Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth (Review)

Brownfoot FC, Crowther CA, Middleton P

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2008, Issue 4

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[Intervention review]

Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth

Fiona C Brownfoot[1], Caroline A Crowther[1], Philippa Middleton[2]

[1]Discipline of Obstetrics and Gynaecology, The University of Adelaide, Adelaide, Australia. [2]ARCH: Australian Research Centre for Health of Women and Babies, Discipline of Obstetrics and Gynaecology, The University of Adelaide, Adelaide, Australia

Contact address: Fiona C Brownfoot, Discipline of Obstetrics and Gynaecology, The University of Adelaide, Women's and Children's Hospital, 1st floor, Queen Victoria Building, 72 King William Road, Adelaide, South Australia, 5006, Australia. fiona.brownfoot@gmail.com. (Editorial group: Cochrane Pregnancy and Childbirth Group.)

Cochrane Database of Systematic Reviews, Issue 4, 2008 (Status in this issue: *New*)

DOI: 10.1002/14651858.CD006764.pub2
This version first published online: 8 October 2008 in Issue 4, 2008.
Last assessed as up-to-date: 30 January 2008. (Dates and statuses?)

This record should be cited as: Brownfoot FC, Crowther CA, Middleton P. Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database of Systematic Reviews* 2008, Issue 4. Art. No.: CD006764. DOI: 10.1002/14651858.CD006764.pub2.

ABSTRACT

Background

Despite the widespread use of antenatal corticosteroids to prevent respiratory distress syndrome in preterm infants, there is currently no consensus as to the type of corticosteroid to use; nor the dose, frequency or timing of use or the route of administration.

Objectives

To assess the effects of different corticosteroid regimens for women at risk of preterm birth.

Search strategy

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (January 2008).

Selection criteria

Randomised and quasi-randomised controlled trials of antenatal corticosteroid regimens in women at risk of preterm birth.

Data collection and analysis

Two authors assessed trial quality and extracted the data independently.

Main results

Ten trials (1089 women and 1161 infants) were included. Dexamethasone decreased the incidence of intraventricular haemorrhage compared with betamethasone (risk ratio (RR) 0.44, 95% confidence interval (CI) 0.21 to 0.92; four trials, 549 infants). No statistically significant differences were seen for other primary outcomes including respiratory distress syndrome, bronchopulmonary dysplasia, severe intraventricular haemorrhage, periventricular leukomalacia, perinatal death, or mean birthweight. Results for biophysical parameters were inconsistent, but mostly no important differences were seen for these, or any other secondary outcome except for neonatal intensive care unit (NICU) admission. In one trial of 105 infants, significantly more infants in the dexamethasone group were admitted to NICU compared with the betamethasone group (RR 3.83, 95% CI 1.24 to 11.87).

Oral dexamethasone compared with intramuscular dexamethasone increased the incidence of neonatal sepsis (RR 8.48, 95% CI 1.11 to 64.93) in one trial of 183 infants. No statistically significant differences were seen for other outcomes reported.

In one small trial of 69 infants comparing betamethasone acetate and phosphate with betamethasone phosphate no differences were seen for any of the outcomes reported.

Authors' conclusions

Dexamethasone may have some benefits compared with betamethasone such as less intraventricular haemorrhage, although perhaps a higher rate of NICU admission (seen in only one trial). Apart from a suggestion from another small trial that the intramuscular route may have advantages over an oral route for dexamethasone, few other conclusions about optimal antenatal corticosteroid regimens were able to be made. Trials of commonly used corticosteroids are most urgently needed, followed by trials of dosages and other variations in regimens.

PLAIN LANGUAGE SUMMARY

Corticosteroid treatments before early birth for reducing death, lung problems and brain haemorrhage in babies

Babies born early are at risk of death, lung problems (respiratory distress syndrome) and bleeding of the brain (intraventricular haemorrhage). Corticosteroids are given to the mother to help stop these problems occurring and there is high-quality evidence that they are effective in preventing many of these problems. These drugs work by maturing the baby's lungs before birth. There are different types of corticosteroids and they can be given in different ways and in different doses. Since there is no clear or agreed best type or dose, hospitals may vary in how they give this drug.

Most trials have compared the two most commonly used corticosteroids before early birth, dexamethasone and betamethasone. In this review of ten trials, nine trials compared dexamethasone and betamethasone; and one trial compared two different ways of giving dexamethasone. We found that dexamethasone and betamethasone showed similar results, although there was less bleeding of the brain (but perhaps more frequent admission to the neonatal intensive care unit) for dexamethasone compared with betamethasone. On the basis of one trial, giving dexamethasone by injection (intramuscularly) may be better than giving the drug to the mother by mouth. We need more studies to establish which is the best drug and which is the best way to give it, and babies in these trials need to be followed up over a long period to monitor any effects on child and adult development.

BACKGROUND

Preterm birth poses a significant health burden affecting approximately 5% to 13% of all babies in industrialised countries with rates increasing in many countries (Goldenberg 2007 ; Haram 2003). Preterm infants (less than 37 weeks' gestation), especially those born before 32 weeks' gestation, are at high risk of respiratory distress syndrome (RDS), a serious complication that remains the primary cause of early neonatal death and disability (Haram 2003). Those infants born preterm who do survive the neonatal period are at a significantly increased risk of long-term neurological disability (Johnson 1993 ; Saigal 2007). RDS develops as a consequence of surfactant deficiency and immature lung development. The risk of RDS and neonatal mortality reduces as gestation increases, reflecting maturity of organ systems (Doyle 2001; Moise 1995; Saigal 2007). Treatments that may reduce the incidence of RDS in infants born preterm, including antenatal corticosteroids, have therefore received considerable attention (Roberts 2006).

Corticosteroids

Corticosteroids act by altering gene expression resulting in glucocorticoid effects, including gluconeogenesis, proteolysis, lipolysis, suppression of immune responses and mineralocorticoid effects, including hypertension, sodium and water retention and potassium loss (AMH 2006). In the fetal lung, the action of corticosteroids leads to an increase in protein production, biosynthesis of phospholipids and the appearance of surfactant (Ballard 1995).
Liggins 1969 demonstrated that the lungs of lambs born preterm became functionally mature following antenatal corticosteroid administration. Following these initial animal studies, Liggins and then other investigators conducted several clinical trials to assess the effects of corticosteroids before preterm birth.
The Cochrane review *'Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth'* showed that a single course of antenatal corticosteroids reduced the incidence of RDS (risk ratio (RR) 0.66, 95% confidence interval (CI) 0.59 to 0.73; 21 trials, 4038 infants) (Roberts 2006). Other beneficial effects included a reduction in neonatal death, cerebroventricular haemorrhage, necrotising enterocolitis, infectious morbidity, need for respiratory support and neonatal intensive care unit admission. For the mother, corticosteroid use was not shown to increase the risk of death, chorioamnionitis or puerperal sepsis (Roberts 2006). Contrary to the concern that corticosteroid treatment may increase infection in those with preterm prelabour rupture of membranes (Imseis 1996) or increase the rate of stillbirth in those with pregnancy-related hypertension (Liggins 1976), this Cochrane review confirmed that antenatal corticosteroid treatment is effective in women at risk of preterm birth with these complications (Roberts 2006). Corticosteroids have become the standard of care for women at risk of preterm birth before 32 to 34 weeks' gestation in many countries (Jobe 2004; NIH 1995).
Despite their widespread use, there is currently variation in clinical practice as to the type of corticosteroid used, the dose and frequency given, and the route of administration of corticosteroid doses.

Corticosteroid type

Currently either betamethasone or dexamethasone are the recommended corticosteroid regimens used in clinical practice (NIH 1995). Betamethasone is available in two different forms: betamethasone sodium phosphate, a solution with a short biological half-life of 36 to 72 hours; and betamethasone acetate, a suspension with a relatively long half-life (Jobe 2004 ; Katzung 2004 ; NNF5 2006). These forms of betamethasone are often used in combination to maximize the drug's efficiency while reducing the number of injections given to the mother (NNF5 2006). Dexamethasone generally comes in the form of dexamethasone sodium

phosphate, a solution with a short biological half-life of 36 to 72 hours (Ballard 1995; Jobe 2004; Katzung 2004; NNF5 2006). Both betamethasone and dexamethasone are able to cross the placenta in their active form and have comparable efficiency (NNF5 2006). The chemical composition of betamethasone and dexamethasone are virtually identical except for the configuration of a methyl group in position 16 (Bar-Lev 2004 ; NNF5 2006). Some dexamethasone preparations contain a sulphite preservative (NNF5 2006). Sulphites have been linked to neurotoxicity in the newborn especially when in combination with peroxy nitrite (Bar-Lev 2004; Baud 1999; Goldenberg 2001; Walfisch 2001).

