Tocolytics for preterm labor: a systematic review
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Authors' objectives
To examine the effectiveness of any tocolytic compared with a placebo or no tocolytic for preterm labour.

Searching
The authors searched the MEDLINE (1966-1998) electronic database and the Cochrane Controlled Trials Register using the search terms: 'randomized controlled trial' (RCT), 'preterm labor', 'tocolysis', 'betamimetics', 'ritodrine', 'terbutaline', 'hexaprenaline', 'isoxuprine', 'prostaglandin synthetase inhibitors', 'indomethacin', sulindac', 'calcium channel blockers', 'nifedipine', 'oxytocin receptor blockers', 'atosiban', 'nitroglyceride', and 'magnesium sulfate'. The search was restricted to English language publications.

Study selection
Randomised controlled trials (RCTs). Studies were excluded where loss to follow-up exceeded 20% of those originally enrolled, or if data was not reported on a per-patient-treated basis.

Specific interventions included in the review
Tocolytics for the intervention group and placebo or no tocolytic for the control group. Tocolytics used in the intervention group included: isoxuprine, ethanol, terbutaline, ritodrine, indomethacin, magnesium sulfate and atosiban. The dosages are not stated.

Participants included in the review
Women in preterm labour.

Outcomes assessed in the review
Perinatal, neonatal or maternal outcomes.

How were decisions on the relevance of primary studies made?
Two authors independently reviewed the articles and abstracted the data. Discrepancies were resolved by consensus.

Assessment of study quality
The authors do not report a method for assessing validity, however they report that the method of randomisation and the use of placebo controls were evaluated in each study. Two authors independently assessed the studies and discrepancies were resolved by consensus.

Data extraction
Data were abstracted independently by two of the authors. Discrepancies were resolved by consensus.

Data were extracted for the categories of trial identification, definition of preterm labour, use of antenatal corticosteroids and antibiotics, method of randomisation, tocolytic type and number of women and infants in the intervention groups, and type of control and number of women and infants in the control groups.

Methods of synthesis
Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each outcome. Peto's fixed-effect model was used to calculate pooled ORs when there was no significant heterogeneity and DerSimonian and Laird's
random-effects model was used when there was significant heterogeneity.

Baseline information and data on co-interventions (e.g. antenatal corticosteroids, antibiotics) were analysed descriptively.

How were differences between studies investigated?
Heterogeneity among trials was assessed using the chi-squared statistic.

Results of the review
Seventeen studies met the inclusion criteria with 1184 women and 1232 infants in the intervention group, and 1100 women and 1155 infants in the control group. One study was reported twice (only 1 set of results included in these numbers).

Tocolytics were associated with statistically significant decreases in the likelihood of delivery with 24 hours (OR 0.47, 95% CI: 0.29, 0.77), 48 hours (OR 0.57, 95% CI: 0.38, 0.83), and 7 days (OR 0.60, 95% CI: 0.38, 0.95). Betamimetics, indomethacin, atosiban and ethanol, but not magnesium sulfate, were associated with significant prolongations in pregnancy. Tocolytics were not associated with a statistically significant reduction in births before 30 weeks’ gestation (OR 1.33, 95% CI: 0.53, 3.33), before 32 weeks’ gestation (OR 0.81, 95% CI: 0.61, 1.07), or before 37 weeks’ gestation (OR 0.17, 95% CI: 0.02, 1.62). Only one study of indomethacin showed a statistically significant decrease in preterm births.

Tocolytics were not associated with a statistically significant reduction in perinatal death (OR 1.22, 95% CI: 0.84, 1.78), respiratory distress syndrome (RDS) (OR 0.82, 95% CI: 0.64, 1.07), intraventricular haemorrhage (OR 0.73, 95% CI: 0.46, 1.15), necrotising enterocolitis (OR 0.96, 95% CI: 0.35, 2.65), patent ductus arteriosus (OR 0.82, 95% CI: 0.52, 1.30), neonatal sepsis (OR 1.09, 95% CI: 0.70, 1.68), seizures (OR 1.05, 95% CI: 0.35, 3.14), hypoglycemia (OR 1.36, 95% CI: 0.87, 2.14), or birth weight under 2500 g (OR 0.62, 95% CI: 0.35, 1.09).

Maternal side-effects statistically significantly associated with tocolytic use were palpitations (OR 10.15, 95% CI: 7.42, 13.87), nausea (OR 2.05, 95% CI: 1.47, 2.85), tremor (OR 8.30, 95% CI: 5.79, 11.89), chorioamnionitis (OR 2.88, 95% CI: 1.13, 7.33), hyperglycemia (OR 3.39, 95% CI: 2.35, 4.90), hypokalemia (OR 6.43, 95% CI: 4.53, 9.14), and need to discontinue treatment (OR 10.09, 95% CI: 4.91, 20.74). Tocolytics were not associated with statistically significant increases in pulmonary edema, chest pain, cardiac arrhythmias, dyspnea, vomiting, headaches, endometritis, or hypertension.

Betamimetics were associated with increases in most maternal side effects.

There were no maternal deaths reported in any study.

Cost information
The authors state that it is reasonable to assume that even a small decrease in preterm labour would translate into reduced costs, considering the frequency of its occurrence (7% to 9% of all births).

Authors' conclusions
The authors state that although tocolytics prolong pregnancy, they have not been shown to improve perinatal or neonatal outcomes and have adverse effects on women in preterm labor.

CRD commentary
The authors have clearly stated their research question and the inclusion and exclusion criteria. The literature search is limited. The authors have restricted the search to English language publications and there is no mention of inclusion of unpublished data. The search terms are also stated in American spellings which may be the journal's style or may mean that other spellings of RCT and labour were not a part of the search strategy. It is not clear therefore whether additional relevant trials may have been missed. The quality of the included studies was not formally assessed and although this
was not discussed the authors state that they examined the method of randomisation and the use of placebo in each included trial. The authors have reported on how the articles were selected. They have also reported how many of the reviewers were involved in data extraction and how the data extraction was performed.

The data extraction is reported in tables and text and the meta-analysis may not have been appropriate because although the authors tested for heterogeneity the results of the tests are not presented, so it is not clear whether statistical pooling was appropriate. The authors stated that they were going to use random-effects models if heterogeneity was found but it is not clear which effects method was used in the presentation of the overall results. The authors conclusions appear to follow from the results but should be viewed with caution because of the stated methodological limitations of the review.

Implications of the review for practice and research
Practice: The authors state that the risks and benefits of indomethacin are uncertain, and its routine use should not be encouraged outside well-designed RCTs.

Research: The authors state that appropriately-sized RCTs of newer tocolytics for perinatal and maternal outcomes are needed.

Bibliographic details

PubMedID
10546776

Other publications of related interest
This additional published commentary may also be of interest. Hsieh C. How effective are tocolytics for the treatment of preterm labor? J Fam Pract 2000;49:186.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.