Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth (Review)

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[Intervention Review]

Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

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Cochrane Database of Systematic Reviews, Issue 4, 2009 (Status in this issue: *Unchanged*)

DOI: 10.1002/14651858.CD004947.pub2
This version first published online: 25 January 2006 in Issue 1, 2006.
Last assessed as up-to-date: 30 December 2008. (Help document - Dates and Statuses explained)

This record should be cited as: Dodd JM, Flenady V, Cincotta R, Crowther CA. Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth. *Cochrane Database of Systematic Reviews* 2006, Issue 1. Art. No.: CD004947. DOI: 10.1002/14651858.CD004947.pub2.

ABSTRACT

Background

Preterm birth is a major complication of pregnancy associated with perinatal mortality and morbidity. Progesterone for the prevention of preterm labour has been advocated.

Objectives

To assess the benefits and harms of progesterone for the prevention of preterm birth for women considered to be at increased risk of preterm birth.

Search strategy

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (December 2008) and the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2008, Issue 1).

Selection criteria

Randomised controlled trials, in which progesterone was given for preventing preterm birth.

Data collection and analysis

Two authors independently evaluated trials for methodological quality and extracted data.

Main results

Eleven randomised controlled trials (2714 women and 3452 infants) were included.

Progesterone versus placebo for women with a past history of spontaneous preterm birth

Progesterone was associated with a statistically significant reduction in the risk of preterm birth less than 34 weeks' gestation (one study; 142 women; risk ratio (RR) 0.15; 95% confidence interval (CI) 0.04 to 0.64); preterm birth less than 37 weeks' gestation (four studies; 1255 women; RR 0.80; 95% CI 0.70 to 0.92); infant birthweight less than 2500 grams (two studies; 501 infants; RR 0.64; 95% CI 0.49 to 0.83).

Progesterone versus placebo for women with a short cervix identified on ultrasound

Progesterone was associated with a statistically significant reduction in the risk of preterm birth less than 34 weeks (one study; 250 women; RR 0.58; 95% CI 0.38 to 0.87); and neonatal sepsis (one study; 274 infants; RR 0.28; 95% CI 0.08 to 0.97).

Progesterone versus placebo for women with a multiple pregnancy

Progesterone was associated with a statistically significant reduction in the risk of antenatal tocolysis (one study; 654 women; RR 0.75; 95% CI 0.57 to 0.97).

Progesterone versus placebo for women following presentation with threatened preterm labour

Progesterone, was associated with a statistically significant reduction in the risk of preterm birth less than 37 weeks (one study; 60 women; RR 0.29; 95% CI 0.12 to 0.69), infant birthweight less than 2500 grams (one study; 70 infants; RR 0.52; 95% CI 0.28 to 0.98); and respiratory distress syndrome (one study; 70 infants; RR 0.30; 95% CI 0.11 to 0.83).

Progesterone versus placebo for women with 'other' risk factors for preterm birth

Progesterone was associated with no statistically significant differences for the reported outcomes.

Authors' conclusions

Further trials are required to assess the benefits and harms of progesterone therapy when given to women considered to be at increased risk of early birth.

PLAIN LANGUAGE SUMMARY

Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Babies who are born before 37 weeks, and particularly those born before 34 weeks, are at greater risk of suffering problems at birth. Progesterone is a hormone that inhibits the uterus from contracting and is involved in maintaining pregnancy. The review of eleven randomised controlled trials, involving a total of 2714 women and 3452 infants, found that where progesterone was given (by injection into the muscle in some studies and as a pessary into the vagina in others), there were some beneficial effects, including prolonging the pregnancy, but there is insufficient information about other possible benefits or harms. Further research is being undertaken.

BACKGROUND

Description of the condition

Preterm birth before 37 weeks' gestation is a common problem in obstetric care, with estimates ranging from 6% to 10% (Lumley 2003). In Australia, approximately 8% of all infants were born preterm in 2000, with 2.7% of these births occurring prior to 34 weeks' gestation (AIHW 2003). Figures are similar for the United States, with a preterm birth rate of 12.1% (Martin 2003). While less than 2% of these infants were born prior to 32 weeks' gestation (Martin 2003), they are at increased risk of complications in infancy, and contribute in excess of 50% of the overall perinatal mortality (AIHW 2003). Infants who are born preterm are at greater risk of dying in their first year of life (Martin 2003), and of those infants who survive, there is an increased risk of repeated admission to hospital (Elder 1999) and adverse outcomes including cerebral palsy and long-term disability (Hack 1999; Stanley 1992), creating a significant burden upon the community (Kramer 2000).

The 'cause' of preterm labour is multifactorial in origin, and it is important to consider the role of any identifiable risk factors in a woman's pregnancy.

The most significant and consistently identified risk factor for preterm birth, is a woman's history of previous preterm birth (Adams 2000; Bakketeig 1979; Berkowitz 1993; Bloom 2001; Goldenberg 1998; Kaminski 1973; Kistka 2007; Papiernik 1974; Petrini 2005; Robinson 2001). Estimates suggest the rate of recurrent preterm birth in this group of women to be 22.5% (Petrini 2005), a 2.5 times increased risk ratio when compared with women with no previous spontaneous preterm birth (Mercer 1999). For women with a history of a single preterm birth, the recurrence risk in a subsequent pregnancy is approximately 15%, increasing to 32% where there have been two previous preterm births (Carr-Hill 1985). Information derived from population-based cohort data suggests that for women who give birth between 20 and 31 weeks' gestation in one pregnancy, 29.3% will give birth prior to 37 weeks in a subsequent pregnancy (Adams 2000). For approximately 10% of these women, the preterm birth will occur at a similar gestational age (Adams 2000; Kistka 2007). In up to 50% of cases of preterm birth, the cause is spontaneous onset of labour or preterm premature rupture of membranes (PPROM) (Hewitt 1988; Mattison 2001; McLaughlin 2002).

Other characteristics in a woman's current pregnancy may place her at increased risk of preterm birth, including women with a short cervix identified by ultrasound assessment, the presence of fetal fibronectin in the vaginal secretions, and presentation with symptoms or signs of threatened preterm labour.

The identification of a short cervix (considered to be less than 2.5cm) on ultrasound examination has been associated with a likelihood ratio of preterm birth before 34 weeks' gestation of 6.29 (95% confidence interval (CI) 3.29 to 12.02) (Honest 2003). The likelihood ratio of preterm birth before 34 weeks associated with a negative ultrasound test result was 0.79 (95% CI 0.65 to 0.95) (Honest 2003).

Identification of fetal fibronectin present in cervico-vaginal secretions has also been proposed as a means of identifying women at risk of preterm birth. Two systematic reviews have assessed the role of fetal fibronectin as a tool to predict preterm birth (Honest 2002; Revah 1998), the largest including 64 studies (40 in symptomatic women) involving almost 27,000 participants (Honest 2002). The conclusion of both reviews was that a negative fetal fibronectin test in women presenting with symptoms of threatened preterm labour was of most benefit in identifying those women who would not proceed to preterm birth before 34 weeks within 7 to 10 days of testing (Honest 2002; Revah 1998), with a likelihood ratio of a negative fetal fibronectin test being 0.32 (95% CI 0.16 to 0.66) (Honest 2002).

Multiple pregnancy is a strong risk factor for preterm birth though the mechanisms may be different to those operating in women with a singleton pregnancy. Up to 50% of women with a twin pregnancy will give birth prior to 37 weeks' gestation (AIHW 2003). The preterm birth risk of early birth before 37 weeks for women with a singleton pregnancy is 6.3% compared with 97% for women with a triplet pregnancy (AIHW 2003).

Description of the intervention

Progesterone may be administered in various forms and by various routes. These different formulations and modes of administration will have different absorption patterns and potentially have differing bio effects. Whilst no teratogenic effects have been described with most progesterones, there is little in the way of long-term safety data. Maternal side-effects from progesterone therapy include headache, breast tenderness, nausea, cough and local irritation if administered intramuscularly. At present, there is little information available regarding the optimal dose of progesterone, mode of administration, gestation to commence therapy, or duration of therapy (Greene 2003; Iams 2003).

How the intervention might work

Progesterone has a role in maintaining pregnancy (Haluska 1997; Pepe 1995; Pieber 2001) and is thought to act by suppressing smooth muscle activity in the uterus (Astle 2003; Grazzini 1998). In many animal species, there is a reduction in the amount of circulating progesterone before the onset of labour. While these changes have not been shown to occur in women (Astle 2003; Block 1984; Lopez-Bernal 2003; Pieber 2001; Smit 1984), it has been suggested that there is a 'functional' withdrawal of progesterone related to changes in the expression of progesterone receptors in the uterus (Astle 2003; Condon 2003; Haluska 2002; Pieber 2001). There have been recent reports in the literature advocating the use of progesterone to reduce the risk of preterm birth (da Fonseca 2003; Meis 2003), rekindling interest that dates back to the 1960s (Le Vine 1964).

This review has been modified from the original protocol published in *The Cochrane Library* in Issue 4, 2004, in order to clarify the scope of the review. The title and objectives have changed, and the description of participants expanded to include the reason the women were considered to be at increased risk of preterm birth. The primary outcome measure of preterm birth less than 32 weeks' gestation has been changed to preterm birth less than 34 weeks' gestation to be consistent with World Health Organization definitions of preterm birth. Secondary outcome measures reflecting childhood developmental assessment have been added, reflecting the need for ongoing evaluation of children participating in randomised trials.

Why it is important to do this review

Preterm birth and its consequences for women and their babies is a significant health problem in pregnancy and childbirth. While the suppression or prevention of preterm labour should lead to improved survival through a lower incidence of premature delivery, there are theoretical reasons why a fetus may not survive without disability. It is possible that an intrauterine mechanism that would trigger preterm labour could also cause neurological injury to the

fetus and that progesterone may prevent labour but not fetal injury. The purpose of this review is to assess the benefits and harms of progesterone administration for the prevention of preterm birth for both women and their infants, when considering the risk factors present for preterm birth.

OBJECTIVES

To assess the benefits and harms of progesterone administration for the prevention of preterm birth in women and their infants.

METHODS

Criteria for considering studies for this review

Types of studies

All published and unpublished randomised controlled trials, in which progesterone was administered for the prevention of preterm birth, subdivided by the reason women were considered to be at risk for preterm birth.
Trials were excluded if:

- they utilised quasi-randomised methodology;
- progesterone was administered for the acute treatment of actual or threatened preterm labour (that is, where progesterone was administered as an acute tocolytic medication); or
- progesterone was administered in the first trimester only for preventing miscarriage.

Types of participants

Pregnant women considered to be at increased risk of preterm birth. These reasons include:

- past history of spontaneous preterm birth (including preterm premature rupture of membranes);
- multiple pregnancy;
- ultrasound identified short cervical length;
- fetal fibronectin testing;
- following acute presentation with symptoms or signs of threatened preterm labour (where a tocolytic medication may have been administered);
- other reason considered to be at increased risk of preterm birth.

Types of interventions

Administration of progesterone by any route for the prevention of preterm birth.

Types of outcome measures

Primary outcomes

1. Perinatal mortality
2. Preterm birth (less than 34 weeks' gestation)
3. Major neurodevelopmental handicap at childhood follow up

Secondary outcomes

Maternal

1. Threatened preterm labour
2. Prelabour spontaneous rupture of membranes
3. Adverse drug reaction
4. Pregnancy prolongation (interval between randomisation and birth)
5. Mode of birth
6. Number of antenatal hospital admissions
7. Satisfaction with the therapy
8. Use of tocolysis

Infant

1. Birth before 37 completed weeks
2. Birth before 28 completed weeks
3. Birthweight less than the third centile for gestational age
4. Birthweight less than 2500 grams
5. Apgar score of less than seven at five minutes
6. Respiratory distress syndrome
7. Use of mechanical ventilation
8. Duration of mechanical ventilation
9. Intraventricular haemorrhage - grades III or IV
10. Periventricular leucomalacia
11. Retinopathy of prematurity
12. Retinopathy of prematurity - grades III or IV
13. Chronic lung disease
14. Necrotising enterocolitis
15. Neonatal sepsis
16. Fetal death
17. Neonatal death
18. Admission to neonatal intensive care unit
19. Neonatal length of hospital stay
20. Teratogenic effects (including virilisation in female infants)

Child

1. Major sensorineural disability (defined as any of legal blindness, sensorineural deafness requiring hearing aids,

moderate or severe cerebral palsy, or developmental delay or intellectual impairment (defined as developmental quotient or intelligence quotient less than -2 standard deviations below mean))
2. Developmental delay (however defined by the authors)
3. Intellectual impairment
4. Motor impairment
5. Visual impairment
6. Blindness
7. Deafness
8. Hearing impairment
9. Cerebral palsy
10. Child behaviour
11. Child temperament
12. Learning difficulties
13. Growth assessments at childhood follow up (weight, head circumference, length, skin fold thickness)

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (December 2008).
The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.
Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.
In addition, we searched CENTRAL (*The Cochrane LIbrary* 2008, Issue 1). See Appendix 1 for search terms.
We did not apply any language restrictions.

Searching other resources

We also manually cross referenced key publications.
We did not apply any language restrictions.
We searched the International Clinical Trials Register (using the terms pregnancy, progesterone and ante/prenatal) to identify ongoing registered clinical trials.

Data collection and analysis

We used the standard methods of The Cochrane Collaboration (Higgins 2008). Review authors independently assessed trials for inclusion in the review and extracted the data. Any differences were resolved by discussion with all co-authors.

Assessment of risk of bias in included studies

The methodology used to assess risk of bias of studies included in the previous version of this review are given in Appendix 2.
For this update, the following methods were used.
Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). Any disagreement was resolved by discussion or by involving a third assessor.

(1) Sequence generation (checking for possible selection bias)

We describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
We assessed the method as:

- adequate (any truly random process, e.g., random number table; computer random number generator),
- inadequate (any non random process, e.g.,, odd or even date of birth; hospital or clinic record number) or
- unclear.

(2) Allocation concealment (checking for possible selection bias)

We describe for each included study the method used to conceal the allocation sequence in sufficient detail and determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.
We assessed the methods as:

- adequate (e.g., telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear.

(3) Blinding (checking for possible performance bias)

We describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which

intervention a participant received. Studies will be judged at low risk of bias if they were blinded, or if we judge that the lack of blinding could not have affected the results. Blinding will be assessed separately for different outcomes or classes of outcomes. We assessed the methods as:

- adequate, inadequate or unclear for participants;
- adequate, inadequate or unclear for personnel;
- adequate, inadequate or unclear for outcome assessors.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We state whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or was supplied by the trial authors, we re-included missing data in the analyses which we undertook. We assessed methods as:

- adequate;
- inadequate:
- unclear;

where 'adequate' is less than 20% losses to follow up.

(5) Selective reporting bias

We describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

- adequate (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- inadequate (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear.

(6) Other sources of bias

We describe for each included study any important concerns we have about other possible sources of bias.
We assessed whether each study was free of other problems that could put it at risk of bias:

- yes;
- no;
- unclear.

(7) Overall risk of bias

We made explicit judgements about whether studies are at high risk of bias, according to the criteria given in the Cochrane Handbook (Higgins 2008). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings. We explored the impact of the level of bias through undertaking sensitivity analyses.

Data management and analysis

We conducted data management and analysis using RevMan software (RevMan 2008). V Flenady, R Cincotta and J Dodd independently extracted data. Results are reported as mean differences for continuous variables, and risk ratios for categorical outcomes, both with 95% confidence intervals.
We conducted the meta-analysis using the fixed-effect model, and assessed heterogeneity by visual inspection of the outcomes tables and by using two statistics (H and I^2 test) of heterogeneity (Higgins 2002). Where we discovered statistical heterogeneity, this was explored.
Results are presented by reason women were considered to be at risk of preterm birth, including:

- past history of spontaneous preterm birth (including preterm premature rupture of membranes);
- multiple pregnancy;
- ultrasound identified short cervical length;
- fetal fibronectin testing;
- presentation with symptoms or signs of threatened preterm labour;
- other reason for risk of preterm birth.

Planned subgroup analyses included an assessment of the effect of: (1) time of treatment commencing (before 20 weeks' gestation versus after 20 weeks' gestation); (2) route of administration (intramuscular, intravaginal, oral, intravenous); and (3) different dosage regimens (divided arbitrarily into a cumulative dose of less than 500 mg per week and a dose of greater than or equal to 500 mg per week). To evaluate the effect of subgroup comparisons, we considered confidence intervals (where non-overlap was taken to indicate a statistically significant difference).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Our search strategy identified 22 studies for consideration. Eleven studies met the inclusion criteria stated (Borna 2008; da Fonseca 2003; Facchinetti 2007; Fonesca 2007; Hartikainen 1980; Hauth 1983; Johnson 1975; Meis 2003; O'Brien 2007; Papiernik 1970; Rouse 2007) involving a total of 2714 women and 3452 infants. The study by Northern (Northen 2007) reports the follow up of children involved in the Meis study (Meis 2003). Refer to table ' Characteristics of included studies' for details.

Included studies

Use of progesterone in women with a history of prior spontaneous preterm birth

Description of studies

Four studies were included involving a total of 1329 women with a past history of spontaneous preterm birth (da Fonseca 2003; Johnson 1975; Meis 2003; O'Brien 2007), of which two compared weekly intramuscular injection with placebo (Johnson 1975; Meis 2003), and two compared nightly vaginal progesterone with placebo (da Fonseca 2003; O'Brien 2007). Dose of progesterone administered varied from 90 mg daily (O'Brien 2007), to 100 mg daily (da Fonseca 2003), to 250 mg weekly (Johnson 1975; Meis 2003). Supplementation commenced prior to 20 weeks' gestation in three trials (Johnson 1975; Meis 2003; O'Brien 2007), and continued up to a gestational age varying from 24 weeks (Johnson 1975), to 28 weeks (da Fonseca 2003), 36 weeks (Meis 2003), and 37 weeks (O'Brien 2007) gestation. The primary outcomes reported by the trials related to the occurrence of preterm birth prior to 32 weeks' gestation (O'Brien 2007), and 37 weeks' gestation (da Fonseca 2003; Johnson 1975; Meis 2003). Two trials involved single centres (da Fonseca 2003; Johnson 1975), and two were multicentre trials (Meis 2003; O'Brien 2007), conducted principally from the United States of America (Johnson 1975; Meis 2003; O'Brien 2007), and Brazil (da Fonseca 2003). The report by Northen 2007 reports childhood follow up of 348 participants in the Meis randomised trial (Meis 2003).

Methodological quality of studies

Intramuscular progesterone

The method of generating the randomisation sequence was assessed as adequate in one study (Meis 2003), with both studies using treatment packs that appeared to be identical (Allocation concealment - adequate) (Johnson 1975; Meis 2003), and blinding of outcome assessment (Blinding - adequate) (Johnson 1975; Meis 2003). There were no reported losses to follow up in the study by Meis 2003, and 14% post-randomisation exclusions in the study by Johnson 1975. Both trials received a quality rating of adequate.

Vaginal progesterone

The method of generating the randomisation sequence was assessed as adequate in both studies (da Fonseca 2003; O'Brien 2007), with both studies using sequentially numbered treatment packs that appeared to be identical (Allocation concealment - adequate), and blinded outcome assessors (Blinding - adequate) (da Fonseca 2003; O'Brien 2007). Both studies reported less than 20% loss to follow up (da Fonseca 2003 10%; O'Brien 2007 7.3%). Both trials received a quality rating of adequate.

Use of progesterone in women with a short cervix identified on transvaginal ultrasound examination

Description of studies

A single study was included involving 250 women who were identified with a short cervix (defined as less than 15 mm) at the time of transvaginal ultrasound examination (Fonesca 2007). Women received either 200 mg nightly intravaginal progesterone or placebo, from 24 to 33 completed weeks of gestation, in a multicentre study conducted in centres in the United Kingdom, Greece, Chile and Brazil. The primary outcome related to the occurrence of preterm birth prior to 34 weeks' gestation.

Methodological quality of studies

Vaginal progesterone

The method of generating the randomisation sequence was not stated (Fonesca 2007). The study utilised central randomisation, with identical appearing treatment packs (Allocation concealment - adequate), and blinded outcome assessors (Blinding - adequate) (Fonesca 2007). There were no reported losses to follow up. The trial received a quality rating of adequate.

Use of progesterone in women with a multiple pregnancy

Description of studies

Two studies were included involving 738 women with a twin pregnancy (Hartikainen 1980; Rouse 2007), who received weekly intramuscular injections in a dose of 250mg or placebo, commencing at 16 to 20 weeks (Rouse 2007) or 28 weeks' gestation (Hartikainen 1980), and continuing to 35 weeks (Rouse 2007) or 37 weeks' gestation (Hartikainen 1980). One study was single centred and recruited women from Finland (Hartikainen 1980), while the other was multicentre, recruiting women from the United States of America (Rouse 2007). The primary outcomes reported included a composite of death or birth prior to 35 weeks' gestation (Rouse 2007).

Methodological quality of studies

Intramuscular progesterone

Only one of the included studies indicated the method of generation of the randomisation sequence (Rouse 2007), while it was not stated in the other (Hartikainen 1980). The study by Hartikainen 1980 did not indicate the method of allocation concealment (Allocation concealment - unclear (B)), but indicated the use of blinded outcome assessors (Blinding - adequate), and reported no losses to follow up, receiving an overall quality rating of unclear. The trial by Rouse 2007 used identical appearing treatment packs (Allocation concealment - adequate), blinded outcome assessors (Blinding - adequate), reported 1% loss to follow up, and received an overall quality rating of adequate.

Use of progesterone in women following symptoms or signs of threatened preterm labour

Description of studies

Two small studies involving a total of 130 women presenting with symptoms or signs of threatened preterm labour between 24 (Borna 2008) and 25 (Facchinetti 2007) weeks and 34 weeks' gestation were included, in which women were randomised following the use of acute tocolysis to arrest uterine activity. Borna 2008 randomised women to receive vaginal progesterone pessaries on a daily basis (400 mg) from randomisation until birth, or no treatment. The study involved a single centre in Iran. The primary outcome reported was the interval from randomisation to birth. Facchinetti 2007 randomised women to receive intramuscular progesterone every four days from randomisation to 36 weeks' gestation, or to no treatment. The study was conducted in Italy, and the primary outcome related to transvaginal ultrasound assessment of cervical length.

Methodological quality of studies

Intramuscular progesterone

Facchinetti 2007 utilised a random number table to generate the randomisation sequence, which was managed by a senior midwife (Allocation concealment - unclear). There was no blinding of outcome assessors (Blinding - unclear), and no reported losses to follow up. The trial received an overall quality rating of unclear.

Vaginal progesterone

Borna 2008 utilised a random number table to generate the randomisation sequence. There was no indication of the method of allocation concealment (Allocation concealment - unclear), did not use blinded outcome assessors (Blinding - unclear), and reported no losses to follow up. The trial received an overall quality rating of unclear.

Use of progesterone in women at risk of preterm birth for 'other' reasons

Description of studies

Papiernik 1970 recruited 99 women from Paris, France, in a single centred trial, with a 'high preterm risk score'. Women were allocated to receive intramuscular progesterone three times per week or placebo, from 28 to 32 weeks' gestation.

Hauth 1983 involved 168 women from the United States of America who were considered to be at risk of preterm birth due to active military service. Women received 1000 mg of progesterone weekly or placebo, from 16 to 20 weeks' gestation, up until 36 weeks' gestation. The primary outcome for the study related to the incidence of preterm birth at less than 37 weeks' gestation.

Methodological quality of studies

Intramuscular Progesterone

Hauth 1983 and Papiernik 1970 did not indicate the method of randomisation utilised, or the process of allocation concealment (Allocation concealment - unclear), but both stated the use of blinded outcome assessors (Blinding - adequate), and reported no losses to follow up. Both trials received an overall quality rating of unclear.

