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Tocolytics for preterm premature rupture of membranes (Review)

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[Intervention Review]

Tocolytics for preterm premature rupture of membranes

A Dhanya Mackeen[1], Jolene Seibel-Seamon[2], Jacqueline Muhammad[3], Jason K Baxter[1], Vincenzo Berghella[1]

[1]Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Jefferson Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania, USA. [2]Division of Maternal Fetal Medicine, Virtua West Jersey Hospital, Voorhees, New Jersey, USA. [3]Division of Maternal Fetal Medicine, Aurora Health Center, Milwaukee, Wisconsin, USA

Contact: A Dhanya Mackeen, Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Jefferson Medical College of Thomas Jefferson University, 834 Chestnut Street, Suite 400, Philadelphia, Pennsylvania, PA 19107, USA. dhanya80@hotmail.com.

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ABSTRACT

Background

In women with preterm labor, tocolysis has not been shown to improve perinatal mortality; however, it is often given for 48 hours to allow for the corticosteroid effect for fetal maturation. In women with preterm premature rupture of membranes (PPROM), the use of tocolysis is still controversial. In theory, tocolysis may prolong pregnancy in women with PPROM, thereby allowing for the corticosteroid benefit and reducing the morbidity and mortality associated with prematurity.

Objectives

To assess the potential benefits and harms of tocolysis in women with preterm premature rupture of membranes.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (15 January 2014).

Selection criteria

We included pregnant women with singleton pregnancies and PPROM (23 weeks to 36 weeks and six days). We included any tocolytic therapy compared to no tocolytic, placebo, or another tocolytic.

Data collection and analysis

All review authors assessed the studies for inclusion. We extracted and quality assessed data.

Main results

We included eight studies with a total of 408 women. Seven of the studies compared tocolysis to no tocolysis. One study compared nifedipine to terbutaline. Compared to no tocolysis, tocolysis was not associated with a significant effect on perinatal mortality in women with PPROM (risk ratio (RR) 1.67; 95% confidence interval (CI) 0.85 to 3.29). Tocolysis was associated with longer latency (mean difference (MD) 73.12 hours; 95% CI 20.21 to 126.03; three trials of 198 women) and fewer births within 48 hours (average RR 0.55; 95% CI 0.32 to 0.95; six trials of 354 women; random-effects, $Tau^2 = 0.18$, $I^2 = 43\%$) compared to no tocolysis. However, tocolysis was associated with increased five-minute Apgar of less than seven (RR 6.05; 95% CI 1.65 to 22.23; two trials of 160 women) and increased need for ventilation of the neonate (RR 2.46; 95% CI 1.14 to 5.34; one trial of 81 women). In the subgroup analysis comparing betamimetic to no betamimetics, tocolysis was associated with increased latency and borderline significance for chorioamnionitis. Prophylactic tocolysis with PPROM was associated with increased overall latency, without additional benefits for maternal/neonatal outcomes. For women with PPROM before 34 weeks, there was a significantly increased risk of chorioamnionitis in women who received tocolysis. However, neonatal outcomes were not

significantly different. There were no significant differences in maternal/neonatal outcomes in subgroup analyses comparing cox inhibitor versus no tocolysis, calcium channel blocker versus betamimetic, antibiotic, corticosteroid or combined antibiotic/corticosteroid.

Authors' conclusions

Our review suggests there is insufficient evidence to support tocolytic therapy for women with PPROM, as there was an increase in maternal chorioamnionitis without significant benefits to the infant. However, studies did not consistently administer latency antibiotics and corticosteroids, both of which are now considered standard of care.

PLAIN LANGUAGE SUMMARY

Tocolytics for preterm premature rupture of membranes

Preterm premature rupture of membranes (PPROM) accounts for one-third of preterm births. Infants who are born before 37 weeks may suffer from problems related to prematurity, including death. Medications that aim to stop labor are often given in an attempt to prevent preterm birth. It is unclear whether these medications should be used in women with PPROM. This review of eight studies (involving 408 women) found that these medications do not effect perinatal death, but do increase latency and may increase maternal (e.g., chorioamnionitis) and neonatal morbidity (e.g., five-minute Apgar of less than seven and increased need for ventilation of the neonate).

BACKGROUND

Description of the condition

Preterm premature rupture of membranes (PPROM) is defined as rupture of the chorioamniotic membranes before the onset of labor prior to 37 weeks of gestation. PPROM is further classified by gestational age: midtrimester (less than 24 weeks), early (24 to 34 weeks), and near-term (34 to 37 weeks). Approximately 1% to 5% of pregnancies are complicated by PPROM (Parry 1998). The etiology of PPROM is not well understood, but is likely to be multifactorial. Associated conditions include smoking, lower socioeconomic status, sexually transmitted infections, vaginal bleeding and uterine distention. Possible mechanisms that could explain these associations include choriodecidual infection/inflammation, decreased membrane collagen content, collagen degradation, membrane stretch or programmed amniotic cell death (Parry 1998).

PPROM contributes to perinatal morbidity and mortality, secondary to premature birth, and maternal morbidity. Overall, PPROM accounts for about one-third of all preterm births (Kaltreider 1980). The related neonatal morbidities associated with prematurity include respiratory distress syndrome (RDS, a complication of lung function resulting in difficulty breathing), intraventricular hemorrhage (IVH, bleeding within the spaces in the brain), necrotizing enterocolitis (NEC, an infectious complication of the intestines that sometimes requires surgery), and infection. Other complications include placental abruption (separation of the afterbirth before birth occurs), cord prolapse (delivery of part of the umbilical cord before the baby is born), and abnormal fetal heart patterns (with periods of decline in the fetal heart rate secondary to compression of the umbilical cord because of less amniotic fluid to cushion the cord). PPROM is strongly associated with maternal infectious morbidity: there is an increase in chorioamnionitis (infection of the fetal membranes), endometritis (infection of the uterine lining), and bacteremia (presence of bacteria in blood).

Description of the intervention

In order to reduce the effects of prematurity, early PPROM (24 to 33 weeks) is best served with conservative management in the absence of labor, infection, or fetal distress (ACOG 2007).

In conservative management of PPROM, the use of adjunctive antibiotic treatment has been recommended. The goal of adjunctive antibiotics is to prevent or treat ascending infection and prolong pregnancy. The choice and regimen of antibiotics have varied (Kenyon 2003). Erythromycin with (Mercer 1995) or without (Kenyon 2001) ampicillin/amoxicillin has been associated with significant maternal and neonatal benefits. An increased risk of NEC has been associated with clavulanic acid. The Cochrane review assessing the effect of antibiotic therapy in women with PPROM showed a 29% reduction in preterm birth within 48 hours and a 20% reduction in preterm birth within seven days when antibiotics were given (Kenyon 2003). Neonatal benefits included a 32% reduction in infection, 17% reduction in surfactant treatment, 12% reduction in oxygen therapy and 18% reduction in abnormal cerebral ultrasound scan (Kenyon 2003). Maternal benefits included a 43% reduction in chorioamnionitis (Kenyon 2003). Antibiotics are not recommended in women with preterm labor without PPROM (King 2000).

In addition to antibiotics, corticosteroid therapy should be administered to women with early PPROM (Crowther 2007; Harding 2001; Roberts 2006). Corticosteroids in the setting of PPROM showed reduction in neonatal death (RR 0.69, 95% CI 0.58 to 0.81), RDS (RR 0.66, 95% CI 0.59 to 0.73) and IVH (RR 0.54, 95% CI 0.43 to 0.69), NEC (RR 0.46, 95% CI 0.29 to 0.74) without any significant increase in maternal or neonatal infection (Roberts 2006). Group B streptococcus (GBS) screening may be considered in women with PPROM (Ohlsson 2009).

With or without the presence of labor, it is unclear whether tocolysis of women with PPROM would be efficacious in reducing the consequences of prematurity.

How the intervention might work

In theory, tocolytic therapy may prolong pregnancy in women with PPROM, thereby reducing the consequences of prematurity. However, the use of tocolytics in women with PPROM is still controversial. Many physicians use tocolytic therapy as a prophylactic measure and others initiate tocolysis only with the onset of contractions. There is also a variety of options for tocolysis: betamimetics, calcium channel blockers, cyclo-oxygenase (COX) inhibitors, oxytocin receptor antagonists and magnesium sulfate. Other Cochrane reviews (Anotayanonth 2004; Crowther 2002; King 2003; King 2005; Papatsonis 2005) have addressed the efficacy of tocolytic therapy in preventing preterm birth without premature rupture of membranes, but there is insufficient evidence to suggest a beneficial role in women with PPROM. The potential benefit from increased latency due to tocolysis must be weighed against the potential harm in increased maternal and perinatal infection, the latter of which can possibly lead to long-term sequelae for the child, including cerebral palsy (Shatrov 2010).

Why it is important to do this review

Though tocolysis may prolong pregnancy in women with PPROM, it is unclear whether this would reduce the morbidity and mortality associated with prematurity without increasing the potential for infection, including chorioamnionitis.

OBJECTIVES

To assess the potential benefits and harms of tocolysis in women with preterm premature rupture of membranes.

METHODS

Criteria for considering studies for this review

Types of studies

We included all published randomized controlled trials (RCTs) evaluating tocolytics in women with singleton gestations and preterm premature rupture of membranes (PPROM) between 23 and 36 weeks and six days. We had planned to include unpublished RCTs and quasi-RCTs, but there were none.

Types of participants

Pregnant women with singleton pregnancies and a gestational age between 23 and 36 weeks and six days who are diagnosed with PPROM.

Types of interventions

We included any tocolytic therapy compared to no tocolytic, another tocolytic or placebo. We classified tocolysis in regards to prophylaxis or treatment. Example of tocolytics include betamimetics, calcium channel blockers, cyclo-oxygenase (COX) inhibitors, oxytocin receptor antagonists and magnesium sulfate. We have also reported the use of interventions like antibiotics and corticosteroids.

Types of outcome measures

Primary outcomes

Perinatal mortality (intrauterine fetal demise and neonatal death).

[Intrauterine fetal demise (fetal demise after 20 weeks' gestation and prior to delivery); neonatal death (death within the first 28 days of life)]

Secondary outcomes

Neonatal morbidity

- Intrauterine fetal demise (fetal demise after 20 weeks' gestation and prior to delivery).
- Neonatal death (death within the first 28 days of life).
- Gestational age at delivery (weeks' gestation).
- Birthweight (grams).
- Very low birthweight (less than 1500 grams).
- Low birthweight (less than 2500 grams).
- Apgar score less than seven at five minutes.
- Neonatal sepsis (positive blood, urine or spinal fluid culture).
- Necrotizing enterocolitis (NEC - as defined in individual trials).
- Intraventricular hemorrhage (IVH - as defined in individual trials).
- Respiratory distress syndrome (RDS - as defined in individual trials).
- Requiring ventilation (number of infants that required ventilation and number of days of ventilation required).
- Length of stay in the neonatal intensive care unit (days).

Latency duration (time from PPROM until birth)

- Latency (hours between PPROM and delivery).
- Birth within 48 hours.
- Birth within seven days.

Maternal morbidity

- Chorioamnionitis (as defined in individual trials).
- Endometritis (as defined in individual trials).
- Need for antibiotics (for treatment of presumed or confirmed infection).
- Length of hospital stay (days).

Search methods for identification of studies

We contacted the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register (15 January 2014).

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. weekly searches of EMBASE;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and EMBASE, 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.

For details of the additional searches we conducted for the previous version of this review (Mackeen 2011), see Appendix 1.

We did not apply any language restrictions.

Data collection and analysis

Selection of studies

All review authors independently assessed all the potential studies that were identified as a result of the search strategy. We resolved any disagreement through discussion.

Data extraction and management

We designed a form to extract data. At least three review authors extracted the data using the agreed form. We resolved discrepancies through discussion. We used the Review Manager software (RevMan 2011) to enter applicable data.

When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement by discussion or by involving a third assessor.

(1) Random 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:

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

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

We describe for each included study the method used to conceal allocation to interventions prior to assignment and assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- low risk of bias (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (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. We consider studies to be at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We describe for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

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 and the numbers included in the analysis at each stage (compared with the total randomized participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or was supplied by the trial authors, we re-include missing data in the analyses which we undertook.

We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomization);
- unclear risk of bias.

(5) Selective reporting (checking for 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:

- low risk of bias (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);
- high risk of bias (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 risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

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:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(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 *Handbook* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered that it is likely to impact on the findings. We explored the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Measures of treatment effect

Dichotomous data

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

Continuous data

For continuous data, we use the mean difference if outcomes are measured in the same way between trials. We use the standardized mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomized trials

We did not identify any cluster-randomized trials for inclusion. If we identify cluster-randomized trials in subsequent updates of this review, we will include them in the analyses along with individually randomized trials. We will adjust their sample sizes using the methods described in the *Handbook* using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if

possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomized trials and individually-randomized trials, we plan to synthesize the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomization unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomization unit and perform a subgroup analysis to investigate the effects of the randomization unit.

Dealing with missing data

For included studies, we noted levels of attrition. We explored the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we included all participants randomized to each group in the analyses, and analyzed all participants in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial was the number randomized minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the Tau^2, I^2 and Chi^2 statistics. We regard heterogeneity as substantial if I^2 is greater than 30% and either Tau^2 is greater than zero, or there is a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

In future updates of this review, if there are 10 or more studies in the meta-analysis we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If we detect asymmetry by visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2011). We used fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. When we identified clinical heterogeneity, we used random-effects meta-analysis to produce an overall summary of an average treatment effect across trials that would be considered clinically meaningful: primary analysis of tocolysis versus no tocolysis for the outcomes of birth within 48 hours and birth within seven days, for the betamimetic subgroup analysis for the outcomes of birth within 48 hours and birth within seven days, for the prophylactic tocolysis subgroup analysis for birth within seven days and for the less than 34-week subgroup analysis for hours of latency and birth within seven days. The random-effects summary is treated as the average range of possible treatment effects and we discussed the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful we will not combine trials. If we use random-effects analyses in subsequent versions of this review, we will present the results as the average treatment effect with its 95% confidence interval, and the estimates of Tau^2 and I^2.

Subgroup analysis and investigation of heterogeneity

We did not identify substantial heterogeneity. If we identify substantial heterogeneity, in future analyses, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.

We carried out the following subgroup analyses.

1. A comparison of each tocolytic type (agent) as compared to no tocolytic or other tocolytic.
2. Women who received tocolysis for prophylaxis compared to tocolysis for treatment.
3. Women who received antibiotics with tocolysis compared to women who received antibiotics without tocolysis.
4. Women who received corticosteroids with tocolysis compared to women who received corticosteroids without tocolysis.
5. Women who received corticosteroids and antibiotics with tocolysis compared to women who received corticosteroids and antibiotics without tocolysis.
6. Women who received tocolysis for PPROM before 34 weeks.

We have used the following outcomes in subgroup analyses: all.

We assessed subgroup differences by interaction tests available within RevMan (RevMan 2011).

Sensitivity analysis

We explored the effect of trial quality and reported studies of lower quality (i.e. high risk of bias for allocation concealment).

RESULTS

Description of studies

We identified a total of 41 studies (71 reports) as potentially eligible for inclusion. The Trials Search Co-ordinator updated the search of the Cochrane Pregnancy and Childbirth Group's Trials Register in January 2014 and identified another two reports, both of which are reports of ongoing trials (El-Sayed 2010; Mol 2012).

Results of the search

We included eight studies (10 reports) in the analysis and excluded 33 studies (61 reports). Two trials identified from the updated search in 2014 are ongoing (El-Sayed 2010; Mol 2012).

Included studies

We included eight studies with a total of 408 women (Dunlop 1986; Garite 1987; Laohapojanart 2007; Levy 1985; Matsuda 1993; Weiner 1988; Christensen 1980; Ehansipoor 2010). Seven of the eight studies compared tocolysis to no tocolysis (Dunlop 1986; Garite 1987; Levy 1985; Matsuda 1993; Weiner 1988; Christensen 1980; Ehansipoor 2010). Four of the seven included studies utilized only ritodrine for tocolysis (Christensen 1980; Dunlop 1986; Garite 1987; Levy 1985); one used both ritodrine and magnesium (Matsuda

1993); one used either ritodrine, terbutaline or magnesium (Weiner 1988); and one used indomethacin as tocolytic (Ehansipoor 2010). One study compared nifedipine to terbutaline (Laohapojanart 2007).

Participants (gestational age of rupture)

All of the studies included women with preterm premature rupture of membranes (PPROM) between the gestational ages of 23 to 36 weeks and six days (Christensen 1980; Dunlop 1986; Ehansipoor 2010; Garite 1987; Laohapojanart 2007; Levy 1985; Matsuda 1993; Weiner 1988).

The Laohapojanart 2007 trial included women between 24 and 36 weeks' gestation with preterm labor irrespective of the membrane status. After contacting the principle investigator, we were able to obtain the data regarding the women with rupture of membranes and the gestational age of rupture was between 30 to 33 weeks.

Five of the studies included only women with PPROM less than 34 weeks and these were included in the subanalysis of PPROM less than 34 weeks (Dunlop 1986; Ehansipoor 2010; Garite 1987; Levy 1985; Weiner 1988)

Tocolytic regimen: tocolytic versus no tocolytic

Seven of the eight studies compared tocolysis to no tocolysis. Four studies used a betamimetic (ritodrine) as the primary tocolytic agent (Christensen 1980; Dunlop 1986; Garite 1987; Levy 1985); one used indomethacin as the primary tocolytic (Ehansipoor 2010); one used ritodrine with the addition of magnesium sulfate as necessary (Matsuda 1993) and one used any tocolytic agent (Weiner 1988).

Tocolytic regimen: tocolytic versus another tocolytic

In the Laohapojanart 2007 trial, women were randomized to receive either nifedipine or terbutaline for tocolysis. The dose of immediate-release nifedipine was 10 mg (max dose 40 mg) within the first hour followed by 10 mg every four to six hours for 72 hours. The initial infusion of terbutaline was 10 µg/min followed by 5 µg/min every 10 minutes until 25 µg/min was reached. Women were then switched to subcutaneous injections of terbutaline 25 mg every four hours for 24 hours.

Prophylactic tocolysis

There were three studies that treated women prophylactically with tocolysis; that is, the women enrolled in the study were not in labor (Dunlop 1986; Ehansipoor 2010; Levy 1985).

Antibiotics

There were two studies that used antibiotics (Dunlop 1986; Ehansipoor 2010). Dunlop 1986 compared four groups: Group A: no ritodrine, no cephalexin; Group B: ritodrine, cephalexin; Group C: ritodrine, no cephalexin; Group D: no ritodrine, cephalexin. For antibiotic subgroup analysis, Group B was compared to Group D. While these two studies did administer prophylactic antibiotics (Dunlop 1986; Ehansipoor 2010), only one administered those currently used for latency (Ehansipoor 2010); that is with the addition of a macrolide antibiotic. However, that study (Ehansipoor 2010) used clavulanate, which is not typically the drug of choice secondary to the increased association with necrotizing enterocolitis (NEC) (Mercer 1995; Kenyon 2001). Ehansipoor 2010 did not show any statistically significant differences in NEC, but the sample size was too small to draw any conclusions regarding the association of clavulanate and NEC. As noted, the antibiotic used in the second study was cephalexin (Dunlop 1986). Studies that administered antibiotics for GBS or other urogenital colonization, cesarean prophylaxis or those that did not administer antibiotics were excluded from this subanalysis as well as from the combined antibiotic/steroid subgroup analyses.

Corticosteroid administration for fetal lung maturity

Two studies administered corticosteroids (Dunlop 1986; Ehansipoor 2010) to all study participants. Dunlop 1986 administered dexamethasone 12 mg IM every 12 hours for four doses and Ehansipoor administered 12 mg of IM betamethasone every 24 hours for two doses. Though Laohapojanart 2007 administered corticosteroids, this study was not included in the corticosteroid or combined antibiotic/corticosteroid subanalysis because the study did not compare a tocolytic to no tocolytic.

Antibiotics and corticosteroid administration for fetal lung maturity

Two studies used some combination of antibiotics and corticosteroids (Dunlop 1986; Ehansipoor 2010). Dunlop 1986 compared four groups: Group A: no ritodrine, no cephalexin; Group B: ritodrine, cephalexin; Group C: ritodrine, no cephalexin; Group D: no ritodrine, cephalexin. For antibiotic/steroid subgroup analyses, Group B was compared to Group D (Dunlop 1986). All women received both antibiotics and corticosteroids in Ehansipoor's study (Ehansipoor 2010)

Excluded studies

We excluded a total of 33 trials. We excluded 12 publications because they included women with preterm labor with intact membranes and did not categorize outcome variables on membrane status (Bisits 2004; El-Sayed 1999; Essed 1978; Ferguson 1989; Gill 2006; Houtzager 2006; Katz 1983; Leake 1983; Papatsonis 1997; Sims 1978; Spearing 1979; Spellacy 1979). We excluded seven trials as they included multiple gestations (Caritis 1984; Cotton 1984; Ferguson 1984; How 1998; Husslein 2007; Koks 1998; Renzo 2003). We excluded four publications because they did not categorize outcomes by membrane status and included women with multiple gestations (Caritis 1982; Lyell 2007; Mittendorf 1997; Moutquin 1992). We excluded two trials because they compared two different regimens of the same tocolytic (Decavalas 1995; Holleboom 1996). Two studies excluded women with rupture of membranes (Ingemarsson 1976; Kashanian 2005) and one study excluded women with rupture of membranes before the onset of labor (Tchilinguirian 1984). We excluded one study because they compared two treatments for preterm labor, ritodrine and placebo against ritodrine and indomethacin (Gamissans 1982). One study did not randomize women by tocolytic therapy (Parsons 1988) and one trial was withdrawn from publication (Freeman 2008). We excluded one study because they studied progesterone administration rather than tocolysis (Briery 2009). One trial compared three groups: corticosteroids with tocolysis, no corticosteroids with tocolysis, and no corticosteroids or tocolysis (Nelson 1985). They were excluded because groups were managed differently with respect to delivery with the first two groups intentionally delivered 24 to 48 hours after PPROM and the latter group managed expectantly.

We attempted to contact the corresponding or lead author for each of the studies that were excluded when outcomes were

not reported based on membrane status. We were able to get applicable results from one author Laohapojanart 2007.

Risk of bias in included studies

See Figure 1 and Figure 2 for a summary of risk of bias assessments.

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

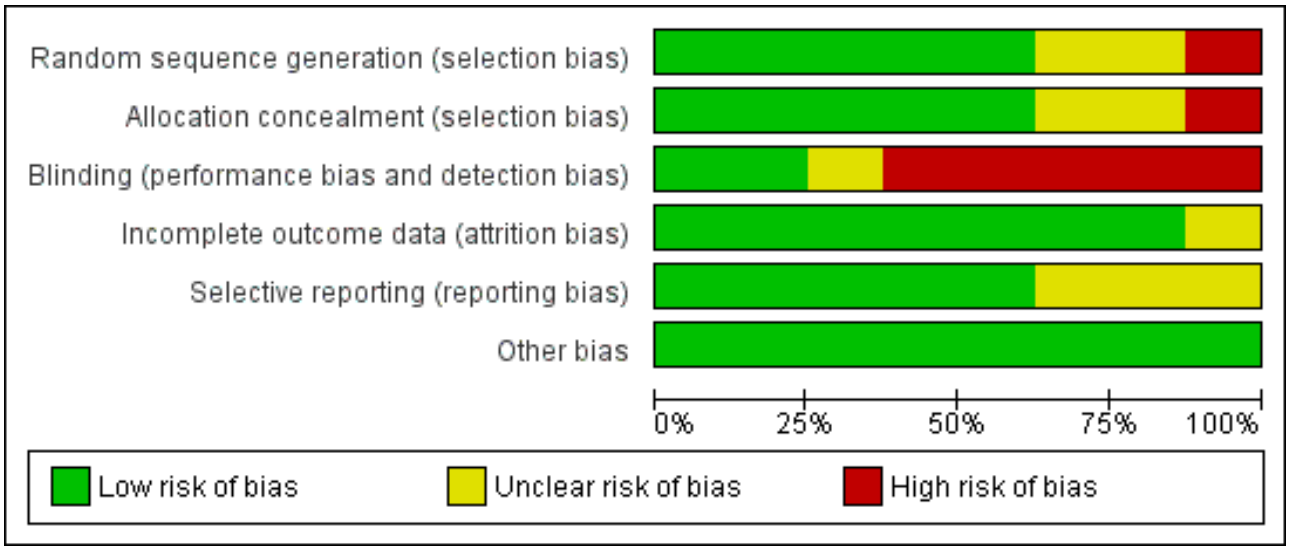
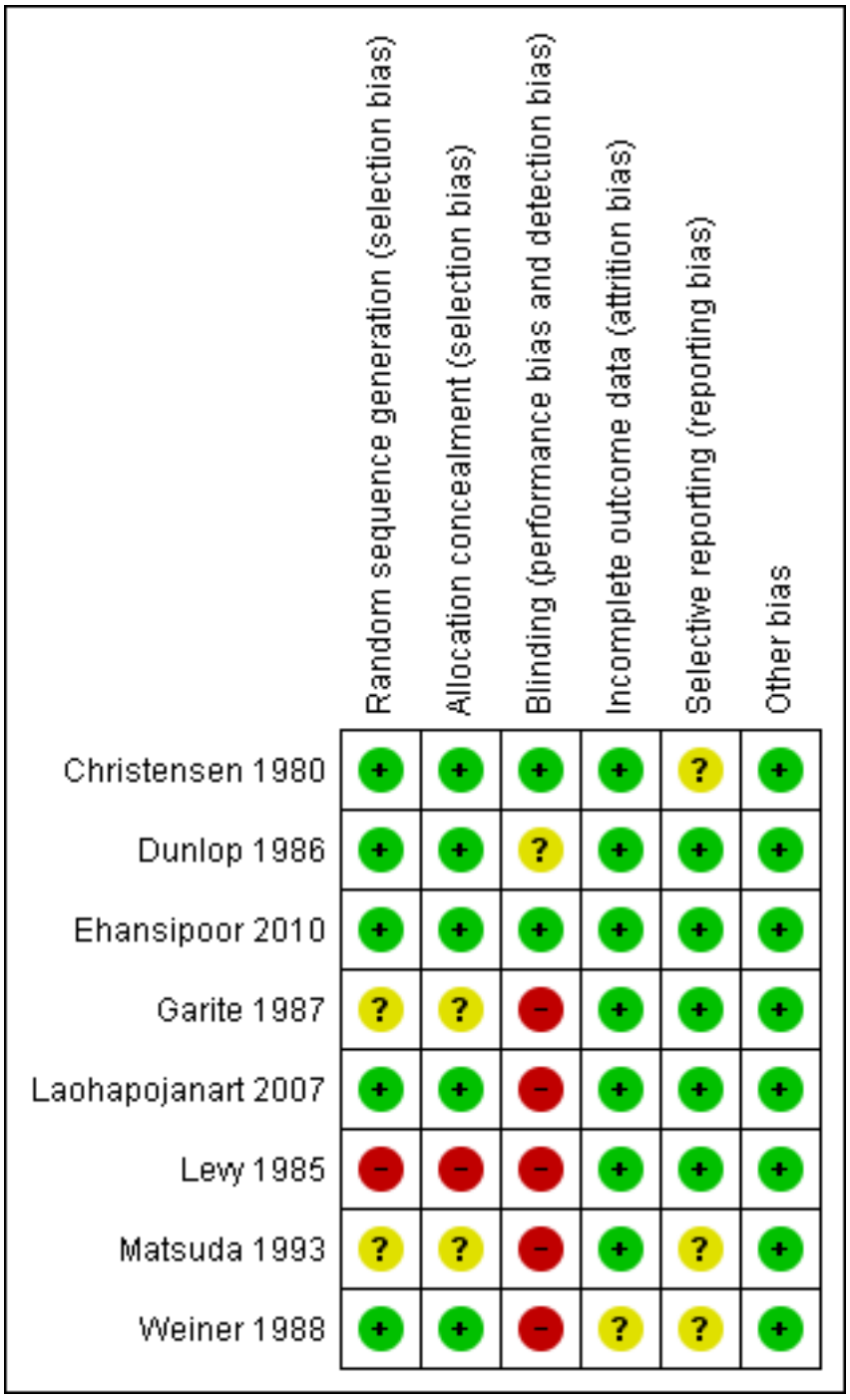


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

We considered five out of eight studies to be at low risk of bias for sequence generation and allocation concealment (Christensen 1980; Dunlop 1986; Ehansipoor 2010; Laohapojanart 2007; Weiner 1988).

