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Appendices

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Screening to prevent spontaneous preterm birth: systematic reviews of accuracy and effectiveness literature with economic modelling

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Appendix 1

Search strategies

Scoping search strategies and results
Rapid appraisal checklist

Objective Scoping searches to identify systematic reviews, published and in progress, and ongoing primary research. Searches were undertaken on 8 March 2005. Update searches in Database of Abstracts of Reviews of Effect (DARE) and Cochrane Database of Systematic Reviews (CDSR) were undertaken on 10 August 2005.

MEDLINE (Ovid Gateway), 2000–2005/ Aug. week 1, 10 August 2005

186 records were retrieved.

1. Meta-Analysis/
2. Review-Literature/
3. meta analysis.pt.
4. review literature.pt.
5. (meta analy$or metaanaly$or meta-analy$).tw.

Completed and ongoing reviews	
Cochrane Database of Systematic Reviews: Cochrane Library 2005:1	74 (complete) 12 (protocol)
Cochrane Database of Systematic Reviews: Cochrane Library 2005:3. Update	1 (complete) 3 (protocols)
Database of Abstracts of Reviews of Effects (DARE) http://www.york.ac.uk/inst/crd/crddatabases.htm/	53
Database of Abstracts of Reviews of Effects (DARE). Update http://www.york.ac.uk/inst/crd/crddatabases.htm/	6
National Research Register [including Centre for Reviews and Dissemination (CRD) ongoing reviews database]	368
Health Technology Assessment Database http://www.york.ac.uk/inst/crd/crddatabases.htm	9
SIGN Guidelines: http://www.sign.ac.uk/	0
National Guideline Clearinghouse: http://www.guideline.gov/index.asp	7
National Coordinating Centre for Health Technology Assessment (also on HTA database): http://www.ncchta.org/	0
NICE web page (published appraisals – also on HTA database) http://www.nice.org.uk/	0
HSTAT: http://text.nlm.nih.gov/	3
Indexes to and summaries of clinical effectiveness sources including reviews, appraisals of reviews, and evidence-based guidelines	
TRIP: http://www.tripdatabase.com/	313 (most already identified)
Clinical Evidence: a compendium of the best available evidence for effective health care. 2004;12	2 (preterm birth bacterial vaginosis)
Health Evidence Bulletins Wales http://hebw.uwcm.ac.uk/	1 (chap. 13)
Searches for ongoing trials – to be conducted by agreement with reviewers	
CENTRAL (Cochrane Library)	1248
Other	
NHS EED: http://www.york.ac.uk/inst/crd/crddatabases.htm	43

6. (systematic adj4 (review$or overview$)).tw.
7. (data adj synthesis).ti,ab.
8. (published adj studies).ti,ab.
9. (data adj extract$).ti,ab.
10. or/1–9
11. letter.pt.
12. comment.pt.
13. editorial.pt.
14. 11 or 12 or 13
15. Animal/
16. Human/
17. 15 not (15 and 16)
18. 10 not (14 or 17)
19. Labor, Premature/
20. ((premature or preterm or pre term or pre-term) adj3 birth$).ti,ab.
21. ((premature or preterm or pre term or pre-term) adj3 deliver$).ti,ab.
22. ((preterm or pre term or pre-term) adj3 (labor or labour)).ti,ab.
23. (premature adj3 (labor or labour or parturition)).ti,ab.
24. Fetal Membranes, Premature Rupture/
25. ((premature or preterm or pre term or pre-term) adj3 rupture$).ti,ab.
26. (PROM or PPROM).ti,ab.
27. or/19–26
28. 18 and 27

Test accuracy

Diagnostic update search strategies and results

MEDLINE (Ovid Gateway), 2002/April–2005/Sept. week 1, 20 September 2005

2858 records were retrieved in MEDLINE and 184 records were retrieved in MEDLINE In-Process & Other Non-Indexed Citations.

1. Labor, Premature/
2. ((premature or preterm or pre term) adj3 birth$).ti,ab.
3. ((premature or preterm or pre term) adj3 deliver$).ti,ab.
4. ((preterm or pre term) adj3 (labor or labour)).ti,ab.
5. (premature adj3 (labor or labour or parturition)).ti,ab.
6. or/1–5
7. exp Socioeconomic Factors/
8. Social Class/
9. Ethnic Groups/
10. risk factors/
11. Life Style/
12. exp Substance-Related Disorders/
13. exp smoking/
14. Pregnancy, High-Risk/
15. Pregnancy in Adolescence/
16. exp Pregnancy, Multiple/
17. Pregnancy Complications/
18. Parity/
19. Reproductive History/
20. Fetal Membranes, Premature Rupture/
21. Cervix Incompetence/
22. exp Abdominal Pain/
23. Uterine Contraction/
24. Uterine Hemorrhage/
25. Cervical Ripening/
26. Treponema pallidum/
27. Neisseria gonorrhoeae/
28. Chlamydia trachomatis/
29. exp Sexually Transmitted Diseases, Bacterial/
30. exp Bacteroidaceae Infections/
31. exp Chlamydiaceae Infections/
32. exp Herpes Genitalis/
33. Vaginosis, Bacterial/
34. mobiluncus/
35. Streptococcus agalactiae/
36. Mycoplasma hominis/
37. Trichomonas vaginalis/
38. Bacteroides Infections/
39. Gardnerella vaginalis/
40. Bacteriuria/
41. Granuloma Inguinale/
42. exp Mycoplasmatales Infections/
43. exp Neisseriaceae Infections/
44. exp Treponemal Infections/
45. exp Staphylococcal Infections/
46. exp Streptococcal Infections/
47. Ureaplasma Infections/
48. exp Lactobacillus/
49. exp Urinary Tract Infections/
50. exp «Diagnostic Techniques, Obstetrical and Gynecological»/
51. exp Diagnostic Equipment/
52. exp Diagnostic Imaging/
53. Diagnostic Tests, Routine/
54. exp Reagent Kits, Diagnostic/
55. exp Ultrasonography, Prenatal/
56. Medical History Taking/
57. Risk Assessment/
58. exp Physical Examination/
59. Uterine Monitoring/
60. exp Culture Techniques/
61. exp Body Constitution/
62. Body Temperature/
63. exp fever/
64. Palpation/
65. exp Corpus Luteum Hormones/
66. Relaxin/
67. exp Prostaglandins/

68. exp Estrogens/
69. exp Inhibins/
70. exp Estradiol/
71. exp Estriol/
72. exp Estrone/
73. exp Estrogen Receptor Modulators/
74. exp Receptors, Estrogen/
75. exp Prostaglandin Antagonists/
76. exp Receptors, Prostaglandin/
77. exp Leukotrienes/
78. exp Thromboxanes/
79. exp Collagenases/
80. Fetal Proteins/
81. Fibronectins/
82. exp Acute-Phase Proteins/
83. exp Immunoproteins/
84. Platelet-Derived Growth Factor/
85. Tumor Necrosis Factor-alpha/
86. Chorioamnionitis/
87. Esterases/
88. exp Cytokines/
89. exp Amniotic Fluid/
90. exp Leukocytes/
91. Saliva/
92. exp Biological Markers/
93. Corticotropin-Releasing Hormone/
94. (risk factor$or socioeconomic factor$or socioeconomic status).ti,ab.
95. (occupation$or socioeconomic or ethnic or ethnicity or manual work or long hours).ti,ab.
96. (cocaine or heroin or narcotics or crack or dope or cannabis or substance abuse$or addiction).ti,ab.
97. (substance disorder$or smoking or tobacco or alcohol$or lifestyle$or life-style$).ti,ab.
98. (low adj3 pregnancy adj3 weight).ti,ab.
99. high parity.ti,ab.
100. (early adj3 bleeding adj3 pregnancy).ti,ab.
101. vaginal bleeding.ti,ab.
102. ((uterine or antepartum) adj3 (hemorrhage or haemorrhage)).ti,ab.
103. (abdominal pain or uterine contraction$). ti,ab.
104. (pyrexia or febrile or fever).ti,ab.
105. (short adj3 pregnancies).ti,ab.
106. (interpregnancy interval$or inter-pregnancy interval$).ti,ab.
107. (older women or elderly women).ti,ab.
108. (adolescent$or teenage$).ti,ab.
109. (clinical histor$or patient histor$or patient record$or pregnan$histor$or birth histor$or reproductive histor$).ti,ab.
110. (obstetric histor$or previous preterm or repeat preterm).ti,ab.
111. (premature adj3 rupture adj3 membrane$). ti,ab.
112. Chorioamnionitis.ti,ab.
113. (estriol or plasma crf or vaginal infection$). ti,ab.
114. ((biophysical or biochemical) adj3 marker$). ti,ab.
115. (bishop$adj1 (score or scores)).ti,ab.
116. (cervical adj1 (change$or length or measurement)).ti,ab.
117. (endocervical adj1 (effacement or assessment or examination)).ti,ab.
118. (cervical adj1 (effacement or assessment or state or examination$)).ti,ab.
119. (risk scor$or physical examination$).ti,ab.
120. (physical exam or physical exams or cervical dilation or (cervix adj3 length)).ti,ab.
121. (dilation adj3 cervix).ti,ab.
122. tocodynamo$.ti,ab.
123. (uterine tocography or uterine anomal$or tocometry).ti,ab.
124. ((cervical or cervix) adj3 (abnormal$or incompetence or incompetent)).ti,ab.
125. ((cervical or cervix) adj3 (ultrasound or ultrasonography or sonography)).ti,ab.
126. ((vaginal or endovaginal or transvaginal or obstetric) adj3 (ultrasound or ultrasonography or sonography)).ti,ab.
127. (uterine activity or huam or uterine excitability).ti,ab.
128. ((myometrial or myometrium) adj3 excitability).ti,ab.
129. ((oncofetal or c-reactive) adj3 protein$).ti,ab.
130. fibronectin.ti,ab.
131. (asymptomatic bacteriuria or genital tract infection$).ti,ab.
132. (leucocyte esterase$or cytokines).ti,ab.
133. (culture$adj3 (amniotic or blood or genital or vaginal or cervical or urine)).ti,ab.
134. (timp or collagenase or relaxin or tissue inhibitor$).ti,ab.
135. plasma corticotropin releasing hormone$. ti,ab.
136. (estrogen or oestrogen or progestogen).ti,ab.
137. (glucose concentration$adj3 amniotic).ti,ab.
138. (zinc adj3 amniotic).ti,ab.
139. or/7–138
140. exp "Sensitivity and Specificity"/
141. ROC Curve/
142. Logistic Models/
143. Likelihood Functions/
144. exp Diagnostic Errors/
145. (predictive value$or reproducibility or logistic regression).ti,ab.
146. (ability adj3 predict$).ti,ab.
147. (logistic model$or sroc or roc or positive rate or positive rates).ti,ab.

148. (likelihood ratio$or negative rate or negative rates).ti,ab.
149. (receiver operating characteristic or correlation or correlated).ti,ab.
150. ((tests or test) adj3 accuracy).ti,ab.
151. (curve or curves or test outcome).ti,ab.
152. ((pretest or pre-test or posttest or post-test) adj3 probabilities).ti,ab.
153. diagnosis.ti,ab.
154. or/140–153
155. 6 and 139 and 154
156. 6 and 139
157. Animals/
158. Humans/
159. 157 not (157 and 158)
160. 155 not 159
161. 156 not 159
162. (200204$or 200205$or 200206$or 200207$or 200208$or 200209$or 200210$or 200211$or 200212$).ed.
163. (2003$or 2004$or 2005$).ed.
164. 162 or 163
165. 161 and 164

EMBASE (Ovid Gateway), 2002/Mar–2005/Sept. week 1, 20 September 2005
4004 records were retrieved.

1. Premature Labor/
2. ((premature or preterm or pre term or pre-term) adj3 birth$).ti,ab.
3. ((premature or preterm or pre term or pre-term) adj3 deliver$).ti,ab.
4. ((preterm or pre term or pre-term) adj3 (labor or labour)).ti,ab.
5. (premature adj3 (labor or labour or parturition)).ti,ab.
6. Premature Fetus Membrane Rupture/
7. ((premature or preterm or pre term or pre-term) adj3 rupture$).ti,ab.
8. (PROM or PPROM).ti,ab.
9. or/1–8
10. exp socioeconomics/
11. Social Class/
12. Risk Factor/
13. exp "Ethnic and Racial Groups"/
14. Smoking/
15. exp Addiction/
16. Substance Abuse/
17. lifestyle/
18. High Risk Pregnancy/
19. Adolescent Pregnancy/
20. parity/
21. ANAMNESIS/
22. Pregnancy Disorder/
23. exp Pregnancy Complication/
24. Obstetric Hemorrhage/
25. Premature Fetus Membrane Rupture/
26. Abdominal Pain/
27. Uterus Contraction/
28. exp Uterine Complication/
29. Uterus Bleeding/
30. Fever/
31. exp Estrogen/
32. Relaxin/
33. Treponema Pallidum/
34. Neisseria Gonorrhoeae/
35. Streptococcus Agalactiae/
36. Mycoplasma Hominis/
37. Chlamydia Trachomatis/
38. Trichomonas Vaginalis/
39. bacteroides/
40. Vaginitis/
41. mobiluncus/
42. Gardnerella Vaginalis/
43. exp Multiple Pregnancy/
44. Uterine Cervix Incompetence/
45. Uterine Cervix Ripening/
46. Fetoprotein/
47. Fibronectin/
48. Bacteriuria/
49. exp Diagnostic Procedure/
50. exp Laboratory Diagnosis/
51. Virus Diagnosis/
52. Venereal Disease Reaction Test/
53. Transvaginal Echography/
54. equipment/
55. Diagnostic Imaging/
56. Test Strip/
57. Reagent/
58. ultrasound/
59. Diagnostic Test/
60. Risk Assessment/
61. exp Physical Examination/
62. exp examination/
63. Home Monitoring/
64. exp Urogenital System Examination/
65. Clinical Observation/
66. Fetus Monitoring/
67. Esterase/
68. exp Tissue Culture/
69. exp Cytokine/
70. Acute Phase Protein/
71. exp Immunoglobulin/
72. Platelet Derived Growth Factor/
73. Tumor Necrosis Factor/
74. Sex Hormone/
75. Progesterone/
76. Inhibin/
77. Estradiol/
78. Estriol/
79. Estrone/

80. exp Estrogen Receptor/
81. exp Prostaglandin Receptor Blocking Agent/
82. exp Leukotriene/
83. exp Thromboxane/
84. Collagenase/
85. Body Constitution/
86. exp «Physical Constitution and Health»/
87. exp Body Temperature/
88. palpation/
89. exp Sexually Transmitted Disease/
90. exp bacteroides/
91. chlamydiaceae/
92. Granuloma Inguinale/
93. mycoplasmatales/
94. Gram Negative Infection/
95. neisseriaceae/
96. Bacterial Infection/
97. Staphylococcus Infection/
98. Streptococcus Infection/
99. exp lactobacillus/
100. Genital Herpes/
101. exp Urinary Tract Infection/
102. exp Chorioamnionitis/
103. exp Amnion Fluid/
104. exp leukocyte/
105. saliva/
106. Biological Marker/
107. Blood Analysis/
108. Blood Culture/
109. exp urinalysis/
110. Amnion Fluid Analysis/
111. Image Analysis/
112. Saliva Analysis/
113. Sputum Analysis/
114. exp assay/
115. exp Chemical Analysis/
116. Corticotropin Releasing Factor/
117. (risk factor$or socioeconomic factor$or socioeconomic status).ti,ab.
118. (occupation$or socioeconomic or ethnic or ethnicity or manual work or long hours).ti,ab.
119. (cocaine or heroin or narcotics or crack or dope or cannabis or substance abuse$or addiction).ti,ab.
120. (substance disorder$or smoking or tobacco or alcohol$or lifestyle$or life-style$).ti,ab.
121. (low adj3 pregnancy adj3 weight).ti,ab.
122. high parity.ti,ab.
123. (early adj3 bleeding adj3 pregnancy).ti,ab.
124. vaginal bleeding.ti,ab.
125. ((uterine or antepartum) adj3 (hemorrhage or haemorrhage)).ti,ab.
126. (abdominal pain or uterine contraction$). ti,ab.
127. (pyrexia or febrile or fever).ti,ab.
128. (short adj3 pregnancies).ti,ab.
129. (interpregnancy interval$or inter-pregnancy interval$).ti,ab.
130. (older women or elderly women).ti,ab.
131. (adolescent$or teenage$).ti,ab.
132. (clinical histor$or patient histor$or patient record$or pregnan$histor$or birth history$or reproductive history$).ti,ab.
133. (obstetric histor$or previous preterm or repeat preterm).ti,ab.
134. (premature adj3 rupture adj3 membrane$). ti,ab.
135. Chorioamnionitis.ti,ab.
136. (estriol or plasma crf or vaginal infection$). ti,ab.
137. ((biophysical or biochemical) adj3 marker$). ti,ab.
138. (bishop$adj1 (score or scores)).ti,ab.
139. (cervical adj1 (change$or length or measurement)).ti,ab.
140. (endocervical adj1 (effacement or assessment or examination)).ti,ab.
141. (cervical adj1 (effacement or assessment or state or examination$)).ti,ab.
142. (risk scor$or physical examination$).ti,ab.
143. (physical exam or physical exams or cervical dilation or (cervix adj3 length)).ti,ab.
144. (dilation adj3 cervix).ti,ab.
145. tocodynamo$.ti,ab.
146. (uterine tocography or uterine anomal$or tocometry).ti,ab.
147. ((cervical or cervix) adj3 (abnormal$or incompetence or incompetent)).ti,ab.
148. ((cervical or cervix) adj3 (ultrasound or ultrasonography or sonography)).ti,ab.
149. ((vaginal or endovaginal or transvaginal or obstetric) adj3 (ultrasound or ultrasonography or sonography)).ti,ab.
150. (uterine activity or huam or uterine excitability).ti,ab.
151. ((myometrial or myometrium) adj3 excitability).ti,ab.
152. ((oncofetal or c-reactive) adj3 protein$).ti,ab.
153. fibronectin.ti,ab.
154. (asymptomatic bacteriuria or genital tract infection$).ti,ab.
155. (leucocyte esterase$or cytokines).ti,ab.
156. (culture$adj3 (amniotic or blood or genital or vaginal or cervical or urine)).ti,ab.
157. (timp or collagenase or relaxin or tissue inhibitor$).ti,ab.
158. plasma corticotropin releasing hormone$. ti,ab.
159. (estrogen or oestrogen or progestogen).ti,ab.
160. (glucose concentration$adj3 amniotic).ti,ab.
161. (zinc adj3 amniotic).ti,ab.
162. or/10–161

163. Diagnostic Error/
164. Diagnostic Accuracy/
165. Diagnostic Value/
166. Differential Diagnosis/
167. Quantitative Diagnosis/
168. exp Statistical Analysis/
169. Discriminant Analysis/
170. statistics/
171. Statistical Model/
172. reliability/
173. variance/
174. Receiver Operating Characteristic/
175. Multiple Regression/
176. (predictive value$or reproducibility or logistic regression).ti,ab.
177. (ability adj3 predict$).ti,ab.
178. (logistic model$or sroc or roc or positive rate or positive rates).ti,ab.
179. (likelihood ratio$or negative rate or negative rates).ti,ab.
180. (receiver operating characteristic or correlation or correlated).ti,ab.
181. ((tests or test) adj3 accuracy).ti,ab.
182. (curve or curves or test outcome).ti,ab.
183. ((pretest or pre-test or posttest or post-test) adj3 probabilities).ti,ab.
184. diagnosis.ti,ab.
185. (sensitivity or specificity).ti,ab.
186. or/163–185
187. 9 and 162 and 186
188. 9 and 162
189. exp animal/
190. Nonhuman/
191. (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dogs or dog or cats or bovine or sheep).ti,ab,sh.
192. 189 or 190 or 191
193. exp human/
194. 192 not (192 and 193)
195. 187 not 194
196. 188 not 194
197. (2002$or 2003$or 2004$or 2005$).em.
198. 196 and 197

BIOSIS (DIALOG), 2002/June–2005/ Sept. week 1, 22 September 2005

1071 records were retrieved.
s (premature or preterm)(3n)birth??
s (premature or preterm)(3n)deliver?
s (premature or preterm)(3n)(labo?r or parturition)
s risk(w)factor?? or socioeconomic(w)factor??
s low(3w)pregnancy(3w)weight
s high(w)parity
s early(3n)bleeding(3n)pregnancy
s vaginal(3n)bleeding
s (uterine or antepartum)(3w)(hemorrhag? or haemorrhag?)
s abdominal(w)pain or uterine(w)contraction??
s pyrexia or febrile
s short(3n)between(3n)pregnancies
s interpregnancy(w)interval??
s pregnancy(3n)multiple
s pregnancy(3n)complication??
s pregnancy(3n)(high(w)risk)
s pregnancy(3n)(adolescen? or teenage?)
s (older or elderly)(n)women
s occupation? or socioeconomic or ethnic or ethnicity or manual(w)work or long(w)hours
s cocaine or heroin or narcotics or crack or dope or cannabis or substance(w)abuse
s substance(w)disorder?? or smoking or tobacco or alcohol? or lifestyle??
s estriol or plasma(w)crf or vaginal(3n)infection??
s (biophysical or biochemical)(3w)marker??
s bishop?(w)score??
s cervical(w)(change? or length or measurement)
s endocervical(w)(effacement or assessment)
s cervical(w)(effacement or assessment or state)
s medical(w)histor? or clinical(w)histor? or patient(w)histor? or patient(w)record??
s obstetric(w)histor? or previous(w)preterm or repeat(w)preterm
s risk(w)scor? or risk(w)assessment
s physical(w)examination? or cervical(w)dilation or cervix(3n)length
s dilation(3n)cervix
s uterine(w)tocography or uterine(w)anomal? or tocometry
s (cervical or cervix)(3n)(abnormal? or incompetence or incompetent)
s (cervical or cervix)(3n)(ultrasound or ultrasonography)
s (vaginal or endovaginal or transvaginal or obstetric)(3n)(ultrasound or ultrasonography)
s diagnostic(n)(technique? or equipment or test??)
s uterine(3n)activity or huam or uterine(3n) excitability
s (myometrial or myometrium)(3n)excitability
s (oncofetal or c-reactive)(w)(protein?)
s fibronectin?
s sexually(w)transmitted(w)disease?
s asymptomatic(w)bacteriuria or genital(w)tract(w) infection?
s chlamydia or gonorrhea or herpes
s leucocyte(w)esterase? or cytokines
s culture?(3n)(amniotic or blood or genital or vaginal or cervical)
s timp or collagenase or relaxin or tissue(w) inhibitor?
s plasma(w)corticotropin(w)releasing(w)hormone?
s estrogen or oestrogen or progestogen

s (glucose(w)concentration?)(n)amniotic
s zinc(n)amniotic
s s1:s3
s s4:s51
s s52 and s53
s s54/2002–2005

PASCAL (DIALOG), 2002/June–2005/ Sept. week 1, 22 September 2005
456 records were retrieved.

s (premature or preterm)(3n)birth??
s (premature or preterm)(3n)deliver?
s (premature or preterm)(3n)(labo?r or parturition)
s risk(w)factor?? or socioeconomic(w)factor??
s low(3w)pregnancy(3w)weight
s high(w)parity
s early(3n)bleeding(3n)pregnancy
s vaginal(3n)bleeding
s (uterine or antepartum)(3w)(hemorrhag? or haemorrhag?)
s abdominal(w)pain or uterine(w)contraction??
s pyrexia or febrile
s short(3n)between(3n)pregnancies
s interpregnancy(w)interval??
s pregnancy(3n)multiple
s pregnancy(3n)complication??
s pregnancy(3n)(high(w)risk)
s pregnancy(3n)(adolescen? or teenage?)
s (older or elderly)(n)women
s occupation? or socioeconomic or ethnic or ethnicity or manual(w)work or long(w)hours
s cocaine or heroin or narcotics or crack or dope or cannabis or substance(w)abuse
s substance(w)disorder?? or smoking or tobacco or alcohol? or lifestyle??
s estriol or plasma(w)crf or vaginal(3n)infection??
s (biophysical or biochemical)(3w)marker??
s bishop?(w)score??
s cervical(w)(change? or length or measurement)
s endocervical(w)(effacement or assessment)
s cervical(w)(effacement or assessment or state)
s medical(w)histor? or clinical(w)histor? or patient(w)histor? or patient(w)record??
s obstetric(w)histor? or previous(w)preterm or repeat(w)preterm
s risk(w)scor? or risk(w)assessment
s physical(w)examination? or cervical(w)dilation or cervix(3n)length
s dilation(3n)cervix
s uterine(w)tocography or uterine(w)anomal? or tocometry
s (cervical or cervix)(3n)(abnormal? or incompetence or incompetent)
s (cervical or cervix)(3n)(ultrasound or ultrasonography)
s (vaginal or endovaginal or transvaginal or obstetric)(3n)(ultrasound or ultrasonography)
s diagnostic(n)(technique? or equipment or test??)
s uterine(3n)activity or huam or uterine(3n) excitability
s (myometrial or myometrium)(3n)excitability
s (oncofetal or c-reactive)(w)(protein?)
s fibronectin?
s sexually(w)transmitted(w)disease?
s asymptomatic(w)bacteriuria or genital(w)tract(w) infection?
s chlamydia or gonorrhea or herpes
s leucocyte(w)esterase? or cytokines
s culture?(3n)(amniotic or blood or genital or vaginal or cervical)
s timp or collagenase or relaxin or tissue(w) inhibitor?
s plasma(w)corticotropin(w)releasing(w)hormone?
s estrogen or oestrogen or progestogen
s (glucose(w)concentration?)(n)amniotic
s zinc(n)amniotic
s s1:s3
s s4:s51
s s52 and s53
s s54/2002–2005

Science Citation Index (SCI) (DIALOG), 2002/June–2005/Sept. week 1, September/22 September 2005
643 records were retrieved.

s (premature or preterm)(3n)birth??
s (premature or preterm)(3n)deliver?
s (premature or preterm)(3n)(labo?r or parturition)
s risk(w)factor?? or socioeconomic(w)factor??
s low(3w)pregnancy(3w)weight
s high(w)parity
s early(3n)bleeding(3n)pregnancy
s vaginal(3n)bleeding
s (uterine or antepartum)(3w)(hemorrhag? or haemorrhag?)
s abdominal(w)pain or uterine(w)contraction??
s pyrexia or febrile
s short(3n)between(3n)pregnancies
s interpregnancy(w)interval??
s pregnancy(3n)multiple
s pregnancy(3n)complication??
s pregnancy(3n)(high(w)risk)
s pregnancy(3n)(adolescen? or teenage?)
s (older or elderly)(n)women
s occupation? or socioeconomic or ethnic or ethnicity or manual(w)work or long(w)hours
s cocaine or heroin or narcotics or crack or dope or cannabis or substance(w)abuse
s substance(w)disorder?? or smoking or tobacco or alcohol? or lifestyle??

s estriol or plasma(w)crf or vaginal(3n)infection??
s (biophysical or biochemical)(3w)marker??
s bishop?(w)score??
s cervical(w)(change? or length or measurement)
s endocervical(w)(effacement or assessment)
s cervical(w)(effacement or assessment or state)
s medical(w)histor? or clinical(w)histor? or patient(w)histor? or patient(w)record??
s obstetric(w)histor? or previous(w)preterm or repeat(w)preterm
s risk(w)scor? or risk(w)assessment
s physical(w)examination? or cervical(w)dilation or cervix(3n)length
s dilation(3n)cervix
s uterine(w)tocography or uterine(w)anomal? or tocometry
s (cervical or cervix)(3n)(abnormal? or incompetence or incompetent)
s (cervical or cervix)(3n)(ultrasound or ultrasonography)
s (vaginal or endovaginal or transvaginal or obstetric)(3n)(ultrasound or ultrasonography)
s diagnostic(n)(technique? or equipment or test??)
s uterine(3n)activity or huam or uterine(3n) excitability
s (myometrial or myometrium)(3n)excitability
s (oncofetal or c-reactive)(w)(protein?)
s fibronectin?
s sexually(w)transmitted(w)disease?
s asymptomatic(w)bacteriuria or genital(w)tract(w) infection?
s chlamydia or gonorrhea or herpes
s leucocyte(w)esterase? or cytokines
s culture?(3n)(amniotic or blood or genital or vaginal or cervical)
s timp or collagenase or relaxin or tissue(w) inhibitor?
s plasma(w)corticotropin(w)releasing(w)hormone?
s estrogen or oestrogen or progestogen
s (glucose(w)concentration?)(n)amniotic
s zinc(n)amniotic
s s1:s3
s s4:s51
s s52 and s53
s s54/2002–2005

Inside Conferences (DIALOG), 2002/June–2005/Sept. week 1, 22 September 2005
12 records were retrieved.

s (premature or preterm)(3n)birth??
s (premature or preterm)(3n)deliver?
s (premature or preterm)(3n)(labo?r or parturition)
s risk(w)factor?? or socioeconomic(w)factor??
s low(3w)pregnancy(3w)weight
s high(w)parity
s early(3n)bleeding(3n)pregnancy
s vaginal(3n)bleeding
s (uterine or antepartum)(3w)(hemorrhag? or haemorrhag?)
s abdominal(w)pain or uterine(w)contraction??
s pyrexia or febrile
s short(3n)between(3n)pregnancies
s interpregnancy(w)interval??
s pregnancy(3n)multiple
s pregnancy(3n)complication??
s pregnancy(3n)(high(w)risk)
s pregnancy(3n)(adolescen? or teenage?)
s (older or elderly)(n)women
s occupation? or socioeconomic or ethnic or ethnicity or manual(w)work or long(w)hours
s cocaine or heroin or narcotics or crack or dope or cannabis or substance(w)abuse
s substance(w)disorder?? or smoking or tobacco or alcohol? or lifestyle??
s estriol or plasma(w)crf or vaginal(3n)infection??
s (biophysical or biochemical)(3w)marker??
s bishop?(w)score??
s cervical(w)(change? or length or measurement)
s endocervical(w)(effacement or assessment)
s cervical(w)(effacement or assessment or state)
s medical(w)histor? or clinical(w)histor? or patient(w)histor? or patient(w)record??
s obstetric(w)histor? or previous(w)preterm or repeat(w)preterm
s risk(w)scor? or risk(w)assessment
s physical(w)examination? or cervical(w)dilation or cervix(3n)length
s dilation(3n)cervix
s uterine(w)tocography or uterine(w)anomal? or tocometry
s (cervical or cervix)(3n)(abnormal? or incompetence or incompetent)
s (cervical or cervix)(3n)(ultrasound or ultrasonography)
s (vaginal or endovaginal or transvaginal or obstetric)(3n)(ultrasound or ultrasonography)
s diagnostic(n)(technique? or equipment or test??)
s uterine(3n)activity or huam or uterine(3n) excitability
s (myometrial or myometrium)(3n)excitability
s (oncofetal or c-reactive)(w)(protein?)
s fibronectin?
s sexually(w)transmitted(w)disease?
s asymptomatic(w)bacteriuria or genital(w)tract(w) infection?
s chlamydia or gonorrhea or herpes
s leucocyte(w)esterase? or cytokines
s culture?(3n)(amniotic or blood or genital or vaginal or cervical)

s timp or collagenase or relaxin or tissue(w) inhibitor?
s plasma(w)corticotropin(w)releasing(w)hormone?
s estrogen or oestrogen or progestogen
s (glucose(w)concentration?)(n)amniotic
s zinc(n)amniotic
s s1:s3
s s4:s51
s s52 and s53
s s54/2002–2005

Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Library, Issue 2:2002–3:20 September 2005
1 new protocol was identified in CDSR and 144 records were retrieved in CENTRAL.

Labor, Premature (MeSH)
(premature or preterm or pre*term) NEAR/3 birth
(premature or preterm or pre*term) NEAR/3 deliver*
(preterm or pre*term) NEAR/3 (labour or labor)
premature NEAR/3 (labour or labor or parturition)
Fetal Membranes, Premature Rupture (MeSH)
(premature or preterm or pre*term) NEAR/3 ruptur*
PROM or PPROM
#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
Socioeconomic Factors (MeSH)
Social Class (MeSH)
Risk Factors (MeSH)
Ethnic Groups (MeSH)
Smoking (MeSH)
Life Style(MeSH)
Substance-Related Disorders(MeSH)
Pregnancy, High-Risk (MeSH)
Parity (MeSH)
Reproductive History (MeSH)
Abdominal Pain (MeSH)
Pregnancy Complications (MeSH)
Uterine Contraction (MeSH)
Uterine Hemorrhage (MeSH)
Fever (MeSH)
Estriol (MeSH)
Relaxin (MeSH)
Treponema pallidum (MeSH)
Neisseria gonorrhoeae (MeSH)
Streptococcus agalactiae (MeSH)
Mycoplasma hominis (MeSH)
Chlamydia trachomatis (MeSH)
Trichomonas vaginalis (MeSH)
Bacteroides Infections (MeSH)
Vaginosis, Bacterial (MeSH)
Mobiluncus (MeSH)
Gardnerella vaginalis (MeSH)
Prostaglandins (MeSH)
Pregnancy, Multiple (MeSH)
Cervix Incompetence (MeSH)
Cervical Ripening (MeSH)
Fetal Proteins (MeSH)
Bacteriuria (MeSH)
Diagnostic Techniques, Obstetrical and Gynecological (MeSH)
Diagnostic Equipment (MeSH)
Diagnostic Imaging (MeSH)
Reagent Kits, Diagnostic (MeSH)
Ultrasonography, Prenatal (MeSH)
Diagnostic Tests, Routine (MeSH)
Medical History Taking (MeSH)
Risk Assessment (MeSH)
Physical Examination (MeSH)
Uterine Monitoring (MeSH)
Esterases (MeSH)
Cytokines (MeSH)
Immunoproteins (MeSH)
Platelet-Derived Growth Factor (MeSH)
Tumor Necrosis Factor-alpha (MeSH)
Gonadal Steroid Hormones (MeSH)
Corpus Luteum Hormones (MeSH)
Estrogens (MeSH)
Inhibins (MeSH)
Estradiol (MeSH)
Estrone (MeSH)
Receptors, Estrogen (MeSH)
Prostaglandin Antagonists (MeSH)
Receptors, Prostaglandin (MeSH)
Leukotrienes (MeSH)
Receptors, Thromboxane (MeSH)
Collagenases (MeSH)
Body Constitution (MeSH)
Body Temperature (MeSH)
Palpation (MeSH)
Sexually Transmitted Diseases, Bacterial (MeSH)
Bacteroidaceae Infections (MeSH)
Chlamydiaceae Infections (MeSH)
Granuloma Inguinale (MeSH)
Mycoplasmatales Infections (MeSH)
Neisseriaceae Infections (MeSH)
Treponemal Infections (MeSH)
Staphylococcal Infections (MeSH)
Streptococcal Infections (MeSH)
Ureaplasma Infections (MeSH)
Lactobacillus (MeSH)
Herpes Genitalis (MeSH)
Urinary Tract Infections (MeSH)
Chorioamnionitis (MeSH)
Amniotic Fluid (MeSH)
Leukocytes (MeSH)
Saliva (MeSH)
Biological Markers (MeSH)

Corticotropin-Releasing Hormone (MeSH)
(older or elderly) NEAR women
fibronectin* or tocodynamo* or (risk NEAR factor*) or (socioeconomic NEAR factor*)
low NEAR pregnancy NEAR weight
(high NEAR parity) or (early NEAR bleeding) or (vaginal NEAR bleeding) or (uterine or antepartum) NEAR hemorrhage or (abdominal NEAR pain) or (uterine NEAR contraction*) or pyrexia or febrile or fever or short NEAR/3 between NEAR/3 pregnancies
interpregnancy and interval* or occupation* or socioeconomic or ethnic or ethnicity or (manual NEAR work) or (long NEAR hours) or cocaine or heroin or narcotics or crack or dope or cannabis or (substance NEAR abuse) or smoking or tobacco or alcohol* or lifestyle* or estriol or (plasma NEAR crf) or (vaginal NEAR infection*)
(biophysical or biochemical) and marker* or bishop* and (score or scores) or cervical NEAR (change* or length or measurement) or endocervical NEAR (effacement or assessment) or cervical NEAR (effacement or assessment or state)
(clinical NEAR histor*) or (patient NEAR histor*) or (patient NEAR record*) or (obstetric NEAR histor*) or (previous NEAR preterm) or (repeat NEAR preterm) or (risk NEAR scor*) or (physical NEAR examination*) or (physical NEAR exam) or (physical NEAR exams) or (cervical NEAR dilation) or (cervix NEAR length) or dilation NEAR cervix
(uterine NEAR tocography) or (uterine NEAR anomal*) or tocometry or (cervical or cervix) NEAR (abnormal* or incompetence or incompetent) or (cervical or cervix) NEAR (ultrasound or ultrasonography) or (vaginal or endovaginal or transvaginal or obstetric) NEAR (ultrasound or ultrasonography) or uterine NEAR (activity or huam or excitability)
(myometrial or myometrium) NEAR excitability or (oncofetal or reactive) NEAR (protein*) or (asymptomatic NEAR bacteriuria) or (genital NEAR tract NEAR infection*) or leucocyte NEAR (esterase* or cytokines) or culture* NEAR (amniotic or blood or genital or vaginal or cervical)
timp or collagenase or relaxin or (tissue NEAR inhibitor*) or plasma NEAR corticotropin NEAR releasing NEAR hormone* or estrogen or oestrogen or progestogen or glucose NEAR concentration* NEAR amniotic or zinc NEAR amniotic
#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20
#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40
#41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60
#61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80
#81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99 OR #100 OR #101
#102 OR #103 OR #104 OR #105 OR #106

National Research Register (NRR), (Update Software), 2002:1–2005:21 September 2005
192 records were retrieved.

LABOR PREMATURE
((premature next birth) or (preterm next birth) or (preterm next birth))
((premature next deliver*) or (preterm next deliver*) or (preterm next deliver*))
((preterm next labour) or (preterm next labour))
((preterm next labor) or (preterm next labor))
((premature next labour) or (premature next labor) or (premature next parturition))
#1 or #2 or #3 or #4 or #5 or #6
SOCIOECONOMIC FACTORS
SOCIAL CLASS
RISK FACTORS
SMOKING
ETHNIC GROUPS
SUBSTANCE RELATED DISORDERS
LIFE STYLE
PREGNANCY HIGH RISK
PREGNANCY IN ADOLESCENCE
PARITY
REPRODUCTIVE HISTORY
PREGNANCY COMPLICATIONS
FETAL MEMBRANES PREMATURE RUPTURE
ABDOMINAL PAIN
UTERINE CONTRACTION
UTERINE HEMORRHAGE
FEVER
ESTRIOL
RELAXIN
TREPONEMA PALLIDUM
NEISSERIA GONORRHOEAE
STREPTOCOCCUS AGALACTIAE
MYCOPLASMA HOMINIS
CHLAMYDIA TRACHOMATIS
TRICHOMONAS VAGINALIS
BACTEROIDES INFECTIONS
VAGINOSIS BACTERIAL

MOBILUNCUS
GARDNERELLA VAGINALIS
PROSTAGLANDINS
PREGNANCY MULTIPLE
CERVIX INCOMPETENCE
CERVICAL RIPENING
FETAL PROTEINS
BACTERIURIA
DIAGNOSTIC TECHNIQUES OBSTETRICAL AND GYNECOLOGICAL
DIAGNOSTIC EQUIPMENT
DIAGNOSTIC IMAGING
REAGENT KITS DIAGNOSTIC
ULTRASONOGRAPHY PRENATAL
DIAGNOSTIC TESTS ROUTINE
MEDICAL HISTORY TAKING
RISK ASSESSMENT
PHYSICAL EXAMINATION
UTERINE MONITORING
ESTERASES
CYTOKINES
TISSUE CULTURE
ACUTE PHASE PROTEINS
IMMUNOPROTEINS
PLATELET DERIVED GROWTH FACTORS
TUMOR NECROSIS FACTOR
CORPUS LUTEUM HORMONES
ESTROGENS
INHIBINS
ESTRADIOL
ESTRIOL
ESTRONE
ESTROGEN RECEPTOR MODULATORS
RECEPTORS ESTROGEN
PROSTAGLANDIN ANTAGONISTS
RECEPTORS PROSTAGLANDIN
LEUKOTRIENES
THROMBOXANES
COLLAGENASES
BODY CONSTITUTION
BODY TEMPERATURE
PALPATION
SEXUALLY TRANSMITTED DISEASES
BACTERIAL
BACTEROIDACEAE INFECTIONS
CHLAMYDIACEAE INFECTIONS
GRANULOMA INGUINALE
MYCOPLASMATALES INFECTIONS
NEISSERIACEAE INFECTIONS
TREPONEMAL INFECTIONS
STAPHYLOCOCCAL INFECTIONS
STREPTOCOCCAL INFECTIONS
UREAPLASMA INFECTIONS
LACTOBACILLUS
HERPES GENITALIS
URINARY TRACT INFECTIONS
CHORIOAMNIONITIS
AMNIOTIC FLUID
LEUKOCYTES
SALIVA
BIOLOGICAL MARKERS
CORTICOTROPIN RELEASING HORMONE
((older near women) or (elderly near women))
fibronectin*
((premature near rupture) near membrane*)
tocodynamo*
((risk near factor*) or (socioeconomic near factor*))
((low near pregnancy) near weight)
(high next parity)
((early near bleeding) near pregnancy)
(vaginal near bleeding)
((uterine near hemorrhage) or (antepartum near hemorrhage))
((abdominal next pain) or (uterine next contraction*))
((pyrexia or febrile) or fever)
((short near between) near pregnancies)
(interpregnancy and interval*)
(((((occupation* or socioeconomic) or ethnic) or ethnicity) or (manual next work)) or (long next hours))
((((((cocaine or heroin) or narcotics) or crack) or dope) or cannabis) or (substance next abuse))
(((((substance and disorder*) or smoking) or tobacco) or alcohol*) or lifestyle*)
((estriol or (plasma near crf)) or (vaginal near infection*))
((biophysical or biochemical) and marker*)
(bishop* and (score or scores))
((cervical near change*) or (cervical near length) or (cervical near measurement))
((endocervical near effacement) or (endocervical near assessment))
((cervical near effacement) or (cervical near assessment) or (cervical near state))
(((clinical near histor*) or (patient near histor*)) or (patient near record*))
(((obstetric near histor*) or (previous near preterm)) or (repeat near preterm))
((risk next scor*) or (physical next examination*))
((((physical next exam) or (physical next exams)) or (cervical next dilation)) or (cervix near length))
(dilation near cervix)
(((uterine near tocography) or (uterine near anomal*)) or tocometry)
((cervical near abnormal*) or (cervical near incompetence) or (cervical near incompetent))
((cervix near abnormal*) or (cervix near incompetence) or (cervix near incompetent))
((cervical near ultrasound) or (cervical near ultrasonography))

((cervix near ultrasound) or (cervix near ultrasonography))
((vaginal near ultrasound) or (ultrasound near endovaginal) or (transvaginal near ultrasound) or (obstetric near ultrasound) or (vaginal near ultrasonography) or (ultrasonography near endovaginal) or (transvaginal near ultrasonography) or (obstetric near ultrasonography))
((uterine near activity) or (uterine near huam) or (uterine near excitability))
((myometrial near excitability) or (myometrium near excitability))
((oncofetal near protein*) or ((c next reactive) near protein*)
((asymptomatic next bacteriuria) or (genital next tract next infection*))
((leucocyte next esterase*) or (leucocyte next cytokines))
((amniotic near culture*) or (blood near culture*) or (genital near culture*) or (vaginal near culture*) or (cervical near culture*))
(((timp or collagenase) or relaxin) or (tissue next inhibitor*))
(plasma next corticotropin next releasing next hormone*)
((estrogen or oestrogen) or progestogen)
((glucose next concentration*) near amniotic)
(zinc near amniotic)
(#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20)
(#21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40)
(#21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40)
(#41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60)
(#61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73 or #74 or #75 or #76 or #77 or #78 or #79 or #80)
(#81 or #82 or #83 or #84 or #85 or #86 or #87 or #88 or #89 or #90 or #91 or #92 or #93 or #94 or #95 or #96 or #97 or #98 or #99 or #100)
(#101 or #102 or #103 or #104 or #105 or #106 or #107 or #108 or #109 or #110 or #111 or #112 or #113 or #114 or #115 or #116 or #117 or #118 or #119 or #120)
(#121 or #122 or #123 or #124 or #125 or #126 or #127 or #128 or #129 or #130 or #131 or #132 or #133 or #134 or #135 or #136 or #137 or #138 or #139)
(#141 or #142 or #143 or #144 or #145 or #146 or #147)
(#7 and #148)

MEDION. 27 September 2005

Eight records were retrieved. Separate searches were performed using the abstract, title and ICPC code fields.

ICPC code: W Pregnancy, childbearing, family planning
Abstract, Title: 'premature', 'preterm', 'pre term', 'pre-term'

Effectiveness

Interventions search strategies and results

MEDLINE (Ovid Gateway), 1966–2005/Aug. week 1, 18 August 2005

5056 records were retrieved in MEDLINE and 54 records were retrieved in MEDLINE In-Process & Other Non-Indexed Citations.

randomized-controlled-trial.pt.
controlled-clinical-trial.pt.
randomized-controlled-trials/
RANDOM ALLOCATION/
DOUBLE-BLIND METHOD/
SINGLE-BLIND METHOD/
clinical trial.pt.
CONTROLLED CLINICAL TRIALS/
CLINICAL TRIALS/
CLINICAL TRIALS, PHASE III/
CLINICAL TRIALS, PHASE IV/
MULTICENTER STUDIES/
Evaluation Studies/
Drug Evaluation/
exp PRODUCT SURVEILLANCE, POSTMARKETING/
(clin$adj3 trial$).ti,ab.
((singl$or doubl$or tripl$or trebl$) adj3 (mask$or blind$)).ti,ab.
Placebos/
placebo$.ti,ab.
random$.ti,ab.
RESEARCH DESIGN/
(control$adj3 (trial$or stud$)).ti,ab.
crossover.ti,ab.
Comparative Study/
1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
Animal/
Human/
26 not (26 and 27)
25 not 28
Labor, Premature/

((premature or preterm or pre term or pre-term) adj3 birth$).ti,ab.
((premature or preterm or pre term or pre-term) adj3 deliver$).ti,ab.
((preterm or pre term or pre-term) adj3 (labor or labour)).ti,ab.
(premature adj3 (labor or labour or parturition)).ti,ab.
Fetal Membranes, Premature Rupture/
((premature or preterm or pre term or pre-term) adj3 rupture$).ti,ab.
(PROM or PPROM).ti,ab.
or/30–37
29 and 38

EMBASE (Ovid Gateway), 1980–2005/ Aug. week 1, 18 August 2005

7830 records were retrieved.

Randomized Controlled Trial/
RANDOMIZATION/
Double Blind Procedure/
Single Blind Procedure/
random$control$trial$.ti,ab.
(clin$adj3 trial$).ti,ab.
exp clinical trial/
exp controlled study/
((singl$or doubl$or trebl$or tripl$) adj3 (blind$or mask$)).ti,ab.
placebo$.ti,ab.
PLACEBO/
EVALUATION/
Follow Up/
Prospective Study/
(control$or prospective$or volunteer$).ti,ab.
random$.ti,ab.
1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
editorial.pt.
note.pt.
18 or 19
(rat or rats or mouse or mice or hamster or hamsters or animal or animals or dogs or dog or cats or bovine or sheep).ti,ab,sh.
exp animal/
Nonhuman/
exp human/
21 or 22 or 23
25 not (25 and 24)
17 not (20 or 26)
Premature Labor/
((premature or preterm or pre term or pre-term) adj3 birth$).ti,ab.
((premature or preterm or pre term or pre-term) adj3 deliver$).ti,ab.
((preterm or pre term or pre-term) adj3 (labor or labour)).ti,ab.
(premature adj3 (labor or labour or parturition)).ti,ab.
Premature Fetus Membrane Rupture/
((premature or preterm or pre term or pre-term) adj3 rupture$).ti,ab.
(PROM or PPROM).ti,ab.
or/28–35
27 and 36

Cumulative Index to Nursing and Allied Health Literature (CINAHL) (Ovid Gateway), 1982–2005/ Aug. week 1, 18 August 2005

1041 records were retrieved.

exp Clinical Trials/
CLINICAL TRIAL.pt.
exp Random Sample/
(clin$adj3 trial$).ti,ab.
((singl$or doubl$or trebl$or tripl$) adj3 (blind$or mask$)).ti,ab.
PLACEBOS/
placebo$.ti,ab.
random$.ti,ab.
exp Study Design/
exp Evaluation Research/
exp Prospective Studies/
(control$or prospectiv$or volunteer$).ti,ab.
or/1–12
Labor, Premature/
((premature or preterm or pre term or pre-term) adj3 birth$).ti,ab.
((premature or preterm or pre term or pre-term) adj3 deliver$).ti,ab.
((preterm or pre term or pre-term) adj3 (labor or labour)).ti,ab.
(premature adj3 (labor or labour or parturition)).ti,ab.
Fetal Membranes, Premature Rupture/
((premature or preterm or pre term or pre-term) adj3 rupture$).ti,ab.
(PROM or PPROM).ti,ab.
or/14–21
13 and 22

BIOSIS (DIALOG), 1969–2005/ Aug. week 1, 19 August 2005

2317 records were retrieved.

s (premature or preterm or pre(w)term)(3n)birth?
s (premature or preterm or pre(w)term)(3n)deliver?
s (premature or preterm or pre(w)term)(3n)(labo?r or parturition)

s (premature or preterm or pre(w)term)(3n) rupture?
s s1:s4
s clinical(2w)trial?
s controlled(2w)(trial? or stud?)
s random or randomi?ation or randomi?ed
s (singl? or doubl? or tripl? or trebl?)(2w)(mask? or blind?)
s placebo?
s crossover
s evaluation
s (prospective(2w)stud?) or (comparative(2w)stud?)
s phase(w)4 or phase(w)four or phase(w)IV
s post(w)market?(w)surveillance
s follow(w)up
s s6:s16
s s5 and s17

PASCAL (DIALOG), 1973–2005/ Aug. week 1, 19 August 2005
2415 records were retrieved.

s (premature or preterm or pre(w)term)(3n)birth?
s (premature or preterm or pre(w)term)(3n)deliver?
s (premature or preterm or pre(w)term)(3n)(labo?r or parturition)
s (premature or preterm or pre(w)term)(3n) rupture?
s s1:s4
s clinical(2w)trial?
s controlled(2w)(trial? or stud?)
s random or randomi?ation or randomi?ed
s (singl? or doubl? or tripl? or trebl?)(2w)(mask? or blind?)
s placebo?
s crossover
s evaluation
s (prospective(2w)stud?) or (comparative(2w)stud?)
s phase(w)4 or phase(w)four or phase(w)IV
s post(w)market?(w)surveillance
s follow(w)up
s s6:s16
s s5 and s17

Science Citation Index (SCI) (Web of Science), 1900–2005/ Aug. week 1, 18 August 2005
1916 records were retrieved.

TS=(clinical* SAME trial*)
TS=(controlled SAME trial*) OR TS=(controlled SAME stud*)
TS=(random OR randomisation OR randomization OR randomized or randomised)
TS=(singl* or doubl* or tripl* or trebl*) SAME TS=(mask* or blind*)
TS=placebo*
TS=crossover
TS=evaluation
TS=(prospective SAME stud*) or TS=(comparative SAME stud*)
TS=(phase 4) or TS=(phase four) or TS=(phase IV)
TS=(post market* surveillance)
#10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
TS=(premature or preterm or pre term or pre-term) SAME TS=(birth*)
TS=(premature or preterm or pre term or pre-term) SAME TS=(deliver*)
TS=(preterm or pre term or pre-term) SAME TS=(labor or labour)
TS=premature SAME TS=(labor or labour or parturition)
TS=(premature or preterm or pre term or pre-term) SAME TS=(rupture*)
#16 OR #15 OR #14 OR #13 OR #12
#17 AND #11

Cochrane Database of Systematic Reviews (CDSR), Cochrane Library, Issue 3:18 August 2005
108 records were retrieved.

Labor, Premature (MeSH)
(premature or preterm or pre*term) NEAR/3 birth in title
(premature or preterm or pre*term) NEAR/3 birth in abstract
(premature or preterm or pre*term) NEAR/3 deliver* in title
(premature or preterm or pre*term) NEAR/3 deliver* in abstract
(preterm or pre*term) NEAR/3 (labour or labor) in title
(preterm or pre*term) NEAR/3 (labour or labor) in abstract
premature NEAR/3 (labour or labor or parturition) in title
premature NEAR/3 (labour or labor or parturition) in abstract
Fetal Membranes, Premature Rupture (MeSH)
(premature or preterm or pre*term) NEAR/3 ruptur* in title
(premature or preterm or pre*term) NEAR/3 ruptur* in abstract
(PROM or PPROM) in title
(PROM or PPROM) in abstract
#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14

Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Library, Issue 3:18 August 2005
1595 records were retrieved.

Labor, Premature (MeSH)
(premature or preterm or pre*term) NEAR/3 birth
(premature or preterm or pre*term) NEAR/3 deliver*
(preterm or pre*term) NEAR/3 (labour or labor)
premature NEAR/3 (labour or labor or parturition)
Fetal Membranes, Premature Rupture (MeSH)
(premature or preterm or pre*term) NEAR/3 ruptur*
PROM or PPROM
#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8

Database of Abstracts of Reviews of Effects (DARE) (CRD internal databases), 1994–2005/Aug. week 1, 18 August 2005
164 records were retrieved.

S (premature or preterm or pre(w)term)(w3)birth$
S (premature or preterm or pre(w)term)(w3) deliver$
S (preterm or pre(w)term)(w3)(labor$or labour$)
S (premature or preterm or pre(w)term)(w3)(labor or labour or parturition)
S (premature or preterm or pre(w)term)(w3) rupture$
S PROM or PPROM
S s1 or s2 or s3 or s4 or s5 or s6

Health Technology Assessment (HTA) (CRD internal databases), 1994–2005/ Aug. week 1, 18 August 2005
12 records were retrieved.

S (premature or preterm or pre(w)term)(w3)birth$
S (premature or preterm or pre(w)term)(w3) deliver$
S (preterm or pre(w)term)(w3)(labor$or labour$)
S (premature or preterm or pre(w)term)(w3)(labor or labour or parturition)
S (premature or preterm or pre(w)term)(w3) rupture$
S PROM or PPROM
S s1 or s2 or s3 or s4 or s5 or s6

System for Information on Grey Literature in Europe (SIGLE), (Ovid Gateway), 1980–2004/ Aug. week 1, 18 August 2005
26 records were retrieved.

((premature or preterm or pre term or pre-term) near3 birth*) in ti,ab
((premature or preterm or pre term or pre-term) near3 deliver*) in ti,ab
((preterm or pre term or pre-term) near3 (labor or labour)) in ti,ab
(premature near3 (labor or labour or parturition)) in ti,ab
((premature or preterm or pre term or pre-term) near3 rupture*) in ti,ab
#1 or #2 or #3 or #4 or #5

Inside Conferences (DIALOG), 1993–2005/Aug. week 1, 19 August 2005
34 records were retrieved.

s (premature or preterm or pre(w)term)(3n)birth?
s (premature or preterm or pre(w)term)(3n)deliver?
s (premature or preterm or pre(w)term)(3n)(labo?r or parturition)
s (premature or preterm or pre(w)term)(3n) rupture?
s s1:s4
s clinical(2w)trial?
s controlled(2w)(trial? or stud?)
s random or randomi?ation or randomi?ed
s (singl? or doubl? or tripl? or trebl?)(2w)(mask? or blind?)
s placebo?
s crossover
s evaluation
s (prospective(2w)stud?) or (comparative(2w)stud?)
s phase(w)4 or phase(w)four or phase(w)IV
s post(w)market?(w)surveillance
s follow(w)up
s s6:s16
s s5 and s17

Dissertation Abstracts (DIALOG), 1861–2005/Aug. week 1, 19 August 2005
124 records were retrieved.

s (premature or preterm or pre(w)term)(3n)birth?
s (premature or preterm or pre(w)term)(3n)deliver?
s (premature or preterm or pre(w)term)(3n)(labo?r or parturition)
s (premature or preterm or pre(w)term)(3n) rupture?
s s1:s4
s clinical(2w)trial?
s controlled(2w)(trial? or stud?)
s random or randomi?ation or randomi?ed
s (singl? or doubl? or tripl? or trebl?)(2w)(mask? or blind?)
s placebo?
s crossover

s evaluation
s (prospective(2w)stud?) or (comparative(2w)stud?)
s phase(w)4 or phase(w)four or phase(w)IV
s post(w)market?(w)surveillance
s follow(w)up
s s6:s16
s s5 and s17

National Research Register (NRR), (Update Software), 2005:19 August 2005
455 records were retrieved.

LABOR PREMATURE single term (MeSH)
(premature NEXT birth*) or (preterm NEXT birth*) or (pre-term NEXT birth*)
(premature NEXT deliver*) or (preterm NEXT deliver*) or (pre-term NEXT deliver*)
(preterm NEXT labour) or (pre-term NEXT labour)
(preterm NEXT labor) or (pre-term NEXT labor)
(premature NEXT labour) or (premature NEXT labor) or (premature NEXT parturition)
FETAL MEMBRANES PREMATURE RUPTURE single term (MeSH)
(premature NEXT rupture*) or (preterm NEXT rupture*) or (pre-term NEXT rupture*)
#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8

National Technical Information Service (NTIS) (US Department of Commerce), 1990–2005/Aug. week 1, 19 August 2005
Seven records were retrieved. Each line was searched separately.

"premature birth" or "preterm birth" or "pre term birth" or "pre-term birth"
"premature delivery" or "preterm delivery" or "pre term delivery" or "pre-term delivery"
"premature labor" or "preterm labor" or "pre term labor" or "pre-term labor"
"premature labour" or "preterm labour" or "pre term labour" or "pre-term labour"
"premature parturition"
"premature rupture" or "preterm rupture" or "pre term rupture" or "pre-term rupture"

ClinicalTrials.gov. (US National Institutes of Health), 2005/ Aug. week 1, 22 August 2005
11 records were retrieved. Each line searched was separately.

premature birth, preterm birth, pre term birth, pre-term birth
premature delivery, preterm delivery, pre term delivery, pre-term delivery
preterm labor, preterm labour, premature labor, premature labour
premature parturition
premature rupture, preterm rupture, pre term rupture, pre-term rupture

Economic analysis

Economic search strategies and results

NHS Economic Evaluation Database (NHS EED) (CRD internal databases), 1994–2005/ Sept. week 1, 21 September 2005

113 records were retrieved.

S (premature or preterm or pre(w)term)(w3)birth$
S (premature or preterm or pre(w)term)(w3) deliver$
S (preterm or pre(w)term)(w3)(labor$or labour$)
S (premature or preterm or pre(w)term)(w3)(labor or labour or parturition)
S (premature or preterm or pre(w)term)(w3) rupture$
S PROM or PPROM
S s1 or s2 or s3 or s4 or s5 or s6

Health Economic Evaluations Database (HEED), (Office of Health Economics), CD-ROM, 1967–2005/ Sept. week 1, 21 September 2005
123 records were retrieved.

AX=(premature birth) or (premature births) or (preterm birth) or (preterm births) or (pre-term birth) or (pre-term births)
AX=(premature deliver) or (premature deliveries) or (premature delivery) or (preterm deliver) or (preterm deliveries) or (preterm delivery) or (pre-term deliver) or (pre-term deliveries) or (preterm delivery)
AX=(premature labor) or (premature labour) or (preterm labor) or (preterm labour) or (pre-term labor) or (pre-term labour)
AX=(premature parturition) or (premature rupture) or (premature ruptures) or (preterm parturition) or (preterm rupture) or (preterm ruptures) or (pre-term parturition) or (pre-term rupture) or (pre-term ruptures)
AX=PROM or PPROM
CS=1 or 2 or 3 or 4 or 5

MEDLINE (Ovid Gateway), 1966–2005/ Sept. week 1, 21 September 2005
610 records were retrieved in MEDLINE and 15 records were retrieved in MEDLINE In-Process & Other Non-Indexed Citations.

economics/
exp "costs and cost analysis"/
economics, dental/
exp "economics, hospital"/
economics, medical/
economics, nursing/
economics, pharmaceutical/
(economic$or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).tw.
(expenditure$not energy).tw.
(value adj1 money).tw.
budget$.tw.
or/1–11
Labor, Premature/
((premature or preterm or pre term or pre-term) adj3 birth$).ti,ab.
((premature or preterm or pre term or pre-term) adj3 deliver$).ti,ab.
((preterm or pre term or pre-term) adj3 (labor or labour)).ti,ab.
(premature adj3 (labor or labour or parturition)).ti,ab.
Fetal Membranes, Premature Rupture/
((premature or preterm or pre term or pre-term) adj3 rupture$).ti,ab.
(PROM or PPROM).ti,ab.
or/13–20
12 and 21
Animals/
Humans/
23 not (23 and 24)
22 not 25

EMBASE (Ovid Gateway), 1980–2005/ Sept. week 1, 21 September 2005
564 records were retrieved.

Health Economics/
exp Economic Evaluation/
exp Health Care Cost/
exp PHARMACOECONOMICS/
or/1–4
(econom$or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
(expenditure$not energy).ti,ab.
(value adj2 money).ti,ab.
budget$.ti,ab.
or/6–9
5 or 10
(metabolic adj cost).ti,ab.
((energy or oxygen) adj cost).ti,ab.
((energy or oxygen) adj expenditure).ti,ab.
or/12–14
11 not 15
editorial.pt.
note.pt.
letter.pt.
or/17–19
16 not 20
(rat or rats or mouse or mice or hamster or hamsters or animal or animals or dogs or dog or cats or bovine or sheep).ti,ab,sh.
exp animal/
Nonhuman/
or/22–24
exp human/
exp human experiment/
26 or 27
25 not (25 and 28)
21 not 29
Premature Labor/
((premature or preterm or pre term or pre-term) adj3 birth$).ti,ab.
((premature or preterm or pre term or pre-term) adj3 deliver$).ti,ab.
((preterm or pre term or pre-term) adj3 (labor or labour)).ti,ab.
(premature adj3 (labor or labour or parturition)).ti,ab.
Premature Fetus Membrane Rupture/
((premature or preterm or pre term or pre-term) adj3 rupture$).ti,ab.
(PROM or PPROM).ti,ab.
or/31–38
30 and 39

Cumulative Index to Nursing and Allied Health Literature (CINAHL) (Ovid Gateway), 1982–2005/Sept. week 1, 21 September 2005
83 records were retrieved.

exp "costs and cost analysis"/or "economic aspects of illness"/or "economic value of life"/or economics, pharmaceutical/
((cost or costs or costed or costly or costing) adj (utilit$or benefit$or effective$or stud$or minimi$or analys$)).ti,ab.
(economic$or pharmacoeconomic$or price$or pricing).ti,ab.
(expenditure$not energy).ti,ab.
(value adj1 money).ti,ab.
budget$.ti,ab.
or/1–6
Labor, Premature/
((premature or preterm or pre term or pre-term) adj3 birth$).ti,ab.
((premature or preterm or pre term or pre-term) adj3 deliver$).ti,ab.

((preterm or pre term or pre-term) adj3 (labor or labour)).ti,ab.
(premature adj3 (labor or labour or parturition)).ti,ab.
Fetal Membranes, Premature Rupture/
((premature or preterm or pre term or pre-term) adj3 rupture$).ti,ab.
(PROM or PPROM).ti,ab.
or/8–15
7 and 16

BIOSIS (Edina), 1969–2005/Sept. week 1, 21 September 2005

282 records were retrieved.

al:(premature n3 birth*) or (preterm n3 birth*) or (pre-term n3 birth*) or (pre term n3 birth*)
al:(premature n3 deliver*) or (preterm n3 deliver*) or (pre-term n3 deliver*) or (pre term n3 deliver*)
al:(premature n3 labo*r*) or (preterm n3 labo*r*) or (pre-term n3 labo*r*) or (pre term n3 labo*r*)
al:(premature n3 parturition)
al:(premature n3 rupture*) or (preterm n3 rupture*) or (pre-term n3 rupture*) or (pre term n3 rupture*)
#1 or #2 or #3 or #4 or #5
al:(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic*)
al:budget*
al:(value w1 money)
al:(expenditure* not energy)
#7 or #8 or #9 or #10
#6 and #11

PASCAL (DIALOG), 1973–2005/ Sept. week 1, 21 September 2005
175 records were retrieved.

s (premature or preterm or pre(w)term)(3n)birth?
s (premature or preterm or pre(w)term)(3n)deliver?
s (premature or preterm or pre(w)term)(3n)(labo?r or parturition)
s (premature or preterm or pre(w)term)(3n) rupture?
s s1:s4
s economic? or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic?
s expenditure? not energy
s value(2w)money
s budget?
s s6:s9
s s5 and s10

Science Citation Index (SCI) (Web of Science), 1900–2005/Sept. week 1, 21 September 2005

388 records were retrieved.

TS=(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic*)
TS=(value SAME money)
TS=budget*
TS=(expenditure* NOT energy)
#1 OR #2 OR #3 OR #4
TS=(premature or preterm or pre term or pre-term) SAME TS=(birth*)
TS=(premature or preterm or pre term or pre-term) SAME TS=(deliver*)
TS=(preterm or pre term or pre-term) SAME TS=(labor or labour)
TS=premature SAME TS=(labor or labour or parturition)
TS=(premature or preterm or pre term or pre-term) SAME TS=(rupture*)
#6 OR #7 OR #8 OR #9 OR #10
#5 AND #11

Inside Conferences (DIALOG), 1993–2005/Sept. week 1, 21 September 2005
Four records were retrieved.

s (premature or preterm or pre(w)term)(3n)birth?
s (premature or preterm or pre(w)term)(3n)deliver?
s (premature or preterm or pre(w)term)(3n)(labo?r or parturition)
s (premature or preterm or pre(w)term)(3n) rupture?
s s1:s4
s economic? or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic?
s expenditure? not energy
s value(2w)money
s budget?
s s6:s9
s s5 and s10
s (prospective(2w)stud?) or (comparative(2w)stud?)
s phase(w)4 or phase(w)four or phase(w)IV
s post(w)market?(w)surveillance
s follow(w)up
s s6:s16
s s5 and s17

Dissertation Abstracts (DIALOG), 1861–2005/Sep. 21 September 2005
51 records were retrieved.

s (premature or preterm or pre(w)term)(3n)birth?
s (premature or preterm or pre(w)term)(3n)deliver?
s (premature or preterm or pre(w)term)(3n)(labo?r or parturition)
s (premature or preterm or pre(w)term)(3n) rupture?
s s1:s4
s economic? or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic?
s expenditure? not energy
s value(2w)money
s budget?
s s6:s9
s s5 and s10

IDEAS, the Research Papers in Economics (RePEC) database, 2005/Sept. 21 September 2005

No records were retrieved. Each line was searched separately

premature birth
preterm birth
preterm labor
preterm labour
premature labor
premature labour
premature parturition
premature rupture
preterm rupture

Appendix 2

List of tests for predicting spontaneous preterm birth

Type of tests or investigation	Predictive and diagnostic tests for preterm birth	Last updated
History	Previous history of spontaneous preterm birth[a]	
Examination	Abdominal palpation[b]	
	Cervical digital examination[b]	
Biochemistry	Cervicovaginal glycoproteins:	2001
	Interleukins (IL-6, IL-8)[b]	
	β-human chorionic gonadotrophin[b]	
	Fetal fibronectin[a,b]	
	Phosphorylated insulin-like growth factor binding protein-1[b]	
	Serum glycoproteins: α-fetoprotein, human chorionic gonadotrophin (as part of Down syndrome screening)[a]	
	Endocrine hormones:	
	Salivary estriolb	
	Cortisol-releasing hormone[b]	
	Inflammatory markers (serum):	
	C-reactive proteina,b	
	Matrix metalloproteases (MMP)b	
	Interleukins[a,b]	
Microbiology	Detection of bacterial vaginosis[a,b]	2002
	Periodontal screening[a]	2006
	Midstream urine culture[a,b]	1989
Physiological	Uterine activity monitoring[a]	
	Rheobase[b]	
	Mammary stimulation test[b]	
Ultrasound scan	Absence of fetal breathing movements[b]	2003
	Measurement of cervical length[a,b]	2003

a Test applied on asymptomatic women.
b Test applied on symptomatic women.

Appendix 3

List of interventions preventing or improving neonatal outcome in spontaneous preterm birth

Intervention	Comparator(s)	Action
Asymptomatic women identified to be at risk of spontaneous preterm birth		
Education for high-risk women	No intervention	Update
Home visits	No intervention	Update
Bed rest (home or hospital)	No intervention	Update
Home uterine monitoring	No intervention	New rapid review
Antibiotic treatment for urogenital infections, including:		
Ureaplasma in vagina	No treatment or placebo	Update
Bacterial vaginosis	No treatment, placebo or alternative antibiotic therapy	Update
Asymptomatic bacteriuria	No treatment	Update
Syphilis	No treatment, placebo or alternative antibiotic therapy	No new trials, use existing Cochrane review
Gonorrhoea	Alternative antibiotic therapy	Update
Symptomatic urinary tract infections	Alternative antibiotic therapy	Update
Duration of asymptomatic bacteriuria	Antimicrobiols of varying duration, e.g. single-dose, short-course, long-course, continuous treatment	Update
Antibiotics for treating intra-amniotic infections	No treatment or alternative antibiotic regimen	Update
Periodontal disease	No treatment, placebo or alternative treatments	New rapid review
Cervical cerclage	No treatment, bed rest, elective versus emergency or alternative therapies (e.g. pessaries)	Update
Nutrition and supplements		
Vitamin C	No treatment or placebo	Update
Vitamin D	No treatment or placebo	Update
Vitamin E	No treatment or placebo	Update
Zinc	No treatment or placebo	Update
Fish oil	No treatment or placebo	Update
Hypnosis	No treatment	New rapid review
Hydration	No treatment	Update
Prophylactic antibiotics (intact membranes)	No treatment or placebo	Update

continued

Intervention	Comparator(s)	Action
Women in late pregnancy symptomatic of threatened preterm labour		
Tocolytic agents		
Nitric oxide donors	No treatment, placebo or alternative tocolytic agent	Update
Cyclo-oxygenase inhibitors	No treatment, placebo or alternative tocolytic agent	Update
Ethanol	No treatment, placebo or alternative tocolytic agent	Update
Terbutaline pump maintenance	No treatment, placebo or alternative tocolytic agent	Update
Oxytocin receptor agonists	No treatment, placebo or alternative tocolytic agent	Update
Calcium channel blockers	No treatment, placebo or alternative tocolytic agent	Update
Calcium channel maintenance	No treatment, placebo or alternative tocolytic agent	Update
Magnesium sulphate	No treatment, placebo or alternative tocolytic agent	Update
Progestational agents	No treatment, placebo, and different routes of administration	Use existing review
In utero transfer		
Planned early birth versus expectant management	Planned early birth versus expectant management	Use Cochrane review (due 2006)
Improvement of neonatal outcomes		
Magnesium sulphate for neuroprotection	No treatment or placebo	Update
Vitamin K for neuroprotection	No treatment or placebo	Update
Prophylactic corticosteroids	No treatment or placebo	
Repeat doses to prevent neonatal respiratory distress	No treatment or placebo	

Appendix 4

Data extraction proforma

Test accuracy

Pro-forma for study inclusion and data extraction

Reviewer	Language	1st author	Publication year	
Selection criteria				
Population – singleton pregnancy (if threatened preterm labour – intact membrane)				Yes/No
Reference standard (outcome) – delivery gestation stated				Yes/No
2x2 table construction possible				Yes/No
Test listed in the list of tests ( )				Yes/No
If all the above yes – select the study (if necessary contact the corresponding author)				Yes/No
Data extraction				
Country				
Population	Asymptomatic	Symptomatic		
Study design	Cohort	Case–control	Cannot tell	Others (state)
Data collection	Prospective	Retrospective	Cannot tell	Others (state)
Enrolment	Consecutive	Arbitrary	Cannot tell	Others (state)
Blinding	Yes	No	Cannot tell	Others (state)
Test description	Yes	No	Cannot tell	Others (state)
Inclusion criteria				
Exclusion criteria				
Testing gestation(s)				
Threshold(s)				
Reference standard(s)				
Sample size				

2 × 2 data extraction here (reproduce table as many times as required)

	Birth < 48 h/7 days/34 weeks/37 weeks	**Birth > 48 h/7 days/34 weeks/37 weeks**	**Total**
Test positive			
Test negative			

Comments:

Effectiveness

Proforma for study inclusion and data extraction

Review details	Methods	Results and conclusions
Authors Title: Type of review: Prevalence: Symptomatic for preterm birth – Preterm birth	Search: Databases searched (Search dates) Other sources Search restrictions Inclusion/exclusion criteria: Study design(s) Population Intervention Outcomes Study selection: Data extraction: Validity assessment: Criteria used Assessment Synthesis: Heterogeneity Methods	Number of studies included: Comparisons No. of studies meeting quality criteria: Adequate randomisation Adequate concealment of allocation Adequate blinding of clinician/patient/researcher Incidence of birth < 34 weeks gestation: Incidence of birth < 37 weeks gestation: Incidence of birth within 24 h of intervention: Incidence of birth within 48 h of intervention: Incidence of birth within 7 days of intervention: Incidence of neonatal intensive care admission: Incidence of perinatal mortality: Incidence of adverse events: Brief summary of findings: Authors' conclusions: Comments:

Decision analyses – economic evaluation (systematic review)

Proforma for study inclusion and data extraction

Author(s):

Title of document:

Source:

Location:

Initial classification of study on the basis of title and abstract:

A. Study reports primary research on the costs or utilisation of care and formal economic evaluation is included.
B. Study discusses economic aspects of care, and contains useful primary or secondary cost or utilisation data.
C. Study may have useful information but does not obviously fall into (A) or (B1).
D. Study discusses economic aspects of policies for care, but is in neither (A) nor (B1).
E. Study does not have any relevance to the economic evaluation of preterm labour.

Final classification of study following systematic review:

1. Economic evaluation
2. Other cost study
3. Effectiveness study with some assessment of implications for cost or quantity of resources used
4. Description of methods used in aspects of economic evaluation of preterm labour
5. Review of economic aspects of care
6. Other, such as, survey of resources and facilities, survey of utilisation, estimate of economic burden of disease, discussion of health finance or policy
7. Not relevant to the economic evaluation of preterm labour
8. Foreign language
9. Quality of life study

Primary focus of study (i.e. what is it about?):

Asymptomatic/symptomatic

Test/intervention

Country of origin:

Document reviewed by:

Comment by reviewer:

Decision analyses – evaluation of economic systematic review quality
Quality assessment form

Author and year:

	Phillips criteria	Y/N/UC
	Structure	
1.	Is there a clear statement of the decision problem?	
2.	Is the objective of the model specified and consistent with the stated decision problem?	
3.	Is the primary decision-maker specified?	
4.	Is the perspective of the model stated clearly?	
5.	Are the model inputs consistent with the stated perspective?	
6.	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	
7.	Are the sources of the data used to develop the structure of the model specified?	
8.	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	
9.	Is there a clear definition of the options under evaluation?	
10.	Have all feasible and practical options been evaluated?	
11.	Is there justification for the exclusion of feasible options?	
12.	Is the chosen model type appropriate given the decision problem and specified casual relationships within the model?	
13.	Is the time horizon of the model sufficient to reflect all the important differences between the options?	
14.	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	
15.	Is the cycle length defined and justified in terms of the natural history of disease?	
	Data	
16.	Are the data identification methods transparent and appropriate given the objectives of the model?	
17.	Where choices have been made between data sources are these justified appropriately?	
18.	Where expert opinion has been used are the methods described and justified?	
19.	Is the choice of baseline data described and justified?	
20.	Are transition probabilities calculated appropriately?	
21.	Has a half-cycle correction been applied to both costs and outcomes?	
22.	If not, has the omission been justified?	
23.	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	
24.	Are the costs incorporated into the model justified?	
25.	Has the source for all costs been described?	
26.	Have discount rates been described and justified given the target decision-maker?	
27.	Are the utilities incorporated into the model appropriate?	
28.	Is the source of utility weights referenced?	
29.	If data have been incorporated as distributions, has the choice of distributions for each parameter been described and justified?	
30.	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	
31.	Has heterogeneity been dealt with by running the model separately for different subgroups?	
32.	Have the results been compared with those of previous models and any differences in results explained?	

Y, yes; N, no; UC, unclear.

Decision analyses – evaluation of economic systematic review quality
Quality assessment form

Author and year:

	Drummond adapted criteria	**Y/N/UC**
1.	Was a well-defined question posed in an answerable form?	
2.	Was a comprehensive description of the competing alternatives given?	
3.	Was there evidence that the programmes' effectiveness was established?	
4.	Were all the important and relevant costs and consequences for each alternative identified?	
5.	Were costs and consequences measured accurately in appropriate physical units?	
6.	Were costs and consequences valued credibly?	
7.	Were costs and consequences adjusted for differential timing?	
8.	Was an incremental analysis of costs and consequences of alternatives performed?	
9.	Was allowance made for uncertainty in the estimates of costs and consequences?	
10.	Did the presentation and discussion of study results include all issues of concern to users?	

Y, yes; N, no; UC, unclear.

Author and year:

	Cost studies criteria – based on ultrasound study	**Y/N/UC**
1.	Methods for the estimation of quantities and unit costs are described (or cited)	
2.	Sources of cost data are stated/apparent	
3.	Indirect costs (if included) are reported separately from direct costs	
4.	Both currency and price data are recorded	
5.	Details of currency or price adjustments for inflation or currency conversion are given (if appropriate)	
6.	The discount rate is stated/apparent and justified (if relevant)	

Y, yes; N, no; UC, unclear.

Decision analyses – cost data extraction

Cost data extraction proforma

Study details	Definition and components	Method for estimation of costs	Results/ statistical analysis	Sensitivity analysis	Comments
Author and year: Research question: Type of cost study: Country/currency: Cost year: Perspective: Study population: Intervention (including comparator):	Definitions: Components:	Estimation of costs:	Costs: Statistical analysis:	Sensitivity analysis: Appropriateness:	Author's conclusions: Implications for practice: Comments:

Decision analyses – data extraction

Data extraction proforma

Study details	Source of data	Method of estimation of benefits/costs	Results/ statistical analysis	Sensitivity analysis	Comments
Author and Year: Research question: Type of economic evaluation: Country/currency: Cost year: Perspective: Study population: Intervention (including comparator):	Source of effectiveness data: Source of cost data:	Valuation for clinical outcomes or benefits: Estimation of costs: Modelling:	Clinical outcome/ benefits: Costs: Synthesis of costs and benefits: Statistical analysis:	Sensitivity analysis: Appropriateness:	Author's conclusions: Magnitude and direction of results: Implications for practice: Comments:

Appendix 5

Characteristics and results of individual included test accuracy studies

TABLE 68 *Characteristics of studies on accuracy of maternal history of previous spontaneous preterm birth in predicting subsequent spontaneous preterm birth*

Authors	Year	Country	*n*	Study designs	Inclusion	Exclusion	Testing gestation	Threshold	Outcome (weeks' gestation)
Goldenberg[68]	1998	USA	1711	Cohort Prospective Test described	Singleton pregnancies	Placenta praevia, congenital fetal anomaly	First antenatal appointment	Previous spontaneous preterm birth	< 35, < 37
Iams[69]	1998	USA	1282	Cohort Prospective Test described	Singleton pregnancies		First antenatal appointment	Previous spontaneous preterm birth before 26, 31 or 36 weeks' gestation	37
Botsis[64]	2004	Greece	104	Cohort Prospective Test described	Singleton pregnancies		First antenatal appointment	Previous spontaneous preterm birth	36
Kristensen[70]	1995	Denmark	13,764	Cohort Retrospective Test described	Singleton pregnancies		First antenatal appointment	Previous spontaneous preterm birth	37
Berkowitz[63]	1998	USA	13,197	Cohort Retrospective Test described	Singleton pregnancies		First antenatal appointment	Previous spontaneous preterm birth	37
Carr-Hill[65]	1985	UK	6072[a] 1463[b]	Cohort Retrospective Test described	Singleton pregnancies		First antenatal appointment	One, two previous spontaneous preterm birth	37
deCarvalho[66]	2005	Brazil	1958	Cohort Retrospective Test described	Singleton pregnancies		First antenatal appointment	Previous spontaneous preterm birth	34
Ancel[62]	1999	France	13,292	Case–control Retrospective Test described	Singleton pregnancies		First antenatal appointment	Previous spontaneous preterm birth	37
Weidinger[71]	1974	Germany	911	Case–control Retrospective Test described	Singleton pregnancies		First antenatal appointment	One, two previous spontaneous preterm birth	37
deHaas[67]	1991	USA	420	Case–control Retrospective Test described	Singleton pregnancies		First antenatal appointment	Previous spontaneous preterm birth	37

a One previous spontaneous preterm birth.
b Two previous spontaneous preterm births.

