Value of maintenance therapy with oral tocolytics: a systematic review
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Authors' objectives
To perform a systematic review of prospective randomised controlled trials evaluating the efficacy of oral tocolytics in the prevention of recurrent preterm labour and its associated complications.

Searching
MEDLINE (1966 onwards) was searched using the following search terms: 'premature labour', 'preterm labour', 'prematurity', 'preterm birth', 'preterm uterine contractions', 'tocolytic agents', 'oral tocolytic therapy', 'tocolysis', 'beta-adrenergic receptor antagonist', 'terbutaline', 'oral terbutaline', 'ritodrine', 'nifedipine', and 'magnesium' and 'prostaglandin inhibitor'. Studies cited in the identified articles were reviewed for possible inclusion. Only full papers published in English were included. Unpublished reports, including those in the Cochrane Library were not included as the authors did not want to include studies that were not peer reviewed.

Study selection
Study designs of evaluations included in the review
Prospective randomised, controlled studies. Studies not including a control group were not included in the review.

Specific interventions included in the review
Oral tocolytic therapy for maintenance after stabilisation with parenteral therapy. Specific pharmacological agents included in the review were: ritodrine, terbutaline and magnesium chloride. Treatment with the assigned agent had to have continued throughout the study, with an intention-to-treat until at least 36 weeks (gestation).

Participants included in the review
Pregnant women at risk of pre-term labour, with intact membranes were included in the review. Participants had to have already been stabilised with parenteral tocolytic therapy prior to receiving maintenance therapy.

Outcomes assessed in the review
Nine outcomes were assessed in the review: incidence of pre-term delivery; incidence of recurrent preterm labour; latency from treatment to delivery; gestational age; birthweight; admission to an intensive care nursery (ICN); incidence of respiratory distress syndrome (RDS); incidence of intraventricular haemorrhage (IVH); and perinatal mortality.

How were decisions on the relevance of primary studies made?
Studies that met the eligibility criteria were reviewed independently by two authors and discrepancies were resolved based on decisions by all authors.

Assessment of study quality
There was no validity assessment beyond checking that studies complied with the inclusion criteria for study design and intervention.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. Data were extracted for the nine outcome variables, and the total number of patients randomised to the treatment, placebo or other control arms of the study.

Methods of synthesis
How were the studies combined?
The odds ratio (OR) with 95% confidence interval (CI) for each categorical outcome variable was computed. If any cell contained a zero 0.5 was added as a correction factor. The results were presented as forest plots. The authors had planned to pool the data across all studies (pooled OR (95%CI)), however, due to the differences in study protocols, particularly the comparators used and the outcomes assessed, this was not possible. For continuous variables the differences in means or medians at delivery between active treatment and control arms were assessed by Student's t-test.

How were differences between studies investigated?
Differences between the studies were investigated qualitatively by reviewing the protocols utilised in the various studies.

Results of the review
Seven studies were included in the review (n=820). The number of patients randomised to active treatment was 456, with 364 randomised to placebo or untreated control. Five of the studies used terbutaline, one of these utilised magnesium chloride as an active treatment control. Two studies used ritodrine, and again one of these utilised magnesium chloride as an active treatment control.

None of the individual studies demonstrated a statistically significant benefit of oral tocolytic therapy in terms of the incidence of pre-term delivery, incidence of recurrent preterm labour, ICN admission, incidence of RDS, incidence of IVH, perinatal mortality or gestational age at delivery.

Authors’ conclusions
The authors concluded 'We do not believe our review has resolved the issue of the effect of oral maintenance tocolysis on pregnancy outcome, but rather has clarified the direction of further research'.

CRD commentary
The review addressed an appropriate question, with well-defined inclusion and exclusion criteria. The literature search was limited being confined to a single electronic database with no supplementary handsearching. The search was further limited by being restricted to full articles in English, with the deliberate exclusion of unpublished data and thus the results of the review may be subject to publication bias. The validity of the papers was not checked against any formal criteria, but were all prospective, randomised, controlled studies. Adequate details of the individual studies are presented in the review, although details of individual study assessments, upon which the decision not to pool the studies was based, are not included in the review. The presentation of the individual study results is comprehensive and the authors conclusions appear to be justified.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated 'Large, well-designed randomised trials that take into account improvements in current practice (related to neonatal outcome) are clearly warranted'.

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