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Ethanol for preventing preterm birth in threatened preterm labor (Review)

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[Intervention Review]

Ethanol for preventing preterm birth in threatened preterm labor

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ABSTRACT

Background

Preterm birth is the leading cause of death and disability in newborns worldwide. A wide variety of tocolytic agents have been utilized to delay birth for women in preterm labor. One of the earliest tocolytics utilized for this purpose was ethanol infusion, although this is not generally used in current practice due to safety concerns for both the mother and her baby.

Objectives

To determine the efficacy of ethanol in stopping preterm labor, preventing preterm birth, and the impact of ethanol on neonatal outcomes.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (31 May 2015) and reference lists of retrieved studies.

Selection criteria

We included randomized and quasi-randomized studies. Cluster-randomized trials and cross-over design trials were not eligible for inclusion. We only included studies published in abstract form if there was enough information on methods and relevant outcomes. Trials were included if they compared ethanol infusion to stop preterm labor versus placebo/control or versus other tocolytic drugs.

Data collection and analysis

At least two review authors independently assessed studies for inclusion and risk of bias. At least two review authors independently extracted data. Data were checked for accuracy.

Main results

Twelve trials involving 1586 women met inclusion criteria for this review. One trial did not report on the outcomes of interest in this review.

Risk of bias of included studies: The included studies generally were of low quality based on inadequate reporting of methodology. Only three trials had low risk of bias for random sequence generation and one had low risk of bias for allocation concealment and participant blinding. Most studies were either high risk of bias or uncertain in these key areas.

Comparison 1: Ethanol versus placebo/control (two trials, 77 women)

Compared to controls receiving pain medications and dextrose solution, ethanol did not improve any of the primary outcomes: **birth < 48 hours after trial entry** (one trial, 35 women; risk ratio (RR) 0.93, 95% confidence interval (CI) 0.43 to 2.00), or **neonatal mortality** (one trial, 35 women; RR 1.06, 95% CI 0.31 to 3.58). **Serious maternal adverse events** and **perinatal mortality** were not reported by either of the two trials in this comparison. Maternal adverse events (overall) were not reported but one trial (42 women) reported that there were no maternal adverse events that required stopping or changing drug) in either group. One trial did report delay until delivery but this outcome was reported as a median with no mention of the standard deviation (median 19 days in ethanol group versus "less than 1" day in the glucose/water group). There were no differences in any secondary outcomes reported: preterm birth < 34 weeks or < 37 weeks; serious infant outcome; fetal alcohol syndrome/fetal alcohol spectrum disorder; or small-for-gestational age.

Comparison 2: Ethanol versus other tocolytic (betamimetics) (nine trials, 1438 women)

Compared to betamimetics (the only tocolytic used as a comparator in these studies), ethanol was associated with no clear difference in the rate of **birth < 48 hours after trial entry** (two trials, 130 women; average RR 1.12, 95% CI 0.53 to 2.37, Tau² = 0.19, I² = 59%), similar rates of **perinatal mortality** (six trials, 698 women; RR1.20, 95% CI 0.78 to 1.84), higher rates of **neonatal mortality** (eight trials, 1238 women; RR 1.43, 95% CI 1.02 to 2.02), higher rates of preterm birth < 34 weeks (two trials, 599 women; RR 1.56, 95% CI 1.11 to 2.19), higher rates of neonatal respiratory distress syndrome (three trials, 823 women; RR 1.76, 95% CI 1.33 to 2.33), and higher rates of low birthweight babies < 2500 g (five trials, 834 women; RR 1.30, 95% CI 1.09 to 1.54). These outcomes are likely all related to the lower incidence of preterm birth seen with other tocolytics, which for all these comparisons were betamimetics. **Serious maternal adverse events** were not reported in any of the nine trial reports. However, ethanol had a trend towards a lower rate of maternal adverse events requiring stopping or changing the drug (three trials, 214 women; RR 0.25, 95% CI 0.06 to 0.97). There were no differences in other secondary outcomes of preterm birth < 37 weeks, number of days delivery was delayed, or overall maternal adverse events.

Planned sensitivity analysis, excluding quasi-randomized trials did not substantially change the results of the primary outcome analyses with the exception of neonatal mortality which no longer showed a clear difference between the ethanol and other tocolytic groups (3 trials, 330 women; RR 1.49, 95% CI 0.82 to 2.72).

Authors' conclusions

This review is based on evidence from twelve studies which were mostly low quality. There is no evidence that to suggest that ethanol is an effective tocolytic compared to placebo. There is some evidence that ethanol may be better tolerated than other tocolytics (in this case betamimetics), but this result is based on few studies and small sample size and therefore should be interpreted with caution. Ethanol appears to be inferior to betamimetics for preventing preterm birth in threatened preterm labor.

Ethanol is generally no longer used in current practice due to safety concerns for the mother and her baby. There is no need for new studies to evaluate the use of ethanol for preventing preterm birth in threatened preterm labour. However, it would be useful for long-term follow-up studies on the babies born to mothers from the existing studies in order to assess the risk of long-term neurodevelopmental status.

PLAIN LANGUAGE SUMMARY

Ethanol (alcohol) for preventing preterm birth

Preterm birth is when a baby is born at less than 37 weeks' gestation. These babies are generally more ill and are less likely to survive than babies born at term. Preterm babies are also more likely to have some disability, and the earlier the baby is born the more likely they are to have problems. Even short-term postponement of preterm birth can improve outcomes for babies, as this gives time for the mother to be given a steroid injection to help develop the baby's lungs prior to birth. Short-term postponement of preterm birth may also give the chance to transfer the mother, if required, to somewhere where there is more expert care for the baby available.

Drugs used to try and stop labor are called tocolytics. These drugs are given to women experiencing preterm labor to try and stop or relax uterine contractions. One of the earliest drugs used to try and stop contractions was ethanol (also known as alcohol), although this is not generally used in current practice due to safety concerns for both the mother and her baby. In this review, we looked at the published studies to see if ethanol was effective in postponing labor and improving outcomes for babies, and also whether ethanol was better than other types of tocolytics used to postpone preterm labor and birth.

We searched for trials evidence on 31 May 2015 and found 12 trials total involving 1586 women, some comparing ethanol with a placebo and others comparing ethanol with other tocolytics (in this instance, all betamimetics). The trials included in this review were considered to be mostly low quality studies.

For our comparison of ethanol versus placebo control (two trials, 77 women). We found that ethanol was no better than placebo (sugar water) for any of the outcomes studied: birth <48 hours after trial entry (one trial, 35 women) or neonatal mortality (one trial, 35 women). Serious maternal adverse events and perinatal mortality was not reported. There was no differences between groups for other outcomes: preterm birth < 37 weeks or < 34 weeks, serious infant outcome, fetal alcohol syndrome/fetal alcohol spectrum disorder, or small-for-gestational age.

We also compared ethanol with other tocolytic drugs (nine trials involving 1438 women; all trials studied betamimetic drugs). We found that ethanol was worse than other betamimetic drugs at postponing birth until after 34 weeks' gestation and led to a higher rate of low birthweight babies, babies with breathing problems at birth and neonatal death (although there was no clear difference in neonatal deaths when we restricted our analyses to the better quality studies), However, we did find that, compared to betamimetics, ethanol was associated with a trend for fewer maternal side effects that required stopping or changing the drug, though this result is based on three small trials. There were no differences in other secondary outcomes of preterm birth < 37 weeks, number of days delivery was delayed, or overall maternal adverse events.

Overall, we found no evidence that ethanol was better than a placebo at postponing preterm labor and birth. Whilst there was some evidence to suggest that ethanol may be better tolerated than betamimetics, we found that ethanol was not as effective as betamimetics at postponing preterm labor and birth. None of the studies were long-term ones and thus none of them reported on the risk of giving ethanol on the babies developing fetal alcohol syndrome, which can cause mental retardation.

There is no need for new studies to evaluate the use of ethanol for preventing preterm birth. However, it would be useful for long-term follow-up studies on the babies born to mothers from the existing studies in order to assess the risk of long-term neurodevelopmental status.

BACKGROUND

Description of the condition

Preterm birth is currently recognized as the leading cause of death in newborns worldwide (Howson 2012). According to the World Health Organization, preterm birth is defined as delivery prior to completion of 37 weeks' gestation (WHO 1977). Of the estimated 3.1 million neonatal deaths in 2010, 35% were directly caused by preterm birth complications (Howson 2012). The premature infants who survive are at risk for several perinatal morbidities, including respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular hemorrhage, sepsis, cerebral palsy, and other neurologic deficits (Gladstone 2011). Neonatal morbidity and mortality rates are inversely proportional to gestational age and birthweight. Thus, as gestational age increases, mortality rate decreases (Lawn 2010). Consequently, research efforts have focused on ways to prolong pregnancy when a woman presents in preterm labor. Research has shown that tocolytic drugs could improve perinatal outcomes by inhibiting uterine contractions during preterm labor (Conde-Agudelo 2011). Though the ultimate goal would

be to decrease the incidence of preterm birth, clinicians also use tocolysis as a short-term treatment to delay birth long enough to administer corticosteroids to the mother for fetal lung maturation and to allow time to transfer the woman to a tertiary care facility (Roberts 2006). A wide variety of tocolytic agents have been utilized, including betamimetics, calcium channel blockers, oxytocin receptor antagonists, magnesium sulfate, and ethanol. Although ethanol is no longer used in clinical practice, this review aims to evaluate ethanol as a tocolytic in preterm labor.

Description of the intervention

Ethanol was previously used as a common tocolytic agent. Research has shown that it is an effective tocolytic when given in high concentrations (Schaefer 2007). However, ethanol has harmful effects on the development of the fetus at these high concentrations in maternal blood (ACOG 2011). Other research has shown that ethanol is an ineffective tocolytic in low concentrations. Both consumption and treatment with ethanol puts the fetus at risk for fetal alcohol syndrome, which is characterized by growth retardation, facial dysmorphia, central nervous system abnormalities, intellec-

tual deficits, and various other birth defects. In addition, maternal adverse effects, including intoxication and withdrawal, were common. According to the American Congress of Obstetricians and Gynecologists (ACOG), no amount of ethanol consumption during pregnancy has been determined to be safe, and, therefore, women should avoid ethanol entirely during pregnancy (ACOG 2011). It is due to these recommendations that the practice of using ethanol as a tocolytic agent has been eliminated.

How the intervention might work

The mechanism for the onset of parturition is complex. There are several known hormones and pathways that play a role in the initiation of labor. One of the most well-understood pathways is the interaction between oxytocin and the uterus. The myometrium has four distinct physiologic phases during pregnancy. In the first phase, uterotropin hormones, such as estrogen, upregulate the production of contraction-associated proteins (CAPs). These CAPs include the myometrial receptor for oxytocin, a hormone released from the posterior pituitary and considered the most potent agent in the stimulation of uterine contractions (Zeeman 1997). Through this mechanism, the receptors exponentially increase in number during pregnancy, peaking during early labor. The oxytocin/oxytocin-receptor complex interacts with a G protein and results in an influx of calcium, stimulating uterine contractions. At high concentrations, ethanol has a tocolytic effect by acting as an inhibitor of oxytocin release (Schaefer 2007), thus reducing the strength of uterine contractions and decreasing the likelihood of preterm labor.

Why it is important to do this review

Early clinical findings supported ethanol as an effective tocolytic agent and it was a standard therapy for many years (Belinkoff 1950; Fuchs 1965; Fuchs 1967). However, ethanol is a teratogen and can affect the fetus at any gestational age (ACOG 2011). Therefore, it is important to assess the evidence surrounding the benefits and harms of the use of ethanol as a tocolytic for women in preterm labor systematically. Even though adverse-effect profiles and potential adverse effects on the fetus have led to this therapy not being used clinically anymore, systematically reviewing the evidence to complete the Cochrane reviews of tocolytic therapies is important.

Other Cochrane reviews of tocolysis include reviews of magnesium sulfate (Crowther 2014), oxytocin receptor antagonists (Flenady 2014a), calcium channel blockers (Flenady 2014b), nitric oxide donors (Duckitt 2014), betamimetics (Neilson 2014), progestational agents (Su 2014), hydration (Stan 2013), relaxin (Bain 2013), cyclo-oxygenase inhibitors (Reinebrant 2015), and combinations of drugs (Vogel 2014).

OBJECTIVES

To determine the efficacy of ethanol in stopping preterm labor, preventing preterm birth, and the impact of ethanol on neonatal outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized and quasi-randomized studies. Cluster-randomized trials and cross-over trials were not eligible for inclusion. We only included studies published in abstract form if there is enough information on methods and relevant outcomes.

Types of participants

Pregnant women admitted to hospital for threatened preterm birth.

Types of interventions

We included any use of ethanol therapy for preterm labor.
This review included comparisons of:
1. ethanol versus placebo/usual care/no tocolytic;
2. ethanol versus a different tocolytic agent.
We planned to exclude trials that used ethanol in combination with another tocolytic agent, unless the use of ethanol was the only difference between the two groups (i.e. betamimetic versus betamimetic plus ethanol).

Types of outcome measures

Primary outcomes

The Cochrane Pregnancy and Childbirth Group's (PCG) Consensus statement, "Adopting a consistent approach to PCG systematic reviews on tocolysis for inhibiting preterm labour" was followed in development of these outcomes. We include the core outcomes in the consensus statement below. These core outcomes are denoted by an asterisk.

Maternal

1. Birth less than 48 hours after trial entry*.
2. Serious maternal adverse events (defined as death, cardiac arrest, respiratory arrest, admission to intensive care unit)*. None of the included trials reported on this outcome and thus no comparisons for it were performed.

Fetal/neonatal/infant

1. Perinatal mortality (fetal death and neonatal death up to 28 days).
2. Neonatal mortality.

Secondary outcomes

Maternal

1. Preterm birth less than 37 weeks.
2. Preterm birth less than 34 weeks*.
3. Number of days that delivery was delayed from start of therapy.
4. Maternal adverse events (overall)*.
5. Maternal adverse events (requiring stopping or changing drug).

Fetal/neonatal/infant

1. Serious infant outcome (defined as death or chronic lung disease (need for supplemental oxygen at 28 days of life or later), grade three or four intraventricular hemorrhage or periventricular leukomalacia, major neurosensory disability (defined as any of legal blindness, sensorineural deafness requiring hearing aids, moderate or severe cerebral palsy, or developmental delay/intellectual impairment (defined as developmental quotient (DQ) or intelligence quotient (IQ) less than two standard deviations below mean)))*.
2. Fetal alcohol syndrome/fetal alcohol spectrum disorder (defined by the trialist or involving brain damage, impaired growth, and head and face abnormalities).
3. Respiratory distress syndrome.
4. Birthweight.
5. Small-for-gestational age (birthweight below 10th percentile for gestational age or as defined by trial authors).

Search methods for identification of studies

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (31 May 2015).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

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

Details of the search strategies for CENTRAL, MEDLINE, Embase and CINAHL, 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.

Searching other resources

We searched the reference lists of identified trials.
We did not apply any language or date restrictions.

Data collection and analysis

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Selection of studies

Two review authors independently assessed for inclusion all the potential studies identified as a result of the search strategy. We resolved any disagreements through discussion. We created a study flow diagram to map out the number of records identified, included, and excluded.

Data extraction and management

We designed a form to extract data. For eligible studies, at least two review authors extracted extract the data using the agreed form. We resolved discrepancies through discussion or, if required, we consulted a third review author. We entered data into Review Manager (RevMan 2014), and checked them for accuracy. When

information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details. We were only successful at contacting one author to clarify an inclusion criteria for his trial (Caritis 1982).

