterm* or pre-term* or prematur* or pre-matur*).tw,kw. 314384 10 (4 or 5 or 6 or 7 or 8) and 9 4910 11 or/1-3,10 95271 12 *Pregnancy, High-Risk/ 3526 13 *Pregnancy Complications/ 77073 14 Uterine Cervical Incompetence/ 2422 15 ((cervix* or cervical* or endocervical* or endo-cervical*) adj3 (incompeten* or insufficien* or short* or weak*)).tw,kw. 4451 16 Cervical Length Measurement/ 859 17 ((cervix* or cervical* or endocervical* or endo-cervical*) adj3 (length* or measur*)).tw,kw. 5786 18 Cervix Uteri/ah [Anatomy & Histology] 754 19 exp Abortion, Spontaneous/ 53294 20 miscarr*.tw,kw. 21218 21 (abort* adj3 (spontaneous* or habitual* or frequen* or recurr* or tubal)).tw,kw. 24562

22 exp fetal death/ 51870

23 ((foetal or fetal or fetus* or foetus* or prenatal* or pre-natal* or perinatal* or peri-natal*) adj3 (death* or loss*)).tw,kw. 33231

24 Stillbirth/ 10441

25 (stillbirth* or still-birth* or stillborn* or still-born*).tw,kw. 22834

26 or/11-25 296809

27 exp Progesterone/ 133660

28 (progesterone* or pregnenedione*).tw,kw. 142955

29 57-83-0.rn. 119113

30 Progestins/ 29825

31 (progestin* or progestogen* or progestagen* or progestational* or gestagen*).tw,kw. (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. 41002 8474

32 33 68-96-2.rn. 5896

34 (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. 791

35 (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

36 (Lingusorbs or Lipo-Lutin or Lucorteum or Luteal hormone* or Luteinique or Luteocrinnormale 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. 150

37 (Membrettes or Methylpregnone or NSC 64377 or NSC 9704 or NSC-9704 or Nalutron or PercutacrineLuteinique 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. 1800

38 Dydrogesterone/ 1795

39 ("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. 1207

40 (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

41 152-62-5.rn. 1744

42 17-Hydroxyprogesterone capro*.tw,kw. 145

43 (17 alpha-hydroxyprogesteronecapro* or 17-alpha-hydroxy-progesterone capro* or hydroxyprogesteronecapro* or hydroxyprogesteronehexanoate).tw,kw. 782

44 (17OHP or Delalutin or Makena or Neolutin or oxyprogesteronecaproate or Prolutin or Proluton).tw,kw. 772

45 MedroxyprogesteroneAcetate.tw,kw. 10013

46 (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* adjMedroxyprogesterone Acetate) or Depo-Provera or DP150 or Depcorlutin or Depo-Clinovir or Depo-Map).tw,kw. 4997

47 (Depo-Prodasone or Depo-Progevera or Depo-Promone or Depo-Provera or Depo-Ralovera or Depo-progestin or Depo-subQprovera 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. 2894

48 (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. 86

49 (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. 3781

50 71-58-9.rn. 17813

51 Allylestrenol/ 364

52 (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. 7076

53 432-60-0.rn. 364

54 Chlormadinone Acetate/ 3539

55 (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. 2098

56 302-22-7.rn. 3524

57 or/27-56 254178

58 26 and 57 8708

59 randomized controlled trial.pt. use prmz 384981

60 exp Randomized Controlled Trials as Topic/ use prmz 102337

61 exp Random Allocation/ use prmz 81084

62 exp Double-Blind Method/ use prmz 130411
63 exp Single-Blind Method/ use prmz 19282
64 exp Placebos/ use prmz 33587
65 (random* or RCT$1 or placebo*).tw. 1715906
66 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. 289241
67 or/59-66 1931623
68 58 and 67 1096
69 exp Animals/ not (exp Animals/ and Humans/) 8095346
70 68 not 69 928
71 limit 70 to yr="2012-current" 177
72 71 use prmz 65
73 premature labor/ 38404
74 ((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw,kw. 72552
75 (PTL or sPTL or PTB or sPTB or PTD or sPTD).tw,kw. 11713
76 uterus contraction/ 7198
77 ((uterus* or uterine) adj3 contraction*).tw,kw. 8600
78 uterine cervix ripening/ 1711
79 ((cervical* or cervix*) adj3 (dilat* or ripen*)).tw,kw. 9244
80 labor onset/ 1893
81 (preterm* or pre-term* or prematur* or pre-matur*).tw,kw. 314384
82 (76 or 77 or 78 or 79 or 80) and 81 4239
83 or/73-75,82 93555
84 *high risk pregnancy/ 3526
85 *pregnancy complication/ 102349
86 uterine cervix incompetence/ 1273
87 ((cervix* or cervical* or endocervical* or endo-cervical*) adj3 (incompeten* or insufficien* or short* or weak*)).tw,kw. 4451
88 cervical length measurement/859
89 ((cervix* or cervical* or endocervical* or endo-cervical*) adj3 (length* or measur*)).tw,kw. 5786
90 spontaneous abortion/ 38550
91 miscarr*.tw,kw. 21218

92 (abort* adj3 (spontaneous* or habitual* or frequen* or recurr* or tubal)).tw,kw. 24562

93 exp fetus death/ 28167

94 ((foetal or fetal or fetus* or foetus* or prenatal* or pre-natal* or perinatal* or peri-natal*) adj3 (death* or loss*)).tw,kw. 33231

95 (stillbirth* or still-birth* or stillborn* or still-born*).tw,kw. 22834

96 or/83-95 296102

97 progesterone/122250

98 (progesterone* or pregnenedione*).tw,kw. 142955

99 57-83-0.rn. 119113

100 expgestagen/ 135192

101 (progestin* or progestogen* or progestagen* or progestational* or gestagen*).tw,kw. 41002

102 (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. 8474

103 68-96-2.rn. 5896

104 (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. 791

105 (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

106 (Lingusorbs or Lipo-Lutin or Lucorteum or Luteal hormone* or Luteinique or Luteocrinnormale 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. 150

107 (Membrettes or Methylpregnone or NSC 64377 or NSC 9704 or NSC-9704 or Nalutron or PercutacrineLuteinique 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. 1800

108 ("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.1207

109 (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

110 152-62-5.rn. 1744

111 17-Hydroxyprogesterone capro*.tw,kw. 145

112 (17 alpha-hydroxyprogesteronecapro* or 17-alpha-hydroxy-progesterone capro* or hydroxyprogesteronecapro* or hydroxyprogesteronehexanoate).tw,kw. 782

113 (17OHP or Delalutin or Makena or Neolutin or oxyprogesteronecaproate or Prolutin or Proluton).tw,kw. 772

114 MedroxyprogesteroneAcetate.tw,kw. 10013

115 (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* adjMedroxyprogesterone Acetate) or Depo-Provera or DP150 or Depcorlutin or Depo-Clinovir or Depo-Map).tw,kw. 4997

116 (Depo-Prodasone or Depo-Progevera or Depo-Promone or Depo-Provera or Depo-Ralovera or Depo-progestin or Depo-subQprovera 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.2894

117 (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. 86

118 (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. 3781

119 71-58-9.rn. 17813

120 (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. 7076

121 432-60-0.rn. 364

122 (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. 2098

123 302-22-7.rn. 3524

124 or/97-123 276964

125 96 and 124 8108

126 Randomized Controlled Trial/ use emez 355507

127 Randomization/ use emez 63366

128 Random Sampling/ use emez 64

129 Double Blind Procedure/ use emez 117458

130 Single Blind Procedure/ use emez 18204

	131 Placebo/ use emez 224986
	132 (random* or RCT$1 or placebo*).tw. 1715906
	133 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. 289241
	134 or/126-133 1946891
	135 125 and 134 1159
	136 exp animals/ 36397898
	137 exp animal experimentation/ 1616611
	138 exp models animal/ 1143709
	139 exp animal experiment/1616611
	140 nonhuman/ 4123486
	141 exp vertebrate/ 35462396
	142 or/136-141 37570478
	143 exp humans/28372137
	144 exp human experimentation/328188
	145 exp human experiment/315911
	146 or/143-145 28374182
	147 142 not 146 9197855
	148 135 not 147 1054
	149 limit 148 to yr="2012-current" 205
	150 149 use emez 145
	151 72 or 150 210
	152 remove duplicates from 151 159
	153 152 use prmz 15
	154 152 use emez 144
Note	

Database	Cochrane Library (Wiley Interface), including CDSR, DARE, Central, HTA, and NHS EED
Date	Cochrane Library (CENTRAL only), Issue 8 of 12, August 2013 Date Run: 10/09/13 00:11:02.356
Search Strategy	#1 MeSH descriptor: [Obstetric Labor, Premature] explode all trees 1002 #2 (labor* or labour* or birth* or deliver*) near/4 (preterm* or pre-term* or prematur* or pre-matur*):ti,ab,kw or (PTL or sPTL or PTB or sPTB or PTD or sPTD):ti,ab,kw 2954 #3 MeSH descriptor: [Uterine Contraction] this term only 334 #4 (uterus* or uterine) near/4 contraction*:ti,ab,kw 654 #5 MeSH descriptor: [Cervical Ripening] this term only 261 #6 (cervical or cervix*) near/4 (dilat* or ripen*):ti,ab,kw 1458 #7 MeSH descriptor: [Labor Onset] explode all trees 468 #8 preterm* or pre-term* or prematur* or pre-matur*:ti,ab,kw 12036 #9 (#3 or #4 or #5 or #6 or #7) and #8 253 #10 #1 or #2 or #9 2988 #11 MeSH descriptor: [Pregnancy, High-Risk] this term only 180 #12 MeSH descriptor: [Pregnancy Complications] this term only 1015 #13 MeSH descriptor: [Uterine Cervical Incompetence] this term only 51 #14 (cervix* or cervical*) near/4 (incompeten* or insufficien* or short* or weak*):ti,ab,kw (Word variations have been searched) 195 #15 MeSH descriptor: [Cervical Length Measurement] this term only 21 #16 (cervix* or cervical* or endocervical* or endo-cervical*) near/3 (length* or measur*):ti,ab,kw (Word variations have been searched) 270 #17 MeSH descriptor: [Abortion, Spontaneous] explode all trees 618 #18 miscarr*:ti,ab,kw or abort* near/4 (spontaneous* or habitual* or frequen* or recurr* or tubal):ti,ab,kw (Word variations have been searched) 1051 #19 MeSH descriptor: [Fetal Death] explode all trees 203 #20 (foetal or fetal or fetus* or foetus* or prenatal* or pre-natal* or perinatal* or peri-natal*) near/4 (death* or loss*):ti,ab,kw (Word variations have been searched) 617 #21 MeSH descriptor: [Stillbirth] this term only 44 #22 stillbirth* or (still next birth*) or stillborn* or (still next born*):ti,ab,kw (Word variations have been searched) 221

#23 MeSH descriptor: [Cervix Uteri] this term only and with qualifiers: [Anatomy & histology - AH] 20

#24 {or #10-#23} 5664

#25 MeSH descriptor: [Progesterone] explode all trees 2240

#26 progesterone* or pregnenedione*:ti,ab,kw (Word variations have been searched) 3841

#27 MeSH descriptor: [Progestins] this term only 362

#28 progestin* or progestogen* or progestagen* or progestational* or gestagen*:ti,ab,kw or 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 or 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 or 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 or Lingusorbs or "Lipo-Lutin" or Lucorteum or (Luteal next hormone*) or Luteinique or "Luteocrinnormale" 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 (Word variations have been searched) 2227

#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 (Word variations have been searched) 45

#30 MeSH descriptor: [Dydrogesterone] this term only 117

#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 or 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 or 17 next Hydroxyprogesterone next capro*:ti,ab,kw or ("17 alpha-hydroxyprogesterone" next capro*) or ("17-alpha-hydroxy-progesterone" next capro*) or (hydroxyprogesterone next capro*) or "hydroxyprogesteronehexanoate":ti,ab,kw or 17OHP or Delalutin or Makena or Neolutin or "oxyprogesteronecaproate" or Prolutin or Proluton:ti,ab,kw (Word variations have been searched) 270

	#32 "Medroxyprogesterone Acetate":ti,ab,kw or "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 or "Depo-Prodasone" or "Depo-Progevera" or "Depo-Promone" or "Depo-Provera" or "Depo-Ralovera" or "Depo-progestin" or "Depo-subQprovera" 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 or "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 or 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 (Word variations have been searched) 1405
	#33 MeSH descriptor: [Allylestrenol] this term only 10
	#34 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 (Word variations have been searched) 104
	#35 MeSH descriptor: [Chlormadinone Acetate] this term only 80
	#36 "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 (Word variations have been searched) 112
	#37 3-#36 6581
	#38 #24 and #37 from 2012 to 2013, in Trials 9
Note	

3.1.4. Secondary prevention: cerclage

3.1.4.1. Cerclage reviews

Database	MEDLINE and EMBASE
Date	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Embase <1980 to 2013 Week 24>
Search Strategy	1 exp Obstetric Labor, Premature/ (42805) 2 ((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw,kw. (69512) 3 (PTL or sPTL or PTB or sPTB or PTD or sPTD).tw,kw. (11061) 4 Uterine Contraction/ (13948) 5 ((uterus* or uterine) adj3 contraction*).tw,kw. (8400) 6 Cervical Ripening/ (2400) 7 ((cervical or cervix*) adj3 (dilat* or ripen*)).tw,kw. (8995) 8 exp Labor Onset/ (4124) 9 (preterm* or pre-term* or prematur* or pre-matur*).tw,kw. (303203) 10 (4 or 5 or 6 or 7 or 8) and 9 (4737) 11 or/1-3,10 (91466) 12 Pregnancy/ (1198814) 13 *Pregnancy, High-Risk/ (3453) 14 *Pregnancy Complications/ (74725) 15 Uterine Cervical Incompetence/ (2371) 16 ((cervix* or cervical*) adj3 (incompeten* or insufficien* or short* or weak*)).tw,kw. (4268) 17 Cervical Length Measurement/ (772) 18 ((cervix* or cervical* or endocervical* or endo-cervical*) adj3 (length* or measur*)).tw,kw. (5533) 19 exp Abortion, Spontaneous/ (52016) 20 miscarr*.tw,kw. (20125) 21 (abort* adj3 (spontaneous* or habitual* or frequen* or recurr* or tubal)).tw,kw. (24109) 22 exp fetal death/ (50984) 23 ((foetal or fetal or fetus* or foetus* or prenatal* or pre-natal* or perinatal* or peri-natal*) adj3 (death* or loss*)).tw,kw. (32285) 24 Stillbirth/ (9917) 25 (stillbirth* or still-birth* or stillborn* or still-born*).tw,kw. (22014) 26 or/11-25 (1293833) 27 Cerclage, Cervical/ (1643) 28 cerclage*.tw,kw. (4786)

29 ((cervix* or cervical*) adj3 (stitch* or sutur*)).tw,kw. (471)
30 (McDonald adj3 (stitch* or sutur*)).tw,kw. (31)
31 (Shirodkar adj3 (stitch* or sutur*)).tw,kw. (45)
32 tracheloplast*.tw,kw. (7)
33 or/27-32 (5461)
34 26 and 33 (3231)
35 limit 34 to systematic reviews [Limit not valid in Embase; records were retained] (1911)
36 meta analysis.pt. (42869)
37 exp meta-analysis as topic/ (21016)
38 (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,kw. (129533)
39 (systematic review* or systematic overview* or technology assessment* or HTA or HTAs).tw,kw. (110608)
40 exp Technology assessment, biomedical/ (20583)
41 health technology assessment winchester england.jn. (1250)
42 (evidence report technology assessment or evidence report technology assessment summary).jn. (400)
43 "cochrane database of systematic reviews".jn. (13249)
44 or/36-43 (251373)
45 34 and 44 (107)
46 35 or 45 (1921)
47 exp Animals/ not (exp Animals/ and Humans/) (7909058)
48 46 not 47 (1911)
49 limit 48 to yr="2008-current" (680)
50 49 use prmz (35)
51 premature labor/ (37331)
52 ((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw,kw. (69512)
53 (PTL or sPTL or PTB or sPTB or PTD or sPTD).tw,kw. (11061)
54 uterus contraction/ (7042)
55 ((uterus* or uterine) adj3 contraction*).tw,kw. (8400)
56 uterine cervix ripening/ (1662)
57 ((cervical or cervix*) adj3 (dilat* or ripen*)).tw,kw. (8995)
58 labor onset/ (1795)
59 (preterm* or pre-term* or prematur* or pre-matur*).tw,kw. (303203)
60 (54 or 55 or 56 or 57 or 58) and 59 (4085)
61 or/51-53,60 (89866)
62 Pregnancy/ (1198814)
63 *high risk pregnancy/ (3453)
64 *pregnancy complication/ (100001)

65 uterine cervix incompetence/ (1243)
66 ((cervix* or cervical*) adj3 (incompeten* or insufficien* or short* or weak*)).tw,kw. (4268)
67 cervical length measurement/ (772)
68 ((cervix* or cervical* or endocervical* or endo-cervical*) adj3 (length* or measur*)).tw,kw. (5533)
69 spontaneous abortion/ (37537)
70 miscarr*.tw,kw. (20125)
71 (abort* adj3 (spontaneous* or habitual* or frequen* or recurr* or tubal)).tw,kw. (24109)
72 exp fetus death/ (27522)
73 ((foetal or fetal or fetus* or foetus* or prenatal* or pre-natal* or perinatal* or peri-natal*) adj3 (death* or loss*)).tw,kw. (32285)
74 (stillbirth* or still-birth* or stillborn* or still-born*).tw,kw. (22014)
75 or/61-74 (1292563)
76 uterine cervix cerclage/ (1643)
77 cerclage*.tw,kw. (4786)
78 ((cervix* or cervical*) adj3 (stitch* or sutur*)).tw,kw. (471)
79 (McDonald adj3 (stitch* or sutur*)).tw,kw. (31)
80 (Shirodkar adj3 (stitch* or sutur*)).tw,kw. (45)
81 tracheloplast*.tw,kw. (7)
82 or/76-81 (5461)
83 75 and 82 (3224)
84 meta-analysis/ or "systematic review"/ or "meta analysis (topic)"/ or biomedical technology assessment/ (176034)
85 (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. (127897)
86 (systematic review* or systematic overview* or technology assessment* or HTA or HTAs).tw. (108942)
87 (data synthes* or data extraction* or data abstraction*).tw. (27341)
88 (health technology assessment or health technology assessment reports or health technology assessment winchester england).jn. (1987)
89 (evidence report technology assessment or evidence report technology assessment summary).jn. (400)
90 "cochrane database of systematic reviews".jn. (13249)
91 ("cochrane database of systematic reviews" or "cochrane database of systematic reviews online").jn. (21215)
92 or/84-91 (300590)
93 83 and 92 (133)
94 exp animals/ (35401329)
95 exp animal experimentation/ (1598052)
96 exp models animal/ (1107058)
97 exp animal experiment/ (1598052)
98 nonhuman/ (4073457)

	99 exp vertebrate/ (34496068) 100 or/94-99 (36562262) 101 exp humans/ (27561859) 102 exp human experimentation/ (325030) 103 exp human experiment/ (313223) 104 or/101-103 (27563896) 105 100 not 104 (8999918) 106 93 not 105 (133) 107 limit 106 to yr="2008-current" (67) 108 107 use emez (43) 109 50 or 108 (78) 110 remove duplicates from 109 (54) 111 110 use prmz (29) MEDLINE UNIQUE HITS 112 110 use emez (25) EMBASE UNIQUE HITS
Note	

Database	**Cochrane Library (Wiley Interface), including CDSR, DARE, Central, HTA, and NHS EED**
Date	Date Run: 11/06/13 22:08:01.771 Description: 2013 Jun 10 - Post PRESS
Search Strategy	#1 [mh "Obstetric Labor, Premature"] 984 #2 ((labor* or labour* or birth* or deliver*) near/4 (preterm* or pre-term* or prematur* or pre-matur*)):ti,ab,kw 2843 #3 (PTL or sPTL or PTB or sPTB or PTD or sPTD):ti,ab,kw 97 #4 [mh "Uterine Contraction"] 333 #5 ((uterus* or uterine) near/4 contraction*):ti,ab,kw 649 #6 [mh "Cervical Ripening"] 258 #7 ((cervical or cervix*) near/4 (dilat* or ripen*)):ti,ab,kw 1452 #8 [mh "Labor Onset"] 463 #9 (preterm* or pre-term* or prematur* or pre-matur*):ti,ab,kw 11797 #10 (#4 or #5 or #6 or #7 or #8) and #9 257 #11 #1 or #2 or #3 or #10 2943 #12 [mh ^Pregnancy] 73

#13	[mh "Pregnancy, High-Risk"] 178
#14	[mh "Pregnancy Complications"] 6985
#15	[mh "Uterine Cervical Incompetence"] 50
#16	((cervix* or cervical*) near/4 (incompeten* or insufficien* or short* or weak*)):ti,ab,kw 191
#17	[mh "Cervical Length Measurement"] 19
#18	((cervix* or cervical* or endocervical* or endo-cervical*) near/3 (length* or measur*)):ti,ab,kw 263
#19	[mh "Abortion, Spontaneous"] 609
#20	miscarr*:ti,ab,kw 561
#21	(abort* near/4 (spontaneous* or habitual* or frequen* or recurr* or tubal)):ti,ab,kw 703
#22	[mh "fetal death"] 202
#23	((foetal or fetal or fetus* or foetus* or prenatal* or pre-natal* or perinatal* or peri-natal*) near/4 (death* or loss*)):ti,ab,kw 607
#24	[mh Stillbirth] 40
#25	(stillbirth* or (still next birth*) or stillborn* or (still next born*)):ti,ab,kw 212
#26	2-#25 9634
#27	[mh "Cerclage, Cervical"] 42
#28	cerclage*:ti,ab,kw 127
#29	((cervix* or cervical*) near/4 (stitch* or sutur*)):ti,ab,kw 35
#30	(McDonald near/4 (stitch* or sutur*)):ti,ab,kw 1
#31	(Shirodkar near/4 (stitch* or sutur*)):ti,ab,kw 2
#32	tracheloplast*:ti,ab,kw 0
#33	{or #27-#32} 142
#34	#26 and #33 from 2008 to 2013 30
DSR - 4	
DARE – 5	
CENTRAL – 21	

Note

3.1.4.2. Cerclage - RCTs

Database	MEDLINE and EMBASE
Date	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Embase <1980 to 2013 Week 36>
Search Strategy	1 exp Obstetric Labor, Premature/44402 2 ((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw,kw.72552 3 (PTL or sPTL or PTB or sPTB or PTD or sPTD).tw,kw. 11713 4 Uterine Contraction/ 14198 5 ((uterus* or uterine) adj3 contraction*).tw,kw.8600 6 Cervical Ripening/ 2500 7 ((cervical or cervix*) adj3 (dilat* or ripen*)).tw,kw.9242 8 exp Labor Onset/4323 9 (preterm* or pre-term* or prematur* or pre-matur*).tw,kw. 314384 10 (4 or 5 or 6 or 7 or 8) and 94910 11 or/1-3,10 95271 12 Pregnancy/1226192 13 *Pregnancy, High-Risk/ 3526 14 *Pregnancy Complications/77073 15 Uterine Cervical Incompetence/2422 16 ((cervix* or cervical*) adj3 (incompeten* or insufficien* or short* or weak*)).tw,kw. 4423 17 Cervical Length Measurement/859 18 ((cervix* or cervical* or endocervical* or endo-cervical*) adj3 (length* or measur*)).tw,kw. 5786 19 exp Abortion, Spontaneous/ 53294 20 miscarr*.tw,kw. 21218 21 (abort* adj3 (spontaneous* or habitual* or frequen* or recurr* or tubal)).tw,kw. 24562 22 exp fetal death/51870 23 ((foetal or fetal or fetus* or foetus* or prenatal* or pre-natal* or perinatal* or peri-natal*) adj3 (death* or loss*)).tw,kw. 33231 24 Stillbirth/ 10441 25 (stillbirth* or still-birth* or stillborn* or still-born*).tw,kw.22834

26	or/11-251323900
27	Cerclage, Cervical/ 1722
28	cerclage*.tw,kw.4921
29	((cervix* or cervical*) adj3 (stitch* or sutur*)).tw,kw.487
30	(McDonald adj3 (stitch* or sutur*)).tw,kw.32
31	(Shirodkar adj3 (stitch* or sutur*)).tw,kw.47
32	tracheloplast*.tw,kw.7
33	or/27-32 5611
34	26 and 33 3339
35	randomized controlled trial.pt. use prmz 384981
36	exp Randomized Controlled Trials as Topic/ use prmz 102337
37	exp Random Allocation/ use prmz 81084
38	exp Double-Blind Method/ use prmz 130411
39	exp Single-Blind Method/ use prmz 19282
40	exp Placebos/ use prmz 33587
41	(random* or RCT$1 or placebo*).tw. 1715906
42	((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. 289241
43	or/35-42 1931623
44	34 and 43 372
45	exp Animals/ not (exp Animals/ and Humans/) 8095346
46	44 not 45 369
47	limit 46 to yr="2011-current" 94
48	47 use prmz 40
49	premature labor/ 38404
50	((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw,kw. 72552
51	(PTL or sPTL or PTB or sPTB or PTD or sPTD).tw,kw. 11713
52	uterus contraction/ 7198
53	((uterus* or uterine) adj3 contraction*).tw,kw. 8600
54	uterine cervix ripening/ 1711

55 ((cervical or cervix*) adj3 (dilat* or ripen*)).tw,kw. 9242
56 labor onset/ 1893
57 (preterm* or pre-term* or prematur* or pre-matur*).tw,kw. 314384
58 (52 or 53 or 54 or 55 or 56) and 57 4239
59 or/49-51,58 93555
60 Pregnancy/ 1226192
61 *high risk pregnancy/ 3526
62 *pregnancy complication/ 102349
63 uterine cervix incompetence/ 1273
64 ((cervix* or cervical*) adj3 (incompeten* or insufficien* or short* or weak*)).tw,kw. 4423
65 cervical length measurement/ 859
66 ((cervix* or cervical* or endocervical* or endo-cervical*) adj3 (length* or measur*)).tw,kw. 5786
67 spontaneous abortion/ 38550
68 miscarr*.tw,kw. 21218
69 (abort* adj3 (spontaneous* or habitual* or frequen* or recurr* or tubal)).tw,kw. 24562
70 exp fetus death/ 28167
71 ((foetal or fetal or fetus* or foetus* or prenatal* or pre-natal* or perinatal* or peri-natal*) adj3 (death* or loss*)).tw,kw. 33231
72 (stillbirth* or still-birth* or stillborn* or still-born*).tw,kw. 22834
73 or/59-72 1322496
74 uterine cervix cerclage/ 1722
75 cerclage*.tw,kw. 4921
76 ((cervix* or cervical*) adj3 (stitch* or sutur*)).tw,kw. 487
77 (McDonald adj3 (stitch* or sutur*)).tw,kw. 32
78 (Shirodkar adj3 (stitch* or sutur*)).tw,kw. 47
79 tracheloplast*.tw,kw. 7
80 or/74-79 5611
81 73 and 80 3332
82 Randomized Controlled Trial/ use emez 355507
83 Randomization/ use emez 63366
84 Random Sampling/ use emez 64

85 Double Blind Procedure/ use emez 117458
86 Single Blind Procedure/ use emez 18204
87 Placebo/ use emez 224986
88 (random* or RCT$1 or placebo*).tw. 1715906
89 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. 289241
90 or/82-89 1946891
91 81 and 90 393
92 exp animals/ 36397898
93 exp animal experimentation/ 1616611
94 exp models animal/ 1143709
95 exp animal experiment/ 1616611
96 nonhuman/ 4123486
97 exp vertebrate/ 35462396
98 or/92-97 37570478
99 exp humans/ 28372137
100 exp human experimentation/ 328188
101 exp human experiment/ 315911
102 or/99-101 28374182
103 98 not 102 9197855
104 91 not 103 391
105 limit 104 to yr="2011-current" 104
106 105 use emez 71
107 48 or 106 111
108 remove duplicates from 107 82
109 108 use prmz 33
110 108 use emez 49

Note

Database	Cochrane Library (Wiley Interface), including CDSR, DARE, Central, HTA, and NHS EED
Date	Cochrane Library (CENTRAL only), Issue 8 of 12, August 2013 Date Run: 09/09/13 23:48:07.773
Search Strategy	#1 MeSH descriptor: [Obstetric Labor, Premature] explode all trees 1002 #2 (labor* or labour* or birth* or deliver*) near/4 (preterm* or pre-term* or prematur* or pre-matur*):ti,ab,kw or (PTL or sPTL or PTB or sPTB or PTD or sPTD):ti,ab,kw 2954 #3 MeSH descriptor: [Uterine Contraction] this term only 334 #4 (uterus* or uterine) near/4 contraction*:ti,ab,kw 654 #5 MeSH descriptor: [Cervical Ripening] this term only 261 #6 (cervical or cervix*) near/4 (dilat* or ripen*):ti,ab,kw 1458 #7 MeSH descriptor: [Labor Onset] explode all trees 468 #8 preterm* or pre-term* or prematur* or pre-matur*:ti,ab,kw 12036 #9 (#3 or #4 or #5 or #6 or #7) and #8 253 #10 #1 or #2 or #9 2988 #11 MeSH descriptor: [Pregnancy] this term only 101 #12 MeSH descriptor: [Pregnancy, High-Risk] this term only 180 #13 MeSH descriptor: [Pregnancy Complications] this term only 1015 #14 MeSH descriptor: [Uterine Cervical Incompetence] this term only 51 #15 (cervix* or cervical*) near/4 (incompeten* or insufficien* or short* or weak*):ti,ab,kw (Word variations have been searched) 195 #16 MeSH descriptor: [Cervical Length Measurement] this term only 21 #17 (cervix* or cervical* or endocervical* or endo-cervical*) near/3 (length* or measur*):ti,ab,kw (Word variations have been searched) 270 #18 MeSH descriptor: [Abortion, Spontaneous] explode all trees 618 #19 miscarr*:ti,ab,kw or abort* near/4 (spontaneous* or habitual* or frequen* or recurr* or tubal):ti,ab,kw (Word variations have been searched) 1051 #20 MeSH descriptor: [Fetal Death] explode all trees 203 #21 (foetal or fetal or fetus* or foetus* or prenatal* or pre-natal* or perinatal* or peri-natal*) near/4 (death* or loss*):ti,ab,kw (Word variations have been searched) 617 #22 MeSH descriptor: [Stillbirth] this term only 44

	#23 stillbirth* or (still next birth*) or stillborn* or (still next born*):ti,ab,kw (Word variations have been searched) 221 #24 {or #10-#23} 5735 #25 MeSH descriptor: [Cerclage, Cervical] this term only 46 #26 cerclage*:ti,ab,kw or (cervix* or cervical*) near/4 (stitch* or sutur*):ti,ab,kw or McDonald near/4 (stitch* or sutur*):ti,ab,kw or Shirodkar near/4 (stitch* or sutur*):ti,ab,kw or tracheloplast*:ti,ab,kw (Word variations have been searched) 147 #27 #25 or #26 147 #28 #24 and #27 from 2011 to 2013, in Trials 6
Note	

3.1.5. Tertiary prevention: repeated doses of corticosteroids

Database	**Medline including pre-medline via OVID**
Date	March 3rd, 2014
Search Strategy	1 exp obstetric labor, premature/ or premature birth/ (17498) 2 labo?r.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (111771) 3 birth.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (233544) 4 deliver*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (474277) 5 2 or 3 or 4 (738528) 6 preterm*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (44675) 7 pre-term*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (2109) 8 prematur*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (150692) 9 pre-matur*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (203) 10 6 or 7 or 8 or 9 (165816)

11	5 and 10 (63928)
12	exp Labor Onset/ (3121)
13	10 and 12 (296)
14	(PTL or sPTL or PTB or sPTB or PTD or sPTD).mp. (4959)
15	1 or 11 or 13 or 14 (67897)
16	exp Betamethasone/ (6190)
17	exp Dexamethasone/ (43376)
18	Glucocorticoids/ad, ae, tu [Administration & Dosage, Adverse Effects, Therapeutic Use] (29209)
19	Adrenal Cortex Hormones/ad, tu [Administration & Dosage, Therapeutic Use] (30920)
20	Premature Birth/dt [Drug Therapy] (102)
21	exp Fetal Organ Maturity/de [Drug Effects] (444)
22	steroid*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (261019)
23	corticosteroid*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (74858)
24	betamethason*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (6470)
25	dexamethason*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (57332)
26	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 (397648)
27	15 and 26 (3806)
28	limit 27 to yr="2011 -Current" (634)
29	randomized controlled trial.pt. (363615)
30	controlled clinical trial.pt. (87597)
31	randomized.ab. (283941)
32	placebo.ab. (150096)
33	randomly.ab. (206454)
34	trial.ti. (121282)
35	clinical trials as topic.sh. (167816)
36	29 or 30 or 31 or 32 or 33 or 34 or 35 (879688)

	37 exp animals/ not humans.sh. (3882912) 38 36 not 37 (811594) 39 38 and 28 (80)
Note	

Database	**EMBASE via embase.com**
Date	March 3rd, 2014
Search Strategy	#22. labor OR labour AND [2011-2014]/py OR (birth AND [2011-2014]/py) OR (deliver* AND [2011-2014]/py) AND (preterm* AND [2011-2014]/py OR (prematur* AND [2011-2014]/py)) OR (ptl OR sptl OR ptb OR sptb OR ptd OR sptd AND [2011-2014]/py) OR (preterm* AND [2011-2014]/py OR (prematur* AND [2011-2014]/py) AND 'labor onset'/exp AND [2011-2014]/py) AND ('steroid hormone'/exp AND [2011-2014]/py OR (dexamethason* AND [2011-2014]/py) OR (betamethason* AND [2011-2014]/py) OR (steroid* AND [2011-2014]/py) OR (corticosteroid* AND [2011-2014]/py)) AND ([controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim) AND [2011-2014]/py
Note	

3.1.6. Tertiary prevention: duration of therapy

3.1.6.1. Systematic reviews

Database	**MEDLINE and EMBASE**
Date	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Embase <1980 to 2013 Week 24>
Search Strategy	1 exp Obstetric Labor, Premature/ (42805) 2 ((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw,kw. (69512) 3 (PTL or sPTL or PTB or sPTB or PTD or sPTD).tw,kw. (11061) 4 Uterine Contraction/ (13948) 5 ((uterus* or uterine) adj3 contraction*).tw,kw. (8400) 6 Cervical Ripening/ (2400) 7 ((cervical or cervix*) adj3 (dilat* or ripen*)).tw,kw. (8995) 8 exp Labor Onset/ (4124) 9 (preterm* or pre-term* or prematur* or pre-matur*).tw,kw. (303203) 10 (4 or 5 or 6 or 7 or 8) and 9 (4737)

11 or/1-3,10 (91466)
12 *Pregnancy, High-Risk/ (3453)
13 *Pregnancy Complications/ (74725)
14 or/11-13 (162727)
15 Tocolysis/ (3605)
16 (tocolys* or tocolytic*).tw,kw. (6660)
17 Tocolytic Agents/ (3287)
18 Maintenance Chemotherapy/ (634)
19 maintenance therap*.tw,kw. (21190)
20 exp Adrenergic beta-Agonists/ (323369)
21 ((adrenergic beta* adj3 agonist*) or (beta-adrenergic adj3 agonist*) or betamimetic* or beta-mimetic*).tw,kw. (10354)
22 (receptor agonist* adj1 (beta-adrenergic or adrenergic beta)).tw,kw. (1146)
23 Calcium Channel Blockers/ (82227)
24 (calcium adj3 (block* or antagonist* or inhibit*)).tw,kw. (89107)
25 (CCB or CCBs).tw. (3595)
26 Albuterol/ (35114)
27 (Aerolin or "AH 3365" or Airomir or Albuterol or Almotex or Alti-Salbutamol or Anebron or Arubendol-Salbutamol or Asmadil or Asmanil or Asmasal or Asmatol or Asmaven or Asmidon or Asmol or Asthalin or "BRN 2213614" or Broncho-Spray or Broncovaleas or Bronter or Bugonol or Bumol or Butamol or Buto-Asma or Butohaler or Butotal or Butovent or Buventol).tw,kw. (5372)
28 (Cobutolin or Dilatamol or dl-Albuterol or dl-Salbutamol or "EINECS 242-424-0" or Eolene or Farcolin or Gerivent or Grafalin or "HSDB 7206" or Levalbuterol or Levosalbutamol or Libretin or Medolin or Mozal or Novosalmol or Parasma or Pneumolat or Proventil or Proventil or Respax or Respolin or Sabutal or Salamol or Salbetol or Salbron or Salbu-BASF or Salbu-Fatol or Salbuhexal or Salbulin or Salbupur or Salbusian or Salbutalan or Salbutamol* or Salbutan or Salbutol or Salbuven or Salbuvent or Sallbupp or Salmaplon or Salomol or Salvent or Saventol or Servitamol or Spreor or Sultanol or Suprasma or Suxar).tw,kw. (15163)
29 (Theosal or Tobybron or UNII-QF8SVZ843E or Vencronyl or Ventamol or Ventilan or Ventiloboi or Ventodisks or Ventolin or Volare easi-breathe or Volmax or Vospire or Xopenex or Zaperin).tw,kw. (2406)
30 18559-94-9.rn. (34222)
31 Fenoterol/ (6781)
32 ("BRN 2157041" or Berotec or Berotek or Fenoterol* or p-Hydroxyphenyl-orciprenaline or p-Hydroxyphenylorciprenaline or Partusisten or Phenoterol or "TH 1165" or "Th-1165a" or UNII-22M9P70OQ9).tw,kw. (4517)
33 13392-18-2.rn. (6734)
34 Isoxsuprine/ (1305)
35 (Dilavase or Duvadilan or "EINECS 206-898-2" or Isoxsuprine or UNII-R15UI3245N or Vasodilian or Vasosurpine).tw,kw. (783)
36 395-28-8.rn. (1299)

37 Nifedipine/ (58375)
38 (Nifedipine or Adalat or Adipine or Afeditab or "BAY A 1040" or BAYA1040 or "BRN 0497773" or "CCRIS 6074" or Citilat or Cordipin* or Corinfar).tw,kw. (41803)
39 ("EINECS 244-598-3" or Fenigidin or Fenihidin or Fenihidine or "HSDB 7775" or Korinfar or Nifangin or Nifediac or Nifedical or Nifedipino or Nifedipinum or Oxcord or Procardia or UNII-I9ZF7L6G2L or Vascard).tw,kw. (934)
40 21829-25-4.rn. (57778)
41 exp Indomethacin/ (92256)
42 (indomethacin* or indometacin* or Amuno or Artracin or Artrinovo or Artrivia or "BRN 0497341" or "CCRIS 3502" or Confortid or Dolovin or "EINECS 200-186-5" or "HSDB 3101").tw,kw. (70790)
43 (Idomethine or Imbrilon or Inacid or Indacin or Indo-lemmon or Indo-rectolmin or Indo-tablinen or Indocid or Indocin or Indomecol or Indomed or Indomee or Indomet, or Indometacyna or Indomethazine or Indometicina or Indoptic or Indoptol or Inflazon or Infrocin).tw,kw. (1980)
44 (Lausit or Metacen or Metartril or Methazine or Metindol or Mezolin or Mikametan or Mobilan or Osmosin or Reumacide or Sadoreum or Tannex or UNII-XXE1CET956).tw,kw. (265)
45 53-86-1.rn. (89545)
46 exp Magnesium Compounds/ (15523)
47 magnesium.tw,kw. (92155)
48 (MgSO4 or "MgSO(4)").tw,kw. (4143)
49 (mag sulfate or mag sulphate).tw,kw. (2)
50 (epsom salt* or Arrosalt 2327 or "CCRIS 8411" or (Caswell adj2 "534") or "EINECS 231-298-2" or "HSDB 664" or Magnesii sulfas or "NSC 146179" or "OT-S" or "SN 00" or Sal Angalis or Sal De sedlitz).tw,kw. (98)
51 7487-88-9.rn. (15004)
52 Nitroglycerin/ (43603)
53 (Adesitrin or Aldonitrin or Angibid or Anginine or Angiolingual or Angiplex or Anglix or Angonist or Angorin or Aquo-Trimitrosan or Blasting gelatin or Blasting oil or "BRN 1802063" or Buccard or Cardabid or Cardamist or Cardinit or Cardiodisco or "CCRIS 4089" or Chitamite or Colenitral or Corangin Nitrokapseln or Cordipatch or Corditrine or Coro-Nitro or Dauxona or Deponit or Diafusor or Discotrine or "EINECS 200-240-8" or Epinitril).tw,kw. (327)
54 (Gepan Nitroglicerin or Gilucor nitro or Gilustenon or Glonoin or Glonoinum or Glycerine trinitrate or Glycerintrinitrate or Glyceroltrinitraat or Glyceryl or Glycerylnitrat or Glytrin or GTN or "GTN-Pohl" or Herwicard or Herzer or "HSDB 30" or Klavikordal or Lenitral or Lentonitrina or Mi-Trates or Millisrol or Minitram or Minitran or Mionitrat or Myocon or Myoglycerin or Myovin).tw,kw. (9889)
55 (Natispray or Neos nitro OPT or NG or Niglin or Niglycon or Niong or Niong Retard or Nirmin or Nit-Ret or Nitora or Nitradisc or Nitradisc Pad or Nitradisc TTS or Nitrek or Nitric acid triester of glycerol or Nitriderm TTS or Nitrin or Nitrine or Nitro Dur TTS or Nitro IV or Nitro Mack Retard or Nitro Retard or Nitro Rorer or Nitro-Bid or Nitro-Dur or Nitro-Gesanit Retard).tw,kw. (362090)

56 (Nitro-Lent or Nitro-M-Bid or Nitro-Par or Nitro-Pflaster or Nitro-Span or Nitro-Time or Nitroard or Nitrobaat or NitroBid or Nitrobid Oint or Nitrobukal or "NitrocapT D" or Nitrocerin or Nitrocine or Nitroclyn or Nitrocontin or NitroCor or Nitrocot or Nitroderm or Nitrodisc or Nitrodyl or Nitrogard or Nitroglicerina or Nitrogliceryna).tw,kw. (563)
57 (Nitroglin or Nitroglycerin* or Nitroglycerol or Nitroglyn or Nitrol or Nitrolan or Nitroletten or Nitrolin or Nitrolingual or Nitrolowe or Nitromack Retard or Nitromel or Nitromex or Nitromint or Nitromist or Nitronal or Nitronet or Nitrong or Nitropatch or Nitropen or Nitropercuten or Nitroperlinit or Nitroplast or Nitroprol or Nitropront*).tw,kw. (23031)
58 (NitroQuick or NitroQuik or Nitrorectal or Nitroretard or Nitrorex or Nitrospan or Nitrostabilin or Nitrostat or Nitrovis or Nitrozell retard or "NK-843" or NTG or NTS or Nysconitrine).tw,kw. (15682)
59 (Nitrangin or Nitrocard or Nitrospan or Percutol or Perganit or Perglottal or Perlinganit or Plastranit or Polnitrin or Propanetriol trinitrate or Ratiopharm or Rectiv).tw,kw. (677)
60 ("SK-106N" or Susadrin or Suscard or Sustac or Sustak or Sustonit or Temponitrin or Top-Nitro or Transderm Nitro or "Transderm-N TTS" or Tridil or Trinalgon or Trinipatch or Triniplas or Trinitrin* or Trinitroglicerin* or Trinitroglycerin or Trinitroglycerol or Trinitrol or Trinitrolong or Trinitron or Trinitrosan or Turicard or UNII-G59M7S0WS3 or Vasoglyn or Vasolator or Vernies or Willong).tw,kw. (1301)
61 55-63-0.rn. (42663)
62 Ritodrine/ (3057)
63 ("BRN 2388728" or "DU-21220" or "EINECS 247-879-9" or Pre-Par or Ritodrin* or Yutopar or UNII-I0Q6O6740J).tw,kw. (2008)
64 26652-09-5.rn. (3039)
65 Sulindac/ (7160)
66 (Aclin or Apo-Sulin or Aflodac or Algocetil or Arthrobid or Arthrocine or Artribid or "BRN 2951842" or "CCRIS 3305" or cis-Sulindac or Chibret or Citireuma or Clinoril or Clisundac or Copal or "EINECS 253-819-2" or "EINECS 256-402-3" or Imbaral or Kenalin or Klinoril or "MK 231" or Mobilin or Novo-Sundac or Nu-Sulindac or Reumofil or Sudac or Sulindac* or Sulindal or Sulinol or Sulreuma or UNII-184SNS8VUH).tw,kw. (4602)
67 38194-50-2.rn. (7081)
68 Terbutaline/ (12732)
69 (Arubendol or Asthmoprotect or Brethaire or Brethine or Bricanyl or "BRN 2370513" or Butaliret or Butalitab or Contimit or "EINECS 245-385-8" or KWD-2019 or Monovent or Taziken or Tedipulmo or Terbasmin or Terbul or Terbutalin* or Terbuturmante or UNII-N8ONU3L3PG).tw,kw. (7873)
70 23031-25-6.rn. (12656)
71 (atosiban or atosibanum or "ORF 22164" or "ORF-22164" or "RWJ 22164" or "RWJ-22164" or Tractocile or UNII-081D12SI0Z).tw,kw. (683)
72 atosiban.rn. (907)
73 (oxytocin adj3 (antagonist* or block* or inhibit*)).tw,kw. (2914)
74 Oxytocin/ai [Antagonists & Inhibitors] (655)
75 Vasotocin/aa [Analogs & Derivatives] (382)
76 or/15-75 (1139607)

77 14 and 76 (12280)
78 limit 77 to systematic reviews [Limit not valid in Embase; records were retained] (7304)
79 meta analysis.pt. (42869)
80 exp meta-analysis as topic/ (21016)
81 (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,kw. (129533)
82 (systematic review* or systematic overview* or technology assessment* or HTA or HTAs).tw,kw. (110608)
83 exp Technology assessment, biomedical/ (20583)
84 health technology assessment winchester england.jn. (1250)
85 (evidence report technology assessment or evidence report technology assessment summary).jn. (400)
86 "cochrane database of systematic reviews".jn. (13249)
87 or/79-86 (251373)
88 77 and 87 (347)
89 78 or 88 (7349)
90 exp Animals/ not (exp Animals/ and Humans/) (7909058)
91 89 not 90 (6901)
92 limit 91 to yr="2008-current" (1749)
93 92 use prmz (89)
94 premature labor/ (37331)
95 ((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw,kw. (69512)
96 (PTL or sPTL or PTB or sPTB or PTD or sPTD).tw,kw. (11061)
97 uterus contraction/ (7042)
98 ((uterus* or uterine) adj3 contraction*).tw,kw. (8400)
99 uterine cervix ripening/ (1662)
100 ((cervical or cervix*) adj3 (dilat* or ripen*)).tw,kw. (8995)
101 labor onset/ (1795)
102 (preterm* or pre-term* or prematur* or pre-matur*).tw,kw. (303203)
103 (97 or 98 or 99 or 100 or 101) and 102 (4085)
104 or/94-96,103 (89866)
105 *high risk pregnancy/ (3453)
106 *pregnancy complication/ (100001)
107 or/104-106 (185846)
108 tocolysis/ (3605)
109 (tocolys* or tocolytic*).tw,kw. (6660)
110 uterus spasmolytic agent/ (1828)
111 exp maintenance therapy/ (733880)
112 maintenance therap*.tw,kw. (21190)

113 exp beta adrenergic receptor stimulating agent/ (220354)
114 ((adrenergic beta* adj3 agonist*) or (beta-adrenergic adj3 agonist*) or betamimetic* or beta-mimetic*).tw,kw. (10354)
115 (receptor agonist* adj1 (beta-adrenergic or adrenergic beta)).tw,kw. (1146)
116 calcium channel blocking agent/ (48770)
117 (calcium adj3 (block* or antagonist* or inhibit*)).tw,kw. (89107)
118 (CCB or CCBs).tw. (3595)
119 salbutamol/ (35114)
120 (Aerolin or "AH 3365" or Airomir or Albuterol or Almotex or Alti-Salbutamol or Anebron or Arubendol-Salbutamol or Asmadil or Asmanil or Asmasal or Asmatol or Asmaven or Asmidon or Asmol or Asthalin or "BRN 2213614" or Broncho-Spray or Broncovaleas or Bronter or Bugonol or Bumol or Butamol or Buto-Asma or Butohaler or Butotal or Butovent or Buventol).tw,kw. (5372)
121 (Cobutolin or Dilatamol or dl-Albuterol or dl-Salbutamol or "EINECS 242-424-0" or Eolene or Farcolin or Gerivent or Grafalin or "HSDB 7206" or Levalbuterol or Levosalbutamol or Libretin or Medolin or Mozal or Novosalmol or Parasma or Pneumolat or Proventil or Proventil or Respax or Respolin or Sabutal or Salamol or Salbetol or Salbron or Salbu-BASF or Salbu-Fatol or Salbuhexal or Salbulin or Salbupur or Salbusian or Salbutalan or Salbutamol* or Salbutan or Salbutol or Salbuven or Salbuvent or Sallbupp or Salmaplon or Salomol or Salvent or Saventol or Servitamol or Spreor or Sultanol or Suprasma or Suxar).tw,kw. (15163)
122 (Theosal or Tobybron or UNII-QF8SVZ843E or Vencronyl or Ventamol or Ventilan or Ventiloboi or Ventodisks or Ventolin or Volare easi-breathe or Volmax or Vospire or Xopenex or Zaperin).tw,kw. (2406)
123 18559-94-9.rn. (34222)
124 ("BRN 2157041" or Berotec or Berotek or Fenoterol* or p-Hydroxyphenyl-orciprenaline or p-Hydroxyphenylorciprenaline or Partusisten or Phenoterol or "TH 1165" or "Th-1165a" or UNII-22M9P70OQ9).tw,kw. (4517)
125 13392-18-2.rn. (6734)
126 isoxsuprine/ (1305)
127 (Dilavase or Duvadilan or "EINECS 206-898-2" or Isoxsuprine or UNII-R15UI3245N or Vasodilian or Vasosurpine).tw,kw. (783)
128 395-28-8.rn. (1299)
129 nifedipine/ (58375)
130 (Nifedipine or Adalat or Adipine or Afeditab or "BAY A 1040" or BAYA1040 or "BRN 0497773" or "CCRIS 6074" or Citilat or Cordipin* or Corinfar).tw,kw. (41803)
131 ("EINECS 244-598-3" or Fenigidin or Fenihidin or Fenihidine or "HSDB 7775" or Korinfar or Nifangin or Nifediac or Nifedical or Nifedipino or Nifedipinum or Oxcord or Procardia or UNII-I9ZF7L6G2L or Vascard).tw,kw. (934)
132 21829-25-4.rn. (57778)
133 exp indomethacin/ (92256)
134 (indomethacin* or indometacin* or Amuno or Artracin or Artrinovo or Artrivia or "BRN 0497341" or "CCRIS 3502" or Confortid or Dolovin or "EINECS 200-186-5" or "HSDB 3101").tw,kw. (70790)

135 (Idomethine or Imbrilon or Inacid or Indacin or Indo-lemmon or Indo-rectolmin or Indo-tablinen or Indocid or Indocin or Indomecol or Indomed or Indomee or Indomet, or Indometacyna or Indomethazine or Indometicina or Indoptic or Indoptol or Inflazon or Infrocin).tw,kw. (1980)
136 (Lausit or Metacen or Metartril or Methazine or Metindol or Mezolin or Mikametan or Mobilan or Osmosin or Reumacide or Sadoreum or Tannex or UNII-XXE1CET956).tw,kw. (265)
137 53-86-1.rn. (89545)
138 magnesium derivative/ (1984)
139 magnesium sulfate/ (15380)
140 magnesium.tw,kw. (92155)
141 (MgSO4 or "MgSO(4)").tw,kw. (4143)
142 (mag sulfate or mag sulphate).tw,kw. (2)
143 (epsom salt* or Arrosalt 2327 or "CCRIS 8411" or (Caswell adj2 "534") or "EINECS 231-298-2" or "HSDB 664" or Magnesii sulfas or "NSC 146179" or "OT- S" or "SN 00" or Sal Angalis or Sal De sedlitz).tw,kw. (98)
144 7487-88-9.rn. (15004)
145 glyceryl trinitrate/ (43603)
146 (Adesitrin or Aldonitrin or Angibid or Anginine or Angiolingual or Angiplex or Anglix or Angonist or Angorin or Aquo-Trimitrosan or Blasting gelatin or Blasting oil or "BRN 1802063" or Buccard or Cardabid or Cardamist or Cardinit or Cardiodisco or "CCRIS 4089" or Chitamite or Colenitral or Corangin Nitrokapseln or Cordipatch or Corditrine or Coro-Nitro or Dauxona or Deponit or Diafusor or Discotrine or "EINECS 200-240-8" or Epinitril).tw,kw. (327)
147 (Gepan Nitroglicerin or Gilucor nitro or Gilustenon or Glonoin or Glonoinum or Glycerine trinitrate or Glycerintrinitrate or Glyceroltrinitraat or Glyceryl or Glycerylnitrat or Glytrin or GTN or "GTN-Pohl" or Herwicard or Herzer or "HSDB 30" or Klavikordal or Lenitral or Lentonitrina or Mi-Trates or Millisrol or Minitram or Minitran or Mionitrat or Myocon or Myoglycerin or Myovin).tw,kw. (9889)
148 (Natispray or Neos nitro OPT or NG or Niglin or Niglycon or Niong or Niong Retard or Nirmin or Nit-Ret or Nitora or Nitradisc or Nitradisc Pad or Nitradisc TTS or Nitrek or Nitric acid triester of glycerol or Nitriderm TTS or Nitrin or Nitrine or Nitro Dur TTS or Nitro IV or Nitro Mack Retard or Nitro Retard or Nitro Rorer or Nitro-Bid or Nitro-Dur or Nitro-Gesanit Retard).tw,kw. (362090)
149 (Nitro-Lent or Nitro-M-Bid or Nitro-Par or Nitro-Pflaster or Nitro-Span or Nitro-Time or Nitroard or Nitrobaat or NitroBid or Nitrobid Oint or Nitrobukal or "NitrocapT D" or Nitrocerin or Nitrocine or Nitroclyn or Nitrocontin or NitroCor or Nitrocot or Nitroderm or Nitrodisc or Nitrodyl or Nitrogard or Nitroglicerina or Nitrogliceryna).tw,kw. (563)
150 (Nitroglin or Nitroglycerin* or Nitroglycerol or Nitroglyn or Nitrol or Nitrolan or Nitroletten or Nitrolin or Nitrolingual or Nitrolowe or Nitromack Retard or Nitromel or Nitromex or Nitromint or Nitromist or Nitronal or Nitronet or Nitrong or Nitropatch or Nitropen or Nitropercuten or Nitroperlinit or Nitroplast or Nitroprol or Nitropront*).tw,kw. (23031)
151 (NitroQuick or NitroQuik or Nitrorectal or Nitroretard or Nitrorex or Nitrospan or Nitrostabilin or Nitrostat or Nitrovis or Nitrozell retard or "NK-843" or NTG or NTS or Nysconitrine).tw,kw. (15682)
152 (Nitrangin or Nitrocard or Nitrospan or Percutol or Perganit or Perglottal or Perlinganit or Plastranit or Polnitrin or Propanetriol trinitrate or Ratiopharm or Rectiv).tw,kw. (677)

153 ("SK-106N" or Susadrin or Suscard or Sustac or Sustak or Sustonit or Temponitrin or Top-Nitro or Transderm Nitro or "Transderm-N TTS" or Tridil or Trinalgon or Trinipatch or Triniplas or Trinitrin* or Trinitroglicerin* or Trinitroglycerin or Trinitroglycerol or Trinitrol or Trinitrolong or Trinitron or Trinitrosan or Turicard or UNII-G59M7S0WS3 or Vasoglyn or Vasolator or Vernies or Willong).tw,kw. (1301)
154 55-63-0.rn. (42663)
155 ("BRN 2388728" or "DU-21220" or "EINECS 247-879-9" or Pre-Par or Ritodrin* or Yutopar or UNII-I0Q6O6740J).tw,kw. (2008)
156 26652-09-5.rn. (3039)
157 sulindac/ (7160)
158 (Aclin or Apo-Sulin or Aflodac or Algocetil or Arthrobid or Arthrocine or Artribid or "BRN 2951842" or "CCRIS 3305" or cis-Sulindac or Chibret or Citireuma or Clinoril or Clisundac or Copal or "EINECS 253-819-2" or "EINECS 256-402-3" or Imbaral or Kenalin or Klinoril or "MK 231" or Mobilin or Novo-Sundac or Nu-Sulindac or Reumofil or Sudac or Sulindac* or Sulindal or Sulinol or Sulreuma or UNII-184SNS8VUH).tw,kw. (4602)
159 38194-50-2.rn. (7081)
160 terbutaline/ (12732)
161 (Arubendol or Asthmoprotect or Brethaire or Brethine or Bricanyl or "BRN 2370513" or Butaliret or Butalitab or Contimit or "EINECS 245-385-8" or KWD-2019 or Monovent or Taziken or Tedipulmo or Terbasmin or Terbul or Terbutalin* or Terbuturmante or UNII-N8ONU3L3PG).tw,kw. (7873)
162 23031-25-6.rn. (12656)
163 (atosiban or atosibanum or "ORF 22164" or "ORF-22164" or "RWJ 22164" or "RWJ-22164" or Tractocile or UNII-081D12SI0Z).tw,kw. (683)
164 90779-69-4.rn. (907)
165 oxytocin antagonist/ (652)
166 (oxytocin adj3 (antagonist* or block* or inhibit*)).tw,kw. (2914)
167 or/108-166 (1744633)
168 107 and 167 (15007)
169 meta-analysis/ or "systematic review"/ or "meta analysis (topic)"/ or biomedical technology assessment/ (176034)
170 (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. (127897)
171 (systematic review* or systematic overview* or technology assessment* or HTA or HTAs).tw. (108942)
172 (data synthes* or data extraction* or data abstraction*).tw. (27341)
173 (health technology assessment or health technology assessment reports or health technology assessment winchester england).jn. (1987)
174 (evidence report technology assessment or evidence report technology assessment summary).jn. (400)
175 ("cochrane database of systematic reviews" or "cochrane database of systematic reviews online").jn. (21215)
176 or/169-175 (300590)
177 168 and 176 (528)

	178 exp animals/ (35401329) 179 exp animal experimentation/ (1598052) 180 exp models animal/ (1107058) 181 exp animal experiment/ (1598052) 182 nonhuman/ (4073457) 183 exp vertebrate/ (34496068) 184 or/178-183 (36562262) 185 exp humans/ (27561859) 186 exp human experimentation/ (325030) 187 exp human experiment/ (313223) 188 or/185-187 (27563896) 189 184 not 188 (8999918) 190 177 not 189 (528) 191 limit 190 to yr="2008-current" (225) 192 191 use emez (160) 193 93 or 192 (249) 194 remove duplicates from 193 (192) 195 194 use prmz (81) MEDLINE UNIQUE HITS 196 194 use emez (111) EMBASE UNIQUE HITS
Note	

Database	**Cochrane Library (Wiley Interface), including CDSR, DARE, Central, HTA, and NHS EED**
Date	Date Run: 16/06/13 00:46:01.201 Description: 2013 Jun 15 - Post PRESS
Search Strategy	#1 [mh "Obstetric Labor, Premature"] 984 #2 ((labor* or labour* or birth* or deliver*) near/4 (preterm* or pre-term* or prematur* or pre-matur*)):ti,ab,kw 2843 #3 (PTL or sPTL or PTB or sPTB or PTD or sPTD):ti,ab,kw 97 #4 [mh "Uterine Contraction"] 333 #5 ((uterus* or uterine) near/4 contraction*):ti,ab,kw 649 #6 [mh "Cervical Ripening"] 258 #7 ((cervical or cervix*) near/4 (dilat* or ripen*)):ti,ab,kw 1452 #8 [mh "Labor Onset"] 463 #9 (preterm* or pre-term* or prematur* or pre-matur*):ti,ab,kw 11798 #10 (#4 or #5 or #6 or #7 or #8) and #9 257 #11 #1 or #2 or #3 or #10 2943

#12 [mh "Pregnancy, High-Risk"] 178
#13 [mh ^"Pregnancy Complications"] 989
#14 #11 or #12 or #13 3910
#15 [mh Tocolysis] 100
#16 (tocolys* or tocolytic*):ti,ab,kw 536
#17 [mh "Tocolytic Agents"] 234
#18 [mh "Maintenance Chemotherapy"] 37
#19 maintenance next therap*:ti,ab,kw 2393
#20 [mh "Adrenergic beta-Agonists"] 1616
#21 ((adrenergic beta* near/4 agonist*) or (beta-adrenergic near/4 agonist*) or betamimetic* or beta-mimetic*):ti,ab,kw 2282
#22 ((receptor next agonist*) near/2 ("beta-adrenergic" or "adrenergic beta")):ti,ab,kw 138
#23 [mh "Calcium Channel Blockers"] 2560
#24 (calcium near/4 (block* or antagonist* or inhibit*)):ti,ab,kw 5444
#25 (CCB or CCBs):ti,ab,kw 183
#26 [mh Albuterol] 2514
#27 (Aerolin or "AH 3365" or Airomir or Albuterol or Almotex or Alti-Salbutamol or Anebron or Arubendol-Salbutamol or Asmadil or Asmanil or Asmasal or Asmatol or Asmaven or Asmidon or Asmol or Asthalin or "BRN 2213614" or Broncho-Spray or Broncovaleas or Bronter or Bugonol or Bumol or Butamol or Buto-Asma or Butohaler or Butotal or Buventol):ti,ab,kw 3144
#28 (Cobutolin or Dilatamol or dl-Albuterol or dl-Salbutamol or "EINECS 242-424-0" or Eolene or Farcolin or Gerivent or Grafalin or "HSDB 7206" or Levalbuterol or Levosalbutamol or Libretin or Medolin or Mozal or Novosalmol or Parasma or Pneumolat or Proventil or Proventil or Respax or Respolin or Sabutal or Salamol or Salbetol or Salbron or Salbu-BASF or Salbu-Fatol or Salbuhexal or Salbulin or Salbupur or Salbusian or Salbutalan or Salbutamol* or Salbutan or Salbutol or Salbuven or Salbuvent or Sallbupp or Salmaplon or Salomol or Salvent or Saventol or Servitamol or Spreor or Sultanol or Suprasma or Suxar):ti,ab,kw 3011
#29 (Theosal or Tobybron or UNII-QF8SVZ843E or Vencronyl or Ventamol or Ventilan or Ventiloboi or Ventodisks or Ventolin or Volare easi-breathe or Volmax or Vospire or Xopenex or Zaperin):ti,ab,kw 144
#30 [mh Fenoterol] 416
#31 ("BRN 2157041" or Berotec or Berotek or Fenoterol* or p-Hydroxyphenyl-orciprenaline or p-Hydroxyphenylorciprenaline or Partusisten or Phenoterol or "TH 1165" or "Th-1165a" or UNII-22M9P70OQ9):ti,ab,kw 851
#32 [mh Isoxsuprine] 19
#33 (Dilavase or Duvadilan or "EINECS 206-898-2" or Isoxsuprine or UNII-R15UI3245N or Vasodilian or Vasosurpine):ti,ab,kw 50
#34 [mh Nifedipine] 1945
#35 (Nifedipine or Adalat or Adipine or Afeditab or "BAY A 1040" or BAYA1040 or "BRN 0497773" or "CCRIS 6074" or Citilat or Cordipin* or Corinfar):ti,ab,kw 3190