TABLE 69 *Individual accuracy results of maternal history of previous spontaneous preterm birth in predicting subsequent spontaneous preterm birth*

Authors	TP	FP	FN	TN	sens	sens_lb	sens_ub	spec	spec_lb	spec_ub	LR+	LR+_lb	LR+_ub	LR–	LR–_lb	LR–_ub
Goldenberg[68]	85	278	119	1229	0.42	0.35	0.49	0.82	0.80	0.83	2.26	1.86	2.74	0.72	0.64	0.81
[a]Goldenberg[68]	55	308	32	1316	0.63	0.52	0.73	0.81	0.79	0.83	3.33	2.76	4.03	0.45	0.34	0.60
[b]Iams[69]	15	83	67	1117	0.18	0.11	0.28	0.93	0.91	0.94	2.64	1.60	4.37	0.88	0.79	0.97
[c]Iams[69]	27	149	55	1051	0.33	0.23	0.44	0.88	0.86	0.89	2.65	1.88	3.74	0.77	0.66	0.89
[c]Iams[69]	55	323	27	877	0.67	0.56	0.77	0.73	0.70	0.76	2.49	2.09	2.98	0.45	0.33	0.61
Botsis[64]	1	10	10	83	0.09	0.00	0.41	0.89	0.81	0.95	0.85	0.12	5.99	1.02	0.83	1.24
Kristensen[70]	55	433	241	13,035	0.19	0.14	0.23	0.97	0.96	0.97	5.78	4.47	7.46	0.84	0.80	0.89
Berkowitz[63]	214	1049	465	11,469	0.32	0.28	0.35	0.92	0.91	0.92	3.76	3.32	4.26	0.75	0.71	0.79
[e]Carr-Hill[65]	76	418	261	537	0.23	0.18	0.27	0.56	0.53	0.59	0.52	0.42	0.64	1.38	1.27	1.49
[f]Carr-Hill[65]	8	17	57	1381	0.12	0.05	0.23	0.99	0.98	0.99	10.12	4.54	22.59	0.89	0.81	0.97
deCarvalho[66]	25	155	41	1737	0.38	0.26	0.51	0.92	0.90	0.93	4.62	3.28	6.52	0.68	0.56	0.82
Ancel[62]	850	526	4477	7439	0.16	0.15	0.17	0.93	0.93	0.94	2.42	2.18	2.68	0.90	0.89	0.91
[e]Weidinger[71]	73	18	370	450	0.16	0.13	0.20	0.96	0.94	0.98	4.28	2.60	7.06	0.87	0.83	0.91
[f]Weidinger[71]	25	4	370	450	0.06	0.04	0.09	0.99	0.98	1.00	7.18	2.52	20.46	0.95	0.92	0.97
deHaas[62]	21	14	119	266	0.15	0.10	0.22	0.95	0.92	0.97	3.00	1.57	5.72	0.89	0.83	0.96

FN, false negative; FP, false positive; lb, lower bound; LR,+, likelihood ratio for positive test; LR–, likelihood ratio for negative test; sens, sensitivity; spec, specificity; TN, true negative; TP, true positive; ub, upper bound.
a Spontaneous preterm birth < 35 weeks' gestation.
b Previous spontaneous preterm birth before 26 weeks' gestation.
c Previous spontaneous preterm birth before 31 weeks' gestation.
d Previous spontaneous preterm birth before 36 weeks' gestation.
e One previous spontaneous preterm birth.
f Two previous spontaneous preterm births.

TABLE 70 *Characteristics of test accuracy studies of digital examination in predicting spontaneous preterm birth stratified according to population of antenatal asymptomatic women and women symptomatic with threatened preterm labour*

Authors	Year	Country	*n*	Study designs	Inclusion	Exclusion	Testing gestation (weeks)	Frequency of testing	Threshold	Outcome (weeks' gestation)
Asymptomatic women										
Leveno[77]	1986	USA	185	Cohort Prospective Consecutive Blinded Test described	Low risk pregnancy		26–30	Single	2 cm dilated	< 34
Parikh[79]	1961	India	463	Cohort Prospective Consecutive Test described	Singleton pregnancies	Pre-eclampsia, infection, placenta praevia, previous history of miscarriages	24–36	Biweekly	Admit digit at internal os	< 37
Iams[76]	2002	USA	270	Cohort Prospective Blinded Test described	Singleton pregnancies	Women who had received or were scheduled to receive an ambulatory monitor or tocolytic medication or to undergo cerclage or were complicated by placenta praevia or a major fetal anomaly detected by ultrasonography. Women who did not have telephones were not enrolled, because the transmission of data collected by the monitoring system required a telephone	< 35	Quads	Bishop score changes	< 35
Stubbs[81]	1986	USA	108	Cohort Prospective Blinded Test described	Singleton pregnancies	Uterine or fetal anomaly, previous history of IUGR, spontaneous preterm birth, or cone biopsy, PPROM, history of second-trimester miscarriage	28, 32 and 34	Thrice	1 cm internal os dilatation, 30% effacement	< 37
Chambers[74]	1990	France	5066	Cohort Prospective Test described	Low-risk pregnancy		28 and < 37	Biweekly	< 1 cm long cervix at 28 weeks, > 1 cm internal os dilatation before 37 weeks	< 37

Authors	Year	Country	*n*	Study designs	Inclusion	Exclusion	Testing gestation (weeks)	Frequency of testing	Threshold	Outcome (weeks' gestation)
Blondel[73]	1990	France	3159	Cohort Prospective Test described	Singleton pregnancies able to attend antenatal clinic at 25–28 and 29–31 weeks' gestation, divided into nulliparous and multiparous groups	Unknown gestation, iatrogenic preterm delivery	25–28, 29–31	Twice	1 cm internal os dilatation, 1 cm long cervix, mid-position, soft cervix	< 37
Newman[78]	1997	USA	2916	Cohort Prospective Test described	Singleton pregnancies		22–24, 26–29	Twice	Bishop score ≥4 or cervical score < 1.5	< 35
Schaffner[80]	1966	USA	83	Cohort Blinded Test described	All pregnant women seen at routine antenatal clinic between 28–32 weeks' gestation, divided into nulliparous and multiparous groups	Operative cervical procedure, threatened or chronic miscarriage, hormone administration during pregnancy, PPROM, previous CS, uncertain dates	28–32	Single	2–3 cm dilated	< 37
Chhabra[75]	1991	India	75	Cohort Prospective Test described	Singleton pregnancies	Polyhydramnios, pre-eclampsia, vaginal bleeding, previous bad obstetrics history or history of preterm birth	28–28	Single	Central cervix position: ≥ 2.6, ≥ 1.5 cm long and posterior cervix position: ≥ 2.6, ≥ 1.5 cm long	< 37
Symptomatic women										
Onderoglu[82]	1997	Turkey	90	Cohort Prospective Blinded Test described	Singletons, intact membrane, cervical dilatation < 3 cm, absence of fetal and maternal complication		25–36	Single	> 2 cm dilated, > 40% effacement	< 37

CS, caesarean section; IUGR, intrauterine growth restriction; PPROM, premature pre-labour rupture of membranes.

TABLE 71 *Individual accuracy results of digital examination in predicting spontaneous preterm birth stratified according to population of asymptomatic antenatal women and symptomatic women with threatened preterm labour.*

Authors	Testing gestation (weeks)	Threshold	TP	FP	FN	TN	sens
Asymptomatic women							
Leveno[77]	26–30	2 cm dilated	4	11	3	167	0.57
Parikh[79]	24–36	Admit finger at internal os	28	174	29	232	0.49
Stubbs[81]	34	30% effacement	2	22	2	104	0.50
Stubbs[81]	32	30% effacement	5	23	5	103	0.50
Stubbs[81]	28	1 cm internal os	2	15	6	85	0.25
Stubbs[81]	32	1 cm internal os	4	28	6	98	0.40
Stubbs[81]	28	30% effacement	0	9	8	91	0.00
Stubbs[81]	34	1 cm internal os	3	51	1	75	0.75
Chambers[74]	< 37	1 cm internal os	65	846	109	4046	0.37
Chambers[74]	28	1 cm long cervix	29	487	109	4046	0.21
Chambers[74]	< 37	Combined	30	146	109	4046	0.22
[a]Blondel[73]	29–31	1 cm long cervix	26	228	92	2271	0.22
[a]Blondel[73]	25–28	1 cm long cervix	22	149	140	2848	0.14
[a]Blondel[73]	25–28	Mid-position cervix	45	520	117	2476	0.28
[a]Blondel[73]	29–31	Mid-position cervix	34	427	84	2072	0.29
[a]Blondel[73]	29–31	1 cm internal os	25	135	386	2071	0.06
[a]Blondel[73]	29–31	Soft cervix	103	1742	15	757	0.87
[a]Blondel[73]	25–28	1 cm internal os	21	48	139	2950	0.13
[a]Blondel[73]	25–28	Soft cervix	130	1870	30	1129	0.81
[b]Blondel[73]	29–31	1 cm long cervix	14	130	56	1509	0.20
[b]Blondel[73]	25–28	Soft cervix	95	1434	21	616	0.82
[b]Blondel[73]	25–28	Mid-position cervix	30	384	88	1664	0.25
[b]Blondel[73]	25–28	1 cm long cervix	12	96	103	1955	0.10
[b]Blondel[73]	29–31	Soft cervix	59	1242	11	397	0.84
[b]Blondel[73]	29–31	1 cm internal os	20	151	49	1489	0.29
[b]Blondel[73]	25–28	1 cm internal os	17	59	98	1992	0.15
[b]Blondel[73]	29–31	Mid-position cervix	16	292	50	1351	0.24
[a]Schaffner[80]	28–32	2–3 cm dilated	0	12	5	56	0.00
[b]Schaffner[80]	28–32	2–3cm dilated	5	60	10	141	0.33
Chhabra[75]	28	Central 1.5 cm long cervix	5	0	36	34	0.12
Chhabra[75]	28	Posterior 2.6 cm long cervix	1	4	6	54	0.14
Chhabra[75]	28	Central 2.6 cm long cervix	24	5	17	29	0.59
Chhabra[75]	28	Posterior 1.5 cm long cervix	7	57	0	1	1.00
Symptomatic women							
Onderoglu[82]	25–36	2 cm dilated cervix	21	16	11	42	0.66
Onderoglu[82]	25–36	40% effacement	20	18	12	40	0.63

FN, false negative; FP, false positive; lb, lower bound; LR,+, likelihood ratio for positive test; LR–, likelihood ratio for negative test; sens, sensitivity; spec, specificity; TN, true negative; TP, true positive; ub, upper bound.
a First examination.
b Second examination.

sens_lb	sens_ub	specs	spec_lb	spec_ub	LR+	LR+_lb	LR+_ub	LR-	LR–_lb	LR–_ub
0.18	0.90	0.94	0.89	0.97	9.25	3.91	21.85	0.46	0.19	1.08
0.36	0.63	0.57	0.52	0.62	1.15	0.86	1.53	0.89	0.68	1.16
0.07	0.93	0.83	0.75	0.89	2.86	1.00	8.19	0.61	0.23	1.62
0.19	0.81	0.82	0.74	0.88	2.74	1.33	5.64	0.61	0.33	1.14
0.03	0.65	0.85	0.76	0.91	1.67	0.46	6.04	0.88	0.59	1.33
0.12	0.74	0.78	0.70	0.85	1.80	0.79	4.11	0.77	0.46	1.29
0.00	0.37	0.91	0.84	0.96	0.59	0.04	9.34	1.04	0.88	1.24
0.19	0.99	0.60	0.50	0.68	1.85	1.01	3.39	0.42	0.08	2.31
0.30	0.45	0.83	0.82	0.84	2.16	1.77	2.64	0.76	0.67	0.85
0.15	0.29	0.89	0.88	0.90	1.96	1.40	2.73	0.88	0.81	0.97
0.15	0.29	0.97	0.96	0.97	6.20	4.35	8.84	0.81	0.74	0.89
0.15	0.31	0.91	0.90	0.92	2.42	1.68	3.47	0.86	0.78	0.95
0.09	0.20	0.95	0.94	0.96	2.73	1.80	4.15	0.91	0.86	0.97
0.21	0.35	0.83	0.81	0.84	1.60	1.23	2.08	0.87	0.79	0.96
0.21	0.38	0.83	0.81	0.84	1.69	1.25	2.27	0.86	0.76	0.96
0.04	0.09	0.94	0.93	0.95	0.99	0.66	1.50	1.00	0.97	1.03
0.80	0.93	0.30	0.28	0.32	1.25	1.16	1.35	0.42	0.26	0.68
0.08	0.19	0.98	0.98	0.99	8.20	5.03	13.35	0.88	0.83	0.94
0.74	0.87	0.38	0.36	0.39	1.30	1.20	1.41	0.50	0.36	0.69
0.11	0.31	0.92	0.91	0.93	2.52	1.53	4.14	0.87	0.77	0.98
0.74	0.88	0.30	0.28	0.32	1.17	1.07	1.28	0.60	0.41	0.89
0.18	0.34	0.81	0.79	0.83	1.36	0.98	1.87	0.92	0.82	1.02
0.06	0.18	0.95	0.94	0.96	2.23	1.26	3.94	0.94	0.88	1.00
0.74	0.92	0.24	0.22	0.26	1.11	1.00	1.24	0.65	0.37	1.12
0.19	0.41	0.91	0.89	0.92	3.15	2.11	4.69	0.78	0.67	0.91
0.09	0.23	0.97	0.96	0.98	5.14	3.10	8.52	0.88	0.81	0.95
0.15	0.36	0.82	0.80	0.84	1.36	0.88	2.12	0.92	0.80	1.06
0.00	0.52	0.82	0.71	0.91	0.46	0.03	6.85	1.12	0.86	1.46
0.12	0.62	0.70	0.63	0.76	1.12	0.53	2.36	0.95	0.66	1.37
0.04	0.26	1.00	0.90	1.00	9.17	0.52	160.08	0.88	0.78	1.00
0.00	0.58	0.93	0.83	0.98	2.07	0.27	16.03	0.92	0.67	1.26
0.42	0.74	0.85	0.69	0.95	3.98	1.70	9.31	0.49	0.33	0.72
0.59	1.00	0.02	0.00	0.09	0.96	0.80	1.16	2.46	0.11	55.35
0.47	0.81	0.72	0.59	0.83	2.38	1.46	3.87	0.47	0.29	0.79
0.44	0.79	0.69	0.55	0.80	2.01	1.26	3.22	0.54	0.34	0.88

TABLE 72 *Characteristic of studies on the accuracy of bedside cervicovaginal fetal fibronectin testing as a predictor of spontaneous preterm birth stratified according to study population of asymptomatic antenatal women and symptomatic women who presented with threatened preterm labour*

Authors	Year	*n*	Study designs	Inclusion criteria	Exclusion criteria	Testing gestation (weeks' gestation)	Reference standards (weeks' gestation)[a]
Asymptomatic women							
Ruiz[105]	2001	78	Cohort Prospective Test described	Asymptomatic women	< 18 or > 40 years old, Rh iso-immunisation, multiple gestation, cervical cerclage, use of tocolytic agents in the current pregnancy, maternal medical disorders, non-English speaking, > 28 weeks' gestation at enrolment, misses > 1 monthly antenatal check-up	23–26, 27–30	< 37 weeks
Arinami[94]	1999	438	Prospective Consecutive Test described	Singleton pregnancies without medical or obstetrical complications	None stated	26–28	< 34 weeks < 37 weeks
Goldenberg[96]	1996	2929	Prospective Blind Test described	Singleton pregnancies	Placenta praevia Fetal anomalies	22, 24, 26, 28, 30	< 34 weeks
Goldenberg[97]	1997	1870	Prospective Blind Test described	Singleton pregnancies of women who are not randomised to treatment for Trichomonas vaginalis or bacterial vaginosis	None stated	8–22	< 35 weeks
Goldenberg[83]	2000	6508	Prospective Blind Test described	Singleton pregnancies	None stated	8–22	< 28 weeks < 32 weeks < 35 weeks < 37 weeks
Hux[98]	1995	54	Prospective Blind Test described	Intact membrane and undilated cervix	Candida infection, fetal anomalies, vaginal bleeding, placenta praevia, and threatened preterm labour	26–29	< 37 weeks
Heath[88]	2000	5146	Prospective Consecutive Blind Test described	Singleton pregnancies of women attending an inner city antenatal clinic	Fetal abnormalities	22–24	< 33 weeks
Chang[95]	1997	234	Prospective Blind Test described	Singleton pregnancies without previous history of spontaneous preterm labour or birth Intact membrane	Vaginal bleeding, pre-eclampsia Placenta praevia Uncertain date Fetal anomaly	28	< 34 weeks < 37 weeks

Authors	Year	*n*	Study designs	Inclusion criteria	Exclusion criteria	Testing gestation (weeks' gestation)	Reference standards (weeks' gestation)[a]
Faron[87]	1997	155	Prospective Consecutive Blind Test described	All asymptomatic women in antenatal clinic with known gestation	Vaginal bleeding	24–33	< 37 weeks
Hellemans[89]	1995	133	Blind Consecutive Prospective Test described	Low-risk singleton pregnancies Intact membrane	Placenta praevia Vaginal bleeding Cervical dilatation > 1 cm or cervical cerclage Threatened preterm labour < 26 weeks, unknown date	26–36	< 37 weeks
Garcia[101]	1999	263	Blind Prospective Test described	Low-risk singleton Intact membrane	Cerclage	24–37	< 32 weeks < 37 weeks
Greenhagen[102]	1996	108	Blind Prospective Test described	Low-risk singleton pregnancies Intact membrane	Previous history of spontaneous preterm labour or birth Vaginal bleeding Fetal anomaly	24–34	< 37 weeks
DiStefano[100]	1999	60	Prospective Test described	Singleton pregnancies Intact membrane	Previous history of spontaneous preterm labour or birth Vaginal bleeding Fetal anomaly Cervical cerclage Genital infection Maternal or fetal complications during gestation and/or examination	24–36	< 37 weeks
Crane[99]	1999	140	Blind Consecutive Prospective Test described	Singleton pregnancies Intact membrane	Cerclage Fetal anomalies or death Vaginal bleeding, recently treated bacterial vaginosis	20–24	< 37 weeks
Inglis[103]	1994	73	Blind Prospective Test described	Intact membrane	Fetal anomalies, placenta praevia, genital or urinary infection, use of antibiotics in the preceding 7 days	< 37	< 37 weeks

continued

TABLE 72 *Characteristic of studies on the accuracy of bedside cervicovaginal fetal fibronectin testing as a predictor of spontaneous preterm birth stratified according to study population of asymptomatic antenatal women and symptomatic women who presented with threatened preterm labour (continued)*

Authors	Year	*n*	Study designs	Inclusion criteria	Exclusion criteria	Testing gestation (weeks' gestation)	Reference standards (weeks' gestation)[a]
Lockwood[104]	1993	429	Blind Prospective Test described	Asymptomatic women from an inner city antenatal clinic	Uncertain date, placenta praevia, iatrogenic preterm delivery	24–37	< 28 days of testing < 37 weeks
Vercoustre[106]	1996	58	Test described	Asymptomatic women	Coitus < 24 h and vaginal bleeding	27–37	< 37 weeks
Zamora[84]	2000	20	Blind Test described	Asymptomatic pregnant women Intact membrane	Coitus < 24 h Recent usage of vaginal pessary	28–36	< 37 weeks
Symptomatic women							
Luzzi[116]	2003	133	Cohort Consecutive Prospective Test described	Preterm labour, intact membrane, < 3 cm cervical dilatation	Scheduled Caesarean section, induced delivery within 21 days of testing	24–35	< 7, < 14 and < 21 days of testing
Tekesin[93]	2005	170	Cohort Consecutive Prospective Blinded Test described	Preterm labour, intact membrane, < 3 cm cervical dilatation	Multiple gestations, cervical manipulations (examination, intercourse, ultrasound), vaginal bleeding, major fetal anomaly, PPROM, cervical cerclage, suspected fetal asphyxia	24–35	< 7, < 14, < 21 days of testing and < 34 and < 37 weeks
Musaad[123]	2005	27	Cohort Consecutive Prospective Test described	Preterm labour, intact membrane, < 3 cm cervical dilatation	Vaginal bleeding	24–33	< 34, < 37
Dolinska[132]	2005	115	Cohort Retrospective Test described	Singleton, preterm labour, intact membrane, < 3 cm cervical dilatation, no cerclage	×	24–34	< 37
Topete[127]	2004	74	Cohort Retrospective Test described	Preterm labour, intact membrane, < 3 cm cervical dilatation	×	24–34	< 37
Foxman[110]	2004	139	Cohort Prospective	×	×	×	< 7

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Authors	Year	*n*	Study designs	Inclusion criteria	Exclusion criteria	Testing gestation (weeks' gestation)	Reference standards (weeks' gestation)[a]
Hincz[128]	2002	82	Cohort Prospective Blinded Test described	Preterm labour, intact membrane, < 3 cm cervical dilatation	Cerclage, clinical criteria of intrauterine infection, vaginal bleeding, IUGR, pre-eclampsia	24–34	< 37
Sakai[119]	2003	116	Cohort Test described	Preterm labour, intact membrane, < 4 cm cervical dilatation	PROM, multiple pregnancy, elective preterm delivery, pre-eclampsia, abruption, placenta praevia, maternal medical conditions	20–36	< 7 days of testing, and < 37 weeks
Closset[109]	2001	61	Cohort Prospective Blinded Test described	Preterm labour, intact membrane, < 3 cm cervical dilatation	×	24–36	< 7, < 14, < 21 days of testing, and < 37 weeks
Gomez[112]	2005	215	Cohort Prospective Test described	Preterm labour, intact membrane, < 3 cm cervical dilatation	×	22–35	< 48 h, < 7, < 14 days of testing and < 32, < 35 weeks
Hansen[115]	2004	41	Cohort Prospective Test described	> 16 years of age, preterm labour, < 3 cm dilatation for primigravida and < 4 cm for multiparous	Multiple gestations, major fetal anomaly, vaginal bleeding, PPROM, cervical cerclage, suspected fetal asphyxia	23–34	< 7, < 14 days of testing, and < 37 weeks
Stevens[135]	2004	185	Cohort Prospective Test described	Preterm labour, intact membrane, ≥ 2 cm dilatation, ≥ 50% effacement		24–34	< 32, < 37 weeks
LaShay[90]	2000	118	Cohort Consecutive Prospective Blind Test described	Singleton pregnancies Intact membrane Cervical dilatation < 3 cm	Coitus or digital vaginal examination within 24 h Vaginal bleeding Placenta praevia Placental abruption Polyhydramnios Pre-eclampsia Known uterine or fetal abnormalities	24–34	< 48 h < 7 days < 37 weeks

continued

TABLE 72 *Characteristic of studies on the accuracy of bedside cervicovaginal fetal fibronectin testing as a predictor of spontaneous preterm birth stratified according to study population of asymptomatic antenatal women and symptomatic women who presented with threatened preterm labour (continued)*

Authors	Year	*n*	Study designs	Inclusion criteria	Exclusion criteria	Testing gestation (weeks' gestation)	Reference standards (weeks' gestation)[a]
Senden[92]	1996		Cohort Consecutive Prospective Blind Test described	Singleton pregnancies Intact membrane Cervical dilatation < 4 cm	Vaginal bleeding Clinical chorioamnionitis Diabetes mellitus	25–35	< 7 days
Bartnicki[107]	1996	112	Cohort Prospective Blind Test described	Intact membrane, cervical dilatation < 2 cm		22–35	< 7 days < 14 days < 21 days < 28 days < 34 weeks
Benattar[108]	1997	124	Cohort Prospective Blind Test described	Singleton and twin pregnancies intact membrane, cervical dilatation < 3 cm	Vaginal bleeding Coitus < 24 h	24–36	< 7 days < 14 days < 21 days < 32 weeks < 34 weeks
Malak[117]	1996	112	Cohort Prospective Blind Test described	Singleton pregnancies Intact membrane Cervical dilatation < 2 cm	Placenta praevia Vaginal bleeding Coitus < 24 h	24–34	< 7 days < 14 days < 21 days < 37 weeks
McKenna[118]	1999	50	Cohort Consecutive Prospective Test described	Cervical dilatation < 3 cm	Coitus < 24 h Vaginal digital examination or transvaginal ultrasound scan procedure Cervical cerclage Uterine anomalies Placenta praevia Placental abruption	22–34	< 7 days < 14 days < 37 weeks
Peaceman[86]	1997	725	Cohort Prospective Blind Test described	Singleton, twin pregnancies and one triplet pregnancy Intact membrane Cervical dilatation < 3 cm	Placenta praevia Cerclage Trauma leading to preterm labour	24–34	< 7 days < 14 days < 37 weeks

Authors	Year	*n*	Study designs	Inclusion criteria	Exclusion criteria	Testing gestation (weeks' gestation)	Reference standards (weeks' gestation)[a]
Iams[113]	1995	192	Cohort Prospective Blind Test described	Intact membrane Cervical dilatation < 3 cm	Placenta praevia Cerclage Uterine anomalies Vaginal bleeding	24–34	< 7 days < 37 weeks
Giles[111]	2000	150	Cohort Prospective Test described	Intact membrane	Vaginal bleeding Coitus < 24 h Recent digital vaginal examination	24–34	< 7 days < 36 weeks
Lopez[114]	2000	85	Cohort Retrospective	Singleton pregnancies Intact membrane Cervical dilatation < 3 cm	Uncertain date Lost to follow up Incomplete data	24–35	< 7 days < 14 days < 34 weeks < 37 weeks
Cox (abstract)[121]	1995	175	Test described	Intact membrane Cervical dilatation < 3 cm	None stated	24–34	< 37 weeks
Chuileannain[124]	1998	50	Cohort Retrospective Test described	Singleton pregnancies Intact membrane Cervical dilatation < 2 cm	Placenta praevia Placental abruption Cerclage Fetal anomalies	< 34	< 34 weeks
Goffeng[122]	1997	63	Cohort Consecutive Prospective Test described	Singleton pregnancies with intact membrane	Pre-eclampsia Uterine or cervical abnormalities Placenta praevia, placental abruption Fetal anomalies Diabetes mellitus	23–34	< 34 weeks < 37 weeks
Parker[125]	1995	36	Cohort Prospective Blind Test described	Singleton pregnancies Intact membrane Cervical dilatation < 2 cm	Placenta praevia Placental abruption Cerclage Fetal anomalies Coitus < 24 h	20–34	< 34 weeks
Burrus[120]	1995	37	Cohort Prospective Blind Test described	Symptomatic women in their first pregnancy Intact membrane Cervical dilatation < 3 cm and changing, no contraindication to tocolytic	Amnionitis Placental abruption	< 34	< 37 weeks

continued

TABLE 72 *Characteristic of studies on the accuracy of bedside cervicovaginal fetal fibronectin testing as a predictor of spontaneous preterm birth stratified according to study population of asymptomatic antenatal women and symptomatic women who presented with threatened preterm labour (continued)*

Authors	Year	*n*	Study designs	Inclusion criteria	Exclusion criteria	Testing gestation (weeks' gestation)	Reference standards (weeks' gestation)[a]
Grandi[85]	1996	26	Cohort	Singleton pregnancies	Placenta praevia	24–36	< 37
			Consecutive	Intact membrane	Placental abruption		
			Prospective	Cervical dilatation < 2 cm	Fetal anomalies		
			Blind		Coitus < 24 h		
			Test described		Iatrogenic preterm labour		
Inglis[103]	1994	38	Cohort	Singleton pregnancies	Fetal anomalies	< 37	< 37
			Prospective	Intact membrane	Placenta praevia		
			Blind		Genital or urinary infection		
			Test described		Use of antibiotics in the preceding 7 days		
Irion[129]	1995	64	Cohort	Intact membrane	Fetal anomalies	24–36	< 37
			Prospective	Cervical dilatation < 2 cm	Vaginal bleeding		
			Blind		Coitus < 24 h		
			Test described		Iatrogenic preterm delivery		
Langer[130]	1997	61	Cohort	Intact membrane	Vaginal bleeding	24–34	< 37
			Prospective		Coitus < 24 h		
			Blind		Progressive cervical dilatation		
			Test described		Abnormal fetal heart rate monitoring		
Lockwood[104]	1991	117	Cohort	Intact membrane	Fetal anomalies	25–35	< 37
			Prospective		Placenta praevia		
			Blind		Coitus < 24 h		
			Test described		Intrauterine growth restriction		
					Fetal distress		
					Previous pregnancy terminated due to severe pre-eclampsia		
Morrison[91]	1993	28	Cohort	Singleton pregnancies	Uterine or cervical abnormalities	24–34	< 37
			Blind	Intact membrane	Vaginal bleeding		
			Consecutive		Placenta praevia		
			Prospective		Suspected placental abruption		
			Test described				

Authors	Year	*n*	Study designs	Inclusion criteria	Exclusion criteria	Testing gestation (weeks' gestation)	Reference standards (weeks' gestation)[a]
					Coitus or douching < 24 h		
					Diabetes mellitus		
					Unknown date		
					Pre-eclampsia		
					< 15 years old		
Rizzo[133]	1997	106	Cohort	Singleton pregnancies	Fetal or maternal complications	24–36	< 37
			Prospective	Intact membrane	Urinary or genital infection		
			Blind	Cervical dilatation < 3 cm	Use of antibiotic in the preceding 14 days		
			Test described				
Rozenberg[134]	1997	76	Cohort	Singleton pregnancies	Gestation < 24 or > 34 weeks	24–34	< 37
			Prospective	Intact membrane	Cerclage		
			Blind	Cervical dilatation < 2 cm	Placenta praevia		
			Test described		Placental abruption		
					Iatrogenic preterm delivery		
Calda[126]	1995	84	Cohort	Intact membrane		24–34	< 36
			Prospective				
			Test described				
Mansouri[131]	1996	90	Cohort	Intact membrane	Vaginal bleeding	24–34	< 37
			Retrospective		Coitus < 24 h		
			Test described				
Vercoustre[106]	1996	86	Test described	Singleton pregnancies with threatened preterm labour	Coitus < 24 h	< 37	< 37
					Vaginal bleeding		
Vetr[136]	1996	46	Cohort	Intact membrane	Fetal anomalies	25–36	< 37
			Prospective		Placenta praevia		
			Test described		Vaginal bleeding		
					Intrauterine growth restriction		
					Fetal distress		
					Diabetes mellitus		
					Pre-eclampsia		

IUGR, intrauterine growth restriction; PPROM, premature pre-labour rupture of membranes.
a Unless otherwise stated.

TABLE 73 *Individual accuracy results of cervicovaginal fetal fibronectin (fFN) in predicting spontaneous preterm birth among symptomatic women with threatened preterm labour*

Authors	Outcome	TP	FP	FN	TN	sens	sens_lb	sens_ub
Tekesin[93]	7	9	37	2	122	0.82	0.48	0.98
Closset[109]	7	5	11	1	44	0.83	0.36	1.00
LaShay[90]	7	3	10	2	103	0.60	0.15	0.95
Luzzi[116]	7	4	34	3	92	0.57	0.18	0.90
Senden[92]	7	4	4	1	20	0.80	0.28	0.99
Bartnicki[107]	7	3	33	1	79	0.75	0.19	0.99
Benattar[108]	7	8	11	1	104	0.89	0.52	1.00
Gomez[112]	7	18	34	10	153	0.64	0.44	0.81
Hansen[115]	7	2	7	1	31	0.67	0.09	0.99
Iams[113]	7	13	32	1	146	0.93	0.66	1.00
Malak[117]	7	8	10	2	92	0.80	0.44	0.97
McKenna[118]	7	5	13	1	35	0.83	0.36	1.00
Peaceman[86]	7	19	123	2	581	0.90	0.70	0.99
Plaut[717]	7	1	8	1	86	0.50	0.01	0.99
Giles[111]	7	11	34	5	100	0.69	0.41	0.89
Sakai[119]	7	11	27	7	71	0.61	0.36	0.83
Foxman[110]	7	6	25	1	107	0.86	0.42	1.00
Lopez[114]	7	8	12	1	64	0.89	0.52	1.00
Musaad[123]	34	5	5	1	21	0.83	0.36	1.00
Tekesin[93]	34	20	26	8	116	0.71	0.51	0.87
Burrus[120]	34	23	6	3	5	0.88	0.70	0.98
Goffeng[122]	34	7	7	4	45	0.64	0.31	0.89
Parker[125]	34	6	7	1	25	0.86	0.42	1.00
Chuileannain[124]	34	9	11	1	49	0.90	0.55	1.00
Cox[121]	34	3	22	11	139	0.21	0.05	0.51
Lopez[114]	34	11	9	4	61	0.73	0.45	0.92
Tekesin[93]	37	31	15	4	120	0.89	0.73	0.97
Closset[109]	37	12	4	11	34	0.52	0.31	0.73
Grandi[85]	37	4	9	4	9	0.50	0.16	0.84
Hincz[128]	37	10	5	4	63	0.71	0.42	0.92
LaShay[90]	37	10	8	24	76	0.29	0.15	0.47
Morrison[91]	37	9	5	1	13	0.90	0.55	1.00
Musaad[123]	37	5	3	5	15	0.50	0.19	0.81
Bartnicki[107]	37	27	7	13	65	0.68	0.51	0.81
Benattar[108]	37	9	9	16	90	0.36	0.18	0.57
Goffeng[122]	37	10	4	18	31	0.36	0.19	0.56
Hansen[115]	37	3	6	6	26	0.33	0.07	0.70
Iams[113]	37	27	18	35	112	0.44	0.31	0.57
Inglis[103]	37	7	2	9	20	0.44	0.20	0.70
Irion[129]	37	15	11	7	31	0.68	0.45	0.86

specs	spec_lb	spec_ub	LR+	LR+_lb	LR+_ub	LR–	LR-_lb	LR–_ub
0.77	0.69	0.83	3.52	2.36	5.23	0.24	0.07	0.83
0.80	0.67	0.90	4.17	2.20	7.89	0.21	0.03	1.25
0.91	0.84	0.96	6.78	2.68	17.16	0.44	0.15	1.29
0.73	0.64	0.81	2.12	1.05	4.28	0.59	0.25	1.39
0.83	0.63	0.95	4.80	1.77	13.00	0.24	0.04	1.40
0.71	0.61	0.79	2.55	1.35	4.80	0.35	0.06	1.94
0.90	0.84	0.95	9.29	5.06	17.06	0.12	0.02	0.78
0.82	0.76	0.87	3.54	2.34	5.33	0.44	0.26	0.72
0.82	0.66	0.92	3.62	1.28	10.27	0.41	0.08	2.04
0.82	0.76	0.87	5.17	3.66	7.30	0.09	0.01	0.58
0.90	0.83	0.95	8.16	4.20	15.87	0.22	0.06	0.77
0.73	0.58	0.85	3.08	1.71	5.53	0.23	0.04	1.38
0.83	0.80	0.85	5.18	4.19	6.40	0.12	0.03	0.43
0.91	0.84	0.96	5.88	1.26	27.30	0.55	0.14	2.19
0.75	0.66	0.82	2.71	1.75	4.21	0.42	0.20	0.87
0.72	0.63	0.81	2.22	1.36	3.62	0.54	0.30	0.97
0.81	0.73	0.87	4.53	2.84	7.20	0.18	0.03	1.08
0.84	0.74	0.92	5.63	3.19	9.94	0.13	0.02	0.84
0.81	0.61	0.93	4.33	1.82	10.29	0.21	0.03	1.25
0.82	0.74	0.88	3.90	2.57	5.93	0.35	0.19	0.63
0.45	0.17	0.77	1.62	0.93	2.83	0.25	0.07	0.88
0.87	0.74	0.94	4.73	2.08	10.75	0.42	0.19	0.93
0.78	0.60	0.91	3.92	1.90	8.06	0.18	0.03	1.13
0.82	0.70	0.90	4.91	2.77	8.70	0.12	0.02	0.79
0.86	0.80	0.91	1.57	0.53	4.60	0.91	0.69	1.20
0.87	0.77	0.94	5.70	2.88	11.28	0.31	0.13	0.71
0.89	0.82	0.94	7.97	4.88	13.03	0.13	0.05	0.32
0.89	0.75	0.97	4.96	1.81	13.56	0.53	0.34	0.83
0.50	0.26	0.74	1.00	0.43	2.30	1.00	0.43	2.30
0.93	0.84	0.98	9.71	3.92	24.05	0.31	0.13	0.71
0.90	0.82	0.96	3.09	1.33	7.15	0.78	0.62	0.98
0.72	0.47	0.90	3.24	1.50	7.02	0.14	0.02	0.91
0.83	0.59	0.96	3.00	0.90	10.01	0.60	0.31	1.15
0.90	0.81	0.96	6.94	3.33	14.49	0.36	0.23	0.57
0.91	0.83	0.96	3.96	1.76	8.93	0.70	0.52	0.95
0.89	0.73	0.97	3.13	1.10	8.91	0.73	0.54	0.98
0.81	0.64	0.93	1.78	0.55	5.74	0.82	0.50	1.34
0.86	0.79	0.92	3.15	1.88	5.26	0.66	0.52	0.82
0.91	0.71	0.99	4.81	1.15	20.18	0.62	0.39	0.97
0.74	0.58	0.86	2.60	1.45	4.66	0.43	0.23	0.82

continued

TABLE 73 *Individual accuracy results of cervicovaginal fetal fibronectin (fFN) in predicting spontaneous preterm birth among symptomatic women with threatened preterm labour (continued)*

Authors	Outcome	TP	FP	FN	TN	sens	sens_lb	sens_ub
Langer[130]	37	10	8	8	35	0.56	0.31	0.78
Lockwood[104]	37	49	10	11	47	0.82	0.70	0.90
Malak[117]	37	17	5	10	109	0.63	0.42	0.81
Peaceman[86]	37	61	81	78	505	0.44	0.35	0.53
Rizzo[133]	37	40	12	9	45	0.82	0.68	0.91
Rozenberg[134]	37	14	17	6	39	0.70	0.46	0.88
Stevens[136]	37	32	20	37	86	0.46	0.34	0.59
Calda[126]	37	19	13	2	50	0.90	0.70	0.99
Giles[111]	37	12	33	7	99	0.63	0.38	0.84
Sakai[119]	37	26	12	36	42	0.42	0.30	0.55
Vetr[136]	37	5	11	4	26	0.56	0.21	0.86
Chuileannain[124]	37	13	7	1	49	0.93	0.66	1.00
Dolinska[132]	37	28	8	10	69	0.74	0.57	0.87
Mansouri[131]	37	13	12	12	53	0.52	0.31	0.72
Topete[127]	37	24	4	10	36	0.71	0.53	0.85
Vercoustre[106]	37	12	21	1	44	0.92	0.64	1.00
Lopez[114]	37	17	3	31	34	0.35	0.22	0.51

FN, false negative; FP, false positive; lb, lower bound; LR,+, likelihood ratio for positive test; LR–, likelihood ratio for negative test; sens, sensitivity; spec, specificity; TN, true negative; TP, true positive; ub, upper bound.

specs	spec_lb	spec_ub	LR+	LR+_lb	LR+_ub	LR–	LR-_lb	LR–_ub
0.81	0.67	0.92	2.99	1.41	6.32	0.55	0.32	0.93
0.82	0.70	0.91	4.66	2.62	8.28	0.22	0.13	0.38
0.96	0.90	0.99	14.36	5.81	35.47	0.39	0.24	0.63
0.86	0.83	0.89	3.17	2.41	4.18	0.65	0.56	0.76
0.79	0.66	0.89	3.88	2.31	6.52	0.23	0.13	0.43
0.70	0.56	0.81	2.31	1.41	3.76	0.43	0.22	0.86
0.81	0.72	0.88	2.46	1.54	3.93	0.66	0.52	0.84
0.79	0.67	0.89	4.38	2.65	7.26	0.12	0.03	0.45
0.75	0.67	0.82	2.53	1.61	3.97	0.49	0.27	0.89
0.78	0.64	0.88	1.89	1.06	3.37	0.75	0.58	0.96
0.70	0.53	0.84	1.87	0.87	4.02	0.63	0.30	1.35
0.88	0.76	0.95	7.43	3.66	15.08	0.08	0.01	0.54
0.90	0.81	0.95	7.09	3.58	14.04	0.29	0.17	0.50
0.82	0.70	0.90	2.82	1.49	5.31	0.59	0.39	0.90
0.90	0.76	0.97	7.06	2.72	18.34	0.33	0.19	0.56
0.68	0.55	0.79	2.86	1.94	4.20	0.11	0.02	0.75
0.92	0.78	0.98	4.37	1.38	13.80	0.70	0.56	0.88

TABLE 74 *Individual accuracy results of cervicovaginal fetal fibronectin (fFN) in predicting spontaneous preterm birth among asymptomatic antenatal women*

Authors	Outcome	TP	FP	FN	TN	sens	sens_lb	sens_ub
34 weeks' gestation								
Arinami[94]	34	1	1	4	432	0.20	0.01	0.72
Heath[88]	34	15	167	30	4934	0.33	0.20	0.49
Chang[95]	34	3	2	3	226	0.50	0.12	0.88
Goldenberg[96]	34	13	144	33	1680	0.28	0.16	0.43
Goldenberg[97]	34	29	88	98	2714	0.23	0.16	0.31
Goldenberg[83]	34	79	457	331	5641	0.19	0.16	0.23
Hux[98]	34	3	5	1	45	0.75	0.19	0.99
37 weeks' gestation								
Arinami[94]	37	1	1	15	421	0.06	0.00	0.30
Crane[99]	37	1	34	8	97	0.11	0.00	0.48
Faron[87]	37	4	6	11	134	0.27	0.08	0.55
Hellemans[89]	37	6	18	4	105	0.60	0.26	0.88
Chang[95]	37	3	2	15	214	0.17	0.04	0.41
Garcia[101]	37	22	9	5	227	0.81	0.62	0.94
Goldenberg[96]	37	118	418	675	5297	0.15	0.12	0.18
Goldenberg[97]	37	24	133	144	1569	0.14	0.09	0.21
Greenhagen[83]	37	5	16	3	84	0.63	0.24	0.91
Inglis[103]	37	2	11	9	51	0.18	0.02	0.52
Lockwood[104]	37	30	108	19	272	0.61	0.46	0.75
Ruiz[103]	37	0	8	6	62	0.00	0.00	0.46
DiStefano[100]	37	4	8	2	46	0.67	0.22	0.96
Zamora[84]	37	4	13	1	15	0.80	0.28	0.99
Vercoustre[106]	37	1	6	0	58	1.00	0.03	1.00

FN, false negative; FP, false positive; lb, lower bound; LR,+, likelihood ratio for positive test; LR–, likelihood ratio for negative test; sens, sensitivity; spec, specificity; TN, true negative; TP, true positive; ub, upper bound.

specs	spec_lb	spec_ub	LR+	LR+_lb	LR+_ub	LR–	LR–_lb	LR–_ub
1.00	0.99	1.00	86.60	6.26	1198.92	0.80	0.52	1.24
0.97	0.96	0.97	10.18	6.56	15.80	0.69	0.56	0.85
0.99	0.97	1.00	57.00	11.57	280.92	0.50	0.23	1.12
0.92	0.91	0.93	3.58	2.20	5.82	0.78	0.65	0.93
0.97	0.96	0.97	7.27	4.97	10.63	0.80	0.72	0.88
0.93	0.92	0.93	2.57	2.07	3.19	0.87	0.83	0.92
0.90	0.78	0.97	7.50	2.74	20.51	0.28	0.05	1.52
1.00	0.99	1.00	26.38	1.73	402.99	0.94	0.83	1.07
0.74	0.66	0.81	0.43	0.07	2.78	1.20	0.93	1.54
0.96	0.91	0.98	6.22	1.97	19.60	0.77	0.56	1.04
0.85	0.78	0.91	4.10	2.11	7.95	0.47	0.22	1.00
0.99	0.97	1.00	18.00	3.21	100.86	0.84	0.68	1.03
0.96	0.93	0.98	21.37	10.98	41.57	0.19	0.09	0.42
0.93	0.92	0.93	2.03	1.68	2.46	0.92	0.89	0.95
0.92	0.91	0.93	1.83	1.22	2.74	0.93	0.87	0.99
0.84	0.75	0.91	3.91	1.94	7.87	0.45	0.18	1.10
0.82	0.70	0.91	1.02	0.26	4.01	0.99	0.74	1.34
0.72	0.67	0.76	2.15	1.64	2.83	0.54	0.38	0.77
0.89	0.79	0.95	0.60	0.04	9.28	1.05	0.84	1.32
0.85	0.73	0.93	4.50	1.92	10.57	0.39	0.13	1.22
0.54	0.34	0.72	1.72	0.95	3.11	0.37	0.06	2.23
0.91	0.81	0.96	7.50	2.54	22.14	0.28	0.03	3.07

TABLE 75 *Characteristics of studies on test accuracy of cervicovaginal prolactin in predicting spontaneous preterm birth stratified according to population of antenatal asymptomatic women and symptomatic women with threatened preterm labour*

Authors	Year	Country	*n*	Study designs	Inclusion	Exclusion	Testing gestation (weeks)	Frequency of testing	Thresholds	Outcome (weeks' gestation)[a]
Asymptomatic women										
O'Brien[137]	1994	USA	40	Cohort Prospective Blinded Test described	Asymptomatic antenatal women	Rupture of membrane, fetal anomalies, vaginal bleeding, contraindication to tocolysis	24–32	Single	2.0 ng/ml	< 34
Koca[138]	1999	Turkey	40	Cohort Prospective Test described	Singleton pregnancies, threatened preterm labour	Rupture of membrane, fetal anomalies, contraindication to tocolysis	24–32	Single	1.5 ng/ml	< 37
Symptomatic women										
Jotterand[140]	1997	France	64	Cohort Prospective Blinded Test described	Singleton pregnancies, threatened preterm labour	Rupture of membrane, fetal anomalies, vaginal bleeding, fetal distress, placenta praevia, contraindication to tocolysis	21–34	Single	2.0 ng/ml	< 34, < 37
O'Brien[137]	1994	USA	40	Cohort Prospective Blinded Test described	Threatened preterm labour	Rupture of membrane, fetal anomalies, vaginal bleeding, contraindication to tocolysis	24–32	Single	2.0 ng/ml	Within 7 and 14 days of testing, < 34, < 37 weeks
Leylek[141]	1997	Turkey	66	Cohort Prospective Test described	Singleton pregnancies, threatened preterm labour		29–36	Single	50 ng/ml	Within 12 days of testing and < 37 weeks
Koca[138]	1999	Turkey	35	Cohort Prospective Test described	Singleton pregnancies, threatened preterm labour	Rupture of membrane, fetal anomalies, contraindication to tocolysis	24–32	Single	1.5 ng/ml	< 34, < 37
Guvenal[139]	2001	Turkey	60	Case–control Retrospective Test described	Singleton pregnancies, threatened preterm labour	Rupture of membrane, fetal anomalies, contraindication to tocolysis, maternal hypertension, IUGR, fetal distress, placenta praevia	24–36	Single	1.8 ng/ml	37

IUGR, intrauterine growth restriction; PPROM, premature pre-labour rupture of membranes.
a Unless otherwise stated.

TABLE 76 *Individual accuracy results of cervicovaginal prolactin measurement in predicting spontaneous preterm birth among asymptomatic antenatal women and symptomatic women with threatened preterm labour*

Authors	Outcome	TP	FP	FN	TN	sens	sens_lb	sens_ub
Asymptomatic women								
O'Brien[137]	34	1	1	1	37	0.50	0.01	0.99
Koca[138]	37	5	9	1	25	0.83	0.36	1.00
Symptomatic women								
O'Brien[137]	7	6	14	3	17	0.67	0.30	0.93
O'Brien[137]	34	16	4	7	13	0.70	0.47	0.87
Koca[138]	34	10	7	3	15	0.77	0.46	0.95
Jotterand[140]	34	4	7	3	50	0.57	0.18	0.90
O'Brien[137]	37	17	3	11	9	0.61	0.41	0.78
Leylek[141]	37	19	0	15	32	0.56	0.38	0.73
Koca[138]	37	14	3	6	12	0.70	0.46	0.88
Guvenal[139]	37	4	2	4	50	0.50	0.16	0.84
Jotterand[140]	37	5	6	11	42	0.31	0.11	0.59

FN, false negative; FP, false positive; lb, lower bound; LR,+, likelihood ratio for positive test; LR–, likelihood ratio for negative test; sens, sensitivity; spec, specificity; TN, true negative; TP, true positive; ub, upper bound.

specs	spec_lb	spec_ub	LR+	LR+_lb	LR+_ub	LR–	LR–_lb	LR–_ub
0.97	0.86	1.00	19.00	1.76	205.15	0.51	0.13	2.06
0.74	0.56	0.87	3.15	1.62	6.12	0.23	0.04	1.37
0.55	0.36	0.73	1.48	0.81	2.70	0.61	0.23	1.62
0.76	0.50	0.93	2.96	1.20	7.26	0.40	0.20	0.78
0.68	0.45	0.86	2.42	1.22	4.77	0.34	0.12	0.95
0.88	0.76	0.95	4.65	1.81	11.97	0.49	0.21	1.16
0.75	0.43	0.95	2.43	0.87	6.76	0.52	0.30	0.92
1.00	0.89	1.00	36.77	2.31	584.80	0.45	0.31	0.65
0.80	0.52	0.96	3.50	1.22	10.02	0.38	0.18	0.77
0.96	0.87	1.00	13.00	2.83	59.76	0.52	0.26	1.04
0.88	0.75	0.95	2.50	0.88	7.10	0.79	0.56	1.11

TABLE 77 *Characteristic of studies on the accuracy of rapid test for phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) in cervical secretion as a predictor of spontaneous preterm birth stratified according to study population of asymptomatic antenatal women and symptomatic women who presented with threatened preterm labour*

Authors	Year	*n*	Study design	Inclusion criteria	Exclusion criteria	Testing gestation (weeks' gestation)	Reference standards (weeks' gestation)[a]
Asymptomatic women							
Bittar[144]	2001	53	Cohort Prospective Test described	Previous premature delivery, intact membrane, no vaginal bleeding, screened and treated for *Trichomonas*, *Candida* spp, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, group B streptococcus	Lost to follow-up	24–34, 3-weekly	< 37
Symptomatic women							
Shine[142]	2001	32	Cohort Prospective Test described	Threatened preterm labour, cervix < 2 cm dilated, intact membrane		24–36	< 34, < 37
Lembet[146]	2002	36	Cohort Prospective Blinded Test described	Threatened preterm labour	Uterine anomaly, congenital fetal abnormality, intrauterine growth restriction, pre-eclampsia, vaginal bleeding	20–36	< 48 h, < 7 days, and < 37
Choi[148]	2003	42	Cohort Prospective Test described	Threatened preterm labour		20–36	< 37
Park[149]	2003	50	Cohort Prospective Test described	Threatened preterm labour, cervix < 3 cm dilated, intact membrane		24–34	< 7 days, < 34, and < 37

Authors	Year	*n*	Study design	Inclusion criteria	Exclusion criteria	Testing gestation (weeks' gestation)	Reference standards (weeks' gestation)[a]
Akercan[147]	2004	45	Cohort Prospective Test described	Threatened preterm labour	Pre-eclampsia, ruptured membrane, vaginal bleeding, intrauterine growth restriction, congenital fetal abnormality, and uterine anomaly	24–36	< 37
Kwek[145]	2004	47	Cohort Consecutive Prospective Test described	Threatened preterm labour	Antepartum haemorrhage, cervix > 3 cm dilated, contraindication to tocolysis, insertion of cervical cerclage	24–34	< 48 h, < 7 days, and < 36
Elizur[150]	2005	35	Cohort Prospective Blinded Test described	Threatened preterm labour		24–35	< 48 hours, < 7 days, < 34, and < 37
Halle[152]	1999	93	Cohort Test described	Threatened preterm labour		23–32	< 37
Paternoster[151]	2005	135	Cohort	Threatened preterm labour	Pre-eclampsia, ruptured membrane, vaginal bleeding, intrauterine growth restriction, congenital fetal abnormality, and uterine anomaly	Not stated	< 37
Turnell[143]	2005	100	Cohort Consecutive	Threatened preterm labour		Not stated	< 37

a Unless otherwise stated.

TABLE 78 *Individual accuracy results of bedside rapid test cervicovaginal phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) in predicting spontaneous preterm birth among symptomatic women with threatened preterm labour*

Authors	Year	Quality	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR– (95% CI)
48 hours										
Lembet[146]	2002	4	14	4	1	17	0.88 (0.62–0.98)	0.81 (0.58–0.95)	4.59 (1.87–11.31)	0.15 (0.04–0.57)
Kwek[145]	2004	4	4	14	2	20	0.67 (0.22–0.96)	0.59 (0.41–0.75)	1.62 (0.81–3.24)	0.57 (0.18–1.82)
Elizur[150]	2005	4	0	7	0	29	0.50 (0.01–0.99)	0.79 (0.63–0.90)	2.38 (1.52–10.82)	0.63 (0.16–2.56)
								Summary LRs	2.53 (1.17–5.48)	0.32 (0.15–0.66)
7 days										
Lembet[146]	2002	4	15	3	1	17	0.94 (0.70–1.00)	0.85 (0.62–0.97)	6.25 (2.19–17.88)	0.07 (0.01–0.49)
Park[149]	2003	3	11	10	2	27	0.85 (0.55–0.98)	0.73 (0.56–0.86)	3.13 (1.76–5.58)	0.21 (0.06–0.77)
Kwek[145]	2004	4	10	8	2	20	0.83 (0.52–0.98)	0.71 (0.51–0.87)	2.92 (1.54–5.52)	0.23 (0.06–0.84)
Elizur[150]	2005	4	0	7	0	29	0.50 (0.01–0.99)	0.79 (0.63–0.90)	2.38 (0.52–10.82)	0.63 (0.16–2.56)
								Summary LRs	3.29 (2.24–4.83)	0.20 (0.10–0.41)
34 weeks										
Shine[142]	2001	3	5	8	0	19	1.00 (0.48–1.00)	0.70 (0.50–0.86)	3.02 (1.64–5.56)	0.12 (0.01–1.72)
Park[149]	2003	3	9	12	2	27	0.82 (0.48–0.98)	0.69 (0.52–0.83)	2.66 (1.54–4.60)	0.26 (0.07–0.94)
Elizur[150]	2005	4	1	6	0	29	1.00 (0.03–1.00)	0.83 (0.66–0.93)	4.15 (1.44–11.99)	0.31 (0.03–3.38)
								Summary LRs	2.96 (2.02–4.33)	0.22 (0.08–0.64)
37 weeks										
Halle[152]	1999	2	22	11	6	54	0.79 (0.59–0.92)	0.83 (0.72–0.91)	4.64 (2.62–8.23)	0.26 (0.13–0.53)
Shine[142]	2001	3	8	5	2	17	0.80 (0.44–0.97)	0.77 (0.55–0.92)	3.52 (1.53–8.08)	0.26 (0.07–0.91)
Lembet[146]	2002	4	17	1	2	16	0.89 (0.67–0.99)	0.94 (0.71–1.00)	15.21 (2.26–102.48)	0.11 (0.03–0.42)
Choi[148]	2003	3	5	17	2	18	0.71 (0.29–0.96)	0.51 (0.34–0.69)	1.47 (0.82–2.62)	0.56 (0.16–1.87)
Park[149]	2003	3	17	1	5	24	0.77 (0.55–0.92)	0.96 (0.80–1.00)	19.32 (2.79–133.58)	0.24 (0.11–0.51)
Akercan[147]	2004	3	11	4	3	27	0.79 (0.49–0.95)	0.87 (0.70–0.96)	6.09 (2.34–15.82)	0.25 (0.09–0.68)
Kwek[145]	2004	4	14	4	5	17	0.74 (0.49–0.91)	0.81 (0.58–0.95)	3.87 (1.54–9.72)	0.33 (0.15–0.71)
Elizur[150]	2005	4	4	3	2	6	0.67 (0.22–0.96)	0.67 (0.30–0.93)	2.00 (0.68–5.91)	0.50 (0.15–1.70)
Paternoster[151]	2005	1	9	9	4	86	0.69 (0.39–0.91)	0.91 (0.83–0.96)	7.31 (3.56–15.0)1	0.34 (0.15–0.77)
								Summary LRs	4.26 (2.54–7.17)	0.28 (0.20–0.38)

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TABLE 79 *Characteristics of the included studies on accuracy of maternal serum α-fetoprotein (MSAFP) testing in predicting spontaneous preterm birth for asymptomatic pregnant women*

Authors	Year	Country	*n*	Study designs	Inclusion	Exclusion	Testing gestation (weeks')	Frequency of testing	Thresholds	Outcome (weeks' gestation)
Goldenberg[159]	2001	USA	2929	Cohort Prospective Blinded Test described	Singleton pregnancies	Pregnant women with cervical dilatation > 2 cm (nulliparous) and > 3 cm (multiparous), placenta praevia, fetal anomaly	23–24	Single	90th centile	< 32, < 35
Tanaka[166]	1994	Japan	1097	Cohort Consecutive Prospective Test described	Singleton pregnancies	Fetal and chromosomal abnormalities	18–20	Single	2.0 MoM	< 37
Simpson[164]	1995	USA	650	Cohort Prospective Blinded Test described	Singleton pregnant women who provided specimen on the two specified occasions	Congenital anomaly	15–20, 24–36	Single	2.0 MoM	< 37
Dugoff[157]	2005	USA	33,145	Cohort Prospective Test described	Singleton gestation, women > 16 years	Fetal chromosomal or structural abnormalities	15–19	Single	2.0 MoM	< 32
Morssink[162]	1995	Netherlands	7992	Cohort Prospective Test described	Singletons who underwent neural tube or Down's syndrome screening	Congenital anomaly, delivery before 25 weeks' gestation, insulin-dependent diabetes mellitus	15–20	Single	2.5 MoM	< 37
Davisa[156]	1992	USA	843	Cohort Prospective Test described	Singleton pregnancies	Non-viable pregnancy, stillbirths, fetal anomaly	14–22	Single	2.5 MoM	< 37
Waller[168]	1996	USA	51,008	Cohort Retrospective Test described	Singleton pregnancies	Fetal anomaly, fetal death, multiple gestations, (non-lethal chromosomal abnormalities might have been included)	15–19	Single	2.0, 2.5 MoM	< 28, < 32, < 34, < 37
Spencer[165]	2000	UK	27,129	Case–control Prospective Test described	Singleton pregnancies	Fetal anomaly, chromosomal abnormality, pregnancy termination, loss before 24 weeks' gestation	14–18	Single	2.0 MoM	< 35, < 37

continued

TABLE 79 *Characteristics of the included studies on accuracy of maternal serum α-fetoprotein (MSAFP) testing in predicting spontaneous preterm birth for asymptomatic pregnant women*

Authors	Year	Country	*n*	Study designs	Inclusion	Exclusion	Testing gestation (weeks')	Frequency of testing	Thresholds	Outcome (weeks' gestation)
Yaron[171]	1999	USA	20,982	Cohort Retrospective Test described	Singleton pregnancies	Fetal anomaly, chromosomal abnormality	14–22	Single	2.5 MoM	< 37
Hsieh[161]	1997	Taiwan	5885	Cohort Retrospective Test described	Singleton pregnancies	Multiple gestation, diabetes mellitus, fetal and chromosomal abnormalities	14–22	Single	2.0 MoM	< 37
[a]Davis[156]	1992	USA	5555	Cohort Retrospective Test described	Singleton pregnancies	Non-viable pregnancy, stillbirths, fetal anomaly	14–22	Single	2.5 MoM	<37
Wenstorm[169]	1996	USA	4574	Cohort Retrospective Test described	Singleton pregnancies	Fetal and chromosomal abnormality	14–20	Single	2.5 MoM	<37
Brazerol[154]	1994	USA	776	Cohort Retrospective Test described	Singleton pregnancies	Fetal anomaly, oligohydramnios, fetal death	15–20	Single	2.0 MoM	<28, <37
Duric[158]	2002	Croatia	672	Cohort Retrospective Test described	Singleton pregnancies	Fetal chromosomal or structural abnormalities	15–22	Single	2.02 MoM	37

Authors	Year	Country	*n*	Study designs	Inclusion	Exclusion	Testing gestation (weeks')	Frequency of testing	Thresholds	Outcome (weeks' gestation)
Sharara[163]	1995	Qatar	360	Case–control Prospective Test described	Singleton pregnancies	Fetal anomaly, chromosomal abnormality, diabetes mellitus, pre-existing hypertension, threatened miscarriage, molar pregnancy	16–18	Single	2.5 MoM	37
Akinbiyi[153]	1996	UK	300	Case–control Retrospective Test described	Singleton pregnancies	Fetal and chromosomal abnormality	16–18	Single	2.0 MoM	37
Cho[155]	1997	USA	255	Case–control Prospective Test described	Singleton pregnancies	Non-viable pregnancies, fetal anomaly, chromosomal abnormality	14–20	Single	2.5 MoM	37
Williams[170]	1992	USA	412	Case–control Retrospective Test described	Singleton pregnancies	Fetal anomaly, chromosomal abnormality, fetal death	14–20	Single	2.0 MoM	37
Hamilton[160]	1985	USA	286	Case–control Retrospective Test described	Singleton pregnancies	Congenital anomaly	16–20	Single, twice	2.5 MoM	< 34, < 37
Wald[167]	1977	UK	188	Case–control Retrospective Test described	Singleton pregnancies	Congenital abnormalities	14–22	Single	3.0 MoM	37

a Initial retrospective study consisted of 5555 pregnant women, followed by a prospective study on 843 women.

TABLE 80 *Individual accuracy results of maternal serum α-fetoprotein (MSAFP) testing in predicting spontaneous preterm birth among antenatal asymptomatic women*

Authors	Threshold (MoM)[a]	Outcome (weeks' gestation)	TP	FP	FN	TN	sens	sens_lb
Goldenberg[159]	90th centile	32	18	184	32	2695	0.36	0.23
Goldenberg[159]	90th centile	35	45	389	82	2490	0.35	0.27
Tanaka[166]	2.0	37	8	65	69	955	0.10	0.05
[b]Simpson[164]	2.0	37	8	119	34	489	0.19	0.09
[c]Simpson[164]	2.0	37	4	62	38	546	0.10	0.03
Dugoff[157]	2.0	32	28	531	229	32,357	0.11	0.07
Morssink[162]	2.5	37	10	60	467	7455	0.02	0.01
Davis[156]	2.5	37	29	3	73	738	0.28	0.20
Waller[168]	2.0	28	48	2418	237	48,305	0.17	0.13
Waller[168]	2.5	28	21	629	264	50,094	0.07	0.05
Waller[168]	2.0	32	118	2348	576	47,966	0.17	0.14
Waller[168]	2.5	32	47	603	647	49,711	0.07	0.05
Waller[168]	2.0	34	227	2239	1149	47,393	0.16	0.15
Waller[168]	2.5	34	79	571	1297	49,061	0.06	0.05
Waller[168]	2.0	37	499	1967	3212	45,330	0.13	0.12
Waller[168]	2.5	37	158	492	3553	46,805	0.04	0.04
Spencer[165]	2.0	35	57	548	607	25,917	0.09	0.07
Spencer[165]	2.0	37	123	482	1429	25,095	0.08	0.07
Yaron[171]	2.5	37	9	75	757	20,141	0.01	0.01
Hsieh[161]	2.0	37	23	153	329	5380	0.07	0.04
Davis[156]	2.5	37	87	19	393	5056	0.18	0.15
Wenstorm[169]	2.5	37	62	99	609	3804	0.09	0.07
Brazerol[154]	2.0	28	6	51	9	710	0.40	0.16
Brazerol[154]	2.0	37	4	53	37	682	0.10	0.03
Duric[158]	2.0	37	1	39	32	601	0.03	0.00
Sharara[163]	2.5	37	18	102	20	220	0.47	0.31
Akinbiyi[153]	2.0	37	9	91	4	196	0.69	0.39
Cho[155]	2.5	37	37	80	16	122	0.70	0.56
Williams[170]	2.0	37	43	158	23	188	0.65	0.52
[d]Hamilton[160]	2.5	34	19	81	1	185	0.95	0.75
[d]Hamilton[160]	2.5	37	26	74	6	180	0.81	0.64
Hamilton[160]	2.5	34	9	78	1	185	0.90	0.55
Hamilton[160]	2.5	37	18	68	6	180	0.75	0.53
Wald[167]	3.0	37	23	4	71	90	0.24	0.16

FN, false negative; FP, false positive; lb, lower bound; LR,+, likelihood ratio for positive test; LR–, likelihood ratio for negative test; sens, sensitivity; spec, specificity; TN, true negative; TP, true positive; ub, upper bound.
Unless otherwise stated.
a Tested at 15–20 weeks' gestation.
b Tested at 24–36 weeks' gestation.
c Tested twice.

sens_ub	specs	spec_lb	spec_ub	LR+	LR+_lb	LR+_ub	LR–	LR–_lb	LR–_ub
0.51	0.94	0.93	0.94	5.63	3.79	8.36	0.68	0.56	0.84
0.44	0.86	0.85	0.88	2.62	2.04	3.38	0.75	0.66	0.85
0.19	0.94	0.92	0.95	1.63	0.81	3.27	0.96	0.89	1.03
0.34	0.80	0.77	0.84	0.97	0.51	1.85	1.01	0.86	1.17
0.23	0.90	0.87	0.92	0.93	0.36	2.44	1.01	0.91	1.12
0.15	0.98	0.98	0.99	6.75	4.71	9.67	0.91	0.87	0.95
0.04	0.99	0.99	0.99	2.63	1.35	5.10	0.99	0.97	1.00
0.38	1.00	0.99	1.00	70.23	21.78	226.38	0.72	0.64	0.81
0.22	0.95	0.95	0.95	3.53	2.72	4.59	0.87	0.83	0.92
0.11	0.99	0.99	0.99	5.94	3.91	9.03	0.94	0.91	0.97
0.20	0.95	0.95	0.96	3.64	3.08	4.31	0.87	0.84	0.90
0.09	0.99	0.99	0.99	5.65	4.24	7.53	0.94	0.92	0.96
0.19	0.95	0.95	0.96	3.66	3.23	4.15	0.87	0.85	0.90
0.07	0.99	0.99	0.99	4.99	3.97	6.28	0.95	0.94	0.97
0.15	0.96	0.96	0.96	3.23	2.95	3.55	0.90	0.89	0.91
0.05	0.99	0.99	0.99	4.09	3.43	4.88	0.97	0.96	0.97
0.11	0.98	0.98	0.98	4.15	3.19	5.39	0.93	0.91	0.96
0.09	0.98	0.98	0.98	4.21	3.47	5.09	0.94	0.92	0.95
0.02	1.00	1.00	1.00	3.17	1.59	6.30	0.99	0.98	1.00
0.10	0.97	0.97	0.98	2.36	1.55	3.61	0.96	0.93	0.99
0.22	1.00	0.99	1.00	48.41	29.74	78.82	0.82	0.79	0.86
0.12	0.97	0.97	0.98	3.64	2.68	4.95	0.93	0.91	0.95
0.68	0.93	0.91	0.95	5.97	3.04	11.71	0.64	0.43	0.97
0.23	0.93	0.91	0.95	1.35	0.51	3.56	0.97	0.88	1.08
0.16	0.94	0.92	0.96	0.50	0.07	3.51	1.03	0.97	1.10
0.64	0.68	0.63	0.73	1.50	1.03	2.17	0.77	0.56	1.05
0.91	0.68	0.63	0.74	2.18	1.46	3.26	0.45	0.20	1.02
0.82	0.60	0.53	0.67	1.76	1.38	2.25	0.50	0.33	0.76
0.76	0.54	0.49	0.60	1.43	1.16	1.76	0.64	0.45	0.90
1.00	0.70	0.64	0.75	3.12	2.53	3.84	0.07	0.01	0.49
0.93	0.71	0.65	0.76	2.79	2.16	3.60	0.26	0.13	0.55
1.00	0.70	0.64	0.76	3.03	2.30	4.01	0.14	0.02	0.91
0.90	0.73	0.67	0.78	2.74	2.01	3.72	0.34	0.17	0.69
0.34	0.96	0.89	0.99	5.75	2.07	15.99	0.79	0.70	0.89

TABLE 81 *Characteristics of studies on test accuracy of maternal serum relaxin in predicting spontaneous preterm birth stratified according to population of antenatal asymptomatic women and symptomatic women with threatened preterm labour*

Authors	Year	Country	*n*	Study designs	Inclusion	Exclusion	Testing gestation (weeks)	Frequency of testing	Threshold	Outcome (weeks' gestation)
Asymptomatic women										
Weiss[173]	1993	USA	76	Cohort Prospective Consecutive Test described	All 18–42-year-old women who achieved singleton pregnancies from ovulatory induction either with or without IVF/ET	No previous history of preterm birth, uterine or fetal abnormalities, more than one major cervical surgery, no previous DES exposure, placenta praevia, pre-eclampsia	6–12	Serial	+3SD [a]	< 37
Vogel[176]	2006	USA	61	Cohort Prospective Consecutive Test described	Asymptomatic women with at least one previous late spontaneous miscarriage or early spontaneous preterm delivery between 16 and 30 weeks' gestation	Multiple gestation, PPROM, uterine or fetal abnormalities, threatened preterm labour	12–25	Single	406 mg/l	< 37
Goldenberg[159]	2001	USA	2929	Case–control Retrospective Blinded Test described	Singleton pregnancy	Cervical dilatation > 3 cm in multipara, > 2 cm in nullipara, PPROM, bulging membrane at cervical os, placenta praevia	24	Single	90th centile	< 32, < 35
Vogel[175]	2006	Denmark	483	Case–control Retrospective Test described	Singleton asymptomatic pregnancies	Multiple gestation, PPROM, fetal abnormalities, diabetes	18–24	Single	932 pg/ml	< 37
Symptomatic women										
Vogel[177]	2002	Denmark	34	Cohort Prospective Test described	Singleton pregnancy presenting with threatened preterm labour and intact membrane and without evidence of ripening cervix	Elevated blood pressure, women with major medical disease, vaginal bleeding	24–34	Single	300 pg/ml	< 34, < 37

DES, diethylstilbestrol; IVF/ET, in vitro fertilisation/embryo transfer; PPROM, premature pre-labour rupture of membranes.
a Standard deviation.

TABLE 82 *Individual accuracy results of maternal serum relaxin measurement in predicting spontaneous preterm birth among asymptomatic antenatal women and symptomatic women with threatened preterm labour*

Authors	Outcome (weeks' gestation)	TP	FP	FN	TN	sens	sens_lb	sens_ub
Asymptomatic women								
Weiss[173]	37	6	37	3	30	0.67	0.30	0.93
Vogel[176]	37	9	33	11	8	0.45	0.23	0.68
Vogel[175]	37	18	50	66	350	0.21	0.13	0.32
Goldenberg[159]	32	11	628	39	2251	0.22	0.12	0.36
Goldenberg[159]	35	43	595	84	2214	0.34	0.26	0.43
Symptomatic women								
Vogel[177]	34	1	7	2	24	0.33	0.01	0.91
Vogel[175]	37	2	6	8	18	0.20	0.03	0.56

FN, false negative; FP, false positive; lb, lower bound; LR,+, likelihood ratio for positive test; LR–, likelihood ratio for negative test; sens, sensitivity; spec, specificity; TN, true negative; TP, true positive; ub, upper bound.

specs	spec_lb	spec_ub	LR+	LR+_lb	LR+_ub	LR–	LR–_lb	LR–_ub
0.45	0.33	0.57	1.21	0.73	2.01	0.74	0.28	1.95
0.20	0.09	0.35	0.56	0.34	0.93	2.82	1.35	5.89
0.88	0.84	0.91	1.71	1.06	2.78	0.90	0.80	1.01
0.78	0.77	0.80	1.01	0.60	1.71	1.00	0.86	1.16
0.79	0.77	0.80	1.60	1.24	2.06	0.84	0.74	0.95
0.77	0.59	0.90	1.48	0.26	8.31	0.86	0.38	1.96
0.75	0.53	0.90	0.80	0.19	3.31	1.07	0.72	1.57

TABLE 83 *Characteristics of studies on test accuracy of corticotrophin-releasing hormone (CRH) in predicting spontaneous preterm birth stratified according to population of antenatal asymptomatic women and symptomatic women with threatened preterm labour*

Authors	Year	Country	Population	Quality of studies	Inclusion criteria	Exclusion criteria	Testing gestation *(weeks' gestation)*	Frequency of testing	Thresholds	Outcome *(weeks' gestation)*
Asymptomatic women										
Leung[181]	1999	Hong Kong	1014	Blinded Cohort Prospective Test described	Singleton pregnancies	Mid-trimester miscarriage	15–20	Single	1.9 MoM	< 34
[a]Berkowitz[178]	1996	USA	396	Cohort Prospective Test described	Asymptomatic Hispanic women	Multiple gestations, stillbirths, congenital malformation, iatrogenic preterm birth, women with chronic hypertension, pre-eclampsia	20–24 24–28 29–33 33–37	Serial	3.1, 41.3, 234, 665.7 pg/ml	< 37
Inder[180]	2001	USA	297	Cohort Prospective Test described	Antenatal women from a local area medical practice	None stated	26	Single[b]	50, 70, 90, 110, 130, 150 pmol/l	< 37
Goldenberg[159]	2001	USA	2929	Blinded Case–control Retrospective Test described	Singleton pregnancies	Fetal anomalies, chromosomal abnormalities, placenta praevia, cervical dilatation > 3 cm, or bulging membrane	23–24	Single	90th centile	< 32, < 35
Holzman[179]	2001	USA	304 (White), 181(Black)	Blinded Case–control Retrospective Test described	Antenatal patients at tertiary referral centre	Other ethnic groups beside black or white, multiple gestations, diabetes before pregnancy, chromosomal abnormalities	15–19	Single	1.0, 1.5 MoM	< 35
Symptomatic women										
Coleman[182]	2000	New Zealand	94	Blinded Cohort Prospective Test described	Non-diabetic singleton pregnancies presenting with preterm labour, intact membrane, and cervical dilatation < 3 cm	Fetal anomaly and chromosomal abnormality	24–36	Single	90th centile	< 10 days of testing and < 37

a Sample was collected weekly from 17–30 weeks' gestation but only the sample closest to 22 weeks' gestation was used in the analysis.
b Sample was collected weekly from 16–20 weeks' gestation but only the sample closest to 26 weeks' gestation was used in the analysis.

TABLE 81 *Individual accuracy results of maternal serum cortisol-releasing hormone (CRH) measurement in predicting spontaneous preterm birth among asymptomatic antenatal women and symptomatic women with threatened preterm labour*

Authors	Thresholds	Outcome (weeks' gestation)	TP	FP	FN	TN	sens	sens_lb
Asymptomatic women								
Leung[181]	1.9 MoM	34	8	217	3	786	0.73	0.39
Berkowitz[178]	3.1 pg/ml	37	4	25	41	326	0.09	0.02
Berkowitz[178]	41.3 pg/ml	37	11	71	34	280	0.24	0.13
Berkowitz[178]	234 pg/ml	37	13	71	32	280	0.29	0.16
Berkowitz[178]	665.7 pg/ml	37	9	74	36	277	0.20	0.10
Inder[180]	90 pmol/l	37	14	16	17	250	0.45	0.27
Inder[180]	70 pmol/l	37	17	29	14	237	0.55	0.36
Inder[180]	110 pmol/l	37	11	9	20	257	0.35	0.19
Inder[180]	130 pmol/l	37	8	6	23	260	0.26	0.12
Inder[180]	150 pmol/l	37	6	2	25	264	0.19	0.07
Inder[180]	50 pmol/l	37	21	60	10	206	0.68	0.49
Goldenberg[159]	90th centile	32	6	242	44	2637	0.12	0.05
Goldenberg[159]	90th centile	35	15	233	112	2569	0.12	0.07
Holzman[179]	1.0 MoM (Black)	35	33	78	8	62	0.80	0.65
Holzman[179]	1.0 MoM (White)	35	34	120	22	128	0.61	0.47
Holzman[179]	1.5 MoM (Black)	35	17	32	24	108	0.41	0.26
Holzman[179]	1.5 MoM (White)	35	16	48	40	200	0.29	0.17
Symptomatic women								
Coleman[182]	90th centile	10	6	12	7	69	0.46	0.19

FN, false negative; FP, false positive; lb, lower bound; LR,+, likelihood ratio for positive test; LR–, likelihood ratio for negative test; sens, sensitivity; spec, specificity; TN, true negative; TP, true positive; ub, upper bound.

sens_ub	specs	spec_lb	spec_ub	LR+	LR+_lb	LR+_ub	LR–	LR–_lb	LR–_ub
0.94	0.78	0.76	0.81	3.36	2.30	4.92	0.35	0.13	0.91
0.21	0.93	0.90	0.95	1.25	0.46	3.42	0.98	0.89	1.08
0.40	0.80	0.75	0.84	1.21	0.69	2.10	0.95	0.80	1.13
0.44	0.80	0.75	0.84	1.43	0.86	2.36	0.89	0.73	1.08
0.35	0.79	0.74	0.83	0.95	0.51	1.76	1.01	0.87	1.18
0.64	0.94	0.90	0.97	7.51	4.07	13.86	0.58	0.42	0.80
0.73	0.89	0.85	0.93	5.03	3.15	8.04	0.51	0.34	0.75
0.55	0.97	0.94	0.98	10.49	4.72	23.31	0.67	0.51	0.87
0.45	0.98	0.95	0.99	11.44	4.25	30.82	0.76	0.62	0.93
0.37	0.99	0.97	1.00	25.74	5.43	122.07	0.81	0.68	0.97
0.83	0.77	0.72	0.82	3.00	2.16	4.18	0.42	0.25	0.70
0.24	0.92	0.91	0.93	1.43	0.67	3.05	0.96	0.87	1.06
0.19	0.92	0.91	0.93	1.42	0.87	2.32	0.96	0.90	1.03
0.91	0.44	0.36	0.53	1.44	1.17	1.78	0.44	0.23	0.84
0.74	0.52	0.45	0.58	1.25	0.98	1.61	0.76	0.54	1.08
0.58	0.77	0.69	0.84	1.81	1.13	2.91	0.76	0.58	1.00
0.42	0.81	0.75	0.85	1.48	0.91	2.40	0.89	0.74	1.06
0.75	0.85	0.76	0.92	3.12	1.42	6.84	0.63	0.38	1.05

TABLE 85 *Characteristics of the included studies on accuracy of β-human chorionic gonadotrophin (β-hCG) testing in predicting spontaneous preterm birth for asymptomatic pregnant women and women who presented with threatened preterm labour*

Authors	Year	Country	*n*	Study designs	Inclusion	Exclusion	Testing gestation (weeks)	Frequency of testing	Threshold (MoM)	Outcome (weeks' gestation)
Yaron[197]	2002	Israel	1622	Cohort Consecutive Prospective Test described	Singleton pregnancies without fetal and chromosomal abnormalities	×	10–13	Single	≥1.0, ≥2.0, ≥3.0, ≥4.0, ≥5.0	< 37
Dugoff[157]	2005	USA	33,145	Cohort Consecutive Prospective Test described	Singleton pregnancies without fetal and chromosomal abnormalities	×	15–19	Single	> 2.0	< 32
Ong[194]	2000	UK	5297	Cohort Consecutive Prospective Test described	Singleton pregnancies without fetal and chromosomal abnormalities	×	10–14	Single	5th, 10th centile	< 34, < 37
Dugoff[157]	2005	USA	34,271	Cohort Prospective Test described	Singleton pregnancies without fetal and chromosomal abnormalities	×	10–14	Single	1st, 5th, and 10th centile	< 32, < 37
Morssink[162]	1995	Netherland	7992	Cohort Prospective Test described	Singleton pregnancies	Unknown pregnancy outcome, a congenital anomaly, delivery before 25 weeks of amenorrhea, or known insulin-dependent diabetes	15–20	Single	≥2.5	< 37
Chandra[187]	2003	Canada	8585	Cohort Prospective Test described	< 35 years, low-risk singleton pregnancies without fetal or chromosomal abnormalities	×	15–20	Single	≥2.0	< 37
Tanaka[166]	1994	Japan	1097	Cohort Consecutive Prospective Test described	Consecutive pregnant women in whom gestation was dated by ultrasonography, with singleton pregnancies	×	18–20	Single	≥2.0	< 37
Haddad[198]	1999	France	169	Cohort Retrospective Test described	IVF singleton pregnancies	No fetal or chromosomal abnormalities	6–7	Serial	90th centile	< 37

Authors	Year	Country	*n*	Study designs	Inclusion	Exclusion	Testing gestation (weeks)	Frequency of testing	Threshold (MoM)	Outcome (weeks' gestation)
Duric[158]	2002	Croatia	672	Cohort Retrospective Test described	< 35 years women with singleton pregnancies without fetal or chromosomal abnormalities	×	15–22	Single	≥2.02	< 37
Spencer[165]	2000	UK	26,918	Case–control Retrospective Test described	Control of singleton uncomplicated pregnancies outcome. Cases were those with spontaneous preterm delivery	×	14–18	Single	≥2.0	< 35, < 37
Lieppman[191]	1993	USA	460	Case–control Retrospective Test described	Non-diabetic women with singleton pregnancies between 15 and 18 weeks' gestation	Multiple gestations, diabetic pregnancies, fetal and chromosomal abnormalities	15–18	Single	≥2.0	< 37
Onderoglu[193]	1997	Turkey	562	Case–control Retrospective Test described	Singleton non-diabetic pregnancies with known outcomes	Fetal and chromosomal abnormalities or maternal serum α-fetoprotein > 2.0 MoM	15–20	Single	≥2.0	< 37
Hsieh[184]	1997	Taiwan	5885	Cohort Retrospective Test described	Taiwanese women under 35 years of age with singleton pregnancies without fetal or chromosomal abnormalities	×	14–22	Single	≥2.0	< 37
Wenstorm[195]	1994	USA	252	Case–control Retrospective Test described	Cases were singleton pregnancies without fetal or chromosomal abnormalities who underwent amniocentesis with matched control who did not have amniocentesis	×	15–20	Single	≥2.0	< 37
Gonen[189]	1992	Israel	493	Case–control Retrospective Test described	Cases were singleton pregnancies with confirmed gestational age	Fetal or chromosomal abnormalities and maternal serum α-fetoprotein > 2.5 MoM	16–20	Single	≥2.5	< 37
Yaron[171]	1999	Israel	45,565	Cohort Retrospective Test described	All singleton pregnancies screened for Down syndrome risks	Fetal or chromosomal abnormalities	14–22	Single	> 2.5	< 37

continued

TABLE 85 *Characteristics of the included studies on accuracy of β-human chorionic gonadotrophin (β-hCG) testing in predicting spontaneous preterm birth for asymptomatic pregnant women and women who presented with threatened preterm labour (continued)*

Authors	Year	Country	*n*	Study designs	Inclusion	Exclusion	Testing gestation (weeks)	Frequency of testing	Threshold (MoM)	Outcome (weeks' gestation)
Benn[185]	1996	USA	1079	Case–control Retrospective Test described	< 35 years, singleton pregnancies without diabetes mellitus, fetal and chromosomal abnormalities	×	15–22	Single	≥3.0	< 37
Brajenovic[186]	2004	Croatia	1507	Case–control Retrospective Test described	Singleton pregnancies without fetal or chromosomal abnormalities		15–20	Single	≥2.0	< 37
Lepage[190]	2003	Canada	2256	Case–control Retrospective Test described	Singleton pregnancies without fetal anomalies	×	15–20	Single	≥4.0	< 37
Liu[192]	1999	USA	72	Case–control Retrospective Test described	Unexplained elevated maternal serum hCG levels compared with controls with normal mshCG levels delivering during the same period	×	15–20	Not stated	≥2.0	< 36
Ramos[200]	2003	USA	86	Cohort Prospective Blinded Test described	Preterm labour, < 4 cm cervical dilatation, intact membrane	PPROM, presence of gross blood in vagina, cervical cerclage, fetal anomaly, IUGR, pre-eclampsia	24–34	Single	25 mIU/ml	<37
Gurbuz[199]	2004	Turkey	102	Cohort Prospective Test described	Preterm labour, < 3 cm cervical dilatation, intact membrane	Fetal compromise, placenta praevia, abruption, fetal anomaly, PPROM, pre-eclampsia.	25–35	Single	32 mIU/ml 42 mIU/ml 30 mIU/ml 33 mIU/ml 27 mIU/ml	<100 hours <100 hours < 7 days <14 days of testing, <35 and <37
Guvenal[139]	2001	Turkey	60	Case–control Prospective Test described	Singleton pregnancies without fetal or chromosomal abnormalities, cervical dilatation < 3 cm	Placenta praevia, vaginal bleeding, pre-eclampsia, hypertension, IUGR, fetal distress, rupture of membrane at presentation	24–36	Single	27.1 mIU/ml	<37

IUGR, intrauterine growth restriction; IVF, in vitro fertilisation; mshCG, maternal serum human chorionic gonadotrophin; PPROM, premature pre-labour rupture of membranes.