Assessment of risk of bias in included studies

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

(1) Random sequence generation (checking for possible selection bias)

For each included study, we described 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);
- unclear risk of bias.

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

For each included study, we described the method used to conceal allocation to interventions prior to assignment and assessed 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)

For each included study, we described the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged 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)

For each included study, we described 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 methods used to blind outcome assessment as:
- low risk of bias;
- high risk of bias;
- unclear risk of bias.

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

For each included study and for each outcome or class of outcomes, we described the completeness of data including attrition and exclusions from the analysis. We stated 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 was reported, or could be supplied by the trial authors, we re-included missing data in the analyses that 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)

For each included study, we described 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 prespecified outcomes and all expected outcomes of interest to the review were reported);
- high risk of bias (where not all the study's prespecified outcomes were reported; one or more reported primary outcomes were not prespecified; outcomes of interest were reported incompletely and so could not be used; study did not 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)

For each included study, described 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 was risk of other bias.

(7) Overall risk of bias

We made explicit judgments about whether studies were at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it is likely to impact on the findings. We planned to explore the impact of the level of bias through undertaking sensitivity analyses (see Sensitivity analysis).

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented the results as summary risk ratio with 95% confidence interval (CI).

Continuous data

For continuous data, we used the mean difference with 95% CI where outcomes are measured in the same way between trials. We planned to use the standardized mean difference with 95% CI to combine trials that measured the same outcome, but used different methods.

Unit of analysis issues

Cluster-randomized trial

Cluster-randomized trials were not eligible for inclusion in this review.

Cross-over trials

Cross-over trials were not eligible for inclusion in this review.

Other unit of analysis issues

As women with multiple gestations are at high risk of preterm labor, it is reasonable to expect that trials will include women with multiple gestations. Had trial authors reported data for multiple gestations separately, we planned to perform a subgroup analysis of women with singleton gestations versus women with multiple gestations. We planned that if a trial excluded multiple gestations, we would include them in the singleton gestation subgroup analysis. For maternal outcomes, we would have counted the number of pregnant women in the trial for outcomes and utilized the number in the denominator. For neonatal/fetal outcomes, the number of individual fetuses/newborns would have been used as the population for outcomes and in the denominator. All of these would have been based on the level of detail reported in the individual trial.

If trials had included more than two treatment groups, we planned to select one pair of interventions for the analysis and exclude the others to avoid double counting as noted in the *Cochrane Handbook for Systematic Reviews of Interventions* Section 16.5 (Higgins 2011). We planned to follow the Pregnancy and Childbirth Group's consensus statement for tocolytic trials. However, as this review is mainly of historical context, we planned to separate the analyses into two comparisons: ethanol versus placebo/control and ethanol versus other tocolytic. As the consensus statement recommends comparisons only between classes of drugs, this is still consistent with this guidance as all of the comparisons that had relevant outcomes compared ethanol to betamimetic drugs. If in future updates, in the highly unlikely event of new trials being found for inclusion that compare ethanol versus a different class of tocolytic, we will separate out the comparisons by class. Because of this, we plan to use a subgroup analysis based on membrane status at admission within these two comparisons.

Dealing with missing data

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

For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis (i.e. we attempted to include all women randomized to each group in the analyses, and all women were analyzed 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 is the number randomized minus any women whose outcomes are known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the Tau², I², and Chi²statistics. We regarded heterogeneity as substantial if an I² was greater than 30% and either a Tau² was greater

than zero, or there was a low P value (less than 0.10) in the Chi² test for heterogeneity.

Assessment of reporting biases

Had there been 10 or more studies in the meta-analysis, we planned to investigate reporting biases (such as publication bias) using funnel plots. We would have assessed funnel plot asymmetry visually. If asymmetry was suggested by a visual assessment, we planned to perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager (RevMan 2014). We used fixed-effect meta-analyses for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect (i.e. where trials were examining the same intervention, and we judged the trials' populations and methods sufficiently similar). If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we used random-effects meta-analyses to produce an overall summary, if a mean treatment effect across trials was considered clinically meaningful. We treated the random-effects summary as the mean of the range of possible treatment effects and we discussed the clinical implications of treatment effects differing between trials. If the mean treatment effect was not clinically meaningful, we would not have combined trials.

Where we used random-effects analyses, we present the results as the mean treatment effect with 95% CI, and the estimates of Tau² and I² statistic.

Subgroup analysis and investigation of heterogeneity

If we identified substantial heterogeneity, we investigated it using subgroup analyses and sensitivity analyses. We considered whether an overall summary was meaningful, and if it was, used random-effects analysis to produce it.

We planned to carry out the following subgroup analyses.

1. Women with multiple gestations versus women with singleton gestations (this subgroup analysis was not carried out due to insufficient data).

2. Women with intact membranes versus women with ruptured membranes. This subgroup analysis was included following current thoughts that preterm labor that accompanies premature preterm ruptured membranes may have a different pathophysiology than simple preterm labor. In addition, many older trials utilized nonspecific definitions of preterm labor for trial entry, such that the presence of regular contractions with minimal or no cervical dilation could qualify a woman for the diagnosis and trial entry. These women would be less likely to delivery preterm in general than women with ruptured membranes. Thus, this subgroup analysis was performed as the outcomes may be very different between them.

Subgroup analyses were restricted to primary outcomes only.

We assessed subgroup differences by interaction tests available within Review Manager (RevMan 2014). We reported the results of subgroup analyses quoting the Chi² statistic and P value, and the interaction test I² statistic.

Sensitivity analysis

We expected many of the trials to be older trials and thus may not robustly report facts related to the methodological quality of the trial. Consequently, we planned to perform a sensitivity analysis of trials found to be at overall low risk of bias versus all trials to explore if there is a risk of bias associated with the quality of some of the included trials. We planned to base this assessment of quality mainly on the risk of bias related to randomization, allocation concealment, and blinding parameters. However, since there were no trials assessed as a low risk of bias, this planned sensitivity analysis was not performed.

We also carried out sensitivity analysis where we included any quasi-randomized trials, to explore the impact of their inclusion on the overall results.

Planned sensitivity analyses for the primary outcomes will be conducted in subsequent updates of this review (if necessary).

R E S U L T S

Description of studies

Results of the search

See: Figure 1.

Figure 1. Study flow diagram.
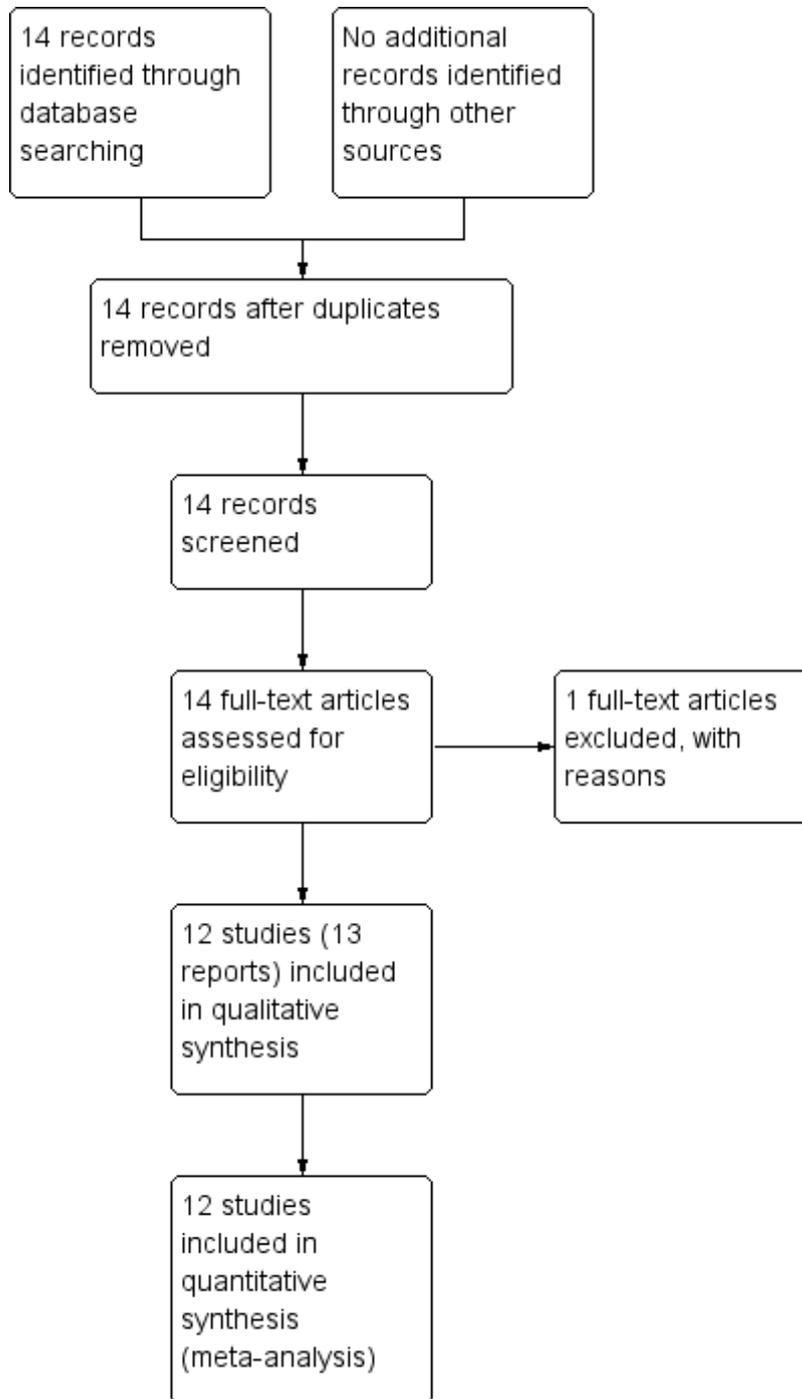
The search of the Cochrane Pregnancy and Childbirth Group's Trials Register identified 14 reports of 13 studies.

Included studies

Twelve trials involving 1586 women met the inclusion criteria for the review. One trial contributed no data to analyses (Steer 1977). Full details on the methods and populations of each trial are available in the Characteristics of included studies.

Two trials compared ethanol with a control/placebo of glucose or dextrose in water (Watring 1976; Zlatnik 1972). The Steer 1977 trial compared ethanol with magnesium sulfate, and also had a small third arm of placebo using 5% dextrose (n = 9). To avoid double counting the ethanol group in two different comparisons, and given the small size of the groups and clear difference in the interventions, we opted to overcome the unit of analysis error issue by selecting one of the pair-wise comparisons (ethanol versus magnesium sulfate) and not including the dextrose group comparison. However, as this trial's reported "success" outcome was defined as stopping contractions and at least a day going by before they started again, and did not report any of our predefined outcomes, it did not contribute to any analyses. The remaining nine studies compared ethanol with a betamimetic - salbutamol (Boyd 1978; Reynolds 1978; Sims 1978; Spearing 1979), terbutaline (Caritis 1982), nylidrin (Castren 1975), fenoterol (Forster 1987 (Part II); Forster 1987 (Part III)), or ritodrine (Lauersen 1977). The Spearing 1979 trial had a third group that received ethanol plus indomethacin. This group was excluded from the analyses.

The trials did not use a single standard definition of preterm labor or successful therapy.

One trial (Forster 1987 (Part II)) reported mean delay of delivery but did not report standard deviations. As it was one of the larger trials (210 women), we believed it important to include for this outcome. After consultation with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and a statistician, we imputed a range of standard deviations from 1.0 up to the largest reported standard deviation of a trial reporting that outcome (Sims 1978) of 24.4. No values within this range significantly altered the results seen. Thus, values similar to the majority of standard deviations in that comparison (~3.3) were utilized in the final analysis. This limits conclusions from this comparison somewhat (Analysis 2.6).

Four trials excluded women with ruptured membranes (Forster 1987 (Part II); Steer 1977; Watring 1976; Zlatnik 1972). Of the other trials, two specified outcomes for those with intact versus ruptured membranes (Caritis 1982; Sims 1978), allowing for the subgroup analyses.

Three trials excluded multiple gestations (Sims 1978; Steer 1977; Watring 1976), and two reported outcomes separately for singleton and multiple gestations (Lauersen 1977; Spearing 1979). However, since there were so few women in the trials with multiple gestations and the outcome reported was birth < 72 hours, which was not a prespecified outcome, we did not perform that planned subgroup analysis.

Six trials (Castren 1975; Forster 1987 (Part II); Forster 1987 (Part III); Reynolds 1978; Spearing 1979; Steer 1977) had randomization methods that qualified as quasi-randomized. In the sensitivity analysis, these trials were excluded.

Excluded studies

One trial was excluded as it did not report trial data regarding ethanol as a tocolytic (Waltman 1969). For more information please see Characteristics of excluded studies.

Risk of bias in included studies

In general, the quality of trial reporting was low. This is likely due to the years of publication of many of the studies being well prior to the CONSORT (Consolidated Standards of Reporting Trials) criteria (Schulz 2010), or any attempts at standard reporting of trials. Thus, the assessment of risk of bias in several areas is unclear simply because they are not stated (see Figure 2; Figure 3).

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.
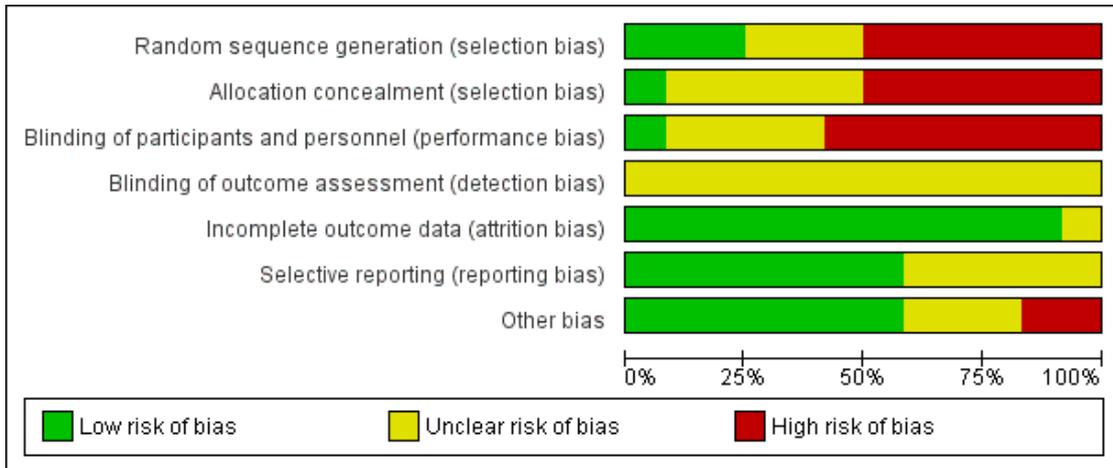
Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

Random sequence generation

Only three trials had a low risk of bias for random sequence generation. (Caritis 1982; Lauersen 1977; Watring 1976). The Zlatnik 1972 trial stated that assignments were "random" in envelopes without any details about how randomization occurred. Six of the trials (Castren 1975; Forster 1987 (Part II); Forster 1987 (Part III); Reynolds 1978; Spearing 1979; Steer 1977) contained high risk of bias for random sequence generation. This is due to generally stating that randomization/allocation was based on alternating allocation or based on last names.

Allocation concealment

While all three of the above trials (Caritis 1982; Lauersen 1977; Watring 1976) used envelopes for allocation, none stated if the envelopes were sequentially numbered or opaque and thus all were unclear in the risk of allocation bias. A fourth had low risk of bias for allocation concealment however, only stated that assignments were "random" in the envelopes (Zlatnik 1972). Six of the trials (Castren 1975; Forster 1987 (Part II); Forster 1987 (Part III); Reynolds 1978; Spearing 1979; Steer 1977) contained high risk of bias for allocation concealment. Often this was due to "alternating" allocation or randomization based on surnames or record numbers.