Excluded studies

Three studies were excluded as they used a quasi-randomised method of treatment allocation (Le Vine 1964; Suvonnakote 1986; Yemini 1985). One study (Hobel 1986) compared an oral progestogen with placebo, but presented outcomes only as percentages. Five studies were excluded as progesterone was administered in the first trimester to prevent miscarriage (Breart 1979; Brenner 1962; Corrado 2002; Turner 1966; Walch 2005), and are covered by the Cochrane review relating to the use of progesterone for prevention of miscarriage (Haas 2008). Refer to table ' Characteristics of excluded studies' for details.

Studies awaiting assessment

Two studies have been identified in abstract form only (Moghtadaei 2008; Rust 2006). Moghtadaei 2008 compares intramuscular progesterone with placebo and Rust 2006 compares the effects of intramuscular progesterone with cervical cerclage. These studies will be assessed for inclusion in subsequent updates of this review, as the full publication becomes available.

Risk of bias in included studies

The overall quality of the included trials varied from good to fair. While all trials were stated to be randomised and placebo controlled, the method of randomisation was described in only five trials (Borna 2008; da Fonseca 2003; Facchinetti 2007; Meis 2003; Rouse 2007). Allocation concealment was assessed as adequate in six trials (da Fonseca 2003; Fonesca 2007; Johnson 1975; Meis 2003; O'Brien 2007; Rouse 2007); and unclear in five trials (Borna 2008; Facchinetti 2007; Hartikainen 1980; Hauth 1983; Papiernik 1970). Nine of the eleven included trials were placebo controlled, with blinding of caregivers and participants (da Fonseca 2003; Fonesca 2007; Hartikainen 1980; Hauth 1983; Johnson 1975; Meis 2003; O'Brien 2007; Papiernik 1970; Rouse 2007). Refer to table 'Characteristics of included studies' for further details.

Effects of interventions

Eleven randomised controlled trials involving a total of 2425 women and 3187 infants were included in the meta-analysis. As the aetiology of preterm birth is multifactorial, results are presented according to the reason considered to be at risk for preterm birth (past history of spontaneous preterm birth (including preterm premature rupture of membranes), ultrasound identified short cervical length, multiple pregnancy, prior presentation with threatened preterm labour, and other reason for risk of preterm birth).

Progesterone versus placebo for women with a past history of spontaneous preterm birth

Primary outcomes

For women administered progesterone during pregnancy, for the primary outcome perinatal death, there was no statistically significant difference identified when compared with placebo. Women administered progesterone were significantly less likely to have a preterm birth less than 34 weeks' gestation (one study; 142 women; risk ration (RR) 0.15; 95% confidence interval (CI) 0.04 to 0.64). Major neurodevelopmental handicap in childhood was not reported.

Secondary infant outcomes

For women administered progesterone during pregnancy, when compared with placebo, there was a statistically significant reduction in the risk of:

- infant birthweight less than 2500 grams (two studies; 501 infants; RR 0.64; 95% CI 0.49 to 0.83); and
- necrotising enterocolitis (two studies; 1070 infants; RR 0.30; 95% CI 0.10 to 0.93); considerable heterogeneity was identified, and when a random-effects model was used, this outcome no longer reached statistical significance (two studies; 1070 infants; RR 0.25; 95% CI 0.03 to 2.46).

For infant outcomes perinatal death, intrauterine fetal death, neonatal death, respiratory distress syndrome, intraventricular haemorrhage (all grades and grade 3 or 4), retinopathy of prematurity, neonatal sepsis, or patent ductus arteriosus, there were no statistically significant differences identified.

Secondary maternal outcomes

For women administered progesterone during pregnancy, when compared with placebo, there was a statistically significant reduction in the risk of:

- preterm birth less than 37 weeks' gestation (four studies; 1255 women; RR 0.80; 95% CI 0.70 to 0.92); considerable heterogeneity was identified, and when a random-effects model was used, this outcome no longer reached statistical significance (four studies; 1255 women; RR 0.68; 95% CI 0.45 to 1.02).

There were no statistically significant differences for the outcomes threatened preterm labour, caesarean birth, use of antenatal corticosteroids, or the use of antenatal tocolysis.

Secondary childhood outcomes

There were no statistically significant differences identified for the outcomes developmental delay, intellectual impairment, motor impairment, visual impairment, hearing impairment, cerebral palsy, learning difficulties, height less than 5th centile or weight less than the 5th centile.

Effect of route of administration, time of commencing therapy, and dose of progesterone

There was no differential effect on these outcomes when considering route of administration of progesterone (intramuscular versus vaginal), time of commencement of supplementation (prior to 20 weeks' gestation versus after 20 weeks' gestation), or by total weekly cumulative dose of progesterone (less than 500 mg versus greater than 500 mg).

Progesterone versus placebo for women with a short cervix identified on ultrasound

Primary outcomes

For women administered progesterone during pregnancy, for the primary outcome perinatal death, there were no statistically significant differences identified when compared with placebo. Women administered progesterone were significantly less likely to have a preterm birth at less than 34 weeks' gestation (one study; 250

women; RR 0.58; 95% CI 0.38 to 0.87). Major neurodevelopmental handicap in childhood was not reported.

Secondary infant outcomes

For women administered progesterone during pregnancy, when compared with placebo, there was a statistically significant reduction in the risk of neonatal sepsis (one study; 274 infants; RR 0.28; 95% CI 0.08 to 0.97).

For infant outcomes infant birthweight less than 2500 grams, respiratory distress syndrome, need for assisted ventilation, intraventricular haemorrhage (all grades), retinopathy of prematurity, necrotising enterocolitis, intrauterine fetal death, or neonatal death, there were no statistically significant differences identified.

Secondary maternal outcomes

There were no secondary maternal outcomes reported.

Secondary childhood outcomes

None of the secondary childhood outcomes were reported.

Effect of route of administration, time of commencing therapy, and dose of progesterone

It was not possible to assess the effect of route of progesterone administration, gestational age at commencing therapy, or total cumulative dose of medication.

Progesterone versus placebo for women with a multiple pregnancy

Primary outcomes

For women administered progesterone during pregnancy, for the primary outcomes perinatal death, and preterm birth less than 34 weeks' gestation, there were no statistically significant differences identified when compared with placebo. Major neurodevelopmental handicap in childhood was not reported.

Secondary infant outcomes

For women administered progesterone during pregnancy, when compared with placebo, there were no statistically significant differences identified in the risk of infant birthweight less than 2500 grams, respiratory distress syndrome, need for ventilation, intraventricular haemorrhage, retinopathy of prematurity, necrotising enterocolitis, neonatal sepsis, or patent ductus arteriosus.

Secondary maternal outcomes

For women administered progesterone during pregnancy, when compared with placebo, there was a statistically significant reduction in the risk of use of antenatal tocolysis (one study; 654 women; RR 0.75; 95% CI 0.57 to 0.97).

There were no statistically significant differences for the outcomes preterm birth less than 37 weeks, caesarean birth, or the use of antenatal corticosteroids.

Secondary childhood outcomes

None of the secondary childhood outcomes were reported.

Effect of route of administration, time of commencing therapy, and dose of progesterone

There was no differential effect observed when considering time of commencement of supplementation (prior to 20 weeks' gestation versus after 20 weeks' gestation).

Progesterone versus placebo for women following presentation with threatened preterm labour

Primary outcomes

For women administered progesterone during pregnancy, for the primary outcomes perinatal death, and preterm birth less than 34 weeks' gestation, there were no statistically significant differences identified when compared with placebo. Major neurodevelopmental handicap in childhood was not reported.

Secondary infant outcomes

For women administered progesterone during pregnancy, when compared with placebo, there was a statistically significant reduction in the risk of:

- preterm birth less than 37 weeks' gestation (one study; 60 women; RR 0.29; 95% CI 0.12 to 0.69);
- infant birthweight less than 2500 grams (one study; 70 infants; RR 0.52; 95% CI 0.28 to 0.98); and
- respiratory distress syndrome (one study; 70 infants; RR 0.30; 95% CI 0.11 to 0.83).

There were no statistically significant differences for the outcomes needed for mechanical ventilation or sepsis.

Secondary maternal outcomes

There were no secondary maternal outcomes reported.

Secondary childhood outcomes

There were no secondary childhood outcomes reported.

Effect of route of administration, time of commencing therapy, and dose of progesterone

It was not possible to assess the effect of route of progesterone administration, gestational age at commencing therapy, or total cumulative dose of medication.

Progesterone versus placebo for women with 'other' risk factors for preterm birth

Primary outcomes

For women administered progesterone during pregnancy, for the primary outcome perinatal death there were no statistically significant differences identified when compared with placebo. The outcomes preterm birth less than 34 weeks' gestation and major neurodevelopmental handicap in childhood were not reported.

Secondary infant outcomes

For women administered progesterone who were considered to be at risk of preterm birth for 'other' reasons, when compared with placebo, there were no statistically significant differences for the outcomes perinatal death, infant birthweight less than 2500 grams, intrauterine fetal death or neonatal death.

Secondary maternal outcomes

For women administered progesterone who were considered to be at risk of preterm birth for 'other' reasons, when compared with placebo, there were no statistically significant differences for the outcome preterm birth less than 37 weeks' gestation.

Secondary childhood outcomes

There were no secondary childhood outcomes reported.

Effect of route of administration, time of commencing therapy, and dose of progesterone

There was no differential effect observed related to cumulative dose of progesterone administered, or gestational age at commencing therapy.

DISCUSSION

The randomised trials identified assessed the use of progesterone in women considered to be at increased risk of preterm birth by virtue of history of spontaneous preterm birth, ultrasonographic evaluation of cervical length, presentation in threatened preterm labour, multiple pregnancy, or other reasons (including 'high preterm risk score' and active military duty).

Progesterone for women with a past history of spontaneous preterm birth

For women with a past history of spontaneous preterm birth, there were no statistically significant differences identified for the primary outcome perinatal death. Women administered progesterone were significantly less likely to have a preterm birth less than 34 weeks' gestation (one study; 142 women; risk ratio (RR) 0.15; 95% confidence interval (CI) 0.04 to 0.64). For the secondary infant outcomes, the use of progesterone was associated with a reduction in the risk of infant birthweight less than 2500 grams (two studies; 501 infants; RR 0.64; 95% CI 0.49 to 0.83). There were no significant differences identified for other secondary infant and maternal health outcomes with the use of progesterone. Information related to childhood health and wellbeing is limited, with a single trial reporting two-year follow-up results to date (Northen 2007), in which there were no documented differences in growth or developmental outcomes between those infants exposed in utero to progesterone and those to placebo. Further information is required about the optimal route of administration of progesterone, with the largest study to date using vaginal progesterone gel suggesting no benefit in this group of women (O'Brien 2007). There are three ongoing randomised trials assessing the role of intramuscular (Rozenberg 2007) and vaginal (Crowther 2007; Perlitz 2007) progesterone in women with a history of spontaneous preterm birth, which will contribute information about the role of progesterone in this group of women.

Progesterone for women with a short cervix identified on ultrasound

In the single trial to date assessing the role of progesterone in women with a short cervix identified on ultrasound (Fonesca 2007), there were no statistically significant differences identified for the primary outcome perinatal death. Women administered progesterone were significantly less likely to have preterm birth less than 34 weeks' gestation (one study; 250 women; RR 0.58; 95% CI 0.38 to 0.87). For the secondary infant outcomes, the use of progesterone was associated with a reduction in the risk of neonatal sepsis (1 study; 274 infants; RR 0.28; 95% CI 0.08 to 0.97). Further information is required about the risk of other infant health outcomes, and maternal health outcomes in this group of women. Reporting of childhood outcomes is lacking, with no trials reporting this information to date. There is a single ongoing randomised trial assessing the role of intramuscular (Grobman 2007) progesterone in nulliparous women with a short cervix, identified on transvaginal ultrasound, which will contribute information about the role of progesterone in this group of women.

Progesterone for women with a multiple pregnancy

The role of progesterone in women with a multiple pregnancy is less clear, with no identified differences in the primary outcomes perinatal death, and preterm birth less than 34 weeks' gestation. While the use of progesterone was associated with a reduction in the use of antenatal tocolysis (one study; 654 women; RR 0.75;

95% CI 0.57 to 0.97), there were no differences identified for the other secondary infant and maternal health outcomes. Information relating to long-term childhood health outcomes is unavailable to date. There are several ongoing randomised trials assessing the role of intramuscular (Bruinse 2007; Maurel 2007; Nassar 2007) and vaginal (Norman 2007; Rode 2007; Serra 2007; Wood 2007) progesterone in women with a multiple pregnancy which will contribute information about the role of progesterone in this group of women.

Progesterone for women following presentation with threatened preterm labour

The role of progesterone for women following presentation with threatened preterm labour remains uncertain. The identified randomised trials indicate a reduction in the risk of preterm birth before 37 weeks, infant birthweight less than 2500 grams, and respiratory distress syndrome. However, the outcomes have been reported in a single study only, and the combined sample size of the two trials are small and underpowered to detect differences in both maternal and infant health outcomes. Furthermore, the failure to use a placebo, and lack of blinding in the assessment of outcomes in both studies increases the potential for bias. There is an ongoing randomised trial assessing the role of vaginal progesterone in women presenting with symptoms or signs of threatened preterm labour which will contribute information about the role of progesterone in this group of women (Martinez 2007).

Progesterone versus placebo for women with 'other' risk factors for preterm birth

The role of progesterone in women considered to be at risk of preterm birth for 'other reasons' is uncertain, with the two randomised trials to date indicating no benefit in terms of perinatal death, preterm birth less than 37 weeks' gestation, or infant birthweight less than 2500 grams. However, the combined sample size of these two trials is significantly underpowered to detect all but large differences in these outcomes.

To date, there remains limited information about the benefits and harms of progesterone, particularly in relation to long-term outcomes for the infants, with only a single randomised trial reporting to date. Ongoing follow up of children exposed to progesterone in utero remains a priority. Maternal outcomes following antenatal progesterone therapy were poorly reported in the available literature, including treatment side-effects, preferences of mode of administration and satisfaction of care. Further information is required on these important issues (Greene 2003; Iams 2003). In addition, there remains uncertainty as to the optimal dose of progesterone to be administered, the optimal route of administration, and the optimal gestational age at which to commence therapy. The American College of Obstetricians and Gynecologists have issued a committee opinion relating to the use of progesterone for the prevention of preterm birth, indicating the need for further information about the optimal mode of administration (ACOG 2003). To date, only three studies have been reported detailing the use of vaginal progesterone therapy (da Fonseca 2003; Fonesca 2007; O'Brien 2007). Further information is required from randomised trials relating to the effect of vaginal progesterone on maternal and infant health outcomes for women at risk of preterm birth.

AUTHORS' CONCLUSIONS

Implications for practice

Summary of the available information

Progesterone for women with a past history of spontaneous preterm birth

The use of progesterone in this group of women is associated with a reduction in the risk of preterm birth before 34 weeks' gestation, preterm birth before 37 weeks' gestation, and infant birthweight less than 2500 grams. Further information is required about the occurrence of other maternal, and infant health outcomes, particularly longer-term childhood health. In addition, further information is required as to the optimal route of administration of progesterone, the optimal dose to be administered, and the best time to commence therapy.

Progesterone for women with a short cervix identified on ultrasound

The use of progesterone in this group of women is associated with a reduction in the risk of preterm birth less than 34 weeks' gestation, and neonatal sepsis. The information relates to a single trial only, and further information is required about other maternal, infant and childhood health outcomes. In addition, further information is required as to the optimal route of administration of progesterone, the optimal dose to be administered, and the best time to commence therapy.

Progesterone for women with a multiple pregnancy

While the use of progesterone in this group of women is associated with a reduction in the use of antenatal tocolysis, there is no reduction in the risk of perinatal death, preterm birth and other maternal, infant, and childhood health outcomes. Further information is required as to the optimal route of administration of progesterone, the optimal dose to be administered, and the best time to commence therapy.

Progesterone for women following presentation with threatened preterm labour

The role of progesterone for women presenting following symptoms or signs of threatened preterm labour is uncertain.

Progesterone for women with 'other' risk factors for preterm birth

The role of progesterone in women considered to be at risk of preterm birth for 'other reasons' is uncertain.

Implications for research

Further well-designed randomised controlled trials are required to assess the benefits and harms of progesterone therapy when given to women considered to be at increased risk of early birth, by virtue of previous history of spontaneous preterm birth, short cervix identified by transvaginal ultrasound, following arrest of symptoms or signs of threatened preterm labour, or on the basis of 'other' risk factors, for important clinical outcomes for both women and their infants. Assessment of longer-term infant and childhood outcomes remains a priority. The use of vaginal progesterone has been under-evaluated to date (four trials only), with most of the identified trials using intramuscular 17-alpha-hydroxyprogesterone caproate. Further information is required to assess the optimal timing, mode of administration and dose of administration of progesterone.

There are several randomised trials that are currently addressing the use of progesterone for preterm birth - *see* 'Characteristics of ongoing studies' for details.

ACKNOWLEDGEMENTS

We thank Lynn Hampson for searching the trials register.

This updated review, which was first published in Issue 1, 2006 of *The Cochrane Library*, has been commented on by a peer, a member of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Borna 2008

Methods	Method of randomisation: random number table. Allocation concealment: unclear. Blinded outcome assessment: no. Completeness of follow up: outcome data available for 70 women.
Participants	70 women presenting between 24 and 34 weeks' gestation with symptoms and signs of threatened preterm labour, where acute symptoms were arrested following use of tocolytic medication.
Interventions	Daily intravaginal pessary (400 mg) versus no treatment.
Outcomes	Interval from randomisation to birth.
Notes	Trial conducted in Tehran, Iran.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Random number table.
Allocation concealment?	Unclear	Unclear.
Blinding? All outcomes	Unclear	No blinding of outcome assessment.
Incomplete outcome data addressed? All outcomes	Yes	Complete data available.
Free of selective reporting?	Yes	
Free of other bias?	Yes	

da Fonseca 2003

Methods	Method of randomisation: random number table. Allocation concealment: sequential sealed envelopes; allocation to either drug A or B; allocation of groups revealed after last woman birthed. Blinded outcome assessment: yes. Completeness of follow up: outcome data available for 142 women (15 women excluded after randomisation).
Participants	157 women considered to be at 'high risk' for preterm birth due to history of previous preterm birth, cervical suture, uterine malformation.
Interventions	Nightly intravaginal pessary of either 100 mg progesterone or placebo from 24 weeks until 28 weeks' gestation, or birth if earlier.
Outcomes	Preterm birth before 37 weeks' gestation; preterm birth before 34 weeks' gestation.
Notes	Trial conducted in Sao Paulo, Brazil.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Random number table.
Allocation concealment?	Yes	Adequate; sequential sealed opaque envelopes.
Blinding? All outcomes	Yes	Outcome assessor blinded.
Incomplete outcome data addressed? All outcomes	Yes	15 women (less than 1%) post-randomisation exclusions.
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Facchinetti 2007

Methods	Method of randomisation: random number table. Allocation concealment: randomisation list managed by senior midwife; allocation to either progesterone or placebo. Blinding of outcome assessment: no. Completeness of follow up: outcome data available for 60 women.

Facchinetti 2007 (*Continued*)

Participants	60 women presenting between 25 and 33 + 6 weeks' gestation with symptoms and signs of threatened preterm labour, where acute symptoms were arrested following use of tocolytic medication (atosiban).
Interventions	341 mg intramuscular 17OHP administered every 4 days to 36 weeks' gestation.
Outcomes	Cervical length as assessed by transvaginal ultrasound. Secondary outcomes included preterm birth < 37 weeks, and infant birthweight.
Notes	Trial conducted in Modena, Italy.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random number table.
Allocation concealment?	Unclear	Unclear; list managed by "senior midwife" with allocation to either progesterone or placebo.
Blinding? All outcomes	No	No blinding of outcome assessor.
Incomplete outcome data addressed? All outcomes	Yes	Outcome data available for all women.
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Fonesca 2007

Methods	Method of randomisation: not stated. Allocation concealment: central randomisation process; identically appearing treatment packs. Blinded outcome assessment: yes. Completeness of follow up: outcome data available for all 250 women randomised.
Participants	250 women undergoing transvaginal ultrasound assessment of cervical length, where the cervical length was measured to be 15 mm or less. Women with both singleton and multiple pregnancies were eligible to participate.
Interventions	Nightly intravaginal pessary of either 200 mg micronised progesterone or placebo from 24 weeks until 33 + 6 weeks' gestation, or birth if earlier.

Fonesca 2007 (*Continued*)

Outcomes	Primary outcome: spontaneous preterm birth less than 34 weeks' gestation. Secondary outcomes: infant birthweight, fetal death, neonatal death, major adverse outcomes (intraventricular haemorrhage, respiratory distress syndrome, retinopathy of prematurity, necrotising enterocolitis), need for neonatal special care (neonatal intensive care unit admission, ventilation, phototherapy, treatment for proven or suspected sepsis, blood transfusion).
Notes	Trial conducted in 5 maternity hospitals in London (UK), Santiago (Chile), Sao Paulo (Brazil), and Greece.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Method of randomisation generation not stated.
Allocation concealment?	Yes	Adequate; central randomisation; identical appearing treatment packs.
Blinding? All outcomes	Yes	Blinding of participants, caregivers, outcome assessors.
Incomplete outcome data addressed? All outcomes	Yes	Complete follow up.
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Hartikainen 1980

Methods	Method of randomisation: stated to be "placebo controlled and double blind". Allocation concealment: not stated. Blinded outcome assessment: yes. Completeness of follow up: outcome data available for 77 women.
Participants	77 women with a twin pregnancy.
Interventions	Weekly intramuscular injection of either 250 mg 17-hydroxyprogesterone caproate or placebo from 28 weeks' gestation until 37 weeks' gestation or birth if earlier.
Outcomes	Perinatal death.
Notes	Trial conducted in Finland.

Hartikainen 1980 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Process of sequence generation not stated.
Allocation concealment?	Unclear	Unclear.
Blinding? All outcomes	Yes	Blinding of outcome assessors.
Incomplete outcome data addressed? All outcomes	Yes	Outcome data available for all participants.
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Hauth 1983

Methods	Method of randomisation: stated to be "randomised, double blind intervention". Allocation concealment: not stated. Blinded outcome assessment: yes. Completeness of follow up: outcome data available for all women randomised.
Participants	168 women on active military duty.
Interventions	Weekly intramuscular injection of either 1000 mg 17-hydroxyprogesterone caproate or placebo from 16 to 20 weeks until 36 weeks' gestation, or birth if earlier.
Outcomes	Preterm birth before 37 weeks' gestation; birthweight less than 2.5 kg; perinatal death.
Notes	Trial conducted in Lackland Airforce Base, Texas, USA.

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Sequence generation not stated.
Allocation concealment?	Unclear	Unclear.
Blinding? All outcomes	Yes	Blinding of outcome assessors.