The optimal type of corticosteroid to use for prenatal treatment remains unclear. The indirect subgroup comparison of betamethasone and dexamethasone in the Roberts 2006 Cochrane review indicates similar short-term neonatal outcomes for both drugs. Maternal outcomes were also similar although the risk of puerperal sepsis was higher in the dexamethasone versus placebo or no treatment group, while betamethasone did not show an increase in puerperal sepsis over placebo or no treatment (Roberts 2006). The results from observational studies are not always consistent with the results from randomised trials. For instance, a National Institute of Child Health and Human Development Neonatal Research Network (NICHD NRN) cohort study of over 300 infants reported a link between betamethasone and reduced risk of neonatal death whereas dexamethasone was associated with an increased risk of neonatal death (Lee 2006). In contrast, the Roberts 2006 Cochrane review showed a reduced risk for fetal and neonatal death for both the betamethasone and dexamethasone groups compared with placebo/no treatment. In a later NICHD NRN report of part of this cohort, Lee 2008 reported reduced adverse childhood neurological outcomes at 18 to 22 months for dexamethasone but not for betamethasone.

The long-term outcomes related to corticosteroid use have largely been positive. Within the Roberts 2006 Cochrane review, overall antenatal corticosteroid treatment was shown to reduce developmental delay and reduce cerebral palsy when compared with no corticosteroid treatment. It is not known if the long-term outcomes vary by type of corticosteroid used. While follow up at 30 years following use showed no clinical differences in adults who were exposed or not exposed to betamethasone as infants (Dalziel 2005), there are no similar long-term follow-up studies reported on dexamethasone use. There are no published data on the long-term effects of betamethasone compared directly with dexamethasone.

Corticosteroid dose, timing and frequency

The optimal corticosteroid dose to use, timing of use and frequency of administration similarly remains unclear. The common regimen of two doses of 12 mg of betamethasone given intramuscularly 24 hours apart and the treatment of four doses of 6 mg of dexamethasone given intramuscularly 12 hours apart was recommended by the NIH Consensus Development Panel on the Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes (NIH 1995). This dose corresponds to a high occupancy of steroid receptors in fetal tissues. Accompanying the benefits of corticosteroids, there is concern that at high doses, corticosteroids may become adverse. There is a suggestion that the current doses used may be higher than needed (Jobe 2004). Similarly, the rationale for two doses of betamethasone and four doses of dexamethasone and the effects of using different formulations for the initial and subsequent injections remain unclear (Jobe 2004; NNF5 2006).

Corticosteroid route

The optimal route of administration of betamethasone and dexamethasone is uncertain. Both drugs may be administered as intramuscular injections. Betamethasone can be given intra-amniotically (Lefebvre 1976; Murphy 1982) and intravenously (Petersen 1983) and dexamethasone can be given orally (Egerman 1998).

Repeat doses of corticosteroid

The reduction in incidence of RDS by antenatal corticosteroid therapy has been shown to be effective up to seven days after treatment (Roberts 2006). A single dose of antenatal corticosteroid does not prevent RDS if it is administered seven days or more prior to birth (Crowther 2007; Roberts 2006). Whether antenatal corticosteroids for women who remain at risk of preterm birth need to be repeated seven days after the initial course is assessed in another Cochrane review (Crowther 2007); therefore, this review will not cover repeat steroid doses compared with single doses.

This review assesses studies making a head-to-head comparison of different regimens of corticosteroid type, dose, timing, frequency of dose per treatment course and route of administration. Other corticosteroid Cochrane reviews have examined inter-study differences between drug regimens, in subgroup analysis. We have assessed these indirect comparisons comparing any corticosteroid with placebo following the methods outlined in an appendix accompanying Song 2003.

OBJECTIVES

To assess the effects on fetal and neonatal morbidity and mortality, on maternal morbidity and mortality, and on the child and adult in later life, of administering different types of corticosteroids (dexamethasone or betamethasone), different corticosteroid dose regimens, including timing, frequency and mode of administration.

METHODS

Criteria for considering studies for this review

Types of studies

All identified published and unpublished randomised controlled trials or quasi-randomised control trials comparing any two corticosteroids (dexamethasone or betamethasone or any other corticosteroid that can cross the placenta), comparing different dose regimens (including frequency and timing of administration) in women at risk of preterm birth were included.

Types of participants

Women with a singleton or multiple pregnancy expected to give birth preterm (before 37 weeks) as a result of either spontaneous preterm labour, preterm prelabour rupture of membranes or elective preterm birth.

Types of interventions

- Different types of corticosteroids including dexamethasone, betamethasone, hydrocortisone or any other corticosteroid that can cross the placenta.
- Different corticosteroid regimens including dose, frequency, timing and route of administration.

Trials which tested the effect of corticosteroids with other interventions have been excluded. Trials assessing repeat corticosteroid doses versus a single corticosteroid dose have been excluded.

Types of outcome measures

These cover outcomes of maternal morbidity, perinatal morbidity and mortality, child morbidity and mortality, child as adult morbidity and mortality and the use of health services by the mother and by the neonate or child.
They are divided into primary outcomes, thought to be the most clinically relevant, and secondary outcomes of importance, including possible complications and also additional measures of effectiveness. Groups include:

- women;
- baby;
- child;
- child as adult;
- health services.

Primary outcomes

For the woman

- Death;
- chorioamnionitis (however defined by authors);
- puerperal sepsis (however defined by authors).

For the baby

- Death (fetal/neonatal);
- respiratory distress syndrome (RDS);
- severity of RDS;
- chronic lung disease (need for continuous supplemental oxygen at 28 days postnatal age or 36 weeks' postmenstrual age, whichever was later);
- bronchopulmonary dyplasia (variously defined);
- intraventricular haemorrhage (diagnosed by ultrasound, diagnosed by autopsy);
- severe intraventricular haemorrhage;
- periventricular leukomalacia;
- birthweight;
- low birthweight.

For the child

- Death;
- neurodevelopmental disability at follow up (blindness, deafness, moderate/severe cerebral palsy (however defined by authors), or developmental delay/intellectual impairment (defined as developmental quotient or intelligence quotient less than -2 standard deviations below population mean) or variously defined).

For the child as adult

- Death;
- neurodevelopmental disability at follow up (blindness, deafness, moderate/severe cerebral palsy (however defined by authors), or developmental delay/intellectual impairment (defined as developmental quotient or intelligence quotient less than -2 standard deviations below population mean) or variously defined.

Secondary outcomes

For the woman

- Fever after trial entry requiring the use of antibiotics;
- intrapartum fever requiring the use of antibiotics;
- postnatal fever requiring the use of antibiotics;
- admission to intensive care unit;
- adverse effects of therapy;
- glucose intolerance (however defined by authors);
- hypertension (however defined by authors).

For the infant

- Apgar score less than seven at five minutes;
- interval between trial entry and birth;
- mean length at birth;
- mean head circumference at birth;

- mean skin fold thickness at birth;
- small-for-gestational age (however defined by authors);
- mean placental weight;
- neonatal blood pressure;
- admission to neonatal intensive care;
- need for inotropic support (days);
- need for mechanical ventilation/continuous positive airways pressure;
- mean duration of mechanical ventilation/continuous positive airways pressure (days);
- air leak syndrome;
- need for oxygen supplementation;
- duration of oxygen supplementation (days);
- surfactant use;
- systemic infection in first 48 hours of life (neonatal sepsis);
- proven infection while in the neonatal intensive care unit;
- necrotising enterocolitis;
- retinopathy of prematurity;
- patent ductus arteriosus;
- hypothalamo-pituitary-adrenal (HPA) axis function (however defined by authors);
- biophysical parameters (however defined by the authors).

For the child

- Mean weight;
- mean head circumference;
- mean length;
- mean skin fold thickness;
- abnormal lung function (however defined by authors);
- mean blood pressure;
- glucose intolerance (however defined by authors);
- HPA axis function (however defined by authors);
- dyslipidaemia (however defined by authors);
- any neurodisability;
- visual impairment (however defined by authors);
- hearing impairment (however defined by authors);
- developmental delay (defined as developmental quotient less than -2 standard deviations below population mean);
- intellectual impairment (defined as intelligence quotient less than -2 standard deviations below population mean);
- cerebral palsy (however defined by authors);
- behavioural/learning difficulties (however defined by authors).

For the child as an adult

- Mean weight;
- mean head circumference;
- mean length;
- mean skin fold thickness;
- abnormal lung function (however defined by authors);
- mean blood pressure;
- glucose intolerance (however defined by authors);
- HPA axis function (however defined by authors);
- dyslipidaemia (however defined by authors);
- mean age at puberty;
- bone density (however defined by authors);
- educational achievement (completion of high school, or however defined by authors);
- any neurodisability;
- visual impairment (however defined by authors);
- hearing impairment (however defined by authors);
- intellectual impairment (defined as intelligence quotient less than -2 standard deviations below population mean);
- behavioural/learning difficulties (however defined by authors);

For health services

- Mean length of antenatal hospitalisation for women (days);
- mean length of postnatal hospitalisation for women (days);
- mean length of neonatal hospitalisation (days).