Blinding

Only the Watring 1976 trial stated that it was "single blind" in the title. However, it was not stated in the trial report which group was blinded. The control group in this study were given morphine or secobarbital so may have appeared similarly "intoxicated" as the ethanol group. Seven trials stated that they were unable to blind providers or women (Caritis 1982; Castren 1975; Forster 1987 (Part II); Forster 1987 (Part III); Lauersen 1977; Reynolds 1978; Sims 1978). In the remaining trials, blinding was not stated for these groups, however it is likely that blinding in a study of ethanol such as this would be difficult. No trial separately reported if the outcomes assessors were blinded, thus all were rated as unclear.

Attrition, reporting, and other sources of bias

Generally, the trials had low risk of bias for attrition and reporting and did not have other sources of bias. The Forster 1987 (Part II) trial initially had a placebo group but after noting "no change" in the first 10 participants, these women were then split into groups one and two for the remainder of the study. This may have led to other bias. The Zlatnik 1972 trial also was rated as a potentially high risk of other bias due to only stopping the trial "when the plot of data indicated one treatment superior to the other" and that while they stated the demographic characteristics were the same for the two groups, they did not show these data.

Thus, none of the trials would easily be categorized as low risk of bias. The Caritis 1982; Lauersen 1977; Watring 1976; Zlatnik 1972 trials appear to be at a lower risk of bias than the rest of the trials of lower quality. As these trials reported different outcomes in different comparisons and they are not clearly low risk of bias, no subgroup analyses based on trial quality was performed.

Effects of interventions

Ethanol versus placebo/control - comparison 1 (two trials, 77 women)

Primary outcomes

The two trials included in this comparison (Watring 1976; Zlatnik 1972), did not report on any of the same outcomes. Both trials excluded women with ruptured membranes so the only subgroup of relevance is that of women with intact membranes for these analyses. There were no significant differences in any of the primary outcomes with data: **birth < 48 hours after trial entry** (one trial, 35 women; risk ratio (RR) 0.93, 95% confidence interval (CI) 0.43 to 2.00 (Analysis 1.1)); **neonatal mortality** (one trial, 35 women; RR 1.06, 95% CI 0.31 to 3.58 (Analysis 1.3)). Both of these results were from the Watring 1976 trial. **Perinatal mortality** was not reported in either trial. **Serious maternal adverse events** were also not reported.

Secondary outcomes

There were no differences in this comparison for any of the secondary outcomes that were reported, although all comparisons were based on only one of the trials: preterm birth < 37 weeks (RR 1.29, 95% CI 0.72 to 2.31 (Analysis 1.4)); preterm birth < 34 weeks (RR 1.69, 95% CI 0.69 to 4.16 (Analysis 1.5)); number of days delivery was delayed (mean difference (MD) -3.43 days, 95% CI -22.74 to 15.88 (Analysis 1.6)); respiratory distress syndrome (RR 0.85, 95% CI 0.27 to 2.64 (Analysis 1.9)), or birthweight < 2500 g (RR 1.41, 95% CI 0.81 to 2.46 (Analysis 1.10)), all from the Watring 1976 trial (one trial, 35 women).

The risk of maternal adverse events requiring stopping or changing the drug was not estimable due to there being no events in either arm for the one trial (42 women) (Analysis 1.8) that reported this (Zlatnik 1972). Additionally, the Zlatnik 1972 trial did report delay until delivery but reported it as a median with no mention of the standard deviation (median 19 days in ethanol group versus "less than 1" day in the glucose/water group). No data were presented for the other prespecified secondary outcomes: maternal adverse

events overall; serious infant outcome; fetal alcohol syndrome/fetal alcohol spectrum disorder; small-for-gestational age.

Ethanol versus other tocolytic (betamimetics) - comparison 2 (nine trials, 1438 women)

The Steer 1977 trial defined success as contractions stopping and not restarting for 24 hours. As it did not have any reported outcomes prespecified in this review, it did not contribute to the analyses. Thus, all comparisons below compare ethanol to a betamimetic drug.

Primary outcomes

Compared to other tocolytic drugs (all involved a comparison of ethanol to betamimetics), ethanol treatment was associated with no clear difference in **births < 48 hours after trial entry** (three trials, 192 women; average RR 1.12, 95% CI 0.53 to 2.37, Tau² = 0.19; I² = 59% Analysis 2.1,) or **perinatal mortality** (six trials, 698 women; RR 1.20, 95% CI 0.78 to 1.84, Analysis 2.2), but higher rates of **neonatal mortality** (eight trials, 1238 women; RR 1.43, 95% CI 1.02 to 2.02, Analysis 2.3)). **Serious maternal adverse events** were not reported

Subgroup analysis

For the subgroup analysis comparing women with intact membranes versus those with ruptured membranes, only one trial presented some data stratified by ruptured or intact membranes (Caritis 1982). Two other trials excluded women with ruptured membranes (Castren 1975; Lauersen 1977) and thus are included in the subgroup of studies limited to women with intact membranes. The other trials either did not specify membrane status in their inclusion/exclusion criteria or in their reporting. These are included in the "women without specified membrane status" subgroup. We carried out subgroup analysis by membrane status, comparing women with intact membranes, those with ruptured membranes and those without specified membrane status. We were able to carry out these subgroup analyses for perinatal mortality and neonatal mortality but these analyses did not change the results - there were no significant subgroup interactions: perinatal mortality (test for subgroup differences: Chi² = 1.00, df = 2 (P = 0.61), I² = 0%); neonatal mortality (test for subgroup differences: Chi² = 1.21, df = 2 (P = 0.55), I² = 0%).

Sensitivity analysis

Excluding quasi-randomized trials did not significantly change the results of the primary outcome analyses with the exception of making the results for neonatal mortality no longer statistically significant (3 trials, 330 women; RR 1.49, 95% CI 0.82 to 2.72).

Secondary outcomes

There was no clear difference in the rate of preterm birth < 37 weeks between the group of women who were given ethanol, compared to those women who received betamimetics (four trials, 741 women; average RR 1.08, 95% CI 0.86 to 1.36, random-effects analysis, Tau² = 0.03; I² = 66% (Analysis 2.4)). In contrast, ethanol was associated with higher rates of preterm birth < 34 weeks (two trials, 599 women; RR 1.56, 95% CI 1.11 to 2.19 (Analysis 2.5)). There was no clear difference between the ethanol group and the betamimetic control in terms of the number of days delivery was delayed (five trials, 585 women; MD -2.51, 95% CI -11.11 to 6.09, random-effects analysis, Tau² = 91.57; Heterogeneity: Tau² = 91.57; I² = 99% (Analysis 2.6)), or overall maternal adverse events (four trials, 350 women, average RR 0.99, 95% CI 0.46 to 2.11, random-effects analysis, Tau² = 0.50; I² = 88% (Analysis 2.7)). Compared to betamimetics, however, ethanol was associated with a trend towards a lower rate of maternal adverse events requiring stopping or changing the drug (three trials, 214 women; RR 0.25, 95% CI 0.06 to 0.97, Analysis 2.8).

Ethanol use was associated with higher rates of neonatal respiratory distress syndrome (three trials, 823 women; RR 1.76, 95% CI 1.33 to 2.33 (Analysis 2.9)), and higher rates for babies with a birthweight of less than < 2500 g (five trials, 834 women; RR 1.30, 95% CI 1.09 to 1.54 (Analysis 2.10)).

These outcomes are likely all related to the lower incidence of preterm birth seen with other tocolytics, which for all these comparisons were betamimetics. The results for neonatal mortality must be viewed with additional caution as some trials did not report both perinatal mortality and neonatal mortality. Due to high measures of heterogeneity, random-effects models were used for the outcomes of preterm birth < 37 weeks, number of days delivery delayed, and overall maternal adverse events (Analysis 2.4; Analysis 2.6; Analysis 2.7).

DISCUSSION

Summary of main results

While early clinical findings supported the use of ethanol as a tocolytic (Fuchs 1965), concerns about its effectiveness and for fetal safety lead to it falling out of favor (ACOG 2011). Consequently, the trials available for this review are all fairly dated with the most recent one being published in 1987. There was much inconsistency in the data reported in these studies. In addition, all of these trials were completed before the routine use of antenatal corticosteroids, which may be responsible for some of the higher rates of neonatal mortality and respiratory distress syndrome seen in these trials.

Twelve studies involving 1586 women were available for review. In two of these studies with 77 women, ethanol was compared with

placeholder/control. The majority, nine studies with 1438 women, compared ethanol with another tocolytic (in this instance, all betamimetic agents). Spearing 1979 had a third group that received ethanol plus indomethacin and they excluded this arm. Steer 1977 compared ethanol and magnesium but contributed no data to the review.

Compared to placebo, ethanol was no different for birth < 48 hours after trial entry, perinatal mortality, neonatal mortality, or any of the secondary outcomes of preterm birth < 37 or < 34 weeks' gestation, adverse events, or neonatal outcomes.

Compared to betamimetic drugs, ethanol had a higher risk of neonatal mortality (although this difference was not apparent when our analysis excluded quasi-RCTs). Compared to betamimetics, ethanol was not different in regards to birth < 48 hours or perinatal mortality, preterm birth < 37 weeks, or number of days delivery was delayed. However, ethanol was associated with a higher rate of preterm birth < 34 weeks and respiratory distress syndrome and low birthweight babies. Compared to betamimetics though, ethanol was associated with a trend towards a lower rate of maternal side effects requiring stopping the drug.

From the available data, there is no evidence of ethanol being superior to placebo and it appears to be inferior to betamimetics in many aspects. Subgroup analysis (for our comparison of ethanol versus betamimetic) did not substantially change these findings, although the number of trials for subgroup analyses was limited. The only advantage shown for ethanol was a trend suggesting that it may be better tolerated than betamimetic therapy, although this is based on few trials with small samples sizes so this result should be interpreted with caution.

Overall completeness and applicability of evidence

There were no data available to investigate any possible association between ethanol as a tocolytic and fetal alcohol syndrome. Alcohol use in pregnancy is the leading cause of preventable mental retardation (ACOG 2011). None of the studies identified using ethanol as a tocolytic contained long-term neurodevelopmental follow-up of the offspring. This does open a potential avenue for future research. Long-term follow-up of the participants in these studies could provide information about any possible cognitive effect that ethanol may have had on the exposed fetuses during labor.

The evidence obtained is relatively old and is complete as ethanol use is essentially obsolete currently due to fetal alcohol syndrome concerns. Thus, it is unlikely any new randomized controlled trials on the topic area will be forthcoming. As such, the evidence's applicability is limited because the therapy is no longer in clinical use.

Quality of the evidence

The quality of the evidence mostly has a high risk of bias, with very few studies that are of at least moderate quality. No truly low 'Risk of bias' studies were identified. Much of the assessments were based on uncertainty because trials in that era did not clearly state all methods for the study as they were before CONSORT.

Potential biases in the review process

As this is a historical therapy no longer used, it is possible that reports were graded more harshly. The two Forster studies Forster 1987 (Part II); Forster 1987 (Part III) were in German and it is possible that the translations missed some information. These reasons are both felt to be unlikely.

Agreements and disagreements with other studies or reviews

We found no difference in outcomes of ethanol compared to placebo, but when compared mainly to betamimetics, that betamimetics were superior in delaying delivery and reducing preterm birth. This corroborates the Cochrane review of betamimetics that found they were superior to placebo/control at delaying delivery (Neilson 2014). This review found that, compared to betamimetics though, ethanol was associated with a trend towards a lower rate of maternal side effects requiring stopping the drug. This is consistent with observations in other studies which report that, compared to placebo, betamimetics are associated with higher levels of side effects resulting in the need for a change in medication (Haas 2012).

AUTHORS' CONCLUSIONS

Implications for practice

Historically, ethanol was used as a common tocolytic agent but is no longer used in practice due to safety concerns for both the mother and her baby. There is no evidence that ethanol is superior to placebo or to betamimetic drugs.

Implications for research

While there is no current need for research regarding ethanol as a tocolytic, long-term follow-up studies on offspring from older trials to assess the risk of long-term neurodevelopmental status would be useful.

ACKNOWLEDGEMENTS

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CHARACTERISTICS OF STUDIES

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

Boyd 1978

Methods	Design: this study randomized and analyzed 96 women in preterm labor. The methods of allocation/randomization are unknown Sample size: 96 (not calculated before trial). Setting: the study was conducted at the Institute of Obstetrics & Gynaecology, Queen Charlotte's Hospital in London
Participants	Patients in spontaneous preterm labor having 6 or more uterine contractions per hour between the 27th and 35th week of pregnancy were included in the study. Patients with cervical dilation of more than 4 cm or uterine bleeding were excluded. A total of 96 women were entered into the trial
Interventions	IV salbutamol: an initial dose of 5 ug/minute being increased to 50 ug/minute until contractions ceased or side effects precluded further increments IV ethanol: an initial dose of 30 mL/hour for 2 hours followed by 3 mL/hour Each regimen was continued for 12 hours and repeated up to 5 times if labor had not ceased. No oral therapy was used
Outcomes	Delivery prevented before the 37th week of gestation. Delivery within 24 hours of admission to the study.
Notes	Only have the abstract.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States "allocated randomly", but it is unclear how.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated.
Selective reporting (reporting bias)	Unclear risk	Not stated.

Boyd 1978 *(Continued)*

Other bias	Unclear risk	Not stated.

Caritis 1982

Methods	Design: this was a randomized controlled trial. Sample size: 92 (not prespecified). Setting: Magee-Women's Hostpital in Pittsburgh.
Participants	Women were included in the study if the following conditions were met (1) Regular painful uterine contractions were documented by a tocodynamometer and occurred at least every 5 to 7 minutes, lasted at least 30 seconds, and occurred for a minimum of 1 hour (2) The gestational age was between 20 and 36 weeks in women with intact membranes and between 24 and 34 weeks in women with ruptured membranes (3) There were no obstetric or medical contraindications to the inhibition of labor or to the use of the labor-inhibiting drug Women were excluded if they had received another labor-inhibiting drug for the current episode of preterm labor or if cervical dilation was greater than 5 cm Patients with rupture of membranes were analyzed as a subgroup This study randomized 92 women, but only analyzed 88 women (4 women were withdrawn because they did not fulfil the inclusion criteria)
Interventions	IV ethanol: a loading dose of 7.5 mL/kg/hour of 10% ethanol in 5% dextrose was infused for 2 hours. This was followed by a maintenance infusion of ethanol at a rate of 1.5 mL/kg/hour for 10 hours. If labor recurred, a second or third course of ethanol was given. For repeated courses, the reloading dose was reduced by 10% for each hour less than 10 elapsing from the end of the previous maintenance infusion IV terbutaline: terbutaline was diluted with physiologic saline solution to a concentration of 20 ug/mL. Physiologic saline solution (400 mL) was infused over 20 minutes before the administration of terbutaline. The rate of infusion of terbutaline was started at 5 ug/minute and was increased by 5 ug/minute every 20 minutes to a maximal dosage of 30 ug/minute or until uterine contractions were abolished or maternal side effects occurred. Once contractions were abolished, the infusion was maintained at that rate for 1 hour, then, the rate of infusion was reduced to the minimal dose (5-10 ug/minute) required to inhibit labor and was maintained at that rate for an additional 8 hours. If labor recurred during the 8-hour maintenance infusion, the rate was increased until labor again subsided, and the entire maintenance infusion was again initiated All women with intact membranes in whom labor was inhibited received 5 mg of terbutaline orally 30 minutes before the end of the IV maintenance infusion. This dosage was repeated 4 times daily for 5 days. No oral medication was given to women with rupture of membranes
Outcomes	Completely successful: pregnancy maintained beyond 36 weeks. Partially successful: prevented delivery or progression of cervical dilation during IV therapy, at least until a mature L/S ratio was obtained or until a full course of betamethasone could be given to the mother to enhance fetal lung maturation Failed: side effects or drug intolerance led to discontinuation of an assigned drug treatment, and the patient continued to experience labor

Caritis 1982 *(Continued)*

Notes	Bethamethasone (12 mg) was given IM 2 times, 24 hours apart to all women. A course was considered to be complete 36 hours after the first injection If treatment failed, a second labor-inhibiting drug, magnesium sulfate, was started Women with rupture of membranes: Objective was to maintain pregnancy for 36 hours. Thus, no further labor-inhibiting therapy was given after 36 hours, but induction of labor was not encouraged until labor recurred or signs of chorioamnionitis or fetal distress were detected

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used random number generator.
Allocation concealment (selection bias)	Unclear risk	Neither physician nor patient was aware of the treatment modality until informed consent had been signed. Then a sealed envelope containing 1 of 2 randomly assigned treatment protocols was opened and the treatment was identified. Thus, no one aware until after randomization. However, unclear if the envelope was opaque
Blinding of participants and personnel (performance bias) All outcomes	High risk	Knew after enveloped was opened.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition bias.
Selective reporting (reporting bias)	Low risk	4 of the 92 women were excluded in the review because they did not meet the inclusion criteria
Other bias	Low risk	None.