In two studies, the treatment allocation was unclear (Garite 1987; Matsuda 1993) and did not specify the randomization scheme in the text of the paper. In one study the treatment allocation was inadequate (Levy 1985) as social security numbers were used to determine randomization - we rated this trial as 'high risk of bias' for allocation concealment.

Blinding

There was double blinding in two of the studies (Christensen 1980; Ehansipoor 2010). The blinding in the Dunlop 1986 trial was unclear because it did not specify whether there was masking of the participants or researchers. There was no blinding in the remaining five trials (Garite 1987; Laohapojanart 2007; Levy 1985; Matsuda 1993; Weiner 1988).

Incomplete outcome data

In seven of the eight trials, all of the women that were randomized were analyzed (Christensen 1980; Dunlop 1986; Ehansipoor 2010; Garite 1987; Laohapojanart 2007; Levy 1985; Matsuda 1993). In one trial, 34 women that were randomized were excluded from the analysis, so the attrition bias is unclear (Weiner 1988).

Selective reporting

There was no selective reporting bias in the eight trials. Six trials had pre-specified outcomes and all expected outcomes were reported. (Dunlop 1986; Ehansipoor 2010; Garite 1987; Laohapojanart 2007; Levy 1985; Matsuda 1993). Primary outcomes were not explicitly stated in two studies (Christensen 1980; Weiner 1988).

Primary outcomes were type of labor, mode of delivery, and neonatal and maternal outcomes (Dunlop 1986); delivery within 48 hours of study drug (Ehansipoor 2010); interval from PPROM until birth (Garite 1987); change in diastolic blood pressure after treatment (Laohapojanart 2007); birthweight, latency, and infection (Levy 1985); efficacy in prolongation of pregnancy; and neonatal outcomes (Matsuda 1993).

Other potential sources of bias

We identified no other potential sources of bias.

Effects of interventions

The following outcomes were not assessed in any of the included trials: very low birthweight (less than 1500 grams), low birthweight (less than 2500 grams), length of stay in the neonatal intensive care unit, need for maternal antibiotics.

Tocolytic versus no tocolytic

Seven trials compared tocolysis to no tocolysis. Four of the seven included studies utilized only ritodrine for tocolysis (Christensen 1980; Dunlop 1986; Garite 1987; Levy 1985); one used both ritodrine and magnesium (Matsuda 1993); one used either ritodrine, terbutaline, or magnesium (Weiner 1988); and one used indomethacin as tocolytic (Ehansipoor 2010).

Primary outcomes

When comparing the tocolytic group to the no tocolytic group, there was no significant difference in perinatal mortality (risk ratio (RR) 1.67; 95% confidence interval (CI) 0.85 to 3.29; seven trials of 402 women; Analysis 1.1).

Secondary outcomes

Tocolytic therapy was associated with an increase in latency (mean difference (MD) 73.12 hrs; 95% CI 20.21 to 126.03; three trials of 198 women, Analysis 1.12), and reduced risk of birth within 48 hours (average RR 0.55; 95% CI 0.32 to 0.95; six trials of 354 women; random-effects, $Tau^2 = 0.18$, $I^2 = 43\%$ Analysis 1.13). However, this was at the expense of an increase in Apgar less than seven at five minutes (RR 6.05; 95% CI 1.65 to 22.23; two trials of 160 women, Analysis 1.6) and need for neonatal ventilation (RR 2.46; 95% CI 1.14 to 5.34; one trial of 81 women, Analysis 1.11).

Treatment with tocolysis versus no tocolysis was not significantly associated with a lower incidence of birth within seven days (average RR 0.81; 95% CI 0.62 to 1.05; four trials of 249 women; random-effects, $Tau^2 = 0.03$, $I^2 = 48\%$; Analysis 1.14) or increased intrauterine fetal demise (RR 1.03; 95% CI 0.07 to 15.83; three trials of 174 women, Analysis 1.2); neonatal death (RR 1.73; 95% CI 0.85 to 3.50; seven trials of 402 women, Analysis 1.3); gestational age at delivery (MD -0.07; 95% CI -0.85 to 0.71; three trials of 198 women, Analysis 1.4); birthweight (mean difference 158.68 g; 95% CI -44.00 to 361.36; two trials of 117 women, Analysis 1.5); neonatal sepsis (average RR 0.73; 95% CI 0.40 to 1.33; five trials of 324 women; random-effects, $Tau^2 = 0.00$, $I^2 = 0\%$; Analysis 1.7); NEC (RR 0.68; 95% CI 0.31 to 1.47; three trials of 170 women, Analysis 1.8); intraventricular hemorrhage (RR 1.15; 95% CI 0.45 to 2.92; three trials of 174 women, Analysis 1.9); RDS (RR 0.90; 95% CI 0.70 to 1.17; five trials of 279 women, Analysis 1.10); maternal endometritis (RR 1.71; 95% CI 0.69 to 4.25; one trial of 79 women, Analysis 1.16); and maternal hospital stay (MD 3.40 days; 95% CI -0.74 to 7.54; one trial of 81 women, Analysis 1.17).

Borderline significance was noted for chorioamnionitis (RR 1.62; 95% CI 1.00 to 2.61; five trials of 279 women, Analysis 1.15).

Cyclo-oxygenase inhibitor versus no Cyclo-oxygenase inhibitor subgroup analysis

One study of 47 women compared tocolysis with a cox inhibitor (specifically indomethacin) to no tocolysis (Ehansipoor 2010).

Primary outcomes

There was no difference in perinatal mortality in pregnancies of women treated with indomethacin versus those not treated with indomethacin (RR 0.88; 95% CI 0.06 to 13.25; Analysis 2.1).

Secondary outcomes

There were no statistically significant differences identified between the treatment groups for any of the secondary outcomes considered. For women treated with indomethacin as compared to those not treated with indomethacin, there was no difference with respect to neonatal death (RR 0.88; 95% CI 0.06 to 13.25; Analysis 2.3), neonatal sepsis (RR 0.53; 95% CI 0.23 to 1.22; Analysis 2.4), NEC (RR 0.88; 95% CI 0.14 to 5.73; Analysis 2.5), RDS (RR 0.74; 95% CI 0.42 to 1.31; Analysis 2.7), latency within 48 hours (RR 0.88; 95% CI 0.14 to 5.73; Analysis 2.8), latency within seven days (RR 1.06; 95% CI 0.57 to1.95; Analysis 2.9), and chorioamnionitis (RR 1.32; 95% CI 0.56 to 3.12; Analysis 2.10).

There was insufficient evidence to evaluate intrauterine fetal demise Analysis 2.2 and IVH Analysis 2.6.

Betamimetic versus no betamimetic subgroup analysis

Four studies compared betamimetic tocolysis (specifically ritodrine) to no tocolysis (Christensen 1980; Dunlop 1986; Garite 1987; Levy 1985). Matsuda 1993 also used ritodrine for tocolysis; however, added magnesium sulfate when ritodrine did not suffice to quell contractions; therefore, Matsuda 1993 was not included in this subgroup analysis.

Primary outcomes

There was no significant difference in perinatal mortality between those who received betamimetics versus those who did not (RR 2.46; 95% CI 0.90 to 6.74; four trials of 199 women; Analysis 3.1)

Secondary outcomes

While the use of betamimetics was associated with an increased latency (MD 147.90 hours; 95% CI 20.17 to 275.63; one trial of 42 women, Analysis 3.11), this was at the expense of a borderline increase in chorioamnionitis (RR 2.06 ; 95% CI 1.01 to 4.23; three trials of 151 women; Analysis 3.14).

Betamimetic therapy was not significantly associated with intrauterine fetal demise (RR 1.03; 95% CI 0.07 to 15.83; two trials of 127 women; Analysis 3.14), neonatal death (RR 2.82; 95% CI 0.93 to 8.59; four trials of 199 women; Analysis 3.3), gestational age at delivery (mean difference (MD) -0.20; 95% CI -1.62 to 1.22; one trial of 42 women, Analysis 3.4), birthweight (MD 212.00; 95% CI -130.72 to 554.72; one trial of 42 women, Analysis 3.5), Apgar less than seven at five minutes (RR 3.59; 95% CI 0.79 to 16.22; one trial of 79 women; Analysis 3.6), neonatal sepsis (average RR 0.51; 95% CI 0.05 to 5.43; two trials of 121 women; random-effects; Analysis 3.7), NEC (RR 0.20; 95% CI 0.01 to 3.96; one trial of 48 women; Analysis 3.8), IVH (RR 1.15; 95% CI 0.45 to 2.92; two trials of 127 women; Analysis 3.9), RDS (RR 0.99; 95% CI 0.69 to 1.43; three trials of 157 women; Analysis 3.10), latency within 48 hours (average RR 0.70; 95% CI 0.35 to 1.40; three trials of 151 women; random-effects, $Tau^2 = 0.16$, $I^2 = 44\%$; Analysis 3.12), latency within seven days (average RR 0.81; 95% CI 0.49 to 1.35; random-effects, $Tau^2 = 0.10$, $I^2 = 72\%$; two trials of 121 women; Analysis 3.13), and maternal endometritis (RR 1.71; 95% CI 0.69 to 4.25; one trial of 79 women; Analysis 3.15).

Tocolytic versus another tocolytic (nifedipine versus terbutaline)

Only one study (Laohapojanart 2007) with a total of six participants compared two different tocolytic therapies (nifedipine versus terbutaline) in women with PPROM.

Primary outcomes

There were insufficient data to assess our primary outcome.

Secondary outcomes

There were no statistically significant differences identified between the treatment groups for any of the secondary outcomes considered. There was no significant difference in RDS (RR 2.00; 95% CI 0.33 to 11.97, Analysis 4.1) or prolongation of pregnancy greater than 48 hours (RR 1.40; 95% CI 0.60 to 3.26; Analysis 4.2). There were insufficient data to assess the remainder of our secondary outcomes.

Though no differences were found, the numbers were very small and power was very low, hence even large differences cannot be excluded.

Tocolytic prophylaxis subgroup analysis

There were three studies that treated women prophylactically with tocolysis: that is, the women that were enrolled in the study were not in labor (Dunlop 1986; Ehansipoor 2010; Levy 1985).

Primary outcomes

There was no difference in perinatal mortality for women treated with tocolysis prophylactically compared with women that had no tocolysis treatment (RR 1.53; 95% CI 0.42 to 5.59; three trials of 137 women; Analysis 5.1).

Secondary outcomes

Hours latency was significantly higher in the group that received tocolysis prophylactically as compared to those who did not (MD 147.90 hours; 95% CI 20.17 to 275.63; one study of 42 women; Analysis 5.10).

There were no significant differences between prophylactic tocolysis versus no tocolysis for neonatal death (RR 1.53; 95% CI 0.42 to 5.59; three trials of 137 women; Analysis 5.3), gestational age (MD -0.20; 95% CI -1.62 to 1.22; one trial of 42 women, Analysis 5.4), birthweight (MD 212.00 g; 95% CI -130.72 to 554.72; one trial of 42 women; Analysis 5.5), neonatal sepsis (RR 0.53; 95% CI 0.23 to 1.22; two trials of 89 women; Analysis 5.6), NEC (RR 0.51; 95% CI 0.11 to 2.33; two trials of 95 women; Analysis 5.7), intraventricular hemorrhage (RR 1.00; 95% CI 0.33 to 3.01; two trials of 95 women; Analysis 5.8), RDS (RR 0.88; 95% CI 0.55 to 1.41; two studies of 95 women; Analysis 5.9), latency within 48 hours (RR 0.35; 95% CI 0.12 to 1.02; two studies of 89 women; Analysis 5.11), latency within seven days (average RR 0.77; 95% CI 0.45 to 1.32; two studies of 89 women; random effects, $Tau^2 = 0.08$, $I^2 = 52\%$; Analysis 5.12) and chorioamnionitis (RR 1.55; 95% CI 0.70 to 3.44; two studies of 89 women; Analysis 5.13).

Differences in rates of Intrauterine fetal demise Analysis 5.2 was not estimable in this comparison.

Antibiotic subgroup analysis

There were two studies that used antibiotics (Dunlop 1986; Ehansipoor 2010). Dunlop compared four groups: Group A: no ritodrine, no cephalexin; Group B: ritodrine, cephalexin; Group C: ritodrine, no cephalexin; Group D: no ritodrine, cephalexin. For antibiotic subgroup analysis, Group B was compared to Group D (Dunlop 1986). Ehansipoor administered IV ampicillin/sulbactam for 48 hours, then amoxicillin/clavulanate for five days (Ehansipoor 2010).

Primary outcomes

There was no difference in perinatal mortality in the group that received antibiotics versus those that did not (RR 1.91; 95% CI 0.39 to 9.44; two trials of 71 women; Analysis 6.1)

Secondary outcomes

There were no statistically significant differences identified between the treatment groups for any of the secondary outcomes considered. There were no significant differences in neonatal death (RR 1.91; 95% CI 0.39 to 9.44; two trials of 71 women; Analysis 6.3), neonatal sepsis (RR 0.53; 95% CI 0.23 to 1.22; one trial of 47 women; Analysis 6.4), NEC (RR 0.65; 95% CI 0.14 to 3.15; two trials of 71 women; Analysis 6.5), IVH (RR 2.00; 95% CI 0.21 to 19.23; two trials of 71 women; Analysis 6.6), RDS (RR 0.80; 95% CI 0.48 to 1.33; two trials of 71 women; Analysis 6.7), latency within 48 hours (RR 0.88; 95% CI 0.14 to 5.73; one trial of 47 women; Analysis 6.8), latency within seven days (RR 1.06; 95% CI 0.57 to 1.95; one trial of 47 women; Analysis 6.9), and chorioamnionitis (RR 1.32; 95% CI 0.56 to 3.12; one trial of 47 women; Analysis 6.10).

There was insufficient evidence to estimate the effect of antibiotics on intrauterine fetal demise Analysis 6.2.

Corticosteroid subgroup analysis

Two studies administered corticosteroids (Dunlop 1986; Ehansipoor 2010). Dunlop compared four groups: Group A: no ritodrine, no cephalexin; Group B: ritodrine, cephalexin; Group C: ritodrine, no cephalexin; Group D: no ritodrine, cephalexin. For this analysis, Groups B and C were combined and compared to the combination of Groups A and D (Dunlop 1986). Dunlop administered dexamethasone and Ehansipoor administered betamethasone (Dunlop 1986; Ehansipoor 2010).

Primary outcomes

There was no significant difference in perinatal mortality (RR 2.39; 95% CI 0.50 to 11.55; two studies of 95 women; Analysis 7.1).

Secondary outcomes

There were no statistically significant differences identified between the treatment groups for any of the secondary outcomes considered. Corticosteroid therapy in addition to tocolysis was not significantly associated with neonatal death (RR 2.39; 95% CI 0.50 to 11.55; two studies of 95 women; Analysis 7.3), neonatal sepsis (RR 0.53; 95% CI 0.23 to 1.22; one study of 47 women; Analysis 7.4), NEC (RR 0.51; 95% CI 0.11 to 2.33; two studies of 95 women; Analysis 7.5), intraventricular hemorrhage (RR 1.00; 95% CI 0.33 to 3.01; two studies of 95 women; Analysis 7.6), RDS (RR 0.88; 95% CI 0.55 to 1.41; two studies of 95 women; Analysis 7.7), latency (birth within 48 hours) (RR 0.88; 95% CI 0.14 to 5.73; one study of 47 women; Analysis 7.8), latency (birth within seven days) (RR 1.06; 95% CI 0.57 to 1.95; one study of 47 women; Analysis 7.9) and chorioamnionitis (RR 1.32; 95% CI 0.56 to 3.12; one study of 47 women; Analysis 7.10).

Insufficient data were available on intrauterine fetal demise; Analysis 7.2.

Corticosteroid and antibiotic subgroup analysis

Two studies used some combination of antibiotics and corticosteroids (Dunlop 1986; Ehansipoor 2010). Dunlop compared four groups: Group A: no ritodrine, no cephalexin; Group B: ritodrine, cephalexin; Group C: ritodrine, no cephalexin; Group D: no ritodrine, cephalexin. For antibiotic/steroid subgroup analyses, Group B was compared to Group D.

Primary outcomes

There was no significant difference in perinatal mortality (RR 1.91; 95% CI 0.39 to 9.44; two studies of 71 women; Analysis 8.1).

Secondary outcomes

There were no statistically significant differences identified between the treatment groups for any of the secondary outcomes considered. Corticosteroid therapy in addition to tocolysis was not significantly associated with neonatal death (RR 1.91; 95% CI 0.39 to 9.44; two studies of 71 women; Analysis 8.3), neonatal sepsis (RR 0.53; 95% CI 0.23 to 1.22; one study of 47 women; Analysis 8.4), NEC (RR 0.65; 95% CI 0.14 to 3.15; two studies of 71 women; Analysis 8.5), intraventricular hemorrhage (RR 2.00; 95% CI 0.21 to 19.23; two studies of 71 women; Analysis 8.6), RDS (RR 0.80; 95% CI 0.48 to 1.33; two studies of 71 women; Analysis 8.7), latency (birth within 48 hours) (RR 0.88; 95% CI 0.14 to 5.73; one study of 47 women; Analysis 8.8), latency (birth within seven days) (RR 1.06; 95% CI 0.57 to 1.95; one study of 47 women; Analysis 8.9) and chorioamnionitis (RR 1.32; 95% CI 0.56 to 3.12; one study of 47 women; Analysis 8.10).

Insufficient data were available on intrauterine fetal demise; Analysis 8.2

PPROM less than 34 weeks subgroup analysis of tocolysis versus no tocolysis

Five studies included only women who had PPROM less than 34 weeks (Dunlop 1986; Ehansipoor 2010; Garite 1987; Levy 1985; Weiner 1988). Levy included women from 25 to 34 weeks, Garite from 25 to 30 6/7 weeks, Dunlop from 26 to 34 weeks, Ehansipoor from 24 to 31 6/7 weeks and Weiner less than 34 weeks.

Primary outcomes

There was no significant difference in perinatal mortality (RR 1.50; 95% CI 0.69 to 3.24; five studies of 291 women; Analysis 9.1).

Secondary outcomes

Chrorioamnionitis was significantly higher in the group that received tocolysis as compared to those who did not (RR 1.79; 95% CI 1.02 to 3.14; three studies of 168 women; Analysis 9.14).

The remainder of the outcomes did not reveal statistically significant differences: intrauterine fetal demise (RR 1.03; 95% CI 0.07 to 15.83; three studies of 174 women; Analysis 9.2), neonatal death (RR 1.55; 95% CI 0.69 to 3.49; five studies of 291 women; Analysis 9.3), gestational age (MD 0.35; 95% CI -0.66 to 1.36; two studies of 117 women; Analysis 9.4), birthweight (MD 158.68 g; 95% CI -44.00 to 361.36; two studies of 117 women; Analysis 9.5), Apgar less than seven at five minutes (RR 3.59; 95% CI 0.79 to 16.22; one study of 79 women; Analysis 9.6), neonatal sepsis (average RR 0.63; 95% CI 0.31 to 1.27; four studies of 243 women; random-effects, $Tau^2 = 0.00$, $I^2 = 0\%$; Analysis 9.7), NEC (RR 0.68; 95% CI 0.31 to 1.47; three studies of 170 women; Analysis 9.8), intraventricular hemorrhage (RR 1.15; 95% CI 0.45 to 2.92; three studies of 174 women; Analysis 9.9), RDS (RR 0.88; 95% CI 0.68 to 1.14; four studies of 249 women; Analysis 9.10), hours latency (MD 79.22; 95% CI -27.56 to 186.01; two studies of 117 women; random-effects, $Tau^2 = 3437.90$, $I^2 = 55\%$; Analysis 9.11), latency (birth within 48 hours) (RR 0.59; 95% CI 0.34 to 1.00; four studies of 243 women; Analysis 9.12), latency (birth within seven days) (average RR 0.87; 95% CI 0.61 to 1.24; three studies of 168 women; random-effects, $Tau^2 = 0.05$, $I^2 = 49\%$; Analysis 9.13), and endometritis (RR 1.71; 95% CI 0.69 to 4.25; one study of 79 women; Analysis 9.15).

DISCUSSION

Compared to no tocolysis, tocolytic therapy is not associated with a significant effect on perinatal mortality in women with PPROM. Tocolysis was associated with longer overall latency and fewer births within 48 hours and seven days compared to no tocolysis. However, tocolysis was associated with significantly more infants with an Apgar less than seven at five minutes and with higher incidence of the neonate requiring ventilation. There were no other significant differences in other maternal or neonatal outcomes. Four of the seven included studies utilized only ritodrine for tocolysis (Christensen 1980; Dunlop 1986; Garite 1987; Levy 1985). One used both ritodrine and magnesium (Matsuda 1993). One used either ritodrine, terbutaline, or magnesium (Weiner 1988). And one used indomethacin as tocolytic (Ehansipoor 2010).

In the subgroup analysis comparing betamimetic to no betamimetics, betamimetic tocolysis is associated with increased overall latency, and increased incidence of chorioamnionitis.

There were no significant differences in any maternal or neonatal outcomes in subgroup analyses comparing cox inhibitor versus no tocolysis, calcium channel blocker versus betamimetic, antibiotic, corticosteroid, or combined antibiotic/corticosteroid.

Prophylactic tocolysis, i.e. tocolysis in women with PPROM and no or minimal uterine contractions, is significantly associated with increased overall latency; and we noted no other significant effects on maternal and neonatal outcomes.

For women with PPROM less than 34 weeks, there is a significantly increased risk of chorioamnionitis in women who received tocolysis. However, neonatal outcomes were not significantly different.

These results should be interpreted with caution because the studies included were in general small and not of high quality. The wide confidence intervals reveal that the sample size is underpowered to detect small differences in outcomes. Moreover, most of these studies did not use antibiotics for latency and corticosteroid therapy to promote fetal maturation, which are the current treatments in the conservative management of PPROM (Kenyon 2003; Roberts 2006) There were too few women randomized (fewer than 100) to receive both antibiotics and corticosteroids for meaningful interpretation of the data. Tocolysis is usually currently considered in women with preterm labor less than 34 weeks, and the subanalysis of PPROM less than 34 weeks was associated with harm (increased risk for chorioamnionitis), not with any benefit. The effect of tocolytics in women with PPROM less than 34 weeks who receive corticosteroids for fetal maturity and antibiotics for latency still remains unanswered. It is unfortunate that many randomized studies had to be excluded because outcomes for women with singleton gestations and PPROM were not reported separately.

While tocolysis is associated with an increase in latency after PPROM, this treatment does not seem justified given worse neonatal outcomes, such as low Apgar scores and higher requirement for ventilation. Perinatal mortality was also not significantly different in any of our analyses. A plausible explanation for an increase in neonatal morbidities despite increase latency is that prolonged pregnancy allows more time for infection to occur. The lack of antibiotics may have influenced the overall incidence of chorioamnionitis.

Furthermore, there are insufficient data on tocolytic therapy in women with PPROM regarding the agent, duration and whether it should be used as a prophylactic or treatment agent. Overall, further evidence from high quality, adequately powered randomized trials are required to assess whether the benefits of prolonged gestation outweigh the potential risks associated with maternal infection and the impact this has on neonatal health outcomes. Once data become available, we plan to perform future subgroup analyses to assess the effects of tocolysis (specifically with calcium channel blockers or cyclo-oxygenase inhibitors) in women with PPROM less than 34 weeks who are treated with both corticosteroids and latency antibiotics.

Summary of main results

In conclusion, there is no neonatal or maternal benefit to tocolytic therapy in the setting of women with PPROM. In fact it may be harmful, resulting in an increase incidence of chorioamnionitis.