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TABLE 86 *Individual accuracy results of β-human chorionic gonadotrophin (β-hCG) testing in predicting spontaneous preterm birth among asymptomatic and symptomatic women with threatened preterm labour*

Authors	TP	FP	FN	TN	sens	sens_lb	sens_ub	specs	spec_lb	spec_ub	LR+	LR+_lb	LR+_ub	LR–	LR–_lb	LR–_ub
Asymptomatic women, threshold 2.0 MoM, < 37 weeks' gestation																
Yaron[197]	32	1246	12	332	0.73	0.57	0.85	0.21	0.19	0.23	0.92	0.77	1.11	1.30	0.79	2.12
Chandra[187]	203	637	1352	6393	0.13	0.11	0.15	0.91	0.90	0.92	1.44	1.24	1.67	0.96	0.94	0.98
Duric[158]	11	97	23	541	0.32	0.17	0.51	0.85	0.82	0.87	2.13	1.27	3.58	0.80	0.63	1.01
Tanaka[166]	8	65	69	955	0.10	0.05	0.19	0.94	0.92	0.95	1.63	0.81	3.27	0.96	0.89	1.03
Brajenovic[186]	5	116	44	1342	0.10	0.03	0.22	0.92	0.91	0.93	1.28	0.55	3.00	0.98	0.89	1.07
Lieppman[191]	25	200	9	226	0.74	0.56	0.87	0.53	0.48	0.58	1.57	1.25	1.96	0.50	0.28	0.88
Onderoglu[193]	27	54	39	442	0.41	0.29	0.54	0.89	0.86	0.92	3.76	2.56	5.52	0.66	0.54	0.81
Shieh[184]	33	383	329	5140	0.09	0.06	0.13	0.93	0.92	0.94	1.31	0.94	1.85	0.98	0.94	1.01
Spencer[165]	250	3713	1302	22,541	0.16	0.14	0.18	0.86	0.85	0.86	1.14	1.01	1.28	0.98	0.96	1.00
Wenstorm[195]	4	18	37	193	0.10	0.03	0.23	0.91	0.87	0.95	1.14	0.41	3.20	0.99	0.88	1.10
[a]Dugoff[157]	54	278	2137	30,926	0.02	0.02	0.03	0.99	0.99	0.99	2.77	2.07	3.69	0.98	0.98	0.99
[b]Dugoff[157]	187	1485	2004	29,719	0.09	0.07	0.10	0.95	0.95	0.95	1.79	1.55	2.07	0.96	0.95	0.97
[c]Dugoff[157]	329	2945	1862	28,259	0.15	0.14	0.17	0.91	0.90	0.91	1.59	1.43	1.77	0.94	0.92	0.96
Symptomatic women, threshold 30 mIU/ml, within 7 days of testing																
Gurbuz[199]	56	7	2	37	0.97	0.88	1.00	0.84	0.70	0.93	6.07	3.07	11.99	0.04	0.01	0.16
Symptomatic women, threshold 30 mIU/ml, < 37 weeks' gestation																
Ramos[200]	18	17	10	41	0.64	0.44	0.81	0.71	0.57	0.82	2.19	1.35	3.56	0.51	0.30	0.85
Gurbuz[199]	61	10	19	12	0.76	0.65	0.85	0.55	0.32	0.76	1.68	1.04	2.69	0.44	0.25	0.75
Guvenal[139]	7	18	1	34	0.88	0.47	1.00	0.65	0.51	0.78	2.53	1.60	3.99	0.19	0.03	1.21

FN, false negative; FP, false positive; lb, lower bound; LR,+, likelihood ratio for positive test; LR–, likelihood ratio for negative test; sens, sensitivity; spec, specificity; TN, true negative; TP, true positive; ub, upper bound.
a Threshold 0.28 MoM (i.e. 1st centile).
b Threshold 0.42 MoM (5th centile).
c Threshold 0.52 MoM (10th centile).

TABLE 87 *Characteristics of studies on test accuracy of estriol in predicting spontaneous preterm birth stratified according to population of antenatal asymptomatic women and symptomatic women with threatened preterm labour*

Authors	Year	Country	*n*	Study designs	Inclusion
Asymptomatic women					
Heine[202]	2000	USA	601	Cohort Prospective Blinded Test described	Singleton gestation, women > 18 years
Dugoff[157]	2005	USA	33,145	Cohort Prospective Test described	Singleton gestation, women > 16 years
Yaron[196]	1999	USA	24,504	Cohort Retrospective Test described	All singleton pregnancies
Kim[203]	2000	Korea	1096	Cohort Test described	All singletons < 35 years old
Duric[158]	2003	Croatia	672	Cohort Retrospective Test described	Singleton pregnancies
Kowalczyk[204]	1998	USA	399	Cohort Retrospective Test described	Singleton pregnancies, <35 years old
Symptomatic women					
Heine[202]	2000	USA	115	Cohort Prospective Blinded Test described	Symptomatic with threatened preterm labour
McGregor[201]	1995	USA	190	Cohort Prospective Test described	Singleton pregnancies presenting with threatened preterm labour

IUGR, intrauterine growth restriction; PPROM, premature pre-labour rupture of membranes.
a Unless otherwise stated.

Exclusion	Testing gestation (weeks')	Frequency of testing	Threshold	Outcome (weeks' gestation)[a]
Placenta praevia, cerclage, PPROM, pre-eclampsia, medications known to affect hormone levels, planned Caesarean section, major congenital abnormalities, intrauterine growth restriction, fetal chromosomal and structural abnormalities, erythroblastosis fetalis, oral conditions that interfere with saliva collections, maternal medical complications	21–25	Single and twice (7 days apart)	2.1 ng/ml	37
Fetal chromosomal or structural abnormalities	15–19	Single	0.5 MoM	32
Fetal chromosomal or structural abnormalities	14–22	Single	0.5 MoM	37
Multiple pregnancies, diabetes mellitus, smoking abnormal α-fetoprotein and or human chorionic gonadotrophin	15–20	Single	0.75 MoM	37
Fetal chromosomal or structural abnormalities	15–22	Single	0.74 MoM	37
Elevated human chorionic gonadotrophin and/or α-fetoprotein	15–21	Single	0.75 MoM	37
Placenta praevia, tocolytics therapy, cerclage, PPROM, pre-eclampsia, medications known to affect hormone levels, planned Caesarean section, major congenital abnormalities, intrauterine growth restriction, fetal chromosomal and structural abnormalities, erythroblastosis fetalis, oral conditions that interfere with saliva collections, maternal medical complications	21–25	Single	1.4 ng/ml and 2.1 ng/ml	Within 14 days of testing
Fetal anomalies, IUGR	22–26	Single	2.1 ng/ml	37

TABLE 88 *Individual accuracy results of maternal estriol measurement in predicting spontaneous preterm birth among asymptomatic antenatal women and symptomatic women with threatened preterm labour*[a]

Authors	Thresholds	Outcome (weeks' gestation)[b]	TP	FP	FN	TN	sens	sens_lb	sens_ub
Asymptomatic women									
Heine[202]	2.1 ng/ml	37	10	46	13	532	0.43	0.23	0.66
[c]Heine[202]	2.1 ng/ml	37	13	128	10	450	0.57	0.34	0.77
Dugoff[157]	0.5 MoM	32	5	369	252	32,519	0.02	0.01	0.04
Yaron[196]	0.5 MoM	37	50	1688	865	21,901	0.05	0.04	0.07
Kim[203]	0.75 MoM	37	7	100	54	935	0.11	0.05	0.22
Duric[158]	0.74 MoM	37	12	104	22	534	0.35	0.20	0.54
Kowalczyk[204]	0.75 MoM	37	12	69	38	190	0.24	0.13	0.38
Symptomatic women									
Heine[202]	1.4 ng/ml	Within 14 days of testing	14	22	9	70	0.61	0.39	0.80
Heine[202]	2.1 ng/ml	Within 14 days of testing	7	1	16	91	0.30	0.13	0.53
McGregor[201]	2.1 ng/ml	37	16	53	6	115	0.73	0.50	0.89

FN, false negative; FP, false positive; lb, lower bound; LR,+, likelihood ratio for positive test; LR–, likelihood ratio for negative test; sens, sensitivity; spec, specificity; TN, true negative; TP, true positive; ub, upper bound.
a Single testing unless otherwise stated.
b Unless otherwise stated.
c Serial testing 7 days apart.

specs	spec_lb	spec_ub	LR+	LR+_lb	LR+_ub	LR–	LR–_lb	LR–_ub
0.92	0.90	0.94	5.46	3.18	9.40	0.61	0.43	0.88
0.78	0.74	0.81	2.55	1.73	3.77	0.56	0.35	0.89
0.99	0.99	0.99	1.73	0.72	4.15	0.99	0.97	1.01
0.93	0.93	0.93	0.76	0.58	1.00	1.02	1.00	1.03
0.90	0.88	0.92	1.19	0.58	2.44	0.98	0.89	1.07
0.84	0.81	0.86	2.17	1.33	3.53	0.77	0.60	0.99
0.73	0.68	0.79	0.90	0.53	1.54	1.04	0.87	1.23
0.76	0.66	0.84	2.55	1.56	4.16	0.51	0.31	0.87
0.99	0.94	1.00	28.00	3.62	216.39	0.70	0.54	0.92
0.68	0.61	0.75	2.31	1.64	3.24	0.40	0.20	0.79

TABLE 89 *Characteristic of studies on accuracy of maternal C-reactive protein (CRP) measurement in predicting spontaneous preterm birth*

Author	Year	*n*	Study quality	Gestation at testing (weeks)	Cut-off [ng/ml]	Reference standard
Amniotic fluid CRP in asymptomatic women						
Ghezzi[210]	2002	306	Cohort, blinding, test described	14–20	110	34 weeks' gestation
Ozer[213]	2005	141	Cohort, consecutive, prospective, test described	15–20	6.5	37 weeks' gestation
Blood serum CRP in asymptomatic women						
Hvilsom[212]	2002	484	Case–control, test described	14–18	7.6	37 weeks' gestation
Karinen[213]	2005	506	Case–control, test described	12–16	4.3	37 weeks' gestation
Rückhäberle[216]	1991	216	Cohort	Not reported	pos/neg	37 weeks' gestation
Blood serum CRP in symptomatic women						
Cammu[206]	1989	87	Cohort, consecutive, blinding, test described	22–35	12.5	7 days after testing 37 weeks' gestation
Cylwik[207]	1997	35	Cohort, retrospective, test described	> 24	10	37 weeks' gestation
Doods[208]	1987	34	Cohort, retrospective, test described	24–35	8	7 days after testing
Foulon[209]	1995	44	Cohort, consecutive, retrospective, test described	20–34	15	34 weeks' gestation
Handwerker[211]	1984	50	Cohort, consecutive, blinding, test described	24–34	0.8–1.0	7 days after testing
Mazor[214]	1993	48	Cohort, consecutive, test described	24–36	8	37 weeks' gestation
Potkul[205]	1985	40	Cohort, consecutive, blinding, test described	24–36	7	37 weeks' gestation
Winkler[217]	1987	98	Cohort, consecutive	Not reported	10	7 days after testing

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TABLE 90 *Sensitivity and specificity [with corresponding 95% confidence Intervals (CI)] of C-reactive protein (CRP) among individual studies in predicting spontaneous preterm birth according to type of tests, reference standards, and populations*

Author	Year	Cut-off (ng/ml)	TP	FP	FN	TN	Sensitivity	95% CI lower limit	95% CI upper limit	Specificity	95% CI lower limit	95% CI upper limit
Amniotic fluid CRP for predicting birth before 34 weeks' gestation												
Asymptomatic women												
Ghezzi[210]	2002	110	8	90	2	206	0.80	0.44	0.97	0.70	0.64	0.75
Amniotic fluid CRP for predicting birth before 37 weeks' gestation												
Asymptomatic women												
Ozer[215]	2005	6.5	13	27	1	100	0.93	0.66	0.99	0.79	0.72	0.85
Blood serum CRP for predicting birth within 7 days of testing												
Symptomatic women												
Cammu[206]	1989	12.5	9	1	2	41	0.82	0.48	0.98	0.98	0.87	1.00
Doods[208]	1987	8	17	4	3	10	0.85	0.62	0.97	0.71	0.42	0.92
Handwerker[211]	1984	0.8–1.0	11	4	2	33	0.85	0.55	0.98	0.89	0.75	0.97
Winkler[217]	1987	10	13	14	27	44	0.33	0.19	0.49	0.76	0.63	0.86
Blood serum CRP for predicting birth before 37 weeks' gestation												
Asymptomatic women												
Hvilsom[212]	2002	7.6	22	58	62	342	0.26	0.17	0.37	0.86	0.82	0.89
Karinen[213]	2005	4.3	36	90	68	312	0.35	0.26	0.46	0.78	0.73	0.82
Rückhäberle[216]	1991	pos/neg	39	20	66	91	0.37	0.28	0.47	0.82	0.74	0.89
Symptomatic women												
Cammu[206]	1989	12.5	14	19	7	47	0.67	0.43	0.85	0.71	0.59	0.82
Cylwik[207]	1997	10	2	4	3	26	0.40	0.05	0.85	0.87	0.69	0.96
[b]Foulon[209]	1995	15	3	2	5	34	0.38	0.09	0.76	0.94	0.81	0.99
Mazor[214]	1993	8	8	8	10	22	0.44	0.22	0.69	0.73	0.54	0.88
Potkul[205]	1985	7	14	2	11	13	0.56	0.35	0.76	0.87	0.60	0.98

FN, false negative; FP, false positive; TN, true negative; TP, true positive.
a Reference standard births < 34 weeks' gestation.

TABLE 91 *Likelihood ratios for positive (LR+) and negative (LR–) test results [with corresponding 95% Confidence Intervals (CI)] of C-reactive protein (CRP) in predicting spontaneous preterm birth among individual studies according to type of tests, reference standard and populations*

Author	Year	Cut-off (ng/ml)	LR+	95% CI lower limit	95% CI upper limit	LR–	95% CI lower limit	95% CI upper limit
Amniotic fluid CRP for predicting birth before 34 weeks' gestation								
Asymptomatic women								
Ghezzi[210]	2002	110	2.63	1.85	3.75	0.29	0.08	0.99
Ozer[215]	2005	6.5	4.37	3.03	6.29	0.09	0.014	0.60
Blood serum CRP for predicting birth within 7 days of testing								
Symptomatic women								
Cammu[206]	1989	12.5	34.36	4.86	243.09	0.19	0.05	0.65
Doods[208]	1987	8	2.98	1.27	6.95	0.21	0.07	0.63
Handwerker[211]	1984	0.8–1.0	7.83	3.01	20.32	0.17	0.05	0.62
Winkler[214]	1987	10	1.35	0.71	2.55	0.89	0.69	1.15
		Summary	*4.54*	*1.48*	*13.91*	*0.30*	*0.08*	*1.15*
Blood serum CRP for predicting birth before 37 weeks' gestation								
Asymptomatic women								
Hvilsom[212]	2002	7.6	1.81	1.17	2.78	0.86	0.76	0.98
Karinen[213]	2005	4.3	1.55	1.22	2.13	0.84	0.73	0.98
Rückhäberle[216]	1991	pos/neg	2.06	1.29	3.29	0.77	0.65	0.91
		Summary	*1.72*	*1.38*	*2.16*	*0.83*	*0.76*	*0.91*
Symptomatic women								
Cammu[206]	1989	12,5	2.32	1.43	3.76	0.47	0.25	0.87
Cylwik[207]	1997	10	3.00	0.73	12.27	0.69	0.33	1.44
[a]Foulon[209]	1995	15	6.75	1.34	34.00	0.66	0.38	1.14
Mazor[214]	1993	8	1.67	0.76	3.66	0.76	0.48	1.21
Potkul[205]	1985	7	4.20	1.10	15.98	0.51	0.31	0.82
		Summary	*2.29*	*1.57*	*3.35*	*0.60*	*0.46*	*0.79*

a Reference standard births < 34 weeks' gestation.
See Table 1 for patient characteristics.

TABLE 92 *Characteristics of the included studies on accuracy of interleukin-6 (I-L6) testing in predicting spontaneous preterm birth for asymptomatic pregnant women and symptomatic women who presented with threatened preterm labour, stratified according to specimen source*

Authors	Year	Country	*n*	Study design	Inclusion criteria	Exclusion criteria	Testing gestations	Frequency of testing	Thresholds	Outcome (weeks' gestation)[a]
Asymptomatic women										
Amniotic fluid										
Wenstorm[220]	1998	USA	482	Case–control Retrospective Test described	Singleton pregnancies that underwent amniocentesis for various reasons (e.g. prenatal diagnosis)	Aneuploidies, anomalies, pregnancy loss within 30 days of amniocentesis	14–18	Single	2.9 ng/ml	34, 37
Ghidini[222]	1997	USA	179	Case–control Retrospective Test described	Singleton uncomplicated pregnancy	Multiple gestations, uterine, fetal or neonatal abnormalities, cytogenetic evidence of karyotypical abnormalities	15–20	Single	1740 pg/ml	34
Cervicovaginal										
Lockwood[221]	1994	USA	161	Cohort Prospective Consecutive Blinding Test described	Singleton pregnancies, intact membrane, cervical dilatation < 3 cm	Unknown dates, placenta praevia, hydatidiform mole, major congenital anomaly, serious maternal medical complications	24–36	Serial 3–4 weekly	125 and 250 pg/ml	37
Inglis[103]	1994	USA	73	Cohort Prospective Consecutive Blinding Test described	All patients between 15 and 40 years old with singleton pregnancies	Congenital anomalies, placenta praevia, known genital or urinary tract infection, use of antibiotics within the past 7 days	20–36	Single	50 pg/ml	37
Goepfert[231]	2001	USA	250	Case–control Retrospective Blinding Test described	Singleton pregnancies, intact membrane, cervical dilatation < 3 cm	Placenta praevia, fetal abnormalities, maternal medical complications, uterine abnormalities	22–24	Single	305 pg/ml	35, 37

Authors	Year	Country	*n*	Study design	Inclusion criteria	Exclusion criteria	Testing gestations	Frequency of testing	Thresholds	Outcome (weeks' gestation)[a]
Symptomatic women										
Amniotic fluid										
Rizzo[227]	1996	Italy	92	Cohort Prospective Consecutive Blinding Test described	Singleton gestation in premature labour with intact membrane, cervical dilatation	Presence of other fetal or maternal complications, known genital or urinary infection, antibiotic use within the last 14 days	24–36	Single	50 pg/ml	37
Romero[230]	1993	USA	146	Cohort Prospective Consecutive Test described	Singleton pregnant women with threatened preterm labour	×	20–34	Single	0.5, 2.0 and 11.30 ng/ml	36
Coultrip[224]	1994	USA	89	Cohort Prospective Blinding Test described	Symptomatic women singleton pregnancies with intact membrane	×	20–36	Single	0.38, 0.617 and 1.13 ng/ml	Within 3 days of testing (0.38 ng/ml only), 37
Greig[238]	1993	USA	57	Cohort Prospective Blinding Test described	Singleton gestation in premature labour with intact membrane	Cervical dilatation > 4 cm, antibiotic treatment in the past 7 days, any medical condition requiring antibiotic treatment	24–34	Single	600 pg/ml	3
Greci[225]	1998	USA	53	Cohort Prospective Blinding Test described	Women who presented with threatened preterm labour and intact membrane	Vaginal bleeding, placenta praevia, abruption, multiple gestations, polyhydramnios, pre-eclampsia, cervical cerclage, known uterine or fetal anomalies	24–34	Single	7586 pg/ml	Within 2 and 7 days of testing

continued

TABLE 92 *Characteristics of the included studies on accuracy of interleukin-6 (I-L6) testing in predicting spontaneous preterm birth for asymptomatic pregnant women and symptomatic women who presented with threatened preterm labour, stratified according to specimen source*

Authors	Year	Country	*n*	Study design	Inclusion criteria	Exclusion criteria	Testing gestations	Frequency of testing	Thresholds	Outcome (weeks' gestation)[a]
Burrus[120]	1995	USA	18	Cohort Prospective Blinding Test described	Symptomatic women in first pregnancy, intact membrane cervical dilatation < 3 cm	Chorio-amnionitis, placental abruption.	24–34	Single	1500 pg/ml	48
Hillier[226]	1993	USA	50	Cohort Prospective Test described	Afebrile women who presented with threatened preterm labour with intact membrane	< 16 or > 40 years old, uterine or fetal abnormalities, multiple pregnancies, polyhydramnios, cervical cerclage, placenta praevia, abruption, hypertension, diabetes or had received antibiotics the previous week	23–34	Single	1500 pg/ml	Within 7 days of testing, 34
Silver[229]	1993	USA	29	Cohort Prospective Test described	Symptomatic women singleton pregnancies with intact membrane	Additional medical or obstetrical problems, e.g. diabetes, chronic hypertension, abruptio placentae	24–37	Single	400 and 500 ng/ml	37
Allbert[223]	1994	USA	23	Cohort Prospective Test described	Singleton gestation in premature labour with intact membrane	Fetal distress, IUGR, abruption, clinical amnionitis, substantial hemorrhage, fetal anomalies, or stillbirth	20–32	Single	20 ng/ml	Within 2 and 7 days of testing
Romero[218]	1993	USA	120	Cohort Test described	Singleton pregnant women with threatened preterm labour	Patients who received antibiotics before amniocentesis, abnormal GTT or diabetes mellitus	22–36	Single	11.30 ng/ml	37
Dudley[718]	1994	USA	75	Cohort Retrospective Test described	Women who presented with threatened preterm labour, intact membrane who delivered within 7 days of testing		×	Single	200 pg/ml	7

Authors	Year	Country	*n*	Study design	Inclusion criteria	Exclusion criteria	Testing gestations	Frequency of testing	Thresholds	Outcome (weeks' gestation)[a]
Romero[228]	1990	USA	56	Cohort Test described	Women admitted with threatened preterm labour and intact membrane		×	Single	46 ng/ml	35
Cervicovaginal										
Inglis[103]	1994	USA	38	Cohort Prospective Consecutive Blinding Test described	All pregnant women between 15 and 40 years, singleton, less than 37 weeks and in those who present within 7 days of testing	Fetal congenital anomalies, placenta praevia, known genital or UTI, use of antibiotics within 7 days of testing	24–37	Single	50 pg/ml	37
LaShay[90]	2000	USA	118	Cohort Prospective Blinding Test described	Singleton pregnancies, intact membrane, cervical dilatation < 3 cm	Coitus or digital vaginal examination within 24 h, vaginal bleeding, placenta praevia, placental abruption, polyhydramnios, pre-eclampsia, known uterine or fetal abnormalities	24–34	Single	100 pg/ml	37
Kurkinen-Raty[223]	2001	Finland	77	Cohort Prospective Consecutive Test described	Consecutive singleton pregnant women between 22 and 32 weeks' gestation who present within 7 days of testing	Coitus or digital vaginal examination within 24 h, vaginal bleeding, placenta praevia, placental abruption, polyhydramnios, pre-eclampsia, known uterine or fetal abnormalities	22–32	Single	61 ng/l	37
Trebeden[236]	2001	France	142	Cohort Prospective Test described	Pregnant women with threatened preterm labour and intact membrane	×	22–34	Single	20 pg/ml	Within 7 days of testing, 34
Holst[232]	2005	Sweden	91	Cohort Prospective Test described	Women with singleton pregnancy presenting with threatened preterm labour and intact membrane	Uterine and fetal abnormalities, vaginal bleeding, imminent delivery and fetal distress	22–34	Single	1.3 ng/ml	7

continued

TABLE 92 *Characteristics of the included studies on accuracy of interleukin-6 (I-L6) testing in predicting spontaneous preterm birth for asymptomatic pregnant women and symptomatic women who presented with threatened preterm labour, stratified according to specimen source*

Authors	Year	Country	*n*	Study design	Inclusion criteria	Exclusion criteria	Testing gestations	Frequency of testing	Thresholds	Outcome (weeks' gestation)[a]
Sozmen[235]	2005	Turkey	40	Cohort Prospective Test described	Singleton pregnancies, intact membrane, cervical dilatation < 3 cm	Vaginal bleeding, placenta praevia, abruption, intercourse within last 24 h, signs of intrauterine infection, polyhydramnios, IUGR, hypertension, diabetes, cervical cerclage, known uterine or fetal anomalies	28–36	Single	172 pg/ml	37
Lange[234]	2003	Germany	27	Cohort Prospective Test described	Singleton pregnancies, intact membrane, cervical dilatation < 3 cm	Multiple gestations	24–34	Single	20 pg/ml	Within 2 and 7 days of testing, 34
Serum										
Greig[238]	1997	USA	56	Cohort Prospective Blinded Test described	Pregnant women who presented to the clinic or hospital in suspected preterm labour	Refusal to participate, PPROM, multiple pregnancy, HIV infection, evidence of chorioamnionitis, UTI, pre-eclampsia, maternal age < 17 or > 40 years	22–34	Single	6 pg/ml	Within 5 days of testing
Alvarez-de-la-Rosa[237]	2000	Spain	49	Cohort Prospective Blinded Test described	Pregnant women who presented to the clinic or hospital in suspected preterm labour	Refusal to participate, multiple pregnancies, HIV infection, evidence of chorioamniontis or fetal distress	26–37	Single	10 pg/ml	Within 2 days of testing, 34

Authors	Year	Country	*n*	Study design	Inclusion criteria	Exclusion criteria	Testing gestations	Frequency of testing	Thresholds	Outcome (weeks' gestation)[a]
Turhan[239]	2000	Turkey	82	Cohort Prospective Test described	Singleton pregnancies with threatened preterm labour, intact membrane	Fetal or uterine abnormalities, diabetes mellitus, placenta praevia, bleeding consistent with placental abruption, cervical cerclage, pre-eclampsia, known or suspected maternal infectious disease, positive urine culture or known maternal medical condition leading to preterm delivery	24–36	Single	8.3 pg/ml	Within 2 and 7 days of testing
von Minckwitz[240]	2000	Germany	72	Cohort Prospective Test described	Singleton pregnancies with threatened preterm labour, intact membrane	Multiple gestation, diabetes mellitus, polyhydramnios, severe concomitant disease, clotting disorders, drug addictions	25–37	Single	4 pg/ml	24
Sozmen[235]	2005	Turkey	40	Cohort Prospective Test described	Singleton pregnancies, intact membrane, cervical dilatation < 3 cm	Vaginal bleeding, placenta praevia, abruption, intercourse within last 24 hours, signs of intrauterine infection, polyhydramnios, IUGR, hypertension, diabetes, cervical cerclage, known uterine or fetal anomalies	28–36	Single	5 pg/ml	37

GTT, glucose tolerance test; HIV, human immunodeficiency virus; IUGR, intrauterine growth restriction; PPROM, premature pre-labour rupture of membrane; UTI, urinary tract infection.
a Unless otherwise stated.

TABLE 93 *Individual accuracy results of interleukin-6 (IL6) testing in predicting spontaneous preterm birth among asymptomatic and symptomatic women with threatened preterm labour, stratified according to outcome (weeks' gestation) and specimen source*

Authors	TP	FP	FN	TN	sens	sens_lb	sens_ub
Asymptomatic women							
34 weeks							
[a]Wenstorm[220]	17	15	107	275	0.14	0.08	0.21
[a]Ghidini[222]	3	13	10	153	0.23	0.05	0.54
[b]Goepfert[231]	10	3	39	46	0.20	0.10	0.34
37 weeks							
[a]Wenstorm[220]	19	15	173	275	0.10	0.06	0.15
[b]Lockwood[221]	17	19	17	108	0.50	0.32	0.68
[b]Lockwood[221]	15	17	19	110	0.44	0.27	0.62
[b]Inglis[103]	1	10	10	52	0.09	0.00	0.41
[b]Goepfert[231]	25	12	100	113	0.20	0.13	0.28
Symptomatic women							
7–10 days							
[a]Grec[225]	17	4	3	29	0.85	0.62	0.97
[a]Hillier[226]	22	8	4	15	0.85	0.65	0.96
[a]Allbert[223]	4	0	1	18	0.80	0.28	0.99
[a]Dudley[718]	26	9	14	26	0.65	0.48	0.79
[b]Trebeden[236]	18	10	26	88	0.41	0.26	0.57
[b]Holst[232]	22	13	7	51	0.76	0.56	0.90
[b]Lange[234]	6	8	0	13	1.00	0.54	1.00
[c]Turhan[239]	36	5	20	21	0.64	0.50	0.77
34 weeks							
[a]Hillier[226]	28	2	4	15	0.88	0.71	0.96
[b]Trebeden[236]	24	4	54	60	0.31	0.21	0.42
[a]Lange[234]	7	7	0	13	1.00	0.59	1.00
[c]Alvarez-de-la-Rosa[237]	7	19	3	20	0.70	0.35	0.93
34 weeks							
[a]Rizzo[227]	18	0	34	40	0.35	0.22	0.49
[a]Coultrip[224]	38	5	9	37	0.81	0.67	0.91
[a]Silver[229]	8	2	5	14	0.62	0.32	0.86
[a]Romero[228]	11	19	0	90	1.00	0.72	1.00
[b]Inglis[103]	1	10	10	52	0.09	0.00	0.41
[b]LaShay[90]	21	59	13	25	0.62	0.44	0.78
[b]Kurkinen-Raty[233]	8	26	3	40	0.73	0.39	0.94
[c]Sozmen[235]	14	1	6	19	0.70	0.46	0.88
[c]Sozmen[235]	9	8	11	12	0.45	0.23	0.68

FN, false negative; FP, false positive; lb, lower bound; LR,+, likelihood ratio for positive test; LR–, likelihood ratio for negative test; sens, sensitivity; spec, specificity; TN, true negative; TP, true positive; ub, upper bound.
a Amniotic fluid specimen.
b Cervicovaginal specimen.
c Maternal serum specimen.

specs	spec_lb	spec_ub	LR+	LR+_lb	LR+_ub	LR–	LR–_lb	LR–_ub
0.95	0.92	0.97	2.65	1.37	5.14	0.91	0.84	0.98
0.92	0.87	0.96	2.95	0.96	9.04	0.83	0.62	1.13
0.94	0.83	0.99	3.33	0.98	11.38	0.85	0.72	0.99
0.95	0.92	0.97	1.91	1.00	3.67	0.95	0.90	1.00
0.85	0.78	0.91	3.34	1.96	5.70	0.59	0.42	0.83
0.87	0.79	0.92	3.30	1.84	5.90	0.65	0.47	0.88
0.84	0.72	0.92	0.56	0.08	3.97	1.08	0.87	1.35
0.90	0.84	0.95	2.08	1.10	3.96	0.88	0.80	0.98
0.88	0.72	0.97	7.01	2.75	17.90	0.17	0.06	0.49
0.65	0.43	0.84	2.43	1.36	4.36	0.24	0.09	0.61
1.00	0.81	1.00	28.50	1.78	456.57	0.26	0.06	1.03
0.74	0.57	0.88	2.53	1.38	4.64	0.47	0.30	0.75
0.90	0.82	0.95	4.01	2.02	7.96	0.66	0.51	0.85
0.80	0.68	0.89	3.73	2.21	6.33	0.30	0.16	0.58
0.62	0.38	0.82	2.40	1.37	4.23	0.12	0.01	1.72
0.81	0.61	0.93	3.34	1.48	7.53	0.44	0.30	0.66
0.88	0.64	0.99	7.44	2.01	27.52	0.14	0.06	0.36
0.94	0.85	0.98	4.92	1.80	13.46	0.74	0.63	0.87
0.65	0.41	0.85	2.63	1.44	4.79	0.10	0.01	1.45
0.51	0.35	0.68	1.44	0.86	2.41	0.59	0.22	1.58
1.00	0.91	1.00	28.62	1.78	461.04	0.66	0.54	0.80
0.88	0.74	0.96	6.79	2.95	15.64	0.22	0.12	0.40
0.88	0.62	0.98	4.92	1.26	19.29	0.44	0.22	0.90
0.83	0.74	0.89	5.41	3.55	8.22	0.05	0.00	0.76
0.84	0.72	0.92	0.56	0.08	3.97	1.08	0.87	1.35
0.30	0.20	0.41	0.88	0.65	1.19	1.28	0.75	2.20
0.61	0.48	0.72	1.85	1.15	2.95	0.45	0.17	1.20
0.95	0.75	1.00	14.00	2.03	96.62	0.32	0.16	0.62
0.60	0.36	0.81	1.13	0.55	2.32	0.92	0.54	1.56

TABLE 94 *Characteristics of the included studies on accuracy of interleukin-8 (IL-8) testing in predicting spontaneous preterm birth for asymptomatic pregnant women and symptomatic women who presented with threatened preterm labour*

Authors	Year	Country	*n*	Study designs	Inclusion criteria	Exclusion criteria	Testing gestation (weeks)	Frequency of testing	Thresholds	Outcomes (weeks' gestation)[a]
Asymptomatic women										
Sakai[243]	2004	Japan	4203	Cohort Prospective Blinding Test described	Asymptomatic women with singleton pregnancy and intact membrane	Preterm pre-labour rupture of membrane, threatened or impending miscarriage or preterm delivery, genital bleeding	20–28	Serial (2-weekly)	360 ng/ml	32, 34, 37
Sakai[244]	2004	Japan	501	Cohort Prospective Test described	Asymptomatic women with singleton pregnancy	Iatrogenic prematurity, fetal asphyxia, abruption, placenta praevia, pre-eclampsia	20–24	Single	377 ng/ml	37
Symptomatic women										
Kurkinen[233]	2001	Finland	77	Cohort Prospective Consecutive Test described	Consecutive singleton pregnant women between 22–32 weeks' gestation who presented with threatened preterm labour	Preterm pre-labour rupture of membrane, impending preterm delivery	22–32	Single	3739 ng/l	37
Holst[232]	2005	Sweden	91	Cohort Prospective Test described	Women with singleton pregnancy presenting with threatened preterm labour and intact membrane	Uterine and fetal abnormalities, vaginal bleeding, imminent delivery and fetal distress	22–34	Single	7.7 ng/ml	Within 7 days of testing
[b]Allbert[223]	1994	USA	23	Cohort Prospective Test described	Singleton gestation in premature labour with intact membrane	Fetal distress, intrauterine growth restriction, abruption, clinical amnionitis, substantial haemorrhage, fetal anomalies, or stillbirth	20–32	Single	15 ng/ml	Within 2 and 7 days of testing

a Unless otherwise stated.
b Amniotic fluid specimen.

TABLE 95 *Individual accuracy results of interleukin-8 (IL-8) testing in predicting spontaneous preterm birth among asymptomatic and symptomatic women with threatened preterm labour and stratified according to outcome (weeks' gestation)*[a]

Authors	Outcome (weeks' gestation)	TP	FP	FN	TN	sens	sens_lb	sens_ub	specs	spec_lb	spec_ub	LR+	LR+_lb	LR+_ub	LR–	LR–_lb	LR–_ub
Asymptomatic women																	
[b]Sakai[243]	32	7	838	11	3347	0.39	0.17	0.64	0.80	0.79	0.81	1.94	1.08	3.48	0.76	0.53	1.10
[b]Sakai[243]	34	12	833	15	3343	0.44	0.25	0.65	0.80	0.79	0.81	2.23	1.46	3.41	0.69	0.50	0.97
[b]Sakai[243]	37	38	807	101	3257	0.27	0.20	0.36	0.80	0.79	0.81	1.38	1.04	1.82	0.91	0.82	1.01
Sakai[243]	37	11	73	15	402	0.42	0.23	0.63	0.85	0.81	0.88	2.75	1.68	4.52	0.68	0.49	0.95
Symptomatic women																	
[c]Allbert[223]	2[d]	4	0	0	19	1.00	0.40	1.00	1.00	0.82	1.00	36.00	2.30	564.54	0.10	0.01	1.42
Holst[252]	7[d]	18	17	11	47	0.62	0.42	0.79	0.73	0.61	0.84	2.34	1.42	3.84	0.52	0.32	0.84
[c]Allbert[223]	7[d]	4	0	1	18	0.80	0.28	0.99	1.00	0.81	1.00	28.50	1.78	456.57	0.26	0.06	1.03
Kurkinen[233]	37	7	30	4	36	0.64	0.31	0.89	0.55	0.42	0.67	1.40	0.83	2.35	0.67	0.30	1.50

FN, false negative; FP, false positive; lb, lower bound; LR,+, likelihood ratio for positive test; LR–, likelihood ratio for negative test; sens, sensitivity; spec, specificity; TN, true negative; TP, true positive; ub, upper bound.

a Unless otherwise stated, testing was done on a single occasion and cervicovaginal samples of IL-8 were used.

b Serial testing.

c Amniotic fluid.

d Birth within the stated number of days of testing.

TABLE 96 *Characteristics of the included studies on accuracy of matrix metalloprotease-9 (MMP-9) testing in predicting spontaneous preterm birth in symptomatic women who presented with threatened preterm labour*

Authors	Year	Country	*n*	Sample	Study designs	Inclusion	Exclusion	Testing gestation (weeks)	Frequency of testing	Threshold	Outcome (weeks' gestation)
Makrakis[246]	2003	Greece	20	Urine, plasma	Cohort Prospective Test described	Symptomatic women who presented with threatened preterm labour, 20–35 years, no other pregnancy complication	Absence of cervical dilatation, no evidence of rupture membrane or chorioamnionitis	24–36	Single	7.71 ng/ml (urine), 68.43 ng/ml (plasma)	< 37
Agrez[245]	1999	Australia	15	Urine	Cohort Prospective Test described	Symptomatic women who presented with threatened preterm labour	×	27–34	Single	5 ng/ml	< 37

TABLE 97 *Individual accuracy results of matrix metalloprotease-9 (MMP-9) testing in predicting spontaneous preterm birth among asymptomatic and symptomatic women with threatened preterm labour*

Authors	Thresholds	TP	FP	FN	TN	sens	sens_lb	sens_ub	specs	spec_lb	spec_ub	LR+	LR+_lb	LR+_ub	LR–	LR–_lb	LR–_ub
Agrez[245]	5 ng/ml	4	1	2	8	0.67	0.22	0.96	0.89	0.52	1.00	6.00	0.87	41.44	0.38	0.12	1.19
Makrakis[246]	7.71 ng/ml	6	1	3	10	0.67	0.30	0.93	0.91	0.59	1.00	7.33	1.07	50.27	0.37	0.14	0.94

FN, false negative; FP, false positive; lb, lower bound; LR,+, likelihood ratio for positive test; LR–, likelihood ratio for negative test; sens, sensitivity; spec, specificity; TN, true negative; TP, true positive; ub, upper bound.

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TABLE 98 *Characteristics of the included studies on accuracy of periodontal health assessment in predicting spontaneous preterm birth among asymptomatic pregnant women*

Authors	Year	Country	*n*	Study designs	Inclusion	Exclusion	Testing gestation	Threshold	Outcome
Jeffcoat[253]	2001	USA	1313	Cohort Prospective Blinded Test described	All pregnant women being studied by the Perinatal Emphasis Research Center at UAB	Women who required antibiotic prophylaxis for dental examination or who is taking antibiotics	21–24	Periodontitis three or more sites with ≥ 3 mm attachment loss (AL), severe periodontitis ≥ 90 sites, and fewer than three healthy sites < 3 mm AL	37
Offenbacher[247]	2001	USA	812	Cohort Prospective Blinded Test described	Pregnant women enrolled before 26 weeks' gestation		Before 26 weeks' gestation and within 48 h of deliveries	Periodontitis: periodontal health (absence of any probe depth (PD) > 3 mm and no sites with AL > 2 mm), moderate severe disease (four or more sites with PD ≥ 5 mm and ≥ 2 mm AL at four or more sites), and mild periodontitis, i.e. less than the moderate to severe group but had more than the healthy group. Progression of periodontitis	37
Moore[255]	2004	UK	539	Cohort Prospective Blinded Test described	Women who attended for nuchal translucency Down syndrome screening at 12 weeks' gestation	Pregnancy less than 10 or more than 15 weeks' gestation, multiple pregnancy and need for antibiotics before dental treatment	10–15	Healthy: < 10% sites with PD ≥ 3 mm and < 5% sites with AL ≥ 2 mm, Severe: more than five sites with PD ≥ 5 mm more than three sites with AL ≥ 3 mm	32, 37
Offenbacher[257]	1996	USA	124	Cohort Prospective Blinded Test described	Pregnant women under routine antenatal care in a University Hospital Prenatal Clinic	Concurrent genitourinary tract infection, use of antibiotics and if at risk for bacterial endocarditis	Day 3 postnatal	PD and AL ≥ 3 mm affecting > 60% (extent 3 : 60) in all women and in primiparous	37

continued

TABLE 98 *Characteristics of the included studies on accuracy of periodontal health assessment in predicting spontaneous preterm birth among asymptomatic pregnant women*

Authors	Year	Country	*n*	Study designs	Inclusion	Exclusion	Testing gestation	Threshold	Outcome
Holbrook[251]	2004	Iceland	96	Cohort Consecutive Prospective Test described	Healthy otherwise unselected pregnant women, bacterial vaginosis testing using Amsel's criteria was also performed on enrolled women		28–30	More than four pockets > 4 mm PD	37
Rajapakse[259]	2005	Sri Lanka	227	Cohort Prospective Test described	Nulliparous, 18–34 years, singleton pregnancy	Hypertension, diabetes, smoking, betel chewing, alcohol and drug abuse	24–37	Mean pocket depth, plaque scores and bleeding scores composite that are greater than the median value in the total cohort.	37
Moore[256]	2005	UK	154	Case–control Prospective Blinded Test described	Cases were women who had spontaneous preterm birth before 37 weeks' gestation, controls were uncomplicated term vaginal or elective Caesarean section delivery	Multiple pregnancy, medical history that required antibiotic cover, iatrogenic preterm delivery, hypertension, pre-eclampsia, diabetes mellitus.	Day 5 postnatal	PD ≥ 4 mm, ≥ 5 mm and AL ≥ 2 mm, ≥ 3 mm	37
Goepfert[250]	2004	USA	103	Case–control Prospective Blinded Test described	Cases were women who delivered between 24 and 32 weeks' gestation		Day 3 postnatal	AL > 3 mm and > 5 mm	32
Dasanayake[248]	2001	USA	80	Case–control Prospective Blinded Test described	Cases were women who had spontaneous preterm birth before 37 weeks' gestation, controls were term delivery.	Missing second trimester samples and elective preterm deliveries	14–24	Median and >75% immunoglobulin *Porphyromonas gingivalis* presence in serology.	37

Authors	Year	Country	*n*	Study designs	Inclusion	Exclusion	Testing gestation	Threshold	Outcome
Dortbudak[249]	2005	Austria	36	Cohort Prospective Test described	Pregnant women undergoing amniocentesis for medical conditions	×	15–20	PD ≥ 5 mm	37
Radnai[258]	2004	Hungary	85	Case–control Retrospective Blinded Test described	Systemically healthy women, cases were spontaneous premature birth before 37 weeks' gestation	Diabetes, asthma, cardiac or renal problems, thyroid problems, chronic infectious disease or multiple pregnancies, patients who needed prophylaxis antibiotics	Day 3 postnatal	PD ≥ 4 mm, bleeding on probing, and combination of probe depth, bleeding on probing	37
Jarjoura[252]	2005	USA	203	Case–control Retrospective Test described	Singleton pregnancies	Fetal or uterine anomalies, cervical incompetence, iatrogenic premature delivery, women who required antibiotics prophylaxis before dental assessment	Day 3 postnatal	Clinical attachment loss (CAL) ≥ 3 mm in five or more sites	37
Konopka[254]	2003	Poland	128	Case–control Retrospective Test described	Cases were women who had spontaneous preterm birth before 37 weeks' gestation of infant who weighed < 2500 g	Multiple pregnancy, developmental defects, treated infertility patients, IVF, iatrogenic preterm births and systemic infection (apart from UTI)	Day 3 postnatal	Periodontal index > 4	37

AL, attachment loss; IVF, in vitro fertilisation; PD, probe depth; UTI, urinary tract infection.

TABLE 99 *Individual accuracy results of periodontal health assessment in predicting spontaneous preterm birth among asymptomatic women*

Authors	Thresholds	TP	FP	FN	TN	sens	sens_lb	sens_ub	specs
Offenbacher[247]	Mild periodontitis	132	434	38	163	0.78	0.71	0.84	0.27
Offenbacher[247]	Moderate to severe periodontitis	18	27	38	163	0.32	0.20	0.46	0.86
Offenbacher[247]	Progressive periodontitis	75	180	113	444	0.40	0.33	0.47	0.71
[a]Moore[255]	Severe periodontitis	9	254	4	272	0.69	0.39	0.91	0.52
[a]Moore[255]	Severe periodontitis	24	239	20	256	0.55	0.39	0.70	0.52
Offenbacher[257]	All women with periodontitis	87	22	6	9	0.94	0.86	0.98	0.29
Offenbacher[257]	Primiparous with periodontitis	41	11	5	9	0.89	0.76	0.96	0.45
Holbrook[251]	PD≥4 mm in > four pockets	0	16	6	74	0.00	0.00	0.46	0.82
Rajapakse[259]	PD≥cohort median value	27	39	12	149	0.69	0.52	0.83	0.79
Moore[256]	PD≥4 mm	5	10	56	83	0.08	0.03	0.18	0.89
Moore[256]	LA≥3 mm	1	2	60	91	0.02	0.00	0.09	0.98
Moore[256]	LA≥2 mm	3	7	58	86	0.05	0.01	0.14	0.92
Moore[256]	PD≥5 mm	1	4	60	89	0.02	0.00	0.09	0.96
[a]Goepfert[250]	Extent 5	11	4	48	40	0.19	0.10	0.31	0.91
[a]Goepfert[250]	Extent 3	28	13	31	31	0.47	0.34	0.61	0.70
Dortbudak[249]	PD≥5 mm	5	6	1	30	0.83	0.36	1.00	0.83
Radnai[258]	PD≥4 mm	22	18	19	26	0.54	0.37	0.69	0.59
Radnai[258]	BOP	20	9	21	35	0.49	0.33	0.65	0.80
Radnai[258]	PD≥4 mm + BOP	19	5	22	39	0.46	0.31	0.63	0.89
Jarjoura[252]	Periodontitis	21	25	62	95	0.25	0.16	0.36	0.79
Konopka[254]	Periodontal index greater than 4	27	12	57	32	0.32	0.22	0.43	0.73

AL, attachment loss; BOP, bleeding on probing; FN, false negative; FP, false positive; lb, lower bound; LR,+, likelihood ratio for positive test; LR–, likelihood ratio for negative test; PD, probing depth; sens, sensitivity; spec, specificity; TN, true negative; TP, true positive; ub, upper bound.
a Spontaneous preterm birth before 32 weeks' gestation.

spec_lb	spec_ub	LR+	LR+_lb	LR+_ub	LR–	LR–_lb	LR–_ub
0.24	0.31	1.07	0.97	1.17	0.82	0.60	1.12
0.80	0.90	2.26	1.35	3.79	0.79	0.65	0.96
0.67	0.75	1.38	1.12	1.71	0.84	0.74	0.96
0.47	0.56	1.43	0.99	2.08	0.60	0.26	1.35
0.47	0.56	1.13	0.85	1.50	0.88	0.63	1.23
0.14	0.48	1.32	1.05	1.66	0.22	0.09	0.57
0.23	0.68	1.62	1.08	2.44	0.24	0.09	0.63
0.73	0.89	0.39	0.03	5.90	1.13	0.90	1.42
0.73	0.85	3.34	2.35	4.73	0.39	0.24	0.63
0.81	0.95	0.76	0.27	2.12	1.03	0.93	1.14
0.92	1.00	0.76	0.07	8.23	1.01	0.96	1.05
0.85	0.97	0.65	0.18	2.43	1.03	0.95	1.12
0.89	0.99	0.38	0.04	3.33	1.03	0.97	1.08
0.78	0.97	2.05	0.70	6.01	0.89	0.77	1.04
0.55	0.83	1.61	0.95	2.73	0.75	0.55	1.02
0.67	0.94	5.00	2.22	11.28	0.20	0.03	1.20
0.43	0.74	1.31	0.83	2.07	0.78	0.52	1.18
0.65	0.90	2.38	1.23	4.62	0.64	0.46	0.90
0.75	0.96	4.08	1.68	9.92	0.61	0.45	0.82
0.71	0.86	1.21	0.73	2.02	0.94	0.81	1.10
0.57	0.85	1.18	0.66	2.09	0.93	0.74	1.18

TABLE 100 *Characteristics of the included studies on accuracy of asymptomatic bacteriuria assessment in predicting spontaneous preterm birth before 37 weeks' gestation for asymptomatic pregnant women*

Authors	Year	Country	*n*	Study designs	Inclusion	Exclusion	Testing gestation (weeks)	Frequency of testing	Outcome (weeks' gestation)
Midstream urine sample									
Wren[287]	1969	Australia	3099	Cohort Consecutive Prospective Test described	All pregnant patients booking at their first antenatal visit	Twin pregnancies and women who moved hospital	Antenatal	Repeat if positive	< 37
Robertson[278]	1968	UK	2184	Cohort Consecutive Prospective Test described	Singleton pregnancies	Miscarriages, treated women, delivered elsewhere	Booking	Single	< 37
Uncu[283]	2002	Turkey	186	Cohort Consecutive Prospective Test described	Singleton pregnancies	Patients with renal disease, recent or current antibiotic treatment, current or recent asymptomatic bacteriuria	<32	Repeat if positive	< 37
Layton[271]	1964	UK	176	Cohort Consecutive Prospective Test described	Antenatal asymptomatic women		<32	Single	< 37
Versi[284]	1997	UK	6864	Cohort Prospective Test described	Singleton pregnancies (Caucasian and Bangladeshi populations only)		11–14	Single	< 37
Patrick[277]	1967	UK	575	Cohort Prospective Test described	Antenatal asymptomatic women		Booking	Single	< 37
Schieve[280]	1994	USA	25,663	Cohort Retrospective Test described	Singleton pregnancies		Antenatal	Single	< 37
LeBlanc[272]	1964	USA	1248	Case–control Retrospective Test described	Singleton pregnancies		< 20	Single	< 37

Authors	Year	Country	*n*	Study designs	Inclusion	Exclusion	Testing gestation (weeks)	Frequency of testing	Outcome (weeks' gestation)
Gold[265]	1966	USA	1246	Case–control Retrospective Test described	Singleton pregnancies		< 20	Single	< 37
Kass[268]	1962	USA	1095	Case–control Retrospective Test described	Singleton pregnancies		< 20	Single	< 37
Hoja[267]	1964	USA	879	Case–control Retrospective Test described	Singleton pregnancies		< 20	Single	< 37
Stuart[282]	1965	UK	817	Case–control Retrospective Test described	Singleton pregnancies		< 20	Single	< 37
Henderson[266]	1965	USA	808	Case–control Retrospective Test described	Singleton pregnancies	Placenta praevia, pre-eclampsia, abruption, induced labour, erythroblastosis fetalis	< 22	Single	< 36
Low[273]	1964	USA	771	Case–control Retrospective Test described	Singleton pregnancies		< 20	Single	< 37
Forkman[264]	1964	Sweden	595	Case–control Retrospective Test described	Singleton pregnancies		< 20	Single	< 37
Schamadan[279]	1965	USA	556	Case–control Retrospective Test described	Singleton pregnancies		< 20	Single	< 37
Kincaid[269]	1964	USA	556	Case–control Retrospective Test described	Singleton pregnancies		< 20	Single	< 37
Whalley[285]	1965	USA	283	Case–control Retrospective Test described	Singleton pregnancies		< 20	Single	< 37

continued

TABLE 100 *Characteristics of the included studies on accuracy of asymptomatic bacteriuria assessment in predicting spontaneous preterm birth before 37 weeks' gestation for asymptomatic pregnant women*

Authors	Year	Country	*n*	Study designs	Inclusion	Exclusion	Testing gestation (weeks)	Frequency of testing	Outcome (weeks' gestation)
Sleigh[281]	1964	UK	200	Case–control Retrospective Test described	Singleton pregnancies		< 20	Single	< 37
Norden[276]	1965	USA	197	Case–control Retrospective Test described	Singleton pregnancies		< 20	Single	< 37
Kubicki[270]	1976	Poland	192	Case–control Retrospective Test described	Singleton pregnancies		18–23	Single	< 37
Bryant[263]	1964	USA	66	Case–control Retrospective Test described	Singleton pregnancies		< 20	Single	< 37
Abdul-Jabbar[262]	1991	Saudi		Case–control Retrospective Test described	Pregnant women without apparent ailments		Booking	Single	< 37
Group B streptococcal bacteriuria									
Moller[275]	1984	Denmark	2745	Cohort Consecutive Prospective Test described	Singleton pregnancies		Antenatal	Single	< 37
McDonald[274]	1989	Australia	692	Cohort Consecutive Prospective Test described	Singleton pregnancies		20–24	Single	< 37
White[286]	1984	UK	8083	Cohort Retrospective Test described	Singleton pregnancies		Antenatal	Single	< 37

TABLE 101 *Individual accuracy results of asymptomatic bacteriuria assessment in predicting spontaneous preterm birth before 37 weeks' gestation among asymptomatic antenatal women*

Authors	TP	FP	FN	TN	sens	sens_lb	sens_ub	specs	spec_lb	spec_ub	LR+	LR+_lb	LR+_ub	LR–	LR–_lb	LR–_ub
Midstream urine sample																
Wren[287]	15	75	204	2805	0.07	0.04	0.11	0.97	0.97	0.98	2.63	1.54	4.50	0.96	0.92	0.99
Robertson[278]	13	191	62	1918	0.17	0.10	0.28	0.91	0.90	0.92	1.91	1.15	3.19	0.91	0.82	1.01
Uncu[283]	6	17	16	147	0.27	0.11	0.50	0.90	0.84	0.94	2.63	1.16	5.96	0.81	0.62	1.05
Layton[271]	4	59	9	104	0.31	0.09	0.61	0.64	0.56	0.71	0.85	0.37	1.97	1.09	0.74	1.59
[a]Versi[284]	13	139	624	6694	0.02	0.01	0.03	0.98	0.98	0.98	1.00	0.57	1.76	1.00	0.99	1.01
[b]Versi[284]	39	393	512	5920	0.07	0.05	0.10	0.94	0.93	0.94	1.14	0.83	1.56	0.99	0.97	1.01
Patrick[277]	7	68	21	479	0.25	0.11	0.45	0.88	0.85	0.90	2.01	1.02	3.97	0.86	0.69	1.06
Schieve[280]	293	1687	2546	21,137	0.10	0.09	0.11	0.93	0.92	0.93	1.40	1.24	1.57	0.97	0.96	0.98
LeBlanc[272]	6	21	133	1088	0.04	0.02	0.09	0.98	0.97	0.99	2.28	0.94	5.55	0.98	0.94	1.01
Gold[265]	0	30	168	1048	0.00	0.00	0.02	0.97	0.96	0.98	0.10	0.01	1.70	1.03	1.01	1.04
Kass[268]	26	69	88	912	0.23	0.15	0.32	0.93	0.91	0.94	3.24	2.16	4.87	0.83	0.75	0.92
Hoja[287]	1	21	54	803	0.02	0.00	0.10	0.97	0.96	0.98	0.71	0.10	5.21	1.01	0.97	1.05
Stuart[282]	20	68	83	646	0.19	0.12	0.28	0.90	0.88	0.93	2.04	1.30	3.21	0.89	0.81	0.98
Henderson[266]	33	15	371	389	0.08	0.06	0.11	0.96	0.94	0.98	2.20	1.21	3.99	0.95	0.92	0.99
Low[273]	5	75	49	642	0.09	0.03	0.20	0.90	0.87	0.92	0.89	0.37	2.10	1.01	0.93	1.11
Forkman[264]	1	33	19	542	0.05	0.00	0.25	0.94	0.92	0.96	0.87	0.13	6.06	1.01	0.91	1.12
Schamadan[279]	8	48	25	475	0.24	0.11	0.42	0.91	0.88	0.93	2.64	1.36	5.11	0.83	0.69	1.01

continued

TABLE 101 *Individual accuracy results of asymptomatic bacteriuria assessment in predicting spontaneous preterm birth before 37 weeks' gestation among asymptomatic antenatal women (continued)*

Authors	TP	FP	FN	TN	sens	sens_lb	sens_ub	specs	spec_lb	spec_ub	LR+	LR+_lb	LR+_ub	LR–	LR–_lb	LR–_ub
Kincaid[269]	12	44	25	475	0.32	0.18	0.50	0.92	0.89	0.94	3.83	2.22	6.59	0.74	0.59	0.92
Whalley[285]	11	96	21	155	0.34	0.19	0.53	0.62	0.55	0.68	0.90	0.54	1.49	1.06	0.81	1.39
Sleigh[281]	7	93	7	93	0.50	0.23	0.77	0.50	0.43	0.57	1.00	0.58	1.72	1.00	0.58	1.72
Norden[276]	11	77	14	95	0.44	0.24	0.65	0.55	0.47	0.63	0.98	0.61	1.58	1.01	0.70	1.47
Kubicki[270]	18	83	5	86	0.78	0.56	0.93	0.51	0.43	0.59	1.59	1.22	2.08	0.43	0.19	0.94
Bryant[263]	2	30	4	40	0.33	0.04	0.78	0.57	0.45	0.69	0.78	0.24	2.49	1.17	0.64	2.13
AbdulJabbar[262]	18	180	16	184	0.53	0.35	0.70	0.51	0.45	0.56	1.07	0.77	1.49	0.93	0.64	1.35
Group B streptococcal bacteriuria																
Moller[275]	14	54	228	2449	0.06	0.03	0.10	0.98	0.97	0.98	2.68	1.51	4.76	0.96	0.93	0.99
McDonald[274]	4	24	46	618	0.08	0.02	0.19	0.96	0.94	0.98	2.14	0.77	5.93	0.96	0.88	1.04

FN, false negative; FP, false positive; lb, lower bound; LR,+, likelihood ratio for positive test; LR–, likelihood ratio for negative test; sens, sensitivity; spec, specificity; TN, true negative; TP, true positive; ub, upper bound.
a Caucasian population.
b Bangladeshi population.

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TABLE 102 *Characteristics of the included studies on accuracy of bacterial vaginosis (BV) testing in predicting spontaneous preterm birth for asymptomatic pregnant women and women who presented with threatened preterm labour*

Study				Population		Test			Reference standards
Author, publication year	**Country**	**Study quality**	***n***	**Inclusion criteria**	**Exclusion criteria**	**Gestational age at testing**	**Site and frequency of testing**	**Criteria for diagnosis of BV**	**Gestational age at birth (weeks' gestation)**
Asymptomatic pregnant women									
Oakeshott 2004[293]	USA	Cohort Consecutive Prospective Test described	887	All consecutive < 10 weeks' gestation	Miscarriages, terminations, multiple gestations, antibiotic treatment, missing specimen slides	< 10	Vaginal swab Single	Gram staining (Nugent's criteria)	< 37
Klebanoff 2005[288]	USA	Cohort Prospective Blindeded Test described	12,937	Did not report genital itching, burning, malodour to questioning, no major medical or obstetric complications in current pregnancy, not received or expected to receive antibiotics, could be followed after delivery		< 13, 13–14, 15–16, 17–18, 19–20, 21–22	Vaginal swab Single	Gram staining (Nugent's criteria)	< 37 (data were collected for 23–26 weeks' gestation births but this was not published)
DeSeta 2005[292]	Italy	Cohort Consecutive Prospective Test described	598	Singleton, negative urine culture the past 2 weeks, no other genitourinary tract infection	Diabetes, hypertension, cardiac or chronic renal disease, Rh iso-immunization, cervical cerclage, antibiotics treatment, unprotected intercourse or vaginal washing in the last 48 h	13–18	Vaginal swab Single	Gram staining (Nugent's criteria)	< 37
Purwar 2001[307]	India	Cohort Blinded Prospective Test described	938	Arbitrary selection of singleton pregnancies	Multiple pregnancy, placenta praevia, symptomatic vaginal discharge, history suggestive of cervical incompetence, vaginal bleeding, leaking membrane, antibiotic use in the preceding 15 days, suspected uterine malformation	16–28	Vaginal swab Single	Gram staining (Nugent's criteria)	< 37

continued

TABLE 102 *Characteristics of the included studies on accuracy of bacterial vaginosis (BV) testing in predicting spontaneous preterm birth for asymptomatic pregnant women and women who presented with threatened preterm labour*

Study				Population		Test			Reference standards
Author, publication year	**Country**	**Study quality**	***n***	**Inclusion criteria**	**Exclusion criteria**	**Gestational age at testing**	**Site and frequency of testing**	**Criteria for diagnosis of BV**	**Gestational age at birth (weeks' gestation)**
Hillier 1995[306]	USA	Cohort Blinded Prospective Test described	8197	Women with singleton pregnancies who have completed 23–26 weeks' gestation and attending routine antenatal clinic	< 16 years old; Rh iso-immunisation disease, preceding 2 weeks or current use of antibiotics, chronic renal disease, organic heart disease, insulin-dependent diabetes mellitus, multiple gestation, cervical cerclage, hypertension requiring treatment	23–26	Posterior fornix Single	Gram staining (Nugent's criteria) or vaginal pH >4.5	< 37
Govender 1996[305]	S Africa	Cohort Blinded Prospective Test described	168	Singleton pregnancies less than 30 weeks' gestation	Previous spontaneous premature birth, antibiotics in the current pregnancy, symptomatic discharge, urinary tract infection, multiple pregnancy	< 30 weeks	Vaginal swab Single	Gram staining (Nugent's criteria)	< 37
Kurki 1992[597]	Finland	Cohort Blinded Prospective Test described	733	Singletons First pregnancy	Antibiotics in current pregnancy, multiple pregnancy, induction before 37 weeks	8–17	Posterior fornix Single	Gram staining (Spiegel's criteria)	< 37
Crane 1999[99]	Canada	Cohort Blinded Prospective Test described	140	Singletons	Multiple pregnancy, pre-labour rupture of membranes, placenta praevia, previously treated for BV in current pregnancy, cervical cerclage, major fetal anomalies	20–24	Posterior fornix Single	Gram staining (Nugent's criteria) or clinical criteria	< 37
Hay 1994[737]	England	Cohort Blinded Prospective Test described	706	Singletons First antenatal visit between 9 and 24 weeks' gestation	Multiple pregnancy, lethal congenital malformations, antibiotics in the current pregnancy	9–24	Posterior fornix Single	Gram staining (Spiegel's criteria)	< 37

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Study				Population		Test			Reference standards
Author, publication year	**Country**	**Study quality**	***n***	**Inclusion criteria**	**Exclusion criteria**	**Gestational age at testing**	**Site and frequency of testing**	**Criteria for diagnosis of BV**	**Gestational age at birth (weeks' gestation)**
McGregor 1990[411]	USA	Cohort Blinded Prospective Test described	194	Singletons Women receiving care at two prenatal clinics	Multiple pregnancy, cerclage, placenta praevia, vaginal bleeding, preterm labour, antibiotics course in preceding 2 weeks, douching within 24 h of examination	24	Mid-vaginal swab Single	Gram staining (Spiegel's criteria)	< 37
Gratacos 1998[303]	Spain	Cohort Blinded Prospective Test described	635	Singletons	Multiple pregnancy, abortion or termination, congenital malformation, lost to follow-up	< 24 and < 35	Posterior fornix Single	Gram staining (Nugent's criteria)	< 37
Helou 1996[304]	Israel	Cohort Blinded Prospective Test described	400	Singletons	Iatrogenic preterm delivery	15–20 and 27–32	Vaginal swab Serial (twice)	Gram staining (Nugent's criteria)	< 37
Balu 2003[291]	USA	Cohort Prospective Test described	646	Singleton pregnancy, access to telephone, > 16 years old, planned to continue care in the same hospital		24–29		Gram staining (Nugent's criteria)	< 32, < 34, and < 37
Riduan 1993[295]	Indonesia	Cohort Prospective Test described	490	Singletons	Medical conditions associated with preterm delivery, previous tocolysis or steroids treatment, antibiotics within 2 weeks of enrolment, incompetent cervix	16–20 and 28–32	Vaginal swab Serial (twice)	Gram staining (Nugent's criteria)	< 37
Meis 1995[294]	USA	Cohort Prospective Test described	2929	Singletons	Cerclage, major congenital anomaly, placenta praevia, polyhydramnios, oligohydramnios, cervix > 2 cm dilated in nulliparous and > 3 cm in multiparous women	24 and 28	Posterior fornix Serial (twice)	Gram staining (Nugent's criteria)	< 35

continued

TABLE 102 *Characteristics of the included studies on accuracy of bacterial vaginosis (BV) testing in predicting spontaneous preterm birth for asymptomatic pregnant women and women who presented with threatened preterm labour*

Study				Population		Test			Reference standards
Author, publication year	**Country**	**Study quality**	***n***	**Inclusion criteria**	**Exclusion criteria**	**Gestational age at testing**	**Site and frequency of testing**	**Criteria for diagnosis of BV**	**Gestational age at birth (weeks' gestation)**
Thorsen 1996[296]	USA	Cohort Test described	2927	Singletons	Congenital malformations, placenta praevia, pre-eclampsia, cerclage, placental abruption, serious medical disease, Rh iso-immunisation	7–24	Posterior fornix Single	Clinical criteria	< 37
Mascagni 2001[289]	USA	Retrospective Case–control	103	Singleton pregnancy, 18–34 years old, asymptomatic from vaginal infection	Medical or obstetrics problem requiring elective preterm delivery, cigarette smoking, diabetes, hypertension, sexually transmitted disease	15–16	Vaginal swab Single	Gram staining (Nugent's criteria)	<37
Women with threatened preterm labour									
Goffinet 2003[308]	France	Cohort Prospective Blinded Test described	212	Singleton with threatened preterm labour and intact membrane.	Rupture of membrane, chorioamnionitis, suspected fetal distress, fetal malformation, maternal disorder requiring delivery, > 3 cm dilatation	24–34	Vaginal swab Single	Gram staining (Nugent's criteria)	< 7 days of testing, < 33, and < 35
Martius 1988[301]	USA	Blinded Prospective Case–control Test described	212	Singletons	Age < 16 years, antibiotics within 2 weeks, insulin-dependent diabetes mellitus, congenital heart disease, pre-eclampsia, renal disease, essential hypertension, placental abruption, placenta praevia, multiple gestation, congenital malformation	20–36	Vaginal swab Single	Gram staining (Spiegel's criteria)	< 37
Holst 1994[241]	Sweden	Prospective Case–control Consecutive Test described	87	Women with singleton pregnancies admitted for preterm labour Control were women admitted in labour at term	Diabetics, pre-eclampsia, placental abruption, placenta praevia, multiple gestation, cervical cerclage, pre-labour preterm rupture of membrane	24–36	Vaginal swab Single	Gram staining (Spiegel's criteria)	< 34 and < 37

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Study				Population		Test			Reference standards
Author, publication year	**Country**	**Study quality**	***n***	**Inclusion criteria**	**Exclusion criteria**	**Gestational age at testing**	**Site and frequency of testing**	**Criteria for diagnosis of BV**	**Gestational age at birth (weeks' gestation)**
Eschenbach 1984[300]	USA	Blinded Prospective Case–control Test described	171	Women admitted in labour and had vaginal exam 2 controls, women who delivered at term, were selected for each case enrolled	Vaginal swab was not obtained Iatrogenic preterm birth Congenital malformation Placental abruption Placenta praevia Vaginal bleeding of indeterminate origin	24–36	Vaginal swab Single	Gas liquid chromatography	< 37
Elliott 1990[297]	Kenya	Retrospective Case–control Test described	276	Preterm singleton pregnancies who presented with preterm labour Control were women who delivered >36 weeks' gestation	None stated	24–36	Vaginal swab Single	Gram staining (Spiegel's criteria)	< 36
Subtil 2002[299]	France	Prospective Case–control Test described	102	Women presented with preterm labour with either cervical dilatation >2 cm or history of previous preterm labour Control matched for gestation and admitted preterm for reasons unrelated to preterm labour (e.g. pre-eclampsia, diabetes, cholestasis)	Gestational age less than 20 or more than 34 weeks' gestation, local or general antibiotic therapy within the past 8 days, premature rupture of membrane, bleeding, or presence of a clear cause for preterm labour (e.g. multiple pregnancy, hydramnios)	20–34	Vaginal swab Single	Clinical criteria	< 37
Krohn 1991[298]	USA	Prospective Test described	211	Women who presented with preterm labour	Less than 16 or more than 40 years old, uterine or fetal anomaly, hypertension, diabetics, cervical cerclage, placenta praevia, placental abruption	22–34	Vaginal swab Single	Gram staining (Nugent's criteria)	< 35
Carlini 2003[290]	USA	Case–control Prospective Test described	753	Singleton with threatened preterm labour and intact membrane	Elective preterm delivery	20–37	Vaginal swab Single	Gram staining (Nugent's criteria)	< 37

a Study quality.

TABLE 103 *Individual accuracy results of bacterial vaginosis (BV) testing in predicting spontaneous preterm birth among symptomatic women with threatened preterm labour*

Authors	TP	FP	FN	TN	sens	sens_lb	sens_ub	specs	spec_lb	spec_ub	LR+	LR+_lb	LR+_ub	LR–	LR–_lb	LR–_ub
Single 37 weeks asymptomatic women																
Oakeshott[293]	6	143	38	700	0.14	0.05	0.27	0.83	0.80	0.86	0.80	0.38	1.72	1.04	0.92	1.17
Crane[99]	1	30	8	101	0.11	0.00	0.48	0.77	0.69	0.84	0.49	0.07	3.16	1.15	0.90	1.48
DeSeta[292]	14	90	35	459	0.29	0.17	0.43	0.84	0.80	0.87	1.74	1.08	2.82	0.85	0.71	1.02
Govender[305]	24	64	11	69	0.69	0.51	0.83	0.52	0.43	0.61	1.43	1.07	1.90	0.61	0.36	1.01
Gratacos[303]	20	105	26	484	0.43	0.29	0.59	0.82	0.79	0.85	2.44	1.68	3.54	0.69	0.53	0.89
Helou[304]	7	53	31	309	0.18	0.08	0.34	0.85	0.81	0.89	1.26	0.62	2.57	0.96	0.82	1.12
Hillier[306]	77	1141	29	6949	0.73	0.63	0.81	0.86	0.85	0.87	5.15	4.53	5.86	0.32	0.23	0.43
Klebanoff[288]	74	121	423	1156	0.15	0.12	0.18	0.91	0.89	0.92	1.57	1.20	2.06	0.94	0.90	0.98
Purwar[307]	30	83	29	783	0.51	0.37	0.64	0.90	0.88	0.92	5.31	3.84	7.33	0.54	0.42	0.71
Balu[291]	71	157	171	350	0.29	0.24	0.36	0.69	0.65	0.73	0.95	0.75	1.20	1.02	0.93	1.13
Riduan[295]	17	67	48	358	0.26	0.16	0.39	0.84	0.80	0.88	1.66	1.04	2.64	0.88	0.75	1.02
Serial 37 weeks asymptomatic women																
Gratacos[303]	8	33	7	38	0.53	0.27	0.79	0.54	0.41	0.65	1.15	0.67	1.96	0.87	0.49	1.56
Helou[304]	3	24	20	330	0.13	0.03	0.34	0.93	0.90	0.96	1.92	0.63	5.92	0.93	0.79	1.10
Riduan[295]	8	31	53	370	0.13	0.06	0.24	0.92	0.89	0.95	1.70	0.82	3.52	0.94	0.85	1.04
Amsel 37 weeks asymptomatic women																
Crane[99]	2	18	7	113	0.22	0.03	0.60	0.86	0.79	0.92	1.62	0.44	5.91	0.90	0.63	1.29
Thorsen[296]	14	438	91	2434	0.13	0.07	0.21	0.85	0.83	0.86	0.87	0.53	1.43	1.02	0.95	1.10
Cauci[302]	11	61	75	356	0.13	0.07	0.22	0.85	0.82	0.89	0.87	0.48	1.59	1.02	0.93	1.12
37 weeks symptomatic women																
Subtil[299] Amsel	6	8	38	50	0.14	0.05	0.27	0.86	0.75	0.94	0.99	0.37	2.64	1.00	0.86	1.17
Goffinet[308] Nugent	4	19	33	156	0.11	0.03	0.25	0.89	0.84	0.93	1.00	0.36	2.76	1.00	0.88	1.13
Carlini[290] Nugent	85	39	321	308	0.21	0.17	0.25	0.89	0.85	0.92	1.86	1.31	2.65	0.89	0.84	0.95
Krohn[298] Nugent	35	20	104	52	0.25	0.18	0.33	0.72	0.60	0.82	0.91	0.57	1.45	1.04	0.87	1.23
Holst[241] Spiegel	9	3	13	24	0.41	0.21	0.64	0.89	0.71	0.98	3.68	1.13	11.97	0.66	0.46	0.96
Martius[301] Spiegel	21	34	40	117	0.34	0.23	0.48	0.77	0.70	0.84	1.53	0.97	2.41	0.85	0.69	1.03
Elliot[297] Spiegel	30	115	27	104	0.53	0.39	0.66	0.47	0.41	0.54	1.00	0.76	1.32	1.00	0.73	1.36

FN, false negative; FP, false positive; lb, lower bound; LR,+, likelihood ratio for positive test; LR–, likelihood ratio for negative test; sens, sensitivity; spec, specificity; TN, true negative; TP, true positive; ub, upper bound.

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TABLE 104 *Characteristics of studies on test accuracy of mammary stimulation test in predicting spontaneous preterm birth among asymptomatic women*

Authors	Year	Country	Population	Quality of studies	Inclusion criteria	Exclusion criteria	Testing gestation (weeks' gestation)	Frequency of testing	Outcome (weeks' gestation)
Eden[309]	1991	USA	94	Cohort Blinded Prospective Test described	Inner city pregnant women	None stated	24–32	Single	< 5 days of testing, < 34 < 37
Guinn[310]	1994	USA	247	Cohort Blinded Prospective Test described	Nulliparous women receiving private antenatal care with singleton pregnancies	Placenta praevia, multiple gestations, preterm pre-labour rupture of membrane	26–28	Single	< 34 and < 37

TABLE 105 *Individual accuracy results of mammary stimulation test in predicting spontaneous preterm birth among asymptomatic women stratified according to testing gestation and outcome gestations*

Authors	Outcome (weeks' gestation)	TP	FP	FN	TN	sens	sens_lb	sens_ub	specs	spec_lb	spec_ub	LR+	LR+_lb	LR+_ub	LR–	LR–_lb	LR–_ub
Guinn[310]	34	7	40	2	198	0.78	0.40	0.97	0.83	0.78	0.88	4.63	2.95	7.25	0.27	0.08	0.91
Guinn[310]	37	3	44	2	198	0.60	0.15	0.95	0.82	0.76	0.86	3.30	1.54	7.08	0.49	0.17	1.43
Eden[309]	37	16	31	3	44	0.84	0.60	0.97	0.59	0.47	0.70	2.04	1.46	2.84	0.27	0.09	0.77
[a]Eden[309]	37	11	8	2	16	0.85	0.55	0.98	0.67	0.45	0.84	2.54	1.38	4.68	0.23	0.06	0.85
Eden[309]	5[b]	12	35	0	47	1.00	0.74	1.00	0.57	0.46	0.68	2.25	1.71	2.95	0.07	0.00	1.02

FN, false negative; FP, false positive; lb, lower bound; LR,+, likelihood ratio for positive test; LR–, likelihood ratio for negative test; sens, sensitivity; spec, specificity; TN, true negative; TP, true positive; ub, upper bound.
a High-risk women according to Creasy risk scoring system.
b Within 5 days of testing.

TABLE 106 *Characteristics of test accuracy studies of uterine activities monitoring in predicting spontaneous preterm birth stratified according to population of antenatal asymptomatic women and women symptomatic with threatened preterm labour*

Authors	Year	Country	n	Test	Study design	Inclusion	Exclusion	Testing gestation (weeks)	Frequency of testing	Threshold	Outcome (weeks' gestation)
Iams[76]	2002	USA	270	Tocogram	Cohort Prospective Blinded Test described	Singleton pregnancies	Women who had received or were scheduled to receive an ambulatory monitor or tocolytic medication or to undergo cerclage, were complicated by placenta praevia or a major fetal anomaly detected by ultrasonography. Women who did not have telephones were not enrolled, because the transmission of data collected by the monitoring system required a telephone	22–30	Four times two sessions at least 2 h apart (one at night, one at day time) before 28 weeks and two more sessions between 28 and 30 weeks	Maximum night-time and day time contraction of four or more per hour	< 35
Iams[312]	1988	USA	100	Tocogram	Cohort Prospective Test described	Asymptomatic singleton pregnancies data only		20–34	Single	Four or more contractions per hour	< 37
Symptomatic women											
Bell[311]	1983	UK	15	Tocogram	Cohort Test described	Singleton pregnancy presenting with threatened preterm labour		20–28	Single	*P*max ≥ 15 mmHg	< 37
Maner[313]	2003	USA	99	Electro-myogram	Case–control Retrospective Test described	Singleton pregnancies presenting with threatened preterm labour leading to vaginal deliveries, intact membrane, dilatation < 2 cm, no evidence of systemic infection or fetal distress	To ensure optimal recording, patient over 230 lb was excluded	24–42	Single	0.463	< 37

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TABLE 107 *Individual accuracy results of uterine activities monitoring in predicting spontaneous preterm birth stratified according to population of asymptomatic antenatal women and symptomatic women with threatened preterm labour*

Authors	TP	FP	FN	TN	sens	sens_lb	sens_ub	specs	spec_lb	spec_ub	LR+	LR+_lb	LR+_ub	LR–	LR–_lb	LR–_ub
Asymptomatic women																
[a]Iams[76]	4	8	42	214	0.09	0.02	0.21	0.96	0.93	0.98	2.41	0.76	7.68	0.95	0.86	1.04
[b]Iams[76]	0	4	48	218	0.00	0.00	0.07	0.98	0.95	1.00	0.51	0.03	9.24	1.01	0.98	1.05
Symptomatic women																
Bell[311]	3	2	1	9	0.75	0.19	0.99	0.82	0.48	0.98	4.13	1.04	16.32	0.31	0.05	1.71
Maner[313]	23	3	19	54	0.55	0.39	0.70	0.95	0.85	0.99	10.40	3.34	32.38	0.48	0.34	0.67

FN, false negative; FP, false positive; lb, lower bound; LR,+, likelihood ratio for positive test; LR–, likelihood ratio for negative test; sens, sensitivity; spec, specificity; TN, true negative; TP, true positive; ub, upper bound.
a Night-time contraction.
b Day-time contraction.

TABLE 108 *Characteristic of studies on test accuracy of rheobase measurement in predicting spontaneous preterm birth among symptomatic women*

Authors	Year	Country	*n*	Quality of studies	Inclusion criteria	Exclusion criteria	Testing gestation (weeks' gestation)	Frequency of testing	Thresholds	Outcome (weeks' gestation)
Symptomatic women										
Arabin[314]	1985	Germany	176	Cohort Prospective Test described	Singleton pregnancies presenting with threatened preterm labour from 20 weeks' gestation onwards	Iatrogenic preterm delivery, suspected chorioamnionitis, fetal distress, placental bleeding, polyhydramnios	20–36	Serial	> 2.8, > 3.4 mA	37

TABLE 109 *Individual accuracy results of rheobase measurement in predicting spontaneous preterm birth among asymptomatic women stratified according to testing gestation and outcome gestations*

Authors	Threshold (mA)	TP	FP	FN	TN	sens	sens_lb	sens_ub	specs	spec_lb	spec_ub	LR+	LR+_lb	LR+_ub	LR–	LR–_lb	LR–_ub
Arabin[314]	2.8	18	34	15	109	0.55	0.36	0.72	0.76	0.68	0.83	2.29	1.50	3.52	0.60	0.41	0.88
Arabin[314]	3.4	25	46	8	97	0.76	0.58	0.89	0.68	0.60	0.75	2.36	1.73	3.20	0.36	0.19	0.66

FN, false negative; FP, false positive; lb, lower bound; LR,+, likelihood ratio for positive test; LR–, likelihood ratio for negative test; sens, sensitivity; spec, specificity; TN, true negative; TP, true positive; ub, upper bound.

TABLE 110 *Characteristics of studies on test accuracy of absence of fetal breathing movements (FBM) in predicting spontaneous preterm birth in symptomatic women*

Study	Year	Language	Study quality	*n*	Inclusion criteria	Exclusion criteria	Frequency of testing	Testing gestation (weeks' gestation)	Definitions of thresholds for abnormality	Outcome
Senden[92]	1996	English	Cohort Prospective Consecutive Blinded Test described	25	Singletons presenting with threatened preterm labour	PPROM, vaginal bleeding, chorioamnionitis, diabetes mellitus, cervical dilatation > 4 cm, history suggestive of cervical incompetence	Single	25–35	Absence of sustained FBM in a 30-s period during 30-min observations	< 7 days
Schreyer[321]	1988	English	Cohort Prospective Consecutive Test described	70	Uncomplicated singleton pregnancies presenting with threatened preterm labour	Multiple pregnancies, PPROM, vaginal bleeding, pyrexia, non-recordable uterine contractions on tocodynamometer, non-reassuring fetal heart rate tocography	Single	32–36	No sustained FBM (lasting > 20 s) in a 45-min observation period	< 24 h < 48 h < 7 days

Study	Year	Language	Study quality	*n*	Inclusion criteria	Exclusion criteria	Frequency of testing	Testing gestation (weeks' gestation)	Definitions of thresholds for abnormality	Outcome
Agustsson[315]	1987	English	Cohort Retrospective Test described	64	Women suspected of preterm labour	Advanced cervical dilatation, regular contraction not detectable	Single	26–36	No sustained FBM (lasting > 20 s) in a 45-min observation period	< 56 h < 7 days
Besinger[316]	1987	English	Cohort Prospective Test described	50	Women suspected of threatened preterm labour	None stated	Single	26–34	No sustained FBM (lasting > 20 s) in a 20-min observation period	< 48 h
Kanaan[319]	1991	English	Cohort Prospective Test described	34	Singletons Healthy volunteers Regular preterm uterine contractions	Vaginal bleeding, PPROM	Single	24–36	Absence of FBM in a 20-s period or decreased FBM in a 15-min observation	< 48 h
Markwitz[320]	2001	Polish	Cohort Retrospective Test described	36	Singleton pregnancies with suspected preterm labour	None stated	Single	28–36	No sustained FBM (lasting > 20 s) in a 30-min observation period	< 7 days
Devoe[318]	1994	English	Cohort Prospective Test described	25	Regular uterine contractions No clinical signs of chorioamnionitis No significant vaginal bleeding Singletons	Congenital abnormalities, maternal medical or obstetrical complications	Single	28–36	Absence of FBM within 6-s period in a 45-min observation	< 7 days
Castle[317]	1983	English	Cohort Prospective Test described	24	Women suspected of preterm labour	None stated	Single	25–34	No sustained FBM (lasting > 20 s) in a 45-min observation period	< 7 days

PPROM, premature pre-labour rupture of membrane.