Castren 1975

Methods	Design: the study was a "quasi" randomized controlled trial. Sample Size:194 (not prespecified). Setting: the trials were performed at the University Central Hospital of Helsinki (nylidrin versus ethanol) and the Midwifery Institute Hospital (isoxuprine versus placebo)
Participants	Partcipants in this study were pregnant women between 24 and 36 weeks' gestation in premature labor. Inclusion criteria were intact membranes and active uterine contractions
Interventions	Treatment with the randomized protocol was started on admission. Treatment was as follows University Central Hospital of Helsinki: Nylidrin (50 mg IV over 6 hours, then approximately 65 mg IM over 57 hours, then 6 mg PO every 5 hours) versus ethanol (128 mL IV over 6 hours, then 40 mL of cognac every 6 hours, which was prescribed to continue at home upon discharge) Midwifery Institute Hospital: isoxuprine (25 mg IV over 1 hour, then 160 mg IM over 60 hours, then 10 mg PO every 4 hours continued after discharge) versus placebo (followed the protocol as described for nylidrin)
Outcomes	The reported outcome as "successful" treatment defined as the premature contractions were arrested and pregnancy prolonged such that the birthweight was >/= 2500 g, or that the pregnancy was prolonged by 7 days and the pregnancy continued until at least the 37th week of gestational age. Thus this trial contained the outcome of preterm birth < 37 weeks only
Notes	We analyzed the women from the University Central Hospital of Helsinki since these women were the group randomized to nylidrin or ethyl alcohol

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Alternating based on admission.
Allocation concealment (selection bias)	High risk	Alternating allocation based on admission.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Based on protocol, it was not possible to blind participants or providers, especially with women who became intoxicated with ethanol
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition bias.

Castren 1975 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Method of reporting makes it unclear if all outcomes are reported for the comparisons. No prespecified outcomes stated in Methods
Other bias	Unclear risk	It was reported that the study obtained their pharmaceuticals directly from the pharmaceutical companies. It was unclear whether these were paid for or not

Forster 1987 (Part II)

Methods	Design: this was a parallel randomized study. Sample size: 223 (not prespecified). Setting: Germany.
Participants	Women were included in this study if they were pregnant and experiencing premature labor. The exclusion criteria were not specified
Interventions	This was a parallel study with 3 groups. Group 1: fenoterol (1-3 ug/minute). Group 2: ethanol 50 in a fructose solution (20 gtt/minute). Group 3: placebo (glucose 50), however the first 10 women showed no change with placebo and were therefore divided into Groups 1 and 2 for the rest of the study
Outcomes	Measured outcomes included birthweight, length of gestation extended, mortality rate, morbidity rate in relation to RDS
Notes	Review was originally written in German. Information here is found on the Cochrane Pregnancy and Childbirth Group Translation Form and original report tables 1 patient's pregnancy ended in abortion, but it appears that they were included in the data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Patients were split into groups by last name, not randomized
Allocation concealment (selection bias)	High risk	Last name would be known on admission.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unable to blind participants and personnel during treatment if women were intoxicated with ethanol

Forster 1987 (Part II)   *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Appears to be no attrition bias noted in the translation document
Selective reporting (reporting bias)	Unclear risk	Not stated in translation form.
Other bias	High risk	There were originally 3 groups but the study designers divided the placebo group into the 2 study groups when there was no change from placebo in the study

Forster 1987 (Part III)

Methods	Design: this was a parallel randomized study. Sample size: 464 (not prespecified). Setting: Germany.
Participants	Women were included in this study if they were pregnant and experiencing premature labor. The exclusion criteria was not specified. All women were approximately 32 weeks' gestation
Interventions	There were 4 treatment groups. Group 1: long-term ethanol. Group 2: long-term partusisten. Group 3: short-term ethanol. Group 4: short-term partusisten. Due to a limited translation form, we combined the data for the long term and short term for both treatments
Outcomes	What determined a success was based on the length of the gestation period; the weight, Apgar score, RDS mortality, maturation level, neonatal morbidity; prolongation index and success score
Notes	Review was originally written in German. Information here is found on the Cochrane Pregnancy and Childbirth Group Translation Form 2 women' participation ended in abortion, but it appears that they were included in the data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Patients were split into groups by last name, not randomized

Forster 1987 (Part III) *(Continued)*

Allocation concealment (selection bias)	High risk	Last name would be known on admission.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unable to blind participants and personnel during treatment if women were intoxicated with ethanol
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated in translation form.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Appears to be no attrition bias noted in the translation document
Selective reporting (reporting bias)	Unclear risk	Not stated in translation form.
Other bias	Unclear risk	Not stated in translation form.

Lauersen 1977

Methods	Design: randomized controlled trial. Sample size: 135 women with threatened premature labor from 3 collaborating centers (not prespecified) Setting: 3 collaborating centers- New York, NY; Cleveland, OH, and East Meadows, NY- all in United States
Participants	Patient included in this study fulfilled the following criteria: (1) regular uterine contractions of 30-60 seconds' duration at least once every 10 minutes and clinically judged as premature labor; (2) pregnancy between 20 and 36 weeks; (3) estimated fetal weight below 2500 g; (4) uterine fundus above the umbilicus; (5) membranes intact and not bulging; (6) cervical effacement; and (7) cervical dilation not exceeding 4 cm. Exclusion criteria were as follows: (1) premature separation of the placenta, (2) pre-eclampsia, chronic renal disease, chronic hypertension, cardiac disease, diabetes mellitus, and other severe maternal diseases, (3) presence of a dead or malformed fetus, (4) placenta previa if bleeding was severe enough to require intervention, and (5) any maternal or fetal complication that required immediate delivery
Interventions	Patients were randomized to either the ritodrine group (68 women) or ethanol group (67 women) Ritodrine group: IV infusion of 50 ug/minute of ritodrine, which was increased by 50 ug every 10 minutes until adequate uterine relaxation occurred, with a maximum infusion rate of 350 ug/minute. The optimal dose for each patient was maintained for 12 hours. 30 minutes prior to termination of infusion, oral ritodrine was started and women were discharged on ritodrine orally in doses ranging from 20 to 60 mg daily maintained for 4 weeks or until 38 weeks' gestation, whichever came first Ethanol group: a loading dose infusion of 7.5 mL/kg/hour ethanol was given for 2

Lauersen 1977 *(Continued)*

	hours, followed by maintenance dose of 1.5 mL/kg/hour for 10 hours. If premature labor recurred after the ethanol infusion, up to 2 additional courses following the same protocol were permitted
Outcomes	Measured outcomes included (1) delivery postponed for more than 72 hours, (2) time gained, (3) gestational age at time of delivery, (4) perinatal mortality, and (5) infant morbidity in relation to RDS
Notes	150 randomized initially, later 15 found to not meet inclusion criteria

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly drawn sealed envelopes were used for randomization.
Allocation concealment (selection bias)	Unclear risk	Likely low risk as stated sealed envelopes. However, unclear if the envelope was opaque thus rated as Unclear
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unable to blind participants and personnel during treatment if women were intoxicated with ethanol
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition bias.
Selective reporting (reporting bias)	Low risk	No reporting bias.
Other bias	Low risk	None identified.

Reynolds 1978

Methods	Design: randomized controlled trial. Sample size: 84 women (not prespecified). Setting: not specified but author from Hammersmith Hospital, London
Participants	In this study, 84 women in premature labor were selected for the trial. Inclusion criteria were gestational age between 20 and 37 weeks and contractions occurring at least every 10 minutes. Exclusions from participation included major maternal complications, the cervix dilated more than 5 cm, amnionitis, or significant hemorrhage

Reynolds 1978   (*Continued*)

Interventions	Group 1: salbutamol infusion until titrated to 40 ug/minute, uterine contractions ceased, or patient became tachycardic. 200 mg sodium phenobarbitone also given to women in this group Group 2: ethanol 10-hour treatment according to the Fuchs 1967 protocol.
Outcomes	The criterion for success was an inhibition of labor for 24 hours
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Patients were alternated to the 2 groups.
Allocation concealment (selection bias)	High risk	Alternate allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unable to blind participants and personnel during treatment if women were intoxicated with ethanol
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition bias.
Selective reporting (reporting bias)	Unclear risk	No prespecified outcomes other than inhibition of labor for 24 hours
Other bias	Low risk	None identified.

Sims 1978

Methods	Design: randomized trial. Sample size: 100 women (not prespecified). Only 88 of the 100 were analyzed. 12 women were withdrawn (8 sets of twins, 2 < 27 weeks, 1 placenta previa, 1 lost records) Setting: Institute of Obstetrics & Gynaecology, Queen Charlotte's Hospital in London
Participants	All women admitted in labor between 27 and 35 weeks' gestation were invited to join the study whether the membranes were intact or ruptured. The diagnosis of labor was made on a history of 6 or more contractions per hour Patients were not considered in cases of multiple pregnancies, if postponement of delivery was contraindicated, or if cervix was more than 4 cm dilated

Sims 1978   *(Continued)*

Interventions	IV ethanol: a solution of 10% v/v ethanol in 5% dextrose in water was prepared. The solution was administered intravenously at the rate of 15 mL/kg of body weight over the first 2-hour period. A maintenance infusion of 1.5 mL/kg of body weight per hour was administered for a further 10 hours. If contractions reappeared after discontinuation, the treatment was repeated IV salbutamol: a solution of 4 mg salbutamol in 500 mL of 5% dextrose in water was prepared. The solution was administered intravenously at 5 ug of salbutamol per minute. The infusion rate was increased by 5 ug of salbutamol per minute every 10 minutes until either (a) contractions were abolished, (b) a maximum rate of 50 ug per minute was attained, or (c) until unacceptable side effects occurred. The infusion rate was maintained at the lowest rate to stop contractions for a total of 12 hours (24 hours for ruptured membranes). If contractions reappeared the treatment was repeated Betamethasone therapy: each patient received either 4 mg of betamethasone IM or saline placebo IM according to a randomized scheme. These injections were repeated 8 hourly for 6 doses
Outcomes	Delay delivery for at least 24 hours. Delay delivery for at least 48 hours. Delivery after 37 weeks.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States there was a "randomized list", but there is not enough detail
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition bias.
Selective reporting (reporting bias)	Low risk	No reporting bias.
Other bias	Low risk	None.

Spearing 1979

Methods	Design: randomized trial. Sample size: 66 women (not prespecified). Only 62 of the 66 were analyzed. 4 women were withdrawn due to drug administration protocol violations Setting: University of Bristol, UK.
Participants	Patients were admitted to the trial if they were in labor (regular painful contractions occurring at least once every 10 minutes) between 26 and 35 completed weeks of gestation inclusive, and in whom arrest of labor was considered advisable. Those women with multiple pregnancy, threatened premature labor with show, and suspected rupture of membranes were included Patients with antepartum hemorrhage, known fetal abnormality, and gross hydramnios were considered reasons for exclusion
Interventions	Treatment was selected in sequence in the labor room. IV ethanol: ethanol was prepared as a 10% solution in 5% dextrose. A loading dose of 15 mL/kg of body weight was infused over 2 hours followed by a maintenance dose of 1.5 mL/kg of body weight IV ethanol + indomethacin: ethanol was given as previously stated. 100 mg of indomethacin was given as a rectal suppository, and a similar dose was given after 12 hours. After 24 hours, this was continued orally with 25 mg every 6 hours for 48 hours after cessation of contractions IV salbutamol: 5 mL of salbutamol to 500 mL of 5% dextrose was prepared, giving a concentration of 10 ug/mL. Infusion began at 20 drops/minute increased by increments of 10 drops/minute every 10 minutes until contractions ceased. The maximum infusion rate was 80 drops/minute or less if the maternal pulse rate exceeded 140 bpm or other maternal distress occurred (palpitations or hypotension). With cessation of contractions the infusion was maintained at the successful level for 6 hours and then gradually decreased. Treatment was continued with oral salbutamol 4 mg four times a day and continued for at least 48 hours 2 infusions of any treatment were allowed.
Outcomes	Success: uterine activity ceased and did not return until 36 weeks or later, or returned only after 48 hours free of labor
Notes	In the cases of failure, treatment was changed. Only the data from the IV ethanol and IV salbutamol were included in our analysis because it was unclear whether the effects of the ethanol + indomethacin were due to the Indomethacin or the combination of the 2

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"Treatment was selected in sequence in the labor room, and the patient's name was added to a list which indicated the treatment to be given."
Allocation concealment (selection bias)	High risk	"Selected in sequence."

Spearing 1979   (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition bias.
Selective reporting (reporting bias)	Low risk	No reporting bias.
Other bias	Low risk	None.

Steer 1977

Methods	Design: randomized controlled trial. Sample size: 71 (not prespecified). Setting: Sloane Hospital for Women of the Columbia-Presbyterian Medical Center in New York
Participants	Patients in the study included those who met all of the following criteria: (1) there was a painful, identifiable contraction pattern with a frequency of 5 minutes or less, (2) the duration of the pregnancy was less than 37 weeks, (3) the estimated fetal weight was less than 2500 g, (4) the amnion was intact, and (5) cervical dilation was less than 5 cm Patients with a fever due to amnionitis or those with bleeding greater than "show" were excluded from the study
Interventions	IV ethanol: a solution of 9.5% v/v ethanol in 5% dextrose in water was administered intravenously at the rate of 15 mL/kg of body weight over the first 2 hours. A maintenance infusion rate of 1.5 mL/kg of body weight per hour was administered until signs of labor had subsided or labor had progressed to an irreversible stage. If contractions reappeared after discontinuation, the procedure was repeated IV magnesium sulfate: a 2% maintenance solution was prepared by adding 200 mL of 10% magnesium sulfate to 800 mL of 5% dextrose in water. 4 g of magnesium sulfate was infused intravenously, slowly enough to avoid flushing and vomiting. A constant infusion of the 2% maintenance solution was then given at 100 mL/hour. This continued until labor had subsided or labor had progressed to an irreversible stage. The rate was reduced if magnesium toxicity was observed. If contractions reappeared, the procedure was repeated IV dextrose in water: a solution of 5% dextrose in water was infused intravenously at 100 mL/hour
Outcomes	Success: contractions stopped and a period of at least 24 hours went by before contractions occurred again
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Patient received treatment according to the last digit of their hospital number (not truly random). A small group of women were chosen at random to receive the dextrose in water for a control group
Allocation concealment (selection bias)	High risk	Last digit of medical record number.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition bias.
Selective reporting (reporting bias)	Low risk	No reporting bias.
Other bias	Low risk	None.

