ClinicalEvidence

Preterm birth

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ABSTRACT

INTRODUCTION: Preterm birth occurs in about 5% to 10% of all births in resource-rich countries, but in recent years the incidence seems to have increased in some countries, particularly in the USA. We found little reliable evidence for incidence in resource-poor countries. The rate in northwestern Ethiopia has been reported to vary from 11% to 22%, depending on the age group of mothers studied, and is highest in teenage mothers. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of preventive interventions in women at high risk of preterm delivery? What are the effects of interventions to improve neonatal outcome after preterm rupture of membranes? What are the effects of treatments to stop contractions in preterm labour? What are the effects of elective compared with selective caesarean delivery for women in preterm labour? What are the effects of interventions to improve neonatal outcome in preterm delivery? We searched: Medline, Embase, The Cochrane Library, and other important databases up to June 2010 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 58 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review, we present information relating to the effectiveness and safety of the following interventions: amnioinfusion for preterm rupture of membranes, antenatal corticosteroids, antibiotic treatment, bed rest, beta-mimetics, calcium channel blockers, elective caesarean, enhanced antenatal care programmes, magnesium sulphate, oxytocin receptor antagonists (atosiban), progesterone, prophylactic cervical cerclage, prostaglandin inhibitors (e.g., indometacin), selective caesarean, and thyrotropin-releasing hormone (TRH) (plus corticosteroids).

QUESTIONS

INTERVENTIONS

IMPROVING NEONATAL OUTCOME IN PRETERM DELIVERY

Beneficial

Unlikely to be beneficial

Likely to be ineffective or harmful

To be covered in future updates

Multiple courses of antenatal corticosteroids

Fish oils

Uterine activity monitoring for singleton and multiple pregnancies in prevention of preterm birth

Antibiotic treatment of bacterial vaginosis to prevent preterm birth: see bacterial vaginosis

Key points

- Around 5% to 10% of all births in resource-rich countries occur before 37 weeks' gestation, leading to increased risks of neonatal and infant death, and of neurological disability in surviving infants.
- Progesterone may reduce preterm birth in women with prior preterm birth and a short cervix, but are unlikely to be beneficial and may even be harmful in women with multiple gestations.
- Enhanced antenatal care programmes and bed rest have repeatedly been shown to be ineffective or harmful.

  Prophylactic cervical cerclage may reduce preterm births in women with cervical changes but is unlikely to be effective — and may increase infection — in women with no cervical changes or with twin pregnancies. We don't know how effective it is in women with protruding membranes.
- A single course of antenatal corticosteroids reduces respiratory distress syndrome, intraventricular haemorrhage, and neonatal mortality compared with placebo in babies born before 37 weeks' gestation.

  Adding TRH to corticosteroids has not been shown to improve outcomes compared with corticosteroids alone, and increases the risk of adverse effects.
- Antibiotics may prolong the pregnancy and reduce infection after premature rupture of the membranes, but are not beneficial when the membranes are intact.
- It is unclear if amnioinfusion for preterm rupture of membranes reduces preterm birth or neonatal mortality, as we found few RCTs.
- Calcium channel blockers may be effective at delaying labour compared with other tocolytics.

  Beta-mimetics and magnesium sulphate do not prevent premature birth, and may increase fetal and maternal adverse effects compared with placebo.

  Oxytocin receptor antagonists (such as atosiban) and prostaglandin inhibitors (such as indometacin) may prevent preterm delivery but we cannot be certain as we found few trials.

  Most tocolytic therapies don't prevent perinatal mortality or morbidity, although trials of these treatments are usually underpowered to detect clinically significant differences in these outcomes.
- Elective caesarean section increases maternal morbidity compared with selective caesarean section, but rates of neonatal morbidity and mortality seem equivalent.

DEFINITION

Preterm or premature birth is defined by the WHO as delivery of an infant before 37 completed weeks of gestation. [1] Clinically, deliveries under 34 weeks' gestation may be a more relevant definition. There is no set lower limit to this definition, but 23 to 24 weeks' gestation is widely accepted, [1] which approximates to an average fetal weight of 500 g.

INCIDENCE/ PREVALENCE

Preterm birth occurs in about 5% to 10% of all births in resource-rich countries, [2] [3] [4] but in recent years the incidence seems to have increased in some countries, particularly in the USA, [5] where the rate reached 12.7% in 2005. [6] We found little reliable evidence for incidence (using the definition of premature birth given above) in resource-poor countries. For example, the rate in northwestern Ethiopia has been reported to vary from 11% to 22% depending on the age group of mothers studied, and is highest in teenage mothers. [7]

AETIOLOGY/ RISK FACTORS

About 30% of preterm births are unexplained and spontaneous. [4] [8] [9] Multiple pregnancy accounts for about another 30% of cases. [4] [8] Other known risk factors include genital tract infection, preterm rupture of the membranes, antepartum haemorrhage, cervical incompetence, and congenital uterine abnormalities, which collectively account for about 20% to 25% of cases. The remaining cases (15–20%) are attributed to elective preterm delivery secondary to hypertensive disorders of pregnancy, intrauterine fetal growth restriction, congenital abnormalities, trauma, and medical dis-

orders of pregnancy. [4] [5] [8] [9] About 50% of women receiving placebo therapy do not give birth within 7 days from the start of treatment. This statistic could be interpreted as indicating either that a large proportion of preterm labour resolves spontaneously, or that there are inaccuracies in the diagnosis. The two strongest risk factors for idiopathic preterm labour are low socioeconomic status and previous preterm delivery. Women with a history of preterm birth had a significantly increased risk of subsequent preterm birth (before 34 weeks' gestation) compared with women who had previously given birth after 35 weeks' gestation (OR 5.6, 95% CI 4.5 to 7.0). [10]

PROGNOSIS

Preterm birth is the leading cause of neonatal death and infant mortality, often as a result of respiratory distress syndrome due to immature lung development. [11] Children who survive are also at high risk of neurological disability. [12] Observational studies have found that one preterm birth significantly raises the risk of another in a subsequent pregnancy. [13]

AIMS OF INTERVENTION

To prevent preterm birth; to prolong the interval between threatened preterm labour and delivery; to optimise the condition of the fetus in preparation for delivery in order to improve neonatal outcome; to minimise maternal morbidity; to minimise adverse effects of treatment.

OUTCOMES

Perinatal **mortality**, neonatal mortality, and **morbidity** (incidence of respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis, neonatal sepsis, and neonatal convulsions); maternal adverse effects, such as infection. Proxy outcomes include duration of pregnancy, number of hours or days between onset of labour and delivery, and incidence of **preterm delivery**. These proxy outcomes, particularly delaying delivery for at least 48 hours, are important markers for therapeutic success of several interventions as they allow for administration of antenatal corticosteroids. **Adverse effects**.

METHODS

Clinical Evidence search and appraisal June 2010. The following databases were used to identify studies for this systematic review: Medline 1966 to June 2010, Embase 1980 to June 2010, and The Cochrane Database of Systematic Reviews, May 2010 (online; 1966 to date of issue). When editing this review we used The Cochrane Database of Systematic Reviews 2010, Issue 3. An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, at least single blinded, and containing >20 individuals of whom >80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 34). The categorisation of the quality of the evidence (into high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of preventive interventions in women at high risk of preterm delivery?

OPTION PROGESTERONE

Mortality

Compared with placebo Progestational agents, including progesterone, seem no more effective at reducing neonatal or perinatal mortality (moderate-quality evidence).

Morbidity

Compared with placebo Progestational agents, including progesterone, may be more effective at decreasing the rate of necrotising enterocolitis in babies born to women with a history of spontaneous preterm birth, but we don't know whether they are more effective at decreasing other morbidity outcomes. Progestational agents, including

progesterone, may be more effective at decreasing the rate of neonatal sepsis in babies born to women with a short cervix identified on ultrasound, but we don't know whether they are more effective at reducing other morbidity outcomes. We don't know whether progestational agents, including progesterone, are more effective at reducing morbidity outcomes in babies born to women with a multiple pregnancy (low-quality evidence).

Preterm birth
Compared with placebo Progestational agents, including progesterone, seem more effective at prolonging pregnancy and lowering the rate of preterm birth in women with a history of prior preterm birth and with a short cervix, but they seem no more effective in women with multiple gestations (moderate-quality evidence).

For GRADE evaluation of interventions for preterm birth, see table, p 34 .

Benefits:

Progesterone versus placebo/no treatment/usual care:
We found two systematic reviews (search date 2008, 11 RCTs [14] [15] and search date 2009, 12 RCTs [16]), which pooled data, comparing progesterone versus placebo. The reviews identified 11 RCTs in common. The first systematic review presented the more complete analysis, and so we have reported the results of this review in full. However, we have also reported data from the second review in women with a history of spontaneous preterm birth, because it included one RCT that was subsequent to the first review, and provided additional data on the outcome of birth before 32 weeks. We found 4 subsequent RCTs — one RCT evaluating treatment for women with a singleton pregnancy with history of at least one spontaneous preterm birth [17] and three RCTs evaluating treatment for women with a multiple pregnancy. [18] [19] [20]

For women with a history of spontaneous preterm birth: The first systematic review found that, in women with a history of spontaneous preterm birth (4 RCTs, 1329 women), progesterone significantly reduced the rate of preterm birth both before 37 weeks' and 34 weeks' gestation compared with placebo (birth before 37 weeks' gestation: 4 RCTs, 1255 women; 252/705 [36%] with progesterone *v* 239/550 [43%] with placebo; RR 0.80, 95% CI 0.70 to 0.92; birth before 34 weeks' gestation: 1 RCT, 142 women; 2/72 [3%] with progesterone *v* 13/70 [18%] with placebo; RR 0.15, 95% CI 0.04 to 0.64). When a random effects model was used because of the considerable heterogeneity among the RCTs (no further information regarding reasons of heterogeneity given), the difference between groups was not significant for birth before 37 weeks' gestation (RR 0.68, 95% CI 0.45 to 1.02). [15] The review found that, compared with placebo, progesterone significantly reduced the risk of infant birth weight under 2500 g and necrotising enterocolitis (infant birth weight <2500 g: 2 RCTs, 501 infants; 86/324 [27%] with progesterone *v* 73/177 [41%] with placebo; RR 0.64, 95% CI 0.49 to 0.83; necrotising enterocolitis: 2 RCTs, 1070 infants; 3/615 [0.3%] with progesterone *v* 9/455 [2%] with placebo; RR 0.30, 95% CI 0.10 to 0.93). It found no significant difference between groups in perinatal mortality, neonatal death, respiratory distress syndrome, intraventricular haemorrhage, or neonatal sepsis (perinatal mortality: 3 RCTs, 1114 infants; 25/633 [4%] with progesterone *v* 29/481 [6%] with placebo; RR 0.65, 95% CI 0.38 to 1.11; neonatal death: 3 RCTs; 14/633 [2%] with progesterone *v* 18/481 [4%] with placebo; RR 0.56, 95% CI 0.28 to 1.10; respiratory distress syndrome: 2 RCTs, 1069 infants; 63/615 [10%] with progesterone *v* 59/454 [13%] with placebo; RR 0.79, 95% CI 0.56 to 1.10; intraventricular haemorrhage: 2 RCTs, 1070 infants; 3/614 [0.4%] with progesterone *v* 1/455 [0.2%] with placebo; RR 0.55, 95% CI 0.25 to 1.19; neonatal sepsis: 1 RCT; 9/306 [2.9%] with progesterone *v* 4/153 [2.6%] with placebo; RR 1.13, 95% CI 0.35 to 3.59).
The second review found that, in women with a history of spontaneous preterm birth, progesterone significantly reduced the rate of preterm birth before 32 weeks' gestation compared with placebo (3 RCTs, 1218 women; absolute results not reported; RR 0.61, 95% CI 0.45 to 0.82). [16]

The subsequent RCT (100 women with a history of at least one spontaneous preterm birth) compared vaginal micronised progesterone (100 mg) nightly from recruitment (20–24 weeks' gestation) until 36 weeks' gestation or delivery versus no progesterone. [17] The RCT found that progesterone significantly reduced rates of preterm birth at <37 weeks' gestation, but found no significant difference between groups in rates of preterm birth at 34 weeks or less (preterm birth <37 weeks' gestation: 6/50 [12%] with progesterone *v* 19/50 [38%] with no progesterone; RR 0.31, 95% CI 0.14 to 0.74; birth 34 weeks' gestation or less: 2/50 [4%] with progesterone *v* 3/50 [6%] with no progesterone; RR 0.67, 95% CI 0.12 to 3.82). The rate of preterm delivery at <37 weeks' gestation was particularly reduced in the subgroup of women with prior preterm birth at <30 weeks' gestation (post-hoc subgroup analysis in women with prior preterm birth at <30 weeks' gestation: birth <37 weeks' gestation: 3/28 [11%] with progesterone *v* 13/27 [48%] with no progesterone; P = 0.002). The RCT found no significant difference between groups in the rates of neonatal outcomes except for birth weight (which was a function of the prolonged gestational age at delivery). [17] It was unclear whether the assessors in this RCT were adequately blinded.

For women with a short cervix identified on ultrasound: The first review found that progesterone significantly reduced preterm birth before 34 weeks' gestation compared with placebo in women

with a short cervix (<15 mm) (1 RCT, 250 women; 26/125 [21%] with progesterone *v* 45/125 [36%] with placebo; RR 0.58, 95% CI 0.38 to 0.87). [15] The review also found that progesterone significantly decreased the rate of neonatal sepsis compared with placebo (1 RCT, 274 infants; 3/136 [2%] with progesterone *v* 11/138 [8%] with placebo; RR 0.28, 95% CI 0.08 to 0.97). [15] However, the review found no significant difference between groups in perinatal mortality, neonatal death, birth weight under 2500 g, respiratory distress syndrome, intraventricular haemorrhage, or necrotising enterocolitis (perinatal mortality: 1 RCT, 274 infants; 3/136 [2%] with progesterone *v* 8/138 [6%] with placebo; RR 0.38, 95% CI 0.10 to 1.40; neonatal death: 1 RCT, 274 infants; 2/136 [1%] with progesterone *v* 7/138 [5%] with placebo; RR 0.29, 95% CI 0.06 to 1.37; birth weight under 2500 g: 1 RCT, 274 infants; 56/136 [41%] with progesterone *v* 59/138 [43%] with placebo; RR 0.96, 95% CI 0.73 to 1.27; respiratory distress syndrome: 1 RCT, 274 infants; 11/136 [8%] with progesterone *v* 19/138 [14%] with placebo; RR 0.65, 95% CI 0.36 to 1.16; intraventricular haemorrhage: 1 RCT; 1/136 [0.7%] with progesterone *v* 2/138 [1.4%] with placebo; RR 0.51, 95% CI 0.05 to 5.53; necrotising enterocolitis: 1 RCT; 0/136 [0%] with progesterone *v* 1/138 [0.7%] with placebo; RR 0.34, 95% CI 0.01 to 8.23). [15]

For women with a multiple pregnancy: When assessing women with a multiple pregnancy, the first review found no significant difference between progesterone and placebo in perinatal mortality (although the trial was underpowered for this outcome), birth before 37 weeks' gestation, birth weight under 2500 g, respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis, or neonatal sepsis (perinatal mortality: 1 RCT, 154 infants; 4/78 [5%] with progesterone *v* 2/76 [3%] with placebo; RR 1.95, 95% CI 0.37 to 10.33; birth before 37 weeks' gestation: 2 RCTs, 732 women; 241/364 [66%] with progesterone *v* 241/368 [65%] with placebo; RR 1.01, 95% CI 0.92 to 1.12; birth weight under 2500 g: 1 large RCT, 1276 infants; 377/628 [60%] with progesterone *v* 415/648 [64%] with placebo; RR 0.94, 95% CI 0.86 to 1.02; respiratory distress syndrome: 1 RCT, 1270 infants; 96/632 [15%] with progesterone *v* 87/648 [13%] with placebo; RR 1.13, 95% CI 0.86 to 1.48; intraventricular haemorrhage: 1 RCT, 1270 infants; 7/632 [1.1%] with progesterone *v* 6/648 [0.9%] with placebo; RR 1.20, 95% CI 0.40 to 3.54; necrotising enterocolitis: 1 RCT, 1270 infants; 3/632 [0.1%] with progesterone *v* 4/648 [0.6%] with placebo; RR 0.77, 95% CI 0.17 to 3.42; neonatal sepsis: 1 RCT, 1270 infants; 24/632 [3.8%] with progesterone *v* 26/648 [4.0%] with placebo; RR 0.95, 95% CI 0.55 to 1.63). [15] The review found that progesterone significantly reduced the need for tocolysis compared with placebo (1 RCT, 654 women; 71/324 [22%] with progesterone *v* 97/330 [29%] with placebo; RR 0.75, 95% CI 0.57 to 0.97). [15]

One subsequent RCT (134 women, 402 infants) [18] compared progesterone versus placebo to prevent preterm birth in women pregnant with triplets. The RCT found no significant difference in rate of birth or fetal loss before 35 weeks' gestation (59/71 [83%] with progesterone *v* 53/63 [84%] with placebo; RR 1.0, 95% CI 0.9 to 1.1) or in the mean gestational age at delivery (mean: 32.4 weeks with progesterone *v* 33.0 weeks with placebo; P = 0.53). [18] There was also no significant difference between groups in neonatal outcomes such as neonatal death or respiratory distress syndrome (neonatal death: 5/212 [2%] with progesterone *v* 2/183 [1%] with placebo; RR 2.2, 95% CI 0.4 to 12.4; respiratory distress syndrome: 65/212 [31%] with progesterone *v* 50/183 [27%] with placebo; RR 1.1, 95% CI 0.7 to 1.8). [18]

A second subsequent RCT (500 women with twin gestation randomised, 494 women, 988 infants in analysis) compared daily vaginal progesterone gel (90 mg) versus vaginal placebo gel for 10 weeks from 24 weeks' gestation. The RCT found no significant difference between groups in the primary outcome of delivery or intrauterine death at <34 weeks (61/247 [25%] with progesterone *v* 48/247 [19%] with placebo; OR 1.36, 95% CI 0.89 to 2.09). [19] The RCT also carried out a prespecified subgroup analysis of this primary outcome in monochorionic and dichorionic twin gestations. It found a significantly increased risk of the primary outcome with progesterone in dichorionic twin gestations but found no significant difference between progesterone and placebo for the subgroup of women with monochorionic twin gestations. However, the RCT found no significant difference between monochorionic and dichorionic groups in its formal test of interaction, and commented that the significant result with dichorionic gestations should therefore be interpreted with caution. The RCT found no significant difference between groups in the secondary outcomes of number of neonatal deaths, rates of admission to the neonatal unit, or length of stay with the infants (neonatal death: P = 0.59; admission to the neonatal unit: P = 0.65; length of stay [for babies admitted to neonatal unit]: P = 0.45; absolute results reported in RCT).