#36 ("EINECS 244-598-3" or Fenigidin or Fenihidin or Fenihidine or "HSDB 7775" or Korinfar or Nifangin or Nifediac or Nifedical or Nifedipino or Nifedipinum or Oxcord or Procardia or UNII-I9ZF7L6G2L or Vascard):ti,ab,kw 22
#37 [mh Indomethacin] 1969
#38 (Idomethine or Imbrilon or Inacid or Indacin or Indo-lemmon or Indo-rectolmin or Indo-tablinen or Indocid or Indocin or Indomecol or Indomed or Indomee or Indomet, or Indometacyna or Indomethazine or Indometicina or Indoptic or Indoptol or Inflazon or Infrocin):ti,ab,kw 49
#39 (Lausit or Metacen or Metartril or Methazine or Metindol or Mezolin or Mikametan or Mobilan or Osmosin or Reumacide or Sadoreum or Tannex or UNII-XXE1CET956):ti,ab,kw 10
#40 [mh "Magnesium Compounds"] 939
#41 magnesium:ti,ab,kw 3456
#42 (MgSO4 or "MgSO(4)"):ti,ab,kw 173
#43 ("mag sulfate" or "mag sulphate"):ti,ab,kw 0
#44 (epsom salt* or "Arrosalt 2327" or "CCRIS 8411" or (Caswell adj2 "534") or "EINECS 231-298-2" or "HSDB 664" or "Magnesii sulfas" or "NSC 146179" or "OT-S" or "SN 00" or "Sal Angalis" or "Sal De sedlitz"):ti,ab,kw 99
#45 [mh Nitroglycerin] 1624
#46 (Adesitrin or Aldonitrin or Angibid or Anginine or Angiolingual or Angiplex or Anglix or Angonist or Angorin or Aquo-Trimitrosan or "Blasting gelatin" or "Blasting oil" or "BRN 1802063" or Buccard or Cardabid or Cardamist or Cardinit or Cardiodisco or "CCRIS 4089" or Chitamite or Colenitral or Corangin Nitrokapseln or Cordipatch or Corditrine or Coro-Nitro or Dauxona or Deponit or Diafusor or Discotrine or "EINECS 200-240-8" or Epinitril):ti,ab,kw 19
#47 (Gepan Nitroglicerin or Gilucor nitro or Gilustenon or Glonoin or Glonoinum or Glycerine trinitrate or Glycerintrinitrate or Glyceroltrinitraat or Glyceryl or Glycerylnitrat or Glytrin or GTN or "GTN-Pohl" or Herwicard or Herzer or "HSDB 30" or Klavikordal or Lenitral or Lentonitrina or Mi-Trates or Millisrol or Minitram or Minitran or Mionitrat or Myocon or Myoglycerin or Myovin):ti,ab,kw 1114
#48 (Natispray or "Neos nitro OPT" or NG or Niglin or Niglycon or Niong or Niong Retard or Nirmin or "Nit-Ret" or Nitora or Nitradisc or Nitradisc Pad or Nitradisc TTS or Nitrek or ("Nitric acid triester" near/1 glycerol) or "Nitriderm TTS" or Nitrin or Nitrine or "Nitro Dur TTS" or "Nitro IV" or Nitro Mack Retard or Nitro Retard or Nitro Rorer or Nitro-Bid or Nitro-Dur or Nitro-Gesanit Retard):ti,ab,kw 9401
#49 (Nitro-Lent or Nitro-M-Bid or Nitro-Par or Nitro-Pflaster or Nitro-Span or Nitro-Time or Nitroard or Nitrobaat or NitroBid or Nitrobid Oint or Nitrobukal or "NitrocapT D" or Nitrocerin or Nitrocine or Nitroclyn or Nitrocontin or NitroCor or Nitrocot or Nitroderm or Nitrodisc or Nitrodyl or Nitrogard or Nitroglicerina or Nitrogliceryna):ti,ab,kw42
#50 (Nitroglin or Nitroglycerin* or Nitroglycerol or Nitroglyn or Nitrol or Nitrolan or Nitroletten or Nitrolin or Nitrolingual or Nitrolowe or Nitromack Retard or Nitromel or Nitromex or Nitromint or Nitromist or Nitronal or Nitronet or Nitrong or Nitropatch or Nitropen or Nitropercuten or Nitroperlinit or Nitroplast or Nitroprol or Nitropront*):ti,ab,kw 2613
#51 (NitroQuick or NitroQuik or Nitrorectal or Nitroretard or Nitrorex or Nitrospan or Nitrostabilin or Nitrostat or Nitrovis or Nitrozell retard or "NK-843" or NTG or NTS or Nysconitrine):ti,ab,kw 377
#52 (Nitrangin or Nitrocard or Nitrospan or Percutol or Perganit or Perglottal or Perlinganit or Plastranit or Polnitrin or Propanetriol trinitrate or Ratiopharm or Rectiv):ti,ab,kw 25

#53 ("SK-106N" or Susadrin or Suscard or Sustac or Sustak or Sustonit or Temponitrin or Top-Nitro or Transderm Nitro or "Transderm-N TTS" or Tridil or Trinalgon or Trinipatch or Triniplas or Trinitrin* or Trinitroglicerin* or Trinitroglycerin or Trinitroglycerol or Trinitrol or Trinitrolong or Trinitron or Trinitrosan or Turicard or UNII-G59M7S0WS3 or Vasoglyn or Vasolator or Vernies or Willong):ti,ab,kw 80
#54 [mh Ritodrine] 132
#55 ("BRN 2388728" or "DU-21220" or "EINECS 247-879-9" or "Pre-Par" or Ritodrin* or Yutopar or UNII-I0Q6O6740J):ti,ab,kw 246
#56 [mh Sulindac] 137
#57 (Aclin or Apo-Sulin or Aflodac or Algocetil or Arthrobid or Arthrocine or Artribid or "BRN 2951842" or "CCRIS 3305" or cis-Sulindac or Chibret or Citireuma or Clinoril or Clisundac or Copal or "EINECS 253-819-2" or "EINECS 256-402-3" or Imbaral or Kenalin or Klinoril or "MK 231" or Mobilin or Novo-Sundac or Nu-Sulindac or Reumofil or Sudac or Sulindac* or Sulindal or Sulinol or Sulreuma or UNII-184SNS8VUH):ti,ab,kw 303
#58 [mh Terbutaline] 712
#59 (Arubendol or Asthmoprotect or Brethaire or Brethine or Bricanyl or "BRN 2370513" or Butaliret or Butalitab or Contimit or "EINECS 245-385-8" or "KWD-2019" or Monovent or Taziken or Tedipulmo or Terbasmin or Terbul or Terbutalin* or Terbuturmante or UNII-N8ONU3L3PG):ti,ab,kw 1287
#60 (atosiban or atosibanum or "ORF 22164" or "ORF-22164" or "RWJ 22164" or "RWJ-22164" or Tractocile or UNII-081D12SI0Z):ti,ab,kw 49
#61 (oxytocin near/4 (antagonist* or block* or inhibit*)):ti,ab,kw 63
#62 [mh Oxytocin/ai] 11
#63 [mh Vasotocin/aa] 37
#64 or #15-#63 34472
#65 #14 and #64 from 2008 to 2013 123
DSR – 33
DARE – 10
CENTRAL – 66
Methods – 1
HTA – 5
NHS EED - 8

Note

3.1.6.2. Calcium blockers - RCTs

Database	MEDLINE and EMBASE
Date	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Embase <1980 to 2013 Week 44>
Search Strategy	1 exp Obstetric Labor, Premature/ (45284) 2 ((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw,kw. (73794) 3 (PTL or sPTL or PTB or sPTB or PTD or sPTD).tw,kw. (12008) 4 Uterine Contraction/ (14299) 5 ((uterus* or uterine) adj3 contraction*).tw,kw. (8686) 6 Cervical Ripening/ (2552) 7 ((cervical or cervix*) adj3 (dilat* or ripen*)).tw,kw. (9345) 8 exp Labor Onset/ (4404) 9 (preterm* or pre-term* or prematur* or pre-matur*).tw,kw. (318375) 10 (4 or 5 or 6 or 7 or 8) and 9 (5005) 11 or/1-3,10 (96810) 12 *Pregnancy, High-Risk/ (3548) 13 *Pregnancy Complications/ (77552) 14 or/11-13 (170614) 15 Calcium Channel Blockers/ (84885) 16 (calcium adj3 (block* or antagonist* or inhibit*)).tw,kw. (91204) 17 (CCB or CCBs).tw. (3819) 18 Nifedipine/ (59169) 19 (Nifedipine or Adalat or Adipine or Afeditab or "BAY A 1040" or BAYA1040 or "BRN 0497773" or "CCRIS 6074" or Citilat or Cordipin* or Corinfar).tw,kw. (42604) 20 ("EINECS 244-598-3" or Fenigidin or Fenihidin or Fenihidine or "HSDB 7775" or Korinfar or Nifangin or Nifediac or Nifedical or Nifedipino or Nifedipinum or Oxcord or Procardia or UNII-I9ZF7L6G2L or Vascard).tw,kw. (938) 21 21829-25-4.rn. (58511) 22 or/15-21 (187507) 23 14 and 22 (1466)

24	randomized controlled trial.pt. (389888)
25	exp Randomized Controlled Trials as Topic/ (144254)
26	exp Random Allocation/ (145521)
27	exp Double-Blind Method/ (250201)
28	exp Single-Blind Method/ (38031)
29	exp Placebos/ (261783)
30	(random* or RCT$1 or placebo*).tw. (1740926)
31	((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (292246)
32	or/24-31 (2112275)
33	23 and 32 (396)
34	exp Animals/ not (exp Animals/ and Humans/) (8153428)
35	33 not 34 (394)
36	35 use prmz (132)
37	premature labor/ (39101)
38	((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw,kw. (73794)
39	(PTL or sPTL or PTB or sPTB or PTD or sPTD).tw,kw. (12008)
40	uterus contraction/ (7277)
41	((uterus* or uterine) adj3 contraction*).tw,kw. (8686)
42	uterine cervix ripening/ (1760)
43	((cervical or cervix*) adj3 (dilat* or ripen*)).tw,kw. (9345)
44	labor onset/ (1952)
45	(preterm* or pre-term* or prematur* or pre-matur*).tw,kw. (318375)
46	(40 or 41 or 42 or 43 or 44) and 45 (4331)
47	or/37-39,46 (95047)
48	*high risk pregnancy/ (3548)
49	*pregnancy complication/ (102828)
50	or/47-49 (193580)
51	calcium channel blocking agent/ (49943)
52	(calcium adj3 (block* or antagonist* or inhibit*)).tw,kw. (91204)
53	(CCB or CCBs).tw. (3819)

54 nifedipine/ (59169)

55 (Nifedipine or Adalat or Adipine or Afeditab or "BAY A 1040" or BAYA1040 or "BRN 0497773" or "CCRIS 6074" or Citilat or Cordipin* or Corinfar).tw,kw. (42604)

56 ("EINECS 244-598-3" or Fenigidin or Fenihidin or Fenihidine or "HSDB 7775" or Korinfar or Nifangin or Nifediac or Nifedical or Nifedipino or Nifedipinum or Oxcord or Procardia or UNII-I9ZF7L6G2L or Vascard).tw,kw. (938)

57 21829-25-4.rn. (58511)

58 or/51-57 (172036)

59 50 and 58 (1431)

60 Randomized Controlled Trial/ (749113)

61 Randomization/ (145521)

62 Random Sampling/ (64)

63 Double Blind Procedure/ (118442)

64 Single Blind Procedure/ (18456)

65 Placebo/ (228016)

66 (random* or RCT$1 or placebo*).tw. (1740926)

67 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (292246)

68 or/60-67 (2093204)

69 59 and 68 (387)

70 exp animals/ (36715474)

Search Strategy

ID Searches Hits

1 exp Obstetric Labor, Premature/ (45284)

2 ((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw,kw. (73794)

3 (PTL or sPTL or PTB or sPTB or PTD or sPTD).tw,kw. (12008)

4 Uterine Contraction/ (14299)

5 ((uterus* or uterine) adj3 contraction*).tw,kw. (8686)

6 Cervical Ripening/ (2552)

7 ((cervical or cervix*) adj3 (dilat* or ripen*)).tw,kw. (9345)

8 exp Labor Onset/ (4404)

9 (preterm* or pre-term* or prematur* or pre-matur*).tw,kw. (318375)

10 (4 or 5 or 6 or 7 or 8) and 9 (5005)
11 or/1-3,10 (96810)
12 *Pregnancy, High-Risk/ (3548)
13 *Pregnancy Complications/ (77552)
14 or/11-13 (170614)
15 Calcium Channel Blockers/ (84885)
16 (calcium adj3 (block* or antagonist* or inhibit*)).tw,kw. (91204)
17 (CCB or CCBs).tw. (3819)
18 Nifedipine/ (59169)
19 (Nifedipine or Adalat or Adipine or Afeditab or "BAY A 1040" or BAYA1040 or "BRN 0497773" or "CCRIS 6074" or Citilat or Cordipin* or Corinfar).tw,kw. (42604)
20 ("EINECS 244-598-3" or Fenigidin or Fenihidin or Fenihidine or "HSDB 7775" or Korinfar or Nifangin or Nifediac or Nifedical or Nifedipino or Nifedipinum or Oxcord or Procardia or UNII-I9ZF7L6G2L or Vascard).tw,kw. (938)
21 21829-25-4.rn. (58511)
22 or/15-21 (187507)
23 14 and 22 (1466)
24 randomized controlled trial.pt. (389888)
25 exp Randomized Controlled Trials as Topic/ (144254)
26 exp Random Allocation/ (145521)
27 exp Double-Blind Method/ (250201)
28 exp Single-Blind Method/ (38031)
29 exp Placebos/ (261783)
30 (random* or RCT$1 or placebo*).tw. (1740926)
31 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (292246)
32 or/24-31 (2112275)
33 23 and 32 (396)
34 exp Animals/ not (exp Animals/ and Humans/) (8153428)
35 33 not 34 (394)
36 35 use prmz (132)
37 premature labor/ (39101)

38 ((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw,kw. (73794)
39 (PTL or sPTL or PTB or sPTB or PTD or sPTD).tw,kw. (12008)
40 uterus contraction/ (7277)
41 ((uterus* or uterine) adj3 contraction*).tw,kw. (8686)
42 uterine cervix ripening/ (1760)
43 ((cervical or cervix*) adj3 (dilat* or ripen*)).tw,kw. (9345)
44 labor onset/ (1952)
45 (preterm* or pre-term* or prematur* or pre-matur*).tw,kw. (318375)
46 (40 or 41 or 42 or 43 or 44) and 45 (4331)
47 or/37-39,46 (95047)
48 *high risk pregnancy/ (3548)
49 *pregnancy complication/ (102828)
50 or/47-49 (193580)
51 calcium channel blocking agent/ (49943)
52 (calcium adj3 (block* or antagonist* or inhibit*)).tw,kw. (91204)
53 (CCB or CCBs).tw. (3819)
54 nifedipine/ (59169)
55 (Nifedipine or Adalat or Adipine or Afeditab or "BAY A 1040" or BAYA1040 or "BRN 0497773" or "CCRIS 6074" or Citilat or Cordipin* or Corinfar).tw,kw. (42604)
56 ("EINECS 244-598-3" or Fenigidin or Fenihidin or Fenihidine or "HSDB 7775" or Korinfar or Nifangin or Nifediac or Nifedical or Nifedipino or Nifedipinum or Oxcord or Procardia or UNII-I9ZF7L6G2L or Vascard).tw,kw. (938)
57 21829-25-4.rn. (58511)
58 or/51-57 (172036)
59 50 and 58 (1431)
60 Randomized Controlled Trial/ (749113)
61 Randomization/ (145521)
62 Random Sampling/ (64)
63 Double Blind Procedure/ (118442)
64 Single Blind Procedure/ (18456)
65 Placebo/ (228016)

66	(random* or RCT$1 or placebo*).tw. (1740926)
67	((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (292246)
68	or/60-67 (2093204)
69	59 and 68 (387)
70	exp animals/ (36715474)
71	exp animal experimentation/ (1629685)
72	exp models animal/ (1157790)
73	exp animal experiment/ (1629685)
74	nonhuman/ (4159520)
75	exp vertebrate/ (35773594)
76	or/70-75 (37897310)
77	exp humans/ (28631631)
78	exp human experimentation/ (330100)
79	exp human experiment/ (317774)
80	or/77-79 (28633677)
81	76 not 80 (9265193)
82	69 not 81 (386)
83	82 use emez (266)
84	(201007* or 201008* or 201009* or 201010* or 201011* or 201012* or 2011* or 2012* or 2013*).ed. (3667779)
85	36 and 84 (25)
86	(2010* or 2011* or 2012* or 2013*).em. (8868488)
87	83 and 86 (74)
88	85 or 87 (99)
89	remove duplicates from 88 (78)
90	89 use prmz (22) MEDLINE UNIQUE RECORDS
91	89 use emez (56) EMBASE UNIQUE RECORDS

Note

Database	Cochrane Library (Wiley Interface) CENTRAL
Date	Date Run: 07/11/13 03:21:36.471 Description: 2013 Nov 6
Search Strategy	#1 [mh "Obstetric Labor, Premature"] 1013 #2 ((labor* or labour* or birth* or deliver*) near/4 (preterm* or pre-term* or prematur* or pre-matur*)):ti,ab,kw 2910 #3 (PTL or sPTL or PTB or sPTB or PTD or sPTD):ti,ab,kw 98 #4 [mh "Uterine Contraction"] 334 #5 ((uterus* or uterine) near/4 contraction*):ti,ab,kw 657 #6 [mh "Cervical Ripening"] 261 #7 ((cervical or cervix*) near/4 (dilat* or ripen*)):ti,ab,kw 1459 #8 [mh "Labor Onset"] 468 #9 (preterm* or pre-term* or prematur* or pre-matur*):ti,ab,kw 12075 #10 (#4 or #5 or #6 or #7 or #8) and #9 254 #11 #1 or #2 or #3 or #10 3004 #12 [mh "Pregnancy, High-Risk"] 179 #13 [mh ^"Pregnancy Complications"] 1025 #14 #11 or #12 or #13 4003 #15 [mh "Calcium Channel Blockers"] 2583 #16 (calcium near/4 (block* or antagonist* or inhibit*)):ti,ab,kw 5529 #17 (CCB or CCBs):ti,ab,kw 187 #18 [mh Nifedipine] 1946 #19 (Nifedipine or Adalat or Adipine or Afeditab or "BAY A 1040" or BAYA1040 or "BRN 0497773" or "CCRIS 6074" or Citilat or Cordipin* or Corinfar):ti,ab,kw 3270 #20 ("EINECS 244-598-3" or Fenigidin or Fenihidin or Fenihidine or "HSDB 7775" or Korinfar or Nifangin or Nifediac or Nifedical or Nifedipino or Nifedipinum or Oxcord or Procardia or UNII-I9ZF7L6G2L or Vascard):ti,ab,kw 22 #21 or #15-#20 7558 #22 #14 and #21 from 2010 to 2013 16 *CENTRAL – 5*
Note	

3.1.6.3. Oral betamimetics - RCTs

Database	MEDLINE and EMBASE
Date	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Embase <1980 to 2013 Week 44>
Search Strategy	1 exp Obstetric Labor, Premature/ (45284) 2 ((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw,kw. (73794) 3 (PTL or sPTL or PTB or sPTB or PTD or sPTD).tw,kw. (12008) 4 Uterine Contraction/ (14299) 5 ((uterus* or uterine) adj3 contraction*).tw,kw. (8686) 6 Cervical Ripening/ (2552) 7 ((cervical or cervix*) adj3 (dilat* or ripen*)).tw,kw. (9345) 8 exp Labor Onset/ (4404) 9 (preterm* or pre-term* or prematur* or pre-matur*).tw,kw. (318375) 10 (4 or 5 or 6 or 7 or 8) and 9 (5005) 11 or/1-3,10 (96810) 12 *Pregnancy, High-Risk/ (3548) 13 *Pregnancy Complications/ (77552) 14 or/11-13 (170614) 15 exp Adrenergic beta-Agonists/ (330285) 16 ((adrenergic beta* adj3 agonist*) or (beta-adrenergic adj3 agonist*) or betamimetic* or beta-mimetic*).tw,kw. (10641) 17 (receptor agonist* adj1 (beta-adrenergic or adrenergic beta)).tw,kw. (1194) 18 Albuterol/ (36402) 19 (Aerolin or "AH 3365" or Airomir or Albuterol or Almotex or Alti-Salbutamol or Anebron or Arubendol-Salbutamol or Asmadil or Asmanil or Asmasal or Asmatol or Asmaven or Asmidon or Asmol or Asthalin or "BRN 2213614" or Broncho-Spray or Broncovaleas or Bronter or Bugonol or Bumol or Butamol or Buto-Asma or Butohaler or Butotal or Butovent or Buventol).tw,kw. (5619) 20 (Cobutolin or Dilatamol or dl-Albuterol or dl-Salbutamol or "EINECS 242-424-0" or Eolene or Farcolin or Gerivent or Grafalin or "HSDB 7206" or Levalbuterol or Levosalbutamol or Libretin or Medolin or Mozal or Novosalmol or Parasma or Pneumolat or Proventil or Proventil or Respax or Respolin or Sabutal or Salamol or Salbetol or Salbron or Salbu-BASF or Salbu-Fatol or

	Salbuhexal or Salbulin or Salbupur or Salbusian or Salbutalan or Salbutamol* or Salbutan or Salbutol or Salbuven or Salbuvent or Sallbupp or Salmaplon or Salomol or Salvent or Saventol or Servitamol or Spreor or Sultanol or Suprasma or Suxar).tw,kw. (15767)
	21 (Theosal or Tobybron or UNII-QF8SVZ843E or Vencronyl or Ventamol or Ventilan or Ventiloboi or Ventodisks or Ventolin or Volare easi-breathe or Volmax or Vospire or Xopenex or Zaperin).tw,kw. (2442)
	22 18559-94-9.rn. (35442)
	23 Fenoterol/ (6862)
	24 ("BRN 2157041" or Berotec or Berotek or Fenoterol* or p-Hydroxyphenyl-orciprenaline or p-Hydroxyphenylorciprenaline or Partusisten or Phenoterol or "TH 1165" or "Th-1165a" or UNII-22M9P70OQ9).tw,kw. (4590)
	25 13392-18-2.rn. (6811)
	26 Isoxsuprine/ (1323)
	27 (Dilavase or Duvadilan or "EINECS 206-898-2" or Isoxsuprine or UNII-R15UI3245N or Vasodilian or Vasosurpine).tw,kw. (792)
	28 395-28-8.rn. (1316)
	29 Ritodrine/ (3095)
	30 ("BRN 2388728" or "DU-21220" or "EINECS 247-879-9" or Pre-Par or Ritodrin* or Yutopar or UNII-I0Q6O6740J).tw,kw. (2042)
	31 26652-09-5.rn. (3069)
	32 or/15-31 (335924)
	33 14 and 32 (5039)
	34 randomized controlled trial.pt. (389888)
	35 Randomized Controlled Trials as Topic/ (143248)
	36 Random Allocation/ (145521)
	37 Double-Blind Method/ (250201)
	38 Single-Blind Method/ (38031)
	39 Placebos/ (261783)
	40 (random* or RCT$1 or placebo*).tw. (1740926)
	41 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (292246)
	42 or/34-41 (2112127)
	43 33 and 42 (756)
	44 exp Animals/ not (exp Animals/ and Humans/) (8153428)
	45 43 not 44 (743)

46 45 use prmz (301)
47 premature labor/ (39101)
48 ((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw,kw. (73794)
49 (PTL or sPTL or PTB or sPTB or PTD or sPTD).tw,kw. (12008)
50 uterus contraction/ (7277)
51 ((uterus* or uterine) adj3 contraction*).tw,kw. (8686)
52 uterine cervix ripening/ (1760)
53 ((cervical or cervix*) adj3 (dilat* or ripen*)).tw,kw. (9345)
54 labor onset/ (1952)
55 (preterm* or pre-term* or prematur* or pre-matur*).tw,kw. (318375)
56 (50 or 51 or 52 or 53 or 54) and 55 (4331)
57 or/47-49,56 (95047)
58 *high risk pregnancy/ (3548)
59 *pregnancy complication/ (102828)
60 or/57-59 (193580)
61 exp beta adrenergic receptor stimulating agent/ (223918)
62 ((adrenergic beta* adj3 agonist*) or (beta-adrenergic adj3 agonist*) or betamimetic* or beta-mimetic*).tw,kw. (10641)
63 (receptor agonist* adj1 (beta-adrenergic or adrenergic beta)).tw,kw. (1194)
64 salbutamol/ (36402)
65 (Aerolin or "AH 3365" or Airomir or Albuterol or Almotex or Alti-Salbutamol or Anebron or Arubendol-Salbutamol or Asmadil or Asmanil or Asmasal or Asmatol or Asmaven or Asmidon or Asmol or Asthalin or "BRN 2213614" or Broncho-Spray or Broncovaleas or Bronter or Bugonol or Bumol or Butamol or Buto-Asma or Butohaler or Butotal or Butovent or Buventol).tw,kw. (5619)
66 (Cobutolin or Dilatamol or dl-Albuterol or dl-Salbutamol or "EINECS 242-424-0" or Eolene or Farcolin or Gerivent or Grafalin or "HSDB 7206" or Levalbuterol or Levosalbutamol or Libretin or Medolin or Mozal or Novosalmol or Parasma or Pneumolat or Proventil or Proventil or Respax or Respolin or Sabutal or Salamol or Salbetol or Salbron or Salbu-BASF or Salbu-Fatol or Salbuhexal or Salbulin or Salbupur or Salbusian or Salbutalan or Salbutamol* or Salbutan or Salbutol or Salbuven or Salbuvent or Sallbupp or Salmaplon or Salomol or Salvent or Saventol or Servitamol or Spreor or Sultanol or Suprasma or Suxar).tw,kw. (15767)
67 (Theosal or Tobybron or UNII-QF8SVZ843E or Vencronyl or Ventamol or Ventilan or Ventiloboi or Ventodisks or Ventolin or Volare easi-breathe or Volmax or Vospire or Xopenex or Zaperin).tw,kw. (2442)
68 18559-94-9.rn. (35442)

69 ("BRN 2157041" or Berotec or Berotek or Fenoterol* or p-Hydroxyphenyl-orciprenaline or p-Hydroxyphenylorciprenaline or Partusisten or Phenoterol or "TH 1165" or "Th-1165a" or UNII-22M9P70OQ9).tw,kw. (4590)

70 13392-18-2.rn. (6811)

71 isoxsuprine/ (1323)

72 (Dilavase or Duvadilan or "EINECS 206-898-2" or Isoxsuprine or UNII-R15UI3245N or Vasodilian or Vasosurpine).tw,kw. (792)

73 395-28-8.rn. (1316)

74 ("BRN 2388728" or "DU-21220" or "EINECS 247-879-9" or Pre-Par or Ritodrin* or Yutopar or UNII-I0Q6O6740J).tw,kw. (2042)

75 26652-09-5.rn. (3069)

76 or/61-75 (245668)

77 60 and 76 (4517)

78 Randomized Controlled Trial/ (749113)

79 Randomization/ (145521)

80 Random Sampling/ (64)

81 Double Blind Procedure/ (118442)

82 Single Blind Procedure/ (18456)

83 Placebo/ (228016)

84 (random* or RCT$1 or placebo*).tw. (1740926)

85 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (292246)

86 or/78-85 (2093204)

87 77 and 86 (692)

88 exp animals/ (36715474)

89 exp animal experimentation/ (1629685)

90 exp models animal/ (1157790)

91 exp animal experiment/ (1629685)

92 nonhuman/ (4159520)

93 exp vertebrate/ (35773594)

94 or/88-93 (37897310)

95 exp humans/ (28631631)

	96 exp human experimentation/ (330100) 97 exp human experiment/ (317774) 98 or/95-97 (28633677) 99 94 not 98 (9265193) 100 87 not 99 (685) 101 100 use emez (460) 102 (200509* or 200510* or 200511* or 200512* or 2006* or 2007* or 2008* or 2009* or 2010* or 2011* or 2012* or 2013*).ed. (7774359) 103 46 and 102 (76) 104 (2005* or 2006* or 2007* or 2008* or 2009* or 2010* or 2011* or 2012* or 2013*).em. (17674856) 105 101 and 104 (172) 106 103 or 105 (248) 107 remove duplicates from 106 (179) 108 107 use prmz (55) MEDLINE UNIQUE HITS 109 107 use emez (124) EMBASE UNIQUE HITS
Note	

Database	**Cochrane Library (Wiley Interface) CENTRAL**
Date	Date Run: 07/11/13 04:46:01.939 Description: 2013 Nov
Search Strategy	#1 [mh "Obstetric Labor, Premature"] 1013 #2 ((labor* or labour* or birth* or deliver*) near/4 (preterm* or pre-term* or prematur* or pre-matur*)):ti,ab,kw 2910 #3 (PTL or sPTL or PTB or sPTB or PTD or sPTD):ti,ab,kw 98 #4 [mh "Uterine Contraction"] 334 #5 ((uterus* or uterine) near/4 contraction*):ti,ab,kw 657 #6 [mh "Cervical Ripening"] 261 #7 ((cervical or cervix*) near/4 (dilat* or ripen*)):ti,ab,kw 1459 #8 [mh "Labor Onset"] 468 #9 (preterm* or pre-term* or prematur* or pre-matur*):ti,ab,kw 12075

#10 (#4 or #5 or #6 or #7 or #8) and #9 254

#11 #1 or #2 or #3 or #10 3004

#12 [mh "Pregnancy, High-Risk"] 179

#13 [mh ^"Pregnancy Complications"] 1025

#14 #11 or #12 or #13 4003

#15 [mh "Adrenergic beta-Agonists"] 1631

#16 ((adrenergic beta* near/4 agonist*) or (beta-adrenergic near/4 agonist*) or betamimetic* or beta-mimetic*):ti,ab,kw 2303

#17 ((receptor next agonist*) near/2 ("beta-adrenergic" or "adrenergic beta")):ti,ab,kw 150

#18 [mh Albuterol] 2530

#19 (Aerolin or "AH 3365" or Airomir or Albuterol or Almotex or Alti-Salbutamol or Anebron or Arubendol-Salbutamol or Asmadil or Asmanil or Asmasal or Asmatol or Asmaven or Asmidon or Asmol or Asthalin or "BRN 2213614" or Broncho-Spray or Broncovaleas or Bronter or Bugonol or Bumol or Butamol or Buto-Asma or Butohaler or Butotal or Buventol):ti,ab,kw 3162

#20 (Cobutolin or Dilatamol or dl-Albuterol or dl-Salbutamol or "EINECS 242-424-0" or Eolene or Farcolin or Gerivent or Grafalin or "HSDB 7206" or Levalbuterol or Levosalbutamol or Libretin or Medolin or Mozal or Novosalmol or Parasma or Pneumolat or Proventil or Proventil or Respax or Respolin or Sabutal or Salamol or Salbetol or Salbron or Salbu-BASF or Salbu-Fatol or Salbuhexal or Salbulin or Salbupur or Salbusian or Salbutalan or Salbutamol* or Salbutan or Salbutol or Salbuven or Salbuvent or Sallbupp or Salmaplon or Salomol or Salvent or Saventol or Servitamol or Spreor or Sultanol or Suprasma or Suxar):ti,ab,kw 3025

#21 (Theosal or Tobybron or UNII-QF8SVZ843E or Vencronyl or Ventamol or Ventilan or Ventiloboi or Ventodisks or Ventolin or Volare easi-breathe or Volmax or Vospire or Xopenex or Zaperin):ti,ab,kw 144

#22 [mh Fenoterol] 416

#23 ("BRN 2157041" or Berotec or Berotek or Fenoterol* or p-Hydroxyphenyl-orciprenaline or p-Hydroxyphenylorciprenaline or Partusisten or Phenoterol or "TH 1165" or "Th-1165a" or UNII-22M9P70OQ9):ti,ab,kw 852

#24 [mh Isoxsuprine] 19

#25 (Dilavase or Duvadilan or "EINECS 206-898-2" or Isoxsuprine or UNII-R15UI3245N or Vasodilian or Vasosurpine):ti,ab,kw 50

#26 [mh Ritodrine] 133

#27 ("BRN 2388728" or "DU-21220" or "EINECS 247-879-9" or "Pre-Par" or Ritodrin* or Yutopar or UNII-I0Q6O6740J):ti,ab,kw 247

#28 or #15-#27 6766

#29 #14 and #28 from 2005 to 2013 47

	CENTRAL – 28
Note	

3.1.6.4. Oxytocine antagonists - RCTs

Database	**MEDLINE and EMBASE**
Date	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Embase <1980 to 2013 Week 44>
Search Strategy	1 exp Obstetric Labor, Premature/ (45284) 2 ((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw,kw. (73794) 3 (PTL or sPTL or PTB or sPTB or PTD or sPTD).tw,kw. (12008) 4 Uterine Contraction/ (14299) 5 ((uterus* or uterine) adj3 contraction*).tw,kw. (8686) 6 Cervical Ripening/ (2552) 7 ((cervical or cervix*) adj3 (dilat* or ripen*)).tw,kw. (9345) 8 exp Labor Onset/ (4404) 9 (preterm* or pre-term* or prematur* or pre-matur*).tw,kw. (318375) 10 (4 or 5 or 6 or 7 or 8) and 9 (5005) 11 or/1-3,10 (96810) 12 *Pregnancy, High-Risk/ (3548) 13 *Pregnancy Complications/ (77552) 14 or/11-13 (170614) 15 (atosiban or atosibanum or "ORF 22164" or "ORF-22164" or "RWJ 22164" or "RWJ-22164" or Tractocile or UNII-081D12SI0Z).tw,kw. (707) 16 atosiban.rn. (928) 17 (oxytocin adj3 (antagonist* or block* or inhibit*)).tw,kw. (2997) 18 Oxytocin/ai [Antagonists & Inhibitors] (667) 19 Vasotocin/aa [Analogs & Derivatives] (393) 20 or/15-19 (4033) 21 14 and 20 (843)

22	randomized controlled trial.pt. (389888)
23	exp Randomized Controlled Trials as Topic/ (144254)
24	exp Random Allocation/ (145521)
25	exp Double-Blind Method/ (250201)
26	exp Single-Blind Method/ (38031)
27	exp Placebos/ (261783)
28	(random* or RCT$1 or placebo*).tw. (1740926)
29	((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (292246)
30	or/22-29 (2112275)
31	21 and 30 (210)
32	exp Animals/ not (exp Animals/ and Humans/) (8153428)
33	31 not 32 (207)
34	33 use prmz (67)
35	premature labor/ (39101)
36	((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw,kw. (73794)
37	(PTL or sPTL or PTB or sPTB or PTD or sPTD).tw,kw. (12008)
38	uterus contraction/ (7277)
39	((uterus* or uterine) adj3 contraction*).tw,kw. (8686)
40	uterine cervix ripening/ (1760)
41	((cervical or cervix*) adj3 (dilat* or ripen*)).tw,kw. (9345)
42	labor onset/ (1952)
43	(preterm* or pre-term* or prematur* or pre-matur*).tw,kw. (318375)
44	(38 or 39 or 40 or 41 or 42) and 43 (4331)
45	or/35-37,44 (95047)
46	*high risk pregnancy/ (3548)
47	*pregnancy complication/ (102828)
48	or/45-47 (193580)
49	(atosiban or atosibanum or "ORF 22164" or "ORF-22164" or "RWJ 22164" or "RWJ-22164" or Tractocile or UNII-081D12SI0Z).tw,kw. (707)
50	90779-69-4.rn. (928)

51 oxytocin antagonist/ (655)
52 (oxytocin adj3 (antagonist* or block* or inhibit*)).tw,kw. (2997)
53 or/49-52 (3824)
54 48 and 53 (856)
55 Randomized Controlled Trial/ (749113)
56 Randomization/ (145521)
57 Random Sampling/ (64)
58 Double Blind Procedure/ (118442)
59 Single Blind Procedure/ (18456)
60 Placebo/ (228016)
61 (random* or RCT$1 or placebo*).tw. (1740926)
62 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (292246)
63 or/55-62 (2093204)
64 54 and 63 (213)
65 exp animals/ (36715474)
66 exp animal experimentation/ (1629685)
67 exp models animal/ (1157790)
68 exp animal experiment/ (1629685)
69 nonhuman/ (4159520)
70 exp vertebrate/ (35773594)
71 or/65-70 (37897310)
72 exp humans/ (28631631)
73 exp human experimentation/ (330100)
74 exp human experiment/ (317774)
75 or/72-74 (28633677)
76 71 not 75 (9265193)
77 64 not 76 (210)
78 77 use emez (145)
79 (200807* or 200808* or 200809* or 200810* or 200811* or 200812* or 2009* or 2010* or 2011* or 2012* or 2013*).ed. (5551926)

	80 34 and 79 (17) 81 (2008* or 2009* or 2010* or 2011* or 2012* or 2013*).em. (12933830) 82 78 and 81 (51) 83 80 or 82 (68) 84 remove duplicates from 83 (53) 85 84 use prmz (14) MEDLINE UNIQUE HITS 86 84 use emez (39) EMBASE UNIQUE HITS
Note	

Database	**Cochrane Library (Wiley Interface) CENTRAL**
Date	Date Run: 07/11/13 04:06:48.74 Description: 2013 Nov 6
Search Strategy	#1 [mh "Obstetric Labor, Premature"] 1013 #2 ((labor* or labour* or birth* or deliver*) near/4 (preterm* or pre-term* or prematur* or pre-matur*)):ti,ab,kw 2910 #3 (PTL or sPTL or PTB or sPTB or PTD or sPTD):ti,ab,kw 98 #4 [mh "Uterine Contraction"] 334 #5 ((uterus* or uterine) near/4 contraction*):ti,ab,kw 657 #6 [mh "Cervical Ripening"] 261 #7 ((cervical or cervix*) near/4 (dilat* or ripen*)):ti,ab,kw 1459 #8 [mh "Labor Onset"] 468 #9 (preterm* or pre-term* or prematur* or pre-matur*):ti,ab,kw 12075 #10 (#4 or #5 or #6 or #7 or #8) and #9 254 #11 #1 or #2 or #3 or #10 3004 #12 [mh "Pregnancy, High-Risk"] 179 #13 [mh ^"Pregnancy Complications"] 1025 #14 #11 or #12 or #13 4003 #15 (atosiban or atosibanum or "ORF 22164" or "ORF-22164" or "RWJ 22164" or "RWJ-22164" or Tractocile or UNII-081D12SI0Z):ti,ab,kw 49

	#16 (oxytocin near/4 (antagonist* or block* or inhibit*)):ti,ab,kw 64 #17 [mh Oxytocin/ai] 11 #18 [mh Vasotocin/aa] 38 #19 or #15-#18 94 #20 #14 and #19 from 2008 to 2013 15 *CENTRAL – 10*
Note	

3.1.7. Tertiary prevention: magnesium sulphate as neuroprotector

3.1.7.1. Magnesium sulphate - reviews

Database	**MEDLINE and EMBASE**
Date	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Embase<1980 to 2013 Week 23>
Search Strategy	1 exp Obstetric Labor, Premature/ (42756) 2 ((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw,kw. (69438) 3 (PTL or sPTL or PTB or sPTB or PTD or sPTD).tw,kw. (11046) 4 Uterine Contraction/ (13946) 5 ((uterus* or uterine) adj3 contraction*).tw,kw. (8399) 6 Cervical Ripening/ (2398) 7 ((cervical* or cervix*) adj3 (dilat* or ripen*)).tw,kw. (8994) 8 exp Labor Onset/ (4122) 9 (preterm* or pre-term* or prematur* or pre-matur*).tw,kw. (302946) 10 (4 or 5 or 6 or 7 or 8) and 9 (4734) 11 or/1-3,10 (91368) 12 Cerebral Palsy/pc [Prevention & Control] (675) 13 (((cerebral adj2 palsy) or (dipleg* adj1 spastic) or Little* Disease) and (prevent* or protect* or neuroprotect* or neuro-protect* or neuroprophyla* or neuro-prophyla*)).tw,kw. (2793) 14 ((infant* or neonat* or newborn* or fetus* or foetus* or fetal* or foetal*) adj5 (protect* or neuroprotect* or neuro-protect* or neuroprophyla* or neuro-prophyla*)).tw,kw. (12371) 15 exp Infant, Premature/ (106470) 16 ((infant* or neonat* or newborn*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw,kw. (85040) 17 or/11-16 (215555)

18 exp magnesium compounds/ (15521)
19 magnesium.tw,kw. (92078)
20 (MgSO4 or "MgSO(4)").tw,kw. (4139)
21 (mag sulphate* or mag sulfate*).tw,kw. (10)
22 (epsom salt* or Arrosalt 2327 or CCRIS 8411 or (Caswell adj2 "534") or "EINECS 231-298-2" or "HSDB 664" or Magnesii sulfas or "NSC 146179" or "OT-S" or "SN 00" or Sal Angalis or Sal De sedlitz).tw,kw. (98)
23 7487-88-9.rn. (14996)
24 Neuroprotective Agents/ (30132)
25 or/18-24 (139650)
26 17 and 25 (3202)
27 limit 26 to systematic reviews [Limit not valid in Embase; records were retained] (1990)
28 meta analysis.pt. (42868)
29 exp meta-analysis as topic/ (20902)
30 (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. (127570)
31 (systematic review* or systematic overview* or technology assessment* or HTA or HTAs).tw. (108716)
32 exp Technology assessment, biomedical/ (20582)
33 (data synthes* or data extraction* or data abstraction*).tw. (27305)
34 health technology assessment winchesterengland.jn. (1250)
35 (evidence report technology assessment or evidence report technology assessment summary).jn. (400)
36 "cochrane database of systematic reviews".jn. (13249)
37 or/28-36 (263658)
38 26 and 37 (157)
39 27 or 38 (2009)
40 exp Animals/ not (exp Animals/ and Humans/) (7906230)
41 39 not 40 (1878)
42 limit 41 to yr="2008-current" (618)
43 42 use prmz (42) MEDLINE
44 premature labor/ (37282)
45 ((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw,kw. (69438)
46 (PTL or sPTL or PTB or sPTB or PTD or sPTD).tw,kw. (11046)
47 uterus contraction/ (7040)
48 ((uterus* or uterine) adj3 contraction*).tw,kw. (8399)
49 uterine cervix ripening/ (1660)
50 ((cervical* or cervix*) adj3 (dilat* or ripen*)).tw,kw. (8994)
51 Labor Onset/ (1793)
52 (preterm* or pre-term* or prematur* or pre-matur*).tw,kw. (302946)

53 (47 or 48 or 49 or 50 or 51) and 52 (4082)
54 or/44-46,53 (89768)
55 Cerebral Palsy/pc [Prevention & Control] (675)
56 (((cerebral adj2 palsy) or (dipleg* adj1 spastic) or Little* Disease) and (prevent* or protect* or neuroprotect* or neuro-protect* or neuroprophyla* or neuro-prophyla*)).tw,kw. (2793)
57 ((infant* or neonat* or newborn* or fetus* or foetus* or fetal* or foetal*) adj5 (protect* or neuroprotect* or neuro-protect* or neuroprophyla* or neuro-prophyla*)).tw,kw. (12371)
58 prematurity/ (66491)
59 ((infant* or neonat* or newborn*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw,kw. (85040)
60 or/54-59 (199265)
61 magnesium sulfate/ (15371)
62 magnesium derivative/ (1982)
63 magnesium.tw,kw. (92078)
64 (MgSO4 or "MgSO(4)").tw,kw. (4139)
65 (mag sulphate* or mag sulfate*).tw,kw. (10)
66 (epsom salt* or Arrosalt 2327 or CCRIS 8411 or (Caswell adj2 "534") or "EINECS 231-298-2" or "HSDB 664" or Magnesii sulfas or "NSC 146179" or "OT-S" or "SN 00" or Sal Angalis or Sal De sedlitz).tw,kw. (98)
67 7487-88-9.rn. (14996)
68 neuroprotective agent/ (30132)
69 or/61-68 (132278)
70 60 and 69 (3145)
71 meta-analysis/ or "systematic review"/ or "meta analysis (topic)"/ or biomedical technology assessment/ (175605)
72 (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. (127570)
73 (systematic review* or systematic overview* or technology assessment* or HTA or HTAs).tw. (108716)
74 (data synthes* or data extraction* or data abstraction*).tw. (27305)
75 (health technology assessment or health technology assessment reports or health technology assessment winchesterengland).jn. (1986)
76 (evidence report technology assessment or evidence report technology assessment summary).jn. (400)
77 ("cochrane database of systematic reviews" or "cochrane database of systematic reviews online").jn. (21215)
78 or/71-77 (299994)
79 70 and 78 (206)
80 exp animals/ (35380104)
81 exp animal experimentation/ (1596558)
82 exp models animal/ (1105876)
83 exp animal experiment/ (1596558)
84 nonhuman/ (4069604)

	85 exp vertebrate/ (34475122) 86 or/80-85 (36540117) 87 exp humans/ (27543462) 88 exp human experimentation/ (324778) 89 exp human experiment/ (312971) 90 or/87-89 (27545499) 91 86 not 90 (8996170) 92 79 not 91 (206) 93 limit 92 to yr="2008-current" (106) 94 93 use emez (73) EMBASE 95 43 or 94 (115) 96 remove duplicates from 95 (86) 97 96 use prmz (38) MEDLINE UNIQUE HITS 98 96 use emez (48) EMBASE UNIQUE HITS
Note	

Database	**Cochrane Library (Wiley Interface), including CDSR, DARE, Central, HTA, and NHS EED**
Date	Date Run: 12/06/13 04:19:35.969 Description: 2013 Jun 11 - Post PRESS
Search Strategy	#1 [mh "Obstetric Labor, Premature"] 984 #2 ((labor* or labour* or birth* or deliver*) near/4 (preterm* or pre-term* or prematur* or pre-matur*)):ti,ab,kw 2843 #3 (PTL or sPTL or PTB or sPTB or PTD or sPTD):ti,ab,kw 97 #4 [mh "Uterine Contraction"] 333 #5 ((uterus* or uterine) near/4 contraction*):ti,ab,kw 649 #6 [mh "Cervical Ripening"] 258 #7 ((cervical or cervix*) near/4 (dilat* or ripen*)):ti,ab,kw 1452 #8 [mh "Labor Onset"] 463 #9 (preterm* or pre-term* or prematur* or pre-matur*):ti,ab,kw 11797 #10 (#4 or #5 or #6 or #7 or #8) and #9 257 #11 #1 or #2 or #3 or #10 2943 #12 [mh "Cerebral Palsy"/pc] 29

	#13 ((cerebral near/3 palsy) or (dipleg* near/1 spastic) or Little* Disease) and (prevent* or protect* or neuroprotect* or neuro-protect* or neuroprophyla* or neuro-prophyla*):ti,ab,kw 1615 #14 ((infant* or neonat* or newborn* or fetus* or foetus* or fetal* or foetal*) near/6 (protect* or neuroprotect* or neuro-protect* or neuroprophyla* or neuro-prophyla*)):ti,ab,kw 339 #15 [mh "Infant, Premature"] 2512 #16 ((infant* or neonat* or newborn*) near/4 (preterm* or pre-term* or prematur* or pre-matur*)):ti,ab,kw 5897 #17 or #11-#16 9253 #18 [mh "magnesium compounds"] 939 #19 magnesium:ti,ab,kw 3456 #20 (MgSO4 or "MgSO(4)"):ti,ab,kw 173 #21 (mag next sulphate*) or (mag next sulfate*):ti,ab,kw 0 #22 (epsom next salt*) or "Arrosalt 2327" or "CCRIS 8411" or (Caswell near/2 534) or "EINECS 231-298-2" or "HSDB 664" or "Magnesii sulfas" or "NSC 146179" or "OT-S" or "SN 00" or "Sal Angalis" or "Sal De sedlitz":ti,ab,kw 125 #23 [mh "Neuroprotective Agents"] 595 #24 or #18-#23 4206 #25 #17 and #24 from 2008 to 2013 63 DSR – 34 DARE -7 CENTRAL – 21 NHS EED - 1
Note	

3.1.7.2. Magnesium sulphate - RCTs

Database	MEDLINE and EMBASE
Date	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Embase <1980 to 2013 Week 44
Search Strategy	1 exp Obstetric Labor, Premature/ (45284) 2 ((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw,kw. (73801) 3 (PTL or sPTL or PTB or sPTB or PTD or sPTD).tw,kw. (12009) 4 Uterine Contraction/ (14299) 5 ((uterus* or uterine) adj3 contraction*).tw,kw. (8688) 6 Cervical Ripening/ (2552) 7 ((cervical or cervix*) adj3 (dilat* or ripen*)).tw,kw. (9346) 8 exp Labor Onset/ (4404) 9 (preterm* or pre-term* or prematur* or pre-matur*).tw,kw. (318399) 10 (4 or 5 or 6 or 7 or 8) and 9 (5005) 11 or/1-3,10 (96817) 12 *Pregnancy, High-Risk/ (3548) 13 *Pregnancy Complications/ (77552) 14 or/11-13 (170621) 15 exp Magnesium Compounds/ (16005) 16 magnesium.tw,kw. (94931) 17 (MgSO4 or "MgSO(4)").tw,kw. (4320) 18 (mag sulfate or mag sulphate).tw,kw. (2) 19 (epsom salt* or Arrosalt 2327 or "CCRIS 8411" or (Caswell adj2 "534") or "EINECS 231-298-2" or "HSDB 664" or Magnesii sulfas or "NSC 146179" or "OT- S" or "SN 00" or Sal Angalis or Sal De sedlitz).tw,kw. (100) 20 7487-88-9.rn. (15436) 21 or/15-20 (113248) 22 14 and 21 (2408) 23 randomized controlled trial.pt. (389900) 24 exp Randomized Controlled Trials as Topic/ (144254)

25	exp Random Allocation/ (145521)
26	exp Double-Blind Method/ (250201)
27	exp Single-Blind Method/ (38031)
28	exp Placebos/ (261783)
29	(random* or RCT$1 or placebo*).tw. (1741114)
30	((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (292259)
31	or/23-30 (2112468)
32	22 and 31 (624)
33	exp Animals/ not (exp Animals/ and Humans/) (8153428)
34	32 not 33 (608)
35	34 use prmz (226)
36	premature labor/ (39101)
37	((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw,kw. (73801)
38	(PTL or sPTL or PTB or sPTB or PTD or sPTD).tw,kw. (12009)
39	uterus contraction/ (7277)
40	((uterus* or uterine) adj3 contraction*).tw,kw. (8688)
41	uterine cervix ripening/ (1760)
42	((cervical or cervix*) adj3 (dilat* or ripen*)).tw,kw. (9346)
43	labor onset/ (1952)
44	(preterm* or pre-term* or prematur* or pre-matur*).tw,kw. (318399)
45	(39 or 40 or 41 or 42 or 43) and 44 (4331)
46	or/36-38,45 (95054)
47	*high risk pregnancy/ (3548)
48	*pregnancy complication/ (102828)
49	or/46-48 (193587)
50	magnesium derivative/ (2050)
51	magnesium sulfate/ (15871)
52	magnesium.tw,kw. (94931)
53	(MgSO4 or "MgSO(4)").tw,kw. (4320)
54	(mag sulfate or mag sulphate).tw,kw. (2)

55 (epsom salt* or Arrosalt 2327 or "CCRIS 8411" or (Caswell adj2 "534") or "EINECS 231-298-2" or "HSDB 664" or Magnesii sulfas or "NSC 146179" or "OT-S" or "SN 00" or Sal Angalis or Sal De sedlitz).tw,kw. (100)
56 7487-88-9.rn. (15436)
57 or/50-56 (105666)
58 49 and 57 (2435)
59 Randomized Controlled Trial/ (749125)
60 Randomization/ (145521)
61 Random Sampling/ (64)
62 Double Blind Procedure/ (118442)
63 Single Blind Procedure/ (18456)
64 Placebo/ (228016)
65 (random* or RCT$1 or placebo*).tw. (1741114)
66 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (292259)
67 or/59-66 (2093397)
68 58 and 67 (620)
69 exp animals/ (36715474)
70 exp animal experimentation/ (1629685)
71 exp models animal/ (1157790)
72 exp animal experiment/ (1629685)
73 nonhuman/ (4159520)

Search Strategy

ID Search Hits
1 exp Obstetric Labor, Premature/ (45284)
2 ((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw,kw. (73801)
3 (PTL or sPTL or PTB or sPTB or PTD or sPTD).tw,kw. (12009)
4 Uterine Contraction/ (14299)
5 ((uterus* or uterine) adj3 contraction*).tw,kw. (8688)
6 Cervical Ripening/ (2552)
7 ((cervical or cervix*) adj3 (dilat* or ripen*)).tw,kw. (9346)
8 exp Labor Onset/ (4404)

9 (preterm* or pre-term* or prematur* or pre-matur*).tw,kw. (318399)
10 (4 or 5 or 6 or 7 or 8) and 9 (5005)
11 or/1-3,10 (96817)
12 *Pregnancy, High-Risk/ (3548)
13 *Pregnancy Complications/ (77552)
14 or/11-13 (170621)
15 exp Magnesium Compounds/ (16005)
16 magnesium.tw,kw. (94931)
17 (MgSO4 or "MgSO(4)").tw,kw. (4320)
18 (mag sulfate or mag sulphate).tw,kw. (2)
19 (epsom salt* or Arrosalt 2327 or "CCRIS 8411" or (Caswell adj2 "534") or "EINECS 231-298-2" or "HSDB 664" or Magnesii sulfas or "NSC 146179" or "OT-S" or "SN 00" or Sal Angalis or Sal De sedlitz).tw,kw. (100)
20 7487-88-9.rn. (15436)
21 or/15-20 (113248)
22 14 and 21 (2408)
23 randomized controlled trial.pt. (389900)
24 exp Randomized Controlled Trials as Topic/ (144254)
25 exp Random Allocation/ (145521)
26 exp Double-Blind Method/ (250201)
27 exp Single-Blind Method/ (38031)
28 exp Placebos/ (261783)
29 (random* or RCT$1 or placebo*).tw. (1741114)
30 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (292259)
31 or/23-30 (2112468)
32 22 and 31 (624)
33 exp Animals/ not (exp Animals/ and Humans/) (8153428)
34 32 not 33 (608)
35 34 use prmz (226)
36 premature labor/ (39101)
37 ((labor* or labour* or birth* or deliver*) adj3 (preterm* or pre-term* or prematur* or pre-matur*)).tw,kw. (73801)

38 (PTL or sPTL or PTB or sPTB or PTD or sPTD).tw,kw. (12009)
39 uterus contraction/ (7277)
40 ((uterus* or uterine) adj3 contraction*).tw,kw. (8688)
41 uterine cervix ripening/ (1760)
42 ((cervical or cervix*) adj3 (dilat* or ripen*)).tw,kw. (9346)
43 labor onset/ (1952)
44 (preterm* or pre-term* or prematur* or pre-matur*).tw,kw. (318399)
45 (39 or 40 or 41 or 42 or 43) and 44 (4331)
46 or/36-38,45 (95054)
47 *high risk pregnancy/ (3548)
48 *pregnancy complication/ (102828)
49 or/46-48 (193587)
50 magnesium derivative/ (2050)
51 magnesium sulfate/ (15871)
52 magnesium.tw,kw. (94931)
53 (MgSO4 or "MgSO(4)").tw,kw. (4320)
54 (mag sulfate or mag sulphate).tw,kw. (2)
55 (epsom salt* or Arrosalt 2327 or "CCRIS 8411" or (Caswell adj2 "534") or "EINECS 231-298-2" or "HSDB 664" or Magnesii sulfas or "NSC 146179" or "OT-S" or "SN 00" or Sal Angalis or Sal De sedlitz).tw,kw. (100)
56 7487-88-9.rn. (15436)
57 or/50-56 (105666)
58 49 and 57 (2435)
59 Randomized Controlled Trial/ (749125)
60 Randomization/ (145521)
61 Random Sampling/ (64)
62 Double Blind Procedure/ (118442)
63 Single Blind Procedure/ (18456)
64 Placebo/ (228016)
65 (random* or RCT$1 or placebo*).tw. (1741114)
66 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (292259)

67	or/59-66 (2093397)
68	58 and 67 (620)
69	exp animals/ (36715474)
70	exp animal experimentation/ (1629685)
71	exp models animal/ (1157790)
72	exp animal experiment/ (1629685)
73	nonhuman/ (4159520)
74	exp vertebrate/ (35773594)
75	or/69-74 (37897310)
76	exp humans/ (28631631)
77	exp human experimentation/ (330100)
78	exp human experiment/ (317774)
79	or/76-78 (28633677)
80	75 not 79 (9265193)
81	68 not 80 (603)
82	81 use emez (391)
83	(200904* or 200905* or 200906* or 200907* or 200908* or 200909* or 200910* or 200911* or 200912* or 2010* or 2011* or 2012* or 2013*).ed. (4881295)
84	35 and 83 (54)
85	(2009* or 2010* or 2011* or 2012* or 2013*).em. (11189819)
86	82 and 85 (145)
87	84 or 86 (199)
88	remove duplicates from 87 (152)
89	88 use prmz (42) MEDLINE UNIQUE HITS
90	88 use emez (110) EMBASE UNIQUE HITS

Note

Database	Cochrane Library (Wiley Interface) CENTRAL
Date	Date Run: 08/11/13 03:36:26.395 Description: 2013 Nov 7
Search Strategy	#1 [mh "Obstetric Labor, Premature"] 1013 #2 ((labor* or labour* or birth* or deliver*) near/4 (preterm* or pre-term* or prematur* or pre-matur*)):ti,ab,kw 2910 #3 (PTL or sPTL or PTB or sPTB or PTD or sPTD):ti,ab,kw 98 #4 [mh "Uterine Contraction"] 334 #5 ((uterus* or uterine) near/4 contraction*):ti,ab,kw 657 #6 [mh "Cervical Ripening"] 261 #7 ((cervical or cervix*) near/4 (dilat* or ripen*)):ti,ab,kw 1459 #8 [mh "Labor Onset"] 468 #9 (preterm* or pre-term* or prematur* or pre-matur*):ti,ab,kw 12075 #10 (#4 or #5 or #6 or #7 or #8) and #9 254 #11 #1 or #2 or #3 or #10 3004 #12 [mh "Pregnancy, High-Risk"] 179 #13 [mh ^"Pregnancy Complications"] 1025 #14 #11 or #12 or #13 4003 #15 [mh "Magnesium Compounds"] 953 #16 magnesium:ti,ab,kw 3519 #17 (MgSO4 or "MgSO(4)"):ti,ab,kw 175 #18 ("mag sulfate" or "mag sulphate"):ti,ab,kw 0 #19 ((epsom next salt*) or "Arrosalt 2327" or "CCRIS 8411" or (Caswell near/2 "534") or "EINECS 231-298-2" or "HSDB 664" or "Magnesii sulfas" or "NSC 146179" or "OT-S" or "SN 00" or "Sal Angalis" or "Sal De sedlitz"):ti,ab,kw 1 #20 or #15-#19 3577 #21 #14 and #20 from 2009 to 2013 22 *CENTRAL - 8*
Note	

4. STUDY SELECTION AND QUALITY APPRAISAL

4.1. Quality appraisal tools

4.1.1. Systematic reviews

AMSTAR criteria were used to assess systematic reviews (Table 2).

Table 2 – 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 ☐ Not applicable
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 ☐ Not applicable
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 ☐ Not applicable
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 ☐ Not applicable
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 ☐ Not applicable

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 ☐ Not applicable
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 ☐ 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 the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
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 ☐ Not applicable
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 ☐ Not applicable
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 ☐ Not applicable

4.1.2. Diagnostic accuracy studies

The quality assessment tool used for the quality assessment of diagnostic accuracy studies was QUADAS-2 Tool (Table 3).

Table 3 – The QUADAS-2 tool

DOMAIN	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING
Description	Describe methods of patient selection: Describe included patients (prior testing, presentation, intended use of index test and setting):	Describe the index test and how it was conducted and interpreted:	Describe the reference standard and how it was conducted and interpreted:	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard:
Signalling questions(yes/no/unclear)	Was a consecutive or random sample of patients enrolled?	Were the index test results interpreted without knowledge of the results of the reference standard?	Is the reference standard likely to correctly classify the target condition?	Was there an appropriate interval between index test(s) and reference standard?
	Was a case-control design avoided?	If a threshold was used, was it pre-specified?	Were the reference standard results interpreted without knowledge of the results of the index test?	Did all patients receive a reference standard?
	Did the study avoid inappropriate exclusions?			Did all patients receive the same reference standard?
				Were all patients included in the analysis?
Risk of bias: High/low/unclear	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Could the patient flow have introduced bias?
Concerns regarding applicability: High/low/unclear	Are there concerns that the included patients do not match the review question?	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Are there concerns that the target condition as defined by the reference standard does not match the review question?	

4.1.3. Randomized controlled trials

To assess risk of bias of randomised controlled trials, we used Cochrane Collaboration's tool (Table 4).

Table 4 – 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
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		

Domain	Support for judgement	Review authors' judgement
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

4.2. Identification of women at risk

4.2.1. fetal fibronectin test or actim partus test

For key question 1 (fFN test performance and effectiveness and Actim Partus test performance), a total of 437 bibliographic records were identified (MEDLINE=177, EMBASE=225, Cochrane Library=24, and Grey Literature= 11). After de-duplicating, 329 records remained (MEDLINE=133, EMBASE=177, Cochrane Library=8, and Grey literature= 11), of which 5 were companions. [4-8] Of these, 208 (83 reviews, and 125 primary studies) met the eligibility criteria based on title and abstract, and 33 (6 systematic reviews, and 27 primary studies) based on full-text. Of the 6 included systematic reviews, 3 were eventually selected for updating based on quality and singleton gestation population (1 for fFN test effectiveness,[9] 1 for fFN test performance,[10] 1 for Actim Partus test performance[4], and none for Actim Partus effectiveness). 27 primary studies met eligibility criteria (4 for fFN test effectiveness,[1, 3, 11, 12] 11 for fFN test performance,[13-23] and 15 for Actim Partus test performance.[6, 13, 15, 20, 24-34] The PRISMA diagram providing further detail on the identified records is presented in Figure 1.

We attempted a *de novo* synthesis to address Actim Partus test effectiveness. 119 bibliographic records were identified (MEDLINE=64, EMBASE=51, and Cochrane Library=4). After de-duplicating, 117 records remained (MEDLINE= 64, EMBASE= 51,and Cochrane Library= 2,) but none met the eligibility criteria even after allowing for comparative observational designs (a post hoc protocol modification specific to Actim Partus). The PRISMA diagram providing further detail on the identified records is presented in Figure 2.

For test performance, no systematic reviews were identified that evaluated the incremental value of adding fFN or Actim Partus to standard or alternative testing strategies. Therefore, it was decided to update reviews that assessed these tests as a standalone testing strategy against the reference standard of preterm birth.

A list of excluded studies based on full text selection with reason for exclusion is available upon request.