TABLE 111 *Individual accuracy results of absence of fetal breathing movement in predicting spontaneous preterm birth among symptomatic women with threatened preterm labour*

Study	Intact membrane (Intact) or pre-labour premature rupture of membrane (PPROM)	Reference standards (hours to delivery or within days of testing)	TP	FP	FN	TN	Likelihood ratios for positive test (LR+) (95% confidence interval)	Likelihood ratios for negative test (LR–) (95% confidence interval)
Agustsson[315]	Intact	< 56 h	17	0	5	42	65.43 (4.12–1039.20)	0.23 (0.11–0.49)
Agustsson[315]	Intact	< 7 days	17	0	14	33	37.19 (2.33–93.09)	0.45 (0.31–0.67)
Besinger[316]	Intact	< 48 h	9	1	4	26	18.69 (2.64–132.33)	0.32 (0.14–0.72)
Besinger[316]	PPROM	< 48 h	7	0	0	3	7.50 (0.56–100.87)	0.07 (0.00–1.07)
Castle[317]	Intact	< 7 days	5	0	2	17	24.75 (1.55–396.04)	0.29 (0.09–0.92)
Castle[317]	PPROM	< 7 days	10	0	6	1	2.47 (0.22–28.05)	0.38 (0.20–0.71)
Devoe[318]	Intact	< 7 days	2	0	10	38	15.00 (0.77–292.61)	0.83 (0.65–1.07)
Devoe[318]	Intact	< 72 h	2	0	8	40	18.64 (0.96–360.56)	0.80 (0.59–1.09)
Devoe[318]	PPROM	< 7 days	9	0	14	2	2.38 (0.18–31.28)	0.61 (0.44–0.84)
Devoe[318]	PPROM	< 72 h	11	0	9	5	6.57 (0.45–96.05)	0.45 (0.28–0.73)
Kanaan[319]	Intact	< 48 h	4	11	1	18	2.11 (1.11–4.00)	0.32 (0.05–1.90)
Markwitz[320]	Intact	< 7 days	8	0	4	24	32.69 (2.04–522.93)	0.33 (0.15–0.74)
Markwitz[320]	PPROM	< 7 days	16	0	6	2	4.30 (0.34–54.76)	0.27 (0.14–0.54)
Schreyer[321]	Intact	< 24 h	7	7	1	55	7.75 (3.68–16.33)	0.14 (0.02–0.88)
Schreyer[321]	Intact	< 48 h	11	3	2	54	16.08 (5.22–49.55)	0.16 (0.05–0.58)
Schreyer[321]	Intact	< 7 days	12	2	4	52	20.25 (5.05–81.23)	0.26 (0.11–0.61)
Senden[92]	Intact	< 7 days	2	2	3	18	4.00 (0.73–21.84)	0.67 (0.32–1.38)

FN, false negative; FP, false positive; PPROM, premature pre-labour rupture of membranes; TN, true negative; TP, true positive.

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TABLE 112 *Characteristics of test accuracy studies of cervical length measurement in predicting spontaneous preterm birth in antenatal asymptomatic women*

Authors	Year	Country	*n*	Study designs	Inclusion	Exclusion	Testing gestation (weeks)	Frequency of testing	Threshold (mm)	Outcome (weeks' gestation)
Leung[329]	2005	HK	2952	Cohort Prospective Consecutive Blinded Test described	Singleton pregnancy of ethnic Chinese women only	Fetal abnormalities, non-viable pregnancies, lack of outcome information, outside test gestation	18–22	Single	< 15, < 20, < 25, < 27, < 30, < 35	< 34
Yazici[335]	2004	Turkey	357	Cohort Prospective Consecutive Blinded Test described	Singleton pregnancies in the absence of history of cervical incompetence, PPROM or previous preterm delivery	Uterine or fetal anomalies, pregnancy-related complications, maternal systemic disease	24	Single	< 32.5	< 36
Owen[331]	2001	USA	183	Cohort Prospective Consecutive Blinded Test described	Singletons with at least one previous spontaneous preterm birth	Cervical cerclage, uterine anomaly, chronic medical problem that may cause iatrogenic preterm delivery	16–18	Single	< 15, < 20, < 25, < 30	< 35
Berghella[326]	1997	USA	96	Cohort Prospective Consecutive Blinded Test described	Singletons, previous spontaneous preterm birth, more than two previous abortions, previous cone biopsy, Ehlers–Danlos syndrome	Cervical cerclage, placenta praevia, major fetal anomaly	14–22	Single	< 16, < 25	< 35
Andrew[325]	2000	USA	69	Cohort Prospective Consecutive Blinded Test described	Singleton pregnancies with previous history of spontaneous preterm birth between 16–30 weeks' gestation	Medical or obstetrical complication, history of incompetent cervix that required cerclage, presented for antenatal care after 28 weeks	< 20	Thrice	< 22, < 25	< 35
To[334]	2001	UK	6334	Cohort Prospective Consecutive Test described	Singleton pregnancies		22–24	Single	< 15	33
Sakai[243]	2004	Japan	4203	Cohort Prospective Blinding Test described	Asymptomatic women with singleton pregnancy and intact membrane	Preterm pre-labour rupture of membrane, threatened or impending miscarriage or preterm delivery, genital bleeding	20–28	Single	25	< 32, < 34, < 37

continued

TABLE 112 *Characteristics of test accuracy studies of cervical length measurement in predicting spontaneous preterm birth in antenatal asymptomatic women (continued)*

Authors	Year	Country	*n*	Study designs	Inclusion	Exclusion	Testing gestation (weeks)	Frequency of testing	Threshold (mm)	Outcome (weeks' gestation)
Taipale[333]	1998	Finland	3694	Cohort Prospective Consecutive Test described	Singleton pregnancies	Inadequate imaging, iatrogenic preterm delivery, fetal death or malformation	18–22	Single	< 25, < 29, < 35, < 40, < 45, < 50	< 35, < 37
Hibbard[328]	2000	USA	760	Cohort Prospective Consecutive Test described	Singleton pregnancies		16–22	Single	< 22, < 27, < 30	< 35
Dilek[327]	2006	Turkey	250	Cohort Prospective Consecutive Test described	Singleton pregnancies in the absence of history of cervical incompetence, PPROM or previous preterm delivery	Uterine or fetal anomalies, pregnancy-related complications, maternal systemic disease	22	Single	< 33.15	< 37
Andersen[324]	1990	USA	113	Cohort Prospective Blinded Test described	Singletons	Placenta praevia, patient thought to be at risk from cervical incompetence	7–30	Single	< 39	< 37
Carvalho[66]	2005	Brazil	1958	Cohort Retrospective Test described	Singleton pregnancy attending routine antenatal care at 21–24 weeks' gestation	Iatrogenic preterm delivery, missing outcomes	21–24	Single	< 10, < 15, < 20, < 25, < 30	< 34
Pires[332]	2005	Brazil	338	Cohort Prospective Test described	Singleton uncomplicated pregnancy	Previous history of preterm delivery, uterine or fetal abnormalities, miscarriage, fetal death, alteration in amniotic fluid, placenta praevia, previous uterine or cervical surgery, surgical procedures during gestation and conditions requiring iatrogenic preterm delivery	21–24	Single	< 20	< 35, < 37
Mara[330]	2002	Czech Republic	247	Case–control Prospective Test described	Singleton viable pregnancy, delivering at investigating institution	Congenital or chromosomal abnormalities, history of uterine or cervix surgery, more than three previous vaginal deliveries	18–20	Single	< 20	< 34

PPROM, premature pre-labour rupture of membranes.

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TABLE 113 *Characteristics of test accuracy studies of cervical length measurement in predicting spontaneous preterm birth in women symptomatic with threatened preterm labour*

Authors	Year	Country	*n*	Study designs	Inclusion	Exclusion	Testing gestation (weeks)	Frequency of testing	Threshold (mm)	Outcome (weeks' gestation)[a]
Crane[326]	1997	USA	136	Cohort Prospective Consecutive Blinded Test described	Singleton pregnancies whose contraction has been arrested by tocolysis	Cervical dilatation > 3 cm, placenta praevia, PPROM	24–34	Single	< 30	< 34
Tsoi[349]	2005	UK	510	Cohort Prospective Blinded Test described	Singleton pregnancy presenting with threatened preterm labour, intact membrane, cervical dilatation < 3 cm	×	24–34	Single	< 5, < 10, < 15, < 20	< 48 h, < 7 days of testing, < 37
Schmitz[345]	2006	France	359	Cohort Prospective Blinded Test described	Singleton pregnancy presenting with threatened preterm labour, intact membrane, cervical dilatation < 3 cm	Cervical manipulation, PPROM, fetal or uterine anomalies, vaginal bleeding, placenta praevia, abruption, IUGR, pre-eclampsia, iatrogenic preterm delivery	18–34	Single	< 15, < 25, < 30	< 7 days of testing, < 35
Fuchs[338]	2004	Germany	253	Cohort Prospective Blinded Test described	Singleton pregnancy presenting with threatened preterm labour, intact membrane, cervical dilatation < 3 cm	PPROM, cervical cerclage, requirement for iatrogenic preterm delivery, abruption, placenta praevia, suspected fetal distress	24–36	Single	< 15	< 7 days of testing
Tsoi[347]	2003	UK	216	Cohort Prospective Blinded Test described	Singleton viable pregnancies presenting with threatened preterm labour	Cervical dilatation > 3 cm or PPROM	24–36	Single	< 15	< 7 days of testing
Onderoglu[82]	1997	Turkey	90	Cohort Prospective Blinded Test described	Singletons, intact membrane, cervical dilatation < 3 cm, absence of fetal and maternal complications	×	25–36	Single	< 28	< 37

continued

TABLE 113 *Characteristics of test accuracy studies of cervical length measurement in predicting spontaneous preterm birth in women symptomatic with threatened preterm labour (continued)*

Authors	Year	Country	*n*	Study designs	Inclusion	Exclusion	Testing gestation (weeks)	Frequency of testing	Threshold (mm)	Outcome (weeks' gestation)[a]
Tekesin[346]	2005	Germany	85	Cohort Prospective Blinded Test described	Singleton pregnancy presenting with threatened preterm labour, intact membrane, cervical dilatation < 3 cm	Fetal abnormalities, PPROM, cervical cerclage, requirement for iatrogenic preterm delivery, abruption, placenta praevia, suspected fetal distress	24–36	Single	< 25	< 37
Kurkinen[233]	2001	Finland	76	Cohort Prospective Consecutive Test described	Consecutive singleton pregnant women between 22 and 32 weeks' gestation who presented with threatened preterm labour	PPROM, impending preterm delivery	22–32	Single	< 29.3	< 37
Tsoi[348]	2004	UK	63	Cohort Prospective Blinded Test described	Singleton pregnancy presenting with threatened preterm labour, intact membrane, cervical dilatation < 3 cm	PPROM	24–36	Single	< 15	< 7 days of testing
Rozenberg[134]	2003	France	28	Cohort Prospective Blinded Test described	Singleton pregnancy presenting with threatened preterm labour, intact membrane, cervical dilatation < 3 cm	History of cervical incompetence with cerclage, suspected chorioamnionitis, PPROM, polyhydramnios, placenta praevia, abruption, IUGR, pre-eclampsia, fetal distress, other maternal or fetal distress requiring preterm delivery	24–34	Single	< 26	< 37
Gomez[112]	2005	Chile	215	Cohort Prospective Test described	Singleton pregnancy presenting with threatened preterm labour, intact membrane, cervical dilatation < 3 cm	×	22–35	Single	< 15, < 30	< 48 h, < 7, < 14 days of testing, < 32, < 35

Authors	Year	Country	*n*	Study designs	Inclusion	Exclusion	Testing gestation (weeks)	Frequency of testing	Threshold (mm)	Outcome (weeks' gestation)[a]
Venditelli[390]	2001	France	174	Cohort Prospective Test described	Singleton pregnancies	Cervical dilatation > 3 cm, PPROM, cervical cerclage, active vaginal bleeding, known fetal malformation or death, placenta praevia	18–36	Single	< 30	< 37
Daskalakis[337]	2005	Greece	172	Cohort Prospective Test described	Singleton pregnancy presenting with threatened preterm labour, intact membrane, cervical dilatation < 3 cm	PPROM, cervical cerclage, requirement for iatrogenic preterm delivery, abruption, placenta praevia, suspected fetal distress	24–34	Single	< 20, < 25, < 30, < 35	< 34
Goffinet[339]	1997	France	108	Cohort Prospective Test described	Singleton pregnancies	Cervical cerclage, PPROM, cervical dilatation > 2 cm, iatrogenic preterm delivery	24–34	Single	< 26	< 37
Rizzo[227]	1996	Italy	108	Cohort Prospective Test described	Singleton pregnancies, intact membrane, cervical dilatation < 3 cm, absence of maternal or fetal complication	×	24–36	Single	< 20	< 37
Botsis[64]	2005	Greece	104	Cohort Prospective Test described	Singleton viable pregnancy presenting with threatened preterm labour between 24 and 36 weeks' gestation with intact fetal membrane and cervical dilatation < 2 cm	×	24–36	Single	< 15	< 7 days of testing
Murakawa[341]	1993	Japan	32	Cohort Prospective Test described	Singleton pregnancies	Suspicion of cervical incompetence	25–35	Single	< 30, < 35	< 37
Rageth[342]	1997	Switzerland	61	Cohort Retrospective Test described	Singleton pregnancies whose contraction has been arrested by tocolysis	IUGR, pre-eclampsia, diabetes	25–35	Single	< 30	< 34

IUGR, intrauterine growth restriction; PPROM, premature pre-labour rupture of membranes

a Unless otherwise stated.

TABLE 114 *Characteristics of test accuracy studies of cervical funnelling assessment in predicting spontaneous preterm birth stratified according to population of antenatal asymptomatic women and women symptomatic with threatened preterm labour*

Authors	Year	Country	*n*	Study designs	Inclusion	Exclusion	Testing gestation (weeks)	Frequency of testing	Threshold	Outcome (weeks' gestation)[a]
Asymptomatic women										
Leung[329]	2005	HK	2952	Cohort Prospective Consecutive Blinded Test described	Singleton pregnancy of ethnic Chinese women only	Fetal abnormalities, non-viable pregnancies, lack of outcome information, outside test gestation	18–22	Single	5 mm length	34
Iams[322]	1996	USA	2915	Cohort Prospective Consecutive Blinded Test described	Singleton pregnancies	Multiple gestations, cervical cerclage, placenta praevia, fetal anomaly	at 28	Twice	3 mm length	35
Andrews[325]	2000	USA	69	Cohort Prospective Consecutive Blinded Test described	Singleton pregnancies with previous history of spontaneous preterm birth between 16 and 30 weeks' gestation	Medical or obstetrical complication, history of incompetent cervix that required cerclage, presented for antenatal care after 28 weeks	25–29	Twice	any	35
To[334]	2001	UK	6334	Cohort Prospective Consecutive Test described	Singleton pregnancies	×	22–24	Single	5 mm width	33
Pires[332]	2005	Brazil	338	Cohort Prospective Test described	Singleton uncomplicated pregnancy	Previous history of preterm delivery, uterine or fetal abnormalities, miscarriage, fetal death, alteration in amniotic fluid, placenta praevia, previous uterine or cervical surgery, surgical procedures during gestation and conditions requiring iatrogenic preterm delivery	21–24	Single	any	35

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Authors	Year	Country	*n*	Study designs	Inclusion	Exclusion	Testing gestation (weeks)	Frequency of testing	Threshold	Outcome (weeks' gestation)[a]
Mara[330]	2002	Czech Republic	247	Case–control Prospective	Singleton viable pregnancy, delivery at investigating institutions	Congenital or chromosomal abnormalities, history of uterine or cervix surgery, greater than 3 previous vaginal deliveries	18–20	Single	any	34
Symptomatic women										
Crane[336]	1997	USA	136	Cohort Prospective Consecutive Blinded Test described	Singleton pregnancies whose contraction has been arrested by tocolysis	Cervical dilatation > 3 cm, placenta praevia, PPROM	24–34	Single	V-shaped	37
Gomez[340]	1994	USA	59	Cohort Prospective Consecutive Blinded Test described	Singleton pregnancies	PPROM, cervix dilatation >3 cm	21–35	Single	6 mm width	36
Kurkinen[233]	2001	Finland	76	Cohort Prospective Consecutive Test described	Consecutive singleton pregnant women between 22 and 32 weeks' gestation who presented with threatened preterm labour	PPROM, impending preterm delivery	22–32	Single	5 mm width	37
Okitsu[323]	1992	Japan	130	Cohort Prospective Test described	Singleton pregnancies	Placenta praevia	25–36	Single	5 mm width	36
Rizzo[227]	1996	Italy	108	Cohort Prospective Test described	Singleton pregnancies, intact membrane, cervical dilatation < 3 cm, absence of maternal or fetal complication		24–36	Single	5 mm width	37

a Unless otherwise stated.

TABLE 115 *Individual accuracy results of cervical length measurement in predicting spontaneous preterm birth among asymptomatic antenatal women stratified according to outcome (weeks' gestation) and testing gestation (weeks' gestation)*

Authors	Thresholds (mm)	Outcome (weeks' gestation)	TP	FP	FN	TN	sens	sens_lb	sens_ub
34 weeks' gestation									
< 20 weeks' gestation									
[a]Andrew[325]	25	35	5	0	10	38	0.33	0.12	0.62
[a]Andrew[325]	22	35	4	0	11	38	0.27	0.08	0.55
Leung[329]	25	34	5	48	15	2884	0.25	0.09	0.49
Leung[329]	15	34	2	0	18	2932	0.10	0.01	0.32
Leung[329]	30	34	7	288	13	2644	0.35	0.15	0.59
Leung[329]	35	34	12	1021	8	1911	0.60	0.36	0.81
Leung[329]	27	34	7	111	13	2821	0.35	0.15	0.59
Leung[329]	20	34	2	4	18	2928	0.10	0.01	0.32
Owen[331]	20	35	5	1	42	135	0.11	0.04	0.23
Owen[331]	25	35	9	3	39	132	0.19	0.09	0.33
Owen[331]	30	35	12	24	29	118	0.29	0.16	0.46
Owen[331]	15	35	5	0	43	135	0.10	0.03	0.23
Hibbard[328]	27	35	15	25	36	684	0.29	0.17	0.44
Hibbard[328]	22	35	11	16	40	693	0.22	0.11	0.35
Hibbard[328]	30	35	21	66	30	643	0.41	0.28	0.56
Mara[330]	20	34	3	0	6	238	0.33	0.07	0.70
20–24 weeks' gestation									
[a]Iams[322]	20	35	29	84	97	2705	0.23	0.16	0.31
[a]Andrews[325]	22	35	4	3	9	41	0.31	0.09	0.61
[a]Iams[322]	25	35	47	218	79	2571	0.37	0.29	0.46
[a]Andrews[325]	25	35	5	5	8	39	0.38	0.14	0.68
[a]Iams[325]	30	35	68	661	58	2128	0.54	0.45	0.63
To[334]	15	33	21	80	38	6195	0.36	0.24	0.49
Carvalho[66]	10	34	3	3	38	1734	0.07	0.02	0.20
Carvalho[66]	10	34	5	5	61	1887	0.08	0.03	0.17
Carvalho[66]	10	34	2	2	23	153	0.08	0.01	0.26
Carvalho[66]	15	34	23	16	43	1876	0.35	0.24	0.48
Carvalho[66]	15	34	11	6	14	149	0.44	0.24	0.65
Carvalho[66]	15	34	12	10	29	1727	0.29	0.16	0.46
Pires[332]	20	37	4	10	17	307	0.19	0.05	0.42
Carvalho[66]	20	34	34	47	32	1845	0.52	0.39	0.64
Carvalho[66]	20	34	18	17	7	138	0.72	0.51	0.88
Carvalho[66]	20	34	16	30	25	1707	0.39	0.24	0.55
Pires[332]	20	35	3	7	8	320	0.27	0.06	0.61
Carvalho[66]	25	34	38	171	28	1721	0.58	0.45	0.70
Carvalho[66]	25	34	19	38	6	117	0.76	0.55	0.91
Carvalho[66]	25	34	19	134	22	1603	0.46	0.31	0.63

specs	spec_lb	spec_ub	LR+	LR+_lb	LR+_ub	LR–	LR–_lb	LR–_ub
1.00	0.91	1.00	26.81	1.57	457.07	0.66	0.47	0.95
1.00	0.91	1.00	21.94	1.25	384.29	0.73	0.53	0.99
0.98	0.98	0.99	15.27	6.80	34.30	0.76	0.59	0.98
1.00	1.00	1.00	698.33	34.56	14,109.00	0.88	0.75	1.03
0.90	0.89	0.91	3.56	1.94	6.54	0.72	0.52	0.99
0.65	0.63	0.67	1.72	1.20	2.47	0.61	0.36	1.05
0.96	0.95	0.97	9.25	4.95	17.26	0.68	0.49	0.93
1.00	1.00	1.00	73.30	14.23	377.66	0.90	0.78	1.04
0.99	0.96	1.00	14.47	1.73	120.69	0.90	0.81	0.99
0.98	0.94	1.00	8.44	2.38	29.88	0.83	0.72	0.95
0.83	0.76	0.89	1.73	0.95	3.15	0.85	0.69	1.05
1.00	0.97	1.00	30.53	1.72	542.02	0.89	0.81	0.98
0.96	0.95	0.98	8.34	4.70	14.80	0.73	0.61	0.87
0.98	0.96	0.99	9.56	4.68	19.50	0.80	0.69	0.93
0.91	0.88	0.93	4.42	2.96	6.60	0.65	0.51	0.82
1.00	0.98	1.00	167.30	9.25	3024.97	0.65	0.41	1.03
0.97	0.96	0.98	7.64	5.21	11.20	0.79	0.72	0.87
0.93	0.81	0.99	4.51	1.15	17.64	0.74	0.51	1.08
0.92	0.91	0.93	4.77	3.68	6.19	0.68	0.59	0.78
0.89	0.75	0.96	3.38	1.16	9.91	0.69	0.45	1.08
0.76	0.75	0.78	2.28	1.91	2.71	0.60	0.50	0.73
0.99	0.98	0.99	27.92	18.59	41.92	0.65	0.54	0.79
1.00	0.99	1.00	42.37	8.81	203.65	0.93	0.85	1.01
1.00	0.99	1.00	28.67	8.51	96.62	0.93	0.86	0.99
0.99	0.95	1.00	6.20	0.91	42.03	0.93	0.83	1.05
0.99	0.99	1.00	41.21	22.87	74.26	0.66	0.55	0.78
0.96	0.92	0.99	11.37	4.62	27.97	0.58	0.41	0.83
0.99	0.99	1.00	50.84	23.31	110.90	0.71	0.58	0.87
0.97	0.94	0.98	6.04	2.07	17.64	0.84	0.68	1.03
0.98	0.97	0.98	20.74	14.37	29.92	0.50	0.39	0.64
0.89	0.83	0.93	6.56	3.94	10.94	0.31	0.17	0.59
0.98	0.98	0.99	22.60	13.41	38.07	0.62	0.49	0.79
0.98	0.96	0.99	12.74	3.79	42.80	0.74	0.52	1.07
0.91	0.90	0.92	6.37	4.95	8.19	0.47	0.35	0.62
0.75	0.68	0.82	3.10	2.18	4.41	0.32	0.16	0.64
0.92	0.91	0.93	6.01	4.16	8.67	0.58	0.44	0.77

continued

TABLE 115 *Individual accuracy results of cervical length measurement in predicting spontaneous preterm birth among asymptomatic antenatal women stratified according to outcome (weeks' gestation) and testing gestation (weeks')*

Authors	Thresholds (mm)	Outcome (weeks' gestation)	TP	FP	FN	TN	sens	sens_lb	sens_ub
[a]Guzman[738]	25	34	12	51	10	285	0.55	0.32	0.76
Carvalho[66]	30	34	42	442	24	1450	0.64	0.51	0.75
Carvalho[66]	30	34	22	372	19	1365	0.54	0.37	0.69
Carvalho[66]	30	34	20	71	5	84	0.80	0.59	0.93
37 weeks' gestation									
<20 weeks' gestation									
Hibbard[328]	22	37	11	10	74	665	0.13	0.07	0.22
Taipale[333]	25	37	5	8	83	3598	0.06	0.02	0.13
Hibbard[328]	27	37	17	23	68	652	0.20	0.12	0.30
Taipale[333]	29	37	14	96	74	3510	0.16	0.09	0.25
Hibbard[328]	30	37	28	59	57	616	0.33	0.23	0.44
Taipale[333]	35	37	31	962	57	2644	0.35	0.25	0.46
Andersen[324]	39	37	13	39	4	56	0.76	0.50	0.93
Taipale[333]	40	37	53	1875	35	1731	0.60	0.49	0.71
Taipale[333]	45	37	78	2731	10	875	0.89	0.80	0.94
Taipale[333]	50	37	87	3261	1	345	0.99	0.94	1.00
20–24 weeks' gestation									
Yazici[335]	32.5	36	16	61	6	274	0.73	0.50	0.89
Dilek[327]	33.15	37	14	29	4	203	0.78	0.52	0.94

FN, false negative; FP, false positive; lb, lower bound; LR,+, likelihood ratio for positive test; LR–, likelihood ratio for negative test; sens, sensitivity; spec, specificity; TN, true negative; TP, true positive; ub, upper bound.
a Women were scanned twice, a few weeks apart within the testing gestation.

specs	spec_lb	spec_ub	LR+	LR+_lb	LR+_ub	LR–	LR–_lb	LR–_ub
0.85	0.81	0.88	3.59	2.27	5.68	0.54	0.34	0.85
0.77	0.75	0.79	2.72	2.23	3.33	0.47	0.34	0.65
0.79	0.77	0.80	2.51	1.86	3.38	0.59	0.42	0.82
0.54	0.46	0.62	1.75	1.35	2.27	0.37	0.17	0.82
0.99	0.97	0.99	8.74	3.82	19.96	0.88	0.81	0.96
1.00	1.00	1.00	25.61	8.55	76.72	0.95	0.90	1.00
0.97	0.95	0.98	5.87	3.27	10.53	0.83	0.74	0.92
0.97	0.97	0.98	5.98	3.56	10.04	0.86	0.79	0.95
0.91	0.89	0.93	3.77	2.55	5.56	0.73	0.63	0.85
0.73	0.72	0.75	1.32	0.99	1.76	0.88	0.76	1.03
0.59	0.48	0.69	1.86	1.30	2.66	0.40	0.17	0.96
0.48	0.46	0.50	1.16	0.97	1.38	0.83	0.64	1.07
0.24	0.23	0.26	1.17	1.08	1.26	0.47	0.26	0.84
0.10	0.09	0.11	1.09	1.07	1.12	0.12	0.02	0.84
0.82	0.77	0.86	3.99	2.84	5.62	0.33	0.17	0.66
0.88	0.83	0.91	6.22	4.09	9.48	0.25	0.11	0.60

TABLE 116 *Individual accuracy results of cervical length measurement in predicting spontaneous preterm birth among women symptomatic with threatened preterm labour stratified according to outcome (within days of testing and according to weeks' gestation)*

Authors	Thresholds (mm)	TP	FP	FN	TN	sens	sens_lb	sens_ub
< 48 h of testing								
Tsoi[348]	5	9	11	12	478	0.43	0.22	0.66
Tsoi[348]	10	17	31	4	458	0.81	0.58	0.95
Tsoi[348]	15	21	74	0	415	1.00	0.84	1.00
Tsoi[348]	20	21	150	0	339	1.00	0.84	1.00
Gomez[340]	15	11	19	6	179	0.65	0.38	0.86
Gomez[340]	30	15	93	2	105	0.88	0.64	0.99
< 7 days of testing								
Tsoi[348]	5	16	4	27	463	0.37	0.23	0.53
Tsoi[348]	10	28	20	15	447	0.65	0.49	0.79
Tsoi[348]	15	42	53	1	414	0.98	0.88	1.00
Tsoi[348]	20	42	129	1	338	0.98	0.88	1.00
Schmitz[345]	15	12	45	11	291	0.52	0.31	0.73
Schmitz[345]	25	20	131	3	205	0.87	0.66	0.97
Schmitz[345]	30	23	193	0	143	1.00	0.85	1.00
Fuchs[338]	15	17	19	4	213	0.81	0.58	0.95
Tsoi[348]	15	16	27	1	172	0.94	0.71	1.00
Tsoi[348]	15	20	10	0	33	1.00	0.83	1.00
Gomez[340]	15	17	13	11	174	0.61	0.41	0.78
Gomez[340]	30	25	83	3	104	0.89	0.72	0.98
Botsis[64]	15	10	9	1	84	0.91	0.59	1.00
Gomez[340]	15	17	13	17	168	0.50	0.32	0.68
Gomez[340]	30	29	79	5	102	0.85	0.69	0.95
< 34 weeks' gestation								
Gomez[340]	15	7	5	2	87	0.78	0.40	0.97
Gomez[340]	30	9	40	0	52	1.00	0.66	1.00
Crane[336]	30	30	35	7	64	0.81	0.65	0.92
Daskalakis[337]	20	21	3	18	60	0.54	0.37	0.70
Daskalakis[337]	25	28	13	11	50	0.72	0.55	0.85
Daskalakis[337]	30	39	21	0	42	1.00	0.91	1.00
Daskalakis[337]	35	39	47	0	16	1.00	0.91	1.00
Daskalakis[337]	20	15	1	10	44	0.60	0.39	0.79
Daskalakis[337]	25	16	9	9	36	0.64	0.43	0.82
Daskalakis[337]	30	25	15	0	30	1.00	0.86	1.00
Daskalakis[337]	35	25	33	0	12	1.00	0.86	1.00
Rageth[342]	30	4	25	0	32	1.00	0.40	1.00
Tsoi[348]	5	17	3	59	431	0.22	0.14	0.33
Tsoi[348]	10	33	15	43	419	0.43	0.32	0.55
Tsoi[348]	15	54	41	22	393	0.71	0.60	0.81

specs	spec_lb	spec_ub	LR+	LR+_lb	LR+_ub	LR–	LR–_lb	LR–_ub
0.98	0.96	0.99	19.05	8.87	40.94	0.58	0.40	0.85
0.94	0.91	0.96	12.77	8.57	19.03	0.20	0.08	0.49
0.85	0.81	0.88	6.43	5.17	8.00	0.03	0.00	0.42
0.69	0.65	0.73	3.18	2.75	3.69	0.03	0.00	0.51
0.90	0.85	0.94	6.74	3.88	11.72	0.39	0.20	0.74
0.53	0.46	0.60	1.88	1.50	2.36	0.22	0.06	0.82
0.99	0.98	1.00	43.44	15.20	124.17	0.63	0.50	0.80
0.96	0.93	0.97	15.20	9.40	24.61	0.36	0.24	0.55
0.89	0.85	0.91	8.61	6.65	11.14	0.03	0.00	0.18
0.72	0.68	0.76	3.54	3.03	4.12	0.03	0.00	0.22
0.87	0.82	0.90	3.90	2.42	6.27	0.55	0.36	0.85
0.61	0.56	0.66	2.23	1.81	2.74	0.21	0.07	0.62
0.43	0.37	0.48	1.71	1.53	1.90	0.05	0.00	0.76
0.92	0.88	0.95	9.88	6.13	15.95	0.21	0.09	0.50
0.86	0.81	0.91	6.94	4.79	10.05	0.07	0.01	0.46
0.77	0.61	0.88	4.09	2.40	6.96	0.03	0.00	0.49
0.93	0.88	0.96	8.73	4.78	15.96	0.42	0.27	0.67
0.56	0.48	0.63	2.01	1.64	2.47	0.19	0.07	0.57
0.90	0.82	0.95	9.39	4.91	17.97	0.10	0.02	0.65
0.93	0.88	0.96	6.96	3.74	12.97	0.54	0.38	0.76
0.56	0.49	0.64	1.95	1.57	2.43	0.26	0.11	0.59
0.95	0.88	0.98	14.31	5.70	35.95	0.23	0.07	0.80
0.57	0.46	0.67	2.18	1.66	2.86	0.09	0.01	1.33
0.65	0.54	0.74	2.29	1.68	3.12	0.29	0.15	0.58
0.95	0.87	0.99	11.31	3.61	35.42	0.48	0.34	0.68
0.79	0.67	0.89	3.48	2.06	5.87	0.36	0.21	0.60
0.67	0.54	0.78	2.94	2.08	4.16	0.02	0.00	0.30
0.25	0.15	0.38	1.33	1.15	1.54	0.05	0.00	0.79
0.98	0.88	1.00	27.00	3.79	192.51	0.41	0.25	0.66
0.80	0.65	0.90	3.20	1.66	6.16	0.45	0.26	0.77
0.67	0.51	0.80	2.91	1.93	4.38	0.03	0.00	0.45
0.27	0.15	0.42	1.35	1.12	1.62	0.07	0.00	1.15
0.56	0.42	0.69	2.05	1.36	3.09	0.18	0.01	2.50
0.99	0.98	1.00	32.36	9.72	107.75	0.78	0.69	0.88
0.97	0.94	0.98	12.56	7.18	21.98	0.59	0.48	0.71
0.91	0.87	0.93	7.52	5.44	10.41	0.32	0.22	0.46

continued

TABLE 116 *Individual accuracy results of cervical length measurement in predicting spontaneous preterm birth among women symptomatic with threatened preterm labour stratified according to outcome (within days of testing and according to weeks' gestation) (continued)*

Authors	Thresholds (mm)	TP	FP	FN	TN	sens	sens_lb	sens_ub
Tsoi[349]	20	59	112	17	322	0.78	0.67	0.86
Schmitz[345]	15	22	35	26	276	0.46	0.31	0.61
Schmitz[345]	25	36	115	12	196	0.75	0.60	0.86
Schmitz[345]	30	43	173	5	138	0.90	0.77	0.97
Gomez[112]	15	19	11	15	170	0.56	0.38	0.73
Gomez[112]	30	30	78	4	103	0.88	0.73	0.97
< 37 weeks' gestation								
Crane[336]	30	30	35	7	64	0.81	0.65	0.92
Gomez[112]	18	16	8	6	29	0.73	0.50	0.89
Onderoglu[86]	28	25	10	7	48	0.78	0.60	0.91
Tekesin[346]	25	17	22	6	40	0.74	0.52	0.90
Rozenberg[134]	26	14	6	2	6	0.88	0.62	0.98
Venditelli[350]	30	55	53	12	54	0.82	0.71	0.90
Rizzo[227]	20	32	13	15	48	0.68	0.53	0.81
Goffinet[339]	26	19	28	5	56	0.79	0.58	0.93
Murakawa[341]	25	7	3	4	18	0.64	0.31	0.89
Murakawa[341]	30	11	6	0	15	1.00	0.72	1.00
Murakawa[341]	35	11	14	0	7	1.00	0.72	1.00

FN, false negative; FP, false positive; lb, lower bound; LR,+, likelihood ratio for positive test; LR–, likelihood ratio for negative test; sens, sensitivity; spec, specificity; TN, true negative; TP, true positive; ub, upper bound.

specs	spec_lb	spec_ub	LR+	LR+_lb	LR+_ub	LR–	LR–_lb	LR–_ub
0.74	0.70	0.78	3.01	2.46	3.67	0.30	0.20	0.46
0.89	0.85	0.92	4.07	2.63	6.31	0.61	0.47	0.79
0.63	0.57	0.68	2.03	1.63	2.52	0.40	0.24	0.65
0.44	0.39	0.50	1.61	1.40	1.85	0.23	0.10	0.54
0.94	0.89	0.97	9.20	4.82	17.54	0.47	0.32	0.69
0.57	0.49	0.64	2.05	1.66	2.52	0.21	0.08	0.52
0.65	0.54	0.74	2.29	1.68	3.12	0.29	0.15	0.58
0.78	0.62	0.90	3.36	1.73	6.54	0.35	0.17	0.70
0.83	0.71	0.91	4.53	2.50	8.20	0.26	0.14	0.51
0.65	0.51	0.76	2.08	1.38	3.15	0.40	0.20	0.82
0.50	0.21	0.79	1.75	0.96	3.17	0.25	0.06	1.03
0.50	0.41	0.60	1.66	1.33	2.07	0.35	0.21	0.61
0.79	0.66	0.88	3.19	1.90	5.38	0.41	0.26	0.63
0.67	0.56	0.77	2.38	1.65	3.42	0.31	0.14	0.69
0.86	0.64	0.97	4.45	1.43	13.91	0.42	0.19	0.95
0.71	0.48	0.89	3.24	1.68	6.25	0.06	0.00	0.90
0.33	0.15	0.57	1.45	1.05	2.01	0.12	0.01	1.96

TABLE 117 *Individual accuracy results of cervical funnelling assessment in predicting spontaneous preterm birth among asymptomatic women and women symptomatic with threatened preterm labour stratified according to outcome (weeks' gestation)*

Authors	Thresholds	Outcome (weeks' gestation)	TP	FP	FN	TN	sens	sens_lb	sens_ub
Asymptomatic women									
[a]Leung[a]	Any	34	6	175	14	2757	0.30	0.12	0.54
[b,c]Andrews[325]	Any	35	5	0	10	38	0.33	0.12	0.62
[b,c]Andrews[325]	Any	35	7	8	2	24	0.78	0.40	0.97
[b]To[334]	5 mm width	33	16	215	43	6103	0.27	0.16	0.40
[a]Pires[332]	Any	37	3	11	18	324	0.14	0.03	0.36
[a]Pires[332]	Any	35	3	11	8	316	0.27	0.06	0.61
[a]Mara[332]	Any	34	7	33	2	205	0.78	0.40	0.97
[a]Mara[332]	Any	37	22	18	11	196	0.67	0.48	0.82
Symptomatic women									
Crane[336]	V-shaped	37	7	9	25	95	0.22	0.09	0.40
Crane[336]	V-shaped	34	4	12	5	115	0.44	0.14	0.79
Gomez[340]	Any	36	17	17	5	20	0.77	0.55	0.92
Gomez[340]	6 mm width	36	14	8	7	25	0.67	0.43	0.85
Gomez[340]	9 mm length	36	15	3	6	30	0.71	0.48	0.89
Rizzo[227]	5 mm width	37	34	20	13	41	0.72	0.57	0.84
Okitsu[323]	5 mm width	36	9	18	4	46	0.69	0.39	0.91

FN, false negative; FP, false positive; lb, lower bound; LR,+, likelihood ratio for positive test; LR–, likelihood ratio for negative test; sens, sensitivity; spec, specificity; TN, true negative; TP, true positive; ub, upper bound.
a Testing < 20 weeks' gestation.
b Testing between 20 and 24 weeks' gestation.
c Tested twice within 2 weeks.

specs	spec_lb	spec_ub	LR+	LR+_lb	LR+_ub	LR–	LR–_lb	LR–_ub
0.94	0.93	0.95	5.03	2.53	9.97	0.74	0.56	0.99
1.00	0.91	1.00	26.81	1.57	457.07	0.66	0.47	0.95
0.75	0.57	0.89	3.11	1.55	6.23	0.30	0.09	1.02
0.97	0.96	0.97	7.97	5.14	12.35	0.75	0.65	0.88
0.97	0.94	0.98	4.35	1.31	14.42	0.89	0.74	1.06
0.97	0.94	0.98	8.11	2.63	25.01	0.75	0.52	1.08
0.86	0.81	0.90	5.61	3.50	8.99	0.26	0.08	0.88
0.92	0.87	0.95	7.93	4.79	13.12	0.36	0.22	0.59
0.91	0.84	0.96	2.53	1.02	6.25	0.86	0.71	1.04
0.91	0.84	0.95	4.70	1.90	11.66	0.61	0.34	1.10
0.54	0.37	0.71	1.68	1.11	2.55	0.42	0.18	0.96
0.76	0.58	0.89	2.75	1.40	5.40	0.44	0.23	0.83
0.91	0.76	0.98	7.86	2.58	23.90	0.31	0.16	0.62
0.67	0.54	0.79	2.21	1.48	3.29	0.41	0.25	0.67
0.72	0.59	0.82	2.46	1.44	4.20	0.43	0.19	0.98

Appendix 6

Characteristics and results of individual included effectiveness studies

Asymptomatic women

TABLE 118 *Antibiotics for urogenital infection*

Review details	Methods	Results and conclusions
Smaill [Cochrane Database of Systematic Reviews 2005, Issue 4][351] ***Title:*** Antibiotics for asymptomatic bacteriuria in pregnancy ***Type of review:*** Cochrane ***Prevalence:*** *Symptomatic for preterm birth –* Not reported *Preterm birth* – OR low birthweight < 2500 g 127 (out of 879 in total) 63 (out of 431 in total) 48 (out of 300 in total)	***Search:*** *Databases searched (Search dates)* Cochrane Pregnancy and Childbirth Group Trials Register (Dec 2000) *Other sources* None stated *Search restrictions* None stated ***Inclusion/exclusion criteria:*** *Study design(s)* RCTs. Quasi-RCTs were also included in the review *Population* Pregnant women with asymptomatic bacteriuria found on screening *Intervention* Any antibiotic regimen vs placebo/no treatment *Outcomes* Persistent bacteriuria, pyelonephritis, preterm delivery, low birthweight ***Study selection:*** Trials were selected for inclusion by one reviewer ***Data extraction:*** This was carried out by one reviewer ***Validity assessment:*** *Criteria used* Allocation concealment, randomisation, blinding of intervention and outcome, completeness of follow-up	***No. of studies included:*** 14 RCTs ($n = 2643$) 8 studies compared treatment with placebo and six studies with no treatment. These are grouped together in the review ***Comparisons*** 01. antibiotics vs no treatment 02. continuous antibiotic therapy vs no treatment 03. short course (3–7 days) antibiotic therapy vs no treatment ***No. of studies meeting quality criteria:*** *Adequate randomisation* – 1 *Adequate concealment of allocation* – 1 *Adequate blinding of clinician/patient/researcher* – 3/3/0 ***Incidence of birth < 34 weeks' gestation:*** Not reported (see below) ***Incidence of birth < 37 weeks' gestation:*** When defined, preterm birth defined as birthweight <2500g 01. OR 0.60 (95% CI: 0.45–0.80) (10 studies, $n = 1923$) 02. OR 0.62 (95% CI: 0.42–0.93) (6 studies, $n = 987$) 03. OR 0.41 (95% CI: 0.25–0.67) (3 studies, $n = 655$) ***Incidence of birth within 24 h of intervention:*** Not applicable ***Incidence of birth within 48 h of intervention:*** Not applicable ***Incidence of birth within 7 days of intervention:*** Not applicable ***Incidence of neonatal intensive care admission:*** Not reported ***Incidence of perinatal mortality:*** Not reported

Review details	Methods	Results and conclusions
	Assessment This was carried out by one reviewer ***Synthesis:*** *Heterogeneity* Heterogeneity was assessed using chi-squared and *I*-squared tests and none was found *Methods* Summary estimates were calculated (Peto odds ratio). Data on the number of participants with each outcome were sought to allow an intention-to-treat analysis	***Incidence of adverse events:*** *Persistent bacteriuria* 01. OR 0.07 (95% CI: 0.05–0.10) (4 studies, $n = 593$) 02. OR 0.21 (95% CI: 0.08–0.56) (1 study, $n = 65$) 03. OR 0.11 (95% CI: 0.04–0.27) (1 study, $n = 69$) *Development of pyelonephritis* 01. OR 0.24 (95% CI: 0.19–0.32) (13 studies, $n = 2189$) 02. OR 0.21 (95% CI: 0.15–0.31) (6 studies, $n = 1005$) 03. OR 0.35 (95% CI: 0.21–0.58) (5 studies, $n = 725$) ***Brief summary of findings:*** Antibiotic treatment compared with placebo/no treatment was effective in clearing asymptomatic bacteriuria and was associated with a reduction in the incidence of pyelonephritis, preterm birth and low birthweight where these two outcomes are conflated ***Authors' conclusions:*** Antibiotic treatment is effective in reducing the risk of pyelonephritis in pregnancy. An apparent association with a reduction in preterm delivery should be interpreted with caution ***Comments:*** Only one person selected studies and extracted the data. The author notes methodological concern about the primary studies and reports that it is difficult to accurately assess their quality because of the lack of detail given. There was no consistent application of standard definitions for the outcomes. Preterm delivery when defined usually referred to birthweight < 2500 g

TABLE 118 *Antibiotics for urogenital infection (continued)*

Review details	Methods	Results and conclusions
Villar et al. [Cochrane Database of Systematic Reviews 2006, Issue 1][363] ***Title:*** Duration of treatment for asymptomatic bacteriuria during pregnancy ***Type of review:*** Cochrane ***Prevalence:*** *Symptomatic for preterm birth –* Not reported *Preterm birth –* Not reported	***Search:*** *Databases searched (Search dates)* Cochrane Pregnancy and Childbirth Group Trials Register (April 2004) *Other sources* Reference lists of identified articles *Search restrictions* None specified ***Inclusion/exclusion criteria:*** *Study design(s)* RCTs and quasi RCTs *Population* Women diagnosed during pregnancy with asymptomatic bacteriuria (1 trial included 24% symptomatic patients in both groups) *Intervention* Antibiotic regimens of differing duration: single-dose, short-course (4–7 days), long-course (14 days), continuous (treatment continued until after delivery). Trials comparing different therapeutic interventions with the same duration of intervention were excluded from the review. Drugs used were ampicillin, cephalexin, fosfomycin trometamol, amoxicillin, cotrimoxazole, trimethoprim and other sulphonamides *Outcomes* Maternal outcomes: cure rate, recurrent asymptomatic bacteriuria, pyelonephritis, need for repeat treatment Newborn outcomes including preterm birth and low birthweight. Side effects were also outcomes of interest ***Study selection:*** Carried out independently ***Data extraction:*** This was conducted independently and data were jointly reviewed before being analysed. Discrepancies were resolved by discussion ***Validity assessment:*** *Criteria used* Allocation concealment, blinding of outcome assessment, blinding of clinicians and patients, contamination in the control groups, attrition bias, co-intervention and protocol deviation	***No. of studies included:*** Eight RCTs, two quasi-RCTs ($n = 568$) All studies compared single-dose treatment with 4–7-day treatments ***No. of studies meeting quality criteria:*** *Adequate randomisation* – 2 *Adequate concealment of allocation* – 1 *Adequate blinding of clinician/patient/researcher* – 1/0/0 ***Incidence of birth < 34 weeks' gestation:*** Not reported ***Incidence of birth < 37 weeks' gestation:*** Single-dose vs short-course (Fixed effects) RR 0.81 (95% CI: 0.26–2.57) (2 studies, $n = 101$) ***Incidence of birth within 24h of intervention:*** Not applicable ***Incidence of birth within 48h of intervention:*** Not applicable ***Incidence of birth within 7 days of intervention:*** Not applicable ***Incidence of neonatal intensive care admission:*** Not reported ***Incidence of perinatal mortality:*** Not reported ***Incidence of adverse events:*** No statistically significant between-group differences found for cure rate, recurrence rate, side effects, or pyelonephritis ***Brief summary of findings:*** No statistically significant between-group differences were found for the outcomes measured (cure rate, recurrence rate, preterm births, pyelonephritis and side effects). The trials were of varying and often poor quality ***Authors' conclusions:*** There is not enough evidence to evaluate whether single-dose or longer duration doses are equivalent in treating asymptomatic bacteriuria in pregnant women

Review details	Methods	Results and conclusions
	Assessment Decisions were made by consensus ***Synthesis:*** *Heterogeneity* This was assessed using the chi-squared test *Methods* Meta-analysis using the fixed effect model. Trials were divided into two groups: trials that used the same drug in treatment and control groups and trials that used different ones. Outcomes were analysed for each group	***Comments:*** This was a well-conducted review. The authors discuss areas of methodological concern about the primary studies, which they considered to be of poor methodological quality

TABLE 118 *Antibiotics for urogenital infection (continued)*

Review details	Methods	Results and conclusions
McDonald et al. [Cochrane Database of Systematic Reviews 2005, Issue 4][375] ***Title:*** Antibiotics for treating bacterial vaginosis in pregnancy ***Type of review:*** Cochrane ***Prevalence:*** *Symptomatic for preterm birth –* Not reported *Preterm birth –* < 37 weeks' gestation: 01. 365 (out of 2607 in total); General population 213 (out of 1866 in total), high-risk population 102 (out of 299 in total). 02. 253 (out of 1690 in total) 03. 80 (out of 781 in total) < 34 weeks' gestation: 01. 21 (out of 418 in total); general population 10 (out of 320 in total), high risk population 11 (out of 98 in total) 02. 20 (out of 397 in total) 03. 1 (out of 11 in total)	***Search:*** *Databases searched (search dates)* Cochrane Pregnancy and Childbirth Group Trials Register (May 2004) *Other sources* None stated *Search restrictions* None stated ***Inclusion/exclusion criteria:*** *Study design(s)* RCTs *Population* Pregnant women with bacterial vaginosis, either symptomatic or asymptomatic, or intermediate vaginal flora *Intervention* Any antibiotic vs placebo/no treatment, or two antibiotic regimens compared *Outcomes* Maternal symptoms, including failure to achieve 'microbiological cure', chorioamnionitis, postpartum uterine infection, pregnancy loss up to 24 weeks' gestation Neonatal outcomes, including perinatal death, severe neonatal morbidity, neonatal sepsis, preterm pre-labour rupture of membranes, preterm birth, low birthweight, admission to neonatal unit, duration of ventilatory support Maternal side effects ***Study selection:*** Two reviewers independently assessed studies for potential inclusion. Study authors were contacted for additional information ***Data extraction:*** Two authors independently extracted data ***Validity assessment:*** *Criteria used* Trials were assessed using standard Cochrane criteria: allocation concealment, blinding of randomisation, blinding of intervention and outcome assessment, completeness of follow-up	***No. of studies included:*** 13 RCTs ($n = 5300$) 12 trials were placebo controlled, one trial compared once daily vs twice daily regimens ***No. of studies meeting quality criteria:*** *Adequate randomisation* – 12 *Adequate concealment of allocation* – 8 *Adequate blinding of clinician/patient/researcher* – 0/0/0 ***Incidence of birth < 34 weeks' gestation:*** 01. OR 1.22 (95% CI: 0.67–2.19) (5 studies, $n = 851$); General population OR 0.95 (95% CI: 0.38–2.37), (2 studies, $n = 628$) high-risk women OR 1.45 (95% CI: 0.67–3.14) (3 studies, $n = 223$) 02. OR 1.30 (95% CI: 0.72–2.35) (3 studies, $n = 819$) 03. OR 1.00 (95% CI: 0.06–17.12) (1 study, $n = 22$) 04. OR 1.21 (95% CI: 0.59–2.49) (4 studies, $n = 257$) ***Incidence of birth < 37 weeks' gestation:*** 01. OR 0.87 (95% CI: 0.74–1.03) (13 studies, $n = 5300$); General population OR 1.01 (95% CI: 0.82–1.24) (6 studies $n = 3703$), high-risk women OR 0.87 (95% CI: 0.74–1.03) (5 studies, $n = 703$) 02. OR 0.84 (95% CI: 0.69–1.02) (6 studies, $n = 3481$) 03. OR 0.92 (95% CI: 0.65–1.28) (4 studies, $n = 1565$) 04. OR 0.83 (95% CI: 0.59–1.17) (5 studies, $n = 622$) 05. OR 0.40 (95% CI: 0.11–1.39) (1 study, $n = 94$) 06. OR 0.51 (95% CI: 0.32–0.81) (1 study, $n = 894$) ***Incidence of birth within 24 h of intervention:*** Not applicable ***Incidence of birth within 48 h of intervention:*** Not applicable. ***Incidence of birth within 7 days of intervention:*** Not applicable ***Incidence of neonatal care admission (unclear if this is intensive care):*** 06. OR 0.73 (95% CI: 0.39–1.39) (1 study, $n = 466$)

Review details	Methods	Results and conclusions
	Assessment Carried out independently by two authors ***Synthesis:*** *Heterogeneity* Heterogeneity was explored using the chi-squared test. *Methods* Trials were stratified by quality to explore the robustness of the findings. Summary estimates were calculated (Peto odds ratio) where there was no evidence of significant heterogeneity. Where significant heterogeneity was found the random effects model was used. Subgroup analyses assessed the effect of oral vs vaginal antibiotics, women with a previous preterm birth and women with intermediate flora/bacterial vaginosis ***Comparisons:*** 01. Any antibiotic vs placebo 02. Oral antibiotics vs placebo 03. Vaginal antibiotics vs placebo 04. Previous preterm delivery: antibiotics vs placebo 05. Single daily dose vs double daily dose vaginal antibiotic 06. Intermediate flora/bacterial vaginosis: antibiotics vs placebo	***Incidence of perinatal mortality:*** 01. OR 2.17 (95% CI: 0.72–6.54) (2 studies, $n = 749$) 02. OR 2.03 (95% CI: 0.67–6.13) (2 studies, $n = 739$) 03. OR 0.35 (95% CI: 0.05–2.52) (1 study, $n = 409$) 04. OR 3.64 (95% CI: 0.86–15.45) (2 studies, $n = 155$) 06. OR 0.50 (95% CI: 0.10–2.48) (2 studies, $n = 894$) ***Incidence of adverse events:*** *PPROM:* 04. OR 0.14 (95% CI: 0.05–0.38) (2 studies, $n = 114$) *Low birthweight:* 01. OR 0.95 (95% CI: 0.77–1.17) (7 studies $n = 4107$) general pop OR 1.00 (95% CI: 0.79–1.27) (4 studies $n = 3151$) high risk 0.33 (95% CI: 0.11–0.93) (1 study, $n = 80$) 04. OR 0.31 (95% CI: 0.13–0.75) (2 studies, $n = 114$) *Late miscarriage:* 06. OR 0.25 (95% CI: 0.08–0.79) (1 study, $n = 485$) No other between group differences were found for the adverse events listed above, or for the other adverse events reported: postpartum infection, neonatal sepsis, side effects sufficient to stop treatment, and side effects not sufficient to stop treatment. ***Brief summary of findings:*** Antibiotic therapy was effective at eradicating bacterial vaginosis during pregnancy. It was not significant in reducing the risk of preterm birth or of preterm pre-labour rupture of membranes. In women with a previous preterm birth, treatment did not affect the risk of subsequent preterm birth but may decrease the risk of preterm pre-labour rupture of membranes and low birthweight ***Authors' conclusions:*** Antibiotics can eradicate bacterial vaginosis in pregnancy but this review provides little evidence that screening and treating all pregnant women with asymptomatic bacterial vaginosis will prevent preterm birth and its consequences. For women with previous preterm birth there is some suggestion that treatment of bacterial vaginosis may reduce the risk of preterm pre-labour rupture of membranes and low birthweight The effect of earlier treatment needs to be studied in further trials ***Comments:*** This was a well-conducted review with clear reporting of the methodology and primary studies. The authors discuss the limitations of the trials Loss to follow-up of < 20% was reported in eight of the included trials

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TABLE 118 *Antibiotics for urogenital infection (continued)*

Study details and design	Description of methods	Results and conclusions
Ugwumadu et al. [Lancet 2003; 361: 983–988][386] ***Country:*** UK ***Setting:*** Outpatient ***Prevalence:*** *Preterm birth* – 28 (of 241 in total) ***Study design:*** RCT Length of follow-up: To delivery ***No. of participants:*** *No. randomised* – 494 *No. analysed* – 485 ***Validity:*** *Adequate randomisation* – Yes *Adequate allocation concealment* – Yes *Blinding of clinician* – Yes *Blinding of patient* – Yes *Blinding of researcher* – Yes ***Type of analysis:*** Sample size calculation showing 239 women/group would detect 9% difference in spontaneous preterm delivery/late miscarriage with 90% power and 5% significance level. Categorical variables analysed using Fisher's exact test and continuous variables with t test.	***Groups compared:*** Clindamycin vs Placebo ***Intervention details:*** Clindamycin 300 mg b.i.d. for 5 days ***Participants:*** Asymptomatic women at 12–22 weeks' gestation who tested positive for abnormal vaginal flora and/or bacterial vaginosis ***Participant inclusion/exclusion criteria:*** Women at their first antenatal clinic visit at between 12 and 16 weeks' gestation (later protocol amendment to 12–22 weeks) that screened positive for abnormal vaginal flora and/or bacterial vaginosis were included. Women with multiple pregnancy, need for/had cervical cerclage, history of cone biopsy, uterine, cervical or fetal anomaly, diabetes, renal disease, collagen disease, lupus, antiphospholipid syndrome, essential hypertension, known allergy to clindamycin, < 16 years old, reported fishy smelling vaginal discharge were excluded ***Outcomes:*** Outcomes of pregnancy including spontaneous preterm delivery, late miscarriage and death in utero; admission to neonatal intensive care unit, low birthweight < 2500 g, < 1500 g	***Incidence of birth < 34 weeks' gestation:*** Not reported ***Incidence of birth < 37 weeks' gestation:*** *No. in intervention group (total no.)* = 11 (244) *No. in control group (total no.)* = 28 (241) ***Incidence of birth within 24 h of intervention:*** Not applicable ***Incidence of birth within 48 h of intervention:*** Not applicable ***Incidence of birth within 7 days of intervention:*** Not applicable ***Incidence of neonatal intensive care admission:*** *No. in intervention group (total no.)* = 18 (238) *No. in control group (total no.)* = 23 (228) ***Incidence of perinatal mortality:*** Not reported ***Incidence of adverse events:*** Late miscarriage *No. in intervention group (total no.)* = 2 (244) *No. in control group (total no.)* = 10 (241) Death in utero *No. in intervention group (total no.)* = 1 (244) *No. in control group (total no.)* = 1 (241) Elective preterm delivery *No. in intervention group (total no.)* = 8 (244) *No. in control group (total no.)* = 3 (241) Low birthweight < 2500g *No. in intervention group (total no.)* = 20 (240) *No. in control group (total no.)* = 23 (227) Low birthweight < 1500g *No. in intervention group (total no.)* = 10 (240) *No. in control group (total no.)* = 4 (227)

Study details and design	Description of methods	Results and conclusions
Kaplan-Meier survival curves used for time to delivery, miscarriage or last known follow-up		Reported side effects *No. in intervention group (total no.)* = 17 (239) *No. in control group (total no.)* = 8 (239) ***Brief summary of findings:*** Significantly fewer preterm deliveries occurred in the clindamycin group ($p = 0.001$) ***Authors' conclusions:*** Treatment of asymptomatic abnormal vaginal flora with oral clindamycin early in the 2nd trimester significantly reduces the rate of late miscarriage and spontaneous preterm birth in a general population ***Comments:*** Good quality RCT. Authors identified differences in baseline history of previous miscarriages (more women in placebo) but say previous history is not associated with increased risk as demonstrated in two previous studies. There were also differences in the number of women of black Caribbean and white origin. The authors caution that their findings may not be generalisable to other populations and state the need to replicate findings in other studies

TABLE 118 *Antibiotics for urogenital infection (continued)*

Review details	Methods	Results and conclusions
Brocklehurst [Cochrane Database of Systematic Reviews, Issue 4, 2005][391] ***Title:*** Antibiotics for gonorrhoea in pregnancy ***Type of review:*** Cochrane ***Prevalence:*** *Symptomatic for preterm birth –* Not reported *Preterm birth –* Not reported	***Search:*** *Databases searched (search dates)* Cochrane Pregnancy and Childbirth Group Trials Register (Feb 2004) *Other sources* None specified *Search restrictions* None specified ***Inclusion/exclusion criteria:*** *Study design(s)* RCTs *Population* Pregnant women at any stage of pregnancy with culture-confirmed genital gonococcal infection, whether symptomatic or asymptomatic *Intervention* Any antibiotic vs penicillin or two or more alternative antibiotics *Outcomes* Neonatal ophthalmia neonatorum; other neonatal gonococcal infection; post partum sepsis in the treated mothers; failure to eradicate gonorrhoea from the genital tract of treated mothers as determined by gonococcal culture after treatment; side effects ***Study selection:*** This was conducted by one reviewer ***Data extraction:*** This was conducted by one reviewer ***Validity assessment:*** *Criteria used* 'Standard Cochrane criteria' were used to assess the studies: allocation concealment, randomisation, blinding of intervention and outcome assessment and completeness of follow-up. *Assessment* Carried out by one reviewer ***Synthesis:*** *Heterogeneity* No information on how this was addressed, as no pooling took place statistical assessment was not possible	***No. of studies included:*** 2 RCTs ($n = 346$) ***No. of studies meeting quality criteria:*** *Adequate randomisation* – 2 *Adequate concealment of allocation* – 0 *Adequate blinding of clinician/patient/researcher* – 0/0/0 ***Incidence of birth < 34 weeks' gestation:*** Not reported ***Incidence of birth < 37 weeks' gestation:*** Not reported ***Incidence of birth within 24h of intervention:*** Not reported ***Incidence of birth within 48h of intervention:*** Not reported ***Incidence of birth within 7 days of intervention:*** Not reported ***Incidence of neonatal intensive care admission:*** Not reported ***Incidence of perinatal mortality:*** Not reported ***Incidence of adverse events:*** One study reported 0/43 events sufficient to stop treatment in intervention group ***Other outcomes:*** *Failure to achieve microbiological cure* Penicillin vs any other antibiotic: OR 2.49 (95% CI: 0.88–7.02) (1 study, $n = 248$) Amoxycillin and probenicid vs spectinomycin: OR 2.29 (95% CI: 0.74–7.08) (1 study, $n = 168$) Amoxicillin and probenicid vs ceftriaxone: OR 2.29 (95% CI: 0.74–7.08) Ceftriaxone vs cefixime: OR 1.22 (95% CI: 0.16–9.01) (1 study, $n = 95$) ***Brief summary of findings:*** The only outcome reported on was the incidence of 'microbiological cure'. Failure to achieve 'microbiological cure' was similar for each antibiotic regimen

Review details	Methods	Results and conclusions
	Methods Summary estimates would have been calculated (Peto odds ratio) if there were no evidence of significant heterogeneity	***Authors' conclusions:*** No differences were seen between treatments but the trials were limited in their ability to detect important but modest differences. For women who are allergic to penicillin, this review provides some reassurance that treatment with ceftriaxone or spectinomycin appears to have similar effectiveness in producing microbiological cure ***Comments:*** There is a lack of detail about the methodology of the review. Only one person selected studies and extracted the data. Neither of the included trials used an intention-to-treat analysis, and both excluded a high proportion of participants from the analysis, which may have introduced bias. The methods of allocation concealment were not specified

TABLE 118 *Antibiotics for urogenital infection (continued)*

Review details	Methods	Results and conclusions
Walker [Cochrane Database of Systematic Reviews 2001, Issue 3][394] ***Title:*** Antibiotics for syphilis diagnosed during pregnancy ***Type of review:*** Cochrane ***Prevalence:*** *Symptomatic for preterm birth* – *Preterm birth* –	***Search:*** *Search dates* Medline 1966 – Oct. 2002, Embase 1974 – Mar. 2000, Cochrane Controlled Trials Register Mar. 2001, Cochrane Pregnancy and Childbirth Group Trials Register Oct. 2002, Cochrane Infectious Diseases Group's Specialised Register of Controlled Trials (Mar. 2001) *Databases searched* See above *Other sources* References of reviews, experts *Search restrictions* None ***Inclusion/exclusion criteria:*** *Study design(s)* RCTs, quasi-RCTs (both published and unpublished) *Population* Pregnant women with a clinical diagnosis of primary, secondary or late-stage syphilis, confirmed by non-treponemal or treponemal tests, with and without concomitant infection with HIV *Intervention* No treatment, alternative antibiotic therapy *Outcomes* Maternal: resolution of clinical symptoms; changes in titres for quantitative reagenic serological tests. Follow-up at 3 months, 6 months, 1 year and 2 years and above Fetal/infant: miscarriage and stillbirth with/without evidence of infected fetus, neonatal death with/without evidence of congenital syphilis; baby born with congenital syphilis or suspicion of congenital syphilis Side effects: Jarisch–Herxheimer reaction in the mother with possible preterm labour, delivery and fetal or neonatal death ***Study selection:*** Titles/abstracts for each potentially relevant study were screened. The authors stated that the review drew on the strategy for the Pregnancy and Childbirth group, which includes the screening of titles/abstracts by two reviewers and resolution of disagreements by consensus or involvement of the editorial team	***No. of studies included:*** 26 studies met criteria for hard copy scrutiny but all were excluded. No RCTs or quasi-RCTs identified ***No. of studies meeting quality criteria:*** *Adequate randomisation* – 0 *Adequate concealment of allocation* – 0 *Adequate blinding of clinician/patient/researcher* – 0 ***Incidence of birth < 34 weeks' gestation:*** ***Incidence of birth < 37 weeks' gestation:*** ***Incidence of birth within 24 h of intervention:*** ***Incidence of birth within 48 h of intervention:*** ***Incidence of birth within 7 days of intervention:*** ***Incidence of neonatal intensive care admission:*** ***Incidence of perinatal mortality:*** ***Incidence of adverse events:*** ***Brief summary of findings:*** No RCTs or quasi-RCTs found ***Authors' conclusions:*** While there is no doubt that penicillin is effective in treatment of syphilis in pregnancy and the prevention of congenital syphilis, uncertainty remains about what are the optimal treatment regimens Future research should address treatment failure cases with recommended regimens, including the role of Hi.v. infection, and the effectiveness of various antibiotic regimens for the treatment of primary and secondary syphilis in pregnant women using RCTs ***Comments:*** The authors have provided clear details of the review methodology and of the excluded studies The authors' conclusions about the efficacy of penicillin in the treatment of syphilis do not follow from this review, which did not include any studies and therefore cannot provide a basis for conclusions about the efficacy of the treatment.

Review details	Methods	Results and conclusions
	Data extraction: The 26 papers potentially meeting the inclusion criteria were checked in full. No studies met the inclusion criteria ***Validity assessment:*** *Criteria used* *Assessment* ***Synthesis:*** *Heterogeneity* *Methods*	

TABLE 118 *Antibiotics for urogenital infection (continued)*

Review details	Methods	Results and conclusions
Gulmezoglu [Cochrane Database of Systematic Reviews 2005 Issue 3][395] ***Title:*** Interventions for trichomoniasis in pregnancy ***Type of review:*** Cochrane ***Prevalence:*** *Symptomatic for preterm birth –* Not reported *Preterm birth –* Preterm birth < 37 weeks: 31 (out of 289 in total)	***Search:*** The Cochrane Pregnancy and Childbirth Group Trials Register (January 2004) *Other sources* *None reported* *Search restrictions* None reported ***Inclusion/exclusion criteria:*** *Study design(s)* RCTs (and quasi-RCTs) *Population:* pregnant women with trichomoniasis diagnosed by wet-mount smear or any other laboratory test in addition to clinical findings (symptomatic women) OR asymptomatic women with a laboratory diagnosis of trichomoniasis *Intervention* 01. Any treatment compared with no treatment 02. Comparison of two different agents 03. Comparison of different doses of same agent 04. Systemic vs local treatment 05. Single dose vs longer (5–10 day) treatment Both included studies compared metronidazole with no treatment *Outcomes* Preterm birth, low birthweight, intrauterine infection. Side effects and complications of treatment ***Study selection:*** Not stated ***Data extraction:*** Performed in accordance with Cochrane reviewers' handbook ***Validity assessment:*** *Criteria used* Allocation concealment, randomisation, blinding *Assessment* Performed in accordance with Cochrane reviewers' handbook (Clarke 2000) ***Synthesis:*** *Heterogeneity* Chi-squared and *I*-squared tests used, trial characteristics discussed	***No. of studies included:*** two studies ($n = 993$): ***No. of studies meeting quality criteria:*** *Adequate randomisation* – 1 *Adequate concealment of allocation* – 0 *Adequate blinding of clinician/patient/researcher* – 1/1/1 ***Incidence of birth < 34 weeks' gestation:*** Not reported ***Incidence of birth < 37 weeks' gestation:*** RR 1.78 (95% CI: 1.19–2.66) (1 study, $n = 604$) ***Incidence of birth within 24 h of intervention:*** Not applicable ***Incidence of birth within 48 h of intervention:*** Not applicable ***Incidence of birth within 7 days of intervention:*** Not applicable ***Incidence of neonatal intensive care admission:*** Not reported ***Incidence of perinatal mortality:*** Not reported ***Incidence of adverse events:*** *Low birthweight < 2500 g* RR 1.38 (95% 0.92–2.06) (1 study, $n = 604$) ***Brief summary of findings:*** Metronidazole was effective in producing parasitological cure but the risk of preterm birth was increased in the intervention group in the trial that reported it. There were no significant differences in incidence of low birthweight ***Authors' conclusions:*** Metronidazole given as a single dose is likely to provide parasitological cure for trichomoniasis but it is not known whether this treatment will have any effect on pregnancy outcomes ***Comments:*** The review does not report how studies were selected. The conclusions are however, appropriately cautious, although given the increase in preterm birth in the good-quality study it is not appropriate to recommend treatment of trichomoniasis with metronidazole. Neither study assessed adverse events

Review details	Methods	Results and conclusions
Raynes-Greenow et al. [Cochrane Database of Systematic Reviews 2005, Issue 4][407] ***Title:*** Antibiotics for ureaplasma in the vagina in pregnancy ***Type of review:*** Cochrane ***Prevalence:*** *Symptomatic for preterm birth –* Not reported *Preterm birth –* Not reported	***Search:*** *Databases searched (Search dates)* Cochrane Pregnancy and Childbirth Group Trials Register (April 2003) *Other sources* None specified *Search restrictions* None specified ***Inclusion/exclusion criteria:*** *Study design(s)* RCTs *Population* Pregnant women < 37 weeks' gestation with ureaplasma in the vagina. Studies of women in preterm labour were excluded *Intervention* Any antibiotic regimen begun before 37 weeks' gestation vs placebo/no treatment *Outcomes* Primary outcome – preterm birth A range of other adverse pregnancy outcomes were sought, including preterm labour > 32 < 36 weeks, < 32 weeks, perinatal death and severe neonatal morbidity ***Study selection:*** Three reviewers independently assessed studies for potential inclusion ***Data extraction:*** Three reviewers independently extracted the data ***Validity assessment:*** *Criteria used* Trials were assessed using Cochrane criteria: allocation concealment, randomisation, blinding of outcome assessment and completeness of follow-up. Outcome data were to be excluded where unavailable for > 20% of participants *Assessment* Carried out independently by three reviewers	***No. of studies included:*** 1 RCT, *n* = 1071 (1105 randomised) ***No. of studies meeting quality criteria:*** *Adequate randomisation* – 1 *Adequate concealment of allocation* – 0 *Adequate blinding of clinician/patient/researcher* – 1/0/0 ***Incidence of birth < 34 weeks' gestation:*** Not reported ***Incidence of birth < 37 weeks' gestation:*** Not reported ***Incidence of birth within 24 h of intervention:*** Not applicable ***Incidence of birth within 48 h of intervention:*** Not applicable ***Incidence of birth within 7 days of intervention:*** Not applicable ***Incidence of neonatal intensive care admission:*** Not reported ***Incidence of perinatal mortality:*** Not reported ***Incidence of adverse events:*** No between-group differences were found for low birthweight and side effects *Low birthweight < 2500 g* RR 0.70 (95% CI: 0.46–1.07) (1 study, *n* = 825) *Maternal side effects sufficient to stop or change treatment* RR 1.25 (95% CI: 0.85–1.85) (1 study, *n* = 1071) ***Brief summary of findings:*** This trial did not report data on the primary outcome, preterm birth. Data were available on low birthweight and side effects, for which no significant between-group differences were found

TABLE 118 *Antibiotics for urogenital infection (continued)*

Review details	Methods	Results and conclusions
	Synthesis: *Heterogeneity* Not applicable *Methods* Categorical data were analysed using relative risk, risk difference and number needed to treat	***Authors' conclusions:*** There is insufficient evidence to assess the effect of giving antibiotics to women with ureaplasma in the vagina on pregnancy outcomes including preterm birth. Well-designed RCTs are needed to determine if antibiotic treatment will reduce the risk of preterm birth in women with ureaplasma in the vagina ***Comments:*** Authors note that intention-to-treat analysis was not conducted (apart from two outcomes) as women who did not comply satisfactorily with treatment were excluded. As this includes women who had symptoms related to the study drug, the analysis is particularly open to bias

Review details	Methods	Results and conclusions
Vazquez and Villar [Cochrane Database of Systematic Reviews 2003, Issue 4][398] ***Title:*** Treatments for symptomatic urinary tract infections during pregnancy ***Type of review:*** Cochrane ***Prevalence:*** *Symptomatic for preterm birth –* Not reported *Preterm birth –* No untreated groups	***Search:*** *Databases searched (Search dates)* Cochrane Pregnancy and Childbirth Group Trials Register (Jan 2003) *Other sources* Reference lists of articles were checked *Search restrictions* None specified ***Inclusion/exclusion criteria:*** *Study design(s)* RCTs *Population* Pregnant women with any symptomatic urinary tract infection of any severity receiving treatment on either an inpatient or an outpatient basis *Intervention* Alternative antibiotic therapies *Outcomes* Primary outcomes: cure rates (symptom relief and/or urine clearance by laboratory test), recurrent infection Secondary outcomes: preterm birth, premature rupture of membranes, admission to neonatal intensive care unit, need for change of antibiotic, incidence of prolonged pyrexia. A range of other outcomes were sought including side effects, resource use and other neonatal outcomes ***Study selection:*** Two authors independently assessed studies for potential inclusion, with differences resolved by discussion ***Data extraction:*** Carried out independently by two authors with discrepancies resolved by discussion ***Validity assessment:*** *Criteria used* Quality ratings were assigned using Cochrane criteria. Studies were assessed for allocation concealment, blinding of outcome assessment and loss to follow-up	***No. of studies included:*** 8 studies ($n = 905$) ***No. of studies meeting quality criteria:*** *Adequate randomisation* – 6 *Adequate concealment of allocation* – 5 *Adequate blinding of clinician/patient/researcher* – not reported ***Incidence of birth < 34 weeks' gestation:*** Not reported ***Incidence of birth < 37 weeks' gestation:*** 02. OR 0.14 (95% CI: 0.00–6.82) (1 study, $n = 120$) 03. OR 1.97 (95% CI: 0.47–8.29) (1 study, $n = 107$) 04. OR 1.10 (95% CI: 0.21–5.68) (1 study, $n = 109$) 05. OR 0.56 (95% CI: 0.13–2.36) (1 study, $n = 102$) 06. OR 1.11 (95% CI: 0.41–3.01) (1 study, $n = 178$) ***Incidence of birth within 24h of intervention:*** Not applicable ***Incidence of birth within 48h of intervention:*** Not applicable ***Incidence of birth within 7 days of intervention:*** Not applicable ***Incidence of neonatal intensive care admission:*** 03. OR 1.50 (95% CI: 0.57–3.95) (1 study, $n = 107$) 04. OR 1.59 (95% CI: 0.62–4.11) (1 study, $n = 109$) 05. OR 1.06 (95% CI: 0.42–2.68) (1 study, $n = 102$) ***Incidence of perinatal mortality:*** Not reported ***Incidence of adverse events:*** Cefuroxime was associated with a higher rate of cure than cephradine. No other between-group differences were found for cure rates, prolonged pyrexia, need for change of antibiotic and recurrent infection

TABLE 118 *Antibiotics for urogenital infection (continued)*

Review details	Methods	Results and conclusions
	Assessment Carried out independently by two authors with differences resolved by discussion ***Synthesis:*** *Heterogeneity* Heterogeneity was looked for and if found would have been explored by sensitivity analyses *Methods* Meta-analysis was conducted using a fixed effects model. Where numbers were given an intention-to treat analysis was performed. Numbers needed to treat were calculated from outcomes. Power calculations were extracted where available Planned subgroup analyses included an assessment of the effect of route of administration, outpatient vs inpatient regimens, dosage and duration of treatment ***Comparisons:*** 01. Intravenous (i.v.) + oral antibiotics vs i.v. only 02. Outpatient vs inpatient antibiotics 03. i.v. cephazolin vs i.v. ampicillin + gentamicin 04. Intramuscular (i.m.) ceftriaxone vs i.v. ampicillin + gentamicin 05. i.m. ceftriaxone vs i.v. cephazolin 06. Cephalosporins daily dose vs multiple doses 07. Oral ampicillin vs oral nitrofurantoin 08. i.v. plus oral cephradine vs i.v. plus oral cefuroxime 09. Oral phosphomycin trometamol vs oral ceftibuten 10. Single vs multiple dose of gentamicin	***Brief summary of findings:*** Cefuroxime was associated with a higher rate of cure and fewer recurrences than cephradine but the sample size is insufficient to give reliable findings. No other significant differences were observed between treatments in respect of any outcomes ***Authors' conclusions:*** There are insufficient data to recommend any specific treatment regimen for symptomatic urinary tract infections during pregnancy. All the antibiotics studied were shown to be effective in decreasing the incidence of adverse outcomes. Complications were very rare ***Comments:*** Authors note that all included trials had small sample sizes and that effects seen are likely to be due to chance. Loss to follow-up is also identified as a problem

Review details	Methods	Results and conclusions
Thinkhamrop et al. [Cochrane Database of Systematic Reviews 2002, Issue 4][409] ***Title:*** Prophylactic antibiotic administration in pregnancy to prevent infectious morbidity and mortality ***Type of review:*** Cochrane ***Prevalence:*** *Symptomatic for preterm birth –* Not estimable *Preterm birth –* 26 (out of a total of 274), based on preterm delivery (not defined) in unselected pregnant women 42 (out of a total 86), based on preterm delivery (not defined) in high-risk women with bacterial vaginosis 40 (out of a total 176), based on preterm delivery (not defined) in high-risk women with previous preterm delivery	***Search:*** *Databases searched (Search dates)* The Pregnancy and Childbirth Group registry was searched for relevant articles (February 2004). *Other sources* Reference lists *Search restrictions* No search restrictions specified ***Inclusion/exclusion criteria:*** *Study design(s)* RCTs *Population* Women in their second or third trimester with a singleton gestation before labour or delivery Unselected, unspecified and high-risk women were included in the review. High-risk women were defined as: previous spontaneous preterm delivery, history of low birthweight (< 2500 g), pre-pregnancy weight < 50 kg, or associate with bacterial vaginosis *Intervention* Prophylactic antibiotics administered vs placebo or no antibiotics *Outcomes* Primary maternal and neonatal outcomes included: preterm labour (not defined), PROM, preterm delivery, chorioamnionitis, intrapartum fever, puerperal sepsis, serious maternal complication of puerperal infection requiring laparotomy for infection, hysterectomy, or death), gonococcal cervicitis, mean gestation age, low birthweight, mean birthweight, clinical neonatal sepsis, blood cultures confirming sepsis. A number of secondary maternal and neonatal outcomes were also sought including side effects, admission to neonatal intensive care unit and perinatal mortality. ***Study selection:*** The authors do not state how articles were selected for inclusion or how many reviewers performed the selection process ***Data extraction:*** The authors do not state how data was extracted or how many reviewers performed the data extraction	***No. of studies included:*** 6 RCTs ($n = 2184$) ***No. of studies meeting quality criteria:*** *Adequate randomisation* – 6 *Adequate concealment of allocation* – 3 *Adequate blinding of clinician/patient/researcher* – 5/6/0 (not reported) ***Incidence of birth < 34 weeks' gestation:*** Not reported ***Incidence of birth preterm birth (no definition of preterm birth given):*** *All women:* Peto OR 0.83 (95% CI; 0.62–1.12) (4 studies, $n = 1310$) *Unselected women:* Peto OR 1.13 (95% CI: 0.64–1.97) (2 studies, $n = 552$) High-risk women with BV < 50 kg pre-pregnancy: Peto OR 0.31 (95% CI: 0.10–0.93) (1 study, $n = 81$) High-risk women with BV > 50 kg pre-pregnancy: Peto OR 0.48 (95% CI: 0.25–0.90) (1 study, $n = 177$) High-risk women with previous history of preterm delivery: Peto OR 1.06 (95% CI: 0.68–1.64) (2 studies, $n = 500$) ***Incidence of birth within 24 h of intervention:*** Not relevant ***Incidence of birth within 48 h of intervention:*** Not relevant ***Incidence of birth within 7 days of intervention:*** Not relevant ***Incidence of neonatal intensive care admission:*** Not estimable ***Incidence of perinatal mortality:*** *All women:* Peto OR 0.52 (95% CI: 0.16–1.71) (3 studies, $n = 624$) *Unselected women:* Peto OR 0.12 (95% CI: 0.01–1.99) (1 study, $n = 229$)

TABLE 118 *Antibiotics for urogenital infection (continued)*

Review details	Methods	Results and conclusions
	Validity assessment: *Criteria used* Trials were assessed according to their allocation concealment (A=adequate, B=unclear, C=inadequate, D=not used). Blinding and loss to follow-up were also assessed *Assessment* The authors do not state how the methodological quality of the primary studies was assessed or how many reviewers performed the validity assessment ***Synthesis:*** *Heterogeneity* Chi squared analysis and *I*-squared statistic were used to assess heterogeneity *Methods* Peto ORs and their 95% CI were presented for categorical data. Sensitivity analyses were planned looking at trial quality	*High-risk women with history of preterm delivery, LBW, stillbirth or perinatal mortality:* Peto OR 0.53 (95% CI: 0.13–2.16) (1 study, *n* = 253) *High-risk women with previous preterm delivery:* Peto OR 7.60 (0.15, 383.33) (1 study, *n* = 142) ***Incidence of adverse events:*** *PPROM:* Unselected women: Peto OR 0.33 (95% CI: 0.08–1.34) (1 study, *n* = 229) *PROM:* Unselected women: Peto OR 0.32 (95% CI: 0.14–0.73) (1 study, *n* = 229) *Chorioamnionitis:* Unselected women: Peto OR 0.61 (95% CI: 0.10–3.60) (1 study, *n* = 229) *Puerperal sepsis/postpartum endometritis:* Unselected women: Peto OR 0.49 (95% CI: 0.23–1.06) (2 studies, *n* = 431) High-risk women with history of preterm delivery, LBW, stillbirth or perinatal mortality: Peto OR 0.46 (95% CI: 0.24–0.89) (1 study, *n* = 196) *Gonococcal infection (detected postpartum)* High-risk women: Peto OR 0.35 (95% CI: 0.13–0.89) (1 study, *n* = 204) *Low birthweight* Unselected women: Peto OR 1.04 (95% CI: 0.64–1.70) (2 studies, *n* = 555) High-risk women with history of preterm delivery, LBW, stillbirth or perinatal mortality: Peto OR 0.48 (95% CI: 0.27–0.84) (1 study, *n* = 253) *Neonatal sepsis:* High-risk women with previous history of preterm delivery: Peto OR 8.07 (95% CI: 1.36–47.77) (1 study, *n* = 142)

Review details	Methods	Results and conclusions
		Other outcomes: Mean birthweight Unselected women: [Fixed effect] WMD –76.00 (–181.03 to 29.03) (2 studies, *n* = 555) High-risk women: WMD 155.00 (6.22, 303.78) (1 study, *n* = 253) ***Brief summary of findings:*** Antibiotic prophylaxis in unselected women reduced the risk of PROM. A reduced incidence of low birthweight and postpartum endometritis was reported in women with a history of previous preterm birth. A reduction in the incidence of preterm delivery was reported in women with a history of preterm birth associated with BV although no reduction was shown in women with a previous history of preterm birth without BV. Vaginal antibiotic prophylaxis did not prevent infectious pregnancy outcomes and there was a possibility of adverse events such as neonatal sepsis ***Authors' conclusions:*** Antibiotic prophylaxis given during the second or third trimester of pregnancy reduces the risk of PROM. Beneficial effects on birthweight and risk of preterm endometritis were demonstrated in high-risk women. The authors note that the sample size for unselected women may not be sufficient to detect differences for important uncommon outcomes ***Comments:*** As the methods undertaken for study selection, data extraction and quality assessment were not described the likelihood of reviewer error or bias cannot be assessed

b.i.d., twice a day; BV, bacterial vaginosis; CI, confidence interval; HIV, human immunodeficiency virus; i.m., intramuscular; i.v., intravenous; LBW, low birthweight; OR, odds ratio; PPROM, premature pre-labour rupture of membranes; PROM, pre-labour rupture of membranes; RCT, randomised controlled trial; RR, relative risk; WMD, weighted mean difference.