Watring 1976

Methods	Design: single-blind randomized trial. Sample size: 35 women (not prespecified). Setting: Tripler Army Medical Center in San Francisco, CA in the United States
Participants	Criteria for inclusion in this study were as follows. (1) a living, single gestation between 24 and 36 weeks. (2) a history of painful uterine contractions less than 10 minutes apart for 1 hour or more. (3) regular uterine contractions as determined by palpation and tokodynamometer. (4) greater than 50% effacement of the cervix with or without dilation. (5) absence of complications such as bleeding, premature rupture of membranes, and fever. (6) no history of incompetent cervical os
Interventions	Study group: received an IV infusion of 5% ethanol in 5% dextrose in water. A loading dose of 15 cc/lb/2 hour and a maintenance dose of 10% of the total loading dose per hour until the contractions had ceased for at least 6 hours. If contractions were still present after 4 hours or if they recurred within 24 hours, one-half of the loading dose was given in 1 hour and the maintenance dose continued for a total of 12 hours. After contractions ceased, women were kept on bed rest for 24 hours. Then, women were on a 24 ambulation period. If no contractions occurred, patient was discharged Control group: usually treated with either morphine sulfate or secobarbital and ambu-

Watring 1976 *(Continued)*

	lated on the same schedule
Outcomes	Success: patient remained without contractions for 72 hours following treatment
Notes	If contractions recurred for a third time, no attempt was made to stop labor

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Groups of 10 cards, 5 treatment and 5 control, were placed in an envelope from which they were drawn by a disinterested, third party. When all cards had been drawn, another group of 10 cards was placed in the envelope and the process repeated
Allocation concealment (selection bias)	Unclear risk	Drawn from envelope. However, unclear if the envelope was opaque
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Single blind" but unclear which group was actually blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition bias.
Selective reporting (reporting bias)	Low risk	No reporting bias.
Other bias	Low risk	None.

Zlatnik 1972

Methods	Design: randomized controlled trial. Sample size: 42 women (not prespecified). Setting: New York Hospital-Cornell Medical Center in the United States
Participants	Patients admitted to the hospital with threatened premature labor were included in the study if stopping labor was deemed advisable Patients were excluded from the study if delivery seemed imminent, the membranes were ruptured, or the patient was bleeding actively or had some other factor which contraindicated the continuation of pregnancy

Zlatnik 1972 *(Continued)*

Interventions	IV ethanol: 9.5% ethanol solution.
	IV glucose: 5% glucose in water.
	Patients received 15 mL/kg of the assigned solution intravenously over a 2 hour period as a loading dose and then 1.5 mL/kg per hour as a maintenance dose for an additional 6 to 10 hours. If labor actively progressed so that delivery seemed imminent, the ethanol was discontinued. If labor stopped, but later recurred, the assigned solution was again administered as outlined above
Outcomes	Success: delivery did not occur within 72 hours.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated "there was random assignment of the two treatments to the numbered envelopes"
Allocation concealment (selection bias)	Low risk	Used serially numbered, sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition bias.
Selective reporting (reporting bias)	Low risk	No reporting bias.
Other bias	High risk	Stopped the study "when the plot of data indicated one treatment superior to the other" Also states that "there were no significant differences between the two groups in regard to age, marital status, race, parity, weeks of gestation, or cervical dilation at the start of treatment, but the data is not shown"

bpm: beats per minute
IM: intramuscular
IV: intravenous
RDS: respiratory distress syndrome

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

Study	Reason for exclusion
Waltman 1969	This study is not a randomized controlled trial.

DATA AND ANALYSES

Comparison 1. Ethanol versus placebo/control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Birth < 48 hours after trial entry	1	35	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.43, 2.00]
1.1 Women with intact membranes	1	35	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.43, 2.00]
1.2 Women with ruptured membranes	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Women without specified membrane status	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Perinatal mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.1 Women with intact membranes	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Women with ruptured membranes	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Women without specified membrane status	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Neonatal mortality	1	35	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.31, 3.58]
3.1 Women with intact membranes	1	35	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.31, 3.58]
3.2 Women with ruptured membranes	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Women without specified membrane status	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Preterm birth < 37 weeks	1	35	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.72, 2.31]
5 Preterm birth < 34 weeks	1	35	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [0.69, 4.16]
6 Number of days delivery delayed	1	35	Mean Difference (IV, Fixed, 95% CI)	-3.43 [-22.74, 15.88]
7 Maternal adverse events (overall)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Maternal adverse events (required stopping or changing drug)	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Respiratory distress syndrome	1	35	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.27, 2.64]
10 Birthweight < 2500 g	1	35	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.81, 2.46]

Comparison 2.   Ethanol versus other tocolytic drug

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Birth < 48 hours after trial entry	2	130	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.53, 2.37]
1.1 Women with intact membranes	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Women with ruptured membranes	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Women without specified membrane status	2	130	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.53, 2.37]
2 Perinatal mortality	6	698	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.78, 1.84]
2.1 Women with intact membranes	2	210	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.40, 2.05]
2.2 Women with ruptured membranes	1	32	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [0.52, 7.30]
2.3 Women without specified membrane status	4	456	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.73, 2.19]
3 Neonatal mortality	8	1238	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [1.02, 2.02]
3.1 Women with intact membranes	3	303	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.49, 2.11]
3.2 Women with ruptured membranes	1	32	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [0.52, 7.30]
3.3 Women without specified membrane status	5	903	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [1.03, 2.35]
4 Preterm birth < 37 weeks	4	741	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.86, 1.36]
5 Preterm birth < 34 weeks	2	599	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [1.11, 2.19]
6 Number of days delivery delayed	5	585	Mean Difference (IV, Random, 95% CI)	-2.51 [-11.11, 6.09]
7 Maternal adverse events (overall)	4	350	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.46, 2.11]
8 Maternal adverse events (required stopping or changing drug)	3	214	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.06, 0.97]
9 Respiratory distress syndrome	3	823	Risk Ratio (M-H, Fixed, 95% CI)	1.76 [1.33, 2.33]
10 Birthweight < 2500 g	5	834	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [1.09, 1.54]

Analysis I.I. Comparison I Ethanol versus placebo/control, Outcome I Birth < 48 hours after trial entry.

Comparison: I Ethanol versus placebo/control

Outcome: I Birth < 48 hours after trial entry

Study or subgroup	Ethanol n/N	Placebo/control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
I Women with intact membranes					
Watring 1976	7/17	8/18	■	100.0 %	0.93 [0.43, 2.00]
Subtotal (95% CI)	**17**	**18**	◆	**100.0 %**	**0.93 [0.43, 2.00]**
Total events: 7 (Ethanol), 8 (Placebo/control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.19 (P = 0.85)					
2 Women with ruptured membranes					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Ethanol), 0 (Placebo/control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Women without specified membrane status					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Ethanol), 0 (Placebo/control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**17**	**18**	◆	**100.0 %**	**0.93 [0.43, 2.00]**
Total events: 7 (Ethanol), 8 (Placebo/control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.19 (P = 0.85)					
Test for subgroup differences: Not applicable					

```
         0.01   0.1    I    10   100
      Favours [ethanol]    Favours [placebo]
```

Analysis 1.3. Comparison 1 Ethanol versus placebo/control, Outcome 3 Neonatal mortality.

Review: Ethanol for preventing preterm birth in threatened preterm labor

Comparison: 1 Ethanol versus placebo/control

Outcome: 3 Neonatal mortality

Study or subgroup	Ethanol n/N	Placebo/control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Women with intact membranes					
Watring 1976	4/17	4/18	■	100.0 %	1.06 [0.31, 3.58]
Subtotal (95% CI)	**17**	**18**	◆	**100.0 %**	**1.06 [0.31, 3.58]**
Total events: 4 (Ethanol), 4 (Placebo/control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.09 (P = 0.93)					
2 Women with ruptured membranes					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Ethanol), 0 (Placebo/control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Women without specified membrane status					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Ethanol), 0 (Placebo/control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**17**	**18**	◆	**100.0 %**	**1.06 [0.31, 3.58]**
Total events: 4 (Ethanol), 4 (Placebo/control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.09 (P = 0.93)					
Test for subgroup differences: Not applicable					

```
        0.01   0.1    1     10    100
     Favours [ethanol]    Favours [placebo]
```

Analysis 1.4. Comparison 1 Ethanol versus placebo/control, Outcome 4 Preterm birth < 37 weeks.

Review: Ethanol for preventing preterm birth in threatened preterm labor

Comparison: 1 Ethanol versus placebo/control

Outcome: 4 Preterm birth < 37 weeks

Study or subgroup	Ethanol n/N	Placebo/control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Watring 1976	11/17	9/18		100.0 %	1.29 [0.72, 2.31]
Total (95% CI)	**17**	**18**		**100.0 %**	**1.29 [0.72, 2.31]**

Total events: 11 (Ethanol), 9 (Placebo/control)

Heterogeneity: not applicable

Test for overall effect: Z = 0.87 (P = 0.38)

Test for subgroup differences: Not applicable

```
        0.01   0.1    1    10    100
      Favours [ethanol]   Favours [placebo]
```

Analysis 1.5. Comparison 1 Ethanol versus placebo/control, Outcome 5 Preterm birth < 34 weeks.

Review: Ethanol for preventing preterm birth in threatened preterm labor

Comparison: 1 Ethanol versus placebo/control

Outcome: 5 Preterm birth < 34 weeks

Study or subgroup	Ethanol n/N	Placebo/control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Watring 1976	8/17	5/18		100.0 %	1.69 [0.69, 4.16]
Total (95% CI)	**17**	**18**		**100.0 %**	**1.69 [0.69, 4.16]**

Total events: 8 (Ethanol), 5 (Placebo/control)

Heterogeneity: not applicable

Test for overall effect: Z = 1.15 (P = 0.25)

Test for subgroup differences: Not applicable

```
        0.01   0.1    1    10    100
      Favours [ethanol]   Favours [placebo]
```

Analysis 1.6. Comparison 1 Ethanol versus placebo/control, Outcome 6 Number of days delivery delayed.

Review: Ethanol for preventing preterm birth in threatened preterm labor

Comparison: 1 Ethanol versus placebo/control

Outcome: 6 Number of days delivery delayed

Study or subgroup	Ethanol		Placebo/control		Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
	N	Mean(SD)	N	Mean(SD)			
Watring 1976	17	20.29 (28.53)	18	23.72 (29.76)		100.0 %	-3.43 [-22.74, 15.88]
Total (95% CI)	**17**		**18**			**100.0 %**	**-3.43 [-22.74, 15.88]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.35 (P = 0.73)

Test for subgroup differences: Not applicable

```
              -100   -50    0    50   100
           Favours [placebo]      Favours [ethanol]
```

Analysis 1.8. Comparison 1 Ethanol versus placebo/control, Outcome 8 Maternal adverse events (required stopping or changing drug).

Review: Ethanol for preventing preterm birth in threatened preterm labor

Comparison: 1 Ethanol versus placebo/control

Outcome: 8 Maternal adverse events (required stopping or changing drug)

Study or subgroup	Ethanol n/N	Placebo/control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Zlatnik 1972	0/21	0/21			Not estimable
Total (95% CI)	**21**	**21**			**Not estimable**

Total events: 0 (Ethanol), 0 (Placebo/control)

Heterogeneity: not applicable

Test for overall effect: not applicable

Test for subgroup differences: Not applicable

```
           0.01  0.1    1    10   100
        Favours [ethanol]      Favours [placebo]
```
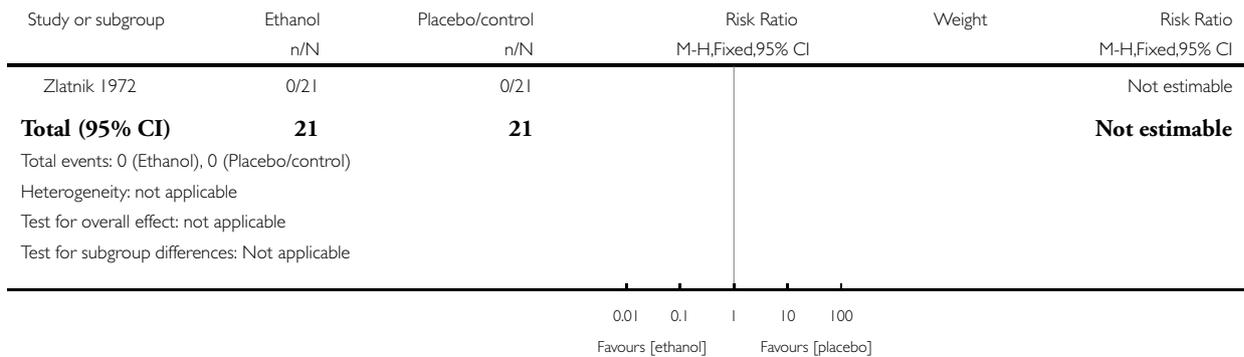
Analysis 1.9. Comparison 1 Ethanol versus placebo/control, Outcome 9 Respiratory distress syndrome.

Review: Ethanol for preventing preterm birth in threatened preterm labor

Comparison: 1 Ethanol versus placebo/control

Outcome: 9 Respiratory distress syndrome

Study or subgroup	Ethanol n/N	Placebo/control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Watring 1976	4/17	5/18		100.0 %	0.85 [0.27, 2.64]
Total (95% CI)	**17**	**18**		**100.0 %**	**0.85 [0.27, 2.64]**
Total events: 4 (Ethanol), 5 (Placebo/control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.29 (P = 0.77)					
Test for subgroup differences: Not applicable					

0.01 0.1 1 10 100

Favours [ethanol]   Favours [placebo]
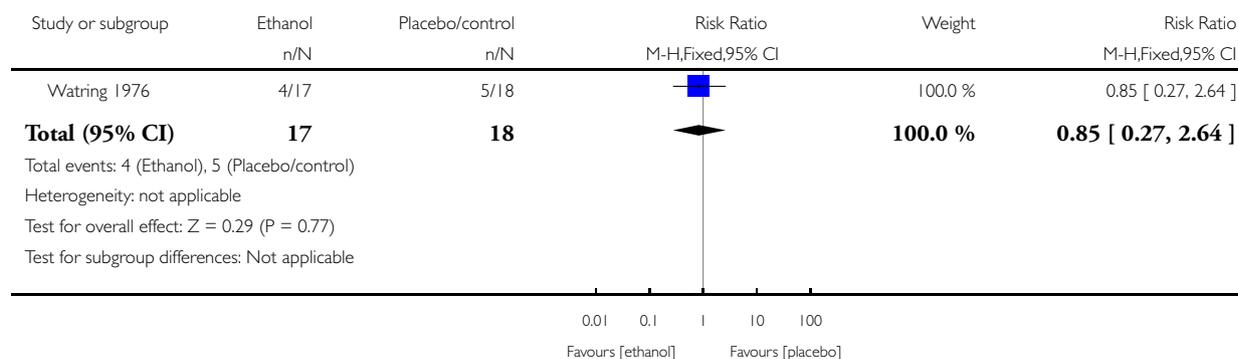
Analysis 1.10. Comparison 1 Ethanol versus placebo/control, Outcome 10 Birthweight < 2500 g.