Table 5 – Fetal fibronectin test: critical appraisal SR

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	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
Honest, 2009[4]	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
Sanchez-Ramos, 2009[10]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
Berhella, 2008[9]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Can't answer	No

Table 6 – Test accuracy fetal fibronectin test: critical appraisal primary studies

		Cooper 2012[13]	Lee 2012[14]	Riboni 2011[15]	Rose 2010[17]	Diaz 2009[18]	Van Baaren 2013[19]	Sumer 2010[21]	Wilms 2009[23]
Domain 1: Patient selection									
A Risk of bias									
Was a consecutive or random sample of patients enrolled?	Yes/No/Unclear	Unclear	No	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Was a case-control design avoided?	Yes/No/Unclear	Yes	No	No	Yes	Yes	Yes	Yes	No
Did the study avoid inappropriate exclusions?	Yes/No/Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes
Could the selection of patients have introduced bias?	RISK: LOW/HIGH/UNCLEAR	Unclear Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	High Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias
B Concerns regarding applicability									
Is there concern that the included patients do not match the review question?	CONCERN: LOW/HIGH/UNCLEAR	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Unclear Concern	Low Concern
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	Unclear	Yes	Yes	Yes	Yes
If a threshold was used, was it pre-specified?	Yes/No/Unclear	Yes	Unclear	Yes	Unclear	Yes	Unclear	Unclear	Yes
Could the conduct or interpretation of the index test have introduced bias?	RISK: LOW/HIGH/UNCLEAR	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Unclear Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias

B. Concerns regarding applicability									
Is there concern that the index test, its conduct, or interpretation differ from the review question?	CONCERN: LOW/HIGH/UNCLEAR	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern
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	Yes	Yes	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes/No/Unclear	Yes	Yes	Unclear	No	No	No	Yes	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	RISK: LOW/HIGH/UNCLEAR	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	High Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias
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	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern
Domain 4: Flow and timing									
A. Risk of bias									
Was there an appropriate interval between index test(s) and reference standard?	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did all patients receive a reference standard?	Yes/No/Unclear	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes

Did patients receive the same reference standard?	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were all patients included in the analysis?	Yes/No/Unclear	No	Unclear	Yes	No	Yes	No	Unclear	No
Could the patient flow have introduced bias?	RISK: LOW/HIGH/UNCLEAR	Unclear Risk of Bias	High Risk of Bias	Low Risk of Bias	High Risk of Bias	Low Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias

Figure 1 – PRISMA diagram identification of women at risk: fFN and Actim Partus test

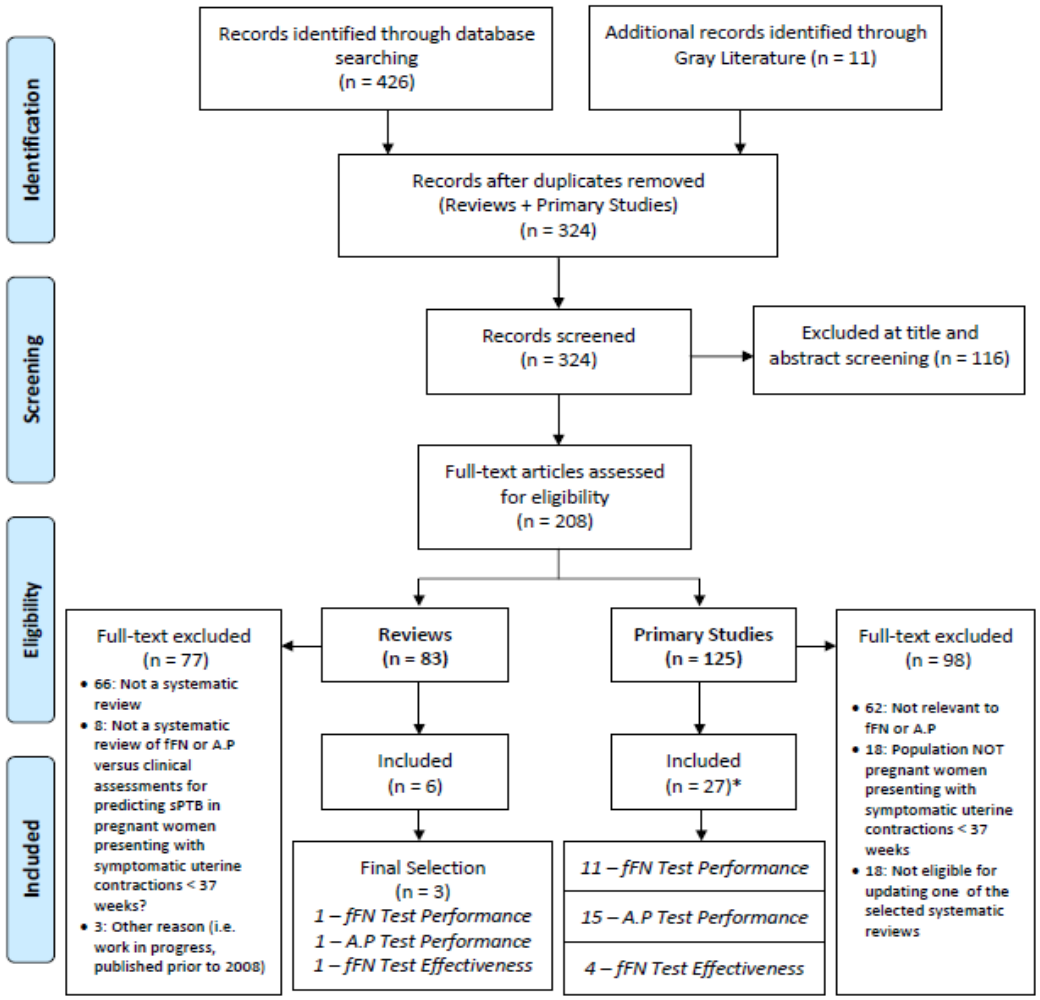


Figure 2 – PRISMA diagram identification of women at risk: clinical effectiveness Actim Partus test

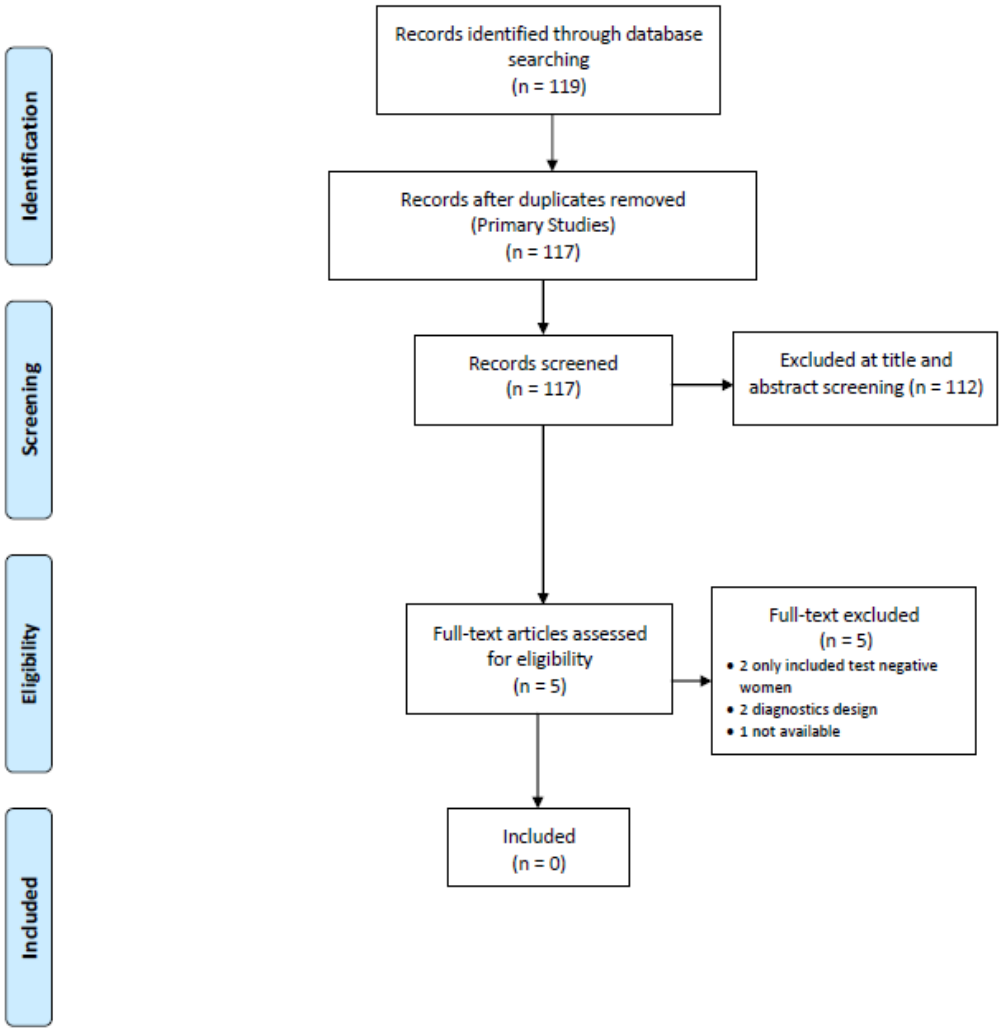


Table 7 – Test accuracy Actim Partus test: critical appraisal primary studies (1)

		Laudanski 2012[24]	Cooper 2012[13]	Riboni 2011[15]	Danti 2011[25]	Azlin 2010[6]	Audibert 2010[26]	Brik 2010[27]
Domain 1: Patient selection								
A Risk of bias								
Was a consecutive or random sample of patients enrolled?	Yes/No/Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Yes
Was a case-control design avoided?	Yes/No/Unclear	Unclear	Yes	Yes	No	Yes	Yes	Yes
Did the study avoid inappropriate exclusions?	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Could the selection of patients have introduced bias?	Risk: low/high/unclear	High Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	Low Risk of Bias
B Concerns regarding applicability								
Is there concern that the included patients do not match the review question?	Concern: low/high/unclear	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern
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	Yes	Yes
If a threshold was used, was it pre-specified?	Yes/No/Unclear	No	Yes	Yes	Yes	Yes	Yes	Yes
Could the conduct or interpretation of the index test have introduced bias?	Risk: low/high/unclear	High Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias
B Concerns regarding applicability								

Is there concern that the index test, its conduct, or interpretation differ from the review question?	concern: low/high/unclear	Unclear Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern
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	Yes	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes/No/Unclear	Unclear	Yes	Unclear	Yes	No	Yes	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Risk: low/high/unclear	Unclear Risk of Bias	Low Risk of Bias	Unclear Risk of Bias	Low Risk of Bias	High Risk of Bias	Low Risk of Bias	Unclear Risk of Bias
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	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern
Domain 4: Flow and timing								
A. Risk of bias								
Was there an appropriate interval between index test(s) and reference standard?	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did all patients receive a reference standard?	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did patients receive the same reference standard?	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were all patients included in the analysis?	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No

Could the patient flow have introduced bias?	Risk: low/high/unclear	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Unclear Risk of Bias	High Risk of Bias

Table 8 – Test accuracy Actim Partus test: critical appraisal primary studies (2)

		Rahkonen 2009[28]	Tanir 2009[29]	Altinkaya 2009[30]	Sunagawa 2008[31]	Latifagic 2008[32]	Eroglu 2007[33]	Ting 2007[34]
Domain 1: Patient selection								
A Risk of bias								
Was a consecutive or random sample of patients enrolled?	Yes/No/Unclear	Unclear	Unclear	Unclear	No	Unclear	Unclear	Unclear
Was a case-control design avoided?	Yes/No/Unclear	Yes	Yes	Yes	Unclear	No	Yes	Yes
Did the study avoid inappropriate exclusions?	Yes/No/Unclear	Yes	Unclear	Unclear	Yes	Unclear	Yes	Yes
Could the selection of patients have introduced bias?	Risk: low/high/unclear	Unclear Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	High Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias
B Concerns regarding applicability								
Is there concern that the included patients do not match the review question?	Concern: low/high/unclear	Unclear Concern	Unclear Concern	Unclear Concern	Low Concern	Unclear Concern	Low Concern	Low Concern
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	Yes	Yes
If a threshold was used, was it pre-specified?	Yes/No/Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear

Could the conduct or interpretation of the index test have introduced bias?	Risk: Low/High/Unclear	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Unclear Risk of Bias	Low Risk of Bias	Low Risk of Bias	Unclear Risk of Bias
B Concerns regarding applicability								
Is there concern that the index test, its conduct, or interpretation differ from the review question?	Concern: Low/High/Unclear	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern
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	Yes	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes/No/Unclear	Yes	Yes	Unclear	No	Unclear	No	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Risk: Low/High/Unclear	Low Risk of Bias	Low Risk of Bias	Unclear Risk of Bias	High Risk of Bias	Unclear Risk of Bias	Low Risk of Bias	Low Risk of Bias
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	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern
Domain 4: Flow and timing								
A. Risk of bias								
Was there an appropriate interval between index test(s) and reference standard?	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did all patients receive a reference standard?	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Did patients receive the same reference standard?	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were all patients included in the analysis?	Yes/No/Unclear	No	Yes	Yes	No	Yes	Yes	No
Could the patient flow have introduced bias?	Risk: Low/High/Unclear	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	High Risk of Bias	Low Risk of Bias	Low Risk of Bias	Unclear Risk of Bias

4.2.2. Vaginal ultrasoud

For the research question on vaginal ultrasound, a total of 1243 bibliographic records were identified (MEDLINE=545, EMBASE=638, Cochrane Library=59, and Grey Literature= 1). After de-duplicating, 1059 records remained (MEDLINE=502, EMBASE=544, Cochrane Library=12, and Grey literature=1), of which 3 were companions.[49-51] Of these, 253 (52 reviews, and 201 primary studies) met the eligibility criteria based on title and abstract, and 56 (11 systematic reviews, and 45 primary studies) based on full-text. Of the 11 included systematic reviews, 2 were eventually selected for updating based on quality and singleton gestation population (1 for test effectiveness[52] and 1 for test performance[53]). A total of 45 primary studies met eligibility criteria (1 for test effectiveness[54] and 44 for test performance[17,32,34,35,38,39,41,42,45,47,55-88]). The PRSIMA diagram providing further detail on the identified records is presented in Figure 3.

A list of excluded studies based on full text selection with reason for exclusion is available upon request.

Figure 3 – PRISMA diagram identification of women at risk: cervical length measurements

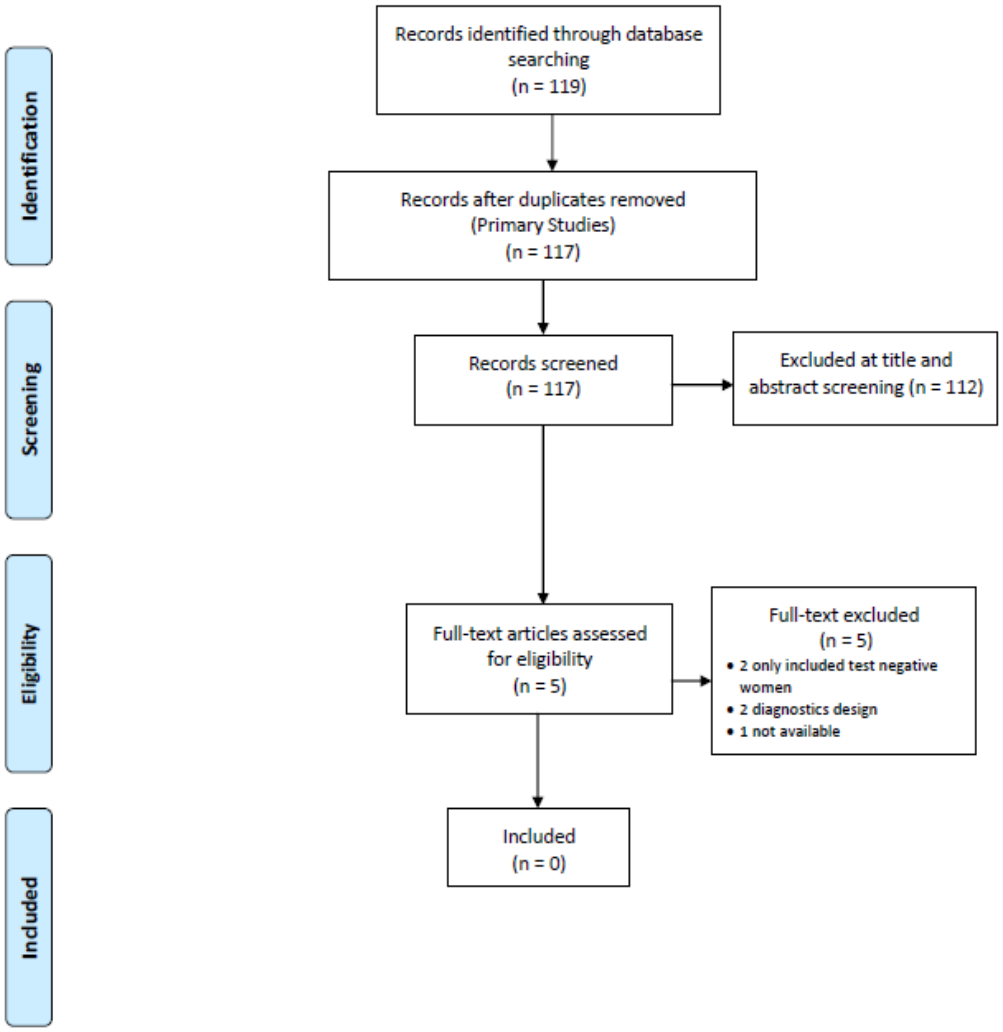


Table 9 – Cervical length measurement: critical appraisal SR

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	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
Berhella, 2013[35]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No

Table 10 – Test accuracy vaginal ultrasound: critical appraisal primary studies (1)

		Priya 2013	Tateyama 2013	Kahyaoglu 2013	Moller 2013	de Oliveira 2012	Romero 2012	Serrano-Gomez 2011
Domain 1: Patient selection								
A Risk of bias								
Was a consecutive or random sample of patients enrolled?	Yes/No/Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	No	Unclear
Was a case-control design avoided?	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the study avoid inappropriate exclusions?	Yes/No/Unclear	Yes	Yes	Yes	Unclear	Yes	No	Yes
Could the selection of patients have introduced bias?	Risk: low/high/unclear	Unclear Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	Low Risk of Bias	Unclear Risk of Bias
B Concerns regarding applicability								
Is there concern that the included patients do not match the review question?	Concern: low/high/unclear	Unclear Concern	Low Concern	Low Concern	Unclear Concern	Low Concern	High Concern	Low Concern
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	Yes	Yes
If a threshold was used, was it pre-specified?	Yes/No/Unclear	No	Yes	No	No	Yes	Yes	Yes
Could the conduct or interpretation of the index test have introduced bias?	Risk: low/high/unclear	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias
B Concerns regarding applicability								
Is there concern that the index test, its conduct, or interpretation differ from the review question?	Concern: low/high/unclear	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern
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	Yes	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes/No/Unclear	No	No	No	No	No	No	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	Risk: low/high/unclear	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias
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	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern
Domain 4: Flow and timing								
A. Risk of bias								

Was there an appropriate interval between index test(s) and reference standard?	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did all patients receive a reference standard?	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did patients receive the same reference standard?	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were all patients included in the analysis?	Yes/No/Unclear	Unclear	Unclear	Unclear	Yes	No	Yes	Unclear
Could the patient flow have introduced bias?	Risk: low/high/unclear	High Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	High Risk of Bias	Unclear Risk of Bias

Table 11 – Test accuracy vaginal ultrasound: critical appraisal primary studies (2)

		Demirci 2011	Kim 2011	Wulff 2011	Adhikari 2011	Brik 2011	Deplagne 2010	Owen 2010
Domain 1: Patient selection								
A Risk of bias								
Was a consecutive or random sample of patients enrolled?	Yes/No/Unclear	Unclear	Unclear	Unclear	Unclear	Yes	No	Unclear
Was a case-control design avoided?	Yes/No/Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Did the study avoid inappropriate exclusions?	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	Yes
Could the selection of patients have introduced bias?	Risk: low/high/unclear	Unclear Risk of Bias	Low Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	Low Risk of Bias	Unclear Risk of Bias	Low Risk of Bias
B Concerns regarding applicability								
Is there concern that the included patients do not match the review question?	Concern: low/high/unclear	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Unclear Concern	Low Concern
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	No	Yes	Yes	Yes	Yes	Yes	Yes
If a threshold was used, was it pre-specified?	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Could the conduct or interpretation of the index test have introduced bias?	Risk: low/high/unclear	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Unclear Risk of Bias
B Concerns regarding applicability								

Is there concern that the index test, its conduct, or interpretation differ from the review question?	Concern: low/high/unclear	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern
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	Yes	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes/No/Unclear	No	No	No	No	No	No	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	Risk: low/high/unclear	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias
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	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern
Domain 4: Flow and timing								
A. Risk of bias								
Was there an appropriate interval between index test(s) and reference standard?	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did all patients receive a reference standard?	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did patients receive the same reference standard?	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were all patients included in the analysis?	Yes/No/Unclear	Yes	Yes	No	Unclear	No	Unclear	No

Could the patient flow have introduced bias?	Risk: Low/High/Unclear	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Unclear Risk of Bias	Low Risk of Bias	Unclear Risk of Bias	Low Risk of Bias

Table 12 – Test accuracy vaginal ultrasound: critical appraisal primary studies (2)

		Wilms 2009	Adhikari 2009	Boudhraa 2008	Park 2008	Schmitz 2008	Van BGJ 2013	Lee 2012
Domain 1: Patient selection								
A Risk of bias								
Was a consecutive or random sample of patients enrolled?	Yes/No/Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Yes
Was a case-control design avoided?	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the study avoid inappropriate exclusions?	Yes/No/Unclear	Yes	Yes	Unclear	No	Yes	Unclear	Unclear
Could the selection of patients have introduced bias?	Risk: low/high/unclear	Unclear Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias
B Concerns regarding applicability								
Is there concern that the included patients do not match the review question?	Concern: low/high/unclear	Low Concern	Low Concern	Unclear Concern	High Concern	Low Concern	Low Concern	Unclear Concern
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	Yes	Yes
If a threshold was used, was it pre-specified?	Yes/No/Unclear	No	Yes	Unclear	No	No	Unclear	No

Could the conduct or interpretation of the index test have introduced bias?	Risk: low/high/unclear	Unclear Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Unclear Risk of Bias
B Concerns regarding applicability								
Is there concern that the index test, its conduct, or interpretation differ from the review question?	Concern: low/high/unclear	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern
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	Yes	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes/No/Unclear	Unclear	No	No	No	No	No	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	Risk: low/high/unclear	Unclear Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias
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	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern
Domain 4: Flow and timing								
A. Risk of bias								
Was there an appropriate interval between index test(s) and reference standard?	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did all patients receive a reference standard?	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Did patients receive the same reference standard?	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were all patients included in the analysis?	Yes/No/Unclear	No	No	Unclear	No	No	No	Unclear
Could the patient flow have introduced bias?	Risk: low/high/unclear	Unclear Risk of Bias	Low Risk of Bias	Unclear Risk of Bias	Low Risk of Bias	Low Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias

Table 13 – Test accuracy vaginal ultrasound: critical appraisal primary studies (3)

		Henrich 2010	Di Renzo 2011	Lopez Farfan 2011	Danti 2011	Azlin 2010	Brik 2010	Paternoster 2009
Domain 1: Patient selection								
A Risk of bias								
Was a consecutive or random sample of patients enrolled?	Yes/No/Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Unclear
Was a case-control design avoided?	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the study avoid inappropriate exclusions?	Yes/No/Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes
Could the selection of patients have introduced bias?	Risk: low/high/unclear	Unclear Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Unclear Risk of Bias
B Concerns regarding applicability								
Is there concern that the included patients do not match the review question?	Concern: low/high/unclear	Unclear Concern	Unclear Concern	Unclear Concern	Low Concern	Low Concern	Low Concern	Low Concern
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	Yes	Yes
If a threshold was used, was it pre-specified?	Yes/No/Unclear	Unclear	Yes	Yes	Yes	Yes	No	No
Could the conduct or interpretation of the index test have introduced bias?	Risk: low/high/unclear	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias
B Concerns regarding applicability								
Is there concern that the index test, its conduct, or interpretation differ from the review question?	Concern: low/high/unclear	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern
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	Yes	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes/No/Unclear	No	No	No	No	Yes	No	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	Risk: low/high/unclear	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias
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	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern
Domain 4: Flow and timing								
A. Risk of bias								

Was there an appropriate interval between index test(s) and reference standard?	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did all patients receive a reference standard?	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did patients receive the same reference standard?	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were all patients included in the analysis?	Yes/No/Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	No	Unclear
Could the patient flow have introduced bias?	Risk: low/high/unclear	Unclear Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	High Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias

Table 14 – Test accuracy vaginal ultrasound: critical appraisal primary studies (4)

		Rahkonen 2009	Sunagawa 2008	Sumer 2010	Gramellini 2007	Eroglu 2007	Bittar 2007	Palacio 2007	Holst 2006
Domain 1: Patient selection									
A Risk of bias									
Was a consecutive or random sample of patients enrolled?	Yes/No/Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Was a case-control design avoided?	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the study avoid inappropriate exclusions?	Yes/No/Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Could the selection of patients have introduced bias?	Risk: low/high/unclear	Unclear Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias
B Concerns regarding applicability									
Is there concern that the included patients do not match the review question?	Concern: low/high/unclear	Low Concern	Low Concern	Unclear Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern

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	Yes	Yes	Yes
If a threshold was used, was it pre-specified?	Yes/No/Unclear	Yes	Yes	No	Yes	No	No	Unclear	No
Could the conduct or interpretation of the index test have introduced bias?	Risk: low/high/unclear	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias
B Concerns regarding applicability									
Is there concern that the index test, its conduct, or interpretation differ from the review question?	Concern: low/high/unclear	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern
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	Yes	Yes	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes/No/Unclear	No	No	No	No	No	No	Yes	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Risk: low/high/unclear	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Unclear Risk of Bias
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	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern
Domain 4: Flow and timing									
A. Risk of bias									
Was there an appropriate interval between index test(s) and reference standard?	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did all patients receive a reference standard?	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did patients receive the same reference standard?	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were all patients included in the analysis?	Yes/No/Unclear	No	No	Unclear	Unclear	Unclear	No	Yes	Yes
Could the patient flow have introduced bias?	Risk: low/high/unclear	High Risk of Bias	High Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	Low Risk of Bias	Low Risk of Bias

Table 15 – Test accuracy vaginal ultrasound: critical appraisal primary studies (5)

		Botsis 2006	Jenkins 2006	Tsoi 2006	Kwasan 2005	Tekesin 2005	Nakai 2005	Sayin 2005	Cardea 2006
Domain 1: Patient selection									
A Risk of bias									
Was a consecutive or random sample of patients enrolled?	Yes/No/Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Was a case-control design avoided?	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the study avoid inappropriate exclusions?	Yes/No/Unclear	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear

Could the selection of patients have introduced bias?	Risk: low/high/unclear	Unclear Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias
B Concerns regarding applicability									
Is there concern that the included patients do not match the review question?	Concern: low/high/unclear	Unclear Concern	Low Concern	Low Concern	Low Concern	Unclear Concern	Low Concern	Low Concern	Unclear Concern
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	Yes	Yes	Yes
If a threshold was used, was it pre-specified?	Yes/No/Unclear	Yes	No	Unclear	No	Yes	Yes	Yes	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Risk: low/high/unclear	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias
B Concerns regarding applicability									
Is there concern that the index test, its conduct, or interpretation differ from the review question?	Concern: low/high/unclear	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern
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	Yes	Yes	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes/No/Unclear	Yes	No	Yes	Yes	Unclear	No	Unclear	Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias?	Risk: low/high/unclear	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Unclear Risk of Bias	High Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias
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	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern	Low Concern
Domain 4: Flow and timing									
A. Risk of bias									
Was there an appropriate interval between index test(s) and reference standard?	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did all patients receive a reference standard?	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did patients receive the same reference standard?	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were all patients included in the analysis?	Yes/No/Unclear	Unclear	No	Unclear	Unclear	Unclear	Yes	Yes	Yes
Could the patient flow have introduced bias?	Risk: low/high/unclear	Unclear Risk of Bias	High Risk of Bias	Low Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias

4.3. Secondary prevention in women at risk

4.3.1. progesterone

Overall, 462 bibliographic records were identified (MEDLINE=118, EMBASE=179, Cochrane Library=116, and Grey Literature= 2). Additionally, we brought in 47 records previously flagged relevant for this question from searches undertaken for other key questions (Key Question 1, 2, and 4),. After de-duplicating and consideration of companion articles, 370 records remained for title/abstract screening. Of these, 119 (107 reviews, and 12 primary studies) met the eligibility criteria based on title and abstract, and 12 (9 systematic reviews and 3 primary studies) based on full-text. Of the 9 included systematic reviews, 2 were eventually selected for updating based on quality and publication year:

- One systematic review (Dodd et al. 2013) on Progesterone versus placebo/no treatment in women with short cervix, or past history of spontaneous preterm birth, or following presentation of threatened preterm birth12
- One systematic review (Conde-Agudelo et al. 2013) on Progesterone versus placebo, and Progesterone versus Cerclage (indirect comparison – to be discussed under Key Question 4) in asymptomatic women with short cervix and past history of preterm birth13 with a companion paper14

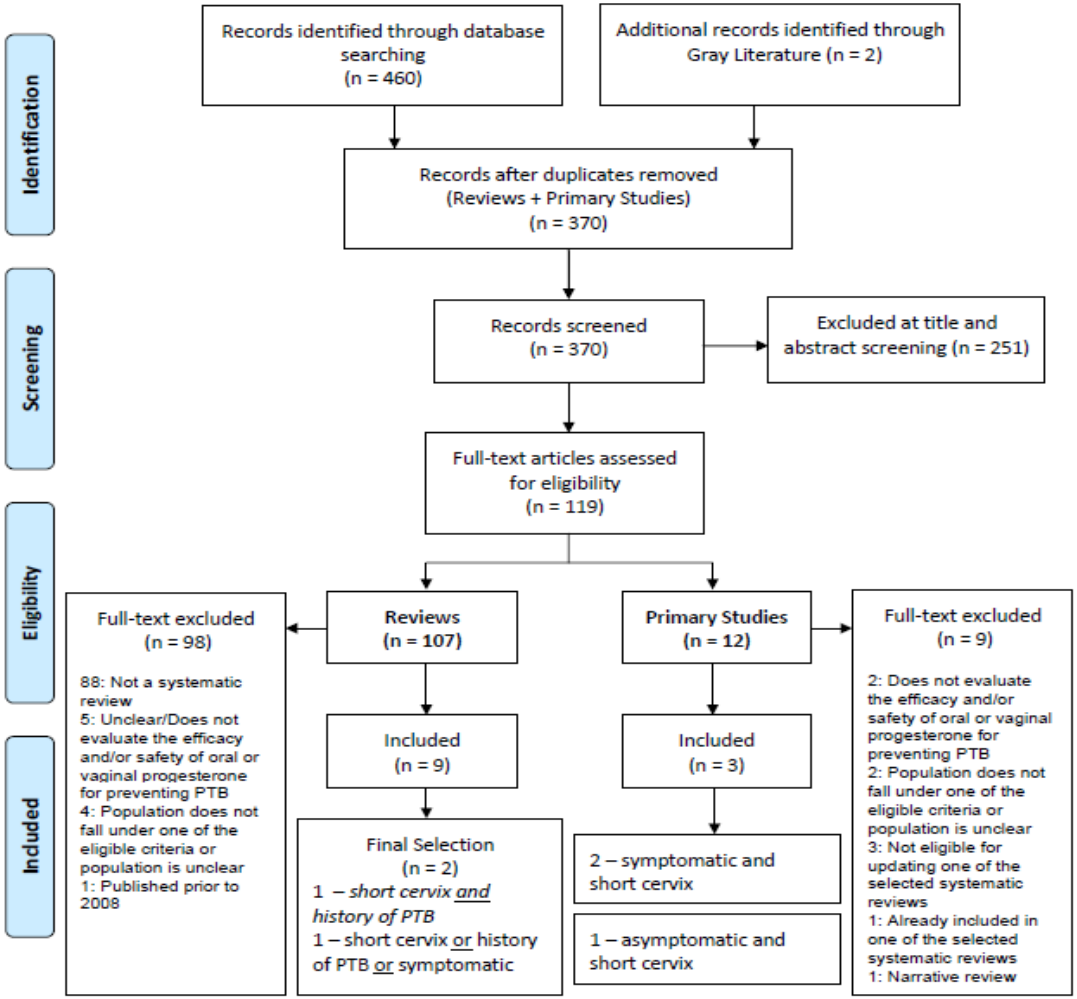
Three primary studies were included for updating the review by Dodd et al.[36-38] No relevant primary studies were identified for updating the review by Conde-Agudelo et al. The PRISMA diagram providing further detail on the identified records is presented in Figure 4.

Critical appraisal of systematic reviews is summarized in Table 16. For randomized controlled trials, critical appraisal is reported in the last column of the evidence tables.

Table 16 – Progesterone: critical appraisal SR

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	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
Conde-Agudelo, 2013[39]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Dodd, 2013[40]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No

Figure 4 – PRISMA diagram secondary prevention: progesterone



4.3.2. Cerclage

For the research question on cerclage, 248 bibliographic records were identified (MEDLINE=62, EMBASE=74, Cochrane Library=38, and Grey Literature= 4), Additionally, we also brought in 70 records that were tagged relevant for this question from searches already undertaken for other key questions. After de-duplicating and consideration of companions, 188 records remained for title/abstract screening. Of these, 62 (44 reviews, and 18 primary studies) met the eligibility criteria based on title and abstract, and 5 (5 systematic reviews, and 0 primary studies) based on full-text. Of the 5 included systematic reviews, 2 were eventually selected for updating based on quality and publication year:

- One systematic review (Alfirevic et al. 2012) on **Cerclage** versus **no cerclage** or **any alternative preventative** treatment (e.g. progesterone) in women considered to be at 'high risk' for pregnancy loss based on history (e.g. previous preterm birth), finding of a short cervix on ultrasound scan, or physical exam-detected cervical changes[10]
- One systematic review (Conde-Agudelo et al. 2013) on **Cerclage** versus **no cerclage**, and **cerclage** versus **progesterone** (indirect comparison) in asymptomatic women with short cervix and past history of preterm birth[18] with a companion paper[19]

No primary study met eligibility criteria to update either of the two selected systematic reviews. The PRISMA diagram providing further detail on the identified records is presented in Figure 5.

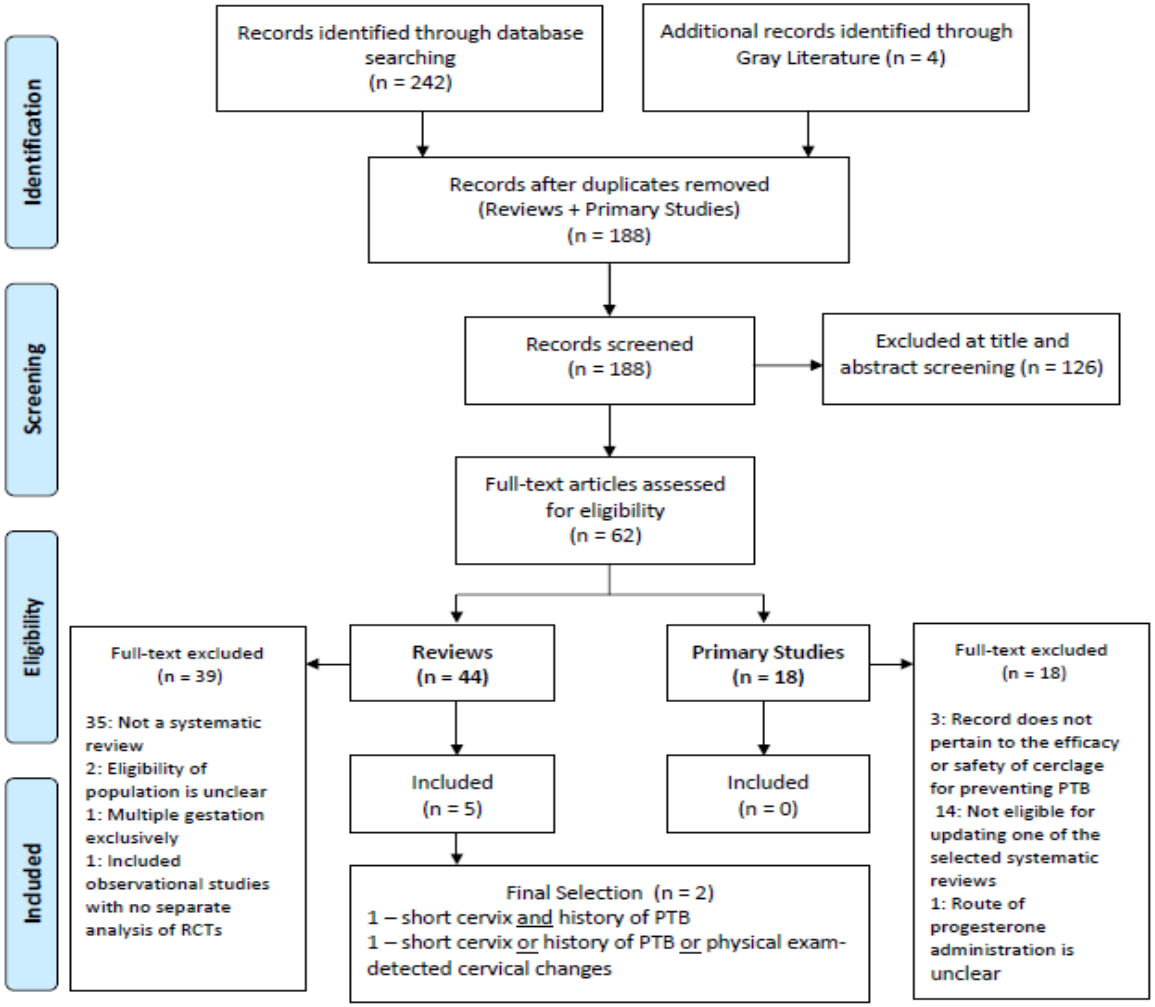
Also, we could not identify any evidence for progesterone (KQ3) and cerclage (KQ4) addressing the subpopulation of pregnancies with advance cervical changes (i.e. cervical dilatation with membranes showing).

Critical appraisal of the systematic reviews is reported in Table 17.

Table 17 – cerclage: critical appraisal SR

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	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
Alfirevic, 2012[41]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Conde-Agudelo, 2013[42]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No

Figure 5 – PRISMA diagram secondary prevention: cerclage



4.4. Tertiary prevention

4.4.1. Repeated doses of prenatal corticosteroids

A recent systematic review of the Cochrane collaboration served as the basis for the evidence review on the comparison of repeated doses corticosteroids versus a single dose.

The SR was judged to of high quality (see Table 18).

Table 18 – repeated doses of prenatal corticosteroids: critical appraisal SR

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	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
Crowther 2012[43]	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**no**

A search for RCTs published since the search date of the review was performed in Mediline, pre-medline and embase.

A total of 369 citations were identified (Medline and pre-medline=80, EMBASE=289). After deduplication, a total of 321 citations were screened based on title and abstract, 27 were retained for full text selection.

Reference	Reason fro exclusion
Ali Khan A, Rodriguez A, Kaakinen M, Pouta A, Hartikainen AL, Jarvelin MR. Does in utero exposure to synthetic glucocorticoids influence birthweight, head circumference and birth length? A systematic review of current evidence in humans. Paediatr. Perinat. Epidemiol. 2011;25(1):20-36.	No comparison of single versus multiple doses, SR of observational studies, no RCTs included
Asztalos EV, Murphy KE, Willan AR, Matthews SG, Ohlsson A, Saigal S, et al. Multiple courses of antenatal corticosteroids for preterm birth study: outcomes in children at 5 years of age (MACS-5). Jama, Pediatr. 2013;167(12):1102-10.	No RCT
Battin M, Bevan C, Harding J. Growth in the neonatal period after repeat courses of antenatal corticosteroids: data from the ACTORDS randomised trial. Arch Dis Child Fetal Neonatal Ed. 2012;97(2):F99-105.	No outcomes of interest reported
Been JV, Degraeuwe PL, Kramer BW, Zimmermann LJI. Antenatal steroids and neonatal outcome after chorioamnionitis: A meta-analysis. BJOG Int. J. Obstet. Gynaecol. 2011;118(2):113-22.	SR, only observational studies included, No comparison of single versus multiple doses

Bennet L, Davidson JO, Koome M, Gunn AJ. Glucocorticoids and preterm hypoxic-ischemic brain injury: the good and the bad. Journal of Pregnancy. 2012;751694.	Narrative review
Bontis N, Vavilis D, Tsolakidis D, Goulis DG, Tzevelekis P, Kellartzis D, et al. Comparison of single versus multiple courses of antenatal betamethasone in patients with threatened preterm labor. Clin. Exp. Obstet. Gynecol. 2011;38(2):165-7.	Prospective, non-randomized trial
Brownfoot FC, Gagliardi DI, Bain E, Middleton P, Crowther CA. Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2013;8:CD006764.	No comparison of single versus multiple doses
Carlo WA, McDonald SA, Fanaroff AA, Vohr BR, Stoll BJ, Ehrenkranz RA, et al. Association of antenatal corticosteroids with mortality and neurodevelopmental outcomes among infants born at 22 to 25 weeks' gestation. J. Am. Med. Assoc. 2011;306(21):2348-58.	Cohort study, No comparison of single versus multiple doses
Contopoulos-Ioannidis DG, Ioannidis JPA. Claims for improved survival from systemic corticosteroids in diverse conditions: An umbrella review. Eur. J. Clin. Invest. 2012;42(3):233-44.	No SR (step-wise approach), no critical appraisal, no comparison of single versus multiple doses
Crowther CA, Doyle LW, Anderson P, Harding JE, Haslam RR, Hiller JE, et al. Repeat dose(S) of prenatal corticosteroids for women at risk of preterm birth: Early school-age outcomes (6 TO 8 YEARS') for children in the actords trial. J. Paediatr. Child Health. 2011;47:52-3.	Abstract only, no data available (“outcomes by treatment group will be available for presentation”)
Crowther CA, Harding JE, Middleton PF, Andersen CC, Ashwood P, Robinson JS, et al. Australasian randomised trial to evaluate the role of maternal intramuscular dexamethasone versus betamethasone prior to preterm birth to increase survival free of childhood neurosensory disability (A*STEROID): study protocol. BMC Pregnancy & Childbirth. 2013;13(104).	Study protocol only, no results reported
Crowther CA, McKinlay CJ, Middleton P, Harding JE. Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes. Cochrane Database Syst Rev. 2011(6):CD003935.	Already included
Harrold J, Ali S, Oleszczuk M, Lacaze-Masmonteil T, Hartling L. Corticosteroids for the prevention of bronchopulmonary dysplasia in preterm infants: An overview of Cochrane reviews. Evid. Based Child Health. 2013;8(6):2063-75.	No systematic review
Kazem M, Hutcheon JA, Joseph KS. A population-based study of antenatal corticosteroid prophylaxis for preterm birth. J Obstet Gynaecol Can. 2012;34(9):842-8.	No RCT, retrospective study
Malloy MH. Antenatal steroid use and neonatal outcome: United States 2007. J Perinatol. 2012;32(9):722-7.	No RCT, retrospective study

McKinlay CJD, Crowther CA, Middleton P, Harding JE. Repeat antenatal glucocorticoids for women at risk of preterm birth: A Cochrane Systematic Review. Am. J. Obstet. Gynecol. 2012;206(3):187-94.	"This review is an abridged version of a Cochrane Review previously published in the Cochrane Database of Systematic Reviews 2011, Issue 6, doi:10.1002/14651858.CD003935.pub3"
McKinlay CJD, Cutfield WS, Battin MR, Dalziel SR, Crowther CA, Harding JE. Repeat antenatal betamethasone does not affect bone mass at early school-age: A randomised controlled trial (actords). J. Paediatr. Child Health. 2013;49:49.	No outcome of interest reported (but summarized as additional information)
McKinlay CJD, Harding JE, Ashwood PJ, Dalziel SR, Doyle LW, Haslam RR, et al. Effect of repeat antenatal betamethasone on childhood lung function: A randomised controlled trial (actords). J. Paediatr. Child Health. 2013;49:92-3.	No outcome of interest reported (but summarized as additional information)
Morris RK, Oliver EA, Malin G, Khan KS, Meads C. Effectiveness of interventions for the prevention of small-for-gestational age fetuses and perinatal mortality: a review of systematic reviews. Acta Obstet Gynecol Scand. 2013;92(2):143-51.	Review of reviews. No SR comparing single versus multiple doses included
Murphy K, Willan A, Hannah M, Ohlsson A, Kelly E, Matthews S, et al. Do antenatal corticosteroids reduce fetal growth or gestational age at birth? A secondary analysis from the multiple courses of antenatal corticosteroids for preterm birth study (MACS). Am. J. Obstet. Gynecol. 2012;206(1):S226.	Abstract only, no report on important outcome (see Obstet. Gynecol. 2012;119(5):917-23)
Murphy KE, Hannah ME, Willan AR, Ohlsson A, Kelly EN, Matthews SG, et al. Maternal side-effects after multiple courses of antenatal corticosteroids (MACS): the three-month follow-up of women in the randomized controlled trial of MACS for preterm birth study. J Obstet Gynaecol Can. 2011;33(9):909-21.	Secondary publication of trial already included in Cochrane review
Murphy KE, Willan AR, Hannah ME, Ohlsson A, Kelly EN, Matthews SG, et al. Effect of antenatal corticosteroids on fetal growth and gestational age at birth. Obstet. Gynecol. 2012;119(5):917-23.	Secondary publication of trial already included in Cochrane review
Nixon PA, Washburn LK, Mudd LM, Webb HH, O'Shea TM. Aerobic fitness and physical activity levels of children born prematurely following randomization to postnatal dexamethasone. J Pediatr. 2011;158(1):65-70.	Postnatal steroids
Onland W, de Laat MW, Mol BW, Offringa M. Effects of antenatal corticosteroids given prior to 26 weeks' gestation: a systematic review of randomized controlled trials. Am J Perinatol. 2011;28(1):33-44.	No comparison single dose versus multiple doses
Peltoniemi OM, Kari MA, Hallman M. Repeated antenatal corticosteroid treatment: a systematic review and meta-analysis. Acta Obstet Gynecol Scand. 2011;90(7):719-27.	included
Porto AMF, Coutinho IC, Correia JB, Amorim MMR. Effectiveness of antenatal corticosteroids in reducing respiratory disorders in late preterm infants: Randomised clinical trial. Bmj. 2011;342(7802).	No comparison single dose versus multiple doses

Romejko-Wolniewicz E, Oleszczuk L, Zareba-Szczudlik J, Czajkowski K. Dosage regimen of antenatal steroids prior to preterm delivery and effects on maternal and neonatal outcomes. J Matern Fetal Neonatal Med. 2013;26(3):237-41.	Two single dose regimens are compared

4.4.2. Maintenance therapy

A total of 941 bibliographic records were identified (MEDLINE=172, EMBASE=330, Cochrane Library=166, Grey Literature= 10, reviewer nomination=1). Additionally, we also brought in 262 records previously flagged relevant for this question from searches undertaken for other key questions (Key Question, 3, and 6). After de-duplicating and consideration of companion articles, 727 records formed the full screening set. At the titles and abstract screen, 71 (49 reviews, and 22 primary studies) records passed to full text review (Figure 6). Of these, 10 records (6 systematic reviews and 4 primary studies) were finally included. Outside of our systematic search and screening of the literature, one systematic review published in October 2013 pertained to maternal harms of magnesium sulphate in a wider pregnant patient population (eclampsia, neuroprotection, tocolysis) was nominated for inclusion to address KQ6.[11] Of note, on AMSTAR this review was rated as of moderate quality, but in reviewers' judgment it was a very comprehensive evaluation of maternal harms of magnesium sulphate with no obvious validity concerns. Following quality assessment of the included systematic reviews, 4 reviews addressing unique maintenance tocolytic drugs (or classes) were selected. We assessed one of the selected reviews to be current because of it's 2013 search date and did not consider it in need of updating,[12] so updated 3 systematic reviews:

- Conde-Agudelo et al., 2011 investigated **nifedipine** maintenance therapy versus placebo/no treatment in patients with preterm labour[13]
- Dodd et al., 2012 compared **oral betamimetics maintenance** therapy with placebo/no treatment, in women with arrested preterm labour[14]
- Papatsonis et al., 2009 evaluated **oxytocin antagonist maintenance** therapy versus placbo in women after threatened preterm labour[15]
- Han et al.'s, 2013 systematic review tested **magnesium maintenance** therapy versus placebo/ no treatment for preventing preterm birth after threatened preterm labour[12]

Four primary studies were included for updating the review by Conde-Agudelo et al.[16-19] No relevant primary studies were identified for updating the reviews by Dodd et al., Papatsonis et al., and Han et al. The PRISMA diagram providing further detail on the identified records for Key Question 5 is presented in Figure 6.

No systematic review addressing the efficacy and safety of **antenatal corticosteroids + tocolysis > 48** hours compared with antenatal steroids + 48 hours tocolysis in women with < and> 32 weeks of gestation) could be located.

Critical appraisal of the systematic reviews is reported in Table 19.

Figure 6 – PRISMA diagram duration of tocolytic therapy

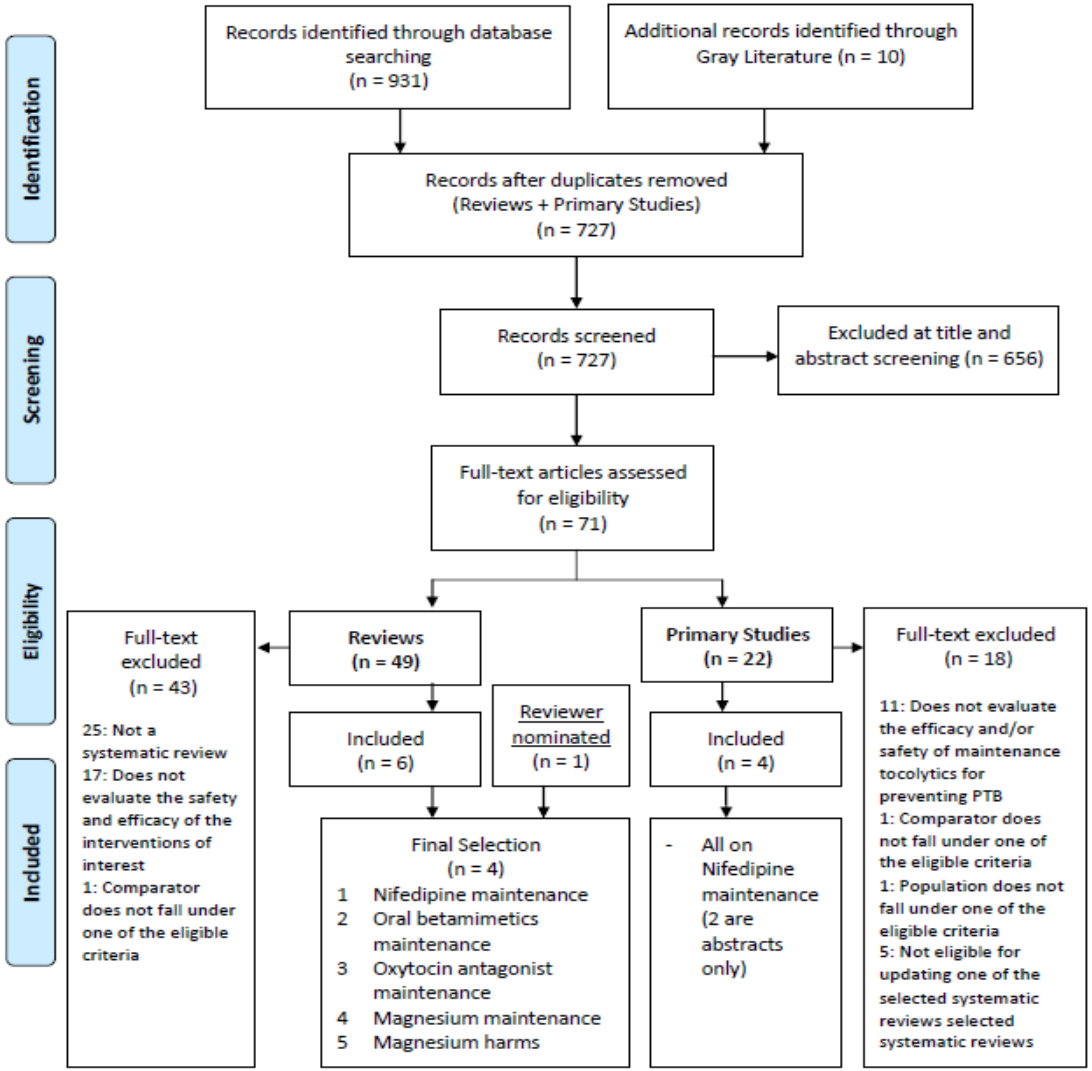


Table 19 – maintenance therapy: critical appraisal SRs

Systematic review	A priori study design	Duplicate study selection and data extraction	Comprehensive literature search	Publication status not used as inclusion (grey literature)	List of in- and excluded studies	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
Han 2013[44]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Dodd 2012[45]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes
Conde Agudelo 2011[46]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes
Papatsonis 2009[47]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes

4.4.3. Neuroprotection magnesium sulphate

A total of 335 bibliographic records were identified (MEDLINE=80, EMBASE=158, Cochrane Library=71, Grey Literature= 9, and reviewer nomination= 1). Additionally, we also brought in 16 records previously flagged relevant for this question from searches undertaken for other key questions (Key Questions 1, 2, 3 and 4). After de-duplicating and consideration of companions, 276 records were available for title/abstract screening, with 34 records (19 reviews, and 15 primary studies) passing to full text screen (Figure 7). Finally 6 unique records (4 systematic reviews, and 2 primary studies) were included. Following quality assessment of the included systematic reviews, 1 most recent and high quality systematic review was selected for updating:

Conde-Agudelo et al., 2009 compared magnesium sulphate versus placebo or **no magnesium sulphate** for women at risk of preterm birth before 34 weeks of gestation to prevent cerebral palsy in the newborn.[20]

Also, the aforementioned reviewer nominated systematic review pertaining to maternal harms of magnesium sulphate was also considered relevant for KQ6:

Bain et al., 2013 investigated maternal adverse effects of different **antenatal magnesium sulphate regimens** for improving maternal and infant outcomes.[11] For the purpose of this project we restricted to the review evidence against placebo/ no treatment comparator.

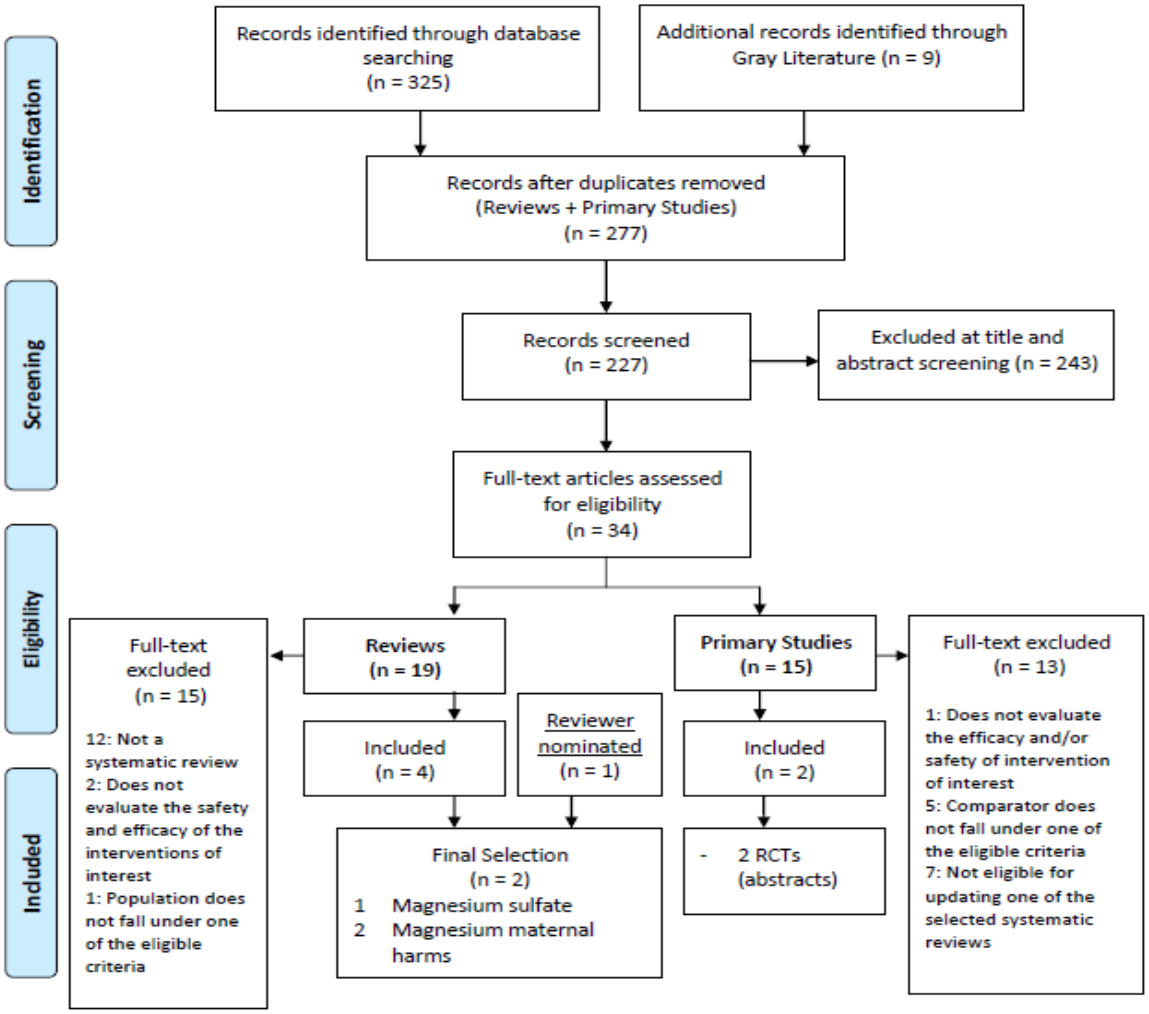
Although, two new primary studies met eligibility criteria for updating Conde-Agudelo et al's., 2009 systematic review, they could not contribute to original meta-analyses because as secondary analyses of RCTs we could not ensure that data were not being double counted. Also, one of the studies did not report usable data.

Critical appraisal of the systematic review is reported in Table 20.

Table 20 – magnesium sulphate for neuroprotection: critical appraisal SR

Systematic review	A priori study design	Duplicate study selection and data extraction	Comprehensive literature search	Publication status not used as inclusion (grey literature)	List of in- and excluded studies	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
Conde Agudelo 2009[48]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes

Figure 7 – PRISMA diagram magnesium sulphate



5. EVIDENCE TABLES

5.1. Identification of women at risk

5.1.1. Fetal fibronectin (fFN) test

Table 21 – Evidence table: SR clinical effectiveness fetal fibronectin test

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome[a]	Results secondary and other outcome(s)[b]	Critical appraisal
Berghella, 2008[9]	**Design:** SR and MA **Sources of funding:** Cochrane review **Search date:** 1966 - Dec. 2007 **Searched databases:** Cochrane Pregnancy and Childbirth Group's Trials Register[c] **Included study designs:** RCT and quasi-RCT	**Eligibility criteria:** Pregnant women between GA of 22-34 weeks screened with fFN for risk of preterm birth. **Patients characteristics** All included studies were in symptomatic PTL populations – analysis based on singletons **(Planned subgroup analyses relevant to the key question):** - Singleton vs. multiple gestations	**Intervention:** Interventions based on knowledge of fFN results[d] **Comparator:** Interventions based on no knowledge of fFN results	**Effect size primary outcome:** ***Preterm birth < 37 weeks*** Knowledge vs. No Knowledge: RR = 0.54 (95% CI: 0.34, 0.87) (N=3 studies)	**Effect size secondary outcomes:** ***(i) Preterm birth < 34 weeks*** Knowledge vs. No Knowledge: RR = 1.01 (95% CI: 0.41, 2.47) (N=3 studies) ***(ii) Preterm birth < 32 weeks*** RR = 0.85 (95% CI: 0.28, 2.58) (N=3 studies) ***(iii) Preterm birth < 28 weeks*** RR = 1.0 (95% CI: 0.15, 6.82) (N=3 studies)	**AMSTAR Score:** 8

[a] Only those outcomes that have been pre-specified in *Phase 1 Protocol: Key Questions 1 & 2* are reported here.

[b] Only those outcomes that have been pre-specified in *Phase 1 Protocol: Key Questions 1 & 2* are reported here.

[c] The Cochrane Pregnancy and Childbirth Group's Trials Register contains trials from the Cochrane Register of Controlled Trials (CENTRAL), MEDLINE, hand searches of 30 journals and proceedings of major conferences, and weekly current awareness alerts for a further 44 journals.

[d] One included study used knowledge of both fFN and transvaginal ultrasound cervical length to guide interventions.

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome[a]	Results secondary and other outcome(s)[b]	Critical appraisal
	Number of included studies: 5 RCTs	- Timing of availability of results - Gestational age at collection of test results (22-23, 24-28, >28 weeks) **Median FU:** NR				

Abbreviations: CI = confidence interval; fFN = fetal fibronectin; FU = follow-up; GA = gestational age; MA = meta-analysis; NR = not reported; RCT = randomized controlled trial; RR = risk ratio; SR = systematic review

Table 22 – Evidence table: RCTs clinical effectiveness fetal fibronectin test

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal
Lee 2013[11]	**Design**: RCT **Sources of funding:** NR **Setting:** Harbor-UCLA Medical Center **Sample size:** 76	**Eligibility criteria:** singleton pregnancy; GA between 24w0d and 33w6d; symptoms suggesting PTL; willingness	**Intervention**[e]**:** Management based on fFN results in addition to cervical exams[f] **Comparator:** Management based on cervical exams only	**Effect size primary outcome:** Time for triage – NA for updating	**Effect size secondary outcome :** ***(i) Preterm birth <37 weeks*** fFN vs. Comparator: 17.1% vs 13.8%; p=0.72 ***(ii) Preterm birth <34 weeks*** fFN vs. Comparator: 7.3% vs 0%; p=0.14	**Dropouts** NR[g] **RoB:** *RSG* – Unclear *AC*-Unclear *Blinding (subjects/ personnel)*-High

[e] Hospital care for PTL included administration of betamethasone and tocolysis with nifedipine. If PTL ceased, the patient was discharged home with instructions for bed rest, limited ambulation for one week, and warning signs for recurrent PTL.

[f] In uncertain cases, a transvaginal ultrasound for cervical length was used to guide management.

[g] Both groups had missing delivery date (3 in fFN group and 3 in comparator group).

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal
	Duration: September 2006 and December 2010	to continue follow-up and contact with the study team; gave permission to obtain medical records for results of a subsequent delivery occurring at an outside hospital; >18 years of age **Exclusion criteria:** advanced cervical dilation (> 3 cm); cerclage *in-situ*; preterm PROM; vaginal bleeding; multi-fetal pregnancy; sexual intercourse, a cervical exam or a TVU within the last 24 hours; already had fFN sampling within prior 2 weeks; received tocolytic drugs or antenatal steroids to prevent RDS during pregnancy; suspicion for placental abruption or known placenta previa; chronic medical conditions which				*Blinding (OA)*-Low *IOD*-Low *SR*-Low *Other*-Unclear

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal
		preclude the use of beta-mimetics, CCBs, or corticosteroids; unable to give informed consent **Patients characteristics:** Pooled age (SD): 27.4 (7.2) years GA (SD) at enrolment: 30.3 (2.8) weeks Nulliparous: 38.2% Majority Hispanic Prior PTD: 27.6% **Median FU:** NR				
Dutta 2011[12]	**Design:** RCT (Pilot study) **Sources of funding**: Greater Glasgow Health Board North Glasgow Hospitals University Operating Division **Setting:** Two large maternity units in the west of Scotland	**Eligibility criteria:** gestation between 24 + 0 and 34 + 6 weeks; primary reason for presentation to hospital being uterine activity	**Intervention:** PTL management with fFN testing **Comparator:** PTL management without fFN testing	**Effect size primary outcome:** Inpatient hospital admission with suspected PTL – NA for updating Gestational age at delivery – NA for updating Incidence of neonatal RDS – NA for updating	**Effect size secondary outcome:** Duration of hospital admission before delivery – NA for updating Length of stay or to delivery – NA for updating Incidence of steroid use between 48h and 7 days – NA for updating	**Dropouts** NR[h] **RoB** *RSG* –Unclear *AC*-Low *Blinding (subjects/ personnel)*-High *Blinding (OA)*-Low

[h] There were missing values.