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Groups Trials Register by contacting the Trials Search Co-ordinator (January 2008).

The Cochrane Pregnancy and Childbirth Groups 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 theCochrane 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.

We did not apply any language restrictions.

Data collection and analysis

Selection of studies

We assessed trials for potential inclusion without consideration of the results. We resolved any differences of opinion by discussion until we reached a consensus. There was no blinding of authorship.

Data extraction and management

Two review authors extracted data using a predesigned form. Any discrepancies were resolved through discussion. We contacted authors of the original reports where further details were required. Dr LA Magee, author of *'A randomised controlled comparison of betamethasone with dexamethasone: effects on the antenatal fetal heart rate'* (Magee 1997) was contacted and supplied the doses of corticosteroids used in the trial. Dr R Figueroa, an author of the *'Betacode trial. Antenatal betamethasone compared to dexamethasone: a randomised control trial [abstract]'* was contacted and supplied a draft of the full trial with data before it was published as Elimian 2007.

Assessment of methodological quality of included studies

The validity of each study was assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2006).

(1) Selection bias (randomisation and allocation concealment)

We have assigned codes, using the following criteria:
(A) adequate concealment of allocation: such as telephone randomisation, consecutively-numbered sealed opaque envelopes;
(B) unclear whether adequate concealment of allocation: such as list or table used, sealed envelopes, or study does not report any concealment approach;
(C) inadequate concealment of allocation: such as open list of random-number tables, use of case record numbers, dates of birth or days of the week.

(2) Attrition bias (loss of participants, e.g. withdrawals, dropouts, protocol deviations)

We have assessed completeness to follow up using the following criteria:
(A) less than 5% loss of participants;
(B) 5% to 9.9% loss of participants;
(C) 10% to 19.9% loss of participants;
(D) more than 20% loss of participants.

(3) Performance bias (blinding of participants, researchers and outcome assessment)

We have assessed blinding using the following criteria:
(1) blinding of participants (yes/no/unclear);
(2) blinding of caregiver (yes/no/unclear);
(3) blinding of outcome assessment (yes/no/unclear).

Measures of treatment effect

Statistical analyses were performed using the Review Manager software (RevMan 2008). We used fixed-effect meta-analysis for combining data in the absence of substantial heterogeneity.

Dichotomous data

For dichotomous data, we presented results as risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we used the mean difference with 95% confidence intervals.

Dealing with missing data

We extracted data from the trials on an intention-to-treat basis. Where this was done in the original report, we re-analysed where possible. When missing data significantly affected the results, we excluded these data in a sensitivity analysis. If missing data later became available, they were included in the analyses.

Assessment of heterogeneity

We have applied tests of heterogeneity between trials, using the I^2 statistic. On identifying high levels of heterogeneity among the trials (exceeding 50%), we have explored it by prespecified subgroup analysis. A random-effects meta-analysis was used as an overall summary as appropriate.

Sensitivity analyses

We planned sensitivity analyses to explore the effect of trial quality assessed by concealment of allocation, by excluding studies with clearly inadequate allocation of concealment (rated C). However only one quasi-randomised trial was included in this version of the review and since no other trials reported the same outcomes as this trial, a sensitivity analysis by adequacy of allocation could not be carried out.

Subgroup analyses

We performed separate comparisons for different types of corticosteroids; and different doses, timings or routes of administration. We planned the following subgroup analyses but were unable to perform them in this version of the review:

- singleton versus multiple pregnancy;
- gestational age at entry to trial (24 to 26 weeks, 27 to 29 weeks, 30 to 34 weeks, 35 to 37 weeks);
- pregnancy-induced hypertension syndromes.

RESULTS

Description of studies

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

Seventeen trials were identified for possible inclusion, and 10 trials met our pre-selected inclusion criteria in that they compared any two corticosteroids (dexamethasone or betamethasone or any other corticosteroid that can cross the placenta), or compared different dose regimens and timing or frequency and route of administration in women at risk of preterm birth.

Seven trials were excluded: three because L-carnitine added to a corticosteroid was compared against a corticosteroid to assess the effect of L-carnitine (Kurz 1993; Salzer 1982; Vytiska 1985); one trial was excluded as thyroxine added to a corticosteroid was compared against a corticosteroid to assess the effects of thyroxine (Romaguera 1997); one trial was excluded as vitamin K added to a corticosteroid was compared against a corticosteroid, vitamin K and no treatment to assess the effects of vitamin K (Liu 2006); one trial was excluded because it assessed levels of corticosteroid post administration of corticosteroid and did not assess fetal/neonatal/child or maternal outcomes (Egerman 1997); and one trial was not randomised (Whitt 1976).

Description of interventions used in the included trials

In the 10 trials included in this review, 1089 women and 1161 infants were recruited (919 women and 973 infants in the nine trials that compared dexamethasone with betamethasone). Four different corticosteroid regimens were used:

- five trials compared 24 mg dexamethasone (6 mg, four doses, 12 hourly) and 24 mg betamethasone (12 mg, two doses, 24 hourly) (Chen 2005; Elimian 2007; Rotmensch 1999; Subtil 2003; Urban 2005);
- two trials compared 24 mg dexamethasone (12 mg, two doses, 12 hourly) and 24 mg betamethasone (12 mg, two doses, 12 hourly) (Magee 1997; Mushkat 2001);
- one trial compared 16 mg dexamethasone (4 mg, four doses, 12 hourly) and 24 mg betamethasone (6 mg, four doses, 12 hourly) (Senat 1998);
- one trial compared 24 mg dexamethasone (12 mg, two doses, 12 hourly) and 24 mg betamethasone (12 mg, two doses, 24 hourly) (Mulder 1997).

One trial of 170 women and 188 infants compared 32 mg oral dexamethasone (8 mg, four doses, 12 hourly) and 24 mg intramuscular dexamethasone (6 mg, four doses, 12 hourly) (Egerman 1998).

The Subtil 2003 trial compared two forms of betamethasone (acetate and phosphate versus phosphate alone) as a third arm.

Four of the trials allowed repeat weekly doses of the allocated corticosteroid (Egerman 1998; Magee 1997; Mushkat 2001; Senat 1998).

The gestational age at trial entry varied widely between trials (from 24 to 35 weeks of gestation). All women were at increased risk of preterm birth or had a medical indication for birth at a preterm gestational age (*see*Characteristics of included studies).

The included studies came from a range of healthcare systems. Two of the trials were conducted in the USA (Egerman 1998; Elimian 2007), two in France (Senat 1998; Subtil 2003), two in Israel (Mushkat 2001; Rotmensch 1999) and one in each of Taiwan (Chen 2005), UK (Magee 1997), Netherlands (Mulder 1997) and Poland (Urban 2005). The trials were conducted over almost two decades from 1990 to 2005.

The primary outcomes varied between the trials. The primary outcomes of five of the trials focused on neonatal outcomes primarily respiratory distress syndrome (RDS), intraventricular haemorrhage (IVH) and death and child outcomes of neurodisability at 18 months (Chen 2005; Egerman 1998; Elimian 2007; Senat 1998; Subtil 2003) while the other five trials concentrated on biophysical parameters of the fetus (Magee 1997; Mulder 1997; Mushkat 2001; Rotmensch 1999; Urban 2005).

Risk of bias in included studies

Randomisation and allocation concealment

We rated three trials as having adequate allocation concealment; one trial used a pharmacy method (Elimian 2007) and two trials used consecutively numbered sealed opaque envelopes to conceal the randomisation (Magee 1997; Urban 2005). A further six trials did not identify their method of concealing the randomisation sequence or did not specify if an opaque envelope was used and were therefore, assessed as having unclear concealment of allocations (Chen 2005; Egerman 1998; Elimian 2007; Mulder 1997; Rotmensch 1999; Senat 1998; Subtil 2003). The remaining trial was quasi-randomised (Mushkat 2001).

Blinding

Two of the trials were able to blind clinicians and participants (Elimian 2007; Magee 1997) and two others were able to achieve some form of partial blinding (Rotmensch 1999; Subtil 2003). Mushkat 2001 stated that blinding was done but as the intervention could not be concealed, any blinding of clinicians may have been compromised.

Losses to follow up

One trial reported no losses to follow up (Elimian 2007). A further four trials did not report losses to follow up. In Magee 1997 and Subtil 2003 losses were greater than 50% at the end of follow up for some of the biophysical parameters, largely due to discharges from hospital.

Sample size calculations had been made prospectively in three studies (Egerman 1998; Elimian 2007; Subtil 2003).
In the Egerman 1998 trial recruitment was discontinued at 39% enrolment after a blinded review of available outcomes.