A third subsequent RCT (30 women with twin gestation between 20 and 30 weeks, 60 infants) compared weekly intramuscular 17-hydroxyprogesterone caproate (250 mg) versus placebo. [20] The RCT found no significant difference in preterm birth at <37 weeks' gestation, birth at <35 weeks' gestation, neonatal death, respiratory distress syndrome, intraventricular haemorrhage, or necrotising enterocolitis (birth <35 weeks' gestation: 7/16 [44%] with progesterone *v* 11/14 [79%] with placebo; P = 0.117; birth <37 weeks' gestation: 14/16 [88%] with progesterone *v* 13/14 [93%] with placebo; P = 0.565; neonatal death: 2/32 [6%] with progesterone *v* 0/28 [0%] with placebo; P = 0.36; respiratory distress syndrome: 10/32 [31%] with progesterone *v* 9/28 [32%] with placebo; P = 0.84;

intraventricular haemorrhage: 3/32 [9%] with progesterone *v* 4/28 [14%] with placebo; P = 0.85; necrotising enterocolitis: 1/32 [3%] with progesterone *v* 0/28 [0%] with placebo; P = 0.95). [20]

Harms:

Progesterone versus placebo/no treatment/usual care:
The first review [15] and one subsequent RCT [20] gave no information on adverse effects of progesterone treatment.

The subsequent RCT (100 women with a history of at least one spontaneous preterm birth), which examined vaginal micronised progesterone, found that 28% of women using progesterone reported mild vaginal discharge and occasional irritation. However, it reported that speculum examination did not show signs of inflammation (no further details reported). [17]

The subsequent RCT (134 women, pregnant with triplets) found no significant difference between groups in adverse effects (69% with progesterone *v* 65% with placebo; RR 1.1, 95% CI 0.8 to 1.3; absolute numbers not reported). Adverse effects included pain, swelling, bruising, itching, or redness at the injection site. However, three women (2/71 [3%] with progesterone *v* 1/63 [1%] with placebo; P = 0.55) experienced severe adverse effects (including constitutional symptoms, elevated liver enzymes, and intense injection site reactions), so the injections were discontinued. [18]

The subsequent RCT (500 women with twin gestation), which compared vaginal progesterone gel with placebo gel, reported on a multitude of adverse effects in mothers. However, it found no significant difference between groups in any of these, except for nausea (proportion of women reporting nausea: 10/187 [5%] with progesterone *v* 22/191 [12%] with placebo; OR 0.43, 95% CI 0.20 to 0.94). [19]

Comment:

Although progestational agents have been shown to reduce preterm delivery in some high-risk women, only limited improvement in neonatal morbidity or mortality has been shown. For example, women with prior preterm birth or short cervix benefit from the therapy whereas women with multiple gestation have no benefit and potentially may have some increased risks in dichorionic twins, although those results should be interpreted with caution.

OPTION PROPHYLACTIC CERVICAL CERCLAGE IN WOMEN AT RISK OF PRETERM LABOUR WITH CERVICAL CHANGES (ULTRASOUND-INDICATED CERCLAGE)

Mortality
Compared with no cerclage We don't know whether cervical cerclage is more effective at reducing perinatal mortality (low-quality evidence).

Morbidity
Compared with no cerclage We don't know whether cervical cerclage is more effective at reducing neonatal morbidity (low-quality evidence).

Preterm birth
Compared with no cerclage Cerclage may be more effective at reducing delivery before 37 weeks' gestation, especially in women with prior preterm birth and cervical shortening, but we don't know whether it is more effective at reducing preterm delivery at other time points or in women with twin gestations (low-quality evidence).

For GRADE evaluation of interventions for preterm birth, see table, p 34 .

Benefits:

Prophylactic cervical cerclage versus no cerclage:
We found two systematic reviews (first review: search date 2002, 2 RCTs, 3 observational studies, and 1 retrospective cohort; 357 women with ultrasound findings of a short cervix 2.5 cm or less; dilation of internal os <2 cm, or funnelling >25%, but not beyond the external os; [21] second review: search date 2004, 4 RCTs; 607 women with ultrasound findings of a short cervix 2.5 cm or less [22]). The second systematic review also included an analysis of raw data. We found one subsequent RCT. [23]

The first systematic review [21] pooled the data from the two RCTs and three observational studies, and it also did a subgroup analysis on the two RCTs alone (149 women). It found no significant difference between cerclage and no cerclage in delivery before 34 weeks' gestation, neonatal mortality, preterm labour, neonatal morbidity, and gestational age at delivery (delivery before 34 weeks' gestation: RR 0.31, 95% CI 0.02 to 6.09; neonatal mortality: RR 0.55, 95% CI 0.07 to 4.10; preterm labour: RR 0.95, 95% CI 0.67 to 1.36; neonatal morbidity: RR 0.41, 95% CI 0.04 to 4.58; gestational age: WMD +2.25 weeks' gestation, 95% CI –2.45 weeks' gestation to +6.94 weeks' gestation). However, it noted significant heterogeneity in the pooled results for delivery before 34 weeks' gestation (P = 0.03), neonatal morbidity (P = 0.02), and gestational age of delivery (P = 0.01).

The second systematic review was limited to 4 RCTs. [22] It found a significant difference in delivery rate before 37 weeks' gestation with cerclage compared with no cerclage, especially in women with prior preterm birth and cervical shortening (133/305 [44%] with cerclage *v* 157/302 [52%] without cerclage; RR 0.84, 95% CI 0.71 to 0.99). It found no significant difference between cerclage and no cerclage in risk of birth before 24, 28, 32, 34, and 35 weeks' gestation, or in perinatal mortality (birth before 24 weeks' gestation: 14/305 [5%] with cerclage *v* 12/302 [4%] without cerclage; RR 1.15, 95% CI 0.53 to 2.49; before 28 weeks' gestation: 44/305 [14.4%] with cerclage *v* 43/302 [14.2%] without cerclage; RR 1.02, 95% CI 0.69 to 1.49; before 32 weeks' gestation: 65/305 [21%] with cerclage *v* 74/302 [25%] without cerclage; RR 0.87, 95% CI 0.65 to 1.16; before 34 weeks' gestation: 80/305 [26%] with cerclage *v* 90/302 [30%] without cerclage; RR 0.88, 95% CI 0.68 to 1.14; before 35 weeks' gestation: 89/305 [29%] with cerclage *v* 105/302 [35%] without cerclage; RR 0.84, 95% CI 0.67 to 1.06; perinatal mortality: 36/335 [11%] with cerclage *v* 27/333 [8%] without cerclage; RR 1.31, 95% CI 0.82 to 2.10). Subgroup analysis of the data for women with singleton pregnancies and a history of preterm birth indicated significantly lower delivery rates before 32, 35, and 37 weeks' gestation for women who had undergone cervical cerclage compared with those who had not (before 32 weeks' gestation: 17/107 [16%] with cerclage *v* 28/101 [28%] without cerclage; RR 0.58, 95% CI 0.34 to 0.98; before 35 weeks' gestation: 25/107 [23%] with cerclage *v* 39/101 [39%] without cerclage; RR 0.61, 95% CI 0.40 to 0.92; before 37 weeks' gestation: 41/107 [38%] with cerclage *v* 61/101 [60%] without cerclage; RR 0.63, 95% CI 0.48 to 0.85). In women with singleton pregnancies and a history of preterm birth, the review found no significant difference between cerclage and no cerclage in perinatal mortality or delivery at any other gestational age cut-off (perinatal mortality: 9/107 [8%] with cerclage *v* 14/101 [14%] without cerclage; RR 0.62, 95% CI 0.29 to 1.30). The systematic review found that, when limiting the analysis to twin gestations, there was a significant increase in preterm birth before 35 weeks' gestation and an insignificant trend to increasing perinatal mortality for cerclage compared with no cerclage (before 35 weeks' gestation: 18/24 [75%] with cerclage *v* 9/25 [36%] without cerclage; OR 2.15, 95% CI 1.15 to 4.01; perinatal mortality: 11/48 [23%] with cerclage *v* 3/50 [6%] without cerclage; OR 2.66, 95% CI 0.83 to 8.54). However, small sample size may limit the statistical power of these results.

The subsequent RCT (302 women) compared cerclage versus no cerclage in women who had a history of a prior spontaneous preterm birth (17–34 weeks' gestation) and had a cervical length <25 mm. [23] The RCT found no significant difference between groups in the primary outcome of birth at <35 weeks' gestation (32% with cerclage *v* 42% with no cerclage; OR 0.67, 95% CI 0.42 to 1.07, absolute numbers not reported). The RCT also stratified this analysis for women by cervical length. It found that cerclage significantly reduced birth at <35 weeks' gestation in women with cervical length <15 mm, but found no significant difference between groups in women with cervical length 15 mm to 24 mm (cervical length <15 mm: OR 0.23, 95% CI 0.08 to 0.66; cervical length 15–24 mm: OR 0.84, 95% CI 0.49 to 1.4; absolute results not reported). The RCT found that cerclage significantly reduced the prespecified secondary outcomes of preterm birth <37 weeks, previable birth (<24 weeks), and perinatal death (preterm birth <37 weeks: 66/148 [45%] with cerclage *v* 91/153 [60%] with no cerclage; P = 0.01; previable birth: 9/148 [6%] with cerclage *v* 21/153 [14%] with no cerclage; P = 0.03; perinatal death: 13/148 [9%] with cerclage *v* 25/153 [16%] with no cerclage; P = 0.046). [23] This RCT allowed the use of progesterone to prevent preterm birth. After 10 of the eventual 302 women were randomised, randomisation was stratified by the participant's stated intent to use progesterone to prevent preterm birth. In the analysis, however, intent to use progesterone did not affect the results (P = 0.94).

Harms:

Prophylactic cervical cerclage versus no cerclage:
The first review gave no information on adverse effects. [21]

The second review [22] found no significant difference in preterm rupture of membranes between cerclage and no cerclage (48/305 [16%] with cerclage *v* 50/302 [17%] without cerclage; OR 0.95, 95% CI 0.66 to 1.35). One of the included RCTs found that, compared with expectant management, cerclage significantly increased symptomatic vaginal discharge (8/127 [6%] with cerclage *v* 1/126 [1%] with expectant management; RR 7.87, 95% CI 1.00 to 62.04; P = 0.036). [24]

The subsequent RCT reported two complications with cerclage, one experienced chorioamnionitis and one experienced postoperative haemorrhage. There were two reported surgical anaesthetic complications. [23]

Comment:

Of the two systematic reviews, the review analysing all RCTs should take precedence when drawing conclusions. [22] These cerclages are now referred to as "ultrasound-indicated cerclage". The subsequent large RCT [23] demonstrates reduction in perinatal mortality, whereas the reviews did not. The size of the RCT, however, may drive the results of a future systematic review to demonstrate benefit in this outcome.

OPTION PROPHYLACTIC CERVICAL CERCLAGE IN WOMEN AT RISK OF PRETERM LABOUR WITH PROTRUDING MEMBRANES (EXAMINATION-INDICATED/RESCUE CERCLAGE)

Morbidity
Compared with bed rest Emergency cerclage may be more effective at reducing compound neonatal morbidity (defined as admission to NICU or death) in women with protruding membranes at or beyond the cervical os (low-quality evidence).

Preterm birth
Compared with bed rest Emergency cerclage seems more effective at reducing preterm delivery in women with membranes at or beyond the cervical os before 27 weeks' gestation (moderate-quality evidence).

For GRADE evaluation of interventions for preterm birth, see table, p 34 .

Benefits:

Prophylactic cervical cerclage versus bed rest:
We found one small RCT (23 women). [25] It found that, compared with bed rest, emergency cerclage significantly reduced delivery before 34 weeks' gestation and neonatal morbidity when membranes were at or beyond the cervical os before 27 weeks' gestation (23 women; delivery before 34 weeks' gestation: 7/13 [54%] with cerclage *v* 10/10 [100%] with bed rest; P = 0.02; compound neonatal morbidity [defined as admission to NICU or death]: 10/16 [63%] with cerclage *v* 14/14 [100%] with bed rest; RR 1.6, 95% CI 1.1 to 2.3). [25] The RCT found no significant difference in neonatal survival (9/16 [54%] with cerclage *v* 4/14 [29%] with bed rest; reported as not significant; P value not reported).

Harms:

Prophylactic cervical cerclage versus bed rest:
The RCT noted one woman in the cerclage group in whom the membranes ruptured during the procedure. Eight of the 13 women with cerclages had them removed owing to maternal or fetal indications, or both, at a mean of 24.7 weeks' gestation, and all 8 women delivered on the day of cerclage removal. Specific indications or any other information on adverse outcomes were not reported. [25]

Comment:

The findings of the small RCT of women with protruding membranes [25] corroborate those of two prospective cohort studies of 37 women [26] and 46 women, [27] which also demonstrated a significantly later gestational age at delivery in those with cerclage compared with those without cerclage. The more recent cohort study also found a higher live-birth rate and a lower preterm-delivery rate before 32 weeks' gestation in women with cerclage compared with controls. [27] These findings are promising, but should be confirmed owing to the small number of women in the studies.

OPTION ENHANCED ANTENATAL CARE FOR SOCIALLY DEPRIVED POPULATION GROUPS/HIGH-RISK GROUPS

Preterm birth
Compared with usual care Enhanced antenatal care seems no more effective at reducing preterm birth in women at high risk of preterm delivery (moderate-quality evidence).

For GRADE evaluation of interventions for preterm birth, see table, p 34 .

Benefits:

Enhanced antenatal care versus usual care:
We found no systematic review but found 11 RCTs. [28] [29] [30] [31] [32] [33] [34] [35] [36] [37] [38] All of the RCTs (carried out in Europe, USA, and Latin America; number of high-risk women ranging from 150 to 2200) found no significant difference in the reduction of preterm birth between enhanced antenatal care and usual antenatal care (see table 1, p 33). The definition of enhanced antenatal care varied between all studies. Examples included: increased numbers of antenatal visits, home visits by midwives, weekly cervical examination, fortnightly social-worker counselling sessions, nutritional education, peer-group education, and counselling by a psychologist.

Harms:

Enhanced antenatal care versus usual care:
The RCTs gave no information on adverse effects. [28] [29] [30] [31] [32] [33] [34] [35] [36] [37] [38]

Comment:

Some women at high risk of preterm birth are seen at decreased intervals in the outpatient setting, whereas many are seen at routine intervals but receive increased teaching about the warning signs of preterm labour. Women at high risk are often counselled to modify other risk behaviours, such as smoking and avoiding STDs. One problem with the methods used in these trials is the varied definition of enhanced antenatal care. Given these varied definitions, these data show no significant difference between any of the interventions and placebo in reducing the incidence of preterm birth in the various socially deprived or high-risk groups studied.

OPTION PROPHYLACTIC CERVICAL CERCLAGE IN WOMEN AT RISK OF PRETERM LABOUR WITH NO CERVICAL CHANGES (HISTORY-INDICATED CERCLAGE)

Mortality
Compared with no cerclage Cervical cerclage seems no more effective at reducing perinatal mortality in women at risk of preterm delivery and with an incompetent cervix, as determined by a history of late miscarriage (moderate-quality evidence).

Preterm birth
Compared with no cerclage We don't know whether cerclage is more effective at reducing preterm birth in women at risk of preterm delivery and with an incompetent cervix, as determined by a history of late miscarriage (low-quality evidence).

Elective cerclage compared with ultrasound surveillance We don't know whether elective cerclage is more effective at reducing deliveries before 37 weeks' gestation (low-quality evidence).

Note
Cervical cerclage has been associated with an increased rate of maternal infection.

For GRADE evaluation of interventions for preterm birth, see table, p 34 .

Benefits:

Prophylactic cervical cerclage versus no cerclage:
We found one systematic review (search date 2002, 4 RCTs, 2062 women) [39] of women with a history of incompetent cervix who either did not have an ultrasound assessment of the cervix, or in whom an ultrasound did not identify any cervical changes. The RCTs included women with twin or singleton pregnancies at risk of preterm delivery because of a history of late miscarriage. The systematic review found no significant difference between cerclage and no cerclage in birth before 24, 28, 32, or 37 weeks' gestation or in perinatal mortality (birth before 24 weeks' gestation: 3 RCTs; 46/767 [6%] with cerclage *v* 55/789 [7%] without cerclage; RR 0.86, 95% CI 0.59 to 1.25; before 28 weeks' gestation: 2 RCTs; 9/120 [8%] with cerclage *v* 10/144 [7%] without cerclage; RR 1.08, 95% CI 0.45 to 2.57; before 32 weeks' gestation: 3 RCTs; 18/388 [5%] with cerclage *v* 16/382 [4%] without cerclage; RR 1.29, 95% CI 0.67 to 2.14; before 37 weeks' gestation: 4 RCTs; 228/1035 [22%] with cerclage *v* 268/1027 [26%] without cerclage; RR 0.88, 95% CI 0.76 to 1.03; perinatal mortality: 4 RCTs; 24/1035 [2%] with cerclage *v* 31/1024 [3%] without cerclage; RR 0.80, 95% CI 0.48 to 1.36). However, it did find a significant reduction in birth rate before 33 weeks' gestation with cerclage compared with no cerclage (1 RCT; 83/647 [13%] with cerclage *v* 110/645 [17%] without cerclage; RR 0.75, 95% CI 0.58 to 0.98).

Elective cerclage compared with ultrasound surveillance:
One subsequent RCT (97 women) compared prophylactic elective cervical cerclage versus cervical ultrasound surveillance. [40] However, 28/52 (54%) of the ultrasound group later received a cerclage for cervical shortening. The RCT found no significant difference between prophylactic cerclage and ultrasound surveillance in median gestational age at delivery, early pregnancy loss before 25 weeks' gestation, or preterm delivery before 37 weeks' gestation (analysis by intention to treat; median gestation at delivery: 38 weeks for cerclage *v* 38 weeks for controls; P = 0.9; early pregnancy loss: 4/45 [9%] with cerclage *v* 5/52 [10%] with ultrasound surveillance; P = 0.7; delivery before 37 weeks' gestation: 9/45 [20%] with cerclage *v* 15/52 [25%] with ultrasound surveillance; P = 0.5). A subgroup analysis comparing outcomes in the 24 women randomised to ultrasound surveillance who did not go on to receive a cerclage versus outcomes in women receiving elective cerclage also yielded no significant difference between groups (reported as not significant; P value not reported). However, this analysis is likely to have been underpowered to detect clinically important differences between the groups.

Harms:

The systematic review found a significant increase in rate of maternal infection (defined as mild pyrexia) and composite minor maternal morbidity (defined as hospital admission and bed rest) after cerclage compared with no cerclage (maternal infection: 36/534 [7%] with cerclage *v* 14/549 [3%] without cerclage; RR 2.57, 95% CI 1.42 to 4.64; composite minor maternal morbidity: 245/743 [33%] with cerclage *v* 185/743 [25%] without cerclage; RR 1.32, 95% CI 1.13 to 1.55). [39] The subsequent RCT gave no information on adverse effects. [40]

Comment:

Although the review found a significant reduction in delivery before 33 weeks' gestation, no reduction was found in any other end points. This result could, therefore, be a statistical anomaly. The increased harms associated with the procedure in these women should be factored when considering these findings. Doubts remain about the effects of this intervention.

OPTION BED REST

Mortality
Compared with no intervention/usual care Hospitalised bed rest is no more effective than hospitalisation for routine care at reducing perinatal death in women with multiple gestations or uncomplicated twin pregnancies at 34 or 37 weeks' gestation, and it increases early neonatal death in women with uncomplicated twin pregnancies before 34 weeks' gestation (high-quality evidence).