Review: Ethanol for preventing preterm birth in threatened preterm labor

Comparison: 1 Ethanol versus placebo/control

Outcome: 10 Birthweight < 2500 g

Study or subgroup	Ethanol n/N	Placebo/control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Watring 1976	12/17	9/18		100.0 %	1.41 [0.81, 2.46]
Total (95% CI)	**17**	**18**		**100.0 %**	**1.41 [0.81, 2.46]**
Total events: 12 (Ethanol), 9 (Placebo/control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.22 (P = 0.22)					
Test for subgroup differences: Not applicable					

0.01 0.1 1 10 100

Favours [ethanol]   Favours [placebo]
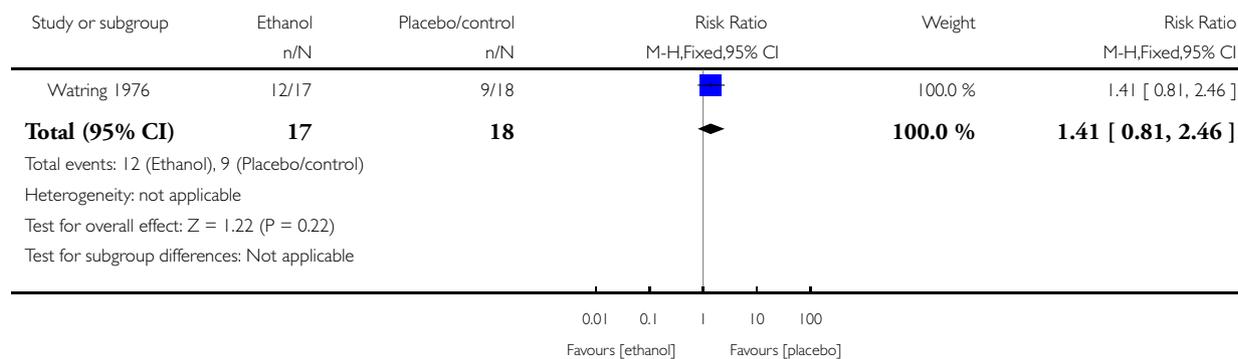
Analysis 2.1. Comparison 2 Ethanol versus other tocolytic drug, Outcome 1 Birth < 48 hours after trial entry.

Review: Ethanol for preventing preterm birth in threatened preterm labor

Comparison: 2 Ethanol versus other tocolytic drug

Outcome: 1 Birth < 48 hours after trial entry

Study or subgroup	Ethanol	Other tocolytic	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
	n/N	n/N			
1 Women with intact membranes					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Ethanol), 0 (Other tocolytic)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Women with ruptured membranes					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Ethanol), 0 (Other tocolytic)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Women without specified membrane status					
Sims 1978	20/46	22/42		62.3 %	0.83 [0.54, 1.29]
Spearing 1979	10/22	5/20		37.7 %	1.82 [0.75, 4.41]
Subtotal (95% CI)	**68**	**62**		**100.0 %**	**1.12 [0.53, 2.37]**
Total events: 30 (Ethanol), 27 (Other tocolytic)					
Heterogeneity: Tau² = 0.19; Chi² = 2.47, df = 1 (P = 0.12); I² =59%					
Test for overall effect: Z = 0.28 (P = 0.78)					
Total (95% CI)	**68**	**62**		**100.0 %**	**1.12 [0.53, 2.37]**
Total events: 30 (Ethanol), 27 (Other tocolytic)					
Heterogeneity: Tau² = 0.19; Chi² = 2.47, df = 1 (P = 0.12); I² =59%					
Test for overall effect: Z = 0.28 (P = 0.78)					
Test for subgroup differences: Not applicable					

```
        0.01   0.1    1    10   100
      Favours [ethanol]    Favours [other tocolytic]
```

Analysis 2.2. Comparison 2 Ethanol versus other tocolytic drug, Outcome 2 Perinatal mortality.

Review: Ethanol for preventing preterm birth in threatened preterm labor

Comparison: 2 Ethanol versus other tocolytic drug

Outcome: 2 Perinatal mortality

Study or subgroup	Ethanol n/N	Other tocolytic n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Women with intact membranes					
Caritis 1982	3/30	8/31		23.3 %	0.39 [0.11, 1.32]
Lauersen 1977	7/76	3/73		9.1 %	2.24 [0.60, 8.34]
Subtotal (95% CI)	**106**	**104**		**32.4 %**	**0.91 [0.40, 2.05]**
Total events: 10 (Ethanol), 11 (Other tocolytic)					
Heterogeneity: Chi² = 3.66, df = 1 (P = 0.06); I² =73%					
Test for overall effect: Z = 0.24 (P = 0.81)					
2 Women with ruptured membranes					
Caritis 1982	4/13	3/19		7.2 %	1.95 [0.52, 7.30]
Subtotal (95% CI)	**13**	**19**		**7.2 %**	**1.95 [0.52, 7.30]**
Total events: 4 (Ethanol), 3 (Other tocolytic)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.99 (P = 0.32)					
3 Women without specified membrane status					
Boyd 1978	3/50	4/55		11.3 %	0.83 [0.19, 3.51]
Forster 1987 (Part II)	13/105	9/118		25.1 %	1.62 [0.72, 3.64]
Reynolds 1978	4/42	6/42		17.8 %	0.67 [0.20, 2.19]
Spearing 1979	5/23	2/21		6.2 %	2.28 [0.49, 10.54]
Subtotal (95% CI)	**220**	**236**		**60.4 %**	**1.26 [0.73, 2.19]**
Total events: 25 (Ethanol), 21 (Other tocolytic)					
Heterogeneity: Chi² = 2.38, df = 3 (P = 0.50); I² =0.0%					
Test for overall effect: Z = 0.82 (P = 0.41)					
Total (95% CI)	**339**	**359**		**100.0 %**	**1.20 [0.78, 1.84]**
Total events: 39 (Ethanol), 35 (Other tocolytic)					
Heterogeneity: Chi² = 7.05, df = 6 (P = 0.32); I² =15%					
Test for overall effect: Z = 0.81 (P = 0.42)					
Test for subgroup differences: Chi² = 1.00, df = 2 (P = 0.61), I² =0.0%					

0.01   0.1   1   10   100

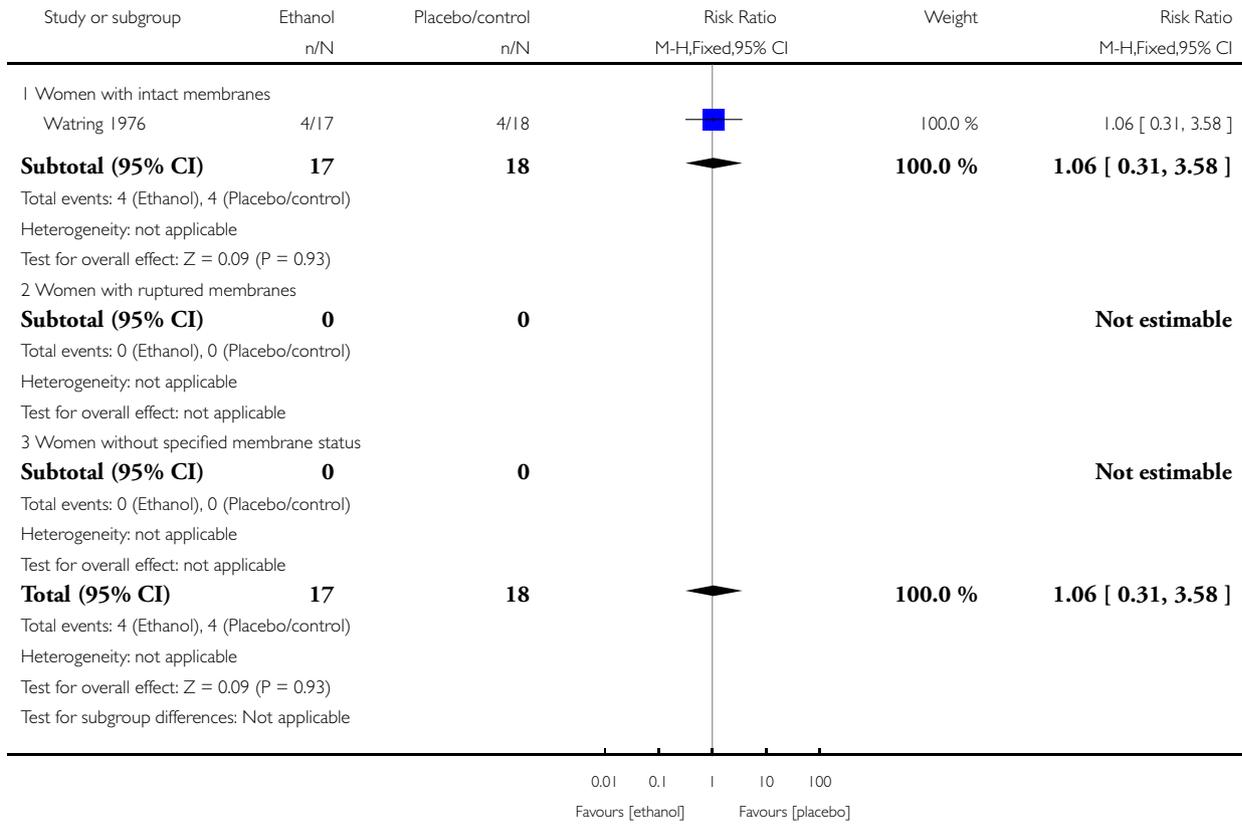Favours [ethanol]   Favours [other tocolytic]

Analysis 2.3. Comparison 2 Ethanol versus other tocolytic drug, Outcome 3 Neonatal mortality.

Review: Ethanol for preventing preterm birth in threatened preterm labor

Comparison: 2 Ethanol versus other tocolytic drug
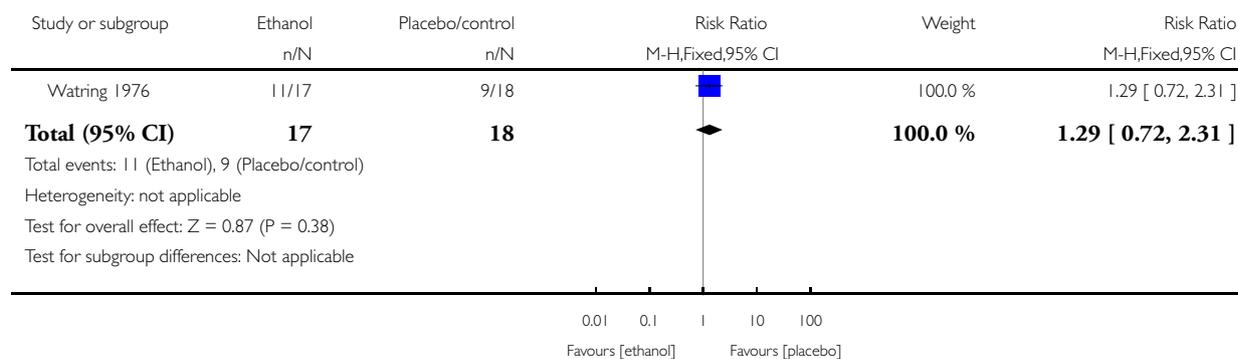
Outcome: 3 Neonatal mortality

Study or subgroup	Ethanol n/N	Other tocolytic n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Women with intact membranes					
Caritis 1982	2/30	6/31		11.9 %	0.34 [0.08, 1.57]
Castren 1975	5/50	4/43		8.7 %	1.08 [0.31, 3.75]
Lauersen 1977	7/76	3/73		6.2 %	2.24 [0.60, 8.34]
Subtotal (95% CI)	**156**	**147**		**26.7 %**	**1.02 [0.49, 2.11]**
Total events: 14 (Ethanol), 13 (Other tocolytic)					
Heterogeneity: Chi² = 3.35, df = 2 (P = 0.19); I² =40%					
Test for overall effect: Z = 0.05 (P = 0.96)					
2 Women with ruptured membranes					
Caritis 1982	4/13	3/19		4.9 %	1.95 [0.52, 7.30]
Subtotal (95% CI)	**13**	**19**		**4.9 %**	**1.95 [0.52, 7.30]**
Total events: 4 (Ethanol), 3 (Other tocolytic)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.99 (P = 0.32)					
3 Women without specified membrane status					
Forster 1987 (Part II)	12/105	9/118		17.1 %	1.50 [0.66, 3.41]
Forster 1987 (Part III)	22/222	17/242		32.8 %	1.41 [0.77, 2.59]
Reynolds 1978	3/42	4/42		8.1 %	0.75 [0.18, 3.15]
Sims 1978	10/46	4/42		8.4 %	2.28 [0.77, 6.73]
Spearing 1979	5/23	1/21		2.1 %	4.57 [0.58, 35.96]
Subtotal (95% CI)	**438**	**465**		**68.4 %**	**1.56 [1.03, 2.35]**
Total events: 52 (Ethanol), 35 (Other tocolytic)					
Heterogeneity: Chi² = 2.63, df = 4 (P = 0.62); I² =0.0%					
Test for overall effect: Z = 2.12 (P = 0.034)					
Total (95% CI)	**607**	**631**		**100.0 %**	**1.43 [1.02, 2.02]**
Total events: 70 (Ethanol), 51 (Other tocolytic)					
Heterogeneity: Chi² = 6.96, df = 8 (P = 0.54); I² =0.0%					
Test for overall effect: Z = 2.06 (P = 0.040)					
Test for subgroup differences: Chi² = 1.21, df = 2 (P = 0.55), I² =0.0%					

```
        0.01   0.1    1    10    100
     Favours [ethanol]      Favours [other tocolytic]
```

Analysis 2.4. Comparison 2 Ethanol versus other tocolytic drug, Outcome 4 Preterm birth < 37 weeks.

Comparison: 2 Ethanol versus other tocolytic drug

Outcome: 4 Preterm birth < 37 weeks

Study or subgroup	Ethanol	Other tocolytic	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
	n/N	n/N			
Boyd 1978	34/48	37/48		28.7 %	0.92 [0.72, 1.17]
Castren 1975	22/50	10/43		10.2 %	1.89 [1.01, 3.54]
Forster 1987 (Part III)	130/222	118/242		33.7 %	1.20 [1.01, 1.42]
Sims 1978	32/46	32/42		27.4 %	0.91 [0.71, 1.18]
Total (95% CI)	**366**	**375**		**100.0 %**	**1.08 [0.86, 1.36]**

Total events: 218 (Ethanol), 197 (Other tocolytic)

Heterogeneity: Tau² = 0.03; Chi² = 8.81, df = 3 (P = 0.03); I² =66%

Test for overall effect: Z = 0.66 (P = 0.51)

Test for subgroup differences: Not applicable

```
       0.01    0.1     1     10    100
```

Favours [ethanol]   Favours [other tocolytic]

Analysis 2.5.   Comparison 2 Ethanol versus other tocolytic drug, Outcome 5 Preterm birth < 34 weeks.