Effects of interventions

Ten trials involving 1089 women and 1161 babies were included. The results are presented by type of corticosteroid compared:

- dexamethasone versus betamethasone;
- oral versus intramuscular dexamethasone; and
- betamethasone acetate and phosphate versus betamethasone phosphate.

1. Dexamethasone versus betamethasone

Nine trials with 919 women and 973 infants.

Primary outcomes

Women

No primary outcomes for women were reported in any of the included trials.

Infants

Dexamethasone decreased the risk of IVH compared with the betamethasone group (risk ratio (RR) 0.44, 95% confidence interval (CI) 0.21 to 0.92; four trials, 549 infants). No difference between the two groups was seen for severe IVH (RR 0.40, 95% CI 0.13 to 1.24; four trials, 563 infants).
No statistically significant differences between those exposed to dexamethasone or betamethasone were seen for RDS (RR 1.06, 95% CI 0.88 to 1.27; five trials; 753 infants); periventricular leukomalacia (RR 0.83, 95% CI 0.23 to 3.03; four trials, 703 infants), bronchopulmonary dysplasia (RR 2.50, 95% CI 0.10 to 61.34; two trials, 464 infants), perinatal death (RR 1.28, 95% CI 0.46 to 3.52; four trials, 596 infants), low birthweight less than 2500 g (RR 0.89, 95% CI 0.65 to 1.24; one trial, 105 infants), mean birthweight (mean difference (MD) 0.01, kg 95% CI -0.11 to 0.12; five trials, 734 infants).

Children

Out of a small subgroup assessed at 18 months, one child in the dexamethasone group was recorded as having a neurosensory disability (RR 1.67, 95% CI 0.08 to 33.75; one trial, 12 infants - Subtil 2003). Death in childhood was not reported as an outcome in any of the included trials.

For the child as adult

No primary outcomes were reported in any of the included trials.

Secondary outcomes

Women

No secondary outcomes were reported in any of the included trials.

Infants

In one trial of 105 infants, significantly more infants were admitted to the neonatal intensive care unit (NICU) in the dexamethasone group compared with the betamethasone group (RR 3.83, 95% CI 1.24 to 11.87; Subtil 2003). Seven of the eight infants in the dexamethasone group were transferred to the NICU because of respiratory distress and the remaining infant was transferred due to suspected infection. The reason for all four infants in the betamethasone group being transferred to NICU was because of respiratory distress.
No statistically significant differences between those exposed to betamethasone or dexamethasone were seen for neonatal sepsis (RR 1.30, 95% CI 0.78 to 2.19; two trials, 516 infants), necrotising enterocolitis (RR 1.29, 95% CI 0.38 to 4.40; three trials, 598 infants), retinopathy of prematurity (RR 0.93, 95% CI 0.59 to 1.47; two trials, 516 infants), patent ductus arteriosus (RR 1.19, 95% CI 0.56 to 2.49; one trial, 359 infants), Apgar score at five minutes (MD -0.20, 95% CI -0.89 to 0.49; one trial, 67 infants), Apgar score less than seven at five minutes (RR 0.97, 95% CI 0.43 to 2.18; two trials, 207 infants), head circumference (MD -0.50 cm, 95% CI -1.55 to 0.55; one trial, 157 infants) or vasopressor use (RR 0.44, 95% CI 0.17 to 1.11; one trial, 359 infants).
Some differences in biophysical parameters were seen:

- the dexamethasone group had a significantly lower fetal heart rate than the betamethasone group at day two (MD -4.20 beats per minute, 95% CI -7.17 to -1.23; one trial, 46 infants - Rotmensch 1999), in Senat 1998 (*see* Other data table); but not in Magee 1997;
- at day two, the dexamethasone group had significantly higher breathing times than the betamethasone group (MD 32.0 more seconds per 30 minutes, 95% CI 4.37 to 59.63; one trial, 46 infants - Rotmensch 1999);
- the dexamethasone group had a significantly higher level of fetal movements detected via ultrasound than the betamethasone group (MD 7.0 movements per hour, 95% CI 2.15 to 11.85; one trial, 33 infants - Mushkat 2001).

No statistically significant differences between those exposed to betamethasone or dexamethasone were seen for other biophysical parameters including fetal movement via maternal perception (MD 3.0 movements per hour, 95% CI -3.20 to 9.20; one trial, 33 infants - Mushkat 2001), fetal movements in 30 minutes (MD 2.30, 95% CI -0.74 to 5.34; one trial, 46 infants - Rotmensch 1999), fetal breathing movements per hour (MD 0.0, 95% CI -2.05 to 2.05; one trial, 33 infants - Mushkat 2001) and accelerations per hour (MD 2.80, 95% CI -0.15 to 5.75; one trial, 46 infants - Rotmensch 1999).

Some additional data in the form of median and interquartile ranges is shown in Other data tables, with no differences seen between dexamethasone and betamethasone except for a lower heart fetal rate in Senat 1998 for dexamethasone.
A range of fetal heart rate indicators were measured in Subtil 2003 but only reported in graphical form; the trial authors reported that none of the indicators showed significant differences between dexamethasone and betamethasone.

Children

No secondary outcomes were reported in any of the included trials.

For the child as adult

No secondary outcomes were reported in any of the included trials.

Indirect comparisons

Using the methods outlined in the additional material accompanying Song 2003, we calculated indirect comparisons of trials of betamethasone versus placebo and no treatment; and dexamethasone versus placebo or no treatment that were included in the Roberts 2006 Cochrane review (*see*Table 1). The indirect calculations (fetal and neonatal death, IVH, severe IVH and RDS) were compatible with the findings of this review, except for RDS. In other words, the data from the dexamethasone and betamethasone subgroups in Roberts 2006 are compatible with a significant difference between dexamethasone and betamethasone for IVH and no significance difference for perinatal death. However, the indirect calculations for RDS from the Roberts review, where a possibly significant difference in favour of RDS was seen for betamethasone over dexamethasone, were inconsistent with the non-significant difference for RDS seen between dexamethasone and betamethasone from the direct calculations in this review.
Although chorioamnionitis was not reported in any trials directly comparing betamethasone and dexamethasone and included in this review, we estimated the indirect RR and 95% CI from Roberts 2006, which suggests that there is no significant difference between dexamethasone and betamethasone for this outcome.

Table 1. Comparison of direct and indirect estimates

Fetal/neonatal death	IVH (any)	severe IVH	Chorioamnionitis	RDS
Direct comparison from this review: dexamethasone v betametasone RR 1.28, 95% CI 0.46 to 3.52 (4 trials, 610 infants).	Direct comparison from this review: dexamethasone v betamethasone: RR 0.44, 95% CI 0.21 to 0.92 (4 trials, 463	Direct comparison from this review: dexamethasone v betamethasone: RR 0.40, 95% CI 0.13 to 1.24 (2 trials, 563	No direct comparison (outcome not reported in any trials included in this review).	Direct comparison from this review: dexamethasone v betamethasone: RR 1.06, 95% CI 0.88 to 1.28 (5 trials, 767

Table 1. Comparison of direct and indirect estimates

(*Continued*)

	infants).	infants).		infants).
Indirect comparison from Roberts Cochrane review: RR 0.96, 95% CI 0.71 to 1.30.	Indirect comparison from Roberts Cochrane review: RR 0.31, 95% CI 0.14 to 0.73.	Indirect comparison from Roberts Cochrane review: RR 0.47, 95% CI 0.09 to 2.33.	Indirect comparison from Roberts Cochrane review: RR 0.96, 95% CI 0.56 to 1.65.	Indirect comparison from Roberts Cochrane review: RR 1.43, 95% CI 1.14 to 1.78.
Nonsignificant discrepancy between direct and indirect results (mean difference -0.29, 95% CI -0.78 to 1.35).	Nonsignificant discrepancy between direct and indirect results (mean difference -1.98, 95% CI -5.92 to 1.96).	Nonsignificant discrepancy between direct and indirect results (mean difference -0.15, 95% CI -5.10 to 4.78).	NA.	Significant discrepancy between direct and indirect results (mean difference -0.30, 95% CI -0.01 to -0.59).

Notes:
[a] CI: confidence interval
IVH: intraventricular haemorrhage
RDS: respiratory distress syndrome
RR: risk ratio
v: versus

2. Dexamethasone (oral versus intramuscular injection)

One trial with 170 women and 188 infants (Egerman 1998).

Primary outcomes

Women

No primary outcomes were reported in any of the included trials.

Infants

No difference was seen between intramuscular and oral dexamethasone for IVH (RR 4.24, 95% CI 0.96 to 18.33) although this did reach statistical significance in favour of the intramuscular route when looking at only the < 34 weeks' gestation at birth subgroup (RR 4.92, 95% CI 1.12 to 21.55). All instances of IVH (10 in oral group and two in the intramuscular group) occurred in babies born before 34 weeks.
No statistically significant differences between oral or intramuscular dexamethasone were seen for RDS (RR 1.15, 95% CI 0.75 to 1.77), perinatal death (RR 1.48, 95% CI 0.45 to 4.90) or birthweight (MD -0.05 kg, 95% CI -0.27 to 0.17).