AUTHORS' CONCLUSIONS

Implications for practice

Tocolytic therapy is commonly used in women with preterm labor with intact membranes. Our review suggests the role of tocolytic therapy for women with PPROM is of no benefit, as there was an increase in maternal chorioamnionitis without significant benefits with regards to maternal and infant morbidity and mortality. However, studies did not consistently administer latency antibiotics and corticosteroids, both of which are now considered standard of care. Further evaluation of tocolysis is required in women with PPROM who are treated with antibiotics and corticosteroids as is currently the standard of care.

Implications for research

Future research is needed to address tocolysis in today's current management of PPROM with antibiotics and corticosteroids. Future studies using tocolytic therapy in women with PPROM should include treatment with adjunctive antibiotics for prolongation of labor and corticosteroids for fetal maturity.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Christensen 1980

Methods	Randomized controlled trial.
Participants	Singleton gestations 28 - 36 weeks with PPROM and ≤ 4 cm cervical dilation. Number of participants: 14 (ritodrine),16 (placebo).
Interventions	Tocolysis: intravenous (IV) ritodrine 100 ug/min with infusion rate increased by 50 µg/min at 10 minute intervals to a max of 400 µg/min until no uterine activity on tocometer; if contractions persisted after 6 hours of 400 µg/min of ritodrine, the infusion was decreased to 100 µg/min; IV ritodrine was continued for 24 hours at which time oral ritodrine therapy of 20 mg 3 times per day was begun and continued until 35 weeks; IV dosing was restarted if contractions recurred. No tocolysis: Placebo of 5.5% glucose solution. Antibiotics: Ampicillin 2 grams intravenously every 4 hours during delivery for those with Group Beta Streptococcus or *Escherichia coli* urogenital colonization. Corticosteroids: use not specified.
Outcomes	Not prespecified, appears to look at delivery < 24 hours.
Notes	Delivered at 36 weeks or signs of infection.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	30 sets of coded ampoules and tablets: 14 with ritodrine and 16 with placebo; each given number from 1-30 at random. Once patient entered the study, the ampoule/tablet was chosen in numerical order.
Allocation concealment (selection bias)	Low risk	Code key was not available to investigator before completion of the study.

Christensen 1980 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete data; all women were analyzed.
Selective reporting (reporting bias)	Unclear risk	Primary outcome was not explicitly stated.
Other bias	Low risk	No other potential sources of bias identified.

Dunlop 1986

Methods	Randomized controlled trial.
Participants	Singleton gestations 26 - 34 weeks with PPROM and no uterine contractions. Number of participants: 12 (Group A), 12 (Group B), 12 (Group C), 12 (Group D).
Interventions	Group A: no ritodrine, no cephalexin. Group B: ritodrine, cephalexin. Group C: ritodrine, no cephalexin. Group D: no ritodrine, cephalexin. Tocolysis: Ritodrine10 mg orally every 6 hours to half of the first 16 cases; thereafter ritodrine was increased to 10 mg every 2 hours (except 2 am and 4 am) for half of the subsequent 32 cases); Duration of therapy was not specified. Antibiotics: Cephalexin 250 mg orally every 6 hours was given to the first half of 32 cases and 500 mg every 6 hours was given to half of the last 16. Corticosteroids: Dexamethasone 4 mg every 8 hours for 6 doses or 12 mg every 24 hours for 2 doses, repeated each week until 32 weeks.
Outcomes	Type of labor (spontaneous, induced, elective cesarean), mode of delivery, neonatal and maternal outcomes including admission to birth interval.
Notes	Delivered if regular, painful contractions, infection or fetal distress. For antibiotic and antibiotic/steroid subgroup analysis, Group B was compared to Group D; for all other analyses, Groups B and C were combined and compared to the combination of Groups A and D.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	First 32 women were randomized by sealed envelopes; the last 16 were entered by order of admission into a 4 by 4 Latin square.
Allocation concealment (selection bias)	Low risk	Sealed envelopes and Latin square.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Does not specify if there was masking of the participants or researchers.

Dunlop 1986 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete data; all women were analyzed.
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes were stated.
Other bias	Low risk	No other potential sources of bias identified.

Ehansipoor 2010

Methods	Randomized controlled trial.
Participants	Singleton gestations 24 - 31 weeks and 6 days with PPROM who presented within 24 hours of rupture of membranes. Number of participants: 25 (indomethacin), 22 (no tocolysis).
Interventions	Tocolysis: indomethacin (50 mg rectal dose initially, then 25 mg orally for subsequent doses for 48 hours). No tocolysis: placebo. Antibiotics: IV ampicillin/sulbactam for 48 hours, then amoxicillin/clavulanate for 5 days. Corticosteroids: Betamethasone 12 mg every 24 hours for 2 doses.
Outcomes	Primary: delivery within 48 hours after starting study drug. Secondary: latency from membrane rupture, weeks gestation at delivery, chorioamnionitis.
Notes	Delivered at 34 weeks or prior if clinically appropriate. Sample size calculation of 65 per group to detect a reduction from 50% to 25% in women delivering within 48 hours; stopped at sample size of 50 secondary to slow enrolment.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated random number table in a block size of ten in a 1:1 ratio.
Allocation concealment (selection bias)	Low risk	Placed in consecutively numbered, opaque, sealed envelopes.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete data; all women were analyzed.
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes were stated.

Ehansipoor 2010 *(Continued)*

Other bias	Low risk	No other potential sources of bias identified.

Garite 1987

Methods	Randomized controlled trial.
Participants	Singleton gestations 25 - 30 weeks and 6 days with PPROM with or without contractions. Number of participants: 39 (ritodrine), 40 (expectant management).
Interventions	No tocolysis: expectant management. Tocolysis: If > 2 contractions/20 minutes, tocolysis was started; IV ritodrine 150 ug/min, increased by 50 µg every 10 minutes until < 1 contraction/10 min, unacceptable side effects or maximum of 350 µg/min; Intravenous ritodrine was continued for 12 to 24 hours after contractions stopped (and no longer than 24 hours at 350 µg/min) and then oral ritodrine was started at 10 mg every 3 hours; an IV ritodrine course was repeated if necessary; tocolysis was stopped at the end of week 31 and the patient was followed expectantly. Expectant management group: no tocolytic. Antibiotics: Prophylactic antibiotics only in women undergoing caesarean section. Corticosteroids: No steroid administration in either group.
Outcomes	Primary outcome: time interval of PPROM to birth.
Notes	Delivery for labor, clinical chorioamnionitis, or fetal distress.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Does not specify randomization scheme in text.
Allocation concealment (selection bias)	Unclear risk	Does not specify allocation concealment in text.
Blinding (performance bias and detection bias) All outcomes	High risk	There was no blinding of participants or researchers.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete data; all women were analyzed.
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes were stated.
Other bias	Low risk	No other potential sources of bias identified.

Laohapojanart 2007

Methods	Randomized trial.

Laohapojanart 2007 *(Continued)*

Participants	Singleton gestations 24 - 36 completed weeks with preterm labor. Author provided data on the women with PPROM: 30 to 33 weeks' gestation PPROM with contractions. Number of participants with rupture of membranes: 3 (nifedipine group), 3 (terbutaline group).
Interventions	Nifedipine group: immediate release nifedipine 10 mg (max dose 40 mg) within first hour followed by 10 mg every 4 to 6 hours for 72 hours. Terbutaline group: terbutaline 10 µg/min followed by 5 µg/min every 10 minutes until 25 µg/min was obtained and then switched to subcutaneous injections of terbutaline 0.25 mg every 4 hours for 24 hours Women defined as having failed tocolysis were treated with 25-50 mg of indomethacin every 6 hours to a maximum daily dose of 200 mg for 48 hours. Antibiotics: not specified. Corticosteroids: Dexamethasone 6 mg IM every 12 hours for 4 doses.
Outcomes	Primary: diastolic blood pressure changed from 1 hour of treatment.
Notes	Indications for delivery were not clarified.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Blocks of size 4, 6, and 8 were used to randomize women.
Allocation concealment (selection bias)	Low risk	Central randomization.
Blinding (performance bias and detection bias) All outcomes	High risk	There was no blinding of the participants or researchers.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete data; all women with ruptured membranes were analyzed.
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes were stated.
Other bias	Low risk	No other potential sources of bias identified.

Levy 1985

Methods	Randomized controlled trial.
Participants	Singleton gestations 25 - 34 weeks with PPROM and no contractions. Number of participants: 21 (ritodrine), 21 (expectant management or placebo).
Interventions	Tocolysis: ritodrine 10 mg orally every 4 hours until labor. No tocolysis: placebo or no medication.

Levy 1985 *(Continued)*

	Antibiotics: perioperative cesarean prophylaxis. Corticosteroids: not administered.
Outcomes	Birthweight at delivery, latency period and evidence of maternal or fetal infection.
Notes	Delivery for labor, clinical chorioamnionitis, or fetal distress.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Women whose social security number ended with an even number received ritodrine 10 mg orally every 4 hours and odd-numbered women received no medication or placebo.
Allocation concealment (selection bias)	High risk	Open allocation.
Blinding (performance bias and detection bias) All outcomes	High risk	There was no blinding of the participants or researchers.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete data; all women were analyzed.
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes were stated.
Other bias	Low risk	No other potential sources of bias identified.

Matsuda 1993

Methods	Randomized study, but no description of randomizations provided.
Participants	Singleton gestations 23 - 34 weeks and 6 days with PPROM in the absence of active labor. Number of participants: 39 (Group 1), 42 (Group 2).
Interventions	Aggressive (Group 1): IV prophylactic antibiotics (ampicillin 2 g/day) and IV ritodrine; initial dose of ritodrine was 50-100 µg/min; this was increased by 50 µg/min every 10-20 minutes until contractions ceased; if contractions did not cease despite a maximum dose of 250 µg/min, 4 g of magnesium sulfate was bolused over 30 minutes and continued at 1-2 g/hr; duration of tocolysis is unclear. Bedrest (Group 2): no tocolysis or antibiotics. Group 3 included women with intact membranes and preterm labor, so this group was not included in our analysis. Antibiotics: Ampicillin 2 g IV/day for Group 1. Corticosteroids: use not specified.
Outcomes	To evaluate the efficacy of tocolytics and antibiotics in prolongation of pregnancy and neonatal outcome in treatment of PPROM without labor; successful therapy for preterm labor defined by latency > 48 hours, latency > 7 days and delivery after 35 weeks.

Matsuda 1993 *(Continued)*

Notes	Delivery for active labor, clinical chorioamnionitis, fetal distress, gestational age > 35 weeks; in addition to tocolysis, Group 1 also received antibiotics, while Group 2 did not receive either.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not clearly stated.
Allocation concealment (selection bias)	Unclear risk	Not clearly stated.
Blinding (performance bias and detection bias) All outcomes	High risk	There was no blinding of the participants or researchers.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete data; all women were analyzed.
Selective reporting (reporting bias)	Unclear risk	Pre-specified outcomes were stated.
Other bias	Low risk	No other potential sources of bias identified.

Weiner 1988

Methods	Randomized controlled trial.
Participants	Singleton gestations with upper limit of gestational age of 34 weeks with PPROM. Number of participants: 33 (tocolysis), 42 (bedrest).
Interventions	Bedrest versus aggressive IV tocolysis (if > 3 contractions/hour) with ritodrine, terbutaline, or magnesium sulfate; drug infusion was increased to quiet uterine activity to a maximum dose of 450 µg/min of ritodrine or 20 µg/min of terbutaline; Magnesium sulfate up to 4.5 gm/hr was added if uterine activity could not be controlled with a beta-mimetic agent; 24 hours after successful tocolysis, oral terbutaline was started. Antibiotics: Administered for bacteriuria or group beta streptococcus genital colonization Corticosteroids: not administered.
Outcomes	No primary outcome clearly stated; aims were to assess therapeutic efficacy, safety and cost-effectiveness of tocolysis for PTL after PPROM.
Notes	Delivery for clinical amnionitis or fetal distress.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table.

Weiner 1988 *(Continued)*

Allocation concealment (selection bias)	Low risk	Sequentially numbered envelopes.
Blinding (performance bias and detection bias) All outcomes	High risk	There was neither blinding of participants nor researchers.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Primary outcome was not explicit; 34 women were excluded from analyses (8 in whom protocol was violated, 6 with chorioamnionitis or advanced dilation, 8 who withdrew from tocolysis, and 12 multiple gestations).
Selective reporting (reporting bias)	Unclear risk	Primary outcome was not explicitly stated.
Other bias	Low risk	No other potential sources of bias identified.

IV: intravenous
PPROM: preterm premature rupture of membranes
ug: micrograms
mg: milligrams

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

Study	Reason for exclusion
Bisits 2004	Included women with preterm labor with intact membranes, but did not categorize outcome variables on membrane status.
Briery 2009	Did not compare tocolysis, but instead compared progesterone versus no progesterone.
Caritis 1982	Included women with preterm labor with intact membranes, but did not categorize outcome variables on membrane status, and included multiple gestations.
Caritis 1984	Included multiple gestations.
Cotton 1984	Included multiple gestations.
Decavalas 1995	Compared short-term versus long-term tocolysis of the same tocolytic; some of the control group did get tocolysis, and separate results for those who did not get tocolysis are not available.
El-Sayed 1999	Included women with preterm labor with intact membranes, but did not categorize outcome variables on membrane status.
Essed 1978	Included women with preterm labor with intact membranes, but did not categorize outcome variables on membrane status.
Ferguson 1984	Included multiple gestations.
Ferguson 1989	Included women with preterm labor with intact membranes but did not categorize outcome variables on membrane status; compared cardiovascular and metabolic effects measured in association with sublingual and oral administration of nifedipine and IV and oral beta adrenergic agents.
Freeman 2008	Study withdrawn from publication.

Study	Reason for exclusion
Gamissans 1982	Compared 2 treatments for preterm labor (ritodrine and placebo against ritodrine and indomethacin).
Gill 2006	Included women with preterm labor with intact membranes, but did not categorize outcome variables on membrane status; compared the neurodevelopment of infants born to women who received glycerol trinitrate patches and beta 2 agonist agents for preterm labor.
Holleboom 1996	Compared 2 different regimens of same tocolytic (ritodrine); included women with preterm labor with intact membranes, but did not categorize outcome variables on membrane status; also included multiple gestations.
Houtzager 2006	Included women with preterm labor with intact membranes, but did not categorize outcome variables on membrane status; compared long-term psychosocial and motor effects on children exposed in utero to nifedipine or ritodrine for preterm labor.
How 1998	Included multiple gestations.
Husslein 2007	Compared atosiban to 'any other tocolytic', and so did not fit our categories (e.g. tocolytic vs no tocolytic; or 1 tocolytic vs another; included multiple gestations).
Ingemarsson 1976	Excluded women with rupture of membranes.
Kashanian 2005	Excluded women with rupture of membranes.
Katz 1983	Included women with preterm labor with intact membranes, but did not categorize outcome variables on membrane status.
Koks 1998	Included multiple gestations.
Leake 1983	Included women with preterm labor with intact membranes, but did not categorize outcome variables on membrane status.
Lyell 2007	Included women with preterm labor with intact membranes, but did not categorize outcome variables on membrane status; also included twins.
Mittendorf 1997	Included women with preterm labor with intact membranes but did not categorize outcome variables on membrane status; included twins.
Moutquin 1992	Included women with preterm labor with intact membranes, but did not categorize outcome variables on membrane status; included multiple gestations.
Nelson 1985	Group 1 received steroid and tocolytic, Group 2 received tocolytic without steroid and Group 3 received neither tocolytic nor steroid. They were excluded because groups were managed differently with respect to delivery with the first 2 groups intentionally delivered 24-48 hours after PPROM and the latter group managed expectantly.
Papatsonis 1997	Included women with preterm labor with intact membranes, but did not categorize outcome variables on membrane status.
Parsons 1988	Not randomized by tocolytic therapy.
Renzo 2003	Included multiple gestations.
Sims 1978	Included women with preterm labor with intact membranes, but did not categorize outcome variables on membrane status.

Study	Reason for exclusion
Spearing 1979	Included women with preterm labor with intact membranes, but did not categorize outcome variables on membrane status.
Spellacy 1979	Included women with preterm labor with intact membranes, but did not categorize outcome variables on membrane status.
Tchilinguirian 1984	Excluded women with rupture of membranes more than 24 hours before onset of labor.

PPROM: preterm premature rupture of membranes

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

El-Sayed 2010

Trial name or title	Progesterone for the Management of Preterm, Premature Rupture of the Membranes: A Randomized Controlled Trial.
Methods	Randomized clinical trial.
Participants	Women greater than 18 years carrying singleton gestations 24 - 33 weeks and 5 days with PPROM.
Interventions	All women will receive standard care in addition to weekly injections of either placebo (castor oil) or 17-hydroxyprogesterone caproate.
Outcomes	*Primary*: delivery at 34 weeks' gestation. *Secondary*: neonatal respiratory distress syndrome; neonatal grade III-IV intraventricular hemorrhage; neonatal necrotizing enterocolitis; neonatal length of NICU and total hospital stay; length of latency.
Starting date	February 2010.
Contact information	Elizabeth S Langen, MD (elizabethlangen@stanford.edu).
Notes	Projected end date: August 2014. Target enrollment 40 women.

Mol 2012

Trial name or title	Assessment of Perinatal Outcome by use of Tocolysis in Early Labour: Nifedipine versus placebo in the treatment of preterm premature rupture of membranes. (APOSTEL IV).
Methods	Randomized clinical trial.
Participants	All women with a fetus 24 - 33 weeks and 6 days with ruptured membranes without other signs of active labour.
Interventions	Random allocation to nifedipine (intervention) or placebo (control) until the start of active labour (≥ 3 contractions per 10 minutes).
Outcomes	*Primary*: neonatal mortality; composite neonatal morbidity (i.e. chronic lung disease, severe intraventricular hemorrhage more than grade 2, periventricular leukomalacia more than grade 1, proven sepsis, necrotizing enterocolitis).

Mol 2012 *(Continued)*	
	*Secon*dary: gestational age at delivery; birth weight; total days in hospital until 3 months corrected age; economic analysis; number of days: in NICU, on supported ventilation, on additional oxygen.
Starting date	April 2012.
Contact information	TS de Lange, Academic Medical Centre, Department of Obstetrics and Gynaecology, Amsterdam, The Netherlands (apostel4@studies-obsgyn.nl) and Prof Dr BWM Mol, PO Box 22700, Academic Medical Centre, Department of Obstetrics and Gynaecology, Room H4-213, 1105 DE, Amsterdam,The Netherlands (b.w.mol@amc.nl).
Notes	Projected end date: December 2014. Target enrollment 120 women.

IVH: intraventricular hemorrhage
NICU: neonatal intensive care unit
PPROM: preterm, premature rupture of the membranes

DATA AND ANALYSES

Comparison 1. Tocolytic versus no tocolytic

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Perinatal mortality	7	402	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.85, 3.29]
2 Intrauterine fetal demise	3	174	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.07, 15.83]
3 Neonatal death	7	402	Risk Ratio (M-H, Fixed, 95% CI)	1.73 [0.85, 3.50]
4 Gestational age	3	198	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.85, 0.71]
5 Birthweight (grams)	2	117	Mean Difference (IV, Fixed, 95% CI)	158.68 [-44.00, 361.36]
6 Apgar < 7 at 5 minutes	2	160	Risk Ratio (M-H, Fixed, 95% CI)	6.05 [1.65, 22.23]
7 Neonatal Sepsis	5	324	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.40, 1.33]
8 Necrotizing enterocolitis	3	170	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.31, 1.47]
9 Intraventricular haemorrhage	3	174	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.45, 2.92]
10 Respiratory distress syndrome	5	279	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.70, 1.17]
11 Neonate required ventilation	1	81	Risk Ratio (M-H, Fixed, 95% CI)	2.46 [1.14, 5.34]
12 Latency (hours)	3	198	Mean Difference (IV, Fixed, 95% CI)	73.12 [20.21, 126.03]
13 Latency (birth within 48 hours)	6	354	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.32, 0.95]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14 Latency (birth within 7 days)	4	249	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.62, 1.05]
15 Chorioamnionitis	5	279	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [1.00, 2.61]
16 Endometritis	1	79	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [0.69, 4.25]
17 Maternal hospital stay (days)	1	81	Mean Difference (IV, Fixed, 95% CI)	3.40 [-0.74, 7.54]

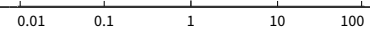
Analysis 1.1. Comparison 1 Tocolytic versus no tocolytic, Outcome 1 Perinatal mortality.

Study or subgroup	Tocolytic n/N	No tocolytic n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Christensen 1980	1/14	0/16		3.8%	3.4[0.15,77.34]
Dunlop 1986	4/24	1/24		8.11%	4[0.48,33.22]
Ehansipoor 2010	1/25	1/22		8.63%	0.88[0.06,13.25]
Garite 1987	6/39	2/40		16.01%	3.08[0.66,14.33]
Levy 1985	0/21	1/21		12.16%	0.33[0.01,7.74]
Matsuda 1993	4/39	2/42		15.62%	2.15[0.42,11.11]
Weiner 1988	3/33	5/42		35.68%	0.76[0.2,2.97]
Total (95% CI)	**195**	**207**		**100%**	**1.67[0.85,3.29]**
Total events: 19 (Tocolytic), 12 (No tocolytic)					
Heterogeneity: Tau^2=0; Chi^2=4.05, df=6(P=0.67); I^2=0%					
Test for overall effect: Z=1.48(P=0.14)					

Favours tocolysis — Favours no tocolysis

Analysis 1.2. Comparison 1 Tocolytic versus no tocolytic, Outcome 2 Intrauterine fetal demise.

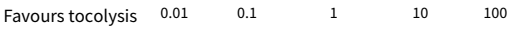
Study or subgroup	Tocolytic n/N	No tocolytic n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dunlop 1986	0/24	0/24			Not estimable
Ehansipoor 2010	0/25	0/22			Not estimable
Garite 1987	1/39	1/40		100%	1.03[0.07,15.83]
Total (95% CI)	**88**	**86**		**100%**	**1.03[0.07,15.83]**
Total events: 1 (Tocolytic), 1 (No tocolytic)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.02(P=0.99)					



Favours tocolysis — Favours no tocolysis

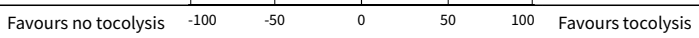
Analysis 1.3. Comparison 1 Tocolytic versus no tocolytic, Outcome 3 Neonatal death.

Study or subgroup	Tocolytic n/N	No tocolytic n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Christensen 1980	1/14	0/16		4.13%	3.4[0.15,77.34]
Dunlop 1986	4/24	1/24		8.81%	4[0.48,33.22]
Ehansipoor 2010	1/25	1/22		9.38%	0.88[0.06,13.25]
Garite 1987	5/39	1/40		8.7%	5.13[0.63,41.93]
Levy 1985	0/21	1/21		13.22%	0.33[0.01,7.74]
Matsuda 1993	4/39	2/42		16.97%	2.15[0.42,11.11]
Weiner 1988	3/33	5/42		38.78%	0.76[0.2,2.97]
Total (95% CI)	**195**	**207**		**100%**	**1.73[0.85,3.5]**
Total events: 18 (Tocolytic), 11 (No tocolytic)					
Heterogeneity: Tau^2=0; Chi^2=4.56, df=6(P=0.6); I^2=0%					
Test for overall effect: Z=1.52(P=0.13)					



Analysis 1.4. Comparison 1 Tocolytic versus no tocolytic, Outcome 4 Gestational age.

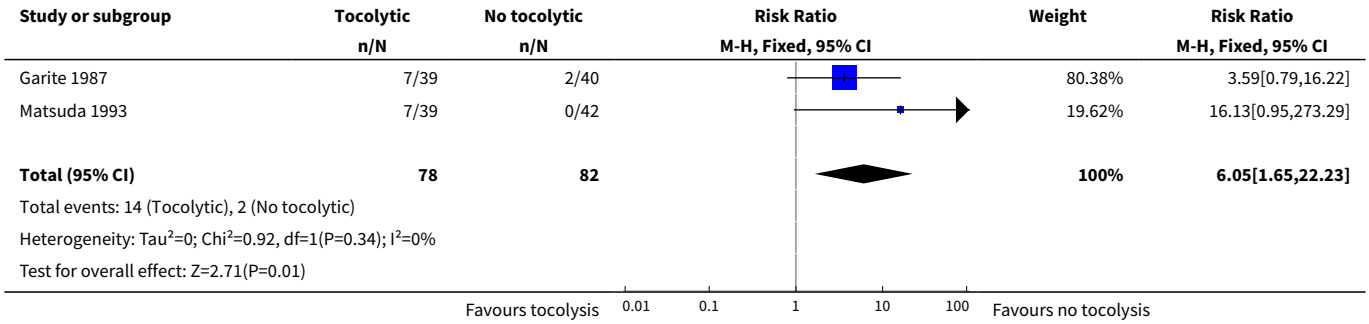
Study or subgroup	Tocolytic N	Tocolytic Mean(SD)	No tocolytic N	No tocolytic Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Levy 1985	21	30.7 (2.4)	21	30.9 (2.3)		30.09%	-0.2[-1.62,1.22]
Matsuda 1993	39	31.3 (3.1)	42	32 (2.5)		40.06%	-0.7[-1.93,0.53]
Weiner 1988	42	31 (2.9)	33	30.1 (3.3)		29.86%	0.9[-0.53,2.33]
Total ***	**102**		**96**			**100%**	**-0.07[-0.85,0.71]**
Heterogeneity: Tau^2=0; Chi^2=2.81, df=2(P=0.25); I^2=28.85%							
Test for overall effect: Z=0.18(P=0.86)							



Analysis 1.5. Comparison 1 Tocolytic versus no tocolytic, Outcome 5 Birthweight (grams).