Hauth 1983 (*Continued*)

Incomplete outcome data addressed? All outcomes	Yes	Outcome data available for all women recruited.
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Johnson 1975

Methods	Method of randomisation: stated to be "random double blind fashion". Allocation concealment: next of identical drug packages. Blinded outcome assessment: yes. Completeness of follow up: outcome data available for 43 women (7 women excluded after randomisation).
Participants	50 women with a history of 2 previous spontaneous abortions or previous preterm birth before 36 weeks' gestation.
Interventions	Weekly intramuscular injection of either 250 mg 17-hydroxyprogesterone caproate or placebo from 'booking' until 24 weeks' gestation.
Outcomes	Preterm birth before 37 weeks' gestation; birthweight less than 2.5 kg; perinatal death.
Notes	Trial conducted in Baltimore, USA.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Generation of sequence not stated.
Allocation concealment?	Yes	Adequate; identical appearing treatment packs.
Blinding? All outcomes	Yes	Outcome assessors blinded.
Incomplete outcome data addressed? All outcomes	Yes	7 women excluded post-randomisation (1%).
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Meis 2003

Methods	Method of randomisation: computer generated 2:1 random number schedule. Allocation concealment: next of identical drug packages. Blinded outcome assessment: yes. Completeness of follow up: outcome data available for 463 women.
Participants	463 women with a history of previous spontaneous preterm birth; exclusion women with multiple pregnancy, known fetal anomaly, progesterone or heparin treatment during pregnancy, current or planned cervical cerclage, hypertension, seizure disorder.
Interventions	Weekly intramuscular injection of either 250 mg 17-hydroxyprogesterone caproate or placebo from 16 to 20 weeks until 36 weeks' gestation, or birth if earlier.
Outcomes	Preterm birth before 37 weeks' gestation; birthweight less than 2.5 kg; stillbirth; neonatal death; intraventricular haemorrhage; respiratory distress syndrome; bronchopulmonary dysplasia; sepsis; necrotising enterocolitis; retinopathy of prematurity; patent ductus arteriosus.
Notes	Trial conducted by the Maternal-Fetal Medicine Network, USA.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated sequence.
Allocation concealment?	Yes	Adequate; identical appearing treatment packs.
Blinding? All outcomes	Yes	Women, caregivers and outcome assessors blinded.
Incomplete outcome data addressed? All outcomes	Yes	Outcome data available for all 463 women recruited.
Free of selective reporting?	Yes	
Free of other bias?	Yes	

O'Brien 2007

Methods	Method of randomisation: random number table. Allocation concealment: identical appearing sequentially numbered treatment packs. Blinded outcome assessment: yes. Completeness of follow up: outcome data available for 611 of 659 women randomised (48 (7.3%) women lost to follow up).
Participants	659 women with a history of prior spontaneous preterm birth. Exclusions: adverse reaction to progesterone; progesterone treatment within 4 weeks of randomisation; medical conditions; suspected genital tract malignancy; thromboembolic disease; fetal anomaly; multiple pregnancy; planned cervical cerclage.
Interventions	Nightly vaginal progesterone gel (90 mg) versus placebo.
Outcomes	Preterm birth less than 32 weeks; Apgar scores, infant birthweight, NICU admission.
Notes	Trial conducted in 53 centres worldwide.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Random number table.
Allocation concealment?	Yes	Adequate; identical appearing treatment packs.
Blinding? All outcomes	Yes	Women, caregivers and outcome assessors blinded.
Incomplete outcome data addressed? All outcomes	Yes	Outcome data available for 611 of 659 women randomied (7.3% women lost to follow up).
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Papiernik 1970

Methods	Method of randomisation: unclear. Allocation concealment: unclear. Blinded outcome assessment: yes. Completeness of follow up: outcome data available for 99 women.
Participants	99 women with a "high preterm risk score".

Papiernik 1970 (*Continued*)

Interventions	Every three days intramuscular injection of either 250 mg 17-hydroxyprogesterone caproate or placebo from 28 weeks' gestation until 32 weeks' gestation.
Outcomes	Preterm birth before 37 weeks' gestation; birthweight less than 2.5 kg; perinatal death.
Notes	Trial conducted in Paris, France.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear.
Blinding? All outcomes	Yes	Outcome assessor blinded.
Incomplete outcome data addressed? All outcomes	Yes	Outcome data available for 99 women randomised.

Rouse 2007

Methods	Method of randomisation: the "urn" method of randomisation. Allocation concealment: next of identical appearing treatment injections. Blinded outcome assessment: yes. Completeness of follow up: 661 women randomised with outcome data available for 655 women.
Participants	661 women with a twin pregnancy; exclusion women with known fetal anomaly, spontaneous fetal death of a fetus after 12 weeks, presumed monoamnionic placenta, suspected twin-twin transfusion syndrome, marked ultrasonographic growth discordance, progesterone or heparin treatment during pregnancy, current or planned cervical cerclage, hypertension, insulin dependent diabetes, and twin pregnancies that were the result of intentional fetal reduction.
Interventions	Weekly intramuscular injection of either 250 mg 17-hydroxyprogesterone caproate or placebo (castor oil) from 16 - 20 + 3 weeks until 34 completed weeks' gestation, or birth if earlier.
Outcomes	Primary outcome: composite of delivery or death prior to 35 weeks' gestation. Secondary outcomes: randomisation to delivery interval; composite adverse outcomes (retinopathy of prematurity, respiratory distress syndrome, sepsis, necrotising enterocolitis, bronchopulmonary dysplasia, grade 3 or 4 intraventricular haemorrhage, periventricular leukomalacia), birthweight (less than 2500 grams and less than 1500 grams), 5-minute Apgar score < 7, patent ductus arteriosus, pneumonia, mechanical ventilation, seizures.

Rouse 2007 (*Continued*)

	Preterm birth before 37 weeks' gestation; birthweight less than 2.5 kg; stillbirth; neonatal death; intraventricular haemorrhage; respiratory distress syndrome; bronchopulmonary dysplasia; sepsis; necrotising enterocolitis; retinopathy of prematurity; patent ductus arteriosus.
Notes	Trial conducted by the Maternal-Fetal Medicine Network, USA.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Urn method of randomisation.
Allocation concealment?	Yes	Adequate; identical appearing treatment packs.
Blinding? All outcomes	Yes	Women, caregivers and outcome assessors blinded.
Incomplete outcome data addressed? All outcomes	Yes	Outcome data available for 655 of 661women (less than 1% loss to follow up).
Free of selective reporting?	Yes	
Free of other bias?	Yes	

NICU: neonatal intensive care unit

Characteristics of excluded studies *[ordered by study ID]*

Breart 1979	Progesterone administration for prevention of miscarriage.
Brenner 1962	Progesterone administration for prevention of miscarriage.
Corrado 2002	Progesterone administered after amniocentesis for the prevention of miscarriage.
Hobel 1986	Compares an oral progesterone agent with placebo but the only outcome reported is the rate of preterm birth as a percentage (not able to determine n = in either progesterone or placebo group). Other results reported as experimental group versus control (this allocation is not randomised but based on risk assessment at first and second antenatal visit).

(*Continued*)

Le Vine 1964	Quasi-randomised trial.
Suvonnakote 1986	Quasi-randomised trial - women were 'divided' into 2 groups (trial group and control group).
Turner 1966	Progesterone administration for prevention of miscarriage.
Walch 2005	Progesterone administration for prevention of miscarriage.
Yemini 1985	Quasi-randomised trial.

Characteristics of ongoing studies *[ordered by study ID]*

Bruinse 2007

Trial name or title	17 alpha hydroxyprogesterone in multiple pregnancies to prevent handicapped infants (The AMPHIA Study).
Methods	
Participants	Women with a multiple pregnancy.
Interventions	IM 17OHP vs placebo.
Outcomes	Composite of neonatal morbidity.
Starting date	August 2006.
Contact information	HW Bruinse: h.w.Bruinse@umcutrecht.nl
Notes	

Creasy 2008

Trial name or title	The effect of vaginal progesterone administration in the prevention of preterm birth in women with a short cervix. NCT00615550.
Methods	
Participants	Women with a singleton gestation and a short cervical length by transvaginal ultrasound (TVU) defined as 10-20mm

Creasy 2008 (*Continued*)

Interventions	Progesterone 8% vaginal gel, 1.125 grams once daily, beginning at 19 0/7 to 23 6/7 weeks gestation through 36 6/7 weeks gestation. Placebo vaginal gel, 1.125 grams once daily, beginning at 19 0/7 to 23 6/7 weeks gestation through 36 6/7 weeks gestation
Outcomes	Reduction in the frequency of preterm birth (less than or equal to 32 6/7 weeks gestation
Starting date	March 2008
Contact information	Joseph R. Parella: jparella@columbialabs.com
Notes	

Crowther 2007

Trial name or title	Progesterone for the prevention of neonatal respiratory distress syndrome (The PROGRESS Study). ISRCTN20269066.
Methods	
Participants	Women with a history of previous spontaneous preterm birth.
Interventions	Daily vaginal progesterone vs placebo.
Outcomes	Neonatal lung disease.
Starting date	October 2005.
Contact information	progress@adelaide.edu.au caroline.crowther@adelaide.edu.au
Notes	

Grobman 2007

Trial name or title	RCT of progesterone to prevent preterm birth in nulliparous women with a short cervix. NCT00439374.
Methods	
Participants	Nulliparous women with a short cervix identified on transvaginal ultrasound.
Interventions	Weekly IM 17OHP vs placebo.

Grobman 2007 (*Continued*)

Outcomes	Preterm birth less than 37 weeks.
Starting date	April 2007.
Contact information	Catherine Spong: spongc@exchange.nih.gov
Notes	

Martinez 2007

Trial name or title	Vaginal progesterone to prevent preterm delivery in women with preterm labour. NCT00536003.
Methods	
Participants	Women presenting with symptoms and signs of preterm labour, and evidence of cervical change or positive fetal fibronectin testing.
Interventions	Vaginal progesterone vs placebo.
Outcomes	Preterm birth less than 37 weeks.
Starting date	July 2006.
Contact information	Begona Martinez de Tejada: begona.mdt@bluewin.ch
Notes	

Maurel 2007

Trial name or title	17OHP for reduction of neonatal morbidity due to preterm birth in twin and triplet pregnancies. NCT00163020.
Methods	
Participants	Women with twin or triplet pregnancy.
Interventions	Weekly IM 17OHP vs placebo.
Outcomes	Composite of adverse neonatal outcomes.
Starting date	November 2004.
Contact information	Diana Abril: diana˙abril@pediatrix.com

Maurel 2007 (*Continued*)

Notes	

Nassar 2007

Trial name or title	Prevention of preterm delivery in twin pregnancies by 17 alpha hydroxyprogesterone caproate. NCT00141908.
Methods	
Participants	Women with a twin pregnancy.
Interventions	Weekly IM 17OHP vs placebo.
Outcomes	Preterm birth.
Starting date	March 2006.
Contact information	Anwar Nassar: an21@aub.edu.lb
Notes	

Norman 2007

Trial name or title	Double blind randomised placebo controlled trial of progesterone for the prevention of preterm birth in twins. ISRCTN35782581.
Methods	
Participants	Women with a twin pregnancy.
Interventions	Daily vaginal progesterone vs placebo.
Outcomes	Preterm birth less than 34 weeks.
Starting date	November 2005.
Contact information	Jane Norman: j.e.norman@clinmed.gla.ac.uk
Notes	

Perlitz 2007

Trial name or title	Prevention of recurrent preterm delivery by a natural progesterone agent. NCT00329316.
Methods	
Participants	Women with preterm labour in a prior pregnancy.
Interventions	Daily vaginal progesterone gel vs placebo.
Outcomes	Not specified.
Starting date	Not yet recruiting.
Contact information	Yuri Perlitz: yperlitz@poria.health.gov.il
Notes	

Rode 2007

Trial name or title	Does progesterone prevent very preterm delivery in twin pregnancies? NCT00329914.
Methods	
Participants	Women with a twin pregnancy.
Interventions	Progesterone vs placebo.
Outcomes	Preterm birth less than 34 weeks.
Starting date	June 2006.
Contact information	Line Rode: line.rode@rh.dk
Notes	

Rozenberg 2007

Trial name or title	Efficacy of 17 alpha hydroxy-progesterone caproate for the prevention of preterm delivery. NCT00331695.
Methods	
Participants	Women with either presentation in threatened preterm labour, history of prior preterm birth, or multiple pregnancy (twin).

Rozenberg 2007 (*Continued*)

Interventions	IM 17OHP vs placebo.
Outcomes	Randomisation to birth interval.
Starting date	June 2006.
Contact information	Patrick Rozenberg: prozenberg@chi-poissy-st-germain.fr
Notes	

Serra 2007

Trial name or title	Natural progesterone and preterm birth in twins. NCT00480402
Methods	
Participants	Women with a twin pregnancy.
Interventions	Natural progesterone vs placebo.
Outcomes	Preterm birth less than 37 weeks.
Starting date	January 2006.
Contact information	Vicente Serra: vserra@ivi.es
Notes	

Starkey 2008

Trial name or title	Comparing intramuscular versus vaginal progesterone for prevention of preterm birth. NCT00579553.
Methods	
Participants	Women with singleton pregnancies and history of prior spontaneous preterm birth.
Interventions	Weekly intramuscular injection of 17 alpha hydroxylprogesterone caproate (250mg) or daily vaginal progesterone (100mg).
Outcomes	Maternal, fetal and neonatal outcomes.
Starting date	October 2006.

Starkey 2008 (*Continued*)

Contact information	Christy Zornes: christina- zornes@ouhsc.edu
Notes	

Swaby 2007

Trial name or title	Pilot randomized controlled trial of vaginal progesterone to prevent preterm birth in multiple pregnancy.
Methods	
Participants	Women with a multiple pregnancy.
Interventions	Vaginal progesterone (90mg) or placebo gel.
Outcomes	Duration of pregnancy.
Starting date	
Contact information	C Swaby. University of Calgary, 1403-29 Street, Calgary, Canada
Notes	

Wood 2007

Trial name or title	Vaginal progesterone versus placebo in multiple pregnancy. NCT00343265.
Methods	
Participants	Women with a multiple pregnancy.
Interventions	Daily vaginal progesterone gel vs placebo.
Outcomes	Primary: Gestational age.
Starting date	June 2006.
Contact information	Stephen Wood: stephen.wood@calgaryhealthregion.ca
Notes	

IM: intramuscular
RCT: randomised controlled trial
vs: versus

DATA AND ANALYSES

Comparison 1. Progesterone versus placebo: previous history spontaneous preterm birth

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Perinatal death	3	1114	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.38, 1.11]
1.1 Intramuscular	2	503	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.23, 0.98]
1.2 Vaginal	1	611	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.43, 2.22]
2 Preterm birth less than 37 weeks	4	1255	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.70, 0.92]
2.1 Intramuscular	2	502	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.51, 0.77]
2.2 Vaginal	2	753	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.79, 1.14]
3 Preterm birth less than 34 weeks	1	142	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.04, 0.64]
3.1 Intramuscular	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.2 Vaginal	1	142	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.04, 0.64]
4 Threatened preterm labour	2	601	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.64, 1.33]
4.1 Intramuscular	1	459	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.73, 1.87]
4.2 Vaginal	1	142	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.35, 1.11]
5 Caesarean section	2	1070	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.82, 1.23]
5.1 Intramuscular	1	459	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.68, 1.30]
5.2 Vaginal	1	611	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.81, 1.35]
6 Antenatal corticosteroids	2	1070	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.73, 1.16]
6.1 Intramuscular	1	459	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.58, 1.30]
6.2 Vaginal	1	611	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.72, 1.26]
7 Antenatal tocolysis	3	1114	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.81, 1.52]
7.1 Intramuscular	2	503	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.73, 1.72]
7.2 Vaginal	1	611	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.70, 1.74]
8 Infant birthweight less than 2500 grams	2	501	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.49, 0.83]
8.1 Intramuscular	2	501	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.49, 0.83]
9 Respiratory distress syndrome	2	1069	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.56, 1.10]
9.1 Intramuscular	1	458	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.38, 1.04]
9.2 Vaginal	1	611	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.59, 1.43]
10 Use of assisted ventilation	1	459	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.35, 1.01]
10.1 Intramuscular	1	459	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.35, 1.01]
11 Intraventricular haemorrhage - all grades	2	1070	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.25, 1.19]
11.1 Intramuscular	1	459	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.08, 0.82]
11.2 Vaginal	1	611	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.36, 3.80]
12 Intraventricular haemorrhage - grade 3 or 4	2	1069	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [0.21, 11.75]
12.1 Intramuscular	1	458	Risk Ratio (M-H, Fixed, 95% CI)	2.52 [0.12, 52.09]
12.2 Vaginal	1	611	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.06, 15.55]
13 Retinopathy of prematurity	1	458	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.15, 1.69]
13.1 Intramuscular	1	458	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.15, 1.69]
14 Necrotising enterocolitis	2	1070	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.10, 0.93]
14.1 Intramuscular	1	459	Risk Ratio (M-H, Fixed, 95% CI)	0.06 [0.00, 1.03]
14.2 Vaginal	1	611	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.14, 2.43]
15 Neonatal sepsis	1	459	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.35, 3.59]

15.1 Intramuscular	1	459	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.35, 3.59]
16 Patent ductus arteriosus	1	459	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.16, 1.18]
16.1 Intramuscular	1	459	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.16, 1.18]
17 Intrauterine fetal death	3	1114	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.35, 2.03]
17.1 Intramuscular	2	503	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.19, 2.13]
17.2 Vaginal	1	611	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.33, 4.51]
18 Neonatal death	3	1114	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.28, 1.10]
18.1 Intramuscular	2	503	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.17, 1.03]
18.2 Vaginal	1	611	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.28, 2.46]
19 Developmental delay	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.36, 2.04]
19.1 Intramuscular	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.36, 2.04]
20 Intellectual impairment	1	274	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.05, 31.34]
20.1 Intramuscular	1	274	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.05, 31.34]
21 Motor Impairment	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.11, 3.76]
21.1 Intramuscular	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.11, 3.76]
22 Visual Impairment	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.16, 4.57]
22.1 Intramuscular	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.16, 4.57]
23 Hearing Impairment	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.09, 1.24]
23.1 Intramuscular	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.09, 1.24]
24 Cerebral palsy	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 3.48]
24.1 Intramuscular	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 3.48]
25 Learning difficulties	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.38, 1.92]
25.1 Intramuscular	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.38, 1.92]
26 Height less than 5th centile	1	270	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.23, 2.49]
26.1 Intramuscular	1	270	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.23, 2.49]
27 Weight less than 5th centile	1	270	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.30, 2.05]
27.1 Intramuscular	1	270	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.30, 2.05]

Comparison 2. Progesterone versus placebo: previous history spontaneous preterm birth, by timing of commencement (< 20 wk v > 20 wk)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Preterm birth less than 37 weeks	4	1256	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.46, 1.02]
1.1 Therapy commences before 20 weeks	3	1114	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.47, 1.16]
1.2 Therapy commences after 20 weeks	1	142	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.25, 0.96]

Comparison 3. Progesterone versus placebo: previous history spontaneous preterm birth by cumulative weekly dose (>= 500 v < 500 mg)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Perinatal death	3	1114	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.38, 1.11]
1.1 Dose < 500 mg per week	2	503	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.23, 0.98]
1.2 Dose >= 500 mg per week	1	611	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.43, 2.22]
2 Preterm birth less than 37 weeks	4	1255	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.45, 1.02]
2.1 Dose < 500 mg per week	2	502	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.19, 1.26]
2.2 Dose >= 500 mg per week	2	753	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.37, 1.56]
3 Threatened preterm labour	2	601	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.47, 1.62]
3.1 Dose < 500 mg per week	1	459	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.73, 1.87]
3.2 Dose >= 500 mg per week	1	142	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.35, 1.11]
4 Caesarean section	2	1070	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.73, 1.16]
4.1 Dose < 500 mg per week	1	459	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.58, 1.30]
4.2 Dose >= 500 mg per week	1	611	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.72, 1.26]
5 Antenatal corticosteroids	2	1070	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.73, 1.16]
5.1 Dose < 500 mg per week	1	459	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.58, 1.30]
5.2 Dose >= 500 mg per week	1	611	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.72, 1.26]
6 Need for tocolysis	3	1114	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.81, 1.52]
6.1 Dose < 500 mg per week	2	503	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.73, 1.72]
6.2 Dose >= 500 mg per week	1	611	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.70, 1.74]
7 Respiratory distress syndrome	2	1070	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.57, 1.10]
7.1 Dose < 500 mg per week	1	459	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.38, 1.05]
7.2 Dose >= 500 mg per week	1	611	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.59, 1.43]
8 Intraventricular haemorrhage - all grades	2	1070	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.12, 2.47]
8.1 Dose < 500 mg per week	1	459	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.08, 0.82]
8.2 Dose >= 500 mg per week	1	611	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.36, 3.80]
9 Intraventricular haemorrhage - grade 3 or 4	2	1070	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [0.21, 11.73]
9.1 Dose < 500 mg per week	1	459	Risk Ratio (M-H, Fixed, 95% CI)	2.51 [0.12, 51.92]
9.2 Dose >= 500 mg per week	1	611	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.06, 15.55]
10 Necrotising enterocolitis	2	1070	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.03, 2.46]
10.1 Dose < 500 mg per week	1	459	Risk Ratio (M-H, Random, 95% CI)	0.06 [0.00, 1.03]
10.2 Dose >= 500 mg per week	1	611	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.14, 2.43]
11 Intrauterine fetal death	3	1114	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.35, 2.03]
11.1 Dose < 500 mg per week	2	503	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.19, 2.13]
11.2 Dose >= 500 mg per week	1	611	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.33, 4.51]
12 Neonatal death	3	1114	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.28, 1.10]
12.1 Dose < 500 mg per week	2	503	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.17, 1.03]
12.2 Dose >= 500 mg per week	1	611	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.28, 2.46]

Comparison 4. Progesterone versus placebo: ultrasound identified short cervix

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Perinatal death	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.10, 1.40]
1.1 Vaginal	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.10, 1.40]
2 Preterm birth less than 34 weeks	1	250	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.38, 0.87]
2.1 Vaginal	1	250	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.38, 0.87]
3 Infant birthweight less than 2500 grams	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.73, 1.27]
3.1 Vaginal	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.73, 1.27]
4 Respiratory distress syndrome	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.29, 1.19]
4.1 Vaginal	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.29, 1.19]
5 Need for assisted ventilation	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.36, 1.16]
5.1 Vaginal	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.36, 1.16]
6 Intraventricular haemorrhage - all grades	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.05, 5.53]
6.1 Vaginal	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.05, 5.53]
7 Retinopathy of prematurity	1	274	Risk Ratio (M-H, Fixed, 95% CI)	5.07 [0.25, 104.70]
7.1 Vaginal	1	274	Risk Ratio (M-H, Fixed, 95% CI)	5.07 [0.25, 104.70]
8 Necrotising enterocolitis	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.23]
8.1 Vaginal	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.23]
9 Neonatal sepsis	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.08, 0.97]
9.1 Vaginal	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.08, 0.97]
10 Intrauterine fetal death	1	274	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.06, 16.06]
10.1 Vaginal	1	274	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.06, 16.06]
11 Neonatal death	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.06, 1.37]
11.1 Vaginal	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.06, 1.37]

Comparison 5. Progesterone versus placebo: multiple pregnancy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Perinatal death	1	154	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [0.37, 10.33]
1.1 Intramuscular	1	154	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [0.37, 10.33]
2 Preterm birth less than 37 weeks	2	732	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.92, 1.12]
2.1 Intramuscular	2	732	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.92, 1.12]
3 Caesarean section	1	652	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.88, 1.12]
3.1 Intramuscular	1	652	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.88, 1.12]
4 Antenatal corticosteroids	1	654	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.70, 1.17]
4.1 Intramuscular	1	654	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.70, 1.17]
5 Antenatal tocolysis	1	654	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.57, 0.97]
5.1 Intramuscular	1	654	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.57, 0.97]
6 Infant birthweight less than 2500 grams	1	1276	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.86, 1.02]
6.1 Intramuscular	1	1276	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.86, 1.02]
7 Respiratory distress syndrome	1	1280	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.86, 1.48]