TABLE 119 *Antioxidants*

Review details	Methods	Results and conclusions
Rumbold A et al. [Cochrane Database of Systematic Reviews 2005, Issue 3][420] ***Title:*** Vitamin C supplementation in pregnancy ***Type of review:*** Cochrane ***Prevalence:*** *Symptomatic for preterm birth –* Not reported *Preterm birth –* 54 (out of 290 in total) based on preterm birth < 37 weeks	***Search:*** *Databases searched (Search dates)* Cochrane Pregnancy and Childbirth Group trials register (June 2004), Central (Issue 2, 2004), MEDLINE (1966–May 2004), Current Contents (1998–May 2004), EMBASE (1980–May 2004) *Other sources* None reported. *Search restrictions* None. ***Inclusion/exclusion criteria:*** *Study design(s)* RCTs, quasi-RCTs *Population* Asymptomatic pregnant women. Of the studies included: three trials recruited women at high risk of pre-eclampsia, one trial involved women with severe early-onset pre-eclampsia, one trial involved women at high risk of preterm birth. *Intervention* Vitamin C supplementation (alone or in combination with other supplements) vs placebo. Interventions using a multivitamin supplement or where the primary supplement was iron were excluded. Of the trials included in the review one trial used vitamin C only supplements, four used a combined supplement. Three trials used 1000 mg vitamin C per day and two used 500 mg vitamin C per day. Combined supplements used vitamin E (2 trials), vitamin E and allopurinal (1 trial), aspirin and fish oil (1 trial) *Outcomes* Primary outcomes: perinatal mortality, iron and folate status, birthweight, intrauterine growth retardation, preterm birth < 37 weeks, PROM, and pre-eclampsia. A number of secondary maternal and infant outcomes were sought, including use of health resources ***Study selection:*** Two authors independently considered trials for inclusion. Differences were resolved through discussion ***Data extraction:*** Two authors independently extracted data. Differences were resolved through discussion. Data were entered separately and double checked	***No. of studies included:*** 5 RCTs ($n = 766$) ***No. of studies meeting quality criteria:*** *Adequate randomisation* – 3 *Adequate concealment of allocation* – 3 *Adequate blinding of clinician/patient/researcher* – 5/5/3 ***Incidence of birth < 34 weeks' gestation:*** Not reported ***Incidence of birth < 37 weeks' gestation:*** (Fixed effects) RR 1.38 (95% CI: 1.04–1.82) (3 studies, $n = 583$) ***Incidence of birth within 24 h of intervention:*** Not applicable ***Incidence of birth within 48 h of intervention:*** Not applicable ***Incidence of birth within 7 days of intervention:*** Not applicable ***Incidence of neonatal intensive care admission:*** Not reported ***Incidence of perinatal mortality:*** (Fixed effects) RR 1.16 (95% CI: 0.61–2.18) (2 studies, $n = 238$) ***Incidence of adverse events:*** *Stillbirth* (Fixed effects) RR 0.87 (95% CI: 0.41–1.87) (3 studies, $n = 539$) *Neonatal death* (Random effects) RR 1.73 (95% CI: 0.25–12.12) (2 studies, $n = 221$). Heterogeneity $\chi^2 = 2.08$ df = 1 $p = 0.15$ $I^2 = 51.9\%$ *Intrauterine growth restriction* (Fixed effects) RR 0.72 (95% CI: 0.49–1.04) (2 studies, $n = 383$) *Apgar score <7 at 5 min* (Fixed effects) RR 0.63 (95% CI: 0.21–1.90) (1 study, $n = 39$) *Pre-eclampsia* (Random effects) RR 0.52 (95% CI: 0.23–1.20) (4 studies, $n = 710$)

Review details	Methods	Results and conclusions
	Validity assessment: *Criteria used* Quality ratings were assigned using Cochrane criteria for blinding, completeness of follow-up, use of placebo, allocation concealment. Where method of allocation concealment was unclear, attempts were made to contact authors for further details *Assessment* Conducted independently by two authors; differences were resolved by consensus ***Synthesis:*** *Heterogeneity* Tests of heterogeneity were applied (I^2 test) and possible causes explored. *Methods* Meta-analysis using a fixed effects model. Where heterogeneity was found, subgroup analyses for the main outcomes were performed. Heterogeneity that was not explained by subgroup analyses was modelled using a random effects model. Sensitivity analyses were carried out to explore the effect of trial quality	*Serious maternal morbidity (subtotals, based on one study)* Eclampsia RR 1.07 (95% CI: 0.07–16.33), renal failure RR 0.36 (95% CI: 0.02–8.41), pulmonary oedema RR 0.54 (95% CI: 0.05–5.59), disseminated intravascular coagulation RR 0.36 (95% CI: 0.02–8.41) *Maternal side effects (subtotals, based on one study)* Acne RR 3.21 (95% CI: 0.14–75.68), transient weakness RR 5.36 (95% CI: 0.27–106.78), skin rash RR 3.21 (95% CI: 0.14–75.68). ***Other outcomes:*** *Birthweight* (Fixed effects) Weighted mean difference –139.00 (95% CI: –517.69 to 239.69) (1 study, $n = 100$) ***Sensitivity analyses:*** *Trial quality* Preterm birth RR 1.40 (95% CI: 1.02–1.93) (2 studies, $n = 483$) Perinatal mortality RR 1.16 (95% CI: 0.61–2.18) (2 studies, $n = 238$) ***Subgroup analyses:*** *Gestation at trial entry* Preterm birth RR 1.40 (95% CI: 1.02–1.93) (3 studies, $n = 583$) Perinatal mortality RR 1.16 (95% CI: 0.61–2.18) (2 studies, $n = 238$) *Supplement type* Preterm birth RR 1.38 (95% CI: 1.04–1.82) (3 studies, $n = 583$) Perinatal mortality RR 1.16 (95% CI: 0.61–2.18) (2 studies, $n = 238$) ***Brief summary of findings:*** Compared with placebo, vitamin C supplements did not reduce the incidence of stillbirth, perinatal death, neonatal death, birthweight or intrauterine growth restriction. Compared to placebo, vitamin C supplements increased the incidence of preterm birth. Women taking vitamin C were at decreased risk of pre-eclampsia using a fixed effect model This difference could not be demonstrated using a random effects model. ***Authors' conclusions:*** The data are too few to demonstrate whether vitamin C, alone or with other supplements, is beneficial in pregnancy. Preterm birth may have been increased with vitamin C supplementation and this is an area that requires further research ***Comments:*** This was a well-conducted review and the authors appear to have taken appropriate steps to reduce bias No study reported > 20% loss to follow-up

TABLE 119 *Antioxidants (continued)*

Study details and design	Description of methods	Results and conclusions
Casanueva et al. [Am J Nutr 2005; 81: 859–863][422] ***Country:*** Mexico ***Setting:*** Prenatal clinic (Instituto Nacional de Perinatologia in Mexico City) ***Prevalence:*** *Symptomatic for preterm birth* – Not reported *Preterm birth* – 14 (out of a total of 57) ***Study design:*** Randomised controlled trial (RCT) ***Length of follow-up:*** Randomisation to delivery ***No. of participants:*** *No. randomised* – 126 *No. analysed* – 109 ***Validity:*** *Adequate randomisation* – No (Random number table used) *Adequate allocation concealment* – No *Blinding of clinician* – Yes *Blinding of patient* – Yes (placebo) *Blinding of researcher* – Yes	***Groups compared:*** Vitamin C (100 mg vitamin C per day) vs Placebo. Both tablet types provided by Roche Pharmaceuticals ***Intervention details:*** All women were initially assessed by nutritionist and obstetric and gynaecological personnel. General information, gynaecological and obstetric history and anthropometric data were taken. Each participant completed a food frequency questionnaire. Vitamin C intake was calculated (corrected for cooking losses by a factor of 50% for boiled/fried food, and a factor of 25% for steamed food). Women were evaluated every 4 weeks from gestation weeks 20 to 36. A vaginal examination was provided, and a swab was taken for Gram staining and microbiological testing. Where infection was diagnosed, women received appropriate antibiotic treatment. Asymptomatic participants with a positive culture did not receive treatment. Adherence to intervention was evaluated through personal record and tablet counting at each clinic visit ***Participants:*** Asymptomatic pregnant women. ***Participant inclusion/exclusion criteria:*** Pregnant women with no acute or chronic diseases, < 20 weeks' gestation, singleton pregnancy, and no consumption of vitamin supplements were eligible for inclusion. Women needing uterine cerclage or having an obstetric indication for Caesarean delivery were excluded ***Outcomes:*** Incidence of incidence of premature births, incidence of PPROM, birthweight, gestational age at birth and plasma and leucocyte vitamin C concentrations	***Incidence of birth < 34 weeks' gestation:*** Not reported ***Incidence of birth < 37 weeks' gestation:*** *No. in intervention group (total no.)* = 7 (52) *No. in control group (total no.)* = 14 (57) ***Incidence of birth within 24 h of intervention:*** Not applicable ***Incidence of birth within 48 h of intervention:*** Not applicable ***Incidence of birth within 7 days of intervention:*** Not applicable ***Incidence of neonatal intensive care admission:*** Not reported ***Incidence of perinatal mortality:*** Not reported ***Incidence of adverse events:*** PROM *No. in intervention group (total no.)* = 4 (52) *No. in control group (total no.)* = 14 (57) ***Other outcomes:*** Birthweight (g) *Mean weight (SD) in intervention group* = 3015 (513) *Mean weight (SD) in control group* = 3015 (629) ***Brief summary of findings:*** A significant reduction in PPROM births was shown for women receiving vitamin C, compared to placebo ($p = 0.018$). No statistically significant between group differences were shown for incidence of preterm birth or birthweight ***Authors' conclusions:*** Daily supplementation with 100 mg vitamin C after 20 weeks' gestation reduces the incidence of PPROM.

Study details and design	Description of methods	Results and conclusions
Type of analysis: Repeated measures analysis of variance, adjusted for multiple comparisons was conducted to evaluate changes in vitamin C concentration in plasma and leucocytes. Chi-squared tests were used to compare maternal characteristics, infections and incidence of PROM. Relative risks (RRs) with their 95% CI were calculated Sample size: 60 cases per group would be needed for an 80% power to test for a 20% reduction in incidence of PROM with a 5% chance of type 1 error. Assumed 10% loss to follow-up		***Comments:*** 13.5% loss to follow-up was observed, which is higher than that estimated for the power calculation Gestational age was verified by clinical examination at delivery. If a difference > 1 week was found from estimated gestational age (based on last menstrual period) the case was excluded from the study

TABLE 119 *Antioxidants (continued)*

Review details	Methods	Results and conclusions
Mahomed and Gulmezoglu [Cochrane Database of Systematic Reviews 2001, Issue 1][419] ***Title:*** Vitamin D supplementation in pregnancy ***Type of review:*** Cochrane ***Prevalence:*** *Symptomatic for preterm birth –* Not reported *Preterm birth –* Not reported	***Search:*** *Databases searched (search dates)* Cochrane Pregnancy and Childbirth Group Trials Register (Oct 2001) and The Cochrane Controlled Trials Register (Issue 3, 2001) *Other sources* None specified *Search restrictions* None specified ***Inclusion/exclusion criteria:*** *Study design(s)* Randomised controlled trials *Population* Pregnant women at risk of vitamin D deficiency *Intervention* Vitamin D supplementation vs no treatment or placebo *Outcomes* Low birthweight, neonatal hypocalcaemia, craniotabes (softening of the skull), perinatal mortality ***Study selection:*** The authors do not report how studies were selected for inclusion, or how many reviewers were involved in this process ***Data extraction:*** Included trial data were processed as described in the Cochrane Collaboration Handbook. This recommends that at least two reviewers extract data ***Validity assessment:*** *Criteria used* Authors refer to data extraction table but do not specifically state the criteria used. Allocation concealment, method of randomisation, and (sometimes) blinding were reported *Assessment* Included trial data were processed as described in the Cochrane Collaboration Handbook. This recommends that at least two reviewers assess the included studies for validity	***No. of studies included:*** 2 RCTs (n = 232) ***No. of studies meeting quality criteria:*** *Adequate randomisation* – 1 *Adequate concealment of allocation* – 1 *Adequate blinding of clinician/patient/researcher* – 1/1/1 ***Incidence of birth < 34 weeks' gestation:*** Not reported ***Incidence of birth < 37 weeks' gestation:*** Not reported ***Incidence of birth within 24h of intervention:*** Not applicable ***Incidence of birth within 48h of intervention:*** Not applicable ***Incidence of birth within 7 days of intervention:*** Not applicable ***Incidence of neonatal intensive care admission:*** Not reported ***Incidence of perinatal mortality:*** Not reported ***Incidence of adverse events:*** *Low birthweight* OR 0.50 (95% CI: 0.20–1.26) (1 study, *n* = 128) *Low weight for gestation* OR 0.47 (95% CI: 0.20–1.09) (1 study, *n* = 126) *Neonatal hypocalcaemia* OR 0.13 (95% CI: 0.02–0.65) (2 studies, *n* = 203). Heterogeneity $\chi^2 = 0.10$ df = 1 $p = 0.75$ $I^2 = 0.0\%$ *Craniotabes* OR 0.40 (95% CI: 0.09–1.65) (1 study, *n* = 126) ***Other outcomes:*** *Maternal daily weight gain (g) in the third trimester* (Fixed effects) WMD 16.90 (95% CI: 8.08–25.72) (1 study, *n* = 126)

Review details	Methods	Results and conclusions
	Synthesis: *Heterogeneity* Heterogeneity was assessed using *H* and I^2 tests *Methods* Fixed effects model, Peto odds ratio	***Brief summary of findings:*** In one trial babies born to women taking vitamin D supplements had lower birthweights, and in the other trial mothers taking vitamin D had higher daily weight gain and fewer babies with low birthweights. Neonatal hypocalcaemia was less common in the supplemented group, compared to the non-supplemented group ***Authors' conclusions:*** There is insufficient evidence to evaluate the effects of vitamin D supplementation in pregnancy ***Comments:*** There is a lack of detail on the methods used to select the primary studies, extract data, and assess trial quality. The number of women included in the trials is small and the authors point out that this may account for the conflicting data on birthweights, which could be due to chance It has also been suggested that reported SDs in one of the primary studies (Mallet *et al.*, 1986[733]) are likely to be SEs One additional trial was identified as 'waiting to be assessed' It is not clear whether singleton and multiple gestations were included in the primary papers

TABLE 119 *Antioxidants (continued)*

Review details	Methods	Results and conclusions
Rumbold et al. [Cochrane Databse of Systematic Reviews 2005, Issue 4][421] ***Title:*** Vitamin E Supplementation in Pregnancy ***Type of review:*** Cochrane ***Prevalence:*** *Symptomatic for preterm birth –* Not reported *Preterm birth –* 19 (out of 190 in total) based on preterm birth at <37 weeks	***Search:*** *Databases searched (search dates)* Cochrane Pregnancy and Childbirth Group Trials Register (June 2004), Central (Issue 2, 2004), MEDLINE (1966 to May 2004), Current Contents (1998 to May 2004), EMBASE (1980 to May 2004) *Other sources* None specified *Search restrictions* None specified ***Inclusion/exclusion criteria:*** *Study design(s)* RCTs and quasi-RCTs *Population* Asymptomatic pregnant women living in areas where there is either inadequate intake of vitamin E or presumed adequate intake. Three trials recruited women 'at high risk of pre-eclampsia', and two trials involved women with established severe early onset pre-eclampsia *Intervention* Vitamin E supplementation (alone or in combination with other separate supplements) vs placebo or no treatment or other supplements. Interventions with a multivitamin supplement (defined as more than two vitamins or minerals in the same tablet) were excluded. All included trials compared supplements of vitamins E and C with placebo *Outcomes* Primary outcomes: perinatal mortality, stillbirth, maternal and infant haematological measures, preterm birth < 37 weeks, pre-eclampsia, intrauterine growth restriction, birthweight, and PPROM A number of secondary maternal and infant outcomes were also sought, including use of health service resources ***Study selection:*** Two reviewers independently assessed trials for inclusion and resolved differences by discussion.	***No. of studies included:*** 4 RCTs ($n = 566$) ***No. of studies meeting quality criteria:*** *Adequate randomisation* – 2 *Adequate concealment of allocation* – 2 *Adequate blinding of clinician/patient/researcher* – 3/3/2 ***Incidence of birth < 34 weeks' gestation:*** Not reported ***Incidence of birth < 37 weeks' gestation:*** (Fixed effect) RR 1.29 (95% CI: 0.78–2.15) (2 studies, $n = 383$) ***Incidence of birth within 24 h of intervention:*** Not applicable ***Incidence of birth within 48 h of intervention:*** Not applicable ***Incidence of birth within 7 days of intervention:*** Not applicable ***Incidence of neonatal intensive care admission:*** Not reported ***Incidence of perinatal mortality:*** (Fixed effect) RR 1.29 (0.67, 2.48) (1 study, $n = 56$) ***Incidence of adverse events:*** *Stillbirth* (Fixed effect) RR 0.77 (95% CI: 0.35–1.71) (2 studies, $n = 339$) *Neonatal death* (Fixed effect) RR 5.00 (95% CI: 0.64–39.06) (1 study, $n = 40$) *Admission to ICU (infants)* (Fixed effect) RR 0.83 (95% CI: 0.30–2.29) (1 study, 40 infants) *Requirement for mechanical ventilation* (Fixed effect) RR 0.33 (95% CI: 0.08–1.46) (1 study, 40 infants) *Clinical pre-eclampsia* (Random effects) RR 0.44 (95% CI: 0.16–1.22) (3 studies, $n = 510$) *Intrauterine growth restriction* (Fixed effect) RR 0.72 (95% CI: 0.49–1.04) (2 studies, $n = 383$)

DOI: 10.3310/hta13430

Review details	Methods	Results and conclusions
	Data extraction: Two reviewers independently extracted data; differences were resolved by discussion. Attempts were made to contact authors for further details if the method of allocation concealment was unclear ***Validity assessment:*** *Criteria used* Blinding of assessment of outcome, completeness of follow-up, use of placebo and allocation concealment were assessed using Cochrane criteria *Assessment* Carried out independently by two authors ***Synthesis:*** *Heterogeneity* Tests of heterogeneity were applied to assess the significance of any differences between trials ($I^2 \geq 50\%$) *Methods* Meta-analysis using the fixed effects model. Where heterogeneity was found subgroup analyses were performed for the main outcomes. Heterogeneity that was not explained by subgroup analyses was modelled using random-effects analysis. Sensitivity analyses were conducted to explore the effect of trial quality	*Bleeding episodes* (Fixed effect) RR 0.35 (95% CI: 0.10–1.23) (2 studies, $n = 339$) *Apgar score less than 7 at 5 min* (Fixed effect) RR 0.63 (95% CI: 0.21–1.90) (1 study, $n = 39$) *Measures of serious maternal morbidity (subtotals only)* Eclampsia RR 1.07 (95% CI: 0.07–16.33) (1 study, $n = 56$), Renal failure RR 0.36 (95% CI: 0.02–8.41) (1 study, $n = 56$), Disseminated intravascular coagulation RR 0.36 (95% CI: 0.02–8.41) (1 study, $n = 56$), pulmonary oedema RR 0.54 (95% CI: 0.05–5.59) *Side effects of vitamin E (subtotals only)* Acne RR 3.21 (95% CI: 0.14–75.68) (1 study, $n = 56$), transient weakness RR 5.36 (95% CI: 0.27–106.78) (1 study, $n = 56$), skin rash RR 3.21 (95% CI: 0.14–75.68) (1 study, $n = 56$) ***Other outcomes:*** *Birthweight* (Fixed effect) weighted mean difference –139.00 (95% CI: –517.69 to 239.69) (1 study, $n = 100$) ***Sensitivity analyses by trial quality:*** *Preterm birth < 37 weeks* (Fixed effects) RR 1.21 (95% CI: 0.38–3.87) (1 study, $n = 283$) *Perinatal death* (Fixed effects) RR 1.29 (0.67–2.48) (1 study, $n = 56$) *Stillbirth* (Fixed effects) RR 0.77 (95% CI: 0.35–1.71) (2 studies, $n = 339$) *Neonatal death* (Fixed effects) RR 5.00 (0.64, 39.06) (1 study, $n = 40$) ***Brief summary of findings:*** Compared with placebo, vitamin E did not alter the incidence of perinatal death, preterm birth, intrauterine growth restriction or birthweight. Substantial heterogeneity was found for pre-eclampsia, with a decreased risk associated with vitamin E supplementation using the fixed effects model, but no difference discernable using random-effects models. No differences were found between groups for any secondary outcomes ***Authors' conclusions:*** There are insufficient data to determine if vitamin E supplementation is beneficial during pregnancy ***Comments:*** The authors highlight a number of considerations when interpreting the review findings: the total number of women involved in the included studies was small, and two trials were of poor quality; all of the women involved were at risk of pre-eclampsia or had established early onset pre-eclampsia; there was no information assessing vitamin E independent of other supplements so the treatment effects may not be a direct consequence of vitamin E supplementation; there are limited data on adverse event outcomes, with many results coming from a single trial; substantial heterogeneity was found for the outcome pre-eclampsia

TABLE 119 *Antioxidants (continued)*

Review details	Methods	Results and conclusions
Mahomed [Cochrane Database of Systematic Reviews 1997, Issue 3] [418] ***Title:*** Zinc supplementation in pregnancy ***Type of review:*** Cochrane ***Prevalence:*** *Symptomatic for preterm birth –* Not reported. *Preterm birth –* 109 (out of 1280 in total)	***Search:*** *Databases searched* Cochrane Pregnancy and Childbirth Group Trials Register; search date not reported *Other sources* None specified *Search restrictions* None specified ***Inclusion/exclusion criteria:*** *Study design(s)* Controlled trials *Population* Asymptomatic pregnant women, at least 26 weeks' gestation, with no systemic illness. Two trials selected women at high risk of low zinc status and one trial selected women with low plasma zinc levels *Intervention* Elemental zinc supplementation (20–62 mg) vs no treatment or placebo *Outcomes* Biochemical assessment of zinc status, plus a range of maternal and neonatal outcomes ***Study selection:*** Carried out by the one reviewer ***Data extraction:*** Additional data was sought where required by contacting the principal author. Studies in which all outcome variables were in the form of mean values with no standard deviation were excluded ***Validity assessment:*** *Criteria used* Satisfactory randomisation of allocation to the study or control group. In addition, studies in which >25% of participants were excluded from the final analysis were excluded from the review *Assessment* This was carried out by one reviewer	***No. of studies included:*** 7 RCTs ($n = 3486$) ***No. of studies meeting quality criteria:*** *Adequate randomisation* – 4 *Adequate concealment of allocation* – 3 *Adequate blinding of clinician/patient/researcher* – 7/7/0 ***Incidence of birth < 34 weeks' gestation:*** Not reported ***Incidence of birth < 37 weeks' gestation:*** OR 0.73 (95% CI: 0.54–0.98) (5 studies, $n = 2539$) NB. Preterm delivery only defined in one trial as PTB < 37 weeks ***Incidence of birth within 24 h of intervention:*** Not applicable ***Incidence of birth within 48 h of intervention:*** Not applicable ***Incidence of birth within 7 days of intervention:*** Not applicable ***Incidence of neonatal intensive care admission:*** Not reported ***Incidence of perinatal mortality:*** *Stillbirth/neonatal death* OR 0.97(95% CI: 0.40–2.35) (4 studies, $n = 1265$) ***Incidence of adverse events:*** *Preterm labour* OR 1.12 (95% CI: 0.72–1.74) (1 study, $n = 1206$) *Pre-labour rupture of membranes* OR 0.01 (95% CI: 0.73–1.15) (2 studies, $n = 1691$) *Smell dysfunction* OR 1.01 (95% CI: 0.47–2.16) (1 study, $n = 170$) *Taste dysfunction* OR 0.70 (95% CI: 0.31–1.59) (1 study, $n = 170$) *Any maternal infection* OR 1.26 (95% CI: 0.76–2.10) (1 study, $n = 487$)

Review details	Methods	Results and conclusions
	Synthesis:	*Antepartum haemorrhage*
	Heterogeneity	OR 1.20 (95% CI: 0.61–2.37) (1 study, *n* = 1206)
	Heterogeneity was assessed using the H and I^2 test of heterogeneity	*5-min Apgar less than 5*
	Methods	OR 1.02 (95% CI: 0.25–4.08) (1 study, *n* = 1692)
	Peto odds ratios were calculated	*Low birthweight*
		OR 0.89 (95% CI: 0.61–1.30) (3 studies, *n* = 1840)
		Congenital malformation
		OR 0.56 (95% CI: 0.21–1.53) (3 studies, *n* = 683)
		Other outcomes:
		A number of other outcomes were obtained, with statistically significant differences detectable only for the following: induction of labour (Peto odds ratio 0.18, 95% CI: 0.06–0.57(1 study, *n* = 54)) and Caesarean section (Peto odds ratio 0.69, 95% CI: 0.49–0.96 (3 studies, *n* = 1747))
		Brief summary of findings:
		Compared with placebo or no treatment, zinc supplementation was associated with lower rates of labour induction, preterm delivery and Caesarean section; it had no detectable effect on any other pregnancy outcome. There was no evidence of any adverse maternal or fetal effect with zinc supplementation
		Authors' conclusions:
		There is insufficient evidence to evaluate the affect of zinc supplementation during pregnancy. The possible beneficial effects on preterm delivery need to be evaluated in further trials
		Comments:
		This review does not appear to have been conducted using all the standard methods of the Cochrane collaboration. Only one reviewer considered trials for inclusion, evaluated trial quality and extracted the data. Search dates are not given. Results are given for 'preterm delivery' and 'preterm labour' but these are not defined. The author notes that apparent inconsistencies between trials in some of the findings (not specified) may be related to the failure to restrict the review to trials of routine zinc supplementation. The association between zinc supplementation and lower rates of induction of labour is based on one study of 54 women, so may be too small to give a reliable result
		It is not clear whether singleton and multiple gestations were included in the primary papers

CI, confidence interval; OR, odds ratio; PPROM, premature pre-labour rupture of membranes; RCT, randomised controlled trials; RR, relative risk.

TABLE 120 *Bed rest*

Review details	Methods	Results and conclusions
Sosa et al. [Cochrane Database of Systematic Reviews 2004, Issue 1] [455] ***Title:*** Bed rest in singleton pregnancies for preventing preterm birth ***Type of review:*** Cochrane ***Prevalence:*** *Symptomatic for preterm birth* – Not reported *Preterm birth* – 71 (out of a total of 834), based on preterm birth less than 37 weeks' gestation	***Search:*** *Search dates* July 2003 *Databases searched* Cochrane Pregnancy and Childbirth Group trials register, Cochrane Central Register of Controlled Trials, Medline, Lilacs, Embase, Poplin *Other sources* Bibliographies *Search restrictions* None ***Inclusion/exclusion criteria:*** *Study design(s)* RCTS, quasi-RCTs *Population* Pregnant women at high risk of spontaneous preterm birth (asymptomatic). Definition given Women with PPROM or multiple pregnancies were not considered *Intervention* Bed rest (home or hospital) vs no intervention *Outcomes* Primary outcomes: preterm birth, perinatal mortality, low birthweight, neonatal intensive care A range of secondary perinatal and maternal outcomes were eligible for inclusion The only reported outcome is preterm birth rate ***Study selection:*** Two reviewers independently assessed the trials for inclusion. Disagreements were resolved by consensus or involvement of a third reviewer ***Data extraction:*** Two reviewers independently extracted the data ***Validity assessment:*** *Criteria used* Randomisation; allocation concealment (rated adequate/uncertain/inadequate); blinding and completeness of follow-up were assessed for each outcome. Quality ratings assigned using Cochrane criteria	***No. of studies included:*** 1 RCT ($n = 1266$). 432 were prescribed bed rest at home and 834 received a placebo ($n = 412$) or no intervention ($n = 422$) ***No. of studies meeting quality criteria:*** *Adequate randomisation* – Unknown (not reported in primary study) *Adequate concealment of allocation* – Unknown (not reported in primary study) *Adequate blinding of clinician/patient/researcher* – Unknown (not reported in primary study) ***Incidence of birth < 34 weeks' gestation:*** Not reported ***Incidence of birth < 37 weeks' gestation:*** (Fixed effects) RR 0.92 (95% CI: 0.62–1.37) (1 study, $n = 1266$) ***Incidence of birth within 24 h of intervention:*** Not relevant ***Incidence of birth within 48 h of intervention:*** Not relevant ***Incidence of birth within 7 days of intervention:*** Not relevant ***Incidence of neonatal intensive care admission:*** Not reported ***Incidence of perinatal mortality:*** Not reported ***Incidence of adverse events:*** Not reported ***Brief summary of findings:*** No statisitically significant between group difference was found for preterm birth <37 weeks' gestation ***Authors' conclusions:*** There is no evidence either supporting or refuting the use of bed rest to prevent preterm birth. Due to the potential adverse effects that bed rest could have on women and their families, and the increased costs for the health-care system, clinicians should not routinely advise women to rest in bed to prevent preterm birth

Review details	Methods	Results and conclusions
	Assessment Carried out by two reviewers independently. Disagreements were resolved by consensus or involvement of a third reviewer ***Synthesis:*** *Heterogeneity* In the case of significant heterogeneity among study outcomes, a sensitivity analysis was to be performed and conclusions based on the results of the highest quality studies. However, only one study was included in the review *Methods* Where estimable, RRs and their 95% CI are reported for each outcome. The included study reported a cluster RCT designed to evaluate a programme for prevention of preterm birth that included an educational intervention plus increased clinic visits. Eight hospitals were randomised to intervention (5) or control (3) units. Besides the prevention programme, women in intervention hospitals were randomised to receive one of five interventions: bed rest, psychosocial support, progestins, placebo or no intervention. For this review the authors only considered the comparison within the intervention hospitals	***Comments:*** The authors have provided good detail about the review methodology and of the included study. Reasons are given for the exclusion of other studies The authors note that the only included trial has uncertain methodological quality and internal validity. They also note that baseline characteristics of randomised women were not reported. In addition, there are discrepancies in the number of women originally included in the intervention hospitals and those in the table of results for which they could find no adequate explanation. One study identified for possible inclusion is awaiting translation into English

CI, confidence interval; RCT, randomised controlled trials; RR, relative risk.

TABLE 121 *Cervical cerclage*

Review details	Methods	Results and conclusions
Bachmann et al. [Acta Obstet Gynecol Scand 2003; 82: 398–404] [22] ***Title:*** Elective cervical cerclage for prevention of preterm birth: a systematic review ***Type of review:*** Other ***Prevalence:*** *Symptomatic for preterm birth* – *Preterm birth* – 182 (out of a total 1188 women), based on preterm birth at less than 34 weeks' gestation 296 (out of a total of 1128 women), based on preterm birth at less than 37 weeks' gestation	***Search:*** *Databases searched (search dates)* MEDLINE (1996 to 2002), EMBASE (1980 to 2002), the Cochrane Library (issue 1, 2002) and the Science Citation Index (1974 to 2001) *Other sources* Reference lists of relevant primary studies and review articles were also searched *Search restrictions* None stated ***Inclusion/exclusion criteria:*** *Study design(s)* Randomised controlled trials (RCTs) were eligible for inclusion. *Population* Pregnant women at risk of spontaneous preterm birth *Intervention* Cervical cerclage vs standard treatment without cerclage *Outcomes* Delivery before 34 weeks' gestation was the primary outcome reported. Data on delivery before 37 weeks' gestation and adverse events was also included ***Study selection:*** One reviewer screened citations of titles and abstracts for relevance. Complete reports of all citations deemed definitely or possibly relevant were independently assessed by two reviewers. The authors do not state how disagreements were resolved ***Data extraction:*** Two reviewers independently extracted data in duplicate ***Validity assessment:*** *Criteria used:* Primary studies were assessed with regard to adequacy of randomisation process, allocation concealment, blinded data analysis and intention-to-treat analysis *Assessment:* The authors do not state who performed the assessment	***No. of studies included:*** Seven RCTs were included in the review ($n = 2354$) ***No. of studies meeting quality criteria:*** *Adequate randomisation* – 2 *Adequate concealment of allocation* – 5 *Adequate blinding of clinician/patient/researcher* – 0/0/3 ***Incidence of birth < 34 weeks' gestation:*** OR 0.72 (95% CI: 0.53–0.97) (1 study, $n = 1292$) Incidence of birth < 37 weeks' gestation: OR 0.80 (95% CI: 0.63–1.02) (1 study, $n = 1292$) ***Incidence of birth within 24 h of intervention:*** Not applicable ***Incidence of birth within 48 h of intervention:*** Not applicable ***Incidence of birth within 7 days of intervention:*** Not applicable ***Incidence of neonatal intensive care admission:*** Not reported ***Incidence of perinatal mortality:*** OR 0.66 (0.31, 1.38) (1 study, $n = 1292$) Mean %: cerclage vs control group 7.79% (SD 8.65) vs 10.20% (SD 7.60) ($p = 0.72$) Data obtained from separate review (Odibo *et al.*, 2003[734]), using six of the primary studies included in the Bachmann review ***Incidence of adverse events (cerclage vs control group):*** *Cervical trauma from cerclage:* 1% *PROM:* 18% vs 12% ($p = 0.50$)

Review details	Methods	Results and conclusions
	Synthesis: *Heterogeneity:* This was assessed graphically by use of funnel plots and statistically with the chi-squared test. Planned exploration of heterogeneity included: method of cerclage used, population, study quality, clinical heterogeneity and methodological heterogeneity *Methods:* Outcome and harm data were abstracted into 2 × 2 tables. Were no heterogeneity was found meta-analysis of the outcome data was performed. Summary ORs and their 95% confidence intervals were presented. A narrative summary was presented for all other results	*Chorioamnionitis:* 20% vs 10.3% ($p = 0.20$); 16.1% vs 6.7% ($p = 0.40$) *Puerperal pyrexia:* 6% vs 3% ($p = 0.03$); 10% vs 3% ($p = 0.07$) *Placental abruption:* 10.9% vs 13.8% ($p = 0.80$); 12.9% vs 16.7% ($p = 0.90$) ***Brief summary of findings:*** Clinical differences between groups precluded meta-anlaysis. Five of the seven trials demonstrated a reduction in preterm birth before 34 weeks' gestation. No statistically significant benefit of cerclage was found compared to standard treatment on the odds of preterm birth < 37 weeks' gestation. Data on complications was sparse ***Authors' conclusions:*** Elective cerclage has a significant effect in preventing spontaneous preterm birth before 34 weeks' gestation The authors also state that further research should focus on clarifying the possible complications associated with cervical cerclage, and with the identification of risk factors and tests that identify high-risk women who are most likely to benefit from this procedure ***Comments:*** This was a well-conducted review; methods were used to minimise bias in the study selection, validity assessment and data abstraction processes. Data was appropriately pooled and heterogeneity assessed Risk of spontaneous preterm birth did not have to be verified by ultrasonographic cervical assessment to be eligible Odds ratios presented for preterm birth outcomes (delivery < 34 or 37 weeks' gestation) and perinatal mortality relate to the largest good quality trial included in the review (MRC/RCOG trial)

TABLE 121 *Cervical cerclage (continued)*

Study details and design	Description of methods	Results and conclusions
Berghella et al. [Am J Obstet Gynecol 2004; 191: 1311–1317][457] ***Country:*** USA ***Setting:*** two university hospitals ***Prevalence:*** *Symptomatic for preterm birth* – Not reported *Preterm birth* – 12 (out of a total 30), based on preterm birth at < 34 weeks' gestation ***Study design:*** RCT ***Length of follow-up:*** Not reported ***No. of participants:*** *No. randomised* – 61 *No. analysed* – 61 ***Validity:*** *Adequate randomisation* – Yes (Computer-generated numbers in permuted blocks of 6) *Adequate allocation concealment* – Yes (sealed opaque envelopes) *Blinding of clinician* – No *Blinding of patient* – No *Blinding of researcher* – No	***Groups compared:*** Cervical cerclage with bed rest vs Bed rest alone Intervention details: *Treatment group* Women received preterm labour education. Within 3 days of randomisation women received a MacDonald cerclage (Mersiline, 5 mm, was the preferred suture). Women were advised to begin bed rest at home, and were followed with ultrasound examination until 28–30 weeks' gestation. Betamethasone for fetal lung maturity was offered after 24 weeks' gestation for overt preterm labour or PROM. Antibiotics, tocolytics and other interventions were left to the discretion of the obstetrician. Fetal fibronectin was not collected *Control group* Women were counselled about preterm labour education, and advised to start bed rest at home. Ultrasound examinations were provided until 28–30 weeks' gestation. Treating obstetricians were allowed to offer rescue cerclage if a cervical dilatation of ≥ 1 cm was detected on digital examination. Treatment for overt preterm labour was as described in the treatment group ***Participants:*** Asymptomatic women at high risk who were identified to have short cervix (< 25 mm) or significant funnelling (> 25%), and unscreened women at low risk who were identified incidentally Participant inclusion/exclusion criteria: Asymptomatic women identified as having high risk factors for preterm birth (one or more preterm births between 14 and 34 weeks' gestation, at least two curettage procedures for spontaneous/voluntary abortions, diethylstilbestrol exposure, cone biopsy, and Müllerian anomaly), and low-risk women incidentally identified as having short cervix or funnelling were eligible. Advanced cervical dilatation or membrane bulging in the vagina were not considered exclusion criteria Prophylactic cerclage due to historic high risk, previous pregnancy delivered to term, major fetal anomaly, triplets or higher order pregnancies were excluded from the study. Post-screening exclusion criteria included: previous inclusion in another trial, current drug abuse, and regular contractions leading to preterm birth after identification of abnormal cervix	***Incidence of birth < 34 weeks' gestation:*** *No. in intervention group (total no.)* = 13 (31) *No. in control group (total no.)* = 12 (30) ***Incidence of birth < 37 weeks' gestation:*** Not reported ***Incidence of birth within 24 h of intervention:*** Not applicable ***Incidence of birth within 48 h of intervention:*** Not applicable ***Incidence of birth within 7 days of intervention:*** Not applicable ***Incidence of neonatal intensive care admission:*** *No. in intervention group (total no.)* = 9 (34) *No. in control group (total no.)* = 11 (31) (includes two sets of twins) ***Incidence of perinatal mortality:*** *No. in intervention group (total no.)* = 9 (34) (includes three sets of twins) *No. in control group (total no.)* = 4 (31) ***Incidence of adverse events:*** Composite morbidity: *No. in intervention group (total no.)* = 7 (34) *No. in control group (total no.)* = 8 (31) (includes two sets of twins) PROM: *No. in intervention group (total no.)* = 11 (31) *No. in control group (total no.)* = 10 (30) Subgroup Analysis According to risk (singleton gestations): High-risk; cervical length < 25 mm: RR 0.66 (95% CI: 0.19–2.30)

Study details and design	Description of methods	Results and conclusions
Type of analysis: Continuous data were analysed with the Student's *t*-test; for binary variables the chi-squared test or Fisher's Exact test was used to describe proportions between groups. Analysis was conducted on an intention-to-treat basis ***Power analysis:*** 30 participants were needed in each study arm to find a 35% reduction in preterm birth at < 35 weeks' gestation ($\alpha = 0.05$, and $\beta = 0.20$)	Outcomes: Primary outcome was preterm birth at <35 weeks' gestation. Secondary outcomes included: gestational age at delivery, preterm labour, PROM, and interval from enrolment to delivery. Neonatal outcomes included death, admission to intensive care unit, days in intensive care unit, and composite morbidity	Previous preterm birth < 35 weeks; cervical length < 25 mm: RR 0.52 (95% CI: 0.12–2.17) Previous preterm birth < 35 weeks; cervical length ≤ 15 mm: RR 0.44 (0.03, 6.70) ***Brief summary of findings:*** Compared to bed rest alone, cerclage did not prevent preterm birth < 34 weeks' gestation (RR 1.05; 95% CI: 0.57–1.92). No statistically significant difference between the groups was shown for incidence of mortality ($p = 0.22$), admission to neonatal care unit ($p = 0.53$), or composite morbidity ($p = 0.80$), birthweight ($p = 0.74$), or PPROM (RR 1.06, 95% CI: 0.53–2.13) ***Authors' conclusions:*** Cerclage did not prevent preterm birth in women with a short cervix. These results should be confirmed by larger trials ***Comments:*** 52% of women eligible for inclusion declined to participate in the trial High-risk women and women without high risk were recruited; no separate analysis for the two groups was reported No loss to follow-up Women were screened with transvaginal ultrasonography

TABLE 121 *Cervical cerclage (continued)*

Study details and design	Description of methods	Results and conclusions
To et al. [Lancet 2004; 363: 1849–1853][458] ***Country:*** Multi-centre trial (UK, Brazil, South Africa, Slovenia, Greece, and Chille) ***Setting:*** Hospital and Home setting ***Prevalence:*** *Symptomatic for preterm birth* – Not reported *Preterm birth* – 33 (out of a total 126), based on preterm birth at < 33 weeks' gestation in high-risk women ***Study design:*** RCT ***Length of follow-up:*** Cervical suture removed in 37th gestational week. All women followed-up until delivery ***No. of participants:*** *No. randomised* – 253 *No. analysed* – 253 ***Validity:*** *Adequate randomisation* – Yes (computer-generated, block randomisation) *Adequate allocation concealment* – Yes (telephone to central trial office) *Blinding of clinician* – No *Blinding of patient* – No *Blinding of researcher* – No	***Groups compared:*** Cervical suture vs Expectant management ***Intervention details:*** Participants in the treatment group received placement of Shirodkar suture with mersilene tape under spinal anaesthesia, and received a single dose of intravenous erythromycin (500 mg) intraoperatively. Cervical suture was removed in the 37th week of pregnancy unless spontaneous onset of labour, rupture of the membranes or need for early delivery arose All women in the trial were given prophylactic steroids (two doses of dexamethasone, 12 mg intramuscularly, 12 h apart) for fetal lung maturation at 26–28 weeks' gestation. No other interventions were routinely recommended ***Participants:*** Asymptomatic women at risk of early preterm birth ***Participant inclusion/exclusion criteria:*** Pregnant women with a cervical length of 15 mm or less were eligible for inclusion Women with major fetal abnormalities, painful regular uterine contractions, or history of ruptured membranes and cervical cerclage in situ were excluded from screening. Women with dilated cervix during screening were excluded from randomisation ***Outcomes:*** Preterm birth < 33 weeks' gestation. A number of secondary outcomes were also considered: birthweight, stillbirth, neonatal death, major adverse event before discharge from hospital, maternal morbidity during antenatal hospital stay, or symptomatic vaginal discharge	***Incidence of birth < 33 weeks' gestation:*** *No. in intervention group (total no.)* = 28 (127) *No. in control group (total no.)* = 33 (126) ***Incidence of birth < 34 weeks' gestation:*** Not reported ***Incidence of birth < 37 weeks' gestation:*** Not reported ***Incidence of birth within 24 h of intervention:*** Not applicable ***Incidence of birth within 48 h of intervention:*** Not applicable ***Incidence of birth within 7 days of intervention:*** Not applicable ***Incidence of neonatal intensive care admission:*** Not reported ***Incidence of perinatal mortality:*** *No. in intervention group (total no.)* = 7 (127) *No. in control group (total no.)* = 10 (126) ***Incidence of adverse events:*** Stillbirth *No. in intervention group (total no.)* = 3 (127) *No. in control group (total no.)* = 5 (126) Retinopathy of prematurity *No. in intervention group (total no.)* = 0 (123) *No. in control group (total no.)* = 3 (121) Bronchopulmonary dysplasia *No. in intervention group (total no.)* = 4 (123) *No. in control group (total no.)* = 4 (121) Intraventricular haemorrhage/periventricular haemorrhage *No. in intervention group (total no.)* = 1 (123) *No. in control group (total no.)* = 2 (121) Maternal pyrexia *No. in intervention group (total no.)* = 5 (127) *No. in control group (total no.)* = 1 (126)

Study details and design	Description of methods	Results and conclusions
Type of analysis: Chi-squared test or Fishers' Exact test was used to detect between-group differences in categorical outcomes. Unpaired *t*-tests or Mann–Whitney tests were used for continuous variables. ITTanalysis was used ***Power analysis:*** It was calculated that 160 participants per arm would be needed to detect a 20% reduction in early preterm birth, power 90%, significance level 5%		Symptomatic vaginal discharge *No. in intervention group (total no.)* = 8 (127) *No. in control group (total no.)* = 1 (126) ***Brief summary of findings:*** Cervical cerclage was not associated with a significant reduction in the rate of preterm birth < 33 weeks' gestaion (RR 0.84, 95% CI: 0.54–1.31). A greater incidence of symptomatic vaginal discharge was shown in women with cerclage than those without (RR 7.87, 95% CI: 1.00–62.04). No other statistically significant differences in perinatal or maternal outcomes were found ***Authors' conclusions:*** Insertion of a Shirodkar suture in women with a short cervix does not substantially reduce risk of early preterm delivery ***Comments:*** Loss to follow-up: one participant from the control group (0.01%), none from the intervention group Of the 47,123 women screened, 470 women met inclusion criteria; 217 declined to participate. Seven participants did not receive their allocated treatment: two declined cerclage, two ruptured membranes before cerclage and one recieved dummy cerclage, and two participants in the expectant management group received cerclage

CI, confidence interval; ITT, intention to treat; OR, odds ratio; PROM, pre-labour rupture of membranes; RCT, randomised controlled trials; RR, relative risks.

TABLE 122 *Educational programmes*

Review details	Methods	Results and conclusions
Hueston [Obstet Gynecol 1995; 86 (4, part 2):705–712][461] ***Title:*** The effectiveness of preterm-birth prevention educational programs for high-risk women: a meta-analysis ***Type of review:*** Other ***Prevalence:*** *Symptomatic for preterm birth –* Not reported *Preterm birth –* Individual numbers were not reported. However, the authors state that the mean rate of preterm delivery in the control groups was 13%, out of a total 3187 women at risk of preterm birth	***Search:*** *Databases searched (Search dates)* MEDLINE (1979 to Feb 1994) *Other sources* Bibliographic handsearching of relevant reviews and articles *Search restrictions* Only articles published in English were sought ***Inclusion/exclusion criteria:*** *Study design(s)* 'Well-controlled studies' were eligible, this appeared to include: RCTs, non-RCTs and historical control studies. Only RCTs were included in the meta-analyses *Population* Pregnant women (asymptomatic). All the studies included in the meta-analysis included only high-risk women, and defined high risk using scoring system described by Creasy et al. (1980) [552] *Intervention* Any type of preterm labour education programme. Interventions from the studies entered in the meta-analyses included provider and patient education with weekly cervical examinations or an education programme with home visitation. These programmes ranged in duration from 16 to 54 months *Outcomes* The primary outcomes of interest included: rate of preterm labour, rate of preterm delivery, low birthweight, rate of neonatal survival, gestational age, and birthweight ***Study selection:*** The authors do not state how the primary studies were selected for the review, or how many reviewers performed the selection ***Data extraction:*** Two reviewers independently extracted the data from the primary studies; disagreements were resolved by a third reviewer. Reviewers were blinded to the identity of the author and the journal. ***Validity assessment:*** *Criteria used* Studies were evaluated in terms of study design, population, study duration, sample size and control for potential confounders	***No. of studies included:*** Six RCTs ***No. of studies meeting quality criteria:*** *Adequate randomisation* – Not reported *Adequate concealment of allocation* – Not reported *Adequate blinding of clinician/patient/researcher* – Not reported ***Incidence of birth < 34 weeks' gestation:*** Not reported ***Incidence of birth < 37 weeks' gestation:*** RR 1.08 (95% CI: 0.92–1.27) (2 studies, *n* = 1345) ***Incidence of birth within 24h of intervention:*** Not applicable ***Incidence of birth within 48h of intervention:*** Not applicable ***Incidence of birth within 7 days of intervention:*** Not applicable ***Incidence of neonatal intensive care admission:*** Not reported ***Incidence of perinatal mortality:*** Not reported ***Incidence of adverse events:*** *Preterm labour:* RR 1.71 (95% CI: 1.41–2.08) (2 studies, *n* = 1345) *Low birthweight:* RR 0.99 (95% CI: 0.88–1.11) (4 studies, *n* = 4130) *Neonatal survival:* RR 1.00 (95% CI: 0.99–1.01) (3 studies, *n* = 2949) ***Brief summary of findings:*** No statistically significant difference was found between women who received an educational programme and those who did not on the primary outcomes for preterm birth, low birthweight, and neonatal survival. When compared to no treatment, women who received a preterm birth educational programme had a greater incidence of diagnosis for preterm labour

Review details	Methods	Results and conclusions
	Assessment The authors do not state how the primary studies were assessed but report that a team of evaluators assessed the methodology of the primary studies ***Synthesis:*** *Heterogeneity* Heterogeneity was considered; the authors do not state what methods were used *Methods* Studies were entered into a meta-analysis using methods described by Rosenthal (1987)[735], grouped by study design. Only results for the RCT group are presented. Risk ratios (RR), with their 95% confidence intervals, were reported for each of the primary outcomes The authors report that statistically significant heterogeneity was found for all outcomes in the meta-analyses performed for studies employing non-randomised and historical control study designs. The authors state that for this reason the analysis was limited to the RCTs	***Authors' conclusions:*** Preterm birth educational programmes appear to have little beneficial effect on reducing the risk of preterm birth. Educational programmes may result in an increased rate of diagnosis for preterm labour ***Comments:*** The procedures involved in study selection were not well described, the quality of the primary studies is not discussed and limited detail is provided regarding the included studies. Caution should be exercised in interpreting the observed results No loss to follow-up in any of the included studies
CI, confidence intervals, RCT, randomised controlled trials; RR, relative risks.		

TABLE 123 *Energy and protein*

Review details	Methods	Results and conclusions
Kramer et al. [Cochrane Database of Systematic Reviews 2003, Issue 4] [427] ***Title:*** Energy and protein intake in pregnancy ***Type of review:*** Cochrane ***Prevalence:*** *Symptomatic for preterm birth –* Not reported *Preterm birth –* 18 (out of 211 in total) 118 (out of 1211 in total) 56 (out of 256 in total) 38 (out of 391 in total) 4 (out of 91 in total) Preterm birth not defined	***Search:*** *Databases searched (Search dates)* Cochrane Pregnancy and Childbirth Group trials register (Oct. 2002) *Other sources* Experts contacted *Search restrictions* None ***Inclusion/exclusion criteria:*** *Study design(s)* RCTs, quasi-RCTs *Population* Pregnant women For dietary restriction, pregnant women with either high pregnancy weight or high gestational weight gain *Intervention* Dietary advice to increase energy and protein intakes, energy/protein supplementation, dietary restriction. For energy/protein supplementation programmes that were balanced, high protein or isocaloric were included *Outcomes* Dietary intake, gestational weight gain, fetal/infant outcomes (stillbirth, neonatal death, fetal growth, gestational duration), child growth and development, maternal outcomes (complications of pregnancy, labour and delivery, postpartum weight retention) ***Study selection:*** Two reviewers independently evaluated studies for inclusion ***Data extraction:*** Data were extracted independently by two reviewers, with disagreements resolved by consensus or involvement of a third party. Additional information was sought from triallists ***Validity assessment:*** *Criteria used* Cochrane method of assigning quality ratings to these criteria: allocation concealment, blinding of randomisation, blinding of intervention and outcome assessment, completeness of follow-up	***No. of studies included:*** 01. Five trials ($n = 1134$) compared nutritional advice to increase energy and protein intake with no advice 02. 13 trials ($n = 4665$) compared balanced energy/protein supplementation with no supplementation or vitamin/mineral only supplementation 0.3 Two trials ($n = 1076$) compared high protein supplementation with other supplementation 0.4 Three trials ($n = 966$) compared isocaloric protein supplements with no supplementation 0.5 Three trials ($n = 384$) compared energy/protein restriction with normal diet ***No. of studies meeting quality criteria:*** *Adequate randomisation* – 2 *Adequate concealment of allocation* – 5 *Adequate blinding of clinician/patient/researcher* – one trial reported blinding of researcher. No blinding in four trials, unknown (not reported in primary study) in 18 ***Incidence of preterm birth (not defined):*** 01. (Fixed effect) RR 0.46 (95% CI: 0.21–0.98) (2 studies, $n = 449$) 02. (Fixed effect) RR 0.83 (95% CI: 0.65–1.06) (5 studies, $n = 2436$) 03. (Fixed effect) RR 1.14 (95% CI: 0.83–1.56) (1 study, $n = 505$) 04. (Fixed effect) RR 1.05 (95% CI: 0.69–1.60) (1 study, $n = 782$) 05. (Fixed effect) RR 0.50 (95% CI: 0.09–2.66) (1 study, $n = 182$) ***Incidence of birth within 24 h of intervention:*** Not reported ***Incidence of birth within 48 h of intervention:*** Not reported ***Incidence of birth within 7 days of intervention:*** Not reported ***Incidence of neonatal intensive care admission:*** Not reported

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Review details	Methods	Results and conclusions
	Assessment Carried out independently by two reviewers with differences resolved by consensus or involvement of third party ***Synthesis:*** *Heterogeneity* Meta-analysis using a fixed effect model. Where significant heterogeneity was found, pooled estimates were recalculated using a random effects model *Methods* Results of trials using nutritional supplements were stratified by initial nutritional status (adequate vs inadequate) of participants for the outcome of mean birthweight For two cluster RCTs with no data on the outcome-specific intra-class correlation coefficients a value of 0.1 was assumed and the corresponding sample sizes adjusted according to the design effect	***Incidence of perinatal mortality:*** *Stillbirth* 01. (Fixed effect) RR 0.37 (95% CI: 0.07–1.90) (1 study, $n = 431$) 02. (Fixed effect) RR 0.55 (0.31, 0.97) (4 studies, $n = 2206$) 03. (Fixed effect) RR 0.81 (0.31, 2.15) (1 study, $n = 529$) *Neonatal death* 01. (Fixed effect) RR 1.28 (95% CI: 0.35–4.72) (1 study, $n = 448$) 02. (Fixed effect) RR 0.62 (95% CI: 0.37–1.05) (4 studies, $n = 2206$) 03. (Fixed effect) RR 2.78 (95% CI: 0.75–10.36) (1 study, $n = 529$) 04. (Fixed effect) RR 0.50 (95% CI: 0.05–5.49) (1 study, $n = 782$) ***Incidence of adverse events:*** *Pre-eclampsia* 01. (Fixed effect) RR 0.89 (95% CI: 0.42–1.88) (1 study, $n = 136$) 02. (Fixed effect) RR 1.20 (95% CI: 0.77–1.89) (3 studies, $n = 516$) 04. (Fixed effect) RR 1.00 (95% CI: 0.57–1.75) (1 study, $n = 782$) 05. (Fixed effect) RR 1.13 (95% CI: 0.59–2.18) (2 studies, $n = 284$) *Pregnancy-induced hypertension* 05. (Fixed effects) RR 0.97 (0.75, 1.26) (3 studies, $n = 384$) ***Other outcomes:*** *Small-for-gestational-age* 01. (Fixed effect) RR 0.97 (95% CI: 0.45–2.11) (1 study, $n = 404$) 02. (Fixed effect) RR 0.68 (95% CI: 0.56–0.84) (6 studies, $n = 3396$) 03. (Fixed effect) RR 1.58 (95% CI: 1.03–2.41) (1 study, $n = 505$) 04. (Fixed effect) RR 1.35 (95% CI: 1.12–1.61) (1 study, $n = 782$) *Birthweight (g)* 01. (Random effects) weighted mean difference 205.75 (95% CI: –242.54 to 654.04) (2 studies, $n = 426$) 02. (Random effects) weighted mean difference 37.62 (–0.21 to 75.45) (14 studies, $n = 4699$) 03. (Fixed effect) weighted mean difference –58.37 (95% CI: –146.23 to 29.50) (2 studies, $n = 529$) 04. (Random effects) weighted mean difference 33.45 (95% CI: –157.88 to 224.77) (3 studies, $n = 966$) 05. (Random effects) weighted mean difference –217.93 (95% CI: –664.73 to 228.87) (2 studies, $n = 282$)

TABLE 123 *Energy and protein*

Review details	Methods	Results and conclusions
		Brief summary of findings: Nutritional advice to increase energy and protein intake was successful in achieving those goals but no consistent benefit was observed on pregnancy outcomes Balanced energy/protein supplementation was associated with modest increases in maternal weight gain and in mean birthweight and a reduction in risk of small-for-gestational-age (SGA) birth and for stillbirth and neonatal death High-protein supplementation and isocaloric protein supplementation were associated with an increased risk of SGA birth Energy/protein restriction of pregnant women who were overweight exhibited high weight gain significantly reduced weekly maternal weight gain but also mean birthweight and had no effect on pregnancy-induced hypertension or pre-eclampsia ***Authors' conclusions:*** Dietary advice appears effective in increasing pregnant women's energy and protein intakes but is unlikely to confer major benefits on infant or maternal health Balanced energy/protein supplementation improves fetal growth and may reduce the risk of fetal and neonatal death. High-protein or balanced protein supplementation alone is not beneficial and may be harmful to the infant Protein/energy restriction of pregnant women who are overweight or exhibit weight gain is unlikely to be beneficial and may be harmful to the infant ***Comments:*** The authors note methodological concern about the trials and highlight a number of possible sources of bias

CI, confidence intervals, RCT, randomised controlled trials; RR, relative risks.

DOI: 10.3310/hta13430

TABLE 124 *Fish oil*

Study details and design	Description of methods	Results and conclusions
Olsen [BJOG 2000; 107: 382–395][369] ***Country:*** Denmark, Scotland, Sweden, England, Italy, the Netherlands, Norway, Belgium and Russia ***Setting:*** 19 hospital-based centres from across participating sites ***Prevalence:*** *Symptomatic for preterm birth* – Not reported *Preterm birth* – 40 (out of a total of 120), based on preterm delivery before 37 weeks' gestation. (Recurrence risks for sample size calculations were based on 17.5% risk of recurrence among controls). ***Study design:*** Six multicentre RCTs included (four prophylactic trials, two therapeutic trials) ***Length of follow-up:*** Four prophylactic trials: randomised at 20 weeks, followed-up until up to 4 weeks after delivery	***Groups compared:*** Fish oil (Pikasol: 32% eicosapentaenoic acid, 23% docosahexaenoic acid and 2 mg tocopherol/ml) was compared with olive oil (oleric acid 72%, linoleic acid 12%). ***Intervention details:*** Prophylactic trials: Participants were given four capsules of either oil per day. For women randomised to fish oil these amounts corresponded to 2.7 g (1.3 g eicosapentaenoic acid, and 0.9 g docosahexaenoic acid) of long-chain *n*-3 fatty acids per day Therapeutic trials: Participants were given nine capsules of either oil per day. For women randomised to fish oil these amounts corresponded to 6.1 g (2.9 g eicosapentaenoic acid, and 2.1 g docosahexaenoic acid) of long-chain *n*-3 fatty acids per day Both oils were provided in identical-looking 1-g gelatine capsules ***Participants:*** Prophylactic trials: Women with uncomplicated pregnancies at high risk of preterm birth Therapeutic trials: Women with threatening pre-eclampsia, or intrauterine growth retardation ***Participant inclusion/exclusion criteria:*** Inclusion criteria (Prophylactic trials): > 16 weeks' gestation; preterm delivery, intrauterine growth retardation, or pregnancy induced hypertension in a previous pregnancy; twin pregnancy (one trial) Inclusion criteria (Therapeutic trials): Women with threatening pre-eclampsia and with or without intrauterine growth restriction (one trial); women with suspected intrauterine growth restriction in current pregnancy Exclusion criteria: Diabetes (in or before pregnancy), diagnosed severe fetal malformation or hydrops in current pregnancy, suspected placental abruption in current pregnancy or occurrence in previous pregnancy, drug or alcohol abuse, regular intake of fish oil or non-steroidal anti-inflammatory agents or any other therapeutic agent that may have an effect on thrombocyte function or eicosanoid metabolism, or allergy to fish products. An additional exclusion criterion for the therapeutic trials was high probability of delivering within 1 week after randomisation	***Incidence of birth < 34 weeks' gestation:*** Earl-PD (combined prophylactic singleton pregnancy groups) *No. in intervention group (total no.)* = 5 (108) *No. in control group (total no.)* = 16 (120) Twin trial (prophylactic study) *No. in intervention group (total no.)* = 37 (286) *No. in control group (total no.)* = 44 (283) ***Incidence of birth < 37 weeks' gestation:*** Earl-PD *No. in intervention group (total no.)* = 23 (108) *No. in control group (total no.)* = 40 (120) Twin trial *No. in intervention group (total no.)* = 129 (286) *No. in control group (total no.)* = 127 (283) ***Incidence of birth within 24 h of intervention:*** Not applicable ***Incidence of birth within 48 h of intervention:*** Not applicable ***Incidence of birth within 7 days of intervention:*** Not applicable ***Incidence of neonatal intensive care admission (figures refer to neonatal care, not stated whether intensive):*** [a] Aggregated trials *No. in intervention group (total no.)* = 258 (1062) *No. in control group (total no.)* = 283 (1076) ***Incidence of perinatal mortality:***[a] Stillbirth *No. in intervention group (total no.)* = 16 (1056)

TABLE 124 *Fish oil (continued)*

Study details and design	Description of methods	Results and conclusions
Two therapeutic trials: randomised at 33 weeks, followed-up until up to 4 weeks after delivery ***No. of participants:*** *No. randomised* – 1647, although only 1619 trial entry forms were received: Four prophylactic trials: 898 women with singleton pregnancies, 579 women with twin pregnancies Two therapeutic trials: 142 women (79 with threatening pre-eclampsia, 63 with suspected intrauterine growth retardation) *No. analysed* – 1595 women ***Validity:*** *Adequate randomisation* – Yes (Restricted blockwise computer-generated randomisation) *Adequate allocation concealment* – Yes *Blinding of clinician* – Yes *Blinding of patient* – No (although identical capsules were provided, oils would taste different: 80% allocated to fish oil group thought they had received fish oil) *Blinding of researcher* – Yes	***Outcomes:*** Risk of preterm delivery, intrauterine growth retardation, pregnancy-induced hypertension. Therapeutic trials also assessed amelioration of threatening pre-eclampsia and suspected intrauterine growth retardation	*No. in control group (total no.)* = 19 (1085) Early neonatal death (aggregated trials) *No. in intervention group (total no.)* = 3 (1126) *No. in control group (total no.)* = 2 (1144) Late neonatal death (aggregated trials) *No. in intervention group (total no.)* = 0 (1125) *No. in control group (total no.)* = 2 (1144) ***Incidence of adverse events:*** Spontaneous abortion (aggregated trials) [a] *No. in intervention group (total no.)* = 4 (804) *No. in control group (total no.)* = 7 (815) Intracranial haemorrhage (aggregated trials) [a] *No. in intervention group (total no.)* = 7 (1107) *No. in control group (total no.)* = 3 (1119) Intrauterine growth retardation (EARL-IUGR) *No. in intervention group (total no.)* = 43 (131) *No. in control group (total no.)* = 37 (132) Pregnancy-induced hypertension (EARL-PIH) *No. in intervention group (total no.)* = 55 (167) *No. in control group (total no.)* = 61 (183) Pre-eclampsia (EARL-PIH) *No. in intervention group (total no.)* = 11 (152) *No. in control group (total no.)* = 17 (169) Vaginal bleeding (aggregated trials) *No. in intervention group (total no.)* = 36 (802) *No. in control group (total no.)* = 39 (816) Maternal anaemia (aggregated trials) *No. in intervention group (total no.)* = 101 (407) *No. in control group (total no.)* = 94 (439) Low birthweight (Earl-PD)

Study details and design	Description of methods	Results and conclusions
Type of analysis: Chi squared and Student's *t*-tests were used to assess group differences. ORs were used to describe dichotomous variables. Multiple linear regression analysis was used to adjust for an observed difference in one continuous variable (gestational age). Cox regression analysis was used to assess the effects on the timing of spontaneous delivery. Intention to treat analysis was used		*No. in intervention group (total no.)* = 15 (108) *No. in control group (total no.)* = 26 (118) Twin trial *No. in intervention group (total no.)* = 238 (556) *No. in control group (total no.)* = 242 (566) ***Brief summary of findings:*** Compared to olive oil, a significant reduction in recurrence of preterm delivery (< 37 weeks' gestation) for women receiving fish oil was found (OR 0.54, 95% CI: 0.30–0.98). Similarly, compared to olive oil, a reduction was found in recurrence of early preterm delivery (< 34 weeks' gestation) (OR 0.32, 95% CI: 0.11–0.89) for women receiving fish oil. No between-group differences for preterm delivery were found in women with twin pregnancies. No statistically significant between group differences were shown for the reported adverse events ***Authors' conclusions:*** Fish oil supplementation reduced the recurrence of preterm delivery, but had no effect on preterm delivery in twin pregnancies. Fish oil had no effect on intrauterine growth retardation and pregnancy-induced hypertension for recurrence risk in singleton or twin pregnancies ***Comments:*** Large, well-conducted study Original sample size calculation (1991): 2740 women would be needed with previous intrauterine growth retardation, pregnancy-induced hypertension/pre-eclampsia, and 2740 women with previous preterm delivery based on recurrence rate of 17.5%, risk reduction of 25%, and a 5% and 20% risk of type I/II error respectively Interim sample size calculation (1995) for six primary hypotheses; based on data from 1065 enrolled women with completed follow-up forms assuming hypothesised effects of 25% risk reductions for all end points and a 5% risk of committing a type I error. Interim analysis indicated that at least one end point would have achieved the cut-off for statistical power (0.9) by 01/01/96. Enrolment was terminated on this date

TABLE 124 *Fish oil (continued)*

Study details and design	Description of methods	Results and conclusions
Smuts et al. [Am J Obstet Gynecol 2003; 101(3): 469–479] [451] ***Country:*** USA ***Setting:*** Ambulatory clinic, Truman Medical Center, Kansas City, Missouri ***Prevalence:*** *Symptomatic for preterm birth* – Not reported *Preterm birth* – 17 (out of a total 149), based on preterm delivery < 37 weeks' gestation ***Study design:*** Randomised, double blind, controlled trial ***Length of follow-up:*** Third trimester of pregnancy ***No. of participants:*** *No. randomised* – 347 (350 pregnancies, 2nd pregnancies only included for adverse events) *No. analysed* – 291 Withdrawal rate: 16.1% ***Validity:*** *Adequate randomisation* – Yes, computerised randomisation schedule, stratified by age	***Groups compared:*** High-docosahexaenoic acid egg consumption vs Ordinary egg consumption ***Intervention details:*** Participants were given 12 eggs per week from enrolment until they gave birth, and were encouraged to eat as many of these as possible. Participants were interviewed bi-weekly to determine how many eggs had been eaten in the previous interval. Subjects were instructed to refrigerate the eggs and to cook the eggs before eating Hens were fed a nutritionally modified feed with 1% docosahexaenoic acid-rich marine microalgae (high-docosahexaenoic acid eggs; Gold Circle Farms, Boulder, CO) or fed without microalgae. Eggs were not commercially available in Kansas City and were shipped via refrigerated trucks as needed. Each batch of eggs provided during the study period was analysed for docosahexaenoic acid by the study sponsor. The high-docosahexaenoic acid eggs contained a mean of 133 mg (SD 15) docosahexaenoic acid per egg. The ordinary eggs contained a mean of 33 mg (SD 11) docosahexaenoic acid per egg ***Participants:*** Asymptomatic pregnant women ***Participant inclusion/exclusion criteria:*** Women with a singleton gestation, 24–28 weeks' gestation, 16–36 years old, able and willing to consume eggs with access to refrigeration and planning to deliver at Truman Medical Center were eligible Exclusion criteria: Age < 16 or > 30 years, weight > 240 lb (109 kg) at baseline, serious illness, e.g. cancer, lupus, hepatitis, untreated serious infectious disease, diabetes or gestational diabetes, elevated blood pressure ***Outcomes:*** Primary outcomes: birthweight and gestational age. A number of additional secondary maternal and infant outcomes were sought including preterm delivery < 37 weeks' gestation and admission to neonatal intensive care	***Incidence of birth < 34 weeks' gestation:*** Not reported ***Incidence of birth < 37 weeks' gestation:*** *No. in intervention group (total no.)* = 14 (142) *No. in control group (total no.)* = 17 (149) ***Incidence of birth within 24 h of intervention:*** Not applicable ***Incidence of birth within 48 h of intervention:*** Not applicable ***Incidence of birth within 7 days of intervention:*** Not applicable ***Incidence of neonatal intensive care admission:*** *No. in intervention group (total no.)* = 21 (142) *No. in control group (total no.)* = 21 (149) ***Incidence of perinatal mortality:*** Not reported ***Incidence of adverse events:*** Birthweight (< 2500 g): *No. in intervention group (total no.)* = 13 (142) *No. in control group (total no.)* = 16 (149) Pre-eclampsia/eclampsia: *No. in intervention group (total no.)* = 5 (142) *No. in control group (total no.)* = 10 (149) Gestational diabetes: *No. in intervention group (total no.)* = 4 (142) *No. in control group (total no.)* = 3 (149) Meconium in amniotic fluid: *No. in intervention group (total no.)* = 26 (142) *No. in control group (total no.)* = 28 (149)

DOI: 10.3310/hta13430

Study details and design	Description of methods	Results and conclusions
Adequate allocation concealment – Unclear, method not reported *Blinding of clinician* – Yes *Blinding of patient* – Yes *Blinding of researcher* – Unclear ***Type of analysis:*** Student's *t*-test was used to compare groups with regard to gestational age and birthweight. Categoric outcomes were assessed using chi-squared tests. An assessment of the relationship of selected risk factors to primary or secondary outcomes was conducted. If a relationship was found, this was included in the final regression analyses to examine the effect of docosahexaenoic acid supplementation on study outcomes. Sample size was calculated based on expected dropout of 25% to reject the null hypothesis for an increase in gestation by 5.25 days assuming an SD of 1.99 weeks, with 90% power and an $\alpha = 0.05$ on a one-tailed *t*-test		***Other findings:*** Mean gestational age in days (Did not smoke during pregnancy): *Intervention group (SD)* = 275.2 (11.8) *Control group (SD)* = 271.5 (15.3) Mean final RBC DHA (g per 100g of fatty acids): *Intervention group (SD)* = 5.53 (1.0) *Control group (SD)* = 5.35 (1.2) Mean infant RBC DHA (g per 100g of fatty acids): *Intervention group (SD)* = 7.61 (3.4) *Control group (SD)* = 7.18 (1.4) ***Brief summary of findings:*** After controlling for various pre-defined risk factors and confounding variables, gestation was shown to significantly increase by 6.0 days (SD 2.3) ($p<0.01$) in the higher docosahexaenoic acid group. No other statistically significant differences were shown. No safety concerns were raised ***Authors' conclusions:*** Modest amounts of dietary docosahexaenoic acid during pregnancy appear to extend gestational age and may lead to enhanced fetal growth Further work is necessary to understand the mechanism by which prenatal docosahexaenoic acid increases gestation and to determine what impact this increase has on developmental outcomes ***Comments:*** Mean egg intake was 7.3 (3.4 per week) for the ordinary egg group and 7.2 (3.4 per week) for the high-docosahexaenoic acid egg consumption group Study sponsored by OmegaTech Inc., Boulder, CO, USA

CI, confidence intervals; OR, odds ratio; RBC DHA, red blood cell; docosahexaenoic acid; RR, relative risks.
a Data refers to combined twin and singleton pregnancies.