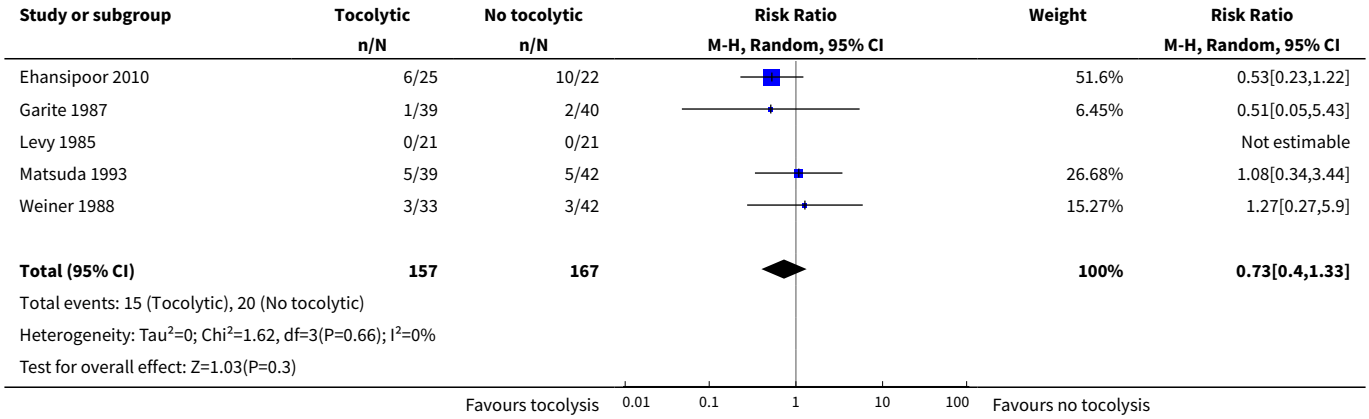
Study or subgroup	Tocolytic N	Tocolytic Mean(SD)	No tocolytic N	No tocolytic Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Levy 1985	21	1941 (671)	21	1729 (438)		34.97%	212[-130.72,554.72]
Weiner 1988	42	1648 (536)	33	1518 (563)		65.03%	130[-121.35,381.35]
Total ***	**63**		**54**			**100%**	**158.68[-44,361.36]**
Heterogeneity: Tau^2=0; Chi^2=0.14, df=1(P=0.71); I^2=0%							
Test for overall effect: Z=1.53(P=0.12)							

Analysis 1.6. Comparison 1 Tocolytic versus no tocolytic, Outcome 6 Apgar < 7 at 5 minutes.



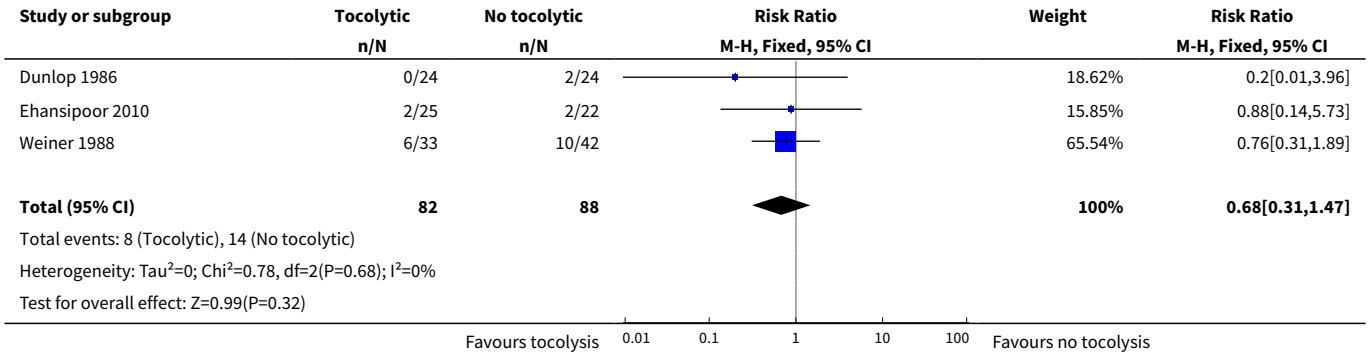
Study or subgroup	Tocolytic n/N	No tocolytic n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Garite 1987	7/39	2/40		80.38%	3.59[0.79,16.22]
Matsuda 1993	7/39	0/42		19.62%	16.13[0.95,273.29]
Total (95% CI)	**78**	**82**		**100%**	**6.05[1.65,22.23]**
Total events: 14 (Tocolytic), 2 (No tocolytic)					
Heterogeneity: Tau^2=0; Chi^2=0.92, df=1(P=0.34); I^2=0%					
Test for overall effect: Z=2.71(P=0.01)					

Analysis 1.7. Comparison 1 Tocolytic versus no tocolytic, Outcome 7 Neonatal Sepsis.



Study or subgroup	Tocolytic n/N	No tocolytic n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Ehansipoor 2010	6/25	10/22		51.6%	0.53[0.23,1.22]
Garite 1987	1/39	2/40		6.45%	0.51[0.05,5.43]
Levy 1985	0/21	0/21			Not estimable
Matsuda 1993	5/39	5/42		26.68%	1.08[0.34,3.44]
Weiner 1988	3/33	3/42		15.27%	1.27[0.27,5.9]
Total (95% CI)	**157**	**167**		**100%**	**0.73[0.4,1.33]**
Total events: 15 (Tocolytic), 20 (No tocolytic)					
Heterogeneity: Tau^2=0; Chi^2=1.62, df=3(P=0.66); I^2=0%					
Test for overall effect: Z=1.03(P=0.3)					

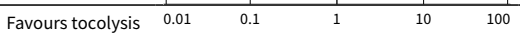
Analysis 1.8. Comparison 1 Tocolytic versus no tocolytic, Outcome 8 Necrotizing enterocolitis.



Study or subgroup	Tocolytic n/N	No tocolytic n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dunlop 1986	0/24	2/24		18.62%	0.2[0.01,3.96]
Ehansipoor 2010	2/25	2/22		15.85%	0.88[0.14,5.73]
Weiner 1988	6/33	10/42		65.54%	0.76[0.31,1.89]
Total (95% CI)	**82**	**88**		**100%**	**0.68[0.31,1.47]**
Total events: 8 (Tocolytic), 14 (No tocolytic)					
Heterogeneity: Tau^2=0; Chi^2=0.78, df=2(P=0.68); I^2=0%					
Test for overall effect: Z=0.99(P=0.32)					

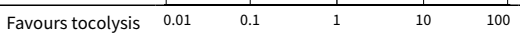
Analysis 1.9. Comparison 1 Tocolytic versus no tocolytic, Outcome 9 Intraventricular haemorrhage.

Study or subgroup	Tocolytic n/N	No tocolytic n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dunlop 1986	5/24	5/24		71.69%	1[0.33,3.01]
Ehansipoor 2010	0/25	0/22			Not estimable
Garite 1987	3/39	2/40		28.31%	1.54[0.27,8.71]
Total (95% CI)	**88**	**86**		**100%**	**1.15[0.45,2.92]**
Total events: 8 (Tocolytic), 7 (No tocolytic)					
Heterogeneity: Tau^2=0; Chi^2=0.17, df=1(P=0.68); I^2=0%					
Test for overall effect: Z=0.3(P=0.76)					



Analysis 1.10. Comparison 1 Tocolytic versus no tocolytic, Outcome 10 Respiratory distress syndrome.

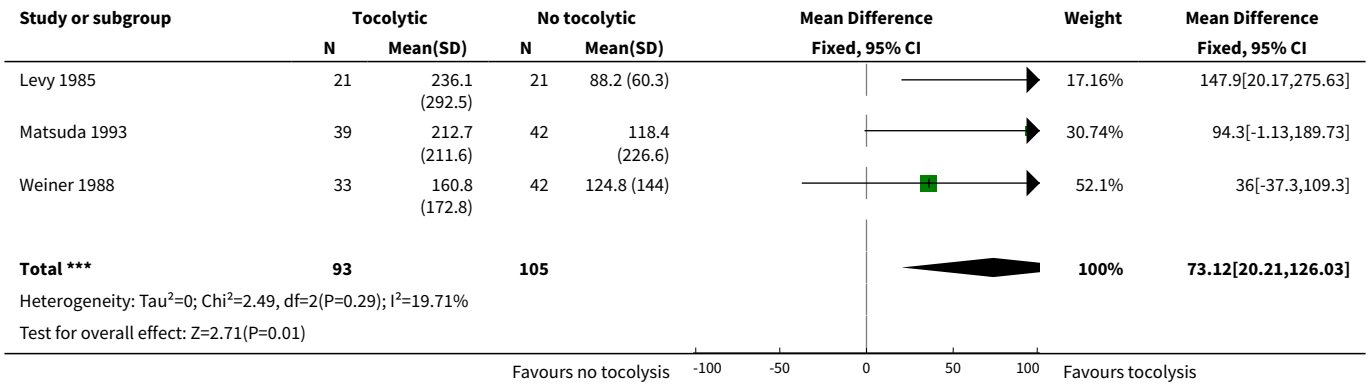
Study or subgroup	Tocolytic n/N	No tocolytic n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Christensen 1980	2/14	1/16		1.46%	2.29[0.23,22.59]
Dunlop 1986	8/24	7/24		10.97%	1.14[0.49,2.65]
Ehansipoor 2010	11/25	13/22		21.67%	0.74[0.42,1.31]
Garite 1987	20/39	23/40		35.58%	0.89[0.59,1.34]
Weiner 1988	15/33	22/42		30.33%	0.87[0.54,1.39]
Total (95% CI)	**135**	**144**		**100%**	**0.9[0.7,1.17]**
Total events: 56 (Tocolytic), 66 (No tocolytic)					
Heterogeneity: Tau^2=0; Chi^2=1.41, df=4(P=0.84); I^2=0%					
Test for overall effect: Z=0.8(P=0.43)					



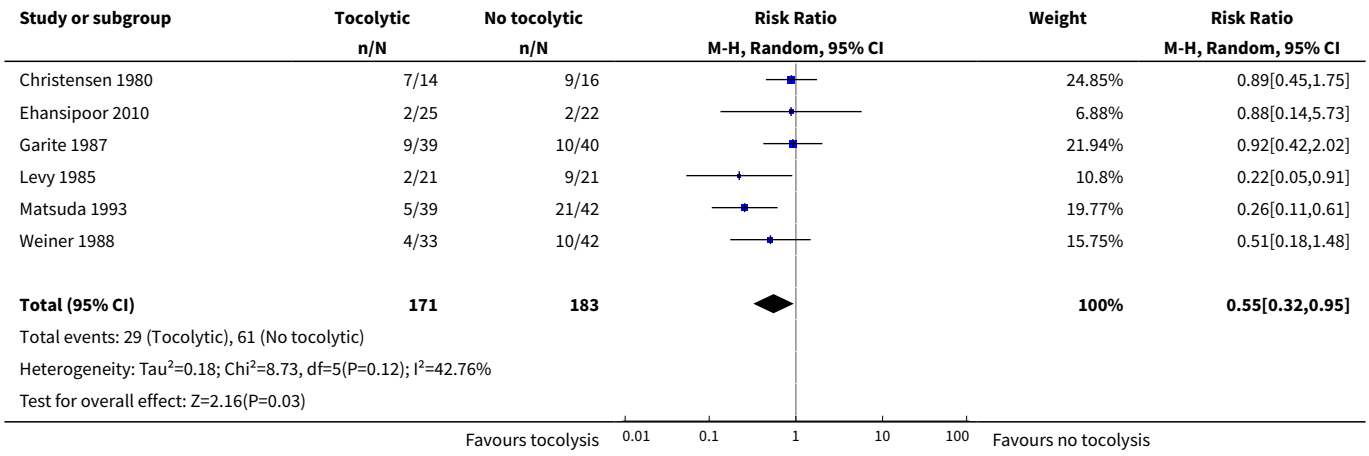
Analysis 1.11. Comparison 1 Tocolytic versus no tocolytic, Outcome 11 Neonate required ventilation.

Study or subgroup	Tocolytic n/N	No tocolytic n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Matsuda 1993	16/39	7/42		100%	2.46[1.14,5.34]
Total (95% CI)	**39**	**42**		**100%**	**2.46[1.14,5.34]**
Total events: 16 (Tocolytic), 7 (No tocolytic)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.28(P=0.02)					

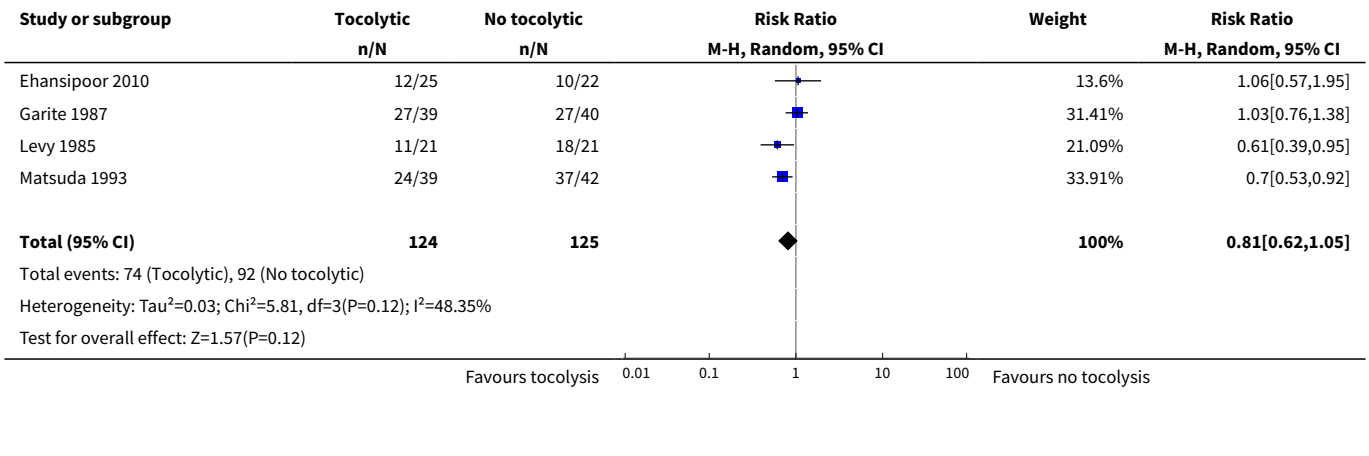
Analysis 1.12. Comparison 1 Tocolytic versus no tocolytic, Outcome 12 Latency (hours).



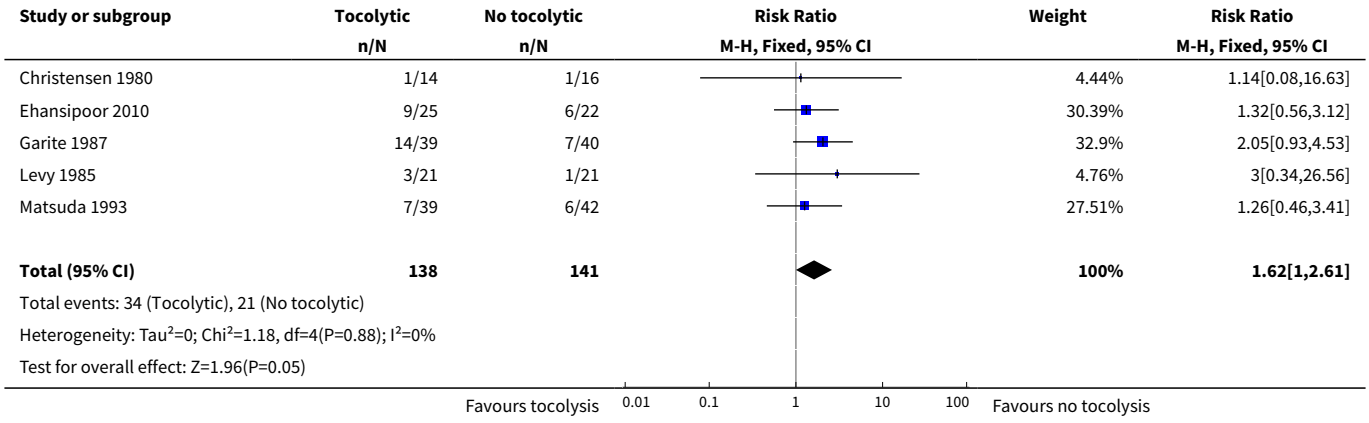
Analysis 1.13. Comparison 1 Tocolytic versus no tocolytic, Outcome 13 Latency (birth within 48 hours).



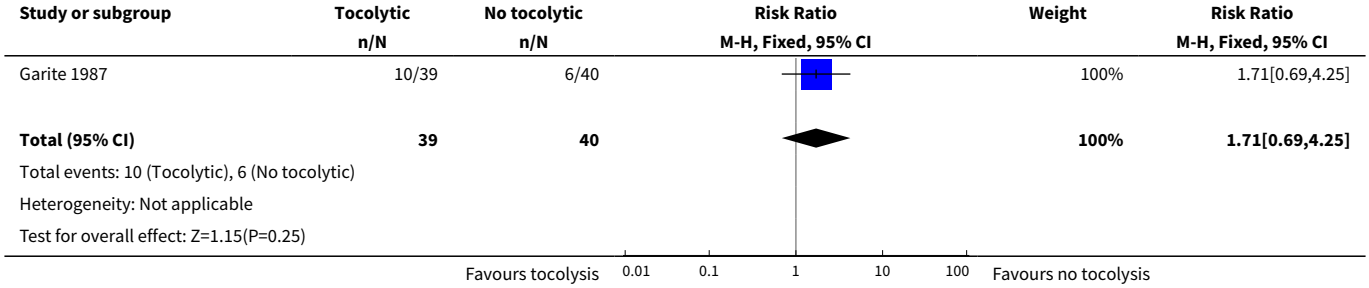
Analysis 1.14. Comparison 1 Tocolytic versus no tocolytic, Outcome 14 Latency (birth within 7 days).



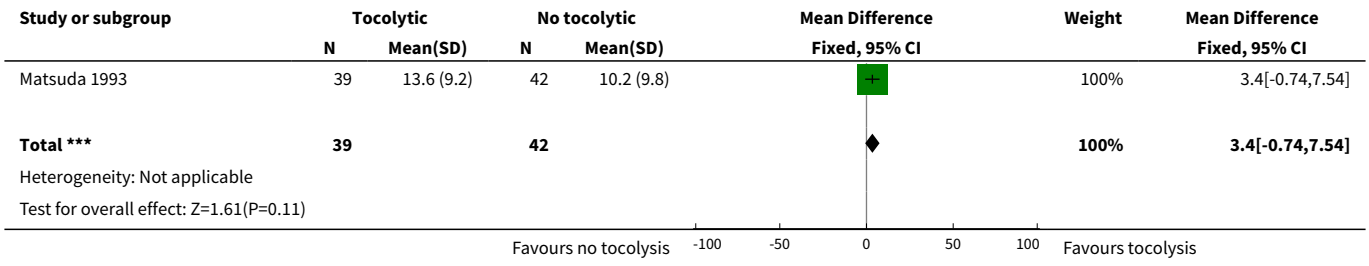
Analysis 1.15. Comparison 1 Tocolytic versus no tocolytic, Outcome 15 Chorioamnionitis.



Analysis 1.16. Comparison 1 Tocolytic versus no tocolytic, Outcome 16 Endometritis.



Analysis 1.17. Comparison 1 Tocolytic versus no tocolytic, Outcome 17 Maternal hospital stay (days).



Comparison 2. Cyclo-oxygenase inhibitor versus no cyclo-oxygenase inhibitor subgroup analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Perinatal mortality	1	47	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.06, 13.25]
2 Intrauterine fetal demise	1	47	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Neonatal death	1	47	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.06, 13.25]
4 Neonatal sepsis	1	47	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.23, 1.22]
5 Necrotizing enterocolitis	1	47	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.14, 5.73]
6 Intraventricular haemorrhage	1	47	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Respiratory distress syndrome	1	47	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.42, 1.31]
8 Latency (birth within 48 hours)	1	47	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.14, 5.73]
9 Latency (birth within 7 days)	1	47	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.57, 1.95]
10 Chorioamnionitis	1	47	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.56, 3.12]

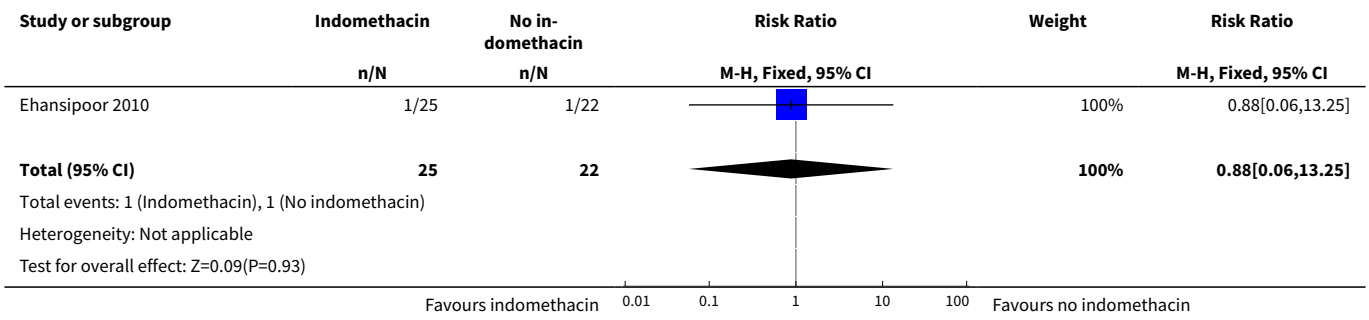
Analysis 2.1. Comparison 2 Cyclo-oxygenase inhibitor versus no cyclo-oxygenase inhibitor subgroup analysis, Outcome 1 Perinatal mortality.

Study or subgroup	Indomethacin n/N	No indomethacin n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ehansipoor 2010	1/25	1/22		100%	0.88[0.06,13.25]
Total (95% CI)	**25**	**22**		**100%**	**0.88[0.06,13.25]**
Total events: 1 (Indomethacin), 1 (No indomethacin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.09(P=0.93)					

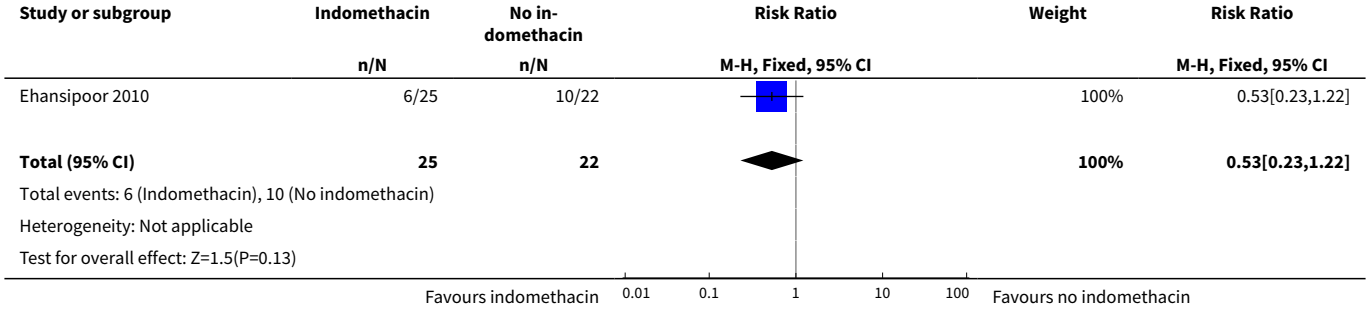
Analysis 2.2. Comparison 2 Cyclo-oxygenase inhibitor versus no cyclo-oxygenase inhibitor subgroup analysis, Outcome 2 Intrauterine fetal demise.

Study or subgroup	Indomethacin n/N	No indomethacin n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ehansipoor 2010	0/25	0/22			Not estimable
Total (95% CI)	**25**	**22**			**Not estimable**
Total events: 0 (Indomethacin), 0 (No indomethacin)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

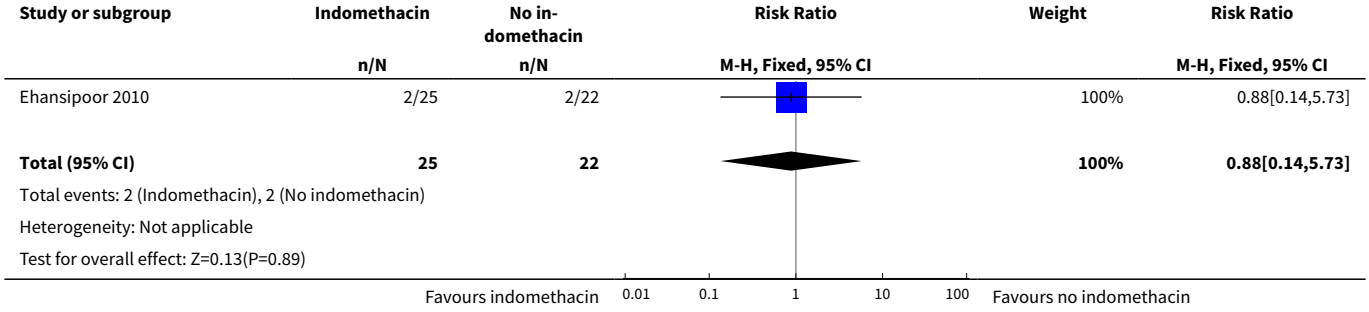
Analysis 2.3. Comparison 2 Cyclo-oxygenase inhibitor versus no cyclo-oxygenase inhibitor subgroup analysis, Outcome 3 Neonatal death.



Analysis 2.4. Comparison 2 Cyclo-oxygenase inhibitor versus no cyclo-oxygenase inhibitor subgroup analysis, Outcome 4 Neonatal sepsis.



Analysis 2.5. Comparison 2 Cyclo-oxygenase inhibitor versus no cyclo-oxygenase inhibitor subgroup analysis, Outcome 5 Necrotizing enterocolitis.



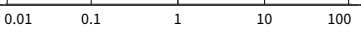
Analysis 2.6. Comparison 2 Cyclo-oxygenase inhibitor versus no cyclo-oxygenase inhibitor subgroup analysis, Outcome 6 Intraventricular haemorrhage.

Study or subgroup	Indomethacin n/N	No indomethacin n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ehansipoor 2010	0/25	0/22			Not estimable
Total (95% CI)	**25**	**22**			**Not estimable**
Total events: 0 (Indomethacin), 0 (No indomethacin)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Favours indomethacin — Favours no indomethacin

Analysis 2.7. Comparison 2 Cyclo-oxygenase inhibitor versus no cyclo-oxygenase inhibitor subgroup analysis, Outcome 7 Respiratory distress syndrome.