7.1 Intramuscular	1	1280	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.86, 1.48]
8 Need for assisted ventilation	1	1280	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.69, 1.26]
8.1 Intramuscular	1	1280	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.69, 1.26]
9 Intraventricular haemorrhage - grades 3 or 4	1	1280	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.40, 3.54]
9.1 Intramuscular	1	1280	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.40, 3.54]
10 Retinopathy of prematurity	1	1280	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.1 Intramuscular	1	1280	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11 Necrotising enterocolitis	1	1280	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.17, 3.42]
11.1 Intramuscular	1	1280	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.17, 3.42]
12 Neonatal sepsis	1	1280	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.55, 1.63]
12.1 Intramuscular	1	1280	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.55, 1.63]
13 Patent ductus arteriosus	1	1280	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.34, 1.05]
13.1 Intramuscular	1	1280	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.34, 1.05]

Comparison 6. Progesterone versus placebo: multiple pregnancy, by timing of commencement (< 20 wk v > 20 wk)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Preterm birth < 37 weeks	2	732	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.92, 1.12]
1.1 Supplementation commenced prior to 20 weeks' gestation	1	655	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.89, 1.09]
1.2 Supplementation commenced after 20 weeks' gestation	1	77	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [0.81, 3.25]

Comparison 7. Progesterone versus no treatment: prior threatened preterm labour

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Preterm birth less than 37 weeks' gestation	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.12, 0.69]
1.1 Intramuscular	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.12, 0.69]
2 Infant birthweight less than 2500 grams	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.28, 0.98]
2.1 Vaginal	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.28, 0.98]
3 Respiratory distress syndrome	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.11, 0.83]
3.1 Vaginal	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.11, 0.83]
4 Need for assisted ventilation	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.06, 1.37]
4.1 Vaginal	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.06, 1.37]
5 Neonatal sepsis	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.06, 1.37]
5.1 Vaginal	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.06, 1.37]

Comparison 8. Progesterone versus placebo: other reason at risk of preterm birth

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Perinatal death	2	264	Risk Ratio (M-H, Fixed, 95% CI)	1.1 [0.23, 5.29]
1.1 Intramuscular	2	264	Risk Ratio (M-H, Fixed, 95% CI)	1.1 [0.23, 5.29]
2 Preterm birth less than 37 weeks	2	267	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.22, 1.24]
2.1 Intramuscular	2	267	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.22, 1.24]
3 Infant birthweight less than 2500 grams	2	267	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.23, 1.18]
3.1 Intramuscular	2	267	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.23, 1.18]
4 Intrauterine fetal death	1	168	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.04, 3.45]
4.1 Intramuscular	1	168	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.04, 3.45]
5 Neonatal Death	1	168	Risk Ratio (M-H, Fixed, 95% CI)	5.49 [0.27, 112.73]
5.1 Intramuscular	1	168	Risk Ratio (M-H, Fixed, 95% CI)	5.49 [0.27, 112.73]

Comparison 9. Progesterone versus placebo: other reason at risk of preterm birth, by timing of commencement (< 20 wk v > 20 wk)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Perinatal death	2	264	Risk Ratio (M-H, Fixed, 95% CI)	1.1 [0.23, 5.29]
1.1 Supplementation commenced prior to 20 weeks' gestation	1	168	Risk Ratio (M-H, Fixed, 95% CI)	1.1 [0.23, 5.29]
1.2 Supplementation commenced after 20 weeks' gestation	1	96	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Preterm birth less than 37 weeks	2	267	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.22, 1.24]
2.1 Supplementation commenced prior to 20 weeks' gestation	1	168	Risk Ratio (M-H, Fixed, 95% CI)	1.1 [0.33, 3.66]
2.2 Supplementation commenced after 20 weeks' gestation	1	99	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.05, 0.96]
3 Infant birthweight less than 2500 grams	2	267	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.23, 1.18]
3.1 Supplementation commenced prior to 20 weeks' gestation	1	168	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.30, 2.27]
3.2 Supplementation commenced after 20 weeks' gestation	1	99	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.05, 1.10]

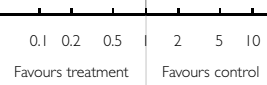
Analysis 1.1. Comparison 1 Progesterone versus placebo: previous history spontaneous preterm birth, Outcome 1 Perinatal death.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 1 Progesterone versus placebo: previous history spontaneous preterm birth

Outcome: 1 Perinatal death

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Intramuscular					
Johnson 1975	0/18	7/26		19.4 %	0.09 [0.01, 1.56]
Meis 2003	14/306	11/153		45.9 %	0.64 [0.30, 1.37]
Subtotal (95% CI)	**324**	**179**		**65.2 %**	**0.48 [0.23, 0.98]**
Total events: 14 (Progesterone), 18 (Placebo)					
Heterogeneity: Chi^2 = 1.83, df = 1 (P = 0.18); I^2 =45%					
Test for overall effect: Z = 2.01 (P = 0.044)					
2 Vaginal					
O'Brien 2007	11/309	11/302		34.8 %	0.98 [0.43, 2.22]
Subtotal (95% CI)	**309**	**302**		**34.8 %**	**0.98 [0.43, 2.22]**
Total events: 11 (Progesterone), 11 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.05 (P = 0.96)					
Total (95% CI)	**633**	**481**		**100.0 %**	**0.65 [0.38, 1.11]**
Total events: 25 (Progesterone), 29 (Placebo)					
Heterogeneity: Chi^2 = 2.77, df = 2 (P = 0.25); I^2 =28%					
Test for overall effect: Z = 1.58 (P = 0.11)					



Analysis 1.2. Comparison 1 Progesterone versus placebo: previous history spontaneous preterm birth, Outcome 2 Preterm birth less than 37 weeks.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 1 Progesterone versus placebo: previous history spontaneous preterm birth

Outcome: 2 Preterm birth less than 37 weeks

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Intramuscular					
Johnson 1975	2/18	12/25		3.8 %	0.23 [0.06, 0.91]
Meis 2003	111/306	84/153		42.0 %	0.66 [0.54, 0.81]
Subtotal (95% CI)	**324**	**178**		**45.8 %**	**0.63 [0.51, 0.77]**
Total events: 113 (Progesterone), 96 (Placebo)					
Heterogeneity: Chi^2 = 2.30, df = 1 (P = 0.13); I^2 =56%					
Test for overall effect: Z = 4.45 (P < 0.00001)					
2 Vaginal					
da Fonseca 2003	10/72	20/70		7.6 %	0.49 [0.25, 0.96]
O'Brien 2007	129/309	123/302		46.6 %	1.03 [0.85, 1.24]
Subtotal (95% CI)	**381**	**372**		**54.2 %**	**0.95 [0.79, 1.14]**
Total events: 139 (Progesterone), 143 (Placebo)					
Heterogeneity: Chi^2 = 4.31, df = 1 (P = 0.04); I^2 =77%					
Test for overall effect: Z = 0.56 (P = 0.58)					
Total (95% CI)	**705**	**550**		**100.0 %**	**0.80 [0.70, 0.92]**
Total events: 252 (Progesterone), 239 (Placebo)					
Heterogeneity: Chi^2 = 15.06, df = 3 (P = 0.002); I^2 =80%					
Test for overall effect: Z = 3.19 (P = 0.0014)					

Analysis 1.3. Comparison 1 Progesterone versus placebo: previous history spontaneous preterm birth, Outcome 3 Preterm birth less than 34 weeks.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 1 Progesterone versus placebo: previous history spontaneous preterm birth

Outcome: 3 Preterm birth less than 34 weeks

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Intramuscular					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Progesterone), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Vaginal					
da Fonseca 2003	2/72	13/70		100.0 %	0.15 [0.04, 0.64]
Subtotal (95% CI)	**72**	**70**		**100.0 %**	**0.15 [0.04, 0.64]**
Total events: 2 (Progesterone), 13 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.56 (P = 0.010)					
Total (95% CI)	**72**	**70**		**100.0 %**	**0.15 [0.04, 0.64]**
Total events: 2 (Progesterone), 13 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.56 (P = 0.010)					

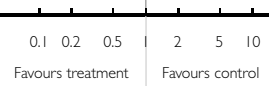
Analysis 1.4. Comparison 1 Progesterone versus placebo: previous history spontaneous preterm birth, Outcome 4 Threatened preterm labour.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 1 Progesterone versus placebo: previous history spontaneous preterm birth

Outcome: 4 Threatened preterm labour

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Intramuscular					
Meis 2003	49/306	21/153		55.7 %	1.17 [0.73, 1.87]
Subtotal (95% CI)	**306**	**153**		**55.7 %**	**1.17 [0.73, 1.87]**
Total events: 49 (Progesterone), 21 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.64 (P = 0.52)					
2 Vaginal					
da Fonseca 2003	14/72	22/70		44.3 %	0.62 [0.35, 1.11]
Subtotal (95% CI)	**72**	**70**		**44.3 %**	**0.62 [0.35, 1.11]**
Total events: 14 (Progesterone), 22 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.61 (P = 0.11)					
Total (95% CI)	**378**	**223**		**100.0 %**	**0.92 [0.64, 1.33]**
Total events: 63 (Progesterone), 43 (Placebo)					
Heterogeneity: Chi^2 = 2.75, df = 1 (P = 0.10); I^2 =64%					
Test for overall effect: Z = 0.43 (P = 0.67)					



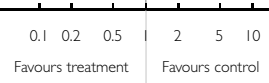
Analysis 1.5. Comparison 1 Progesterone versus placebo: previous history spontaneous preterm birth, Outcome 5 Caesarean section.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 1 Progesterone versus placebo: previous history spontaneous preterm birth

Outcome: 5 Caesarean section

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Intramuscular					
Meis 2003	77/306	41/153		39.4 %	0.94 [0.68, 1.30]
Subtotal (95% CI)	**306**	**153**		**39.4 %**	**0.94 [0.68, 1.30]**
Total events: 77 (Progesterone), 41 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.38 (P = 0.70)					
2 Vaginal					
O'Brien 2007	89/309	83/302		60.6 %	1.05 [0.81, 1.35]
Subtotal (95% CI)	**309**	**302**		**60.6 %**	**1.05 [0.81, 1.35]**
Total events: 89 (Progesterone), 83 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.36 (P = 0.72)					
Total (95% CI)	**615**	**455**		**100.0 %**	**1.01 [0.82, 1.23]**
Total events: 166 (Progesterone), 124 (Placebo)					
Heterogeneity: Chi^2 = 0.27, df = 1 (P = 0.60); I^2 =0.0%					
Test for overall effect: Z = 0.05 (P = 0.96)					



Analysis 1.6. Comparison 1 Progesterone versus placebo: previous history spontaneous preterm birth, Outcome 6 Antenatal corticosteroids.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 1 Progesterone versus placebo: previous history spontaneous preterm birth

Outcome: 6 Antenatal corticosteroids

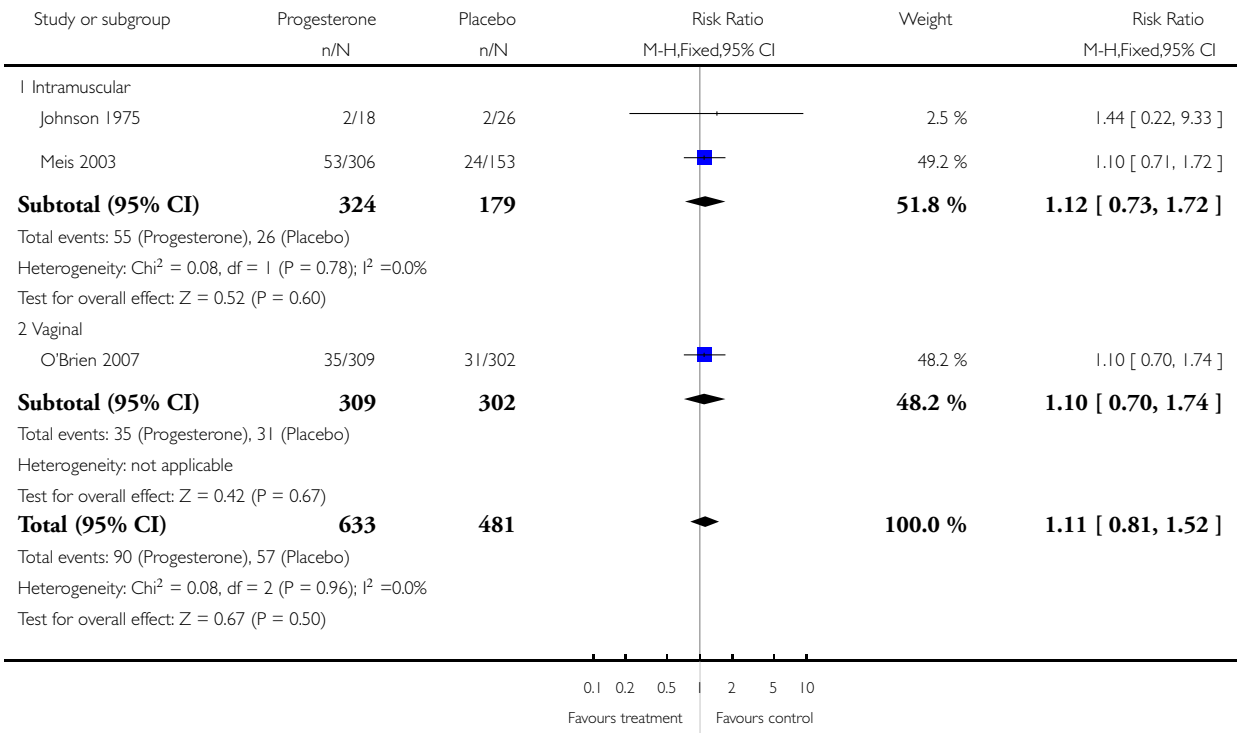
Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Intramuscular					
Meis 2003	52/306	30/153		34.8 %	0.87 [0.58, 1.30]
Subtotal (95% CI)	**306**	**153**		**34.8 %**	**0.87 [0.58, 1.30]**
Total events: 52 (Progesterone), 30 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.69 (P = 0.49)					
2 Vaginal					
O'Brien 2007	72/309	74/302		65.2 %	0.95 [0.72, 1.26]
Subtotal (95% CI)	**309**	**302**		**65.2 %**	**0.95 [0.72, 1.26]**
Total events: 72 (Progesterone), 74 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.35 (P = 0.73)					
Total (95% CI)	**615**	**455**		**100.0 %**	**0.92 [0.73, 1.16]**
Total events: 124 (Progesterone), 104 (Placebo)					
Heterogeneity: Chi^2 = 0.14, df = 1 (P = 0.71); I^2 =0.0%					
Test for overall effect: Z = 0.69 (P = 0.49)					

Analysis 1.7. Comparison 1 Progesterone versus placebo: previous history spontaneous preterm birth, Outcome 7 Antenatal tocolysis.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 1 Progesterone versus placebo: previous history spontaneous preterm birth

Outcome: 7 Antenatal tocolysis



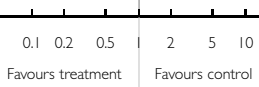
Analysis 1.8. Comparison 1 Progesterone versus placebo: previous history spontaneous preterm birth, Outcome 8 Infant birthweight less than 2500 grams.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 1 Progesterone versus placebo: previous history spontaneous preterm birth

Outcome: 8 Infant birthweight less than 2500 grams

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Intramuscular					
Johnson 1975	4/18	11/26		9.8 %	0.53 [0.20, 1.39]
Meis 2003	82/306	62/151		90.2 %	0.65 [0.50, 0.85]
Total (95% CI)	**324**	**177**		**100.0 %**	**0.64 [0.49, 0.83]**
Total events: 86 (Progesterone), 73 (Placebo)					
Heterogeneity: Chi^2 = 0.18, df = 1 (P = 0.67); I^2 =0.0%					
Test for overall effect: Z = 3.40 (P = 0.00068)					



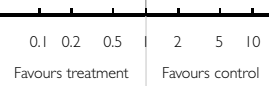
Analysis 1.9. Comparison 1 Progesterone versus placebo: previous history spontaneous preterm birth, Outcome 9 Respiratory distress syndrome.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 1 Progesterone versus placebo: previous history spontaneous preterm birth

Outcome: 9 Respiratory distress syndrome

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Intramuscular					
Meis 2003	29/306	23/152		45.8 %	0.63 [0.38, 1.04]
Subtotal (95% CI)	**306**	**152**		**45.8 %**	**0.63 [0.38, 1.04]**
Total events: 29 (Progesterone), 23 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.79 (P = 0.073)					
2 Vaginal					
O'Brien 2007	34/309	36/302		54.2 %	0.92 [0.59, 1.43]
Subtotal (95% CI)	**309**	**302**		**54.2 %**	**0.92 [0.59, 1.43]**
Total events: 34 (Progesterone), 36 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.36 (P = 0.72)					
Total (95% CI)	**615**	**454**		**100.0 %**	**0.79 [0.56, 1.10]**
Total events: 63 (Progesterone), 59 (Placebo)					
Heterogeneity: Chi^2 = 1.27, df = 1 (P = 0.26); I^2 =21%					
Test for overall effect: Z = 1.41 (P = 0.16)					



Analysis 1.10. Comparison 1 Progesterone versus placebo: previous history spontaneous preterm birth, Outcome 10 Use of assisted ventilation.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 1 Progesterone versus placebo: previous history spontaneous preterm birth

Outcome: 10 Use of assisted ventilation

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Intramuscular					
Meis 2003	26/306	22/153		100.0 %	0.59 [0.35, 1.01]
Total (95% CI)	**306**	**153**		**100.0 %**	**0.59 [0.35, 1.01]**
Total events: 26 (Progesterone), 22 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.93 (P = 0.053)					

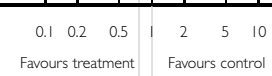
Analysis 1.11. Comparison 1 Progesterone versus placebo: previous history spontaneous preterm birth, Outcome 11 Intraventricular haemorrhage - all grades.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 1 Progesterone versus placebo: previous history spontaneous preterm birth

Outcome: 11 Intraventricular haemorrhage - all grades

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Intramuscular					
Meis 2003	4/306	8/153		67.8 %	0.25 [0.08, 0.82]
Subtotal (95% CI)	**306**	**153**		**67.8 %**	**0.25 [0.08, 0.82]**
Total events: 4 (Progesterone), 8 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.29 (P = 0.022)					
2 Vaginal					
O'Brien 2007	6/309	5/302		32.2 %	1.17 [0.36, 3.80]
Subtotal (95% CI)	**309**	**302**		**32.2 %**	**1.17 [0.36, 3.80]**
Total events: 6 (Progesterone), 5 (Placebo)					
Heterogeneity: not applicable					



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Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 0.27 (P = 0.79)					
Total (95% CI)	**615**	**455**		**100.0 %**	**0.55 [0.25, 1.19]**
Total events: 10 (Progesterone), 13 (Placebo)					
Heterogeneity: Chi^2 = 3.29, df = 1 (P = 0.07); I^2 =70%					
Test for overall effect: Z = 1.52 (P = 0.13)					

Analysis 1.12. Comparison 1 Progesterone versus placebo: previous history spontaneous preterm birth, Outcome 12 Intraventricular haemorrhage - grade 3 or 4.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 1 Progesterone versus placebo: previous history spontaneous preterm birth

Outcome: 12 Intraventricular haemorrhage - grade 3 or 4

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Intramuscular					
Meis 2003	2/305	0/153		39.7 %	2.52 [0.12, 52.09]
Subtotal (95% CI)	**305**	**153**		**39.7 %**	**2.52 [0.12, 52.09]**
Total events: 2 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.60 (P = 0.55)					
2 Vaginal					
O'Brien 2007	1/309	1/302		60.3 %	0.98 [0.06, 15.55]
Subtotal (95% CI)	**309**	**302**		**60.3 %**	**0.98 [0.06, 15.55]**
Total events: 1 (Treatment), 1 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.02 (P = 0.99)					
Total (95% CI)	**614**	**455**		**100.0 %**	**1.59 [0.21, 11.75]**
Total events: 3 (Treatment), 1 (Control)					
Heterogeneity: Chi^2 = 0.21, df = 1 (P = 0.65); I^2 =0.0%					
Test for overall effect: Z = 0.45 (P = 0.65)					

Analysis 1.13. Comparison 1 Progesterone versus placebo: previous history spontaneous preterm birth, Outcome 13 Retinopathy of prematurity.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 1 Progesterone versus placebo: previous history spontaneous preterm birth

Outcome: 13 Retinopathy of prematurity

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Intramuscular					
Meis 2003	5/306	5/152		100.0 %	0.50 [0.15, 1.69]
Total (95% CI)	**306**	**152**		**100.0 %**	**0.50 [0.15, 1.69]**
Total events: 5 (Progesterone), 5 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.12 (P = 0.26)					

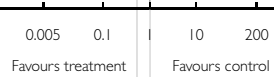
Analysis 1.14. Comparison 1 Progesterone versus placebo: previous history spontaneous preterm birth, Outcome 14 Necrotising enterocolitis.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 1 Progesterone versus placebo: previous history spontaneous preterm birth

Outcome: 14 Necrotising enterocolitis

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Intramuscular					
Meis 2003	0/306	4/153		54.2 %	0.06 [0.00, 1.03]
Subtotal (95% CI)	**306**	**153**		**54.2 %**	**0.06 [0.00, 1.03]**
Total events: 0 (Progesterone), 4 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.94 (P = 0.052)					
2 Vaginal					
O'Brien 2007	3/309	5/302		45.8 %	0.59 [0.14, 2.43]
Subtotal (95% CI)	**309**	**302**		**45.8 %**	**0.59 [0.14, 2.43]**
Total events: 3 (Progesterone), 5 (Placebo)					
Heterogeneity: not applicable					



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Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 0.74 (P = 0.46)					
Total (95% CI)	**615**	**455**		**100.0 %**	**0.30 [0.10, 0.93]**
Total events: 3 (Progesterone), 9 (Placebo)					
Heterogeneity: Chi^2 = 2.14, df = 1 (P = 0.14); I^2 =53%					
Test for overall effect: Z = 2.08 (P = 0.038)					

Analysis 1.15. Comparison 1 Progesterone versus placebo: previous history spontaneous preterm birth, Outcome 15 Neonatal sepsis.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 1 Progesterone versus placebo: previous history spontaneous preterm birth

Outcome: 15 Neonatal sepsis

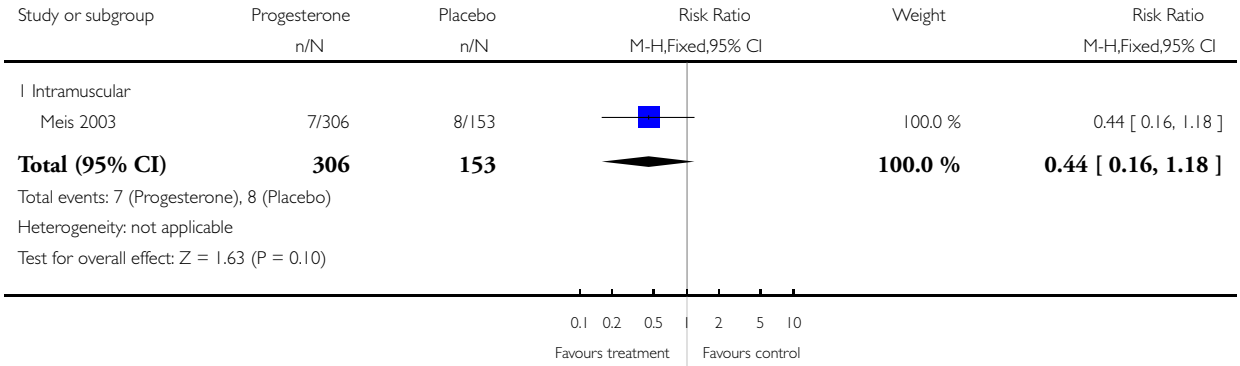
Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Intramuscular					
Meis 2003	9/306	4/153		100.0 %	1.13 [0.35, 3.59]
Total (95% CI)	**306**	**153**		**100.0 %**	**1.13 [0.35, 3.59]**
Total events: 9 (Progesterone), 4 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.20 (P = 0.84)					