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal
	Sample size: 88 **Duration:** December 2007 to March 2009	**Exclusion criteria:** vaginal bleeding; membrane rupture; multiple pregnancies; history of recent intercourse; recent digital examination of the cervix in the last 24 hours; cervical dilation ≥ 3 cm **Patients characteristics:** Pooled age (SD): 27.3 (5.6) years 100% Caucasian GA (SD): 30.8 (2.9) weeks **Median FU:** NR			Incidence of tocolysis – NA for updating	*IOD*-Unclear *SR*-Unclear *Other*-Unclear
Burwick 2011[3]	**Design:** RCT **Sources of funding:** none **Setting:** Harbor-UCLA Medical Center. **Sample size:** 52 **Duration:** NR	**Eligibility criteria:** Symptomatic women between 24 and 34 weeks gestation; uterine contractions; cervical dilation < 3 cm; intact membranes; singleton gestation **Exclusion Criteria:** recent intercourse; vaginal bleeding; cervical cerclage	**Intervention:** Cervilenz-measured CL **Comparator:** fFN testing	**Effect size primary outcome:** No usable data presented	**Effect size secondary outcome:** No usable data presented	**Dropouts** NR **RoB** *RSG* –Unclear *AC*-Unclear *Blinding (subjects/ personnel)*-High *Blinding (OA)*-Low

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal
		Patients characteristics: Age (SD): 27.9 (7.3) years GA Entry (SD): 30.4 (2.8) weeks Nulliparous: 38.5% Prior PTD: 28.9% Majority Hispanic **Median FU:** NR				*IOD*-Unclear *SR*-Low *Other*-Unclear
Osorio 2010[1] (Abstract)	**Design:** RCT **Sources of funding:** NR **Setting:** Centro Hospitalar de Vila Nova de Gaia, Portugal **Sample size:** 66 **Duration:** April 2007 and December 2009	**Eligibility criteria:** GA between 24 and 34 weeks 6 days **Patients characteristics:** NR **Median FU:** NR	**Intervention:** Knowledge of fFN test results **Comparator:** No fFN testing	**Effect size (unclear if primary or secondary outcomes)** Hospital admissions – NA for updating Length of stay – NA for updating	**Effect size secondary outcome:** none	**Dropouts** NR **RoB** *RSG* –Unclear *AC*-Unclear *Blinding (subjects/ personnel)*-High *Blinding (OA)*-Low *IOD*-Unclear *SR*-Unclear *Other*-Unclear

Abbreviations: *AC = allocation concealment; CCB = calcium channel blocker; CL = cervical length; FU = follow-up; GA = gestational age; IOD = incomplete outcome data; NA = not applicable; NR = not reported; OA = outcome assessment; PROM = premature rupture of membranes; PTD = preterm delivery; PTL = preterm labour; RCT = randomized controlled trial; RDS = respiratory distress syndrome; RoB = risk of bias; RSG = random sequence generation; SD = standard deviation; SR = selective reporting; TVU = transvaginal ultrasound*

Table 23 – Evidence table: SR test performance fetal fibronectin test

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Sanchez-Ramos 2009[10]	**Design**: SR and MA **Sources of funding:** NR **Search date:** 1966-April 2008 **Searched databases:** MEDLINE, EMBASE, Current Contents, Index Medicus, Silver Platter, and the Cochrane Library **Included study designs:** Cohort **Number of included studies:** 32	**Eligibility criteria:** signs and symptoms of PTL; underwent fFN testing before 37 weeks of gestation; described the assay employed; had known gestational ages after spontaneous labour and delivery; used PTD within 7 days of testing as the reference standard. **Patient characteristics:**	**Index test:** fFN **Reference standard:** PTD	**PTD prediction within 7 days of testing:** *Pooled estimates using bivariate random effect model:* • **Sensitivity:** 0.76 (95% CI 0.69- 0.82) • **Specificity:** 0.82 (95% CI 0.79- 0.84) • **LR+:** 4.20 (95% CI 3.5-5.0) • **LR-:** 0.29 (95% CI 0.22-0.38) **Diagnostic Odds Ratio:** 14.4 (95% CI 9.7- 21.3) **Note:** Data is also presented based on high versus low quality studies **ROC curve:** presented **Meta regression:** conducted	**Effect size secondary outcome** The authors performed a meta-analysis of these four studies using the 48-hour outcome and found that fFN was even less accurate than when using the 7-day outcome (results not shown)	**AMSTAR** 9

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
		All symptomatic women: singleton pregnancies in 17 of the included studies, multifetal pregnancies in 5 of the studies, and not known if multifetal were included in 10 of the studies ***(updating is based on the set of singleton studies and unknown multifetal studies only)***				

Abbreviations: *MA = meta-analysis; NR = not reported; PTD = preterm delivery; PTL = preterm labour; SR = systematic review*

Table 24 – Evidence table: primary studies test performance fetal fibronectin test

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal
Van Baaren (2013)[19] **(Abstract)**	**Design:** Cohort **Sources of funding:** NR **Setting:** 10 perinatal centres in the Netherlands **Sample size:** 559	**Eligibility criteria:** Women with threatened labour between 24-34 weeks GA and with intact membrane **Exclusion criteria:** NR	**Index test:** fFN (cut-off value not indicated) **Reference standard:** PTD within 7 days of inclusion	• **Sensitivity:** 76% (95% CI: 66, 83) • **Specificity:** 58% (95% CI: 54, 62) • **LR+:** NR • **LR-:** NR	**Excluded from Analysis:** 101 **RoB:** Unclear **Applicability Concern:** Low

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal
	Duration: December 2009-May 2012	**Patients characteristics:** NR **Prevalence of disease:** 15.5% (PTD within 7 days of inclusion)			
Cooper (2012)[13]	**Design:** Cohort (prospective) **Sources of funding:** NR **Setting:** Foothills Medical Centre or Peter Lougheed Centre labour, Calgary **Sample size:** 288 **Duration:** October 2005-May 2009	**Eligibility criteria:** Suspected labour between 24 – 34 weeks GA **Exclusion criteria:** Ruptured membranes; antepartum hemorrhage; active labour; suspected chorioamnionitis **Patients characteristics:** *Age (SD):* 29 (5) years *Nulliparous:* 43.3% *Previous PTD:* 16.1% *Singleton:* 93.7% *GA range at visit:* 24-34 weeks **Prevalence of disease:** 2.1% (PTD within 7 days of testing)	**Index test:** fFN (cut-off 50 ng/mL) **Reference standard:** PTD within 7 days of testing	• **Sensitivity:** 33% (95% CI: 0, 71) • **Specificity:** 91% (95% CI: 87, 94) • **LR+:** 3.62 (95% CI: 1.10, 11.88) • **LR-:** 0.73 (95% CI: 0.42, 1.29)	**Excluded from Analysis:** 61 **RoB:** Unclear **Applicability Concern:** Low
Lee (2012)[14]	**Design:** Cohort (retrospective)	**Eligibility criteria:**	**Index test:** fFN (cut-off value not indicated) **Reference standard:** PTD	• **Sensitivity:** 66.7% (95% CI: 41.7, 84.8)	**Excluded from Analysis:** 6[i]

[i] Lost to follow-up and delivery outcome not available

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal
	Sources of funding: Not-for-Profit **Setting:** Seoul National University Hospital **Sample size:** 64 **Duration:** April 2005-November 2010	PTL < 35 weeks of gestation; no evidence of ROM; singleton; Amnisure ROM test performed within 72 h of amniocentesis **Exclusion criteria:** PTL and clinical ROM **Patients characteristics:** NR for fFN population **Prevalence of disease:** 23.4% (PTD < 7 days of testing)	< 7 days of testing	• **Specificity:** 62.5% (95% CI: 48.5, 74.6) • **LR+:** 3.18 • **LR-:** 0.31	**RoB:** High **Applicability Concern:** Low
Thandayathany (2012)[20] (Abstract)	**Design:** Cohort **Sources of funding:** NR **Setting:** NR **Sample size:** 174 **Duration:** NR	**Eligibility criteria:** Between 24-34 weeks GA with documented contractions on cardiotocography **Exclusion criteria:** NR **Patients characteristics:** NR **Prevalence of disease:** NR	**Index test:** fFN (cut-off value not indicated) **Reference standard:** Delivery within 7 days of testing	No usable data for meta-analysis	**Excluded from Analysis:** NR **RoB and Applicability:** Not assessed
Riboni (2011)[15]	**Design:** Cohort (prospective)	**Eligibility criteria:**	**Index test:** fFN (cut-off 50 ng/mL)	• **Sensitivity:** 50% (95% CI: 22, 78)	**Excluded from Analysis:** NR

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal
	Sources of funding: NR **Setting:** Departments of obstetrics in Padua and Milan **Sample size:** 210 **Duration:** January 2006-December 2006	Symptomatic (documented uterine contractions); 24-34 weeks GA; singleton; intact membranes **Exclusion criteria:** >2 cm dilatation of the cervix; undergone cervical examination or sexual intercourse <24 h previously; vaginal bleeding; placenta previa; multiple gestations; fetal abnormalities; uterine anomalies **Patients characteristics:** *Mean GA at sampling;* 28.7 weeks *Ethnicity:* Caucasian **Prevalence of disease:** 3.8% (PTD within 7 days of admission)	**Reference standard:** PTD within 7 days of admission	• **Specificity:** 80.2% (95% CI: 75, 86) • **LR+:** NR • **LR-:** NR	**RoB:** Unclear **Applicability Concern:** Low
Yoneda (2011)[16]	**Design:** Cohort (prospective) **Sources of funding:** NR **Setting:** Toyama University Hospital, Japan	**Eligibility criteria:** PTL; intact membranes; singleton **Exclusion criteria:** multiple gestation; IUGR; fetal anomalies; preeclampsia; GDM; neonatal hypoxic-ischemic encephalopathy	**Index test:** fFN (cut-off 90 ng/mL) **Reference standard:** PTD within 3 days	No useable data for meta-analysis	**Excluded from Analysis:** NR **RoB and Applicability**: Not assessed

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal
	Sample size: 126 **Duration:** January 2001-December 2009	**Patients characteristics:** NR **Prevalence of disease:** NR (PTD within 7 days)			
Henrich (2010)[22] (Abstract)	**Design:** Cohort **Sources of funding:** NR **Setting:** NR **Sample size:** 125 **Duration:** NR	**Eligibility criteria:** Singleton pregnancies and regular uterine contractions between 23+0 and 33+6 weeks GA **Exclusion criteria:** NR **Patients characteristics:** NR **Prevalence of disease:** NR (PTD within 7 days of testing)	**Index test:** fFN (cut-off value not indicated) **Reference standard:** PTD within 7 days of testing	No useable data for meta-analysis	**Excluded from Analysis:** NR **RoB and Applicability**: Not assessed
Rose (2010)[17]	**Design:** Cohort (prospective) **Sources of funding:** NR **Setting:** Mayo Clinic, United States	**Eligibility criteria:** Symptoms of PTL; **Exclusion criteria:** NR **Patients characteristics:** NR **Prevalence of disease:** 0.7% (PTD within 7 days of testing)???	**Index test:** fFN (cut-off not reported) **Reference standard:** PTD within 7 days of admission	**Sensitivity:** 25% (95% CI: 2.7, 80) • **Specificity:** 96% (95% CI: 92, 98) • **LR+:** 6.41 (95% CI: 0.51, 80.97) • **LR-:** 0.78 (95% CI: 0.35, 1.74)	**Excluded from analysis:** 60 **RoB:** High **Applicability Concern:** Unclear

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal
	Sample size: Initial sample of 201 – 141 analyzed without protocol violations **Duration:** December 2007-November 2008				
Sümer (2010)[21] (English Abstract)	**Design:** Cohort (prospective) **Sources of funding:** NR **Setting:** Etlik Zubeyde Hanim Women's Hospital Ankara **Sample size:** 67 **Duration:** NR	**Eligibility criteria:** Singleton pregnancies presenting at 26- 36 weeks GA with intact membranes and threatened labour **Exclusion criteria:** NR **Patients characteristics:** NR **Prevalence of disease:** 7.4% (PTD within 7 days of presentation)	**Index test:** fFN (cut-off value not indicated) **Reference standard:** PTD within 7 days of presentation	• **Sensitivity:** 20% (95% CI: 4, 62) • **Specificity:** 88.7% (95% CI: 78, 94) • **LR+:** 1.62 • **LR-:** 0.9	**Excluded from Analysis:** NR **RoB:** Unclear **Applicability Concern:** Unclear
Díaz (2009)[18]	**Design:** Cohort (prospective) **Sources of funding:** For-Profit	**Eligibility criteria:** Live normal singleton pregnancy; intact membranes; between 24-36 weeks 6 days GA; threatened PTL	**Index test:** fFN (cut-off 50 ng/mL) **Reference standard:** PTD ≤ 7 days of testing	• **Sensitivity:** 75% (95% CI: 52.9, 89.4) • **Specificity:** 78 (95% CI: 70.7, 84.2) • **LR+:** NR	**Excluded from Analysis**: NR **RoB:** High **Applicability Concern:** Low

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal
	Setting: Antenatal high risk pregnancy unit of Enrique C. Sotomayor Hospital Guayaquil, Ecuador **Sample size:** 180 **Duration:** January 2006-January 2007	**Exclusion criteria:** Ruptured membranes; acute fetal distress; abnormal trans-vaginal bleeding; in labour with ≥ 3 cm dilation; major fetal congenital malformation; multiple gestation; history of cervical cerclage or previous conisation; coitus or digitally examined in another medical facility within 24 h **Patients characteristics:** *Pooled age (SD):* 22.4 (6) years *Pooled GA recruitment:* 33.3 (2.2) weeks *Nulliparous:* 46.7% *Previous PTD:* 16.7% **Prevalence of disease:** 13.3% (PTD ≤ 7 days of testing)		• **LR-:** NR	

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal
Wilms (2009)[23] **Companion**[49]	**Design:** Cohort **Sources of funding:** NR **Setting:** Netherlands **Sample size:** 108 – 101 included in analysis **Duration:** NR	**Eligibility criteria:** symptoms of PTL; GA between 24 and 34 weeks; **Exclusion criteria:** NR **Patients characteristics:** NR **Prevalence of disease:** 12% (PTD within 7 days of inclusion)	**Index test:** fFN (cut-off 50 ng/mL) **Reference standard:** PTD within 7 days of inclusion	• **Sensitivity:** 92% (95% CI: 66.7, 98.6) • **Specificity:** 60.2% (95% CI: 49.8, 69.8) • **LR+:** 2.3 (95% CI: 1.7, 3.1) • **LR-:** 0.13 (95% CI: 0.02, 0.85)	**Excluded from Analysis:** 7 **RoB:** Unclear **Applicability Concern:** Low

Abbreviations: *CI = confidence interval; fFN = fetal fibronectin; GA = gestational age; GDM = gestational diabetes mellitus; IUGR = intrauterine growth restriction; LR = likelihood ratio; NA = not applicable; NR = not reported; PTD = preterm delivery; PTL = preterm labour; RoB = risk of bias; ROM = rupture of membranes; SD = standard deviation*

5.1.2. Actim Partus test

Table 25 – Evidence table: SR test performance Actim Partus test

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Honest 2009[4]	**Design**: SR and MA **Sources of funding:** NIHR **Search date:** Sep 2005 **Searched databases:**	**Eligibility criteria:** Symptomatic singleton women (also asymptomatic women) - ***updating based on symptomatic women only***	**Index test:** Actim Partus **Reference standard:** PTD at <37 weeks, <34 weeks, ≤ 48h, ≤ 24 h, ≤ 7 days of testing	• **Sensitivity** No Pooled estimates • **Specificity** No Pooled estimates • **PPV** No info • **NPV** No info	**Effect size secondary outcome:** NA	**AMSTAR** 8

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	Cochrane Library, the National Research Register (NRR), the HTA database, the National Guideline Clearinghouse, MEDLINE, EMBASE, BIOSIS, MEDION, Pascal, Science Citation Index, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE) and HTA database. **Included study designs:** Systematic Reviews of test accuracy when available.	**Patient characteristics:** Mostly women with threatened PTL		***(i)SPTB within 48 hours of testing:*** • ***LR+*** **=** 2.53 (95%CI 1.17–5.48) • **LR- =** 0.32 (95% CI 0.15–0.66) ***(ii)SPTB within 7 days of testing:*** • ***LR+*** =3.29 (95% CI 2.24 - 4.83) • **LR-** = 0.20 (95% CI 0.10 – 0.41) ***(iii)SPTB <34 weeks:*** ***LR+*** = 2.96 (95% CI 2.02–4.33) **LR**- = 0.22 (95% CI 0.08–0.64) ***(iv)SPTB <37 weeks:*** ***LR+*** = 4.26 (95% CI 2.54–7.17) **LR-** = 0.28 (95% CI 0.20–0.38)		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	Primary test accuracy studies (observational: prospective or retrospective) of defined nonrandomised populations in which the results of the test of interest were compared with the outcomes (reference standard) to generate 2 × 2 tables to compute indices of test accuracy. If unavailable, case-control studies of test accuracy. **Number of included studies:** 11 (for Actim Partus)					

Abbreviations: *LR = likelihood ratio; MA = meta-analysis; NA = not applicable; NIHR = National Institute for Health Research; NPV = negative predictive value; PPV = positive predictive value; PTD = preterm delivery; PTL = preterm labour; SPTB = spontaneous preterm birth; SR = systematic review*

Table 26 – Evidence table: primary studies test performance Actim Partus test

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of review quality
Cooper (2012)[13]	**Design:** Cohort (prospective) **Sources of funding:** NR	**Eligibility criteria:** Suspected labour between 24 – 34 weeks GA **Exclusion criteria:**	**Index test:** Actim Partus (cut-off 10 µg/L) **Reference standard:** PTD within 7 days of testing and < 37 weeks	***PTD within 7 days of testing*** • **Sensitivity:** 33% (95% CI: 0, 71) • **Specificity:** 74% (95% CI: 69, 79) • **LR+:** 1.28 (95% CI: 0.41, 4.04)	**Excluded from Analysis:** 15 **RoB:** Low **Applicability Concern:** Low

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of review quality
	Setting: Foothills Medical Centre or Peter Lougheed Centre labour, Calgary **Sample size:** 349 **Duration:** October 2005-May 2009	Ruptured membranes; antepartum hemorrhage; active labour; suspected chorioamnionitis **Patients characteristics:** *Age (SD):* 29 (5) years *Nulliparous:* 43.3% *Previous PTD:* 16.1% *Singleton:* 93.7% *GA range at visit:* 24-34 weeks **Prevalence of disease:** 1.7% (PTD within 7 days of testing) 16.3% (PTD < 37 weeks gestation)		• **LR-:** 0.90 (95% CI: 0.51, 1.59) ***PTD < 37 weeks*** • **Sensitivity:** 39% (95% CI: 26, 51) • **Specificity:** 76% (95% CI: 72, 81) • **LR+:** 1.63 (95% CI: 1.11, 2.41) • **LR-:** 0.80 (95% CI: 0.65-1.00)	
Laudanski (2012)[24]	**Design:** Cohort **Sources of funding:** Not-for-Profit **Setting:** NR **Sample size:** 74 **Duration:** NR	**Eligibility criteria:** Hospitalized for threatened PTL **Exclusion criteria:** Signs of infection; antibiotic treatment during 3 weeks directly before the inclusion tests; placenta previa; placental abruption; multiple pregnancy; patients in labour in whom the time from rupture of fetal membranes till the first uterine contractions exceeded 2 h; cervical incompetence	**Index test:** Actim Partus (cut-off 158.83 pg/mL) **Reference standard:** PTD < 37 weeks (assumed)	• **Sensitivity:** 60.8% (95% CI 46, 74) • **Specificity:** 60.9% (95% 38, 83) • **LR+:** 1.55 (95% CI: 0.89, 2.71) • **LR-:** 0.64 (95% CI: 0.40, 1.03)	**Excluded from Analysis:** NR **RoB:** High **Applicability Concern:** Low

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of review quality
		Patients characteristics: NR **Prevalence of disease:** 68.9% (PTD < 37 weeks)			
Thandayathany (2012)[20] (Abstract)	**Design:** Cohort **Sources of funding:** NR **Setting:** NR **Sample size:** 174 **Duration:** NR	**Eligibility criteria:** Between 24-34 weeks GA with documented contractions on cardiotocography **Exclusion criteria:** NR **Patients characteristics:** NR **Prevalence of disease:** NR	**Index test:** Actim Partus (cut-off value not indicated) **Reference standard:** Delivery within 48 hours or 7 days of testing or PTD < 34 weeks	No usable data for meta-analysis	**Excluded from Analysis:** NR **RoB:** Not assessed **Applicability Concern:** Not assessed
Danti (2011)[25]	**Design:** Cohort (prospective) **Sources of funding:** NR **Setting:** Maternal-Fetal Medicine Unit, University of Brescia, Italy	**Eligibility criteria:** Between 24- 32 weeks GA; singleton; uterine contractions (at least 4 in 20 min); cervical length ≤30 mm. **Exclusion criteria:**	**Index test:** Actim Partus (cut-off 10 µg/L) **Reference standard:** PTD within 7 days of testing and < 34 weeks	*All estimates are for cervical length ≤30 mm* ***PTD within 7 days of testing*** • **Sensitivity:** 50% (95% CI: 7, 93) • **Specificity:** 70% (95% CI: 56, 81) • **LR+:** 1.65 (95% CI: 0.57, 4.74)	**Excluded from Analysis:** NR **RoB:** Low **Applicability Concern:** Unclear

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of review quality
	Sample size: 60 (received Actim Partus test) **Duration:** December 2004-December 2006	Vaginal bleeding; ruptured membranes; cervical dilatation ≥3 cm; cervical cerclage; known uterine abnormalities; fetal abnormalities; other pregnancy complications (placenta previa, abruption placentae, fetal growth restriction, and pre-eclampsia). **Patients characteristics:** Women were divided in 2 groups according to cervical length measurements (20-30 mm, <20 mm) Mean gestational age at assessment 30.0 weeks (cervical length ≤30 mm). **Prevalence of disease:** In group with cervical length ≤30 mm: 6.7% (PTD within 7 days of testing) 13.3 % (PTD <34 weeks)		• **LR-:** 0.72 (95% CI: 0.27, 1.94) ***PTD < 34 weeks*** • **Sensitivity:** 63% (95% CI: 24, 91) • **Specificity:** 73% (95% CI: 59, 84) • **LR+:** 2.32 (95% CI: 1.15, 4.67) • **LR-:** 0.51 (95% CI: 0.21, 1.27)	
Riboni (2011)[15]	**Design:** Cohort (prospective) **Sources of funding:** NR	**Eligibility criteria:** Symptomatic (documented uterine contractions); 24-34 weeks GA; singleton; intact membranes **Exclusion criteria:**	**Index test:** Actim Partus (positive result indicated by 2 blue lines, test has detection limit of 10 µg/L) **Reference standard:**	***PTD within 7 days of admission*** • **Sensitivity:** 50% (95% CI: 21.5, 78.5) • **Specificity**: 83.7% (95% CI: 77.9, 88.1)	**Excluded from Analysis:** NR **RoB:** Unclear **Applicability Concern:** Low

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of review quality
	Setting: Departments of obstetrics in Padua and Milan **Sample size:** 210 **Duration:** January 2006-December 2006	>2 cm dilatation of the cervix; undergone cervical examination or sexual intercourse <24 h previously; vaginal bleeding; placenta previa; multiple gestations; fetal abnormalities; uterine anomalies **Patients characteristics:** *Mean GA at sampling;* 28.7 weeks *Ethnicity:* Caucasian **Prevalence of disease:** 3.8% (PTD within 7 days of admission); 7.6 % (PTD <34 weeks' gestation); 16.2 % (PTD <37 weeks' gestation);	PTD within 7 days of admission, <34 weeks, and <37 weeks	• **LR+:** 3.06 (95% CI: 1.43, 6.54) • **LR-:** 0.60 (95% CI: 0.30, 1.20) ***PTD < 34 weeks*** • **Sensitivity:** 64.3% (95% CI: 40.3, 82.8) • **Specificity:** 85.7% (95% CI: 80.1, 90) • **LR+:** 4.51 (95% CI: 2.73, 7.45) • **LR-:** 0.42 (95% CI: 0.22, 0.80) ***PTD < 37 weeks*** • **Sensitivity:** 52.9% (95% CI: 36.7, 68.5) • **Specificity:** 89.2% (95% CI: 83.8, 93) • **LR+:** 4.90 (95% CI: 2.89, 8.33) • **LR-:** 0.53 (95% CI: 0.37, 0.76)	
Audibert (2010)[26]	**Design:** Cohort (prospective) **Sources of funding:** NR	**Eligibility criteria:** Between 24-34 weeks GA; singleton; signs and symptoms of labour. **Exclusion criteria:**	**Index test:** Actim Partus (cut-off 10 µg/L) **Reference standard:** PTD < 34 weeks and < 37 weeks	***PTD < 34 weeks*** • **Sensitivity:** 14% (95% CI: 2, 43) • **Specificity:** 94% (95% CI: 83, 99) • **LR+:** 2.3 (95% CI: 0.4, 12.4)	**Excluded from Analysis:** 9 **RoB:** Unclear **Applicability Concern:** Low

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of review quality
	Setting: Tertiary care unit in Montreal **Sample size:** 62 **Duration:** January 2006-January 2007	PPROM; cervical incompetence or a cervical cerclage suture; placenta previa or abruption placenta; multiple pregnancies and those with cervical dilation ≥3 cm on vaginal examination. **Patients characteristics:** *Age (SD):* 27.6 (6.2) years *GA inclusion (SD):* 29.4 (2.5) weeks *Nulliparous:* 29% **Prevalence of disease:** 22.6% (PTD < 34 weeks) 37.1% (PTD < 37 weeks)		• **LR-:** 0.9 (95% CI: 0.7, 1.1) ***PTD < 37 weeks*** • **Sensitivity:** 13% (95% CI: 5, 21) • **Specificity:** 95% (95% CI: 89, 100) • **LR+:** 2.5 (95% CI: 0.5, 14) • **LR-:** 0.9 (95% CI: 0.8, 1.1)	
Azlin (2010)[50] **Companion[6]**	**Design:** Cohort (prospective) **Sources of funding:** Not-for-Profit **Setting:** University Kebangsaan Malaysia **Sample size:** 51 **Duration:** NR	**Eligibility criteria:** Between 24-36 weeks GA; evidence of PTL; singleton **Exclusion criteria:** PPROM; cervical incompetence; cervical cerclage suture; placenta previa; abruption placenta; multiple pregnancies; cervical dilatation ≥ 3 cm **Patients characteristics:** *Pooled Age (SD):* 28.5 (4.2) years	**Index test:** Actim Partus (cut-off: qualitative – blue line) **Reference standard:** Delivery within 7 days	• **Sensitivity:** 80% (95% CI: 37.6, 96.4) • **Specificity:** 93.5% (95% CI: 82.5, 97.8) • **LR+:** 12.27 (95% CI: 3.78, 39.86) • **LR-:** 0.21 (95% CI: 0.04, 1.24)	**Excluded from Analysis:** NR **RoB:** High **Applicability Concern:** Low

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of review quality
		Prevalence of disease: 9.8% (Delivery within 7 days)			
Brik (2010)[27] **Companion[7]**	**Design:** Cohort (prospective) **Sources of funding:** Not-for-Profit **Setting:** University Hospital La Fe, Spain **Sample size:** 276 **Duration:**June 2004 to July 2008	**Eligibility criteria:** Singleton; between 24-34 weeks GA; intact membranes; threatened PTL **Exclusion criteria:** PPROM; moderate to intense vaginal bleeding; pregnancies ending in PTD because of placental abruption, fetal distress leading to induction of labour or cord prolapse; active labour (cervix 100% effaced, >3 cm dilation); fetal anomalies; presence of a cerclage suture **Patients characteristics:** *Age (SD):* 29.4 (5.9) years *GA at examination:* 29.9 (2.8) weeks *Nulliparous:* 58.3% *Previous PTD:* 9.4% **Prevalence of disease:** 6.9% (PTD within 48 h) 9.4% (PTD within 7 days) 14.1% (PTD < 34 weeks)	**Index test:** Actim Partus (cut-off 30 µg/L) **Reference standard:** PTD within 48 h, 7 days, or <34 weeks	***PTD within 48 h:*** • **Sensitivity:** 73.7% (95% CI: 51.2, 88.2) • **Specificity:** 64.9% (95% CI: 59, 70.6) • **LR+:** 2.1 (95% CI: 1.52, 2.91) **LR-:** 0.41 (95% CI: 0.19, 0.87) ***PTD within 7 days:*** • **Sensitivity:** 73.1% (95% CI: 53.9, 86.3) • **Specificity:** 66.2% (95% CI: 60.1, 71.8) • **LR+:** 2.16 (95% CI: 1.60, 2.92) **LR-:** 0.41 (95% CI: 0.21, 0.78) ***PTD <34 weeks:*** • **Sensitivity:** 59% (95% CI: 43.4, 72.9) • **Specificity:** 66% (95% CI: 59.6, 71.6)	**Excluded from Analysis:** 49 **RoB:** High **Applicability Concern:** Low

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of review quality
				• **LR+:** 1.76 (95% CI: 1.25, 2.41) **LR-:** 0.62 (95% CI: 0.41, 0.93)	
Altinkaya (2009)[30]	**Design:** Cohort **Sources of funding:** NR **Setting:** Zekai Tahir Burak Women's Health Care Education and Research Hospital, Turkey **Sample size:** 105 **Duration:** NR	**Eligibility criteria:** Between 24-34 weeks GA; singleton; uterine contractions. **Exclusion criteria:** Multiple gestation; premature rupture of membranes; cervical dilatation ≥2cm; preeclampsia; vaginal bleeding; IUGR; congenital fetal anomalies; uterine anomalies; history of PTD; smoking **Patients characteristics:** *Age (SD):* 24.5 (5.2) years *GA at enrolment:* 29.6 (4.4) weeks **Prevalence of disease:** 13.3% (Delivery within 7 days of admission) 19% (PTD < 37 weeks)	**Index test:** Actim Partus (cut-off 30 µg/L) **Reference standard:** Delivery within 7 days of admission and PTD < 37 weeks	***Delivery within 7 days of admission:*** • **Sensitivity:** 64.3% (95% CI: 38.8, 83.7) • **Specificity:** 82.4% (95% CI: 73.3, 88.9) • **LR+:** 3.66 (95% CI: 2.02, 6.61) • **LR-:** 0.43 (95% CI: 0.21, 0.88) ***PTD < 37 weeks*** • **Sensitivity:** 70.0% (95% CI: 48.1, 85.5) • **Specificity:** 87.0% (95% CI: 78.3, 92.6) • **LR+:** 5.41 (95% CI: 2.91, 10.07) • **LR-:** 0.34 (95% CI: 0.18, 0.68)	**Excluded from Analysis:** NR **RoB:** Unclear **Applicability Concern:** Unclear
Rahkonen (2009)[28]	**Design:** Cohort (prospective) **Sources of funding:** Not-for-Profit	**Eligibility criteria:** Uterine contractions **Exclusion criteria:** Major fetal anomalies; vaginal	**Index test:** Actim Partus (cut-off 10 µg/L) **Reference standard:** PTD < 34 weeks	• **Sensitivity:** 50.0% (95% CI: 23.7, 76.3) • **Specificity:** 86.9% (95% CI: 82, 90.6)	**Excluded from Analysis:** 3 **RoB:** Unclear

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of review quality
	Setting: Department of Obstetrics and Gynecology, University Hospital, Finland **Sample size:** 246 **Duration:** April 2005-December 2006	bleeding at presentation; placenta previa **Patients characteristics:** *Age Range:* 18-40 years *GA at examination range:* 22-34 weeks *Nulliparous:* 41.9% **Prevalence of disease:** 4.1% (PTD < 34 weeks)		• **LR+:** 3.8 (95% CI: 1.89, 7.68) • **LR-:** 0.6 (95% CI: 0.31, 1.07)	**Applicability Concern:** Low
Latifagić (2008)[32]	**Design:** Cohort (prospective) **Sources of funding:** NR **Setting:** Gynaecology and obstetrics department, University Clinical Centre, Tuzla **Sample size:** 30 **Duration:** During 2006	**Eligibility criteria:** Between 24-34 weeks GA; singleton; hospitalized for threatened PTD; intact fetal membranes **Exclusion criteria:** Chronic disease (hypertension, diabetes, renal or cardiac diseases); genital tract anomalies of the mother; genetic or anatomic defects of the fetus; previous PTD **Patients characteristics:** *Age (SD):* 25.1 (5.2) years *GA at testing (SD):* 31.2 (1.9) weeks	**Index test:** Actim Partus (cut-off 10 µg/L) **Reference standard:** PTD < 37 weeks	• **Sensitivity:** 80% (95% CI: 54.8, 93) • **Specificity:** 53.3% (95% CI: 30.1, 75.2) • **LR+:** 1.71 (95% CI: 0.94, 3.12) • **LR-:** 0.38 (95% CI: 0.12, 1.15)	**Excluded from Analysis:** NR **RoB:** Unclear **Applicability Concern:** Unclear

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of review quality
		Prevalence of disease: 50% (PTD < 37 weeks)			
Sunagawa (2008)[31]	**Design:** Case-control (conducted as retrospective cohort) **Sources of funding:** NR **Setting:** Department of Obstetrics, Center for Perinatal Medicine, Nagano Children's Hospital, Nagano, Japan **Sample size:** 76 **Duration:** April 2001-October 2006	**Eligibility criteria:** <37 weeks GA; singleton; PTL **Exclusion criteria:** Multiple gestation; obvious rupture of membranes; herniation of membranes protruding beyond the external cervical os; PTD due to medical indications; congenital anomalies of the fetus; any fetal or maternal contraindications to tocolysis (fetal asphyxia, IUGR, placenta previa, abruption placentae, pre-eclampsia, and other fetal or maternal contraindications for the use of tocolytic agents). **Patients characteristics: (for IGFBP-1 Positive)** *Pooled Age (SD):* 30.4 (4.2) years *GA at admission (SD):* 27.6 weeks **Prevalence of disease:** 26.3% (Delivery within 7 days of admission)	**Index test:** Actim Partus (cut-off: qualitative) **Reference standard:** Delivery within 7 days of admission	• **Sensitivity:** 30.0% (95% CI: 14.5, 51.9) • **Specificity:** 67.9% (95% CI: 54.8, 78.6) • **LR+:** 0.93 (95% CI: 0.43, 2.02) • **LR-:** 1.03 (95% CI: 0.74, 1.45)	**Excluded from Analysis:** 43 **RoB:** High **Applicability Concern:** Low

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of review quality
Tanir (2008)[29]	**Design:** Cohort (prospective) **Sources of funding:** NR **Setting:** Perinatology Unit at Eskisehir Osmangazi University School of Medicine, Turkey **Sample size:** 68 **Duration:** January 2004-June 2006	**Eligibility criteria:** PTL; between 24-37 weeks GA; <3 cm cervical dilatation; intact membranes **Exclusion criteria:** Cervical cerclage; massive vaginal bleeding; received tocolysis at admission; cervical manipulation such as vaginal douche, intercourse or digital examination within the previous 24 h; pre-eclampsia; multiple pregnancy; DM; hyperthyroidism; asthma **Patients characteristics:** *Pooled Age (SD):* 28.4 (5.0) years *Pooled GA at admission:* 30.0 (2.8) weeks *Cesarean Delivery:* 56% **Prevalence of disease:** 22.1% (PTD within 7 days of admission) 25.0% (PTD < 34 weeks)	**Index test:** Actim Partus (cut-off: qualitative – two lines) **Reference standard:** Delivery within 7 days of admission or PTD < 34 weeks	**Delivery within 7 days of admission:** • **Sensitivity:** 93.3% (95% CI: 70.2, 99) • **Specificity:** 79.2% (95% CI: 67, 88) • **LR+:** 4.4 (95% CI: 2.1, 5.2) • **LR-:** 0.8 (95% CI: 0.4, 0.9) **PTD < 34 weeks:** • **Sensitivity:** 70% (95% CI: 47, 87) • **Specificity:** 74.5% (95% CI: 61, 85) • **LR+:** 2.8 (95% CI: 1.1, 3.8) • **LR-:** 0.3 (95% CI: 0.1, 0.9)	**Excluded from Analysis:** NR **RoB:** Unclear **Applicability Concern:** Unclear
Eroglu (2007)[33]	**Design:** Cohort (prospective) **Sources of funding:** NR **Setting:**	**Eligibility criteria:** Between 24-35 weeks GA; regular premature uterine contractions (>10/h) **Exclusion criteria:**	**Index test:** Actim Partus (cut-off 30 µg/L) **Reference standard:** Delivery within 7 days of admission	• **Sensitivity:** 83.3% (95% CI: 43.6, 97) • **Specificity:** 84.4% (95% CI: 71.2, 92.3) • **LR+:** 5.36 (95% CI: 2.3, 12.2)	**Excluded from Analysis:** NR **RoB:** Unclear **Applicability Concern:** Low

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of review quality
	Department of Obstetrics and Gynecology, Baskent University Faculty of Medicine, Turkey **Sample size:** 51 (with PTL) **Duration:** February 2004-February 2006	Vaginal bleeding; cervical dilatation of ≥ 3cm; confirmed rupture of membranes; sexual intercourse within the past 24 h; multiple pregnancy; uterine anomalies; congenital fetal abnormality; placenta previa; abruption placenta; IUGR; pre-eclampsia. **Patients characteristics:** Gestational age at enrolment: 29.5 ± 2.6 weeks **Prevalence of disease:** 11.8% (Delivery within 7 days of admission)		• **LR-:** 0.20 (95% CI: 0.01, 0.7)	
Ting (2007)[34]	**Design:** Cohort **Sources of funding:** Singhealth Research Grant **Setting:** KK Women's and Children's Hospital, Singapore **Sample size:** 94 **Duration:**	**Eligibility criteria:** Between 24-34 weeks GA; symptomatic; singleton; intact membranes **Exclusion criteria:** Multiple gestation; premature rupture of membranes; cervical cerclage; cervical dilatation ≥ 3 cm; placenta previa; chorioamnionitis; IUGR; preeclampsia; suspected fetal asphyxia; major fetal anomaly **Patients characteristics:**	**Index test:** Actim Partus (cut-off: qualitative) **Reference standard:** Delivery within 48 h or 7 days	***Delivery within 48 h*** • **Sensitivity:** 100% (95% CI: 51.7, 99.1) • **Specificity:** 74% (95% CI: 64, 81.9) • **LR+:** 3.51 (95% CI: 2.3, 5.36) • **LR-:** 0.11 (95% CI: 0.01, 1.61) ***Delivery within 7 days*** • **Sensitivity:** 69% (95% CI: 44.4, 85.8) • **Specificity:** 78% (95% CI: 67.8, 85.9)	**Excluded from Analysis:** 14 **RoB:** Unclear **Applicability Concern:** Low

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of review quality
	January 2003 - January 2005	*Age:* 27 years *GA at admission:* 31.7 weeks **Prevalence of disease:** 5.3% (Delivery within 48 h) 17% (Delivery within 7 days)		• **LR+:** 3.15 (95% CI: 1.85, 5.38) • **LR-:** 0.4 (95% CI: 0.19, 0.83)	

Abbreviations: *CI = confidence interval; DM = diabetes mellitus; GA = gestational age; IUGR = intrauterine growth restriction; LR = likelihood ratio; PPROM = preterm premature rupture of membranes; PTD = preterm delivery; PTL = preterm labour; RoB = risk of bias; SD = standard deviation*

5.1.3. Transvaginal ultrasound- cervical length measurement

Table 27 – Evidence table: SR clinical effectiveness cervical length measurement

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal
Berghella, 2013[35]	**Design:** SR and MA **Sources of funding:** National Institute for Health Research, UK **Search date:** 31 August 2012 **Searched databases:** Cochrane Pregnancy and Childbirth Group's Trials Register **Included study designs:** RCTs **Number of included studies:** 5	**Eligibility criteria:** Pregnant women between GA 14 and 34 weeks screened with TVU and CL for risk of PTD **Patients characteristics:** -Asymptomatic singleton (no trials found) - Asymptomatic twins (1 trial) -Symptomatic singletons with PTL (3 trials)	**Intervention:** Knowledge of TVU CL test results **Comparator:** No knowledge of TVU CL test results	**Effect size primary outcome:** In symptomatic singleton: ***(i) Preterm birth < 37 weeks*** Knowledge vs. No Knowledge: RR= 0.59; 95% CI (0.26, 1.32)	**Effect size secondary outcome** In symptomatic singleton: ***(i) Preterm birth < 34 weeks*** Knowledge vs. No Knowledge: RR= 0.55; 95% CI (0.25, 1.20) ***(i) Preterm birth < 28 weeks*** Knowledge vs. No Knowledge: RR= 0.0; 95% CI (0.0, 0.0)	**AMSTAR** 8

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal
		- Symptomatic singletons with signs and symptoms of PPROM (1 trial) -Symptomatic twins with PTL (0 trials) **Median FU:** NR				

Abbreviations: *CL = cervical length; FU = follow-up; GA = gestational age; MA = meta-analysis; NR = not reported; PPROM = preterm premature rupture of membranes; PTD = preterm delivery; PTL = preterm labour; RCT = randomized controlled trial; SR = systematic review; UK = United Kingdom; TVU = transvaginal ultrasound*

Table 28 – Evidence table: RCTs clinical effectiveness cervical length measurement

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Hosseini 2012[51] **(Abstract)**	**Design:** RCT **Sources of funding**: NR **Setting:** Hafez Hospital affiliated to Shiraz University of Medical Sciences **Sample size:** 120 **Duration:** NR	**Eligibility criteria:** singleton pregnancies diagnosed to have preterm labor according to the following criteria: uterine contractions before 34 completed weeks of gestation (at least 4 contractions in 20 minutes	**Intervention:** TVU CL (those with CL < 15 mm received tocolysis; those with CL ≥ 15 mm were managed expectantly) **Comparator:** No TVU CL	**Effect size primary outcome**: No usable numerical data presented.	**Effect size secondary outcome** NA	**Dropouts** NR **RoB** *RSG* –Unclear *AC*-Unclear *Blinding (subjects/ personnel)*-High *Blinding (OA)*-Low *IOD*-Unclear *SR*-Unclear *Other*-Unclear

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
		interval) and who were selected for receiving tocolytic and steroid therapy according to the decision of the present obstetrician **Patients characteristics**: *Pooled age (SD):* 24.8 (4.4) years *Nulliparous:* 53.3% **Median FU:** NR				

Abbreviations: *CL = cervical length; FU = follow-up; NA = not applicable; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; TVU = transvaginal ultrasound*

Table 29 – Evidence table: SR test performance cervical length measurement

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Honest 2009[4]	**Design**: SR and MA **Sources of funding:** NIHR **Search date:** Sep 2005 **Searched databases:** Cochrane Library, the National Research Register (NRR), the HTA database, the National Guideline Clearinghouse, MEDLINE, EMBASE, BIOSIS, MEDION, Pascal, Science Citation Index, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE) and HTA database. **Included study designs:** Systematic Reviews of Test accuracy when available.	**Eligibility criteria:** Singleton symptomatic and asymptomatic women **Patient characteristics** Symptomatic: women with threatened PTL Asymptomatic: only 2 studies on women with history of PTD	**Index test:** TVU (length measurement) **Reference standard:** *For symptomatic women:* PTD at <37 weeks, <34 weeks, ≤ 48h, ≤ 7 days of testing *For asymptomatic women:* PTD <37 weeks, <34 weeks	• **Sensitivity** No pooling (individual study data provided) • **Specificity** No pooling (individual study data provided) • **PPV** No pooling (individual study data provided) • **NPV** No pooling (individual study data provided) • **LR+** No pooling (individual study data provided) • **LR-** No pooling (individual study data provided)	**Effect size secondary outcome** NA	**AMSTAR** 8

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	Primary test accuracy studies (observational: prospective or retrospective) of defined nonrandomised populations in which the results of the test of interest were compared with the outcomes (reference standard) to generate 2 × 2 tables to compute indices of test accuracy. If unavailable, case-control studies of test accuracy. **Number of included studies:** ***Cervical Length:*** 31 (13 primary studies on asymptomatic – mix of those with and without history of PTD, and 19 primary studies on symptomatic women) ***Cervical Funnelling:*** Presented but not relevant to updating exercise.					

Abbreviations: *LR = likelihood ratio; MA = meta-analysis; NA = not applicable; NIHR = National Institute for Health Research; NPV = negative predictive value; PPV = positive predictive value; PTD = preterm delivery; PTL = preterm labour; SPTB = spontaneous preterm birth; SR = systematic review; TVU = transvaginal ultrasound*

5.1.3.1. Primary studies test performance vaginal ultrasound

TVU Test Performance - Aymptomatic women with history of PTD (Reference Standard: PTD < 34 weeks)																							
Author of Primary Study	Reference Standard, weeks	Testing Period, weeks	Thresholds, mm		FP	FN	TN	Total Analyzed	Sensitivity	LCI	UCI	Specificity	LCI	UCI	LR+	LCI	UCI	LR-	LCI	UCI	Prevalence (%)	Quality	Blinding	Gestation
Andrew 2000[21]	34	20-24	25	5	5	8	39	57	0.38	0.14	0.68	0.89	0.75	0.96	3.38	1.16	9.91	0.69	0.45	1.08	22.8%	High	Y	S
Andrew 2000[21]	34	20-24	22	4	3	9	41	57	0.31	0.09	0.61	0.93	0.81	0.99	4.51	1.15	17.64	0.74	0.51	1.08	22.8%	High	Y	S
Owen 2001[21]	34	<20	20	5	1	42	135	183	0.11	0.04	0.23	0.99	0.96	1	14.47	1.73	120.7	0.9	0.81	0.99	25.7%	High	Y	S
Owen 2001[21]	34	<20	25	9	3	39	132	183	0.19	0.09	0.33	0.98	0.94	1	8.44	2.38	29.88	0.83	0.72	0.95	26.2%	High	Y	S
Owen 2001[21]	34	<20	30	12	24	29	118	183	0.29	0.16	0.46	0.83	0.76	0.89	1.73	0.95	3.15	0.85	0.69	1.05	22.4%	High	Y	S
Owen 2001[21]	34	<20	15	5	0	43	135	183	0.1	0.03	0.23	1	0.97	1	30.53	1.72	542	0.89	0.81	0.98	26.2%	High	Y	S
Priya 2013[36]	34	≥24	27	14	23	4	49	90	0.77	0.523	0.935	0.68	0.56	0.786	2.435	1.603	3.698	0.327	0.136	0.786	20.0%	Low	U/N	S
Romero 2012[37]	34	16-32	25	7	60	2	107	176	0.778	0.453	0.937	0.641	0.566	0.71	2.04	1.446	3.241	0.35	0.102	1.184	5.1%	Low	U/N	S
Owen 2010[38]	35	16-21	25	64	89	107.5	564.5	825	0.373	0.304	0.448	0.864	0.835	0.888	2.74	2.084	3.603	0.726	0.644	0.818	20.8%	Unlear	U/N	S
Adhikari 2009[39]	34	20-37	26.5	3	10	3	59	75	0.5	0.188	0.812	0.855	0.753	0.919	3.45	1.289	9.231	0.585	0.261	1.309	8.0%	Unclear	U/N	S
Brik 2010[27]	34	24-34	20.5	34	109	5	128	276	0.88	0.733	0.944	0.54	0.476	0.602	1.896	1.578	2.276	0.237	0.104	0.543	14.1%	Unclear	U/N	S
Bittar 2007[40]	34	22-24	20	10	13	2	80	105	0.833	0.552	0.953	0.86	0.775	0.916	5.962	3.391	10.48	0.194	0.055	0.688	11.4%	Unclear	U/N	S
Bittar 2007[40]	34	22-24	25	10	37	2	56	105	0.833	0.552	0.953	0.602	0.501	0.696	2.095	1.468	2.989	0.277	0.077	0.991	11.4%	Unclear	U/N	S

Abbreviations: FN = false negative; FP = false positive; LCI = lower confidence interval; LR = likelihood ratio; N = not blinded; PTD = preterm delivery; S = singleton; TN = true negative; TP = true positive; TVU = transvaginal ultrasound; UCI = upper confidence interval; U = unknown; Y = blinded

TVU Test Performance - Aymptomatic women with history of PTD (Reference Standard: PTD < 37 weeks)																				Prevalence (%)	Quality	Blinding	Gestation
Author of Primary Study	Reference Standard, weeks	Testing Period, weeks	Thresholds, mm	TP	FP	FN	TN	Total Analyzed	Sensitivity	LCI	UCI	Specificity	LCI	UCI	LR+	LCI	UCI	LR-	LCI	UCI				
Priya 2013[36]	37	24-32	27	25	11	13	41	90	0.65	0.486	0.804	0.79	0.653	0.889	3.11	1.754	5.514	0.434	0.273	0.689	42.2%	Low	U/N	S
Priya 2013[36]	37	24-28	28	25	11	13	41	90	0.66	0.486	0.804	0.79	0.653	0.889	3.11	1.754	5.514	0.434	0.273	0.689	42.2%	Low	U/N	S
Priya 2013[36]	37	28-32	26	30	14	8	38	90	0.79	0.627	0.904	0.73	0.59	0.844	2.932	1.82	4.724	0.288	0.152	0.545	42.2%	Low	U/N	S
Adhikari 2009[39]	37	20-37	29.5	15	11	5	44	75	0.75	0.531	0.888	0.801	0.676	0.884	3.75	2.087	6.738	0.313	0.145	0.675	26.7%	Unclear	U/N	S
Bittar 2007[40]	37	22-24	20	16	7	9	73	105	0.64	0.445	0.798	0.913	0.83	0.957	7.314	3.399	15.74	0.395	0.233	0.668	23.8%	Unclear	U/N	S
Bittar 2007[40]	37	22-24	25	19	28	6	52	105	0.76	0.566	0.885	0.65	0.541	0.745	2.171	1.498	3.147	0.369	0.18	0.755	23.8%	Unclear	U/N	S

Abbreviations: FN = false negative; FP = false positive; LCI = lower confidence interval; LR = likelihood ratio; N = not blinded; PTD = preterm delivery; S = singleton; TN = true negative; TP = true positive; TVU = transvaginal ultrasound; UCI = upper confidence interval; U = unknown

TVU Test Performance - Symptomatic women (Reference Standard: Delivery within 48 hours)																				Prevalence (%)	Quality	Blinding	Gestation
Author of Primary Study	Reference Standard, weeks	Testing Period, weeks	Thresholds, mm	TP	FP	FN	TN	Total Analyzed	Sensitivity	LCI	UCI	Specificity	LCI	UCI	LR+	LCI	UCI	LR-	LCI	UCI				
Tsoi 2005[21]	<48 hours	NR	5	9	11	12	478	510	0.43	0.22	0.66	0.98	0.96	0.99	19.05	8.87	40.94	0.58	0.4	0.85	4.1%	Low	Y	S
Tsoi 2005[21]	<48 hours	NR	10	17	31	4	458	510	0.81	0.58	0.95	0.94	0.91	0.96	12.77	8.57	19.03	0.2	0.08	0.49	4.1%	Low	Y	S
Tsoi 2005[21]	<48 hours	NR	15	21	74	0	415	510	1	0.84	1	0.85	0.81	0.88	6.43	5.17	8	0.03	0	0.42	4.1%	Low	Y	S
Tsoi 2005[21]	<48 hours	NR	20	21	150	0	339	510	1	0.84	1	0.69	0.65	0.73	3.18	2.75	3.69	0.03	0	0.51	4.1%	Low	Y	S
Gomez 2005[21]	<48 hours	NR	15	11	19	6	179	215	0.65	0.38	0.86	0.9	0.85	0.94	6.74	3.88	11.72	0.39	0.2	0.74	7.9%	High	Y	S
Gomez 2005[21]	<48 hours	NR	30	15	93	2	105	215	0.88	0.64	0.99	0.53	0.46	0.6	1.88	1.5	2.36	0.22	0.06	0.82	7.9%	High	Y	S
Wulff 2011[41]	Within 48 hours of presentation	23-33	15	9	27	4	106	146	0.692	0.424	0.873	0.797	0.721	0.857	3.41	2.079	5.593	0.386	0.17	0.876	8.9%	Unclear	U/N	S
Adhikari 2011[42]	Within 48 hours of admission	26-37	25	15	8	9	68	100	0.625	0.427	0.788	0.895	0.806	0.946	5.938	2.876	12.26	0.419	0.249	0.707	24.0%	Unclear	U/N	S
Boudhraa 2008[43]	< 48 hours	28-34	25	8	20	0	28	56	1	0.629	0.994	0.59	0.443	0.709	2.257	1.565	3.256	0.096	0.006	1.427	14.3%	Unclear	U/N	S
Schmitz 2008[44]	Within 48 hours of admission	24-34	30	15	227	2	151	395	0.88	0.64	0.98	0.4	0.35	0.46	1.48	1.22	1.8	0.29	0.08	1.07	4.3%	High	Y	S

Abbreviations: FN = false negative; FP = false positive; LCI = lower confidence interval; LR = likelihood ratio; N = not blinded; PTD = preterm delivery; S = singleton; TN = true negative; TP = true positive; TVU = transvaginal ultrasound; UCI = upper confidence interval; U = unknown; Y = blinded

TVU Test Performance - Symptomatic women (Reference Standard: Delivery within 7 days)																				Prevalence (%)	Quality	Blinding	Gestation
Author of Primary Study	Reference Standard, weeks	Testing Period, weeks	Thresholds, mm	TP	FP	FN	TN	Total Analyzed	Sensitivity	LCI	UCI	Specificity	LCI	UCI	LR+	LCI	UCI	LR-	LCI	UCI				
Tsoi 2005[21]	<7days	NR	5	16	4	27	463	510	0.37	0.23	0.53	0.99	0.98	1	43.44	15.2	124.2	0.63	0.5	0.8	8.4%	Low	Y	S
Tsoi 2005[21]	<7days	NR	10	28	20	15	447	510	0.65	0.49	0.79	0.96	0.93	0.97	15.2	9.4	24.61	0.36	0.24	0.55	8.4%	Low	Y	S
Tsoi 2005[21]	<7days	NR	15	42	53	1	414	510	0.98	0.88	1	0.89	0.85	0.91	8.61	6.65	11.14	0.03	0	0.18	8.4%	Low	Y	S
Tsoi 2005[21]	<7days	NR	20	42	129	1	338	510	0.98	0.88	1	0.72	0.68	0.76	3.54	3.03	4.12	0.03	0	0.22	8.4%	Low	Y	S
Schmitz 2006[21]	<7days	NR	15	12	45	11	291	359	0.52	0.31	0.73	0.87	0.82	0.9	3.9	2.42	6.27	0.55	0.36	0.85	6.4%	Low	Y	S
Schmitz 2006[21]	<7days	NR	25	20	131	3	205	359	0.87	0.66	0.97	0.61	0.56	0.66	2.23	1.81	2.74	0.21	0.07	0.62	6.4%	Low	Y	S
Schmitz 2006[21]	<7days	NR	30	23	193	0	143	359	1	0.85	1	0.43	0.37	0.48	1.71	1.53	1.9	0.05	0	0.76	6.4%	Low	Y	S
Fuchs 2004[21]	<7days	NR	15	17	19	4	213	253	0.81	0.58	0.95	0.92	0.88	0.95	9.88	6.13	15.95	0.21	0.09	0.5	8.3%	Low	Y	S
Tsoi 2003[21]	<7days	NR	15	16	27	1	172	216	0.94	0.71	1	0.86	0.81	0.91	6.94	4.79	10.05	0.07	0.01	0.46	7.9%	Low	Y	S
Tsoi 2004[21]	<7days	NR	15	20	10	0	33	63	1	0.83	1	0.77	0.61	0.88	4.09	2.4	6.96	0.03	0	0.49	31.7%	Low	Y	S
Gomez 2005[21]	<7days	NR	15	17	13	11	174	215	0.61	0.41	0.78	0.93	0.88	0.96	8.73	4.78	15.96	0.42	0.27	0.67	13.0%	High	Y	S
Gomez 2005[21]	<7days	NR	30	25	83	3	104	215	0.89	0.72	0.98	0.56	0.48	0.63	2.01	1.64	2.47	0.19	0.07	0.57	13.0%	High	Y	S
Botsis 2005[21]	<7days	NR	15	10	9	1	84	104	0.91	0.59	1	0.9	0.82	0.95	9.39	4.91	17.97	0.1	0.02	0.65	10.6%	Low	U/N	S
Demirci 2011[45]	Within 7 days of presentation	24-34	15	15	11	4	179	209	0.789	0.567	0.915	0.942	0.899	0.967	13.636	7.344	25.32	0.223	0.093	0.534	9.1%	Low	Y	S
Wulff 2011[41]	Within 7 days of presentation	23-33	15	14	22	10	100	146	0.583	0.388	0.755	0.82	0.742	0.878	3.235	1.948	5.373	0.508	0.314	0.822	16.4%	Unclear	U/N	S
Adhikari 2011[42]	Within 7 days of admission	26-37	25	21	2	14	63	100	0.6	0.436	0.744	0.969	0.895	0.992	19.5	4.852	78.37	0.413	0.274	0.621	35.0%	Unclear	U/N	S
Deplagne 2010[46]	Within 7 days of testing	24-34	20	5	53	1	52	111	0.8	0.436	0.97	0.495	0.401	0.589	1.651	1.101	2.475	0.337	0.056	2.035	5.4%	Unclear	U/N	U
Park 2008[47]	Within 7 days of amniocentesis	22-35	20	8	7	4	43	62	0.667	0.391	0.862	0.86	0.738	0.93	4.762	2.15	10.55	0.388	0.173	0.869	19.4%	Unclear	U/N	S
Schmitz 2008[44]	Within 7 days of admission	24-34	30	30	210.5	2	152.5	395	0.94	0.79	0.99	0.42	0.37	0.47	1.63	1.43	1.84	0.15	0.04	0.57	8.1%	High	Y	S
van Baaren 2013[9]	Within 7 days of inclusion	24-34	25	81	208	6	264	559	0.93	0.86	0.97	0.56	0.51	0.6	2.113	1.88	2.374	0.123	0.057	0.268	15.6%	Unclear	U/N	U
van Baaren 2013[9]	Within 7 days of inclusion	24-34	30	84	269	3	203	559	0.97	0.9	0.99	0.43	0.38	0.47	1.694	1.552	1.85	0.08	0.026	0.245	15.6%	Unclear	U/N	U

Danti 2011[23]	Within 7 days of assessment	24-32	30	4	56	0	42	102	0.9	0.463	0.989	0.429	0.336	0.528	1.577	1.124	2.212	0.233	0.017	3.262	3.9%	Low	U/N	S
Danti 2011[23]	Within 7 days of assessment	24-32	20	3	16	1	82	102	0.75	0.301	0.954	0.837	0.751	0.897	4.594	2.232	9.455	0.299	0.055	1.635	3.9%	Low	U/N	S
Azlin 2010[25]	<7days	24-36	25	4	13	1	33	51	0.8	0.376	0.964	0.717	0.575	0.827	2.831	1.499	5.345	0.279	0.048	1.624	9.8%	High	Y	S
Azlin 2010[25]	<7days	24-36	15	0	1	5	45	51	0	0.009	0.483	0.978	0.873	0.993	2.611	0.119	57.14	0.947	0.74	1.212	9.8%	High	Y	S
Azlin 2010[25]	<7days	24-36	20	1	4	4	42	51	0.2	0.036	0.624	0.913	0.797	0.966	2.3	0.315	16.78	0.876	0.56	1.37	9.8%	High	Y	S
Azlin 2010[25]	<7days	24-36	30	4	17	1	29	51	0.8	0.376	0.964	0.63	0.486	0.755	2.165	1.214	3.86	0.317	0.054	1.857	9.8%	High	Y	S
Azlin 2010[25]	<7days	24-36	35	5	26	0	20	51	1	0.517	0.991	0.435	0.305	0.577	1.626	1.147	2.304	0.191	0.013	2.769	9.8%	High	Y	S
Sunagawa 2008[32]	Delivery within 7 days	NR	25	11	33	9	23	76	0.55	0.342	0.742	0.411	0.292	0.541	0.933	0.593	1.468	1.096	0.615	1.951	26.3%	Low	U/N	S
Sümer 2010[17]	Delivery within 7 days of	26-36	30	4	11	1	51	67	0.8	0.376	0.964	0.823	0.71	0.898	4.509	2.256	9.011	0.243	0.042	1.409	7.5%	Unclear	Y	S
Gramellini 2007[48]	Delivery within 7 days of testing	20-33	15	5	4	14	85	108	0.263	0.118	0.488	0.955	0.89	0.982	5.855	1.732	19.79	0.772	0.588	1.013	17.6%	Unclear	Y	S
Gramellini 2007[48]	Delivery within 7 days of testing	20-33	25	14	18	7	69	108	0.667	0.454	0.828	0.793	0.696	0.865	3.222	1.934	5.369	0.42	0.227	0.777	19.4%	Unclear	Y	S
Eroglu 2007[34]	Delivery within 7 days of	24-35	20	4	2	2	43	51	0.667	0.3	0.903	0.956	0.852	0.988	15	3.7	88.9	0.35	0.07	0.7	11.8%	Unclear	U/N	S
Eroglu 2007[34]	Delivery within 7 days of	24-35	25	4	5	2	40	51	0.667	0.3	0.903	0.889	0.765	0.952	6	1.9	17.3	0.38	0.07	0.8	11.8%	Unclear	U/N	S
Palacio 2007[49]	Delivery within 7 days of	24-36	15	6	11	15	301	333	0.286	0.138	0.5	0.965	0.938	0.98	8.104	3.324	19.76	0.74	0.564	0.971	6.3%	Unclear	Y	S
Palacio 2007[49]	Delivery within 7 days of	24-36	20	10	29	11	283	333	0.476	0.283	0.676	0.907	0.87	0.935	5.123	2.906	9.031	0.577	0.384	0.87	6.3%	Unclear	Y	S
Palacio 2007[49]	Delivery within 7 days of	24-36	25	15	65	6	247	333	0.714	0.5	0.862	0.792	0.743	0.833	3.429	2.425	4.848	0.361	0.183	0.711	6.3%	Unclear	Y	S
Holst 2006[50]	Delivery within 7 days of testing	22-33	15	19	14	8	46	87	0.704	0.515	0.841	0.767	0.646	0.856	3.016	1.793	5.072	0.386	0.213	0.703	31.0%	Unclear	U/N	S
Botis 2006[51]	Delivery within 7 days of	24-36	15	9	4	2	47	62	0.818	0.523	0.949	0.922	0.815	0.969	10.432	3.911	27.83	0.197	0.056	0.693	17.7%	Unclear	Y	S