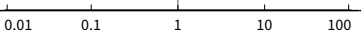
Study or subgroup	Indomethacin n/N	No indomethacin n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ehansipoor 2010	11/25	13/22		100%	0.74[0.42,1.31]
Total (95% CI)	**25**	**22**		**100%**	**0.74[0.42,1.31]**
Total events: 11 (Indomethacin), 13 (No indomethacin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.03(P=0.3)					



Favours indomethacin — Favours no indomethacin

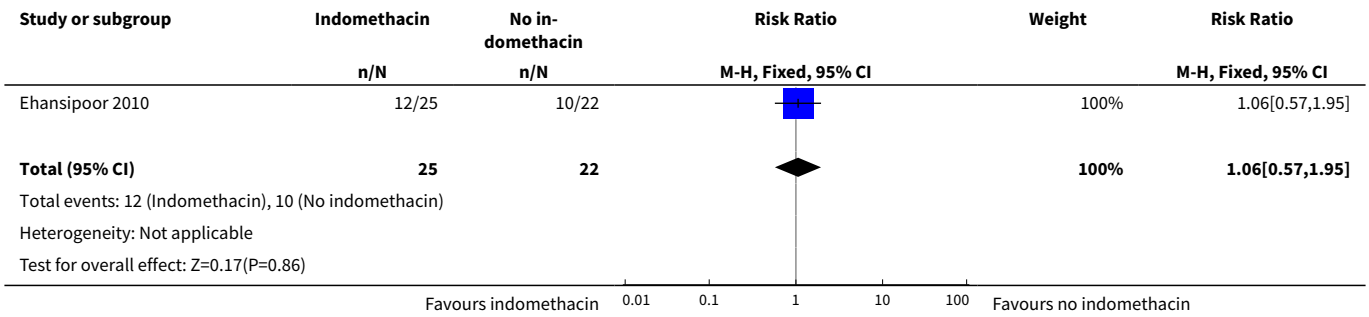
Analysis 2.8. Comparison 2 Cyclo-oxygenase inhibitor versus no cyclo-oxygenase inhibitor subgroup analysis, Outcome 8 Latency (birth within 48 hours).

Study or subgroup	Indomethacin n/N	No indomethacin n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ehansipoor 2010	2/25	2/22		100%	0.88[0.14,5.73]
Total (95% CI)	**25**	**22**		**100%**	**0.88[0.14,5.73]**
Total events: 2 (Indomethacin), 2 (No indomethacin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.13(P=0.89)					

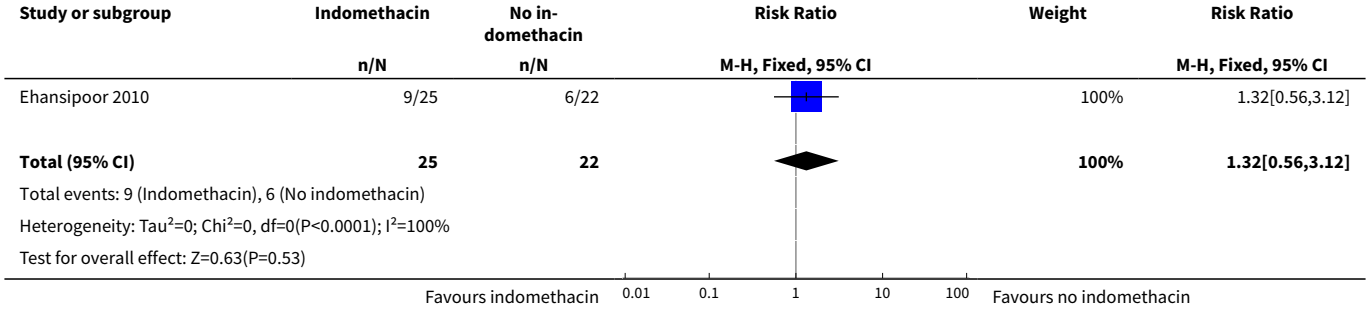


Favours indomethacin — Favours no indomethacin

Analysis 2.9. Comparison 2 Cyclo-oxygenase inhibitor versus no cyclo-oxygenase inhibitor subgroup analysis, Outcome 9 Latency (birth within 7 days).



Analysis 2.10. Comparison 2 Cyclo-oxygenase inhibitor versus no cyclo-oxygenase inhibitor subgroup analysis, Outcome 10 Chorioamnionitis.

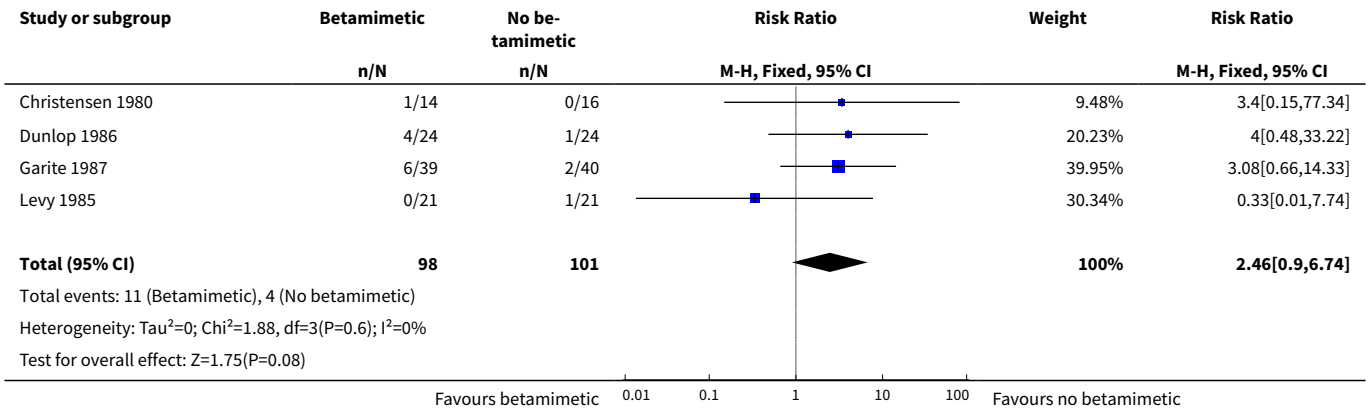


Comparison 3. Betamimetic versus no betamimetic

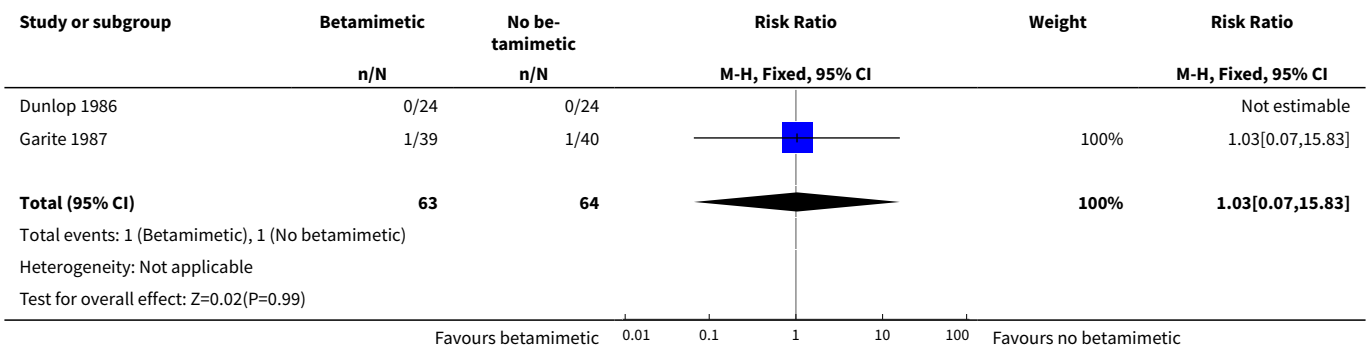
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Perinatal mortality	4	199	Risk Ratio (M-H, Fixed, 95% CI)	2.46 [0.90, 6.74]
2 Intrauterine fetal demise	2	127	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.07, 15.83]
3 Neonatal death	4	199	Risk Ratio (M-H, Fixed, 95% CI)	2.82 [0.93, 8.59]
4 Gestational age	1	42	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-1.62, 1.22]
5 Birthweight (grams)	1	42	Mean Difference (IV, Fixed, 95% CI)	212.0 [-130.72, 554.72]
6 Apgar < 7 at 5 minutes	1	79	Risk Ratio (M-H, Fixed, 95% CI)	3.59 [0.79, 16.22]
7 Neonatal sepsis	2	121	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.05, 5.43]
8 Necrotizing enterocolitis	1	48	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.01, 3.96]
9 Intraventricular haemorrhage	2	127	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.45, 2.92]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10 Respiratory distress syndrome	3	157	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.69, 1.43]
11 Latency (hours)	1	42	Mean Difference (IV, Fixed, 95% CI)	147.90 [20.17, 275.63]
12 Latency (birth within 48 hours)	3	151	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.35, 1.40]
13 Latency (birth within 7 days)	2	121	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.49, 1.35]
14 Chorioamnionitis	3	151	Risk Ratio (M-H, Fixed, 95% CI)	2.06 [1.01, 4.23]
15 Maternal endometritis	1	79	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [0.69, 4.25]

Analysis 3.1. Comparison 3 Betamimetic versus no betamimetic, Outcome 1 Perinatal mortality.

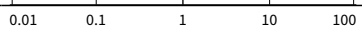


Analysis 3.2. Comparison 3 Betamimetic versus no betamimetic, Outcome 2 Intrauterine fetal demise.



Analysis 3.3. Comparison 3 Betamimetic versus no betamimetic, Outcome 3 Neonatal death.

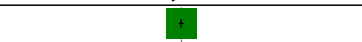
Study or subgroup	Betamimetic n/N	No betamimetic n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Christensen 1980	1/14	0/16		11.85%	3.4[0.15,77.34]
Dunlop 1986	4/24	1/24		25.28%	4[0.48,33.22]
Garite 1987	5/39	1/40		24.96%	5.13[0.63,41.93]
Levy 1985	0/21	1/21		37.92%	0.33[0.01,7.74]
Total (95% CI)	**98**	**101**		**100%**	**2.82[0.93,8.59]**
Total events: 10 (Betamimetic), 3 (No betamimetic)					
Heterogeneity: Tau²=0; Chi²=2.2, df=3(P=0.53); I²=0%					
Test for overall effect: Z=1.83(P=0.07)					



Favours betamimetic — Favours no betamimetic

Analysis 3.4. Comparison 3 Betamimetic versus no betamimetic, Outcome 4 Gestational age.

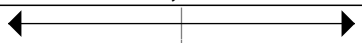
Study or subgroup	Betamimetic N	Mean(SD)	No betamimetic N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Levy 1985	21	30.7 (2.4)	21	30.9 (2.3)		100%	-0.2[-1.62,1.22]
Total ***	**21**		**21**			**100%**	**-0.2[-1.62,1.22]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.28(P=0.78)							



Favours no betamimetic — Favours betamimetic

Analysis 3.5. Comparison 3 Betamimetic versus no betamimetic, Outcome 5 Birthweight (grams).

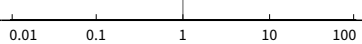
Study or subgroup	Betamimetic N	Mean(SD)	No betamimetic N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Levy 1985	21	1941 (671)	21	1729 (438)		100%	212[-130.72,554.72]
Total ***	**21**		**21**			**100%**	**212[-130.72,554.72]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.21(P=0.23)							



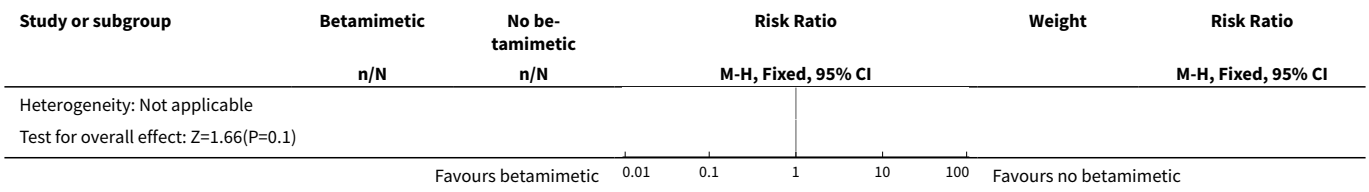
Favours no betamimetic — Favours betamimetic

Analysis 3.6. Comparison 3 Betamimetic versus no betamimetic, Outcome 6 Apgar < 7 at 5 minutes.

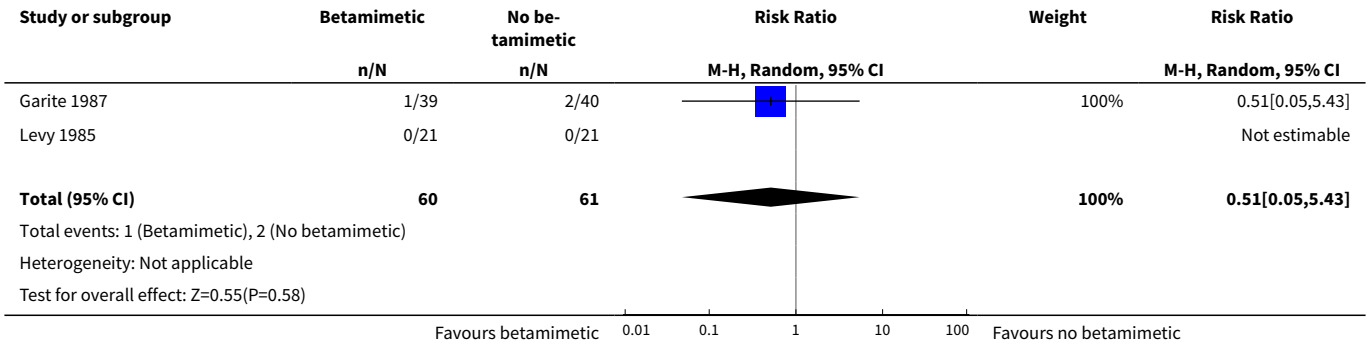
Study or subgroup	Betamimetic n/N	No betamimetic n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Garite 1987	7/39	2/40		100%	3.59[0.79,16.22]
Total (95% CI)	**39**	**40**		**100%**	**3.59[0.79,16.22]**
Total events: 7 (Betamimetic), 2 (No betamimetic)					



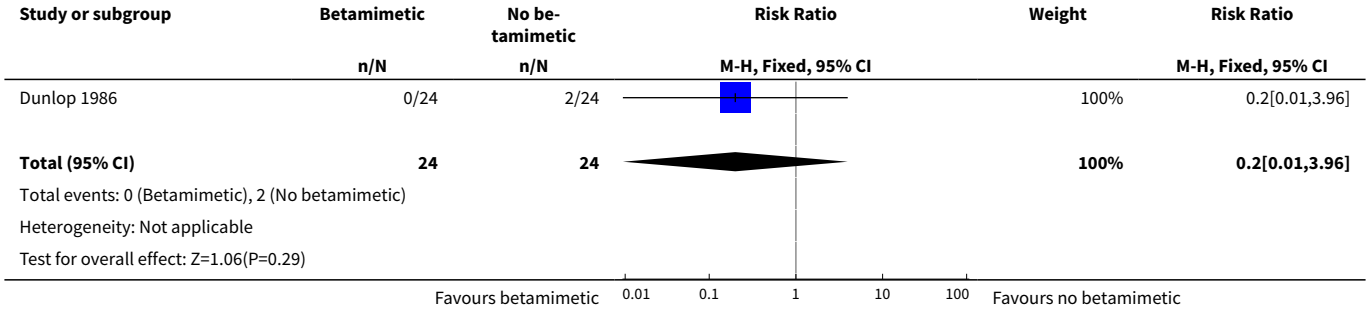
Favours betamimetic — Favours no betamimetic



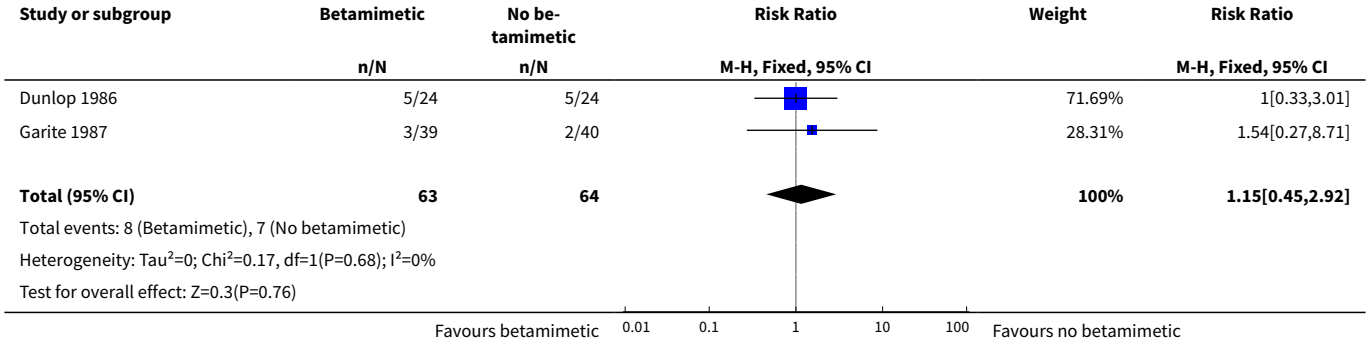
Analysis 3.7. Comparison 3 Betamimetic versus no betamimetic, Outcome 7 Neonatal sepsis.



Analysis 3.8. Comparison 3 Betamimetic versus no betamimetic, Outcome 8 Necrotizing enterocolitis.

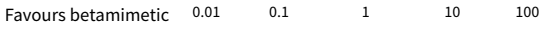


Analysis 3.9. Comparison 3 Betamimetic versus no betamimetic, Outcome 9 Intraventricular haemorrhage.



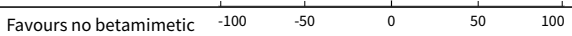
Analysis 3.10. Comparison 3 Betamimetic versus no betamimetic, Outcome 10 Respiratory distress syndrome.

Study or subgroup	Betamimetic n/N	No betamimetic n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Christensen 1980	2/14	1/16		3.05%	2.29[0.23,22.59]
Dunlop 1986	8/24	7/24		22.84%	1.14[0.49,2.65]
Garite 1987	20/39	23/40		74.11%	0.89[0.59,1.34]
Total (95% CI)	**77**	**80**		**100%**	**0.99[0.69,1.43]**
Total events: 30 (Betamimetic), 31 (No betamimetic)					
Heterogeneity: Tau^2=0; Chi^2=0.88, df=2(P=0.64); I^2=0%					
Test for overall effect: Z=0.04(P=0.96)					



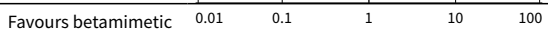
Analysis 3.11. Comparison 3 Betamimetic versus no betamimetic, Outcome 11 Latency (hours).

Study or subgroup	Betamimetic N	Mean(SD)	No betamimetic N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Levy 1985	21	236.1 (292.5)	21	88.2 (60.3)		100%	147.9[20.17,275.63]
Total ***	**21**		**21**			**100%**	**147.9[20.17,275.63]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.27(P=0.02)							

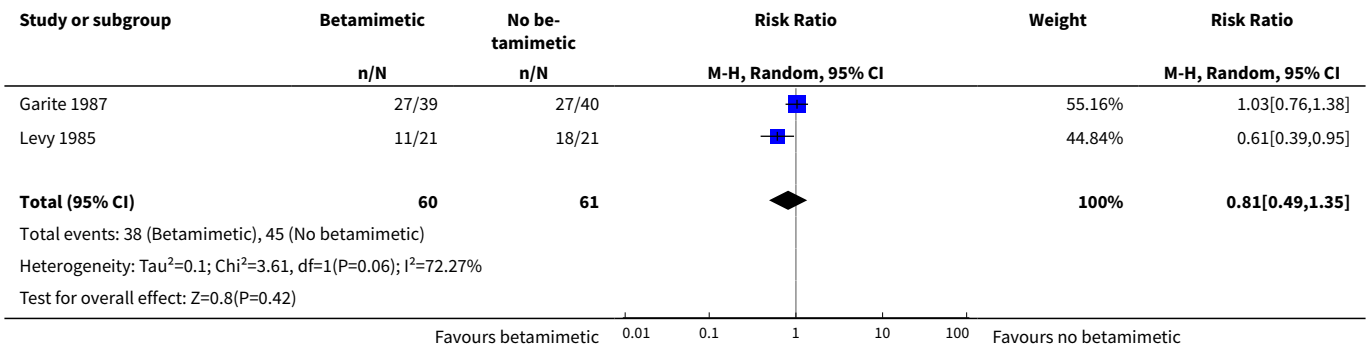


Analysis 3.12. Comparison 3 Betamimetic versus no betamimetic, Outcome 12 Latency (birth within 48 hours).

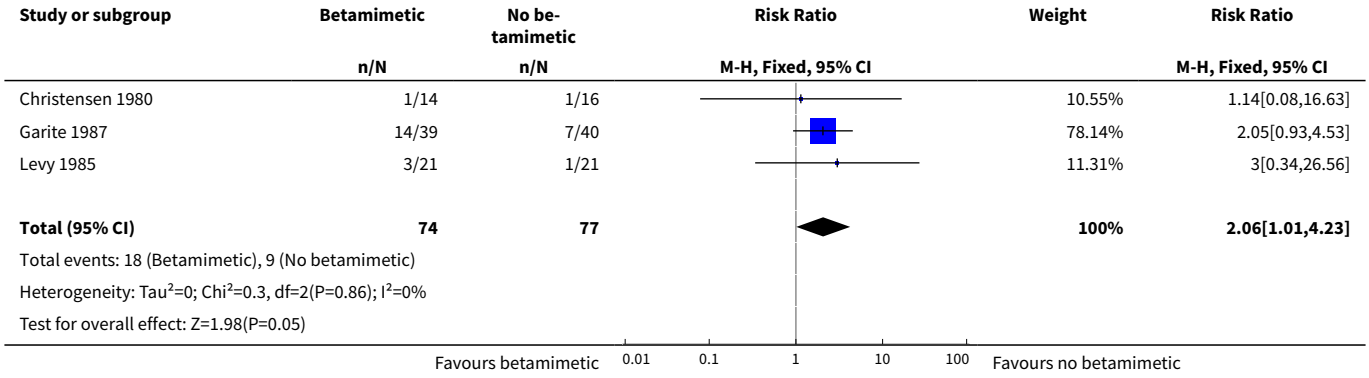
Study or subgroup	Betamimetic n/N	No betamimetic n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Christensen 1980	7/14	9/16		43.6%	0.89[0.45,1.75]
Garite 1987	9/39	10/40		38.17%	0.92[0.42,2.02]
Levy 1985	2/21	9/21		18.23%	0.22[0.05,0.91]
Total (95% CI)	**74**	**77**		**100%**	**0.7[0.35,1.4]**
Total events: 18 (Betamimetic), 28 (No betamimetic)					
Heterogeneity: Tau^2=0.16; Chi^2=3.6, df=2(P=0.17); I^2=44.4%					
Test for overall effect: Z=1.01(P=0.31)					



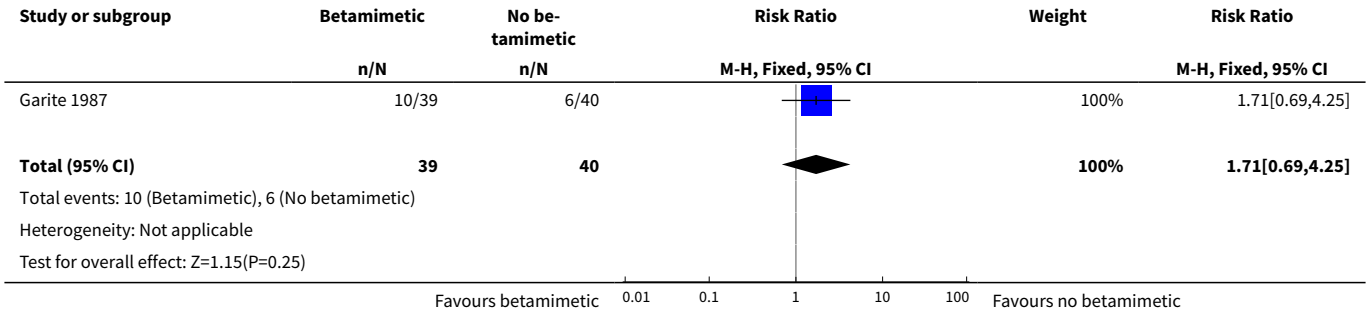
Analysis 3.13. Comparison 3 Betamimetic versus no betamimetic, Outcome 13 Latency (birth within 7 days).



Analysis 3.14. Comparison 3 Betamimetic versus no betamimetic, Outcome 14 Chorioamnionitis.



Analysis 3.15. Comparison 3 Betamimetic versus no betamimetic, Outcome 15 Maternal endometritis.