Analysis 1.16. Comparison 1 Progesterone versus placebo: previous history spontaneous preterm birth, Outcome 16 Patent ductus arteriosus.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 1 Progesterone versus placebo: previous history spontaneous preterm birth

Outcome: 16 Patent ductus arteriosus

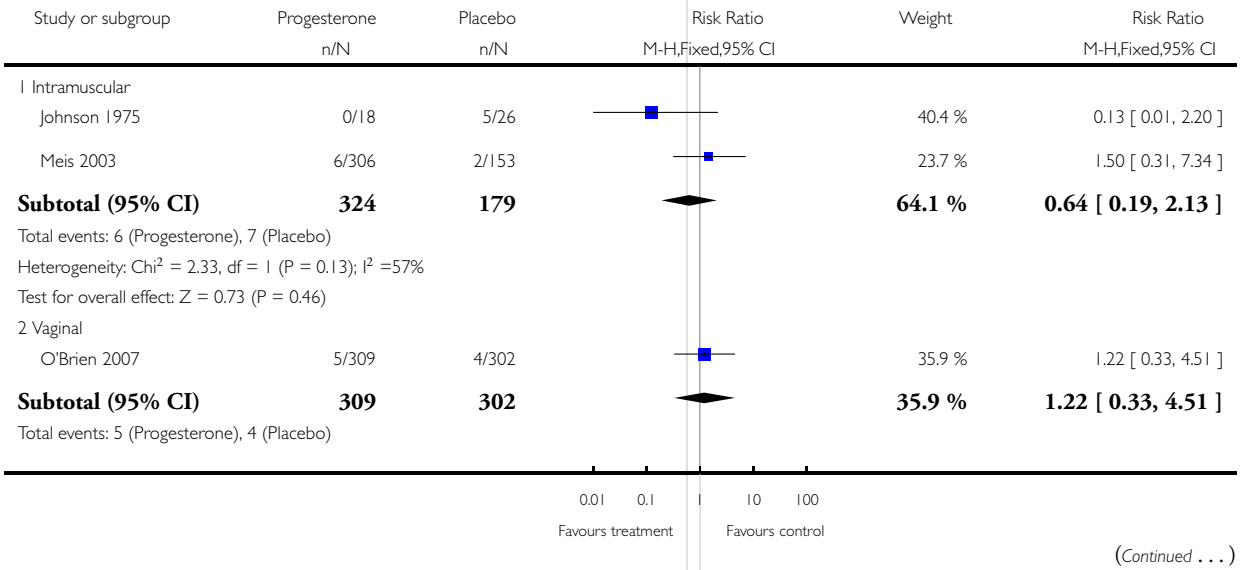


Analysis 1.17. Comparison 1 Progesterone versus placebo: previous history spontaneous preterm birth, Outcome 17 Intrauterine fetal death.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 1 Progesterone versus placebo: previous history spontaneous preterm birth

Outcome: 17 Intrauterine fetal death



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Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heterogeneity: not applicable					
Test for overall effect: Z = 0.30 (P = 0.76)					
Total (95% CI)	**633**	**481**		**100.0 %**	**0.85 [0.35, 2.03]**
Total events: 11 (Progesterone), 11 (Placebo)					
Heterogeneity: Chi^2 = 2.49, df = 2 (P = 0.29); I^2 =20%					
Test for overall effect: Z = 0.37 (P = 0.71)					

Analysis 1.18. Comparison 1 Progesterone versus placebo: previous history spontaneous preterm birth, Outcome 18 Neonatal death.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 1 Progesterone versus placebo: previous history spontaneous preterm birth

Outcome: 18 Neonatal death

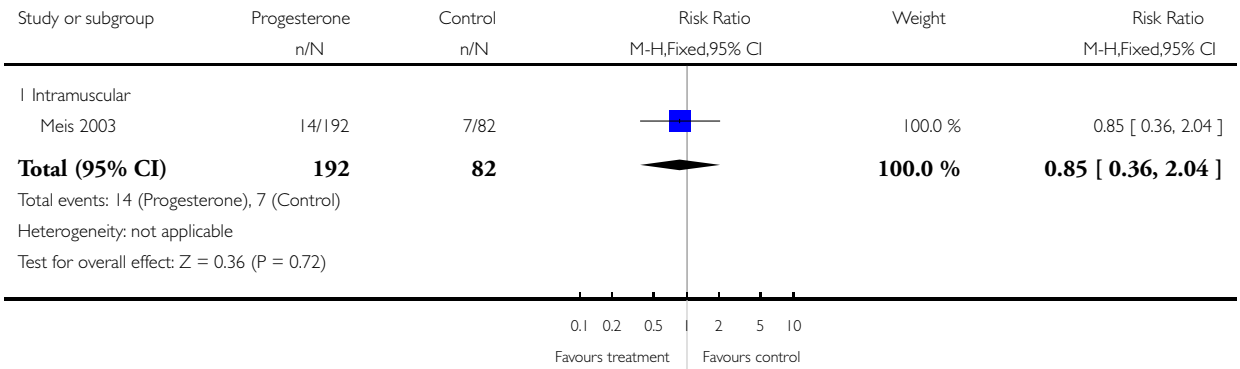
Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Intramuscular					
Johnson 1975	0/18	2/26		9.8 %	0.28 [0.01, 5.59]
Meis 2003	8/306	9/153		56.7 %	0.44 [0.17, 1.13]
Subtotal (95% CI)	**324**	**179**		**66.5 %**	**0.42 [0.17, 1.03]**
Total events: 8 (Progesterone), 11 (Placebo)					
Heterogeneity: Chi^2 = 0.08, df = 1 (P = 0.78); I^2 =0.0%					
Test for overall effect: Z = 1.90 (P = 0.058)					
2 Vaginal					
O'Brien 2007	6/309	7/302		33.5 %	0.84 [0.28, 2.46]
Subtotal (95% CI)	**309**	**302**		**33.5 %**	**0.84 [0.28, 2.46]**
Total events: 6 (Progesterone), 7 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.32 (P = 0.75)					
Total (95% CI)	**633**	**481**		**100.0 %**	**0.56 [0.28, 1.10]**
Total events: 14 (Progesterone), 18 (Placebo)					
Heterogeneity: Chi^2 = 0.97, df = 2 (P = 0.62); I^2 =0.0%					
Test for overall effect: Z = 1.67 (P = 0.094)					

Analysis 1.19. Comparison 1 Progesterone versus placebo: previous history spontaneous preterm birth, Outcome 19 Developmental delay.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 1 Progesterone versus placebo: previous history spontaneous preterm birth

Outcome: 19 Developmental delay

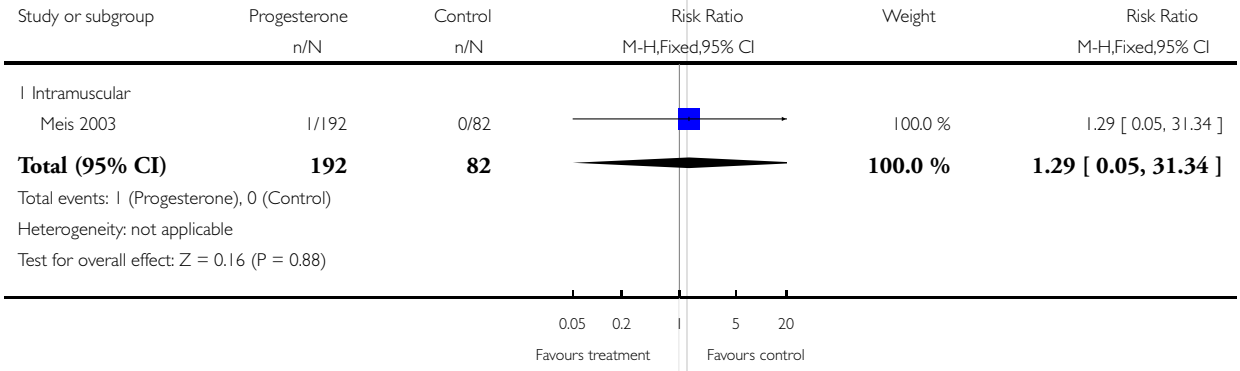


Analysis 1.20. Comparison 1 Progesterone versus placebo: previous history spontaneous preterm birth, Outcome 20 Intellectual impairment.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 1 Progesterone versus placebo: previous history spontaneous preterm birth

Outcome: 20 Intellectual impairment

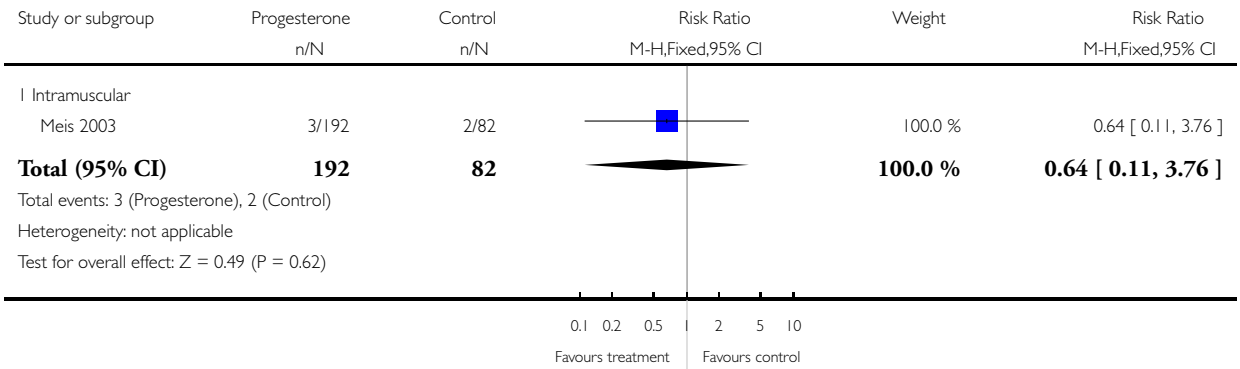


Analysis 1.21. Comparison 1 Progesterone versus placebo: previous history spontaneous preterm birth, Outcome 21 Motor Impairment.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 1 Progesterone versus placebo: previous history spontaneous preterm birth

Outcome: 21 Motor Impairment

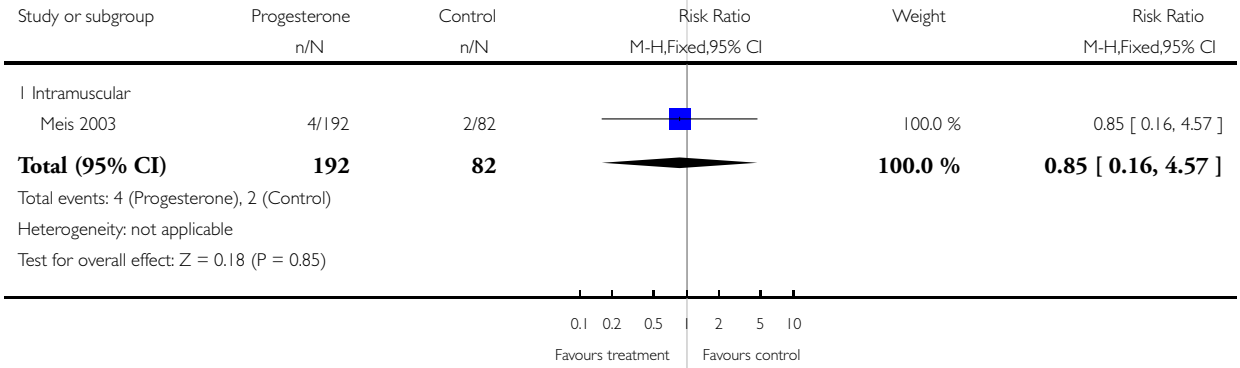


Analysis 1.22. Comparison 1 Progesterone versus placebo: previous history spontaneous preterm birth, Outcome 22 Visual Impairment.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 1 Progesterone versus placebo: previous history spontaneous preterm birth

Outcome: 22 Visual Impairment

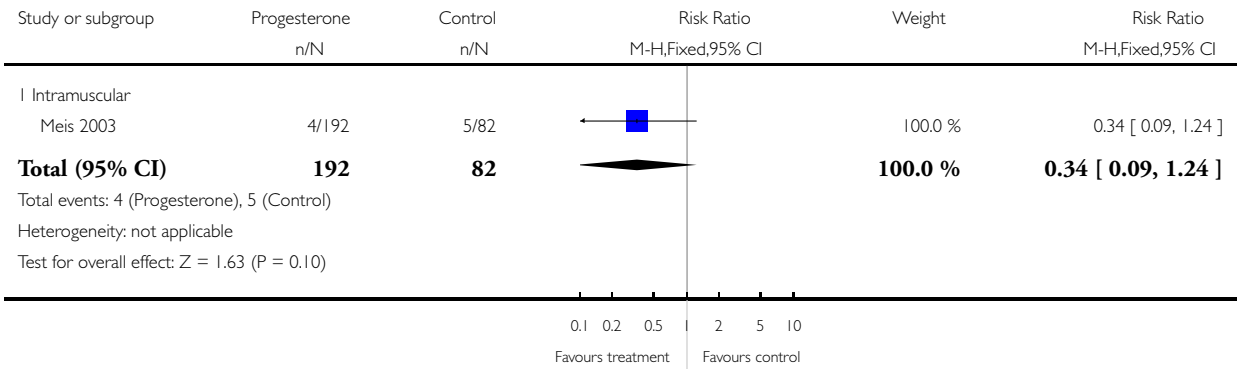


Analysis 1.23. Comparison 1 Progesterone versus placebo: previous history spontaneous preterm birth, Outcome 23 Hearing Impairment.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 1 Progesterone versus placebo: previous history spontaneous preterm birth

Outcome: 23 Hearing Impairment

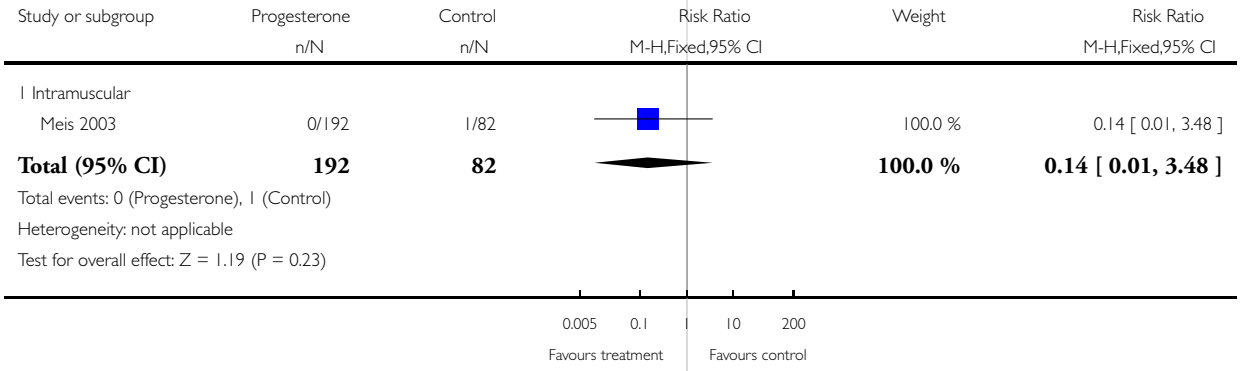


Analysis 1.24. Comparison 1 Progesterone versus placebo: previous history spontaneous preterm birth, Outcome 24 Cerebral palsy.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 1 Progesterone versus placebo: previous history spontaneous preterm birth

Outcome: 24 Cerebral palsy

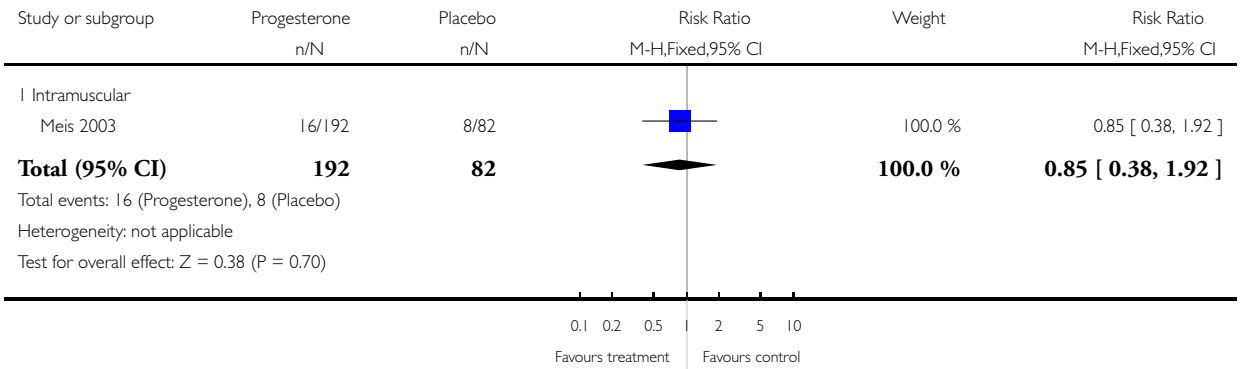


Analysis 1.25. Comparison 1 Progesterone versus placebo: previous history spontaneous preterm birth, Outcome 25 Learning difficulties.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 1 Progesterone versus placebo: previous history spontaneous preterm birth

Outcome: 25 Learning difficulties

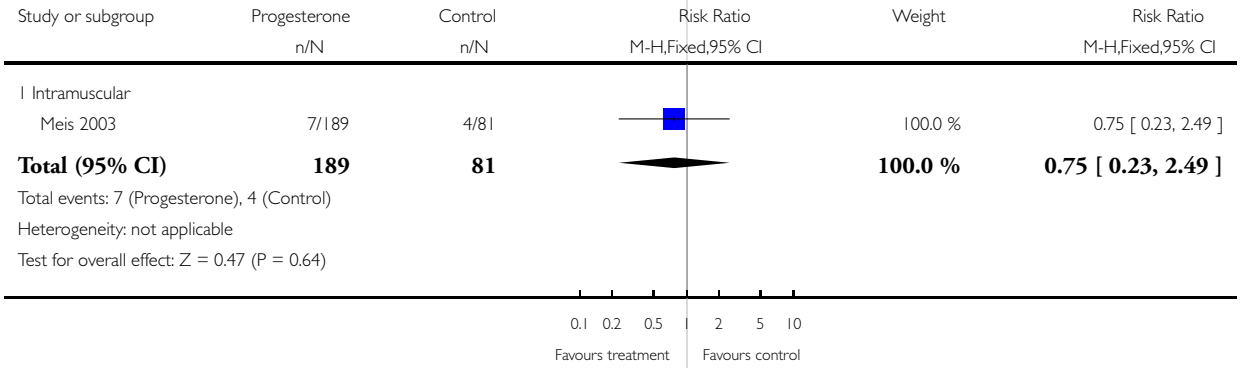


Analysis 1.26. Comparison 1 Progesterone versus placebo: previous history spontaneous preterm birth, Outcome 26 Height less than 5th centile.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 1 Progesterone versus placebo: previous history spontaneous preterm birth

Outcome: 26 Height less than 5th centile



Analysis 1.27. Comparison 1 Progesterone versus placebo: previous history spontaneous preterm birth, Outcome 27 Weight less than 5th centile.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 1 Progesterone versus placebo: previous history spontaneous preterm birth

Outcome: 27 Weight less than 5th centile

Study or subgroup	Progesterone n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Intramuscular					
Meis 2003	11/189	6/81		100.0 %	0.79 [0.30, 2.05]
Total (95% CI)	**189**	**81**		**100.0 %**	**0.79 [0.30, 2.05]**
Total events: 11 (Progesterone), 6 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.49 (P = 0.62)					

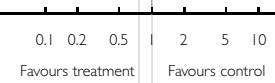
Analysis 2.1. Comparison 2 Progesterone versus placebo: previous history spontaneous preterm birth, by timing of commencement (< 20 wk v > 20 wk), Outcome 1 Preterm birth less than 37 weeks.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 2 Progesterone versus placebo: previous history spontaneous preterm birth, by timing of commencement (< 20 wk v > 20 wk)

Outcome: 1 Preterm birth less than 37 weeks

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Therapy commences before 20 weeks					
Johnson 1975	2/18	12/26		7.2 %	0.24 [0.06, 0.95]
Meis 2003	111/306	84/153		36.7 %	0.66 [0.54, 0.81]
O'Brien 2007	129/309	123/302		37.3 %	1.03 [0.85, 1.24]
Subtotal (95% CI)	**633**	**481**		**81.2 %**	**0.74 [0.47, 1.16]**
Total events: 242 (Progesterone), 219 (Placebo)					
Heterogeneity: Tau^2 = 0.10; Chi^2 = 12.58, df = 2 (P = 0.002); I^2 =84%					
Test for overall effect: Z = 1.32 (P = 0.19)					
2 Therapy commences after 20 weeks					
da Fonseca 2003	10/72	20/70		18.8 %	0.49 [0.25, 0.96]



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Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**72**	**70**		**18.8 %**	**0.49 [0.25, 0.96]**
Total events: 10 (Progesterone), 20 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.07 (P = 0.039)					
Total (95% CI)	**705**	**551**		**100.0 %**	**0.68 [0.46, 1.02]**
Total events: 252 (Progesterone), 239 (Placebo)					
Heterogeneity: Tau^2 = 0.11; Chi^2 = 14.85, df = 3 (P = 0.002); I^2 =80%					
Test for overall effect: Z = 1.84 (P = 0.065)					

Analysis 3.1. Comparison 3 Progesterone versus placebo: previous history spontaneous preterm birth by cumulative weekly dose (>= 500 v < 500 mg), Outcome 1 Perinatal death.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 3 Progesterone versus placebo: previous history spontaneous preterm birth by cumulative weekly dose (>= 500 v < 500 mg)

Outcome: 1 Perinatal death

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Dose < 500 mg per week					
Johnson 1975	0/18	7/26		19.4 %	0.09 [0.01, 1.56]
Meis 2003	14/306	11/153		45.9 %	0.64 [0.30, 1.37]
Subtotal (95% CI)	**324**	**179**		**65.2 %**	**0.48 [0.23, 0.98]**
Total events: 14 (Progesterone), 18 (Placebo)					
Heterogeneity: Chi^2 = 1.83, df = 1 (P = 0.18); I^2 =45%					
Test for overall effect: Z = 2.01 (P = 0.044)					
2 Dose >= 500 mg per week					
O'Brien 2007	11/309	11/302		34.8 %	0.98 [0.43, 2.22]
Subtotal (95% CI)	**309**	**302**		**34.8 %**	**0.98 [0.43, 2.22]**
Total events: 11 (Progesterone), 11 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.05 (P = 0.96)					
Total (95% CI)	**633**	**481**		**100.0 %**	**0.65 [0.38, 1.11]**
Total events: 25 (Progesterone), 29 (Placebo)					
Heterogeneity: Chi^2 = 2.77, df = 2 (P = 0.25); I^2 =28%					
Test for overall effect: Z = 1.58 (P = 0.11)					

Analysis 3.2. Comparison 3 Progesterone versus placebo: previous history spontaneous preterm birth by cumulative weekly dose (>= 500 v < 500 mg), Outcome 2 Preterm birth less than 37 weeks.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 3 Progesterone versus placebo: previous history spontaneous preterm birth by cumulative weekly dose (>= 500 v < 500 mg)