Tsoi 2006[52]	Delivery within 7 days of	24-36	15	18	17	1	159	195	0.947	0.754	0.991	0.903	0.851	0.939	9.8	6.166	15.6	0.05	0.009	0.393	9.7%	Unclear	Y	S
Cardea 2006[53]	Delivery within 7 days of	24-36	15	8	14	0	86	108	0.944	0.629	0.994	0.856	0.775	0.912	6.579	3.982	10.87	0.065	0.004	0.96	7.4%	Unclear	U/N	U
Wilms 2009[20]	Delivery within 7 days of	24-34	5	2	2	9	78	91	0.182	0.051	0.477	0.975	0.913	0.993	7.273	1.137	46.53	0.839	0.634	1.111	12.1%	Unclear	U/N	S
Wilms 2009[20]	Delivery within 7 days of	24-34	35	11	51	0	29	91	0.958	0.699	0.996	0.364	0.268	0.473	1.507	1.231	1.846	0.114	0.007	1.752	12.1%	Unclear	U/N	S
Wilms 2009[20]	Delivery within 7 days of	24-34	15	5	17	6	63	91	0.455	0.213	0.72	0.788	0.686	0.863	2.139	0.988	4.632	0.693	0.399	1.202	12.1%	Unclear	U/N	S
Wilms 2009[20]	Delivery within 7 days of	24-34	25	8	33	3	47	91	0.727	0.434	0.903	0.588	0.478	0.689	1.763	1.128	2.755	0.464	0.174	1.24	12.1%	Unclear	U/N	S

Abbreviations: FN = false negative; FP = false positive; LCI = lower confidence interval; LR = likelihood ratio; N = not blinded; PTD = preterm delivery; S = singleton; TN = true negative; TP = true positive; TVU = transvaginal ultrasound; UCI = upper confidence interval; U = unknown; Y = blinded

TVU Test Performance - Symptomatic women (Reference Standard: PTD < 34 weeks)																				Prevalence (%)	Quality	Blinding	Gestation
Author of Primary Study	Reference Standard, weeks	Testing Period, weeks	Thresholds, mm	TP	FP	FN	TN	Total Analyzed	Sensitivity	LCI	UCI	Specificity	LCI	UCI	LR+	LCI	UCI	LR-	LCI	UCI				
Gomez 2005[21]	34	NR	15	7	5	2	87	101	0.78	0.4	0.97	0.95	0.88	0.98	14.31	5.7	35.95	0.23	0.07	0.8	8.9%	High	Y	S
Gomez 2005[21]	34	NR	30	9	40	0	52	101	1	0.66	1	0.57	0.46	0.67	2.18	1.66	2.86	0.09	0.01	1.33	8.9%	High	Y	S
Crane 1997[21]	34	NR	30	30	35	7	64	136	0.81	0.65	0.92	0.65	0.54	0.74	2.29	1.68	3.12	0.29	0.15	0.58	27.2%	High	Y	S
Daskalakis 2005[21]	34	NR	20	36	4	28	104	172	0.563	0.441	0.677	0.963	0.909	0.986	15.188	5.668	40.7	0.454	0.343	0.601	37.2%	Low	U/N	S
Daskalakis 2005[21]	34	NR	25	44	22	20	86	172	0.688	0.566	0.788	0.796	0.711	0.861	3.375	2.245	5.074	0.392	0.27	0.571	37.2%	Low	U/N	S
Daskalakis 2005[21]	34	NR	30	64	36	0	72	172	0.992	0.93	0.999	0.665	0.572	0.747	2.963	2.272	3.864	0.012	0.001	0.184	37.2%	Low	U/N	S
Daskalakis 2005[21]	34	NR	35	64	80	0	28	172	0.992	0.93	0.999	0.261	0.188	0.351	1.344	1.199	1.505	0.029	0.002	0.474	37.2%	Low	U/N	S
Rageth 1997[21]	34	NR	30	4	25	0	32	61	1	0.4	1	0.56	0.42	0.69	2.05	1.36	3.09	0.18	0.01	2.5	6.6%	Low	U/N	S
Tsoi 2005[21]	34	NR	5	17	3	59	431	510	0.22	0.14	0.33	0.99	0.98	1	32.36	9.72	107.8	0.78	0.69	0.88	14.9%	Low	Y	S
Tsoi 2005[21]	34	NR	10	33	15	43	419	510	0.43	0.32	0.55	0.97	0.94	0.98	12.56	7.18	21.98	0.59	0.48	0.71	14.9%	Low	Y	S
Tsoi 2005[21]	34	NR	15	54	41	22	393	510	0.71	0.6	0.81	0.91	0.87	0.93	7.52	5.44	10.41	0.32	0.22	0.46	14.9%	Low	Y	S
Tsoi 2005[21]	34	NR	20	59	112	17	322	510	0.78	0.67	0.86	0.74	0.7	0.78	3.01	2.46	3.67	0.3	0.2	0.46	14.9%	Low	Y	S
Schmitz 2006[21]	34	NR	15	22	35	26	276	359	0.46	0.31	0.61	0.89	0.85	0.92	4.07	2.63	6.31	0.61	0.47	0.79	13.4%	Low	Y	S
Schmitz 2006[21]	34	NR	25	36	115	12	196	359	0.75	0.6	0.86	0.63	0.57	0.68	2.03	1.63	2.52	0.4	0.24	0.65	13.4%	Low	Y	S
Schmitz 2006[21]	34	NR	30	43	173	5	138	359	0.9	0.77	0.97	0.44	0.39	0.5	1.61	1.4	1.85	0.23	0.1	0.54	13.4%	Low	Y	S
Gomez 2005[21]	34	NR	15	19	11	15	170	215	0.56	0.38	0.73	0.94	0.89	0.97	9.2	4.82	17.54	0.47	0.32	0.69	15.8%	Low	U/N	S
Gomez 2005[21]	34	NR	30	30	78	4	103	215	0.88	0.73	0.97	0.57	0.49	0.64	2.05	1.66	2.52	0.21	0.08	0.52	15.8%	Low	U/N	S
Kahyaoglu 2013[54]	34	24-34	30	18	25	14	28	85	0.563	0.393	0.718	0.528	0.397	0.656	1.193	0.785	1.811	0.828	0.519	1.322	37.6%	Unclear	U/N	U
Kahyaoglu 2013[54]	34	24-34	20	13	13	19	40	85	0.406	0.255	0.577	0.755	0.624	0.851	1.656	0.881	3.114	0.787	0.568	1.089	37.6%	Unclear	U/N	U
de Oliveira 2012[55]	35	22-34	20	18	15	5	32	70	0.783	0.581	0.903	0.681	0.538	0.796	2.452	1.533	3.923	0.319	0.144	0.71	32.9%	Unclear	U/N	S
Wulff 2011[41]	34	23-33	15	18	18	13	97	146	0.581	0.408	0.736	0.843	0.766	0.899	3.71	2.207	6.234	0.497	0.326	0.758	21.2%	Unclear	U/N	S
Deplagne 2010[46]	34	24-34	20	13	45	4	49	111	0.75	0.527	0.904	0.522	0.421	0.619	1.597	1.14	2.239	0.451	0.187	1.087	15.3%	Unclear	U/N	U
Deplagne 2010[46]	34	24-34	15	9	21	8	73	111	0.5	0.31	0.738	0.772	0.682	0.849	2.37	1.319	4.256	0.606	0.362	1.015	15.3%	Unclear	U/N	U
Di Renzo 2011[56]	34	24-32	25	16	38	2	40	96	0.889	0.672	0.969	0.513	0.404	0.621	1.825	1.379	2.415	0.217	0.058	0.812	18.8%	Unclear	U/N	U

Danti 2011[23]	34	24-32	30	8	52	0	42	102	0.944	0.629	0.994	0.447	0.351	0.547	1.709	1.344	2.174	0.124	0.008	1.853	7.8%	Low	U/N	S
Danti 2011[23]	34	24-32	20	5	14	3	80	102	0.625	0.306	0.863	0.851	0.765	0.909	4.196	2.038	8.641	0.441	0.179	1.082	7.8%	Low	U/N	S
Rahkonen 2009[30]	34	22-34	25	4	14	6	222	246	0.4	0.168	0.687	0.941	0.903	0.964	6.8	2.705	16.81	0.6	0.384	1.059	4.1%	Low	U/N	S
Gramellini 2007[48]	34	20-33	15	6	5	19	78	108	0.24	0.115	0.434	0.94	0.867	0.974	3.984	1.327	11.96	0.809	0.645	1.015	23.1%	Unclear	Y	S
Gramellini 2007[48]	34	20-33	25	14	14	11	69	108	0.56	0.371	0.733	0.831	0.737	0.897	3.32	1.839	5.993	0.529	0.337	0.832	23.1%	Unclear	Y	S
Eroglu 2007[34]	35	24-35	20	6	0	4	41	51	0.6	0.316	0.819	1	0.896	0.999	49.636	3.022	815.3	0.414	0.203	0.843	19.6%	Unclear	U/N	S
Eroglu 2007[34]	35	24-35	25	6	3	4	38	51	0.6	0.313	0.832	0.927	0.806	0.975	8.2	2.6	32.8	0.4	0.16	0.8	19.6%	Unclear	U/N	S
Palacio 2007[49]	34	24-36	15	2	5	13	193	213	0.133	0.037	0.379	0.975	0.942	0.989	5.28	1.117	24.97	0.889	0.728	1.086	7.0%	Unclear	Y	S
Palacio 2007[49]	34	24-36	20	3	17	12	181	213	0.2	0.07	0.452	0.914	0.867	0.946	2.329	0.768	7.065	0.875	0.677	1.131	7.0%	Unclear	Y	S
Palacio 2007[49]	34	24-36	25	9	30	6	168	213	0.6	0.357	0.802	0.528	0.473	0.583	1.272	0.828	1.954	0.757	0.404	1.419	7.0%	Unclear	Y	S
Holst 2006[50]	34	22-33	15	24	9	10	44	87	0.706	0.538	0.832	0.83	0.708	0.908	4.157	2.206	7.833	0.354	0.208	0.605	39.1%	Unclear	U/N	S
Tekesin 2005[57]	34	24-34	25	11	41	2	63	117	0.846	0.578	0.957	0.606	0.51	0.694	2.146	1.539	2.993	0.254	0.07	0.917	11.1%	High	Y	S
Nakai 2005[58]	34	22-28	25	13	83	6	59	161	0.684	0.46	0.846	0.415	0.338	0.498	1.171	0.837	1.637	0.76	0.381	1.515	11.8%	Low	U/N	S

Abbreviations: FN = false negative; FP = false positive; LCI = lower confidence interval; LR = likelihood ratio; N = not blinded; PTD = preterm delivery; S = singleton; TN = true negative; TP = true positive; TVU = transvaginal ultrasound; UCI = upper confidence interval; U = unknown; Y = blinded

TVU Test Performance - Symptomatic women (Reference Standard: PTD < 37 weeks)																				Prevalence (%)	Quality	Blinding	Gestation
Author of Primary Study	Reference Standard, weeks	Testing Period, weeks	Thresholds, mm	TP	FP	FN	TN	Total Analyzed	Sensitivity	LCI	UCI	Specificity	LCI	UCI	LR+	LCI	UCI	LR-	LCI	UCI				
Crane 1997[21]	37	NR	30	30	35	7	64	136	0.81	0.65	0.92	0.65	0.54	0.74	2.29	1.68	3.12	0.29	0.15	0.58	27.2%	High	Y	S
Gomez 1994[21]	37	NR	18	16	8	6	29	59	0.73	0.5	0.89	0.78	0.62	0.9	3.36	1.73	6.54	0.35	0.17	0.7	37.3%	Low	U/N	S
Onderoglu 1997[21]	37	NR	28	25	10	7	48	90	0.78	0.6	0.91	0.83	0.71	0.91	4.53	2.5	8.2	0.26	0.14	0.51	35.6%	Low	Y	S
Tekesin 2005[21]	37	NR	25	17	22	6	40	85	0.74	0.52	0.9	0.65	0.51	0.76	2.08	1.38	3.15	0.4	0.2	0.82	27.1%	Low	Y	S
Rozenberg 1997[21]	37	NR	26	14	6	2	6	28	0.88	0.62	0.98	0.5	0.21	0.79	1.75	0.96	3.17	0.25	0.06	1.03	57.1%	Low	Y	S
Venditelli 2001[21]	37	NR	30	55	53	12	54	174	0.82	0.71	0.9	0.5	0.41	0.6	1.66	1.33	2.07	0.35	0.21	0.61	38.5%	Low	U/N	S
Rizzo 1996[21]	37	NR	20	32	13	15	48	108	0.68	0.53	0.81	0.79	0.66	0.88	3.19	1.9	5.38	0.41	0.26	0.63	43.5%	Low	U/N	S
Goffinet 1997[21]	37	NR	26	19	28	5	56	108	0.79	0.58	0.93	0.67	0.56	0.77	2.38	1.65	3.42	0.31	0.14	0.69	22.2%	Low	U/N	S
Murakawa 1993[21]	37	NR	25	7	3	4	18	32	0.64	0.31	0.89	0.86	0.64	0.97	4.45	1.43	13.91	0.42	0.19	0.95	34.4%	Low	U/N	S
Murakawa 1993[21]	37	NR	30	11	6	0	15	32	1	0.72	1	0.71	0.48	0.89	3.24	1.68	6.25	0.06	0	0.9	34.4%	Low	U/N	S
Murakawa 1993[21]	37	NR	35	11	14	0	7	32	1	0.72	1	0.33	0.15	0.57	1.45	1.05	2.01	0.12	0.01	1.96	34.4%	Low	U/N	S
Tateyama 2013[59]	37	22-31	25	12	19	6	31	68	0.667	0.437	0.837	0.62	0.482	0.741	1.754	1.084	2.84	0.538	0.27	1.07	26.5%	Unclear	U/N	S
errano-Gómez 2011	38	22-36	25	10	1	4	58	73	0.714	0.454	0.883	0.983	0.91	0.997	42.143	5.869	302.6	0.291	0.127	0.666	19.2%	Unclear	U/N	S
Kim 2011[61]	37	22-37	17	62.4	14.6	39.6	58.4	175	0.612	0.515	0.701	0.8	0.694	0.876	3.059	1.885	4.964	0.485	0.371	0.635	58.3%	Unclear	U/N	S
Deplagne 2010[46]	37	24-34	20	20	37	11	43	111	0.655	0.469	0.789	0.532	0.429	0.643	1.395	0.981	1.984	0.66	0.394	1.106	27.9%	Unclear	U/N	U
Lopez Farfan 2011[6]	37	24-33	25	16	2	13	35	66	0.552	0.375	0.716	0.946	0.823	0.985	10.207	2.549	40.87	0.474	0.314	0.715	43.9%	Unclear	U/N	U

Danti 2011[23]	37	24-32	30	21	39	2	40	102	0.913	0.732	0.976	0.506	0.398	0.614	1.849	1.431	2.39	0.172	0.045	0.657	22.5%	Low	U/N	S
Paternoster 2009[63]	37	24-34	26	29	49.5	5	126.5	210	0.864	0.699	0.936	0.719	0.648	0.78	3.69	2.305	3.99	0.22	0.091	0.462	16.2%	Unclear	U/N	S
Palacio 2007[49]	36	24-36	25	27	53	24	229	333	0.529	0.395	0.659	0.812	0.762	0.853	2.817	1.976	4.016	0.58	0.431	0.779	15.3%	Unclear	Y	S
Jenkins 2006[64]	37	23-34	30	12	16	6	32	66	0.667	0.437	0.837	0.667	0.525	0.783	2	1.193	3.352	0.5	0.252	0.99	27.3%	Low	U/N	S
Jenkins 2006[64]	37	23-34	20	6	5	12	43	66	0.333	0.163	0.563	0.896	0.778	0.955	3.2	1.113	9.199	0.744	0.529	1.046	27.3%	Low	U/N	S
Kwasan 2005[65]	37	24-36	30	28	7	2	32	69	0.933	0.875	0.992	0.82	0.73	0.911	5.2	2.64	10.24	0.081	0.021	0.312	43.5%	Unclear	Y	S
Kwasan 2005[65]	37	24-36	19	6	0	24	39	69	0.2	0.106	0.294	1	1	1	16.774	0.982	286.5	0.8	0.665	0.963	43.5%	Unclear	Y	S
Tekesin 2005[57]	37	24-34	25	21	31	10	55	117	0.677	0.501	0.814	0.64	0.534	0.733	1.879	1.296	2.726	0.504	0.296	0.861	26.5%	High	Y	S
Sayin 2005[66]	37	25-36	35	19	9	15	13	56	0.559	0.395	0.711	0.591	0.387	0.767	1.366	0.762	2.45	0.747	0.447	1.248	60.7%	Unclear	U/N	S

Abbreviations: FN = false negative; FP = false positive; LCI = lower confidence interval; LR = likelihood ratio; N = not blinded; PTD = preterm delivery; S = singleton; TN = true negative; TP = true positive; TVU = transvaginal ultrasound; UCI = upper confidence interval; U = unknown; Y = blinded

5.2. Secondary prevention of preterm labour

Table 30 – Evidence table: SRs progesterone

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary outcome(s)	Critical appraisal
Conde-Agudelo 2013[39] **Companion**[52]	**Design:** SR and IPD MA for progesterone vs. placebo/no treatment **Sources of funding:** in part by the Intramural Research Program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development **Search date:** Inception – Oct 31 2012 **Sources Searched:** MEDLINE; EMBASE; CINAHL; LILACS; Cochrane Central Register of Controlled Trials; ISI Web of Science; registers of ongoing trials; Google Scholar; congress proceedings; reference lists of identified studies, textbooks, and reviews; contacting experts	**Eligibility criteria:** Asymptomatic women with a sonographic short cervix (<25 mm) in mid trimester, singleton gestation, and previous spontaneous preterm birth < 37 weeks **Exclusion criteria:** Quasi-randomized; multiple gestations; women with actual or threated PTL, 2nd trimester bleeding, or PROM; administration of progesterone in 1st trimester to prevent miscarriage	**Intervention:** Vaginal progesterone • gel-90 mg/d; • capsule – 200 mg/d; • suppository – 100 mg/d) **Comparator:** Placebo or no treatment	***Preterm birth < 32 weeks:*** RR = 0.47 (95% CI: 0.24, 0.91) NNT = 7 (95% CI: 5-38)	***Preterm birth < 37 weeks:*** RR = 0.84 (95% CI: 0.61, 1.14) ***Preterm birth < 35 weeks:*** RR = 0.66 (95% CI: 0.42, 1.04) ***Preterm birth < 28 weeks:*** RR = 0.51 (95% CI: 0.22, 1.18) ***RDS:*** RR = 0.38 (95% CI: 0.13, 1.07) ***NEC:*** RR = 0.47 (95% CI: 0.02, 10.32) ***Grade III/IV IVH:*** RR = 0.50 (95% CI: 0.08, 2.96) ***Neonatal Sepsis:*** RR = 0.25 (95% CI: 0.05, 1.37)	**AMSTAR Score:** 10

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary outcome(s)	Critical appraisal
	Included study designs: RCTs **Number of included studies:** 4 (vaginal progesterone vs. placebo)				***BPD:*** RR = 0.31 (95% CI: 0.01, 7.32)	
Dodd 2013[40]	**Design:** SR and MA **Sources of funding:** NIHR (Cochrane Review) **Search date:** Jan 14 2013 **Sources Searched:** Cochrane Pregnancy and Childbirth Group's Trials Register[j]; reference lists of articles **Included study designs:** RCTs **Number of included studies:** 36	**Eligibility criteria:** Pregnant women at increased risk of preterm birth: • Previous history of spontaneous preterm birth (including PPROM) • Multiple gestation (we focused on singleton gestation only) • Short cervical length identified by ultrasound • fFN testing • Following acute presentation of threatened PTL	**Intervention:** Progesterone (by any route – we focused on PV and PO routes only) **Comparator:** Placebo/no treatment	• **Women with previous history of spontaneous preterm birth:** ***Preterm Birth < 34 weeks:*** PV: RR = 0.21 (95% CI: 0.10, 0.44) PO: RR = 0.59 (95% CI: 0.39, 0.90) ***Perinatal Mortality:*** PV: RR = 0.67 (95% CI: 0.34, 1.29) PO: RR = 0.43 (95% CI: 0.12, 1.59) • **Women with short cervix:**	1. **Women with previous history of spontaneous preterm birth:** ***Preterm Birth < 37 weeks:*** PV: RR = 0.52 (95% CI: 0.29, 0.92) PO: RR = 0.46 (95% CI: 0.19, 1.11) ***Adverse Drug Reaction:*** PO: RR = 0.71 (95% CI: 0.24, 2.15) ***RDS:*** PV: RR = 0.92 (95% CI: 0.59, 1.43) PO: RR = 0.10 (95% CI: 0.03, 0.30)	**AMSTAR Score:** 10

[j] Contains trials identified from the following databases: CENTRAL (monthly searches), MEDLINE (weekly searches), Embase (weekly searches), hand searches of 30 journals and major conference proceedings, weekly current awareness alerts for a further 44 journals, and monthly BioMed Central email alerts.

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary outcome(s)	Critical appraisal
		Exclusion criteria: Quasi-randomized; cross-over design; progesterone administered for acute treatment of actual or threatened PTL (i.e. acute tocolytic); progesterone administered in 1st trimester for preventing miscarriage		***Preterm Birth < 34 weeks:*** PV: RR = 0.58 (95% CI: 0.38, 0.87) ***Perinatal Mortality:*** PV: RR = 0.56 (95% CI: 0.27, 1.17) • **Women with threatened PTL (i.e. symptomatic)** ***Preterm Birth < 34 weeks:*** PV: RR = 0.92 (95% CI: 0.37, 2.27)	***Use of Mechanical Ventilation:*** PV: RR = 0.24 (95% CI: 0.07, 0.81) PO: RR = 0.11 (95% CI: 0.01, 1.92) ***Grade III/IV IVH:*** PV: RR = 0.98 (95% CI: 0.06, 15.55) ***PVL:*** PV: RR = 3.13 (95% CI: 0.13, 75.52) ***NEC:*** PV: RR = 0.53 (95% CI: 0.15, 1.92) ***Neonatal Sepsis:*** PV: RR = 0.13 (95% CI: 0.02, 1.01) ***Neonatal Death:*** PV: RR = 0.53 (95% CI: 0.24, 1.18) PO: RR = 0.43 (95% CI: 0.12, 1.59) **2. Women with short cervix:**	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary outcome(s)	Critical appraisal
					Preterm Birth < 37 weeks: PV: RR = 0.89 (95% CI: 0.68, 1.16) ***Preterm Birth < 28 weeks:*** PV: RR = 0.50 (95% CI: 0.25, 0.97) ***RDS:*** PV: RR = 0.49 (95% CI: 0.29, 0.85) ***Use of Mechanical Ventilation:*** PV: RR = 0.65 (95% CI: 0.36, 1.16) ***Grade III/IV IVH:*** PV: RR = 0.32 (95% CI: 0.01, 7.73) ***PVL:*** PV: RR = 0.0 (95% CI: 0.0, 0.0) **Retinopathy of Prematurity:**	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary outcome(s)	Critical appraisal
					PV: RR = 5.07 (95% CI: 0.25, 104.70) ***NEC:*** PV: RR = 0.96 (95% CI: 0.30, 3.11) ***Neonatal Sepsis:*** PV: RR = 0.58 (95% CI: 0.15, 2.25) ***Neonatal Death:*** PV: RR = 0.41 (95% CI: 0.15, 1.15) **3. Women with threatened PTL (i.e. symptomatic)** ***Preterm Birth < 37 weeks:*** PV: RR = 0.76 (95% CI: 0.55, 1.06) ***Preterm Birth < 28 weeks:*** PV: RR = 0.99 (95% CI: 0.06, 15.60) ***RDS:***	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary outcome(s)	Critical appraisal
					PV: RR = 0.48 (95% CI: 0.20, 1.15) ***Use of Mechanical Ventilation:*** PV: RR = 0.30 (95% CI: 0.06, 1.37) ***Neonatal Sepsis:*** PV: RR = 0.26 (95% CI: 0.07, 1.00) ***Neonatal Death:*** PV: RR = 0.17 (95% CI: 0.02, 1.40)	

Abbreviations: BPD = bronchopulmonary dysplasia; BW = birthweight; CI = confidence interval; fFN = fetal fibronectin; IPD = individual patient data; IVH = intraventricular hemorrhage; MA = meta-analysis; NEC = necrotizing enterocolitis; NICU = neonatal intensive care unit; NIHR = National Institute for Health Research; NNT = number needed to treat; PO = per os; PPROM = preterm premature rupture of membranes; PROM = premature rupture of membranes; PTL = preterm labour; PV = per vaginal; PVL = periventricular leukomalacia; QoL = quality of life; RCT = randomized controlled trial; RDS = respiratory distress syndrome; RR = relative risk; SR = systematic review

Table 31 – Evidence table: RCTs progesterone

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary outcome(s)	Critical appraisal
Saleh Gargari , 2012[36]	• **Design:** Randomized control study • **Sources of funding:**	• **Eligibility criteria:** ***Inclusion criteria:*** all singleton pregnancies at ≥24 and <34 weeks complicated with preterm labor	• **Intervention(s):** Progesterone (vaginal) • **Comparator(s):**	• **Effect size primary outcome** <u>*Neonatal death*</u>: Progesterone group (n/N): 3/72	• **Effect size secondary outcome** NR	• **RoB:** ***Random sequence generation:*** Low risk of bias

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary outcome(s)	Critical appraisal
	NR • **Setting:** Mahdieh Tertiary Care Hospital affiliated to Shahid Beheshti University of Medical Sciences in Tehran, Iran • **Sample size:** 144 • **Duration:** March 2007 through March 2010	The criteria used for the diagnosis of acute preterm labor included persistent uterine contractions (e.g., at least four every 20 minutes or eight every 60 minutes), cervical dilation of 1 to 3 cm, effacement exceeding 50 percent, a change in cervical dilation, or effacement detected by serial examinations] ***Exclusion criteria:*** preterm premature rupture of membranes, premature termination for obstetric indications and fetal anomaly, vaginal bleeding, polyhydramnios, fetal anomalies, suspected chorioamnionitis or intrauterine growth retardation (IUGR), and concomitant cardiovascular disease of woman (e.g., preeclampsia, gestational or chronic hypertension). • **Patients characteristics:** Mean Age±SD (years): Progesterone: 24.2±3.7 No drug: 25.4 ± 2.9 Mean initial gestational age±SD (years): Progesterone: 32.2 ±2.8 No drug: 32.7 ± 2.6 Mean length of cervix ±SD (cm): Progesterone:1.8 ±0.3	No drug	No-drug group (n/N): (4.2%), 8/72 (11.1%) ; p=0.08		***Allocation concealment:*** Unclear risk of bias ***Blinding Participants and Personnel:*** Low risk of bias ***Blinding Outcome Assessment:*** Unclear risk of bias ***Incomplete Outcome Data:*** High risk of bias ***Selective Reporting:*** High risk of bias ***Other Bias:*** Unclear risk of bias

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary outcome(s)	Critical appraisal
		No drug: 1.7 ± 0.4 Mean dilation of cervix ±SD (cm): Progesterone:1.5 ±0.2 No drug: 1.6 ± 0.3 • **Median FU:** NR				
Bimbashi 2013[37]	• **Design:** Randomized control trial • **Sources of funding:** NR • **Setting:** University Hospital of Obstetrics and Gynecology, Tirana, Albania • Sample size: NR • Duration: NR	• **Eligibility criteria:** Singleton pregnancy. CL <30 mm at two independent measurements. • **Patients characteristics:** NR • **Median FU**: NR	• **Intervention(s):** Vaginal Progesterone • **Comparator(s):** No treatment	• **Effect size primary outcome** ***PTB< 34 weeks:*** 9.2% progesterone vs 17.2% without treatment ***Women with short cervix:*** Asymptomatic women with a short cervix between 20-24 weeks gestation was associated with a reduction of preterm birth rate before 34 weeks. Note: No exact numbers were reported.	• **Effect size secondary outcome** NR	• **RoB** *Unclear risk of Bias for all domains*

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary outcome(s)	Critical appraisal
Palacio 2013[38]	• **Design:** prospective, randomized, double blind, clinical trial • **Sources of funding:** NR • **Setting:** 12 centers all over Spain • **Sample size:** 265 • **Duration:** NR	• **Eligibility criteria:** single pregnancy and preterm labor successfully arrested, in whom decision of discharge was made, gestational age between 24.0-34.0 weeks and cervical length<25mm • **Patients characteristics:** Gestational age at delivery (weeks, mean ± SD) Progesterone: 37.5 ± 5.2 Placebo: 37.2 ± 5.9 • **Median FU**: NR	• **Intervention(s):** Progesterone (vaginal) • **Comparator(s):** • Placebo control	**PTB <34 weeks:** 10/127 (7.9%) vs 12/132 (9.1%), p =0.82 **PTB<37 weeks:** • 38/127 (29.9%) vs 33/132 (25%), p=0.40	NR	• **RoB** ***Random sequence generation:*** low risk of bias ***Allocation concealment:*** Low risk of bias ***Blinding Participants and Personnel:*** Unclear risk of bias ***Blinding Outcome Assessment:*** Unclear risk of bias ***Incomplete Outcome Data:*** Unclear risk of bias ***Selective Reporting:*** Unclear risk of bias ***Other Bias:*** • Unclear risk of bias

Abbreviations: FU = follow up; n= number of events; N: Sample size; NR = not reported; RCT = randomized controlled trial; RR = relative risk; SD = standard deviation

Table 32 – Evidence table: SRs cerclage

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary outcome(s)	Critical appraisal
Alfirevic 2012[41]	**Design:** SR and MA **Sources of funding:** Cochrane review **Search date:** Oct 31st, 2012 **Searched databases:** Cochrane Pregnancy and Childbirth Group's Trials Register **Included study designs:** RCT and e cluster-randomised **Number of included studies:** 12 RCTs (51 reports)	**Eligibility criteria:** Women with singleton pregnancies considered to be at 'high risk' for pregnancy loss based on women's history (e.g. previous preterm birth), finding of a short cervix on ultrasound scanning, or physical exam-detected cervical changes. **Patients characteristics** Asymptomatic , and singletons **(Planned subgroup analyses relevant to the key question):**	**Intervention:** Cervical stitch in singleton pregnancies considered to be at high risk for pregnancy loss **Comparator:** - Cervical stitch (cerclage) versus no stitch. - Cervical stitch (cerclage) versus any alternative preventative treatment (e.g. progesterone).	**Effect size primary outcome:** Not of interest to this review	**Effect size secondary outcomes:** **First comparison (cerclage vs. No cerclage)** **Neonatal outcomes:** ***Neonatal deaths before discharge*** 1- History-indicated RR = 0.67 (95% CI: 0.33, 1.36) (N=3 studies) 2- One-off ultrasound indicated cerclage in high risk for PTL RR = 2.31 (95% CI: 0.22, 24.01) (N=1 study) 3- Physical exam-indicated cerclage in high risk for PTL RR = 0(95% CI: 0.0, 0.0) (N=0 study) 4- Serial Ultrasound indicated cerclage in high risk for PTL RR = 0.87 (95% CI: 0.13, 5.89) (N=2 studies) ***Preterm birth < 37 weeks*** 1- History-indicated RR = 0.86 (95% CI: 0.59, 1.27)	**AMSTAR Score:** 10

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary outcome(s)	Critical appraisal
		1- Cervical stitch based on previous obstetric history, e.g. previous PTB versus no cerclage. 2- Cervical stitch based on one off ultrasound scan of the cervix in high risk for preterm birth (previous history, versus no cerclage. 3- Cervical stitch based on physical exam in high risk for preterm birth (previous history, versus no cerclage.			(N=4 studies) 2- One-off ultrasound indicated cerclage in high risk for PTL RR = 0.55 (95% CI: 0.30, 0.99) (N=1 study) 3- Physical exam-indicated cerclage in high risk for PTL RR = 0(95% CI: 0.0, 0.0) (N=0 study) 4- Serial Ultrasound indicated cerclage in high risk for PTL RR = 0.78 (95% CI: 0.60, 1.02) (N=4 studies) ***Preterm birth < 34 weeks*** 1- History-indicated cerclage RR = 0.76 (95% CI: 0.40, 1.46) (N=3 studies) 2- One-off ultrasound indicated cerclage in high risk for PTL RR = 0.63 (95% CI: 0.27, 1.46) (N=1 study) 3- Physical exam-indicated cerclage in high risk for PTL RR = 0(95% CI: 0.0, 0.0)	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary outcome(s)	Critical appraisal
					(N=0 study) 4- Serial Ultrasound indicated cerclage in high risk for PTL RR = 0.77 (95% CI: 0.55, 1.10) (N=4 studies) ***Preterm birth < 28 weeks*** 1- History-indicated cerclage RR = 0.82 (95% CI: 0.59, 1.13) (N=3 studies) 2- One-off ultrasound indicated cerclage in high risk for PTL RR = 0.69 (95% CI: 0.18, 2.62) (N=1 study) 3- Physical exam-indicated cerclage in high risk for PTL RR = 0(95% CI: 0.0, 0.0) (N=0 study) 4- Serial Ultrasound indicated cerclage in high risk for PTL RR = 0.71 (95% CI: 0.48, 1.04) (N=4 studies) ***Serious respiratory morbidity (RDS or oxygen dependency after 28 days of life)*** 1- History-indicated cerclage RR = 3.06 (95% CI: 0.32, 28.93)	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary outcome(s)	Critical appraisal
					(N=1 study) 2- One-off ultrasound indicated cerclage in high risk for PTL RR = 0.58 (95% CI: 0.06, 6.00) (N=1 study) 3- Physical exam-indicated cerclage in high risk for PTL RR = 0(95% CI: 0.0, 0.0) (N=0 study) 4- Serial Ultrasound indicated cerclage in high risk for PTL RR = 0.98 (95% CI: 0.53, 1.81) (N=3 studies) ***Necrotising enterocolitis*** 1- History-indicated cerclage RR = 0.00 (95% CI: 0.00, 0.00) (N=0 study) 2- One-off ultrasound indicated cerclage in high risk for PTL RR = 0.00 (95% CI: 0.00, 0.00) (N=0 study) 3- Physical exam-indicated cerclage in high risk for PTL RR = 0(95% CI: 0.0, 0.0)	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary outcome(s)	Critical appraisal
					(N=0 study) 4- Serial Ultrasound indicated cerclage in high risk for PTL RR = 0.81 (95% CI: 0.16, 4.12) (N=3 studies) ***Retinopathy of prematurity*** 1- History-indicated cerclage RR = 0.00 (95% CI: 0.00, 0.00) (N=0 study) 2- One-off ultrasound indicated cerclage in high risk for PTL RR = 0.23 (95% CI: 0.01, 4.58) (N=1 study) 3- Physical exam-indicated cerclage in high risk for PTL RR = 0.00 (95% CI: 0.00, 0.00) (N=0 study) 4- Serial Ultrasound indicated cerclage in high risk for PTL RR = 0.62 (95% CI: 0.15, 2.53) (N=1 study) ***Serious intracranial pathology (IVH or periventricular leucomalacia)*** 1- History-indicated cerclage RR = 1.02 (95% CI: 0.06, 16.09)	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary outcome(s)	Critical appraisal
					(N=1 study) 2- One-off ultrasound indicated cerclage in high risk for PTL RR = 0.38 (95% CI: 0.02, 9.01) (N=1 study) 3- Physical exam-indicated cerclage in high risk for PTL RR = 0.00 (95% CI: 0.00, 0.00) (N=0 study) 4- Serial Ultrasound indicated cerclage in high risk for PTL RR = 0.96 (95% CI: 0.05, 19.53) (N=3 studies) **Maternal outcomes:** ***Cesarean section*** 1- History-indicated cerclage RR = 1.21 (95% CI: 0.96, 1.52) (N=3 studies) 2- One-off ultrasound indicated cerclage in high risk for PTL RR = 1.35 (95% CI: 0.52, 3.50) (N=1 study) 3- Physical exam-indicated	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary outcome(s)	Critical appraisal
					cerclage in high risk for PTL RR = 0(95% CI: 0.0, 0.0) (N=0 study) 4- Serial Ultrasound indicated cerclage in high risk for PTL RR = 1.10 (95% CI: 0.82, 1.46) (N=4 studies) ***Maternal side effects (vaginal discharge, bleeding, pyrexia not requiring antibiotic)*** 1- History-indicated cerclage RR = 1.57 (95% CI: 0.76, 3.24) (N=2 studies) 2- One-off ultrasound indicated cerclage in high risk for PTL RR = 0.00 (95% CI: 0.00, 0.00) (N=0 study) 3- Physical exam-indicated cerclage in high risk for PTL RR = 0.00 (95% CI: 0.00, 0.00) (N=0 study) **Second comparison (cerclage vs.** versus any alternative preventative treatment (e.g. progesterone)**)** No outcome data was provided for Oral or Vaginal Progesterone	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary outcome(s)	Critical appraisal
Conde-Agudelo 2013[42] **Companion**[53]	**Design:** SR, IPD MA for cerclage vs. no cerclage, and indirect comparison MA for cerclage vs. progesterone **Sources of funding:** in part by the Intramural Research Program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development **Search date:** Inception – Oct 31 2012	**Eligibility criteria:** Asymptomatic women with a sonographic short cervix (<25 mm) in mid trimester, singleton gestation, and previous spontaneous preterm birth < 37 weeks	**Intervention:** Cerclage •4 studies - McDonald •1 study - Shirodkar **Comparator:** No cerclage Vaginal Progesterone (indirect comparison)	***Preterm birth < 32 weeks:*** • ***vs. no cerclage*** RR = 0.66 (95% CI: 0.48, 0.91) NNT = 10 (95% CI: 7, 38) • ***vs. vaginal progesterone*** RR = 1.41 (95% CI: 0.67, 2.94)	***Preterm birth < 37 weeks:*** • ***vs. no cerclage*** RR = 0.70 (95% CI: 0.58, 0.83) • ***vs. vaginal progesterone*** RR = 0.83 (95% CI: 0.58, 1.19) ***Preterm birth < 35 weeks:*** • ***vs. no cerclage*** RR = 0.70 (95% CI: 0.55, 0.89) • ***vs. vaginal progesterone*** RR = 1.06 (95% CI: 0.63, 1.78) ***Preterm birth < 28 weeks:*** • ***vs. no cerclage*** RR = 0.64 (95% CI: 0.43, 0.96) • ***vs. vaginal progesterone*** RR = 0.20 (95% CI: 0.50, 3.22) ***RDS:*** • ***vs. no cerclage*** RR = 0.61 (95% CI: 0.32, 1.19) • ***vs. vaginal progesterone*** RR = 1.61 (95% CI: 0.46, 5.55) ***NEC:*** • ***vs. no cerclage***	**AMSTAR Score:** 10

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary outcome(s)	Critical appraisal
	Sources Searched: MEDLINE; EMBASE; CINAHL; LILACS; Cochrane Central Register of Controlled Trials; ISI Web of Science; registers of ongoing trials; Google Scholar; congress proceedings; reference lists of identified studies, textbooks, and reviews; contacting experts **Included study designs:** RCTs **Number of included studies:** 4 (vaginal progesterone vs. placebo) 5 (cerclage vs. no cerclage)	**Exclusion criteria:** Quasi-randomized; multiple gestations; women with actual or threated PTL, 2nd trimester bleeding, or PROM; administration of progesterone in first trimester to prevent miscarriage; assessed history-indicated cerclage (placed for the sole indication of poor obstetric history), physical examination-indicated cerclage (placed for 2nd trimester cervical dilation), or compared different cerclage techniques or outpatient vs. inpatient cerclage; compared cerclage with 17P			RR = 0.62 (95% CI: 0.08, 4.67) • ***vs. vaginal progesterone*** RR = 1.32 (95% CI: 0.03, 50) ***Grade III/IV IVH:*** • ***vs. no cerclage*** RR = 0.28 (95% CI: 0.05, 1.64) • ***vs. vaginal progesterone*** RR = 0.56 (95% CI: 0.04, 6.67) ***Neonatal Sepsis:*** • ***vs. no cerclage*** RR = 0.47 (95% CI: 0.21, 1.05) • ***vs. vaginal progesterone*** RR = 1.89 (95% CI: 0.30, 12.5) ***BPD:*** • ***vs. no cerclage*** RR = 1.10 (95% CI: 0.38, 3.18) • ***vs. vaginal progesterone*** RR = 3.57 (95% CI: 0.11, 100)	

Abbreviations: 17P = 17α-hydroxyprogesterone caproate; BPD = bronchopulmonary dysplasia; CI = confidence interval; IPD = individual patient data; IVH = intraventricular hemorrhage; MA = meta-analysis; N = number; NEC = nectrotizing enterocolitis; NICU = neonatal intensive care unit; NNT = number needed to treat; PROM = premature rupture of membranes; PTL = preterm labour; RCT = randomized controlled trial; RDS = respiratory distress syndrome; RR = relative risk; SR = systematic review; VS. = versus

5.3. Tertiary prevention of preterm labour

Table 33 – Evidence table: SR repeated doses of corticosteroids

Crowther 2011[43]	
Methods	
• **Design**	Systematic review of RCTs and meta-analysis
• **Source of funding and competing interest**	• Discipline of Obstetrics and Gynaecology, The University of Adelaide, Australia. • Liggins Institute, University of Auckland, New Zealand. • Australian Department of Health and Ageing, Australia.
• **Search date**	18 April 2011
• **Searched databases**	The Cochrane Pregnancy and Childbirth Group's Trials Register (including searches in CENTRAL, MEDLINE, EMBASE, hand searches, awareness alerts)
• **Included study designs**	RCT
• **Number of included studies**	10
• **Statistical analysis**	Fixed-effect meta-analysis except if clinical heterogeneity or substantial statistical heterogeneity detected. Review manager software.
Patient characteristics	
• **Eligibility criteria**	Women considered to be at risk of pretermbirth who have already received a single course of prenatal corticosteroid seven or more days previously
• **Exclusion criteria**	None stated
• **Patient & disease characteristics**	No overall summary reported
Interventions	
• **Intervention group**	In five trials: two doses of 12 mg/dose betamethasone at weekly intervals One trial: two doses of 12 mg/dose betamethasone every 14 days Three trials planned only a single repeat course of treatment (betamethasone two doses of 12 mg)
• **Control group**	No repeat dose of corticosteroids, with or without the administration of placebo
Results	

• **RDS (infant)**	RR 0.83; 95%CI 0.75-0.91. NNTB 17; 95%CI 11-32
• **Composite serious outcome for the infant (however defined by authors)**	RR 0.84; 95%CI 0.75-0.94. NNT 30; 95%CI 19-79
• **Total deaths up to early childhood FU**	RR 1.01; 95%CI 0.77-1.34
• **Survival free of any disability**	RR 1.00; 95%CI 0.97-1.04
• **Survival free of major disability**	RR 1.01; 95%CI 0.92-1.11
• **Chorioamnionitis**	RR 1.16; 95%CI 0.92-1.46
• **Puerperal sepsis**	RR 1.15; 95%CI 0.83-1.60
Limitations and other comments	
• **Limitations**	Serious shortcomings unlikely

Table 34 – Evidence table: SR maintenance therapy magnesium

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary outcome(s)	Critical appraisal
Han, 2013[44]	**Design:** SR of RCTs **Sources of funding:** None **Search date:** 31 January 2013 **Sources Searched:** Cochrane Pregnancy and Childbirth Group's Trials	**Eligibility criteria:** Magnesium maintenance therapy administered to the woman by any route prior to delivery, compared with either placebo, no treatment or alternative maintenance tocolytic therapy.	**Intervention:** Magnesium **Comparator:** placebo or no treatment **Time of initiation of Maintenance tocolysis in terms of:**	**Outcome of interest Effect estimate and 95% CI** **Preterm birth<37 Weeks**: RR 1.05 (95% CI: 0.80, 1.40) **Preterm birth<32 Weeks** Not estimable **Preterm birth<32 Weeks** Not estimable **Death before discharge**: RR 5.00 (95%CI: 0.25, 99.16)	**Outcome of interest** **Effect estimate and 95% CI** **Respiratory distress syndrome:** RR 3.00 (95% CI: 0.13, 70.30) **Maternal side effects** (Diarrhea): RR 7.67 (95% CI: 2.41, 24.41) **Maternal side effects** (nausea, vomiting, tachycardia):	**AMSTAR Score:** 10

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary outcome(s)	Critical appraisal
	Register (reviews identified from CENTRAL, MEDLINE, EMBASE, handsearches of 30 journals and proceedings of major conferences, weekly awareness alerts for a further 44 journals, monthly BioMed Central email alerts) **Included study designs:** RCTs **Number of included studies:** 3 *Note: 1 study used Mg(SO)4, 2 used MgCl and 1 used Mg oxide*	*Note:* Gestation at inclusion was not reported. In the included primary studies the gestation ranged from 20 to 36 weeks. **Exclusion criteria:** Magnesium sulphate was used together with an alternative tocolytic as maintenance therapy	1) **Hours after presentation:** NR 2) **Relationship with symptoms:** NR **Time of maintenance tocolysis discontinuation:** NR		Various estimates (Not significant)	

Abbreviations: *CI= confidence interval; NR= not reported; RCT = randomized controlled trial; RDS = respiratory distress syndrome; RR = relative risk; SR = systematic review*

Table 35 – Evidence table: SR maintenance therapy nifedipine

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary outcome(s)	Critical appraisal
Conde-Agudelo, 2012[46]	**Design:** SR of RCTs **Sources of funding:** This research was supported by the Intramural Research Program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services **Search date:** 1960 to June 30, 2010 for MEDLINE,EMBASE, CINAHL, and LILACS Other databases were searched from inception to June 30, 2010 **Sources Searched:**	**Eligibility criteria:** Patient with preterm labor received nifedipine for tocolysis and compared with alternative tocolytic agents, placebo or no treatment (we focused on comparison of no treatment /placebo) **Exclusion criteria:** If patients received different doses of nifedipine or other calcium channel blockers, or if nifedipine was given in addition to or following failure of another tocolytic drug	**Intervention:** Nifedipine maintenance **Comparator:** No treatment or placebo **Time of initiation and discontinuation of maintenance tocolysis in terms of:** **1) Hours after presetnation:** Time of initiation was after arrest of preterm labour via acute tocolysis but the exact hours not reported. All studies evaluating maintenance	**Outcome of interest Effect estimate and 95% CI** **Preterm birth<34 weeks** RR 1.33 (95% CI: 0.64, 2.78) **Preterm birth<37 weeks** RR 0.87 (95% CI: 0.69, 1.08) **Preterm birth<34 weeks among women enrolled at< 32 weeks' gestation:** RR 0.96 (95% CI: 0.43, 2.15) **Preterm birth<37 weeks among women enrolled at< 32 weeks' gestation:** RR 0.93 (95% CI: 0.72, 1.20)	**Outcome of interest Effect estimate and 95% CI** **Neonatal Sepsis:** RR 2.00 (95% CI: 0.19, 21.18) **Necrotizing enterocolitis:** RR 1.67 (95% CI: 0.23, 12.33) **Intraverntricular Haemorrhage:** RR 0.71 (95% CI: 0.14, 3.54) **Pregnancy Prolongation (days):** Mean difference 6.3 (95% CI: 1.2, 11.4) **Pregnancy Prolongation (days) among women enrolled at< 32 weeks' gestation:** Mean difference 11.0 (95% CI: -2.1, 24.2)	**AMSTAR Score:** 9

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary outcome(s)	Critical appraisal
	MEDLINE, EMBASE, CINAHL, and LILACS, Cochrane Central Register of Controlled Trials, ISI Web of Science, Research Registers of ongoing trials (www.clinicaltrials.gov, www.controlledtrials.com, www.centerwatch.com, www.anzctr.org.au, http://www.nihr.ac.uk, and www.umin.ac.jp/ctr), and Google scholar **Included study designs:** RCTs. Published abstracts alone were excluded if additional information on methodological issues and results could not be obtained. Trials were excluded if they were quasi-randomized. **Number of included studies:** 26 included studies (3 evaluated maintenance tocolytics)		Tocolysis used nifedipine 20 mg orally every 4 to 6 hours until 37 weeks of gestation or delivery, whichever occurred first. 2) **Relationship with symptoms:** NR		**Respiratory distress syndrome** RR 0.78 (95% CI: 0.31, 1.98) **Neonatal death** RR 0.20 (95% CI: 0.01, 4.04)	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary outcome(s)	Critical appraisal
	The focus of updated was ONLY the maintenance tocolytics.					

Abbreviations: *CI= confidence interval; NR= not reported; RCT = randomized controlled trial; RDS = respiratory distress syndrome; RR = relative risk; SR = systematic review*

Table 36 – Evidence table: RCTs maintenance therapy nifedipine

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Roos (2013)[54] **Companions:**[55-58]	**Design:** RCT **Sources of funding:** This trial was funded by ZonMw, the Netherlands Organization for Health Research and Development Healthcare Efficiency Program grant 80-82310-98-08210. **Setting:** 11 perinatal units including all tertiary centers in the Netherlands	**Eligibility criteria:** Women with threatened preterm labor and a gestational age between weeks 26 (plus 0 days) and 32 (plus 2 days), who had not delivered after a complete 48-hour course of tocolytics and corticosteroids, were eligible for participation. Included women were singleton and multiple pregnancies with and without ruptured membranes.	**Intervention:** Nifidipine **Comparator:** Placebo	**Outcome of interest Effect estimate and 95% CI** **Neonatal Sepsis:** RR 0.85 (95% CI: 0.26 , 2.7) **IVH> grade 2:** RR 0.91 (95% CI: 0.48 , 1.7) **Necrotizing enterocolitis:** RR 1.7 (95% CI: 0.41 , 7.0) **Ventilation support:** RR 1.1 (95% CI: 0.67 , 1.7)	**Outcome of interest Effect estimate and 95% CI** **Prolongation of pregnancy (days):** HR 1.0 (95% CI: 0.84 , 1.2) **Preterm birth<32 weeks** RR 0.95 (95% CI: 0.73 , 1.3) **Preterm birth<34 weeks** RR 1.0 (95% CI: 0.83 , 1.3) **Preterm birth<37 weeks** RR 1.0 (95% CI: 0.89 , 1.2)	**Dropouts:** Nine women (3 in nifedipine, and 6 in placebo group) did not start study medication for these reasons: withdrawal (n=6), need for emergency tocolysis for transfer to another centre (n=1), and signs of intra uterine infection (n=1). **RoB Random sequence generation:** Low risk of bias

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	Sample size: 406 **Duration:** June 2008 and February 2010; follow-up was completed in August 2010.	**Exclusion criteria:** Maternal exclusion criteria were signs of intrauterine infection, hypertension (≥140/90 mm Hg), preeclampsia, HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count), placenta previa, and contraindications for nifedipine. Fetal exclusion criteria included signs of fetal distress, known lethal congenital anomalies, and intrauterine death.			**Serious adverse events** (maternal mortality, perinatal mortality, and severe maternal morbidity with admittance to the intensive care unit or critical care unit): RR 1.2 (95% CI: 0.38, 4.0) **Hemorrhage>1000ml:** RR 2.6 (0.73, 9.3)	**Allocation concealment:** Unclear risk of bias **Blinding Participants and Personnel:** Low risk of bias **Blinding Outcome assessment:** Unclear risk of bias **Incomplete Outcome data:** Low risk of bias **Selective Reporting:** Low risk of bias **Other Bias:** Low risk of bias

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
		Patients characteristics: 22% of the women had multiple gestations, mean age was 30.2 years with standard deviation of 5.1. Additional tocolysis was given to 6% of women in treatment arm and 4.4% in placebo arm. **Prevalence of disease:** PTB<37: 67%				
Chawanpaiboon **(2012)**[59] **Companion:**[60]	**Design:** RCT **Sources of funding:** NR **Setting:** Siriraj Hospital **Sample size:** 100 **Duration:** 1 May 2007 to 31 December 2008	**Eligibility criteria:** singleton pregnancies Women with threatened preterm between at 28–35 weeks of gestation **Exclusion criteria:** Women in active labor, defined by the presence of cervical dilatation > 3 cm, those with cervical insufficiency, and those with ruptured membranes	**Intervention:** nifidipine **Comparator:** bed rest	**Outcome of interest Effect estimate and 95% CI** No outcomes of interest	**Outcome of interest Effect estimate and 95% CI** No outcomes of interest	**Dropouts:** NR **RoB: Random sequence generation:** Unclear Risk of Bias **Allocation concealment:** Unclear Risk of Bias **Blinding Participants and Personnel:** Unclear Risk of Bias

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
		Patients characteristics: Patients with cervical length <3 cm were enrolled in this study **Prevalence of disease:** NR				**Blinding Outcome assessment:** Unclear Risk of Bias **Incomplete Outcome data:** Low risk of Bias **Selective Reporting:** High risk of Bias **Other Bias:** Unclear Risk of Bias
Uma (2012)[61] (Abstract only)	**Design:** RCT **Sources of funding:** NR **Setting:** NR **Sample size:** 98 **Duration:** January 2010-August 2011	**Eligibility criteria:** NR **Exclusion criteria:** NR **Patients characteristics:** Women with preterm labour at 22-34 weeks **Prevalence of disease:** Preterm birth 50%	**Intervention:** maintenance nifidipine up to 36 weeks **Comparator:** standard dose of nifedipine for 72 hours	**Outcome of interest Effect estimate and 95% CI** ***Prolongation of pregnancy:*** Significant prolongation of pregnancy (of about 9 days) with maintenance nifedipine Note: no effect size or pvalue is given in abstract	**Outcome of interest Effect estimate and 95% CI** NR	**Dropouts:** NR **RoB**: **Random sequence generation:** Unclear Risk of Bias **Allocation concealment:** Unclear Risk of Bias **Blinding Participants and Personnel:** Unclear Risk of Bias

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
				Preterm Birth: More full term deliveries in treatment group (60%) than in control group (40%)but not statistically significant		**Blinding Outcome assessment:** Unclear Risk of Bias **Incomplete Outcome data:** Unclear Risk of Bias **Selective Reporting:** Unclear Risk of Bias **Other Bias:** Unclear Risk of Bias
Parry (2012)[62] (Abstract only)	**Design:** RCT **Sources of funding:** NR **Setting:** NR **Sample size:** 60 **Duration**: 2003 and 2008	**Eligibility criteria:** women with a singleton pregnancy in threatened preterm labour (24+0 weeks to 33+6 weeks) with a positive Fetal Fibronectin swab who had completed a course of corticosteroids and 48 hours of acute nifedipine tocolysis **Exclusion criteria:**	**Intervention:** Nifidipine maintenance (continued until week 37) **Comparator:** Placebo	**Outcome of interest Effect estimate and 95% CI** **Prolongation of pregnancy** **by >7 days**: RR 0.94 (95% CI: 0.72 , 1.2)	**Outcome of interest Effect estimate and 95% CI** NR	**Dropouts:** NR **RoB: Random sequence generation:** Unclear Risk of Bias **Allocation concealment:** Unclear Risk of Bias **Blinding Participants and Personnel:** Unclear Risk of Bias

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
		ruptured membranes, bleeding, fetal anomaly, suspected chorioamnionitis or contraindication to nifedipine **Patients characteristics:** NR **Prevalence of disease:** NR				**Blinding Outcome assessment:** Unclear Risk of Bias **Incomplete Outcome data:** Unclear Risk of Bias **Selective Reporting:** Unclear Risk of Bias **Other Bias:** Unclear Risk of Bias

Abbreviations: *FU = follow up; N: Sample size; NR = not reported; RCT = randomized controlled trial; RoB= risk of bias; RR = relative risk*

Table 37 – Evidence table: SR maintenance therapy oral betamimetics

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary outcome(s)	Critical appraisal
Dodd, 2012[45]	**Design:** SR of RCTs (quasi-randomised studies and those presented only in abstract form were not included.) **Sources of funding:** NR	**Eligibility criteria:** Women who have had at least one episode of threatened preterm labour that settled without preterm birth.	**Intervention:** Oral Betamimetics	**Outcome of interest Effect estimate and 95% CI** ***Very preterm birth (< 34 weeks):*** RR = 2.81 (95% CI: 0.30, 26.22) Ritodrine versus placebo/no treatment:	**Outcome of interest Effect estimate and 95% CI** ***Preterm birth (< 37 weeks):*** RR = 1.11 (95% CI: 0.91, 1.35) Ritodrine versus placebo/no treatment:	**AMSTAR Score:** 9

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary outcome(s)	Critical appraisal
	Search date: 25 January 2011 **Sources Searched:** MEDLINE, and CENTRAL database. Details of the search strategies for CENTRAL and MEDLINE, the list of hand searched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group. **Included study designs:** RCTs **Number of included studies:** 10 RCTs on oral betamimetics maintenance	**Exclusion criteria:** Women who received an oral betamimetic in combination with another tocolytic.	**Comparator:** placebo/no treatment, and alternative tocolytic therapy (we focused only on placebo/no treatment) **Time of initiation of Maintenance tocolysis in terms of:** No information at SR level 1) **Hours after presetnation:** NR 2) **Relationship with symptoms:** 3) NR **Time of maintenance tocolysis discontinuation:** NR	RR = 2.81 (95% CI: 0.30, 26.22) ***Maternal death or serious maternal morbidity:*** (not estimable)	RR = 1.08 (95% CI: 0.75, 1.57) Terbutaline versus placebo/no treatment: RR = 1.12 (95% CI: 0.89, 1.41) ***Respiratory distress syndrome:*** RR = 1.10 (95% CI: 0.61, 1.98) Ritodrine versus placebo/no treatment: RR = 1.46 (95% CI: 0.57, 3.73) Terbutaline versus placebo/no treatment: RR = 0.93 (95% CI: 0.43, 1.98) **Necrotising enterocolitis:** RR = 0.98 (95% CI: 0.22, 4.28) Terbutaline versus placebo/no treatment: RR = 0.98 (95% CI:0.22, 4.28) **Intraventricular haemorrhage:**	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary outcome(s)	Critical appraisal
					RR = 0.97 (95% CI: 0.27, 3.580 Ritodrine versus placebo/no treatment: RR = 3.0 (95% CI: 0.13, 70.30) Terbutaline versus placebo/no treatment: RR = 0.72 (95% CI: 0.16, 3.24) ***Need for mechanical ventilation:*** RR = 0.94 (95% CI: 0.06, 14.61) Ritodrine versus placebo/no treatment: RR = 0.94 (95% CI: 0.06, 14.61)	

Abbreviations: CI= confidence interval; NR= not reported; RCT = randomized controlled trial; RDS = respiratory distress syndrome; RR = relative risk; SR = systematic review

Table 38 – Evidence table: SR maintenance therapy oxytocin antagonist

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary outcome(s)	Critical appraisal
Papatsonis, 2009[47]	**Design:** SR of RCTs **Sources of funding:** NR **Search date:** June 2008 *Note:* does not state start date. **Sources Searched:** Cochrane Pregnancy and Childbirth Group's Trials Register (identified from the Cochrane Central Register of Controlled Trials, MEDLINE, handsearches of 30 journals and the proceedings of major Conferences and weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts) **Included study designs:** RCT **Number of included studies:** 1	**Eligibility criteria:** Pregnant women with preterm labour, with intactmembranes and≤3 cm cervical dilatation, with a live fetus, after uterine quiescence was achieved with intravenous atosiban (not placebo) in a multi-centre trial comparing placebo or atosiban for the treatment of preterm labour. Gestation at inclusion ranged from 20 to 33 6/7 weeks. **Exclusion criteria:** Fetal or placental abnormalities by ultrasonography, maternal indications for delivery, urinary tract infection, and overt clinical manifestations of substance abuse	**Intervention:** Oxytocin antagonist (atosiban) **Comparator:** Placebo **Time of initiation of Maintenance tocolysis in terms of:** **1) Hours after presetnation:** **2) Relationship with symptoms:** NR **Time of maintenance tocolysis discontinuation:** NR at SR level but according to the primary study:	**Outcome of interest Effect estimate and 95% CI** **Preterm birth< 28 Week** RR 0.75 (95% CI: 0.28, 2.01) **Preterm birth< 32 Week** RR 0.85 (95% CI: 0.47, 1.55) **Neonatal death** RR 0.58(95% CI: 0.14, 2.39)	**Outcome of interest Effect estimate and 95% CI** **Preterm birth< 37 Week** RR 0.89 (95% CI: 0.71, 1.12) **Maternal death** Not estimable **Necrotising enterocolitis** RR 2.34 (95% CI: 0.46, 11.93) **Patent ductus arteriosius** RR 1.17 (95%CI: 0.47, 2.91) **Respiratory distress syndrome** RR 1.06 (95%CI 0.66, 1.70)	**AMSTAR Score:** 10

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary outcome(s)	Critical appraisal
			Both active drug and placebo were administered until the end of week 36 of gestation, delivery, or progression of labour requiring an alternative tocolytic agent			

Abbreviations: *CI= confidence interval; NR= not reported; RCT = randomized controlled trial; RDS = respiratory distress syndrome; RR = relative risk; SR = systematic review*

5.3.1. Magnesium sulphate for neuroprotection

Table 39 – Evidence table: SR magnesium sulphate for neuroprotection

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary outcome(s)	Critical appraisal
Conde-Agudelo, 2009[48]	**Design:** SR of RCTs **Sources of funding:** This research was supported by the Intramural Research Program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services **Search date:** PubMed, Embase, Cinahl, and Lilacs (inception to March 30, 2009) All other databases from 1960 to March 30, 2009. **Sources Searched:** PubMed, Embase, Cinahl, and Lilacs, ISI Web of Science, the Cochrane Central Register of Controlled Trials and Research Registers of	**Eligibility criteria:** Women at risk of preterm birth before 34 weeks of gestation, who received magnesium sulfate versus placebo or no magnesium sulfate to prevent cerebral palsy and other neurologic abnormalities in the unborn baby or if the primary aim was otherwise but data on cerebral palsy were reported for the infants. **Exclusion criteria:** Quasi-randomized studies were excluded.	**Intervention:** magnesium sulfate **Comparator:** Placebo or no treatment	**Outcome of interest Effect estimate and 95% CI** ***Cerebral palsy and pediatric mortality*** **Cerebral palsy:** RR= 0.69 (95% CI: 0.55–0.88) **Moderate/severe cerebral palsy:** RR=0.64; (95% CI: 0.44–0.92) **Mild cerebral palsy:** **RR=**0.74 (95%CI: 0.52–1.04) **Total pediatric mortality:** **RR=** 1.01 (95% CI: 0.84–1.19)	**Outcome of interest Effect estimate and 95% CI** ***Neonatal outcomes:*** **Apgar Score<7 at 5 minutes:**RR= 1.03(95% CI: 0.90– 1.18) **Neonatal Seizures: RR=** 0.80(95% CI: 0.56–1.13) **Need for supplemental oxygen at 36 weeks:** RR= 1.12(95% CI: 0.95–1.32) **Mechanical ventilation: RR=** 0.99(95% CI: 0.89–1.09) ***Maternal outcomes:*** **Death: RR=** 0.32(95%CI: 0.01–7.92) **Cardiac or respiratory arrest:** Not estimable	**AMSTAR Score:9**

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary outcome(s)	Critical appraisal
	ongoing trials (www.clinicaltrials.gov, www.controlled-trials.com, www.centerwatch.com, www.actr.org.au, www.nrr.nhs.uk, and www.umin.ac.jp/ct **Included study designs:** RCTs **Number of included studies:** 5 studies (6 trials) Note: The aim of one trial was eclampsia prevention; one study was counted as two trials because it had on two arms: tocolytic and neuroprotective effects of magnesium sulphate				**Pulmonary edema:** RR= 2.79(95% CI: 0.74–10.47) **Respiratory depression:** RR= 1.31 (95% CI: 0.83–2.07) **Severe postpartum hemorrhage:** RR=1.06(95% CI: 0.63–1.79)	

Abbreviations: *CI= confidence interval; NR= not reported; RCT = randomized controlled trial; RR = relative risk; SR = systematic review*

Table 40 – Evidence table: RCTs magnesium sulphate for neuroprotection

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Horton (2012)[63] **Abstract only**	**Design:** Secondary analysis of an RCT **Sources of funding:** NR **Setting:** NR **Sample size:** 1377 **Duration:** NR	**Eligibility criteria:** NR **Exclusion criteria:** NR **Patients characteristics:** Gravid women between 24-31(6/7) weeks of gestation with preterm premature rupture of membranes without evidence of preterm labour received magnesium sulphate for prevention of cerebral palsy in newborn **Prevalence of disease:** NR	**Intervention:** Magnesium sulfate **Comparator:** Placebo	**Outcome of interest** **Effect estimate and 95% CI** NR	**Outcome of interest** **Effect estimate and 95% CI** ***RDS:*** OR= 1.00 (95% CI:[0.81, 1.23 ***IVH (Grade 3 or 4):*** OR= 0.45 (95% CI: 0.20, 1.00) ***Culture proven sepsis:*** OR=1.00 (95% CI: 0.74, 1.34) ***Necrotizing enterocolitis:*** OR= 1.22 (95% CI: 0.83, 1.79) ***Retinopathy of prematurity:*** OR= 1.04 (95% CI: 0.80, 1.36) ***Death:*** OR= 0.97 (95% CI: 0.64, 1.46)	**Dropouts:** NR **RoB** **Random sequence generation:** Unclear Risk of Bias **Allocation concealment:** Unclear Risk of Bias **Blinding Participants and Personnel:** Unclear Risk of Bias **Blinding Outcome assessment:** Unclear Risk of Bias **Incomplete Outcome data:** Unclear Risk of Bias **Selective Reporting:** Unclear Risk of Bias **Other Bias:** Unclear Risk of Bias

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Leveno (2013)[64] **Abstract only**	**Design:** Secondary analysis of an RCT **Sources of funding:** NR **Setting:** NR **Sample size:** 99 had CP of 1811 infants examined **Duration:** NR	**Eligibility criteria:** Women who delivered infants without major anomalies between 24 and 32 weeks. **Exclusion criteria:** NR **Patients characteristics:** Pregnant women received magnesium sulphate for prevention of cerebral palsy in newborn **Prevalence of disease:** Cerebral Palsy 5.5%	**Intervention:** Magnesium sulphate **Comparator:** Placebo	**Outcome of interest** **Effect estimate and 95% CI** NR	**Outcome of interest** **Effect estimate and 95% CI** **MgSO4 exposure:** Adjusted OR= 0.58 (95% CI: 0.35, 0.95) **Preterm labour:** Adjusted OR= 1.98 (95% CI: 1.06, 3.71) **IVH (Grade 3 and 4):** Adjusted OR= 5.96 (95% CI: 2.5, 14.24) **PVL:** Adjusted OR= 45.38 (95% CI: 18.01, 114.34)	**Dropouts:** NR **RoB:** **Random sequence generation:** Unclear Risk of Bias **Allocation concealment:** Unclear Risk of Bias **Blinding Participants and Personnel:** Unclear Risk of Bias **Blinding Outcome assessment:** Unclear Risk of Bias **Incomplete Outcome data:** Unclear Risk of Bias **Selective Reporting:** Unclear Risk of Bias **Other Bias:** Unclear Risk of Bias

Abbreviations: *CP= cerebral palsy; FU = follow up; IVH = intraventricular hemorrhage; MgSO4= magnesium sulphate; n= number of events; N: Sample size; NR = not reported; PVL = periventricular leukomalacia; RCT = randomized controlled trial; RDS = respiratory distress syndrome; RoB= risk of bias; RR = relative risk;*

6. SUMMARY OF FINDINGS TABLES AND GRADE PROFILES

6.1. Secondary prevention: progesterone

Table 41 – GRADE evidence profile: vaginal progesterone versus no progesterone in asymptomatic women with a history of prior preterm birth

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaginal progesterone	No progesterone	Relative (95% CI)	Absolute		
Neonatal death												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	9/378 (2.4%)	8%[3] (n/N = 17/374)	RR 0.53 (0.24 to 1.18)	38 fewer per 1000 (from 61 fewer to 14 more)	⊕⊕OO LOW	
Necrotising enterocolitis												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	3/359 (0.84%)	2%[3] (n/N = 6/352)	RR 0.53 (0.15 to 1.92)	9 fewer per 1000 (from 17 fewer to 18 more)	⊕⊕OO LOW	
Intraventricular haemorrhage, Grade III or IV												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	1/309 (0.32%)	1/302 (0.33%)[6]	RR 0.98 (0.06 to 15.55)	0 fewer per 1000 (from 3 fewer to 48 more)	⊕⊕OO LOW	
Periventricular Leucomalacia												
1	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	very serious[5]	none	1/69 (1.4%)	0/72 (0%)[6]	RR 3.13 (0.13 to 75.52)	-	⊕OOO VERY LOW	
Neonatal sepsis												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	0/119 (0%)	6%[3] (n/N = 7/122)	RR 0.13 (0.02 to 1.01)	52 fewer per 1000 (from 59 fewer to 1 more)	⊕⊕OO LOW	
Respiratory distress syndrome												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	34/309 (11%)	36/302 (11.9%)[6]	RR 0.92 (0.59 to 1.43)	10 fewer per 1000 (from 49 fewer to 51 more)	⊕⊕OO LOW	
Use of assisted ventilation												
1	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	serious[2]	none	3/69 (4.3%)	13/72 (18.1%)[6]	**RR 0.24 (0.07 to 0.81)**	137 fewer per 1000 (from 34 fewer to 168 fewer)	⊕⊕OO LOW	
Preterm birth <34 weeks												

4	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	8/228 (3.5%)	20%[3] (n/N=41/226)	**RR 0.21 (0.1 to 0.44)**	158 fewer per 1000 (from 112 fewer to 180 fewer)	⊕⊕OO LOW	
Preterm birth <37 weeks												
5	randomised trials	no serious risk of bias	very serious[4]	serious[1]	no serious imprecision	none	162/537 (30.2%)	38%[3] (n/N = 202/528)	**RR 0.52 (0.29 to 0.92)**	182 fewer per 1000 (from 30 fewer to 270 fewer)	⊕OOO VERY LOW	

[1] Preterm birth is of concern not per se but because it predicts short-term and longterm adverse health outcomes associated with preterm birth. However, there is some uncertainty whether drug induced prolongation of pregnancy would improve adverse health outcomes of prematurity.
[2] Although statistically significant difference, the estimate is deemed fragile because it originates in small sample size and event rates (i.e. GRADE optimal information size criterion not met)
[3] Median control event rate across contributing studies
[4] Largest trial (n=611) showed no important difference. Other trials were less than 145 sample size.
[5] GRADE optimal information size criteria not met and also imprecise 95% CI allowing for the possibilities of important benefit and no difference or even possible harm if the upper bound of 95% CI is judged to be importantly above the null.
[6] Single study control event rate
[7] Although in general we did not downgrade on risk of bias when the body of evidence comprised of several studies with unclear risk, this very small single study had all risk of bias domains rated as unclear except for selective reporting. As such, the concerns about risk of bias became important.