Morbidity
Compared with cerclage Bed rest may be less effective than emergency cerclage at reducing compound neonatal morbidity (defined as admission to NICU or death) in women with protruding membranes at or beyond the cervical os (low-quality evidence).

Preterm birth
Compared with no intervention/usual care Bed rest, including hospitalised bed rest, is no more effective at reducing preterm births at 34 or 37 weeks' gestation in singleton, multiple gestation, or uncomplicated twin pregnancies, and it increases early preterm delivery before 34 weeks' gestation in uncomplicated twin pregnancies (high-quality evidence).

Compared with cerclage Bed rest seems less effective than emergency cerclage at reducing preterm delivery in women with membranes at or beyond the cervical os before 27 weeks' gestation (moderate-quality evidence).

For GRADE evaluation of interventions for preterm birth, see table, p 34 .

Benefits:

Bed rest versus no intervention/usual care:
We found one systematic review evaluating bed rest in singleton pregnancies at high risk for preterm birth (search date 2003, 1 RCT, 1266 women). [41] This was a cluster RCT with 5 different assigned groups. The included analysis compared 432 women assigned to bed rest with 834 other women (412 assigned to placebo [not further defined] and 422 assigned to no intervention). It found no significant difference in preterm birth before 37 weeks' gestation for bed rest compared with placebo or no intervention (34/432 [8%] with bed rest *v* 71/834 [9%] with placebo or no intervention; RR 0.92, 95% CI 0.62 to 1.37). No other outcomes were reported.

We also found a systematic review specifically evaluating hospitalised bed rest for multiple-gestation pregnancies (search date 2010, 7 RCTs, 713 women and 1452 babies). [42] It found no significant difference between routine hospitalisation for bed rest and hospitalisation for routine care in women with multiple gestations, in reducing delivery before 34 or 37 weeks' gestation, rates of perinatal mortality, or low birth weight (<2500 g) (delivery before 34 weeks' gestation: 5 RCTs; 50/210 [24%] with hospitalisation for bed rest *v* 39/214 [18%] with hospitalisation for routine care; RR 1.31, 95% CI 0.91 to 1.89; delivery before 37 weeks' gestation: 7 RCTs; 179/347 [52%] with hospitalisation for bed rest *v* 176/366 [48%] with hospitalisation for routine care; RR 0.99, 95% CI 0.86 to 1.13; perinatal mortality: 7 RCTs; 26/703 [4%] with hospitalisation for bed rest *v* 26/745 [3%] with hospitalisation for routine care; RR 1.06, 95% CI 0.42 to 2.64; low birth weight: 7 RCTs; 359/707 [51%] with hospitalisation for bed rest *v* 401/745 [54%] with hospitalisation for routine care; RR 0.92, 95% CI 0.85 to 1.00). The review found that bed rest significantly increased rate of spontaneous labour in multiple-gestation pregnancies compared with routine care (300/312 [96%] with hospitalisation for bed rest *v* 291/317 [92%] with hospitalisation for routine care; RR 1.05, 95% CI 1.02 to 1.09). The review further analysed outcomes for hospitalised bed rest in the subgroup of uncomplicated twin pregnancies. [42] It found no significant difference between hospitalisation for bed rest compared with routine care in delivery before 37 weeks' gestation, delivery before 34 weeks' gestation, early neonatal death, or in total perinatal mortality in this subgroup (delivery before 37 weeks: 4 RCTs; 117/264 [44%] with hospitalisation for bed rest *v* 108/284 [38%] with hospitalisation for routine care; RR 1.12, 95% CI 0.89 to 1.42; delivery before 34 weeks' gestation: 2 RCTs; 33/127 [26%] with hospitalisation for bed rest *v* 21/132 [16%] with hospitalisation for routine care; RR 1.57, 95% CI 0.72 to 3.43; early neonatal death: 4 RCTs; 11/528 [2%] with hospitalisation for bed rest *v* 4/568 [1%] with hospitalisation for routine care; RR 2.54, 95% CI 0.83 to 7.75; total perinatal mortality: 4 RCTs; 23/524 [4%] with hospitalisation for bed rest *v* 19/568 [3%] with hospitalisation for routine care; RR 1.64, 95% CI 0.45 to 6.08). However, it found that hospitalised bed rest for uncomplicated twin pregnancies significantly increased rates of very low birth weight (<1500 g) (very low birth weight: 4 RCTs; 29/528 [6%] with hospitalisation for bed rest *v* 17/568 [3%] with hospitalisation for routine care; RR 1.82, 95% CI 1.02 to 3.27). [42] The confidence intervals were too wide to adequately judge results analysed for triplet pregnancies.

Best rest versus prophylactic cerclage (in women with protruding membranes):
See benefits of prophylactic cerclage in women with protruding membranes, p 8 .

Harms:

Bed rest versus no intervention/usual care:
The systematic review regarding bed rest for singleton pregnancies gave no information on adverse effects. [41]

The systematic review regarding bed rest for multiple-gestation pregnancies found no significant differences between hospitalisation for bed rest and routine care in premature ruptured membranes, rate of caesarean delivery, Apgar scores of under 7, admission to the NICU, or nursery stay of >7 days. [42] For uncomplicated twin pregnancies, there were no significant differences in Apgar scores, admission to the NICU, or nursery stay of >7 days.

Best rest versus prophylactic cerclage (in women with protruding membranes):
See harms of prophylactic cerclage in women with protruding membranes, p 8 .

Comment: None.

QUESTION What are the effects of interventions to improve neonatal outcome after preterm rupture of membranes?

OPTION ANTIBIOTIC TREATMENT FOR PRETERM RUPTURE OF THE MEMBRANES

Mortality
Any antibiotic compared with placebo Antibiotic treatments may be no more effective at reducing perinatal mortality before discharge from hospital (very low-quality evidence).

Morbidity
Any antibiotic compared with placebo Antibiotics (including erythromycin, amoxicillin−clavulanic acid [co-amoxiclav], benzylpenicillin, ampicillin, piperacillin, and clindamycin) may be more effective at reducing the risk of neonatal infection, requirement for supplementary oxygen, surfactant use, and abnormal cerebral ultrasound (low-quality evidence).

Penicillins (excluding amoxicillin−clavulanic acid) compared with placebo Penicillin may be more effective at reducing the risk of neonatal infection and major cerebral abnormality on ultrasound. Mezlocillin may be more effective at reducing composite neonatal morbidity (infection, respiratory distress syndrome, grade III or IV intraventricular haemorrhage, and necrotising enterocolitis) (very low-quality evidence).

Amoxicillin−clavulanic acid compared with placebo Amoxicillin−clavulanic acid may be more effective at reducing the proportion of babies requiring supplementary oxygen; however, it increases the proportion of babies with necrotising enterocolitis (low-quality evidence).

Preterm birth
Any antibiotic compared with placebo Antibiotics (including erythromycin, amoxicillin–clavulanic acid [co-amoxiclav], benzylpenicillin, ampicillin, piperacillin, and clindamycin) may be more effective at reducing the proportion of babies born within 48 hours and within 7 days of treatment after preterm rupture of membranes (low-quality evidence).

Penicillins (excluding amoxicillin–clavulanic acid) compared with placebo Penicillins may be more effective at reducing the proportion of babies born within 48 hours and within 7 days after preterm premature rupture of membranes. Mezlocillin may be more effective at prolonging pregnancy by >7 days in women with preterm premature ruptured membranes (very low-quality evidence).

Amoxicillin−clavulanic acid compared with placebo Amoxicillin−clavulanic acid may be more effective at reducing the proportion of babies born within 48 hours and within 7 days of treatment after preterm premature rupture of membranes (low-quality evidence).

Erythromycin compared with placebo Erythromycin may be more effective at reducing the proportion of babies born within 48 hours and within 7 days of treatment after preterm premature rupture of membranes (low-quality evidence).

For GRADE evaluation of interventions for preterm birth, see table, p 34 .

Benefits:

Any antibiotic (analysed as a group) versus placebo:
One systematic review (search date 2004, 22 RCTs, >6000 women with rupture of membranes before 37 weeks' gestation) [43] found that antibiotics (including erythromycin, amoxicillin−clavulanic acid [co-amoxiclav], benzylpenicillin, ampicillin, piperacillin, and clindamycin) significantly reduced the proportion of babies born within 48 hours and within 7 days after preterm premature rupture of the membranes compared with placebo (within 48 hours: 7 RCTs; RR 0.71, 95% CI 0.58 to 0.87; within 7 days: 6 RCTs; RR 0.80, CI 0.71 to 0.90). It found that antibiotics significantly reduced neonatal infection, requirement for supplementary oxygen, surfactant use, and abnormal cerebral ultrasound compared with placebo (neonatal infection: 11 RCTs; RR 0.68, CI 0.53 to 0.87; requirement for supplementary oxygen: 1 RCT; RR 0.88, 95% CI 0.81 to 0.96; surfactant use: 1 RCT; RR

0.83, 95% CI 0.72 to 0.96; abnormal cerebral ultrasound: 12 RCTs; RR 0.82, 95% CI 0.68 to 0.98). It found no significant difference between antibiotics and placebo in perinatal mortality before discharge from hospital when additional data were included from 5 studies that were randomised but not placebo controlled (18 trials, 6951 babies; RR 0.87, 95% CI 0.72 to 1.05).

Penicillins (excluding amoxicillin−clavulanic acid) versus placebo:
The review found that any penicillin (except amoxicillin−clavulanic acid) significantly reduced the proportion of babies born within 48 hours and within 7 days of treatment compared with placebo (birth within 48 hours: 5 RCTs, 512 babies; RR 0.41, 95% CI 0.25 to 0.66; birth within 7 days: 3 RCTs, 220 babies; RR 0.68, 95% CI 0.56 to 0.82). [43] It found that penicillins significantly reduced neonatal infection and major cerebral abnormality on ultrasound before discharge (neonatal infection: 4 RCTs, 416 babies; RR 0.33, 95% CI 0.14 to 0.81; major cerebral abnormality: 3 RCTs, 267 babies; RR 0.49, 95% CI 0.25 to 0.97). We found one subsequent RCT (105 women) comparing mezlocillin versus placebo in women with preterm premature ruptured membranes. [44] It found a significant increase in the incidence of pregnancy prolonged by >7 days with mezlocillin compared with placebo (30/47 [64%] with mezlocillin *v* 26/58 [45%] with placebo; P <0.05). The RCT, which failed to state some of the methods used, reported significantly less composite neonatal morbidity (infection, respiratory distress syndrome, grade III or IV intraventricular haemorrhage, and necrotising enterocolitis) with mezlocillin compared with placebo (neonatal morbidity: 9/47 [19%] with mezlocillin *v* 23/58 [40%] with placebo; P = 0.02). [44]

Amoxicillin−clavulanic acid versus placebo:
The review found that amoxicillin−clavulanic acid significantly reduced the proportion of babies born within 48 hours and within 7 days of treatment compared with placebo (birth within 48 hours: 1 RCT, 2430 babies; RR 0.75, 95% CI 0.67 to 0.84; birth within 7 days: 1 RCT, 2430 babies; RR 0.91, 95% CI 0.85 to 0.97). It found that amoxicillin−clavulanic acid significantly reduced the proportion of babies requiring supplementary oxygen compared with placebo (1 RCT, 4809 babies; RR 0.80, CI 0.71 to 0.90). [43] The review found that amoxicillin−clavulanic acid significantly increased the proportion of babies with necrotising enterocolitis compared with placebo (2 RCTs, 2492 babies; RR 4.60, 95% CI 1.98 to 10.72). [43]

Erythromycin versus placebo:
The review found that erythromycin significantly reduced the proportion of babies born within 48 hours (2 RCTs, 2635 babies; RR 0.84, 95% CI 0.76 to 0.93). [43]

Harms:

Any antibiotic (analysed as a group) versus placebo:
The review gave no information on adverse effects of treatment for antibiotics. [43] We found one 7-year follow-up of an RCT included in the review. The RCT (3298 7-year-old children, born to 4148 women) compared erythromycin (375 mg) or amoxicillin−clavulanic acid (250 mg), or both, versus placebo for women with preterm rupture of the membranes without overt signs of clinical infections, and assessed the long-term effects on children of these interventions. [45] The RCT found no significant difference in the proportion of children born to mothers given erythromycin with or without amoxicillin−clavulanic acid for the composite outcome of mortality and any functional impairment (750/2323 [32%] with antibiotics *v* 827/2389 [35%] with placebo; OR 0.90, 95% CI 0.80 to 1.02), or after amoxicillin with or without erythromycin (808/2336 [35%] with antibiotics *v* 769/2376 [32%] with placebo; OR 1.11, 95% 0.98 to 1.25) compared with placebo. [45] There were no significant differences between groups at 7 years' follow-up in the proportion of children with respiratory problems with either erythromycin or amoxicillin−clavulanic acid compared with placebo (erythromycin: 305/1590 [19%] with erythromycin *v* 320/1671 [19%] with placebo; OR 1.00, 95% CI 0.84 to 1.19; amoxicillin−clavulanic acid: 309/1632 [19%] with amoxicillin−clavulanic acid *v* 316/1629 [19%] with placebo; OR 0.97, 95% CI 0.82 to 1.16). [45] The RCT also reported that children whose mothers had been exposed to amoxicillin−clavulanic acid were significantly more likely to suffer from bowel problems (including hospital admission for constipation, diarrhoea, stomach problems, or under the care of a doctor for bowel problems: RR 1.71, 95% CI 1.05 to 2.79) compared with placebo. [45]

Penicillins (excluding amoxicillin−clavulanic acid) versus placebo:
The review gave no information on adverse effects of treatment for antibiotics. [43] The subsequent RCT gave no information on adverse effects. [44]

Amoxicillin−clavulanic acid versus placebo:
The review gave no information on adverse effects of treatment for antibiotics. [43]

Erythromycin versus placebo:
The review gave no information on adverse effects of treatment for antibiotics. [43]

Comment: Most of the RCTs in the review did not include antenatal administration of corticosteroids, but 77% of the women in one large RCT (the ORACLE trial) received corticosteroids. [46] Most of the women in the review (>4800 women) came from this trial. All but one of the RCTs in the review gave data on the percentage of withdrawals, which was always under 20%. All women in the subsequent RCT received corticosteroids. [44] The subsequent RCT did not disclose randomisation technique or sample size calculations, but its results are consistent with the systematic review.

OPTION AMNIOINFUSION FOR PRETERM RUPTURE OF MEMBRANES

Mortality
Compared with no treatment/expectant management We don't know whether amnioinfusion is more effective than expectant management at reducing neonatal mortality (very low-quality evidence).

Preterm birth
Compared with no treatment/expectant management We don't know whether amnioinfusion is more effective than expectant management at prolonging pregnancy in women with oligohydramnios after preterm rupture of membranes (very low-quality evidence).

For GRADE evaluation of interventions for preterm birth, see table, p 34 .

Benefits:

Amnioinfusion versus no treatment/usual care:
We found one systematic review (search date 2001, 1 RCT, 66 women) [47] and two subsequent RCTs [48] [49] comparing amnioinfusion versus no amnioinfusion. The systematic review found no significant differences between amnioinfusion and no amnioinfusion in rates neonatal mortality (neonatal death: 1/29 [3%] with amnioinfusion *v* 2/32 [6%] with no amnioinfusion; RR 0.55, 95% CI 0.05 to 5.77). It also found no significant difference between amnioinfusion and no amnioinfusion in rates of caesarean section, low Apgar scores,or endometritis. [47]

The first subsequent RCT (34 women), comparing amnioinfusion with controls, found that, compared with expectant management, women with preterm ruptured membranes and oligohydramnios had a significantly reduced incidence of delivery within 7 days of treatment, increased mean rupture to delivery interval, and lower pulmonary hypoplasia (delivery within 7 days: 2/17 [12%] with amnioinfusion *v* 11/17 [65%] with expectant management; RR 0.18, 95% CI 0.04 to 0.69; rupture to delivery interval: 21 days with amnioinfusion *v* 8 days with expectant management; P <0.05; pulmonary hypoplasia: 2/17 [12%] with amnioinfusion *v* 9/17 [53%] with expectant management; RR 0.22, 95% CI 0.05 to 0.87). It found similar birth weight, rates of admission to the NICU, and abnormal neurological outcomes with both amnioinfusion and expectant management. [48]

The second subsequent RCT (60 women with singleton pregnancy) also compared amnioinfusion versus expectant management in women with preterm premature ruptured membranes (PPROM) and oligohydramnios (amniotic fluid index <5th percentile). [49] The RCT found no significant difference between groups in prolongation of pregnancy, mean gestational age at delivery, or birth weight (mean PPROM to delivery interval: 7.3 days with amnioinfusion *v* 6.7 days with expectant management; P = 0.75; gestational age at delivery: 222 days with amnioinfusion *v* 220 days with expectant management; P = 0.56; birth weight: 1.43 kg with amnioinfusion *v* 1.32 kg with expectant management; P = 0.28). [49] However, the RCT found that amnioinfusion significantly reduced neonatal deaths and early neonatal sepsis compared with expectant management (neonatal death: 5/30 [17%] with amnioinfusion *v* 19/30 [63%] with expectant management; P <0.01; early neonatal sepsis: 5/30 [17%] with amnioinfusion *v* 19/30 [63%] with expectant management; P <0.01). [49] It also found that amnioinfusion significantly reduced maternal postpartum sepsis compared with control (2/30 [7%] with amnioinfusion *v* 10/30 [33%] with expectant management; P = 0.02). [49]

Harms:

Amnioinfusion versus no treatment/usual care:
The RCT identified by the review and the first subsequent RCT gave no information on adverse effects. [47] [48] The second subsequent RCT noted fewer neonatal deaths and maternal cases of sepsis (see benefits section), but did not comment on other adverse effects. [49]

Comment: The RCT in the review was too small to detect clinically important changes in some of the outcomes (rates of caesarean section, neonatal mortality, and infectious morbidity) and had shortcomings in methods used (unspecified method of random assignment of women; blinding of treatment not possible). [47] Both subsequent RCTs used adequate methods. Notably, the subsequent RCTs only included women with oligohydramnios, and while the amnioinfusion was not standardised, investigators aimed to achieve an Amniotic Fluid Index at greater than the tenth centile and fifth centile, respectively. [48] [49] Further research is needed to confirm these findings.

QUESTION What are the effects of treatments to stop contractions in preterm labour?

OPTION CALCIUM CHANNEL BLOCKERS

Mortality

Compared with other tocolytics (analysed as a group) Calcium channel blockers and other tocolytics are equally effective at reducing perinatal mortality (high-quality evidence).

Compared with beta-mimetics We don't know how effective calcium channel blockers and beta-mimetics are, compared with each other, at reducing perinatal mortality (low-quality evidence).

Compared with magnesium sulphate Calcium channel blockers and magnesium sulphate seem equally effective at reducing perinatal mortality (moderate-quality evidence).

Morbidity

Compared with other tocolytics (analysed as a group) Calcium channel blockers are more effective at reducing neonatal morbidity, including respiratory distress syndrome, necrotising enterocolitis, and intraventricular haemorrhage (high-quality evidence).

