Effectiveness and safety of ritodrine hydrochloride for the treatment of preterm labour: a systematic review

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CRD summary
The review assessed the effectiveness and safety of ritodrine hydrochloride in delaying delivery and decreasing the incidence of pre-term birth. Ritodrine may be useful for the short-term prolongation of pregnancy, but the high incidence of adverse reactions means that administration should be limited. The authors' conclusions reflect the evidence presented but the studies may be of poor quality.

Authors' objectives
To assess the effectiveness and safety of ritodrine hydrochloride in delaying delivery and decreasing the incidence of pre-term birth.

Searching
MEDLINE (1966 to October 2004), the Cochrane CENTRAL Register (Issue 3, 2004) and Igaku-Chuo-Zasshi (1983 to 2004) were searched for English language studies; the search terms were reported. The reference lists of all retrieved articles were also screened.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) that included a description of random allocation, and using either a placebo control or a non-treatment control, were eligible for inclusion.

Specific interventions included in the review
Studies of intravenous ritodrine hydrochloride for acute tocolysis, or maintenance therapy after acute tocolysis with oral ritodrine hydrochloride, were eligible for inclusion. Twelve studies assessed intravenous therapy, and 5 studies assessed oral maintenance therapy. Three studies reported also using antenatal steroids.

Participants included in the review
Studies of pregnant women with threatened pre-term delivery were eligible for inclusion. Studies of intravenous ritodrine hydrochloride involving only women with multiple pregnancy and studies of oral ritodrine hydrochloride involving only women with premature rupture of the membranes (PROM) were excluded. The gestation period for the included participants ranged from 20 to 37 weeks. Nine studies assessed singleton pregnancy only, 5 studies included twins, and 3 studies did not state the number in the pregnancy. Patients experiencing PROM were included in 5 studies, one of which was a study of acute tocolysis using intravenous therapy where all participants experienced PROM.

Outcomes assessed in the review
Studies assessing any of the following were eligible for inclusion: perinatal mortality, proportion of neonatal respiratory distress syndrome (RDS), proportion of pre-term birth, proportion of birth within 48 hours or 7 days of treatment initiation. The primary end points were perinatal death and incidence of RDS.

How were decisions on the relevance of primary studies made?
The bibliographic records and abstracts for each retrieved article were checked against the inclusion and exclusion criteria. The authors did not state how many reviewers performed the selection.

Assessment of study quality
Two reviewers independently assessed the methodological quality of the included studies using five criteria based on
the Cochrane Reviewers’ Handbook: method of allocation concealment, blinding, sample size calculation, completeness of follow-up and explicit definition of threatened pre-term delivery.

Data extraction
A predefined set of data was extracted from the selected trials to create structured abstract tables. Relative risks (RRs) and 95% confidence intervals (CIs) were extracted. The data were extracted on an intention-to-treat (ITT) basis. The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
How were the studies combined?
Pooled RRs and 95% CIs were estimated using the DerSimonian and Laird random-effects model and the Mantel-Haenszel fixed-effect model, though only the former was reported. Publication bias was visually assessed using a funnel plot.

How were differences between studies investigated?
Clinical and statistical heterogeneity were assessed by comparing study quality and participant characteristics. Studies of acute intravenous therapy and oral maintenance therapy were pooled separately for each of the outcomes. In addition to an overall pooling of all studies, the following subgroups were also pooled: only studies that provided accurate data for ITT analysis; studies of women with multiple pregnancy; studies that did not involve women with PROM; studies that involved a certain proportion of women with PROM and studies that did not involve women with PROM; and studies in which steroids were used. Statistical heterogeneity was then assessed using the Q-statistic (p<0.1 was considered statistically significant) and an I-squared test (I-squared>50% was considered to demonstrate significant heterogeneity).

Results of the review
Seventeen RCTs (n=1,928) were included.

Methodological quality.
The quality of the included studies was reported as being low, but no significant variation in quality was observed. No evidence of publication bias was identified using the funnel plot.

Intravenous ritodrine hydrochloride.
There was no statistically significant difference in perinatal mortality with intravenous ritodrine hydrochloride compared with control for the overall pooling (RR 1.19, 95% CI: 0.78, 1.81, p=0.46) or for any of the 5 subgroups. Similar results were found for neonatal RDS.

There was a statistically significant decrease in the proportion of births within 48 hours of initiation of treatment with intravenous ritodrine compared with control for the overall pooling and 2 subgroup analyses (studies reporting adequate ITT data, RR 0.68, 95% CI: 0.51, 0.91; excluding trials of only PROM, RR 0.72, 95% CI: 0.53, 0.98). However, statistical heterogeneity was found between the 7 studies in the subgroup analyses excluding trials of only PROM.

Subgroup analysis of studies reporting adequate ITT data suggested that ritodrine was effective for reducing the proportion of births within 7 days of treatment initiation among all pregnant women, including those with multiple pregnancy and those with PROM (RR 0.85, 95% CI: 0.74, 0.97). Subgroup analysis of studies excluding trials with only PROM showed similar effects.

No statistically significant decrease in the proportion of pre-term delivery (birth before 37 weeks’ gestation) was observed in the overall pooling or subgroup analyses.

Analysis of studies reporting adequate ITT data showed a decrease in low birth weight infants (the proportion of live-born infants weighing less than 2,500 g) (RR 0.89, 95% CI 0.81, 0.99). There was no statistical heterogeneity across the
trials. No statistically significant decrease was observed in any other pooling groups.

A statistically significant increase was found in the incidence of palpitation (RR 8.28, 95% CI: 5.70, 12.02; 5 studies) and chest pain (RR 10.55, 95% CI 3.55, 31.38; 2 studies). No statistical heterogeneity was found across studies.

Maintenance therapy with oral ritodrine hydrochloride.

There was no statistically significant difference between maintenance therapy with oral ritodrine hydrochloride and control for any outcomes.

**Authors' conclusions**
The effectiveness of intravenous ritodrine is limited. It may be useful for short-term prolongation of pregnancy, but the high incidence of adverse reactions means that administration should be limited. Current evidence fails to support the use of oral ritodrine and its use should be reconsidered.

**CRD commentary**
The review addressed a clear question that was defined in terms of the participants, interventions, outcomes and study design. Some relevant sources were searched and references of retrieved articles were screened, thereby limiting the possibility of publication bias. Furthermore, a formal assessment of publication bias suggests that this was not present in the review. However, the review was based on only a small number of studies. Only English language articles were included, which means that other relevant studies published in other languages might have been missed. The methods used to select the studies and extract the data were not described, and so it is not known whether any efforts were made to reduce reviewer error and bias. Study quality was assessed but the findings were not reported for individual studies, making it difficult to judge the quality of the evidence. However, the authors did comment that the quality was generally low.

Sensitivity analyses examined the effect of excluding studies which did not provide accurate data for ITT analysis. The characteristics of the included studies were presented in tables. Little information was presented about the intervention (in terms of dosage) and control, so comparability could not be adequately assessed. Sensitivity and subgroup analyses examining relevant differences did not significantly change the results. The review methods were poorly reported, and the potential for bias in the review should not be ignored. The authors' conclusions reflect the evidence presented but, given the limited information provided, the studies may be of poor quality.

**Implications of the review for practice and research**
Practice: The use of oral ritodrine should not be reconsidered as its use is not supported by current evidence. Although ritodrine may be useful for acute tocolysis or short-term prolongation of pregnancy, the high incidence of adverse reactions indicates that administration should be limited.

Research: Further research using well-controlled clinical trials should be conducted to assess the benefits of tocolytic agents in combination with antenatal steroids.

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