Table 42 – GRADE evidence profile: oral progesterone in asymptomatic women with a history of prior preterm birth

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral progesterone	No progesterone	Relative (95% CI)	Absolute		
Neonatal death												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	3/74 (4.1%)	7/74 (9.5%)[3]	RR 0.43 (0.12 to 1.59)	54 fewer per 1000 (from 83 fewer to 56 more)	⊕⊕OO LOW	
Respiratory distress syndrome												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	3/74 (4.1%)	31/74 (41.9%)[3]	**RR 0.10 (0.03 to 0.3)**	377 fewer per 1000 (from 293 fewer to 406 fewer)	⊕⊕⊕O MODERATE	
Use of assisted ventilation												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	0/19 (0%)	3/14 (21.4%)[3]	RR 0.11 (0.01 to 1.92)	191 fewer per 1000 (from 212 fewer to 197 more)	⊕⊕OO LOW	
Preterm birth <34 weeks												

1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	22/74 (29.7%)	37/74 (50%)[3]	**RR 0.59 (0.39 to 0.9)**	205 fewer per 1000 (from 50 fewer to 305 fewer)	⊕⊕OO LOW	
Preterm birth <37 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[4]	none	5/19 (26.3%)	8/14 (57.1%)[3]	RR 0.46 (0.19 to 1.11)	309 fewer per 1000 (from 463 fewer to 63 more)	⊕OOO VERY LOW	

[1] Preterm birth is of concern not per se but because it predicts short-term and longterm adverse health outcomes associated with preterm birth. However, there is some uncertainty whether drug induced prolongation of pregnancy would improve adverse health outcomes of prematurity.
[2] Although statistically significant difference, the estimate is deemed fragile because it originates in small sample size and event rates (i.e. GRADE optimal information size criterion not met)
[3] Single study control event rate
[4] GRADE optimal information size criteria not met and also imprecise 95% CI allowing for the possibilities of important benefit and no difference or even possible harm if the upper bound of 95% CI is judged to be importantly above the null.

Table 43 – GRADE evidence profile: vaginal progesterone versus no progesterone in asymptomatic women with a short cervix

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaginal progesterone	No progesterone	Relative (95% CI)	Absolute		
Neonatal death												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	5/371 (1.3%)	2%[5] (n/N= 12/361)	RR 0.41 (0.15 to 1.15)	12 fewer per 1000 (from 17 fewer to 3 more)	⊕⊕OO LOW	
Necrotising enterocolitis												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	5/371 (1.3%)	1%[5] (n/N= 5/361)	RR 0.96 (0.3 to 3.11)	0 fewer per 1000 (from 7 fewer to 21 more)	⊕⊕OO LOW	
Intraventricular haemorrhage, Grade III or IV												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	0/235 (0%)	1/223 (0.45%)[3]	RR 0.32 (0.01 to 7.73)	3 fewer per 1000 (from 4 fewer to 30 more)	⊕⊕OO LOW	
Periventricular Leucomalacia												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	0/235 (0%)	0/223 (0%)[3]	Not estimable	-	⊕⊕OO LOW	
Neonatal sepsis												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	10/371 (2.7%)	5%[5] (n/N= 17/361)	RR 0.58 (0.15 to 2.25)	21 fewer per 1000 (from 43 fewer to 62 more)	⊕⊕OO LOW	
Retinopathy or prematurity												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	2/136 (1.5%)	0/138 (0%)[3]	RR 5.07 (0.25 to 104.7)	-	⊕⊕OO LOW	
Respiratory distress syndrome												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	18/371 (4.9%)	11%[5] (n/N= 36/361)	**RR 0.49 (0.29 to 0.85)**	56 fewer per 1000 (from 16 fewer to 78 fewer)	⊕⊕⊕O MODERATE	
Use of assisted ventilation												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	16/136 (11.8%)	25/138 (18.1%)[3]	RR 0.65 (0.36 to 1.16)	63 fewer per 1000 (from 116 fewer to 29 more)	⊕⊕OO LOW	
Preterm birth <28 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	12/235 (5.1%)	23/223 (10.3%)[3]	**RR 0.50 (0.25 to 0.97)**	52 fewer per 1000 (from 3 fewer to 77 fewer)	⊕⊕OO LOW	
Preterm birth <34 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	26/125 (20.8%)	45/125 (36%)[3]	**RR 0.58 (0.38 to 0.87)**	151 fewer per 1000 (from 47 fewer to 223 fewer)	⊕⊕OO LOW	
Preterm birth <37 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[4]	none	71/235 (30.2%)	76/223 (34.1%)[3]	RR 0.89 (0.68 to 1.16)	37 fewer per 1000 (from 109 fewer to 55 more)	⊕OOO VERY LOW	

[1] Preterm birth is of concern not per se but because it predicts short-term and longterm adverse health outcomes associated with preterm birth. However, there is some uncertainty whether drug induced prolongation of pregnancy would improve adverse health outcomes of prematurity.
[2] Although statistically significant difference, the estimate is deemed fragile because it originates in small sample size and event rates (i.e. GRADE optimal information size criterion not met)
[3] Single study control event rate.
[4] GRADE optimal information size criteria not met and also imprecise 95% CI allowing for the possibilities of important benefit and no difference or even possible harm if upper bound of 95% confidence interval was judged to be importantly above the null.
[5] Median control event rate across contributing studies

6.2. Secondary prevention: cerclage

Table 44 – GRADE evidence profile: cerclage versus no cerclage in asymptomatic women with a history of prior preterm birth

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cerclage	No cerclage	Relative (95% CI)	Absolute		
Neonatal death (in-hospital)												
3	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	13/999 (1.3%)	2%[4] (n/N= 19/965)	RR 0.67 (0.33 to 1.36)	7 fewer per 1000 (from 13 fewer to 7 more)	⊕OOO VERY LOW	
Intraventricular haemorrhage or leucomalacia												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/96 (1%)	1/98 (1%)[6]	RR 1.02 (0.06 to 16.09)	0 more per 1000 (from 10 fewer to 154 more)	⊕OOO VERY LOW	
Respiratory distress syndrome or oxygen dependency (after 28 days of birth)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/96 (3.1%)	1/98 (1%)[6]	RR 3.06 (0.32 to 28.93)	21 more per 1000 (from 7 fewer to 285 more)	⊕OOO VERY LOW	
Preterm birth <28 weeks												
3	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	60/770 (7.8%)	7%[4] (n/N= 73/769)	RR 0.82 (0.59 to 1.13)	13 fewer per 1000 (from 29 fewer to 9 more)	⊕OOO VERY LOW	
Preterm birth <34 weeks												
3	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[5]	none	106/770 (13.8%)	18%[4] (n/N= 138/769)	RR 0.76 (0.4 to 1.46)	43 fewer per 1000 (from 108 fewer to 83 more)	⊕OOO VERY LOW	
Preterm birth <37 weeks												
4	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[5]	none	215/1038 (20.7%)	31%[4] (n/N= 249/1007)	RR 0.86 (0.59 to 1.27)	43 fewer per 1000 (from 127 fewer to 84 more)	⊕OOO VERY LOW	
Cesarean section												
3	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	very serious[3]	none	143/999 (14.3%)	12%[4] (n/N= 115/965)	RR 1.21 (0.96 to 1.52)	25 more per 1000 (from 5 fewer to 62 more)	⊕OOO VERY LOW	
Maternal side effects (discharge, bleeding, pyrexia not requiring antibiotics)												

2	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	very serious[3]	none	71/364 (19.5%)	11%[4] (n/N= 47/336)	RR 1.57 (0.76 to 3.24)	63 more per 1000 (from 26 fewer to 246 more)	⊕OOO VERY LOW	

[1] *High risk of performance bias*
[2] *Preterm birth is of concern not per se but because it predicts short-term and longterm adverse health outcomes associated with preterm birth. However, there is some uncertainty whether procedure induced prolongation of pregnancy would improve adverse health outcomes of prematurity.*
[3] *GRADE optimal information size criteria not met; and also imprecise 95% CI allowing for the possibilities of important benefit and no difference, or even possible harm if upper bound of CI is judged to be importantly above the null.*
[4] *Median control event rate across data contributing studies*
[5] *Very wide 95% confidence interval allowing for the possibilities of important benefit and no difference or even possible harm if upper bound of CI is judged to be importantly above the null*
[6] *Single study control event rate*
[7] *High risk of performance and "other bias"*

Table 45 – GRADE evidence profile: cerclage versus no cerclage in asymptomatic women with a short cervix identified on serial ultrasound

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cerclage	No cerclage	Relative (95% CI)	Absolute		
Neonatal Death (in-hospital)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/44 (2.3%)	3%[3] (n/N= 1/38)	RR 0.87 (0.13 to 5.89)	4 fewer per 1000 (from 26 fewer to 147 more)	⊕OOO VERY LOW	
Necrotising Enterocolitis												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/192 (1.6%)	0%[3] (n/N= 2/170)	RR 0.81 (0.16 to 4.12)	-	⊕OOO VERY LOW	
Intraventricular Hemorrhage or Periventricular Leucomalacia												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/192 (1%)	0%[3] (n/N= 2/190)	RR 0.96 (0.05 to 19.53)	-	⊕OOO VERY LOW	
Retinopathy of Prematurity												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/148 (2%)	5/152 (3.3%)[6]	RR 0.62 (0.15 to 2.53)	13 fewer per 1000 (from 28 fewer to 50 more)	⊕OOO VERY LOW	
Respiratory Distress Syndrome or Oxygen Dependency (after 28 days of life)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	18/192 (9.4%)	9%[3] (n/N= 18/190)	RR 0.98 (0.53 to 1.81)	2 fewer per 1000 (from 42 fewer to 73 more)	⊕OOO VERY LOW	

Preterm Birth < 28 weeks												
4	randomised trials	serious[1]	no serious inconsistency	serious[4]	very serious[2]	none	36/253 (14.2%)	20%[3] (n/N= 52/257)	RR 0.71 (0.48 to 1.04)	58 fewer per 1000 (from 104 fewer to 8 more)	⊕OOO VERY LOW	
Preterm Birth < 34 weeks												
4	randomised trials	serious[1]	no serious inconsistency	serious[4]	very serious[2]	none	65/253 (25.7%)	41%[3] (n/N= 90/257)	RR 0.77 (0.55 to 1.1)	94 fewer per 1000 (from 184 fewer to 41 more)	⊕OOO VERY LOW	
Preterm Birth < 37 weeks												
4	randomised trials	serious[1]	no serious inconsistency	serious[4]	very serious[2]	none	110/253 (43.5%)	61%[3] (n/N= 144/257)	RR 0.78 (0.6 to 1.02)	134 fewer per 1000 (from 244 fewer to 12 more)	⊕OOO VERY LOW	
Cesarean Section												
4	randomised trials	serious[1]	no serious inconsistency	serious[5]	very serious[2]	none	70/253 (27.7%)	26%[3] (n/N= 65/257)	RR 1.10 (0.82 to 1.46)	26 more per 1000 (from 47 fewer to 120 more)	⊕OOO VERY LOW	

[1] High risk of performance bias
[2] GRADE optimal information size criteria not met; and also imprecise 95% CI allowing for the possibilities of important benefit and no difference, or even possible harm if the upper bound of CI is judged to be importantly above the null.
[3] Median control event rate across data contributing studies
[4] Preterm birth is of concern not per se but because it predicts short-term and longterm adverse health outcomes associated with preterm birth. However, there is some uncertainty whether procedure induced prolongation of pregnancy would improve adverse health outcomes of prematurity.
[5] Cesarean section is not of concern per se
[6] Single study control event rate

Table 46 – GRADE evidence profile: vaginal progesterone versus cervical cerclage (indirect meta-analysis) in asymptomatic women with a short cervix or prior history of preterm birth

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaginal progesterone	Cerclage (indirect meta-analysis)	Relative (95% CI)	Absolute		
Bronchopulmonary dysplasia												
3	randomised trials	no serious risk of bias	no serious inconsistency[1]	serious[5]	very serious[3]	none	0/51 (0%)	7/135 (5.2%)[4]	RR 0.28 (0.01 to 9.01)	37 fewer per 1000 (from 51 fewer to 415 more)	⊕OOO VERY LOW	
Necrotising enterocolitis												
8	randomised trials	no serious risk of bias	no serious inconsistency[1]	serious[5]	very serious[3]	none	0/75 (0%)	1/207 (0.48%)[4]	RR 0.76 (0.02 to 31.49)	1 fewer per 1000 (from 5 fewer to 147 more)	⊕OOO VERY LOW	
Intraventricular haemorrhage, Grade III or IV												
8	randomised trials	no serious risk of bias	no serious inconsistency[1]	serious[5]	very serious[3]	none	1/75 (1.3%)	0/207 (0%)[4]	RR 1.79 (0.15 to 22)	-	⊕OOO VERY LOW	
Neonatal sepsis												
8	randomised trials	no serious risk of bias	no serious inconsistency[1]	serious[5]	very serious[3]	none	0/75 (0%)	8/207 (3.9%)	RR 0.53 (0.08 to 3.35)	18 fewer per 1000 (from 36 fewer to 91 more)	⊕OOO VERY LOW	
Respiratory distress syndrome												
8	randomised trials	no serious risk of bias	no serious inconsistency[1]	serious[5]	very serious[3]	none	3/75 (4%)	13/207 (6.3%)[4]	RR 0.62 (0.18 to 2.16)	24 fewer per 1000 (from 51 fewer to 73 more)	⊕OOO VERY LOW	
Preterm birth <28 weeks												
9	randomised trials	no serious risk of bias	no serious inconsistency[1]	very serious[2]	very serious[3]	none	6/75 (8%)	32/250 (12.8%)[4]	RR 0.80 (0.31 to 2.02)	26 fewer per 1000 (from 88 fewer to 131 more)	⊕OOO VERY LOW	
Preterm birth <32 weeks												
9	randomised trials	no serious risk of bias	no serious inconsistency[1]	very serious[2]	very serious[3]	none	9/75 (12%)	48/250 (19.2%)[4]	RR 0.71 (0.34 to 1.49)	56 fewer per 1000 (from 127 fewer to 94 more)	⊕OOO VERY LOW	
Preterm birth <35 weeks												
9	randomised trials	no serious risk of bias	no serious inconsistency[1]	very serious[2]	very serious[3]	none	20/75 (26.7%)	71/250 (28.4%)[4]	RR 0.94 (0.56 to 1.58)	17 fewer per 1000 (from 125 fewer to 165 more)	⊕OOO VERY LOW	

Preterm birth <37 weeks												
9	randomised trials	no serious risk of bias	no serious inconsistency[1]	very serious[2]	very serious[3]	none	34/75 (45.3%)	105/250 (42%)[4]	RR 1.20 (0.84 to 1.72)	84 more per 1000 (from 67 fewer to 302 more)	⊕OOO VERY LOW	

[1] Statistical measures of inconsistency in direct pairwise comparisons were reported as low or nonsignificant. As such we assumed homogeneity across pairwise evidence. Given the reported clinical characteristics of study populations, we assumed that all studies were similar to each other except interventions. Consistency could not be assessed because there were no direct head-to-head comparisons.
[2] Downgraded because: 1) preterm birth is of concern not per se but because it predicts short-term and longterm adverse health outcomes associated with preterm birth. However, there is some uncertainty whether drug/proceduare induced prolongation of pregnancy would improve adverse health outcomes of prematurity. 2) evidence originates in indirect comparsions using the Bucher method.
[3] GRADE optimal information size criteria not met for the pairwise comparisions. Also imprecise 95% CI for indirect comparison allowing for the possibilities of important benefit and no difference or even possible harm if upper bound of CI is judged to be importantly above the null.
[4] Because the control event rates were obtained from individual patient data meta-analysis, we used this rate to estimate risk difference
[5] Downgraded because evidence originates in indirect comparison

Table 47 – GRADE evidence profile: repeated doses antenatal corticosteroids

Quality assessment							No of events/patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Incon-sistency	Indirectness	Imprecision	Other considerations	Repeated dose(s)	Placebo or no treatment	Relative (95% CI)	Absolute		
Respiratoyr distress syndrome												
8	RCT	No serious RoB	no serious inconsistency	no serious indirectness	Serious imprecision[2]	none	463/1603	565/1603 (29%)[1]	0.83 (0.75 to 0.91)	49 fewer per 1000 (from 72 fewer to 26 fewer)	moderate	critical
Composite serious outcome												
7	RCT	No serious RoB	no serious inconsistency	no serious indirectness	Serious imprecision[2]	none	438/2561	519/2533 (27%)[1]	0.84 (0.75-0.94)	43 fewer per 1000 (from 67 fewer to 16 fewer)	moderate	critical
Fetal and neonatal mortality												
9	RCT	No serious RoB	no serious inconsistency	no serious indirectness	Very serious imprecision[3]	none	96/2791	102/2763 (2.4%)[1]	0.94 (0.71-1.23)	1 fewer per 1000 (from 7 fewer to 6 more)	low	critical
Mean head circumference (cm)												
9	RCT	No serious RoB	no serious inconsistency	serious indirectness	Serious imprecision[2]	none				MD -0.32 [-0.49, -0.15] cm	low	important

[1] Median control event rate across contributing studies
[2] Confidence interval includes clinical decision threshold
[3] Confidence interval includes both appreciable benefit and harm

6.3. Tertiary prevention: maintenance therapy

Table 48 – GRADE evidence profile: maintenance therapy with magnesium versus placebo/no maintenance treatment

Quality assessment							No of events/patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Magnesium maintenance tocolysis	Placebo or no treatment	Relative (95% CI)	Absolute		
Death before discharge among live borns												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/25 (8%)	0/25 (0%)[5]	RR 5 (0.25 to 99.16)	-	⊕OOO VERY LOW	critical
Respiratory distress syndrome												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/25 (4%)	0/25 (0%)[5]	RR 3 (0.13 to 70.3)	-	⊕OOO VERY LOW	critical
Brith <37 weeks												
2	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	31/50 (62%)	31/49 (61%)[4]	RR 1.05 (0.8 to 1.4)	30 more per 1000 (from 122 fewer to 244 more)	⊕OOO VERY LOW	important

[1] Performance and "other bias" in Ricci 1991
[2] Preterm birth is of concern not per se but because it predicts short-term and longterm adverse health outcomes associated with preterm birth. As such, there is some uncertainty whether drug induced prolongation of pregnancy would improve adverse neonatal health outcomes of prematurity
[3] GRADE optimal information size criteria not met and also imprecise 95% CI allowing for possibilities of important benefit, no difference, or even possible harm if the upper bound of 95% CI is judged to be importantly above the null.
[4] Median control event rate across contributing studies
[5] Single study control event rate

Table 49 – GRADE evidence profile: maintenance therapy with nifedipine versus placebo/no maintenance treatment

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nifedipine maintenance tocolytic therapy	Placebo/no treatment	Relative (95% CI)	Absolute		
Neonatal death												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	0/40 (0%)	2/40 (5%)[7]	RR 0.20 (0.01 to 4.04)	40 fewer per 1000 (from 49 fewer to 152 more)	⊕⊕OO LOW	critical
Necrotising enterocolitis												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	7/278 (2.5%)	4/282 (1%[3])	RR 1.78 (0.53 to 6)[6]	8 more per 1000 (from 5 fewer to 50 more)	⊕⊕OO LOW	critical
Intraventricular haemorrhage												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	4/278 (1.4%)	8/282 (3%[3])	RR 0.51 (0.15 to 1.66)[6]	15 fewer per 1000 (from 25 fewer to 20 more)	⊕⊕OO LOW	critical
Neonatal sepsis												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	18/241 (7.5%)	19/245 (6%[3])	RR 0.96 (0.51 to 1.78)	2 fewer per 1000 (from 29 fewer to 47 more)	⊕⊕OO LOW	critical
Respiratory distress syndrome												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	7/77 (9.1%)	9/77 (11.7%)[9]	RR 0.78 (0.31 to 1.98)	26 fewer per 1000 (from 81 fewer to 115 more)	⊕⊕OO LOW	critical
Ventilatory support												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	35/201 (17.4%)	34/205 (16.6%)[7]	RR 1.1 (0.67 to 1.7)	17 more per 1000 (from 55 fewer to 116 more)	⊕⊕OO LOW	critical
Preterm birth <34weeks												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[4]	none	108/238 (45.4%)	105/242 (36%[3])	RR 1.04 (0.85 to 1.27)	14 more per 1000 (from 54 fewer to 97 more)	⊕⊕OO LOW	important
Preterm birth <34weeks in women at <32 weeks gestation												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[4]	none	104/226 (46%)	104/229 (40%[3])	RR 1.02 (0.83 to 1.24)	8 more per 1000 (from 68 fewer to 96 more)	⊕⊕OO LOW	important
Preterm birth <37weeks												

4	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	196/308 (63.6%)	206/314 (65%[3])	RR 0.97 (0.85 to 1.12)	19 fewer per 1000 (from 97 fewer to 78 more)	⊕⊕OO LOW	important
Preterm birth <37weeks in women at <32 weeks gestation												
3	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	171/251 (68.1%)	175/257 (71%[3])	RR 1.00 (0.89 to 1.13)	0 fewer per 1000 (from 78 fewer to 92 more)	⊕⊕OO LOW	important
Pregnancy prolongation in days (Better indicated by higher values)												
3	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[5,10]	none	107 days	108 days	-	MD 6.3 higher (1.2 to 11.4 higher)	⊕⊕OO LOW	important
Pregnancy prolongation amongst women enrolled at <32 weeks gestation (Better indicated by higher values)												
3	randomised trials	no serious risk of bias	serious[8]	serious[1]	very serious[5]	none	66 days	75 days	-	MD 11 days higher (2.1 lower to 24.2 higher)	⊕OOO VERY LOW	important

[1] Preterm birth is of concern not per se but because it predicts short-term and longterm adverse health outcomes associated with preterm birth. As such, there is some uncertainty whether drug induced prolongation of pregnancy would improve adverse neonatal health outcomes of prematurity
[2] Although the RR point estimate is close to 1 suggesting no difference, the associated confidence interval indicates arguable imprecision. When converted into absolute risk difference, however, the imprecision appears more pronounced posing concerns about the potential for important improvement and as well as important harms.
[3] Median control event rate across contributing studies
[4] Some uncertainty about study power (OIS criteria) and imprecision around absolute risk difference
[5] GRADE optimal information size criteria not met; also wide 95% CI allowing for the possibilities of important benefit, no difference, and/or possible harm
[6] Because sparse event rate, odds ratio was approximated as relative risk
[7] Single study control event rate
[8] Of the 3 trials, (Carr 1999, Sayin 2004 and Leyll 2008), Sayin 2004 showed strong effect favouring (MD 23.26 days, 95% CI 12.41, 34.11) nifedipine as opposed to Carr 1999 and Leyll 2008 which showed no significant differences (I-squared 75%) [9] Individual study data not available, so this baseline risk is crude average
[10] Although pooled estimate significantly favours the intervention group, there are some concerns about the stability of estimate of effect given small sample size for the body of evidence. A future study may render the mean difference nonsignificant.

Table 50 – GRADE evidence profile: maintenance therapy with oral betamimetics versus placebo/no maintenance treatment

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral betamimetic maintenance tocolysis	Placebo/no treatment	Relative (95% CI)	Absolute		
Intraventricular haemorrhage												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	4/237 (1.7%)	4/229 (1%[3])	RR 0.97 (0.27 to 3.58)	0 fewer per 1000 (from 7 fewer to 26 more)	⊕⊕OO LOW	critical
Respiratory distress syndrome												
6	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[2]	none	20/388 (5.2%)	19/382 (6%[3])	RR 1.10 (0.61 to 1.98)	6 more per 1000 (from 23 fewer to 59 more)	⊕OOO VERY LOW	critical
Birth <37 weeks												
6	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	111/336 (33%)	98/308 (40%[3])	RR 1.11 (0.91 to 1.35)	44 more per 1000 (from 36 fewer to 140 more)	⊕OOO VERY LOW	important
Tachycardia												
4	randomised trials	no serious risk of bias[5]	no serious inconsistency	no serious indirectness	No serious imprecision	none	68/210 (32.4%)	31/204 (17%3)	RR 2.13 (1.52 to 2.98)	192 more per 1000 (from 88 more to 337 more)	⊕⊕⊕⊕ HIGH	critical
Palpitations												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[6]	none	12/72 (16.7%)	2/68 (2.9%)	RR 5.67 (1.32 to 24.40)	137 more per 1000 (from 9 more to 688 more)	⊕⊕⊕O MODERATE	critical
Tachypnoe												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[2,6]	none	15/134 (11.2%)	4/126 (3.2%)	RR 3.52 (1.2 to 10.33)	80 more per 1000 (from 6 more to 296 more)	⊕⊕⊕O MODERATE	critical
Hypotension												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[6]	none	21/85 (24.7%)	11/81 (13.6%)	RR 1.89 (1.13 to 3.19)	121 more per 1000 (from 18 more to 297 more)	⊕⊕⊕O MODERATE	critical

[1] *Preterm birth is of concern not per se but because it predicts short-term and long-term adverse health outcomes associated with preterm birth. As such, there is some uncertainty whether drug induced prolongation of pregnancy would improve adverse neonatal health outcomes of prematurity*
[2] *GRADE optimal information size criteria not met; also imprecise 95% CI allowing for possibilities of important benefit, no difference, or even possible harm if the upper bound of 95% CI is judged to be importantly above the null.*
[3] *Median control event rate across contributing studies*
[4] *Creasy 1980 added relatively substantial weight to the meta-analysis but was at high risk of attrition bias*
[5] *Only one study at high risk of attrition bias contributing <30% weight and no extreme estimate for the body of evidence*
[6] *Few events in few patients -- fragile estimates*

Table 51 – GRADE evidence profile: maintenance therapy with oxytocin antagonists versus placebo/no maintenance treatment

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Subcutaneous atosiban maintenance tocolysis	Placebo	Relative (95% CI)	Absolute		
Neonatal death												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	3/261 (1.1%)	5/251 (2%)[3]	RR 0.58 (0.14 to 2.39)	8 fewer per 1000 (from 17 fewer to 28 more)	⊕⊕OO LOW	critical
Infant death up to 12 months												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	4/288 (1.4%)	5/269 (1.9%)[3]	RR 0.74 (0.2 to 2.74)	5 fewer per 1000 (from 15 fewer to 32 more)	⊕⊕OO LOW	critical
Necrotising enterocolitis												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	5/288 (1.7%)	2/269 (0.74%)[3]	RR 2.34 (0.46 to 11.93)	10 more per 1000 (from 4 fewer to 81 more)	⊕⊕OO LOW	critical
Respiratory distress syndrome												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	33/288 (11.5%)	29/269 (10.8%)[3]	RR 1.06 (0.66 to 1.7)	6 more per 1000 (from 37 fewer to 75 more)	⊕⊕OO LOW	critical
Patent ductus arteriosus												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	10/288 (3.5%)	8/269 (3%)[3]	RR 1.17 (0.47 to 2.91)	5 more per 1000 (from 16 fewer to 57 more)	⊕⊕OO LOW	critical
Birth <28 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	7/45 (15.6%)	6/29 (20.7%)[3]	RR 0.75 (0.28 to 2.01)	52 fewer per 1000 (from 149 fewer to 209 more)	⊕OOO VERY LOW	important
Birth <32 weeks												

1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	19/158 (12%)	18/127 (14.2%)[3]	RR 0.85 (0.47 to 1.55)	21 fewer per 1000 (from 75 fewer to 78 more)	⊕OOO VERY LOW	important
Birth <37 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	90/267 (33.7%)	92/243 (37.9%)[3]	RR 0.89 (0.71 to 1.12)	42 fewer per 1000 (from 110 fewer to 45 more)	⊕OOO VERY LOW	important
Maternal death												

[1] Preterm birth is of concern not per se but because it predicts short-term and longterm adverse health outcomes associated with preterm birth. As such, there is some uncertainty whether drug induced prolongation of pregnancy would improve adverse neonatal health outcomes of prematurity
[2] GRADE optimal information size criteria not met and also imprecise 95% CI allowing for possibilities of important benefit, no difference, or even possible harm if the upper bound of 95% CI is judged to be importantly above the null.
[3] Single study control event rate

Table 52 – GRADE evidence profile: vaginal progesterone versus no progesterone in symptomatic women with a singleton pregnancy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaginal progesterone	No progesterone	Relative (95% CI)	Absolute		
Neonatal death												
2	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	serious[8]	none	4/152 (2.6%)	9%[3] (n/N= 14/155)	**RR 0.30 (0.1 to 0.91)**	63 fewer per 1000 (from 8 fewer to 81 fewer)	⊕⊕OO LOW	
Neonatal sepsis												
2	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/117 (1.7%)	11%[3] (n/N= 9/116)	RR 0.26 (0.07 to 1)	81 fewer per 1000 (from 102 fewer to 0 more)	⊕OOO VERY LOW	
Respiratory distress syndrome												
2	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/117 (9.4%)	24%[3] (n/N= 22/116)	RR 0.48 (0.2 to 1.15)	125 fewer per 1000 (from 192 fewer to 36 more)	⊕OOO VERY LOW	
Use of assisted ventilation												
1	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/37 (5.4%)	6/33 (18.2%)[4]	RR 0.30 (0.06 to 1.37)	127 fewer per 1000 (from 171 fewer to 67 more)	⊕OOO VERY LOW	
Pretrem birth <28 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	1/97 (1%)	1/96 (1%)[4]	RR 0.99 (0.06 to 15.6)	0 fewer per 1000 (from 10 fewer to 152 more)	⊕OOO VERY LOW	

Preterm birth <34 weeks												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	18/207 (8.7%)	10%[3] (n/N= 21/215)	RR 0.89 (0.49 to 1.62)	11 fewer per 1000 (from 51 fewer to 62 more)	⊕OOO VERY LOW	
Preterm birth <37 weeks												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	71/207 (34.3%)	40%[3] (n/N= 78/215)	RR 0.94 (0.6 to 1.47)	24 fewer per 1000 (from 160 fewer to 188 more)	⊕OOO VERY LOW	

[1] Preterm birth is of concern not per se but because it predicts short-term and longterm adverse health outcomes associated with preterm birth. However, there is some uncertainty whether drug induced prolongation of pregnancy would improve adverse health outcomes of prematurity.
[2] GRADE optimal information size criteria not met and also imprecise 95% CI allowing for the possibilities of important benefit and no difference or even possible harm if the upper bound of 95% CI is judged to be importantly above the null.
[3] Median control event rate across contributing studies
[4] Single study control event rate
[5] Single study at high risk of performance and detection bias
[6] High risk of performance and determination of outcome bias in one study
[7] One of the two studies at high risk of attrition bias
[8] Although statistically significant difference, the estimate is deemed fragile because it originates in small sample size and event rates (i.e. GRADE optimal information size criterion not met)

6.4. Tertiary prevention: Magnesium sulphate as neuroprotector

Table 53 – GRADE evidence profile: MgSO4 neuroprotection versus no MgSO4

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intravenous magnesium sulphate**	**Placebo or no magnesium sulphate**	**Relative (95% CI)**	**Absolute**		
Total paediatric mortality												
5[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	401/2658 (15.1%)	400/2699 (14.8%[4])	RR 1.01 (0.89 to 1.14)	1 more per 1000 (from 16 fewer to 21 more)	⊕⊕⊕⊕ HIGH	
Cerebral palsy (assessed with: various definitions or definition not reported)												
5[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	104/2658 (3.9%)	152/2699 (6%[2])	RR 0.69 (0.55 to 0.88)	19 fewer per 1000 (from 7 fewer to 27 fewer)	⊕⊕⊕⊕ HIGH	
Moderate to severe cerebral palsy (assessed with: various definitions or definition not reported)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	45/2169 (2.1%)	72/2218 (3.2%[4])	RR 0.64 (0.44 to 0.92)	12 fewer per 1000 (from 3 fewer to 18 fewer)	⊕⊕⊕O MODERATE	

Need for oxygen at 36 weeks												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[6]	serious[7]	none	220/981 (22.4%)	195/962 (20.3%[4])	RR 1.12 (0.95 to 1.32)	24 more per 1000 (from 10 fewer to 65 more)	⊕⊕OO LOW	
Mechanical ventilation												
3	randomised trials	no serious risk of bias	no serious inconsistency[8]	no serious indirectness[9]	no serious imprecision	none	1381/2169 (63.7%)	1446/2218 (65.2%[4])	RR 0.99 (0.89 to 1.09)	7 fewer per 1000 (from 72 fewer to 59 more)	⊕⊕⊕⊕ HIGH	
Apgar score <7 at 5 minutes												
3	randomised trials	no serious risk of bias	no serious inconsistency	serious[5]	no serious imprecision	none	351/2169 (16.2%)	351/2218 (15.8%[4])	RR 1.03 (0.9 to 1.18)	5 more per 1000 (from 16 fewer to 28 more)	⊕⊕⊕O MODERATE	

[1] Mittendorf et al. had two arms (tocolytic and neuroprotective) which Conde-Agudelo considered as two trials giving a total of 6 trials and 5 studies
[2] Median control event rate across contributing studies
[3] Given the total number of events, there are some concerns about the fragility of effect estimates -- slight changes in proportion could change the conclusions from significant benefit to no difference
[4] Median control event rate across studies could not be obtained from the review report, so we used the crude average control event rate across studies
[5] Apgar score measures vitality shortly after birth. There is correlation between low Apgar scores and cerebral palsy, but some uncertainty exists about the magnitude of the correlation. Kent A stated that "90% of children with a low Apgar score did not develop cerebral palsy.[23]
[6] Some uncertainty about the causal association between this outcome and cerebral palsy
[7] Imprecise 95% CI allowing for the possibilities of important benefit, no difference and/or even possible harm if upper bound of CI is judged to be importantly above the null
[8] I-squared value was reported as 82.1%. However, an equivalent meta-analysis on the same trials in the 2009 Cochrane review by Doyle et al .[24] showed no serious inconsistency and similar effect estimate -- Cochrane review analysis 1.25.
[9] Although the requirement for mechanical ventilation may be an indirect proxy for cerebral palsy, one could argue that in and of itself, the outcome is of direct concern.
[10] Although the 95% CI is wide allowing for the possibilities of important benefit, no difference, or even possible harm, the absolute difference in risk was deemed clinically unimportant and small

Note: unless otherwise specified, the evidence of maternal harms of magnesium sulphate presented below originates in a wider pregnant population (i.e. includingpre-eclampsia/eclampsia patients.

Table 54 – GRADE evidence profile maternal side effects: MgSO4 versus no MgSO4

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intravenous or intramuscular magnesium sulphate	Placebo/no treatment	Relative (95% CI)	Absolute		
Death												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[1]	none	11/7317 (0.15%)	21/7345 (0.34%[2])	RR 0.53 (0.26 to 1.09)	2 fewer per 1000 (from 3 fewer to 0 more)	⊕⊕⊕⊕ HIGH	
Death in pregnant women with preterm labour < 30-32 weeks												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[10]	none	0/1917 (0%)	1/1950 (0.05%[4])	RR 0.32 (0.01 to 7.92)	0 fewer per 1000 (from 1 fewer to 4 more)	⊕⊕⊕⊕ HIGH	
Cardiac arrest												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[1]	none	4/6972 (0.06%)	5/7005 (0.07%)[3]	RR 0.80 (0.21 to 2.98)	0 fewer per 1000 (from 1 fewer to 1 more)	⊕⊕⊕⊕ HIGH	
Respiratory arrest												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[1]	none	5/6972 (0.07%)	2/7005 (0.03%)[3]	RR 2.50 (0.49 to 12.88)	0 more per 1000 (from 0 fewer to 3 more)	⊕⊕⊕⊕ HIGH	
Respiratory depression in pregnant women with preterm labour < 30-32 weeks												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[10]	none	41/1631 (2.5%)	31/1672 (1.9%[4])	RR 1.31 (0.83 to 2.07)	6 more per 1000 (from 3 fewer to 20 more)	⊕⊕⊕⊕ HIGH	
ICU admission												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[1]	none	83/5590 (1.5%)	86/5582 (1.5%)[3]	RR 0.97 (0.72 to 1.3)	0 fewer per 1000 (from 4 fewer to 5 more)	⊕⊕⊕⊕ HIGH	
Postpartum haemorrhage												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	842/5303 (15.9%)	875/5232 (9.60%[2])	RR 0.95 (0.87 to 1.03)	5 fewer per 1000 (from 12 fewer to 3 more)	⊕⊕⊕⊕ HIGH	
Severe postpartum haemorrhage in pregnant women with preterm labour < 30-32 weeks												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[10]	none	28/821 (3.4%)	26/805 (3.2%[4])	RR 1.06 (0.63 to 1.79)	2 more per 1000 (from 12 fewer to 26 more)	⊕⊕⊕⊕ HIGH	
Pulmonary oedema												

4	randomised trials	no serious risk of bias[4]	no serious inconsistency	no serious indirectness	no serious imprecision[1]	none	41/6362 (0.64%)	37/6425 (0.46%[2])	RR 1.12 (0.72 to 1.74)	1 more per 1000 (from 1 fewer to 3 more)	⊕⊕⊕⊕ HIGH	
Pulmonary oedema in pregnant women with preterm labour < 30-32 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[10]	none	8/1096 (0.73%)	3/1145 (0.26%[4])	RR 2.79 (0.74 to 10.47)	5 more per 1000 (from 1 fewer to 25 more)	⊕⊕⊕⊕ HIGH	
Discontinuation due to adverse events												
5	randomised trials	no serious risk of bias[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	449/6811 (6.6%)	162/6855 (1.42%[2])	RR 2.77 (2.32 to 3.3)	25 more per 1000 (from 19 more to 33 more)	⊕⊕⊕⊕ HIGH	

[1] *While the relative risk estimate is wide, the absolute risk difference is very precise*
[2] *Median control event rate across contributing studies*
[3] *Control event rate from a single study with events*
[4] *One study contributing small weight was judged to be impacted by detection and/or performance bias*

7. DATA SYNTHESIS

7.1. Identification of women at risk

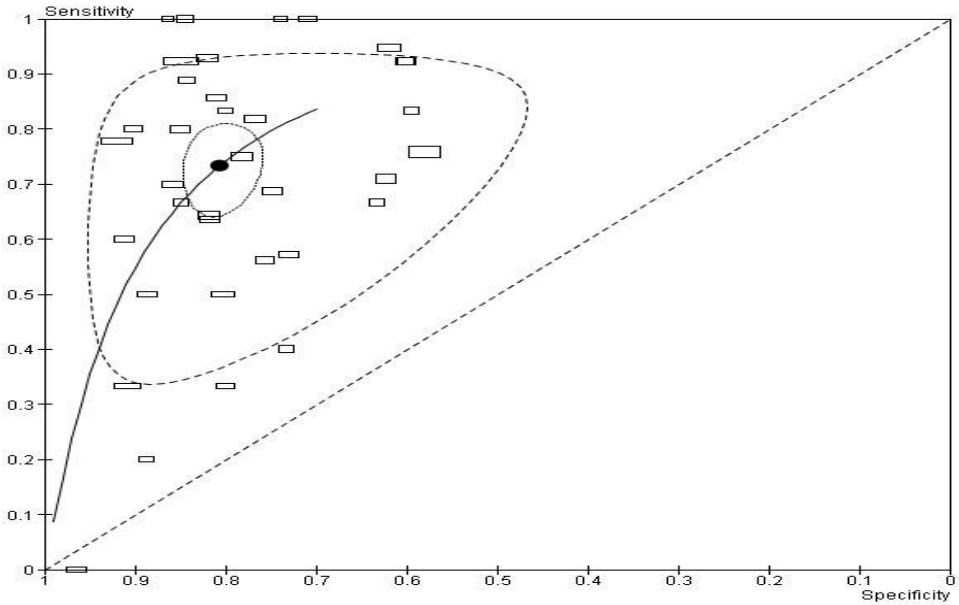
7.1.1. Fetal fibronect test

Table 55 – Primary Studies used in fFN Test Performance Review Update

Number of Included Relevant Studies in Analyses		Study Design				Quality					Search Date		Blinding	
Original SR	New Primary Studies	SR		New Primary		SR		New Primary*			Original SR	New Primary Studies	Original SR	New Primary Studies*
		Cohort	RCT	Cohort	RCT	High	Low	High	Low	Unclear				
27	11	27	0	11	0	20	7	3	0	5	Apr 2008	Apr 2008-present (Jun 11th , 2013)	Yes=14 No: 7 U:6 `	Yes=2 No/U: 6

Abbreviations: RCT = randomized controlled trial; SR = systematic review; U = unknown

Figure 8 – sROC plot for fFN test



The summary point is located at a sensitivity of 0.73 (95% CI: 0.67, 0.80) and specificity of 0.81 (95% CI: 0.77, 0.84). The corresponding estimates for LR+ and LR- are 3.79 (95% CI: 3.10, 4.49) and 0.33 (95% CI: 0.25, 0.41) respectively.

Figure 9 – Coupled sensitivity and specificity plots for fFN

Study	TP	FP	FN	TN	Sensitivity	Specificity
Bartnicki	2	32	0	78	1.00 [0.16, 1.00]	0.71 [0.61, 0.79]
Senden	3	3	0	19	1.00 [0.29, 1.00]	0.86 [0.65, 0.97]
Mansouri	13	12	0	65	1.00 [0.75, 1.00]	0.84 [0.74, 0.92]
McKenna	4	12	0	34	1.00 [0.40, 1.00]	0.74 [0.59, 0.86]
Tsoi	18	67	1	109	0.95 [0.74, 1.00]	0.62 [0.54, 0.69]
Iams	13	32	1	146	0.93 [0.66, 1.00]	0.82 [0.76, 0.87]
Woodworth	12	88	1	498	0.92 [0.64, 1.00]	0.85 [0.82, 0.88]
Wilms	12	38	1	57	0.92 [0.64, 1.00]	0.60 [0.49, 0.70]
Lopez	8	12	1	64	0.89 [0.52, 1.00]	0.84 [0.74, 0.92]
Foxman	6	25	1	107	0.86 [0.42, 1.00]	0.81 [0.73, 0.87]
Closset	5	11	1	44	0.83 [0.36, 1.00]	0.80 [0.67, 0.90]
O'Brien	10	15	2	22	0.83 [0.52, 0.98]	0.59 [0.42, 0.75]
Tekesin	9	37	2	122	0.82 [0.48, 0.98]	0.77 [0.69, 0.83]
Skoll	12	20	3	114	0.80 [0.52, 0.96]	0.85 [0.78, 0.91]
Malak	8	10	2	92	0.80 [0.44, 0.97]	0.90 [0.83, 0.95]
Ray	7	38	2	434	0.78 [0.40, 0.97]	0.92 [0.89, 0.94]
van Baaren	66	198	21	274	0.76 [0.65, 0.84]	0.58 [0.53, 0.63]
Diaz	18	34	6	122	0.75 [0.53, 0.90]	0.78 [0.71, 0.84]
Sakai	39	49	16	81	0.71 [0.57, 0.82]	0.62 [0.53, 0.71]
groom	7	24	3	145	0.70 [0.35, 0.93]	0.86 [0.80, 0.91]
Giles	11	34	5	101	0.69 [0.41, 0.89]	0.75 [0.67, 0.82]
Lee	10	18	5	31	0.67 [0.38, 0.88]	0.63 [0.48, 0.77]
Tanir	10	8	5	45	0.67 [0.38, 0.88]	0.85 [0.72, 0.93]
Gomez	18	34	10	153	0.64 [0.44, 0.81]	0.82 [0.76, 0.87]
Schmitz	7	27	4	121	0.64 [0.31, 0.89]	0.82 [0.75, 0.88]
LaShay	3	10	2	103	0.60 [0.15, 0.95]	0.91 [0.84, 0.96]
Luzzi	4	34	3	92	0.57 [0.18, 0.90]	0.73 [0.64, 0.81]
Ting	9	19	7	59	0.56 [0.30, 0.80]	0.76 [0.65, 0.85]
Pelaez	1	14	1	110	0.50 [0.01, 0.99]	0.89 [0.82, 0.94]
Riboni	4	40	4	162	0.50 [0.16, 0.84]	0.80 [0.74, 0.85]
Sunagawa	8	15	12	41	0.40 [0.19, 0.64]	0.73 [0.60, 0.84]
Cooper	2	26	4	256	0.33 [0.04, 0.78]	0.91 [0.87, 0.94]
Mateus	1	18	2	72	0.33 [0.01, 0.91]	0.80 [0.70, 0.88]
Sumer	1	7	4	55	0.20 [0.01, 0.72]	0.89 [0.78, 0.95]
Rose	0	5	1	135	0.00 [0.00, 0.97]	0.96 [0.92, 0.99]

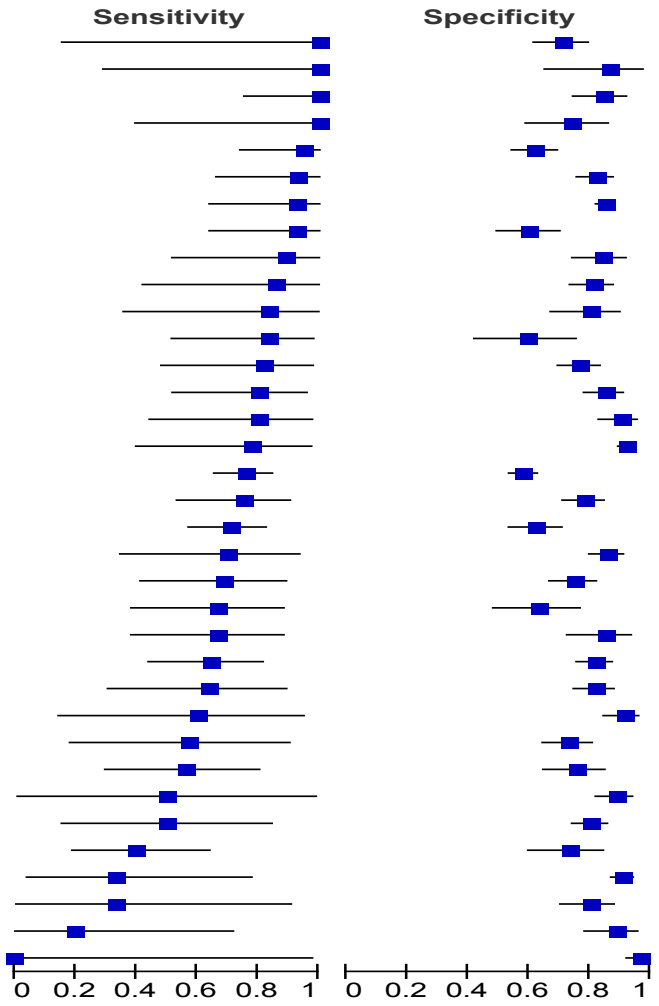


Table 56 – fFN subgroup analysis by pre-specified covariates

Characteristic	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)
All studies	0.73 (0.67-0.80)	0.81 (0.77-0.84)	3.79 (3.10-4.49)	0.33 (0.25-0.41)
Publication year				
Before 2008	0.77 (0.70-0.85)	0.80 (0.76-0.84)	3.84 (3.02-4.66)	0.29 (0.19-0.38)
2008 and afterward	0.63 (0.48-0.78)	0.82 (0.75-0.90)	3.58 (2.12-5.05)	0.45 (0.28-0.62)
Methodologic quality (v1)				
High quality	0.76 (0.68-0.84)	0.81 (0.76-0.86)	3.96 (2.98-4.93)	0.30 (0.20-0.40)
Low quality	0.68 (0.56-0.80)	0.81 (0.75-0.86)	3.50 (2.36-4.63)	0.40 (0.24-0.55)
Methodologic quality (v2)				
High quality	0.73 (0.63-0.83)	0.82 (0.78-0.87)	4.13 (3.18-5.08)	0.32 (0.22-0.44)
Low quality	0.62 (0.58-0.67)	0.75 (0.73-0.77)	2.50 (2.28-2.73)	0.50 (0.44-0.56)
Prevalence (%)				
<6	0.66 (0.55-0.78)	0.82 (0.75-0.88)	3.64 (2.38-4.90)	0.41 (0.28-0.54)
6-11.3	0.74 (0.58-0.90)	0.79 (0.73-0.86)	3.58 (2.20-4.97)	0.33 (0.12-0.53)
>11.3	0.78 (0.68-0.87)	0.81 (0.74-0.87)	3.98 (2.67-5.30)	0.28 (0.16-0.39)
Blinded				
Yes	0.71 (0.59-0.83)	0.82 (0.75-0.88)	3.88 (2.56-5.20)	0.36 (0.22-0.50)
No	0.75 (0.67-0.83)	0.80 (0.76-0.84)	3.73 (2.92-4.54)	0.31 (0.21-0.42)
Gestation				
S	0.69 (0.61-0.76)	0.82 (0.77-0.86)	3.72 (2.82-4.63)	0.38 (0.29-0.47)
U	0.83 (0.69-0.97)	0.79 (0.74-0.84)	3.95 (2.85-5.04)	0.22 (0.04-0.40)

Abbreviations: CI = confidence interval; fFN = fetal fibronectin; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; S = singleton; U = unknown

7.1.2. Actim Partus test

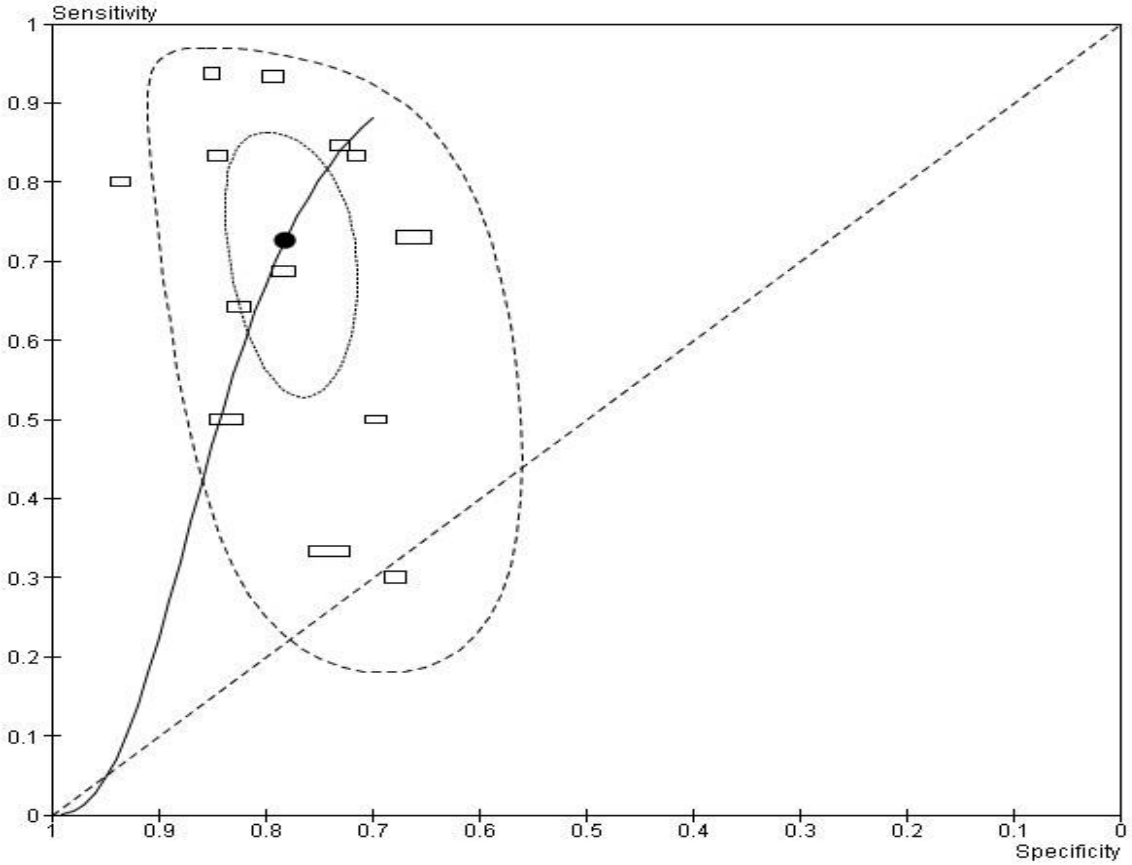
Table 57 – Primary studies used in Actim Partus Test Performance Review Update

Number of Included Studies in Relevant Analyses		Study Design				Quality					Search Date		Blinding	
Original SR	New Primary Studies	SR		New Primary		SR		New Primary*			Original SR	New Primary Studies	Original SR	New Primary Studies*
		Cohort	RCT	Cohort	RCT	High	Low	High	Low	Unclear				
9	15	9	0	15	0	3	6	2	1	11	Sep 2005	Sep 2005-present (Jul 24th, 2013)	Yes: 2 No: 7	Yes: 7 No/U: 7

Abbreviations: RCT = randomized controlled trial; SR = systematic review; U = unknown

7.1.2.1. Reference standard preterm birth within 7 days

Figure 10 – sROC plot for Actim Partus for PTD within 7 days



The summary point is located at a sensitivity of 0.73 (95% CI: 0.59, 0.86) and specificity of 0.78 (95% CI: 0.73, 0.83). The corresponding estimates for LR+ and LR- are 3.33 (95% CI: 2.24, 4.41) and 0.35 (95% CI: 0.17, 0.53) respectively.

Table 58 – Actim Partus Subgroup Analysis by Pre-specified Covariates (PTD within 7 days)

Characteristic	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)
All studies	0.73 (0.59-0.86)	0.78 (0.73-0.83)	3.33 (95% CI 2.24-4.41)	0.35 (95% CI 0.17-0.53)
Publication year				
Before 2008	Convergence issues	Convergence issues	Convergence issues	Convergence issues
After 2008	0.63 (0.40-0.85)	0.78 (0.70-0.85)	2.80 (1.21-4.38)	0.48 (0.17-0.79)
Methodologic quality (v1)				
High quality	0.73 (0.58-0.90)	0.80 (0.75-0.84)	3.60 (2.37-4.82)	0.33 (0.13-0.53)
Low quality	0.70 (0.13-1.00)	0.76 (0.48-1.00)	2.91 (0-7.74)	0.40 (0-1.21)
Methodologic quality (v2)				
High quality	Convergence issues	Convergence issues	Convergence issues	Convergence issues
Low quality	0.72 (0.55-0.89)	0.79 (0.73-0.86)	3.45 (1.92-4.98)	0.36 (0.14-0.58)
Prevalence (%)				
<=13	0.65 (0.47-0.84)	0.79 (0.70-0.88)	3.09 (1.50-4.69)	0.44 (0.20-0.68)
>13	Convergence issues	Convergence issues	Convergence issues	Convergence issues
Blinded				
Yes	Convergence issues	Convergence issues	Convergence issues	Convergence issues
no	0.67 (0.46-0.88)	0.78 (0.68-0.87)	3.06 (1.34-4.78)	0.42 (0.14-0.70)
Threshold				
10 ug	Convergence issues	Convergence issues	Convergence issues	Convergence issues
30+ug	Convergence issues	Convergence issues	Convergence issues	Convergence issues

Abbreviations: *CI = confidence interval; LR+ = positive likelihood ratio; LR- = negative likelihood ratio*

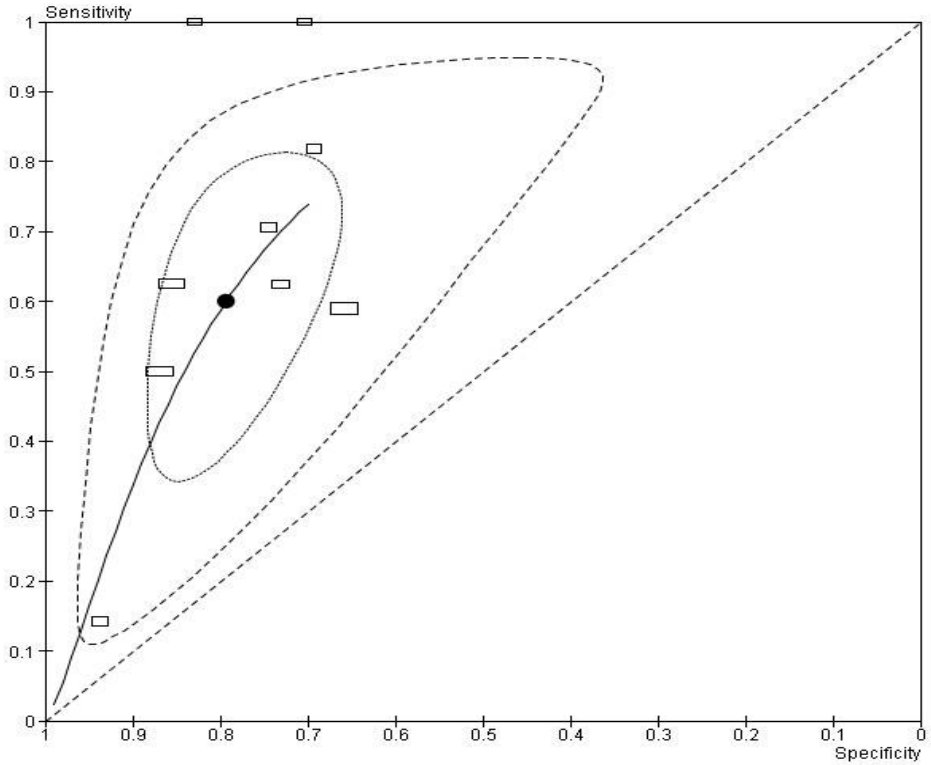
Table 59 – Direct comparison of performance of fFN and Actim Partus test to predict PTD within 7 days

Authors		fFN	Actim Plus
Cooper 2012	Sensitivity	33% (0; 71)	33% (0; 71)
	Specificity	91% (87; 94)	74% (69; 79)
	LR+	3.62 (1.10; 11.88)	1.28 (0.41; 4.04)
	LR -	0.73 (0.42; 1.29)	0.90 (0.51; 1.59)
Riboni 2011	Sensitivity	50% (22; 78)	50% (21; 78)
	Specificity	80% (75; 86)	84% (78; 88)
	LR+	NR	3.06 (1.43; 6.54)
	LR -	NR	0.60 (0.30; 1.20)

7.1.2.2. Reference standard preterm birth before 34 weeks of pregnancy

A total of 9 studies (6 new) contributed to evidence synthesis. Approximately 50% of the studies employed a test cut-off of 10 µg/L. In keeping with the original review, our updated meta-analysis yielded evidence of test performance unlikely to yield substantial changes between pre- and post test probabilities (see overall pooled estimates of sensitivity, specificity and likelihood ratios in Table 60 and Figure 11). Compared with estimates of specificity, substantial heterogeneity was observed across studies in estimates of test sensitivity (Figure 12). When we considered studies of unclear risk of bias together with higher quality studies, subgroup analyses improved estimates of test sensitivity (by about 30%) and LR- but did not substantially alter test specificity and LR+ (Methodologic quality v1, Table 60). The implication of this observation is unclear because the 95% confidence interval remained imprecise with the lower bound of sensitivity lower than 70% and upper bound of negative likelihood ratio approaching 0.5. No other meaningful effect modification was observed in subgroup analyses (Table 60). Also, because of the limitation in the number of studies contributing data, threshold related effect modification in effect estimates could not be explored (i.e. the bivariate models did not converge).