Compared with beta-mimetics We don't know how effective calcium channel blockers and beta-mimetics are, compared with each other, at reducing neonatal morbidity outcomes including proportion of infants transferred to ICU, respiratory distress syndrome, infection, or longer-term childhood outcomes measured at 2 years after birth (low-quality evidence).

Compared with magnesium sulphate Calcium channel blockers and magnesium sulphate seem equally effective at reducing a composite morbidity outcome including respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis, sepsis, and fetal or neonatal mortality (moderate-quality evidence).

Preterm birth

Compared with placebo We don't know whether nifedipine is more effective at reducing delivery within 48 hours or at delaying delivery beyond 36 weeks, in women with preterm labour and single gestations between 30 and 34 weeks (very low-quality evidence).

Compared with other tocolytics (analysed as a group) Calcium channel blockers are more effective at reducing deliveries before 34 weeks' gestation, and within 7 days of treatment, but not within 48 hours of treatment (high-quality evidence).

Compared with beta-mimetics Nifedipine may be more effective at reducing delivery within 48 hours (low-quality evidence).

Compared with atosiban We don't know how effective nifedipine and atosiban are, compared with each other, at increasing the proportion of women with delivery delayed by 48 hours or 7 days (moderate-quality evidence).

Compared with magnesium sulphate We don't know how effective nifedipine and magnesium sulphate are, compared with each other, at delaying pregnancy by 48 hours or in reducing delivery before 32 weeks (moderate-quality evidence).

Adverse effects

Calcium channel blockers are more effective than other tocolytics (mainly beta-mimetics) at reducing withdrawals caused by adverse effects.

For GRADE evaluation of interventions for preterm birth, see table, p 34 .

Benefits:

We found one RCT comparing calcium channel blockers versus placebo. [50] We found one systematic review (search date 2002, 12 RCTs, 1029 women) [51] and 7 subsequent RCTs comparing calcium channel blockers versus other tocolytics. [52] [53] [54] [55] [56] [57] [58]

Calcium channel blockers versus placebo:

The RCT (89 women with preterm labour, singleton gestations between 30 to 34 weeks) compared calcium channel blockers versus placebo. [50] The RCT found that, compared with placebo, calcium channel blockers (nifedipine) had fewer deliveries within 48 hours (8/45 [18%] with nifedipine *v* 39/44 [89%] with placebo; significance assessment for this outcome not reported). However, it found similar rates of deliveries delayed beyond 36 weeks' gestation between groups (2/45 [4%] with nifedipine *v* 0/44 [0%] with placebo, significance assessment for this outcome not reported). [50] No neonatal outcomes were reported. It was unclear whether this RCT was adequately blinded.

Calcium channel blockers versus other tocolytics (analysed as a group):
The systematic review found that, compared with other tocolytics, calcium channel blockers significantly reduced delivery within 7 days and before 34 weeks' gestation (delivery within 7 days: 4 RCTs, 453 women; 71/229 [31%] with calcium channel blocker *v* 86/224 [38%] with other tocolytics; RR 0.76, 95% CI 0.60 to 0.97; delivery before 34 weeks' gestation: 6 RCTs, 619 women; 107/311 [34%] with calcium channel blocker *v* 122/308 [40%] with other tocolytics; RR 0.83, 95% CI 0.69 to 0.99). It found no significant difference between calcium channel blockers and other tocolytics in delivery within 48 hours; however, this was lower with calcium channel blockers (delivery within 48 hours: 9 RCTs, 761 women; 74/383 [19%] with calcium channel blocker *v* 87/378 [23%] with other tocolytics; RR 0.80, 95% CI 0.61 to 1.05). It found that calcium channel blockers significantly reduced neonatal morbidity, including respiratory distress syndrome, necrotising enterocolitis, and intraventricular haemorrhage (respiratory distress syndrome: 9 RCTs, 763 newborns; 48/386 [12%] with calcium channel blocker *v* 72/377 [19%] with other tocolytics; RR 0.63, 95% CI 0.46 to 0.88; necrotising enterocolitis: 3 RCTs, 323 newborns; 1/166 [0.6%] with calcium channel blocker *v* 8/157 [5%] with other tocolytics; RR 0.21, 95% CI 0.05 to 0.96; intraventricular haemorrhage: 3 RCTs, 340 newborns; 19/173 [11%] with calcium channel blocker *v* 31/167 [19%] with other tocolytics; RR 0.59, 95% CI 0.36 to 0.98). It found no significant differences in perinatal mortality (10 RCTs, 810 newborns; 13/400 [3%] with calcium channel blocker *v* 7/410 [2%] with other tocolytics; RR 1.65, 95% CI 0.74 to 3.64). [51]

Calcium channel blockers versus beta-mimetics:
When the review analysis was limited to nifedipine compared with beta-mimetics, the resulting maternal benefits were similar, with the exception that nifedipine significantly reduced birth within 48 hours compared with beta-mimetics (6 RCTs, 470 women; 55/242 [23%] with nifedipine *v* 71/228 [31%] with beta-mimetics; RR 0.72, 95% CI 0.53 to 0.97). However, the review found no significant difference between groups in neonatal mortality (8 RCTs, 592 women; 13/304 [4%] with nifedipine *v* 8/288 [3%] with beta-mimetics; RR 1.40, 95% CI 0.63 to 3.12). [51]

However, the first, second, and third subsequent RCTs found no significant difference in delay of delivery by 48 hours between calcium channel blockers and beta-mimetics (first RCT: 22/31 [71%] with nifedipine *v* 23/30 [77%] with ritodrine; P >0.05; [52] second RCT: 26/32 [81%] with nifedipine *v* 21/30 [70%] with isoxsuprine; P = 0.30; [53] third RCT: 48 women randomised, 45 women in analysis: 88% with nicardipine *v* 86% with salbutamol, absolute results not reported; P >0.05). [54] The third RCT found no significant difference between groups in neonatal outcomes (perinatal mortality: 0/24 [0%] with nicardipine *v* 1/21 [5%] with salbutamol; P >0.05; proportion of infants transferred to intensive care unit: 6/24 [25%] with nicardipine *v* 4/21 [19%] with salbutamol; P >0.05). [54] The third RCT did not describe whether assessors were blinded; however, it commented that it was not double-blind because of the well-known adverse effects of both treatments.

The fourth subsequent RCT (93 women) comparing nifedipine versus ritodrine also found no significant difference between groups in rates of delayed delivery for 48 hours, delayed for 7 days, and after 34 weeks' gestation (delayed for 48 hours: 36/48 [75%] with nifedipine *v* 33/43 [77%] with ritodrine; P = 1.0; delayed for 7 days: 33/48 [69%] with nifedipine *v* 25/43 [58%] with ritodrine; P = 0.6; after 34 weeks' gestation: 28/48 [58%] with nifedipine *v* 20/43 [46%] with ritodrine; P = 0.5). [55] The RCT found no significant differences between the groups for any neonatal outcomes, including respiratory distress syndrome, infection, or longer-term childhood outcomes measured at 2 years after birth (respiratory distress syndrome: 3/48 [6%] with nifedipine *v* 3/43 [7%] with ritodrine; P = 0.5; infection: 5/48 [10%] with nifedipine *v* 4/43 [10%] with ritodrine; P = 0.5; longer-term childhood outcomes measured at 2 years after birth: P = 0.9; no further data reported). [55]

Calcium channel blockers versus atosiban:
The fifth subsequent RCT found no significant difference between nifedipine and atosiban in the proportion of women with delivery delayed by 48 hours or 7 days (delayed by 48 hours: 30/40 [75%] with nifedipine *v* 33/40 [83%] with atosiban; P value not significant; delayed by 7 days: 26/40 [65%] with nifedipine *v* 30/40 [75%] with atosiban; P value not significant). [56]

Calcium channel blockers versus magnesium sulphate:
The sixth and seventh subsequent RCTs both compared nifedipine versus magnesium sulphate. [57] [58] The sixth subsequent RCT (192 women) found that nifedipine significantly decreased the rate of delay of delivery by 48 hours compared with magnesium sulphate (72/100 [72%] with nifedipine *v* 80/92 [87%] with magnesium sulphate; P = 0.01), even when excluding twins and women with ruptured membranes. [57] The RCT found no significant difference between groups in delivery before 32 weeks' gestation (7/100 [7%] with nifedipine *v* 10/92 [11%] with magnesium sulphate; P = 0.39) or before 37 weeks' gestation (52/100 [52%] with nifedipine *v* 50/92 [54%] with magnesium sulphate; P = 0.97), the mean estimated gestational age at delivery (36 weeks with nifedipine *v* 35.8 weeks with magnesium sulphate; P = 0.61), or the number of episodes of recurrent preterm labour (P = 0.32). [57] The RCT found no significant difference between groups in the

composite outcome of neonatal morbidity, birth weight of under 2500 g, respiratory distress syndrome, sepsis, and mortality (neonatal morbidity including respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis, sepsis, and fetal or neonatal mortality: 22/110 [20%] with nifedipine *v* 27/106 [25%] with magnesium sulphate; P = 0.32; birth weight of under 2500 g: 46/110 [42%] with nifedipine *v* 52/106 [49%] with magnesium sulphate; P = 0.48; respiratory distress syndrome: 21/110 [19%] with nifedipine *v* 24/106 [23%] with magnesium sulphate; P = 0.48; sepsis: 3/110 [3%] with nifedipine *v* 5/106 [5%] with magnesium sulphate; P = 0.43; mortality: 0/110 [0%] with nifedipine *v* 1/106 [1%] with magnesium sulphate; P = 0.31). The RCT found nifedipine significantly decreased the rate of NICU admission compared with magnesium sulphate (41/110 [37%] with nifedipine *v* 55/106 [52%] magnesium sulphate; P = 0.04). [57]

The seventh subsequent RCT (120 women) found no significant difference between nifedipine and magnesium sulphate in the proportion of women who did not deliver or require a different medication in the first 48 hours (22/57 [39%] with nifedipine *v* 31/63 [49%] with magnesium sulphate, ARR –10%, 95% CI –28% to –7%) or in mean gestational age at delivery (mean: 34.3 weeks with nifedipine *v* 34.1 weeks with magnesium sulphate, ARR –0.20 weeks, 95% CI –0.72 weeks to –0.32 weeks). [58]

Harms:

Calcium channel blockers versus placebo:
The RCT found a higher rate of adverse effects with nifedipine compared with placebo (proportion of women reporting adverse effects: 25/45 [55%] with nifedipine *v* 0/44 [0%] with placebo). The most commonly reported adverse effect with nifedipine was flushing (40%). [50]

Calcium channel blockers versus other tocolytics (analysed as a group):
The review found that calcium channel blockers significantly reduced discontinuation caused by adverse effects compared with other tocolytics (10 RCTs, 833 women; 1/419 [0.2%] with calcium channel blocker *v* 29/414 [7%] with other tocolytics; RR 0.14, 95% CI 0.05 to 0.36). [51] The review did not report specific adverse effects of calcium channel blockers. [51]

Calcium channel blockers versus beta-mimetics:
The effect of reduced discontinuation caused by adverse effects, noted by the review, [51] was more pronounced when the comparison was limited to calcium channel blockers versus beta-mimetic agents (withdrawals: 7 RCTs, 542 women; 0/278 [0%] with calcium channel blockers *v* 19/264 [7%] with beta-mimetics; RR 0.09, 95% CI 0.02 to 0.38). [51] A follow-up analysis of an RCT identified by the review found significantly lower mean diastolic blood pressure, increased mean fasting glucose, and a lower potassium level after 48 hours' treatment with ritodrine compared with nifedipine (diastolic blood pressure: 71 mmHg with nifedipine *v* 65 mmHg with ritodrine; P = 0.004; fasting glucose level: 4.93 mmol/L with nifedipine *v* 6.68 mmol/L with ritodrine; P <0.001; potassium level: 3.81 mmol/L with nifedipine *v* 3.52 mmol/L with ritodrine; P = 0.04). [59]

The first subsequent RCT comparing nifedipine versus ritodrine found that ritodrine significantly increased the proportion of women with adverse effects compared with nifedipine (87% with ritodrine *v* 26% with nifedipine; P <0.05), with palpitations and tachycardia being the most common adverse effects reported. In women taking nifedipine, the most common adverse effects reported were hypotension and vertigo (hypotension: 11/40 [28%]; vertigo: 9/40 [23%]). [52] The second subsequent RCT comparing nifedipine versus isoxsuprine noted similar rates of medication discontinuation for nifedipine compared with isoxsuprine (2/32 [6.3%] with nifedipine *v* 2/30 [6.7%] with isoxsuprine), mostly because of hypotension. [53] The third RCT found significantly fewer adverse effects with nifedipine compared with salbutamol (proportion of women with adverse effects: 2/25 [8%] with nifedipine *v* 11/23 [48%] with salbutamol; P = 0.02). [54] The fourth subsequent RCT found a significantly lower rate of adverse effects with nifedipine compared with ritodrine, but a similar number of severe adverse effects (adverse effects: 2/48 [4%] with nifedipine *v* 2/43 [29%] with ritodrine; P <0.05; severe adverse effects: 1/48 [2%] with nifedipine *v* 2/43 [5%] with ritodrine; P = 0.1). [55]

Calcium channel blockers versus atosiban:
The fifth subsequent RCT noted significantly greater cumulative adverse effects with nifedipine compared with atosiban (16/40 [40%] with nifedipine *v* 7/40 [18%] with atosiban; P = 0.027). [56]

Calcium channel blockers versus magnesium sulphate:
The sixth subsequent RCT found significantly fewer adverse effects with nifedipine compared with magnesium sulphate (any adverse effects: 34/100 [34%] with nifedipine *v* 60/92 [65%] with magnesium sulphate; P <0.001; serious adverse effects: 10/100 [10%] with nifedipine *v* 20/92 [22%] with magnesium sulphate; P = 0.03). [57]

The seventh subsequent RCT noted a similar rate of adverse effects with nifedipine compared with magnesium sulphate (7/57 [12%] with nifedipine *v* 8/63 [13%] with magnesium; difference –0.4, 95% CI –12.3 to +11.4). [58]

Comment: The new RCT comparing nifedipine versus placebo is the first placebo-controlled trial for calcium channel blockers that we have identified in the tocolytic literature. [50]

Some of the conclusions of the three subsequent RCTs [52] [53] [54] comparing nifedipine with beta-mimetics are limited, owing to insufficiently documented randomisation methods, but are included for completeness.

We found one systematic review (58 RCTs, 7176 women) comparing tocolytic drugs (including beta-mimetics, calcium channel blockers, magnesium sulphate, oxytocin inhibitors, and prostaglandin inhibitors) versus each other or placebo. [60] Data were extracted for the following outcomes: delay of delivery for 48 hours, 7 days, and until 37 weeks' gestation; adverse effects causing discontinuation of treatment; absence of respiratory distress syndrome; and neonatal survival. These data were then combined by drug category to calculate weighted mean and standard error for proportions of successful outcomes for all treatments included in studies. As the review aggregated data from individual trials according to treatment group, effectively disassembling the trials, weighted proportions were generated based on the number of people in each study group (the total number of individual participants across all the relevant trials for each comparison). Disassembling the trials precluded direct comparisons required for odds ratios, so they are not reported. It is also noteworthy that the indirect comparisons reported by the review remove the benefits of randomisation of the original trials, which may bias the results. The percentage of women with a successful delay of delivery by 48 hours was 53% with control/placebo and 76% with calcium channel blockers. The percentage of women with successful delay of labour until 37 weeks' gestation was 36% with control/placebo and 47% with calcium channel blockers. Neonatal mortality was 2% with placebo and 1% with calcium channel blockers. Overall rates for adverse effects were 1% in both groups. [60]

OPTION OXYTOCIN RECEPTOR ANTAGONISTS

Mortality
Compared with beta-mimetics Atosiban and beta-mimetics seem equally effective at reducing perinatal mortality (moderate-quality evidence).

Preterm birth
Compared with placebo Atosiban is more effective at increasing the proportion of women with preterm labour undelivered without needing to use an alternative tocolytic at 24 hours, 48 hours, and 7 days after starting treatment. Atosiban is also more effective at prolonging pregnancies over 28 weeks' gestation for up to 24 hours, 48 hours, and 7 days (high-quality evidence).

Compared with beta-mimetics Atosiban and beta-mimetics are equally effective at reducing the proportion of women with delivery before 37 weeks' gestation, or birth within 48 hours or 7 days of initiation of treatment (high-quality evidence).

Compared with calcium channel blockers We don't know how effective nifedipine and atosiban are, compared with each other, at increasing the proportion of women with delivery delayed by 48 hours or 7 days (moderate-quality evidence).

Adverse effects
Compared with placebo Atosiban is more likely to cause adverse effects, such as nausea and injection-site reactions, and is also more likely to lead to stopping of treatment because of adverse effects (high-quality evidence).

Note
We found no clinically important results from RCTs about the effects of oxytocin receptor antagonists other than atosiban.

For GRADE evaluation of interventions for preterm birth, see table, p 34 .

Benefits: **Atosiban versus placebo:**
We found two systematic reviews (search date 1998, 2 RCTs; [61] search date 2004, 2 RCTs [62]) comparing atosiban versus placebo. Both the reviews reported on the same two trials, but with some different outcome measures.

The first RCT identified by the reviews found no significant difference between atosiban (300 micrograms/minute for 2 hours) and placebo in premature delivery, although there was an increase in delivery within 48 hours in women taking atosiban (5/56 [9%] with atosiban *v* 2/56 [4%] with placebo; RR 2.50, 95% CI 0.51 to 12.35). [63] However, as noted by the study author, the trial was a dose-finding study and not an efficacy trial, and many of the doses were lower than those currently recommended.

The second, larger RCT identified by the reviews found that atosiban significantly increased the proportion of women undelivered without needing to use an alternative tocolytic at 24 hours, 48 hours, and 7 days (501 women with preterm labour diagnosed by uterine contractions and cervical changes at 20–33 weeks' gestation; undelivered at 24 hours: 179/246 [73%] with atosiban *v* 148/255 [58%] with placebo; OR 1.93, 95% CI 1.30 to 2.86; undelivered at 48 hours: 165/246 [67%] with atosiban *v* 124/255 [49%] with placebo; OR 1.62, 95% CI 1.10 to 2.37; undelivered at 7 days: 153/246 [62%] with atosiban *v* 125/254 [49%] with placebo; OR 1.70, 95% CI 1.17 to 2.46). [64] It found no significant difference between atosiban and placebo in the median time to delivery (25.6 days with atosiban *v* 21.0 days with placebo; reported as not significant; P value not reported). For pregnancies over 28 weeks' gestation, it found that, compared with placebo, atosiban significantly prolonged pregnancy for up to 24 hours, 48 hours, and 7 days (424 pregnancies; delay up to 24 hours: 150/203 [74%] with atosiban *v* 128/221 [58%] with placebo; RR 1.28, 95% CI 1.11 to 1.47; NNT 7, 95% CI 4 to 15; delay up to 48 hours: 140/203 [69%] with atosiban *v* 122/221 [55%] with placebo; RR 1.25, 95% CI 1.08 to 1.45; NNT 8, 95% CI 5 to 23; delay up to 7 days: 131/203 [65%] with atosiban *v* 105/220 [48%] with placebo; RR 1.35, 95% CI 1.14 to 1.60; NNT 6, 95% CI 4 to 14).