TABLE 125 *Home uterine activity monitoring*

Study details and design	Description of methods	Results and conclusions
Brown [Am J Obstet Gynecol 1999; 180(4): 798–805][473] ***Country:*** USA ***Setting:*** Home monitoring ***Prevalence:*** *Symptomatic for preterm birth* – 997 (out of mean of 2600/ year over 4.5 years – extrapolated total: 11,700) *Preterm birth* – 48 (out of a total of 80), based on delivery ≤ 37 weeks ***Study design:*** RCT Length of follow-up: Until birth or 37 weeks' gestation ***No. of participants:*** *No. randomised* – 186 *No. analysed* – 162 ***Validity:*** *Adequate randomisation* – Unclear (process not described) *Adequate allocation concealment* – Yes (sealed, opaque envelopes) *Blinding of clinician* – No *Blinding of patient* – No *Blinding of researcher* – Unclear	***Groups compared:*** Home uterine activity monitoring vs No home uterine activity monitoring ***Intervention details*** All participants were treated with a maintenance regimen of oral terbutaline tocolysis (following i.v. magnesium sulphate treatment) for the duration of the pregnancy or until discontinuation at 37 weeks' gestation. Before discharge from hospital all women received preterm labour and delivery education: this included recognition of signs and symptoms of preterm labour and instructions on perinatal follow-up. In addition, all participants received daily contact with a perinatal nurse who asked about any signs or symptoms of recurrent labour. Participants were followed-up weekly in a preterm labour clinic by one of the researchers. Participants in the monitored group were asked to transmit a uterine activity monitor strip by telephone to the Tokos Monitor Centre twice daily until 37 weeks' gestation or until instructed to stop monitoring. If a participant exceeded the baseline contraction frequency of six contractions/h, the study physician, or perinatal nurse were informed by the monitoring centre, and the patient was instructed on immediate management and follow-up. Parenteral tocolysis was not reinitiated for women with recurrent preterm labour after 35 weeks' gestation ***Participants:*** Asymptomatic women who had been treated for threatened preterm labour Participants were all being managed at Wishard Memorial Hospital, the primary hospital for disadvantaged inner-city population of Marion county ***Participant inclusion/exclusion criteria:*** Women with a singleton gestation treated for idiopathic preterm labour between 24 and 34 weeks' gestation, Medicaid coverage, and functioning telephone services were eligible for inclusion. Women with premature rupture of membranes or any obstetric condition warranting early delivery were excluded ***Outcomes:*** Preterm delivery < 35 weeks' gestation and < 37 weeks' gestation, neonatal intensive care admission, mechanical ventilation, antenatal corticosteroid treatment, birthweight, Caesarean delivery Secondary outcomes were readmissions for recurrent preterm labour necessitating parenteral tocolysis and unscheduled hospital visits lasting < 24 h	***Incidence of birth < 34 weeks' gestation:*** Not reported ***Incidence of birth < 35 weeks' gestation:*** *No. in intervention group (total no.)* = 9 (82) *No. in control group (total no.)* = 12 (80) ***Incidence of birth ≤37 weeks' gestation:*** *No. in intervention group (total no.)* = 40 (82) *No. in control group (total no.)* = 48 (80) ***Incidence of birth within 24 h of intervention:*** Not reported ***Incidence of birth within 48 h of intervention:*** Not reported ***Incidence of birth within 7 days of intervention:*** Not reported ***Incidence of neonatal intensive care admission:*** *No. in intervention group (total no.)* = 20 (82) *No. in control group (total no.)* = 22 (80) ***Incidence of perinatal mortality:*** Not reported ***Birthweight*** Intervention group: 2933 (SD: 639.9) Control group: 2943.5 (SD: 547.0) ***Incidence of adverse events:*** Mechanical ventilation *No. in intervention group (total no.)* = 2 (82) *No. in control group (total no.)* = 3 (80) Antenatal corticosteroid treatment *No. in intervention group (total no.)* = 56 (82) *No. in control group (total no.)* = 54 (80) Mean length of neonatal unit stay (days) *Intervention group (SD)* = 3.3 (11.4) *Control group (SD)* = 2.2 (6.5)

Study details and design	Description of methods	Results and conclusions
Type of analysis: Chi-squared test was used to analyse categoric data, Mantel–Haenszel test was used for ordinal variables, and Student's *t*-test was used for continuous data. Multivariate logistic regression model was performed to determine the probability of preterm birth at < 35 weeks' gestation Power calculation: 82 women per arm were required to determine a 20% reduction in the risk of preterm delivery with 80% power, and 5% significance level		***Brief summary of findings:*** No statistically significant differences were shown for any of the measures predicting preterm birth except cervical dilatation at enrolment. Women with cervical dilatation ≥ 2 cm at enrolment had an OR of 4.35 (95% CI: 1.07–17.66) for delivery at < 35 weeks' gestation. The OR for preterm delivery women with ≥ 2 cm dilatation was 2.07 (95% CI: 0.47–9.20); the OR for women with < 2 cm dilatation was 1.06 995% CI: 0.22–5.23) No difference was shown between groups in neonatal intensive care admissions, number of infants receiving mechanical ventilation, or percentage of women receiving corticosteroid treatment for prevention of neonatal complications ***Authors' conclusions:*** Home uterine monitoring, as an adjunctive treatment to oral terbutaline therapy, does not reduce the likelihood of preterm delivery before 35 weeks' gestation ***Comments:*** Mean compliance with home uterine activity monitoring (based on actual number of HUM transmissions vs expected number of transmissions) was 64.5% (delivery < 35 weeks' gestation) and 59.7% (delivery > 35 weeks' gestation) There was a 12.9% loss to follow-up

TABLE 125 *Home uterine activity monitoring (continued)*

Study details and design	Description of methods	Results and conclusions
Corwin et al. [Am J Obstet Gynecol 1996; 175: 1281–1285][474] ***Country:*** USA ***Setting:*** Recruitment was conducted at three centres: the Truman Medical Center, Kansas City; the State University of New York, Syracuse Health Sciences Center; and the University of Illinois Hospital Chicago. Home uterine monitoring was performed in the participant's home ***Prevalence:*** *Symptomatic for preterm birth* – Not reported *Preterm birth* – 35 (out of a total 154), based on preterm delivery at less than 37 weeks' gestation in women at high risk of preterm birth ***Study design:*** RCT ***Length of follow-up:*** Monitoring was started no earlier than 24 weeks' gestation, and was continued until 37 weeks' gestation or until delivery if delivery occurred < 37 weeks ***No. of participants:*** *No. randomised* – 339 *No. analysed* – 318 (339 women with singleton pregnancies and 38 women with twin gestations were separately randomised to the trial. However, the report is limited to the outcomes for the 339 singleton gestations)	***Groups compared:*** Home uterine activity monitoring (HUM) without increased nursing support vs Routine high-risk prenatal care ***Intervention details:*** Both groups received education regarding preterm labour risk and information about preterm labour precautions, including the signs and symptoms of preterm labour. Participants also received education about the monitoring protocol and self-palpation. Participants were instructed to notify their physician or the clinic if they suspected preterm labour. Treatment protocols at each site included intensive tocolytic therapy; the specific therapy provided for preterm labour was at the discretion of the treating physician The monitored group received standard high-risk obstetric care plus twice daily home uterine monitoring (Genesis System). Women were instructed in the use of this device and told to monitor for 1 h twice a day, every day. Participants were scheduled for twice-daily transmission of uterine data (morning and evening) via phone. The receiver personnel reported the number of contractions to the patient. No additional medical advice or instructions were given to the participants at these times. The control group received standard high-risk obstetric care ***Participants:*** Asymptomatic women at risk of preterm delivery ***Participant inclusion/exclusion criteria:*** Women between 24 and 32 weeks' gestation with an increased risk for preterm labour as judged by a Creasy risk score ≥ 10 were eligible for inclusion. Women with a psychiatric problem that precluded compliance with study protocol, or who did not speak English, and pregnancies > 32 weeks' gestation were excluded. In addition, all participants were required to have telephone access ***Outcomes:*** Preterm birth at < 37 weeks and < 31 weeks' gestation, birthweight and admission to neonatal care unit	***Incidence of birth < 34 weeks' gestation:*** Not reported ***Incidence of birth < 37 weeks' gestation:*** *No. in intervention group (total no.)* = 22 (164) *No. in control group (total no.)* = 35 (154) ***Incidence of birth within 24 h of intervention:*** Not applicable ***Incidence of birth within 48 h of intervention:*** Not applicable ***Incidence of birth within 7 days of intervention:*** Not applicable ***Incidence of neonatal intensive care admission:*** *No. in intervention group (total no.)* = 17 (164) *No. in control group (total no.)* = 32 (154) ***Incidence of perinatal mortality:*** Not reported ***Incidence of adverse events:*** Incidence of birth < 31 weeks' gestation *No. in intervention group (total no.)* = 2 (164) *No. in control group (total no.)* = 9 (154) Birthweight < 2500 g *No. in intervention group (total no.)* = 19 (155) *No. in control group (total no.)* = 37 (142) Birthweight < 2000 g *No. in intervention group (total no.)* = 9 (155) *No. in control group (total no.)* = 20 (142) Birthweight < 1500 g *No. in intervention group (total no.)* = 0 (155) *No. in control group (total no.)* = 7 (142) Mean length of stay in neonatal care unit (days) *Intervention group* = 0.89 *Control group* = 3.90

Study details and design	Description of methods	Results and conclusions
Validity: *Adequate randomisation* – Yes (Random number table) *Adequate allocation concealment* – Unclear (envelopes, not stated whether opaque or sealed) *Blinding of clinician* – Yes *Blinding of patient* – No *Blinding of researcher* – Unclear ***Type of analysis:*** Group comparisons were assessed using Fisher's Exact test (categorical data) and independent *t*-test (continuous data). Kaplan–Meier plots were used for survival curves (women remaining undelivered between 26 and 37 weeks). Group comparisons were performed with log-rank test for survival analyses Power calculation: 320 women were required to detect an improvement from 30% to 60% in the proportion of women with preterm labour with early diagnosis (alpha 0.05, and beta 0.20; power 80%). The sample obtained had a power of 80% to detect a reduction in preterm birth from 22.7% to 11%		***Brief summary of findings:*** Compared to routine care, home uterine monitoring was shown to reduce risk of preterm delivery at < 37 weeks' gestation (RR 0.59, 95% CI: 0.37–0.95), and at < 31 weeks' gestation (RR 0.21, 95% CI: 0.05–0.95). In addition, infants from women receiving home uterine monitoring were less likely to need neonatal care admission (RR 0.50, 95% CI: 0.29–0.85), or have a low birthweight (< 2500 g, < 2000 g and < 1500 g) ***Authors' conclusions:*** The use of uterine activity monitoring improved pregnancy outcomes in women with singleton pregnancies, including: prolonged gestation, decreased risk for preterm birth, larger-birthweight infants, and a decreased need for neonatal intensive care ***Comments:*** Loss to follow-up rate: 6.19% 377 of 509 women with Creasy scores of ≥ 10 were enrolled in the trial. Reasons for lack of enrolment: 55 women refused to participate, consent for 37 women was not requested because of lack of telephone access, and 40 women were not approached because of logistical problems related to staff availability or lack of equipment

TABLE 125 *Home uterine activity monitoring (continued)*

Study details and design	Description of methods	Results and conclusions
Dyson et al. [Am J Obstet Gynecol 1991; 164: 756–762] [475] ***Country:*** USA ***Setting:*** Home monitoring ***Prevalence:*** *Symptomatic for preterm birth –* 51 (out of a total of 253), based on preterm labour at < 34 weeks in women at risk of preterm birth *Preterm birth –* 15 (out of a total 63), based on preterm labour at < 34 weeks in women at risk of preterm birth ***Study design:*** RCT ***Length of follow-up:*** From 24 weeks' gestation to 36 weeks' gestation ***No. of participants:*** *No. randomised* – 247 *No. analysed* – 247 Results presented relate to the 138 singleton pregnancies only A group of 143 participants receiving standard care were also entered in the study. Participants had received their prenatal care and were delivered of infants at the same hospital in the 30 months preceding the start of the prospective study and were selected by presence of risk factors	***Groups compared:*** Home uterine monitoring (tracings analysed and used in patient management) vs Education-palpation group (tracings not analysed or used in patient management) ***Intervention details:*** All women were contacted at least 5 days per week by a study nurse to review signs/symptoms of preterm labour, record number of contractions by palpation, and in the home monitoring group to review monitoring information. Women in the education–palpation group routinely transmitted to a monitor in such a way that the nurse could tell which participant had transmitted but could not analyse the uterine activity data All women were instructed to report to the hospital for evaluation if they experienced more than five contractions an hour that persisted for more than 1 h despite bed rest and oral hydration. Women in the home uterine monitoring group who had five contractions per hour on routine monitoring were instructed to lie down, drink fluids and remonitor for 1 h; if contractions persisted they were referred for evaluation. Women were initially asked to monitor themselves for 1 h/day and to transmit daily. Two years into the trial the protocol was changed to twice-daily monitoring and transmission. In addition, women in the home monitoring group were given the capability to transmit an emergency tracing at any time The clinical protocol recommended tocolysis for persistent uterine contractions if the cervix was dilated to 2 cm or documented cervical change before tocolysis. Prophylactic tocolytic agents were not administered. If tocolysis was successful, the participant was discharged home to bed rest taking oral tocolytic agents and maintaining pretreatment protocols. All gestational ages were confirmed by first or second trimester ultrasonography ***Participants:*** Asymptomatic women at risk of preterm birth ***Participant inclusion/exclusion criteria:*** Women with at least one risk factor (twin gestations, premature delivery at < 34 weeks' gestation after premature rupture of membranes in preceding pregnancy, premature labour requiring parenteral tocolysis but with term delivery in preceding pregnancy, incompetent cervix with cerclage in place, and nullipara with bicornuate, subseptate or didelphic uterus), < 28 weeks' gestation without evidence of preterm labour in the current pregnancy were eligible	***Incidence of birth < 34 weeks' gestation:*** *No. in intervention group (total no.)* = 8 (68) (11.8%) *No. in control group (total no.)* = 8 (70) (11.4%) ***Incidence of birth < 37 weeks' gestation:*** Not reported ***Incidence of birth within 24 h of intervention:*** Not applicable ***Incidence of birth within 48 h of intervention:*** Not applicable ***Incidence of birth within 7 days of intervention:*** Not applicable ***Neonatal intensive care admission (percentage):*** *Intervention group* = 22.1 ($n = 15$) *Control group* = 16.4% ***Incidence of perinatal mortality:*** Not reported ***Incidence of adverse events:*** Birthweight < 2500 g (percentage) *Intervention group* = 20.6 ($n = 14$) *Control group* = 18.6 (n = 13) Birthweight < 1500 g (percentage) *Intervention group* = 5.9 ($n = 4$) *Control group* = 8.6 ($n = 6$) ***Standard care:*** The incidence of preterm birth < 34 weeks' gestation was reduced in the education-palpation and home uterine monitoring group compared to standard care ($p = 0.05$ and 0.06, respectively). Neonatal outcomes, such as birthweight, infant hospital stay and development of respiratory distress syndrome were improved in the education-palpation and home uterine monitoring groups compared to standard care, but differences were not statistically significant except for infant hospital stay compared with education–palpation ($p = 0.04$)

Study details and design	Description of methods	Results and conclusions
Validity: *Adequate randomisation* – Unclear, method not reported *Adequate allocation concealment* – Unclear, not reported *Blinding of clinician* – No (study nurse), Unclear, not reported (obstetrician) *Blinding of patient* – Yes *Blinding of researcher* – No ***Type of analysis:*** Chi-squared test or the Student's *t*-test was used as appropriate. Results are expressed as mean ± SEM	***Outcomes:*** Preterm birth (< 34 weeks), preterm labour (< 34 or < 36 weeks' gestation), birthweight (< 2500 g and < 1500 g), respiratory distress syndrome, admission to neonatal intensive care unit, and infant hospital stay, days gained, gestational age at delivery, and delay > 48 h	***Brief summary of findings:*** The between-group difference in incidence of preterm birth was not statistically significant. There was no apparent difference between education–palpation and home uterine monitoring on any of the reported outcomes in women with singleton gestations ***Authors' conclusions:*** Addition of home uterine monitoring to the educational programme was not found to significantly improve pregnancy outcomes. However, the number of singleton pregnancies was too small to rule out possible benefit from home uterine monitoring in that group ***Comments:*** Small sample sizes and unclear internal validity limit confidence in the conclusions

CI, confidence intervals, i.v., intravenous; OR, odds ratio; RCT, randomised controlled trial; RR, relative risks.

TABLE 126 *Home visits*

Review details	Methods	Results and conclusions
Blondel [Semin Perinatol 1995; 19(4): 263–271][489] ***Title:*** Home visits during pregnancy: consequences on pregnancy outcome, use of health services, and women's situations. ***Type of review:*** Other ***Prevalence:*** *Symptomatic for preterm birth* – Not stated *Preterm birth* – 387 (out of a total 2986), based on preterm delivery rate < 37 weeks' gestation	***Search:*** *Search dates* Not reported *Databases searched* Cochrane Pregnancy and Childbirth Database *Other sources* Personal contacts *Search restrictions* No search restrictions applied ***Inclusion/exclusion criteria:*** *Study design(s)* RCTs *Population* Women at risk of pregnancy complications. Trials focusing on home visits for social support included women at risk of preterm or unfavourable social conditions. Trials focusing on home visits for medical care included mostly women at risk of preterm birth *Intervention* Home visits compared with no treatment. Home visits for social support: The goal of the midwife or family member was to increase emotional support, act as confidante, strengthen social networks and/or offer educational advice Home visits for medical care: The midwives' main task was medical examination, although they also encouraged women to rest and friends/ family to help with housework *Outcomes* Primary outcomes of interest: Preterm birth < 37 weeks' gestation, incidence of hospital admission during pregnancy and effect on women's health, support, attitudes, satisfaction with care and health habits ***Study selection:*** RCTs ***Data extraction:*** The authors do not state how data was extracted from the primary studies, or how many reviewers performed the data extraction.	***No. of studies included:*** Eight RCTs ($n = 7401$) ***No. of studies meeting quality criteria:*** *Adequate randomisation* – Not reported *Adequate concealment of allocation* – Not reported *Adequate blinding of clinician/patient/researcher* – Not reported ***Incidence of birth < 34 weeks' gestation:*** Not reported ***Incidence of birth < 37 weeks' gestation:*** All home visits: OR 1.0 (95% CI: 0.8–1.1) (8 studies, $n = 7401$) Social support: OR 0.9 (95% CI: 0.8–1.1) (5 studies, $n = 6005$) Medical care: OR 1.4 (95% CI: 0.9–1.9) (3 studies, $n = 1403$) ***Incidence of birth within 24h of intervention:*** Not applicable ***Incidence of birth within 48h of intervention:*** Not applicable ***Incidence of birth within 7 days of intervention:*** Not applicable. ***Incidence of neonatal intensive care admission:*** Not reported ***Incidence of perinatal mortality:*** Not reported ***Incidence of adverse events:*** *Prenatal hospital admission* All home visits: OR 0.8 (95% CI: 0.7–1.0) (4 studies, $n = 1893$) Social support: OR 0.6 (95% CI: 0.4–0.9) (1 study, $n = 486$) Medical care: OR 0.9 (95% CI: 0.7–1.2) (3 studies, $n = 1407$) ***Brief summary of findings:*** Incidence of preterm delivery did not significantly differ between the intervention and control group. Home visits did not significantly reduce the incidence of prenatal hospital admission. A reduction in the number of hospital visits during pregnancy was found for home visits (social support) compared to no treatment

Review details	Methods	Results and conclusions
	Validity assessment: *Criteria used* *Assessment* The authors do not state how the validity of the primary studies was assessed, or how many reviewers performed the quality assessment ***Synthesis:*** *Heterogeneity* Statistical heterogeneity does not appear to have been formally assessed *Methods* Odds ratios were used to measure associations for each trial. Confidence intervals were obtained using the Cornfield method. Pooled estimates and their 95% confidence intervals were obtained by meta-analysis using the Mantel–Haenzel method for each of the primary outcomes. Studies were also grouped by type of home visit (visits to provide social support, and visits to provide medical care)	***Authors' conclusions:*** Results do not support programmes offering home visits to pregnant women who are at risk for or suffering complications; visits do not improve their pregnancy outcome or reduce the rate of prenatal hospital admission ***Comments:*** Methods for the selection of the primary studies and data extraction were not reported so the possibility of reviewer error and bias cannot be assessed. Validity of the primary studies is not reported, so the quality of the included trials is uncertain. ***Related publication of interest:*** Belzian JM *et al* (1995). Impact of health education during pregnancy on behaviour and utilisation of health resources. *Am J Obstet Gynecol* **173**: 894–9. This study is included in the review described but reports on different outcomes that are not of primary interest to this review

TABLE 126 *Home visits (continued)*

Study details and design	Description of methods	Results and conclusions
Goulet et al.[CMAJ 2001; 164(7): 985–991][481] ***Country:*** Canada ***Setting:*** Two regional perinatal centres (Montreal and Quebec City) associated with teaching hospitals ***Prevalence:*** *Symptomatic for preterm birth* – Not stated *Preterm birth* – 55 (out of a total of 125), based on preterm birth less than 37 weeks' gestation ***Study design:*** RCT ***Length of follow-up:*** Women were followed-up until delivery ***No. of participants:*** *No. randomised* – 250 *No. analysed* – 250 ***Validity:*** *Adequate randomisation* – Yes *Adequate allocation concealment* – Yes *Blinding of clinician* – No *Blinding of patient* – No *Blinding of researcher* – Not stated	***Groups compared:*** Home care vs Hospital care for women with preterm labour ***Intervention details:*** *Intervention group* (early discharge and home care): the care plan and frequency of visits was determined on an individual basis. Medical prescription was completed by attending obstetrician, external uterine monitoring and fetal heart monitoring were carried out in the home by a nurse. Visits were provided between 09.00 and 17.00 h. The average visit lasted 1 h. Blood and urine samples were also taken at each visit. Individual teaching and psychosocial support were provided. The goal was to maximise the mother's ability to participate in her own care and to react quickly should a problem arise. Teaching was based around individual needs. Participants were given a self-monitoring diary to record uterine activity, fetal movements, maternal activity, medication etc. An assessment of additional needs was completed, including child-care. Services were arranged through family and community resources as required. The nurse could be contacted by telephone to address concerns *Control group* (hospital care): women received usual in-hospital medical care according to their medical status. Nurses provided the same teaching received by the experimental group. Women were also provided with a self-monitoring diary. Women discharged from the hospital were encouraged to call regarding concerns on an emergency basis or to go direct to the emergency/obstetrics ward ***Participants:*** Pregnant women with preterm labour were approached about participation after their contractions had resolved spontaneously or in response to tocolytic treatment ***Participant inclusion/exclusion criteria:*** Women with a first episode of preterm labour, singleton pregnancy, no previous history of preterm delivery, gestational age between 20 and 35 weeks, minimum maternal age of 18, resident within 50 km of the hospital were eligible. Women were excluded if there was more than one pregnancy complication at time of randomisation, cervical dilatation was > 4 cm and effacement was > 80%, or there was a diagnosis of intrauterine death or suspicion of fetal malformation	***Incidence of birth < 34 weeks' gestation:*** Not reported ***Incidence of birth < 37 weeks' gestation:*** *No. in intervention group (total no.)* = 53 (125) *No. in control group (total no.)* = 55 (125) ***Incidence of birth within 24 h of intervention:*** Not applicable ***Incidence of birth within 48 h of intervention:*** Not applicable ***Incidence of birth within 7 days of intervention:*** Not applicable ***Incidence of neonatal intensive care admission:*** *No. in intervention group (total no.)* = 13 (125) *No. in control group (total no.)* = 11 (125) ***Incidence of perinatal mortality:*** Not reported ***Incidence of adverse events:*** Neonatal intermediate care *No. in intervention group (total no.)* = 20 (125) *No. in control group (total no.)* = 21 (125) Neonatal haematological problems *No. in intervention group (total no.)* = 2 (125) *No. in control group (total no.)* = 1 (125) Multiple neonatal problems *No. in intervention group (total no.)* = 30 (125) *No. in control group (total no.)* = 28 (125) Duration of hospital stay (neonatal) *Mean (SD) number of days, intervention group= 7.9 (14.4)* *Mean (SD) number of days, control group= 6.1 (10.8)* Number of hospital re-admissions (maternal) 1: *No. in intervention group (total no.)* = 14 (125)

Study details and design	Description of methods	Results and conclusions
Type of analysis: Student's *t*-test was used to compare means, chi-squared and the Fisher exact test were used to compare proportions. One-way analysis of variance and Pearson's chi-squared tests were used to examine differences between the two groups in neonatal and maternal outcomes. Power: A sample size of 132 per group was required based on the assumptions of a two-tailed α of 5%, a 10% probability of type II error (β), a 1-week difference between the means and standard deviation of 2.5 weeks for gestational age	***Outcomes:*** Primary neonatal outcomes: gestational age and birthweight Secondary neonatal outcomes: incidence of preterm birth, duration of neonatal hospital stay, admission to neonatal intensive care Maternal outcomes: incidence of maternal hospital admission and length of hospital stay	*No. in control group (total no.)* = 18 (125) 2: *No. in intervention group (total no.)* = 3 (125) *No. in control group (total no.)* = 5 (125) 3: *No. in intervention group (total no.)* = 3 (125) *No. in control group (total no.)* = 0 (125) Duration of all maternal hospital stays *Mean (SD) number of days, intervention group= 3.7 (3.4)* *Mean (SD) number of days, control group= 5.0 (5.5)* ***Brief summary of findings:*** There were no statistically significant differences between the two groups in incidence of preterm delivery, neonatal admission to intensive care or intermediate care, birthweight, number of maternal hospital re-admissions. The mean duration of all maternal hospital stays was slightly shorter for women in the home visit group ***Authors' conclusions:*** Home care management is an efficient and acceptable alternative to hospital care for women experiencing preterm labour ***Comments:*** Analysis was by intention to treat A sample of 125 per group produced a power of 89% to detect a difference in the means for gestational age of more than a week

TABLE 126 *Home visits (continued)*

Study details and design	Description of methods	Results and conclusions
Kitzman [JAMA 1997; 278(8): 644–652][482] ***Country:*** USA ***Setting:*** Home visits for pregnant women recruited at the Regional medical centre, Memphis ***Prevalence:*** *Symptomatic for preterm birth* – Not stated *Preterm birth* – 13%, based on preterm birth less than 37 weeks' gestation. Individual numbers not reported ***Study design:*** RCT ***Length of follow-up:*** Prenatal phase: until delivery Postnatal phase: 24 months postpartum ***No. of participants:*** *No. randomised* – 1139 (intervention group, $n = 458$) *No. analysed* – 1139, based on preterm birth, however, final numbers varied depending on outcome.	***Groups compared:*** Four treatment arms are described: 1. Free transport for scheduled prenatal care appointments, 2. Free transport for scheduled prenatal care appointments plus developmental screening and referral services for the child at 6, 12 and 24 months, 3. Free transportation and screening offered plus intensive nurse home visitation services during pregnancy and 1 home visit post partum, 4. Same treatment as group 3 plus nurse visits through to the child's 2nd birthday For evaluation of the prenatal phase treatments 3 and 4 were combined to form a single comparison group (nurse visited group) and contrasted with treatments 1 and 2 (non-nurse visited group) ***Intervention details:*** *Home visitation, prenatal phase*: Nurses completed an average of seven home visits during pregnancy and 26 home visits postpartum. A visit-by-visit protocol was followed. Nurses helped women complete 24-h diet histories, plot weight gain, assess and facilitate reduction in smoking habits, use of alcohol and illicit drugs through behavioural analysis. Nurses taught women to identify signs and symptoms of pregnancy complications, encouraged women to inform the hospital of those conditions, and facilitated compliance with treatment. They co-ordinated care with office-based staff and measured blood flow when needed *Postpartum*: Nurses helped mothers and other care-givers improve the physical and emotional care of their children ***Participants:*** Pregnant women at risk of spontaneous preterm birth (asymptomatic) ***Participant inclusion/exclusion criteria:*** Women, less than 29 weeks pregnant, with no previous history of live births, no chronic illnesses thought to contribute to fetal growth retardation or preterm delivery, and at least two sociographic risk factors (unmarried, < 12 years education, and unemployed) were eligible for inclusion ***Outcomes:*** Primary outcomes: pregnancy-induced hypertension, preterm delivery, low birthweight, and a number of infant child health-care encounters and maternal life course outcomes	***Incidence of birth < 34 weeks' gestation:*** Not reported ***Incidence of birth < 37 weeks' gestation:*** *Intervention group (%)* = 11 *Control group (%)* = 13 ***Incidence of birth within 24 h of intervention:*** Not applicable. ***Incidence of birth within 48 h of intervention:*** Not applicable. ***Incidence of birth within 7 days of intervention:*** Not applicable ***Incidence of neonatal intensive care admission:*** Not reported ***Incidence of perinatal mortality:*** Not reported ***Incidence of adverse events:*** Low birthweight (< 2500 g) *Intervention group (%)* = 15 *Control group (%)* = 14 5-min Apgar *Intervention group (Mean)* = 8.6 *Control group (Mean)* = 8.7 Pregnancy-induced hypertension *Intervention group (%)* = 13 *Control group (%)* = 20 Number of yeast infections *Intervention group Incidence (log-incidence)* = 0.14 (–1.94) *Control group Incidence (log-incidence)* = 0.19 (–1.65)

Study details and design	Description of methods	Results and conclusions
Validity: *Adequate randomisation* – Yes (computerised programme) *Adequate allocation concealment* – Unknown *Blinding of clinician* – No *Blinding of patient* – No *Blinding of researcher* – No ***Type of analysis:*** Linear and logistic-linear models were used to analyse dependent variables. Odds ratios and their 95% confidence intervals are presented. Estimates were adjusted for all covariates, classification factors and interactions Homogeneity of regressions was considered ***Power:*** A sample of 1468 was need for the prenatal phase and a sample of 734 for the postnatal phase of the trial, based on a series of calculations using $\alpha = 0.5$ and $\beta = 0.20$ for two-tailed tests		***Brief summary of findings:*** Preterm delivery, low birthweight, and Apgar scores did not significantly differ between women receiving nurse home visit programmes and those who did not. Nurse-visited women had fewer yeast infections and lower incidence of pregnancy-induced hypertension ***Authors' conclusions:*** Home visits by nurses can reduce pregnancy-induced hypertension, childhood injuries and subsequent pregnancies among low-income women with no previous live births ***Comments:*** Intention to treat analysis conducted The majority of participants were young, unmarried, low-income African Americans, which may limit the generalisability of the findings

CI, confidence intervals; OR, odds ratio; RCT, randomised controlled trials.

TABLE 127 *Periodontal treatment*

Study details and design	Description of methods	Results and conclusions
Lopez [J Periodontol 2002; 73:911–924] [490] ***Country:*** Chile ***Setting:*** Dental clinic located within the same building in which routine prenatal care was given. Women invited to participate in the study were of low socioeconomic status receiving uniform prenatal care in a public health clinic in Santiago ***Prevalence:*** *Symptomatic for preterm birth* – *Preterm birth* – 12 (out of a total of 188) ***Study design:*** Quasi-RCT ***Length of follow-up:*** Periodontal therapy was completed by 28 weeks' gestation. Maintenance therapy continued until delivery ***No. of participants:*** *No. randomised* – 400 (200 in each group) *No. analysed* – 351 (Treatment group: 163, Control group: 188) Trial stopped early, after 160 deliveries in both arms of the study	***Groups compared:*** Periodontal treatment vs No treatment ***Intervention details:*** *Treatment group* Periodontal therapy consisted of: plaque control instructions, scaling, and root planing performed under local anaesthesia. Women were also instructed to rinse once a day with 0.12% chlorhexidine. A full periodontal examination was given before and after completing the therapy period. The same examiner performed measurements for a given participant. As a consequence of severe aggressive periodontitis, 29 women (18%) received metronidazole 250 mg and amoxicillin 500 mg for 7 days in addition to the mechanical treatment. All women in the treatment group also received routine prenatal care *Control group* In addition to the routine prenatal care programme women were monitored every 4–6 weeks during their pregnancy to determine any change in their periodontal condition. A full periodontal examination was performed at study entry and after 28 weeks' gestation. Participants were to receive periodontal therapy after delivery ***Participants:*** Pregnant women (asymptomatic) ***Participant inclusion/exclusion criteria:*** *Inclusion criteria:* Pregnant women aged 18 to 35, with a singleton gestation, between 9 and 21 weeks' gestation, with periodontal disease and fewer than 18 of their natural teeth *Exclusion criteria:* women with a history of congenital heart disease requiring prophylactic antibiotics for invasive procedures, diabetes, current use of corticosteroids, chronic renal disease, and the intention to deliver at a hospital other than that designated by the study ***Outcomes:*** Primary outcomes of interest: preterm birth (spontaneous delivery < 37 weeks' gestation), and low birthweight (< 2500 g)	***Incidence of birth < 34 weeks' gestation:*** Not reported ***Incidence of birth < 37 weeks' gestation:*** *No. in intervention group (total no.)* = 2 (163) *No. in control group (total no.)* = 12 (188) ***Incidence of birth within 24 h of intervention:*** Not applicable ***Incidence of birth within 48 h of intervention:*** Not applicable ***Incidence of birth within 7 days of intervention:*** Not applicable ***Incidence of neonatal intensive care admission:*** Not reported. ***Incidence of perinatal mortality:*** Not reported. ***Incidence of adverse events:*** Low birthweight (< 2500 g): *No. in intervention group (total no.)* = 1 (163) *No. in control group (total no.)* = 7 (188) Fetal death (spontaneous abortion): *No. in intervention group (total no.)* = 8 (200) *No. in control group (total no.)* = 6 (200) ***Brief summary of findings:*** Compared to those not receiving treatment, the periodontal therapy group had statistically fewer preterm deliveries < 37 weeks' gestation ($p = 0.017$). In addition, a reduction in infants with low birthweight was found in the periodontal therapy group, although this was not statistically significant ($p = 0.083$) ***Authors' conclusions:*** Periodontal disease appears to be an independent risk factor for preterm birth and low birthweight. In addition, periodontal therapy reduced the rate of preterm birth and low birthweight in this population with periodontal disease

Study details and design	Description of methods	Results and conclusions
Validity: *Adequate randomisation* – No *Adequate allocation concealment* – No (coin toss) *Blinding of clinician* – Periodontal specialist (no), obstetrician (yes) *Blinding of patient* – No *Blinding of researcher* – Not stated ***Type of analysis:*** Incidence rates were reported in relation to the outcomes of interest. In addition, univariate and multivariate logistic regression analyses were performed for a combined preterm birth/ low birthweight group. ORs and their 95% CI were presented		***Comments:*** Allocation to treatment groups was conducted by a coin toss. Residual confounding from variables such as lifetime smoking or smoking during pregnancy did not appear to be accounted for 49 participants were excluded from the analysis; 37 in the treatment group (12.7%). Reasons for exclusion included: spontaneous abortion; preterm delivery due to pre-eclampsia, gestational diabetes, placenta praevia, or polyhydramnios; withdrawal due to discomfort with treatment; or lost to follow-up Participants in the treatment group were slightly older than those in the control group (28 (SD 4.5) vs 27 9 (SD 4.3), $p = 0.04$; and more likely to be single (30% vs 19%; $p = 0.001$)

CI, confidence intervals; OR, odds ratio; RCT, randomised controlled trials.

TABLE 128 *Progesterone*

Review details	Methods	Results and conclusions
Dodd et al. [Cochrane Database of Systematic Reviews Issue 1, 2006][736] ***Title:*** Prenatal administration of progesterone for preventing preterm birth ***Type of review:*** Cochrane ***Prevalence:*** *Symptomatic for preterm birth –* Not reported *Preterm birth –* 130 (out of 338 in total), based on preterm birth less than 37 weeks' gestation 13 (out of 70 in total), based on preterm birth less than 34 weeks' gestation	***Search:*** *Databases searched (search dates)* Cochrane Pregnancy and Childbirth Group Trials Register (Mar. 2005), Cochrane Controlled Trials Register (Issue 3, 2004), MEDLINE (1965 to Jan. 2005), EMBASE (1988 to Aug. 2004), Current Contents (1997 to Aug. 2004) *Other sources* Hand searching of bibliographic references *Search restrictions* None specified ***Inclusion/exclusion criteria:*** *Study design(s)* RCTs *Population* Pregnant women at high risk of preterm birth (asymptomatic) *Intervention* Trials comparing progesterone (administered by any route) with placebo. Trials were excluded if progesterone was administered for the treatment of preterm labour or administered in the first trimester for preventing miscarriage *Outcomes* Primary outcomes included: perinatal mortality, preterm birth < 34 weeks' gestation, and major neurodevelopmental handicap at childhood follow-up A number of other maternal and neonatal outcomes were sought, including preterm birth < 37 weeks and admission to neonatal care unit ***Study selection:*** Two reviewers independently assessed studies for potential inclusion; disagreements were resolved by consensus ***Data extraction:*** Two reviewers independently extracted data from the primary studies; disagreements were resolved by consensus ***Validity assessment:*** *Criteria used* Four sources of potential bias were considered: Allocation concealment, randomisation, blinding, and completeness of follow-up. A quality rating for blinding of randomisation was given to each trial (A: adequate, B: unclear, C: inadequate, or D: not used). A quality rating of A: Yes, b: Cannot tell, C: No, was used for all other validity outcomes	***No. of studies included:*** Five RCTs ($n = 911$). Four trials compared intramuscular 17-hydroxyprogesterone caproate with placebo one trial compared vaginal progesterone with placebo ***No. of studies meeting quality criteria:*** *Adequate randomisation* – 2 *Adequate concealment of allocation* – 3 *Adequate blinding of clinician/patient/researcher* – 6/6/Not stated ***Incidence of birth < 34 weeks' gestation:*** (Fixed effects) RR 0.15 (95% CI: 0.04–0.64) (1 study, $n = 142$) ***Incidence of birth < 37 weeks' gestation:*** (Fixed effects) RR 0.60 (95% CI: 0.49–0.73) (5 studies, $n = 988$). ***Incidence of birth within 24 h of intervention:*** Not reported ***Incidence of birth within 48 h of intervention:*** Not reported ***Incidence of birth within 7 days of intervention:*** Not reported ***Incidence of neonatal intensive care admission:*** Need for assisted ventilation (Fixed effects) RR 0.59 (95% CI: 0.35–1.00) (1 study, $n = 454$) ***Incidence of perinatal mortality:*** (Fixed effects) RR 0.55 (95% CI: 0.29–1.06) (4 studies, $n = 9767$) ***Incidence of adverse events:*** *Intrauterine fetal death* (Fixed effects) RR 0.56 (95% CI: 0.19–1.61) (3 studies, $n = 671$) *Neonatal death* (Fixed effects) RR 0.59 (95% CI: 0.27–1.30) (3 studies, $n = 671$) *Birthweight < 2500 g* (Fixed effects) RR 0.63 (95% CI: 0.49–0.81) (4 studies, $n = 763$). *Intraventricular haemorrhage* RR 0.25 (95% CI: 0.08–0.82) (1 study, $n = 458$)

Review details	Methods	Results and conclusions
	Assessment Two reviewers independently assessed the methodological quality of the primary studies; disagreements were resolved by consensus ***Synthesis:*** *Heterogeneity* This was assessed visually by an inspection of the outcomes tables, and statistically using the *I*-squared statistic and the chi-squared test. Planned subgroup analyses included: time of treatment commencement, route of administration, dose and plurality of the pregnancy *Methods* Pooled risk ratio (RRs), with their associated 95% confidence intervals (CIs), were calculated for each outcome using a fixed effects model	*Use of antenatal corticosteroids* RR 0.87 (95% CI: 0.58–1.30) (1 study, $n = 459$) *Use of antenatal tocolytics* (Fixed effects) RR 1.12 (95% CI: 0.73–1.72) (2 studies, $n = 503$) *Respiratory distress syndrome* RR 0.63 (95% CI: 0.38–1.05) (1 study, $n = 457$) *Retinopathy of prematurity* RR 0.50 (95% CI: 0.50–1.70) (1 study, $n = 457$) *Necrotising enterocolitis* RR 0.06 (95% CI: 0.00–1.03) (1 study, $n = 457$) *Neonatal sepsis* RR 1.12 (95% CI: 0.35–3.58) (1 study, $n = 457$) *Patent duct arteriosus* RR 0.43 (95% CI: 0.16–1.17) (1 study, $n = 457$) ***Subgroup analyses:*** ***Preterm birth < 37 weeks' gestation:*** Route of administration Intramuscular injection: (Fixed effects) RR 0.61 (95% CI: 0.50–0.75) (5 studies, $n = 846$) Vaginal pessary: RR 0.49 (95% CI: 0.25–0.96) (1 study, $n = 142$) Timing of treatment administration < 20 weeks gestation: (Fixed effects) RR 0.64 (95% CI: 0.52–0.79) (3 studies, $n = 670$) > 20 weeks gestation: (Fixed effects) RR 0.40 (95% CI: 0.22–0.75) (3 studies, $n = 318$) Cumulative weekly dose ≥500 mg: (Fixed effects) RR 0.50 (95% CI: 0.29–0.86) (3 studies, $n = 409$) < 500 mg: (Fixed effects) RR 0.63 (95% CI: 0.51–0.77) (2 studies, $n = 579$) ***Perinatal mortality:*** Timing of treatment administration < 20 weeks gestation: (Fixed effects) RR 0.55 (95% CI: 0.29–1.06) (3 studies, $n = 671$) > 20 weeks gestation: Not estimable Cumulative weekly dose ≥500 mg: RR 1.10 (95% CI: 0.23–5.29) (1 study, $n = 168$) < 500 mg: (Fixed effects) RR 0.48 (95% CI: 0.23–0.98) (2 studies, $n = 503$)

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TABLE 128 *Progesterone (continued)*

Review details	Methods	Results and conclusions
		Brief summary of findings: A reduction in the risk of preterm birth < 37 weeks' gestation, and < 34 weeks' gestation was shown for women prescribed progesterone compared to placebo. A reduction in the risk of birthweight < 2500 g was also shown for infants born to mothers receiving progesterone. No other differences were reported for maternal or infant outcomes ***Authors' conclusions:*** That intramuscular progesterone is associated with reduced risk of preterm birth at < 37 weeks' gestation and infant birthweight < 2500 g. Further research is needed on the use of vaginal progesterone for the prevention of preterm birth. Other infant and maternal outcomes are not well reported, with most outcomes reported from a single study ***Comments:*** This was a well-conducted review and the authors appear to have taken appropriate steps to reduce bias The authors note that the sample size of trials reporting outcomes is underpowered to detect significant differences in important neonatal outcomes One study, focusing on twin gestations, was excluded from the original review
CI, confidence intervals; RCT, randomised controlled trials; RR, relative risks		

TABLE 129 *Smoking cessation programmes*

Review details	Methods	Results and conclusions
Lumley et al. [Cochrane Database of Systematic Reviews 2004, Issue 4] [500] ***Title:*** Interventions for promoting smoking cessation during pregnancy	***Search:*** *Search dates:* July 2003 *Databases searched:* Cochrane Pregnancy and Childbirth Group trials register, Cochrane Tobacco Addiction Group trials register, MEDLINE, EMBASE, PsychLIT, CINAHL, AUSTHEALTH	***No. of studies included:*** 64 of which 16 reported relevant maternal or perinatal outcomes ***No. of studies meeting quality criteria:*** *Adequate randomisation* – *Adequate concealment of allocation* – *Adequate blinding of clinician/patient/researcher* – ***Incidence of birth < 34 weeks' gestation:*** Not reported

Review details	Methods	Results and conclusions
Type of review: Cochrane ***Prevalence:*** *Symptomatic for preterm birth* – Not applicable *Preterm birth* – 341 (of 5403 in total)	*Other sources:* References of identified trials. Handsearching of journals including *American Journal of Obstetrics and Gynecology*, *Obstetrics and Gynecology*, *BJOG*; *Acta Obstetrica et Gynecologica Scandinavica*, *Tobacco Control*, *BMJ*, the *Lancet* *Search restrictions:* None reported ***Inclusion/exclusion criteria:*** *Study design(s)* RCTs and quasi-RCTs *Population* Pregnant women, women seeking a pre-pregnancy consultation, health professionals in trials of strategies to change knowledge, attitudes and behaviour with respect to smoking cessation *Intervention:* Any programme that aimed to promote smoking cessation during pregnancy *Outcomes* Preterm birth < 37 weeks, preterm birth < 32 weeks, preterm birth < 30 weeks, low birthweight < 1500 g low birthweight < 2500 g, perinatal mortality. A range of outcomes relating to intervention success and maternal wellbeing and satisfaction were also included ***Study selection:*** Methods of study selection were not reported ***Data extraction:*** Two reviewers independently extracted data from the studies ***Validity assessment:*** *Criteria used* Cochrane reviewers' handbook criteria, which include randomisation, allocation concealment, blinding, treatment of drop-outs and loss to follow-up, sample size calculation *Assessment* Two reviewers assessed studies independently ***Synthesis:*** *Heterogeneity* Heterogeneity was assessed using the chi-squared and *I*-squared tests. Subgroup analyses for treatment intensity and trial quality were conducted *Methods* Pooled relative risks were calculated in a fixed-effect meta-analysis	***Incidence of birth < 37 weeks' gestation*** RR 0.84 (95% CI: 0.72–0.98) (11 trials, *n* = 10932) ***Incidence of birth within 24 h of intervention:*** Not applicable ***Incidence of birth within 48 h of intervention:*** Not applicable ***Incidence of birth within 7 days of intervention:*** Not applicable ***Incidence of neonatal intensive care admission:*** Not reported ***Incidence of perinatal mortality:*** RR 1.13 (95% CI 0.72–1.77) (3 studies, *n* = 4335) ***Incidence of adverse events:*** *Low birthweight < 2500 g* RR 0.82 (95% CI: 0.70–0.95) (13 studies, *n* = 8930) *Low birthweight < 1500 g* RR 1.26 (95% CI: 0.69–2.32) (3 trials, *n* = 4765) *Stillbirth* RR 1.16 (95% CI: 0.71–1.88) (5 trials, *n* = 4525) *Neonatal death* RR 1.17 (95% CI: 0.34–4.01) (3 trials, *n* = 4143) ***Brief summary of findings:*** Interventions to promote smoking cessation significantly reduced the incidence of preterm birth at less than 37 weeks' gestation and the incidence of low birthweight < 2500 g, but did not significantly affect the incidence of perinatal mortality or very low birthweight < 1500 g ***Authors' conclusions:*** Smoking cessation programmes in pregnancy reduce the proportion of women who continue to smoke and reduce low birthweight and preterm birth. Pooled trials have inadequate power to detect reductions in perinatal mortality or very low birthweight ***Comments:*** This was a well-conducted review that includes a substantial number of large trials reporting primary outcomes and the authors' conclusions are likely to be reliable

CI, confidence intervals; RCT, randomised controlled trials; RR, relative risks.

Symptomatic women

TABLE 130 *Hydration*

Review details	Methods	Results and conclusions
Stan et al. [Cochrane Database of Systematic Reviews 2005, Issue 3][516] ***Title:*** Hydration for treatment of preterm labour ***Type of review:*** Cochrane ***Prevalence:*** *Symptomatic for preterm birth* –Not reported *Preterm birth* – 24 (out of 93 in total) for preterm birth < 37 weeks' gestation 5 (out of 56 in total) for preterm birth < 34 weeks' gestation	***Search:*** *Search dates* June 2004 *Databases searched* Cochrane Pregnancy and Childbirth Group Trials Register *Other sources* Bibliographies of identified studies were also searched *Search restrictions* No search restrictions reported ***Inclusion/exclusion criteria:*** *Study design(s)* RCTs with < 20% loss to follow-up *Population* Pregnant women at risk of preterm birth (symptomatic) *Intervention* Intravenous or oral hydration compared with no treatment. Studies comparing tocolytic agents with intravenous fluids used in the control group were not considered in the review *Outcomes* Primary outcomes included prolongation of pregnancy (> 48 h, > 7 days), gestational age at delivery (> 28 weeks, > 32 weeks, > 34 weeks, > 37 weeks), a number of perinatal outcomes including perinatal death and admission to neonatal intensive care unit, long-term sequelae. A number of maternal outcomes were also considered ***Study selection:*** Two reviewers independently screened the titles/abstracts and full papers. Disagreements were resolved by consensus ***Data extraction:*** Two reviewers independently extracted data from the primary studies	***No. of studies included:*** 2 RCTs ($n = 228$) ***No. of studies meeting quality criteria:*** *Adequate randomisation* – 2 *Adequate concealment of allocation* – 2 *Adequate blinding of clinician/patient/researcher* – 0/0/0 (not stated) ***Incidence of birth < 34 weeks' gestation:*** (Fixed effects) RR 0.72 (95% CI: 0.20–2.56) (1 study, $n = 118$) ***Incidence of birth < 37 weeks' gestation:*** (Fixed effects) RR 1.09 (95% CI: 0.71–1.68) (2 studies, $n = 228$) ***Incidence of birth within 24 h of intervention:*** Not reported ***Incidence of birth within 48 h of intervention:*** Not estimable ***Incidence of birth within 7 days of intervention:*** Not estimable ***Incidence of neonatal intensive care admission:*** (Fixed effects) RR 0.99 (95% CI: 0.46–2.16) or (1 study, $n = 118$) Incidence of perinatal mortality: Not estimable ***Incidence of adverse events:*** Low birthweight (< 2500 g, < 1500 g), severe neonatal morbidity and maternal death were not estimable ***Brief summary of findings:*** Compared to bed rest alone, intravenous hydration did not prolong gestation; no statistical difference was found between the groups for preterm birth less than 34 or 37 weeks' gestation. No statistical difference was found between groups for admission to neonatal intensive care unit. The impact of hydration on the other outcomes sought was not estimable

Review details	Methods	Results and conclusions
	Validity assessment: *Criteria used* A methodological grade was given to each study primarily based on allocation concealment: grade A (adequate concealment), grade B (uncertain), grade C (inadequate concealment). Blinding and loss to follow-up were also considered *Assessment* Carried out independently by two reviewers, disagreements resolved by consensus ***Synthesis:*** *Heterogeneity* Heterogeneity was formally assessed using the chi-squared test and the *I*-squared test *Methods* Results were expressed as relative risks (RRs) for dichotomous outcomes and weighted means difference (WMD) for continuous outcomes. Where more than one study was considered, meta-analysis was performed. Separate analyses were also carried out for women included before 34 weeks	***Authors' conclusions:*** There are insufficient data to support the use of hydration for the treatment of women presenting with preterm labour. The two included studies do not demonstrate any benefit of intravenous hydration compared to bed rest alone, even during the period of evaluation soon after admission. The authors add that women with evidence of dehydration may, however, benefit from hydration ***Comments:*** This was a well-conducted review and the authors appear to have taken appropriate steps to reduce possible biases Both included studies used intravenous hydration. No trials evaluated oral hydration It appears likely that multiple pregnancies were included as subgroup analyses were planned but not completed due to insufficient data Both studies reported less than 20% drop-out rates

CI, confidence intervals; RCT, randomised controlled trials; RR, relative risks.

TABLE 131 *Prophylactic antibiotics (intact membrane)*

Review details	Methods	Results and conclusions
King and Flenady [Cochrane Database of Systematic Reviews 2002, Issue 4][520] ***Title:*** Prophylactic antibiotics for inhibiting preterm labour with intact membranes ***Type of review:*** Cochrane review ***Prevalence:*** *Symptomatic for preterm birth –* Not reported *Preterm birth –* 852 (out of a total 2087), based on delivery less than 36 or 37 weeks' gestation	***Search:*** *Databases searched (Search dates)* The Cochrane Pregnancy and Childbirth Group database (May 2002), the Cochrane Controlled Trials Registry (2002, Issue 1), and MEDLINE (1965 to May 2002) *Other sources* Bibliographic references of all retrieved articles were also searched. In addition the authors contacted experts in the field and cross-referenced relevant material. *Search restrictions* No restrictions reported ***Inclusion/exclusion criteria:*** *Study design(s)* RCTs *Population* Women thought to be in preterm labour with intact membranes *Intervention* Any antibiotics, administered intravenously or orally, in the management of preterm labour with intact membranes *Outcomes* Delivery < 28, 36 and 37 weeks' gestation, time to delivery, chorioamnionitis, post-partum pyrexia, adverse drug reaction, length of hospital stay (maternal), adverse drug reaction, fetal death, neonatal death, perinatal mortality, Apgar scores, neonatal sepsis, admission to neonatal care unit, mechanical ventilation, respiratory distress syndrome, necrotising enterocolitis, retinopathy of prematurity, intraventricular haemorrhage, cerebral cystic lesions, chronic lung disease, long term neurosensory impairment and length of hospital stay (infant) ***Study selection:*** The authors independently selected studies for inclusion; disagreements were resolved by discussion ***Data extraction:*** The authors independently extracted data from the primary studies; disagreements were resolved by discussion. Missing or incomplete data were sought from the trial authors where necessary	***No. of studies included:*** 11 RCTs ($n = 7428$) ***No. of studies meeting quality criteria:*** *Adequate randomisation* – 10 *Adequate concealment of allocation* – 10 *Adequate blinding of clinician/patient/researcher* – 9/10/10 ***Incidence of birth < 34 weeks' gestation:*** Not reported ***Incidence of birth < 36 or < 37 weeks' gestation:*** Any antibiotic vs no antibiotic [Fixed effect] RR 0.99 (95% CI: 0.92–1.05) (9 studies, $n = 7291$) Betalactam antibiotic alone vs no antibiotic [Fixed effect] RR 0.99 (95% CI: 0.88–1.11) (4 studies, $n = 2334$) Macrolide antibiotics alone vs no antibiotic [Fixed effect] RR 1.02 (95% CI: 0.90–1.15) (2 studies, $n = 2235$) Macorilde and betalactam antibiotic vs no antibiotic [Fixed effect] RR 0.99 (95% CI: 0.89–1.10) (4 studies, $n = 2613$) Antibiotic active against anaerobic bacteria vs no antibiotics: [Fixed effect] RR 0.85 (95% CI: 0.68–1.05) (2 studies, $n = 226$) ***Incidence of birth within 24 h of intervention:*** Not reported ***Incidence of birth within 48 h of intervention:*** Any antibiotic vs no antibiotic [Fixed effect] RR 1.04 (95% CI: 0.89–1.23) (4 studies, $n = 6800$) Betalactam antibiotic alone vs no antibiotic [Fixed effect] RR 1.01 (95% CI: 0.75–1.36) (1 study, $n = 2053$) Macrolide antibiotics alone vs no antibiotic [Fixed effect] RR 1.06 (95% CI: 0.78–1.42) (1 study, $n = 2119$) Macorilde and betalactam antibiotic vs no antibiotic [Fixed effect] RR 1.12 (95% CI: 0.86–1.45) (3 studies, $n = 2520$) Antibiotic active against anaerobic bacteria vs no antibiotics [Fixed effect] RR 0.55 (95% CI: 0.19–1.57) (1 study, $n = 109$)

Review details	Methods	Results and conclusions
	Validity assessment: *Criteria used* Blinding, allocation concealment and follow-up *Assessment* The authors independently assessed the methodological quality of the included studies; disagreements were resolved by discussion ***Synthesis:*** *Heterogeneity* Chi-squared test and *I*-squared statistic were used to assess differences between trials. *Methods* Meta-analysis was conducted using a fixed effects model; one outcome with significant heterogeneity, not explained by sensitivity analyses, was recalculated using a random effects model. Results are presented as relative risks (RR) for categorical data and weighted mean difference (WMD) for continuous data with their 95% confidence intervals Subgroup analysis was planned (treatment commenced prior to 24 weeks and between 25 and 33 weeks), treatment with macrolide antibiotics alone, treatment with beta-lactam antibiotics alone, treatment with both macrolide and beta-lactam antibiotics, treatment with antibiotics active against anaerobic bacteria	***Incidence of birth within 7 days of intervention:*** Any antibiotic vs no antibiotic [Fixed effect] RR 0.98 (95% CI: 0.87–1.10) (7 studies, *n* = 6957) Betalactam antibiotic alone vs no antibiotic [Fixed effect] RR 0.99 (95% CI: 0.80–1.22) (3 studies, *n* = 2248) Macrolide antibiotics alone vs no antibiotic [Fixed effect] RR 1.04 (95% CI: 0.82–1.31) (1 study, *n* = 2119) Macrolide and betalactam antibiotic vs no antibiotic [Fixed effect] 1.03 (95% CI: 0.84–1.26) (3 studies, *n* = 2401) Antibiotic active against anaerobic bacteria vs no antibiotic RR 0.62 (95% CI: 0.42–0.90) (1 study, *n* = 190) ***Incidence of neonatal intensive or special care nursery admission:*** Any antibiotic vs no antibiotics [Fixed effect] RR 1.03 (95% CI: 0.94–1.13) (4 studies, *n* = 6795) Betalactam antibiotic alone vs no antibiotic [Fixed effect] RR 1.07 (95% CI: 0.90–1.28) (1 study, *n* = 2053) Macrolide antibiotics alone vs no antibiotic [Fixed effect] RR 1.08 (95% CI: 0.91–1.29) (1 study, *n* = 2119) Macrolide and betalactam antibiotic vs no antibiotic [Fixed effect] RR 1.01 (95% CI: 0.87–1.18) (3 studies, *n* = 2515) Antibiotic active against anaerobic bacteria vs no antibiotics: [Fixed effect] RR 0.63 (95% CI: 0.43–0.93) (1 study, *n* = 109) ***Incidence of perinatal mortality:*** Any antibiotic vs no antibiotics [Fixed effect] RR 1.22 (95% CI: 0.88–1.70) (9 studies, *n* = 7208) Betalactam antibiotic alone vs no antibiotic [Fixed effect] RR 1.14 (95% CI: 0.63–2.04) (3 studies, *n* = 2227) Macrolide antibiotics alone vs no antibiotic [Fixed effect] RR 1.17 (95% CI: 0.64–2.11) (2 studies, *n* = 2222) Macrolide and betalactam antibiotic vs no antibiotic [Fixed effect] RR 1.39 (95% CI: 0.79–2.43) (4 studies, *n* = 2569) Antibiotic active against anaerobic bacteria vs no antibiotics [Fixed effect] RR 1.63 (95% CI: 0.36–7.39) (3 studies, *n* = 294)

TABLE 131 *Prophylactic antibiotics (intact membrane) (continued)*

Review details	Methods	Results and conclusions
		Incidence of adverse events:
		Maternal adverse drug reaction
		Any antibiotic vs no antibiotic
		[Fixed effect] RR 1.11 (95% CI: 0.99–1.24) (4 studies, *n* = 626)
		Maternal infection
		[Fixed effect] RR 0.74 (95% CI: 0.64–0.87) (9 studies, *n* = 7242)
		Fetal death
		[Fixed effect] RR 0.72 (95% CI: 0.42–1.25) (7 studies, *n* = 6986) (5 not estimable)
		Neonatal death
		[Fixed effect] RR 1.52 (95% CI: 0.99–2.34) (7 studies, *n* = 6877) (1 not estimable)
		Respiratory distress syndrome
		[Fixed effect] RR 0.99 (95% CI: 0.84–1.16) (8 studies, *n* = 7104)
		Mechanical ventilation
		[Fixed effect] RR 1.02 (95% CI: 0.84–1.24) (1 study, *n* = 6241)
		Chronic lung disease
		[Fixed effect] RR 1.17 (95% CI: 0.78–1.76) (1 study, *n* = 6241)
		Neonatal sepsis
		[Fixed effect] RR 0.86 (95% CI: 0.64–1.16) (9 studies, *n* = 7290)
		Necrotising enterocolitis
		[Fixed effect] RR 1.06 (95% CI: 0.64–1.73) (6 studies, *n* = 6880)
		Neonatal positive blood culture
		[Fixed effect] RR 1.01 (95% CI: 0.69–1.49) (3 studies, *n* = 6526)
		Intraventricular haemorrhage
		[Fixed effect] RR 0.76 (95% CI: 0.48–1.19) (4 studies, *n* = 6717)
		Major cerebral abnormality
		[Fixed effect] RR 1.00 (95% CI: 0.66–1.51) (1 study, *n* = 6241)

Review details	Methods	Results and conclusions
		Brief summary of findings: Maternal infection was significantly reduced in the group receiving antibiotics. No statistically significant differences were reported in any other maternal outcomes. No statistically significant benefit from antibiotic administration was found in any of the neonatal outcomes including perinatal mortality and admission to neonatal intensive care unit. When grouped by type of antibiotic, a reduction in the risk of admission to neonatal intensive care unit was reported for the group receiving antibiotics active against anaerobic bacteria compared to no antibiotics; based on the results of one small study ***Authors' conclusions:*** The review fails to demonstrate a clear overall benefit from prophylactic antibiotic treatment for preterm labour with intact membranes on neonatal outcomes and raises concerns about increased neonatal mortality for those who received antibiotics. Prophylactic antibiotic treatment for preterm labour is not recommended for routine practice. Further research may be warranted to determine if there is a subgroup of women who may benefit from this treatment when sensitive markers for subclinical infection become available ***Comments:*** This was a well-conducted review and the authors appear to have taken appropriate steps to reduce possible biases Seven of the included studies specifically stipulate singleton gestation in their inclusion criteria or multiple gestations in their exclusion criteria The review is dominated by the data from one trial (ORACLE II 2001), which is six times larger than the other 10 trials combined Nine of the studies used antibiotics as an adjunct to tocolysis Five trials were stopped early because of low recruitment rates or low baseline outcome rates

CI, confidence intervals; RCT, randomised controlled trials; RR, relative risks.

TABLE 132 *Betamimetics*

Review details	Methods	Results and conclusions
Anotayanonth et al. [Cochrane Database of Systematic Reviews 2004, Issue 3][532] ***Title:*** Betamimetics for inhibiting preterm labour ***Type of review:*** Cochrane ***Prevalence:*** *Symptomatic for preterm birth* – Not reported *Preterm birth* – 383 (out of a total 558), based on preterm birth < 37 weeks' gestation in women at high risk of preterm delivery	***Search:*** *Databases searched (Search dates)* Cochrane Pregnancy and Childbirth Group Register (May 2003) *Other sources* Reference lists of retrieved articles *Search restrictions* Search was not restricted by language ***Inclusion/exclusion criteria:*** *Study design(s)* RCTs with ≤20% loss to follow-up *Population* Women assessed as being in spontaneous preterm labour (defined by trial authors) and considered suitable for tocolytic therapy. Women with intact or ruptured membranes were included in the review. *Intervention* Betamimetics, administered by any route or any dose compared with other betamimetics, placebo or no treatment *Outcomes* Primary outcomes included: delivery within 48 hrs, perinatal death, neonatal morbidity, respiratory distress syndrome, chronic lung disease/ bronchopulmonary dysplasia, severe neuroradiological abnormality, abnormal long-term developmental status and neonatal length of hospital stay. A number of secondary perinatal, neonatal, infant and maternal outcomes were also sought including preterm birth < 34 and < 37 weeks' gestation, delivery within 7 days and admission to neonatal intensive care unit ***Study selection:*** Two reviewers independently selected papers for inclusion in the review; any disagreements were resolved by discussion or consultation with an additional reviewer(s) ***Data extraction:*** Two reviewers independently extracted data from the primary studies; any disagreements were resolved by discussion or consultation with an additional reviewer(s). Additional information was sought from the authors of the primary studies where necessary	***No. of studies included:*** 16 RCTs ($n = 2282$) ***No. of studies meeting quality criteria:*** *Adequate randomisation* – 9 *Adequate concealment of allocation* – 5 *Adequate blinding of clinician/patient/researcher* – 9/10/2 ***Incidence of birth < 34 weeks' gestation:*** Ritodrine loading dose vs incremental dose: [Fixed effect] RR 1.02 (95% CI: 0.57–1.80) (1 study, $n = 222$) ***Incidence of birth < 37 weeks' gestation:*** All betamimetics vs placebo: [Fixed effect] RR 1.06 (95% CI: 0.61–1.84) (10 studies, $n = 1212$) Ritodrine loading dose vs incremental dose: [Fixed effect] RR 0.78 (95% CI: 0.40–1.24) (1 study, $n = 203$) ***Incidence of birth within 24h of intervention:*** Not reported ***Incidence of birth within 48h of intervention:*** All betamimetics vs placebo: [Fixed effect] RR 0.63 (95% CI: 0.53–0.75) (10 studies, $n = 1209$) Terbutaline vs ritodrine: [Fixed effect] RR 2.05 (95% CI: 0.77–5.48) (1 study, $n = 83$) Ritodrine loading dose vs incremental dose: [Fixed effect] RR 1.08 (95% CI: 0.53–2.21) (1 study, $n = 203$) ***Incidence of birth within 7 days of intervention:*** All betamimetics vs placebo: [Fixed effect] RR 0.78 (95% CI: 0.68–0.90) (5 studies, $n = 911$) Terbutaline vs ritodrine: [Fixed effect] RR 0.80 (95% CI: 0.57–1.10) (1 study, $n = 100$) ***Incidence of neonatal intensive care admission:*** Not reported

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Review details	Methods	Results and conclusions
	Validity assessment: *Criteria used* Quality scores were assigned to each trial for method of randomisation, method of allocation concealment, use of placebo, completeness of follow-up, and blinding of outcome *Assessment* At least two reviewers independently assessed the methodological quality of the primary studies; disagreements would have been resolved by discussion. Reviewers were not blinded to authorship ***Synthesis:*** *Heterogeneity* Chi-squared test and *I*-squared statistic were used to assess heterogeneity. Sensitivity analysis was carried out to assess the effect of trial quality. A funnel plot was performed to assess publication bias *Methods* Weighted mean difference (WMD) was used for continuous data. Relative risks (RR) were calculated with 95% confidence intervals for binary data. A 10% level of statistical significance was used. Results were pooled using a fixed effect model. If significant heterogeneity was found, a random effects model was used	***Incidence of perinatal mortality:*** All betamimetics vs placebo: [Fixed effect] RR 0.84 (95% CI: 0.46–1.55) (11 studies, $n = 1332$) Fenoterol vs ritodrine: [Fixed effect] RR 0.11 (95% CI: 0.01–2.01) (1 study, $n = 98$) ***Incidence of adverse events:*** *Preterm birth < 28 weeks' gestation* Terbutaline vs ritodrine: [Fixed effect] RR 2.08 (95% CI: 0.55–7.87) (1 study, $n = 100$) *Neonatal death* All betamimetics vs placebo: [Fixed effect] RR 1.00 (95% CI: 0.48–2.09) (6 studies, $n = 1174$) Terbutaline vs ritodrine: [Fixed effect] RR 1.27 (95% CI: 0.42–3.91) (2 studies, $n = 184$) Fenoterol vs ritodrine: [Fixed effect] OR 0.11 (95% CI: 0.01–0.89) (1 study, $n = 98$) Ritodrine loading dose vs incremental dose: [Fixed effect] RR 0.11 (95% CI: 0.01–2.04) (1 study, $n = 222$) *Respiratory distress syndrome* All betamimetics vs placebo: [Fixed effect] RR 0.87 (95% CI: 0.71–1.08) (8 studies, $n = 1239$) Terbutaline vs ritodrine: [Fixed effect] RR 1.99 (95% CI: 0.93–4.27) (1 study, $n = 101$) Fenoterol vs ritodrine: [Fixed effect] RR 2.00 (95% CI: 0.38–10.42) (1 study, $n = 98$) Ritodrine loading dose vs incremental dose: [Fixed effect] RR 0.71 (95% CI: 0.35–1.41) (1 study, $n = 222$) *Periventricular haemorrhage (grades 3 and 4)* Ritodrine loading dose vs incremental dose: [Fixed effect] RR 0.14 (95% CI: 0.01–2.73) (1 study, $n = 222$) *Cerebral palsy* All betamimetics vs placebo: [Fixed effect] RR 0.19 (95% CI: 0.02–1.63) (1 study, $n = 246$) *Treatment cessation due to adverse drug reaction* All betamimetics vs placebo:

TABLE 132 *Betamimetics (continued)*

Review details	Methods	Results and conclusions
		[Fixed effect] RR 11.38 (95% CI: 5.21–24.86) (4 studies, *n* = 1051) Terbutaline vs ritodrine: [Fixed effect] RR 0.83 (95% CI: 0.24–2.92) (1 study, *n* = 100) Hexoprenaline vs ritodrine: [Fixed effect] RR 0.27 (95% CI: 0.08–0.93) (1 study, *n* = 466) *Any maternal side effects* Terbutaline vs ritodrine: [Fixed effect] RR 0.95 (95% CI: 0.84–1.07) (1 study, *n* = 83) Hexoprenaline vs ritodrine: [Fixed effect] RR 0.83 (95% CI: 0.76–0.91) (1 study, *n* = 466) Ritodrine loading dose vs incremental dose: [Fixed effect] RR 0.69 (95% CI: 0.43–1.11) (1 study, *n* = 203) *Palpitations* All betamimetics vs placebo: [Fixed effect] RR 10.11 (95% CI: 6.56–15.58) (4 studies, *n* = 1042) Terbutaline vs ritodrine: [Fixed effect] RR 1.18 (95% CI: 0.78–1.79) (1 study, *n* = 83) Hexoprenaline vs ritodrine: [Fixed effect] RR 0.75 (95% CI: 0.60–0.94) (1 study, *n* = 466) Ritodrine loading dose vs incremental dose: [Fixed effect] RR 0.50 (95% CI: 0.23–1.13) (1 study, *n* = 203) *Tachycardia* All betamimetics vs placebo: [Fixed effect] RR 4.08 (95% CI: 1.55–10.73) (2 studies, *n* = 229) Terbutaline vs ritodrine: [Fixed effect] RR 0.66 (95% CI: 0.43–1.00) (1 study, *n* = 100) Fenoterol vs ritodrine: [Fixed effect] RR 0.71 (95% CI: 0.35–1.45) (1 study, *n* = 96) Ritodrine loading dose vs incremental dose: [Fixed effect] RR 0.88 (95% CI: 0.33–2.35) (1 study, *n* = 203)

Review details	Methods	Results and conclusions
		Cardiac arrhythmias All betamimetics vs placebo: [Fixed effect] RR 3.54 (95% CI: 0.74–16.92) (1 study, *n* = 708) Terbutaline vs ritodrine: [Fixed effect] RR 0.35 (95% CI: 0.04–3.22) (1 study, *n* = 100) *Pulmonary oedema* All betamimetics vs placebo: [Fixed effect] RR 3.03 (95% CI: 0.12–74.23) (3 studies, *n* = 852) *Myocardial ischaemia* All betamimetics vs placebo: [Fixed effect] RR 12.53 (95% CI: 0.72–216.91) (1 studies, *n* = 106) *Chest pain* All betamimetics vs placebo: [Fixed effect] RR 11.29 (95% CI: 3.81–33.46) (2 studies, *n* = 814) Terbutaline vs ritodrine: [Fixed effect] RR 1.11 (95% CI: 0.55–2.25) (2 studies, *n* = 183) *Shortness of breath/dyspnoea* All betamimetics vs placebo: [Fixed effect] RR 3.86 (95% CI: 2.21–6.77) (2 studies, *n* = 814) Terbutaline vs ritodrine: [Fixed effect] RR 0.83 (95% CI: 0.41–1.67) (2 studies, *n* = 183) *Tremor* All betamimetics vs placebo: [Fixed effect] RR 10.74 (95% CI: 6.20–18.59) (1 study, *n* = 708) *Hypotension* All betamimetics vs placebo: [Fixed effect] RR 1.77 (95% CI: 0.39–8.06) (2 studies, *n* = 136) Terbutaline vs ritodrine: [Fixed effect] RR 1.00 (95% CI: 0.67–1.49) (2 studies, *n* = 183) Hexoprenaline vs ritodrine: [Fixed effect] RR0.77 (95% CI: 0.61–0.96) (1 study, *n* = 466) *Hyperglycaemia* All betamimetics vs placebo: [Fixed effect] RR 2.90 (95% CI: 2.05–4.09) (1 study, *n* = 708)

TABLE 132 *Betamimetics (continued)*

Review details	Methods	Results and conclusions
		Terbutaline vs ritodrine: [Fixed effect] RR 1.78 (95% CI: 1.05–3.03) (1 study, *n* = 100) Fenoterol vs ritodrine: [Fixed effect] RR 1.33 (95% CI: 0.31–5.65) (1 study, *n* = 98) *Hypokalaemia* All betamimetics vs placebo: [Fixed effect] RR 6.07 (95% CI: 4.00–9.20) (1 study, *n* = 708) *Nausea/vomiting* All betamimetics vs placebo: [Fixed effect] RR 1.76 (95% CI: 1.29–2.42) (3 studies, *n* = 932) Terbutaline vs ritodrine: [Fixed effect] RR 1.50 (95% CI: 0.71–3.20) (1 study, *n* = 100) Hexoprenaline vs ritodrine: [Fixed effect] RR 0.63 (95% CI: 0.45–0.89) (1 study, *n* = 466) Ritodrine loading dose vs incremental dose: [Fixed effect] RR 1.23 (95% CI: 0.36–4.15) (1 study, *n* = 203) *Headache* Terbutaline vs ritodrine: [Fixed effect] RR 0.48 (95% CI: 0.23–0.99) (1 study, *n* = 83) Ritodrine loading dose vs incremental dose: [Fixed effect] RR 1.01 (95% CI: 0.06–15.93) (1 study, *n* = 203) *Anxiety* Terbutaline vs ritodrine: [Fixed effect] RR 1.08 (95% CI: 0.67–1.75) (1 study, *n* = 83) *Fetal hypoglycaemia* All betamimetics vs placebo: [Fixed effect] RR 1.89 (95% CI: 0.35–10.04) (3 studies, *n* = 857) *Fetal tachycardia* All betamimetics vs placebo: [Fixed effect] RR 2.40 (95% CI: 1.12–5.13) (1 studies, *n* = 30)

Review details	Methods	Results and conclusions
		Increase in fetal heart rate Hexoprenaline vs ritodrine: [Fixed effect] OR 0.65 (95% CI: 0.43–0.98) (1 study, *n* = 466 *Sepsis/infection* All betamimetics vs placebo: [Fixed effect] RR 2.72 (95% CI: 0.19–39.63) (2 studies, *n* = 809) Ritodrine loading dose vs incremental dose: [Fixed effect] RR 0.71 (95% CI: 0.23–2.18) (1 study, *n* = 222) *Necrotising enterocolitis* All betamimetics vs placebo: [Fixed effect] RR 0.42 (95% CI: 0.06–2.78) (2 studies, *n* = 149) Terbutaline vs ritodrine: [Fixed effect] RR 0.53 (95% CI: 0.05–5.67) (1 study, *n* = 101) ***Brief summary of findings:*** Betamimetics vs placebo/no treatment: Betamimetics decreased the number of women in preterm labour delivering within 48 h; there was no decrease in the incidence of deliveries within 7 days after sensitivity analysis for adequate allocation concealment. No statistically significant between-group differences for perinatal death, neonatal death, respiratory distress syndrome, cerebral palsy or necrotising enterocolitis was shown. Betamimetics were significantly associated with withdrawal from treatment due to side effects: chest pains, dyspnoea, tachycardia, palpitations, headaches, hypokalaemia, hyperglycaemia, nausea/vomiting, and fetal tachycardia ***Authors' conclusions:*** While betamimetics help delay delivery for women transferred to tertiary care or completed course of antenatal corticosteroids, the multiple adverse effects should be considered. There are insufficient data to recommend one betamimetic agent over another ***Comments:*** This was a well-conducted review and the authors appear to have taken appropriate steps to reduce possible biases Few of the primary studies included in the review were of high quality 14 of the included studies report using a maintenance regimen: of these 13 continue beyond 48 h; the duration of the remaining two trials was unclear. Maintenance therapy is treatment after the initial bolus beyond 48 h. It is therefore difficult to extract the influence of the acute tocolytic treatment from the effects of maintenance therapy for outcomes beyond this period Only one trial explicitly excluded multiple pregnancies Some studies included women with ruptured membranes

TABLE 132 *Betamimetics (continued)*

Review details	Methods	Results and conclusions
Dodd et al. [Cochrane Database of Systematic Reviews 2006, Issue 1][549] ***Title:*** Oral betamimetics for maintenance therapy after threatened preterm labour ***Type of review:*** Cochrane ***Prevalence:*** *Symptomatic for preterm birth* – Not reported *Preterm birth* – 88 (out of a total 190), based on preterm delivery less than 37 weeks' gestation	***Search:*** *Databases searched (Search dates)* The Cochrane Pregnancy and Childbirth Group Trials Register (June 2005) and MEDLINE (1966 to August 2003) were searched. *Other sources* None reported *Search restrictions* No language restrictions were applied ***Inclusion/exclusion criteria:*** *Study design(s)* Published RCTs *Population* Women who have had at least one episode of threatened preterm labour that settled without delivery *Intervention* Oral betamimetic therapy compared with an alternative tocolytic or no tocolytic treatment for maintenance therapy. Trials in which women are administered an oral betamimetic in combination with another tocolytic agent were excluded *Outcomes* Primary measures included: preterm birth < 34 weeks, low birthweight (< 2500 g), admission to neonatal intensive care unit, perinatal mortality, serious infant morbidity, maternal death or serious maternal morbidity. A number of additional infant and maternal outcomes were also sought including preterm birth < 28 weeks and < 37 weeks, preterm birth within 24 h, 48 h and 7 days of treatment, and side effects ***Study selection:*** Two reviewers selected articles for inclusion in the review; any disagreements were resolved by discussion ***Data extraction:*** Two reviewers extracted and double entered data from the primary studies; any disagreements were resolved by discussion. Reviewers were not blinded to authorship	***No. of studies included:*** 11 RCTs ($n = 1238$) ***No. of studies meeting quality criteria:*** *Adequate randomisation* – 6 *Adequate concealment of allocation* – 3 *Adequate blinding of clinician/patient/researcher* – 4/5/1 ***Incidence of birth < 34 weeks' gestation:*** Terbutaline vs indomethacin: [Fixed effect] RR 0.64 (95% CI: 0.24–1.76) (1 study, $n = 65$) Terbutaline vs ritodrine: [Fixed effect] RR 0.29 (95% CI: 0.01–6.86) (1 study, $n = 91$) ***Incidence of birth < 37 weeks' gestation:*** Ritodrine/terbutaline vs placebo/no treatment: [Fixed effect] RR 1.08 (0.88, 1.32) (4 studies, $n = 384$) Ritodrine vs placebo/no treatment: [Fixed effect] RR 0.98 (95% CI: 0.64–1.50) (2 studies, $n = 145$) Terbutaline vs placebo/no treatment: [Fixed effect] RR 1.12 (95% CI: 0.89–1.41) (2 studies, $n = 239$) Terbutaline vs ritodrine: [Fixed effect] RR 0.80 (95% CI: 0.44–1.46) (1 study, $n = 91$) Betamimetic vs magnesium: [Fixed effect] RR 1.02 (95% CI: 0.58–1.79) (2 studies, $n = 100$) Ritodrine vs magnesium: [Fixed effect] RR 1.00 (95% CI: 0.54–1.87) (1 study, $n = 50$) Terbutaline vs magnesium: [Fixed effect] RR 1.06 (95% CI: 0.32–3.50) (1 study, $n = 50$) ***Incidence of birth within 24 h of intervention:*** Terbutaline vs placebo/no treatment: [Fixed effect] RR 0.67 (95% CI: 0.12–3.62) (1 study, $n = 46$) ***Incidence of birth within 48 h of intervention:*** Terbutaline vs placebo/no treatment: [Fixed effect] RR 0.78 (95% CI: 0.30–2.01) (1 study, $n = 200$)

Review details	Methods	Results and conclusions
	Validity assessment: *Criteria used* Quality scores were assigned to each trial on the basis of allocation concealment (A = adequate, B = unclear, C = inadequate, D = not used). Completeness of follow-up and blinding (investigators, participants and outcome assessors) were also assessed *Assessment* The authors do not state how methodological quality was assessed or how many reviewers performed the quality assessment ***Synthesis:*** *Heterogeneity* The chi-squared and *I*-squared statistic was used to evaluate statistical heterogeneity. Sensitivity analyses were planned to evaluate the effect of trial quality *Methods* Categorical data were compared using RRs and 95% CIs using a fixed effect model. Planned subgroup analyses included: dosage administered, type of betamimetic, gestational age maintenance begun, type of therapy (control group); however, there were insufficient data to do this	***Incidence of birth within 7 days of intervention:*** Ritodrine/terbutaline vs placebo: [Fixed effect] RR 0.67 (95% CI: 0.40–1.13) (2 studies, *n* = 295) Ritodrine vs placebo/no treatment: [Fixed effect] RR 0.23 (95% CI: 0.03–1.94) (1 study, *n* = 95) Terbutaline vs placebo/no treatment: [Fixed effect] RR 0.75 (95% CI: 0.44–1.29) (1 study, *n* = 200) Terbutaline vs indomethacin: [Fixed effect] RR 0.26 (95% CI: 0.03–2.18) (1 study, *n* = 65) ***Incidence of neonatal intensive care admission:*** Terbutaline vs placebo/no treatment: [Fixed effect] RR 1.29 (95% CI: 0.64–2.60) (1 study, *n* = 140) Betamimetic vs magnesium: [Fixed effect] RR 0.80 (95% CI: 0.43–1.46) (1 study, *n* = 137) ***Incidence of perinatal mortality (death before discharge among live births):*** Ritodrine/terbutaline vs placebo: [Fixed effect] RR 2.41 (95% CI: 0.86–6.74) (6 studies, *n* = 681) Ritodrine vs placebo/no treatment: [Fixed effect] RR 1.85 (95% CI: 0.41–8.39) (3 studies, *n* = 214) Terbutaline vs placebo/no treatment: [Fixed effect] RR 2.96 (95% CI: 0.72–12.14) (3 studies, *n* = 467) Betamimetic vs magnesium: [Fixed effect] RR 0.20 (95% CI: 0.01–3.97) (1 study, *n* = 50) ***Incidence of adverse events:*** *Respiratory distress syndrome* Ritodrine/terbutaline vs placebo: [Fixed effect] RR1.10 (95% CI: 0.61–1.98) (5 studies, *n* = 577) Ritodrine vs placebo/no treatment: [Fixed effect] RR 1.46 (95% CI: 0.57–3.73) (2 studies, *n* = 110) Terbutaline vs placebo/no treatment: [Fixed effect] RR 0.93 (95% CI: 0.43–1.98) (3 studies, *n* = 467) Ritodrine vs magnesium: [Fixed effect] RR 2.00 (95% CI: 0.19–20.67) (1 study, *n* = 50)

TABLE 132 *Betamimetics (continued)*

Review details	Methods	Results and conclusions
		Necrotising enterocolitis Terbutaline vs placebo/no treatment: [Fixed effect] RR 0.98 (95% CI: 0.22–4.28) (2 studies, *n* = 416) *Intraventricular haemorrhage* Ritodrine/terbutaline vs placebo: [Fixed effect] RR 0.97 (95% CI: 0.27–3.58) (3 studies, *n* = 466) Ritodrine vs placebo/no treatment: [Fixed effect] RR 3.00 (95% CI: 0.13–70.30) (1 study, *n* = 50) Terbutaline vs placebo/no treatment: [Fixed effect] RR 0.72 (95% CI: 0.16–3.24) (2 studies, *n* = 416) Ritodrine vs magnesium: [Fixed effect] RR 1.00 (95% CI: 0.07–15.12) (1 study, *n* = 50) *Neonatal jaundice/Hyperbilirubinaemia requiring treatment* Ritodrine vs placebo/no treatment: [Fixed effect] RR 1.67 (95% CI: 0.71–3.89) (1 study, *n* = 50) Terbutaline vs ritodrine: [Fixed effect] RR 1.45 (95% CI: 0.84–2.51) (1 study, *n* = 91) Ritodrine vs magnesium: [Fixed effect] RR 0.91 (95% CI: 0.47–1.75) (1 study, *n* = 50) *Side effects to stop therapy* Ritodrine vs placebo/no treatment: [Fixed effect] RR 2.71 (95% CI: 0.11–64.79) (1 study, *n* = 95) Terbutaline vs indomethacin: [Fixed effect] RR 3.09 (95% CI: 0.13–73.19) (1 study, *n* = 65) Betamimetic vs magnesium: [Fixed effect] RR 0.90 (95% CI: 0.24–3.46) (2 studies, *n* = 100) Ritodrine vs magnesium: [Fixed effect] RR 0.50 (95% CI: 0.05–5.17) (1 study, *n* = 50) Terbutaline vs magnesium: [Fixed effect] RR 1.28 (95% CI: 0.23–7.00) (1 study, *n* = 50) *Tachycardia* Ritodrine/terbutaline vs placebo: [Fixed effect] RR 1.55 (95% CI: 1.02–2.37) (2 studies, *n* = 101)

Review details	Methods	Results and conclusions
		Ritodrine vs placebo/no treatment: [Fixed effect] RR 1.61 (95% CI: 0.84–3.09) (1 study, *n* = 55) Terbutaline vs placebo/no treatment: [Fixed effect] RR 1.50 (95% CI: 0.86–2.61) (1 study, *n* = 46) Terbutaline vs ritodrine: [Fixed effect] RR 0.57 (95% CI: 0.22–1.47) (1 study, *n* = 91) Betamimetic vs magnesium: [Fixed effect] RR 5.61 (95% CI: 2.41–13.04) (3 studies, *n* = 237) Ritodrine vs magnesium: [Fixed effect] RR 17.00 (95% CI: 1.03–279.53) (1 study, *n* = 50) Terbutaline vs magnesium: [Fixed effect] RR 4.54 (95% CI: 1.86–11.07) (2 studies, *n* = 187) *Tachypnoea* Terbutaline vs placebo/no treatment: [Fixed effect] RR 2.83 (95% CI: 0.59–13.56) (1 study, *n* = 140) Terbutaline vs Ritodrine: [Fixed effect] RR 2.57 (95% CI: 0.55–12.07) (1 study, *n* = 91) Terbutaline vs magnesium: [Fixed effect] RR 1.35 (95% CI: 0.40–4.59) (1 study, *n* = 137) *Hypotension* Terbutaline vs placebo/no treatment: [Fixed effect] RR 1.80 (95% CI: 1.08–3.01) (1 study, *n* = 46) *Nausea* Terbutaline vs placebo/no treatment: [Fixed effect] RR 0.95 (95% CI: 0.43–2.13) (2 studies, *n* = 186) Betamimetic vs magnesium: [Fixed effect] RR 1.07 (95% CI: 0.57–0.57–1.98) (3 studies, *n* = 237) Ritodrine vs magnesium: [Fixed effect] RR 0.50 (95% CI: 0.05–5.17) (1 study, *n* = 50) Terbutaline vs magnesium: [Fixed effect] RR 1.15 (95% CI: 0.60–2.19) (2 studies, *n* = 187) *Vomiting* Ritodrine/terbutaline vs placebo: [Fixed effect] RR 1.28 (95% CI: 0.44–3.70) (2 studies, *n* = 235)

TABLE 132 *Betamimetics (continued)*

Review details	Methods	Results and conclusions
		Ritodrine vs placebo/no treatment: [Fixed effect] RR 2.71 (95% CI: 0.11–64.79) (1 study, *n* = 95) Terbutaline vs placebo/no treatment: [Fixed effect] RR 1.13 (95% CI: 0.36–3.54) (1 study, *n* = 140) Terbutaline vs ritodrine: [Fixed effect] RR 0.57 (95% CI: 0.17–1.89) (1 study, *n* = 91) Terbutaline vs magnesium: [Fixed effect] RR 0.88 (95% CI: 0.39–1.98) (2 studies, *n* = 187) *Palpitations* Terbutaline vs placebo/no treatment: [Fixed effect] RR 5.67 (95% CI: 1.32–24.40) (1 study, *n* = 140) *Headache* Ritodrine vs placebo/no treatment: [Fixed effect] RR 2.71 (95% CI: 0.11–64.79) (1 study, *n* = 95) ***Brief summary of findings:*** No statistically significant differences were reported for admission to neonatal care unit when betamimetics were compared with placebo or magnesium, or preterm birth < 37 weeks when ritodrine or terbutaline were compared with placebo. No statistically significant between-group differences was reported for perinatal mortality and morbidity outcomes. A number of cardiovascular effects were reported compared to placebo ***Authors' conclusions:*** Available evidence does not support the use of oral betamimetics for maintenance therapy after threatened preterm labour ***Comments:*** This was a well-conducted review and the authors appear to have taken appropriate steps to reduce possible biases Few of the primary studies included in the review were of high quality Most trials included multiple gestations

Review details	Methods	Results and conclusions
Nanda et al. [Cochrane Database of systematic Reviews 2002, Issue 4] [561] ***Title:*** Terbutaline pump maintenance therapy after threatened preterm labor for preventing preterm birth ***Type of review:*** Cochrane ***Prevalence:*** *Symptomatic for preterm birth –* Not reported *Preterm birth –* 17 (out of a total 28), based on preterm delivery at less than 37 weeks' gestation in women at risk of preterm birth 12 (out of a total 28), based on preterm delivery at less than 34 weeks' gestation in women at risk of preterm birth	***Search:*** *Databases searched (Search dates)* The Cochrane Pregnancy and Childbirth Group Register (May 2002), and the Cochrane Controlled Trials Register (2002, Issue 2) were searched for relevant articles *Other sources* Reference list and experts in the field *Search restrictions* No restrictions stated. Published, unpublished and ongoing trials were included ***Inclusion/exclusion criteria:*** *Study design(s)* RCTs *Population* Women with intact membranes and either singleton or multiple gestations who had had at least one episode of threatened preterm labour that was successfully stopped with tocolytic therapy before delivery *Intervention* Terbutaline pump maintenance therapy vs alternative drug therapy, placebo or no therapy *Outcomes* A number of infant maternal and health-care outcomes were sought including: gestational age, preterm, very preterm and extremely preterm birth, perinatal mortality, admission to neonatal intensive care unit, side effects (maternal), cardiovascular and other serious complications (maternal) ***Study selection:*** Two reviewers independently selected studies from inclusion in the review; discrepancies were resolved by consensus ***Data extraction:*** Two reviewers independently extracted data from the primary studies. A third reviewer checked the abstracted data for accuracy; discrepancies were resolved by discussion ***Validity assessment:*** *Criteria used* A quality score was given to each trial for allocation concealment. Other aspects of study quality were individually discussed for each trial in the body of the text	***No. of studies included:*** 2 RCTs ($n = 94$) ***No. of studies meeting quality criteria:*** *Adequate randomisation* – 2 *Adequate concealment of allocation* – 2 *Adequate blinding of clinician/patient/researcher* – 2/2/2 ***Incidence of birth < 34 weeks' gestation:*** Terbutaline pump vs saline pump: [Fixed effect] RR 0.97 (95% CI: 0.51–1.84) (1 study, $n = 52$) ***Incidence of birth < 37 weeks' gestation:*** Terbutaline pump vs saline pump: [Fixed effect] RR 1.17 (95% CI: 0.79–1.73) (1 study, $n = 52$) ***Incidence of birth within 24 h of intervention:*** Not applicable ***Incidence of birth within 48 h of intervention:*** Not applicable ***Incidence of birth within 7 days of intervention:*** Not applicable ***Incidence of neonatal intensive care admission (> 24 h):*** Terbutaline pump vs saline pump: [Fixed effect] RR 0.94 (95% CI: 0.51–1.73) (1 study, $n = 51$) ***Incidence of perinatal mortality:*** Not reported ***Incidence of adverse events:*** *Early discontinuation* Terbutaline pump vs saline pump [Fixed effect] RR 1.15 (95% CI: 0.68–1.95) (2 studies, $n = 79$) Terbutaline pump vs oral terbutaline [Fixed effect] RR 3.00 (95% CI: 0.72–12.55) (1 study, $n = 30$) *Respiratory distress syndrome* Terbutaline pump vs saline pump [Fixed effect] RR 0.82 (95% CI: 0.23–2.93) (2 studies, $n = 79$) Terbutaline pump vs oral terbutaline [Fixed effect] RR 1.00 (95% CI: 0.16–6.20) (1 study, $n = 30$)

TABLE 132 *Betamimetics (continued)*

Review details	Methods	Results and conclusions
	Assessment Two reviewers independently assessed the primary studies for methodological quality; discrepancies were resolved by consensus. Reviewers were not blinded to authorship ***Synthesis:*** *Heterogeneity* Chi-squared test and *I*-squared statistic were used to assess heterogeneity *Methods* WMD differences with 95% confidence intervals were calculated for continuous data, and RRs were calculated with 95% confidence intervals for all dichotomous outcomes. Estimates were pooled in meta-analysis were appropriate using a fixed effects model	***Other outcomes:*** *Gestational age at delivery* Terbutaline pump vs saline pump [Fixed effect] WMD −0.14 (95% CI: −1.66 to 1.38) (2 studies, $n = 79$) Terbutaline pump vs oral terbutaline [Fixed effect] WMD 1.40 (95% CI: −1.13 to 3.93) (1 study, $n = 30$) *Birthweight* Terbutaline pump vs saline pump [Fixed effect] WMD 107.90 (95% CI: −216.25 to 432.04) (2 studies, $n = 79$) Terbutaline pump vs oral terbutaline [Fixed effect] WMD 484.00 (95% CI: −25.01 to 993.01) (1 study, $n = 30$) ***Brief summary of findings:*** Terbutaline pump maintenance did not offer any advantage over saline pump or oral terbutaline in preventing preterm birth or its complications. No data were reported for long-term infant outcomes, costs, or maternal assessment of therapy ***Authors' conclusions:*** Terbutaline pump maintenance has not been shown to decrease the risk of preterm birth by prolonging pregnancy; in addition there is a lack of information on the safety of the therapy. Further well-conducted RCTs are needed ***Comments:*** This was a well-conducted review that attempted to limit reviewer error or bias Small dataset, with most results limited to one trial One of the two trials included a mixed population of singleton/multiple pregnancies. It is not stated how many multiple pregnancies were included Two additional studies were identified; the authors of these primary studies did not respond to requests for further information and so these studies could not be included in the review

CI, confidence intervals; RCT, randomised controlled trials; RR, relative risks; WMD, weighted mean difference.