Outcome: 2 Preterm birth less than 37 weeks

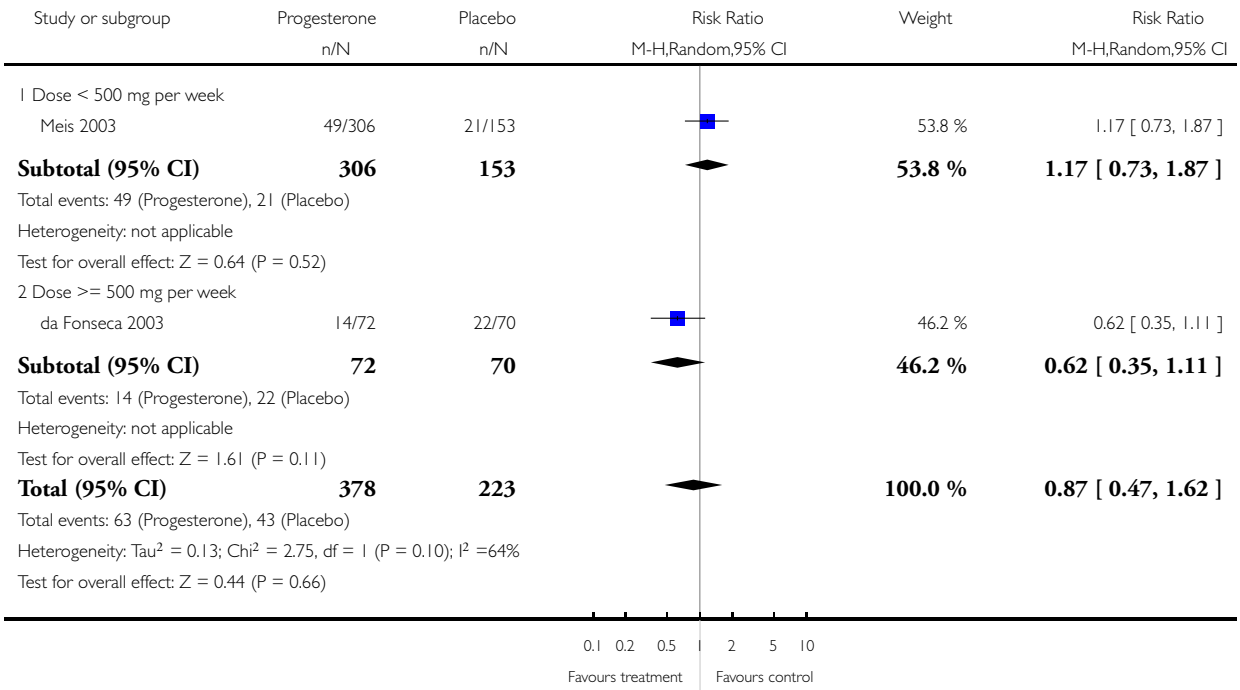
Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Dose < 500 mg per week					
Johnson 1975	2/18	12/25		7.3 %	0.23 [0.06, 0.91]
Meis 2003	111/306	84/153		36.6 %	0.66 [0.54, 0.81]
Subtotal (95% CI)	**324**	**178**		**43.9 %**	**0.49 [0.19, 1.26]**
Total events: 113 (Progesterone), 96 (Placebo)					
Heterogeneity: Tau^2 = 0.32; Chi^2 = 2.30, df = 1 (P = 0.13); I^2 =56%					
Test for overall effect: Z = 1.48 (P = 0.14)					
2 Dose >= 500 mg per week					
da Fonseca 2003	10/72	20/70		18.9 %	0.49 [0.25, 0.96]
O'Brien 2007	129/309	123/302		37.2 %	1.03 [0.85, 1.24]
Subtotal (95% CI)	**381**	**372**		**56.1 %**	**0.76 [0.37, 1.56]**
Total events: 139 (Progesterone), 143 (Placebo)					
Heterogeneity: Tau^2 = 0.22; Chi^2 = 4.31, df = 1 (P = 0.04); I^2 =77%					
Test for overall effect: Z = 0.74 (P = 0.46)					
Total (95% CI)	**705**	**550**		**100.0 %**	**0.68 [0.45, 1.02]**
Total events: 252 (Progesterone), 239 (Placebo)					
Heterogeneity: Tau^2 = 0.11; Chi^2 = 15.06, df = 3 (P = 0.002); I^2 =80%					
Test for overall effect: Z = 1.85 (P = 0.064)					

Analysis 3.3. Comparison 3 Progesterone versus placebo: previous history spontaneous preterm birth by cumulative weekly dose (>= 500 v < 500 mg), Outcome 3 Threatened preterm labour.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 3 Progesterone versus placebo: previous history spontaneous preterm birth by cumulative weekly dose (>= 500 v < 500 mg)

Outcome: 3 Threatened preterm labour



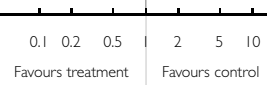
Analysis 3.4. Comparison 3 Progesterone versus placebo: previous history spontaneous preterm birth by cumulative weekly dose (>= 500 v < 500 mg), Outcome 4 Caesarean section.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 3 Progesterone versus placebo: previous history spontaneous preterm birth by cumulative weekly dose (>= 500 v < 500 mg)

Outcome: 4 Caesarean section

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Dose < 500 mg per week					
Meis 2003	52/306	30/153		34.8 %	0.87 [0.58, 1.30]
Subtotal (95% CI)	**306**	**153**		**34.8 %**	**0.87 [0.58, 1.30]**
Total events: 52 (Progesterone), 30 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.69 (P = 0.49)					
2 Dose >= 500 mg per week					
O'Brien 2007	72/309	74/302		65.2 %	0.95 [0.72, 1.26]
Subtotal (95% CI)	**309**	**302**		**65.2 %**	**0.95 [0.72, 1.26]**
Total events: 72 (Progesterone), 74 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.35 (P = 0.73)					
Total (95% CI)	**615**	**455**		**100.0 %**	**0.92 [0.73, 1.16]**
Total events: 124 (Progesterone), 104 (Placebo)					
Heterogeneity: Chi^2 = 0.14, df = 1 (P = 0.71); I^2 =0.0%					
Test for overall effect: Z = 0.69 (P = 0.49)					



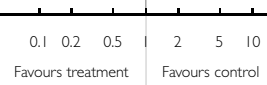
Analysis 3.5. Comparison 3 Progesterone versus placebo: previous history spontaneous preterm birth by cumulative weekly dose (>= 500 v < 500 mg), Outcome 5 Antenatal corticosteroids.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 3 Progesterone versus placebo: previous history spontaneous preterm birth by cumulative weekly dose (>= 500 v < 500 mg)

Outcome: 5 Antenatal corticosteroids

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Dose < 500 mg per week					
Meis 2003	52/306	30/153		34.8 %	0.87 [0.58, 1.30]
Subtotal (95% CI)	**306**	**153**		**34.8 %**	**0.87 [0.58, 1.30]**
Total events: 52 (Progesterone), 30 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.69 (P = 0.49)					
2 Dose >= 500 mg per week					
O'Brien 2007	72/309	74/302		65.2 %	0.95 [0.72, 1.26]
Subtotal (95% CI)	**309**	**302**		**65.2 %**	**0.95 [0.72, 1.26]**
Total events: 72 (Progesterone), 74 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.35 (P = 0.73)					
Total (95% CI)	**615**	**455**		**100.0 %**	**0.92 [0.73, 1.16]**
Total events: 124 (Progesterone), 104 (Placebo)					
Heterogeneity: Chi^2 = 0.14, df = 1 (P = 0.71); I^2 =0.0%					
Test for overall effect: Z = 0.69 (P = 0.49)					



Analysis 3.6. Comparison 3 Progesterone versus placebo: previous history spontaneous preterm birth by cumulative weekly dose (>= 500 v < 500 mg), Outcome 6 Need for tocolysis.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 3 Progesterone versus placebo: previous history spontaneous preterm birth by cumulative weekly dose (>= 500 v < 500 mg)

Outcome: 6 Need for tocolysis

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Dose < 500 mg per week					
Johnson 1975	2/18	2/26		2.5 %	1.44 [0.22, 9.33]
Meis 2003	53/306	24/153		49.2 %	1.10 [0.71, 1.72]
Subtotal (95% CI)	**324**	**179**		**51.8 %**	**1.12 [0.73, 1.72]**
Total events: 55 (Progesterone), 26 (Placebo)					
Heterogeneity: Chi² = 0.08, df = 1 (P = 0.78); I² =0.0%					
Test for overall effect: Z = 0.52 (P = 0.60)					
2 Dose >= 500 mg per week					
O'Brien 2007	35/309	31/302		48.2 %	1.10 [0.70, 1.74]
Subtotal (95% CI)	**309**	**302**		**48.2 %**	**1.10 [0.70, 1.74]**
Total events: 35 (Progesterone), 31 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.42 (P = 0.67)					
Total (95% CI)	**633**	**481**		**100.0 %**	**1.11 [0.81, 1.52]**
Total events: 90 (Progesterone), 57 (Placebo)					
Heterogeneity: Chi² = 0.08, df = 2 (P = 0.96); I² =0.0%					
Test for overall effect: Z = 0.67 (P = 0.50)					

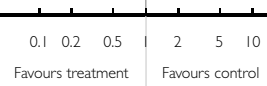
Analysis 3.7. Comparison 3 Progesterone versus placebo: previous history spontaneous preterm birth by cumulative weekly dose (>= 500 v < 500 mg), Outcome 7 Respiratory distress syndrome.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 3 Progesterone versus placebo: previous history spontaneous preterm birth by cumulative weekly dose (>= 500 v < 500 mg)

Outcome: 7 Respiratory distress syndrome

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Dose < 500 mg per week					
Meis 2003	29/306	23/153		45.7 %	0.63 [0.38, 1.05]
Subtotal (95% CI)	**306**	**153**		**45.7 %**	**0.63 [0.38, 1.05]**
Total events: 29 (Progesterone), 23 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.77 (P = 0.077)					
2 Dose >= 500 mg per week					
O'Brien 2007	34/309	36/302		54.3 %	0.92 [0.59, 1.43]
Subtotal (95% CI)	**309**	**302**		**54.3 %**	**0.92 [0.59, 1.43]**
Total events: 34 (Progesterone), 36 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.36 (P = 0.72)					
Total (95% CI)	**615**	**455**		**100.0 %**	**0.79 [0.57, 1.10]**
Total events: 63 (Progesterone), 59 (Placebo)					
Heterogeneity: Chi^2 = 1.22, df = 1 (P = 0.27); I^2 =18%					
Test for overall effect: Z = 1.39 (P = 0.16)					



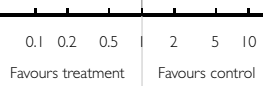
Analysis 3.8. Comparison 3 Progesterone versus placebo: previous history spontaneous preterm birth by cumulative weekly dose (>= 500 v < 500 mg), Outcome 8 Intraventricular haemorrhage - all grades.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 3 Progesterone versus placebo: previous history spontaneous preterm birth by cumulative weekly dose (>= 500 v < 500 mg)

Outcome: 8 Intraventricular haemorrhage - all grades

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Dose < 500 mg per week					
Meis 2003	4/306	8/153		49.9 %	0.25 [0.08, 0.82]
Subtotal (95% CI)	**306**	**153**		**49.9 %**	**0.25 [0.08, 0.82]**
Total events: 4 (Progesterone), 8 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.29 (P = 0.022)					
2 Dose >= 500 mg per week					
O'Brien 2007	6/309	5/302		50.1 %	1.17 [0.36, 3.80]
Subtotal (95% CI)	**309**	**302**		**50.1 %**	**1.17 [0.36, 3.80]**
Total events: 6 (Progesterone), 5 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.27 (P = 0.79)					
Total (95% CI)	**615**	**455**		**100.0 %**	**0.54 [0.12, 2.47]**
Total events: 10 (Progesterone), 13 (Placebo)					
Heterogeneity: Tau^2 = 0.83; Chi^2 = 3.29, df = 1 (P = 0.07); I^2 =70%					
Test for overall effect: Z = 0.79 (P = 0.43)					

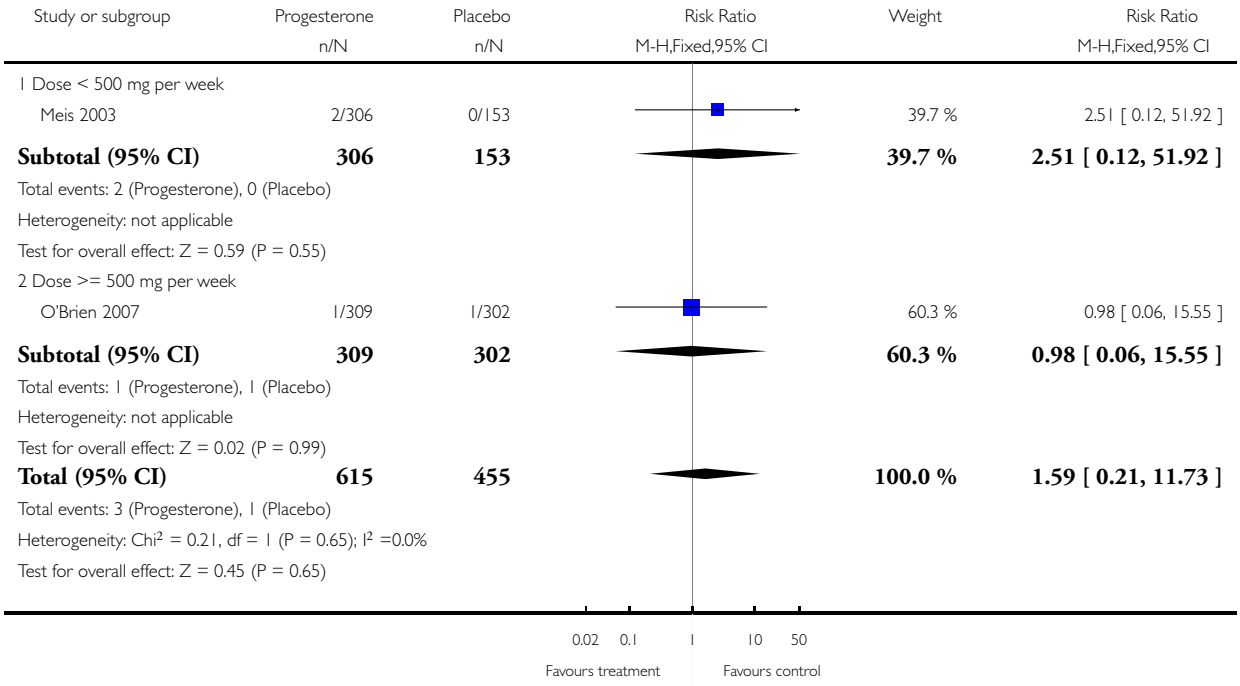


Analysis 3.9. Comparison 3 Progesterone versus placebo: previous history spontaneous preterm birth by cumulative weekly dose (>= 500 v < 500 mg), Outcome 9 Intraventricular haemorrhage - grade 3 or 4.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 3 Progesterone versus placebo: previous history spontaneous preterm birth by cumulative weekly dose (>= 500 v < 500 mg)

Outcome: 9 Intraventricular haemorrhage - grade 3 or 4



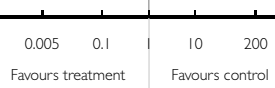
Analysis 3.10. Comparison 3 Progesterone versus placebo: previous history spontaneous preterm birth by cumulative weekly dose (>= 500 v < 500 mg), Outcome 10 Necrotising enterocolitis.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 3 Progesterone versus placebo: previous history spontaneous preterm birth by cumulative weekly dose (>= 500 v < 500 mg)

Outcome: 10 Necrotising enterocolitis

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Dose < 500 mg per week					
Meis 2003	0/306	4/153		35.6 %	0.06 [0.00, 1.03]
Subtotal (95% CI)	**306**	**153**		**35.6 %**	**0.06 [0.00, 1.03]**
Total events: 0 (Progesterone), 4 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.94 (P = 0.052)					
2 Dose >= 500 mg per week					
O'Brien 2007	3/309	5/302		64.4 %	0.59 [0.14, 2.43]
Subtotal (95% CI)	**309**	**302**		**64.4 %**	**0.59 [0.14, 2.43]**
Total events: 3 (Progesterone), 5 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.74 (P = 0.46)					
Total (95% CI)	**615**	**455**		**100.0 %**	**0.25 [0.03, 2.46]**
Total events: 3 (Progesterone), 9 (Placebo)					
Heterogeneity: Tau^2 = 1.56; Chi^2 = 2.14, df = 1 (P = 0.14); I^2 =53%					
Test for overall effect: Z = 1.18 (P = 0.24)					

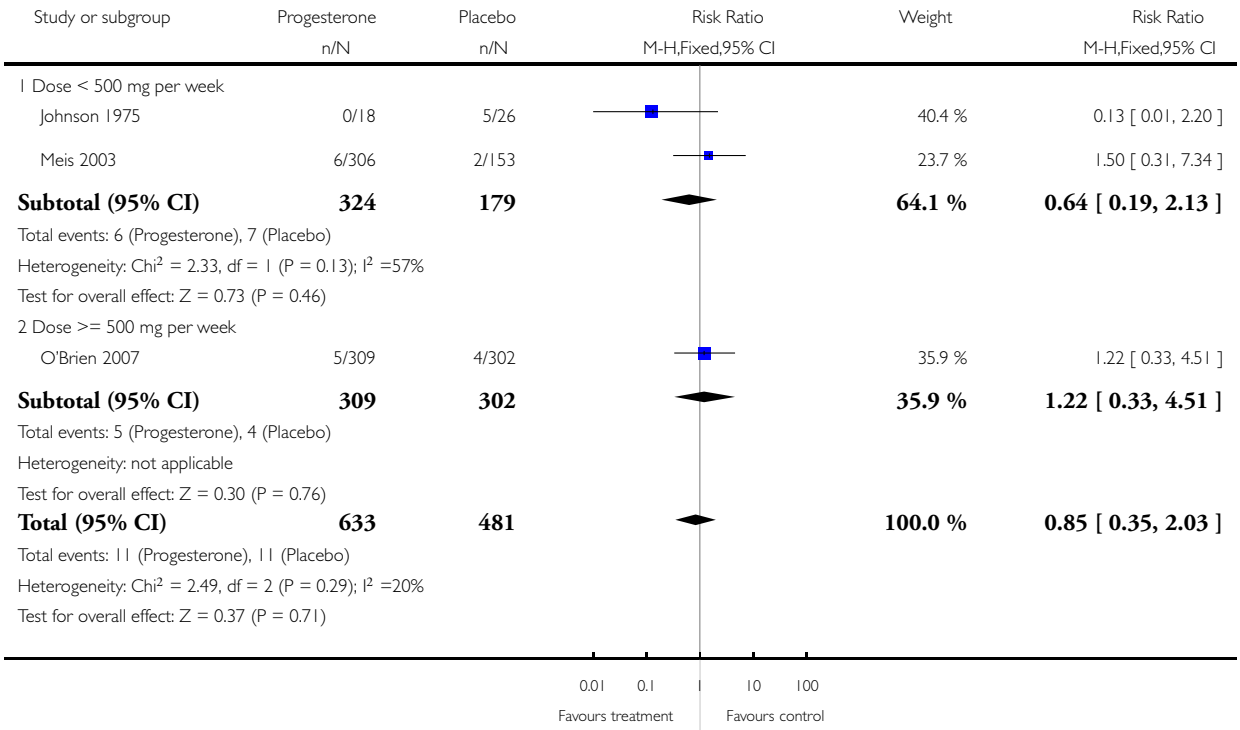


Analysis 3.11. Comparison 3 Progesterone versus placebo: previous history spontaneous preterm birth by cumulative weekly dose (>= 500 v < 500 mg), Outcome 11 Intrauterine fetal death.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 3 Progesterone versus placebo: previous history spontaneous preterm birth by cumulative weekly dose (>= 500 v < 500 mg)

Outcome: 11 Intrauterine fetal death



Analysis 3.12. Comparison 3 Progesterone versus placebo: previous history spontaneous preterm birth by cumulative weekly dose (>= 500 v < 500 mg), Outcome 12 Neonatal death.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 3 Progesterone versus placebo: previous history spontaneous preterm birth by cumulative weekly dose (>= 500 v < 500 mg)

Outcome: 12 Neonatal death

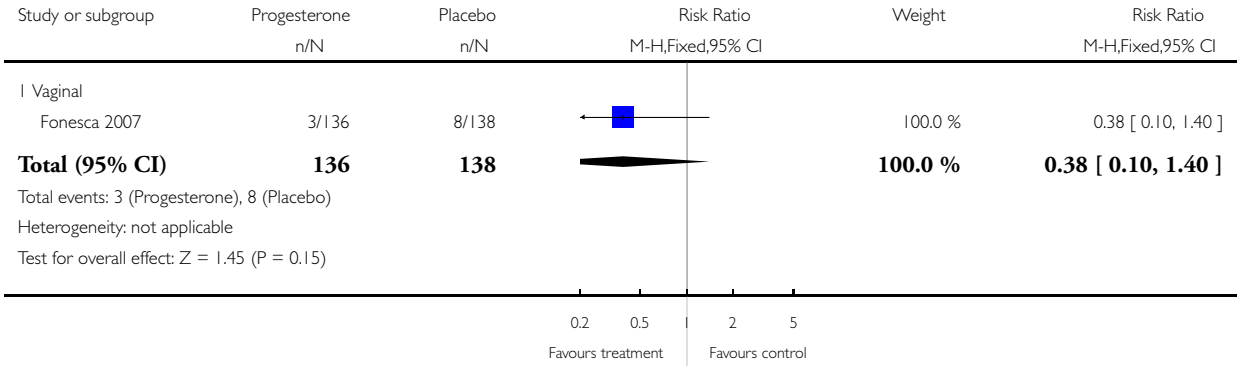
Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Dose < 500 mg per week					
Johnson 1975	0/18	2/26		9.8 %	0.28 [0.01, 5.59]
Meis 2003	8/306	9/153		56.7 %	0.44 [0.17, 1.13]
Subtotal (95% CI)	**324**	**179**		**66.5 %**	**0.42 [0.17, 1.03]**
Total events: 8 (Progesterone), 11 (Placebo)					
Heterogeneity: Chi^2 = 0.08, df = 1 (P = 0.78); I^2 =0.0%					
Test for overall effect: Z = 1.90 (P = 0.058)					
2 Dose >= 500 mg per week					
O'Brien 2007	6/309	7/302		33.5 %	0.84 [0.28, 2.46]
Subtotal (95% CI)	**309**	**302**		**33.5 %**	**0.84 [0.28, 2.46]**
Total events: 6 (Progesterone), 7 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.32 (P = 0.75)					
Total (95% CI)	**633**	**481**		**100.0 %**	**0.56 [0.28, 1.10]**
Total events: 14 (Progesterone), 18 (Placebo)					
Heterogeneity: Chi^2 = 0.97, df = 2 (P = 0.62); I^2 =0.0%					
Test for overall effect: Z = 1.67 (P = 0.094)					

Analysis 4.1. Comparison 4 Progesterone versus placebo: ultrasound identified short cervix, Outcome 1 Perinatal death.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 4 Progesterone versus placebo: ultrasound identified short cervix