Atosiban versus beta-mimetics:
We found one systematic review (search date 2004) [62] and two subsequent RCTs [65] [66] comparing atosiban versus beta-mimetics.

The systematic review found no significant difference between atosiban and beta-mimetics in perinatal mortality, delivery before 37 weeks' gestation, and birth within 48 hours or 7 days of initiation of treatment (perinatal mortality: 3 RCTs; 6/405 [1%] with atosiban *v* 10/431 [2%] with beta-mimetics; RR 0.66, 95% CI 0.24 to 1.83; delivery before 37 weeks' gestation: 1 RCT; 60/115 [52%] with atosiban *v* 75/129 [58%] with beta-mimetics; RR 0.90, 95% CI 0.71 to 1.13; birth within 48 hours: 4 RCTs; 58/604 [10%] with atosiban *v* 49/429 [11%] with beta-mimetics; RR 0.98, 95% CI 0.68 to 1.41; birth within 7 days: 3 RCTs; 73/360 [20%] with atosiban *v* 83/371 [22%] with beta-mimetics; RR 0.91, 95% CI 0.69 to 1.20). [62] The review also found no significant difference in any neonatal outcomes between atosiban and other tocolytics, with the exception of significantly more infants weighing under 1500 g in women receiving atosiban (2 RCTs; 46/384 [12%] with atosiban *v* 16/191 [8%] with beta-mimetics; RR 1.96, 95% CI 1.15 to 3.35). [62] An analysis of the pooled data from three RCTs included in the systematic review found no significant difference in perinatal mortality between atosiban and beta-mimetics (14.7/1000 with atosiban *v* 27.7/1000 with beta-mimetics; P value not reported). [67] It also found that significantly fewer women receiving atosiban than beta-mimetics needed to use an alternative tocolytic (134/361 [37%] with atosiban *v* 173/372 [46%] with beta-mimetics; P = 0.01). The analysis of the pooled data from three RCTs also contained a subgroup analysis of women with twin gestations. [67] It found that, in this subgroup, atosiban was significantly less effective than beta-mimetics in delaying delivery by 48 hours, but it found no significant difference between groups in delivery at 7 days (undelivered at 48 hours: 33/44 [75%] with atosiban *v* 56/60 [93%] with beta-mimetics; OR 0.21, CI not estimable; P = 0.003; undelivered at 7 days: 27/44 [61%] with atosiban *v* 46/60 [77%] with beta-mimetics; OR 0.24, 95% CI 0.05 to 1.13). [67]

The first subsequent RCT (128 women) found no significant difference between atosiban and ritodrine in the proportion of women undelivered at 48 hours or at 7 days, although more women in the atosiban group were both undelivered and did not require an alternative tocolytic at 7 days (undelivered at 48 hours: 58/63 [92%] with atosiban *v* 59/63 [94%] with ritodrine; OR 0.79, 95% CI 0.20 to 3.08; undelivered at 7 days: 57/63 [90%] with atosiban *v* 56/63 [89%] with ritodrine; OR 1.19, 95% CI 0.38 to 3.75; undelivered and no alternative tocolytic at 7 days: 38/63 [60%] with atosiban *v* 22/63 [35%] with ritodrine; OR 2.83, 95% CI 1.37 to 5.84). [65] The RCT found no significant difference in neonatal morbidity (including infection, intraventricular haemorrhage, and respiratory distress syndrome) between atosiban and ritodrine (reported as not significant; significance assessment not reported).

The second subsequent open-label RCT (45 women) compared atosiban versus ritodrine. It found no significant difference between groups in the proportion of women undelivered at 48 hours, undelivered at 7 days, or any neonatal outcomes (undelivered at 48 hours: 19/23 [83%] with atosiban *v* 19/22 [86%] with ritodrine; P = 1.00; undelivered at 7 days: 18/23 [78%] with atosiban *v* 19/22 [86%] with ritodrine; P = 0.70; respiratory distress syndrome: 0/23 [0%] with atosiban *v* 1/22 [5%] with ritodrine; P = 0.49). [66] We have included this RCT despite it being open label — blinding would have been difficult because of potential differences in adverse effects between groups.

Atosiban versus calcium channel blockers:
See benefits of calcium channel blockers, p 14 .

Harms:

Atosiban versus placebo:

Maternal adverse effects: The first review found that atosiban significantly increased nausea compared with placebo, but it found no significant difference in vomiting (nausea: 2 RCTs; 33/306 [11%] with atosiban *v* 15/307 [5%] with placebo; OR 2.3, 95% CI 1.3 to 4.1; vomiting: 2 RCTs; 10/306 [3%] with atosiban *v* 13/307 [4%] with placebo; OR 0.8, 95% CI 0.3 to 1.8). [61] Atosiban significantly reduced chest pain and dyspnoea compared with placebo (chest pain: 2 RCTs; 3/306 [1%] with atosiban *v* 13/307 [4%] with placebo; OR 0.3, 95% CI 0.1 to 0.8; dyspnoea: 1 RCT; 1/250 [0.4%] with atosiban *v* 7/251 [2.8%] with placebo; OR 0.22, 95% CI 0.05 to 0.89). The subsequent full report of one of the included RCTs found that atosiban significantly increased injection-site reactions after prolonged use, and significantly increased withdrawal caused by adverse effects (injection-site reaction: 110/250 [44%] with atosiban *v* 58/251 [23%] with placebo; RR 1.90, 95% CI 1.46 to 2.48; NNH 4, 95% CI 3 to 7; withdrawal: 16% with atosiban *v* 4% with placebo). [64] The second review found that, overall, atosiban caused significantly more maternal adverse effects requiring stopping of treatment compared with placebo (40/306 [13%] with atosiban *v* 10/307 [3%] with placebo; RR 4.02, 95% CI 2.05 to 7.85). [62]

Neonatal adverse effects: Analysis by gestational age at admission found that all the excess mortality with atosiban occurred in pregnancies before 26 weeks' gestation (mortality in pregnancies <26 weeks' gestation: 10/27 [37%] with atosiban *v* 0/16 [0%] with placebo). [64] This difference may, therefore, be a spurious finding that can be explained by the study design (see comment).

Atosiban versus beta-mimetics:

Maternal adverse effects: The review reported significantly fewer maternal adverse effects requiring stopping of treatment with atosiban compared with beta-mimetics (4/604 [1%] with atosiban *v* 75/430 [17%] with beta-mimetics; RR 0.04, 95% CI 0.02 to 0.11). [62] The first subsequent RCT also found that atosiban caused significantly lower rates of adverse effects than ritodrine (5/63 [8%] with atosiban *v* 46/65 [71%] with ritodrine; P <0.001). [65] The second small subsequent RCT found no significant difference between groups in maternal adverse effects (defined as any except tachycardia; 3/23 [13%] with atosiban *v* 4/22 [18%] with ritodrine; P = 0.7). It found no significant difference between groups in tachycardia (defined as heart rate >120 bpm); however, it found that ritodrine significantly increased the proportion of women with heart rate >100 bpm compared with atosiban (proportion of women with heart rate >120 bpm: 4/23 [18%] with ritodrine *v* 0/22 [0%] with atosiban; P = 0.108; proportion of women with heart rate >100 bpm: 20/22 [91%] with ritodrine *v* 3/22 [14%] with atosiban; P = 0.0001). [66]

Neonatal adverse effects: The review [62] and subsequent RCT [65] gave no information on neonatal adverse effects.

Comment:

In the first placebo-controlled RCT identified by the review, infusions were stopped in two people (1 in each treatment group), who were subsequently excluded from analysis. [63] Tocolytic rescue with ritodrine was used in the second RCT comparing atosiban versus placebo. [64] In this RCT, 24/246 (10%) women randomised to receive atosiban and 13/255 (5%) women randomised to receive placebo were recruited before 26 weeks' gestation. This may have contributed to a higher incidence of fetal mortality before 26 weeks' gestation in the atosiban group. The comparison of atosiban with beta-mimetics seems to indicate similar effectiveness with fewer adverse effects. The subgroup analysis regarding twin gestations is limited by its small sample size. [67] Overall, atosiban seems effective at delaying delivery compared with placebo in pregnancies greater than 28 weeks' gestation, and seems as effective at delaying delivery as beta-mimetics, and with fewer adverse effects.

We found one systematic review (58 RCTs, 7176 women) comparing tocolytic drugs (including beta-mimetics, calcium channel blockers, magnesium sulphate, oxytocin inhibitors, and prostaglandin inhibitors) versus each other or placebo. [60] Data were extracted for the following outcomes: delay of delivery for 48 hours, 7 days, and until 37 weeks' gestation; adverse effects causing discontinuation of treatment; absence of respiratory distress syndrome; and neonatal survival. These data were then combined by drug category to calculate weighted mean and standard error for proportions of successful outcomes for all treatments included in studies. As the review aggregated data from individual trials according to treatment group, effectively disassembling the trials, weighted proportions were generated based on the number of people in each study group (the total number of individual participants across all the relevant trials for each comparison). Disassembling the trials precluded direct comparisons required for odds ratios, so they are not reported. It is also noteworthy that the indirect comparisons reported by the review remove the benefits of randomisation of the original trials, which may bias the results. The percentage of women with a successful delay of delivery by 48 hours was 53% with control/placebo and 86% with oxytocin receptor antagonists. The percentage of women with successful delay of labour until 37 weeks' gestation was 36% with control/placebo; the review did not assess delay in labour for oxytocin receptor antagonist. Neonatal mortality and adverse effects were 2% with placebo and 1% with oxytocin receptor antagonists. [60]

OPTION PROSTAGLANDIN INHIBITORS

Mortality
Compared with placebo Indometacin is no more effective at reducing perinatal mortality (moderate-quality evidence).

Compared with other tocolytics (analysed as a group) Prostaglandin inhibitors and other tocolytics are equally effective at reducing perinatal mortality (high-quality evidence).

Morbidity
Compared with placebo Indometacin seems no more effective at reducing respiratory distress syndrome, necrotising enterocolitis, or neonatal sepsis (moderate-quality evidence).

Compared with other tocolytics (analysed as a group) Prostaglandin inhibitors and other tocolytics are equally effective at reducing respiratory distress syndrome, necrotising enterocolitis, premature closing of the ductus, or persistent pulmonary hypertension of the newborn (high-quality evidence).

Preterm birth
Compared with placebo Indometacin seems more effective at reducing delivery within 48 hours and within 7 days of receiving treatment, and before 37 weeks' gestation (moderate-quality evidence).

Compared with other tocolytics (analysed as a group) Prostaglandin inhibitors are more effective at reducing the proportion of women who deliver before 37 weeks' gestation, but not within 48 hours or 7 days of treatment (high-quality evidence).

Adverse effects
Compared with other tocolytics Prostaglandin inhibitors are less likely to cause maternal adverse effects leading to cessation of treatment (high-quality evidence).

For GRADE evaluation of interventions for preterm birth, see table, p 34 .

Benefits:

We found one systematic review comparing prostaglandin inhibitors, mainly indometacin, with placebo or other tocolytics (search date 2004, 13 RCTs, 713 women). [68]

Prostaglandin inhibitors versus placebo:
The systematic review found that, compared with placebo, indometacin significantly reduced delivery within 48 hours and 7 days of treatment, and delivery before 37 weeks' gestation. However, the number of women studied was small (within 48 hours: 2 RCTs; 4/34 [12%] with indometacin *v* 22/36 [61%] with placebo; RR 0.19, 95% CI 0.07 to 0.51; within 7 days: 2 RCTs; 11/34 [32%] with indometacin *v* 27/36 [75%] with placebo; RR 0.44, 95% CI 0.26 to 0.74; before 37 weeks' gestation: 1 RCT; 3/18 [17%] with indometacin *v* 14/18 [78%] with placebo; RR 0.21, 95% CI 0.07 to 0.62). [68] It found no significant difference between indometacin and placebo in perinatal mortality, respiratory distress syndrome, necrotising enterocolitis, or neonatal sepsis (perinatal mortality: 3 RCTs; 4/53 [8%] with indometacin *v* 5/53 [9%] with placebo; RR 0.80, 95% CI 0.25 to 2.58; respiratory distress syndrome: 3 RCTs; 8/53 [15%] with indometacin *v* 8/53 [15%] with placebo; RR 1.00, 95% CI 0.40 to 2.49; necrotising enterocolitis: 2 RCTs; 3/35 [8.6%] with indometacin *v* 3/35 [8.6%] with placebo; RR 0.97, 95% CI 0.24 to 4.43; neonatal sepsis: 2 RCTs; 0/35 [0%] with indometacin *v* 1/35 [3%] with placebo; RR 0.31, 95% CI 0.01 to 7.15). [68] The number of newborns assessed for these outcomes may have been too small to detect a clinically important difference between groups.

Prostaglandin inhibitors versus other tocolytics (analysed as a group):
The systematic review found that, compared with other tocolytics, prostaglandin inhibitors significantly reduced the proportion of women delivering before 37 weeks' gestation, but did not significantly reduce delivery within 48 hours or 7 days of treatment, perinatal mortality, respiratory distress syndrome, necrotising enterocolitis, premature closure of the ductus, or persistent pulmonary hypertension of the newborn (8 RCTs, 557 women; 5 RCTs using indometacin; 4 trials comparing with beta-mimetics; 4 trials comparing with magnesium sulphate; delivery before 37 weeks' gestation: 3 RCTs; 13/85 [15%] with prostaglandin inhibitors *v* 24/83 [29%] with other tocolytics; RR 0.53, 95% CI 0.31 to 0.94; delivery within 48 hours of treatment: 4 RCTs; 18/206 [9%] with prostaglandin inhibitors *v* 31/209 [15%] with other tocolytics; RR 0.59, 95% CI 0.34 to 1.02; delivery within 7 days: 2 RCTs; 20/74 [27%] with prostaglandin inhibitors *v* 22/72 [30%] with other tocolytics; RR 0.88, 95% CI 0.52 to 1.46; perinatal mortality: 8 RCTs; 9/326 [3%] with prostaglandin inhibitors *v* 6/334 [2%] with other tocolytics; RR 1.46, 95% CI 0.57 to 3.74; respiratory distress syndrome: 6 RCTs; 27/247 [11%] with prostaglandin inhibitors *v* 27/258 [10%] with other tocolytics; RR 1.08, 95% CI 0.66 to 1.76; necrotising enterocolitis: 4 RCTs; 4/144 [3%] with prostaglandin inhibitors *v* 0/154 [0%] with other tocolytics; RR 3.82, 95% CI 0.65 to 22.51; premature closure of the ductus: 4 RCTs; 1/167 with prostaglandin inhibitors *v* 0/170 with other tocolytics; RR 3.05, 95% CI 0.13 to 73.39;

persistent pulmonary hypertension: 5 RCTs; 5/240 [2.1%] with prostaglandin inhibitors *v* 1/250 [0.4%] with other tocolytics; RR 2.85, 95% CI 0.56 to 14.38). [68]

Harms:

Prostaglandin inhibitors versus placebo:
The review found that, compared with placebo, indometacin showed an insignificant trend towards increasing the incidence of postpartum haemorrhage (1 RCT: 7/16 [44%] with indometacin *v* 2/18 [11%] with placebo or no treatment; RR 3.94, 95% CI 0.95 to 16.29), [68] but it found no significant difference in nausea, chorioamnionitis, or maternal drug reaction requiring cessation of therapy. [68] The number of women assessed for these outcomes may have been too small to detect a clinically important difference.

We found one additional systematic review focusing on neonatal safety of indometacin (11 RCTs, 628 infants). [69] This review found an increased risk of bronchopulmonary dysplasia in babies of women receiving indometacin compared with no tocolysis (15/76 [20%] with indometacin *v* 6/80 [8%] with no tocolysis; OR 2.80, 95% CI 1.07 to 7.31). It found no significant difference in risk of neonatal patent ductus arteriosus, intraventricular haemorrhage, necrotising enterocolitis, or mortality with indometacin compared with no tocolysis (patent ductus arteriosus: 21/153 [14%] with indometacin *v* 18/155 [12%] with no tocolysis; OR 1.25, 95% CI 0.64 to 2.54; intraventricular haemorrhage: 22/263 [8.4%] with indometacin *v* 23/270 [8.5%] with no tocolysis; OR 1.02, 95% CI 0.55 to 1.89; necrotising enterocolitis: 7/162 [4%] with indometacin *v* 2/167 [1%] with no tocolysis; OR 2.43, 95% CI 0.73 to 8.03; neonatal mortality: 15/283 [5%] with indometacin *v* 11/289 [4%] with no tocolysis; OR 1.39, 95% CI 0.65 to 2.97). Pooled data in the review from 17 observational studies (5380 infants) showed no significant difference in any of the above neonatal outcomes. [69]

Prostaglandin inhibitors versus other tocolytics (analysed as a group):
The review reported significantly fewer maternal adverse drug effects requiring stopping of treatment with prostaglandin inhibitors compared with other tocolytics (5 RCTs; 0/178 [0%] with prostaglandin inhibitors *v* 27/177 [15%] with other tocolytics; RR 0.07, 95% CI 0.02 to 0.29). There was no increased risk of oligohydramnios in women taking prostaglandin inhibitors (8/146 [5%] with prostaglandin inhibitors *v* 3/149 [2%] with other tocolytics; RR 2.53, 95% CI 0.76 to 8.46). [68]

Comment:

Because of the small numbers of people in the placebo comparison, estimation of effects in subgroup analyses should be interpreted with caution. Prostaglandin inhibitors seem as effective as other tocolytics, and with fewer adverse maternal reactions. However, the small number of participants in the studies limit conclusions about some aspects of neonatal safety.

We found one systematic review (58 RCTs, 7176 women) comparing tocolytic drugs versus each other (including beta-mimetics, calcium channel blockers, magnesium sulphate, oxytocin inhibitors, and prostaglandin inhibitors) or placebo. [60] Data were extracted for the following outcomes: delay of delivery for 48 hours, 7 days, and until 37 weeks' gestation; adverse effects causing discontinuation of therapy; absence of respiratory distress syndrome; and neonatal survival. These data were then combined by drug category to calculate weighted mean and standard error for proportions of successful outcomes. As the data were aggregated from individual trials according to treatment group, effectively disassembling the trials, weighted proportions were generated based on the number of people in each study. Disassembling the trials precluded direct comparisons required for odds ratios, so they are not reported. It is also noteworthy that the indirect comparisons reported by the review remove the benefits of randomisation of the original trials, which may bias the results. The percentage of women with a successful delay of delivery by 48 hours was 53% with control/placebo and 93% with prostaglandin inhibitors. The percentage of women with successful delay until 37 weeks' gestation was 36% with control/placebo and 43% with prostaglandin inhibitors. Neonatal death rates were 2% with placebo and 2% with prostaglandin inhibitors, and adverse effects were 1% with placebo and 0% with prostaglandin inhibitors. [60] This review also included a decision model to determine the optimal first-line tocolytic therapy, and concluded that prostaglandin inhibitors should be considered the optimal first-line agent before 32 weeks of gestation to delay delivery. [60]

Another subsequent systematic review and decision analysis confirmed that prostaglandin inhibitor agents were found to be the most effective tocolytic agent in terms of reducing spontaneous preterm birth and prolonging pregnancy, although evidence to support their safety or a reduction in perinatal mortality and morbidity was "less convincing". [70]

OPTION BETA-MIMETICS

Mortality
Compared with placebo/no treatment Beta-mimetics are no more effective at reducing perinatal and neonatal mortality (high-quality evidence).

Compared with calcium channel blockers We don't know how effective calcium channel blockers and beta-mimetics are, compared with each other, at reducing perinatal mortality (low-quality evidence).

Compared with atosiban Atosiban and beta-mimetics seem equally effective at reducing perinatal mortality (moderate-quality evidence).

Morbidity
Compared with placebo/no treatment Beta-mimetics are no more effective at reducing respiratory distress syndrome (high-quality evidence).

Compared with calcium channel blockers We don't know how effective beta-mimetics and calcium channel blockers are, compared with each other, at reducing neonatal morbidity outcomes including proportion of infants transferred to ICU, respiratory distress syndrome, infection, or longer-term childhood outcomes measured at 2 years after birth (low-quality evidence).

Preterm birth
Compared with placebo/no treatment Beta-mimetics are more effective at reducing preterm birth within 48 hours of treatment (high-quality evidence).

Compared with calcium channel blockers Beta-mimetics may be less effective at reducing delivery within 48 hours (low-quality evidence).

Compared with atosiban Beta-mimetics and atosiban are equally effective at reducing the proportion of women with delivery before 37 weeks' gestation, or birth within 48 hours or 7 days of initiation of treatment (high-quality evidence).

Adverse effects
Compared with placebo/no treatment Beta-mimetics are more likely to increase fetal tachycardia and to cause maternal adverse effects such as chest pain, palpitations, dyspnoea, tremor, nausea, vomiting, headache, hyperglycaemia, and hypokalaemia, thus increasing treatment discontinuation (high-quality evidence).

For GRADE evaluation of interventions for preterm birth, see table, p 34 .

Benefits:

Beta-mimetics versus placebo:
We found one systematic review (search date 2006, 11 RCTs, 1320 women). [71] The review found that, compared with placebo or no treatment, beta-mimetics significantly reduced birth within 48 hours, and also found a trend towards reduction after 7 days (after sensitivity analysis); it found no significant reduction in delivery before 37 weeks' gestation (birth within 48 hours: 10 RCTs; 151/652 [23%] with beta-mimetics *v* 218/557 [39%] with placebo or no treatment; RR 0.63, 95% CI 0.53 to 0.75; birth within 7 days [after sensitivity analysis]: 5 RCTs; 184/454 [41%] with beta-mimetics *v* 238/457 [52%] with placebo or no treatment; RR 0.67, 95% CI 0.48 to 1.01; delivery before 37 weeks' gestation: 10 RCTs; 404/654 [62%] with beta-mimetics *v* 383/558 [69%] with placebo or no treatment; RR 0.95, 95% CI 0.88 to 1.03). The review found no significant difference between beta-mimetics and placebo or no treatment in perinatal mortality, neonatal mortality, respiratory distress syndrome, or any other morbidity outcomes (8 RCTs ritodrine; 2 RCTs terbutaline; and 1 RCT isoxsuprine, fenoterol, and hexoprenaline; perinatal mortality: 16/712 [2%] with beta-mimetics *v* 20/620 [3%] with placebo or no treatment; RR 0.84, 95% CI 0.46 to 1.55; neonatal mortality: 6 RCTs; 19/629 [3%] with beta-mimetics *v* 12/545 [2%] with placebo or no treatment; RR 1.00, 95% CI 0.48 to 2.09; respiratory distress syndrome: 8 RCTs; 123/664 [19%] with beta-mimetics *v* 136/575 [24%] with placebo or no treatment; RR 0.87, 95% CI 0.71 to 1.08).

Beta-mimetics versus other tocolytics:
See benefits of calcium channel blockers, p 14 , oxytocin receptor antagonists , p 17 , and magnesium sulphate, p 23 .

Harms:

Beta-mimetics versus placebo:
The review found that, compared with placebo or no treatment, beta-mimetics significantly increased maternal adverse effects such as chest pain, palpitations, tachycardia, dyspnoea, tremor, nausea, vomiting, headache, hyperglycaemia, and hypokalaemia (chest pain: 2 RCTs; 39/406 [10%] with beta-mimetics *v* 3/408 [1%] with placebo or no treatment; RR 11.3, 95% CI 3.8 to 33.5; palpitations: 4 RCTs; 213/570 [37%] with beta-mimetics *v* 19/472 [4%] with placebo or no treatment; RR 10.1, 95% CI 6.5 to 15.6; tachycardia: 2 RCTs; 65/165 [39%] with beta-mimetics *v* 19/64 [30%] with placebo or no treatment; RR 4.1, 95% CI 1.6 to 10.7; dyspnoea: 2 RCTs; 55/406 [14%] with beta-mimetics *v* 14/408 [3%] with placebo or no treatment; RR 3.9, 95% CI 2.2 to 6.7; tremor: 1 RCT; 138/352 [39%] with beta-mimetics *v* 13/356 [4%] with placebo or no treatment; RR 10.7, 95% CI 6.2 to 18.6; nausea/vomiting: 3 RCTs; 107/516 [21%] with beta-mimetics *v* 50/416 [12%] with placebo or no treatment; RR 1.8, 95% CI 1.3 to 2.4; headache: 3 RCTs; 98/516 [19%] with beta-mimetics *v* 22/420 [5%] with placebo or no treatment; OR 4.1, 95% CI 2.6 to 6.4; hyperglycaemia:

1 RCT; 106/352 [30%] with beta-mimetics *v* 37/356 [10%] with placebo or no treatment; RR 2.9, 95% CI 2.0 to 4.1; hypokalaemia: 1 RCT; 138/352 [39%] with beta-mimetics *v* 23/356 [7%] with placebo or no treatment; RR 6.1, 95% CI 4.0 to 9.2). [71] These adverse effects were associated with significantly higher treatment discontinuation with beta-mimetics compared with placebo or no treatment (5 RCTs; 77/590 [13%] with beta-mimetics *v* 5/491 [1%] with placebo or no treatment; RR 11.4, 95% CI 5.2 to 24.9). The systematic review also found that beta-mimetics significantly increased rate of fetal tachycardia compared with placebo or no treatment (1 RCT; 12/15 [80%] with beta-mimetics *v* 5/15 [33%] with placebo or no treatment; RR 2.4, 95% CI 1.1 to 5.1).

Beta-mimetics versus other tocolytics:
See harms of calcium channel blockers, p 14 , oxytocin receptor antagonists, p 17 , and magnesium sulphate, p 23 .

Drug safety alert:
A drug safety alert has been issued by the FDA that terbutaline should not be used in pregnant women for prevention or prolonged treatment of preterm labour because of the associated risks of serious maternal heart problems and death. (www.fda.gov)

Comment:

The systematic review noted that all of the trials were carried out before routine use of antenatal corticosteroids, and were performed in tertiary care centres. It suggested that effectiveness could perhaps be demonstrated if beta-mimetics could delay delivery by 48 hours to enable completion of a course of corticosteroids and transfer of the patient to a tertiary care facility from a community setting, or both. [71]

We found one systematic review (58 RCTs, 7176 women) comparing tocolytic drugs (including beta-mimetics, calcium channel blockers, magnesium sulphate, oxytocin inhibitors, and prostaglandin inhibitors) versus each other or placebo. [60] Data were extracted for the following outcomes: delay of delivery for 48 hours, 7 days, and until 37 weeks' gestation; adverse effects causing discontinuation of treatment; absence of respiratory distress syndrome; and neonatal survival. These data were then combined by drug category to calculate weighted mean and standard error for proportions of successful outcomes for all treatments included in studies. As the review aggregated data from individual trials according to treatment group, effectively disassembling the trials, weighted proportions were generated based on the number of people in each study group (the total number of individual participants across all the relevant trials for each comparison). Disassembling the trials precluded direct comparisons required for odds ratios, so they are not reported. It is also noteworthy that the indirect comparisons reported by the review remove the benefits of randomisation of the original trials, which may bias the results. The percentage of women with a successful delay of delivery by 48 hours was 53% with control/placebo and 75% with beta-mimetics. The percentage of women with successful delay of labour until 37 weeks' gestation was 36% with control/placebo and 46% with beta-mimetics. Neonatal mortality occurred in 2% of both groups. Overall rates of adverse effects were 1% with placebo and 14% with beta-mimetics. [60]

Despite evidence of benefit of beta-mimetics over placebo for some proxy outcomes such as delaying delivery, the lack of benefit compared with other tocolytic medications and the higher rate of adverse events over both placebo and other tocolytic medications prompts this categorisation.

OPTION MAGNESIUM SULPHATE

Mortality
Compared with placebo Magnesium sulphate seems no more effective at reducing perinatal mortality (moderate-quality evidence).

Compared with calcium channel blockers Magnesium sulphate and calcium channel blockers seem equally effective at reducing perinatal mortality (moderate-quality evidence).

Morbidity
Compared with placebo Magnesium sulphate seems no more effective at reducing respiratory distress syndrome, necrotising enterocolitis, intraventricular haemorrhage, seizures, or neonatal sepsis in newborns (moderate-quality evidence).

Compared with calcium channel blockers Magnesium sulphate and calcium channel blockers seem equally effective at reducing a composite morbidity outcome including respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis, sepsis, and fetal or neonatal mortality (moderate-quality evidence).

Preterm birth
Compared with placebo Magnesium sulphate seems no more effective at reducing delivery before 36 weeks' gestation (moderate-quality evidence).

Compared with other tocolytics (analysed as a group) We don't know whether magnesium sulphate is more effective than other tocolytics (including beta-mimetics, calcium channel blockers, prostaglandin synthetase inhibitors, nitroglycerine, alcohol, and dextrose infusion) at delaying delivery within 48 hours of treatment (low-quality evidence).

Compared with calcium channel blockers We don't know how effective nifedipine and magnesium sulphate are, compared with each other, at delaying pregnancy by 48 hours or in reducing delivery before 32 weeks (moderate-quality evidence).

Compared with calcium channel blockers We don't know how effective nifedipine and magnesium sulphate are, compared with each other, at delaying pregnancy by 48 hours or in reducing delivery before 32 weeks (moderate-quality evidence).

For GRADE evaluation of interventions for preterm birth, see table, p 34 .

Benefits:

Magnesium sulphate versus placebo:
We found two systematic reviews (search date 1998, 4 RCTs; [61] search date 2002, 5 RCTs [72]).

The first systematic review found no significant difference in delivery before 36 weeks' gestation between magnesium sulphate and placebo or no treatment (2 RCTs, 191 women; 61/92 [66%] with magnesium sulphate *v* 74/99 [75%] with placebo or no treatment; OR 0.67, 95% CI 0.36 to 1.26). [61] It found no significant difference in perinatal mortality or respiratory distress syndrome between magnesium sulphate and placebo or no treatment (perinatal mortality: 4 RCTs; 11/169 [7%] with magnesium sulphate *v* 7/182 [4%] with placebo or no treatment; OR 1.83, 95% CI 0.70 to 4.77; respiratory distress syndrome: 3 RCTs; 22/139 [16%] with magnesium sulphate *v* 22/153 [14%] with placebo or no treatment; OR 1.19, 95% CI 0.61 to 2.31). [61] It also found no significant difference between magnesium sulphate and placebo or no treatment in birth weight under 2500 g, necrotising enterocolitis, intraventricular haemorrhage, seizures, or neonatal sepsis. The number of newborns assessed for these outcomes was small.

The second systematic review compared magnesium sulphate versus placebo/controls, as well as with other interventions. The studies included in the second review comparing magnesium sulphate versus placebo, no treatment, or sedation were the same as those included in the first systematic review, except for the addition of a study comparing magnesium sulphate versus barbiturate and bed rest. In the second systematic review, subgroup analysis of magnesium sulphate compared with placebo or controls showed a trend towards reduced delivery within 48 hours (birth within 48 hours: 3 RCTs; 36/91 [40%] with magnesium sulphate *v* 73/99 [72%] with placebo or controls; RR 0.57, 95% CI 0.28 to 1.15). [72]

Magnesium sulphate versus other tocolytics (analysed as a group):
We found one systematic review (search date 2002, 20 RCTs) which compared magnesium sulphate versus other tocolytics (beta-mimetics, calcium channel blockers, prostaglandin inhibitors, nitroglycerine, alcohol, and dextrose infusion). [72] The review found no significant difference between magnesium sulphate and other treatments in delivery within 48 hours, although there was significant statistical heterogeneity (11 RCTs, 881 women; RR 0.85, 95% CI 0.58 to 1.25). Subgroup analysis comparing magnesium sulphate versus individual classes of tocolytic medications also failed to show any significant differences between the treatments in perinatal mortality, delivery within 48 hours, delivery before 37 weeks' gestation, or in any other outcomes. [72] The review found no significant difference in perinatal mortality between magnesium sulphate and other tocolytics (2 RCTs, 166 women; 1/62 [2%] with magnesium sulphate *v* 1/104 [1%] with beta-mimetics; RR 1.19, CI 0.08 to 17.51; 1 RCT: 80 women; 0/41 [0%] with magnesium sulphate *v* 2/39 [5%] with calcium channel blockers; RR 0.19, CI 0.01 to 3.85; 1 RCT: 117 women; 1/59 [2%] with magnesium sulphate *v* 1/58 [2%] with prostaglandin inhibitors; RR 0.98, CI 0.06 to 15.35). [72]

Magnesium sulphate versus calcium channel blockers:
See benefits of calcium channel blockers , p 14 .

Harms:

Magnesium sulphate versus placebo:
The first systematic review found that magnesium sulphate significantly increased discontinuation of treatment compared with placebo or no treatment (3 RCTs; 10/137 [7%] with magnesium sulphate *v* 0/144 [0%] with placebo or no treatment; OR 8.36, 95% CI 2.36 to 29.61). [61] The second review did not report on adverse effects for this comparison. [72]

We found one subsequent RCT (1062 women at risk of preterm birth before 30 weeks) comparing magnesium sulphate or placebo, which predominantly examined long-term outcomes in surviving children at 2 years. However, it gave information on adverse effects of magnesium sulphate, and so we have included these data here. It found that, compared with placebo, magnesium sulphate significantly increased minor maternal adverse effects, including tachycardia, nausea, and dizziness

(tachycardia: 56/535 [11%] with magnesium sulphate *v* 36/527 [7%] with placebo; RR 1.53, 95% CI 1.03 to 2.29; nausea: 137/535 [26%] with magnesium sulphate *v* 55/527 [10%] with placebo; RR 2.45, 95% CI 1.84 to 3.28; dizziness: 83/535 [16%] with magnesium sulphate *v* 37/527 [7%] with placebo; RR 2.21, 95% CI 1.53 to 3.19). [73] The RCT found that magnesium sulphate significantly increased discontinuation of treatment compared with placebo (78/535 [15%] with magnesium sulphate *v* 28/527 [5%] with placebo; RR 2.74, 95% CI 1.81 to 4.15).

Magnesium sulphate versus other tocolytics (analysed as a group):
The reviews found fewer maternal adverse effects requiring stopping of treatment with magnesium sulphate compared with beta-mimetics (3 RCTs; 1/108 [1%] with magnesium sulphate *v* 44/156 [28%] with beta-mimetics; RR 0.07, 95% CI 0.02 to 0.31). [72] For data on maternal adverse effects in comparisons of magnesium sulphate versus other classes of tocolytics, see prostaglandin inhibitors, p 20 and calcium channel blockers, p 14 .

Comment:

We found one systematic review (58 RCTs, 7176 women) comparing tocolytic drugs (including beta-mimetics, calcium channel blockers, magnesium sulphate, oxytocin inhibitors, and prostaglandin inhibitors) versus each other or placebo. [60] Data were extracted for the following outcomes: delay of delivery for 48 hours, 7 days, and until 37 weeks' gestation; adverse effects causing discontinuation of treatment; absence of respiratory distress syndrome; and neonatal survival. These data were then combined by drug category to calculate weighted mean and standard error for proportions of successful outcomes for all treatments included in studies. As the review aggregated data from individual trials according to treatment group, effectively disassembling the trials, weighted proportions were generated based on the number of people in each study group (the total number of individual participants across all the relevant trials for each comparison). Disassembling the trials precluded direct comparisons required for odds ratios, so they are not reported. It is also noteworthy that the indirect comparisons reported by the review remove the benefits of randomisation of the original trials, which may bias the results. The percentage of women with a successful delay of delivery by 48 hours was 53% with control/placebo and 89% with magnesium sulphate. The percentage of women with successful delay of labour until 37 weeks' gestation was 36% with control/placebo and 42% with magnesium sulphate. Neonatal mortality was 2% with placebo and 1% with magnesium sulphate. Overall rates of adverse effects were 1% with placebo and 3% with magnesium sulphate. [60]

While not specifically addressed currently in this review, one systematic review regarding magnesium sulphate given before preterm delivery for neuroprotection has demonstrated a reduction in cerebral palsy and substantial gross motor dysfunction. [74] This intervention will be added to future searches. The data, however, should add to the context of the harms information. [74]

QUESTION What are the effects of elective compared with selective caesarean delivery for women in preterm labour?

OPTION ELECTIVE VERSUS SELECTIVE CAESAREAN DELIVERY

Mortality
Elective compared with selective caesarean delivery We don't know whether elective caesarean delivery is more effective at reducing neonatal mortality (very low-quality evidence).

Morbidity
Elective compared with selective caesarean delivery We don't know whether elective caesarean delivery is more effective at improving Apgar scores at 5 minutes, at reducing the need for neonatal intubation, or at reducing intracranial haemorrhage (very low-quality evidence).

Note
Elective caesarean delivery has been associated with maternal complications, and may occasionally result in unnecessary preterm delivery.

For GRADE evaluation of interventions for preterm birth, see table, p 34 .

Benefits:

Elective versus selective caesarean delivery:
We found one systematic review (search date not reported, 6 RCTs, 122 women). [75] It found no significant difference in neonatal morbidity and mortality between elective caesarean delivery and selective caesarean delivery (6 RCTs included for each intervention; low Apgar score at 5 minutes: OR 0.68, 95% CI 0.29 to 1.60; need for neonatal intubation: OR 0.58, 95% CI 0.26 to 1.31; intracranial haemorrhage: OR 0.86, 95% CI 0.20 to 3.67; perinatal death: OR 0.32, 95% CI 0.07 to 1.36). About a sixth of women in each group delivered by an alternative method, but the analysis was by intention to treat. Three RCTs included only breech presentation.

Harms:

Elective versus selective caesarean delivery:
The review found that major maternal complications were reported in 7/84 (8%) women all after caesarean delivery, although one of these women was allocated to expectant management. [75] Maternal complications were significantly higher in women allocated to elective compared with selective caesarean (4 RCTs, 84 women; AR: 6/44 [14%] with elective caesarean delivery *v* 1/40 [3%] with selective caesarean; OR 6.18, 95% CI 1.27 to 30.10). Elective caesarean delivery may occasionally result in unnecessary preterm delivery; two women allocated to the selective delivery group did not deliver until some weeks after entry to one trial.

Comment:

The confidence intervals in the systematic review suggest that RCTs were underpowered, and no meaningful conclusions can be drawn here on the neonatal effects of elective caesarean section. [75] The sample size of the trials was small, and most were terminated because of recruitment difficulties. Doubts remain about the effects of this treatment.

QUESTION What are the effects of interventions to improve neonatal outcome in preterm delivery?

OPTION CORTICOSTEROIDS (ANTENATAL)

Mortality
Compared with placebo/no treatment Antenatal corticosteroids are more effective at reducing perinatal mortality (high-quality evidence).

Morbidity
Compared with placebo/no treatment Antenatal corticosteroids are more effective at reducing respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis, and neonatal infections in the first 48 hours of life, but they are no more effective at reducing chronic lung disease (high-quality evidence).

For GRADE evaluation of interventions for preterm birth, see table, p 34 .

Benefits:

Corticosteroids versus placebo or no treatment:
We found two systematic reviews (search date 2005 [76] and search date 2009 [77]). The reviews identified many of the same RCTs, and the second review also identified the meta-analysis carried out by the first review. The first systematic review presented the more complete analysis, and so we have reported the results of this review in full. However, the second review carried out a separate meta-analysis of RCTs from middle-income countries only, and so we have also included these data.

The first systematic review (21 RCTs, 3885 women, 4269 babies), [76] in women experiencing anticipated preterm delivery, compared a single course of corticosteroids (betamethasone, dexamethasone, or hydrocortisone) versus placebo or no treatment. The review pooled results and found that antenatal corticosteroids significantly reduced perinatal mortality, respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis, neonatal infection in the first 48 hours of life, and NICU admissions, but it found no significant difference in chronic lung disease (perinatal mortality: 13 RCTs; 261/1813 [14%] with corticosteroids *v* 341/1814 [19%] with placebo or no treatment; RR 0.77, 95% CI 0.67 to 0.89; respiratory distress syndrome: 21 RCTs; 351/2030 [17%] with corticosteroids *v* 523/2008 [26%] with placebo or no treatment; RR 0.66, 95% CI 0.59 to 0.73; intraventricular haemorrhage: 13 RCTs; 88/1445 [6%] with corticosteroids *v* 155/1427 [11%] with placebo or no treatment; RR 0.54, 95% CI 0.43 to 0.69; necrotising enterocolitis: 8 RCTs; 25/853 [3%] with corticosteroids *v* 52/822 [6%] with placebo or no treatment; RR 0.46, 95% CI 0.29 to 0.74; newborn infection in first 48 hours of life: 5 RCTs; 32/665 [5%] with corticosteroids *v* 56/654 [8%] with placebo or no treatment; RR 0.56, 95% CI 0.38 to 0.85; NICU admission: 2 RCTs; 65/138 [47%] with corticosteroids *v* 82/139 [59%] with placebo or no treatment; RR 0.80, 95% CI 0.65 to 0.99; chronic lung disease: 6 RCTs; 48/413 [12%] with corticosteroids *v* 50/405 [12%] with placebo or no treatment; RR 0.86, 95% CI 0.61 to 1.22). The decrease in perinatal mortality was present whether the corticosteroid was betamethasone or dexamethasone, and if the birth occurred both less than 24 hours or 48 hours after administration. The small number of evaluable neonates from twin pregnancies did not allow a confident statement to be made regarding the treatment in multiple gestations (perinatal mortality in twin gestations: 2 RCTs; 19/131 [14%] with corticosteroids *v* 24/121 [20%] with placebo or no treatment; RR 0.71, 95% CI 0.41 to 1.22). In addition, the decrease in respiratory distress syndrome was seen when corticosteroids were given in all gestational age ranges between 26 and 34 weeks. [76]

The second systematic review included a meta-analysis of antenatal corticosteroids versus placebo in middle-income countries (4 RCTs, all of which were included in the first review; 672 women). It found that antenatal corticosteroids significantly reduced both neonatal mortality and morbidity (neonatal mortality: 46/338 [14%] with corticosteroids *v* 96/334 [29%] without corticosteroids; RR

0.47, 95% CI 0.35 to 0.64; respiratory distress syndrome: 668 neonates in analysis; absolute numbers not reported; RR 0.63, 95% CI 0.49 to 0.81). [77]

Harms:

Corticosteroids versus placebo or no treatment:
The first systematic review found evidence from one RCT of an increased risk of glucose intolerance in the mother with antenatal corticosteroids compared with placebo or no treatment (16/61 [26%] with corticosteroids *v* 6/62 [10%] with placebo or no treatment; RR 2.71, 95% CI 1.14 to 6.46). [76] The review found no increased risk of maternal chorioamnionitis and no significant difference in birth weight (chorioamnionitis: 12 RCTs; 91/1234 [7%] with corticosteroids *v* 100/1251 [8%] with placebo or no treatment; RR 0.91, 95% CI 0.70 to 1.18; birth weight: 11 RCTs; mean difference –17.5 g, 95% CI –62.1 g to +27.1 g). Pooled analysis failed to reveal any other maternal or neonatal harms of corticosteroid treatment. [76] The second review gave no information on adverse effects. [77]

Comment:

For commonly reported outcomes, such as perinatal mortality and respiratory distress syndrome, the above first review noted no differences in outcomes whether betamethasone or dexamethasone was used, or with single compared with multiple courses of corticosteroids. [76] Although the RCTs in this review were not designed to evaluate single versus multiple courses of corticosteroids, these subgroup analyses were performed to address the potential effects of repeated doses of antenatal corticosteroids, and (as one retrospective cohort study [883 babies delivered between 24–31 weeks' gestation] suggests) whether one form of corticosteroid was more harmful than another. [78] In addition, the second review looking at the effectiveness in "middle income countries" is relevant as those countries often have higher mortality and morbidity from preterm birth and thus this intervention may be even better suited to improving outcomes in those settings. [77]

OPTION ANTIBIOTIC TREATMENT FOR PRETERM LABOUR WITH INTACT MEMBRANES

Mortality
Compared with placebo/no treatment Antibiotics seem no more effective at reducing perinatal mortality (moderate-quality evidence).

Morbidity
Compared with placebo/no treatment Antibiotics seem no more effective at reducing neonatal morbidity, respiratory distress syndrome, necrotising enterocolitis, or intraventricular haemorrhage (moderate-quality evidence).

Maternal infections
Compared with placebo/no treatment Antibiotics seem more effective at reducing chorioamnionitis and endometriosis (moderate-quality evidence).

Compared with no antibiotics Beta-lactams alone or in combination with macrolides seem more effective at reducing chorioamnionitis and endometriosis (moderate-quality evidence).

Compared with no antibiotics Macrolides alone or anti-anaerobics used to treat anaerobic infections seem no more effective at reducing maternal infections (moderate-quality evidence).

Preterm birth
Compared with placebo/no treatment Antibiotics seem no more effective at reducing delivery within 48 hours or within 7 days of treatment, or delivery before 37 weeks' gestation, in women in preterm labour and with intact membranes (moderate-quality evidence).

For GRADE evaluation of interventions for preterm birth, see table, p 34 .

Benefits:

Antibiotic treatment versus placebo/no treatment:
We found two systematic reviews. [79] [80] The first review (search date 2002, 11 RCTs), [79] comparing single or combined antibiotics versus placebo or no antibiotic in women in preterm labour and with intact membranes, found no significant difference in delivery within 48 hours or within 7 days between antibiotics and placebo or no antibiotics (within 48 hours: 4 RCTs, 6800 women; 509/4959 [10.3%] with antibiotics *v* 183/1841 [9.9%] without antibiotics; OR 1.04, 95% CI 0.89 to 1.23; within 7 days: 7 RCTs, 6957 women; 813/5044 [16%] with antibiotics *v* 337/1913 [18%] without antibiotics; OR 0.98, 95% CI 0.87 to 1.10). It found no significant difference between both groups in neonatal morbidity including respiratory distress syndrome, necrotising enterocolitis, or intraventricular haemorrhage, or in perinatal mortality (respiratory distress syndrome: 8 RCTs, 7104 newborns; 460/5112 [9%] with antibiotics *v* 194/1992 [10%] without antibiotics; RR 0.99, 95% CI 0.84 to 1.16; necrotising enterocolitis: 6 RCTs, 6880 newborns; 62/5004 [1.2%] with antibiotics *v* 25/1876 [1.3%] without antibiotics; RR 1.06, 95% CI 0.64 to 1.73; intraventricular haemorrhage: 4 RCTs, 6717 newborns; 59/4921 [1%] with antibiotics *v* 30/1796 [2%] without antibiotics; RR 0.76,

95% CI 0.48 to 1.19; perinatal mortality: 9 RCTs, 7208 newborns; 140/5166 [3%] with antibiotics *v* 42/2042 [2%] without antibiotics; RR 1.22, 95% CI 0.88 to 1.70).

The second review (search date 2006, 10 RCTs, 6771 deliveries, 9 RCTs also included in the first review plus one additional RCT not included in the first review) [80] compared antibiotics versus placebo/control (not further defined) in women in preterm labour with intact membranes. The review found no significant difference in average latency period between antibiotics and placebo/control (6 RCTs, 4542 women; WMD +0.21 days, 95% CI –1.36 days to +1.78 days). [80] The review also found that antibiotics significantly reduced neonatal infection compared with placebo/control (9 RCTs, 1004 neonates, 29/506 [6%] with antibiotics *v* 59/498 [12%] without antibiotics; OR 0.43, 95% CI 0.27 to 0.68). [80] The review also found no significant difference between groups for perinatal mortality (9 RCTs; 114/4782 [2%] with antibiotics *v* 46/1904 [2%] without antibiotics; OR 0.98, 95% CI 0.69 to 1.39). [80]

Maternal infections: The first review found that antibiotics significantly reduced maternal infection — namely chorioamnionitis and endometritis — compared with no antibiotics (9 RCTs; 7242 women: 456/5185 [9%] with antibiotics *v* 230/2057 [11%] without antibiotics; RR 0.74, 95% CI 0.64 to 0.87). [79] It found that beta-lactams, either alone or in combination with a macrolide, significantly reduced chorioamnionitis and endometritis compared with no antibiotics (beta-lactams alone: 3 RCTs; 144/1635 [9%] with beta-lactams *v* 70/621 [11%] with no antibiotics; RR 0.75, 95% CI 0.56 to 0.98; beta-lactam plus macrolide: 4 RCTs; 165/1790 [9%] with beta-lactam plus macrolide *v* 97/773 [13%] with no antibiotics; RR 0.75, 95% CI 0.59 to 0.95). It found no significant difference between either a macrolide alone or antibiotics used to treat anaerobic bacteria compared with no antibiotic (macrolide alone: 2 RCTs; 157/1653 [10%] with macrolide *v* 64/569 [11%] with no antibiotics; RR 0.81, 95% CI 0.62 to 1.07; antibiotics used to treat anaerobic bacteria: 3 RCTs; 5/155 [3%] with anti-anaerobic antibiotic *v* 6/139 [4%] with no antibiotic; RR 0.76, 95% CI 0.25 to 2.34). [79]

Harms:

Antibiotic treatment versus placebo/no treatment:
The first review found a trend towards increased neonatal deaths in the group receiving antibiotics compared with no antibiotics (7 RCTs, 6877 newborns: 99/5005 [2%] with antibiotics *v* 24/1872 [1%] with no antibiotics; RR 1.52, 95% CI 0.99 to 2.34), but the increase was not statistically significant. [79] The second review gave no information on adverse effects. [80]

A 7-year follow-up study (3196 children) of the largest RCT in the two reviews found an increased proportion of children with any functional impairment and proportion of children with total death or cerebral palsy whose mothers had received erythromycin compared with no erythromycin (any functional impairment: 42% with any erythromycin *v* 38% with no erythromycin; OR 1.18, 95% CI 1.02 to 1.37; total death or cerebral palsy: 6% with any erythromycin *v* 4% with no erythromycin; OR 1.40, 95% CI 1.07 to 1.82). [81] A further subgroup analysis found that the increase in any functional impairment was present if erythromycin was given alone or with amoxicillin−clavulanic acid (co-amoxiclav). [81]

Comment:

The ORACLE trial, [82] being 6 times larger than all of the previous RCTs, contributed the largest number of women in the first review. [79] It differed from the other RCTs in that the diagnosis of preterm labour was made by each clinician (as distinct from the other studies, which used similar definitions of preterm labour, including uterine contractions and cervical dilation), and it was one of only two trials in the review in which antibiotics were administered orally and in which some women were recruited after 34 weeks' gestation. Tocolysis was used in 9 of the 11 RCTs in the first review (56% in the ORACLE RCT) and in the subsequent RCT included in the second review, and 30% to 100% of women received corticosteroids. [79] [82] [83] Maternal chorioamnionitis and endometritis is reduced by the prescription of prophylactic beta-lactam antibiotics, but about 88% of women with threatened preterm birth and intact membranes would receive antibiotics unnecessarily for an infection that is easily diagnosed and treated. The harms noted with erythromycin should lead to its non-use in this patient population.

OPTION TRH PLUS CORTICOSTEROIDS BEFORE PRETERM DELIVERY

Mortality
Compared with corticosteroids alone TRH plus corticosteroids seems no more effective at reducing the risk of neonatal death before hospital discharge (moderate-quality evidence).

Morbidity
Compared with corticosteroids alone TRH plus corticosteroids seems no more effective at reducing respiratory distress syndrome, or periventricular or intraventricular haemorrhage, and increases maternal and fetal adverse effects (moderate-quality evidence).

For GRADE evaluation of interventions for preterm birth, see table, p 34 .

Benefits:

TRH plus corticosteroids versus corticosteroids alone:
We found one systematic review (search date 2009, 13 RCTs, >4600 women at risk of preterm birth, with a mean gestational age of 32 weeks) [11] comparing TRH plus corticosteroids versus corticosteroids alone. It found no significant difference in gestational age at delivery, respiratory distress syndrome, periventricular or intraventricular haemorrhage, necrotising enterocolitis, or neonatal death before hospital discharge between TRH plus corticosteroids and corticosteroids alone (gestational age at delivery: 2 RCTs; absolute numbers not reported; mean difference between groups –0.43 weeks, 95% CI –0.86 weeks to +0.01 weeks; respiratory distress syndrome: 9 RCTs; 712/1917 [37%] with TRH plus corticosteroids *v* 667/1916 [35%] with corticosteroids alone; RR 1.07, 95% CI 0.98 to 1.16; periventricular or intraventricular haemorrhage: 6 RCTs; 282/1819 [16%] with TRH plus corticosteroids *v* 262/1826 [14%] with corticosteroids alone; RR 1.08, 95% CI 0.93 to 1.26; necrotising enterocolitis: 4 RCTs; 56/1555 [4%] with TRH plus corticosteroids *v* 61/1548 [4%] with corticosteroids alone; RR 0.91, 95% CI 0.64 to 1.30; death before hospital discharge: 6 RCTs; 185/1842 [10.0%] with TRH plus corticosteroids *v* 177/1852 [9.6%] with corticosteroids alone; RR 1.05, 95% CI 0.86 to 1.27). A subgroup analysis based on timing of delivery after randomisation found that, compared with corticosteroids alone, TRH plus corticosteroids showed significant benefit (less-severe respiratory distress syndrome), but only in births between 24 hours and 10 days after randomisation (3 RCTs, 874 infants, severity of respiratory distress syndrome: RR 0.65, 95% CI 0.49 to 0.85). A large proportion of births (49%) occurred after this period, and had poorer outcomes (see harms). Another subgroup analysis found no significant difference in death, need for oxygen at 28 days of life, respiratory distress syndrome, or need for respiratory support between the TRH plus corticosteroids group and 1618 mothers "optimally" treated with corticosteroids (1618 mothers optimally treated received at least all doses of study medication before delivery; death before discharge: 80/587 [14%] with TRH plus corticosteroids *v* 85/563 [15%] with corticosteroids alone; OR 0.90, 95% CI 0.68 to 1.19; respiratory distress syndrome: 335/778 [43%] with TRH plus corticosteroids *v* 355/757 [47%] with corticosteroids alone; OR 0.91, 95% CI 0.82 to 1.02; need for oxygen at 28 days of life: 141/503 [28%] with TRH plus corticosteroids *v* 140/478 [29%] with corticosteroids alone; OR 0.96, 95% CI 0.79 to 1.17; need for respiratory support: 177/266 [67%] with TRH plus corticosteroids *v* 149/240 [62%] with corticosteroids alone; OR 1.07, 95% CI 0.94 to 1.22). [11]

Harms:

TRH plus corticosteroids versus corticosteroids alone:
The review found that, compared with corticosteroids alone, TRH plus corticosteroids significantly increased the risk of low Apgar score at 5 minutes, and increased the requirement for assisted ventilation (low Apgar: OR 1.80, 95% CI 1.14 to 1.92; assisted ventilation: OR 1.16, 95% CI 1.02 to 1.29). [11] TRH plus corticosteroids significantly increased maternal blood pressure compared with corticosteroids alone (1 RCT; risk of an increase of 25 mmHg in systolic blood pressure: 36/506 [7%] with TRH plus corticosteroids *v* 20/505 [4%] with corticosteroids alone; RR 1.80, 95% CI 1.05 to 3.06; risk of an increase of 15 mmHg in diastolic blood pressure: 115/506 [23%] with TRH plus corticosteroids *v* 71/505 [14%] with corticosteroids alone; RR 1.62, 95% CI 1.24 to 2.12). The review also found that, compared with corticosteroids alone, TRH plus corticosteroids significantly increased other maternal adverse effects, including nausea, vomiting, light-headedness, urgency of micturition, and facial flushing (nausea: 3 RCTs; 303/1175 [26%] with TRH plus corticosteroids *v* 77/1195 [6%] with corticosteroids alone; RR 3.92, 95% CI 3.13 to 4.90; vomiting: 1 RCT; 40/506 [8%] with TRH plus corticosteroids *v* 17/505 [3%] with corticosteroids alone; RR 2.35, 95% CI 1.35 to 4.09; light-headedness: 1 RCT; 139/506 [28%] with TRH plus corticosteroids *v* 80/505 [16%] with corticosteroids alone; RR 1.73, 95% CI 1.36 to 2.20; urgency of micturition: 1 RCT; 115/506 [23%] with TRH plus corticosteroids *v* 48/505 [10%] with corticosteroids alone; RR 2.39, 95% CI 1.75 to 3.27; facial flushing: 3 RCTs; 397/1252 [32%] with TRH plus corticosteroids *v* 149/1271 [12%] with corticosteroids alone; RR 2.67, 95% CI 2.26 to 3.16). [11] In the subgroup analysis based on time from randomisation to delivery, almost half (49%) of the babies were born 10 days or more after the first dose of medication. The analysis found that, compared with corticosteroids alone, the group treated with TRH had a significantly increased need for oxygen therapy or neonatal death within 28 days of life, and significantly increased rate of respiratory distress syndrome (oxygen therapy or neonatal death at 28 days: 5 RCTs, 1685 women; RR 1.35, 95% CI 1.02 to 1.78; respiratory distress syndrome: 4 RCTs, 1515 women; RR 1.33, 95% CI 1.05 to 1.68). [11]

Comment:

TRH regimens varied in the RCTs identified by the review. [11] Nine of the RCTs were analysed by intention to treat.

GLOSSARY

Neonatal mortality refers to the number of deaths in the neonatal period (from birth to 28 days of life).

Perinatal mortality refers to fetal deaths after 22 weeks' gestation plus neonatal deaths in the first 7 days of life.

Amnioinfusion is the infusion of physiological saline or Ringer's lactate through a catheter transabdominally or transcervically into the amniotic cavity.

Apgar score is a clinical scoring method that assesses neonatal heart rate, respirations, tone, colour, and reflexes immediately after delivery.

Cervical cerclage is the insertion of a cervical suture, using non-absorbable suture material, circumferentially around the cervix. May be done transvaginally or transabdominally.

Perinatal Refers to the period after 24 weeks' gestation and includes the first 7 days of postnatal life for the neonate.

Preterm labour Onset of labour (regular uterine contractions with cervical effacement and dilatation) in the preterm period.

Preterm rupture of membranes Leakage of amniotic fluid from the amniotic cavity during the preterm period owing to rupture of the fetal membranes.

Tocolytics Pharmacological agents that inhibit uterine contractions.

Elective caesarean section is when the operation is performed at a preselected time before the onset of labour, usually after 38 weeks' gestation.

Enhanced antenatal care includes various programmes of increased medical, midwifery, psychological, social, and nutritional support during pregnancy.

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Selective caesarean section is when the operation is performed after the onset of labour.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Amnioinfusion for preterm rupture of membranes New evidence added. [49] Categorisation unchanged (Unknown effectiveness) as there remains insufficient evidence to judge effects of this intervention.

Bed rest New evidence added. [42] Categorisation unchanged (Likely to be ineffective or harmful).

Beta-mimetics New evidence added. [54] [66] Categorisation unchanged (Unlikely to be beneficial).

Calcium channel blockers New evidence added. [50] [54] Categorisation unchanged (Likely to be beneficial).

Corticosteroids (antenatal) New evidence added. [77] Categorisation unchanged (Beneficial).

Oxytocin receptor antagonists New evidence added. [66] Categorisation unchanged (Unknown effectiveness) as new evidence was a small RCT comparing atosiban with ritodrine, and so there remains insufficient evidence to judge effects of this intervention.

Prophylactic cervical cerclage in women at risk of preterm labour with cervical changes New evidence added. [23] Categorisation unchanged (Likely to be beneficial).

TRH plus corticosteroids before preterm delivery Search updated for already included systematic review. [11] No new evidence added. Categorisation unchanged (Likely to be ineffective or harmful).

Progesterone New evidence added. [16] [17] [19] [20] Categorisation changed from Likely to be beneficial to Trade-off between benefits and harms.

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Disclaimer

TABLE 1 **Summary of RCTs addressing effects of enhanced care compared with usual care on preterm birth rates**

Ref	Nature of intervention*	Preterm delivery before 37 weeks' gestation		
		Intervention group	Control group†	Results
[28]	1 or 2 home visits/week by lay workers with no formal training in a client-led role; from booking in before 20 weeks' gestation until birth	6/60 (10%)	5/54 (9%)	P >0.05
[29]	1 home visit/week by trained nurses for cervical examination, education about preterm labour symptoms and signs; from 20 to 37 weeks' gestation	143/1024 (14%)	168/1197 (14%)	P >0.05
[30]	1 clinic visit/week with trained nurses for cervical examination, education about preterm labour symptoms and signs; from 22 weeks' gestation until birth	78/491 (16%)	68/478 (14%)	P >0.05
[31]	1 home visit every 1 or 2 weeks by trained midwife plus access to domiciliary midwives by telephone for measurement of blood pressure, urinary glucose and protein levels, cervical examination, monitoring of fundal height, fetal heart rate, and movements; from 26 weeks' gestation until birth	12/79 (15%)	13/73 (18%)	P >0.05
[32]	4 home visits at around 22, 26, 30, and 34 weeks' gestation with 2 more optional at discretion of woman and study staff by trained social workers or obstetric nurses. Additional access to special support office at any time in person or by telephone. Aiming to strengthen social network, providing strategies to address worries, health education including nutrition, smoking, alcohol, and drug use. Assessed at 36 weeks' gestation and 40 weeks' postpartum	123/1115 (11%)	140/1120 (13%)	OR 0.88, 95% CI 0.67 to 1.16
[33]	1 home visit/week by trained nurse for routine obstetric care and education about preterm labour symptoms and signs from 20 to 24 weeks' gestation until birth. All people identified as low income	192/1200 (16.0%)	185/1195 (15.5%)	P >0.05
[34]	1 telephone call/week by trained nurse assessing health status, recommendations from this, and discussion of any other issues concerning the mother; from time of home visit at 22 to 32 weeks' gestation until 37th week	72/718 (10%)	79/715 (11%)	RR 0.87, 95% CI 0.62 to 1.22; P = 0.42
[35]	1 home visit every 2 weeks by trained nurses for parent health education and awareness of preterm labour symptoms and signs, enhancement of informal support systems, and linkage of parents with community services. Each mother had an average of 9 visits	12/166 (7%)	10/142 (7%)	P >0.05
[36]	17 home visits from first or second trimester to end of first year of birth (1–2 antenatal visits), for preparation for motherhood classes during third trimester	2/62 (3%)	5/59 (9%)	Not significant; P value not reported
[37]	1 home visit every 1 to 2 weeks by trained midwives for gentle cervical examination and recommendations to decrease physical activity if necessary; from booking in until birth	107/667 (16%)	122/679 (18%)	P >0.05
[38]	1 clinic visit every 2 weeks with trained nurses for educationally orientated peer groups, strengthening of social support, smoking-cessation programmes as necessary, discussion of problems, health education, and additional appointments as needed, and extended time with clinicians from before 26 weeks' gestation until birth	33/318 (10%)	42/301 (14%)	P = 0.22

This table shows the results from year 1 (of 3). No significant difference seen over whole length of study compared with control group. *The definition of high risk varied between RCTs. †Antenatal care in outpatient clinic.

TABLE **GRADE evaluation of interventions for preterm birth**

Important outcomes	**Neonatal/perinatal mortality, morbidity (incidence of respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis, neonatal sepsis, and neonatal convulsions), incidence of preterm births, maternal infections, and adverse effects**								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of interventions to improve neonatal outcome after preterm rupture of membranes?									
8 (2992 babies) [15] [18] [19] [20]	Mortality	Progesterone *v* placebo	4	0	0	−1	0	Moderate	Directness point deducted for small number of events
At least 8 (at least 4164 babies) [15] [17] [18] [19] [20]	Morbidity	Progesterone *v* placebo	4	0	−1	−1	0	Low	Consistency point deducted for conflicting results between studies. Directness point deducted for small number of events
At least 11 (at least 2995 women) [15] [16] [17] [18] [19] [20]	Preterm birth	Progesterone *v* placebo	4	0	−1	0	0	Moderate	Consistency point deducted for conflicting results between studies and statistical heterogeneity present in analysis
7 (1118 babies) [21] [22] [23]	Mortality	Prophylactic cervical cerclage in women at risk of preterm labour with cervical changes *v* no cerclage	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for small number of events
2 (149) [21]	Morbidity	Prophylactic cervical cerclage in women at risk of preterm labour with cervical changes *v* no cerclage	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for statistical heterogeneity
7 (1057) [21] [22] [23]	Preterm birth	Prophylactic cervical cerclage in women at risk of preterm labour with cervical changes *v* no cerclage	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for statistical heterogeneity and different results for subgroup analysis
1 (23 babies) [25]	Morbidity	Prophylactic cervical cerclage in women at risk of preterm labour with protruding membranes *v* bed rest	4	−1	0	−1	0	Low	Quality point deducted for sparse data. Directness point deducted for composite outcome
1 (23) [25]	Preterm birth	Prophylactic cervical cerclage in women at risk of preterm labour with protruding membranes *v* bed rest	4	−1	0	0	0	Moderate	Quality point deducted for sparse data
11 (12,013) [28] [29] [30] [31] [32] [33] [34] [35] [36] [37] [38]	Preterm birth	Enhanced antenatal care *v* usual care	4	0	0	−1	0	Moderate	Directness point deducted for different definitions of enhanced antenatal care and high risk
4 (2059) [39]	Mortality	Prophylactic cervical cerclage in women at risk of preterm labour with no cervical changes *v* no cerclage	4	0	0	−1	0	Moderate	Directness point deducted for inclusion of women with no ultrasound assessment of cervix
4 (2062) [39]	Preterm birth	Prophylactic cervical cerclage in women at risk of preterm labour with no cervical changes *v* no cerclage	4	0	−1	−1	0	Low	Consistency point deducted for different results at different end points. Directness point deducted for inclusion of women with no ultrasound assessment of cervix
1 (97) [40]	Preterm birth	Elective cervical cerclage *v* cervical ultrasound surveillance	4	−1	0	−1	0	Low	Quality point deducted for sparse data. Directness point deducted for high crossover between groups

Important outcomes	Neonatal/perinatal mortality, morbidity (incidence of respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis, neonatal sepsis, and neonatal convulsions), incidence of preterm births, maternal infections, and adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
7 (1448 babies) [42]	Mortality	Bed rest (including hospitalisation) *v* placebo/no intervention/routine care hospitalisation	4	0	0	0	0	High	
8 (at least 1979) [41] [42]	Preterm birth	Bed rest (including hospitalisation) *v* placebo/no intervention/routine care hospitalisation	4	0	0	0	0	High	
What are the effects of interventions to improve neonatal outcome after preterm rupture of membranes?									
18 trials (6951 babies) [43]	Mortality	Any antibiotic *v* placebo	4	−2	0	−1	0	Very low	Quality points deducted for incomplete reporting of results and inclusion of trials that were not placebo controlled. Directness point deducted for inclusion of other intervention in some studies
At least 12 RCTs (number not reported) [43] [45]	Morbidity	Any antibiotic *v* placebo	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for inclusion of other intervention in some studies
At least 13 RCTs (number not reported) [43]	Preterm birth	Any antibiotic *v* placebo	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for inclusion of intervention in some studies
8 (788 babies) [43] [44]	Morbidity	Penicillins (excluding amoxicillin−clavulanic acid [co-amoxiclav]) *v* placebo	4	−2	0	−1	0	Very low	Quality points deducted for incomplete reporting of results and methodological flaws. Directness point deducted for inclusion of other intervention in some studies
12 (545 babies) [44] [43]	Preterm birth	Penicillins (excluding amoxicillin−clavulanic acid) *v* placebo	4	−2	0	−1	0	Very low	Quality points deducted for incomplete reporting of results and methodological flaws. Directness point deducted for inclusion of other intervention in some studies
At least 2 (at least 4809 babies) [43]	Morbidity	Amoxicillin−clavulanic acid *v* placebo	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for inclusion of other intervention in some studies
2 (4860 babies) [43]	Preterm birth	Amoxicillin−clavulanic acid *v* placebo	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for inclusion of other intervention in some studies
2 (2635 babies) [43]	Preterm birth	Erythromycin *v* placebo	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for inclusion of other intervention in some studies
2 (126) [47] [49]	Mortality	Amnioinfusion *v* no treatment/expectant management	4	−3	0	0	0	Very low	Quality points deducted for sparse data, methodological flaws, and incomplete reporting of results
2 (94) [48] [49]	Preterm birth	Amnioinfusion *v* no treatment/expectant management	4	−2	0	−1	0	Very low	Quality points deducted for sparse data and lack of standardisation of intervention. Directness point deducted for narrow inclusion criteria

Important outcomes	**Neonatal/perinatal mortality, morbidity (incidence of respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis, neonatal sepsis, and neonatal convulsions), incidence of preterm births, maternal infections, and adverse effects**								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of treatments to stop contractions in preterm labour?									
1 (89) [50]	Preterm birth	Calcium channel blockers *v* placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, uncertainty about blinding and no direct statistical comparison
10 (810 newborns) [51]	Mortality	Calcium channel blockers *v* other tocolytics (analysed as a group)	4	0	0	0	0	High	
At least 9 RCTs (at least 763 newborns) [51]	Morbidity	Calcium channel blockers *v* other tocolytics (analysed as a group)	4	0	0	0	0	High	
At least 9 RCTs (at least 761) [51]	Preterm birth	Calcium channel blockers *v* other tocolytics (analysed as a group)	4	0	0	0	0	High	
10 (833) [51]	Adverse effects	Calcium channel blockers *v* other tocolytics (analysed as a group)	4	0	0	0	+2	High	Effect-size points added for RR <0.2
1 (45) [54]	Mortality	Calcium channel blockers *v* beta-mimetics	4	−2	0	0	0	Low	Quality point deducted for sparse data and methodological flaws (uncertainty about blinding).
2 (136) [54] [55]	Morbidity	Calcium channel blockers *v* beta-mimetics	4	−2	0	0	0	Low	Quality point deducted for sparse data and methodological flaws in 1 RCT (uncertainty about blinding)
10 (729) [51] [52] [53] [54] [55]	Preterm birth	Calcium channel blockers *v* beta-mimetics	4	−1	−1	0	0	Low	Quality point deducted for uncertainty about method of randomisation. Consistency point deducted for conflicting results
1 (80) [56]	Preterm birth	Calcium channel blockers *v* atosiban	4	−1	0	0	0	Moderate	Quality point deducted for sparse data
1 (216 babies) [57]	Mortality	Calcium channel blockers *v* magnesium sulphate	4	0	0	−1	0	Moderate	Directness point deducted for uncertainty about statistical significance of result
1 (216 babies) [57]	Morbidity	Calcium channel blockers *v* magnesium sulphate	4	0	0	−1	0	Moderate	Directness point deducted for use of composite outcome
2 (312) [57] [58]	Preterm birth	Calcium channel blockers *v* magnesium sulphate	4	0	−1	0	0	Moderate	Consistency point deducted for conflicting results
2 (613) [63] [64]	Preterm birth	Atosiban *v* placebo	4	0	0	0	0	High	
2 (607) [61] [62] [64]	Adverse effects	Atosiban *v* placebo	4	0	0	0	0	High	
3 (836) [62]	Mortality	Atosiban *v* beta-mimetics	4	0	0	−1	0	Moderate	Directness point deducted for small number of events
At least 6 (at least 1206) [62] [65] [66]	Preterm birth	Atosiban *v* beta-mimetics	4	0	0	0	0	High	
3 (106) [68]	Mortality	Prostaglandin inhibitors *v* placebo	4	−1	0	0	0	Moderate	Quality point deducted for sparse data
At least 3 RCTs (at least 106) [68]	Morbidity	Prostaglandin inhibitors *v* placebo	4	−1	0	0	0	Moderate	Quality point deducted for sparse data

Important outcomes	**Neonatal/perinatal mortality, morbidity (incidence of respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis, neonatal sepsis, and neonatal convulsions), incidence of preterm births, maternal infections, and adverse effects**								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
At least 2 RCTs (at least 70) [51]	Preterm birth	Prostaglandin inhibitors *v* placebo	4	−1	0	0	0	Moderate	Quality point deducted for sparse data
8 (660) [68]	Mortality	Prostaglandin inhibitors *v* other tocolytics	4	0	0	0	0	High	
At least 6 RCTs (at least 505) [68]	Morbidity	Prostaglandin inhibitors *v* other tocolytics (analysed as a group)	4	0	0	0	0	High	
At least 4 RCTs (at least 415) [68]	Preterm birth	Prostaglandin inhibitors *v* other tocolytics (analysed as a group)	4	0	0	0	0	High	
5 (355) [68]	Adverse effects	Prostaglandin inhibitors *v* other tocolytics (analysed as a group)	4	0	0	0	0	High	
11 (1332) [71]	Mortality	Beta-mimetics *v* placebo/no treatment	4	0	0	0	0	High	
8 (1239) [71]	Morbidity	Beta-mimetics *v* placebo/no treatment	4	0	0	0	0	High	
At least 10 (at least 1212) [71]	Preterm birth	Beta-mimetics *v* placebo/no treatment	4	0	0	0	0	High	
At least 5 RCTs (at least 1081) [71]	Adverse effects	Beta-mimetics *v* placebo/no treatment	4	0	0	0	0	High	
4 (351) [61]	Mortality	Magnesium sulphate *v* placebo	4	0	0	−1	0	Moderate	Directness point deducted for small number of events
3 (292) [61]	Morbidity	Magnesium sulphate *v* placebo	4	0	0	−1	0	Moderate	Directness point deducted for small number of events
2 (191) [61]	Preterm birth	Magnesium sulphate *v* placebo	4	−1	0	0	0	Moderate	Quality point deducted for sparse data
11 (881) [72]	Preterm birth	Magnesium sulphate *v* other tocolytics	4	−2	0	0	0	Low	Quality points deducted for incomplete reporting of results and statistical heterogeneity
What are the effects of elective compared with selective caesarean delivery for women in preterm labour?									
6 (122) [75]	Mortality	Elective *v* selective caesarean delivery	4	−3	0	−1	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and for short follow-up. Directness point deducted for uncertainty about benefit
6 (122) [75]	Morbidity	Elective *v* selective caesarean delivery	4	−3	0	−1	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and for short follow-up. Directness point deducted for uncertainty about benefit
What are the effects of interventions to improve neonatal outcome in preterm delivery?									
13 (3627) [76]	Mortality	Antenatal corticosteroids *v* placebo/no treatment	4	0	0	0	0	High	
21 (at least 4038 babies) [76]	Morbidity	Antenatal corticosteroids *v* placebo/no treatment	4	0	0	0	0	High	

Important outcomes	**Neonatal/perinatal mortality, morbidity (incidence of respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis, neonatal sepsis, and neonatal convulsions), incidence of preterm births, maternal infections, and adverse effects**								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
9 (7208) [43]	Mortality	Antibiotics *v* placebo/no antibiotics in women in preterm labour and with intact membranes	4	0	0	−1	0	Moderate	Directness point deducted for inclusion of intervention
At least 8 RCTs (at least 7104 babies) [79] [80]	Morbidity	Antibiotics *v* placebo/no antibiotics in women in preterm labour and with intact membranes	4	0	0	−1	0	Moderate	Directness point deducted for inclusion of intervention
12 (at least 6771 deliveries) [43] [80]	Preterm birth	Antibiotics *v* placebo/no antibiotics in women with in preterm labour and with intact membranes	4	0	0	−1	0	Moderate	Directness point deducted for inclusion of intervention
9 (7242) [43]	Maternal infection	Antibiotics *v* placebo/no antibiotics in women with in preterm labour and with intact membranes	4	0	0	−1	0	Moderate	Directness point deducted for inclusion of different combinations
6 (3694) [11]	Mortality	TRH plus corticosteroids before preterm delivery *v* corticosteroids alone	4	0	0	−1	0	Moderate	Directness point deducted for differences in TRH regimens
At least 9 RCTs (at least 3833 babies) [11]	Morbidity	TRH plus corticosteroids before preterm delivery *v* corticosteroids alone	4	0	0	−1	0	Moderate	Directness point deducted for differences in TRH regimens

Type of evidence: 4 = RCT
Consistency: similarity of results across studies. TRH, thyrotrophin-releasing hormone
Directness: generalisability of population or outcomes
Effect size: based on relative risk or odds ratio