Figure 11 – sROC plot for Actim Partus for PTD <34 weeks of gestation



The summary point is located at a sensitivity of 0.60 (95% CI: 0.40, 0.80) and specificity of 0.79 (95% CI: 0.71, 0.88). The corresponding estimates for LR+ and LR- are 2.91 (95% CI: 1.86, 3.95) and 0.50 (95% CI: 0.0.28, 0.72) respectively.

Figure 12 – Coupled sensitivity and specificity plots for Actim Partus (PTD < 34 weeks)

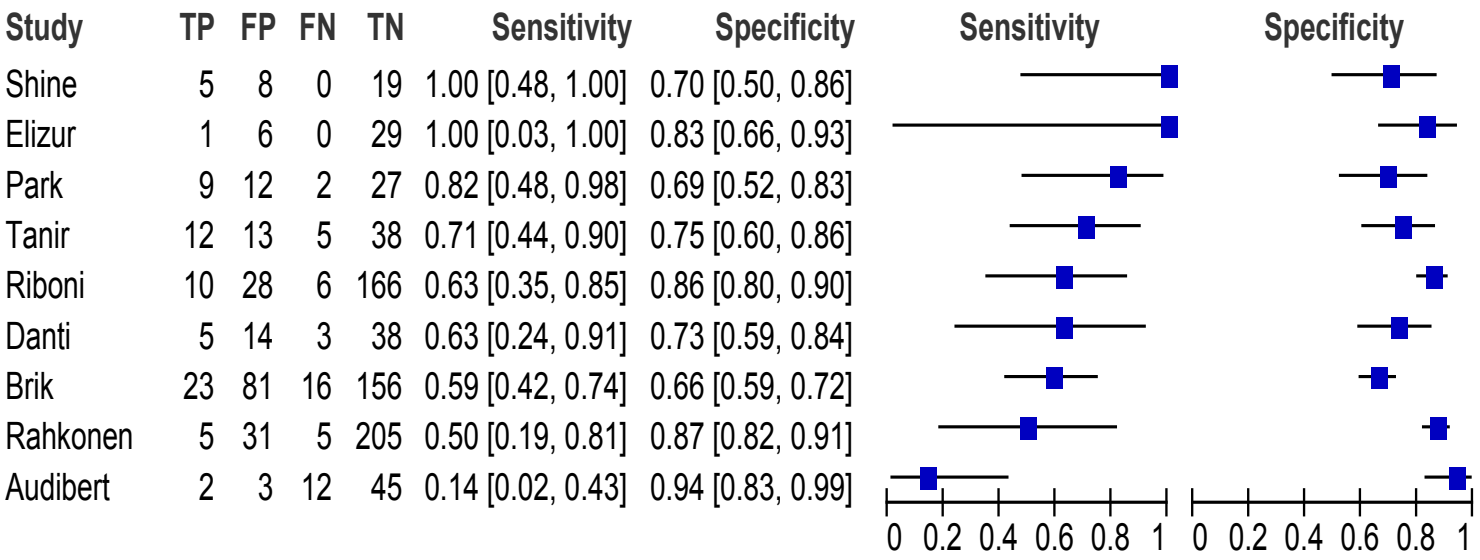


Table 60 – Actim Partus Subgroup Analysis by Pre-specified Covariates (PTD < 34 weeks)

Characteristic	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)
All studies	0.60 (0.40-0.80)	0.79 (0.71-0.88)	2.91 (95% CI 1.86-3.95)	0.50 (95% CI 0.28-0.72)
Publication year				
Before 2008	Convergence issues	Convergence issues	Convergence issues	Convergence issues
After 2008	0.51 (0.30-0.73)	0.82 (0.69-0.94)	2.82 (1.36-4.28)	0.59 (0.38-0.81)
Methodologic quality (v1)				
High quality	0.88 (0.66-1.10)	0.73 (0.64-0.83)	3.28 (1.75-4.80)	0.16 (-0.14 to 0.47)
Low quality	Convergence issues	Convergence issues	Convergence issues	Convergence issues

Methodologic quality (v2)					
	High quality	Convergence issues	Convergence issues	Convergence issues	Convergence issues
	Low quality	0.60 (0.34-0.85)	0.80 (0.68-0.91)	2.94 (1.64-4.24)	0.51 (0.23-0.78)
Prevalence (%)					
	<=14	Convergence issues	Convergence issues	Convergence issues	Convergence issues
	>14	0.61 (0.15-1.00)	0.75 (0.55-0.94)	2.42 (0.82-4.02)	0.52 (0.0-1.06)
Blinded					
	Yes	Convergence issues	Convergence issues	Convergence issues	Convergence issues
	No	Convergence issues	Convergence issues	Convergence issues	Convergence issues
Threshold					
	10ug	Convergence issues	Convergence issues	Convergence issues	Convergence issues
	30+ug	Convergence issues	Convergence issues	Convergence issues	Convergence issues

Abbreviations: *CI = confidence interval; LR+ = positive likelihood ratio; LR- = negative likelihood ratio*

7.1.2.3. Reference standard preterm birth before 37 weeks

A total of 15 studies (6 new) contributed to evidence synthesis. Approximately 30% of the studies employed a test cut-off of 10 µg/L or lower – cut-offs employed in other studies were between 30-40 µg/L. In keeping with the original review, our updated meta-analysis yielded evidence of test performance unlikely to yield substantial changes between pre- and post test probabilities (see overall pooled estimates of sensitivity, specificity and likelihood ratios in Table 61 and Figure 13). Substantial heterogeneity was observed across studies in estimates of test sensitivity and specificity (Figure 14). Subgroup analysis of studies employing test threshold of ≥ 30 µg/L improved test sensitivity and negative likelihood ratio but without substantial reduction in imprecision associated with the overall meta-analytic estimates (i.e. test sensitivity could truly be as low as 68% and LR- as high as 0.4) (Table 61 – Actim Partus Subgroup Analysis by Pre-Specified Covariates (PTD < 37 weeks)). No meaningful effect modification was observed in other subgroup analyses.

Figure 13 – sROC plot for Actim Partus for PTD <37 weeks of gestation

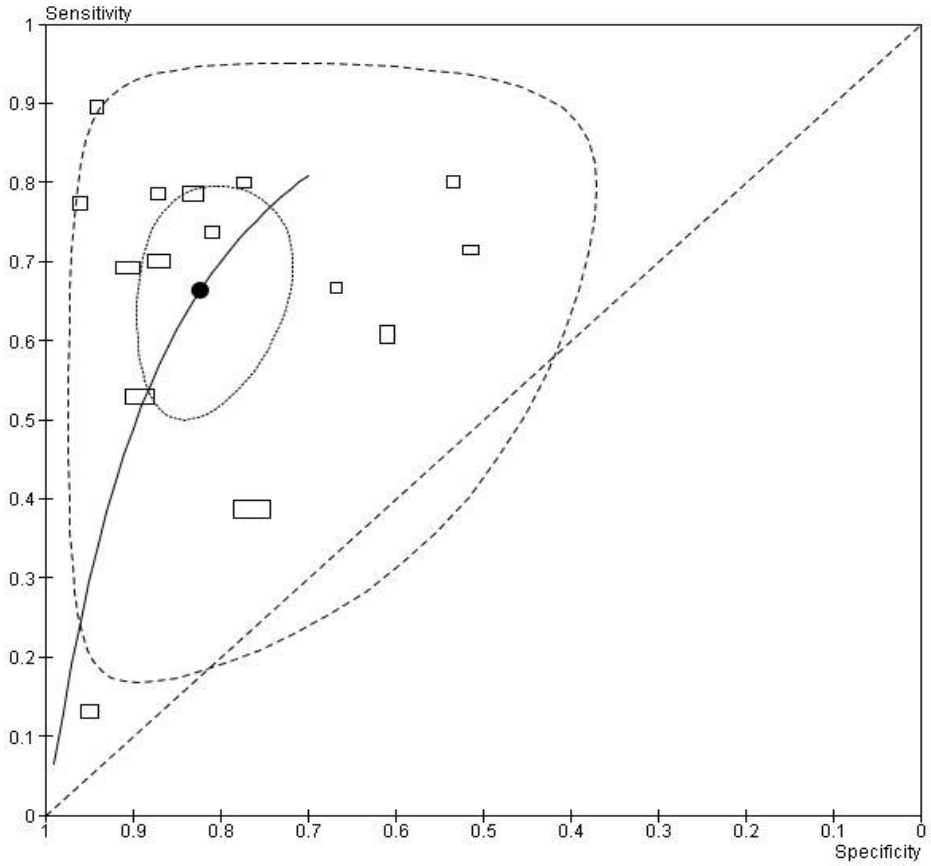


Figure 14 – Coupled sensitivity and specificity plots for Actim Partus (PTD < 37 weeks)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Lembet	17	1	2	16	0.89 [0.67, 0.99]	0.94 [0.71, 1.00]
Shine	8	5	2	17	0.80 [0.44, 0.97]	0.77 [0.55, 0.92]
Latifagic	12	7	3	8	0.80 [0.52, 0.96]	0.53 [0.27, 0.79]
Halle	22	11	6	54	0.79 [0.59, 0.92]	0.83 [0.72, 0.91]
Akercan	11	4	3	27	0.79 [0.49, 0.95]	0.87 [0.70, 0.96]
Park	17	1	5	24	0.77 [0.55, 0.92]	0.96 [0.80, 1.00]
Kwek	14	4	5	17	0.74 [0.49, 0.91]	0.81 [0.58, 0.95]
Choi	5	17	2	18	0.71 [0.29, 0.96]	0.51 [0.34, 0.69]
Altinkaya	14	11	6	74	0.70 [0.46, 0.88]	0.87 [0.78, 0.93]
Paternoster	9	9	4	86	0.69 [0.39, 0.91]	0.91 [0.83, 0.96]
Elizur	4	3	2	6	0.67 [0.22, 0.96]	0.67 [0.30, 0.93]
Laudanski	31	9	20	14	0.61 [0.46, 0.74]	0.61 [0.39, 0.80]
Riboni	18	19	16	157	0.53 [0.35, 0.70]	0.89 [0.84, 0.93]
Cooper	22	69	35	223	0.39 [0.26, 0.52]	0.76 [0.71, 0.81]
Audibert	3	2	20	37	0.13 [0.03, 0.34]	0.95 [0.83, 0.99]

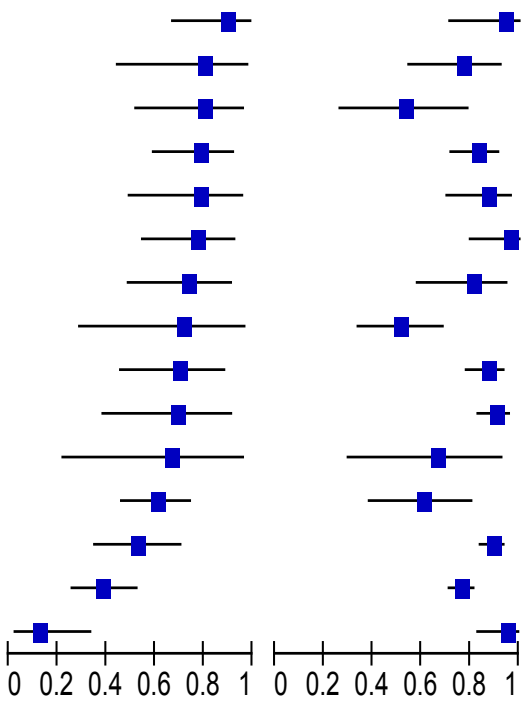


Table 61 – Actim Partus Subgroup Analysis by Pre-Specified Covariates (PTD < 37 weeks)

Characteristic	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)
All studies	0.67 (0.55-0.79)	0.83 (0.75-0.90)	3.83 (95% CI 2.24-5.42)	0.40 (0.25-0.54)
Publication year				
Before 2002	Convergence issues	Convergence issues	Convergence issues	Convergence issues
After 2002	0.51 (0.23-0.79)	0.81 (0.65-0.98)	2.75 (0.86-4.64)	0.60 (0.32-0.88)
Methodologic quality (v1)				
High quality	0.61 (0.37-0.86)	0.83 (0.74-0.93)	3.67 (1.56-5.78)	0.47 (0.19-0.74)
Low quality	Convergence issues	Convergence issues	Convergence issues	Convergence issues
Methodologic quality (v2)				
High quality	Convergence issues	Convergence issues	Convergence issues	Convergence issues
Low quality	0.64 (0.50-0.79)	0.82 (0.74-0.91)	3.63 (1.92-5.33)	0.44 (0.27-0.61)
Prevalence (%)				
<=32	0.66 (0.50-0.81)	0.83 (0.74-0.91)	3.78 (1.64-5.92)	0.42 (0.22-0.61)
>32	0.67 (0.41-0.94)	0.83 (0.66-0.99)	3.99 (0.14-7.83)	0.39 (0.08-0.70)
Blinded				
Yes	Convergence issues	Convergence issues	Convergence issues	Convergence issues
no	0.70 (0.62-0.78)	0.81 (0.73-0.90)	3.76 (1.91-5.62)	0.37 (0.26-0.48)
Threshold				
10ug	0.47 (0.12-0.83)	0.80 (0.55-1.00)	2.35 (0.47-4.22)	0.66 (0.34-0.98)
30+ug	0.76 (0.68-0.84)	0.84 (0.76-0.92)	4.79 (2.18-7.40)	0.28 (0.18-0.39)

Abbreviations: *CI = confidence interval; LR+ = positive likelihood ratio; LR- = negative likelihood ratio*

7.1.3. Cervical length measurement – symptomatic population

Table 62 – Primary studies used in Transvaginal Ultrasound Test Performance Review – Symptomatic Population

Number of Included Studies in Relevant Analyses		Study Design				Quality					Search Date		Blinding	
Original SR	New Primary Studies	SR		New Primary		SR		New Primary*			Original SR	New Primary Studies	Original SR	New Primary Studies*
		Cohort	RCT	Cohort	RCT	High	Low	High	Low	Unclear				
18*	38**	18	0	38	0	2	16	6	2	26	Sep 2005	Sep 2005-present (Jul 29th, 2013)	Yes:10 N/U: 8	Yes:10 N/U:24

Abbreviations: RCT = randomized controlled trial; SR = systematic review; U = unknown

** There were 19 studies in the original review. The original review did not present numerical data for one study.*
*** Four studies did not have extractable numerical data.*

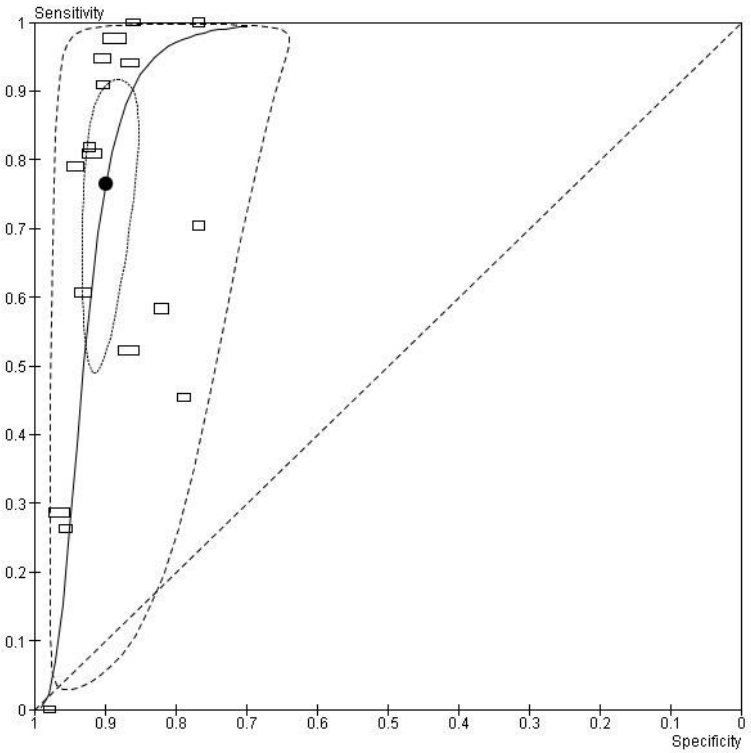
7.1.3.1. Reference standard preterm birth within 48 hours

See scientific report

7.1.3.2. Reference standard preterm birth within 7 days

15 mm Threshold

Figure 15 – sROC plot for ultrasound cervical length for PTD < 7 days – cut-off 15 mm, symptomatic singleton pregnancy

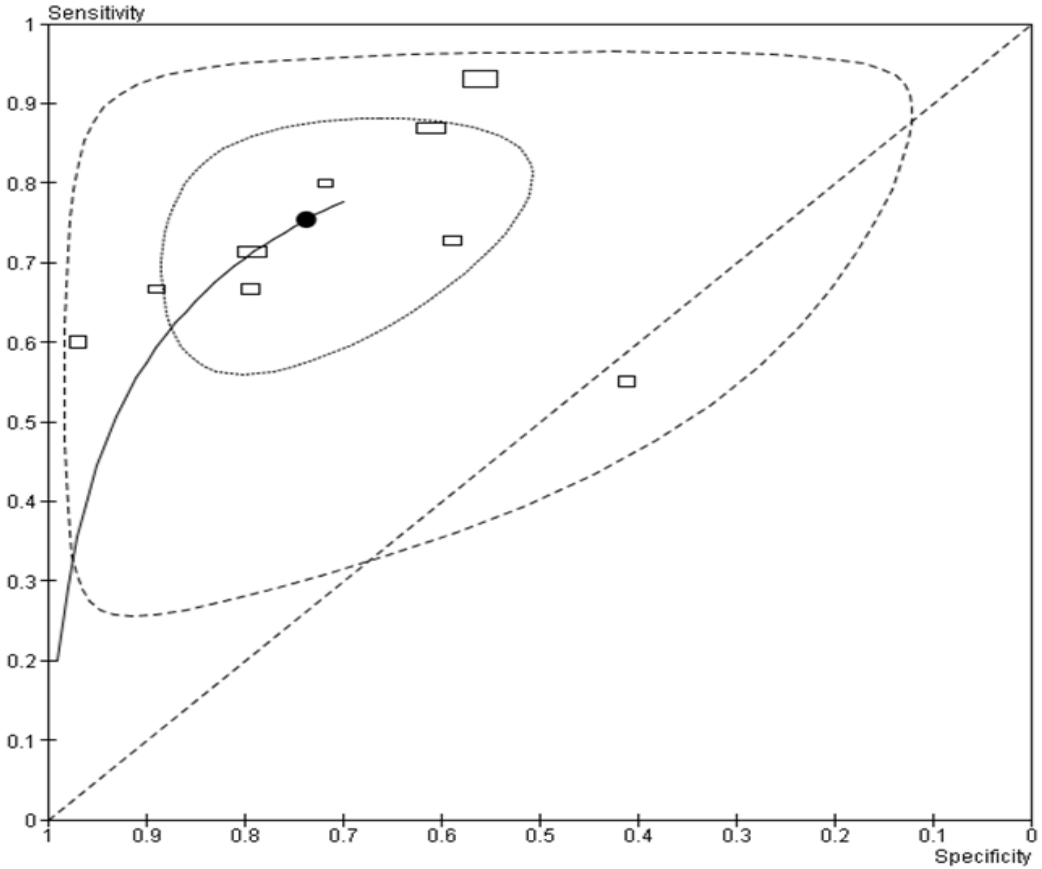


The summary point is located at a sensitivity of 0.77 (95% CI: 0.59, 0.94) and specificity of 0.90 (95% CI: 0.88, 0.93). The corresponding estimates for LR+ and LR- are 7.57 (95% CI: 5.34, 9.79) and 0.26 (95% CI: 0.07, 0.45) respectively.

25 mm Threshold

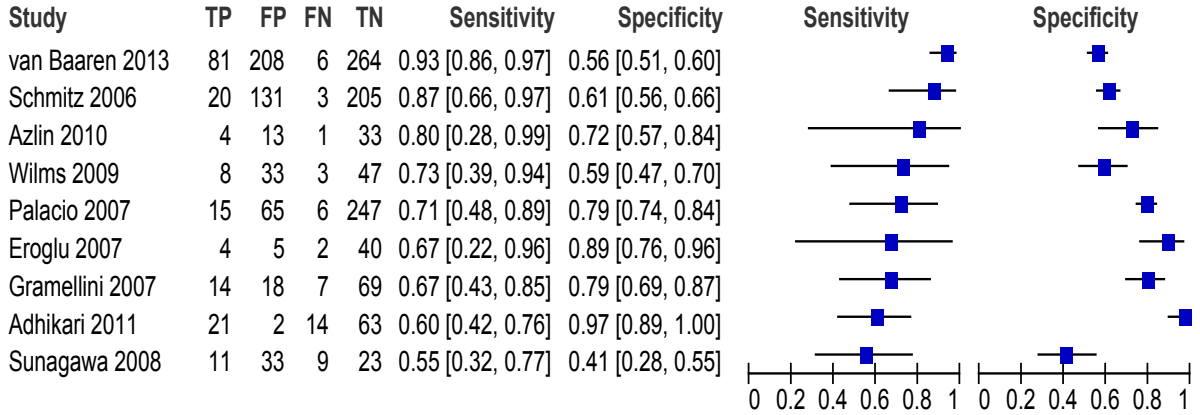
A total of 9 studies (8 new) contributed to evidence synthesis. In keeping with the original review, our updated meta-analysis yielded evidence of limited test performance (Figure 16). The pooled sensitivity was 0.75 (95% CI: 0.63, 0.88) and specificity 0.74 (95% CI: 0.59, 0.89); corresponding estimates LR+ and LR- were 2.87 (95% CI: 1.33, 4.40) and 0.33 (95% CI: 0.17, 0.50), respectively. Substantial heterogeneity was observed across studies in estimates of test sensitivity and specificity (Figure 17). This heterogeneity is reflected as a broad prediction ellipse around the summary point (Figure 16). Model non-convergence precluded exploration of heterogeneity in subgroup analyses. In a qualitative exploration, no obvious explanation was found for the variability in test performance estimates across studies.

Figure 16 – sROC plot for ultrasound cervical length for PTD <7days – cut-off 25 mm, symptomatic singleton pregnancy



The summary point is located at a sensitivity of 0.75 (95% CI: 0.63, 0.88) and specificity of 0.74 (95% CI: 0.59, 0.89). The corresponding estimates for LR+ and LR- are 2.87 (95% CI: 1.33, 4.40) and 0.33 (95% CI: 0.17, 0.50) respectively.

Figure 17 – Coupled sensitivity and specificity plots for ultrasound cervical length (25mm cut-off) for PTD <7days in symptomatic singleton pregnancy



Other Thresholds

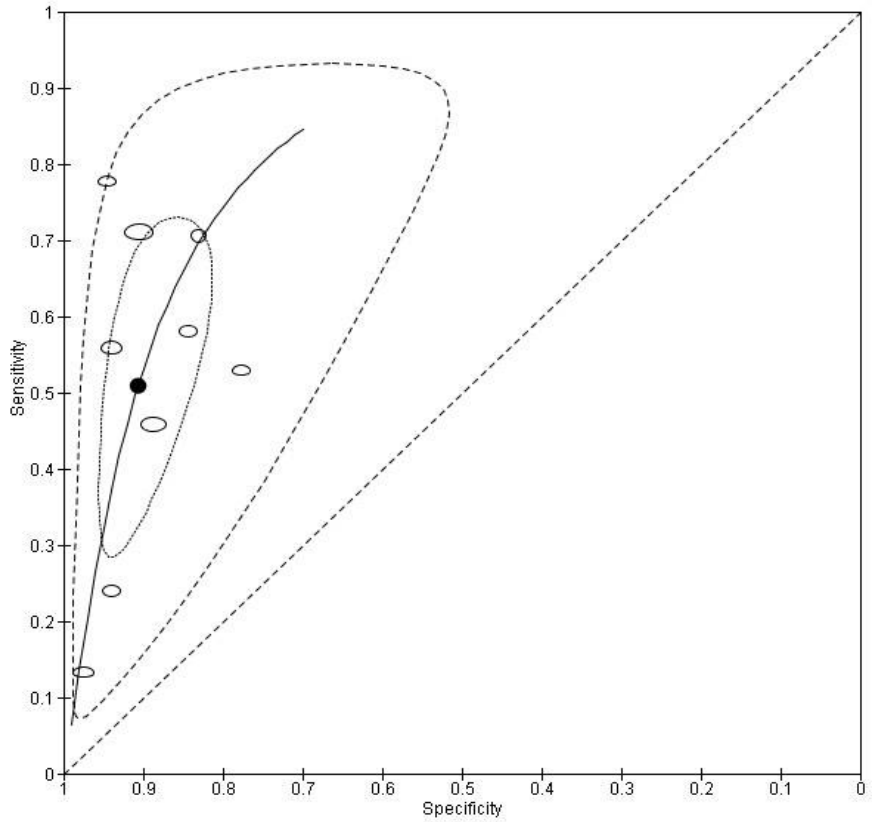
Underpowered evidence evaluated thresholds of 5, 10, 20, 25, and 35 mm. Because of very few studies or model convergence issues, no meta-analysis was performed. Although 7 studies (6 new) were available for 20 mm cut-off, most contributed low numbers of true positives and false negatives. Overall estimates for test sensitivity were substantially imprecise such that possibilities of both high and low test sensitivity were included in the confidence intervals. Test specificity estimates were relatively more precise, stable, and generally over >0.80 except for 35 mm threshold for which the test specificity was low but the estimates were fragile given small study information size.

7.1.3.3. Reference standard preterm birth before 34 weeks of gestation

15 mm Threshold:

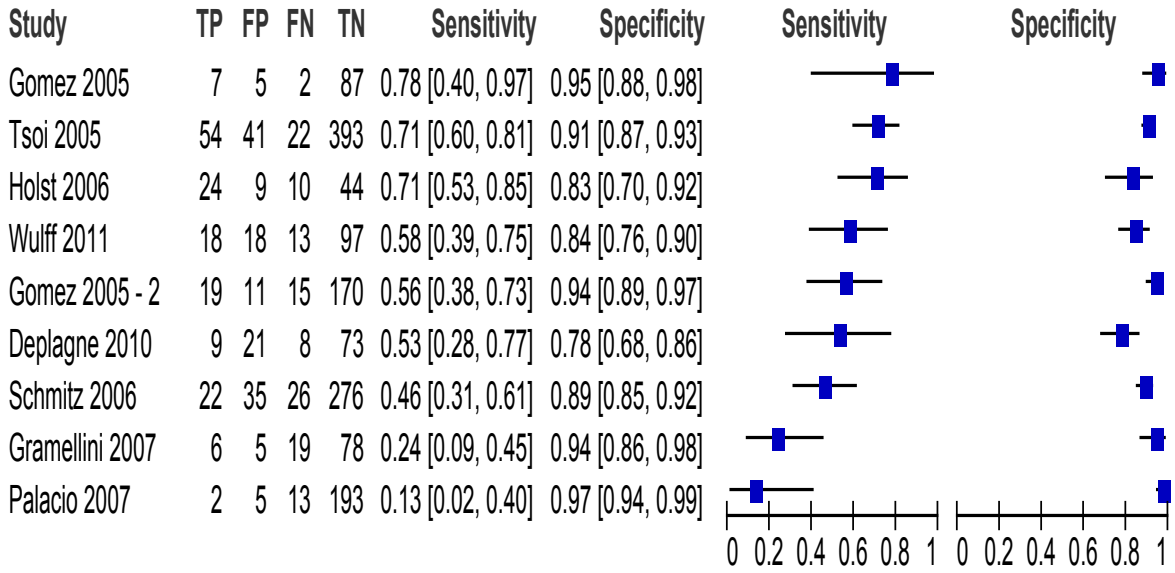
A total of 9 studies (5 new) contributed to evidence synthesis. In keeping with the original review, our updated meta-analysis yielded evidence of low test performance unlikely to yield important changes between pre- and post test probabilities (Figure 18). The pooled sensitivity was 0.51 (95% CI: 0.32, 0.70) and specificity 0.91 (95% CI: 0.85, 0.96); corresponding estimates for LR+ and LR- were 5.44 (95% CI: 2.92, 7.95) and 0.54 (95% CI: 0.35, 0.73) respectively. Substantially more heterogeneity was observed across studies in estimates of test sensitivity than specificity (Figure 19). This heterogeneity is reflected in a vertically oriented prediction ellipse around the summary point (Figure 18). Model non-convergence precluded exploration of heterogeneity in subgroup analyses. In a qualitative exploration, no obvious explanation was found for the variability in test performance estimates across studies.

Figure 18 – sROC plot for ultrasound cervical length for PTD <34 weeks – cut-off 15 mm, symptomatic singleton pregnancy



The summary point is located at a sensitivity of 0.51 (95% CI: 0.32, 0.70) and specificity of 0.91 (95% CI: 0.85, 0.96). The corresponding estimates for LR+ and LR- are 5.44 (95% CI: 2.92, 7.95) and 0.54 (95% CI: 0.35, 0.73) respectively.

Figure 19 – Coupled sensitivity and specificity plots for plots of ultrasound cervical length test (15mm cut-off) for PTD <34 weeks in symptomatic singleton pregnancy

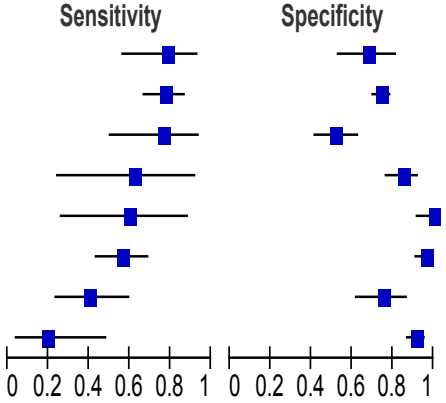


20 mm Threshold:

A total of 9 studies (7 new) contributed to evidence synthesis (Figure 20). The bivariate model did not converge to elicit a reliable estimate of test accuracy because of inadequate power in the evidence base and the heterogeneity in the body of evidence. Heterogeneity in test performance estimates was substantial. The pooled estimates were: Sensitivity = 0.63 (95% CI: 0.54, 0.70); Specificity = 0.82 (95% CI: 0.79, 0.85); LR+ = 3.41 (95% CI: 2.67, 4.15); LR- = 0.46 (95% CI: 0.37, 0.56). Across the studies, the extreme values of confidence interval were LR+ 0.77 and 815.26; and LR- 0.14 and 1.13. In a qualitative investigation of heterogeneity we found no obvious explanation that could be explained by publication year, blinding status, overall study risk of bias, or prevalence of preterm birth. Given the fragility of the pooled estimates, existing evidence is imprecise but is unlikely to yield important changes between pre- and post test probabilities for a negative test.

Figure 20 – Coupled sensitivity and specificity plots for ultrasound cervical length (20mm cut-off) for PTD <34 weeks in symptomatic singleton pregnancy

Study	TP	FP	FN	TN	Sensitivity	Specificity
de Oliveira 2012	18	15	5	32	0.78 [0.56, 0.93]	0.68 [0.53, 0.81]
Tsoi 2005	59	112	17	322	0.78 [0.67, 0.86]	0.74 [0.70, 0.78]
Deplagne 2010	13	45	4	49	0.76 [0.50, 0.93]	0.52 [0.42, 0.63]
Danti 2011	5	14	3	80	0.63 [0.24, 0.91]	0.85 [0.76, 0.92]
Eroglu 2007	6	0	4	41	0.60 [0.26, 0.88]	1.00 [0.91, 1.00]
Daskalakis 2005	36	4	28	104	0.56 [0.43, 0.69]	0.96 [0.91, 0.99]
Kahyaoglu 2013	13	13	19	40	0.41 [0.24, 0.59]	0.75 [0.62, 0.86]
Palacio 2007	3	17	12	181	0.20 [0.04, 0.48]	0.91 [0.87, 0.95]

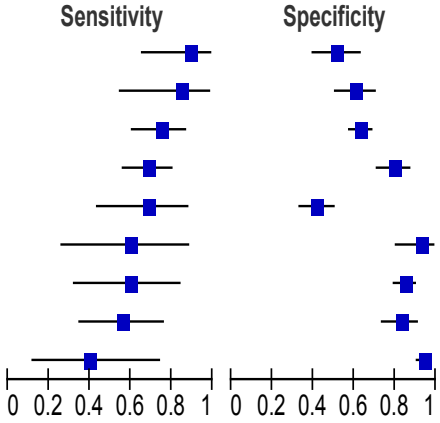


25 mm Threshold:

A total of 9 studies (7 new) contributed to evidence synthesis (Figure 21). The bivariate model did not converge to elicit a reliable estimate of test accuracy because of inadequate power in the evidence base and the observed heterogeneity in the body of evidence. Heterogeneity in test performance estimates was substantial. The pooled estimates were: Sensitivity = 0.69 (95% CI: 0.62, 0.76); Specificity = 0.72 (95% CI: 0.69, 0.75); LR+ = 2.49 (95% CI: 2.12, 2.87); LR- = 0.43 (95% CI: 0.32, 0.53). Across the studies, the extreme values of confidence interval were LR+ 0.83 and 32.80; and LR- 0.06 and 1.52. In a qualitative investigation of heterogeneity we found no obvious explanation that could be explained by publication year, blinding status, overall study risk of bias, or prevalence of preterm birth. Given the fragility of the pooled estimates, existing evidence is best considered imprecise.

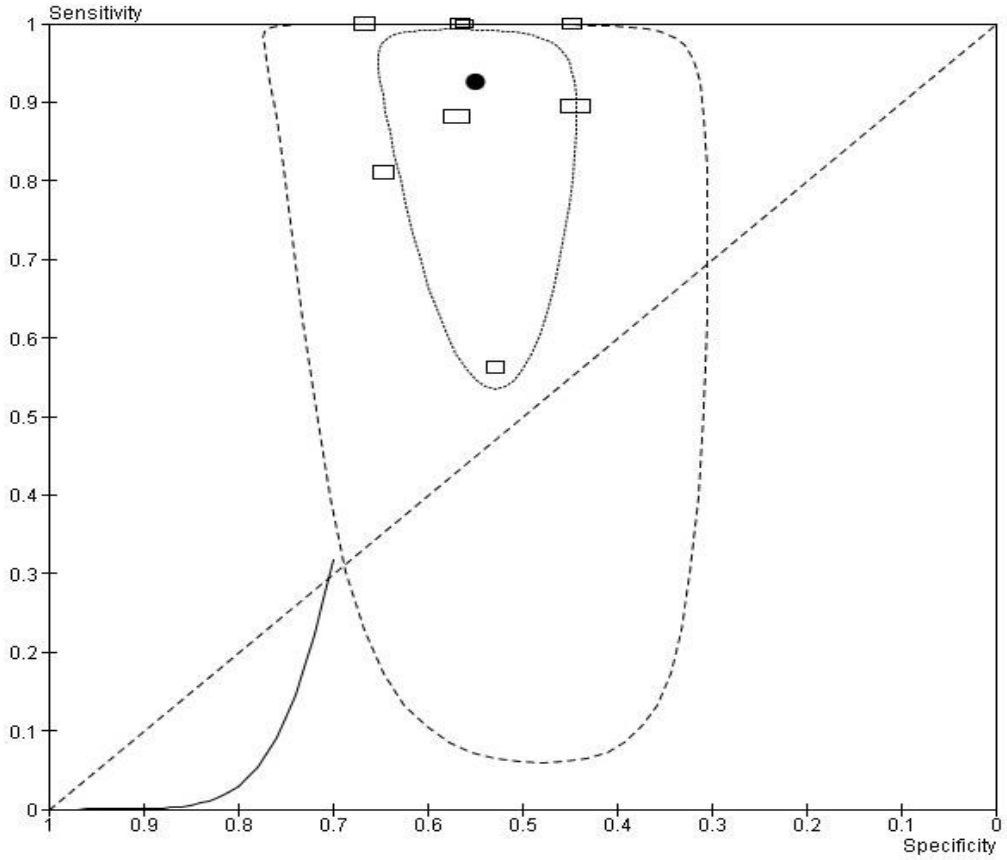
Figure 21 – Coupled sensitivity and specificity plots for ultrasound cervical length (25mm cut-off) for PTD <34 weeks in symptomatic singleton pregnancy

Study	TP	FP	FN	TN	Sensitivity	Specificity
Di Renzo 2011	16	38	2	40	0.89 [0.65, 0.99]	0.51 [0.40, 0.63]
Tekesin 2005	11	41	2	63	0.85 [0.55, 0.98]	0.61 [0.51, 0.70]
Schmitz 2006	36	115	12	196	0.75 [0.60, 0.86]	0.63 [0.57, 0.68]
Daskalakis 2005	44	22	20	86	0.69 [0.56, 0.80]	0.80 [0.71, 0.87]
Nakai 2005	13	83	6	59	0.68 [0.43, 0.87]	0.42 [0.33, 0.50]
Eroglu 2007	6	3	4	38	0.60 [0.26, 0.88]	0.93 [0.80, 0.98]
Palacio 2007	9	30	6	168	0.60 [0.32, 0.84]	0.85 [0.79, 0.90]
Gramellini 2007	14	14	11	69	0.56 [0.35, 0.76]	0.83 [0.73, 0.90]
Rahkonen 2009	4	14	6	222	0.40 [0.12, 0.74]	0.94 [0.90, 0.97]



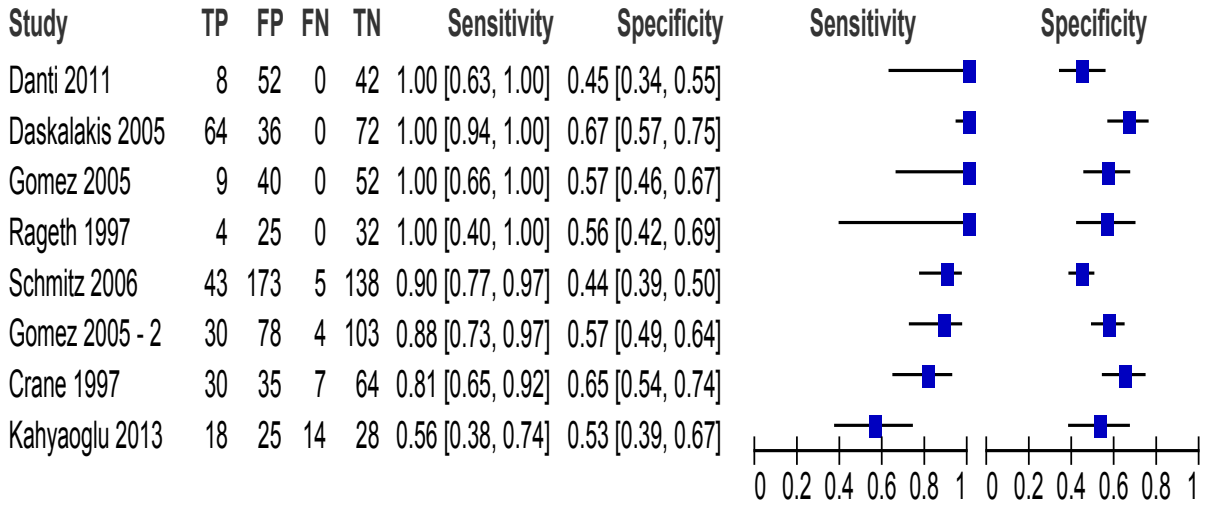
30 mm Threshold: A total of 8 studies (2 new) contributed to evidence synthesis. Our updated meta-analysis yielded evidence of imprecise test performance incorporating both possibilities of high and low test accuracy in ruling out high risk of preterm birth before 34 weeks of gestation in singleton symptomatic women (Figure 22). This was because 50% of studies were small (n<75) and with no false negative results. Specificity of the test to rule in high risk pregnancies was consistently poor. The pooled sensitivity was 0.93 (95% CI: 0.80, 1.06) and specificity 0.55 (95% CI: 0.46, 0.63); corresponding estimates for LR+ and LR- were 2.05 (95% CI: 1.53, 2.58) and 0.14 (95% CI: 0.11, 0.38) respectively. Substantially more heterogeneity was observed across studies in estimates of test sensitivity (Figure 23). This heterogeneity is reflected in a vertically oriented prediction ellipse around the summary point (Figure 22). Model non-convergence precluded exploration of heterogeneity in subgroup analyses. In a qualitative exploration, no obvious explanation was found for the variability in test performance estimates across studies.

Figure 22 – sROC plot for ultrasound cervical length for PTD <34 weeks – cut-off 30 mm, symptomatic singleton pregnancy



The summary point is located at a sensitivity of 0.93 (95% CI: 0.80, 1.06) and specificity of 0.55 (95% CI: 0.46, 0.63). The corresponding estimates for LR+ and LR- are 2.05 (95% CI: 1.53, 2.58) and 0.14 (95% CI: 0.11, 0.38) respectively.

Figure 23 – Coupled sensitivity and specificity plots for ultrasound cervical length (30 mm cut-off) for PTD <34 weeks in symptomatic singleton pregnancy

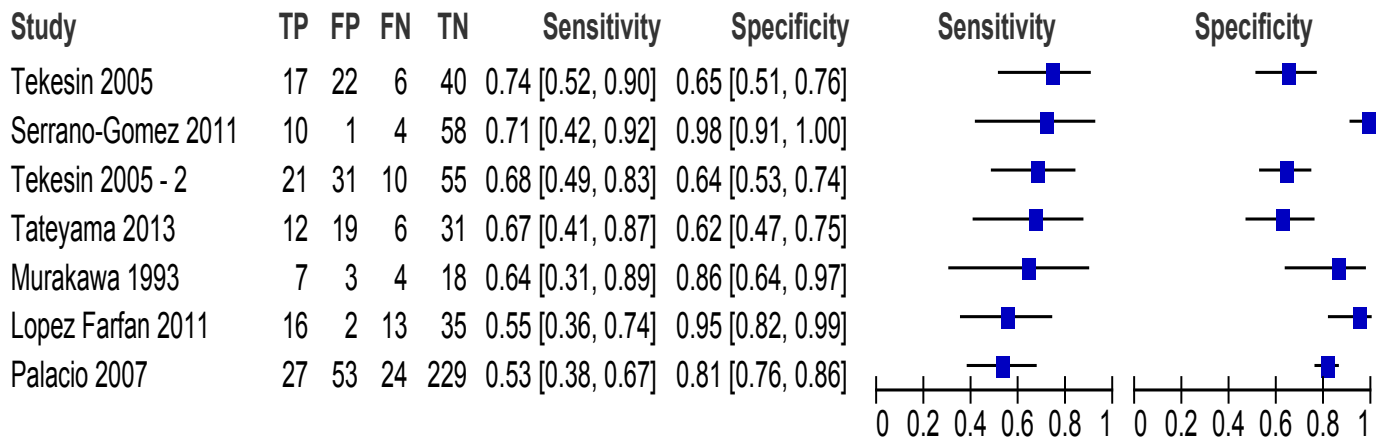


Other Thresholds*:* Single study evidence from unclear risk of bias studies precluded meaningful conclusions for other thresholds of 4, 10 and 35mm that were investigated in this population

7.1.3.4. Reference standard preterm birth before 37 weeks of gestation

A total of 21 studies (12 new) investigated the accuracy of transvaginal ultrasound cervical length measurement for prediction of birth before 37 weeks of gestation. Various testing thresholds were examined. For all thresholds, few underpowered evidence yielding imprecise estimates of test performance precluded meaningful conclusions – meta-analyses could not be performed. In general, wide confidence intervals ranged from low to substantial test performance. For test threshold of 25 mm we attempted to meta-analyse 7 studies (2 new), but studies were mostly small not permitting convergence of the bivariate model (Figure 24). Pooled results for 25mm threshold reported below suggest low test performance of cervical length measurement in predicting the preterm birth before 37 weeks of gestation. The results, however, are fragile. Sensitivity = 0.64 (95% CI : 0.0.53, 0.74); Specificity = 0.71 (95% CI : 0.65, 0.78); LR+ = 2.20 (95% CI : 1.59, 2.81); LR- = 0.51 (95% CI : 0.36, 0.67). Across the studies, the extreme values of confidence interval were LR+ 1.08 and 302.59; and LR- 0.13 and 1.07. These results are best considered imprecise.

Figure 24 – Coupled sensitivity and specificity plots for ultrasound cervical length (25 mm cut-off) for PTD <37 weeks in symptomatic singleton pregnancy



7.1.4. Cervical length measurement – asymptomatic population

Table 63 – Primary studies used in Transvaginal Ultrasound Test Performance Review – Asymptomatic Population

Number of Included Studies in Relevant Analyses		Study Design				Quality					Search Date		Blinding	
		SR		Primary		SR		Primary*						
Original SR	Primary Studies	Cohort	RCT	Cohort	RCT	High	Low	High	Low	Unclear	Original SR	Primary Studies	Original SR	Primary Studies
2	6	2	0	5	1*	2	0	2	0	4	Sep 2005	Sep 2005-present (Jul 29th, 2013)	Yes: 2 No: 0	Yes: 0 No/U: 6

Abbreviations: RCT = randomized controlled trial; SR = systematic review; U = unknown
Secondary analysis of an RCT.

Reference Standard: Preterm Delivery < 34 weeks.

Figure 25 – Forest plot of ultrasound cervical length test sensitivity and specificity (15 mm cut-off) for PTD < 34 weeks in asymptomatic pregnant women with singleton gestation

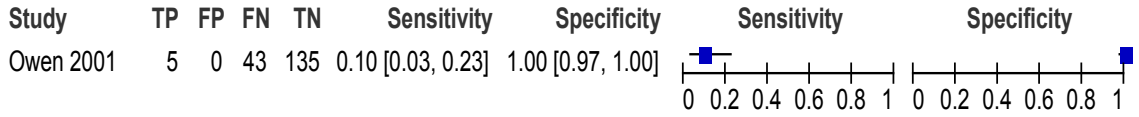


Figure 26 – Coupled sensitivity and specificity plots of ultrasound cervical length (25 mm cut-off) for PTD < 34 weeks in asymptomatic pregnant women with singleton gestation

Study	TP	FP	FN	TN	Sensitivity	Specificity
Bittar 2007 25mm	10	37	2	56	0.83 [0.52, 0.98]	0.60 [0.50, 0.70]
Romero 2012	7	60	2	107	0.78 [0.40, 0.97]	0.64 [0.56, 0.71]
Andrew 2000	5	5	8	39	0.38 [0.14, 0.68]	0.89 [0.75, 0.96]
Owen 2010	64	89	108	565	0.37 [0.30, 0.45]	0.86 [0.84, 0.89]
Owen 2001	9	3	39	132	0.19 [0.09, 0.33]	0.98 [0.94, 1.00]

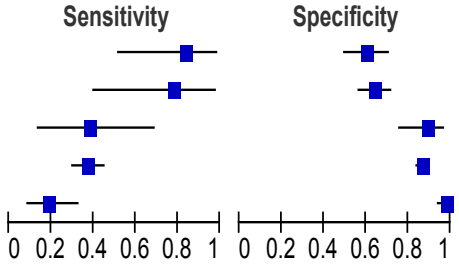
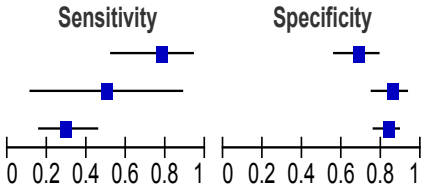


Figure 27 – Coupled sensitivity and specificity plots of ultrasound cervical length (26.5-30 mm cut-off) for PTD < 34 weeks in asymptomatic pregnant women with singleton gestation

Study	TP	FP	FN	TN	Sensitivity	Specificity
Priya 2013 27mm	14	23	4	49	0.78 [0.52, 0.94]	0.68 [0.56, 0.79]
Adhikari 2009	3	10	3	59	0.50 [0.12, 0.88]	0.86 [0.75, 0.93]
Owen 2001	12	24	29	118	0.29 [0.16, 0.46]	0.83 [0.76, 0.89]



7.2. Tertiary prevention

7.2.1. Maintenance therapy

Figure 28 – Neonatal sepsis: nifedipine maintenance therapy versus placebo/no treatment

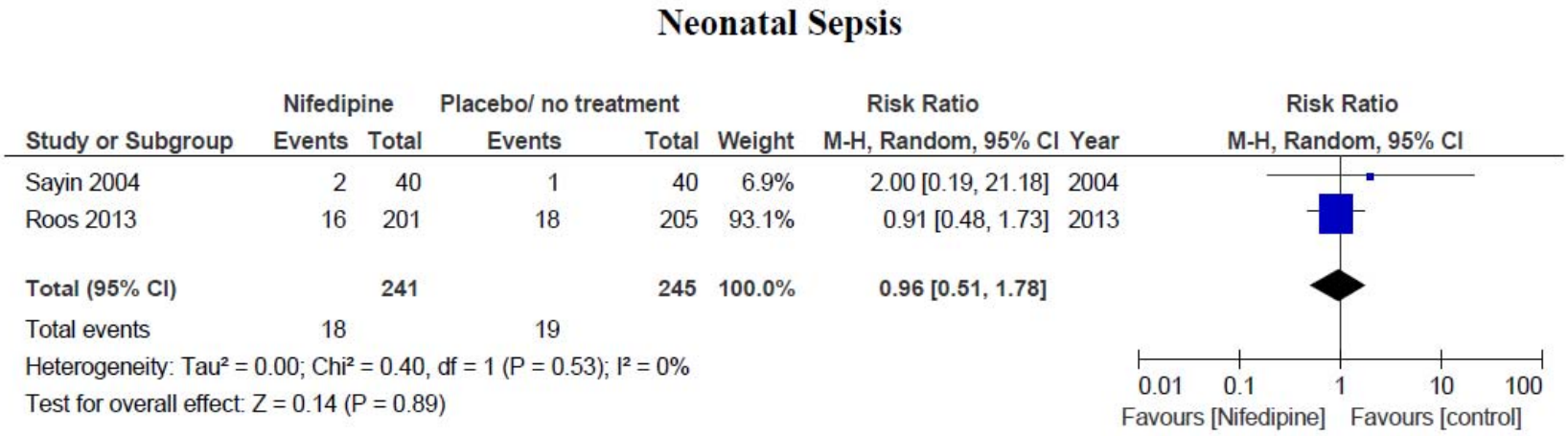


Figure 29 – Necrotizing enterocolitis: nifedipine maintenance therapy versus placebo/no treatment

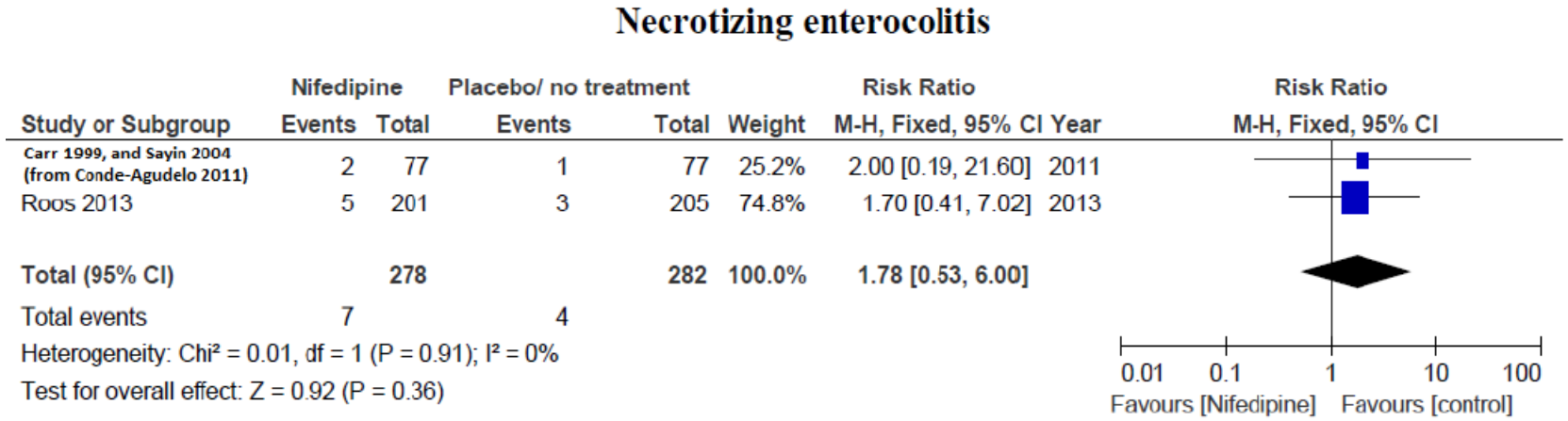


Figure 30 – Intraventricular haemorrhage: nifedipine maintenance therapy versus placebo/no treatment



Figure 31 – Preterm birth < 37 weeks: nifedipine maintenance therapy versus placebo/no treatment

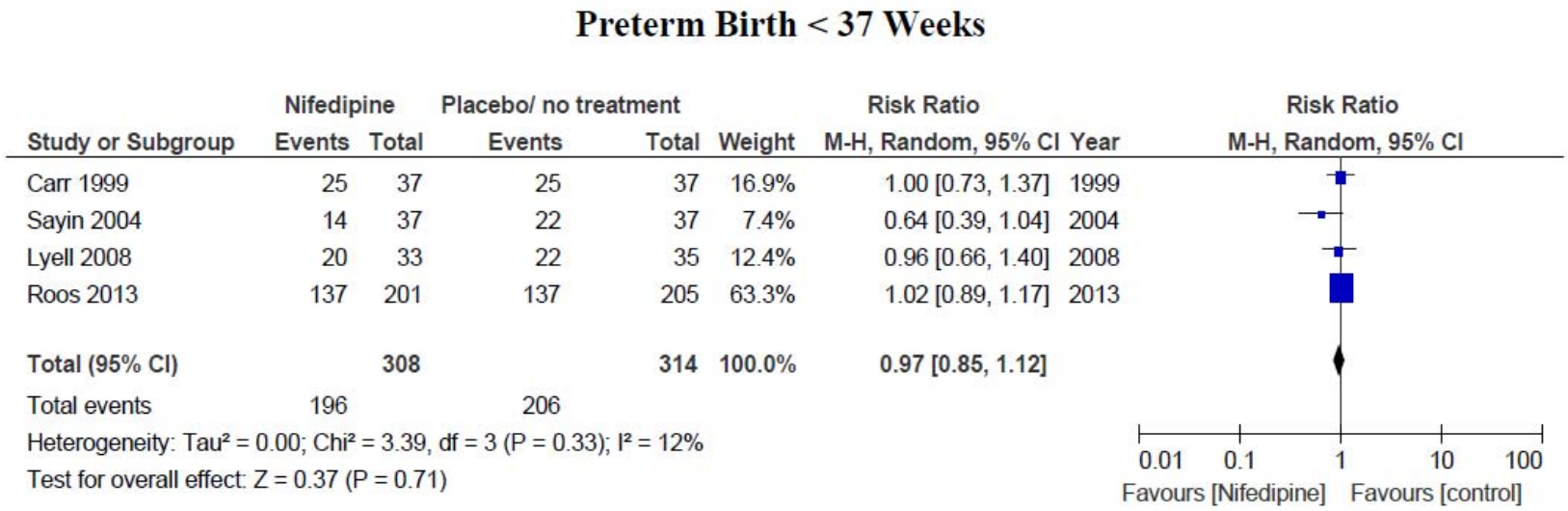


Figure 32 – Preterm birth < 37 weeks among women enrolled at < 32 weeks: nifedipine maintenance therapy versus placebo/no treatment

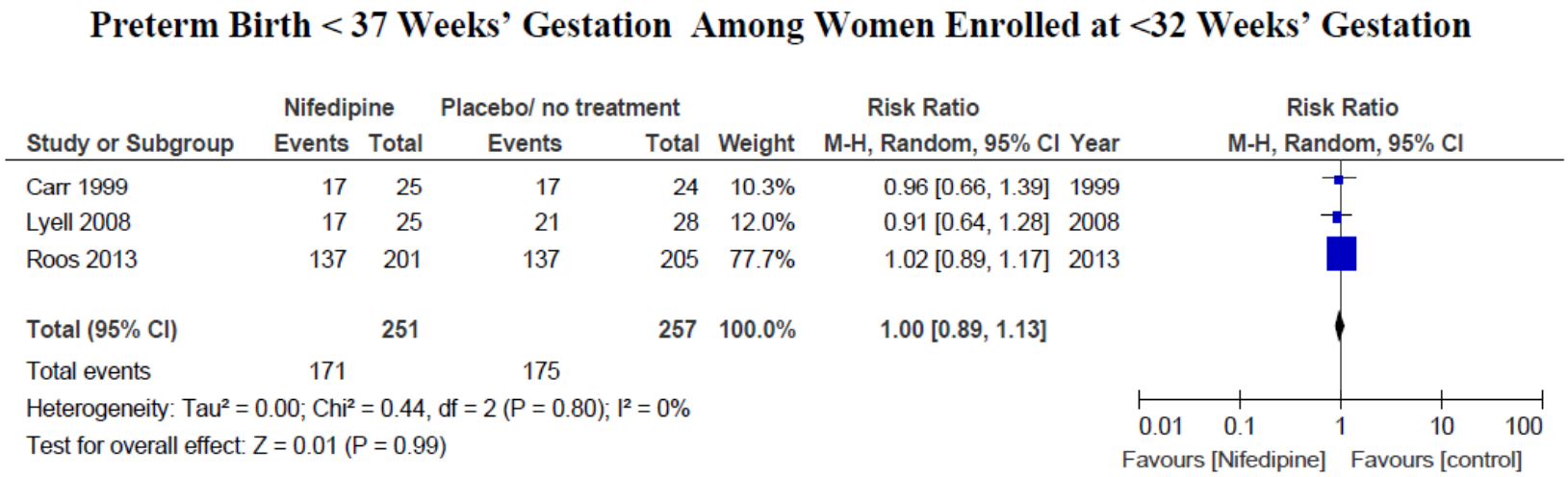


Figure 33 – Preterm birth < 34 weeks: nifedipine maintenance therapy versus placebo/no treatment

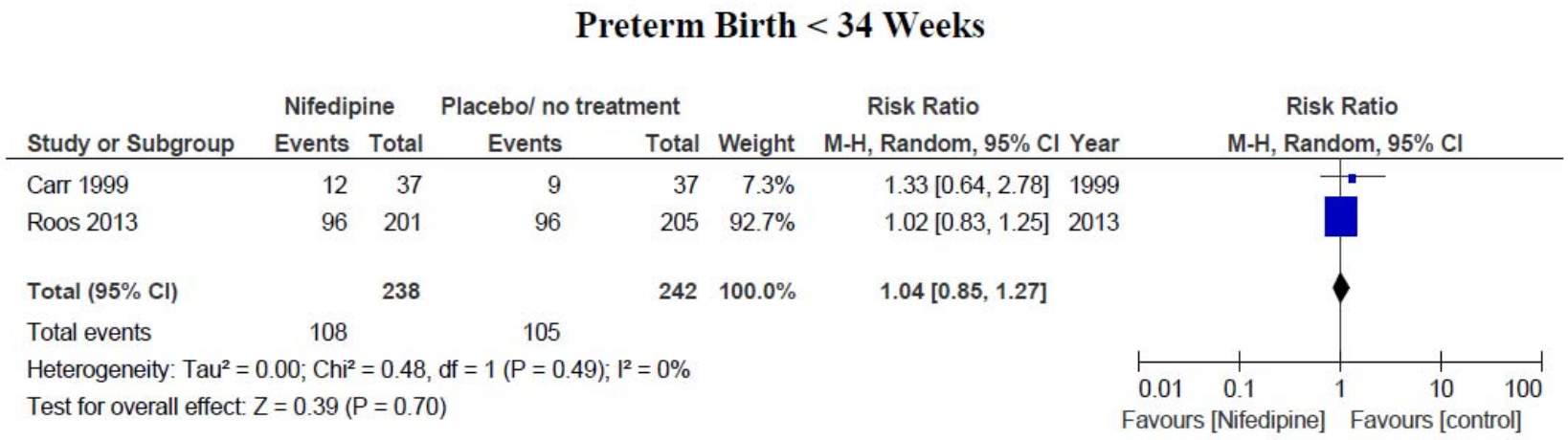


Figure 34 – Preterm birth < 34 weeks among women enrolled at < 32 weeks: nifedipine maintenance therapy versus placebo/no treatment

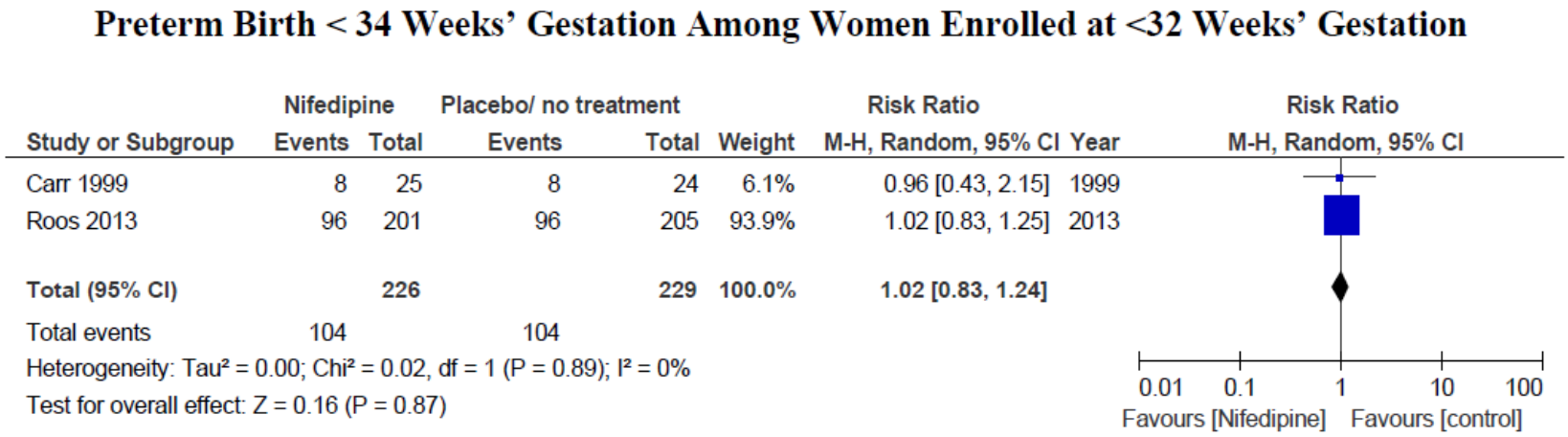


Figure 35 – Neonatal death: vaginal progesterone maintenance therapy versus placebo/no treatment

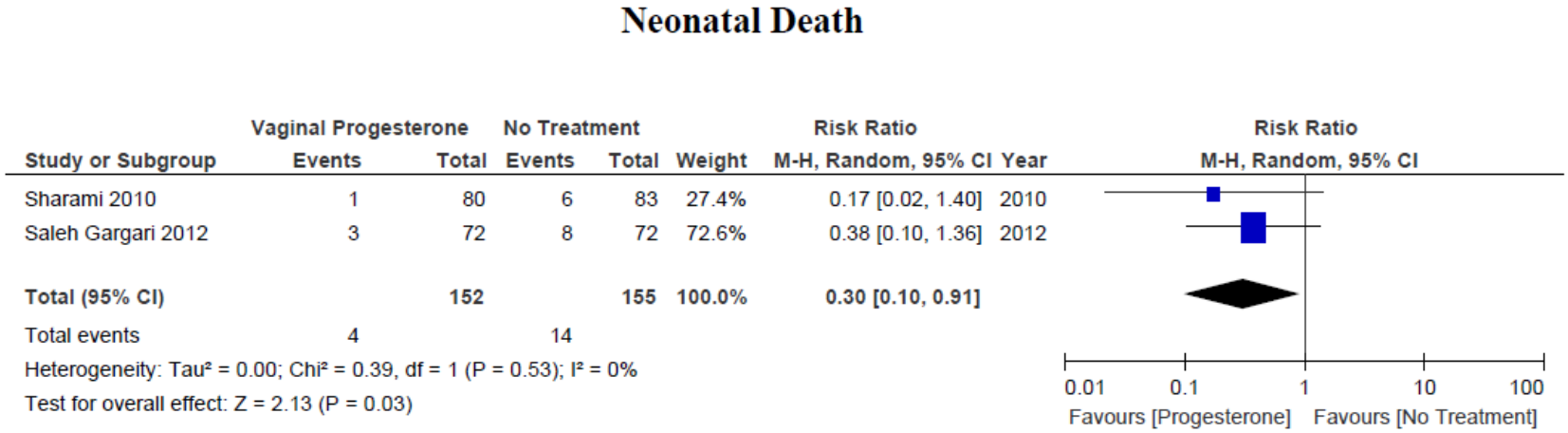


Figure 36 – Preterm birth < 34 weeks: vaginal progesterone maintenance therapy versus placebo/no treatment

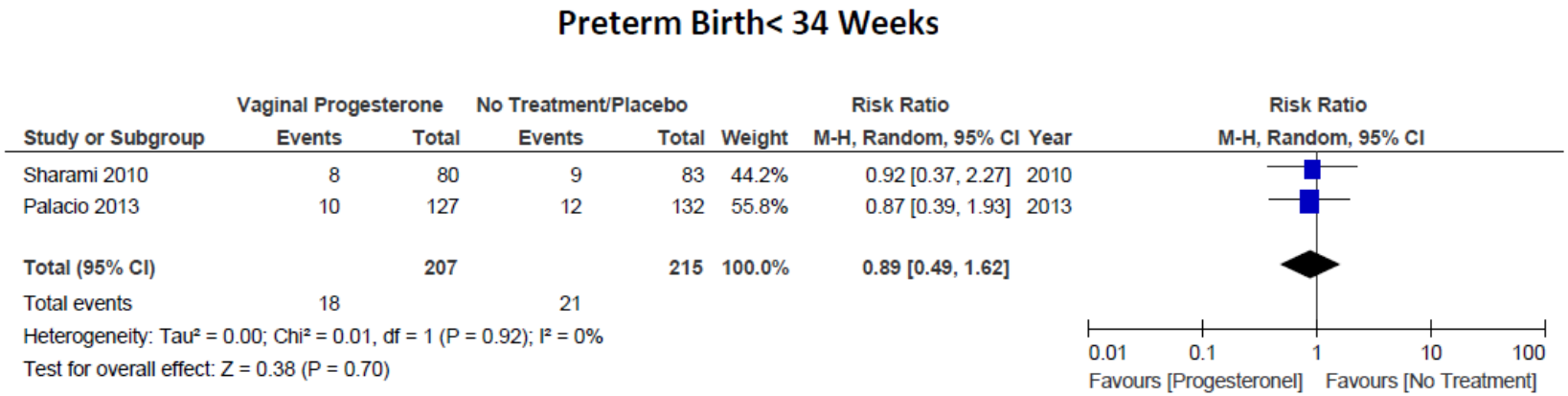
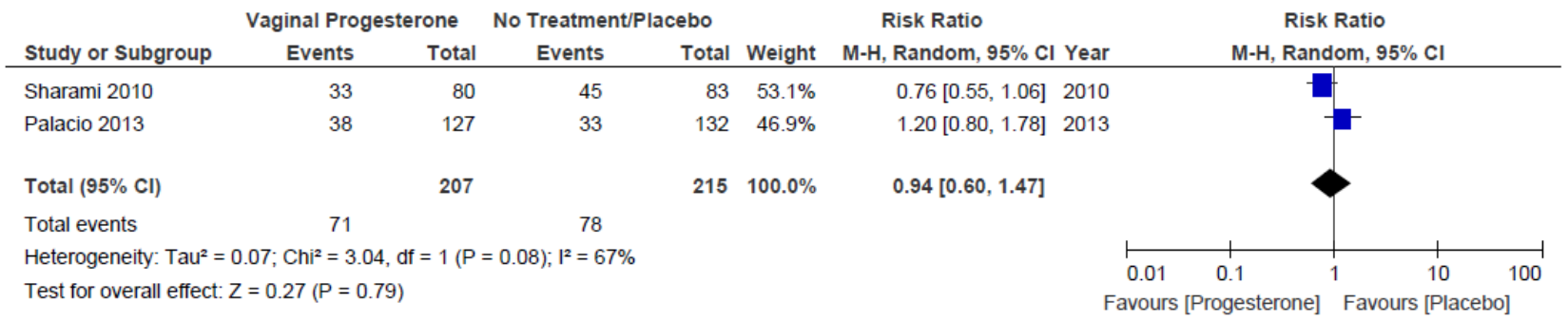


Figure 37 – Preterm birth < 37 weeks: vaginal progesterone maintenance therapy versus placebo/no treatment



8. EXTERNAL REVIEW

8.1. Consultation of stakeholders

The draft recommendations developed by the Guideline Development Group were presented to the members of four LOK/GLEM groups to gather feedback on clarity and completeness, to gain acceptance of the guideline and to assess applicability and feasibility. LOK/GLEM group members consist of second and teriary line gynaecologists. For the pupose of reviewing the draft guideline, midwifes and neonatologists were also invited.