Children

No primary outcomes were reported in any of the included trials.

For the child as adult

No primary outcomes were reported in any of the included trials.

Secondary outcomes

Women

No secondary outcomes were reported in any of the included trials.

Infants

Treatment with oral dexamethasone was associated with an increase in neonatal sepsis compared with intramuscular dexamethasone (RR 8.48, 95% CI 1.11 to 64.93) with all neonatal sepsis cases occurring in the less than 34 weeks' gestation subgroup (RR 9.84, 95% CI 1.30 to 74.60).
There was no statistically significant difference between oral and im dexamethasone seen for necrotising enterocolitis (RR 5.09, 95% CI 0.63 to 41.45).

Children

No secondary outcomes were reported in any of the included trials.

For the child as adult

No secondary outcomes were reported in any of the included trials.

3. Betamethasone acetate+phosphate versus betamethasone phosphate

One trial with 69 infants (Subtil 2003).

Primary outcomes

Women

No primary outcomes were reported in any of the included trials.

Infants

No statistically significant differences between those exposed to betamethasone acetate and phosphate versus betamethasone phosphate was seen for RDS (RR 0.19, 95% CI 0.01 to 3.91), IVH (RR 0.32, 95% CI 0.01 to 7.69), perinatal death (RR 0.32, 95% CI 0.01 to 7.69), low birthweight (RR 1.21, 95% CI 0.86 to 1.72) or birthweight (MD -0.10 kg, 95% CI -0.44 to 0.24). No instances of periventricular leukomalacia and bronchopulmonary dysplasia were reported in this trial.

Children

None of the children were reported to have a neurodevelopmental disability at 18 months.

For the child as adult

No primary outcomes were reported in any of the included trials.

Secondary outcomes

No infants from the betamethasone acetate+phosphate group were transferred to NICU compared with four in the betamethasone phosphate group, all four due to respiratory distress (RR 0.11, 95% CI 0.01 to 1.93).

A range of fetal heart rate indicators were measured but only reported in graphical form. The trial authors reported that none of the indicators showed significant differences between the different betamethasone formulations.

DISCUSSION

That antenatal corticosteroids are effective in preventing neonatal morbidity is not in dispute (Roberts 2006) and this life-saving therapy is now widely used throughout the world (Abeywandana 2005; Brocklehurst 1999; Foix-L'Helias 2008; NIH 2000; Quinlivan 1998; Saengwaree 2005). However, it is not yet clear which corticosteroid and which regimen performs best. Determining the optimal corticosteroid and optimal regimens is very important since most pregnant women at risk of preterm birth will be considered candidates for antenatal corticosteroid treatment (NIH 2000) and these numbers will increase as rate of preterm birth is increasing in a number of countries (Abeywandana 2005; Goldenberg 2007). There is considerable variation reported between countries as to whether dexamethasone or betamethasone is preferred by health practitioners, with many likely reasons for these differences including availability and costs (dexamethasone is cheaper than betamethasone so is widely used in low-income countries) (Henderson-Smart 2007; Saengwaree 2005), impact of inconsistent findings from observational studies (Baud 1999; Lee 2006) and influence of opinion leaders (Jobe 2004).

Although we were able to include nine trials of moderate to good quality and one quasi-randomised trial in this review, our ability to reach conclusions was limited by the small number of comparisons of different antenatal steroid regimens. Most of the data available focused on the type of corticosteroid used, with nine of the studies comparing the two most commonly used corticosteroids, dexamethasone and betamethasone (with some variation in frequency and timing of administration).

The results of this review are broadly consistent with results of the Roberts 2006 Cochrane review of antenatal corticosteroids when they are recalculated as indirect comparisons of dexamethasone versus betamethasone (*see* Table 1). However, the suggestion of increased benefit of dexamethasone over betamethasone from this review for intraventricular haemorrhage is not sufficient evidence to support dexamethasone over betamethasone. A recent observational study, which reported reduced adverse neurological outcomes at 18 to 22 months for betamethasone but not for dexamethasone, highlights this uncertainty by stating that "to elucidate more fully predictive or causative neonatal or neurodevelopmental outcomes, a randomised clinical trial comparing dexamethasone and betamethasone should be performed" (Lee 2008). Such a trial would need to measure long-term effects, particularly for dexamethasone, as there have been no long-term follow-up studies for the antenatal use of this type of corticosteroid.

Although extensively reported in several of the included trials (Magee 1997; Mushkat 2001;Rotmensch 1999; Senat 1998; Subtil 2003), the clinical significance of differences in biophysical parameters such as fetal heart rate and respiratory rate is not clear (Rotmensch 1999). Overall these trials generally show few differences between dexamethasone and betamethasone. Some authors suggest that the influence of antenatal corticosteroids on parameters such as fetal heart rate is not clinically important, being a transient physiological response (Magee 1997; Rotmensch 1999; Subtil 2003).

Evidence about optimal doses, timing and frequency of administration of specific antenatal corticosteroids is even more sparse than that for type of corticosteroid. However, we feel it is important for emphasis for future research to be first directed towards establishing which corticosteroid (dexamethasone or betamethasone) is most effective in reducing neonatal morbidity, including assessment of long-term outcomes.

AUTHORS' CONCLUSIONS

Implications for practice

Dexamethasone may have some benefits compared with betamethasone such as less intraventricular haemorrhage and possibly some improved biophysical parameters, although a higher rate of neonatal intensive care unit admission was seen for dexamethasone in one trial. Apart from the superiority of an intramuscular compared with an oral route for dexamethasone in one trial, very few other conclusions about optimal antenatal corticosteroid regimens were able to be made.

Implications for research

Further trials directly comparing the type, dose, frequency and route of betamethasone with dexamethasone for women at risk of preterm birth are required. They should be of high quality, large enough to assess morbidity and mortality of the fetus/infant, long-term outcomes and maternal outcomes. It would be helpful to start by conducting high-quality trials to establish which of the commonly used corticosteroids is most effective and causes least harm, followed by trials of dosages and other variations in regimens.

ACKNOWLEDGEMENTS

Special thanks to Sonja Henderson, Denise Atherton and Lynn Hampson of the Cochrane Pregnancy and Childbirth Group for their support throughout this review. Thanks to Dr Reinaldo Figueroa and Dr Laura Magee, authors of included trials, for providing additional information.

As part of the pre-publication editorial process, this review has been commented on by three peers (an editor and three referees who are external to the editorial team) 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]*

Chen 2005

Methods	Randomisation and allocation concealment: unclear - "these women were randomly divided into 2 groups". Blinding: unclear - not reported. Losses to follow up: 28/168 (16%) women (1 intrauterine fetal death, 4 immediate expiration of baby after birth, 15 women gave birth after 37 weeks' gestation, 8 women did not give birth at the study hospital); not reported which groups (dexamethasone or betamethasone) the losses were from.

Participants	168 women "received antenatal corticosteroids" so we have assumed 168 is the number randomised. After exclusions (*see* above) 140 women giving birth to 157 infants (17 sets of twins) were included. Inclusion criteria: preterm prelabour rupture of membranes between 24-32 weeks and preterm labour 24-34 weeks. Taiwan.
Interventions	Dexamethasone - 24 mg: 4 x 6 mg doses IM 12 hours apart (76 infants). Betamethasone - 24 mg: 2 x 12 mg doses IM 24 hours apart (81 infants).
Outcomes	Infant: RDS; IVH (grade 3-4); PVL; birthweight; Apgar score < 7 at 5 mins; head circumference; neonatal sepsis; NEC; ROP. Mother: caesarean birth.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Egerman 1998

Methods	Randomisation and allocation concealment: unclear "patients were randomly assigned (by computer-generated numbers placed in sealed envelopes". Blinding: not reported. Losses to follow up: 5/170 (3%) women were unavailable for follow up.
Participants	170 women randomised; recruited at 24 to 33 weeks' gestation. Inclusion criteria: preterm birth between 24-33 weeks' gestation, preterm labour, preterm rupture of membranes, medical indication for delivery. Exclusion criteria: received corticosteroids during the pregnancy (except immediately before transfer), anticonvulsant therapy, rifampin, infection other than cystitis or cervicitis, advanced cervical dilatation, fetal pulmonary maturity. Tennessee, USA.
Interventions	Oral v IM dexamethasone 32 mg oral dexamethasone: 4 x 8 mg, 12 hourly (n = 92 women; 99 infants); 24 mg IM dexamethasone: 4 x 6 mg IM, 12 hourly (n = 78 women; 84 infants); repeated weekly until 34 weeks' gestation if birth had not yet occurred.
Outcomes	Infant:

Egerman 1998

(*Continued*)

	death; RDS; IVH; birthweight; sepsis; NEC; gestational age at birth. Mother: gestational age at entry (weeks); dilatation (cm); latency; caesarean birth; antibiotic use.
Notes	The study was discontinued at 39% enrolment (170 women) after a blinded review of available outcomes.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Elimian 2007

Methods	Randomisation: "double blind placebo- controlled randomised trial". Allocation concealment: "allocation to 1 of 2 groups by the pharmacy using computer-generated random numbers". Blinding: "syringes covered with opaque material" and participants and healthcare providers were reported as being blinded. Losses to follow up: no losses to follow up; only 105/178 infants in the dexamethasone group and 100/181 in the betamethasone group were assessed for IVH and PVL.
Participants	299 women randomised. Inclusion criteria: preterm birth. Exclusion criteria: clinical chorioamnionitis, major fetal structural abnormalities, major fetal chromosomal abnormalities, prior antenatal corticosteroid exposure, use of betamethasone or dexamethasone for other medical indications, quadruplets. New York, USA.
Interventions	Dexamethasone v betamethasone. 24 mg dexamethasone: 4 x 6 mg doses of dexamethasone IM 12 hours apart (149 women; 178 infants). 24 mg betamethasone: 2 x 12 mg doses of betamethasone IM 24 hours apart (placebo 2 doses given at 12 hour intervals) (150 women; 181 infants).
Outcomes	Infant: death;

Elimian 2007

(*Continued*)

	IVH (diagnosed by ultrasound, diagnosed by autopsy); RDS; PVL; birthweight; BPD; NEC; neonatal sepsis; surfactant use; ROP; neonatal blood pressure; need for inotropic support; mean duration of inotropic support (days); PDA; need for a vasopressor. Women: chorioamnionitis; fever after trial entry requiring the use of antibiotics; intrapartum fever requiring the use of antibiotics.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Magee 1997

Methods	Randomisation and allocation concealment: "random number table-generated assignments contained within consecutively numbered, sealed opaque envelopes". Blinding: participant, clinician, outcome assessor all blinded adequately. Losses to follow up: 1/30 postrandomisation exclusions in the betamethasone group (a woman with a twin pregnancy was enrolled in error); then 9/29 losses from the betamethasone group at day 2 (1 transfer, 3 early births, 5 early discharges); 7/29 losses from the dexamethasone group (1 self-discharge, 3 early births, 3 early discharges).
Participants	59 women with singleton pregnancies at risk of birth between 26 to 34 weeks' gestation inclusive, who had not received steroids in the preceding week. Oxford, UK.
Interventions	Dexamethasone v betamethasone. 24 mg dexamethasone: 2 x 12 mg IM; 12 hourly (n = 29). 24 mg betamethasone: 2 x 12 mg IM; 12 hourly (n = 29).
Outcomes	Infant: biophysical parameters (day 0, 1, 2); FHR;

Magee 1997

(*Continued*)

	LTV/STV; number of movements/hour; number of accelerations; number of decelerations; Apgar score at 5 mins; caesarean birth.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Mulder 1997

Methods	Randomisation and allocation concealment: "sealed envelope method". Blinding: not stated. Losses to follow up: 17%; 6/30 from the dexamethasone group and 4/30 from the betamethasone group.
Participants	60 women with premature contractions or at risk of preterm labour, between 26 to 33 weeks' gestation, small-for-gestational age (estimated fetal size < 5th centile), premature contractions, placenta praevia or other cause of vaginal blood loss, preterm rupture of membranes without evidence of intrauterine infection, pre-eclampsia, essential hypertension, poor obstetrical history, or leiomyoma. Exclusion criteria: cervical dilatation > 5 cm, signs of intrauterine infection, ritodrine hydrochloride treatment for < 4 days at the start of the study. Netherlands.
Interventions	Dexamethasone v betamethasone. 24 mg dexamethasone: 2 x 12 mg IM, 12 hourly (n = 24). 24 mg betamethasone: 2 x 12 mg IM, 24 hourly (n = 26).
Outcomes	Infant: birthweight; biophysical parameters - FHR, LTV/STV, breathing movement, breathing bout length, number of breaths, breath-to-breath interval, body movement incidence, body movement number of bursts, body movement burst length; Apgar score less than 7 at 5 mins; mode of birth.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Mushkat 2001

Methods	Allocation concealment: quasi-randomised - "each consecutive candidate got an even or an uneven number drawn out of preformed random computer-generated list. Even numbers were assigned to betamethasone treatment, while uneven numbers were assigned to dexamethasone treatment". Blinding: participant and clinician stated to be blinded, outcome assessor not stated - blinding may have been compromised because of the inadequate allocation concealment. Losses to follow up: not stated.
Participants	33 women with preterm labour between 26 to 33 weeks' gestation. Exclusion criteria: chronic or acute hypertension, gestational diabetes, vaginal bleeding due to placenta praevia or abruptio placenta, IUGR, fetal distress. Israel.
Interventions	Dexamethasone v betamethasone. 24 mg dexamethasone: 2 x 12 mg IM, 12 hourly (n = 16). 24 mg betamethasone: 12 mg betamethasone sodium and 12 mg betamethasone acetate IM, divided into two doses 12 hours apart (n = 17).
Outcomes	Infant: biophysical parameters (0, 6, 12, 18, 36 hours): maternal perception of fetal movements, body movement, breathing movements; gestational age.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Rotmensch 1999

Methods	Randomisation: randomised by "computer-generated randomisation tables". Allocation concealment: details not reported. Blinding: clinician blinded, participant and outcome assessor unclear. Losses to follow up: none reported.
Participants	46 women with preterm birth at 27 to 34 weeks' gestation, preterm premature rupture of membranes with no clinical evidence of infection, pregnancy-induced hypertension syndromes, IUGR, third trimester bleeding due to placenta praevia. Israel and Italy.
Interventions	Dexamethasone v betamethasone. 24 mg dexamethasone: 2 x 12 mg IM, 24 hourly (n = 24). 24 mg betamethasone: 2 x 12 mg IM, 24 hourly (n = 22).
Outcomes	Infant: birthweight; biophysical parameters (0, 2 ,4 days): FHR, acceleration > 10 bpm, deceleration > 10 bpm, LTV/STV,

Rotmensch 1999

(*Continued*)

	breathing time (sec in 30 mins), movement in 30 mins.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Senat 1998

Methods	Randomisation and allocation concealment: "randomly allocated by a table of random numbers held by an independent investigator". Blinding: participant and clinician not blinded; unclear if outcome assessor was blinded. Losses to follow up: none reported.
Participants	82 women with preterm labour < 34 weeks' gestation. Exclusion criteria: uncertain pregnancy history, clinical infection in women, vaginal bleeding, suspicion of premature rupture of membranes. France.
Interventions	Dexamethasone v betamethasone. 16 mg dexamethasone: 4 x 4 mg IM, 12 hourly (n = 40 women, 44 babies - 40 babies analysed). 24 mg betamethasone: 4 x 3 mg betamethasone sodium and 3 mg betamethasone acetate IM, 12 hourly (n = 42 women, 53 babies - 42 babies analysed).
Outcomes	Infant: death; RDS; IVH; PVL; birthweight; NEC; biophysical parameters (0, 24-48 hours, 4-7 days): FHR, LTV/STV, high/low variation, acceleration > 10 bpm; deceleration > 10 bpm; uterine contractions; gestational age; CTG.
Notes	In the case of multiple pregnancy, 1 fetus was randomly selected for analysis.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Subtil 2003

Methods	Randomisation and allocation concealment: "system of envelopes". Blinding: clinician blinded, participant and outcome assessor not blinded. Losses to follow up: none at day 0; 1/105 (1%) at day 1; 16 (15%) at day 2, 44 (42%) at day 3; and 57 (54%) at day 4 (because of discharge and birth).
Participants	105 women at high risk of preterm birth, recruited at 27 to 35 weeks' gestation, with singleton pregnancies. Exclusion criteria: imminent birth, multiple pregnancy, previously participated in the protocol, received corticosteroid therapy < 10 days prior. France.
Interventions	Dexamthasone v betamethasone (acetate + phosphate v phosphate). 24 mg dexamethasone phosphate: 4 x 6 mg IM, 12 hourly (n = 36). 24 mg betamethasone acetate and phosphate: 2 x 12 mg IM, 24 hourly (n = 35). 24 mg betamethasone phosphate: 4 x 6 mg IM, 12 hourly (n = 34).
Outcomes	Infant: death; RDS; bronchopulmonary dysplasia; IVH (grade 1 and 2); severe IVH (grade 3 and 4); hyperechoic > 10 days; PVL; birthweight. For the child (18mths): neurodevelopmental disability at follow up; biophysical parameters: duration of tracing; STV/LTV; FHR; acceleration/deceleration number per hr; movement number per hr; neonatal intensive care; patient age; parity; reason for hospitalisation; other treatments; gestation at inclusion; corticosteroid course in same pregnancy; FHR recording period; protocol withdrawal during study; gestational age at delivery; tests of the specific drug effect, time effect, and interaction by analysis of variance.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Urban 2005

