Progesterone for the prevention of preterm birth among women at increased risk: a systematic review and meta-analysis of randomized controlled trials

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CRD summary
This review evaluated the effects of progestational agents on the prevention of pre-term birth. The authors concluded that treatment initiated in the second trimester of pregnancy reduces the risks of pre-term delivery, but the effect on other clinical outcomes is uncertain. Although the conclusions are likely to be reliable, limited evidence means that their wider applicability is unclear.

Authors' objectives
To evaluate the effectiveness of progestational agents initiated in the second trimester to prevent pre-term birth.

Searching
MEDLINE (1996 to 2003), EMBASE (1980 to 2003), and the Cochrane Library were searched for published studies; the search terms were reported. The reference lists of retrieved studies and relevant systematic reviews were also checked for additional articles. There was no attempt to retrieve unpublished papers.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion in the review. The comparators were placebo or no treatment.

Specific interventions included in the review
Studies of progestational agents initiated during the second trimester of pregnancy were eligible for inclusion. The interventions evaluated were weekly intramuscular 17 alpha-hydroxyprogesterone caproate, compared with caster oil (with or without benzyl benzoate), or a daily natural progesterone vaginal suppository, compared with a placebo suppository comparable in appearance. Treatment started between 16 and 24 weeks and continued to 37 weeks' gestation, or delivery if earlier. All participants received tocolytics for pre-term labour; some received cervical cerclage or antenatal corticosteroids.

Participants included in the review
Studies of women considered to be at risk of spontaneous pre-term birth were eligible for inclusion. Studies were excluded where there were signs or symptoms of threatened abortion, pre-term labour, or ruptured membranes at enrolment or initiation of treatment. Studies of women with twins and those with singleton pregnancies were included where the loss to follow-up of the women or infants was less than 20%. The mean gestational age at enrolment varied from 14 to 26 weeks.

Outcomes assessed in the review
The primary outcome was delivery less than 37 weeks' gestation. The secondary outcomes were: delivery before 35, 34 and 32 weeks; birth weight less than 2,500 g; birth weight less than 1,500 g; spontaneous abortion or perinatal death; measures of serious neonatal morbidity; and congenital anomalies. Studies were excluded where the outcome data were not presented according to intention-to-treat.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected the studies. Any disagreements were resolved by consensus.

Assessment of study quality
The authors reported on the method of randomisation, concealment of allocation, and whether the studies were blinded. The authors did not state how the validity assessment was performed.

**Data extraction**
Two reviewers independently extracted the data. Event rates were extracted for the outcomes in each comparison group.

**Methods of synthesis**

- **How were the studies combined?**
  Where possible, the results were pooled in a meta-analysis using the random-effects model of DerSimonian and Laird. Summary relative risks (RRs) or weighted mean differences (WMDs), and corresponding 95% confidence intervals (CIs), were calculated.

- **How were differences between studies investigated?**
  Heterogeneity was explored using the chi-squared test. Subgroup analyses were planned but not carried out, owing to the small number of eligible trials.

**Results of the review**
Three RCTs were included in the analysis (data from 648 women and 643 infants followed up). The women received progestational agents (n=399) or placebo (n=249).

All of the trials were double-blind. Two trials described the method of randomisation and the third reported concealment of allocation.

The use of progestational agents resulted in a statistically significantly lower risk of delivery less than 37 weeks' gestation than the placebo group (RR 0.57, 95% CI: 0.36, 0.90; 3 RCTs). There were no statistically significant effects on the risks of congenital anomalies (2 RCTs), spontaneous abortion (3 RCTs) or perinatal death (2 RCTs). There was no reported statistical heterogeneity in any of the pooled analyses.

Individual trials comparing progestational treatment with placebo showed statistically significant results for lower risk of delivery before 35 weeks' gestation (RR 0.67, 95% CI: 0.48, 0.93), 34 weeks' (RR 0.15, 95% CI: 0.04, 0.64) and 32 weeks' (RR 0.58, 95% CI: 0.37, 0.91) gestation. In addition, the risk of birth weight less than 2,500g was lower (RR 0.66, 95% CI: 0.51, 0.87) and mean birth weight was higher (WMD 475.0, 95% CI: 16.56, 933.44) in the treatment groups.

**Authors' conclusions**
Progestational agents initiated in the second trimester of pregnancy might reduce the risk of delivery less than 37 weeks' gestation for women at increased risk of spontaneous pre-term birth. The effect on neonatal outcome is uncertain.

**CRD commentary**
The review question was clear, with specific inclusion criteria for the interventions, participants, outcomes and study design. The search strategy was adequate, but the decision to exclude unpublished studies means that relevant articles might have been missed and could indicate publication bias. The review process appeared largely systematic and transparent, the validity assessment criteria applied were relevant, and the method of synthesis was appropriate. Although the authors' conclusions are likely to be reliable, the limited number of studies containing small sample sizes means that their generalisability to all women at risk is unclear. The authors appropriately acknowledged the importance of continued research in this area and made recommendations.

**Implications of the review for practice and research**
Practice: The authors stated that recommendations for the use of progestational agents should be offered cautiously and
should consider uncertainties about their impact on other important clinical outcomes and possible adverse events.

Research: The authors stated that large, well-designed RCTs are needed to determine the effects of progestational treatment on perinatal mortality or serious neonatal morbidity. Future trials should also consider women with a wider range of risk factors for pre-term birth.

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