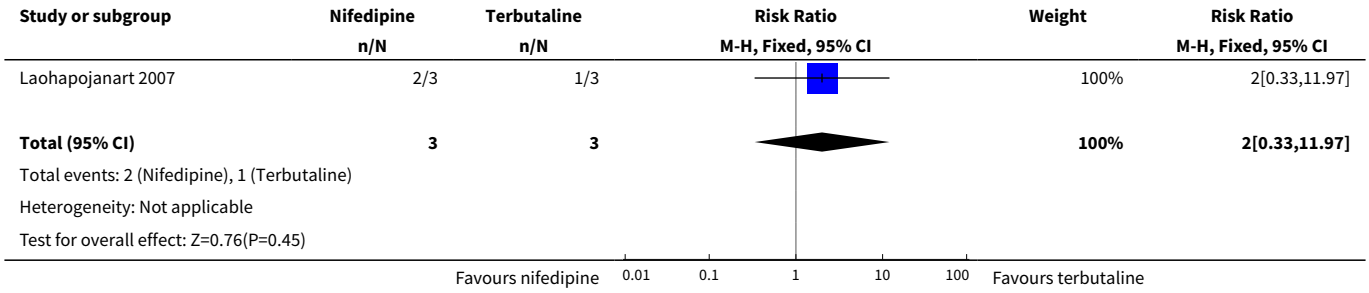


Comparison 4. Nifedipine versus Terbutaline

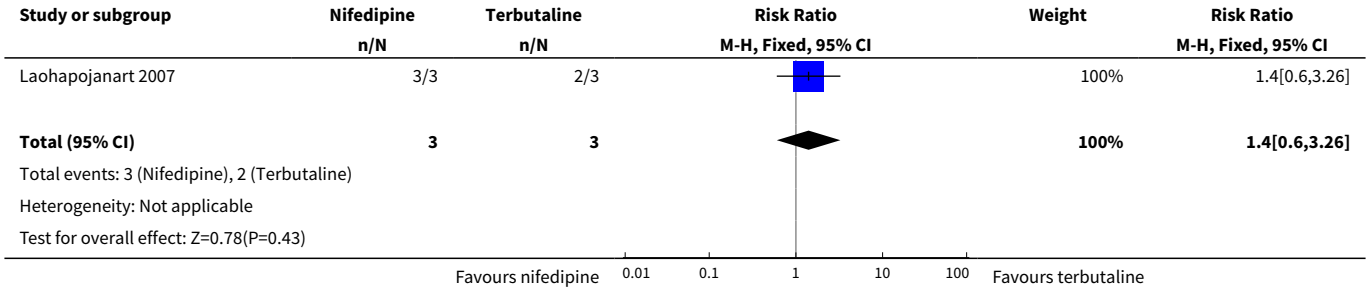
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Respiratory distress syndrome	1	6	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.33, 11.97]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Latency (birth within 48 hours)	1	6	Risk Ratio (M-H, Fixed, 95% CI)	1.4 [0.60, 3.26]

Analysis 4.1. Comparison 4 Nifedipine versus Terbutaline, Outcome 1 Respiratory distress syndrome.



Analysis 4.2. Comparison 4 Nifedipine versus Terbutaline, Outcome 2 Latency (birth within 48 hours).



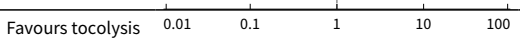
Comparison 5. Prophylactic tocolysis (PPROM without contractions)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Perinatal mortality	3	137	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.42, 5.59]
2 Intrauterine fetal demise	2	95	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Neonatal death	3	137	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.42, 5.59]
4 Gestational age	1	42	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-1.62, 1.22]
5 Birthweight (grams)	1	42	Mean Difference (IV, Fixed, 95% CI)	212.0 [-130.72, 554.72]
6 Neonatal sepsis	2	89	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.23, 1.22]
7 Necrotizing enterocolitis	2	95	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.11, 2.33]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Intraventricular haemorrhage	2	95	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.33, 3.01]
9 Respiratory distress syndrome	2	95	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.55, 1.41]
10 Latency (hours)	1	42	Mean Difference (IV, Fixed, 95% CI)	147.90 [20.17, 275.63]
11 Latency (birth within 48 hours)	2	89	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.12, 1.02]
12 Latency (birth within 7 days)	2	89	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.45, 1.32]
13 Chorioamnionitis	2	89	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [0.70, 3.44]

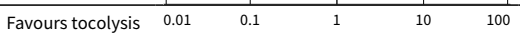
Analysis 5.1. Comparison 5 Prophylactic tocolysis (PPROM without contractions), Outcome 1 Perinatal mortality.

Study or subgroup	Tocolysis n/N	No tocolysis n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dunlop 1986	4/24	1/24		28.06%	4[0.48,33.22]
Ehansipoor 2010	1/25	1/22		29.85%	0.88[0.06,13.25]
Levy 1985	0/21	1/21		42.09%	0.33[0.01,7.74]
Total (95% CI)	**70**	**67**		**100%**	**1.53[0.42,5.59]**
Total events: 5 (Tocolysis), 3 (No tocolysis)					
Heterogeneity: Tau^2=0; Chi^2=1.85, df=2(P=0.4); I^2=0%					
Test for overall effect: Z=0.64(P=0.52)					

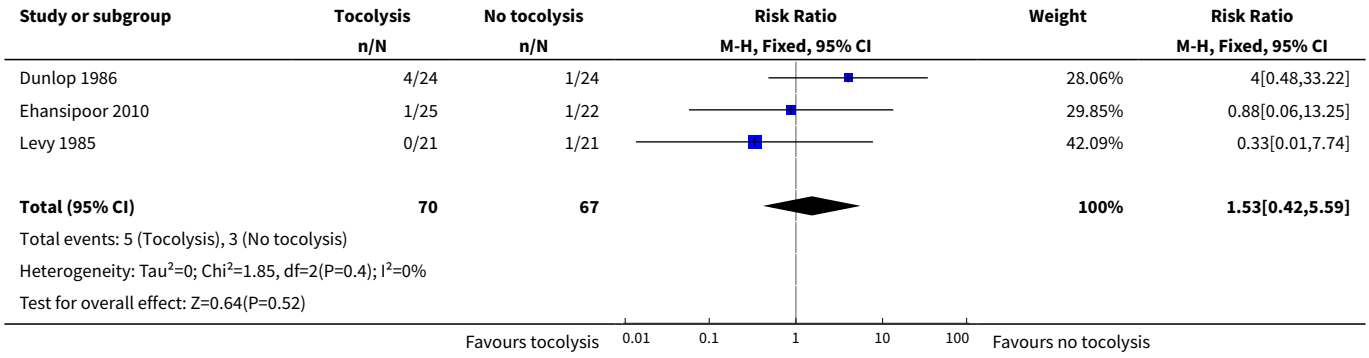


Analysis 5.2. Comparison 5 Prophylactic tocolysis (PPROM without contractions), Outcome 2 Intrauterine fetal demise.

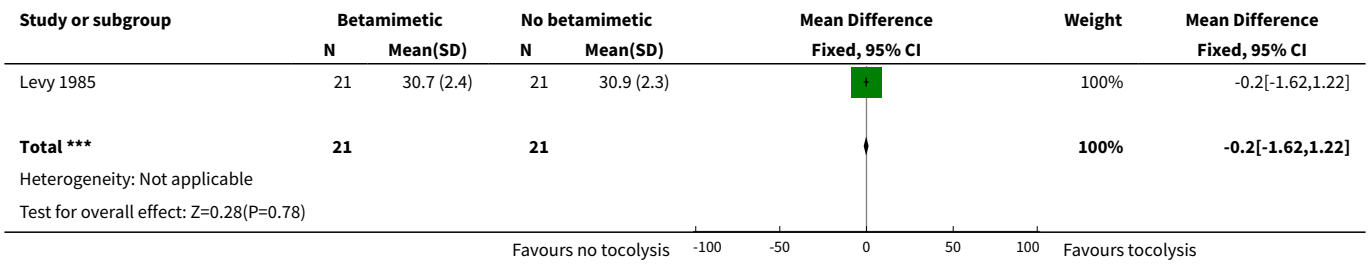
Study or subgroup	Tocolysis n/N	No tocolysis n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dunlop 1986	0/24	0/24			Not estimable
Ehansipoor 2010	0/25	0/22			Not estimable
Total (95% CI)	**49**	**46**			**Not estimable**
Total events: 0 (Tocolysis), 0 (No tocolysis)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



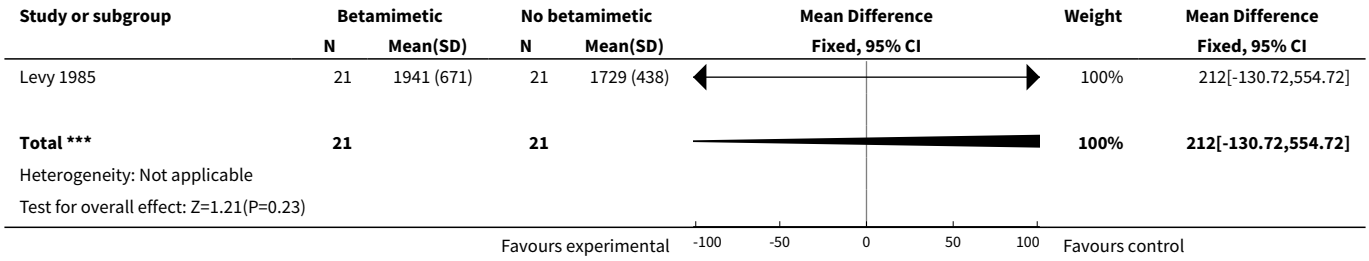
Analysis 5.3. Comparison 5 Prophylactic tocolysis (PPROM without contractions), Outcome 3 Neonatal death.



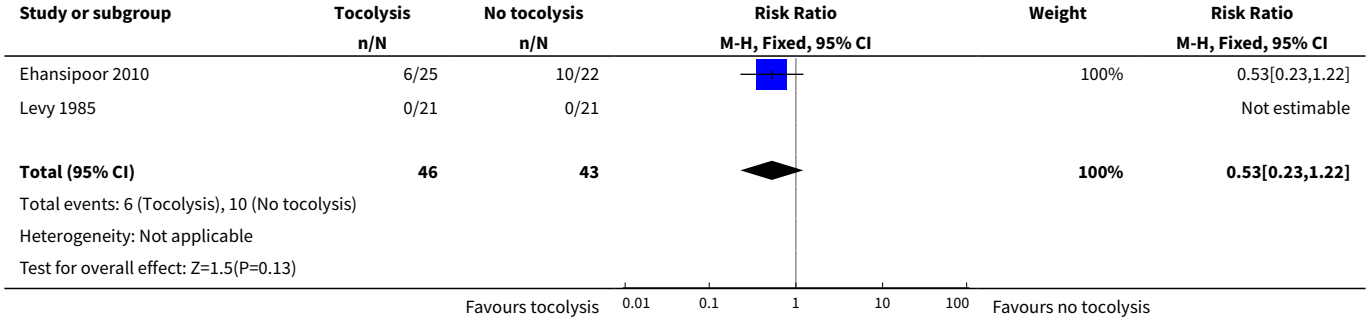
Analysis 5.4. Comparison 5 Prophylactic tocolysis (PPROM without contractions), Outcome 4 Gestational age.



Analysis 5.5. Comparison 5 Prophylactic tocolysis (PPROM without contractions), Outcome 5 Birthweight (grams).



Analysis 5.6. Comparison 5 Prophylactic tocolysis (PPROM without contractions), Outcome 6 Neonatal sepsis.

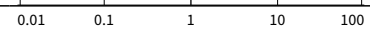


Analysis 5.7. Comparison 5 Prophylactic tocolysis (PPROM without contractions), Outcome 7 Necrotizing enterocolitis.

Study or subgroup	Tocolysis n/N	No tocolysis n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dunlop 1986	0/24	2/24		54.02%	0.2[0.01,3.96]
Ehansipoor 2010	2/25	2/22		45.98%	0.88[0.14,5.73]
Total (95% CI)	**49**	**46**		**100%**	**0.51[0.11,2.33]**
Total events: 2 (Tocolysis), 4 (No tocolysis)					
Heterogeneity: Tau^2=0; Chi^2=0.7, df=1(P=0.4); I^2=0%					
Test for overall effect: Z=0.87(P=0.39)					

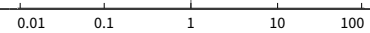
Analysis 5.8. Comparison 5 Prophylactic tocolysis (PPROM without contractions), Outcome 8 Intraventricular haemorrhage.

Study or subgroup	Tocolysis n/N	No tocolysis n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dunlop 1986	5/24	5/24		100%	1[0.33,3.01]
Ehansipoor 2010	0/25	0/22			Not estimable
Total (95% CI)	**49**	**46**		**100%**	**1[0.33,3.01]**
Total events: 5 (Tocolysis), 5 (No tocolysis)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



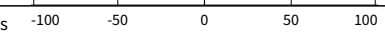
Analysis 5.9. Comparison 5 Prophylactic tocolysis (PPROM without contractions), Outcome 9 Respiratory distress syndrome.

Study or subgroup	Tocolysis n/N	No tocolysis n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dunlop 1986	8/24	7/24		33.61%	1.14[0.49,2.65]
Ehansipoor 2010	11/25	13/22		66.39%	0.74[0.42,1.31]
Total (95% CI)	**49**	**46**		**100%**	**0.88[0.55,1.41]**
Total events: 19 (Tocolysis), 20 (No tocolysis)					
Heterogeneity: Tau^2=0; Chi^2=0.71, df=1(P=0.4); I^2=0%					
Test for overall effect: Z=0.54(P=0.59)					



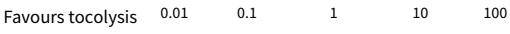
Analysis 5.10. Comparison 5 Prophylactic tocolysis (PPROM without contractions), Outcome 10 Latency (hours).

Study or subgroup	Betamimetic N	Betamimetic Mean(SD)	No betamimetic N	No betamimetic Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Levy 1985	21	236.1 (292.5)	21	88.2 (60.3)		100%	147.9[20.17,275.63]
Total ***	**21**		**21**			**100%**	**147.9[20.17,275.63]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.27(P=0.02)							



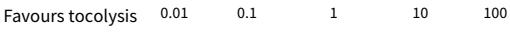
Analysis 5.11. Comparison 5 Prophylactic tocolysis (PPROM without contractions), Outcome 11 Latency (birth within 48 hours).

Study or subgroup	Tocolysis n/N	No tocolysis n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ehansipoor 2010	2/25	2/22		19.12%	0.88[0.14,5.73]
Levy 1985	2/21	9/21		80.88%	0.22[0.05,0.91]
Total (95% CI)	**46**	**43**		**100%**	**0.35[0.12,1.02]**
Total events: 4 (Tocolysis), 11 (No tocolysis)					
Heterogeneity: Tau^2=0; Chi^2=1.33, df=1(P=0.25); I^2=24.87%					
Test for overall effect: Z=1.93(P=0.05)					



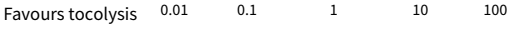
Analysis 5.12. Comparison 5 Prophylactic tocolysis (PPROM without contractions), Outcome 12 Latency (birth within 7 days).

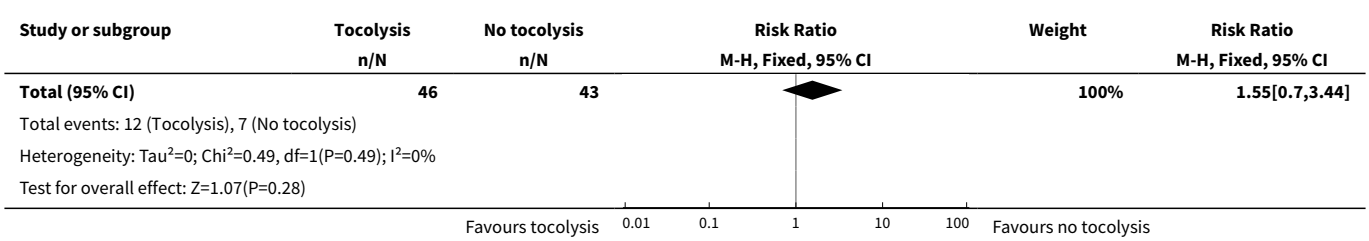
Study or subgroup	Tocolysis n/N	No tocolysis n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Ehansipoor 2010	12/25	10/22		42.5%	1.06[0.57,1.95]
Levy 1985	11/21	18/21		57.5%	0.61[0.39,0.95]
Total (95% CI)	**46**	**43**		**100%**	**0.77[0.45,1.32]**
Total events: 23 (Tocolysis), 28 (No tocolysis)					
Heterogeneity: Tau^2=0.08; Chi^2=2.09, df=1(P=0.15); I^2=52.04%					
Test for overall effect: Z=0.94(P=0.35)					



Analysis 5.13. Comparison 5 Prophylactic tocolysis (PPROM without contractions), Outcome 13 Chorioamnionitis.

Study or subgroup	Tocolysis n/N	No tocolysis n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ehansipoor 2010	9/25	6/22		86.46%	1.32[0.56,3.12]
Levy 1985	3/21	1/21		13.54%	3[0.34,26.56]

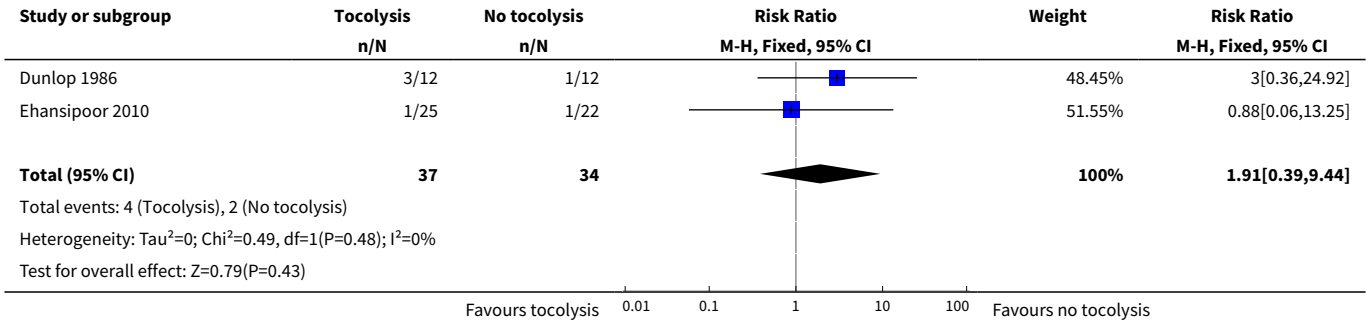




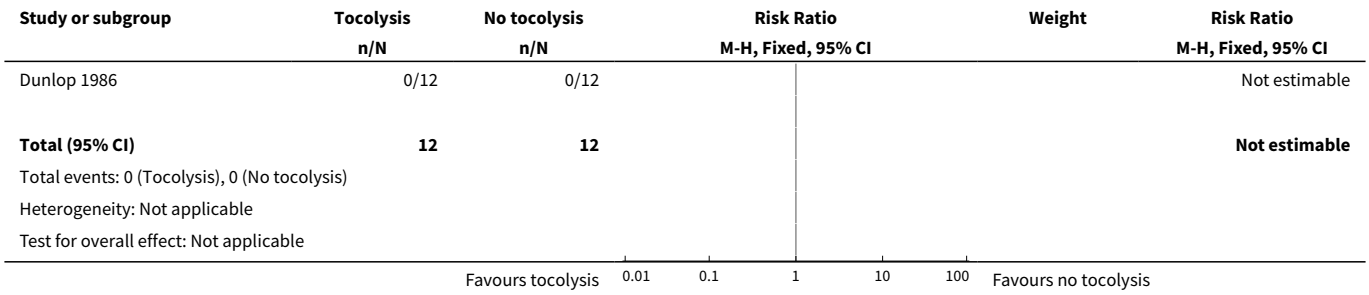
Comparison 6. Antibiotic subgroup analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Perinatal mortality	2	71	Risk Ratio (M-H, Fixed, 95% CI)	1.91 [0.39, 9.44]
2 Intrauterine fetal demise	1	24	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Neonatal death	2	71	Risk Ratio (M-H, Fixed, 95% CI)	1.91 [0.39, 9.44]
4 Neonatal sepsis	1	47	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.23, 1.22]
5 Necrotizing enterocolitis	2	71	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.14, 3.15]
6 Intraventricular haemorrhage	2	71	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.21, 19.23]
7 Respiratory distress syndrome	2	71	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.48, 1.33]
8 Latency (birth within 48 hours)	1	47	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.14, 5.73]
9 Latency (birth within 7 days)	1	47	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.57, 1.95]
10 Chorioamnionitis	1	47	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.56, 3.12]

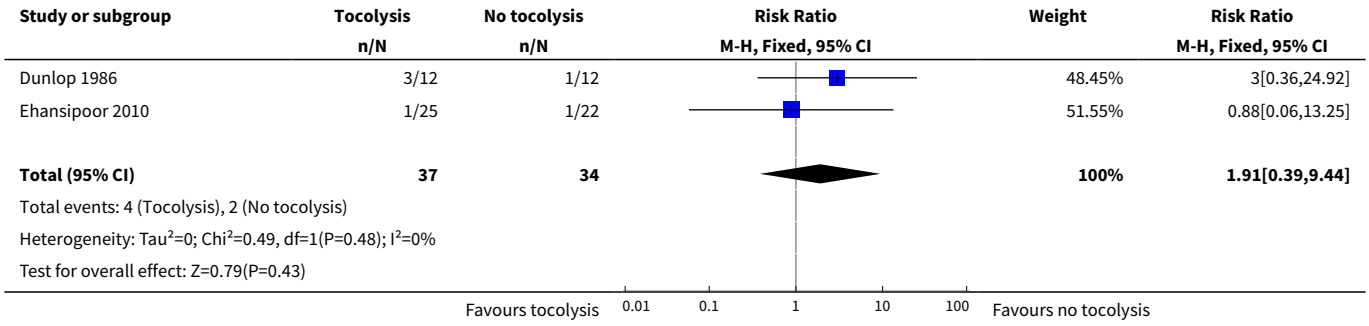
Analysis 6.1. Comparison 6 Antibiotic subgroup analysis, Outcome 1 Perinatal mortality.



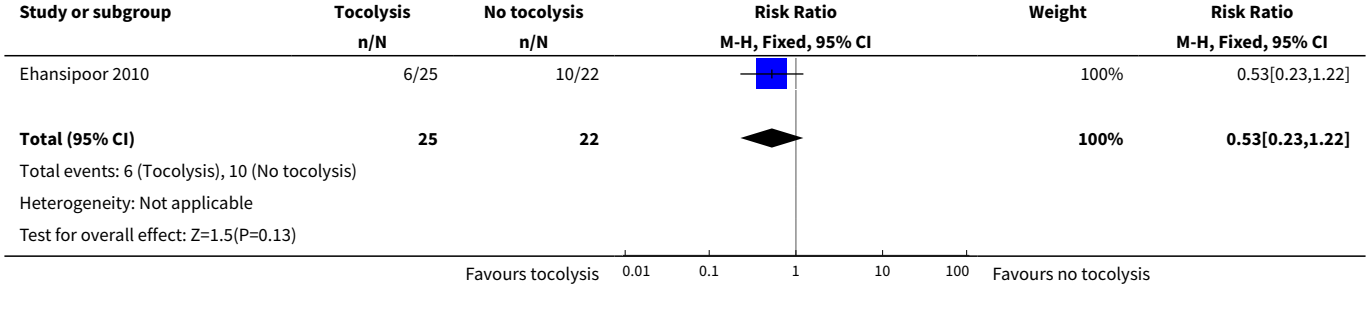
Analysis 6.2. Comparison 6 Antibiotic subgroup analysis, Outcome 2 Intrauterine fetal demise.



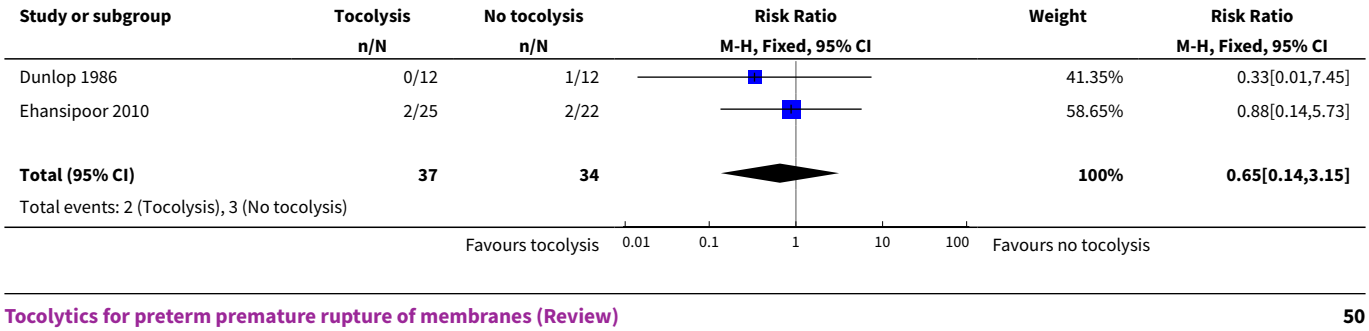
Analysis 6.3. Comparison 6 Antibiotic subgroup analysis, Outcome 3 Neonatal death.

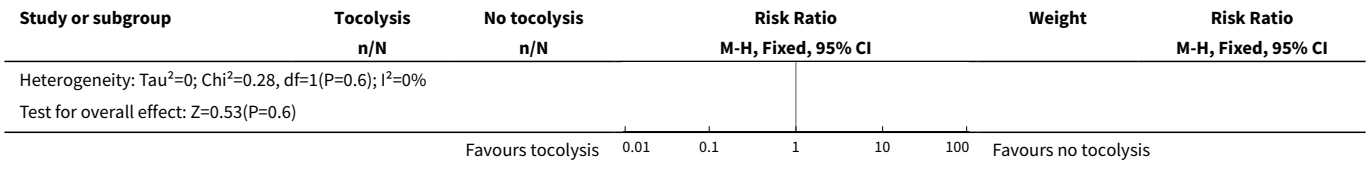


Analysis 6.4. Comparison 6 Antibiotic subgroup analysis, Outcome 4 Neonatal sepsis.

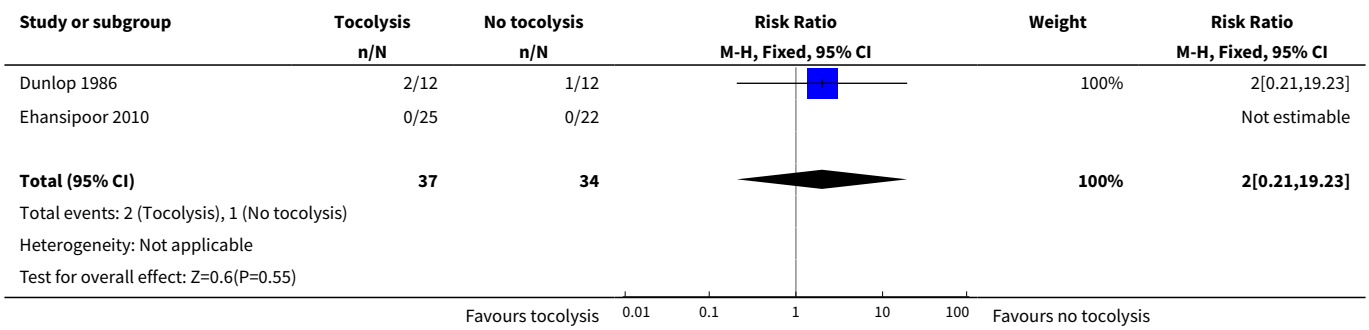


Analysis 6.5. Comparison 6 Antibiotic subgroup analysis, Outcome 5 Necrotizing enterocolitis.