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TABLE 133 *Calcium channel blockers*

Review details	Methods	Results and conclusions
King et al. [Cochrane Database of Systematic Reviews 2003, Issue 1][565] ***Title:*** Calcium channel blockers for inhibiting preterm labour ***Type of review:*** Cochrane ***Prevalence:*** *Symptomatic for preterm birth* – Not reported *Preterm birth* – Not reported No placebo/no treatment trials	***Search:*** *Databases searched (Search dates)* Cochrane Pregnancy and Childbirth Group Trials Register (June 2002), Cochrane Controlled Trials Register (Issue 2, 2002), Medline (1965–June 2002), Embase (1988–June 2002), Current Contents (1997–June 2002) *Other sources* Experts contacted, cross-referencing of relevant material *Search restrictions* None ***Inclusion/exclusion criteria:*** *Study design(s)* RCTs *Population* Women in labour between 20 and 36 weeks' gestation considered suitable for tocolysis *Intervention* Calcium channel blockers administered by any route vs alternative tocolytic agent. The planned comparison of calcium channel blockers and no treatment or placebo could not be conducted as no trials were found that addressed this *Outcomes* Maternal outcomes: pregnancy prolongation, delivery before 34 and 37 weeks, delivery within 48 h/7 days of treatment, adverse drug reaction, cessation of treatment for adverse drug reaction, antepartum/postpartum haemorrhage, maternal death, length of hospital stay, satisfaction with treatment, admission to intensive care unit Fetal outcomes: death, death excluding congenital abnormality, oligohydramnios A range of neonatal outcomes were sought, including gestation at birth, neonatal and perinatal mortality ***Study selection:*** The authors state that 'the standard methods of the Cochrane Collaboration were used for the consideration of trials for inclusion' i.e. independent assessment by at least two people and resolution of differences by consensus/involvement of third person	***No. of studies included:*** 12 RCTs ($n = 1029$) 10 trials compared oral nifedipine with other tocolytic agents. One trial compared intravenous nicardipine with salbutamol and one compared oral nicardipine with magnesium sulphate. Results given for two comparisons: 01. Any calcium channel blocker vs any other tocolytic agent 02. Any dihydropyridine calcium channel blocker compared with any betamimetic agent ***No. of studies meeting quality criteria:*** *Adequate randomisation* – 10 *Adequate concealment of allocation* – 10 *Adequate blinding of clinician/patient/researcher* – 0/0/0 ***Incidence of birth < 34 weeks' gestation:*** 01. (Fixed effects) RR 0.83 (95% CI: 0.69–0.99) (6 studies, $n = 619$) 02. (Fixed effects) RR 0.79 (95% CI: 0.65–0.96) (3 studies, $n = 328$) ***Incidence of birth < 37 weeks' gestation:*** 01. (Fixed effects) RR 0.95 (95% CI:0.83, 1.09) (6 studies, $n = 558$) 02. (Fixed effects) RR 0.89 (95% CI: 0.76, 1.05) (4 studies, $n = 389$) ***Incidence of birth within 24 h of intervention:*** Not reported ***Incidence of birth within 48 h of intervention:*** 01. (Fixed effects) RR 0.80 (95% CI:0.61, 1.05) (9 studies, $n = 761$) 02. (Fixed effects) RR 0.72 (95% CI:0.53–0.97) (6 studies, $n = 470$) ***Incidence of birth within 7 days of intervention:*** 01. (Fixed effects) RR 0.76 (95% CI: 0.60–0.97) (4 studies, $n = 453$) 02. (Fixed effects) RR 0.76 (95% CI: 0.59–0.99) (2 studies, $n = 242$) ***Incidence of neonatal intensive care admission:*** 01. (Fixed effects) RR 0.78 (95% CI:0.64–0.95) (9 studies, $n = 771$) 02. (Fixed effects) RR 0.84 (95% CI:0.71–1.00) (7 studies, $n = 572$) ***Incidence of perinatal mortality:*** *Perinatal mortality:* 01. (Fixed effects) RR 1.65 (95% CI:0.74–3.64) (10 studies, $n = 810$) 02. (Fixed effects) RR 1.39 (95% CI: 0.60–3.24) (7 studies, $n = 529$)

TABLE 133 *Calcium channel blockers (continued)*

Review details	Methods	Results and conclusions
	Data extraction: Three authors independently extracted data with differences in interpretation resolved by discussion. Additional information was sought to enable assessment of methodology and conduct of intention-to-treat analyses ***Validity assessment:*** *Criteria used* Blinding of randomisation, blinding of intervention, complete follow-up, blinding of outcome assessment. Quality ratings assigned using Cochrane criteria *Assessment* Carried out independently by three authors with differences in interpretation resolved by discussion ***Synthesis:*** *Heterogeneity* Statistical heterogeneity between trials was assessed using the chi-squared test *Methods* Meta-analysis using the fixed effects model, or a random effects model where heterogeneity was found. One subgroup analysis was performed comparing the dihydropiridine class of calcium channel blockers with betamimetics in nine trials. An attempt was made to conduct an intention-to-treat analysis for all outcomes	*Excluding congenital abnormality:* 01. (Fixed effects) RR 1.42 (95% CI: 0.61–3.31) (10 studies, $n = 820$) 02. (Fixed effects) RR 1.20 (95% CI: 0.49–2.94) (7 studies, $n = 529$) *Fetal death:* 01. (Fixed effects) RR 3.00 (95% CI: 0.13–71.08) (10 studies, $n = 820$) 02. (Fixed effects) RR3.00 (95% CI:0.13–71.08) (studies, $n = 529$) *Neonatal death:* 01. (Fixed effects) RR 1.58 (95% CI: 0.74–3.39) (11 studies, $n = 883$) 02. (Fixed effects) RR 1.40 (95% CI:0.63–3.12) (8 studies, $n = 592$) *Excluding congenital abnormality:* 01. (Fixed effects) RR 1.42 (95% CI: 0.61–3.31) (10 studies, $n = 820$) 02. (Fixed effects) RR 1.20 (95% CI: 0.49–2.94) (7 studies, $n = 529$) ***Incidence of adverse events:*** *Maternal adverse drug reaction:* 01. (Fixed effects) RR 0.32 (95% CI:0.24–0.41) (8 studies, $n = 717$) 02. (Fixed effects) RR0.40 (95% CI: 0.30–0.55) (5 studies, $n = 426$) *Maternal adverse drug reaction requiring cessation of treatment:* 01. (Fixed effects) RR 0.14 (95% CI: 0.05–0.36) (10 studies, $n = 833$) 02. (Fixed effects) RR 0.09 (95% CI:0.02–0.38) (7 studies, $n = 542$) *Neonatal respiratory distress syndrome:* 01. (Fixed effects) RR 0.63 (95% CI: 0.46–0.88) (9 studies, $n = 763$) 02. (Fixed effects) RR 0.64 (95% CI: 0.45–0.91) (7 studies, $n = 552$) *Necrotising enterocolitis:* 01. (Fixed effects) RR 0.21 (95% CI: 0.05–0.96) (3 studies, $n = 323$) 02. (Fixed effects) RR 0.21 (95% CI: 0.04–1.25) (2 studies, $n = 234$) *Intraventricular haemorrhage:* 01. (Fixed effects) RR 0.59 (95% CI: 0.36–0.98) (3 studies, $n = 340$) 02. (Fixed effects) RR 0.62 (95% CI: 0.37–1.04) (2 studies, $n = 251$) *Neonatal jaundice:* 01. (Fixed effects) RR 0.73 (95% CI: 0.57–0.93) (2 studies, $n = 227$) 02. (Fixed effects) RR 0.73 (95% CI: 0.57–0.93) (2 studies, $n = 277$) *Neonatal sepsis:* 01. (Fixed effects) RR 0.73 (95% CI: 0.46–1.16) (4 studies, $n = 375$) 02. (Fixed effects) RR 0.73 (95% CI: 0.46–1.16) (4 studies, $n = 375$)

Review details	Methods	Results and conclusions
		Other: a range of other perinatal and maternal outcomes were reported ***Brief summary of findings:*** When compared with any other tocolytic agent calcium channel blockers reduced the number of women giving birth within 7 days of receiving treatment and before 34 weeks' gestation. Calcium channel blockers also reduced the need for cessation of treatment because of maternal adverse drug reaction, frequency of neonatal respiratory distress syndrome, necrotising enterocolitis, intraventricular haemorrhage and neonatal jaundice ***Authors' conclusions:*** When tocolysis is indicated for women in preterm labour, calcium channel blockers are preferable to other tocolytic agents compared, mainly betamimetics. They have fewer adverse effects for women and appear at least as good at postponing preterm birth. Further research should address the effects of different dosage regimens and formulations of calcium channel blockers on maternal and neonatal outcomes ***Comments:*** This was a well-conducted review with the methodology clearly reported and details given of the included studies. The authors note that a sensitivity analysis by trial quality could not be conducted because there were insufficient data. They also comment that neonatal outcomes often lacked clear definition Additional information is being sought on 12 trials for possible inclusion

TABLE 133 *Calcium channel blockers (continued)*

Study details and design	Description of methods	Results and conclusions
Al-Qattan et al. [Medical Principles and Practice 2001; 9: 164–173] [578] ***Country:*** Kuwait ***Setting:*** Hospital ***Prevalence:*** *NA – no placebo group* ***Study design:*** RCT ***Length of follow-up:*** To delivery and neonatal outcome ***No. of participants:*** *No. randomised* – 60 *No. analysed* – 53 ***Validity:*** *Adequate randomisation* – Random number table *Adequate allocation concealment* – No *Blinding of clinician* – No *Blinding of patient* – No *Blinding of researcher* – No ***Type of analysis:*** per protocol	***Groups compared:*** Nifedipine vs ritrodine ***Intervention details:*** Nifedipine 30 mg loading dose, second dose 20 mg after 2 h if contractions persisted, if suppressed maintenance dose 20 mg every 6 h vs Ritrodine 50 μg/min i.v. If contractions stopped 10 mg p.o. every 4–6 h started 1 h before i.v. treatment discontinued Maintenance therapy continued to 34 weeks' gestation ***Participants:*** Women in preterm labour between 24 and 34 weeks' gestation ***Participant inclusion/exclusion criteria:*** Inclusion criteria: Women in preterm labour between 24 and 34 weeks' gestation. Preterm labour was defined as regular uterine contractions at a frequency of 2–3/10 min with documented change in cervical dilatation or effacement. Exclusion criteria: cardiac disease, placental abruption, hyperthyroidism, severe pre-eclampsia, eclampsia, clinical signs of infection like fever and vaginal discharge or white cell count > 15,000/cm^3 and positive vaginal swab cultures. Medical conditions contraindicating tocolytic therapy: polyhydramnios, cervix dilated ≥4 cm, fetal pathology, breech presentation, PROM, intrauterine fetal death, fetal distress, congenital malformation ***Outcomes:*** Time to uterine quiescence, time to delivery, side effects, perinatal outcome, Apgar score, birthweight, respiratory distress syndrome, intraventricular haemorrhage, admission to special care baby unit	***Incidence of birth < 34 weeks' gestation:*** *No. in intervention group (total no.)* = 15 (30) *No. in control group (total no.)* = 18 (23) ***Incidence of birth < 37 weeks' gestation:*** *No. in intervention group (total no.)* = 20 (30) *No. in control group (total no.)* = 20 (23) ***Incidence of birth within 24 h of intervention:*** *No. in intervention group (total no.)* = 4 (30) *No. in control group (total no.)* = 8 (23) ***Incidence of birth within 48 h of intervention:*** *No. in intervention group (total no.)* = 12 (30) *No. in control group (total no.)* = 14 (23) Incidence of birth within 7 days of intervention: *No. in intervention group (total no.)* = 15 (30) *No. in control group (total no.)* = 18 (23) ***Incidence of neonatal intensive care admission (special care not intensive care):*** *No. in intervention group (total no.)* = 14 (30) *No. in control group (total no.)* = 17 (23) ***Incidence of perinatal mortality:*** *No. in intervention group (total no.)* = 0 (30) *No. in control group (total no.)* = 0 (23) ***Incidence of adverse events:*** *Neonatal* Respiratory distress syndrome *No. in intervention group (total no.)* = 4 (30) *No. in control group (total no.)* = 4 (23) Intraventricular haemorrhage *No. in intervention group (total no.)* = 0 (30) *No. in control group (total no.)* = 0 (23) Low birthweight < 1500 g *No. in intervention group (total no.)* = 8 (30) *No. in control group (total no.)* = 11 (23)

Study details and design	Description of methods	Results and conclusions
		Low birthweight < 2500g *No. in intervention group (total no.)* = 22 (30) *No. in control group (total no.)* = 20 (23) *Maternal* Treatment stopped due to adverse events (hypotension, tachycardia, palpitations, chest pain) *No. in intervention group (total no.)* = 0 (30) *No. in control group (total no.)* = 5 (28) Headache *No. in intervention group (total no.)* = 0 (30) *No. in control group (total no.)* = 1 (28) Hypotension *No. in intervention group (total no.)* = 1 (30) *No. in control group (total no.)* = 2 (28) Nausea *No. in intervention group (total no.)* = 2 (30) *No. in control group (total no.)* = 11 (28) Vomiting *No. in intervention group (total no.)* = 2 (30) *No. in control group (total no.)* = 5 (28) Palpitations *No. in intervention group (total no.)* = 3 (30) *No. in control group (total no.)* = 16 (28) Chest pain *No. in intervention group (total no.)* = 0 (30) *No. in control group (total no.)* = 9 (28) ***Brief summary of findings:*** Nifedipine was more effective than ritrodine in postponing delivery for more than 24 h and in reducing births < 37 weeks. It also caused fewer maternal adverse events ***Authors' conclusions:*** Nifedipine is an effective tocolytic with fewer side effects than ritrodine and it is easier to administer. A larger study is required to confirm these findings ***Comments:*** Small study with per protocol analysis, although it is clear why treatment was not adhered to. Allocation concealment not reported and blinding not used. A sample size calculation was conducted

TABLE 133 *Calcium channel blockers (continued)*

Study details and design	Description of methods	Results and conclusions
Fan et al. [Chinese J Practical Gynecol Obstet 2003, 19: 87–89][579] ***Country:*** China ***Setting:*** Hospital ***Prevalence:*** Not applicable (no placebo group) ***Study design:*** RCT ***Length of follow-up:*** To delivery ***No. of participants:*** *No. randomised* – 61 *No. analysed* – 61 ***Validity:*** *Adequate randomisation* – Not reported *Adequate allocation concealment* – Not reported *Blinding of clinician* – No *Blinding of patient* – No *Blinding of researcher* – No Type of analysis: ITT	***Groups compared:*** Nifedipine vs ritodrine ***Intervention details:*** Nifedipine 20 mg p.o. (sublingual), repeated after 30 min if required. If contractions ceased, 20 mg p.o. thereafter to 35 weeks' gestation Ritodrine 50 mg i.v. at 50 μg/min increased by 50 μg/min every 15 min until contractions ceased or a maximum of 350 μg/min was reached. The effective dose was maintained for 12 h after contractions ceased. Nifedipine 20 mg every 2 h p.o. started 30 min before i.v. ritodrine ceased, then 10 mg every 6 h until 35 weeks' gestation ***Participants:*** Women in preterm labour ***Participant inclusion/exclusion criteria:*** Women in preterm labour were included. Both single and multiple gestations (twins) were included ***Outcomes:*** Birth within 48 h of initiation of treatment, birth within 7 days of initiation of treatment, birth after 35 weeks' gestation, birthweight, respiratory distress, side effects, change of treatment required	***Incidence of birth < 34 weeks' gestation:*** *Not reported* ***Incidence of birth < 37 weeks' gestation:*** *Not reported* ***Incidence of birth within 24 h of intervention:*** *Not reported* ***Incidence of birth within 48 h of intervention:*** *No. in intervention group (total no.)* = 9 (31) *No. in control group (total no.)* = 9 (30) ***Incidence of birth within 7 days of intervention:*** *No. in intervention group (total no.)* = 13 (31) *No. in control group (total no.)* = 14 (30) ***Incidence of neonatal intensive care admission:*** *Not reported* ***Incidence of perinatal mortality:*** *No. in intervention group (total no.)* = 0 (31) *No. in control group (total no.)* = 1 (30) (twin) ***Incidence of adverse events:*** Respiratory distress *No. in intervention group (total no.)* = 2 (31) *No. in control group (total no.)* = 1 (30) Birth < 35 weeks' gestation *No. in intervention group (total no.)* = 14 (31) *No. in control group (total no.)* = 16 (30) Maternal side effects (including headache, fever, weakness, palpitations and tachycardia) of mother *No. in intervention group (total no.)* = 8 (31) *No. in control group (total no.)* = 26 (30) Maternal side effects requiring treatment change *No. in intervention group (total no.)* = 0 (31) *No. in control group (total no.)* = 3 (30)

Study details and design	Description of methods	Results and conclusions
		Brief summary of findings: There were no significant differences in primary outcomes including birth within 48 h and 7 days of intervention. Fewer women experienced side effects in the nifedipine group ***Authors' conclusions:*** Nifedipine is safe and effective in the management of preterm labour ***Comments:*** Twin pregnancies were included in the study and were not identified as a subgroup for the analyses. There is no description of the methods used for randomisation so methodological quality is difficult to assess, and the sample size is small

TABLE 133 *Calcium channel blockers (continued)*

Study details and design	Description of methods	Results and conclusions
Floyd RC et al. 1995 [J Matern-Fetal Invest 1995; 5: 25–29] [580] ***Country***: USA ***Setting:*** Hospital ***Prevalence:*** *Not applicable – no placebo group* ***Study design:*** RCT ***Length of follow-up:*** To delivery ***No. of participants:*** *No. randomised* – 90 *No. analysed* – 90 ***Validity:*** *Adequate randomisation* – computer generated *Adequate allocation concealment* – Yes *Blinding of clinician* – Yes *Blinding of patient* – Yes *Blinding of researcher* – No ***Type of analysis:*** ITT	***Groups compared:*** Nifedipine vs magnesium sulphate ***Intervention details:*** Nifedipine 30 mg p.o. then 20 mg every 8 h until cessation of contractions. Maintenance therapy 20 mg every 8 h until 37 weeks' gestation or delivery Magnesium sulphate 4 g i.v. then 4–6 g i.v. for uterine quiescence. After 6 h uterine quiescence magnesium gluconate 2 g p.o every 4 h until 37 weeks' gestation or delivery Oral medication continued to delivery or 37 weeks in both groups ***Participants:*** Women in preterm labour between 20 and 34 weeks' gestation ***Participant inclusion/exclusion criteria:*** Inclusion criteria: singleton gestation, preterm labour between 20 and 34 weeks' gestation, intact membranes Exclusion criteria: medical or obstetric problems precluding continuation of pregnancy, previous tocolytic therapy in current pregnancy, chorioamnionitis ***Outcomes:*** Primary outcomes: delivery < 34 weeks' gestation, delivery < 37 weeks' gestation, delivery > 37 weeks' gestation, extension of gestation following treatment Secondary outcomes: maternal complications, birthweight, Apgar score, hypoglycaemia, respiratory complications, lethargy, depression at birth	***Incidence of birth < 34 weeks' gestation:*** *No. in intervention group (total no.)* = 10 (50) *No. in control group (total no.)* = 8 (40) ***Incidence of birth < 37 weeks' gestation:*** *No. in intervention group (total no.)* = 18 (50) *No. in control group (total no.)* = 18 (40) ***Incidence of birth within 24 h of intervention:*** *Not reported* ***Incidence of birth within 48 h of intervention:*** *Not reported* ***Incidence of birth within 7 days of intervention:*** *Not reported* ***Incidence of neonatal intensive care admission:*** *Not reported* ***Incidence of perinatal mortality:*** *Not reported* ***Incidence of adverse events:*** Respiratory distress syndrome *No. in intervention group (total no.)* = 5 (50) *No. in control group (total no.)* = 4 (40) Transient tachypnoea of newborn *No. in intervention group (total no.)* = 0 (50) *No. in control group (total no.)* = 2 (40) Low birthweight < 1500 g *No. in intervention group (total no.)* = 3 (50) *No. in control group (total no.)* = 2 (40) Low birthweight < 2500 g *No. in intervention group (total no.)* = 14 (50) *No. in control group (total no.)* = 19 (40)

Study details and design	Description of methods	Results and conclusions
		Apgar < 7 at 5 min *No. in intervention group (total no.)* = 7 (50) *No. in control group (total no.)* = 6 (40) Adverse events requiring cessation of treatment *No. in intervention group (total no.)* = 2 (50) *No. in control group (total no.)* = 3 (40) ***Brief summary of findings:*** No significant difference between groups in incidence of preterm birth < 37 weeks or other outcome ***Authors' conclusions:*** Both nifedipine and magnesium sulphate are effective tocolytic agents. No evidence of fetal neonatal or maternal compromise in either group ***Comments:*** Small well-conducted RCT. No sample-size calculation reported

TABLE 133 *Calcium channel blockers (continued)*

Study details and design	Description of methods	Results and conclusions
Haghighi [Int J Gynecol Obstet 1999; 66: 297–298][581] ***Country:*** Iran ***Setting:*** Hospital ***Prevalence:*** *Not applicable – no placebo group* ***Study design:*** RCT ***Length of follow-up:*** To delivery or neonatal intensive care unit discharge ***No. of participants:*** *No. randomised* – 74 *No. analysed* – 74 ***Validity:*** *Adequate randomisation* – Not reported *Adequate allocation concealment* – Not reported *Blinding of clinician* – No *Blinding of patient* – No *Blinding of researcher* – No ***Type of analysis:*** ITT	***Groups compared:*** Nifedipine vs magnesium sulphate ***Intervention details:*** Nifedipine 10 mg every 20 min p.o. (sublingual) up to maximum dose 40 mg in first hour of treatment if contractions persisted. If contractions stopped then 20 mg every 6 h p.o. for 24 h then 20 mg every 8 h p.o. for 24 h Magnesium sulphate loading dose 6 g i.v. over 15 min then 2 g/h increasing to a maximum of 4 g/h as required to stop contractions for up to 48 h. Infusion continued for 12 h after contractions stopped then terbutaline 5 mg every 6 h p.o. ***Participants:*** Primigravid women in preterm labour ***Participant inclusion/exclusion criteria:*** Inclusion criteria: Primigravid women with singleton pregnancies at 23–36 weeks' gestation in preterm labour defined as regular contractions < 10 min apart despite bed rest, 50 mg i.v. meperidine and 500 cm^3 bolus of Ringer's solution ***Outcomes:*** Birth within 48 h of intervention, maternal side effects, birthweight, Apgar score, stay in neonatal intensive care	***Incidence of birth < 34 weeks' gestation:*** *Not reported* ***Incidence of birth < 37 weeks' gestation:*** *Not reported* ***Incidence of birth within 24 h of intervention:*** *Not reported* ***Incidence of birth within 48 h of intervention:*** *No. in intervention group (total no.)* = 8 (34) *No. in control group (total no.)* = 12 (40) ***Incidence of birth within 7 days of intervention:*** *Not reported* ***Incidence of neonatal intensive care admission:*** *Not reported* ***Incidence of perinatal mortality:*** *Not reported* ***Incidence of adverse events:*** Maternal side effects (chest pain, nausea and vomiting, headache, transient hypotension) *No. in intervention group (total no.)* = 8 (34) *No. in control group (total no.)* = 3 (40) Maternal side effects requiring cessation of treatment *No. in intervention group (total no.)* = 0 (34) *No. in control group (total no.)* = 0 (40) Apgar score at 1 min: mean (SD) Intervention 7.15 (1.3) Control 7.2 (1.25) Apgar score at 5 min: mean (SD) Intervention 8.5 (1.4) Control 8.6 (1.0) Days in NICU: mean (SD) Intervention 24 (3) Control 26 (2)

Study details and design	Description of methods	Results and conclusions
		Brief summary of findings:
		There were no significant differences in birth within 48 h of intervention, maternal side effects or neonatal outcomes including length of stay in intensive care unit
		Authors' conclusions:
		Oral nifedipine has the same efficacy and side effects and a faster action than magnesium sulphate and could be a suitable and more convenient alternative to intravenous magnesium sulphate in arresting preterm labour
		Comments:
		Methods are reported extremely briefly so it is unclear how well conducted the study was. However, a sample size calculation indicated the study was appropriately powered

TABLE 133 *Calcium channel blockers (continued)*

Study details and design	Description of methods	Results and conclusions
Kashanian et al. [Int J Gynecol Obstet 2005; 91: 10–14][582] ***Country:*** Iran ***Setting:*** Hospital ***Prevalence:*** *Not applicable, no placebo group* ***Study design:*** RCT ***Length of follow-up:*** To delivery ***No. of participants:*** *No. randomised* – 80 *No. analysed* – 80 ***Validity:*** *Adequate randomisation* – Yes *Adequate allocation concealment* – No *Blinding of clinician* – No *Blinding of patient* – No *Blinding of researcher* – No ***Type of analysis:*** ITT	***Groups compared:*** Nifedipine vs atosiban ***Intervention details:*** Nifedipine 10 mg p.o. (sublingual) every 20 min for four doses. If contractions were inhibited, 20 mg every 6 h for 24 h then every 8 h for 24 h then 10 mg every 8 h for 24 h Atosiban 300 μg/min i.v. Therapy continued for a maximum of 12 h or 6 h after cessation of contractions Dexamethasone 5 mg i.m. every 12 h for 48 h in both groups No maintenance therapy in either group ***Participants:*** Symptomatic women ***Participant inclusion/exclusion criteria:*** Inclusion criteria: Women between 26 and 34 weeks' gestation with pregnancy documented by a definite last menstrual period and sonography in first trimester, in preterm labour. Labour defined as contractions at a frequency of 4/20 or 8/60 min with cervical dilatation ≥ 1 cm and cervical effacement of ≥ 50%. Exclusion criteria: PROM, vaginal bleeding, fetal death, fetal distress, intrauterine growth restriction, history of trauma, cervical dilatation > 3 cm, systemic disorders of the mother, known uterine anomaly, blood pressure > 90/50 mmHg ***Outcomes:*** Birth within 48 h of intervention, birth within 7 days of intervention, time to delivery, maternal side effects	***Incidence of birth < 34 weeks' gestation:*** *Not reported* ***Incidence of birth < 37 weeks' gestation:*** *Not reported* ***Incidence of birth within 24 h of intervention:*** *Not reported* ***Incidence of birth within 48 h of intervention:*** *No. in intervention group (total no.)* = 10 (40) *No. in control group (total no.)* = 7 (40) ***Incidence of birth within 7 days of intervention:*** *No. in intervention group (total no.)* = 14 (40) *No. in control group (total no.)* = 10 (40) *n = Not reported* ***Incidence of perinatal mortality:*** *Not reported* ***Incidence of adverse events:*** Total maternal side effects (women) *No. in intervention group (total no.)* = 16 (40) *No. in control group (total no.)* = 7 (40) Headache *No. in intervention group (total no.)* = 3 (40) *No. in control group (total no.)* = 3 (40) Vertigo *No. in intervention group (total no.)* = 9 (40) *No. in control group (total no.)* = 3 (40) Flank pain *No. in intervention group (total no.)* = 0 (40) *No. in control group (total no.)* = 1 (40) Hypotension *No. in intervention group (total no.)* = 11 (40) *No. in control group (total no.)* = 0 (40)

Study details and design	Description of methods	Results and conclusions
		Palpitation *No. in intervention group (total no.)* = 3 (40) *No. in control group (total no.)* = 0 (40) Tachycardia *No. in intervention group (total no.)* = 3 (40) *No. in control group (total no.)* = 0 (40) ***Brief summary of findings:*** There were no significant differences between the groups in birth within 48 h or within 7 days. Significantly more women in the nifedipine group experienced side effects ***Authors' conclusions:*** Atosiban is an effective and safe drug for acute treatment of preterm labour with minimal side effects and may be an option ***Comments:*** Twin pregnancies were included in the study and were not identified as a subgroup for the analyses

CI, confidence interval; ITT, intention to treat; i.v., intravenous; p.o. per os; PROM, pre-labour rupture of membranes; RCT, randomised controlled trials; RR, relative risks.

TABLE 134 *Cyclo-oxygenase inhibitors*

Review details	Methods	Results and conclusions
King et al. [Cochrane Database of Systematic Reviews, 2005, Issue 2][594] ***Title:*** Cyclo-oxygenase (COX) inhibitors for treating preterm labour ***Type of review:*** Cochrane ***Prevalence:*** *Symptomatic for preterm birth* 14 (out of a total of 18)	***Search:*** *Search dates* August 2004 *Databases searched* Cochrane Pregnancy and Childbirth Group trials register *Other sources:* Experts contacted for ongoing and unpublished trials *Search restrictions* None reported ***Inclusion/exclusion criteria:*** *Study design(s)* RCTs *Population* Women assessed as being in preterm labour between 20 and 36 weeks' gestation and suitable for tocolysis *Intervention* COX inhibitors administered by any route for the management of preterm labour *Outcomes* Death or major sensoneural disability at two years of age, preterm birth < 28 weeks' gestation, < 34 weeks, < 37 weeks, birth < 48 h after trial entry, birth < 7 days after trial entry, low birthweight < 2500 g, neonatal death, admission to neonatal intensive care unit. A range of other neonatal outcomes including respiratory distress syndrome, use and duration of mechanical ventilation, intraventricular haemorrhage, sepsis and necrotising enterocolitis were sought Maternal death, cardiac arrest, respiratory arrest, admission to ICU and a range of outcomes including oligohydramnios, haemorrhage and requirement for blood transfusion ***Study selection:*** Three reviewers independently selected trials for inclusion. Differences were resolved by discussion ***Data extraction:*** Three reviewers independently extracted data. Differences were resolved by discussion ***Validity assessment:*** *Criteria used:* Cochrane criteria of allocation concealment, randomisation, blinding and loss to follow-up *Assessment:* Three reviewers independently assessed study validity. Differences were resolved by discussion	***No. of studies included:*** 13 RCTs ($n = 713$) 01. COX inhibitor vs placebo (3 studies, $n = 106$) 02. COX inhibitor vs any other tocolytic (8 studies, $n = 660$) 03. Indomethacin compared with COX-2 inhibitor (2 studies, $n = 54$) ***No. of studies meeting quality criteria:*** *Adequate randomisation* – 12 *Adequate concealment of allocation* – 12 *Adequate blinding of clinician/patient/researcher* – 7/7/7 ***Incidence of birth < 34 weeks' gestation:*** Not reported ***Incidence of birth < 37 weeks' gestation:*** 01. RR 0.21 (95% CI: 0.07–0.62) (1 study, $n = 36$) 02. RR 0.53 (95% CI: 0.31–0.94) (3 studies, $n = 168$) compared with betamimetic: RR 0.53 (95% CI: 0.28–0.99) (2 studies, $n = 80$) compared with magnesium sulphate: RR 0.55 (95% CI: 0.17–1.73) (1 study, $n = 88$) 03. RR 1.00 (95% CI: 0.31–3.19) (2 studies, $n = 54$) ***Incidence of birth within 24 h of intervention:*** Not reported ***Incidence of birth within 48 h of intervention:*** 01. RR 0.19 (95% CI: 0.07–0.51) (2 studies, $n = 70$) 02. RR 0.59 (95% CI: 0.34–1.02) (4 studies, $n = 415$) compared with betamimetic: RR 0.27 (95% CI: 0.08–0.96) (2 studies, $n = 100$) compared with magnesium sulphate: RR 0.75 (95% CI: 0. 40–1.40) (2 studies, $n = 15$) ***Incidence of birth within 7 days of intervention:*** 01. RR 0.44 (5% CI: 0.26–0.74) (2 studies, $n = 70$) 02. RR 0.88 (95% CI: 0.52–1.46) (2 studies, $n = 146$) compared with betamimetic: RR 0.88 (95% CI: 0.52–1.46) (2 studies, $n = 146$) 03. RR 3.00 (95% CI: 0.13–67.06) (1 study, $n = 24$)

Review details	Methods	Results and conclusions
	Synthesis:	***Incidence of neonatal intensive care admission:***
	Heterogeneity:	01. RR 0.80 (95% CI: 0.56–1.15) (1 study, *n* = 39)
	Subgroup analyses were planned for:	02. RR 0.83 (95% CI: 0.48–1.43) (1 study, *n* = 194)
	women < 28 weeks' gestation vs > 28 weeks	compared with magnesium sulphate: RR 0.83 (95% CI: 0.48–1.43) (1 study, *n* = 194)
	women with multiple vs singleton gestation	03. RR 1.00 (95% CI: 0.34–2.91) (2 studies, *n* = 54)
	women with ruptured vs intact membranes	***Incidence of perinatal mortality:***
	type of tocolytic agent used as comparator (specifically betamimetics, magnesium sulphate, calcium channel blockers, oxytocin receptor antagonists)	01. RR 0.80 (95% CI: 0.25–2.58) (3 studies, *n* = 106)
	high-quality vs low-quality trials	02. RR 1.46 (95% CI: 0.57–3.74) (8 studies, *n* = 660)
	Methods: Chi-squared tests for heterogeneity were used and an *I*-squared statistic was calculated. Where significant statistical heterogeneity was present a random-effects model was employed for meta-analysis in place of a fixed effect model	compared with betamimetic: RR 0.99 (95% CI: 0.27–3.57) (4 studies, *n* = 237)
		compared with magnesium sulphate: RR 2.31 (95% CI: 0.54–9.90) (4 studies, *n* = 423)
		Incidence of adverse events:
		Respiratory distress syndrome
		01. RR 1.00 (95% CI: 0.40–2.49) (3 studies, *n* = 106)
		02. RR 1.08 (95% CI: 0.66–1.76) (6 studies, *n* = 503)
		compared with betamimetic: RR 1.50 (95% CI: 0.27–8.34) (2 studies, *n* = 80)
		compared with magnesium sulphate: RR 1.04 (95% CI: 0.62–1.74) (4 studies, *n* = 423)
		03. RR 1.00 (95% CI: 0.07–14.21) (1 study, *n* = 24)
		Neonatal mechanical ventilation
		02. RR 1.50 (95% CI: 0.47–4.78) (1 study, *n* = 60)
		03. RR 1.00 (95% CI: 0.07–14.21) (1 study, *n* = 24)
		Intraventricular haemorrhage (all grades)
		02. RR 1.18 (95% CI: 0.66–2.11) (7 studies, *n* = 548)
		compared with betamimetic: RR 5.34 (95% CI: 0.66–43.10) (3 studies *n* = 125)
		compared with magnesium sulphate: RR 0.92 (95% CI: 0.49–1.73) (4 studies, *n* = 223)
		Intraventricular haemorrhage Grade III or IV
		01. RR 3.15 (95% CI: 0.14–72.88) (1 study, *n* = 39)
		02. RR 0.61(95% CI: 0.08–4.40) (3 studies, *n* = 249)
		compared with betamimetic: RR not estimable (1 study *n* = 20)
		compared with magnesium sulphate: RR 0.61(95% CI: 0.08–4.40) (3 studies, *n* = 229)
		03. RR not estimable (1 study, *n* = 24)

TABLE 134 *Cyclo-oxygenase inhibitors (continued)*

Review details	Methods	Results and conclusions
		Necrotising enterocolitis 01. RR 0.97 (95% CI: 0.21–4.43) (2 studies, *n* = 70) 02. RR 3.82 (95% CI: 0.65–22.51) (4 studies, *n* = 298) compared with betamimetic: RR 3.00 (95% CI: 0.13–70.83) (2 studies, *n* = 80) compared with magnesium sulphate: RR 4.24 (95% CI: 0.49–36.45) (2 studies, *n* = 218) 03. RR not estimable (1 study, *n* = 24) *Chronic neonatal lung disease* 01. RR 1.24 (95% CI: 0.39–3.94) (2 studies, *n* = 70) *Persistent pulmonary hypertension of the newborn* 01. RR not estimable (3 studies, *n* = 106) 02. RR 2.85 (95% CI: 0.56–14.38) (6 studies, *n* = 490) compared with betamimetic: RR 5.63 (95% CI: 0.31–103.46) (3 studies, *n* = 177) compared with magnesium sulphate: RR 1.78 (95% CI: 0.23–13.44) (3 studies, *n* = 313) *Neonatal sepsis* 01. RR 0.31 (95% CI: 0.01–7.15) (2 studies, *n* = 70) 02. RR 1.00 (95% CI: 0.07–15.26) (2 studies, *n* = 80) 03. RR 0.33 (95% CI: 0.01–7.45) (1 study, *n* = 24) *Apgar score < 7 at 5 min* 01. RR 0.53 (95% CI: 0.05–5.34) (1 study, *n* = 39) 02. RR 0.53 (95% CI: 0.21–1.30) (2 studies, *n* = 254) compared with betamimetic: RR 3.00 (95% CI: 0.13–70.83) (1 study, *n* = 60) compared with magnesium sulphate: RR 0.43 (95% CI: 0.16–1.15) (1 study, *n* = 200) 03. RR 3.00 (95% CI: 0.13–67.06) (1 study, *n* = 24) *Oligohydramnios* 02. RR 2.53 (95% CI: 0.76–8.46) (3 studies, *n* = 295) compared with betamimetic: RR 2.08 (95% CI: 0.55–7.87) (1 study, *n* = 106) compared with magnesium sulphate: RR 5.30 (95% CI: 0.26–107.70) (2 studies, *n* = 189) 03. RR = 4.00 (95% CI: 0.52–30.76) (1 study, *n* = 24)

Review details	Methods	Results and conclusions
		Maternal adverse drug reaction 01. RR 1.58 (95% CI: 0.66–3.78) (3 studies, *n* = 101) 02. RR 0.22 (95% CI: 0.15–0.33) (7 studies, *n* = 629) compared with betamimetic: RR 0.10 (95% CI: 0.05–0.20) (4 studies, *n* = 226) compared with magnesium sulphate: RR 0.41 (95% CI: 0.26–0.66) (3 studies, *n* = 403) 03. RR not estimable (2 studies, *n* = 54) *Maternal adverse drug reaction requiring cessation of treatment* 02. RR 0.07 (95% CI: 0.02–0.29) (5 studies, *n* = 355) compared with betamimetic: RR 0.07 (95% CI: 0.01–0.37) (3 studies, *n* = 166) compared with magnesium sulphate: RR 0.06 (95% CI: 0.00–1.05) (2 studies, *n* = 189) *Postpartum haemorrhage* 01. RR = 3.94 (95% CI: 0.95–16.29) (1 study, *n* = 34) *Antepartum haemorrhage* 03. RR 0.33 (95% CI: 0.01–7.45) (1 study, *n* = 24) *Chorioamnionitis or endometritis* 01. RR 1.94 (95% CI: 0.44–8.60) (2 studies, *n* = 64) 02. RR not estimable (1 study, n = 88) 03. RR 2.00 (95% CI: 0.21–19.23) (1 study, *n* = 24) ***Brief summary of findings:*** COX inhibitors (indomethacin) produced a significant reduction in birth < 37 weeks compared with placebo. Compared to other tocolytics COX inhibitors reduced birth < 37 weeks' gestation, and maternal drug reactions requiring cessation of treatment. There were no differences between selective COX-2 inhibitors and non-selective COX-2 inhibitors ***Authors' conclusions:*** There is insufficient information on which to base decisions about the role of COX inhibition for women in preterm labour. Further well-designed trials are needed ***Comments:*** Well-conducted review. The authors are appropriately cautious about their conclusions because of the small numbers of patients involved

TABLE 134 *Cyclo-oxygenase inhibitors (continued)*

Study details and design	Description of methods	Results and conclusions
Golding [BJOG 1998; 105: 293–299] [608] ***Country:*** Jamaica ***Setting:*** Outpatient ***Prevalence:*** *Symptomatic for preterm birth* –NA *Preterm birth* – 463 (of 3026 in total) ***Study design:*** RCT ***Length of follow-up:*** To 6-week postnatal visit following delivery ***No. of participants:*** *No. randomised* – 6275 *No. analysed* – 6096 ***Validity:*** *Adequate randomisation* – *Yes* *Adequate allocation concealment* – Yes *Blinding of clinician* – Yes *Blinding of patient* – Yes *Blinding of researcher* – No ***Type of analysis:*** Not ITT	***Groups compared:*** Low-dose aspirin vs Placebo ***Intervention details:*** Aspirin 60 mg p.o. daily vs placebo ***Participants:*** Primiparae < 32 weeks' gestation ***Participant inclusion/exclusion criteria:*** Primiparae < 32 weeks' gestation at recruitment resident in two parishes in Jamaica were eligible ***Outcomes:*** Development of hypertension, proteinuric pre-eclampsia or pre-eclamptic fits; birthweight, preterm delivery < 37 weeks, perinatal mortality, bleeding in pregnancy, antepartum haemorrhage, haematemesis, postpartum haemorrhage, admission to neonatal special care, low birthweight < 2500 g, Apgar < 5 at 5 min	***Incidence of birth < 34 weeks' gestation:*** *Not reported* ***Incidence of birth < 37 weeks' gestation:*** *No. in intervention group (total no.)* = 447 (3023) *No. in control group (total no.)* = 463 (3026) ***Incidence of birth within 24 h of intervention:*** *Not applicable* ***Incidence of birth within 48 h of intervention:*** *Not applicable* ***Incidence of birth within 7 days of intervention:*** *Not applicable* ***Incidence of neonatal intensive care admission:*** *No. in intervention group (total no.)* = 285 (3023) *No. in control group (total no.)* = 263 (3026) ***Incidence of perinatal mortality:*** *No. in intervention group (total no.)* = 86 (3023) *No. in control group (total no.)* = 103 (3026) ***Incidence of adverse events:*** Apgar < 5 at 5 min *No. in intervention group (total no.)* = 38 (3023) *No. in control group (total no.)* = 25 (3026) Low birthweight (< 2500 g) *No. in intervention group (total no.)* = 303 (3023) *No. in control group (total no.)* = 325 (3026) Intercranial haemorrhage *No. in intervention group (total no.)* = 1 (3023) *No. in control group (total no.)* = 0 (3026) Other neonatal bleeding *No. in intervention group (total no.)* = 3 (3023) *No. in control group (total no.)* = 2 (3026) Stopped medication due to adverse events *No. in intervention group (total no.)* = 35 (3023) *No. in control group (total no.)* = 35 (3026)

Study details and design	Description of methods	Results and conclusions
		Vaginal bleeding in pregnancy *No. in intervention group (total no.)* = 75 (3023) *No. in control group (total no.)* = 67 (3026) Vomiting blood *No. in intervention group (total no.)* = 15 (3023) *No. in control group (total no.)* = 17 (3026) Other maternal bleeding *No. in intervention group (total no.)* = 58 (3023) *No. in control group (total no.)* = 38 (3026) Severe stomach pains *No. in intervention group (total no.)* = 34 (3023) *No. in control group (total no.)* = 36 (3026) Skin rash *No. in intervention group (total no.)* = 58 (3023) *No. in control group (total no.)* = 47 (3026) Wheezing or asthma *No. in intervention group (total no.)* = 21 (3023) *No. in control group (total no.)* = 21 (3026) Admitted antenatally *No. in intervention group (total no.)* = 540 (3023) *No. in control group (total no.)* = 504 (3026) Postpartum haemorrhage *No. in intervention group (total no.)* = 213 (3023) *No. in control group (total no.)* = 155 (3026) Alive but ill at 6 weeks postpartum (maternal) *No. in intervention group (total no.)* = 38 (3023) *No. in control group (total no.)* = 34 (3026) ***Brief summary of findings:*** There was no effect of aspirin on rates of preterm delivery or low birthweight infants. Aspirin did show an increase in maternal bleeding disorders including postpartum haemorrhage ***Authors' conclusions:*** Low-dose aspirin has no consistent beneficial effect in primiparae ***Comments:*** Large reasonably well-conducted study. Analysis not ITT. Multiple pregnancies were excluded from the analyses

TABLE 134 *Cyclo-oxygenase inhibitors (continued)*

Study details and design	Description of methods	Results and conclusions
Groom et al. [BJOG 2005; 112: 725–730][609] ***Country:*** UK ***Setting:*** Outpatient ***Prevalence:*** *Symptomatic for preterm birth* – 19 (of 47 in total) *Preterm birth* – 19 (of 47 in total) ***Study design:*** RCT ***Length of follow-up:*** To delivery (maternal); to discharge from hospital (neonatal) ***No. of participants:*** *No. randomised* – 92 women in 101 pregnancies *No. analysed* – 89 women in 98 pregnancies ***Validity:*** *Adequate randomisation* – computer-generated *Adequate allocation concealment* – yes *Blinding of clinician* – yes *Blinding of patient* – yes *Blinding of researcher* – no Type of analysis: Described as ITT but excluded three who did not receive treatment due to withdrawal from PPROM	***Groups compared:*** Rofecoxib vs placebo ***Intervention details:*** Rofecoxib 12.5 mg p.o. or placebo once daily ***Participants:*** Women at high risk of preterm delivery ***Participant inclusion/exclusion criteria:*** Inclusion criteria: at least one of: (1) Two or more previous second-trimester losses or preterm deliveries < 30 weeks; (2) One previous second-trimester loss or preterm delivery < 30 weeks and cervical length ≤ 15 mm from 14 to 24 weeks; (3) Cervical changes requiring cerclage in current pregnancy determined by ultrasound criteria or clinically (rescue cerclage) Women were eligible from 16 weeks' gestation if (1) applied, and when clinically indicated in (2) and (3) up to 26 weeks Exclusion criteria were multiple pregnancy, previous allergy to non-steroidal anti-inflammatory agents, maternal renal dysfunction ***Outcomes:*** Preterm delivery and neonatal outcome including neonatal intensive care unit admission, need for assisted ventilation, chronic lung disease. Maternal postpartum haemorrhage. Also fetal renal function and ductus arteriosus blood flow changes	***Incidence of birth < 34 weeks' gestation:*** *Not reported* ***Incidence of birth < 37 weeks' gestation:*** *No. in intervention group (total no.)* = 34 (51) *No. in control group (total no.)* = 19 (47) ***Incidence of birth within 24 h of intervention:*** *Not applicable* ***Incidence of birth within 48 h of intervention:*** *Not applicable* ***Incidence of birth within 7 days of intervention:*** Not applicable ***Incidence of neonatal intensive care admission:*** *No. in intervention group (total no.)* = 17 (51) *No. in control group (total no.)* = 10 (47) ***Incidence of perinatal mortality:*** *Not reported* ***Incidence of adverse events:*** Neonate requiring assisted ventilation *No. in intervention group (total no.)* = 6 (51) *No. in control group (total no.)* = 3 (47) Number of days requiring assisted ventilation: Mean (SD) *Intervention:* 5.2 (3.4) *Control:* 1.5 (16.3) Number of days given continuous positive airway pressure Mean (SD) *Intervention:* 10.2 (18.8) *Control:* 3.4 (5.1) Neonate with chronic lung disease *No. in intervention group (total no.)* = 3 (51) *No. in control group (total no.)* = 3 (47) Necrotising enterocolitis confirmed *No. in intervention group (total no.)* = 1 (51) *No. in control group (total no.)* = 0 (47)

Study details and design	Description of methods	Results and conclusions
		Postpartum haemorrhage *No. in intervention group (total no.)* = 1 (51) *No. in control group (total no.)* = 0 (47) Stop treatment < 32 weeks *No. in intervention group (total no.)* = 21 (51) *No. in control group (total no.)* = 16 (47) Oligohydramnios *No. in intervention group (total no.)* = 9 (51) *No. in control group (total no.)* = 1 (47) PPROM *No. in intervention group (total no.)* = 24 (51) *No. in control group (total no.)* = 9 (47) Neonate discharged alive and well *No. in intervention group (total no.)* = 38 (51) *No. in control group (total no.)* = 39 (47) ***Brief summary of findings:*** Rofecoxib increased the incidence of oligohydramnios, PPROM, and the occurrence of delivery < 37 weeks in high-risk women, without reducing the risk of earlier delivery (< 30 weeks) ***Authors' conclusions:*** Rofecoxib has a significant but reversible effect on fetal renal function and the ductus arteriosus. It does not reduce incidence of delivery < 30 weeks and is associated with an increased risk of delivery < 37 weeks in high-risk women ***Comments:*** Well conducted RCT, although true ITT analysis was not performed, sample size was small but an appropriate power calculation was performed

TABLE 134 *Cyclo-oxygenase inhibitors (continued)*

Study details and design	Description of methods	Results and conclusions
Humphrey et al. [Obstet Gynecol 2001; 98: 555–562][610] ***Country:*** USA ***Setting:*** Hospital ***Prevalence:*** *Symptomatic for preterm birth* – Not reported *Preterm birth* – Not reported ***Study design:*** RCT ***Length of follow-up:*** To discharge *No. of participants:* *No. randomised* – 95 *No. analysed* – 89 ***Validity:*** *Adequate randomisation* – computer generated *Adequate allocation concealment* – Yes *Blinding of clinician* – Yes *Blinding of patient* – Yes *Blinding of researcher* – Yes ***Type of analysis:*** per protocol	***Groups compared:*** Sulindac vs Placebo ***Intervention details:*** Sulindac 100 mg p.o b.i.d. (every 12 h) until 34 weeks' gestation vs placebo ***Participants:*** Women with gestational age > 24 < 34 weeks, singleton gestation, intact amniotic membranes, no cerclage, diagnosis of arrested preterm labour, cervical dilatation ≤ 4 cm ***Participant inclusion/exclusion criteria:*** Inclusion criteria: gestational age > 24 < 34 weeks, singleton gestation, intact amniotic membranes, no cerclage, diagnosis of arrested preterm labour, cervical dilatation ≤ 4 cm. Preterm labour defined as progressive cervical dilatation or effacement associated with regular uterine contractions at a rate of ≥ 4 in 20 min or 8 in 60 min. Arrested preterm labour defined as 12-h contraction-free period after discontinuation of i.v. tocolysis Exclusion criteria were: clinical evidence of intra-amniotic infection, pyelonephritis, medical complications contraindicating tocolysis, evidence of fetal growth retardation, sonographic evidence of congenital anomalies inconsistent with life ***Outcomes:*** Birth within 48 hours intervention, birth within 7 days of intervention, birth after 35 weeks' gestation, birth before 37 weeks' gestation or at least one admission for repeat tocolysis before 34 weeks, birth before 34 weeks' gestation or repeat tocolysis, readmission for tocolysis, birthweight, estimated gestational age at delivery, length of stay in neonatal intensive care, length of stay in hospital (neonatal), length of time neonate on ventilator	***Incidence of birth < 34 weeks' gestation:*** *Not reported* ***Incidence of birth < 37 weeks' gestation:*** *Not reported* ***Incidence of birth within 24 h of intervention:*** *Not reported* ***Incidence of birth within 48 h of intervention:*** *No. in intervention group (total no.)* = 2 (44) *No. in control group (total no.)* = 1 (45) ***Incidence of birth within 7 days of intervention:*** *No. in intervention group (total no.)* = 4 (44) *No. in control group (total no.)* = 4 (45) ***Incidence of neonatal intensive care admission:*** *Not reported* ***Incidence of perinatal mortality:*** *Not reported* ***Incidence of adverse events:*** Respiratory distress syndrome *No. in intervention group (total no.)* = 3 (44) *No. in control group (total no.)* = 2 (45) Neonatal sepsis *No. in intervention group (total no.)* = 2 (44) *No. in control group (total no.)* = 2 (45) Days in neonatal intensive care unit *Intervention*: 2.8 (9.2) *Control*: 2.4 (8.6) Days in hospital *Intervention:* 6.8 (10.3) *Control:* 4.3 (8.1) Days on ventilator *Intervention*: 0.3 (1.7) *Control*: 0.1 (0.6)

Study details and design	Description of methods	Results and conclusions
		Patent ductus arteriosus *No. in intervention group (total no.)* = 1 (44) *No. in control group (total no.)* = 0 (45) ***Brief summary of findings:*** There were no significant differences between the groups in births within 48 h or 7 days of treatment, and no differences in incidence of adverse events ***Authors' conclusions:*** Use of oral sulindac until 34 weeks' gestation after successful parenteral tocolysis failed to reduce the incidence of readmission for preterm labour ***Comments:*** Well-conducted RCT, although ITT analysis was not performed. A power analysis suggested that 43 patients per group would be required

b.i.d., twice a day; CI, confidence interval; COX, cyclo-oxygenase; ITT, intention to treat; i.v., intravenous; p.o. per os; PPROM, premature pre-labour rupture of membranes; RCT, randomised controlled trials; RR, relative risks

TABLE 135 *Ethanol*

Study details and design	Description of methods	Results and conclusions
Caritis et al. [Am J Obstet Gynecool 1982; 142(2): 183–190][612] ***Country:*** USA ***Setting:*** Magee-Women's Hospital, Pittsburgh ***Prevalence:*** *Symptomatic for preterm birth* – Not reported *Preterm birth* – Not estimable ***Study design:*** RCT ***Length of follow-up:*** Enrolment to neonatal period No. of participants: *No. randomised* – 92 *No. analysed* – 85 ***Validity:*** *Adequate randomisation* – (randomisation method not described) *Adequate allocation concealment* – Yes *Blinding of clinician* – No *Blinding of patient* – No *Blinding of researcher* – Not stated ***Type of analysis:*** Chi-squared analysis was used to assess differences between the treatment groups	***Groups compared:*** Ethanol vs Terbutaline ***Intervention details:*** A loading dose of 7.5 ml/kg/h of 10% ethanol in 5% dextrose was infused for 2 h. This was followed by a maintenance infusion of ethanol at a rate of 1.5 ml/kg/h for 10 h. If labour recurred, a second or third course of ethanol was given. For repeated course, the reloading dose was reduced by 10% for each hour less than 10 elapsing from the end of the previous maintenance infusion Terbutaline was diluted with physiological saline solution to a concentration of 20 μg/min. Physiological saline solution 400 ml was infused over 20 min before administering the terbutaline. The rate of terbutaline infusion was started at 5 μg/min and increased by 5 μg/min every 20 min to a maximal dosage of 30 μg/min or until uterine contractions ceased. Once contractions had stopped, the infusion was maintained for 1 h, after which the infusion rate was decreased to the minimal dose (5–10 μg/min) required to inhibit labour for an additional 8 h. If labour reoccurred during this maintenance period, the rate of infusion was increased until labour subsided, and the maintenance regimen was started again. During infusion, vital signs were recorded every 15 min. The infusion was stopped if the patient reported any tightness in the chest or shortness of breath, and the participant was evaluated by a physician All women with intact membranes in whom labour was inhibited received 5 mg terbutaline orally 30 min before the end of the intravenous maintenance infusion. This dosage was repeated four times daily for 5 days After successful inhibition with either treatment regimen, women were observed for 36 h, after which those with intact membranes were discharged ***Participants:*** Women experiencing symptoms of preterm labour ***Participant inclusion/exclusion criteria:*** Women with regular painful contractions (documented by tocodynamometer) occurring every 5–7 min for at least 30 seconds for a minimum of 1 h, gestational age between 20 and 36 weeks in women with intact membranes and 24 and 34 weeks in women with ruptured membranes, and no obstetric or medical contraindications to the inhibition of labour or the use of labour-inhibiting drugs were eligible	***Incidence of birth < 34 weeks' gestation:*** Not reported ***Incidence of birth < 37 weeks' gestation:*** Women with intact membranes *No. in intervention group (total no.)* = 23 (28) *No. in control group (total no.)* = 23 (28) ***Incidence of birth within 24 h of intervention:*** Women with intact membranes *No. in intervention group (total no.)* = 10 (28) *No. in control group (total no.)* = 4 (28) ***Incidence of birth within 48 h of intervention:*** Not reported ***Incidence of birth up to and including 7 days of intervention:*** Women with intact membranes *No. in intervention group (total no.)* = 21 (28) *No. in control group (total no.)* = 15 (28) ***Incidence of neonatal intensive care admission:*** Not reported ***Incidence of perinatal mortality:*** All women *No. in intervention group (total no.)* = 3 (40) *No. in control group (total no.)* = 8 (45) ***Incidence of adverse events:*** *Stillbirth:* Women with intact membranes: *No. in intervention group (total no.)* = 1 (28) *No. in control group (total no.)* = 2 (28) Women with ruptured membranes: *No. in intervention group (total no.)* = 0 (12) *No. in control group (total no.)* = 0 (17)

Study details and design	Description of methods	Results and conclusions
	Women who had received an alternative labour-inhibiting drug for their current episode of preterm labour and those with cervical dilatation greater than 5 cm were excluded ***Outcomes:*** Prolongation of pregnancy, birthweight, incidence of neonatal death, fetal death and hyaline membrane disease, Apgar scores and maternal side effects	*Neonatal death:* Women with intact membranes: *No. in intervention group (total no.)* = 2 (28) *No. in control group (total no.)* = 6 (28) Women with ruptured membranes: *No. in intervention group (total no.)* = 4 (12) *No. in control group (total no.)* = 3 (17) *Hyaline membrane disease:* Women with intact membranes: *No. in intervention group (total no.)* = 9 (28) *No. in control group (total no.)* = 9 (28) Women with ruptured membranes: *No. in intervention group (total no.)* = 7 (12) *No. in control group (total no.)* = 7 (17) *Loss of consciousness:* All women *No. in intervention group (total no.)* = 9 (40) *No. in control group (total no.)* = 0 (45) *Nausea/vomiting:* All women *No. in intervention group (total no.)* = 32 (40) *No. in control group (total no.)* = 13 (45) *Chest pain:* All women *No. in intervention group (total no.)* = 0 (40) *No. in control group (total no.)* = 7 (45) *Shortness of breath:* All women *No. in intervention group (total no.)* = 0 (40) *No. in control group (total no.)* = 5 (45) *Cardiac arrhythmia:* All women *No. in intervention group (total no.)* = 1 (40) *No. in control group (total no.)* = 0 (45)

TABLE 135 *Ethanol (continued)*

Study details and design	Description of methods	Results and conclusions
		Pulmonary arrhythmia: All women *No. in intervention group (total no.)* = 0 (40) *No. in control group (total no.)* = 0 (45) ***Other outcomes:*** Birthweight (g) Women with intact membranes: *Intervention group (SD)* = 1773 *Control group (SD)* = 1815 Women with ruptured membranes: *No. in intervention group (total no.)* = 1531 (436) *No. in control group (total no.)* = 1565 (487) ***Subgroup analysis:*** *Prolongation of pregnancy by cervical dilatation (days gained)* Cervix > 2 cm dilated or ≥ 75% effaced Women with intact membranes *Intervention group (SD)* = 2 (0.5) *Control group (SD)* = 9 (2.6) Cervix ≤ 2 cm dilated or < 75% effaced Women with intact membranes *Intervention group (SD)* = 25 (6.6) *Control group (SD)* = 39 (9.9) ***Brief summary of findings:*** Tocolytic success was demonstrated in 18% of both treatment groups in women with intact membranes. Terbutaline was shown to prolong pregnancy for a greater number of days than ethanol in women with intact membranes and cervix > 2 cm dilated or effacement ≥ 75%. No statistically significant difference was shown between treatment groups in women with intact membranes and cervix < 2 cm dilated or < 75% effacement. In women with ruptured membranes, the tocolytic success rate was similar in both treatment groups when all cases are considered. However, terbutaline was better at maintaining pregnancy for a minimum of 36 h in women with cervical dilatation < 4 cm. Fetal or neonatal outcomes were not significantly different between the two treatment groups when compared by gestational age

Study details and design	Description of methods	Results and conclusions
		Authors' conclusions: Terbutaline is more effective than ethanol in treating preterm labour. No serious complications occurred from the use of terbutaline, either in the mother or her infant ***Comments:*** Cervical dilatation and cervical effacement were similar in the two groups at study onset Five sets of twins were recorded in the intact membrane group (two ethanol, three terbutaline), and three sets of twins were recorded in the ruptured membrane group (one ethanol, two terbutaline) 8% loss to follow-up

TABLE 135 *Ethanol (continued)*

Study details and design	Description of methods	Results and conclusions
Lauersen et al. [Am J Obstet Gynecol 1977; 127: 837–845][613] ***Country:*** USA ***Setting:*** Three collaborating centres: The New York Hospital, University Hospitals of Cleveland, and Nassau County Medical Center ***Prevalence:*** *Symptomatic for preterm birth* – Not reported *Preterm birth* – No non-treatment group included ***Study design:*** RCT ***Length of follow-up:*** Enrolment to neonatal period ***No. of participants:*** *No. randomised* – 135 *No. analysed* – 135 ***Validity:*** *Adequate randomisation* – Not reported *Adequate allocation concealment* – Yes *Blinding of clinician* – Not reported *Blinding of patient* – Not reported *Blinding of researcher* – Not reported	***Groups compared:*** Ethanol vs Ritodrine ***Intervention details:*** A loading dose of ethanol 10% in 5% dextrose (i.v.) 7.5 ml/kg/h of body weight for 2 h, followed by a maintenance dose of 1.5 ml/kg/h for 10 or more hours. If premature labour recurred after the initial ethanol infusion up to two additional courses were permitted. If labour recurred less than 10 h after discontinuation of first infusion, the repeat loading was reduced and followed by the maintenance dose described A total of 250 mg of ritodrine hydrochloride 10 mg/ml added to 450 ml of 5% dextrose in water for a final concentration of 526 μg/ml (administered intravenously). Infusion rate started at 50 μg/min and increased by 50 μg every 10 min until adequate uterine relaxation occurred (max 350 μg/min), then maintained for 12 h. 30 min before termination of the intravenous infusion, oral ritodrine was initiated at a dose schedule of up to 10 mg every 2 h and maintained for 24 h. Women were discharged from hospital receiving oral doses of ritodrine ranging from 20 to 60 mg daily. Oral therapy was maintained for up to 4 weeks or until 38th week of gestation, whichever came first. If premature labour recurred with oral therapy, up to two repeat courses of intravenous ritodrine were given Vital signs were monitored and recorded every 15 min for the first 2 h of infusion in all participants. After 2 h, vital signs were monitored and recorded every 2–4 h during the participants' entire hospital stay ***Participants:*** Women experiencing symptoms of preterm labour ***Participant inclusion/exclusion criteria:*** Inclusion criteria included regular uterine contractions of 30–60 seconds at least once every 10 min and clinically judged as premature labour, gestation between 20 and 36 weeks, estimated fetal weight below 2500 g, uterine fundus above the umbilicus, intact membranes and not bulging, cervical effacement, and cervical dilatation not exceeding 4 cm Exclusion criteria included premature separation of the placenta, pre-eclampsia, chronic renal disease, diabetes mellitus and other severe maternal diseases, presence of a dead or malformed fetus, placenta praevia, if bleeding required intervention, and any maternal or fetal complication which required immediate delivery	***Incidence of birth < 34 weeks' gestation:*** All women *No. in intervention group (total no.)* = 19 (67) *No. in control group (total no.)* = 10 (68) Singleton gestations *No. in intervention group (total no.)* = 17 (58) *No. in control group (total no.)* = 9 (62) ***Incidence of birth < 37 weeks' gestation:*** All women *No. in intervention group (total no.)* = 41 (67) *No. in control group (total no.)* = 33 (68) Singleton gestations *No. in intervention group (total no.)* = 37 (58) *No. in control group (total no.)* = 29 (62) ***Incidence of birth within 24 h of intervention:*** Not reported ***Incidence of birth within 48 h of intervention:*** Not reported ***Incidence of birth within 7 days of intervention:*** All women *No. in intervention group (total no.)* = 23 (67) *No. in control group (total no.)* = 9 (68) Singleton gestations *No. in intervention group (total no.)* = 21 (58) *No. in control group (total no.)* = 8 (62) ***Incidence of neonatal intensive care admission:*** Not reported ***Incidence of perinatal mortality:*** *No. in intervention group (total no.)* = 6 (76) *No. in control group (total no.)* = 3 (73) ***Incidence of adverse events:*** Stillbirths *No. in intervention group (total no.)* = 0 (76) *No. in control group (total no.)* = 0 (73)

Study details and design	Description of methods	Results and conclusions
Type of analysis:	***Outcomes:***	Neonatal death
Differences between the two treatment groups were assessed using the Student *t*-test and chi-squared test, as appropriate	Labour postponed for more than 3 days, time gained, week of delivery, birthweight, infant survival, and cardiovascular effects of treatment	*No. in intervention group (total no.)* = 7 (76) *No. in control group (total no.)* = 3 (73) Respiratory distress syndrome *No. in intervention group (total no.)* = 15 (76) *No. in control group (total no.)* = 6 (73) Birthweight ≤2500 g *No. in intervention group (total no.)* = 44 (76) *No. in control group (total no.)* = 17 (73) Birthweight ≤1500 g *No. in intervention group (total no.)* = 11 (76) *No. in control group (total no.)* = 6 (73) Maternal heart rate acceleration (beats per/min) *Intervention group (SD)* = 15.7 (10.2) *Control group (SD)* = 37.9 (16.1) Fetal heart rate acceleration (beats per/min) *Intervention group (SD)* = 11.1 (9.3) *Control group (SD)* = 21.5 (16.1) Maternal systolic blood pressure increase (mmHg) *Intervention group (SD)* = 4.2 (8.8) *Control group (SD)* = 13.4 (11.9) Fetal systolic blood pressure decrease (mmHg) *Intervention group (SD)* = 13.5 (11.2) *Control group (SD)* = 19.3 (9.7) ***Other outcomes:*** Postponed delivery > 72 h *No. in intervention group (total no.)* = 49 (67) *No. in control group (total no.)* = 61 (68) ***Brief summary of findings:*** Ritodrine was more effective than ethanol in singleton pregnancies ($p < 0.05$), but no statistically significant differences between the two treatment groups in control of premature labour in twin gestations was shown ***Authors' conclusions:*** Ethanol and ritodrine were both found to be effective inhibitors of premature labour with ritodrine giving the most favourable results ***Comments:*** 11% had multiple pregnancies: nine sets of twins were reported in the ethanol group and six sets of twins were reported in the ritodrine group The authors' conclusions do not seem to follow from the data presented

TABLE 135 *Ethanol (continued)*

Study details and design	Description of methods	Results and conclusions
Reynolds [Aust NZ J Obstet Gynecol 1978; 18: 107–109][615] ***Country:*** Australia ***Setting:*** Crown Street Women's Hospital, Sydney, Australia ***Prevalence:*** *Symptomatic for preterm birth* – Not reported *Preterm birth* – Not estimable ***Study design:*** Quasi-RCT ***Length of follow-up:*** Enrolment to delivery No. of participants: *No. randomised* – 84 *No. analysed* – 84 ***Validity:*** *Adequate randomisation* – No (alternate allocation) *Adequate allocation concealment* – No *Blinding of clinician* – No *Blinding of patient* – Not reported *Blinding of researcher* – No reported ***Type of analysis:*** Not reported	***Groups compared:*** Ethanol vs Salbutamol ***Intervention details:*** Ethanol was administered intravenously [as described by Fuchs *et al*. (1967), *Am J Obstet Gynecol* **99**:672)] with a 2-h loading dose infusion, followed by an 8-h maintenance infusion. Solu-medrol 500 mg was given intravenously to all women in the ethanol group. Maternal blood pressure, pulse and fetal heart rate were recorded at 30-min intervals and degree of consciousness was closely observed. After cessation of the 10-h treatment women were observed for any uterine activity. If activity recurred within 12 h of initial treatment the maintenance dose was recommenced. If the membranes had been ruptured for more than 24 h, labour was allowed to proceed Salbutamol was diluted in a 5% dextrose solution to a concentration of 50 mg per 250 ml and intravenously infused. The initial dose was 2 μg/min which was increased by 100% increments until a rate of 40 μg/min, uterine activity ceased or a tachycardia of 140 beats/min developed. A cardiac monitor was used continuously during the infusion. Maternal pulse, blood pressure and fetal heart rate were recorded every 5 min until the maintenance infusion was achieved. Salbutamol infusion was usually stopped after 12 h, if labour had been successfully inhibited, but was recommenced if uterine activity returned. Intramuscular phenobarbitone 200 mg was given to all women in the salbutamol group ***Participants:*** Women experiencing symptoms of preterm labour ***Participant inclusion/exclusion criteria:*** Women between 20 and 37 weeks' gestation, with painful contractions occurring less than 10 min apart, usually verified by external tocograph were eligible. Women with major medical complications, cervix dilated more than 5 cm, amnionitis, or significant antepartum haemorrhage were excluded ***Outcomes:*** The primary outcome was inhibition of labour for more than 24 h. Secondary outcomes included: delayed delivery more than 7 days, perinatal mortality, Apgar score, and other maternal and fetal side effects	***Incidence of birth < 34 weeks' gestation:*** Not reported ***Incidence of birth < 37 weeks' gestation:*** Not reported ***Incidence of birth within 24 h of intervention:*** *No. in intervention group (total no.)* = 10 (42) *No. in control group (total no.)* = 13 (42) ***Incidence of birth within 48 h of intervention:*** Not reported ***Incidence of birth within 7 days of intervention:*** *No. in intervention group (total no.)* = 28 (42) *No. in control group (total no.)* = 24 (42) ***Incidence of neonatal intensive care admission:*** Not reported ***Incidence of perinatal mortality:*** *No. in intervention group (total no.)* = 4 (44) (Two sets of twins included) *No. in control group (total no.)* = 6 (45) (Set of triplets and set of twins included) ***Incidence of adverse events:*** Mean Apgar score at 1 min of babies born within 24 h of treatment *Intervention group (SD)* = 7.4 (not reported) *Control group (SD)* = 7.4 (not reported) Mean Apgar score at 5 min *Intervention group (SD)* = 9.2 (not reported) *Control group (SD)* = 8.7 (not reported) Mean maternal heart rate acceleration (beats per/min) *Intervention group (SD)* = 4 (not reported) *Control group (SD)* = 40 (not reported) Mean maternal systolic blood pressure (mmHg) *Intervention group (SD)* = –6 (not reported) *Control group (SD)* = –5 (not reported)

Study details and design	Description of methods	Results and conclusions
		A number of individual maternal side effects were reported for each treatment group; 19% of the sabutamol group complained of palpitations and 29% were noted to have occasional ventricular ectopic beats, 74% of the ethanol group complained of nausea and vomiting ***Brief summary of findings:*** Ethanol was successful at suppressing labour for more than 24 h in 76% of the women receiving this treatment, compared to 69% of women in the salbutamol group. Labour was successfully delayed for more than 7 days in 33% of the ethanol group and 43% of the salbultamol group ***Authors' conclusions:*** Ethanol and salbutamol were equally effective in the inhibition of premature labour, but the side effects were less marked with salbutamol ***Comments:*** Method of randomisation and allocation concealment was inadequate The mothers of a set of triplets and a set of twins were treated with salbutamol. Two mothers with sets of twins were treated with ethanol

TABLE 135 *Ethanol (continued)*

Study details and design	Description of methods	Results and conclusions
Sims et al. [BJOG 1978; 85: 761–766] [614] ***Country:*** UK ***Setting:*** Queen Charlotte's Hospital, London ***Prevalence:*** *Symptomatic for preterm birth* – Not reported *Preterm birth* – No non-treatment control group assigned. ***Study design:*** RCT ***Length of follow-up:*** Enrolment to neonatal period ***No. of participants:*** *No. randomised* – 100 *No. analysed* – 88 ***Validity:*** *Adequate randomisation* – Yes (randomised list) *Adequate allocation concealment* – Not reported *Blinding of clinician* – Not reported *Blinding of patient* – Not reported *Blinding of researcher* – Not reported ***Type of analysis:*** Differences between treatments were examined with the chi-squared test	***Groups compared:*** 01. Ethanol vs Salbutamol 01.1 Ethanol + betamethasone vs Salbutamol + betamethasone ***Intervention details:*** A solution of 10% v/v ethanol in 5% dextrose in water was prepared. 50 ml ethanol to 450 ml 5% dextrose in water was administered intravenously at a rate of 15 ml/kg of body weight over 2 h. A maintenance infusion of 1.5 ml/kg/h was administered for a further 10 h. If contractions reoccurred after discontinuation then the treatment was repeated A solution of 4 mg salbutamol in 500 ml 5% dextrose in water was prepared. The solution was administered intravenously at 5 μg of salbutamol per minute. The infusion rate was increased by 5 μg every 10 min until either contractions had ceased, a maximum of rate of 50 μg/min was attained, or until unacceptable side effects occurred. The infusion was then maintained at the lowest rate to stop contractions for a total of 12 h. Treatment was continued for 24 h in women with ruptured membranes, if the cervix showed progressive dilatation or contraction had not stopped. If contractions recurred then the treatment was repeated At commencement of therapy 23 women in each group also received either 4 mg betamethasone intramuscularly or saline placebo intramuscularly. These injections were repeated 8-hourly for six doses ***Participants:*** Women experiencing symptoms of preterm labour. ***Participant inclusion/exclusion criteria:*** Women admitted in labour between 27 and 35 weeks' gestation, regardless of whether the membranes were intact or not, were eligible. Women were excluded if postponement of delivery was contraindicated or if the cervix was more than 4 cm dilated. ***Outcomes:*** Delay of delivery for at least 24 h and 48 h, delivery after 37 weeks' gestation, mean number of days delivery postponed, number of infants surviving neonatal period	***Incidence of birth < 34 weeks' gestation:*** Not reported ***Incidence of birth < 37 weeks' gestation:*** All women *No. in intervention group (total no.)* = 32 (46) *No. in control group (total no.)* = 32 (42) ***Incidence of birth within 24 h of intervention:*** All women *No. in intervention group (total no.)* = 12 (46) *No. in control group (total no.)* = 7 (42) Women with intact membranes with cervical dilatation 2 cm or less *No. in intervention group (total no.)* = 4 (29) *No. in control group (total no.)* = 3 (21) ***Incidence of birth within 48 h of intervention:*** All women *No. in intervention group (total no.)* = 20 (46) *No. in control group (total no.)* = 22 (42) Women with intact membranes with cervical dilatation 2 cm or less *No. in intervention group (total no.)* = 7 (29) *No. in control group (total no.)* = 8 (21) ***Incidence of birth within 7 days of intervention:*** Not reported ***Incidence of neonatal intensive care admission:*** Not reported ***Incidence of perinatal mortality:*** Not reported. ***Incidence of adverse events:*** Neonatal mortality: *No. in intervention group (total no.)* = 10 (46) *No. in control group (total no.)* = 4 (42)

Study details and design	Description of methods	Results and conclusions
		Other outcomes:
		Days delivery postponed
		Intervention group (SD) = 20.4 (24)
		Control group (SD.) = 15.0 (24.5)
		Brief summary of findings:
		No significant difference was found between ethanol and salbutamol, as used in this study, on prevention of premature delivery (<37 weeks), incidence of birth within 24 or 48 h of intervention, although greater maternal side effects were found with salbutamol
		Authors' conclusions:
		Neither treatment was terribly effective. Salbutamol acted more rapidly than ethanol but produced more cardiovascular side effects
		Comments:
		Small data set with uncertain randomisation/concealment of allocation
		No significant differences were shown between the two treatment groups in terms of parity, gestational age, cervical dilatation, membrane status or tocolytic index at the start of the study
		13 women required more than one course of salbutamol, and 10 women received two or more courses of ethanol
		23 women in the salbutamol group and 23 women in the ethanol group also received betamethasone. Participants receiving betamethasone had no outcome differences, so far as delay of labour was concerned
		12% loss to follow-up

TABLE 135 *Ethanol (continued)*

Study details and design	Description of methods	Results and conclusions
Watring et al. [J Reprod Med 1976; 16(1): 35–38][616] ***Country:*** USA ***Setting:*** Tripler General Hospital, San Fransisco ***Prevalence:*** *Symptomatic for preterm birth* – Not reported *Preterm birth* – 9 (out of a total of 18 women) ***Study design:*** Single blind RCT ***Length of follow-up:*** Enrolment to postneonatal period ***No. of participants:*** *No. randomised* – 35 *No. analysed* – 35 ***Validity:*** *Adequate randomisation* – No (Numbered cards, selected by disinterested third party) *Adequate allocation concealment* – No *Blinding of clinician* – No *Blinding of patient* – Yes *Blinding of researcher* – No ***Type of analysis:*** Differences between the two treatment groups were assessed using the chi-squared test	***Groups compared:*** Intravenous alcohol vs Control ***Intervention details:*** The study group received an intravenous infusion of 5% ethanol in 5% dextrose in water. A loading dose of 15ml/lb/2 h and a maintenance dose of 10% of the total loading dose per hour until contractions had ceased for at least 6 h was administered. If contractions were still present after four hours or if they returned within 24 h, 1.5 of the loading dose was given in 1 h and the maintenance dose was continued for a total of 12 h. On cessation of contractions complete bed rest was advised for an additional 24 h. Ambulation was begun in the third 24-h period. If contractions recurred the participant was given a repeat course of ethanol as above. If contractions had ceased for 72 h following the last ethanol infusion the participant was discharged home. If contractions recurred for the third time, no attempt was made to stop labour Contractions were monitored by an external tocodynamometer. A broad liver and renal function profile was taken of all participants in the ethanol group before and after treatment. Control participants were given conventional treatment (sedation, morphine, vasodilan, bed rest, demerol, and seconal) ***Participants:*** Pregnant women experiencing symptoms of preterm labour ***Participant inclusion/exclusion criteria:*** Women with a viable pregnancy, between 24 and 36 weeks, experiencing labour symptoms (uterine contractions less than 10 min apart for 1 h or more), regular uttering contractions determined by palpation of tocodynamometer, greater than 50% effacement of the cervix with or without dilatation, and no complications such as bleeding, PROM or fever were eligible for inclusion. Women with a history of incompetent cervical os were excluded ***Outcomes:*** Delayed delivery for 72 h, time gained, gestation age at delivery, weight at delivery, and neonatal complications including neonatal death	***Incidence of birth < 34 weeks' gestation:*** *No. in intervention group (total no.)* = 8 (17) *No. in control group (total no.)* = 5 (18) ***Incidence of birth < 37 weeks' gestation:*** *No. in intervention group (total no.)* = 11 (17) *No. in control group (total no.)* = 9 (18) ***Incidence of birth within 24 h of intervention:*** *No. in intervention group (total no.)* = 6 (17) *No. in control group (total no.)* = 8 (18) ***Incidence of birth within 48 h of intervention:*** *No. in intervention group (total no.)* = 7 (17) *No. in control group (total no.)* = 8 (18) ***Incidence of birth within 7 days of intervention:*** *No. in intervention group (total no.)* = 10 (17) *No. in control group (total no.)* = 9 (18) ***Incidence of neonatal intensive care admission:*** *No. in intervention group (total no.)* = 3 (17) *No. in control group (total no.)* = 1 (18) ***Incidence of perinatal mortality:*** Not reported ***Incidence of adverse events:*** Neonatal death *No. in intervention group (total no.)* = 4 (17) *No. in control group (total no.)* = 3 (18) Respiratory distress syndrome *No. in intervention group (total no.)* = 4 (17) *No. in control group (total no.)* = 5 (18) ***Other outcomes:*** Mean weight (g) *Intervention group* = 2137.35 (981.39) *Control group* = 2568.78 (841.31)

Study details and design	Description of methods	Results and conclusions
		Brief summary of findings: No statistically significant difference was found between the two treatment groups on prevention of premature delivery, neonatal mortality or respiratory distress syndrome. The ethanol group was 14% smaller, in terms of weight, than the control group at birth ***Authors' conclusions:*** The success rate of preventing premature delivery was not statistically different between the two treatment groups ***Comments:*** Quasi-RCT although authors state that trial is an RCT. Conventional treatment varies among participants. Data set is very small

i.v., intravenous; RCT, randomised controlled trial.