Review: Ethanol for preventing preterm birth in threatened preterm labor

Comparison: 2 Ethanol versus other tocolytic drug

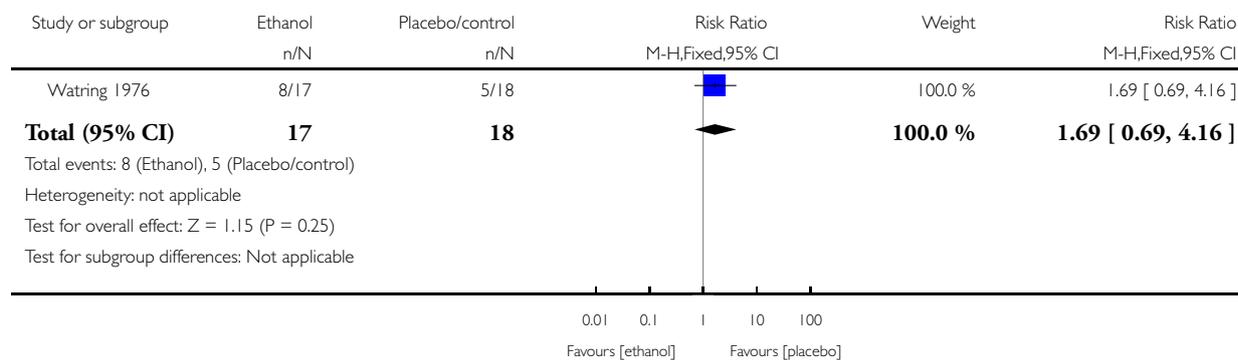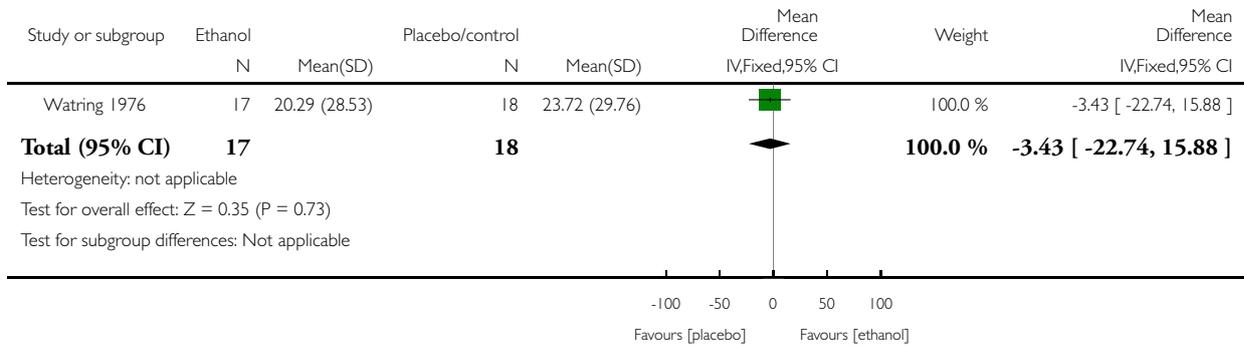Outcome: 5 Preterm birth < 34 weeks

Study or subgroup	Ethanol	Other tocolytic	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
Forster 1987 (Part III)	48/222	36/242		77.6 %	1.45 [0.98, 2.15]
Lauersen 1977	19/67	10/68		22.4 %	1.93 [0.97, 3.83]
Total (95% CI)	**289**	**310**		**100.0 %**	**1.56 [1.11, 2.19]**

Total events: 67 (Ethanol), 46 (Other tocolytic)

Heterogeneity: Chi² = 0.49, df = 1 (P = 0.48); I² =0.0%

Test for overall effect: Z = 2.56 (P = 0.010)

Test for subgroup differences: Not applicable

```
        0.01    0.1    1    10    100
   Favours [ethanol]      Favours [other tocolytic]
```

Analysis 2.6. Comparison 2 Ethanol versus other tocolytic drug, Outcome 6 Number of days delivery delayed.

Review: Ethanol for preventing preterm birth in threatened preterm labor

Comparison: 2 Ethanol versus other tocolytic drug

Outcome: 6 Number of days delivery delayed

Study or subgroup	Ethanol		Other tocolytic		Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
	N	Mean(SD)	N	Mean(SD)			
Boyd 1978	48	18.8 (3.4)	48	15.2 (3.4)		20.9 %	3.60 [2.24, 4.96]
Caritis 1982	28	10 (3.2)	28	15 (3.7)		20.8 %	-5.00 [-6.81, -3.19]
Forster 1987 (Part II)	105	21.5 (3.3)	105	19.9 (3.3)		21.0 %	1.60 [0.71, 2.49]
Lauersen 1977	67	27.6 (3.1)	68	44 (3.9)		21.0 %	-16.40 [-17.59, -15.21]
Sims 1978	46	20.4 (24)	42	15 (24.5)		16.3 %	5.40 [-4.75, 15.55]
Total (95% CI)	**294**		**291**			**100.0 %**	**-2.51 [-11.11, 6.09]**

Heterogeneity: Tau² = 91.57; Chi² = 688.23, df = 4 (P<0.00001); I² =99%

Test for overall effect: Z = 0.57 (P = 0.57)

Test for subgroup differences: Not applicable

-10   -5   0   5   10

Favours [other tocolytic]   Favours [ethanol]

Analysis 2.7. Comparison 2 Ethanol versus other tocolytic drug, Outcome 7 Maternal adverse events (overall).

Review: Ethanol for preventing preterm birth in threatened preterm labor

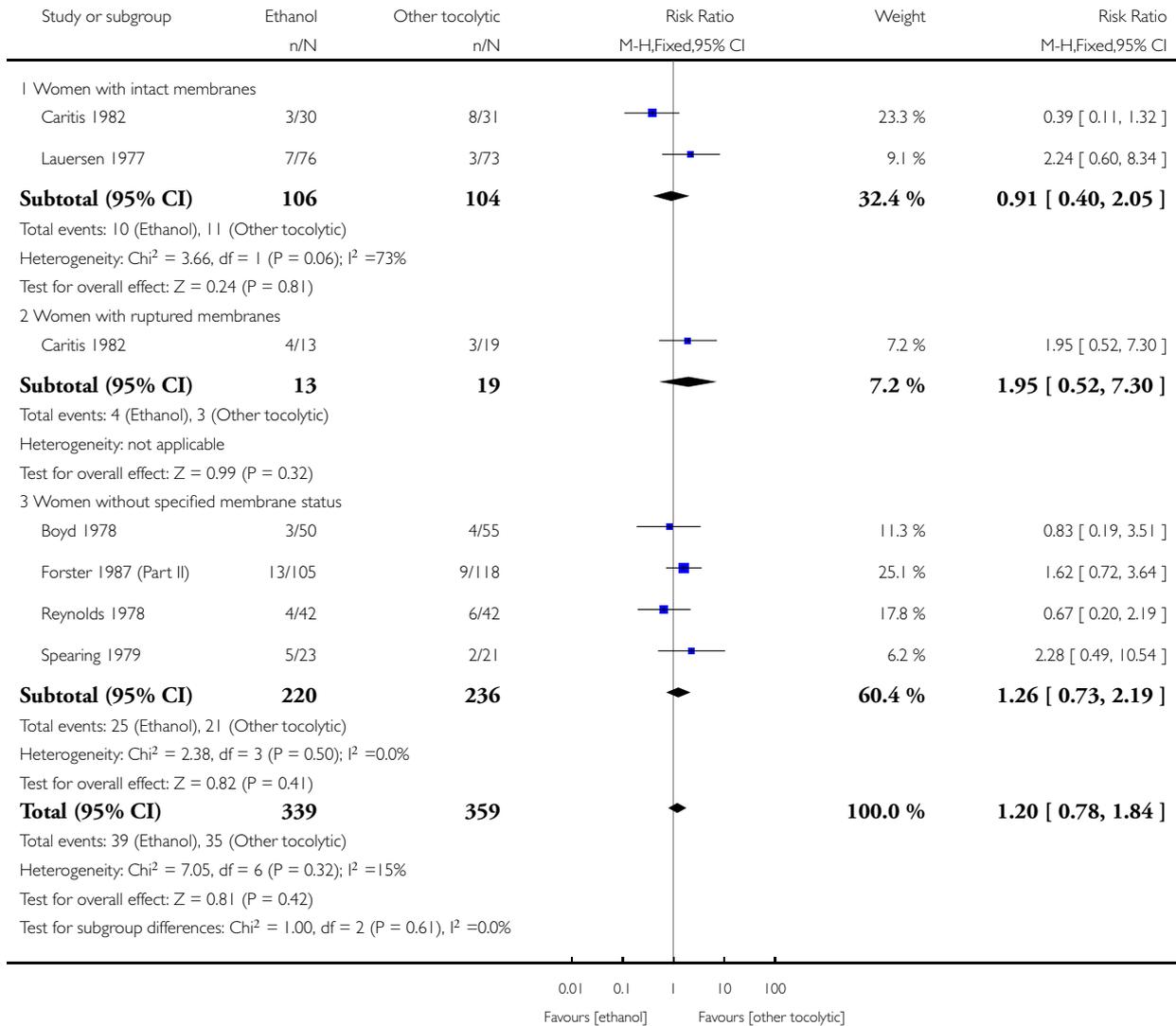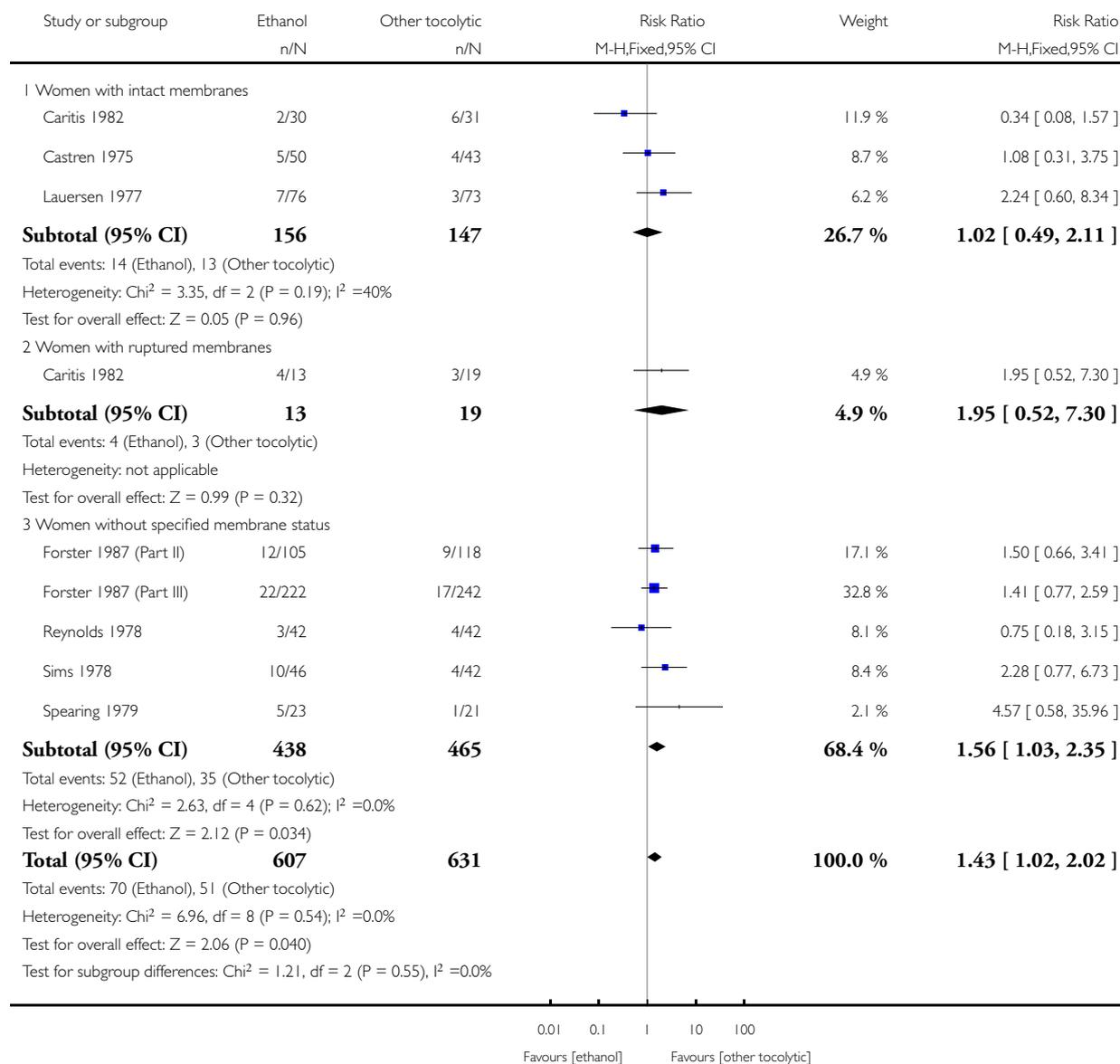Comparison: 2 Ethanol versus other tocolytic drug

Outcome: 7 Maternal adverse events (overall)

Study or subgroup	Ethanol n/N	Other tocolytic n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Caritis 1982	32/40	13/45		26.6 %	2.77 [1.71, 4.49]
Castren 1975	5/50	9/43		19.5 %	0.48 [0.17, 1.32]
Reynolds 1978	32/42	26/42		28.6 %	1.23 [0.92, 1.65]
Sims 1978	11/46	22/42		25.3 %	0.46 [0.25, 0.82]
Total (95% CI)	**178**	**172**		**100.0 %**	**0.99 [0.46, 2.11]**

Total events: 80 (Ethanol), 70 (Other tocolytic)

Heterogeneity: Tau^2 = 0.50; Chi^2 = 25.22, df = 3 (P = 0.00001); I^2 =88%

Test for overall effect: Z = 0.03 (P = 0.98)

Test for subgroup differences: Not applicable

```
        0.01   0.1    1    10   100
```

Favours [ethanol]   Favours [other tocolytic]

Analysis 2.8. Comparison 2 Ethanol versus other tocolytic drug, Outcome 8 Maternal adverse events (required stopping or changing drug).