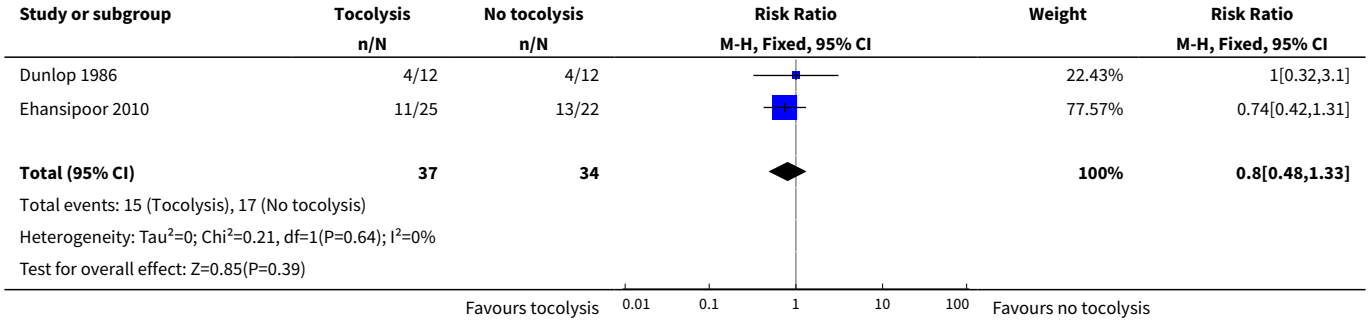




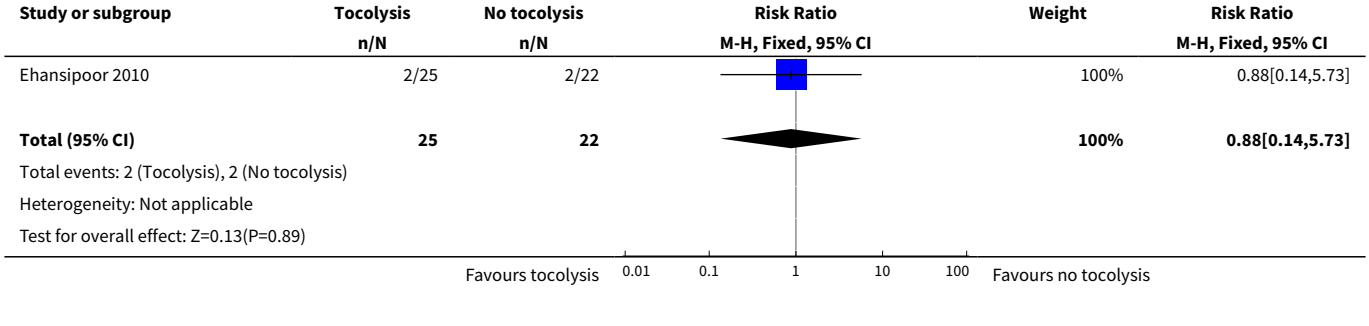
Analysis 6.6. Comparison 6 Antibiotic subgroup analysis, Outcome 6 Intraventricular haemorrhage.



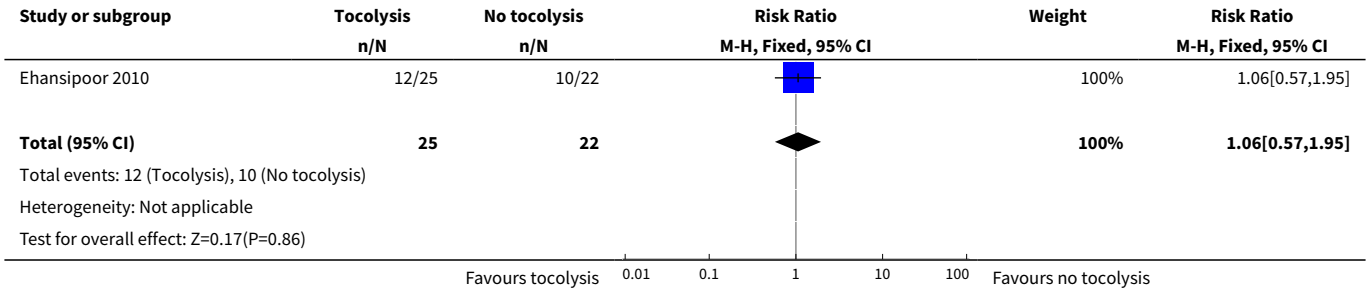
Analysis 6.7. Comparison 6 Antibiotic subgroup analysis, Outcome 7 Respiratory distress syndrome.



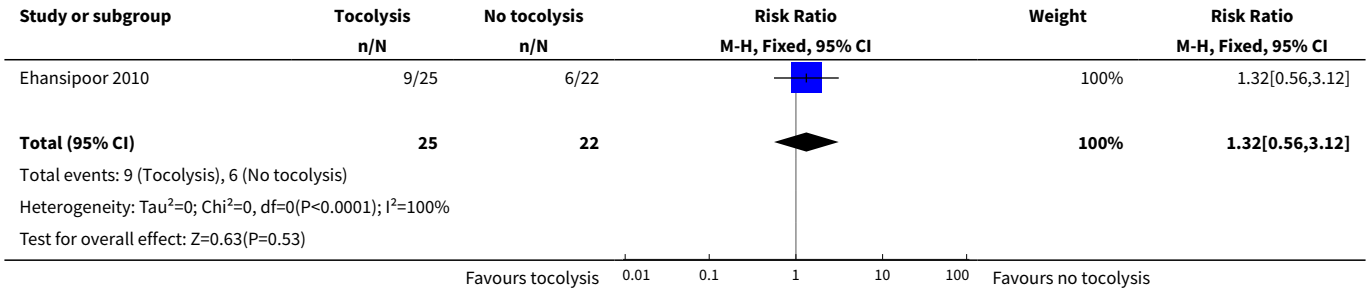
Analysis 6.8. Comparison 6 Antibiotic subgroup analysis, Outcome 8 Latency (birth within 48 hours).



Analysis 6.9. Comparison 6 Antibiotic subgroup analysis, Outcome 9 Latency (birth within 7 days).



Analysis 6.10. Comparison 6 Antibiotic subgroup analysis, Outcome 10 Chorioamnionitis.



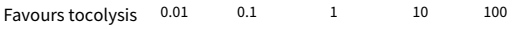
Comparison 7. Steroid subgroup analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Perinatal mortality	2	95	Risk Ratio (M-H, Fixed, 95% CI)	2.39 [0.50, 11.55]
2 Intrauterine fetal demise	2	95	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Neonatal death	2	95	Risk Ratio (M-H, Fixed, 95% CI)	2.39 [0.50, 11.55]
4 Neonatal sepsis	1	47	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.23, 1.22]
5 Necrotizing enterocolitis	2	95	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.11, 2.33]
6 Intraventricular haemorrhage	2	95	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.33, 3.01]
7 Respiratory distress syndrome	2	95	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.55, 1.41]
8 Latency (birth within 48 hours)	1	47	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.14, 5.73]
9 Latency (birth within 7 days)	1	47	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.57, 1.95]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10 Chorioamnionitis	1	47	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.56, 3.12]

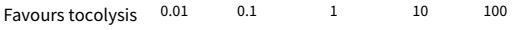
Analysis 7.1. Comparison 7 Steroid subgroup analysis, Outcome 1 Perinatal mortality.

Study or subgroup	Tocolysis n/N	No tocolysis n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dunlop 1986	4/24	1/24		48.45%	4[0.48,33.22]
Ehansipoor 2010	1/25	1/22		51.55%	0.88[0.06,13.25]
Total (95% CI)	**49**	**46**		**100%**	**2.39[0.5,11.55]**
Total events: 5 (Tocolysis), 2 (No tocolysis)					
Heterogeneity: Tau^2=0; Chi^2=0.75, df=1(P=0.39); I^2=0%					
Test for overall effect: Z=1.09(P=0.28)					



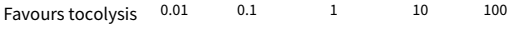
Analysis 7.2. Comparison 7 Steroid subgroup analysis, Outcome 2 Intrauterine fetal demise.

Study or subgroup	Tocolysis n/N	No tocolysis n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dunlop 1986	0/24	0/24			Not estimable
Ehansipoor 2010	0/25	0/22			Not estimable
Total (95% CI)	**49**	**46**			**Not estimable**
Total events: 0 (Tocolysis), 0 (No tocolysis)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



Analysis 7.3. Comparison 7 Steroid subgroup analysis, Outcome 3 Neonatal death.

Study or subgroup	Tocolysis n/N	No tocolysis n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dunlop 1986	4/24	1/24		48.45%	4[0.48,33.22]
Ehansipoor 2010	1/25	1/22		51.55%	0.88[0.06,13.25]
Total (95% CI)	**49**	**46**		**100%**	**2.39[0.5,11.55]**
Total events: 5 (Tocolysis), 2 (No tocolysis)					
Heterogeneity: Tau^2=0; Chi^2=0.75, df=1(P=0.39); I^2=0%					
Test for overall effect: Z=1.09(P=0.28)					

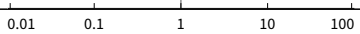


Analysis 7.4. Comparison 7 Steroid subgroup analysis, Outcome 4 Neonatal sepsis.

Study or subgroup	Tocolysis n/N	No tocolysis n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ehansipoor 2010	6/25	10/22		100%	0.53[0.23,1.22]
Total (95% CI)	**25**	**22**		**100%**	**0.53[0.23,1.22]**
Total events: 6 (Tocolysis), 10 (No tocolysis)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.5(P=0.13)					

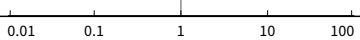
Analysis 7.5. Comparison 7 Steroid subgroup analysis, Outcome 5 Necrotizing enterocolitis.

Study or subgroup	Tocolysis n/N	No tocolysis n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dunlop 1986	0/24	2/24		54.02%	0.2[0.01,3.96]
Ehansipoor 2010	2/25	2/22		45.98%	0.88[0.14,5.73]
Total (95% CI)	**49**	**46**		**100%**	**0.51[0.11,2.33]**
Total events: 2 (Tocolysis), 4 (No tocolysis)					
Heterogeneity: Tau^2=0; Chi^2=0.7, df=1(P=0.4); I^2=0%					
Test for overall effect: Z=0.87(P=0.39)					



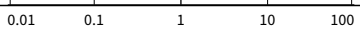
Analysis 7.6. Comparison 7 Steroid subgroup analysis, Outcome 6 Intraventricular haemorrhage.

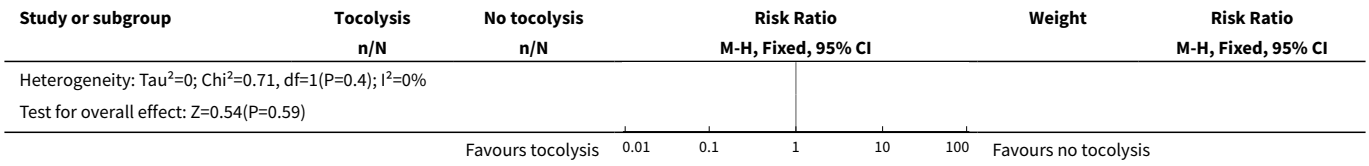
Study or subgroup	Tocolysis n/N	No tocolysis n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dunlop 1986	5/24	5/24		100%	1[0.33,3.01]
Ehansipoor 2010	0/25	0/22			Not estimable
Total (95% CI)	**49**	**46**		**100%**	**1[0.33,3.01]**
Total events: 5 (Tocolysis), 5 (No tocolysis)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



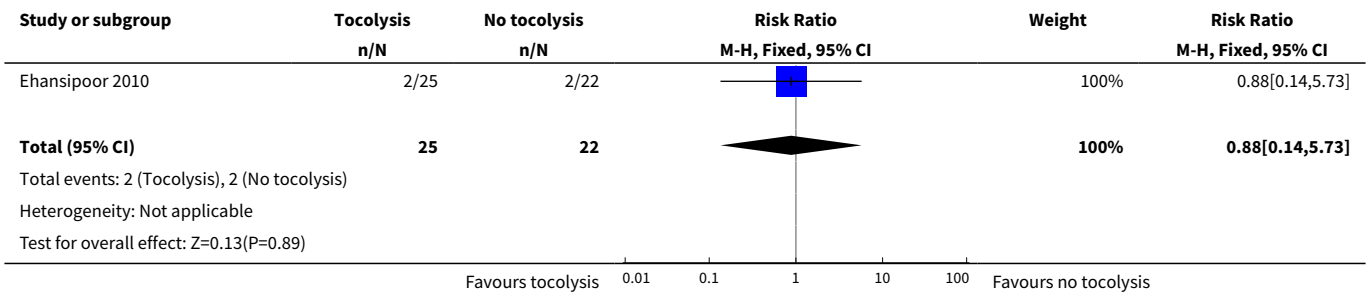
Analysis 7.7. Comparison 7 Steroid subgroup analysis, Outcome 7 Respiratory distress syndrome.

Study or subgroup	Tocolysis n/N	No tocolysis n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dunlop 1986	8/24	7/24		33.61%	1.14[0.49,2.65]
Ehansipoor 2010	11/25	13/22		66.39%	0.74[0.42,1.31]
Total (95% CI)	**49**	**46**		**100%**	**0.88[0.55,1.41]**
Total events: 19 (Tocolysis), 20 (No tocolysis)					

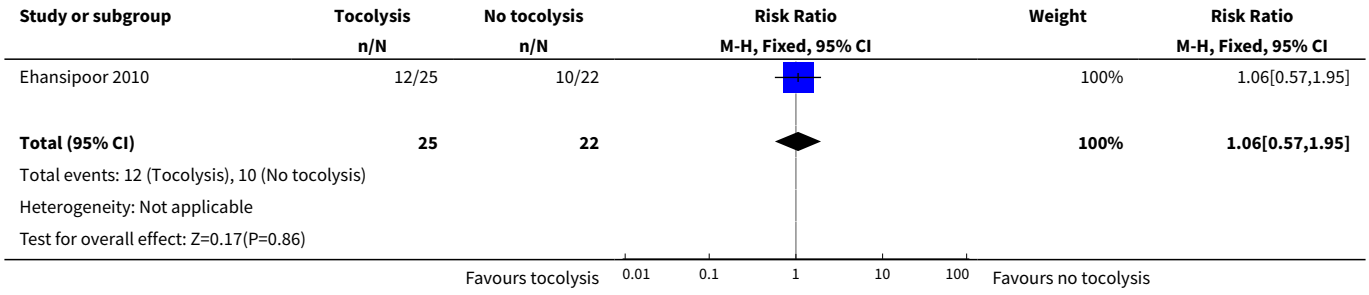




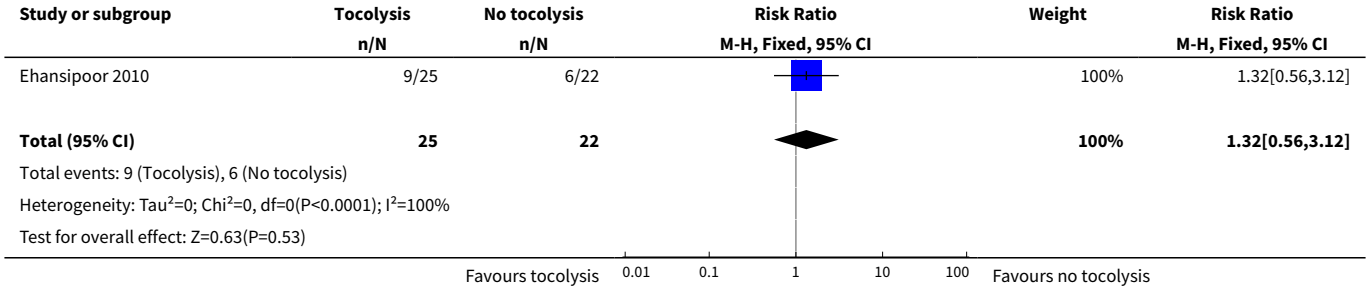
Analysis 7.8. Comparison 7 Steroid subgroup analysis, Outcome 8 Latency (birth within 48 hours).



Analysis 7.9. Comparison 7 Steroid subgroup analysis, Outcome 9 Latency (birth within 7 days).



Analysis 7.10. Comparison 7 Steroid subgroup analysis, Outcome 10 Chorioamnionitis.

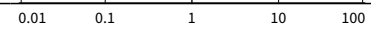


Comparison 8. Antibiotic and steroid subgroup analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Perinatal mortality	2	71	Risk Ratio (M-H, Fixed, 95% CI)	1.91 [0.39, 9.44]
2 Intrauterine fetal demise	1	24	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Neonatal death	2	71	Risk Ratio (M-H, Fixed, 95% CI)	1.91 [0.39, 9.44]
4 Neonatal sepsis	1	47	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.23, 1.22]
5 Necrotizing enterocolitis	2	71	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.14, 3.15]
6 Intraventricular haemorrhage	2	71	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.21, 19.23]
7 Respiratory distress syndrome	2	71	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.48, 1.33]
8 Latency (birth within 48 hours)	1	47	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.14, 5.73]
9 Latency (birth within 7 days)	1	47	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.57, 1.95]
10 Chorioamnionitis	1	47	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.56, 3.12]

Analysis 8.1. Comparison 8 Antibiotic and steroid subgroup analysis, Outcome 1 Perinatal mortality.

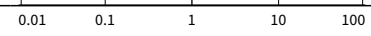
Study or subgroup	Tocolysis n/N	No tocolysis n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dunlop 1986	3/12	1/12		48.45%	3[0.36,24.92]
Ehansipoor 2010	1/25	1/22		51.55%	0.88[0.06,13.25]
Total (95% CI)	**37**	**34**		**100%**	**1.91[0.39,9.44]**
Total events: 4 (Tocolysis), 2 (No tocolysis)					
Heterogeneity: Tau^2=0; Chi^2=0.49, df=1(P=0.48); I^2=0%					
Test for overall effect: Z=0.79(P=0.43)					



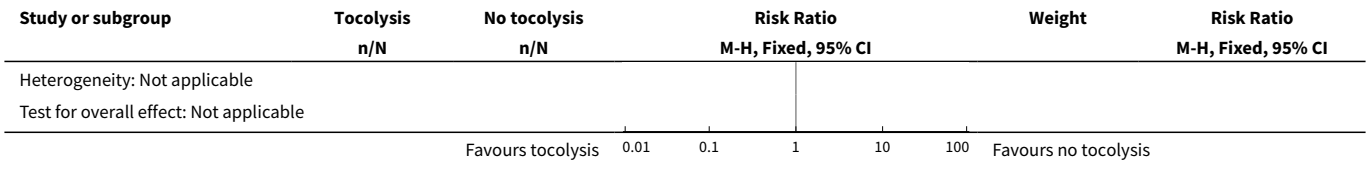
Favours tocolysis — Favours no tocolysis

Analysis 8.2. Comparison 8 Antibiotic and steroid subgroup analysis, Outcome 2 Intrauterine fetal demise.

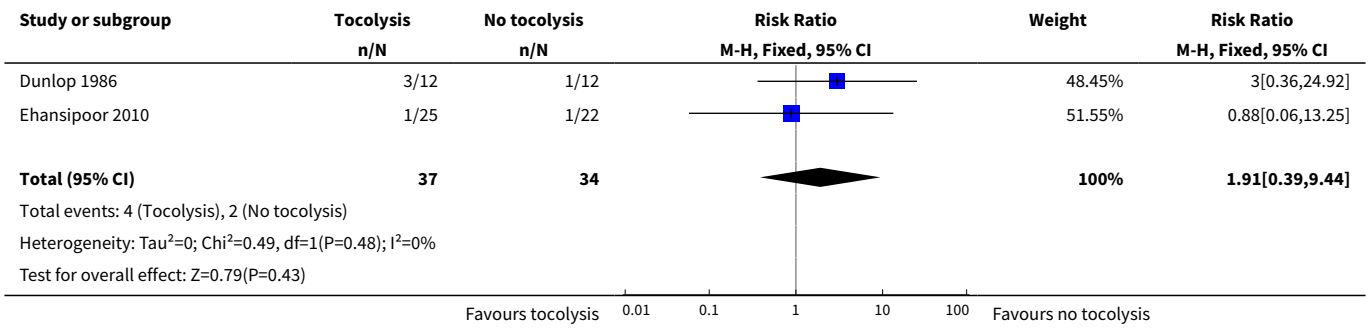
Study or subgroup	Tocolysis n/N	No tocolysis n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dunlop 1986	0/12	0/12			Not estimable
Total (95% CI)	**12**	**12**			**Not estimable**
Total events: 0 (Tocolysis), 0 (No tocolysis)					



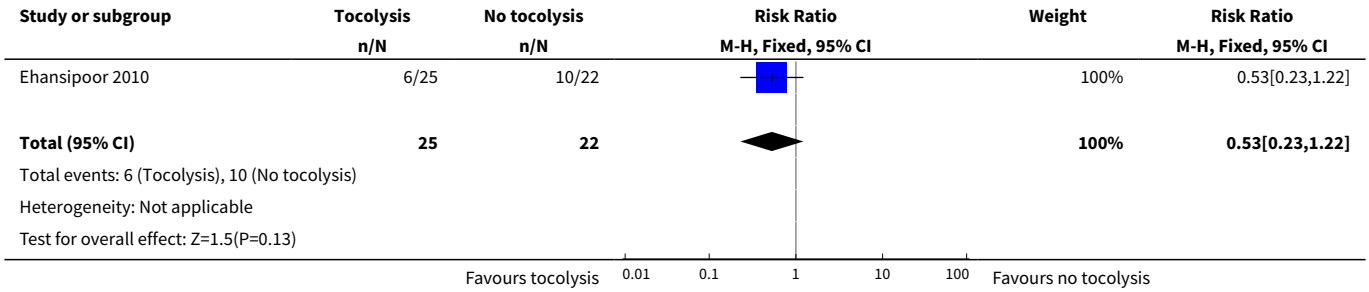
Favours tocolysis — Favours no tocolysis



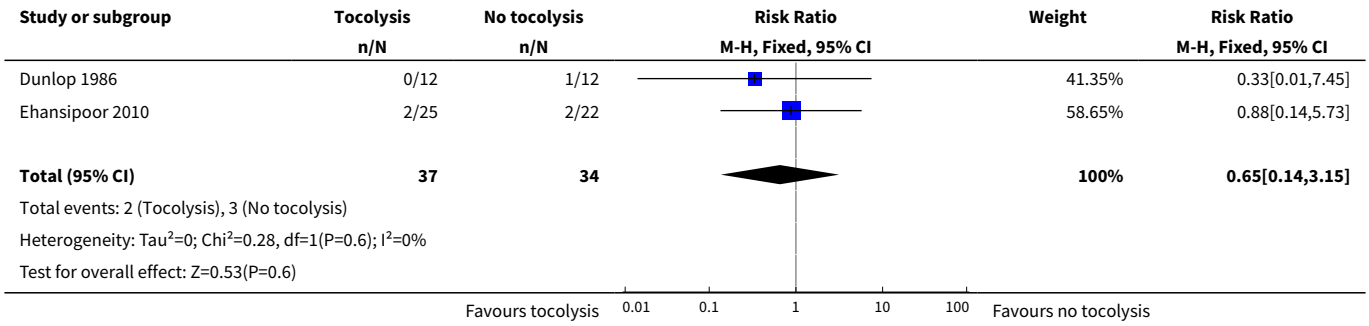
Analysis 8.3. Comparison 8 Antibiotic and steroid subgroup analysis, Outcome 3 Neonatal death.



Analysis 8.4. Comparison 8 Antibiotic and steroid subgroup analysis, Outcome 4 Neonatal sepsis.



Analysis 8.5. Comparison 8 Antibiotic and steroid subgroup analysis, Outcome 5 Necrotizing enterocolitis.



Analysis 8.6. Comparison 8 Antibiotic and steroid subgroup analysis, Outcome 6 Intraventricular haemorrhage.

Study or subgroup	Tocolysis n/N	No tocolysis n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dunlop 1986	2/12	1/12		100%	2[0.21,19.23]
Ehansipoor 2010	0/25	0/22			Not estimable
Total (95% CI)	**37**	**34**		**100%**	**2[0.21,19.23]**
Total events: 2 (Tocolysis), 1 (No tocolysis)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.6(P=0.55)					

Analysis 8.7. Comparison 8 Antibiotic and steroid subgroup analysis, Outcome 7 Respiratory distress syndrome.

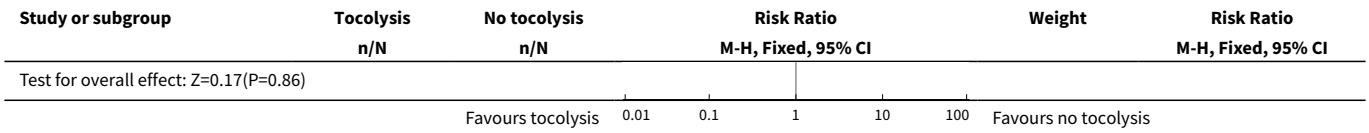
Study or subgroup	Tocolysis n/N	No tocolysis n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dunlop 1986	4/12	4/12		22.43%	1[0.32,3.1]
Ehansipoor 2010	11/25	13/22		77.57%	0.74[0.42,1.31]
Total (95% CI)	**37**	**34**		**100%**	**0.8[0.48,1.33]**
Total events: 15 (Tocolysis), 17 (No tocolysis)					
Heterogeneity: Tau^2=0; Chi^2=0.21, df=1(P=0.64); I^2=0%					
Test for overall effect: Z=0.85(P=0.39)					

Analysis 8.8. Comparison 8 Antibiotic and steroid subgroup analysis, Outcome 8 Latency (birth within 48 hours).