TABLE 136 *Magnesium sulphate*

Review details	Methods	Results and conclusions
Crowther et al. [Cochrane Database of Systematic Reviews 2002, Issue 4][632] ***Title:*** Magnesium sulphate for preventing preterm birth in threatened preterm labour ***Type of review:*** Cochrane ***Prevalence:*** *Symptomatic for preterm birth –* Not reported. *Preterm birth –* No placebo control data for this outcome	***Search:*** *Databases searched (Search dates)* The Cochrane Pregnancy and Childbirth Groups trials register (May 2002), and The Cochrane Controlled Trials Register (2002, Issue 2) were searched for relevant articles *Other sources* None reported *Search restrictions* No search restrictions stated ***Inclusion/exclusion criteria:*** *Study design(s)* RCTs and quasi-RCTs were eligible *Population* Women thought to be experiencing preterm labour *Intervention* Magnesium sulphate given as a tocolytic, administered intravenously or orally, compared with placebo, no placebo, or alternative tocolytic agent. Trials where magnesium sulphate was used together with an alternative tocolytic were excluded *Outcomes* Primary outcomes included: birth < 48 h after treatment, extremely preterm birth (< 28 weeks), serious infant outcomes (death, chronic lung disease, cerebroventricular haemorrhage, periventricular leukomalacia, or major sensorineural disability), and serious maternal outcomes (death, cardiac arrest, respiratory arrest, or admission to intensive care unit) A number of infant and maternal secondary outcomes were also assessed ***Study selection:*** Three reviewers independently selected the primary studies for the review; any disagreements were resolved by discussion. There was no blinding of authorship ***Data extraction:*** Two reviewers independently extracted and double entered data from the primary studies; any disagreement was resolved by discussion ***Validity assessment:*** *Criteria used* Quality scores were assigned to each trial for concealment of allocation, use of placebo, completeness of follow-up and blinding of outcomes assessments. Details of scoring procedures reported	***No. of studies included:*** 21 RCTs and two quasi-RCTs (*n* = at least 2000 women) ***No. of studies meeting quality criteria:*** *Adequate randomisation* – 10 *Adequate concealment of allocation* – 9 *Adequate blinding of clinician/patient/researcher* – 0/2/0 ***Incidence of birth < 34 weeks' gestation:*** Magnesium sulphate vs all comparators: [Fixed effects] RR 0.82 (95% CI: 0.45–1.50) (1 study, *n* = 80) ***Incidence of birth < 37 weeks' gestation:*** Magnesium sulphate vs all comparators: [Fixed effects] RR 0.91 (95% CI: 0.75–1.11) (6 studies, *n* = 424) ***Incidence of birth within 24 h of intervention:*** Not reported ***Incidence of birth within 48 h of intervention:*** Magnesium sulphate vs all comparators: [Random effects] RR 0.85 (95% CI: 0.58–1.25) (11 studies, *n* = 881) ***Incidence of birth within 7 days of intervention:*** Not reported ***Incidence of neonatal intensive care admission:*** Magnesium sulphate vs all comparators: [Fixed effects] RR 0.49 (95% CI: 0.18–1.32) (1 study, *n* = 165) ***Incidence of perinatal mortality:*** Not reported ***Incidence of adverse events:*** *Total deaths (fetal, neonatal and infant)* Magnesium sulphate vs all comparators: [Fixed effects] RR 2.82 (95% CI: 1.20–6.62) (7 studies, *n* = 727) *Respiratory distress syndrome* Magnesium sulphate vs all comparators: [Fixed effects] RR 1.12 (95% CI: 0.99–1.27) (5 studies, *n* = 437) *Need for assisted ventilation* Magnesium sulphate vs all comparators: [Fixed effects] RR 1.17 (95% CI: 0.61–2.24) (1 study, *n* = 165)

Review details	Methods	Results and conclusions
	Assessment Two reviewers independently assessed the methodological quality of the primary studies; any disagreement was resolved by consensus. ***Synthesis:*** *Heterogeneity* Chi-squared test and the *I*-squared test were used to assess statistical heterogeneity, where appropriate *Methods* Data were pooled using a fixed effects model; if significant statistical heterogeneity was found pooled estimates were re-calculated using a random effects model. Categorical data were presented as relative risks (RR) and continuous data were presented as weighted mean difference (WMD)	*Cerebroventricular haemorrhage (all grades)* Magnesium sulphate vs all comparators: [Fixed effects] RR 1.07 (95% CI: 0.56–2.05) (5 studies, $n = 495$) *Severe cerebroventricular haemorrhage (grades 3/4) or periventricular leukomalacia* Magnesium sulphate vs all comparators: [Fixed effects] RR 1.39 (95% CI: 0.24–8.21) (3 studies, $n = 296$) *Necrotising enterocolitis* Magnesium sulphate vs all comparators: [Fixed effects] RR 1.19 (95% CI: 0.33–4.29) (3 studies, $n = 289$) *Cerebral palsy* Magnesium sulphate vs all comparators: [Fixed effects] RR 0.14 (95% CI: 0.01–2.60) (1 study, $n = 73$) *Proven neonatal infection* Magnesium sulphate vs all comparators: [Fixed effects] RR 0.36 (95% CI: 0.09–1.49) (1 study, $n = 34$) *Maternal respiratory arrest* Magnesium sulphate vs all comparators: [Fixed effects] RR 3.16 (95% CI: 0.13–76.30) (1 study, $n = 156$) *Nausea* Magnesium sulphate vs all comparators: [Fixed effects] RR 1.47 (95% CI: 0.75–2.90) (2 studies, $n = 128$) *Vomiting* Magnesium sulphate vs all comparators: [Fixed effects] RR 0.86 (95% CI: 0.23–3.19) (2 studies, $n = 128$) *Hypotension* Magnesium sulphate vs all comparators: [Fixed effects] RR 3.16 (95% CI: 0.13–76.30) (2 studies, $n = 171$) *Tachycardia* Magnesium sulphate vs all comparators: [Fixed effects] RR 0.23 (95% CI: 0.03–1.90) (2 studies, $n = 133$) *Maternal side effects leading to discontinuation of treatment* Magnesium sulphate vs all comparators: [Fixed effects] RR 0.63 (95% CI: 0.37–1.06) (10 studies, $n = 838$)

TABLE 136 *Magnesium sulphate (continued)*

Review details	Methods	Results and conclusions
		Subgroup analyses:
		Magnesium sulphate vs trials with good allocation concealment:
		Total deaths (fetal, neonatal and infant)
		[Fixed effects] RR 1.84 (95% CI: 0.67–5.06) (4 studies, *n* = 454)
		Maternal side effects leading to discontinuation of treatment
		[Fixed effects] RR 9.16 (95% CI: 2.48–33.90) (5 studies, *n* = 457)
		No other significant outcome differences were shown when only trials with good treatment allocation procedures were selected
		Magnesium sulphate subgrouped by alternative tocolytic therapy:
		Total deaths (fetal, neonatal and infant)
		Betamimetics
		[Fixed effects] RR 1.19 (95% CI: 0.08–17.51) (2 studies, *n* = 166)
		Calcium channel blockers
		[Fixed effects] RR 0.19 (95% CI: 0.01–3.85) (1 study, *n* = 80)
		Prostaglandin inhibitors
		[Fixed effects] RR 0.98 (95% CI: 0.06–15.35) (1 study, *n* = 117)
		No alternative tocolytic agent
		[Fixed effects] RR 1.74 (95% CI: 0.63–4.77) (3 studies, *n* = 292)
		Maternal side effects leading to discontinuation of treatment
		Betamimetics
		[Fixed effects] RR 0.07 (95% CI: 0.02–0.31) (3 studies, *n* = 264)
		No other significant outcome differences where shown when magnesium sulphate was compared to alternative tocolytic agents
		Magnesium sulphate subgrouped by dose:
		Total deaths (fetal, neonatal and infant)
		Dose protocol 2 g/h or less
		[Fixed effects] RR 1.19 (95% CI: 0.08–17.51) (1 study, *n* = 35)
		Dose protocol > 2 g/h
		[Fixed effects] RR 3.07 (95% CI: 1.24–7.61) (6 studies, *n* = 692)
		No other significant outcome differences were shown when magnesium sulphate was grouped by dose.

Review details	Methods	Results and conclusions
		Brief summary of findings:
		When all studies were combined, no statistically significant between group differences were shown for risk of birth within 48 h of treatment, preterm birth < 37 weeks and very preterm birth < 34 weeks' gestation. The risk of fetal/neonatal death was higher for infants exposed to magnesium sulphate, although no statistical difference was found when categorised by tocolytic agent, dose or quality. A non-significant reduction in risk of cerebral palsy was reported at follow-up at 18 months corrected age. No beneficial effect of magnesium sulphate was found for other neonatal or maternal outcomes
		Authors' conclusions:
		Magnesium sulphate, given to women in threatened preterm labour, does not reduce the risk of preterm birth or the risk of developing serious health problems, and is associated with an increased risk of infant death. Any further trials should be of high quality and large enough to assess serious morbidity and mortality, as well as compare different dose regimens and provide data on neurodevelopmental status
		Comments:
		This was a well-conducted review and the authors appear to have taken appropriate steps to reduce possible biases
		Few of the primary studies included in the review were of high quality
		Where stated loss to follow-up ranged from 2% to 21%

TABLE 136 *Magnesium sulphate (continued)*

Review details	Methods	Results and conclusions
Crowther and Moore [Cochrane Database of Systematic Reviews 1998, Issue 1][633] ***Title:*** Magnesium maintenance therapy for preventing preterm birth after threatened preterm labour ***Type of review:*** Cochrane ***Prevalence:*** *Symptomatic for preterm birth –* Not reported *Preterm birth –* 13 (out of a total of 25), based on preterm birth < 37 weeks' gestation	***Search:*** *Databases searched (dates)* Cochrane Pregnancy and Childbirth Group (August 2002) *Other sources* None reported *Search restrictions* No search restrictions reported ***Inclusion/exclusion criteria:*** *Study design(s)* RCTs *Population* Women who have had at least one episode of threatened preterm labour that settled without delivery *Intervention* Magnesium maintenance therapy administered by any route before delivery, compared with placebo, no treatment or an alternative maintenance tocolytic therapy Trials where magnesium sulphate was used in combination with an alternative tocolytic were excluded *Outcomes* Primary outcomes of the trial were preterm birth, perinatal mortality and any neurological disability at follow-up. Secondary outcomes included hospital re-admission for threatened preterm labour, neonatal morbidity, maternal side effects of therapy and cost ***Study selection:*** Two reviewers independently selected the studies; any discrepancies were resolved by discussion ***Data extraction:*** Two reviewers independently extracted data from the primary studies; any discrepancies were resolved by discussion. Unpublished data was sought from authors where possible ***Validity assessment:*** *Criteria used* Quality scores were assigned to each trial with regard to allocation concealment, completeness of follow-up, and blinding	***No. of studies included:*** 3 RCTs ($n = 303$) ***No. of studies meeting quality criteria:*** *Adequate randomisation* – 1 *Adequate concealment of allocation* – 1 *Adequate blinding of clinician/patient/researcher* – 1/1/0 ***Incidence of birth < 34 weeks' gestation:*** Not reported ***Incidence of birth < 37 weeks' gestation:*** Magnesium maintenance vs placebo/no treatment: RR 0.85 (95% CI: 0.47–1.51) (1 study, $n = 50$) Magnesium maintenance vs alternative tocolytic: RR 0.98 (95% CI: 0.56–1.72) (2 studies, $n = 100$) ***Incidence of birth within 24 h of intervention:*** Not applicable ***Incidence of birth within 48 h of intervention:*** Not applicable ***Incidence of birth within 7 days of intervention:*** Not applicable ***Incidence of neonatal intensive care admission:*** Magnesium maintenance vs placebo/no treatment RR 1.57 (95% CI: 0.76–3.24) (1 study, $n = 133$) Magnesium maintenance vs alternative tocolytic RR 0.98 (95% CI: 0.53–1.80) (1 study, $n = 137$) ***Incidence of perinatal mortality:*** Not reported ***Incidence of adverse events:*** *Death before discharge* Magnesium maintenance vs placebo/no treatment: RR 5.00 (95% CI: 0.25–99.16) (1 study, $n = 50$) Magnesium maintenance vs alternative tocolytic RR 5.00 (95% CI: 0.25–99.16) (1 study, $n = 50$)

Review details	Methods	Results and conclusions
	Assessment Two reviewers independently assessed the quality of the primary studies; any discrepancies were resolved by discussion ***Synthesis:*** *Heterogeneity* Where appropriate, statistical heterogeneity was assessed using chi-squared test and *I*-squared test *Methods* Studies were pooled using meta-analysis (fixed effects model). Dichotomous data were presented as relative risks (RR), and continuous data were presented as weighted mean difference (WMD). Sensitivity analyses were performed (quality of trials)	*Maternal re-admission for threatened preterm labour* Magnesium maintenance vs placebo/no treatment: RR 0.79 (95% CI: 0.45–1.38) (1 study, $n = 50$) Magnesium maintenance vs alternative tocolytic: RR 1.01 (95% CI: 0.63–1.65) (2 studies, $n = 100$) *Respiratory distress syndrome* Magnesium maintenance vs placebo/no treatment: RR 3.00 (95% CI: 0.13–70.30) (1 study, $n = 50$) *Periventricular haemorrhage* Magnesium maintenance vs placebo/no treatment: RR 3.00 (95% CI: 0.13–70.30) (1 study, $n = 50$) Magnesium maintenance vs alternative tocolytic: RR 1.00 (95% CI: 0.07–15.12) (1 study, $n = 50$) *Any maternal side effects* Magnesium maintenance vs placebo/no treatment: RR 1.88 (95% CI: 1.11–3.20) (1 study, $n = 133$) Magnesium maintenance vs alternative tocolytic: RR 0.69 (95% CI: 0.52–0.91) (3 studies, $n = 237$) *Nausea* Magnesium maintenance vs placebo/no treatment: RR 0.73 (95% CI: 0.30–1.81) (1 study, $n = 133$) Magnesium maintenance vs alternative tocolytic: RR 0.94 (95% CI: 0.50–1.75) (3 studies, $n = 237$) *Vomiting* Magnesium maintenance vs placebo/no treatment: RR 0.42 (95% CI: 0.08–2.08) (1 study, $n = 133$) Magnesium maintenance vs alternative tocolytic: RR 0.92 (95% CI: 0.39–2.17) (3 studies, $n = 237$) *Diarrhoea* Magnesium maintenance vs placebo/no treatment: RR 7.67 (95% CI: 2.41–24.41) (1 study, $n = 133$) Magnesium maintenance vs alternative tocolytic: RR 10.67 (95% CI: 3.35–33.99) (3 studies, $n = 237$)

TABLE 136 *Magnesium sulphate (continued)*

Review details	Methods	Results and conclusions
		Palpitations/tachycardia Magnesium maintenance vs placebo/no treatment: RR 1.05 (95% CI: 0.15–7.21) (1 study, *n* = 133) Magnesium maintenance vs alternative tocolytic: RR 0.22 (95% CI: 0.11–0.44) (3 studies, *n* = 237) *Discontinued therapy* Magnesium maintenance vs alternative tocolytic: RR 1.11 (95% CI: 0.29–4.23) (2 studies, *n* = 100) *Neonatal length of stay (days)* Magnesium maintenance vs placebo/no treatment: WMD 1.18 (95% CI: −0.46 to 2.82) (2 studies, *n* = 180) Magnesium maintenance vs alternative tocolytic: WMD −2.63 (95% CI: −5.70 to 0.43) (2 studies, *n* = 180) ***Brief summary of findings:*** No statistically significant differences were shown between treatment groups in risk of preterm birth < 37 weeks' gestation, stillbirth, death before discharge, or admission to neonatal intensive care unit. Women receiving magnesium sulphate were more likely to experience side effects than those receiving placebo/no treatment and more likely to report diarrhoea but less likely to report palpitations/tachycardia than those women on alternative maintenance tocolytic therapy or placebo/no treatment ***Authors' conclusions:*** There is not enough evidence to show any difference between magnesium maintenance therapy and placebo or alternative tocolytic agents after threatened preterm labour ***Comments:*** This was a well-conducted review and the authors appear to have taken appropriate steps to reduce possible biases The authors note that the trials were too small to exclude either important benefits or harms from magnesium maintenance therapy Loss to follow-up was less than 20% in all included trials Only one of the trials was rated of reasonable quality

CI, confidence interval; RCT, randomised controlled trial; RR, relative risk; WMD, weighted mean difference.

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TABLE 137 *Nitric oxide donors*

Review details	Methods	Results and conclusions
Duckitt and Thornton [Cochrane Database of Systematic Reviews 2002, Issue 3] [639] ***Title:*** Nitric oxide donors for the treatment of preterm labour ***Type of review:*** Cochrane ***Prevalence:*** *Symptomatic for preterm birth –* Not reported *Preterm birth –* Not reported	***Search:*** *Databases searched (Search dates)* Cochrane Pregnancy and Childbirth Group Register (March 2002), and the Cochrane Controlled Trials Register (2002, Issue 1) were searched for relevant articles *Other sources* None reported *Search restrictions* No search restrictions included Inclusion/exclusion criteria: *Study design(s)* RCTs and quasi-RCTs were eligible. Studies where less than 20% of data was unavailable were excluded *Population* Pregnant women assessed as being in preterm labour and considered suitable for tocolysis. Preterm labour was defined as uterine contractions, in the presence or absence of ruptured membranes, with or without cervical dilatation *Intervention* Nitric oxide donors compared with placebo, no treatment or any other tocolytic agent *Outcomes* A number of maternal and infant outcomes were assessed including: prolongation of pregnancy greater than 24 h, 48 h, 72 h, 7 days and 14 days, delivery before 37, 34, 32 and 28 weeks' gestation, adverse drug reactions, serious maternal outcomes, birthweight, mortality, delivery for presumed fetal distress, intraventricular haemorrhage, respiratory distress syndrome, chronic lung disease, long-term neurological development and use of health services ***Study selection:*** Two reviewers independently selected studies for inclusion; any disagreements were resolved by discussion ***Data extraction:*** Two reviewers independently extracted data form the primary studies; any disagreement was resolved by discussion	***No. of studies included:*** 5 RCTs ($n = 466$) ***No. of studies meeting quality criteria:*** *Adequate randomisation* – 2 *Adequate concealment of allocation* – 5 *Adequate blinding of clinician/patient/researcher* – 1/1/1 ***Incidence of birth < 34 weeks' gestation:*** Nitric oxide vs any other tocolytic agent (Fixed effects) RR 0.75 (95% CI: 0.52–1.10) (3 studies, $n = 365$); $I^2 = 66.8\%$, p=0.08 ***Incidence of birth < 37 weeks' gestation:*** Nitric oxide vs any other tocolytic agent (Fixed effects) RR 0.69 (95% CI: 0.53–0.88) (3 studies, $n = 391$) ***Incidence of birth within 24 h of intervention:*** Nitric oxide vs any other tocolytic agent (Fixed effects) RR 0.50 (95% CI: 0.05–4.86) (1 study, $n = 26$) ***Incidence of birth within 48 h of intervention:*** Nitric oxide vs any other tocolytic agent (Fixed effects) RR 0.73 (95% CI: 0.27–1.98) (1 study, $n = 132$) Nitric oxide vs placebo/no treatment (Fixed effects) RR 0.56 (95% CI: 0.27–1.19) (1 study, $n = 33$) ***Incidence of birth within 7 days of intervention:*** Nitric oxide vs any other tocolytic agent (Fixed effects) RR 1.24 (95% CI: 0.80–1.91) (3 studies, $n = 391$) ***Incidence of neonatal intensive care admission:*** Not reported ***Incidence of perinatal mortality:*** Not reported ***Incidence of adverse events:*** *Adverse drug reaction* Nitric oxide vs any other tocolytic agent

TABLE 137 *Nitric oxide donors (continued)*

Review details	Methods	Results and conclusions
	Validity assessment: *Criteria used* Methodological quality was categorised as low, moderate or high risk of bias depending on randomisation methods, allocation concealment, blinding and use of placebo *Assessment* Two reviewers independently assessed the methodological quality of the primary studies; any disagreement was resolved by discussion ***Synthesis:*** *Heterogeneity* The chi-squared test and *I*-squared test were used to assess heterogeneity *Methods* Results are presented using relative risks for categorical data and weighted mean difference for continuous variables Subgroup analysis was planned for treatment commenced before 24 weeks' gestation, between 24 and 34 weeks' gestation, after 34 weeks' gestation, treatment commenced with cervical dilatation < 3 cm, equal to or > 3 cm, treatment commenced before membrane rupture and after membrane rupture, single and multiple gestations, and nontransdermal and transdermal administration	Headache (Fixed effects) RR 4.14 (95% CI: 2.44–7.04) (4 studies, *n* = 379) Dizziness (Fixed effects) RR 2.34 (95% CI: 0.76–6.89) (2 studies, *n* = 221) Flushing (Fixed effects) RR 0.15 (95% CI: 0.04–0.54) (1 study, *n* = 30) Palpitations (Fixed effects) RR 0.09 (95% CI: 0.02–0.32) (3 studies, *n* = 353) Hypotension (Fixed effects) RR 7.94 (95% CI: 0.46–135.65) (1 study, *n* = 30) Shortness of breath (Fixed effects) RR 0.09 (95% CI: 0.02–0.46) (1 study, *n* = 217) Nausea (Fixed effects) RR 0.38 (95% CI: 0.09–1.55) (2 studies, *n* = 227) Tachycardia (Fixed effects) RR 0.03 (95% CI: 0.01–0.10) (2 studies, *n* = 323) Chest pain/tightness (Fixed effects) RR 0.12 (95% CI: 0.02–0.64) (2 studies, *n* = 323) Nitric oxide vs placebo/no treatment (Fixed effects) RR 2.07 (95% CI: 0.92–4.64) (1 study, *n* = 33) *Neonatal death unrelated to congenital abnormalities* Nitric oxide vs placebo/no treatment (Fixed effects) RR 0.94 (95% CI: 0.06–13.82) (1 study, *n* = 33 *Birthweight* Nitric oxide vs placebo/no treatment (Fixed effects) WMD 327.00 (95% CI: –272.13 to 926.13) (1 study, *n* = 33 ***Brief summary of findings:*** Nitric oxide donors did not delay delivery or improve neonatal outcomes when compared with placebo, no treatment or alternative tocolytic agents. A reduction in the number of deliveries less than 37 weeks was shown when compared with other tocolytic agents, but no statistical difference between the groups was shown for number of deliveries less than 34 weeks' gestation. Side effects, other than headaches, were reduced in women receiving nitric oxide donors rather than other tocolytic agents

Review details	Methods	Results and conclusions
		Authors' conclusions: There is currently insufficient evidence to support the routine use of nitric oxide donors in the treatment of threatened preterm labour ***Comments:*** This was a well-conducted review with clearly reported methodology and details given of the included studies Nitroglycerine was the nitric oxide donor used in all included trials Other tocolytic agents assessed: ritodrine, albuterol, and magnesium sulphate

TABLE 137 *Nitric oxide donor (continued)*

Study details and design	Description of methods	Results and conclusions
Bisits et al. [Am J Obstet Gynecol 2004; 191: 683–690][636] ***Country:*** Australia ***Setting:*** Four tertiary obstetric care centres; two in South East Asia and two in Australia ***Prevalence:*** *Symptomatic for preterm birth* – Not reported *Preterm birth* – Not estimable ***Study design:*** RCT ***Length of follow-up:*** Randomisation to 18 months of age ***No. of participants:*** *No. randomised* – 238 *No. analysed* – 238 ***Validity:*** *Adequate randomisation* – Yes (random number sequence) *Adequate allocation concealment* – Yes (sealed opaque envelopes) *Blinding of clinician* – Not reported *Blinding of patient* – No *Blinding of researcher* – Not reported	***Groups compared:*** Glyceryl trinitrate (GTN) patches vs beta-sympathomimetics β2 agonists included were salbutamol and ritodrine ***Intervention details:*** GTN: Participants received one 50-g Transiderm Nitro 50 patch; patches were placed on the skin of the anterior chest wall. Steroids were administered according to local protocols. If contractions did not settle within 1 h, a second patch was administered. If contractions settled, the patch (or patches) was left on for 21 h and then removed. If contractions did not settle after 2 h of GTN treatment, the patches were removed and beta-sympathomimetic treatment was commenced Beta-sympathomimetic administration not reported ***Participants:*** Pregnant women experiencing symptoms of preterm labour ***Participant inclusion/exclusion criteria:*** Women experiencing at least two contractions in 10 min with a singleton pregnancy between 24 and 35 weeks' gestation, with either a positive test for cervicovaginal fetal fibronectin or the presence of ruptured membranes were eligible for inclusion. Women with multiple pregnancies, chorioamnionitis, cervical dilatation of 5 cm or more, a history of hypotension or a negative fetal fibronectin test in the presence of intact membranes were excluded ***Outcomes:*** Primary outcomes included: number of days from randomisation until delivery, delivery at 24 h, 48 h, 7 days, and before 37 weeks' gestation. A number of maternal and infant secondary outcomes were sought, including infant mortality and admission to neonatal intensive care unit	***Incidence of birth < 34 weeks' gestation:*** Not reported ***Incidence of birth < 37 weeks' gestation:*** *No. in intervention group (total no.)* = 71 (121) *No. in control group (total no.)* = 68 (117) ***Incidence of birth within 24 h of intervention:*** *No. in intervention group (total no.)* = 35 (121) *No. in control group (total no.)* = 27 (117) ***Incidence of birth within 48 h of intervention:*** *No. in intervention group (total no.)* = 45 (121) *No. in control group (total no.)* = 34 (117) ***Incidence of birth within 7 days of intervention:*** *No. in intervention group (total no.)* = 57 (121) *No. in control group (total no.)* = 48 (117) ***Incidence of neonatal intensive care admission:*** Not reported ***Incidence of perinatal mortality:*** *No. in intervention group (total no.)* = 1 (121) *No. in control group (total no.)* = 3 (117) ***Incidence of adverse events:*** Chronic lung disease *No. in intervention group (total no.)* = 9 (121) *No. in control group (total no.)* = 9 (117) Necrotising enterocolitis *No. in intervention group (total no.)* = 10 (121) *No. in control group (total no.)* = 10 (117) Patent ductus arteriosus *No. in intervention group (total no.)* = 3 (121) *No. in control group (total no.)* = 11 (117)

Study details and design	Description of methods	Results and conclusions
Type of analysis: Data were analysed by using time to delivery or with the use of rescue treatment; Kaplan–Meier survival curves were plotted. All survival curves were compared using log rank test and risk ratios with Mantel–Haenzel assessment for effect from different centres. Multivariant techniques were used to adjust for baseline differences. Subgroup analysis for women with ruptured membranes, intact membranes and closed cervices were performed Intention to treat analysis was used ***Sample size:*** It was calculated that 120 women were needed in each arm of the trial to show a median difference of 10 days in time to delivery between GTN and beta-sympathomimetic groups (80% power and two-tailed alpha 0.5)		Intracerebral haemorrhage *No. in intervention group (total no.)* = 2 (121) *No. in control group (total no.)* = 8 (117) GTN was reported to be associated with more maternal headaches but lower incidence of cardiovascular side effects; no further details provided ***Subgroup analysis:*** The authors reported that no statistically significant differences between the treatment groups were found for time to delivery in women with ruptured membranes, intact membranes, and closed cervices ***Brief summary of findings:*** Survival curves and log rank tests showed no statistically significant differences between the two treatment groups for time to delivery or prolongation of pregnancy. A higher risk of earlier delivery was found within the GTN group, although this was not statistically significant. No statistically significant differences between the two treatment groups were found for incidence of chronic lung disease or necrotising enterocolitis, but a higher proportion of infants with patent ductus arteriosus and intracranial haemorrhage were found in the beta-sympathomimetic group ***Authors' conclusions:*** GTN is a less efficacious tocolytic than beta-sympathomimetics ***Comments:*** 40 women from the GTN group required rescue tocolysis after unsuccessful application of a second patch
GTN, glyceryl trinitrate; RCT, randomised controlled trials.		

TABLE 138 *Oxytocin receptor antagonists*

Review details	Methods	Results and conclusions
Papatsonis et al [Cochrane Database of Systematic Reviews 2005, Issue 3][586] ***Title:*** Oxytocin receptor antagonists for inhibiting preterm labour ***Type of review:*** Cochrane ***Prevalence:*** *Symptomatic for preterm birth –* Not reported *Preterm birth –* 128 (out of 255 in total), based on preterm birth less than 37 weeks	***Search:*** *Databases searched (Search dates)* Cochrane Pregnancy and Childbirth Group trials register (Sept. 2004), Central (Issue 3, 2004), Medline (1966 to June 2004), Embase (1988 to June 2004) *Other sources* Experts contacted *Search restrictions* None ***Inclusion/exclusion criteria:*** *Study design(s)* RCTs *Population* Women in labour between 26 and 36 weeks' gestation and considered suitable for tocolysis *Intervention* Oxytocin receptor antagonists administered as a tocolytic by any route vs placebo, no treatment or alternative tocolytic therapy *Outcomes* Predefined clinical outcome measures relating to the prolongation of pregnancy, infant morbidity and mortality and maternal side effects ***Study selection:*** Two authors independently considered trials for inclusion. Differences were resolved by consensus ***Data extraction:*** Two authors independently extracted data. Differences were resolved by consensus. Additional information was sought from trial authors and if there was consensus about theses data they were included in the analysis. If there was no consensus or if data were incomplete the original authors were asked for additional data or comments ***Validity assessment:*** *Criteria used* Quality ratings were applied to four criteria: blinding of randomisation, blinding of intervention, completeness of follow-up and blinding of outcome assessment	***No. of studies included:*** Six RCTs Two trials compared the oxytocin receptor antagonist atosiban with placebo ($n = 651$) and four trials compared atosiban with betamimetic agents ($n = 1044$) ***No. of studies meeting quality criteria:*** *Adequate randomisation* –6 *Adequate concealment of allocation* –6 *Adequate blinding of clinician/patient/researcher* – blinding of intervention in five trials; blinding of outcome assessment not known ***Incidence of birth < 34 weeks' gestation:*** Atosiban vs placebo: < 28 weeks' gestation (Fixed effects) RR 2.25 (95% CI: 0.80–6.35) (1 study, $n = 77$) ***Incidence of birth < 37 weeks' gestation:*** Atosiban vs placebo: (Fixed effects) RR 1.17 (95% CI: 0.99–1.37) (1 study, $n = 501$) Atosiban vs betamimetics (Fixed effects) RR 0.90 (95% CI: 0.71–1.13) (1 study, $n = 244$) ***Incidence of birth within 24 h of intervention:*** Not reported ***Incidence of birth within 48 h of intervention:*** Atosiban vs placebo: (Fixed effects) RR 2.50 (95% CI: 0.51–12.35) (1 study, $n = 112$) Atosiban vs betamimetics (Fixed effects) RR 0.98 (95% CI: 0.68–1.41) (4 studies, $n = 1033$) ***Incidence of birth within 7 days of intervention:*** Atosiban vs betamimetics: (Fixed effects) RR 0.91 (95% CI: 0.69–1.20) (3 studies, $n = 731$) ***Incidence of neonatal intensive care admission:*** Atosiban vs placebo: (Fixed effects) RR 1.09 (95% CI: 0.89–1.34) (1 study, $n = 560$) Atosiban vs betamimetics: (Fixed effects) RR 1.03 (95% CI: 0.84–1.26) (3 studies, $n = 836$) ***Incidence of perinatal mortality:*** *Perinatal death* Atosiban vs placebo: (Fixed effects) RR 2.25 (95% CI: 0.79–6.40) (1 study, $n = 583$) Atosiban vs betamimetics: (Fixed effects) RR 0.66 (95% CI: 0.24–1.83) (3 studies, $n = 836$). Heterogeneity: $\chi^2 = 4.97$, df=2, p=0.08; I^2=59.7%.

Review details	Methods	Results and conclusions
	Assessment: This was carried out independently by two authors and disagreements were resolved by consensus ***Synthesis:*** *Heterogeneity* Heterogeneity was assessed by visual inspection of the outcomes table and by using two statistics (*H* and I^2 test) of heterogeneity. One trial was identified as an outlier; the authors suggest that this may be because more women with a multiple pregnancy were randomised to the atosiban group *Methods* Meta-analysis using the fixed effects model. Where heterogeneity was found, pooled estimates were re-calculated using a random effects model. The authors report that use of a random effects model for these outcomes did not alter their interpretation of the results. Due to insufficient data, planned subgroup analyses were not undertaken	*Fetal death* Atosiban vs placebo: (Fixed effects) RR 1.02 (95% CI: 0.21–5.03) (2 studies, $n = 585$) Atosiban vs betamimetics: (Fixed effects) RR 0.55 (95% CI: 0.05–6.04) (3 studies, $n = 836$) *Neonatal death (up to 28 days)* Atosiban vs placebo: (Fixed effects) RR 4.10 (95% CI: 0.88–19.13) (1 study, $n = 583$) Atosiban vs betamimetics: (Fixed effects) RR 0.70 (95% CI: 0.27–1.81) (4 studies, $n = 1130$) *Infant death (up to 12 months)* Atosiban vs placebo: (Fixed effects) RR 6.15 (95% CI: 1.39–27.22) (1 study, $n = 583$) ***Incidence of adverse events:*** *Maternal adverse drug reaction* Atosiban vs betamimetics: (Fixed effects) RR 0.86 (95% CI: 0.72–1.03) (2 studies, $n = 486$) Maternal drug reaction requiring cessation of treatment Atosiban vs placebo: (Fixed effects) RR 4.02 (95% CI: 2.05–7.85) (2 studies, $n = 613$) Atosiban vs betamimetics: (Fixed effects) RR 0.04 (95% CI: 0.02–0.11) (4 studies, $n = 1034$) *Respiratory distress syndrome* Atosiban vs placebo: (Fixed effects) RR 1.28 (95% CI: 0.93–1.76) (2 studies, $n = 689$) Atosiban vs betamimetics: (Fixed effects) RR 0.99 (95% CI: 0.76–1.29) (4 studies, $n = 1129$). Heterogeneity: $\chi^2 = 6.69$, df = 2, $p = 0.08$; $I^2 = 55.2\%$ *Intraventricular haemorrhage* Atosiban vs placebo: (Fixed effects) RR 0.21 (95% CI: 0.02–1.76) (1 study, $n = 575$) *Necrotising enterocolitis* Atosiban vs placebo: (Fixed effects) RR 0.21 (95% CI: 0.02–1.76) (1 study, $n = 575$) Atosiban vs betamimetics: (Fixed effects) RR 0.48 (95% CI: 0.12–1.98) (2 studies, $n = 576$) *Hypoglycaemia* Atosiban vs placebo: (Fixed effects) RR 0.75 (95% CI: 0.18–3.20) (1 study, $n = 114$) Atosiban vs betamimetics: (Fixed effects) RR 1.07 (95% CI: 0.63–1.82) (3 studies, $n = 837$) *Patent ductus arteriosus* Atosiban vs placebo: (Fixed effects) RR 1.28 (95% CI: 0.68–2.40) (2 studies, $n = 689$) Atosiban vs betamimetics: (Fixed effects) RR 1.02 (95% CI: 0.58–1.79) (4 studies, $n = 1129$)

TABLE 138 *Oxytocin receptor antagonists (continued)*

Review details	Methods	Results and conclusions
		Neonatal sepsis Atosiban vs betamimetics: (Fixed effects) RR 0.91 (95% CI: 0.56–1.46) (4 studies, $n = 1129$) ***Brief summary of findings:*** Compared with placebo, atosiban did not reduce the incidence of preterm birth or improve neonatal outcomes. In one trial (583 infants) atosiban was associated with an increase in infant deaths at 12 months of age compared with placebo: RR 6.15 (95% CI: 1.39–27.22). Use of atosiban resulted in lower infant birthweight and more maternal adverse drug reactions ***Authors' conclusions:*** This review failed to demonstrate the superiority of atosiban over betamimetics or placebo in terms of tocolytic efficacy or infant outcomes, although atosiban results in fewer maternal side effects than betamimetics. The finding of an increase in infant deaths in one placebo-controlled trial warrants caution Further RCTs of tocolytic therapy, with a placebo arm and long-term infant follow-up, are needed ***Comments:*** This was a well-conducted review and the authors appear to have taken appropriate steps to reduce bias The authors note methodological concern for one of the trials; an imbalance in the randomisation of women before 26 weeks' gestation between atosiban and placebo groups was observed. The authors indicate this might explain results found for infant deaths. They also note that in both trials comparing atosiban with placebo the high level of rescue tocolysis used may have confounded the estimation of true effects of atosiban. Three trials identified for possible inclusion are awaiting classification pending further information from the authors
CI, confidence intervals; RCT, randomised controlled trial; RR, relative risks.		

TABLE 139 *Corticosteroids*

Review details	Methods	Results and conclusions
Crowley [Cochrane Database of Systematic Reviews 1996, Issue 1][24] ***Title:*** Prophylactic corticosteroids for preterm birth ***Type of review:*** Cochrane ***Prevalence:*** *Symptomatic for preterm birth –* Not applicable *Preterm birth –* Not applicable	***Search:*** *Databases searched (Search dates)* The Pregnancy and Childbirth Group Register (search date not reported) were searched for relevant articles *Other sources* No other sources reported *Search restrictions* No search restrictions stipulated ***Inclusion/exclusion criteria:*** *Study design(s)* RCTs *Population* Women expected to deliver preterm as a result of spontaneous labour, PROM, or elective delivery *Intervention* Antenatal administration of corticosteroids capable of crossing the placenta (betamethasone, dexamethasone, or hydrocortisone) compared with placebo/no treatment given to women before expected preterm delivery (elective or following spontaneous labour). Trials that tested the effect of corticosteroids with other co-interventions were excluded *Outcomes* Primary outcomes included respiratory distress syndrome (RDS), perinatal and neonatal mortality and morbidity, and long-term neurological abnormality ***Study selection:*** Eligibility was assessed by one reviewer ***Data extraction:*** Data were extracted by one reviewer ***Validity assessment:*** *Criteria used* Elimination of selection bias, performance bias, exclusion bias and detection bias were assessed in each trial	***No. of studies included:*** 18 trials (n = over 3700 infants) ***No. of studies meeting quality criteria:*** *Adequate randomisation* – 6 *Adequate concealment of allocation* – 8 *Adequate blinding of clinician/patient/researcher* – 1/12/0 ***Incidence of birth < 34 weeks' gestation:*** Not reported ***Incidence of birth < 37 weeks' gestation:*** Not reported ***Incidence of birth within 24 h of intervention:*** NA ***Incidence of birth within 48 h of intervention:*** NA ***Incidence of birth within 7 days of intervention:*** NA ***Incidence of neonatal intensive care admission:*** Not reported ***Incidence of perinatal mortality:*** Not reported ***Incidence of adverse events:*** *Respiratory distress syndrome* All babies: OR 0.53 (95% CI: 0.44–0.63) (18 studies, n = 3735) Babies delivered at < 28 weeks: OR 0.64 (95% CI: 0.16–2.50) (2 studies, n = 48) Babies delivered at < 30 weeks: OR 0.48 (95% CI: 0.30–0.77) (7 studies, n = 349) Babies born at < 32 weeks: OR 0.33 (95% CI: 0.21–0.50) (7 studies, n = 393)

DOI: 10.3310/hta13430

TABLE 139 *Corticosteroids*

Review details	Methods	Results and conclusions
	Assessment Trial quality was assessed by one reviewer ***Synthesis:*** *Heterogeneity* Chi-squared test and *I*-squared statistic were used to assess statistical heterogeneity *Methods* A weighted estimate of the treatment effect was calculated using Peto odds ratio (OR). The effect of respiratory distress syndrome in a number of infant subgroups was explored	Babies delivered at < 34 weeks: OR 0.36 (95% CI: 0.27–0.48) (7 studies, *n* = 1048) Babies delivered at > 34 weeks: OR 0.65 (95% CI: 0.33–1.29) (8 studies, *n* = 719) Babies born <24 h after first dose: OR 0.70 (95% CI: 0.43–1.16) (5 studies, *n* = 335) Babies born <48 h after first dose: OR 0.34 (95% CI: 0.08–1.47) (1 study, *n* = 42) Babies born 24 h to 7 days after first dose: OR 0.38 (95% CI: 0.25–0.57) (4 studies, *n* = 728) Babies delivered > 7 days after first dose: OR 0.41 (95% CI: 0.18–0.98) (3 studies, *n* = 265) Dexamethasone: OR 0.56 (95% CI: 0.43–0.73) (5 studies, *n* = 1400) Betamethasone: OR 0.49 (95% CI: 0.39–0.63) (11 studies, *n* = 2176) Hydrocortisone: OR 0.69 (95% CI: 0.32–1.47) (2 studies, 172) Male infants: OR 0.43 (95% CI: 0.29–0.64) (3 studies, *n* = 627) Female infants: OR 0.36 (95% CI: 0.23–0.57) (3 studies, *n* = 555) Twins/triplets: OR 0.72 (95% CI: 0.31–1.68) (2 studies, *n* = 140) *Neonatal death* All babies: OR 0.60 (95% CI: 0.48–0.75) (14 studies, *n* = 3517) Treated before 1980: OR 0.51 (95% CI: 0.38–0.68) (8 studies, *n* = 2133) Treated after 1980: OR 0.78 (95% CI: 0.54–1.12) (6 studies, *n* = 1384)

Review details	Methods	Results and conclusions
		Stillbirth All babies: OR 0.83 995% CI: 0.57–1.22) (12 studies, *n* = 3306) Women with hypertension: OR 3.75 (95% CI: 1.24–11.30) (1 study, *n* = 90; 3 studies unestimable) *Surfactant use* OR 0.41 (95% CI: 0.18–0.89) (1 study, *n* = 189) *Chronic lung disease* OR 1.57 (95% CI: 0.87–2.84) (3 studies, *n* = 411) *Intraventricular haemorrhage* Diagnosed by ultrasound OR 0.48 (95% CI: 0.32–0.72) (4 studies, *n* = 596) Diagnosed at autopsy OR 0.29 (95% CI: 0.14–0.61) (4 studies, *n* = 863) *Necrotising enterocolitis* OR 0.59 (95% CI: 0.32–1.09) (4 studies, *n* = 1154) *Fetal and neonatal infection* All babies: OR 0.82 (95% CI: 0.57–1.19) (15 studies, *n* = 2675) After PROM > 24 h: OR 2.31 (95% CI: 0.77–6.99) (2 studies, *n* = 163) With PROM at trial entry: OR 1.11 (95% CI: 0.50–2.43) (4 studies, *n* = 329) *Maternal infection* All mothers: OR 1.31 (95% CI: 0.99–1.73) (11 studies, *n* = 2109) After PROM > 24 h: OR 6.04 (95% CI: 1.47–24.71) (1 study, *n* = 42) With PROM at trial entry: OR 1.26 (95% CI: 0.69–2.28) (3 studies, *n* = 320) *Long-term neurological abnormality* OR 0.62 (95% CI: 0.36–1.08) (3 studies, *n* = 778)

TABLE 139 *Corticosteroids (continued)*

Review details	Methods	Results and conclusions
		Brief summary of findings:
		Antenatal corticosteroids reduce the incidence of respiratory distress syndrome across a variety of gestational ages compared to placebo/no treatment; greatest benefits reported for babies delivered < 28 weeks to < 34 weeks' gestation. Beneficial effect of antenatal corticosteroids appears greatest after 24 h. Administration of antenatal corticosteroids to women expected to give birth prematurely also reduces the risk of neonatal mortality compared to placebo/no treatment
		Authors' conclusions:
		Corticosteroids given before preterm delivery are effective in preventing respiratory distress syndrome and neonatal mortality
		Comments:
		Processes undertaken for the selection of papers, data extraction and assessment of trial quality increase the possibility of reviewer error or bias
		Although the inclusion criteria states that only RCTs were eligible for inclusion in the review, one quasi-randomised trial has also been included
		Most trials included multiple gestations

DOI: 10.3310/hta13430

Review details	Methods	Results and conclusions
Crowther and Harding [Cochrane Database of Systematic Reviews 2003, Issue 2][661] ***Title:*** Repeat doses of prenatal corticosteroids for women at risk of preterm birth for preventing neonatal respiratory disease ***Type of review:*** Cochrane ***Prevalence:*** *Symptomatic for preterm birth –* Not reported *Preterm birth –* No untreated control group	***Search:*** *Databases searched (Search dates)* The Cochrane Pregnancy and Childbirth Group trials register (January 2003), the Cochrane Controlled Trials Register (Issue 1, 2003), MEDLINE (1965 to January 2003), EMBASE (1988 to January 2003), and Current Contents (1997 to January 2003) *Other sources* Bibliographic references from all retrieved articles were also searched. In addition, the authors contacted experts and searched conference abstracts *Search restrictions* No search restrictions stated ***Inclusion/exclusion criteria:*** *Study design(s)* RCTs *Population* Pregnant women at risk of preterm birth who have already received a single course of prenatal corticosteroids seven or more days previously *Intervention* Repeat dose(s) of prenatal corticosteroids vs single dose of prenatal corticosteroids. Eligible comparators included: placebo or no placebo. Trials in which the fetus receives corticosteroids directly were excluded *Outcomes* Primary outcomes included: incidence of respiratory distress syndrome, severity of lung disease, birthweight, fetal/neonatal/infant mortality, chronic lung disease, periventricular haemorrhage, periventricular leukomalacia, disability at childhood follow-up, chorioamnionitis, and puerperal sepsis A number of secondary infant and maternal outcomes were also sought including measures of effectiveness, complications, satisfaction with care and health service use ***Study selection:*** The authors do not state how studies were selected for inclusion or how many reviewers performed the selection ***Data extraction:*** Data extraction was completed independently by two reviewers. Data were extracted from the trials on an intention to treat basis	***No. of studies included:*** Three RCTs ($n = 551$) ***No. of studies meeting quality criteria:*** *Adequate randomisation* – 3 *Adequate concealment of allocation* – 3 *Adequate blinding of clinician/patient/researcher* – 3/3/3 ***Incidence of birth < 34 weeks' gestation:*** [Fixed effect] RR 1.09 (95% CI: 0.96–1.25) (2 studies, $n = 500$) ***Incidence of birth < 37 weeks' gestation:*** [Fixed effect] RR 1.26 (95% CI: 0.66–2.41) (2 studies, $n = 49$) ***Incidence of birth within 24 h of intervention:*** Not applicable ***Incidence of birth within 48 h of intervention:*** Not applicable ***Incidence of birth within 7 days of intervention:*** Not applicable ***Incidence of neonatal intensive care admission:*** Not reported ***Incidence of perinatal mortality:*** Not reported ***Incidence of adverse events:*** Respiratory distress syndrome [Fixed effect] RR 0.96 (95% CI: 0.72–1.26) (2 studies, $n = 516$) Severity of lung disease [Fixed effect] RR 0.64 (95% CI: 0.44–0.93) (1 study, $n = 500$) Fetal, neonatal, or infant death [Fixed effect] RR 0.53 (95% CI: 0.18–1.57) (2 studies, $n = 518$) Chronic lung disease [Fixed effect] RR 1.01 (95% CI: 0.63–1.65) (2 studies, $n = 516$) Periventricular haemorrhage [Fixed effect] RR 1.15 (95% CI: 0.70–1.90) (1 study, $n = 500$) Periventricular haemorrhage (Grades 3/4) [Fixed effect] RR 2.50 (95% CI: 0.76–8.22) (2 studies, $n = 516$)

TABLE 139 *Corticosteroids (continued)*

Review details	Methods	Results and conclusions
	Validity assessment:	Periventricular leukomalacia
	Criteria used	[Fixed effect] RR 0.64 (95% CI: 0.11–3.80) (2 studies, *n* = 516)
	Studies were assessed in terms of randomisation, allocation concealment, blinding, use of placebo and completeness of follow-up, and assigned a score. Details of the scoring procedure were described	Chorioamnionitis
	Assessment	[Fixed effect] RR 1.35 (95% CI: 0.95–1.92) (2 studies, *n* = 497)
	The authors independently assessed the methodological quality of the primary studies; any disagreements were resolved by discussion. Reviewers were not blinded to authorship	Puerperal sepsis
	Synthesis:	[Fixed effect] RR 0.88 (95% CI: 0.42–1.83) (2 studies, *n* = 497)
	Heterogeneity	Preterm birth < 28 weeks' gestation
	Chi-squared test and *I*-squared test were used to assess statistical heterogeneity. Sensitivity analysis, using trial quality, was performed	[Fixed effect] RR 1.08 (95% CI: 0.67–1.74) (1 study, *n* = 488)
	Methods	Necrotising enterocolitis
	Where appropriate studies were combined in a meta-analysis using a fixed effects model. Categorical data were presented as relative risks (RR) and continuous data were presented as weighted mean difference (WMD). If statistical heterogeneity was found, data were recalculated using a random effects model. Subgroup analyses (singletons/multiple gestation; presence or absence of ruptured membranes; type of corticosteroid given; dosage and method of administration) were planned	[Fixed effect] RR 1.07 (95% CI: 0.44–2.58) (2 studies, *n* = 516)
		Infection while in neonatal intensive care unit
		[Fixed effect] RR 1.09 (95% CI: 0.52–2.30) (2 studies, *n* = 516)
		Patent ductus arteriosus requiring treatment
		[Fixed effect] RR 1.56 (95% CI: 0.17–13.87) (1 study, *n* = 16)
		Retinopathy of prematurity
		[Fixed effect] RR 0.78 (95% CI: 0.22–2.74) (1 study, *n* = 16)
		Use of postnatal steroids
		[Fixed effect] RR 1.13 (95% CI: 0.61–2.11) (1 study, *n* = 500)
		Postpartum haemorrhage
		[Fixed effect] RR 0.60 (95% CI: 0.33–1.07) (1 study, *n* = 485)
		Composite serious morbidity
		[Fixed effect] RR 0.80 (95% CI: 0.60–1.07) (2 studies, *n* = 518)
		Other outcomes:
		Birthweight
		[Fixed effect] WMD – 137.67 (95% CI: –281.54 to 6.20) (2 studies, *n* = 539)
		Length of postnatal hospitalisation
		[Fixed effect] WMD 0.00 (95% CI: –0.22 to 0.22) (1 study, *n* = 485)
		Duration of oxygen supplementation (days)
		[Fixed effect] WMD 3.30 (95% CI: –2.31 to 8.91) (1 study, *n* = 37)
		Duration of respiratory support (days)
		[Fixed effect] WMD 0.30 (95% CI: –0.90 to 1.50) (1 study, *n* = 37)
		Use of surfactant
		[Fixed effect] RR 0.65 (95% CI: 0.46–0.92) (2 studies, *n* = 537)

Review details	Methods	Results and conclusions
		Brief summary of findings: A reduced risk of severe lung disease was shown for repeat dose corticosteroid administration compared to single dose, and fewer infants in the repeat-dose group received surfactant compared to the single-dose group. No statistically significant differences between the treatment groups were shown on the other infant and maternal outcomes ***Authors' conclusions:*** Repeat dose(s) of prenatal corticosteroids may reduce the severity of neonatal lung disease. However, there is insufficient evidence regarding risks and benefits to recommend the use of repeat dose prenatal corticosteroids for women at risk of preterm birth for the prevention of neonatal respiratory disease. Further trials are needed ***Comments:*** Procedures undertaken for selection of the primary studies were not reported Datasets appeared to include both singleton and multiple pregnancies

CI, confidence interval; OR, odds ratio; PROM, pre-labour rupture of membranes; RCT, randomised controlled trial; RR, relative risk; WMD, weighted mean difference.

TABLE 140 *Magnesium sulphate for neuroprotection*

Study details and design	Description of methods	Results and conclusions
Crowther et al. [JAMA 2003; 290(20): 2669–2676][668] ***Country:*** Australia and New Zealand ***Setting:*** 16 tertiary hospitals with neonatal intensive care units ***Prevalence:*** *Symptomatic for preterm birth* – Not reported *Preterm birth* – Not reported ***Study design:*** RCT ***Length of follow-up:*** From enrolment with follow-up of surviving children at 2 years ***No. of participants:*** *No. randomised* – 1062 (women) *No. analysed* – 1062 (women), 1047 (infants; 99%) ***Validity:*** *Adequate randomisation* – Yes (computer-generated random numbers) *Adequate allocation concealment* – Yes (study number placed on masked treatment packs) *Blinding of clinician* – Yes *Blinding of patient* – Yes *Blinding of researcher* – Yes	***Groups compared:*** Magnesium sulphate vs placebo (isotonic sodium chloride solution) ***Intervention details:*** Each pack contained an infusion bag of 60 ml of either a 0.5-g/ml solution of magnesium sulphate or isotonic sodium chloride solution (0.9%). Women were given a loading infusion of 8 ml [4 g (16 mmol) of magnesium sulphate or isotonic sodium chloride solution] for 20 min followed by a maintenance infusion of 2 ml/h until birth (if occurred within 24 h) or up to 24 h Pulse rate, blood pressure and respiratory rates were monitored throughout the infusion and any maternal adverse effects recorded. Loading or maintenance infusions were stopped if the respiratory rate decreased more than 4/min or diastolic blood pressure decreased more than 15 mmHg below baseline level. The infusion could be resumed once respiratory rate and blood pressure had returned to baseline levels. Magnesium levels were not measured. The care that women and infants received was otherwise according to standard practice at each centre ***Participants:*** Women with planned or expected very preterm birth within 24 h ***Participant inclusion/exclusion criteria:*** Women with single or multiple fetuses at < 30 weeks' gestation were eligible for inclusion. No lower limit on gestational age at enrolment was enforced. Women were excluded if they had received magnesium sulphate therapy in current pregnancy, or if there were any contraindications to magnesium sulphate ***Outcomes:*** Primary: Total paediatric mortality, cerebral palsy in survivors, and combined death or cerebral palsy Secondary: Major maternal adverse effects (e.g. death, cardiac arrest, haemorrhage or respiratory arrest), minor maternal adverse effects (e.g. nausea, sleepiness, dizziness, discomfort, sweating, blurred vision, mouth dryness and warmth over body), infant intraventricular haemorrhage, cystic periventricular leukomalacia, chronic lung disease, necrotising enterocolitis, mechanical ventilation, neurosensory disability, blindness, deafness, delayed development, and gross motor dysfunction	***Incidence of birth < 34 weeks' gestation:*** Not applicable ***Incidence of birth < 37 weeks' gestation:*** Not applicable ***Incidence of birth within 24 h of intervention:*** Not applicable ***Incidence of birth within 48 h of intervention:*** Not applicable ***Incidence of birth within 7 days of intervention:*** Not applicable ***Incidence of neonatal intensive care admission:*** Not reported ***Incidence of perinatal mortality:*** Not reported ***Incidence of adverse events:*** Stillbirths *No. in intervention group (total no.)* = 9 (629) *No. in control group (total no.)* = 11 (626) Infant deaths born live before initial discharge *No. in intervention group (total no.)* = 76 (629) *No. in control group (total no.)* = 92 (626) Post discharge deaths (up to corrected age of 2 yrs) *No. in intervention group (total no.)* = 2 (629) *No. in control group (total no.)* = 4 (626) Total deaths *No. in intervention group (total no.)* = 87 (629) *No. in control group (total no.)* = 107 (626) Cerebral palsy *No. in intervention group (total no.)* = 36 (629) *No. in control group (total no.)* = 42 (626) Periventricular leukomalacia *No. in intervention group (total no.)* = 22 (620) *No. in control group (total no.)* = 21 (615)

Study details and design	Description of methods	Results and conclusions
Type of analysis: Baseline variables were included as confounders if there was an imbalance between treatment groups. Binary outcomes are presented as RRs with 95% CIs; RRs were calculated using log binomial regression. Robust variance estimation was used to account for clustering of infants within mothers Intention to treat analysis was undertaken for women randomised to the trial but not for infants ***Sample size:*** To detect a 50% reduction in risk of cerebral palsy at 2 years in survivors from 10% to 5%, with 80% probability at an alpha level of 0.5, 848 children were needed. This number was adjusted upward to 1250 infants to account for a predicted 20% mortality rate and the effect of non-independence of observations from multiple births		Intraventricular haemorrhage *No. in intervention group (total no.)* = 165 (620) *No. in control group (total no.)* = 148 (615) Primary postpartum haemorrhage *No. in intervention group (total no.)* = 86 (629) *No. in control group (total no.)* = 99 (626) Major postpartum haemorrhage *No. in intervention group (total no.)* = 26 (629) *No. in control group (total no.)* = 25 (626) Clinical and self-assessed maternal adverse effects of infusion stopped due to adverse effects *No. in intervention group (total no.)* = 78 (629) *No. in control group (total no.)* = 28 (626) Substantial gross motor dysfunction *No. in intervention group (total no.)* = 18 (629) *No. in control group (total no.)* = 34 (626) ***Brief summary of findings:*** A reduction in number of stillbirths, deaths before initial discharge home, post-discharge deaths and total paediatric mortality was observed in the magnesium sulphate group, although no statistically significant differences were found. The incidence of cerebral palsy was less frequent in the magnesium sulphate group compared to placebo, but again this difference was not statistically significant. A significant reduction in substantial gross motor dysfunction was found in the magnesium sulphate group. No statistically significant differences were shown for other neurosensory outcomes assessed at a corrected age of 2 years, or other infant outcomes. Significantly more women stopped their infusion because of adverse effects in the magnesium sulphate group. A decrease in diastolic blood pressure > 15 mmHg was found in the magnesium sulphate group compared to placebo ***Authors' conclusions:*** Magnesium sulphate given immediately before very preterm birth may improve important paediatric outcomes but the evidence is not strong enough to recommend widespread use of magnesium sulphate. No serious harmful effects were shown ***Comments:*** Magnesium sulphate was given for neuroprotection only and not as a tocolytic 16.6% had a multiple pregnancy

TABLE 140 *Magnesium sulphate for neuroprotection (continued)*

Study details and design	Description of methods	Results and conclusions
Mittendorf et al., 2002 [Am J Obstet Gynecol 2002; 186: 1111–1118] ***Country:*** USA ***Setting:*** Hospital based ***Prevalence:*** *Symptomatic for preterm birth* – Not reported *Preterm birth* – Not reported. ***Study design:*** Randomised, controlled trial (RCT) ***Length of follow-up:*** Infants were followed from randomisation up to 18 corrected months of age ***No. of participants:*** *No. randomised* – Toclysis: 92 Neuroprotection: 57 *No. analysed* – Toclysis: 92 Neuroprotection: 57 ***Validity:*** *Adequate randomisation* – Yes, 1 and 2 (computer-generated numbers) *Adequate allocation concealment* – *Blinding of clinician* – 1. No, 2. Yes *Blinding of patient* – Yes, 1 & 2 *Blinding of researcher* – Dependent on outcome	***Groups compared:*** Tandem trials: Tocolytic magnesium sulphate vs Other tocolytic agents Neuroprotective magnesium sulphate vs saline ***Intervention details:*** In the tocolytic arms women were randomised to receive magnesium sulphate as a 4-g bolus followed by an infusion of 2–3 g of magnesium sulphate per hour or other tocolytic therapy (ritodrin, terbutaline, indomethacin, or nifedipine, according to the attending obstetrician's preference) In the neuroprotective arms women were randomised to receive a 4-g intravenous bolus of magnesium sulphate without further infusion or saline solution. In the neonatal period, infants underwent a minimum of three cranial ultrasounds (weeks 1, 2 and 4 of life). Final ultrasound diagnoses were made by consensus decisions of two paediatric radiologists. Follow-up neurodevelopmental examinations were conducted in special clinic visits at 4, 8, 12 and 18 corrected months of age ***Participants:*** (Symptomatic) pregnant women ***Participant inclusion/exclusion criteria:*** Women > 24 and < 34 weeks' gestation, reassuring fetal assessment, and absence of clinical features suggestive of infection or pre-eclampsia were eligible for the trial. Women in active labour with cervical dialation ≤4 cm considered legitimate candidates for aggressive tocolysis were eligible for the tocolytic arm. Women in active labour with cervical dilatation ≥4 cm were eligible for the prevention arm. Women with triplet or higher order gestations were excluded ***Outcomes:*** Adverse paediatric outcomes, such as mortality, cerebral palsy, neonatal intraventricular haemorrhage and periventricular haemorrhage, and obstetric and neonatal risk factors for adverse paediatric outcomes were considered	***Incidence of birth < 34 weeks' gestation:*** Not reported ***Incidence of birth < 37 weeks' gestation:*** Not reported ***Incidence of birth within 24 h of intervention:*** Not reported ***Incidence of birth within 48 h of intervention:*** Not reported ***Incidence of birth within 7 days of intervention:*** Not reported ***Incidence of neonatal intensive care admission:*** Not reported ***Incidence of perinatal mortality:*** Not reported ***Incidence of adverse events:*** *Composite adverse events* Tocolytic group: *No. in intervention group (total no.)* = 16 (46) *No. in control group (total no.)* = 9 (46) Neuroprotection group: *No. in intervention group (total no.)* = 11 (29) *No. in control group (total no.)* = 6 (28) *Intraventricular haemorrhage (grades 1–3)* Tocolytic group: *No. in intervention group (total no.)* = 8 (55) *No. in control group (total no.)* = 6 (51) Neuroprotection group: *No. in intervention group (total no.)* = 5 (30) *No. in control group (total no.)* = 5 (29) *Periventricular leukomalacia* Neuroprotection group: *No. in intervention group (total no.)* = 1 (30) *No. in control group (total no.)* = 0 (29)

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Study details and design	Description of methods	Results and conclusions
Type of analysis: Chi-squared test, Student's *t*-test, Mann–Whitney *U*-test and the Fisher exact test and multivariate logistic regression were used were appropriate. Analyses were conducted on an intention-to-treat basis. ***Sample size:*** Power analyses were based on anticipated reductions in the occurrence of neonatal intraventricular haemorrhage after the use of antenatal intravenous magnesium sulphate (18.9% to 4.4%). To obtain an alpha of 0.5 and a beta of 80%, 140 infants would be needed, increasing to 188 infants for a beta of 90%		*Cerebral palsy* Tocolytic group: *No. in intervention group (total no.)* = 0 (46) *No. in control group (total no.)* = 3 (46) Neuroprotection group: *No. in intervention group (total no.)* = 3 (30) *No. in control group (total no.)* = 0 (29) *Mortality (fetal, neonatal + postnatal)* Tocolytic group: *No. in intervention group (total no.)* = 8 *No. in control group (total no.)* =0 Neuroprotection group: *No. in intervention group (total no.)* = 2 (30) *No. in control group (total no.)* =1 (29) ***Brief summary of findings:*** A greater number of composite adverse paediatric outcomes were shown in the individual magnesium sulphate groups compared with control groups; however, between-group differences were not statistically significant When trial data were combined, multivariate regression analyses found that cord ionised magnesium was shown to be a significant risk factor for adverse paediatric outcome (i.e. intraventricular haemorrhage) ***Authors' conclusions:*** Use of antenatal magnesium sulphate was associated with worse perinatal outcomes in a dose-dependent fashion ***Comments:*** Randomisation occurred after separation into the two parallel arms. The distributions of women in each trial arm were similar in terms of ethnicity, gestational length and fetal plurality 15.2% (14) randomised to the tocolytic arm had a multiple gestation 3.5% (2) randomised to the neuroprotection arm had a multiple gestation. Individually the two arms would be underpowered to detect significant differences between the two groups The trial was stopped early because of concerns of a higher total paediatric mortality rate in the magnesium group

CI, confidence interval; RCT, randomised controlled trial; RR, relative risk.

TABLE 141 *Vitamin K for the premature neonates' neuroprotection*

Review details	Methods	Results and conclusions
Crowther et al. [Cochrane Database of Systematic Reviews 2001, Isssue1][672] ***Title:*** Vitamin K prior to preterm birth for preventing neonatal periventricular haemorrhage ***Type of review:*** Cochrane ***Prevalence:*** *Symptomatic for preterm birth –* Not reported *Preterm birth –* Not reported	***Search:*** *Search dates* September 2000 *Databases searched* The Cochrane Controlled Trials Register and the Pregnancy and Childbirth Group Register were searched using the search term 'vitamin' *Other sources* None reported *Search restrictions* None specified ***Inclusion/exclusion criteria:*** *Study design(s)* RCTs or quasi-randomised trials were eligible for inclusion *Population* Women at risk of imminent very preterm labour *Intervention* Administration of vitamin K (parentally or orally) to the mother before preterm birth *Outcomes* Primary outcomes included: neonatal mortality and neonatal neurological morbidity (periventricular haemorrhage and long-term neurodevelopment). Secondary outcomes included: any maternal side effects and other neonatal morbidity ***Study selection:*** Two reviewers independently selected the studies for inclusion. There was no blinding of authorship ***Data extraction:*** Two reviewers independently extracted data from the primary studies; All data was double entered. Any disagreements were resolved through consensus. Where possible authors of the primary studies were contacted for additional information	***No. of studies included:*** Five trials (*n* at least 420) ***No. of studies meeting quality criteria:*** *Adequate randomisation* – 2 *Adequate concealment of allocation* – 2 *Adequate blinding of clinician/patient/researcher* – 5/Unclear/Unclear ***Incidence of birth < 34 weeks' gestation:*** Not reported ***Incidence of birth < 37 weeks' gestation:*** Not reported ***Incidence of birth within 24 h of intervention:*** Not applicable ***Incidence of birth within 48 h of intervention:*** Not applicable ***Incidence of birth within 7 days of intervention:*** Not applicable ***Incidence of neonatal intensive care admission:*** Not reported ***Incidence of perinatal mortality:*** (Fixed effect) RR 0.79 (95% CI: 0.46–1.35) (4 studies, *n* = 539) ***Incidence of adverse events:*** All periventricular haemorrhage (Fixed effect) RR 0.82 (95% CI: 0.67–1.00) (5 studies, *n* = 606) Severe periventricular haemorrhage (grades 3–4) (Fixed effect) RR 0.75 (95% CI: 0.45–1.25) (5 studies, *n* = 606) Low Apgar score at 5 min (Fixed effect) RR 0.99 (95% CI: 0.63–1.57) (2 studies, *n* = 475) Respiratory distress syndrome (Fixed effect) RR 1.02 (95% CI: 0.76–1.37) (3 studies, *n* = 167)

Review details	Methods	Results and conclusions
	Validity assessment:	Use of mechanical ventilation
	Criteria used	(Fixed effect) RR 0.96 (95% CI: 0.84–1.10) (5 studies, *n* = 642)
	Quality scores for concealment of allocation were assigned to each study; A = adequate, B = unclear, C = inadequate and D = not used. In addition, quality scores were also assigned for completeness of follow-up, and blinding of outcome assessment; details reported	Pulmonary air leak
	Assessment	(Fixed effect) RR 1.74 (95% CI: 0.59–5.10) (2 studies, *n* = 475)
	Two reviewers independently assessed the included studies for methodological quality	Patent ductus arteriosus
	Synthesis:	(Fixed effect) RR 0.96 (95% CI: 0.57–1.63) (3 studies, *n* = 528)
	Heterogeneity	Maternal side effects
	Chi-squared test and the *I*-squared statistic were used to assess statistical heterogeneity. Planned sensitivity analysis was carried out, looking at trial quality	(Fixed effect) RR 3.78 (95% CI: 0.41–35.07) (4 studies, *n* = 474)
	Methods	***Sensitivity analyses:***
	Categorical data were compared using RRs and their 95% CIs. Meta-analyses were used to pool data, using a fixed effects model; where statistically significant heterogeneity was found a random effects model was used	*Incidence of perinatal mortality*
		Excluding non-concealment of randomisation – (Fixed effect) RR 0.78 (95% CI: 0.43–1.42) (3 studies, *n* = 486)
		Excluding non-concealment of randomisation and unclear follow-up – (Fixed effect) RR 0.79 (95% CI: 0.41–1.52) (1 study, *n* = 372)
		Brief summary of findings:
		Compared to no treatment, antenatal administration of vitamin K did not statistically reduce the incidence of perinatal mortality or periventricular haemorrhage. No statistically significant between-group differences were shown on any of the other reported outcomes
		Neurodevelopmental outcomes were not reported in the primary studies
		Authors' conclusions:
		Vitamin K, administered to women before very preterm birth did not significantly prevent periventricular haemorrhages in preterm infants
		Comments:
		This was a well-conducted review; methods were used to minimise bias in the study selection, validity assessment and data abstraction processes. Data were appropriately pooled and heterogeneity assessed

CI, confidence interval; RCT, randomised controlled trial; RR, relative risk.

Appendix 7

Adjusted indirect comparisons data

TABLE 142 *Details of the data used for adjusted indirect comparisons included in the economic model*

Indirect comparison	Outcome [indirect RR (95% CI)]	Direct comparisons used in indirect estimate	RR (95% CI)	Size (*n*) and quality
Calcium channel blockers vs placebo	Birth before 34 weeks 0.74 (95% CI: 1.43–0.38)	Calcium channel blockers vs betamimetic maintenance therapy	0.76 (95% CI: 0.64–0.91)	Meta-analysis of five trials: *n* = 86, questionable quality[571] *n* = 185, reasonable quality[575] *n* = 57, reasonable quality[572] *n* = 53, poor quality[578] *n* = 89, reasonable quality[577]
		Betamimetic maintenance (terbutaline pump) vs placebo	0.97 (95% CI: 0.51–1.84)	One trial *n* = 52, good quality[562]
	Birth before 37 weeks 0.98 (95% CI: 0.65–1.50)	Calcium channel blockers vs betamimetic maintenance therapy	0.84 (95% CI: 0.73–0.98)	Meta-analysis of five trials: *n* = 90, questionable quality[571] *n* = 52, reasonable quality[568] *n* = 65, reasonable quality[567] *n* = 185, reasonable quality[575] *n* = 90, reasonable quality[577]
		Betamimetic maintenance (terbutaline pump) vs placebo	1.17 (95% CI: 0.79–1.73)	One trial *n* = 52, good quality[562]
	Admission to neonatal intensive care unit 0.67 (95% CI: 0.35–1.26)	Calcium channel blockers vs betamimetic maintenance therapy	0.71 (95% CI: 0.59–0.86)	Meta-analysis of nine trials: *n* = 62, reasonable quality[570] *n* = 42, reasonable quality[566] *n* = 82, questionable quality[573] *n* = 86, questionable quality[571] *n* = 173, reasonable quality[575] *n* = 52, reasonable quality[568] *n* = 63, reasonable quality[572] *n* = 53, poor quality[578] *n* = 89, reasonable quality[577]
		Terbutaline pump maintenance (betamimetic) vs placebo	0.94 (95% CI: 0.51–1.73)	One trial *n* = 140, good quality[560]
	Birth within 48 h after treatment 0.44 (95% CI: 0.16–1.26)	Calcium channel blockers vs magnesium sulphate – no maintenance therapy	0.78 (95% CI: 0.36–1.69)	One trial *n* = 74,questionable quality[581]
		Magnesium sulphate vs no tocolytic agent	0.57 (95% CI: 0.28–1.15)	Meta-analysis of three trials: *n* = 35,questionable quality[578] *n* = 65,questionable quality[624] *n* = 90, reasonable quality[622]
	Birth within 7 days after treatment 0.46 (95% CI: 0.30–0.71)	Calcium channel blockers vs terbutaline (betamimetic)	0.78 (95% CI: 0.64–0.94)	Meta-analysis of five trials: *n* = 185, reasonable quality[575] *n* = 57, reasonable quality[572] *n* = 53, poor quality[578] *n* = 89, reasonable quality[577] *n* = 61, questionable quality[579]
		Terbutaline (betamimetic) vs placebo	0.59 (95% CI: 0.40–0.87)	Meta-analysis of two trials: *n* = 30, good quality[578] *n* = 38, questionable quality[578]

TABLE 142 *Details of the data used for adjusted indirect comparisons included in the economic model*

Indirect comparison	Outcome [indirect RR (95% CI)]	Direct comparisons used in indirect estimate	RR (95% CI)	Size (*n*) and quality
Fenoterol (betamimetic) vs placebo	Perinatal mortality	Fenoterol (betamimetic) vs ritodrine (betamimetic)	0.11 (95% CI: 0.01–2.01)	One trial *n* = 98, questionable quality[538]
		Ritodrine (betamimetic) vs placebo	0.88 (95% CI: 0.48–1.63)	Meta-analysis of eight trials: *n* = 29, questionable quality[547] *n* = 25, questionable quality[535] *n* = 33, questionable quality[539] *n* = 199, questionable quality[539,542] *n* = 11, questionable quality[539,545] *n* = 33, questionable quality[539,546] *n* = 111, reasonable quality[539,543] *n* = 771, good quality[533,539]
Oxytocin receptor antagonists (atosiban) vs placebo	Birth before 37 weeks	Oxytocin receptor antagonists (atosiban) vs betamimetics	0.90 (95% CI: 0.71–1.13)	One trial *n* = 244, good quality[588]
		Betamimetic (terbutaline) vs placebo	0.64 (95% CI: 0.45–0.91)	Meta-analysis of two trials: *n* = 30, good quality[578] *n* = 38, questionable quality[537]
	Birth within 48 h after treatment	Oxytocin receptor antagonists (atosiban) vs betamimetics	0.98 (95% CI: 0.68–1.41)	Meta-analysis of four trials: *n* = 302, poor quality[590] *n* = 247, good quality[591] *n* = 244, good quality[588] *n* = 240, good quality[587]
		Betamimetic (terbutaline) vs placebo	0.45 (95% CI: 0.25–0.81)	Meta-analysis of two trials: *n* = 30, good quality[578] *n* = 38, questionable quality[537]
	Birth within 7 days after treatment	Oxytocin receptor antagonists (atosiban) vs betamimetics	0.91 (95% CI: 0.69–1.20)	Meta-analysis of three trials: *n* = 247, good quality[591] *n* = 244, good quality[588] *n* = 240, good quality[587]
		Betamimetic (terbutaline) vs placebo	0.59 (95% CI: 0.40–0.87)	Meta-analysis of two trials: *n* = 30, good quality[578] *n* = 38, questionable quality[537]

95% CI, 95% confidence interval; RR, relative risk.

Appendix 8

Estimation of cost of spontaneous preterm birth

The data presented in *Table 143* represent the cost of low birthweight babies, for a specific weight range, for the neonatal period. It was derived from Petrou,[60] and was used to estimate the Costs during the neonatal period (Cost of spontaneous preterm birth) for up to 34 and up to 37 weeks' gestation, which refers to the cost of looking after the infant only and only covered the period of the initial hospitalisation.

We need to estimate the proportion of surviving infants for each of the weight ranges presented above so as to estimate the weighted mean (statistical term) of the costs during the neonatal period of the above ranges for up to 34 weeks' and up to 37 weeks' of gestation. *Table 144* contains average birthweight for all gestational ages.

From *Table 144*, we can calculate the average birthweight per range of gestational age. For example the average birthweight of babies born up to 24 weeks is estimated by the average of the birthweight for 22, 23 and 24 weeks' gestation.

Thus: Average birthweight up to 24 weeks = (500 + 590 + 690)/3 = 593 grams (as presented in *Table 145*). We proceed accordingly for the remaining gestational weeks.

Table 146 presents the number of surviving babies by gestational age.

To estimate the proportion of survivors by weight range to correspond with *Table 143* we use the data in *Table 146* and *Table 145*.

Therefore, from *Tables 145* and *146*, we calculate the number of babies who survived according to their average birthweight (< 1000 g, 1000–1499 g, ≥ 1500 g) for up to 34 weeks and the same for up to 37 weeks.

For the 34 weeks: the < 1000 g range (in *Table 143*) corresponds to up to 26 weeks' gestation (from *Table 145*). From *Table 146*, there are 17 (7 + 10) babies who survived to up to 26 weeks' gestation.

TABLE 143 *Costs during and after the neonatal period per average birthweight (weeks)*[a]

Average birthweight (g)	**< 1000**	**1000–1499**	**≥ 1500**
Costs during the neonatal period	£29,757 (£19,711–£39,803)	£14,896 (£9,310–£20,662)	£9207 (£4295–£14,119)

a Costs are in 1998 values.

TABLE 144 *Average birthweight (g) by gestational age (weeks)*

Gestational age (weeks)	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**
Average birthweight (g)	500	590	690	790	900	1000	1150	1300
Gestational age (weeks)	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**
Average birthweight (g)	1500	1650	1850	2050	2300	2550	2800	3000

Source: Data extrapolated from Figure 2 in Fenton.[712]

TABLE 145 *Average birthweight (g) per gestational age (weeks)*

Gestational age (weeks)	**≤24**	**25–26**	**27–28**	**29–30**	**31–32**	**33–34**	**35–36**	**≥37**
Average birthweight (g)	593	845	1075	1400	1750	2175	2675	3000

TABLE 146 *Number of babies survived per gestational age (weeks)*

Gestational age (weeks)	**≤24**	**25–26**	**27–28**	**29–30**	**31–32**	**33–34**	**35–36**	**≥37**	**Total**
Number of babies survived	7	10	33	41	49	130	298	6092	6660
Source: Morgan, 2003, Birmingham Women's Hospital.[713]									

The 1000–1499 g range (in *Table 143*) corresponds to 27–30 weeks' gestation (from *Table 145*). From *Table 146*, there are 74 babies (i.e. 33 + 41) who survived between 27 and 30 weeks' gestation.

The ≥1500-g range (in *Table 143*) corresponds to 31–34 weeks' gestation (from *Table 145*). From *Table 145*, there are 179 babies (i.e. 49 + 130) who survived between 31 and 34 weeks' gestation.

For the 37 weeks: the babies who survived for the < 1000 g and the 1000–1499 g ranges were the same as before.

The ≥1500-g range (in *Table 143*) corresponds to 31–37 weeks' gestation (from *Table 145*). From *Table 146*, there are 6569 babies (49 + 130 + 298 + 6092) who survived between 31 and 37 weeks' gestation.

The above as well as the weightings (statistical term) for each weight range are summarised in *Table 147*.

These proportions are then used to estimate the 'weighted' (statistical definition) mean for weight ranges corresponding to *Table 143* for both gestational weeks.

For example, for up to 34 weeks, the cost of preterm birth was estimated to be £12,084.76 (in 1998 values) which we inflated to 2005 prices:

> 0.0663 × £29,757 (*Table 143*) + 0.2741 × £14,896 (*Table 143*) + 0.663 × £9207 (*Table 143*) = **£12,084.76** as shown in *Table 148* for 34 weeks in 1998 prices which is then inflated to £15,688.75.

TABLE 147 *Summary of the weightings for each premature neonate weight range*

Average birthweight (g)	**< 1000**	**1000–1499**	**≥1500**
Proportions required for up to 34 weeks			
Gestational age (weeks)	≤26	27–30	31–34
Number of babies survived	17	74	179
Weightings (per total number of babies survived)	0.0630	0.2741	0.6630
Proportions required for up to 37 weeks			
Gestational age (weeks)	≤26	27–30	31–37
Number of babies survived	17	74	6569
Weightings (per total number of babies survived)	0.0026	0.0111	0.9863

TABLE 148 *Cost of preterm birth*

	Average birthweight (g)			1998 values	2005 values
	< 1000	**1000–1499**	**≥1500**	**Total cost**	**Total cost**
34 weeks					
Costs during the neonatal period	£1873.59	£4107.27	£6103.90	£12,084.76	£15,688.75[a]
37 weeks					
Costs during the neonatal period	£75.96	£166.51	£9,081.20	£9,323.67	£12,104.23

a Also used in the 48-h and 7-day perinatal mortality models.

Appendix 9

Estimation of spontaneous preterm birth prevalence

From the meta-analysis of the accuracy data (likelihood ratios positive and negative for each test) and the effectiveness data (relative risk of each intervention) the following data were available:

- Prevalence of symptomatic women having spontaneous preterm birth, e.g. 0.3 (30/100)
- Prevalence of asymptomatic women having spontaneous preterm birth, e.g. 0.048 (12/250).

We had to assume that data were from separate studies (i.e. there was no overlap) and so we assumed that populations were comparable. We could then simply add the Total number of cases and divide it by the Total size of the studies. The result is the Overall Prevalence of symptomatic women having spontaneous preterm birth and the Overall Prevalence of asymptomatic women having spontaneous preterm birth. For example, Overall Prevalence of symptomatic women having spontaneous preterm birth =

$$\frac{30+40+30}{100+500+400}=\frac{100}{1000}=0.1,$$

where 0.3 (30/100), 0.08 (40/500) and 0.075 (30/400) are the prevalences from three separate studies. Technically the appropriate distribution for the Overall Prevalence is the β-distribution, i.e. Overall Prevalence $\sim \beta(n, r)$, where n = Total number of cases and r = Total number of studies size. In practice, the confidence intervals are expected to be sufficiently narrow that a normal distribution can be used instead. Using the β-distribution we calculate the variance of the Overall Prevalence of asymptomatic women having spontaneous preterm birth and the variance of the Overall Prevalence of symptomatic women having spontaneous preterm birth by the standard function

$$\text{var}(x)=\frac{r(n-r)}{n^2(n+1)},$$

which will be used in the normal distribution as well as below. Next we have to determine the Overall Prevalence of asymptomatic women becoming symptomatic with threatened preterm labour.

Having calculated the Overall Prevalence of asymptomatic women having spontaneous preterm birth and the Overall Prevalence of symptomatic women having spontaneous preterm birth, we can simply divide these two and obtain the Overall Prevalence of asymptomatic women becoming symptomatic. The variance of the Overall Prevalence of asymptomatic women becoming symptomatic can be calculated using the formula:

$$\text{var}(y)=\frac{\text{var}(x_1)}{\{E(x_2)\}^2}+\frac{E(x_1)\}^2}{E(x_2)\}^4}\text{var}\,x^2,$$

where, $y = x_1/x_2$, y is the Overall Prevalence of asymptomatic women becoming symptomatic, x_1 is the Overall Prevalence of asymptomatic women having spontaneous preterm birth and x_2 is the Overall Prevalence of symptomatic women having spontaneous preterm birth.

Feedback

The HTA programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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