Participants of the LOK/GLEM meeting received the summary guideline two weeks in advance and were asked to assign a score to each recommendation for clarity and a separate score for feasibility. Received scores and comments were summarized and further discussed during the meetings. Final changes of the recommendations following the review were considered in collaboration with the GDG.

Particpants, scores and comments of each LOK/GLEM meeting are summarized below.

8.1.1. Meeting LOK group Gent, April 4th, 2014

8.1.1.1. Participants

Name, title	Name, title
Tom Bovyn, Gynaecologist	Tessa Van Oostveldt, Gynaecologist
Ann Mortier, Gynaecologist	Veerle Verhaeghe, Gynaecologist
Tessie Declercq, Gynaecologist	Caroline Van Turnhout, Gynaecologist
Geert Braems, Gynaecologist	Ellen Roets, Gynaecologist
Sandra Delanote, Gynaecologist	Regine Goemaes, midwife
Inge Dierickx, Gynaecologist	Ann Van Holsbeek, midwife
Kristien Roelens, Gynaecologist	Sofie Daninck, midwife
Kristin Van Mensel, Gynaecologist	Ann Huygevelt, midwife
Kathleen Van Mulders, Gynaecologist	

8.1.1.2. Overview scoring and comments

	SoR	LoE	Score Content	Score Content	Score Content	Comment
Secondary prevention						
Vaginal ultrasound to identify women eligible for secondary prevention						
Consider performing (serial) cervical length measurement in women with a history of birth prior to 32 weeks to select women eligible for cerclage.	**weak**	**NA**	4	4	5	When will you measure? Between 14 and 24 weeks? During the whole pregnancy?
Progesterone for women at risk						
Offer vaginal progesterone to asymptomatic pregnant women with a history of spontaneous preterm birth, from the start of the second trimester onwards until at least 34 weeks.	**Strong**	**Low**	5	4	5	
Cerclage						
Do not routinely offer cerclage as secondary prevention of preterm birth to women at high risk based on the woman's history of preterm birth (between 24 and 37 weeks) alone.	**weak**	**Very low**	5	5	5	
Consider a cerclage in women with a history of preterm birth before 32 weeks and a short cervix on ultrasound.	**weak**	**Very low**	2	4	5	only if measured between 14 and 24 weeks pregnancy in the current one
Consider offering a primary cerclage to women with a history of recurrent second trimester birth.	**Weak**	**Very low**	4	5	5	
Tertiary prevention						
Identification of symptomatic women eligible for treatment: vaginal ultrasound						
Consider performing cervical length measurement in women presenting with symptoms of threatened preterm labour and less than 3cm cervical dilatation to avoid overtreatment (avoid unnecesarry admissions to hospital, transfer to tertiary level and administration of tocolytic therapy), using a threshold of ≥ 30mm to decline treatment. If cervical length is < 15mm, consider treatment.	**Weak**	**NA**	5	5	4	cut-off is wel zeer laag gekozen: komt niet zoveel voor en als de cx lengte minder dan 15mm is, heb je sowieso al veel bevallingen
Identification of symptomatic women eligible for treatment: fetal fibronectin test or Actim Partus test						
In women presenting with symptoms of threatened preterm labour and less than 3cm cervical dilatation, consider further assessment using a fetal fibronectin test or actim partus test if measured cervical length is between 16 and 29mm. If test result is negative, no treatment is indicated.	**Weak**	**NA**	4	4	4	ook vooral als weerhouden therapie te gebruiken
Repeated dose corticosteroid treatment						
Consider a second course of antenatal corticosteroids in women with threatened preterm birth before 30 weeks if the first dose was administered at least seven days earlier. More than two courses of corticosteroids are not recommended.	**Weak**	**Moderate**	5	5	4	

Type of tocolytic therapy						
•Consider tocolytic therapy in women with threatened preterm birth between 23+5/7 and 33+5/7 weeks of gestation to delay birth with 48h while administering corticosteroid therapy and/or transfer to tertiary level. Calcium channel blockers and oxytocin antagonists are considered first choice tocolytic agents.	**Weak**	**NA**	5	4	4	I suspect the parents have the choice to start treatment or not before they reach 25+5/7. This is not clear in the recommendation
Duration of therapy						
Do not offer magnesium maintenance therapy to pregnant women with arrested preterm labour.	**Strong**	**Very low**	5	5	5	
Do not routinely offer nifedipine maintenance therapy to pregnant women with arrested preterm labour. It can be considered to prolong pregnancy in women with threatened preterm labour before 28 weeks if no contraindication is present.	**Weak**	**Low**	4	5	5	
Do not offer oral betamimetics maintenance therapy to pregnant women with arrested preterm labour.	**Strong**	**Low**	5	5	5	
Do not offer oxytocin antagonist maintenance therapy to pregnant women with arrested preterm labour.	**Strong**	**Very low**	5	5	5	may add: after 48h treatment
Consider offering progesterone maintenance therapy to pregnant women with arrested preterm labour.	**Weak**	**Very low**	5	5	5	
Offer magnesium sulphate for neuroprotection to women presenting with imminent preterm birth and/or failed tocolytic therapy (before 32-34 weeks) of pregnancy.	**Strong**	**High**		5	5	maybe add: for 24 hours maximum

Legend

1	I completely disagree with the recommendation
2	I somewhat disagree with the recommendation
3	I don't agree or disagree
4	I somewhat agree with the recommendation
5	I completely agree with the recommendation
NA	No opinion

	SoR	LoE	Score Feasibility	Score Content	Score Content	Comment
Secondary prevention						
Vaginal ultrasound to identify women eligible for secondary prevention						
Consider performing (serial) cervical length measurement in women with a history of birth prior to 32 weeks to select women eligible for cerclage.	**weak**	**NA**	5	4	5	
Progesterone for women at risk						
Offer vaginal progesterone to asymptomatic pregnant women with a history of spontaneous preterm birth, from the start of the second trimester onwards until at least 34 weeks.	**Strong**	**Low**	5	5	5	
Cerclage						
Do not routinely offer cerclage as secondary prevention of preterm birth to women at high risk based on the woman's history of preterm birth (between 24 and 37 weeks) alone.	**weak**	**Very low**	5		5	
Consider a cerclage in women with a history of preterm birth before 32 weeks and a short cervix on ultrasound.	**weak**	**Very low**	5	4	5	
Consider offering a primary cerclage to women with a history of recurrent second trimester birth.	**Weak**	**Very low**	4	4	5	
Tertiary prevention						
Identification of symptomatic women eligible for treatment: vaginal ultrasound						
Consider performing cervical length measurement in women presenting with symptoms of threatened preterm labour and less than 3cm cervical dilatation to avoid overtreatment (avoid unnecesarry admissions to hospital, transfer to tertiary level and administration of tocolytic therapy), using a threshold of ≥ 30mm to decline treatment. If cervical length is < 15mm, consider treatment.	**Weak**	**NA**	5	5	3	is niet zo gemakkelijk on 's nachts uit te voeren wanneer geen gynaecoloog aanwezig is, partosure is dan gemakkelijk gezien niet cervicaal
Identification of symptomatic women eligible for treatment: fetal fibronectin test or Actim Partus test						
In women presenting with symptoms of threatened preterm labour and less than 3cm cervical dilatation, consider further assessment using a fetal fibronectin test or actim partus test if measured cervical length is between 16 and 29mm. If test result is negative, no treatment is indicated.	**Weak**	**NA**	1	4		fibronectine test bij ons niet gebruikt dus zouden we nu eerder actim partus of partosure gebruiken
Repeated dose corticosteroid treatment						
Consider a second course of antenatal corticosteroids in women with threatened preterm birth before 30 weeks if the first dose was administered at least seven days earlier. More than two courses of corticosteroids are not recommended.	**Weak**	**Moderate**	5	5		
Type of tocolytic therapy						

•Consider tocolytic therapy in women with threatened preterm birth between 23+5/7 and 33+5/7 weeks of gestation to delay birth with 48h while administering corticosteroid therapy and/or transfer to tertiary level. Calcium channel blockers and oxytocin antagonists are considered first choice tocolytic agents.	**Weak**	**NA**	5	4	gebeurt overal nog te veel zeker
Duration of therapy					
Do not offer magnesium maintenance therapy to pregnant women with arrested preterm labour.	**Strong**	**Very low**	5	5	nooit gedaan
Do not routinely offer nifedipine maintenance therapy to pregnant women with arrested preterm labour. It can be considered to prolong pregnancy in women with threatened preterm labour before 28 weeks if no contraindication is present.	**Weak**	**Low**	5	4	nooit gedaan
Do not offer oral betamimetics maintenance therapy to pregnant women with arrested preterm labour.	**Strong**	**Low**	5	5	nooit gedaan
Do not offer oxytocin antagonist maintenance therapy to pregnant women with arrested preterm labour.	**Strong**	**Very low**	5	5	nooit gedaan
Consider offering progesterone maintenance therapy to pregnant women with arrested preterm labour.	**Weak**	**Very low**	5	4	lijkt logisch
Offer magnesium sulphate for neuroprotection to women presenting with imminent preterm birth and/or failed tocolytic therapy (before 32-34 weeks) of pregnancy.	**Strong**	**High**		5	

Legend

1	Very low
2	Low
3	Average
4	High
5	Very high
NA	No opinion

Comments received during the meeting

Secondary prevention

- Change order of recommendations so that chronology is respected: start with progesterone, then FU cervical length measurement and possible cerclage
- For progesterone: add remark on dose, timing and stress that recommendation is only applicable to singleton pregnancies
- For vaginal ultrasound: discuss in text that FU of cervical length may also be considered for other interventions that are not discussed in the guideline (e.g. reduce physical activity). Vaginal ultrasound may be difficult to perform during on call hours, as assessment of women with threatened preterm labour is often performed by midwifes.

- For cerclage: recommendation not to perform a cerclage based on women's history alone should be a strong recommendation. Add that no cerclage should be performed after 24-26 weeks of pregnancy.
- Fetal fibronectin test: for small hospitals where the test is not frequently used, fFN has the disadvantage that it quickly passes its expiration date. Furthermore, if not performed frequently, it is not very easy in use. Newer tests, with vaginal in stead of cervical sampling are considered more user friendly.

Tertiary prevention

- Tocolytic treatment: nifedipine has often side effects such as headache and it is not registered for use as tocolytic agent. Tablets of 10 mg are not available in Belgium, leading to difficulties with dosing.
- Repeated dose steroids: proposal to leave out "before 30 weeks" as this limitation is not clear in the evidence (example of threatened preterm labour at 32 weeks in a woman who received a first course of steroids at 26 weeks: following the evidence, repeated dose would be beneficial).
- Magnesium sulphate: add proposed dose: 4g loading doase followed by 1g per hour for maximum 24 hours.

8.1.2. Meeting LOK group Anderlecht (Erasme hospital), April 25th, 2014

8.1.2.1. Partipants

Name, title	Name, title
ALVARO MERCADAL Beatriz, Gynaecologist	HOLOYE Anne, Gynaecologist
BOGNE KAMDEM Valéry, Gynaecologist	KIRKPATRICK Christine, Gynaecologist
CHAMIEC Martine, Gynaecologist	KOENIG Isabelle, Gynaecologist
DELBAERE Anne, Gynaecologist	LEJEUNE Rosine, Gynaecologist
DEROOVER Jacques, Gynaecologist	NAOME Geneviève, Gynaecologist
DEVREKER Fabienne, Gynaecologist	SASSI Asma, Gynaecologist
DIKETE EKANGA Miche, Gynaecologist l	SIMON Philippe, Gynaecologist
DONNER Catherine, Gynaecologist	THOMAS Christine, Gynaecologist
ENGLERT Yvon, Gynaecologist	TWAGIRAYEZU Pierre, Gynaecologist
GAJEWSKA Kalina, Gynaecologist	ZAHRAOUI Laila, Gynaecologist
HANNES Michel, Gynaecologist	HERINCKX Alain, Gynaecologist
HOING Louise, Gynaecologist	SBERA Ioana, Gynaecologist
HENNEQUIN Yves, Paediatrician	

8.1.2.2. Overview scoring and comments

R		FdR	LoE	Score Contenu	Score Contenu	Commentaires	Score Faisabilité
	Prévention secondaire						
	Echographie vaginale pour identifier les femmes éligibles pour une prévention secondaire						
R1	**Consider performing (serial) cervical length measurement in women with a history of birth prior to 32 weeks to select women eligible for cerclage.** ***Envisager une mesure (répétée) de la longueur du col en cas d'antécédents d'accouchement prématuré avant 32 semaines pour identifier les femmes éligibles pour un cerclage.***	**Faible**	**NA**	1	3	comment identifier? Plus le col est court, plus le cerclage sera difficile; le cerclage n'a jamais été démontré efficace dans les antécédents de MAP	2
	Progestérone pour les femmes à risque						
R2	**Offer vaginal progesterone to asymptomatic pregnant women with a history of spontaneous preterm birth, from the start of the second trimester onwards until at least 34 weeks.** ***Proposer de la progestérone vaginale aux femmes asymptomatiques avec des antécédents d'accouchement prématuré, du début du second trimestre jusqu'à la 34ème semaine au minimum.***	**Forte**	**Basse**	4	3		3
R3	**Consider offering vaginal progesterone to asymptomatic women with a short cervix identified on vaginal ultrasound.** ***Envisager l'utilisation de progestérone vaginale chez les femmes asymptomatiques présentant un col court à l'échographie vaginale.***	**Faible**	**Basse**	1	1	diagnostic col court augmente angoisse et risque AP!	2
	Cerclage						
R4	**Do not routinely offer cerclage as secondary prevention of preterm birth to women at high risk based on the woman's history of preterm birth (between 24 and 37 weeks) alone.** ***Ne pas proposer automatiquement de cerclage pour la prévention secondaire de la prématurité chez des femmes avec des antécédents d'accouchement prématuré (entre 24 et 37 semaines) comme seul facteur de risque.***	**Faible**	**Très basse**	5	5		4
R5	**Consider a cerclage in women with a history of preterm birth before 32 weeks and a short cervix on ultrasound.** ***Envisager un cerclage chez les femmes avec des antécédents d'accouchement prématuré avant 32 semaines de gestation et un col court à l'échographie.***	**Faible**	**Très basse**	1	2		1
R6	**Consider offering a primary cerclage to women with a history of recurrent second trimester birth.**	**Faible**	**Très basse**	5	2		2

	Envisager de proposer un cerclage primaire aux femmes avec des antécédents d'accouchements prématurés répétés au second trimestre.						
	Prévention tertiaire						
	Identification des femmes symptomatiques susceptibles de recevoir un traitement : échographie vaginale						
R7	**Consider performing cervical length measurement in women presenting with symptoms of threatened preterm labour and less than 3cm cervical dilatation to avoid overtreatment (avoid unnecesarry admissions to hospital, transfer to tertiary level and administration of tocolytic therapy), using a threshold of ≥ 30mm to decline treatment. If cervical length is < 15mm, consider treatment.**						
	Envisager de mesurer la longueur du col chez les femmes avec des symptômes de menace d'accouchement prématuré et une ouverture du col de moins de 3 cm afin d'éviter le surtraitement (admission à l'hôpital, transfert au niveau tertiaire, administration de tocolytiques). Si la longueur du col est ≥30 mm, aucun traitement n'est requis. Si la longueur du col est <15 mm, envisager un traitement.	**Faible**	**NA**	5	2		2
	Identification des femmes symptomatiques susceptibles de recevoir un traitement : échographie vaginale						
R8	**In women presenting with symptoms of threatened preterm labour and less than 3cm cervical dilatation, consider further assessment using a fetal fibronectin test or actim partus test if measured cervical length is between 16 and 29mm. If test result is negative, no treatment is indicated.**						
	Envisager d'appliquer un test de fibronectine foetale ou un test Actim Partus chez les femmes avec des symptômes de menace d'accouchement prématuré, une ouverture du col de moins de 3 cm et une longueur du col comprise entre 16 mm et 29 mm à l'échographie vaginale. Si le test est négatif, aucun traitement n'est requis.	**Faible**	**NA**	5	3		3
	Utilisation répétée des corticostéroides						
R9	**Consider a second course of antenatal corticosteroids in women with threatened preterm birth before 30 weeks if the first dose was administered at least seven days earlier. More than two courses of corticosteroids are not recommended.**						
	Envisager un second traitement de corticostéroides prénatal chez les femmes avec une menace d'accouchement prématuré avant 30 semaines si la première dose a été administrée au moins 7 jours plus tôt. Il n'est pas recommandé d'appliquer plus de deux traitements aux corticostéroides.	**Faible**	**Modérée**	4	3	plutôt cure de rapperl (12 mg 1 fois) et 15j depuis cure précédente et < 32 sem	4
	Type de traitement tocolytique						

R10	**Consider tocolytic therapy in women with threatened preterm birth between 23+5/7 and 33+5/7 weeks of gestation to delay birth with 48h while administering corticosteroid therapy and/or transfer to tertiary level. Calcium channel blockers and oxytocin antagonists are considered first choice tocolytic agents.** ***Envisager une tocolyse chez les femmes avec menace d'accouchement prématuré entre 23+5/7 et 33+5/7 semaines de gestation pour retarder l'accouchement de 48 heures et permettre d'administrer des corticostéroides et/ou référer la femme au niveau tertiaire. Les antagonistes du calcium et les antagonistes de l'ocytocine sont considérés comme les tocolytiques de premier choix.***	**Faible**	**NA**	5	5		4
	Durée du traitement						
R11	**Do not offer magnesium maintenance therapy to pregnant women with arrested preterm labour.** ***Ne pas utiliser le magnesium en traitement de maintenance chez les femmes avec un travail prématuré stoppé***	**Forte**	**Très basse**	5	4		4
R12	**Do not routinely offer nifedipine maintenance therapy to pregnant women with arrested preterm labour. It can be considered to prolong pregnancy in women with threatened preterm labour before 28 weeks if no contraindication is present.** ***Ne pas utiliser en routine la nifédipine en traitement de maintenance chez les femmes avec un travail prématuré stoppé. Ce traitement peut être envisagé chez des femmes avec une menace d'accouchement prématuré avant 28 semaines de gestation en l'absence de contre-indications.***	**Faible**	**Basse**	5	4	5 pour la 1ère phrase, 1 pour la 2ème	2
R13	**Do not offer oral betamimetics maintenance therapy to pregnant women with arrested preterm labour.** ***Ne pas utiliser les beta-mimétiques oraux en traitement de maintenance chez les femmes avec un travail prématuré stoppé.***	**Forte**	**Basse**	5	5		4
R14	**Do not offer oxytocin antagonist maintenance therapy to pregnant women with arrested preterm labour.** ***Ne pas utiliser les antagonistes de l'ocytocine en traitement de maintenance chez les femmes avec un travail prématuré stoppé.***	**Forte**	**Très basse**	5	5		4
R15	**Consider offering progesterone maintenance therapy to pregnant women with arrested preterm labour.** ***Envisager un traitement de maintenance à la progestérone chez les femmes avec un travail prématuré stoppé.***	**Faible**	**Très basse**	5	3		3
R16	**Offer magnesium sulphate for neuroprotection to women presenting with imminent preterm birth and/or failed tocolytic therapy (before 32-34 weeks) of pregnancy.**	**Forte**	**Haute**	5	3		3

Administrer du sulphate de magnésium pour la neuro-protection chez les femmes avec un accouchement prématuré imminent et/ou échec de la tocolyse (avant 32-34 semaines de gestation).

Comments received during the meeting

Secondary prevention

- Measurement of cervical length: the group mentions that the recommendation lacks of clarity about the number and timing of ultrasound tests recommended, and emphasizes that this strategy could generate anxiety. It is also mentions that the goal of such strategy should be clarified, as a cerclage is unlikely to be appropriate in all cases. One participant also emphasizes the need to account for other clinical parameters such as the opening and the consistency of the cervix.
- The formulation of recommendation 5 needs to be clarified because as now it seems to indicate that a cerclage is indicated up to 32 weeks
- Recommendation 6 should be graded as strong because there is a large consensus about the appropriateness of that intervention and further RCTs are unlikely to be set up.

Tertiary prevention

- It is mentioned that applying an fFN test directly after a vaginal ultrasound might be difficult because the gel used for the ultrasound might impact on the validity of the fFN test. Solutions proposed by participants would be to take a vaginal swab before making the ultrasound and to send the swab to lab only when the cervix is shortened (in the case of Actim Partus). Another approach would be to wait until the day after the ultrasound to test the fFN.
- Participants underlines that the recommendation on the administration of Magnesium Sulphate for neuroprotection might be lowly feasible as it should be administered in case of imminent delivery whereas 4 hours after the injection are needed for the drug to be effective.

8.1.3. Meeting LOK group Brugge, April 25th, 2014

8.1.3.1. Participants

Name, title	Name, title
Hilde Logghe, Gynaecologist	Véronique Verhulst, Gynaecologist
Filip Claerhout, Gynaecologist	Wim Decaluwé, Neonatologist
Barbara Lebbe, Gynaecologist	Alexandra Chanteloup, Midwife
Christine Colmant, Gynaecologist	Chris Quintens, Midwife
Guy Bouwens, Gynaecologist	
Bart Boone, Gynaecologist	
Benoit Rombaut, Gynaecologist	
Anne Loccufier, Gynaecologist	
Karine Helsen, Gynaecologist	

8.1.3.2. Overview scoring and comments

	SoR	LoE	Score Content SH1	Score Content SH2	Score Content SH3	Score Content SH4	Score Content SH5	Score Content SH6	Score Content SH7	Comment
Secondary prevention										
Vaginal ultrasound to identify women eligible for secondary prevention										
Consider performing (serial) cervical length measurement in women with a history of birth prior to 32 weeks to select women eligible for cerclage.	**Weak**	**NA**	1	5	5	4	3	1	4	SH5: literatuur lijkt eerder aan te geven bij deze patiënten, die reeds onder Utrogestan staan, rond ca 20 wkn een cervixlengte te doen en als < 25mm een cerclage uit te voeren (oa publicaties van Romero) - je gaat toch geen cerclage aanleggen op 30w?
Progesterone for women at risk										
Offer vaginal progesterone to asymptomatic pregnant women with a history of spontaneous preterm birth, from the start of the second trimester onwards until at least 34 weeks.	**Strong**	**Low**	5	5	5	5	5	5	5	SH5: misschien bij specifiëren wat de dosis is? nog te veel gyn geven 3x200
Consider offering vaginal progesterone to asymptomatic women with a short cervix identified on vaginal ultrasound.	**Weak**	**Low**	4	5	2	5	5	4	5	SH5: termijn specifiëren: cxlengte rond 20w
Cerclage										
Do not routinely offer cerclage as secondary prevention of preterm birth to women at high risk based on the woman's history of preterm birth (between 24 and 37 weeks) alone.	**Weak**	**Very low**	5	2	3	4	5	5	4	
Consider a cerclage in women with a history of preterm birth before 32 weeks and a short cervix on ultrasound.	**Weak**	**Very low**	3	5	5	2	4	3	4	SH5: misschien specifiëren dat deze patiënten in principe reeds op Utrogestan staan - waarom termijn van 32 en niet van 34 wkn?
Consider offering a primary cerclage to women with a history of recurrent second trimester birth.	**Weak**	**Very low**	5	5	5		5	5	4	
Tertiary prevention										
Identification of symptomatic women eligible for treatment: vaginal ultrasound										
Consider performing cervical length measurement in women presenting with symptoms of threatened preterm labour and less than 3cm cervical dilatation to avoid overtreatment (avoid unnecesarry	**Weak**	**NA**	3	1	5	4	5	3	4	SH5: obv literatuur niet gemakkelijk vast te stellen wat de cutoff zou moeten zijn: 30 of 25 mm - je zou kunnen denken: we doen heel vaak aan overbehandeling, zou het dan niet beter zijn de grens lager te

admissions to hospital, transfer to tertiary level and administration of tocolytic therapy), using a threshold of ≥ 30mm to decline treatment. If cervical length is < 15mm, consider treatment.										leggen? - ik ben idd ook voorstander voor groep tussen 15 en 25/30 een Actim Partus test te doen
Identification of symptomatic women eligible for treatment: fetal fibronectin test or Actim Partus test										
In women presenting with symptoms of threatened preterm labour and less than 3cm cervical dilatation, consider further assessment using a fetal fibronectin test or actim partus test if measured cervical length is between 16 and 29mm. If test result is negative, no treatment is indicated.	**Weak**	**NA**	5	4	5	4	5	5	4	SH5: ik zou kiezen voor Actim Partus test: zelfde NPW en een aanzienlijk stuk goedkoper - extra voordelen: wattenstaafjes apart verkrijgbaar zodat je niet steeds een set dient open te doen (als cx > 30 mm of < 15 mm blijkt te zijn kan staafje weggegooid worden) - idem als Actim prom test, die ingeburgerd is - geen analyser nodig)
Repeated dose corticosteroid treatment										
Consider a second course of antenatal corticosteroids in women with threatened preterm birth before 30 weeks if the first dose was administered at least seven days earlier. More than two courses of corticosteroids are not recommended.	**Weak**	**Moderate**	5	5	5	3	4	5	4	SH5: waarom termijn van 30 weken? Ik zou tot 34 weken geneigd zijn te herhalen
Type of tocolytic therapy										
Consider tocolytic therapy in women with threatened preterm birth between 23+5/7 and 33+5/7 weeks of gestation to delay birth with 48h while administering corticosteroid therapy and/or transfer to tertiary level. Calcium channel blockers and oxytocin antagonists are considered first choice tocolytic agents.	**Weak**	**NA**	4		5	5	5		4	als we beslissen om in België Adalat aan te raden, dan zal de Adalat 10 mg wel beschikbaar gemaakt moeten worden (of zullen apothekers bereid moeten zijn om het uit Nederland te importeren)
Duration of therapy										
Do not offer magnesium maintenance therapy to pregnant women with arrested preterm labour.	**Strong**	**Very low**	NA	5	5	4	5	NA	5	
Do not routinely offer nifedipine maintenance therapy to pregnant women with arrested preterm labour. It can be considered to prolong pregnancy in women with threatened preterm labour before 28 weeks if no contraindication is present.	**Weak**	**Low**	3	3	5	4	4	3	4	SH5: hier zetten we wel weer een deur open naar onderhoudstocolyse (net nu we verlost zijn van de Prepar po)

Do not offer oral betamimetics maintenance therapy to pregnant women with arrested preterm labour.	**Strong**	**Low**	3	5	5	5	5	3	5	voor zover ik weet is Prepar po uit de handel en is deze aanbeveling eigenlijk in België niet meer van toepassing?
Do not offer oxytocin antagonist maintenance therapy to pregnant women with arrested preterm labour.	**Strong**	**Very low**	3	5	5	5	5	3	5	
Consider offering progesterone maintenance therapy to pregnant women with arrested preterm labour.	**Weak**	**Very low**	5	5	5	4	3	5	4	hier is eigenlijk geen evidentie voor…, hoewel ik er wel kan inkomen (opnieuw dosering specifiëren, 1x200 vag)
Offer magnesium sulphate for neuroprotection to women presenting with imminent preterm birth and/or failed tocolytic therapy (before 32-34 weeks) of pregnancy.	**Strong**	**High**	4	5	5	5		4	5	NNT is best onder 32 weken (dus bovenbrens 32 lijkt beter) - dosering vermelden: uit de literatuur niet eenduidig, persoonlijke voorkeur: 4g oplaad en 1g/u onderhoud omdat we bij PE hierbij zelden bijwerkingen zien en omdat vroedvrouwen met deze bereiding vertrouwd zijn

	SoR	LoE	Score Feasibility SH1	Score Feasibility SH2	Score Feasibility SH3	Score Feasibility SH4	Score Feasibility SH5	Score Feasibility SH6	Score Feasibility SH7	Comment
Secondary prevention										
Vaginal ultrasound to identify women eligible for secondary prevention										
Consider performing (serial) cervical length measurement in women with a history of birth prior to 32 weeks to select women eligible for cerclage.	**Weak**	**NA**	3	5	3	4		3	4	SH3: afhankelijk van de compliance van de patiënte
Progesterone for women at risk										
Offer vaginal progesterone to asymptomatic pregnant women with a history of spontaneous preterm birth, from the start of the second trimester onwards until at least 34 weeks.	**Strong**	**Low**	5	5	4	5	5	5	5	SH3: opnnieuw cave patient compliance: niet iedereen steekt graag comprimés vaginaal op gezien het belang van TVE in het volledige preterme arbeid verhaal, lijkt het met maar normaal dat dergelijke echografie ook vergoed wordt…
Consider offering vaginal progesterone to asymptomatic women with a short cervix identified on vaginal ultrasound.	**Weak**	**Low**	3	5	3	5	5	3	5	SH3: belangrijker om nadruk te leggen op het belang van utrogestan bij VG van premature

										partus. Er wordt al voldoende 'gesmeten' met utrogestan
Cerclage										
Do not routinely offer cerclage as secondary prevention of preterm birth to women at high risk based on the woman's history of preterm birth (between 24 and 37 weeks) alone.	**Weak**	**Very low**	3	3	3	4	5	3	5	SH3: wordt sowieso al weing geplaatst
Consider a cerclage in women with a history of preterm birth before 32 weeks and a short cervix on ultrasound.	**Weak**	**Very low**	4	5	4	2	5	4	4	
Consider offering a primary cerclage to women with a history of recurrent second trimester birth.	**Weak**	**Very low**	4	5	4		5	4	4	
Tertiary prevention										
Identification of symptomatic women eligible for treatment: vaginal ultrasound										
Consider performing cervical length measurement in women presenting with symptoms of threatened preterm labour and less than 3cm cervical dilatation to avoid overtreatment (avoid unnecesarry admissions to hospital, transfer to tertiary level and administration of tocolytic therapy), using a threshold of ≥ 30mm to decline treatment. If cervical length is < 15mm, consider treatment.	**Weak**	**NA**	NA	5	1	2	5	NA	3	SH3: compliance in perifeer centrum op >20 minuten van tertiair centrum met 'expectant policy' is zeer laag. In sommige centra soms ook geen vag echo beschikbaar tijdens wachtdienst
Identification of symptomatic women eligible for treatment: fetal fibronectin test or Actim Partus test										
In women presenting with symptoms of threatened preterm labour and less than 3cm cervical dilatation, consider further assessment using a fetal fibronectin test or actim partus test if measured cervical length is between 16 and 29mm. If test result is negative, no treatment is indicated.	**Weak**	**NA**	5	5	1	3	5	5	2	SH3: In centra met slechte indiciatie voor tocolyse, is fibronectine een (dure) druppel op een veel te hete plaat.
Repeated dose corticosteroid treatment										
Consider a second course of antenatal corticosteroids in women with threatened preterm birth before 30 weeks if the first dose was administered at least seven days earlier. More than	**Weak**	**Moderate**	4	5	5	3	5	4	4	

two courses of corticosteroids are not recommended.										
Type of tocolytic therapy										
Consider tocolytic therapy in women with threatened preterm birth between 23+5/7 and 33+5/7 weeks of gestation to delay birth with 48h while administering corticosteroid therapy and/or transfer to tertiary level. Calcium channel blockers and oxytocin antagonists are considered first choice tocolytic agents.	**Weak**	**NA**	NA		5	5	5	NA	4	
Duration of therapy										
Do not offer magnesium maintenance therapy to pregnant women with arrested preterm labour.	**Strong**	**Very low**	NA	5	5	5	2	NA	5	
Do not routinely offer nifedipine maintenance therapy to pregnant women with arrested preterm labour. It can be considered to prolong pregnancy in women with threatened preterm labour before 28 weeks if no contraindication is present.	**Weak**	**Low**	NA	4	2	4		NA	2	SH3: Snelwerkende vorm van nifedipine is niet meer beschikbaar in belgie!! Moet geimporteerd worden uit nederland SH5: volgens mij gaan veel gyn dit toepassen, en niet enkel bij termijn < 28 weken (vervanging van Prepar)
Do not offer oral betamimetics maintenance therapy to pregnant women with arrested preterm labour.	**Strong**	**Low**	NA	5	5	5	5	NA	5	
Do not offer oxytocin antagonist maintenance therapy to pregnant women with arrested preterm labour.	**Strong**	**Very low**	3	5	5	5	5	3	3	
Consider offering progesterone maintenance therapy to pregnant women with arrested preterm labour.	**Weak**	**Very low**	5	5	4	4	5	5	4	
Offer magnesium sulphate for neuroprotection to women presenting with imminent preterm birth and/or failed tocolytic therapy (before 32-34 weeks) of pregnancy.	**Strong**	**High**	4	5	3	5	5	4	4	SH3: wordt te vaak vergeten SH5: vraag is: wanneer start je MgSO4: als je ook tocolyse start of als je zegt nu geraak ik er niet meer met mijn tocolyse, deze patiënte moet naar VK - ook specifiêren hoe lang het gegeven mag worden en

			wat minimumduur is dat het gegeven moet worden alvorens voordelig

Comments received during the meeting

Secondary prevention

- The recommendation on the use of primary cerclage is somewhat unclear. On the one hand, for women with a history of 'cervical incompetence' (asymptomatic dilatation of the cervix and immature birth), a primary cerclage may already be considered in the second pregnancy. On the other hand, for women with a history of (recurrent) preterm birth at the end of the second trilmester due to infection or extremely preterm labour, a cerclage may be contra-indicated.
- The recommendation on the use of progesterone in women with a short cervix may refer to primary prevention, as it suggests that screening of all pregnant women may be useful.

Tertiary prevention

- It is suggested that the recommendations on the use of predictive tests (vaginal ultrasound, fFN, actim partus) are essentially 'strong' recommendations, as they apply to the vast majority of women presenting with suspected preterm labour and less than 3 cm dilatation.
- A note on the use of combination tocolytic therapy should be added. There is no proof that combining tocolytic agents improves outcomes but combination therapy is associated with increased toxicity. Nevertheless, it is still often done in practice.
- It is difficult to organise the administration of antenatal magnesium sulphate for neuroprotection, as timeframe for administration is often very short in women with immanent preterm labour or failed tocolysis.

8.1.4. Meeting LOK group Ixelles, April 29th, 2014

8.1.4.1. Participants

Name, title	Name, title
ATALLAH W. , Gynaecologist	AFEICHE C. , Gynaecologist
BEECKMANS D. , Gynaecologist	BRANS A. , Gynaecologist
BEERNAERT J. , Gynaecologist	BRAT M. , Gynaecologist
BOSSENS M. , Gynaecologist	BUISSON, Gynaecologist
BUCELLA D. , Gynaecologist	COBIN Laurence, Gynaecologist
BUXANT F, Gynaecologist	KARLIN S. , Gynaecologist
CAMACHO E. , Gynaecologist	LASZLO Emeric, Gynaecologist

DE BRUYNE G. , Gynaecologist	MAHILLON I. , Gynaecologist
DUPOND Isabelle, Gynaecologist	MAKHOUL J. , Gynaecologist
FELLEMANS C. , Gynaecologist	MELICE H. , Gynaecologist
FLORENCE N. , Gynaecologist	PEELLAERT C. , Gynaecologist
GREGOIRE M. , Gynaecologist	PREUMONT P. , Gynaecologist
HOUBEN S. , Gynaecologist	THEUNISSEN I. , Gynaecologist
KHAKBAZ S. , Gynaecologist	THOMAS D. , Gynaecologist
LAMY C; , Gynaecologist	TSINA Georgia, Gynaecologist
LEFEBVRE C. , Gynaecologist	VAN HENTENRYCK M. , Gynaecologist
LOTOKO J.P. , Gynaecologist	ZIEREISEN V. , Gynaecologist
NEIRYNCK, Gynaecologist	
NOTERMAN D, Gynaecologist	
NUTTIN R. , Gynaecologist	
SCHMITT J. , Gynaecologist	
SIOZIOS, Gynaecologist	
ZARZYCKA Marzenna, Gynaecologist	
ZIANE Samir, Gynaecologist	
ZUCKER M. , Gynaecologist	

8.1.4.2. Overview scoring and comments

	FdR	LoE	Score Contenu	Score Contenu	Score Contenu	Score Contenu	Score Contenu	Commentaires
Prévention secondaire								
Echographie vaginale pour identifier les femmes éligibles pour une prévention secondaire								
Consider performing (serial) cervical length measurement in women with a history of birth prior to 32 weeks to select women eligible for cerclage.	**Faible**	**NA**	4	4	1	5	5	
Envisager une mesure (répétée) de la longueur du col en cas d'antécédents d'accouchement prématuré avant 32 semaines pour identifier les femmes éligibles pour un cerclage.								
Progestérone pour les femmes à risque								
Offer vaginal progesterone to asymptomatic pregnant women with a history of spontaneous preterm birth, from the start of the second trimester onwards until at least 34 weeks.	**Forte**	**Basse**	2	4	5	5	3	Not enough evidence especially regarding: (i) type of progesterone, (ii) route, (iii) dosage, (iv) long term follow-up. Also unclear what a history of SPTB means: including 36 weeks, twins..
Proposer de la progestérone vaginale aux femmes asymptomatiques avec des antécédents d'accouchement prématuré, du début du second trimestre jusqu'à la 34ème semaine au minimum.								
Consider offering vaginal progesterone to asymptomatic women with a short cervix identified on vaginal ultrasound.	**Faible**	**Basse**	3	4	5	5	3	Col court ou très court?
Envisager l'utilisation de progestérone vaginale chez femmes asymptomatiques présentant un col court à l'échographie vaginale.								
Cerclage								
Do not routinely offer cerclage as secondary prevention of preterm birth to women at high risk based on the woman's history of preterm birth (between 24 and 37 weeks) alone.	**Faible**	**Très basse**	5	4	5	4	5	
Ne pas proposer automatiquement de cerclage pour la prévention secondaire de la prématurité chez des femmes avec des antécédents d'accouchement prématuré (entre 24 et 37 semaines) comme seul facteur de risque.								
Consider a cerclage in women with a history of preterm birth before 32 weeks and a short cervix on ultrasound.	**Faible**	**Très basse**	4	3	5	2	5	Si col très court
Envisager un cerclage chez les femmes avec des antécédents d'accouchement prématuré avant 32								

semaines de gestation et un col court à l'échographie.								
Consider offering a primary cerclage to women with a history of recurrent second trimester birth.								
Envisager de proposer un cerclage primaire aux femmes avec des antécédents d'accouchements prématurés répétés au second trimestre.	**Faible**	**Très basse**	5	4	5	4	5	
Prévention tertiaire								
Identification des femmes symptomatiques susceptibles de recevoir un traitement : échographie vaginale								
Consider performing cervical length measurement in women presenting with symptoms of threatened preterm labour and less than 3cm cervical dilatation to avoid overtreatment (avoid unnecesarry admissions to hospital, transfer to tertiary level and administration of tocolytic therapy), using a threshold of ≥ 30mm to decline treatment. If cervical length is < 15mm, consider treatment.								
Envisager de mesurer la longueur du col chez les femmes avec des symptômes de menace d'accouchement prématuré et une ouverture du col de moins de 3 cm afin d'éviter le surtraitement (admission à l'hôpital, transfert au niveau tertiaire, administration de tocolytiques). Si la longueur du col est ≥30 mm, aucun traitement n'est requis. Si la longueur du col est <15 mm, envisager un traitement.	**Faible**	**NA**	4	4	2	5	5	si on ne traite que des patientes qui ont un col en dessous de 15mm on ne va pas éviter beaucoup d'accouchement prématurés, il faut les prendre en charge à 25 mm
Identification des femmes symptomatiques susceptibles de recevoir un traitement : échographie vaginale								
In women presenting with symptoms of threatened preterm labour and less than 3cm cervical dilatation, consider further assessment using a fetal fibronectin test or actim partus test if measured cervical length is between 16 and 29mm. If test result is negative, no treatment is indicated.								
Envisager d'appliquer un test de fibronectine foetale ou un test Actim Partus chez les femmes avec des symptômes de menace d'accouchement prématuré, une ouverture du col de moins de 3 cm et une longueur du col comprise entre 16 mm et 29 mm à l'échographie vaginale. Si le test est négatif, aucun traitement n'est requis.	**Faible**	**NA**	4	4	NA	2	5	
Utilisation répétée des corticostéroides								

Consider a second course of antenatal corticosteroids in women with threatened preterm birth before 30 weeks if the first dose was administered at least seven days earlier. More than two courses of corticosteroids are not recommended.								
Envisager un second traitement de corticostéroides prénatal chez les femmes avec une menace d'accouchement prématuré avant 30 semaines si la première dose a été administrée au moins 7 jours plus tôt. Il n'est pas recommandé d'appliquer plus de deux traitements aux corticostéroides.	**Faible**	**Modérée**	4	4	3	5	5	si elle a reçu 1 dose à 25 semaines, il parait licite de lui redonner une nouvelle dose à 30 semaines si elle accouche à ce terme
Type de traitement tocolytique								
Consider tocolytic therapy in women with threatened preterm birth between 23+5/7 and 33+5/7 weeks of gestation to delay birth with 48h while administering corticosteroid therapy and/or transfer to tertiary level. Calcium channel blockers and oxytocin antagonists are considered first choice tocolytic agents.								
Envisager une tocolyse chez les femmes avec menace d'accouchement prématuré entre 23+5/7 et 33+5/7 semaines de gestation pour retarder l'accouchement de 48 heures et permettre d'administrer des corticostéroides et/ou référer la femme au niveau tertiaire. Les antagonistes du calcium et les antagonistes de l'ocytocine sont considérés comme les tocolytiques de premier choix.	**Faible**	**NA**	5	4	5	5	5	Why not 33+6?
Durée du traitement								
Do not offer magnesium maintenance therapy to pregnant women with arrested preterm labour.								
Ne pas utiliser le magnesium en traitement de maintenance chez les femmes avec un travail prématuré stoppé	**Forte**	**Très basse**	5	4	NA	5	3	Not dangerous, not expensive
Do not routinely offer nifedipine maintenance therapy to pregnant women with arrested preterm labour. It can be considered to prolong pregnancy in women with threatened preterm labour before 28 weeks if no contraindication is present.								
Ne pas utiliser en routine la nifédipine en traitement de maintenance chez les femmes avec un travail prématuré stoppé. Ce traitement peut être envisagé chez des femmes avec une menace d'accouchement prématuré avant 28 semaines de gestation en l'absence de contrindications.	**Faible**	**Basse**	4	4	4	2		Unclear where the evidence about offering might come from?

Do not offer oral betamimetics maintenance therapy to pregnant women with arrested preterm labour. ***Ne pas utiliser les beta-mimétiques oraux en traitement de maintenance chez les femmes avec un travail prématuré stoppé.***	**Forte**	**Basse**	5	4	5	5	5	
Do not offer oxytocin antagonist maintenance therapy to pregnant women with arrested preterm labour. ***Ne pas utiliser les antagonistes de l'ocytocine en traitement de maintenance chez les femmes avec un travail prématuré stoppé.***	**Forte**	**Très basse**	5	4	5	5	5	What is atosiban maintenance therapy?
Consider offering progesterone maintenance therapy to pregnant women with arrested preterm labour. ***Envisager un traitement de maintenance à la progestérone chez les femmes avec un travail prématuré stoppé.***	**Faible**	**Très basse**	4	4	5	5	5	
Offer magnesium sulphate for neuroprotection to women presenting with imminent preterm birth and/or failed tocolytic therapy (before 32-34 weeks) of pregnancy. ***Administrer du sulphate de magnésium pour la neuro-protection chez les femmes avec un accouchement prématuré imminent et/ou échec de la tocolyse (avant 32-34 semaines de gestation).***	**Forte**	**Haute**	3	5	4	NA	3	30 weeks

	FdR	LoE	Score Faisabilité	Score Faisabilité	Score Faisabilité	Score Faisabilité	Commentaires
Prévention secondaire							
Echographie vaginale pour identifier les femmes éligibles pour une prévention secondaire							
Consider performing (serial) cervical length measurement in women with a history of birth prior to 32 weeks to select women eligible for cerclage. ***Envisager une mesure (répétée) de la longueur du col en cas d'antécédents d'accouchement prématuré avant 32 semaines pour identifier les femmes éligibles pour un cerclage.***	**Faible**	**NA**	3	5	4	5	il est très facile de faire une écho de col à 12semaines et même lors de l'échographie de 22 semaines, ça ne coûte pas plus cher à la sécurité sociale, les patientes sont souvent demandeuses
Progestérone pour les femmes à risque							
Offer vaginal progesterone to asymptomatic pregnant women with a history of spontaneous preterm birth, from the start of the second trimester onwards until at least 34 weeks.	**Forte**	**Basse**	3	5	5	5	

Proposer de la progestérone vaginale aux femmes asymptomatiques avec des antécédents d'accouchement prématuré, du début du second trimestre jusqu'à la 34ème semaine au minimum.							
Consider offering vaginal progesterone to asymptomatic women with a short cervix identified on vaginal ultrasound.	**Faible**	**Basse**	3	5	5	5	
Envisager l'utilisation de progestérone vaginale chez femmes asymptomatiques présentant un col court à l'échographie vaginale.							
Cerclage							
Do not routinely offer cerclage as secondary prevention of preterm birth to women at high risk based on the woman's history of preterm birth (between 24 and 37 weeks) alone.	**Faible**	**Très basse**	4	5	3	5	
Ne pas proposer automatiquement de cerclage pour la prévention secondaire de la prématurité chez des femmes avec des antécédents d'accouchement prématuré (entre 24 et 37 semaines) comme seul facteur de risque.							
Consider a cerclage in women with a history of preterm birth before 32 weeks and a short cervix on ultrasound.	**Faible**	**Très basse**	4	5	2	5	
Envisager un cerclage chez les femmes avec des antécédents d'accouchement prématuré avant 32 semaines de gestation et un col court à l'échographie.							
Consider offering a primary cerclage to women with a history of recurrent second trimester birth.	**Faible**	**Très basse**	5	5	5	5	
Envisager de proposer un cerclage primaire aux femmes avec des antécédents d'accouchements prématurés répétés au second trimestre.							
Prévention tertiaire							
Identification des femmes symptomatiques susceptibles de recevoir un traitement : échographie vaginale							
Consider performing cervical length measurement in women presenting with symptoms of threatened preterm labour and less than 3cm cervical dilatation to avoid overtreatment (avoid unnecesarry admissions to hospital, transfer to tertiary level and administration of tocolytic therapy), using a threshold of ≥ 30mm to decline treatment. If cervical length is < 15mm, consider treatment.	**Faible**	**NA**	4		5	5	
Envisager de mesurer la longueur du col chez les femmes avec des symptômes de menace d'accouchement prématuré et une ouverture du col de moins de 3 cm afin d'éviter le surtraitement (admission à l'hôpital, transfert au niveau tertiaire, administration de tocolytiques). Si la longueur du col est ≥30 mm, aucun traitement n'est requis. Si la longueur du col est <15 mm, envisager un traitement.							
Identification des femmes symptomatiques susceptibles de recevoir un traitement : échographie vaginale							
In women presenting with symptoms of threatened preterm labour and less than 3cm cervical dilatation, consider further assessment using a fetal fibronectin test or actim partus test if measured cervical length is	**Faible**	**NA**	4	2	2	5	le test de fibronectine fœtale est cher par rapport au bénéfice rendu

between 16 and 29mm. If test result is negative, no treatment is indicated.						
Envisager d'appliquer un test de fibronectine foetale ou un test Actim Partus chez les femmes avec des symptômes de menace d'accouchement prématuré, une ouverture du col de moins de 3 cm et une longueur du col comprise entre 16 mm et 29 mm à l'échographie vaginale. Si le test est négatif, aucun traitement n'est requis.						
Utilisation répétée des corticostéroides						
Consider a second course of antenatal corticosteroids in women with threatened preterm birth before 30 weeks if the first dose was administered at least seven days earlier. More than two courses of corticosteroids are not recommended.						
Envisager un second traitement de corticostéroides prénatal chez les femmes avec une menace d'accouchement prématuré avant 30 semaines si la première dose a été administrée au moins 7 jours plus tôt. Il n'est pas recommandé d'appliquer plus de deux traitements aux corticostéroides.	**Faible**	**Modérée**	4	5	5	5
Type de traitement tocolytique						
Consider tocolytic therapy in women with threatened preterm birth between 23+5/7 and 33+5/7 weeks of gestation to delay birth with 48h while administering corticosteroid therapy and/or transfer to tertiary level. Calcium channel blockers and oxytocin antagonists are considered first choice tocolytic agents.						
Envisager une tocolyse chez les femmes avec menace d'accouchement prématuré entre 23+5/7 et 33+5/7 semaines de gestation pour retarder l'accouchement de 48 heures et permettre d'administrer des corticostéroides et/ou référer la femme au niveau tertiaire. Les antagonistes du calcium et les antagonistes de l'ocytocine sont considérés comme les tocolytiques de premier choix.	**Faible**	**NA**	5	5	5	5
Durée du traitement						
Do not offer magnesium maintenance therapy to pregnant women with arrested preterm labour.	**Forte**	**Très basse**	5	5	5	5
Ne pas utiliser le magnesium en traitement de maintenance chez les femmes avec un travail prématuré stoppé						
Do not routinely offer nifedipine maintenance therapy to pregnant women with arrested preterm labour. It can be considered to prolong pregnancy in women with threatened preterm labour before 28 weeks if no contraindication is present.						
Ne pas utiliser en routine la nifédipine en traitement de maintenance chez les femmes avec un travail prématuré stoppé. Ce traitement peut être envisagé chez des femmes avec une menace d'accouchement prématuré avant 28 semaines de gestation en l'absence de contrindications.	**Faible**	**Basse**	4	5	2	5
Do not offer oral betamimetics maintenance therapy to pregnant women with arrested preterm labour.	**Forte**	**Basse**	5	5	5	5

Ne pas utiliser les beta-mimétiques oraux en traitement de maintenance chez les femmes avec un travail prématuré stoppé.						
Do not offer oxytocin antagonist maintenance therapy to pregnant women with arrested preterm labour. ***Ne pas utiliser les antagonistes de l'ocytocine en traitement de maintenance chez les femmes avec un travail prématuré stoppé.***	**Forte**	**Très basse**	5	5	5	5
Consider offering progesterone maintenance therapy to pregnant women with arrested preterm labour. ***Envisager un traitement de maintenance à la progestérone chez les femmes avec un travail prématuré stoppé.***	**Faible**	**Très basse**	5	5	5	5
Offer magnesium sulphate for neuroprotection to women presenting with imminent preterm birth and/or failed tocolytic therapy (before 32-34 weeks) of pregnancy. ***Administrer du sulphate de magnésium pour la neuro-protection chez les femmes avec un accouchement prématuré imminent et/ou échec de la tocolyse (avant 32-34 semaines de gestation).***	**Forte**	**Haute**	3	5	NA	5

Comments received during the meeting

Secondary prevention

- One participant proposes to dissociate the 2 elements of the first recommendation, i.e. it is important to follow up the cervical length of women with a history of preterm birth, but not necessarily to make a cerclage which is a preventative strategy much debated. The question of reviewing the evidence regarding the utilization of the pessary is put forward.
- INAMI/RIZIV currently reimbursed one vaginal ultrasound in pregnancy at risk. Will a recommendation be made about reimbursing serial vaginal ultrasounds? A recommendation on the number and timing of vaginal ultrasounds would be considered helpful.
- It is underlined that the group “women with a history of preterm birth” groups many different patient profiles, and that in women with a cervical incompetency, a cerclage could be appropriate even in women with no other risk factors (as currently stated in recommendation 4).
- The formulation of recommendation 5 needs to be clarified because as now it seems to indicate that a cerclage is indicated up to 32 weeks

Tertiary prevention

- It is mentioned that the second course of corticosteroids should be only one dose
- One participant suggests that magnesium sulphate should not be given after 30 weeks of gestation, and that the utilization of this drug should be limited to cases transferred to MICs.
- The terminology should be standardized across recommendations (e.g. spontaneous preterm birth)

8.1.5. Overview implementation of stakeholder comments

	SoR	LoE	Adaptation after stakeholder review
Secondary prevention			
Vaginal ultrasound to identify women eligible for secondary prevention			
Consider performing (serial) cervical length measurement in women with a history of birth prior to 32 weeks to select women eligible for cerclage.	**Weak**	**NA**	during the second trimester' added, recommendation listed with recommendations on cerclage for cliarity
Progesterone for women at risk			
Offer vaginal progesterone to asymptomatic pregnant women with a history of spontaneous preterm birth, from the start of the second trimester onwards until at least 34 weeks.	**Strong**	**Low**	no change
Consider offering vaginal progesterone to asymptomatic women with a short cervix identified on vaginal ultrasound.	**Weak**	**Low**	evidence reviewed and note added on primary screening
Cerclage			
Do not routinely offer cerclage as secondary prevention of preterm birth to women at high risk based on the woman's history of preterm birth (between 24 and 37 weeks) alone.	**Weak**	**Very low**	changed to strong recommendation
Consider a cerclage in women with a history of preterm birth before 32 weeks and a short cervix on ultrasound.	**Weak**	**Very low**	during the second trimester' added Note added on the importance of patient selection Note added on cervical pessary as an alternative
Consider offering a primary cerclage to women with a history of recurrent second trimester birth.	**Weak**	**Very low**	no change
Tertiary prevention			
Identification of symptomatic women eligible for treatment: vaginal ultrasound			
Consider performing cervical length measurement in women presenting with symptoms of threatened preterm labour and less than 3cm cervical dilatation to avoid overtreatment (avoid unnecesarry admissions to hospital, transfer to tertiary level and administration of tocolytic therapy), using a threshold of ≥ 30mm to decline treatment. If cervical length is < 15mm, consider treatment.	**Weak**	**NA**	strength of recommendation rediscussed with GDG
Identification of symptomatic women eligible for treatment: fetal fibronectin test or Actim Partus test			
In women presenting with symptoms of threatened preterm labour and less than 3cm cervical dilatation, consider further assessment using a fetal fibronectin test or actim partus test if measured cervical length is between 16 and 29mm. If test result is negative, no treatment is indicated.	**Weak**	**NA**	strength of recommendation rediscussed with GDG
Repeated dose corticosteroid treatment			
Consider a second course of antenatal corticosteroids in women with threatened preterm birth before 30 weeks if the first dose was administered at least seven days earlier. More than two courses of corticosteroids are not recommended.	**Weak**	**Moderate**	before 30 weeks removed'
Type of tocolytic therapy			
Consider tocolytic therapy in women with threatened preterm birth between 23+5/7 and 33+5/7 weeks of gestation to delay birth with 48h while administering corticosteroid therapy and/or transfer to tertiary level. Calcium channel blockers and oxytocin antagonists are considered first choice tocolytic agents.	**Weak**	**NA**	Other tocolytic agents are not routinely recommended because of their side effects.' added Note added on off label use of nifedipine Note added on combination tocolytic treatment: should be avoided
Duration of therapy			

Do not offer magnesium maintenance therapy to pregnant women with arrested preterm labour.	**Strong**	**Very low**	no change
Do not routinely offer nifedipine maintenance therapy to pregnant women with arrested preterm labour. It can be considered to prolong pregnancy in women with threatened preterm labour before 28 weeks if no contraindication is present.	**Weak**	**Low**	no change
Do not offer oral betamimetics maintenance therapy to pregnant women with arrested preterm labour.	**Strong**	**Low**	no change
Do not offer oxytocin antagonist maintenance therapy to pregnant women with arrested preterm labour.	**Strong**	**Very low**	no change
Consider offering progesterone maintenance therapy to pregnant women with arrested preterm labour.	**Weak**	**Very low**	no change
Offer magnesium sulphate for neuroprotection to women presenting with imminent preterm birth and/or failed tocolytic therapy (before 32-34 weeks) of pregnancy.	**Strong**	**High**	no change

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