Tocolytic therapy for preterm delivery: systematic review and network meta-analysis
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CRD summary
This review concluded that prostaglandin inhibitors and calcium channel blockers had the highest probability of delaying delivery and improving neonatal and maternal outcomes. This was a generally well-conducted review and the conclusions are likely to be reliable based on the information available.

Authors' objectives
To determine the most effective tocolytic agent at delaying delivery in women at risk of preterm delivery.

Searching
MEDLINE, EMBASE, CINAHL and Cochrane Central Register of Controlled Trials (CENTRAL) were searched without language restrictions to 2012; search terms were reported. Bibliographies of Cochrane reviews were searched for additional studies. Abstracts and personal communications cited in Cochrane reviews were excluded.

Study selection
Eligible randomised controlled trials (RCTs) were of women at risk of preterm delivery and compared a tocolytic therapy with placebo, usual care or an alternative tocolytic therapy for delaying delivery. Trials that evaluated combination drug therapies for tocolysis, or that did not report maternal or neonatal outcomes in relation to preterm delivery, were excluded.

There were 89 RCTs for which information was available; 44% of studies were conducted in North America, 27% in Asia and 24% in Europe. Studies were published between 1966 and 2011. The treatment classes evaluated were: beta-mimetics; calcium channel blockers; magnesium sulphate; nitrates; oxytocin receptor blockers; prostaglandin inhibitors; others (alcohol, human chorionic gonadotropin, combination tocolytic drugs); and placebo (including usual/standard care).

At least two reviewers selected studies for the review; disagreements were resolved by consensus.

Assessment of study quality
Quality was assessed with the Cochrane risk of bias tool which assessed random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other sources of bias. Each study was allocated a score out of seven. When at least four domains had a low risk score (and one of these was sequence generation or allocation concealment), the study was considered to be high quality.

Study quality was assessed by two reviewers.

Data extraction
Data were extracted on the incidence of each outcome, all of which were binary, from which odds ratios (OR) were calculated. The primary maternal outcomes were the incidence of delivery delayed by 48 hours and tocolytic-related side effects. The primary neonatal outcomes were rates of respiratory distress syndrome and death.

At least two reviewers extracted data.

Methods of synthesis
Posterior median odds ratios and 95% credible intervals (CrI) were calculated using a random-effects network meta-analysis; trials with zero or 100% events on all arms were excluded from the analysis. Goodness of fit was measured by the posterior mean of the residual deviance. When head-to-head data was available, pairwise comparisons were made and odds ratios with 95% credible intervals were calculated using a random-effects model, unless only two trials were available, when a fixed-effect model was used. Statistical heterogeneity was assessed using the posterior median between trial variance for the network meta-analysis, and $X^2$ and $I^2$ for the pairwise analyses. Sensitivity analyses were used to examine the impact of multiple gestations, ruptured membranes and study quality. A meta-regression
investigated the impact of duration of treatment. The treatments classes and presumed to have a class effect.

**Results of the review**

The review included 95 RCTs which evaluated 18 treatments across eight tocolytic classifications (10,096 in the network analysis; range 30 to 1,749 across treatment comparisons). Of the 95 RCTs, 89 addressed incomplete data, 82 were free from reporting bias, 50 used adequate allocation concealment. 49 used an adequate method for random number generation, 30 reported blinding patients or personnel, 32 reported blinding outcome assessors and 92 were free from other biases. The results reported in this abstract were those from the network meta-analysis.

**Delaying outcome delivery by 48 hours (55 trials):** All active treatments were superior to placebo; this benefit did not reach statistical significance for the nitrates and other classes. Prostaglandin inhibitors were suggested as having a greater beneficial effect than any other active class, with an 83% probability of being the best. The probability of being ranked in the top three most efficacious classes was 96% for prostaglandin inhibitors, 63% for magnesium sulphate, 57% for calcium channel blockers, 33% for beta-mimetics, 24% for nitrates, 14% for oxytocin receptor blockers, 13% for others and 0% for placebo. Heterogeneity was observed ($I^2>50\%$) for both beta mimetic and magnesium sulphate when compared to placebo.

**Maternal tocolytic-related adverse events (58 trials):** Placebo was ranked first, with a probability of 61%, and a 98% probability of being ranked in the top three drug classes. The closest active competitor for reducing all cause maternal side effects was prostaglandin inhibitors, with a probability of 79%, followed by oxytocin receptor blockers (70%).

**Reducing neonatal mortality (40 trials):** Calcium channel blockers appeared to be the best, but the probability of this was only 41%. Prostaglandin inhibitors had the next highest probability of being the best (28%). The probability of being ranked in the top three most efficacious classes was 85% for calcium channel blockers, 58% for beta-mimetics, 56% for oxytocin receptor blockers and 54% for prostaglandin. There was substantial uncertainty around which class was associated with the fewest neonatal deaths. Heterogeneity was observed ($I^2=78\%$) for beta mimetic compared to placebo.

**Reducing neonatal respiratory distress syndrome (42 trials):** There was no evidence of a difference between the classes, with no clear benefit of any active treatment over placebo.

The overlap between the available direct estimates and network meta-analysis estimates were considered substantial (results from both were reported in the paper). Results for a range of secondary outcomes were reported. Sensitivity analyses and meta-regression showed no impact on the finding for prostaglandin inhibitors.

**Authors’ conclusions**

Prostaglandin inhibitors and calcium channel blockers had the highest probability of delaying delivery and improving neonatal and maternal outcomes.

**CRD commentary**

The review addressed a clear research question with reproducible inclusion criteria. The treatment classification of "other" included combination tocolytic drugs, but these were specifically stated as being excluded from the review. Several relevant sources were searched without language restrictions. There did not appear to have been a specific search for unpublished studies, so no attempts to mitigate for potential publication bias. Each stage of the review was conducted in duplicate, which reduced the risk of error and bias. Study quality was assessed using appropriate criteria; the results were reported in full in an online appendix.

Overall, the analytical methods were appropriate, but three studies may have been an insufficient number to inform the distribution of effects within the random-effects model used for the pairwise comparisons, and some relevant trials were excluded from the network meta-analysis. This was a generally well-conducted review and the conclusions seem likely to be reliable.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that given the small amount of direct evidence and considerable uncertainty identified for
the neonatal outcomes, the findings from the network meta-analysis suggested that a head-to-head trial of tocolytic agents needed to investigate further the effectiveness, adverse effects and costs of these regimens to women; the authors plan to conduct an expected value of information analysis. They also stated that an individual participant meta-analysis might overcome the difficulties of extrapolating a composite of the primary neonatal outcomes. The authors suggested that future trials should use a standard list of both maternal safety and neonatal short-term and long-term outcomes to allow researchers to understand the benefits or lack of benefits of tocolytic therapy.

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