Review: Ethanol for preventing preterm birth in threatened preterm labor

Comparison: 2 Ethanol versus other tocolytic drug

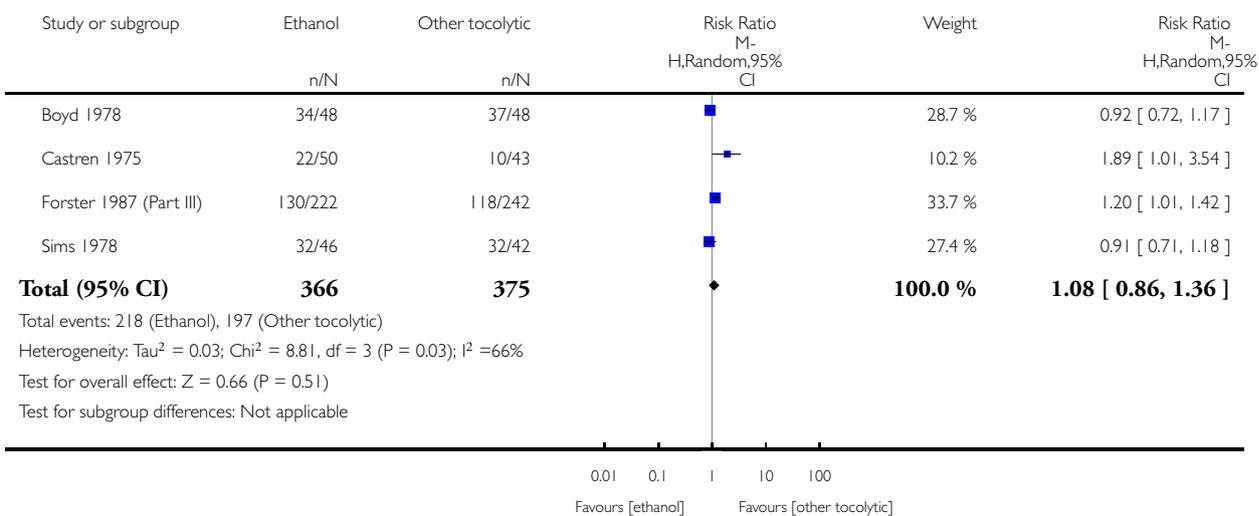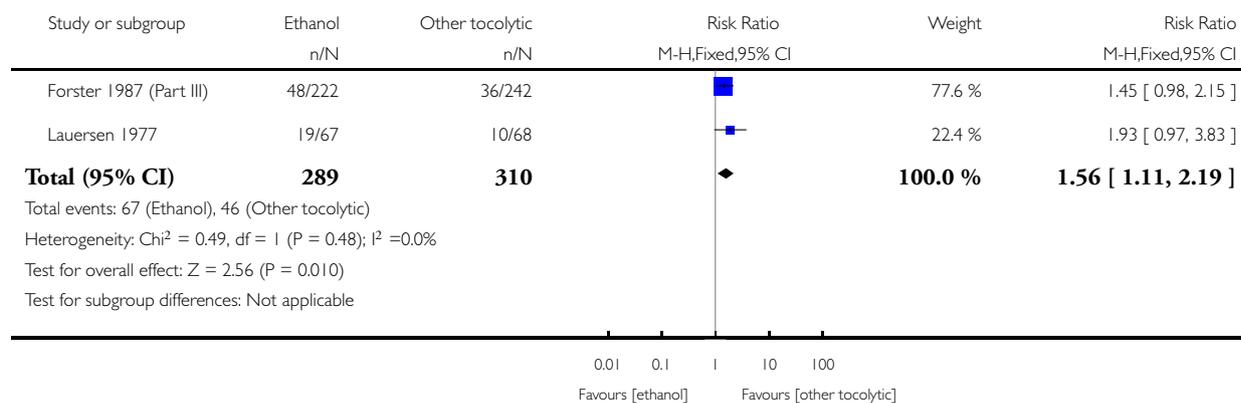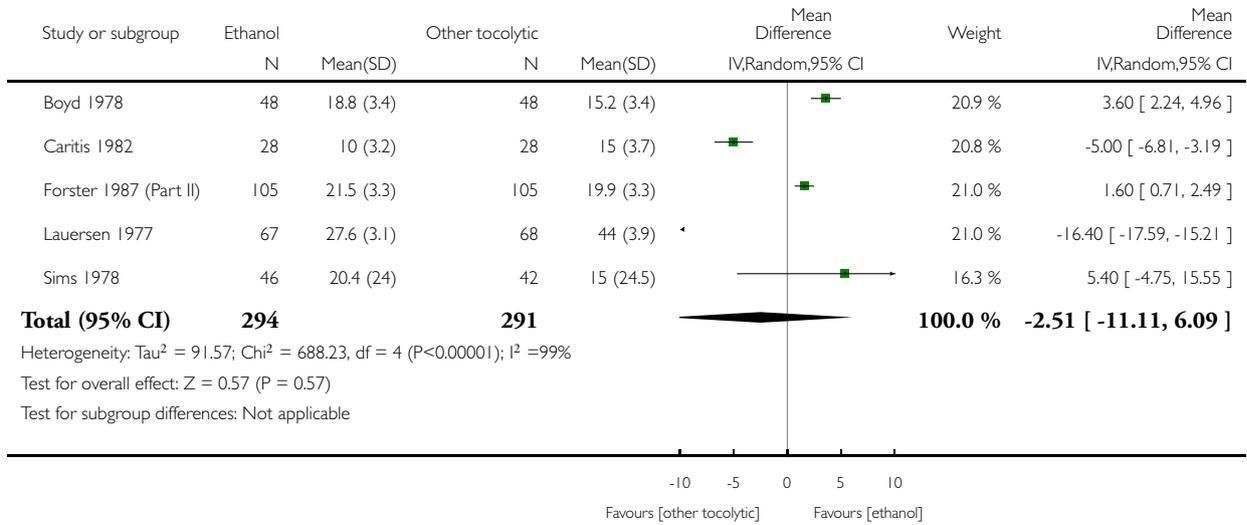Outcome: 8 Maternal adverse events (required stopping or changing drug)

Study or subgroup	Ethanol n/N	Other tocolytic n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Reynolds 1978	0/42	3/42		35.8 %	0.14 [0.01, 2.68]
Sims 1978	1/46	5/42		53.5 %	0.18 [0.02, 1.50]
Spearing 1979	1/22	1/20		10.7 %	0.91 [0.06, 13.59]
Total (95% CI)	**110**	**104**		**100.0 %**	**0.25 [0.06, 0.97]**

Total events: 2 (Ethanol), 9 (Other tocolytic)

Heterogeneity: Chi² = 1.11, df = 2 (P = 0.58); I² =0.0%

Test for overall effect: Z = 2.00 (P = 0.046)

Test for subgroup differences: Not applicable

0.01 0.1 1 10 100

Favours [ethanol]   Favours [other tocolytic]

Analysis 2.9. Comparison 2 Ethanol versus other tocolytic drug, Outcome 9 Respiratory distress syndrome.

Review: Ethanol for preventing preterm birth in threatened preterm labor

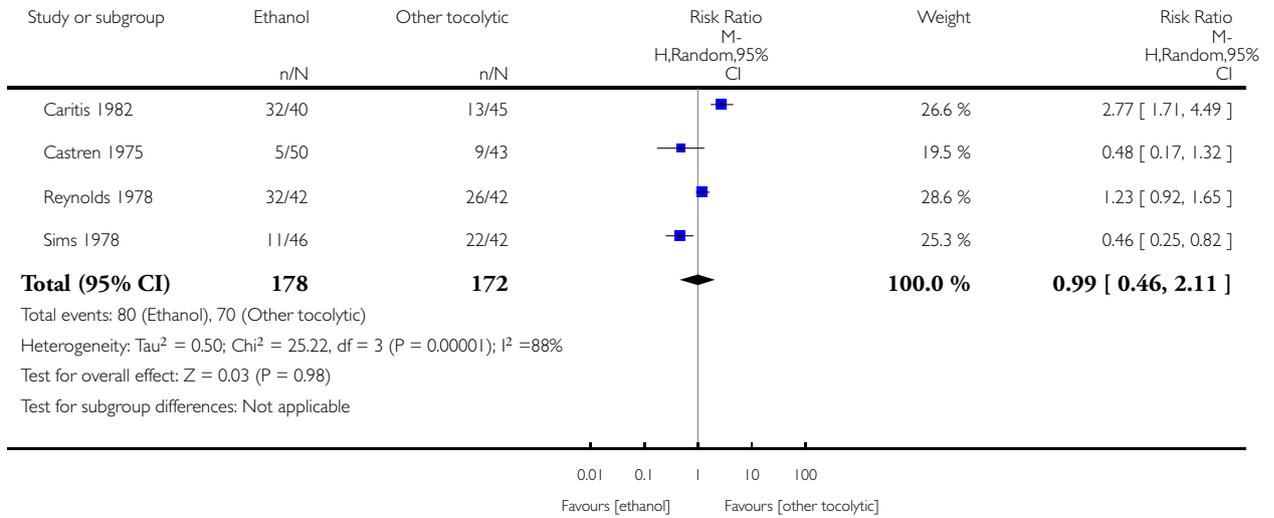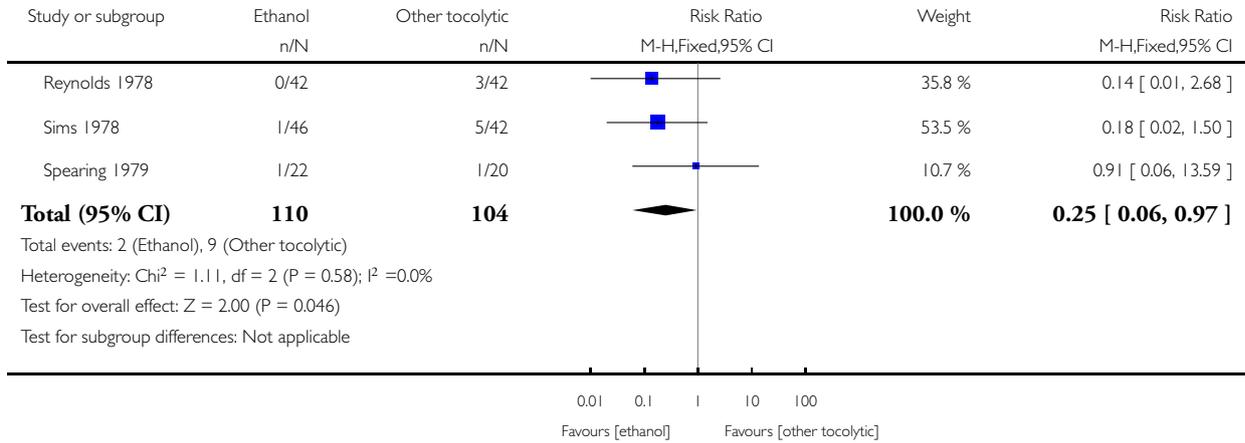Comparison: 2 Ethanol versus other tocolytic drug

Outcome: 9 Respiratory distress syndrome

Study or subgroup	Ethanol n/N	Other tocolytic n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Forster 1987 (Part II)	32/105	20/105		32.5 %	1.60 [0.98, 2.61]
Forster 1987 (Part III)	59/222	37/242		57.5 %	1.74 [1.20, 2.51]
Lauersen 1977	15/76	6/73		9.9 %	2.40 [0.99, 5.85]
Total (95% CI)	**403**	**420**		**100.0 %**	**1.76 [1.33, 2.33]**

Total events: 106 (Ethanol), 63 (Other tocolytic)
Heterogeneity: Chi² = 0.62, df = 2 (P = 0.73); I² =0.0%
Test for overall effect: Z = 3.96 (P = 0.000074)
Test for subgroup differences: Not applicable

```
        0.01   0.1    1    10   100
      Favours [ethanol]   Favours [other tocolytic]
```
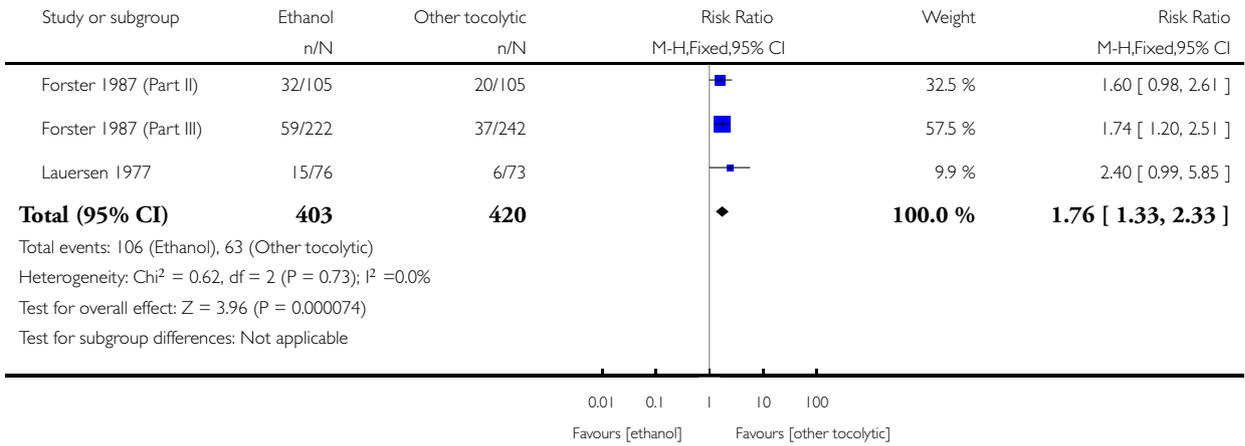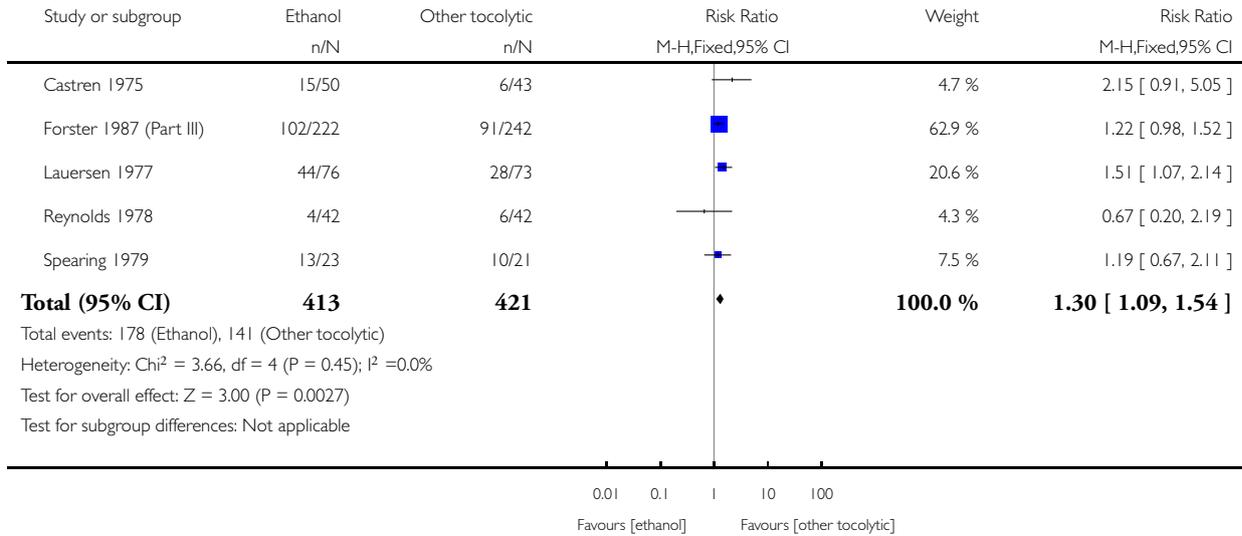
Analysis 2.10. Comparison 2 Ethanol versus other tocolytic drug, Outcome 10 Birthweight < 2500 g.

Review: Ethanol for preventing preterm birth in threatened preterm labor

Comparison: 2 Ethanol versus other tocolytic drug

Outcome: 10 Birthweight < 2500 g

Study or subgroup	Ethanol n/N	Other tocolytic n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Castren 1975	15/50	6/43		4.7 %	2.15 [0.91, 5.05]
Forster 1987 (Part III)	102/222	91/242		62.9 %	1.22 [0.98, 1.52]
Lauersen 1977	44/76	28/73		20.6 %	1.51 [1.07, 2.14]
Reynolds 1978	4/42	6/42		4.3 %	0.67 [0.20, 2.19]
Spearing 1979	13/23	10/21		7.5 %	1.19 [0.67, 2.11]
Total (95% CI)	**413**	**421**		**100.0 %**	**1.30 [1.09, 1.54]**

Total events: 178 (Ethanol), 141 (Other tocolytic)

Heterogeneity: Chi² = 3.66, df = 4 (P = 0.45); I² =0.0%

Test for overall effect: Z = 3.00 (P = 0.0027)

Test for subgroup differences: Not applicable

0.01 0.1 1 10 100

Favours [ethanol]   Favours [other tocolytic]

CONTRIBUTIONS OF AUTHORS

David Haas (DMH) and Amanda Morgan (AM) originally conceived the protocol.

DMH, AM, Samantha Deans, and Frank Schubert subsequently developed the final protocol, abstracted and entered data, wrote and approved the final version of this review.

DMH is the guarantor for this review.

DECLARATIONS OF INTEREST

David M Haas: none known

Amanda Morgan: none known

Samantha Deans: none known

Frank Schubert: none known

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

INDEX TERMS
Medical Subject Headings (MeSH)

*Obstetric Labor, Premature; Ethanol [*therapeutic use]; Pregnancy Outcome; Premature Birth [*prevention & control]; Randomized Controlled Trials as Topic; Tocolytic Agents [*therapeutic use]

MeSH check words

Female; Humans; Pregnancy