Methods	Randomisation: computer-generated randomisation table. Allocation concealment: "consecutively numbered sealed opaque envelopes". Blinding: unclear. No losses to follow up reported.
Participants	67 women at risk for preterm labour, with singleton pregnancies, recruited at < 34 weeks. Inclusion criteria: preterm labour, preterm contractions of the uterus, preterm premature rupture of membranes, cervical length less than 20 mm, placenta praevia before 34 weeks, singleton pregnancy. Exclusion criteria: fetal major structural malformations or abnormal karyotype. Poland.
Interventions	Dexamethasone v betamethasone. 24 mg dexamethasone: 4 x 6 mg IM, 12 hourly (n = 34). 24 mg betamethasone: 2 x 12 mg IM, 24 hourly (n = 33).
Outcomes	Infant: birthweight; UA PI; MCA PI; abnormal FHR patterns (at 0, 24 and 72 hours); Apgar score at 1 and 5 minutes; umbilical cord artery pH; base deficit.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

[a] BPD: biparietal diameter
bpm: beats per minute
CTG: cardiotocography
FHR: fetal heart rate
hr: hour
IM: intramuscular
IUGR: intrauterine growth restriction
IVH: intraventricular haemorrhage
LTV: long-term variation
MCA PI: middle cerebral artery pulsatility index
mins: minutes
mths: months
NEC: necrotising enterocolitis
PDA: patent ductus arteriosus
PVL: periventricular leukomalacia
RDS: respiratory distress syndrome
ROP: retinopathy of prematurity
secs: seconds
STV: short-term variation

UA PI: umbilical artery pulsatility index
v: versus

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

Study	Reason for exclusion
Egerman 1997	Assessed bioavailability of dexamethasone post oral or IM administration; no fetal, neonatal, child, child as adult or maternal outcomes were assessed.
Kurz 1993	L-carnitine was added to betamethasone and compared against betamethasone alone to assess the effect it had on RDS.
Liu 2006	Vitamin K was added to dexamethasone and compared against dexamethasone injection alone, vitamin K injection alone or no treatment to determine which treatment was most effective at reducing the incidence of IVH.
Romaguera 1997	Intra-amniotic thyroxine and im betamethasone versus betamethasone alone to assess the effect it had on maturity.
Salzer 1982	Carnitine and dexamethasone versus dexamethasone to assess the effect it had on lung maturity.
Vytiska 1985	Carnitine and betamethasone versus betamethasone to assess the effect it had on RDS prophylaxis.
Whitt 1976	Trial not randomised.

[a] IM: intramuscular
IVH: intraventricular haemorrhage
RDS: respiratory distress syndrome

DATA AND ANALYSES

Comparison 1. Dexamethasone versus betamethasone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Respiratory distress syndrome	5	753	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.88, 1.27]
1.1 Dexamethasone (24 mg - 4 x 6 mg; 12 hourly) v betamethasone (24 mg - 2 x 12 mg; 24 hourly)	3	621	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.89, 1.30]
1.2 Dexamethasone (16 mg - 4 x 4 mg; 12 hourly) v betamethasone (24 mg - 4 x 6 mg; 12 hourly)	1	82	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 8.34]
1.3 Dexamethasone (24 mg - 2 x 12 mg; 12 hourly) v betamethasone (24 mg - 2 x 12 mg; 24 hourly)	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.02, 8.43]
2 Intraventricular haemorrhage			Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Dexamethasone (24 mg - 4 x 6 mg; 12 hourly) v betamethasone (24 mg - 2 x 12 mg; 24 hourly)	3	467	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.21, 0.92]
2.2 Dexamethasone (16 mg - 4 x 4 mg; 12 hourly) v betamethasone (24 mg - 4 x 6 mg; 12 hourly)	1	82	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.3 Intraventricular haemorrhage (any dose)	4	549	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.21, 0.92]
2.4 Severe intraventricular haemorrhage (any dose)	4	549	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.13, 1.24]
3 Periventricular leukomalacia	4	703	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.23, 3.03]
3.1 Dexamethasone (24 mg - 4 x 6 mg; 12 hourly) v betamethasone (24 mg - 2 x 12 mg; 24 hourly)	3	621	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.23, 3.03]
3.2 Dexamethasone (16 mg - 4 x 4 mg; 12 hourly) v betamethasone (24 mg - 4 x 6 mg; 12 hourly)	1	82	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4 Perinatal death	4	596	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.46, 3.52]
4.1 Dexamethasone (24 mg - 4 x 6 mg; 12 hourly) v betamethasone (24 mg - 2 x 12 mg; 24 hourly)	2	464	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.38, 3.33]

4.2 Dexamethasone (16 mg - 4 x 4 mg; 12 hourly) v betamethasone (24 mg - 4 x 6 mg; 12 hourly)	1	82	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.3 Dexamethasone (24 mg - 2 x 12 mg; 12 hourly) v betamethasone (24 mg - 2 x 12 mg; 24 hourly)	1	50	Risk Ratio (M-H, Fixed, 95% CI)	3.25 [0.14, 75.91]
5 Bronchopulmonary dysplasia	2	464	Risk Ratio (M-H, Random, 95% CI)	2.50 [0.10, 61.34]
5.1 Dexamethasone (24 mg - 4 x 6 mg, 12 hourly) v betamethasone (24 mg - 2 x 12 mg, 24 hourly)	2	464	Risk Ratio (M-H, Random, 95% CI)	2.50 [0.10, 61.34]
6 Neurosensory disability as a child	1	12	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.08, 33.75]
6.1 Dexamethasone (24 mg - 4 x 6 mg; 12 hourly) v betamethasone (24 mg - 2 x 12 mg; 24 hourly)	1	12	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.08, 33.75]
7 Neonatal sepsis	2	516	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.78, 2.19]
7.1 Dexamethasone (24 mg - 4 x 6 mg; 12 hourly) v betamethasone (24 mg - 2 x 12 mg; 24 hourly)	2	516	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.78, 2.19]
8 Necrotising enterocolitis	3	598	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.38, 4.40]
8.1 Dexamethasone (24 mg - 4 x 6 mg; 12 hourly) v betamethasone (24 mg - 2 x 12 mg; 24 hourly)	2	516	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.38, 4.40]
8.2 Dexamethasone (16 mg - 4 x 4 mg; 12 hourly) v betamethasone (24 mg - 4 x 6 mg; 12 hourly)	1	82	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9 Retinopathy of prematurity	2	516	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.59, 1.47]
9.1 Dexamethasone (24 mg - 4 x 6 mg; 12 hourly) v betamethasone (24 mg - 2 x 12 mg; 24 hourly)	2	516	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.59, 1.47]
10 Apgar score at 5 minutes	1	67	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.89, 0.49]
10.1 Dexamethasone (24 mg - 4 x 6 mg; 12 hourly) v betamethasone (24 mg - 2 x 12 mg; 24 hourly)	1	67	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.89, 0.49]
11 Apgar score < 7 at 5 minutes	2	207	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.43, 2.18]
11.1 Dexamethasone (24 mg - 4 x 6 mg; 12 hourly) v betamethasone (24 mg - 2 x 12 mg; 24 hourly)	1	157	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.45, 2.54]
11.2 Dexamethasone (24 mg - 2 x 12 mg; 12 hourly) v betamethasone (24 mg - 2 x 12 mg; 24 hourly)	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.05, 5.60]

12 Apgar score at 5 minutes			Other data	No numeric data
13 Fetal heart rate, bpm (day 2)	1	46	Mean Difference (IV, Fixed, 95% CI)	-4.20 [-7.17, -1.23]
13.1 Dexamethasone (24 mg - 4 x 6 mg; 12 hourly) v betamethasone (24 mg - 2 x 12 mg; 24 hourly)	1	46	Mean Difference (IV, Fixed, 95% CI)	-4.20 [-7.17, -1.23]
14 Fetal heart rate (day 2)			Other data	No numeric data
15 Accelerations per hour	1	46	Mean Difference (IV, Fixed, 95% CI)	2.80 [-0.15, 5.75]
15.1 Dexamethasone (24 mg - 4 x 6 mg; 12 hourly) v betamethasone (24 mg - 2 x 12 mg, 24 hourly)	1	46	Mean Difference (IV, Fixed, 95% CI)	2.80 [-0.15, 5.75]
16 Accelerations per hour			Other data	No numeric data
17 Fetal movements in 30 minutes	1	46	Mean Difference (IV, Fixed, 95% CI)	2.04 [-0.74, 5.34]
17.1 Dexamethasone (24 mg - 4 x 6 mg; 12 hourly) v betamethasone (24 mg - 2 x 12 mg; 24 hourly)	1	46	Mean Difference (IV, Fixed, 95% CI)	2.04 [-0.74, 5.34]
18 Fetal movements per hour (maternal perception)	1	33	Mean Difference (IV, Fixed, 95% CI)	3.01 [-3.20, 9.20]
18.1 Dexamethasone (24 mg - 2 x 12 mg; 12 hourly) v betamethasone (24 mg - 2 x 12 mg; 12 hourly)	1	33	Mean Difference (IV, Fixed, 95% CI)	3.01 [-3.20, 9.20]
19 Fetal movements per hour (ultrasound)	1	33	Mean Difference (IV, Fixed, 95% CI)	7.00 [2.15, 11.85]
19.1 Dexamethasone (24 mg - 2 x 12 mg; 12 hourly) v betamethasone (24 mg - 2 x 12 mg; 12 hourly)	1	33	Mean Difference (IV, Fixed, 95% CI)	7.00 [2.15, 11.85]
20 Fetal movements per hour			Other data	No numeric data
21 Fetal breathing movements per hour	1	33	Mean Difference (IV, Fixed, 95% CI)	Not estimable
21.1 Dexamethasone (24 mg - 2 x 12 mg; 12 hourly) v betamethasone (24 mg - 2 x 12 mg; 12 hourly)	1	33	Mean Difference (IV, Fixed, 95% CI)	Not estimable
22 Breathing time at 2 days (seconds in 30 minutes)	1	46	Mean Difference (IV, Fixed, 95% CI)	32.01 [4.37, 59.63]
22.1 Dexamethasone (24 mg - 4 x 6 mg; 12 hourly) v betamethasone (24 mg - 2 x 12 mg; 24 hourly)	1	46	Mean Difference (IV, Fixed, 95% CI)	32.01 [4.37, 59.63]
23 Low birthweight	1	105	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.65, 1.24]
23.1 Dexamethasone (24 mg - 4 x 6 mg; 12 hourly) v betamethasone (24 mg - 2 x 12 mg; 24 hourly)	1	105	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.65, 1.24]
24 Birthweight (kg)	5	734	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.11, 0.12]

24.1 Dexamethasone (24 mg - 4 x 6 mg; 12 hourly) v betamethasone (24 mg - 2 x 12 mg; 24 hourly)	5	734	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.11, 0.12]
25 Birthweight (kg)			Other data	No numeric data
26 Head circumference (cm)	1	157	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-1.55, 0.55]
26.1 Dexamethasone (24 mg - 4 x 6 mg; 12 hourly) v betamethasone (24 mg - 2 x 12 mg; 24 hourly)	1	157	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-1.55, 0.55]
27 Vasopressor use	1	359	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.17, 1.11]
27.1 Dexamethasone (24 mg - 4 x 6 mg; 12 hourly) v betamethasone (24 mg - 2 x 12 mg; 24 hourly)	1	359	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.17, 1.11]
28 Patent ductus arteriosus	1	359	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.56, 2.49]
28.1 Dexamethasone (24 mg - 4 x 6 mg; 12 hourly) v betamethasone (24 mg - 2 x 12 mg; 24 hourly)	1	359	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.56, 2.49]
29 Neonatal intensive care unit admission	1	105	Risk Ratio (M-H, Fixed, 95% CI)	3.83 [1.24, 11.87]
29.1 Dexamethasone (24 mg - 4 x 6 mg; 12 hourly) v betamethasone (24 mg - 2 x 12 mg; 24 hourly)	1	105	Risk Ratio (M-H, Fixed, 95% CI)	3.83 [1.24, 11.87]

Comparison 2. Dexamethasone: oral versus intramuscular

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Respiratory distress syndrome			Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Dexamethasone: oral (32 mg - 4 x 8 mg, 12 hourly) v IM (24 mg - 4 x 6 mg, 12 hourly)	1	183	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.75, 1.77]
1.2 < 34 weeks' gestation at birth	1	125	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.85, 1.86]
2 Intraventricular haemorrhage			Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Dexamethasone: oral (32 mg - 4 x 8 mg, 12 hourly) v IM (24 mg - 4 x 6 mg, 12 hourly)	1	183	Risk Ratio (M-H, Fixed, 95% CI)	4.24 [0.96, 18.83]
2.2 < 34 weeks' gestation at birth	1	125	Risk Ratio (M-H, Fixed, 95% CI)	4.92 [1.12, 21.55]
3 Perinatal death			Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Dexamethasone: oral (32 mg - 4 x 8 mg, 12 hourly) v IM (24 mg - 4 x 6 mg, 12 hourly)	1	183	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [0.45, 4.90]
3.2 < 34 weeks' gestation	1	125	Risk Ratio (M-H, Fixed, 95% CI)	1.72 [0.53, 5.59]

4 Neonatal sepsis			Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Dexamethasone: oral (32 mg - 4 x 8 mg, 12 hourly) v IM (24 mg - 4 x 6 mg, 12 hourly)	1	183	Risk Ratio (M-H, Fixed, 95% CI)	8.48 [1.11, 64.93]
4.2 < 34 weeks' gestation at birth	1	125	Risk Ratio (M-H, Fixed, 95% CI)	9.84 [1.30, 74.60]
5 Necrotising enterocolitis			Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Dexamethasone: oral (32 mg - 4 x 8 mg, 12 hourly) v IM (24 mg - 4 x 6 mg, 12 hourly)	1	183	Risk Ratio (M-H, Fixed, 95% CI)	5.09 [0.63, 41.45]
5.2 < 34 weeks' gestation at birth	1	125	Risk Ratio (M-H, Fixed, 95% CI)	4.92 [0.59, 40.92]
6 Birthweight			Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Dexamethasone: oral (32 mg - 4 x 8 mg, 12 hourly) v IM (24 mg - 4 x 6 mg, 12 hourly)	1	183	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.27, 0.17]

Comparison 3. Betamethasone acetate + phosphate versus betamethasone phosphate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Respiratory distress syndrome	1	69	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.01, 3.91]
1.1 24 mg beta a+p (2 x 12 mg, 24 hourly) v 24 mg beta p (4 x 6 mg, 12 hourly)	1	69	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.01, 3.91]
2 Intraventricular haemorrhage	1	69	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.69]
2.1 24 mg beta a+p (2 x 12 mg, 24 hourly) v 24 mg beta p (4 x 6 mg, 12 hourly)	1	69	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.69]
3 Periventricular leukomalacia	1	69	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.1 24 mg beta a+p (2 x 12 mg, 24 hourly) v 24 mg beta p (4 x 6 mg, 12 hourly)	1	69	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4 Perinatal death	1	69	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.69]
4.1 24 mg beta a+p (2 x 12 mg, 24 hourly) v 24 mg beta p (4 x 6 mg, 12 hourly)	1	69	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.69]
5 Bronchopulmonary dysplasia	1	69	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.1 24 mg beta a+p (2 x 12 mg, 24 hourly) v 24 mg beta p (4 x 6 mg, 12 hourly)	1	69	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Neurodevelopmental disability	1	69	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.1 24 mg beta a+p (2 x 12 mg, 24 hourly) v 24 mg beta p (4 x 6 mg, 12 hourly)	1	69	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Low birthweight	1	69	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.86, 1.72]

7.1 24 mg beta a+p (2 x 12 mg, 24 hourly) v 24 mg beta p (4 x 6 mg, 12 hourly)	1	69	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.86, 1.72]
8 Birthweight	1	69	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.44, 0.24]
8.1 beta a+p (2 x 12 mg, 24hrly) and beta p (4 x 6 mg,12hrly)	1	69	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.44, 0.24]
9 Neonatal intensive care unit admission	1	69	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 1.93]
9.1 24 mg beta a+p (2 x 12 mg, 24 hourly) x 24 mg beta p (4 x 6 mg, 12 hourly)	1	69	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 1.93]

WHAT'S NEW

Last assessed as up-to-date: 30 January 2008

Date	Event	Description
9 May 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 4, 2007

Review first published: Issue 4, 2008

CONTRIBUTIONS OF AUTHORS

Fiona Brownfoot researched and wrote the initial draft of the review, and extracted data together with Philippa Middleton. Caroline Crowther and Philippa Middleton edited the subsequent drafts.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Discipline of Obstetrics and Gynaecology, The University of Adelaide, Australia.

External sources

- Department of Health and Ageing, Australia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added the outcome of any neurodisability for the child, and for the child as an adult.

We deleted the following subgroup analyses as they may be affected by the intervention:

- gestational age at birth (24 to 26 weeks, 27 to 29 weeks, 30 to 34 weeks, 35 to 37 weeks);
- preterm prelabour rupture of membranes (at trial entry, more than 24 hours before birth, more than 48 hours before birth).