Outcome: 1 Perinatal death

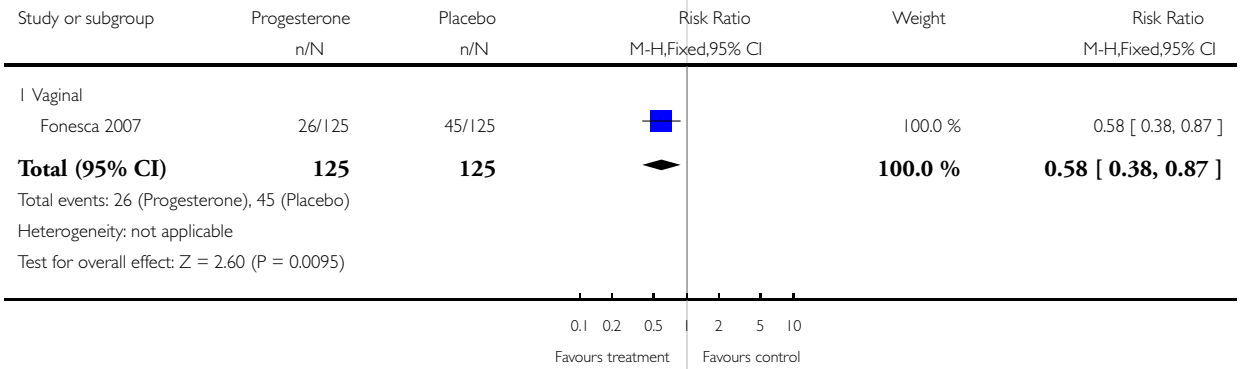


Analysis 4.2. Comparison 4 Progesterone versus placebo: ultrasound identified short cervix, Outcome 2 Preterm birth less than 34 weeks.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 4 Progesterone versus placebo: ultrasound identified short cervix

Outcome: 2 Preterm birth less than 34 weeks

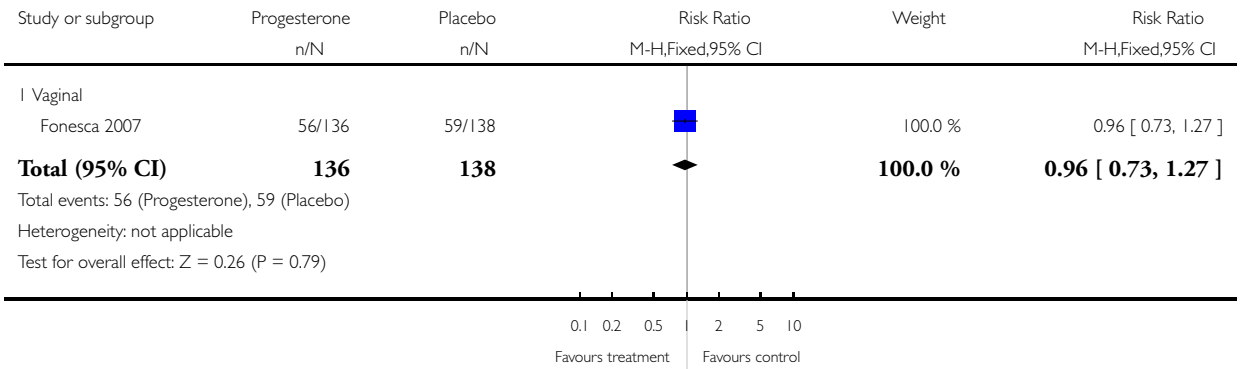


Analysis 4.3. Comparison 4 Progesterone versus placebo: ultrasound identified short cervix, Outcome 3 Infant birthweight less than 2500 grams.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 4 Progesterone versus placebo: ultrasound identified short cervix

Outcome: 3 Infant birthweight less than 2500 grams

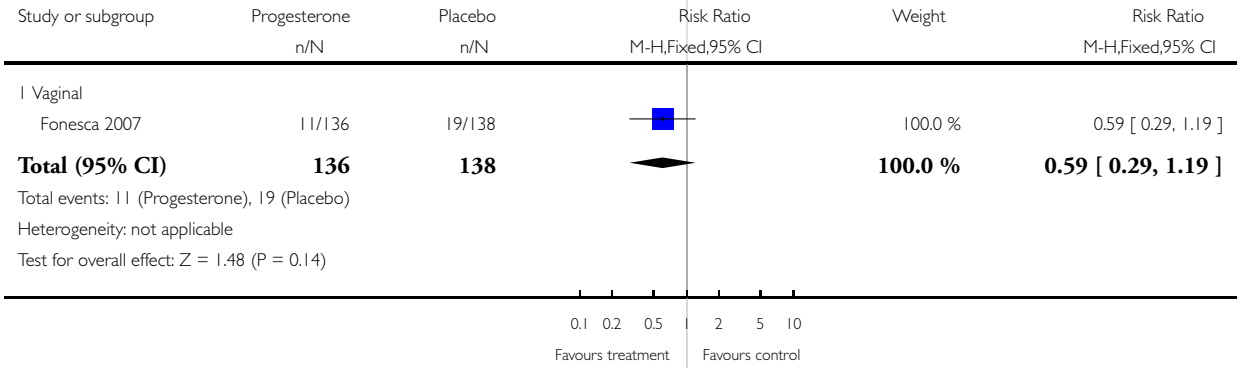


Analysis 4.4. Comparison 4 Progesterone versus placebo: ultrasound identified short cervix, Outcome 4 Respiratory distress syndrome.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 4 Progesterone versus placebo: ultrasound identified short cervix

Outcome: 4 Respiratory distress syndrome



Analysis 4.5. Comparison 4 Progesterone versus placebo: ultrasound identified short cervix, Outcome 5 Need for assisted ventilation.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 4 Progesterone versus placebo: ultrasound identified short cervix

Outcome: 5 Need for assisted ventilation

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Vaginal					
Fonesca 2007	16/136	25/138		100.0 %	0.65 [0.36, 1.16]
Total (95% CI)	**136**	**138**		**100.0 %**	**0.65 [0.36, 1.16]**
Total events: 16 (Progesterone), 25 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.46 (P = 0.15)					

Analysis 4.6. Comparison 4 Progesterone versus placebo: ultrasound identified short cervix, Outcome 6 Intraventricular haemorrhage - all grades.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 4 Progesterone versus placebo: ultrasound identified short cervix

Outcome: 6 Intraventricular haemorrhage - all grades

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Vaginal					
Fonesca 2007	1/136	2/138		100.0 %	0.51 [0.05, 5.53]
Total (95% CI)	**136**	**138**		**100.0 %**	**0.51 [0.05, 5.53]**
Total events: 1 (Progesterone), 2 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.56 (P = 0.58)					

Analysis 4.7. Comparison 4 Progesterone versus placebo: ultrasound identified short cervix, Outcome 7 Retinopathy of prematurity.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 4 Progesterone versus placebo: ultrasound identified short cervix

Outcome: 7 Retinopathy of prematurity

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Vaginal					
Fonesca 2007	2/136	0/138		100.0 %	5.07 [0.25, 104.70]
Total (95% CI)	**136**	**138**		**100.0 %**	**5.07 [0.25, 104.70]**
Total events: 2 (Progesterone), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.05 (P = 0.29)					

Analysis 4.8. Comparison 4 Progesterone versus placebo: ultrasound identified short cervix, Outcome 8 Necrotising enterocolitis.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 4 Progesterone versus placebo: ultrasound identified short cervix

Outcome: 8 Necrotising enterocolitis

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Vaginal					
Fonesca 2007	0/136	1/138		100.0 %	0.34 [0.01, 8.23]
Total (95% CI)	**136**	**138**		**100.0 %**	**0.34 [0.01, 8.23]**
Total events: 0 (Progesterone), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.67 (P = 0.51)					

Analysis 4.9. Comparison 4 Progesterone versus placebo: ultrasound identified short cervix, Outcome 9 Neonatal sepsis.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 4 Progesterone versus placebo: ultrasound identified short cervix

Outcome: 9 Neonatal sepsis

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Vaginal					
Fonesca 2007	3/136	11/138		100.0 %	0.28 [0.08, 0.97]
Total (95% CI)	**136**	**138**		**100.0 %**	**0.28 [0.08, 0.97]**
Total events: 3 (Progesterone), 11 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.01 (P = 0.045)					

Analysis 4.10. Comparison 4 Progesterone versus placebo: ultrasound identified short cervix, Outcome 10 Intrauterine fetal death.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 4 Progesterone versus placebo: ultrasound identified short cervix

Outcome: 10 Intrauterine fetal death

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Vaginal					
Fonesca 2007	1/136	1/138		100.0 %	1.01 [0.06, 16.06]
Total (95% CI)	**136**	**138**		**100.0 %**	**1.01 [0.06, 16.06]**
Total events: 1 (Progesterone), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.01 (P = 0.99)					

Analysis 4.11. Comparison 4 Progesterone versus placebo: ultrasound identified short cervix, Outcome 11 Neonatal death.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 4 Progesterone versus placebo: ultrasound identified short cervix

Outcome: 11 Neonatal death

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Vaginal					
Fonesca 2007	2/136	7/138		100.0 %	0.29 [0.06, 1.37]
Total (95% CI)	**136**	**138**		**100.0 %**	**0.29 [0.06, 1.37]**
Total events: 2 (Progesterone), 7 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.56 (P = 0.12)					

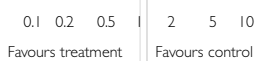
Analysis 5.1. Comparison 5 Progesterone versus placebo: multiple pregnancy, Outcome 1 Perinatal death.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 5 Progesterone versus placebo: multiple pregnancy

Outcome: 1 Perinatal death

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Intramuscular					
Hartikainen 1980	4/78	2/76		100.0 %	1.95 [0.37, 10.33]
Total (95% CI)	**78**	**76**		**100.0 %**	**1.95 [0.37, 10.33]**
Total events: 4 (Progesterone), 2 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.78 (P = 0.43)					



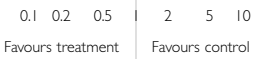
Analysis 5.2. Comparison 5 Progesterone versus placebo: multiple pregnancy, Outcome 2 Preterm birth less than 37 weeks.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 5 Progesterone versus placebo: multiple pregnancy

Outcome: 2 Preterm birth less than 37 weeks

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Intramuscular					
Hartikainen 1980	15/39	9/38		3.8 %	1.62 [0.81, 3.25]
Rouse 2007	226/325	232/330		96.2 %	0.99 [0.89, 1.09]
Total (95% CI)	**364**	**368**		**100.0 %**	**1.01 [0.92, 1.12]**
Total events: 241 (Progesterone), 241 (Placebo)					
Heterogeneity: Chi^2 = 1.99, df = 1 (P = 0.16); I^2 =50%					
Test for overall effect: Z = 0.26 (P = 0.80)					



Analysis 5.3. Comparison 5 Progesterone versus placebo: multiple pregnancy, Outcome 3 Caesarean section.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 5 Progesterone versus placebo: multiple pregnancy

Outcome: 3 Caesarean section

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Intramuscular					
Rouse 2007	200/324	204/328		100.0 %	0.99 [0.88, 1.12]
Total (95% CI)	**324**	**328**		**100.0 %**	**0.99 [0.88, 1.12]**
Total events: 200 (Progesterone), 204 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.12 (P = 0.90)					

Analysis 5.4. Comparison 5 Progesterone versus placebo: multiple pregnancy, Outcome 4 Antenatal corticosteroids.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 5 Progesterone versus placebo: multiple pregnancy

Outcome: 4 Antenatal corticosteroids

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Intramuscular					
Rouse 2007	80/324	90/330		100.0 %	0.91 [0.70, 1.17]
Total (95% CI)	**324**	**330**		**100.0 %**	**0.91 [0.70, 1.17]**
Total events: 80 (Progesterone), 90 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.75 (P = 0.45)					

Analysis 5.5. Comparison 5 Progesterone versus placebo: multiple pregnancy, Outcome 5 Antenatal tocolysis.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 5 Progesterone versus placebo: multiple pregnancy

Outcome: 5 Antenatal tocolysis

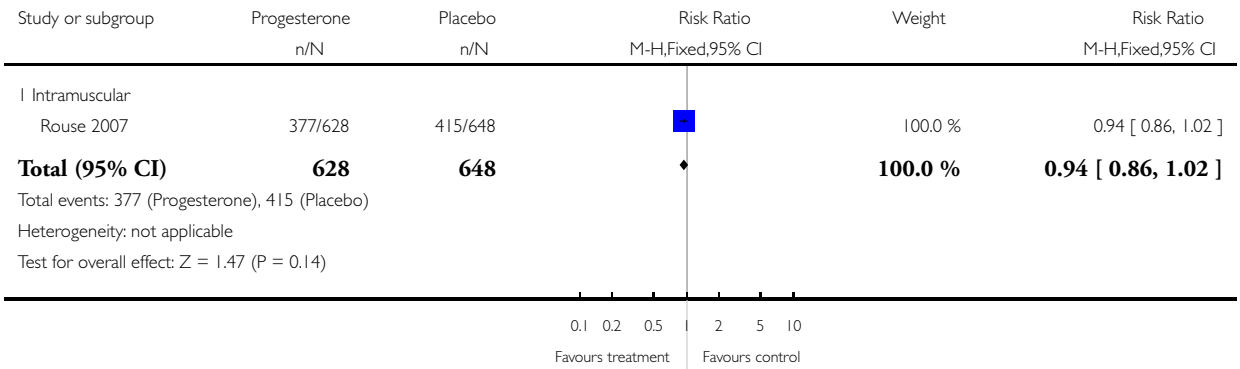
Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Intramuscular					
Rouse 2007	71/324	97/330		100.0 %	0.75 [0.57, 0.97]
Total (95% CI)	**324**	**330**		**100.0 %**	**0.75 [0.57, 0.97]**
Total events: 71 (Progesterone), 97 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.17 (P = 0.030)					

Analysis 5.6. Comparison 5 Progesterone versus placebo: multiple pregnancy, Outcome 6 Infant birthweight less than 2500 grams.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 5 Progesterone versus placebo: multiple pregnancy

Outcome: 6 Infant birthweight less than 2500 grams

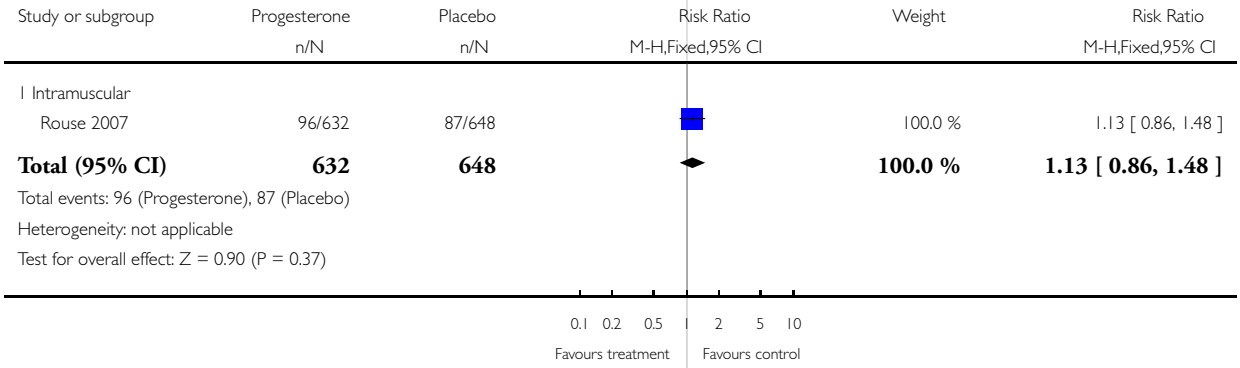


Analysis 5.7. Comparison 5 Progesterone versus placebo: multiple pregnancy, Outcome 7 Respiratory distress syndrome.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 5 Progesterone versus placebo: multiple pregnancy

Outcome: 7 Respiratory distress syndrome

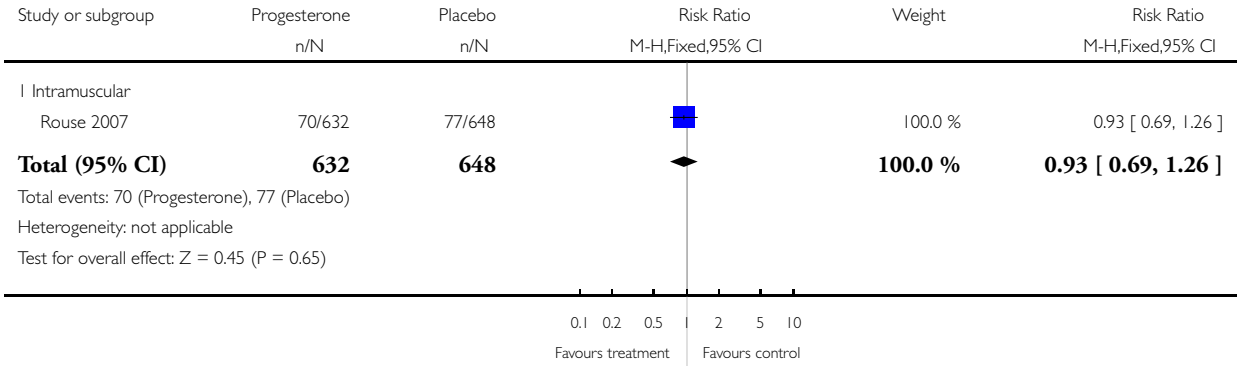


Analysis 5.8. Comparison 5 Progesterone versus placebo: multiple pregnancy, Outcome 8 Need for assisted ventilation.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 5 Progesterone versus placebo: multiple pregnancy

Outcome: 8 Need for assisted ventilation

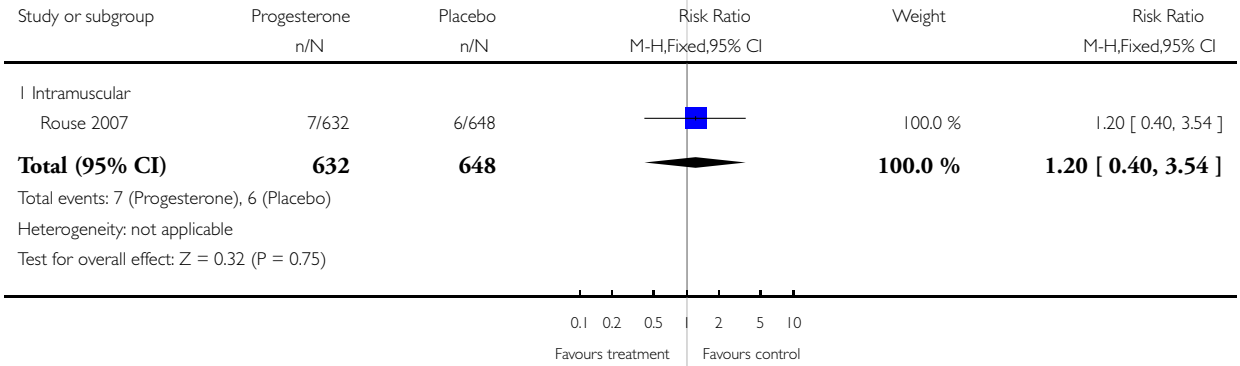


Analysis 5.9. Comparison 5 Progesterone versus placebo: multiple pregnancy, Outcome 9 Intraventricular haemorrhage - grades 3 or 4.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 5 Progesterone versus placebo: multiple pregnancy

Outcome: 9 Intraventricular haemorrhage - grades 3 or 4



Analysis 5.10. Comparison 5 Progesterone versus placebo: multiple pregnancy, Outcome 10 Retinopathy of prematurity.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 5 Progesterone versus placebo: multiple pregnancy

Outcome: 10 Retinopathy of prematurity

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Intramuscular				
Rouse 2007	0/632	0/648		0.0 [0.0, 0.0]
Total (95% CI)	**632**	**648**		**0.0 [0.0, 0.0]**
Total events: 0 (Progesterone), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				

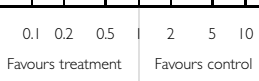
Analysis 5.11. Comparison 5 Progesterone versus placebo: multiple pregnancy, Outcome 11 Necrotising enterocolitis.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 5 Progesterone versus placebo: multiple pregnancy

Outcome: 11 Necrotising enterocolitis

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Intramuscular					
Rouse 2007	3/632	4/648		100.0 %	0.77 [0.17, 3.42]
Total (95% CI)	**632**	**648**		**100.0 %**	**0.77 [0.17, 3.42]**
Total events: 3 (Progesterone), 4 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.34 (P = 0.73)					

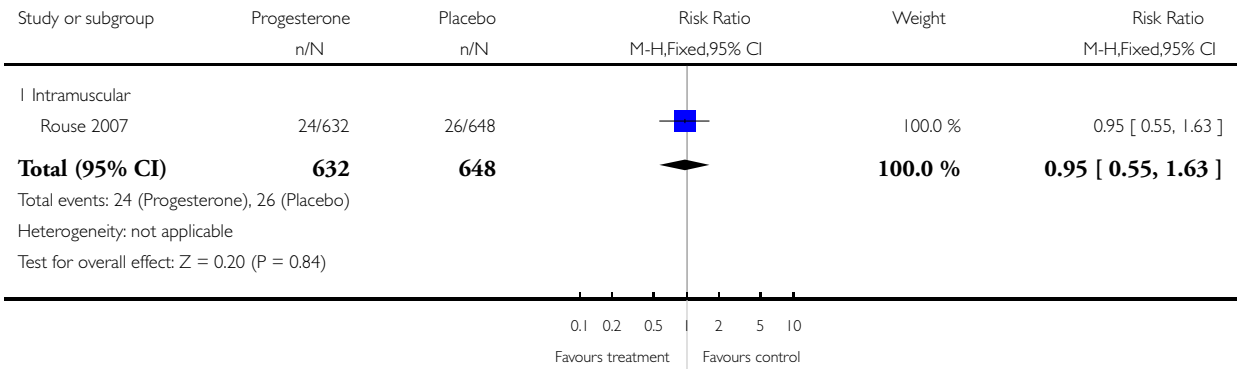


Analysis 5.12. Comparison 5 Progesterone versus placebo: multiple pregnancy, Outcome 12 Neonatal sepsis.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 5 Progesterone versus placebo: multiple pregnancy

Outcome: 12 Neonatal sepsis

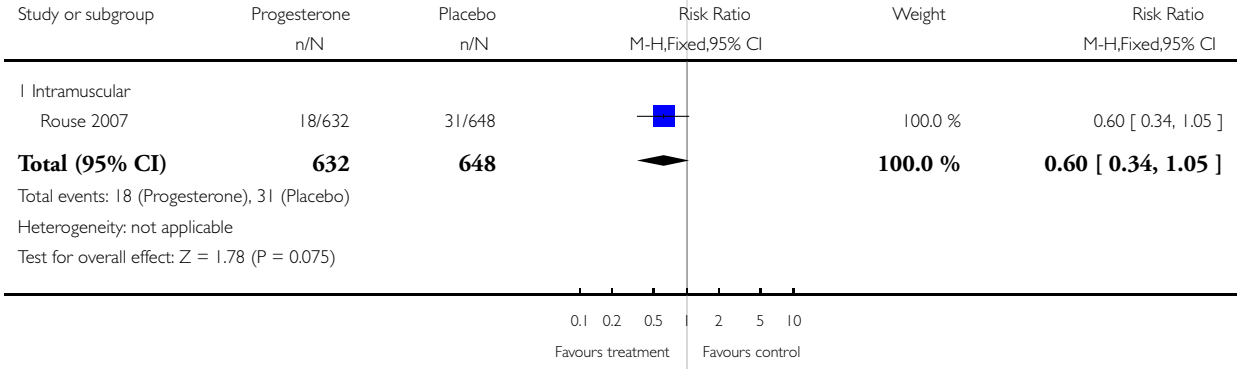


Analysis 5.13. Comparison 5 Progesterone versus placebo: multiple pregnancy, Outcome 13 Patent ductus arteriosus.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 5 Progesterone versus placebo: multiple pregnancy

Outcome: 13 Patent ductus arteriosus



Analysis 6.1. Comparison 6 Progesterone versus placebo: multiple pregnancy, by timing of commencement (< 20 wk v > 20 wk), Outcome 1 Preterm birth < 37 weeks.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 6 Progesterone versus placebo: multiple pregnancy, by timing of commencement (< 20 wk v > 20 wk)