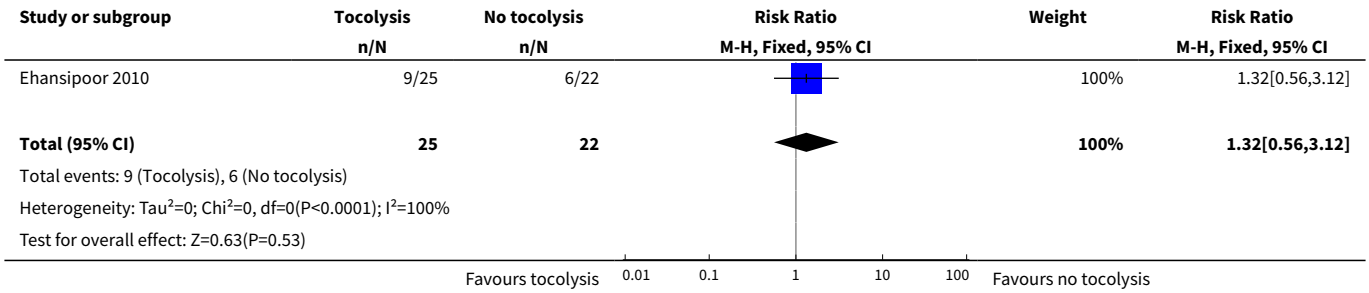
Study or subgroup	Tocolysis n/N	No tocolysis n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ehansipoor 2010	2/25	2/22		100%	0.88[0.14,5.73]
Total (95% CI)	**25**	**22**		**100%**	**0.88[0.14,5.73]**
Total events: 2 (Tocolysis), 2 (No tocolysis)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.13(P=0.89)					

Analysis 8.9. Comparison 8 Antibiotic and steroid subgroup analysis, Outcome 9 Latency (birth within 7 days).

Study or subgroup	Tocolysis n/N	No tocolysis n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ehansipoor 2010	12/25	10/22		100%	1.06[0.57,1.95]
Total (95% CI)	**25**	**22**		**100%**	**1.06[0.57,1.95]**
Total events: 12 (Tocolysis), 10 (No tocolysis)					
Heterogeneity: Not applicable					



Analysis 8.10. Comparison 8 Antibiotic and steroid subgroup analysis, Outcome 10 Chorioamnionitis.



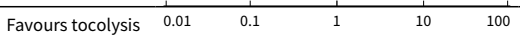
Comparison 9. Less than 34 week PPROM subgroup analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Perinatal mortality	5	291	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.69, 3.24]
2 Intrauterine fetal demise	3	174	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.07, 15.83]
3 Neonatal death	5	291	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [0.69, 3.49]
4 Gestational age	2	117	Mean Difference (IV, Fixed, 95% CI)	0.35 [-0.66, 1.36]
5 Birthweight (grams)	2	117	Mean Difference (IV, Fixed, 95% CI)	158.68 [-44.00, 361.36]
6 Apgar < 7 at 5 minutes	1	79	Risk Ratio (M-H, Fixed, 95% CI)	3.59 [0.79, 16.22]
7 Neonatal sepsis	4	243	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.31, 1.27]
8 Necrotizing enterocolitis	3	170	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.31, 1.47]
9 Intraventricular haemorrhage	3	174	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.45, 2.92]
10 Respiratory distress syndrome	4	249	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.68, 1.14]
11 Latency (hours)	2	117	Mean Difference (IV, Random, 95% CI)	79.22 [-27.56, 186.01]
12 Latency (birth within 48 hours)	4	243	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.34, 1.00]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13 Latency (birth within 7 days)	3	168	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.61, 1.24]
14 Chorioamnionitis	3	168	Risk Ratio (M-H, Fixed, 95% CI)	1.79 [1.02, 3.14]
15 Endometritis	1	79	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [0.69, 4.25]

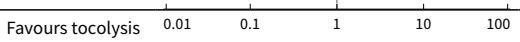
Analysis 9.1. Comparison 9 Less than 34 week PPROM subgroup analysis, Outcome 1 Perinatal mortality.

Study or subgroup	Tocolytic n/N	No tocolytic n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dunlop 1986	4/24	1/24		10.06%	4[0.48,33.22]
Ehansipoor 2010	1/25	1/22		10.7%	0.88[0.06,13.25]
Garite 1987	6/39	2/40		19.87%	3.08[0.66,14.33]
Levy 1985	0/21	1/21		15.09%	0.33[0.01,7.74]
Weiner 1988	3/33	5/42		44.27%	0.76[0.2,2.97]
Total (95% CI)	**142**	**149**		**100%**	**1.5[0.69,3.24]**
Total events: 14 (Tocolytic), 10 (No tocolytic)					
Heterogeneity: Tau^2=0; Chi^2=3.64, df=4(P=0.46); I^2=0%					
Test for overall effect: Z=1.02(P=0.31)					



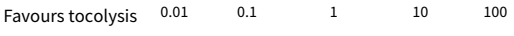
Analysis 9.2. Comparison 9 Less than 34 week PPROM subgroup analysis, Outcome 2 Intrauterine fetal demise.

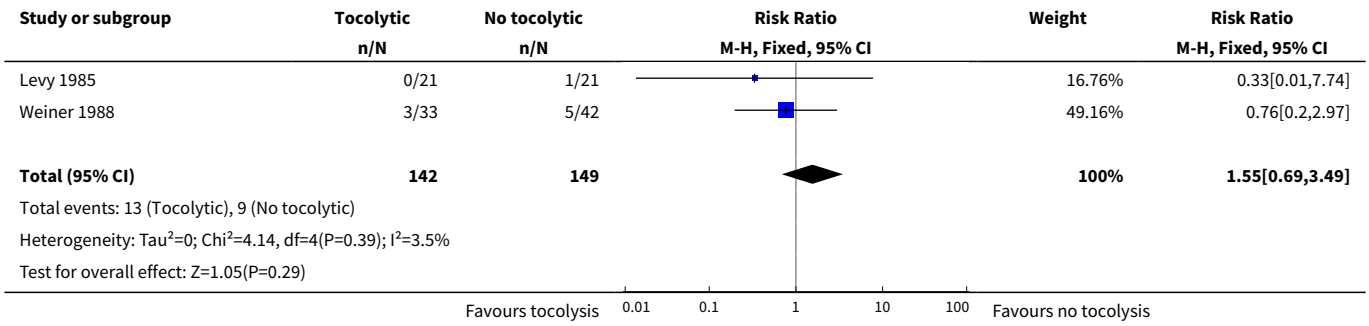
Study or subgroup	Tocolytic n/N	No tocolytic n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dunlop 1986	0/24	0/24			Not estimable
Ehansipoor 2010	0/25	0/22			Not estimable
Garite 1987	1/39	1/40		100%	1.03[0.07,15.83]
Total (95% CI)	**88**	**86**		**100%**	**1.03[0.07,15.83]**
Total events: 1 (Tocolytic), 1 (No tocolytic)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.02(P=0.99)					



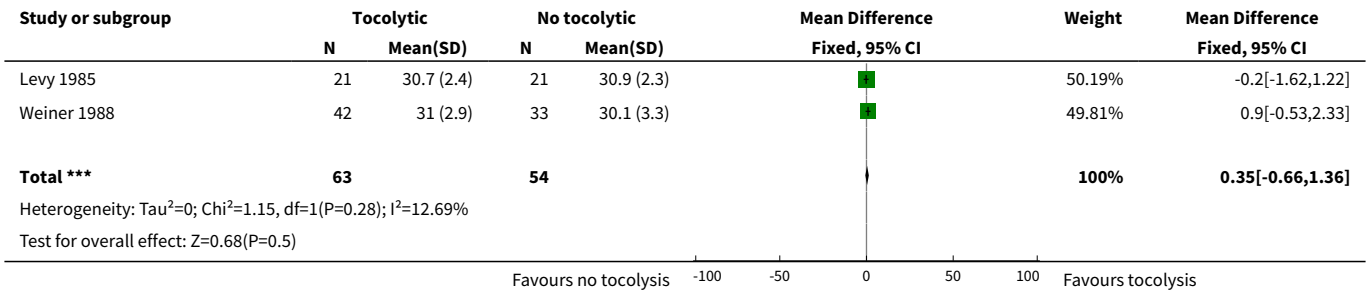
Analysis 9.3. Comparison 9 Less than 34 week PPROM subgroup analysis, Outcome 3 Neonatal death.

Study or subgroup	Tocolytic n/N	No tocolytic n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dunlop 1986	4/24	1/24		11.17%	4[0.48,33.22]
Ehansipoor 2010	1/25	1/22		11.88%	0.88[0.06,13.25]
Garite 1987	5/39	1/40		11.03%	5.13[0.63,41.93]

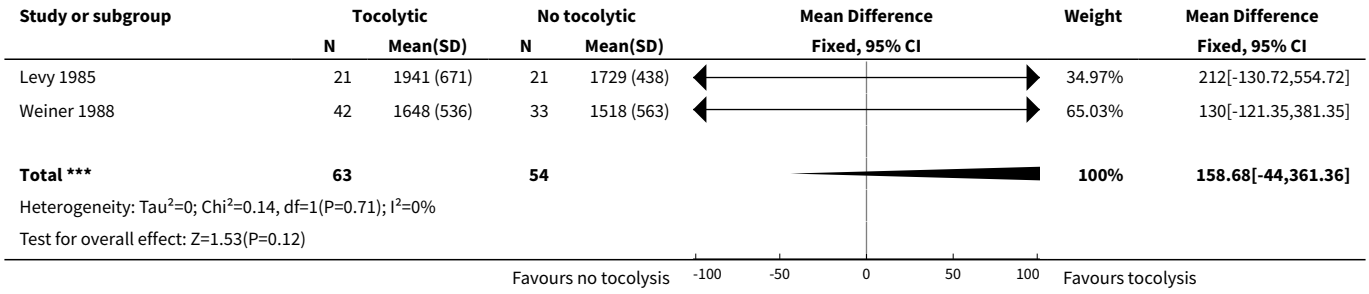




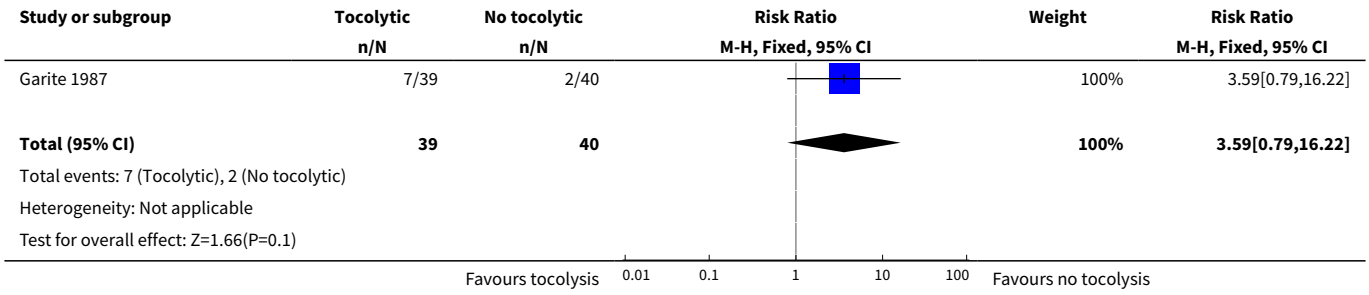
Analysis 9.4. Comparison 9 Less than 34 week PPROM subgroup analysis, Outcome 4 Gestational age.



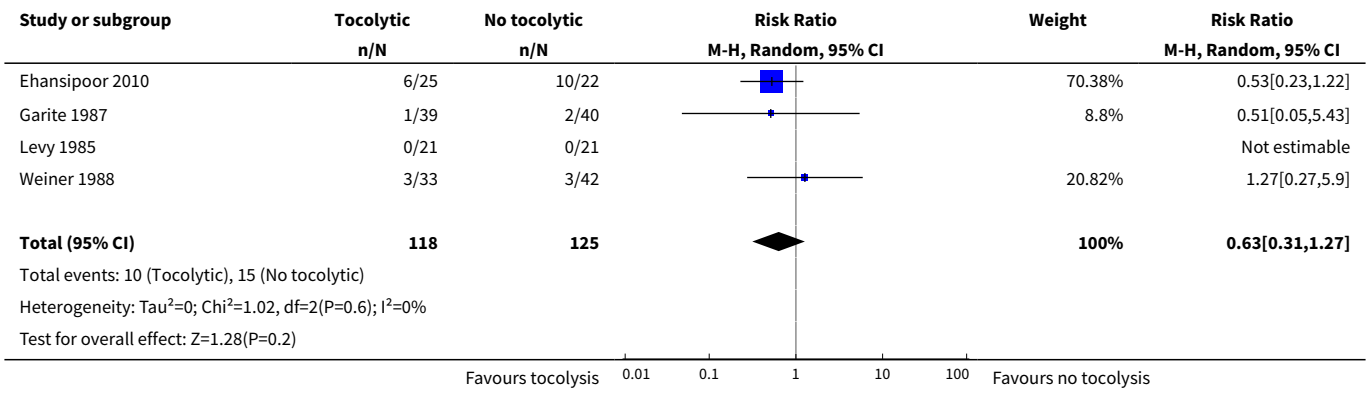
Analysis 9.5. Comparison 9 Less than 34 week PPROM subgroup analysis, Outcome 5 Birthweight (grams).



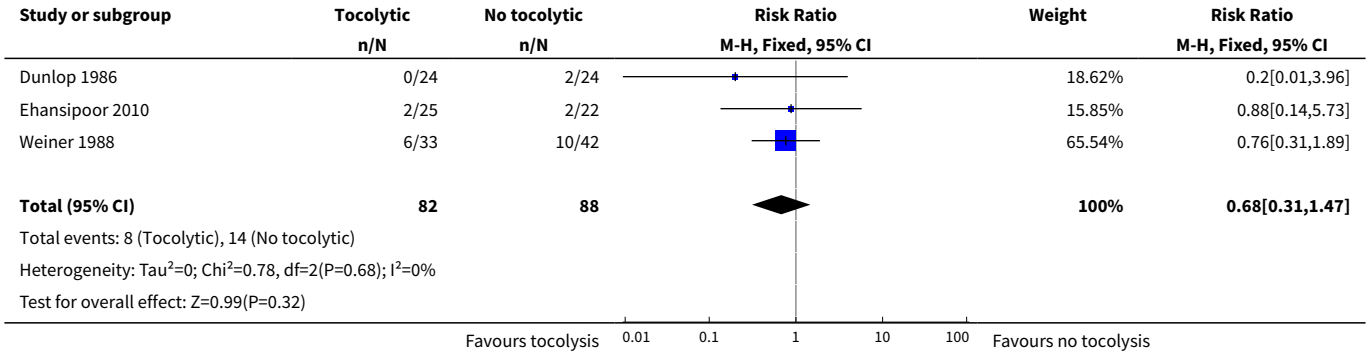
Analysis 9.6. Comparison 9 Less than 34 week PPROM subgroup analysis, Outcome 6 Apgar < 7 at 5 minutes.



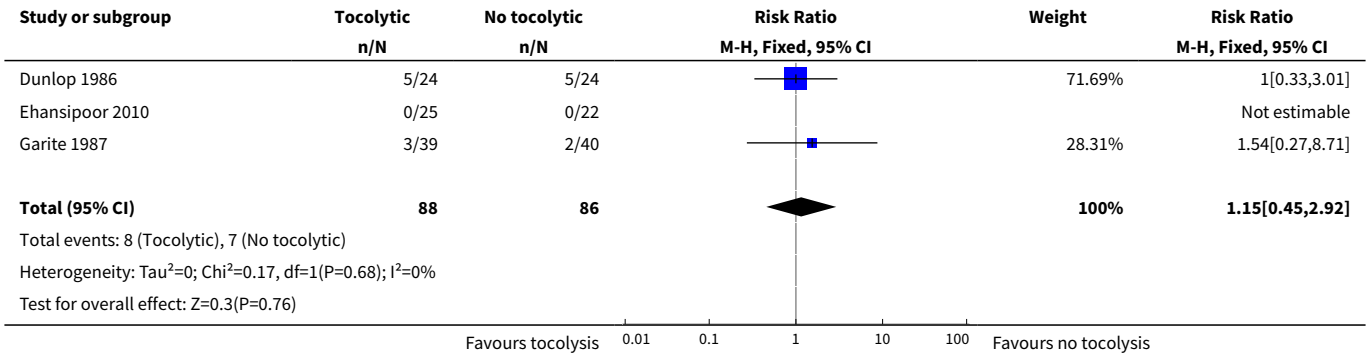
Analysis 9.7. Comparison 9 Less than 34 week PPROM subgroup analysis, Outcome 7 Neonatal sepsis.



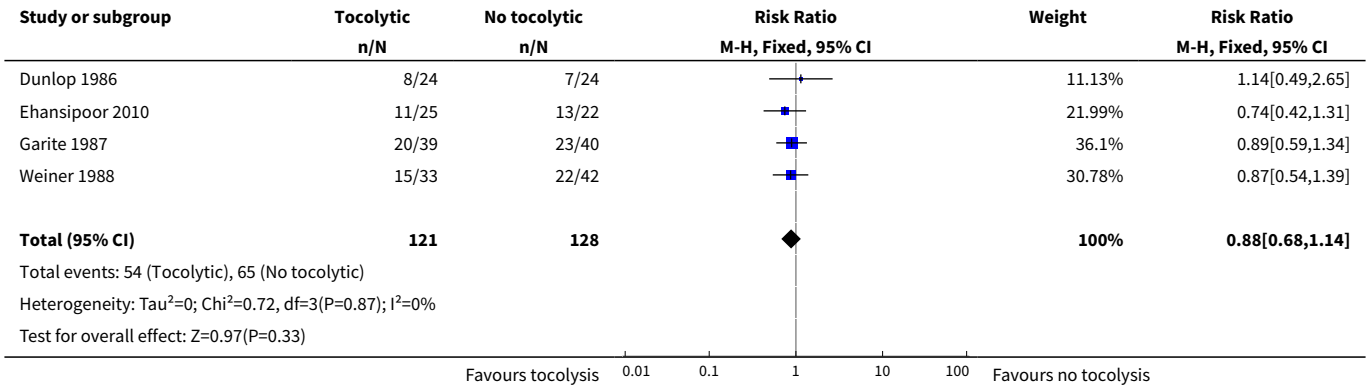
Analysis 9.8. Comparison 9 Less than 34 week PPROM subgroup analysis, Outcome 8 Necrotizing enterocolitis.



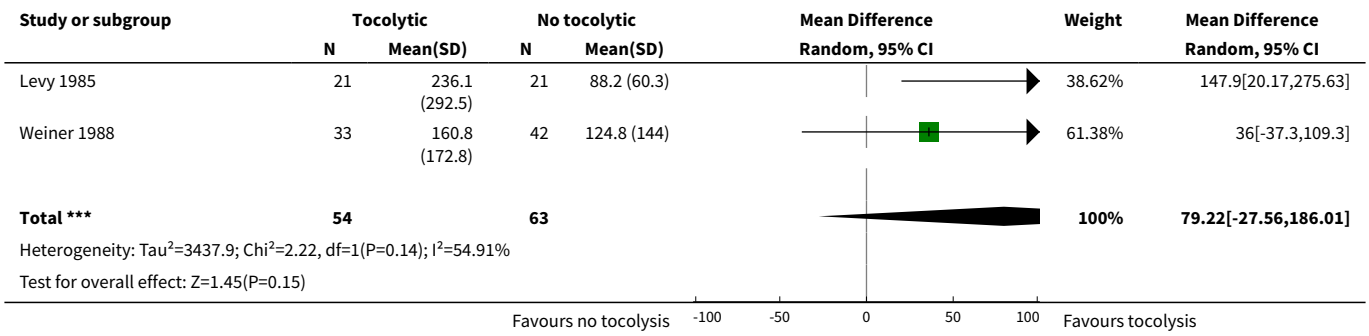
Analysis 9.9. Comparison 9 Less than 34 week PPROM subgroup analysis, Outcome 9 Intraventricular haemorrhage.



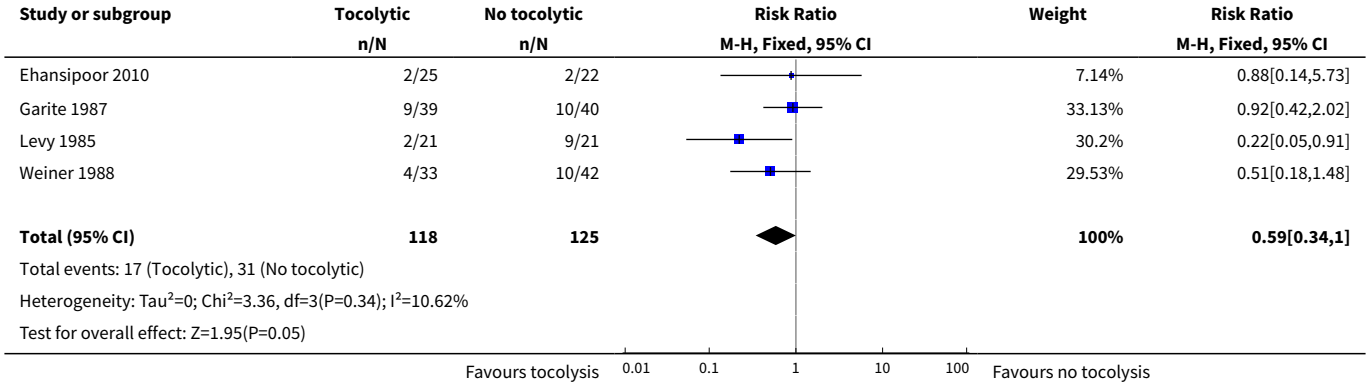
Analysis 9.10. Comparison 9 Less than 34 week PPROM subgroup analysis, Outcome 10 Respiratory distress syndrome.



Analysis 9.11. Comparison 9 Less than 34 week PPROM subgroup analysis, Outcome 11 Latency (hours).



Analysis 9.12. Comparison 9 Less than 34 week PPROM subgroup analysis, Outcome 12 Latency (birth within 48 hours).

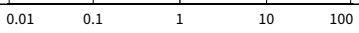


Analysis 9.13. Comparison 9 Less than 34 week PPROM subgroup analysis, Outcome 13 Latency (birth within 7 days).

Study or subgroup	Tocolytic n/N	No tocolytic n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Ehansipoor 2010	12/25	10/22		22.08%	1.06[0.57,1.95]
Garite 1987	27/39	27/40		45.36%	1.03[0.76,1.38]
Levy 1985	11/21	18/21		32.55%	0.61[0.39,0.95]
Total (95% CI)	**85**	**83**		**100%**	**0.87[0.61,1.24]**
Total events: 50 (Tocolytic), 55 (No tocolytic)					
Heterogeneity: Tau^2=0.05; Chi^2=3.91, df=2(P=0.14); I^2=48.9%					
Test for overall effect: Z=0.76(P=0.44)					

Analysis 9.14. Comparison 9 Less than 34 week PPROM subgroup analysis, Outcome 14 Chorioamnionitis.

Study or subgroup	Tocolytic n/N	No tocolytic n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ehansipoor 2010	9/25	6/22		44.65%	1.32[0.56,3.12]
Garite 1987	14/39	7/40		48.35%	2.05[0.93,4.53]
Levy 1985	3/21	1/21		7%	3[0.34,26.56]
Total (95% CI)	**85**	**83**		**100%**	**1.79[1.02,3.14]**
Total events: 26 (Tocolytic), 14 (No tocolytic)					
Heterogeneity: Tau^2=0; Chi^2=0.81, df=2(P=0.67); I^2=0%					
Test for overall effect: Z=2.03(P=0.04)					



Analysis 9.15. Comparison 9 Less than 34 week PPROM subgroup analysis, Outcome 15 Endometritis.

Study or subgroup	Tocolytic n/N	No tocolytic n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Garite 1987	10/39	6/40		100%	1.71[0.69,4.25]
Total (95% CI)	**39**	**40**		**100%**	**1.71[0.69,4.25]**
Total events: 10 (Tocolytic), 6 (No tocolytic)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.15(P=0.25)					

APPENDICES

Appendix 1. Search strategies

Database	Search strategy
CENTRAL (The Cochrane Library 2011, Issue 1)	#1MeSH descriptor Fetal Membranes, Premature Rupture explode all trees #2(rupture* near membrane*) or prom or pprom #3tocoly* #4MeSH descriptor Tocolysis, this term only #5MeSH descriptor Tocolytic Agents explode all trees #6(#1 OR #2) #7(#3 OR #4 OR #5) #8(#6 AND #7)
MEDLINE (1966 to 6 April 2011)	1 exp Fetal Membranes, Premature Rupture/ 2 exp Tocolytic Agents/ 3 Tocolysis/ 4 2 or 3 5 1 and 4
EMBASE (1974 to 6 April 2011)	1.Premature-Fetus-Membrane-Rupture/ 2. Tocolysis/ 3. exp Uterus-Spasmolytic-Agent 4. 2 or 3 5. 1 and 4

WHAT'S NEW

Date	Event	Description
15 January 2014	New citation required but conclusions have not changed	Review updated.
15 January 2014	New search has been performed	Search updated. Two new ongoing trials identified and added to Ongoing studies (El-Sayed 2010; Mol 2012).

CONTRIBUTIONS OF AUTHORS

Drs. Berghella and Baxter conceived and applied for this review. Drs. Mackeen, Seibel-Seamon, Grimes-Dennis, Berghella and Baxter searched the literature; contributed to the extraction of the data and the analysis using RevMan 2011; and the writing of this Review.

Dr. Mackeen finalized the 2014 update, which was approved by all authors.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support, Not specified.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The following secondary outcomes were added: need for antibiotics and length of stay, gestational age at delivery, birth weight, latency (hours). The outcome of prolongation of pregnancy for 48 hours/seven days was changed to birth within 48 hours and birth within seven days.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [therapeutic use]; Adrenergic beta-Agonists [therapeutic use]; Anti-Bacterial Agents [therapeutic use]; Fetal Membranes, Premature Rupture [*drug therapy]; Nifedipine [adverse effects] [therapeutic use]; Randomized Controlled Trials as Topic; Terbutaline [adverse effects] [therapeutic use]; Tocolysis [methods]; Tocolytic Agents [adverse effects] [*therapeutic use]

MeSH check words

Female; Humans; Pregnancy