Outcome: 1 Preterm birth < 37 weeks

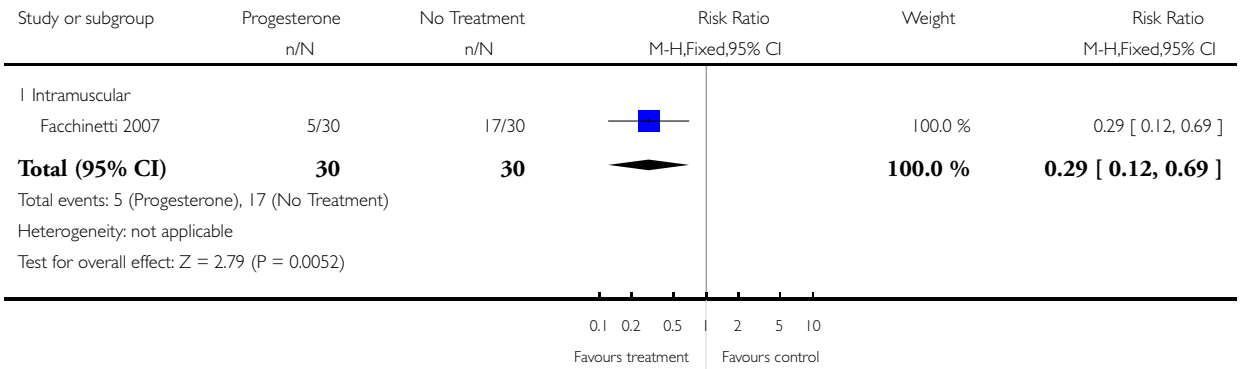
Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Supplementation commenced prior to 20 weeks' gestation					
Rouse 2007	226/325	232/330		96.2 %	0.99 [0.89, 1.09]
Subtotal (95% CI)	**325**	**330**		**96.2 %**	**0.99 [0.89, 1.09]**
Total events: 226 (Progesterone), 232 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.21 (P = 0.83)					
2 Supplementation commenced after 20 weeks' gestation					
Hartikainen 1980	15/39	9/38		3.8 %	1.62 [0.81, 3.25]
Subtotal (95% CI)	**39**	**38**		**3.8 %**	**1.62 [0.81, 3.25]**
Total events: 15 (Progesterone), 9 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.37 (P = 0.17)					
Total (95% CI)	**364**	**368**		**100.0 %**	**1.01 [0.92, 1.12]**
Total events: 241 (Progesterone), 241 (Placebo)					
Heterogeneity: Chi^2 = 1.99, df = 1 (P = 0.16); I^2 =50%					
Test for overall effect: Z = 0.26 (P = 0.80)					

Analysis 7.1. Comparison 7 Progesterone versus no treatment: prior threatened preterm labour, Outcome 1 Preterm birth less than 37 weeks' gestation.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 7 Progesterone versus no treatment: prior threatened preterm labour

Outcome: 1 Preterm birth less than 37 weeks' gestation

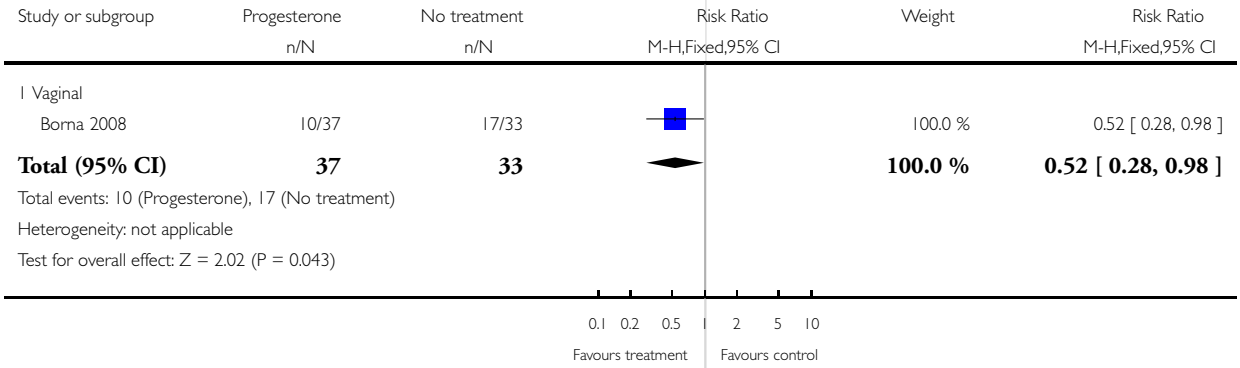


Analysis 7.2. Comparison 7 Progesterone versus no treatment: prior threatened preterm labour, Outcome 2 Infant birthweight less than 2500 grams.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 7 Progesterone versus no treatment: prior threatened preterm labour

Outcome: 2 Infant birthweight less than 2500 grams



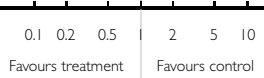
Analysis 7.3. Comparison 7 Progesterone versus no treatment: prior threatened preterm labour, Outcome 3 Respiratory distress syndrome.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 7 Progesterone versus no treatment: prior threatened preterm labour

Outcome: 3 Respiratory distress syndrome

Study or subgroup	Progesterone n/N	No treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Vaginal					
Borna 2008	4/37	12/33		100.0 %	0.30 [0.11, 0.83]
Total (95% CI)	**37**	**33**		**100.0 %**	**0.30 [0.11, 0.83]**
Total events: 4 (Progesterone), 12 (No treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.31 (P = 0.021)					



Analysis 7.4. Comparison 7 Progesterone versus no treatment: prior threatened preterm labour, Outcome 4 Need for assisted ventilation.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 7 Progesterone versus no treatment: prior threatened preterm labour

Outcome: 4 Need for assisted ventilation

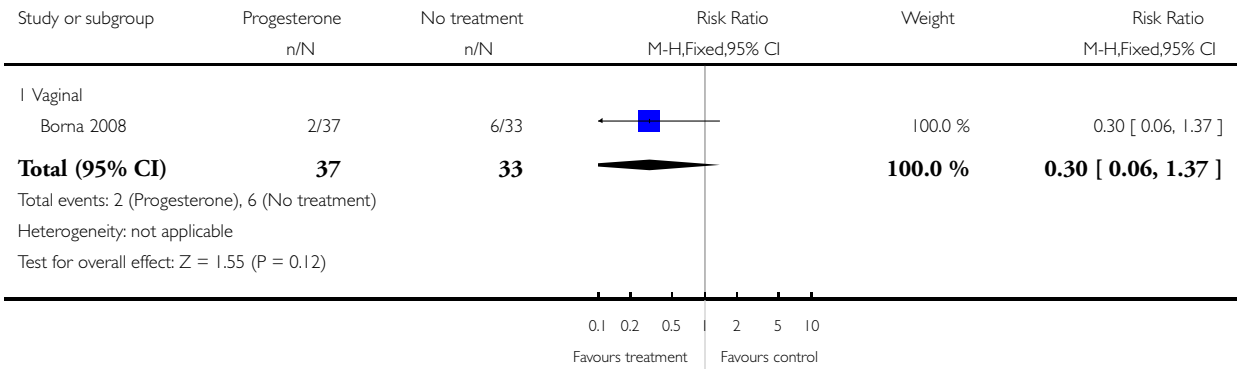
Study or subgroup	Progesterone n/N	No treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Vaginal					
Borna 2008	2/37	6/33		100.0 %	0.30 [0.06, 1.37]
Total (95% CI)	**37**	**33**		**100.0 %**	**0.30 [0.06, 1.37]**
Total events: 2 (Progesterone), 6 (No treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.55 (P = 0.12)					

Analysis 7.5. Comparison 7 Progesterone versus no treatment: prior threatened preterm labour, Outcome 5 Neonatal sepsis.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 7 Progesterone versus no treatment: prior threatened preterm labour

Outcome: 5 Neonatal sepsis

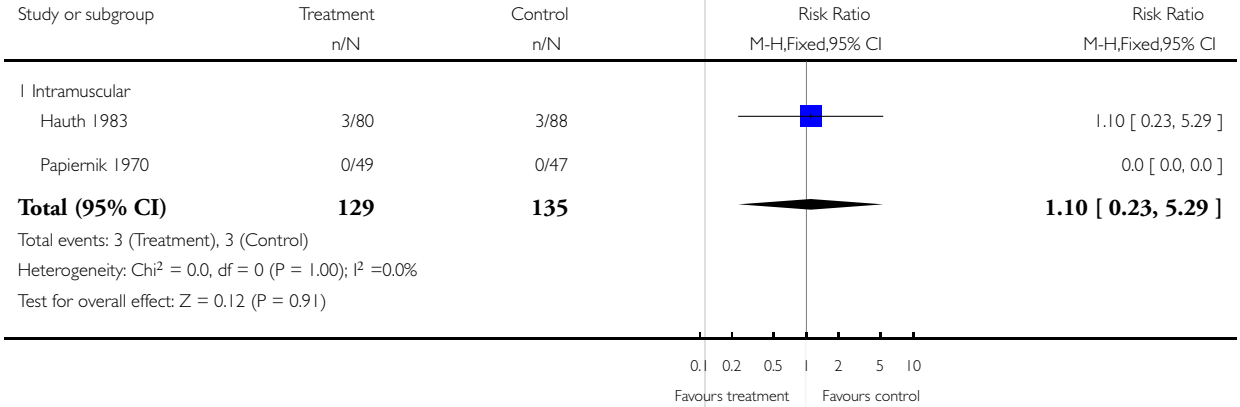


Analysis 8.1. Comparison 8 Progesterone versus placebo: other reason at risk of preterm birth, Outcome 1 Perinatal death.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 8 Progesterone versus placebo: other reason at risk of preterm birth

Outcome: 1 Perinatal death



Analysis 8.2. Comparison 8 Progesterone versus placebo: other reason at risk of preterm birth, Outcome 2 Preterm birth less than 37 weeks.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 8 Progesterone versus placebo: other reason at risk of preterm birth

Outcome: 2 Preterm birth less than 37 weeks

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Intramuscular					
Hauth 1983	5/80	5/88		34.4 %	1.10 [0.33, 3.66]
Papiernik 1970	2/50	9/49		65.6 %	0.22 [0.05, 0.96]
Total (95% CI)	**130**	**137**		**100.0 %**	**0.52 [0.22, 1.24]**
Total events: 7 (Progesterone), 14 (Placebo)					
Heterogeneity: Chi^2 = 2.82, df = 1 (P = 0.09); I^2 =65%					
Test for overall effect: Z = 1.47 (P = 0.14)					

Analysis 8.3. Comparison 8 Progesterone versus placebo: other reason at risk of preterm birth, Outcome 3 Infant birthweight less than 2500 grams.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 8 Progesterone versus placebo: other reason at risk of preterm birth

Outcome: 3 Infant birthweight less than 2500 grams

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Intramuscular					
Hauth 1983	6/80	8/88		48.5 %	0.83 [0.30, 2.27]
Papiernik 1970	2/50	8/49		51.5 %	0.25 [0.05, 1.10]
Total (95% CI)	**130**	**137**		**100.0 %**	**0.53 [0.23, 1.18]**
Total events: 8 (Progesterone), 16 (Placebo)					
Heterogeneity: Chi^2 = 1.75, df = 1 (P = 0.19); I^2 =43%					
Test for overall effect: Z = 1.55 (P = 0.12)					

Analysis 8.4. Comparison 8 Progesterone versus placebo: other reason at risk of preterm birth, Outcome 4 Intrauterine fetal death.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 8 Progesterone versus placebo: other reason at risk of preterm birth

Outcome: 4 Intrauterine fetal death

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Intramuscular					
Hauth 1983	1/80	3/88		100.0 %	0.37 [0.04, 3.45]
Total (95% CI)	**80**	**88**		**100.0 %**	**0.37 [0.04, 3.45]**
Total events: 1 (Progesterone), 3 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.88 (P = 0.38)					

Analysis 8.5. Comparison 8 Progesterone versus placebo: other reason at risk of preterm birth, Outcome 5 Neonatal Death.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 8 Progesterone versus placebo: other reason at risk of preterm birth

Outcome: 5 Neonatal Death

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Intramuscular					
Hauth 1983	2/80	0/88		100.0 %	5.49 [0.27, 112.73]
Total (95% CI)	**80**	**88**		**100.0 %**	**5.49 [0.27, 112.73]**
Total events: 2 (Progesterone), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.11 (P = 0.27)					

Analysis 9.1. Comparison 9 Progesterone versus placebo: other reason at risk of preterm birth, by timing of commencement (< 20 wk v > 20 wk), Outcome 1 Perinatal death.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 9 Progesterone versus placebo: other reason at risk of preterm birth, by timing of commencement (< 20 wk v > 20 wk)

Outcome: 1 Perinatal death

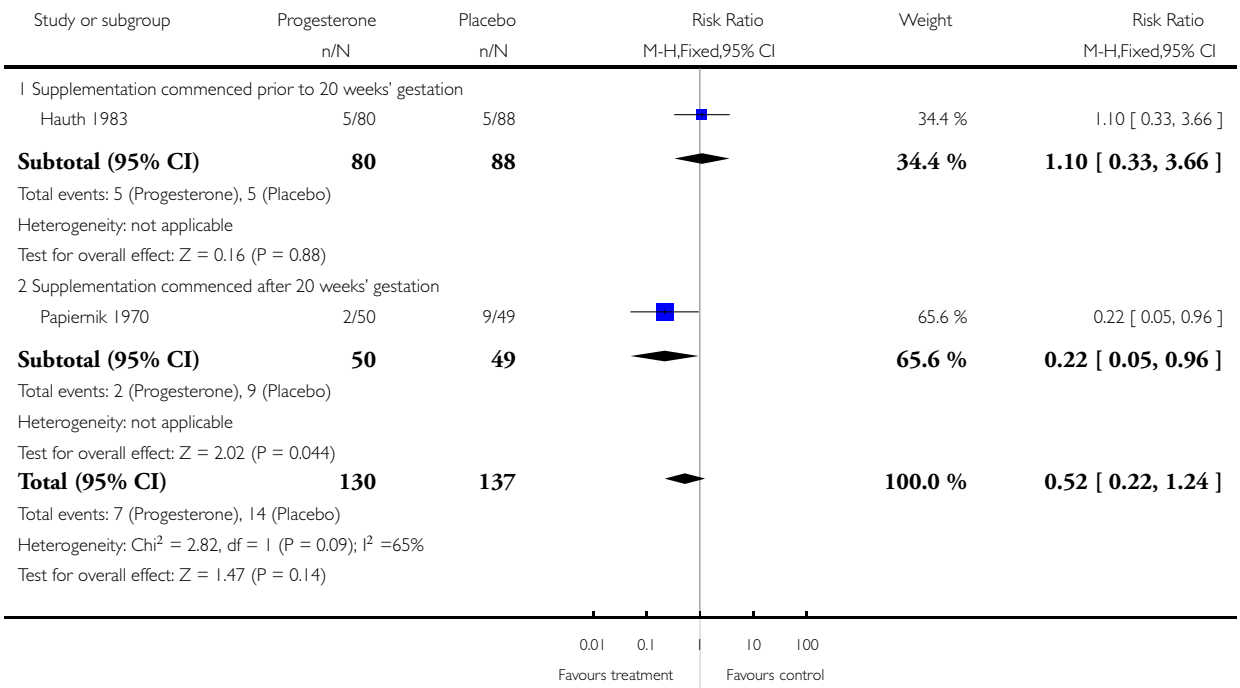
Study or subgroup	Progesterone n/N	Placbeo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Supplementation commenced prior to 20 weeks' gestation				
Hauth 1983	3/80	3/88		1.10 [0.23, 5.29]
Subtotal (95% CI)	**80**	**88**		**1.10 [0.23, 5.29]**
Total events: 3 (Progesterone), 3 (Placbeo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.12 (P = 0.91)				
2 Supplementation commenced after 20 weeks' gestation				
Papiernik 1970	0/49	0/47		0.0 [0.0, 0.0]
Subtotal (95% CI)	**49**	**47**		**0.0 [0.0, 0.0]**
Total events: 0 (Progesterone), 0 (Placbeo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Total (95% CI)	**129**	**135**		**1.10 [0.23, 5.29]**
Total events: 3 (Progesterone), 3 (Placbeo)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 0.12 (P = 0.91)				

Analysis 9.2. Comparison 9 Progesterone versus placebo: other reason at risk of preterm birth, by timing of commencement (< 20 wk v > 20 wk), Outcome 2 Preterm birth less than 37 weeks.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 9 Progesterone versus placebo: other reason at risk of preterm birth, by timing of commencement (< 20 wk v > 20 wk)

Outcome: 2 Preterm birth less than 37 weeks

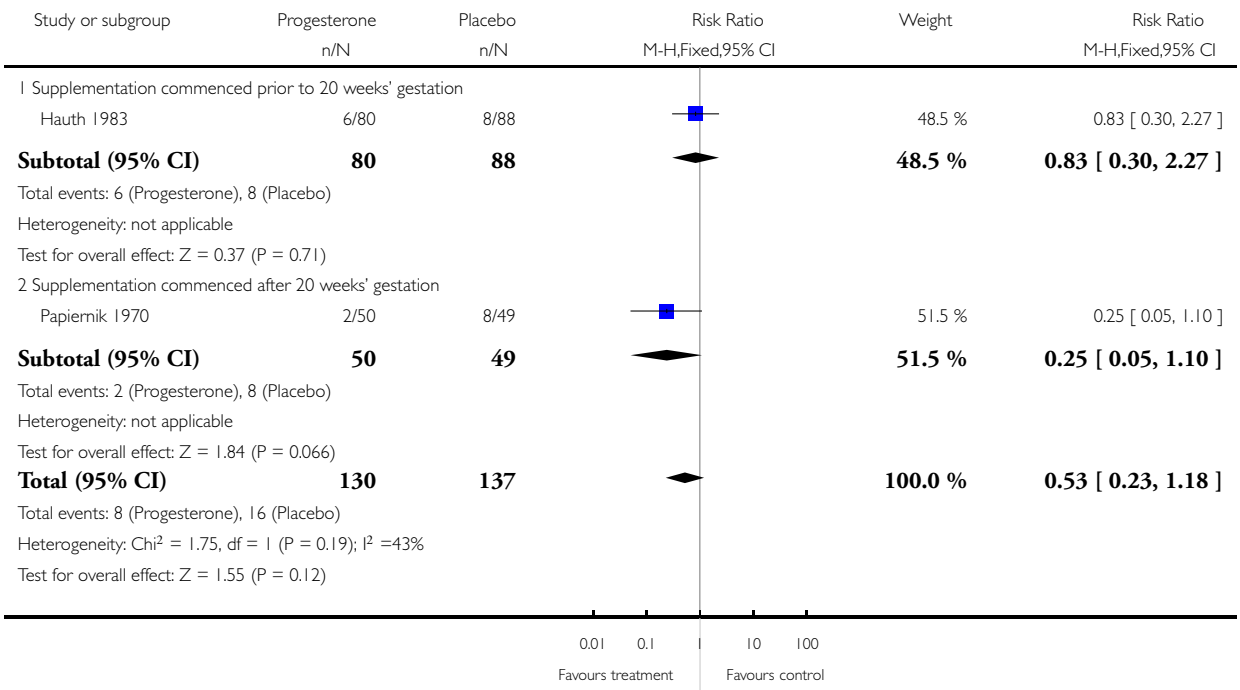


Analysis 9.3. Comparison 9 Progesterone versus placebo: other reason at risk of preterm birth, by timing of commencement (< 20 wk v > 20 wk), Outcome 3 Infant birthweight less than 2500 grams.

Review: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

Comparison: 9 Progesterone versus placebo: other reason at risk of preterm birth, by timing of commencement (< 20 wk v > 20 wk)

Outcome: 3 Infant birthweight less than 2500 grams



APPENDICES

Appendix 1. Search terms for CENTRAL

Search terms included free text terms pregnancy, preterm birth, progesterone, progestogen, intramuscular, vaginal, oral, perinatal morbidity, perinatal mortality, and randomis(z)ed controlled trial. Please contact review author for exact strategy.

Appendix 2. Methods for the previous version of this review

Quality assessment

We considered four major sources of potential bias and methods of avoidance of these biases when assessing trial quality: (1) selection bias - allocation concealment, (2) performance bias - blinding of intervention, (3) attrition bias - completeness of follow up, (4) detection bias - blinding of outcome assessment. We assigned a quality rating for blinding of randomisation to each trial, using the criteria outlined in the Cochrane Reviewers' Handbook (Clarke 2003a): (A) adequate, (B) unclear, (C) inadequate, or (D) not used. We assigned a quality rating of (A) yes, (B) cannot tell, or (C) no, to the other quality components (blinding of intervention, completeness of follow up and blinding of outcome assessment). We defined high-quality trials as those receiving an A rating for the criterion of blinding of randomisation (central-computerised randomisation service or consecutively numbered, sealed, opaque envelopes) blinding of the intervention (use of a placebo) and less than 20% loss to follow up for major outcomes.

WHAT'S NEW

Last assessed as up-to-date: 30 December 2008.

31 December 2008	New search has been performed	Search updated. A search in October 2007 identified 17 new trials. We included five (Borna 2008; Facchinetti 2007; Fonesca 2007; O'Brien 2007; Rouse 2007); added a follow-up report to Meis 2003; and excluded one (Walch 2005). Ten trials are ongoing (Bruinse 2007; Maurel 2007; Grobman 2007; Martinez 2007; Nassar 2007; Perlitz 2007; Rode 2007; Rozenberg 2007; Serra 2007; Wood 2007). A further updated search in December 2008 identified one more report of Borna 2008; five more reports of O'Brien 2007; six more reports of Rouse 2007; one more report of Crowther 2007; one more report of Bruinse 2007; three ongoing studies (Creasy 2008; Starkey 2008; Swaby 2007); and one study which is awaiting classification (Moghtadaei 2008). The review's conclusions have not changed.

HISTORY

Protocol first published: Issue 4, 2004

Review first published: Issue 1, 2006

5 November 2008	Amended	Converted to new review format.
31 March 2005	New search has been performed	Search updated and new studies found and included or excluded.

CONTRIBUTIONS OF AUTHORS

V Flenady commented on drafts of the original protocol prior to publication; identified studies and assessed eligibility for inclusion; extracted data; and also commented on all drafts of the review.

R Cincotta drafted the original protocol and commented on subsequent drafts prior to publication; he also assessed studies for inclusion and extracted data.

CA Crowther identified studies for inclusion and commented on all drafts of the review.

J Dodd revised the review; conducted the MEDLINE search; identified studies and assessed their eligibility for inclusion. She also extracted data and entered it into RevMan, wrote the first version of the results, discussion and conclusions of the review, as well as commenting on each draft of the review prior to publication.

DECLARATIONS OF INTEREST

All authors are investigators in a randomised trial assessing the use of progesterone for prevention of respiratory distress syndrome (The PROGRESS Trial).

SOURCES OF SUPPORT

Internal sources

- Mater Research Support Centre, Mater Health Services Brisbane, South Brisbane, Queensland, Australia.
- Department of Maternal Fetal Medicine, Mater Mothers' Hospital, South Brisbane, Queensland, Australia.
- The University of Adelaide, Division of Obstetrics and Gynaecology, Australia.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In view of the increase in the number of trials published, along with the huge variation in the patient populations recruited, we have decided to categorise the studies by the reason women were considered to be at increased risk of preterm birth. We have also included longer-term childhood health outcomes, in recognition of the need for ongoing follow up of children exposed antenatally to progesterone.

INDEX TERMS

Medical Subject Headings (MeSH)

17-alpha-Hydroxyprogesterone [administration & dosage; adverse effects]; Premature Birth [*prevention & control]; Progesterone [*administration & dosage; adverse effects]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy