Progesterone for the prevention of preterm birth: a critical evaluation of evidence
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CRD summary
The authors concluded that progestational agents should be given to women at high risk of pre-term delivery. These conclusions appear to reflect the data presented, but poor reporting of review methods and a lack of detail about the participants and interventions mean it is not possible to assess the reliability of these conclusions and their general applicability.

Authors' objectives
To evaluate the effects of progestational agents on the prevention of pre-term delivery.

Searching
MEDLINE, EMBASE, the Cochrane Library and SciSearch were searched from inception to 2004 using the reported search terms. In addition, the reference lists of known primary studies and reviews were screened, while frequently cited citations were used to identify further studies using the Science Citation Index.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion in the review.

Specific interventions included in the review
Studies that evaluated progesterone or a progesterone metabolite were eligible for inclusion in the review. Studies of synthetic progestagens were excluded. Over half of the included studies evaluated 17-hydroxyprogesterone caproate; other studies evaluated vaginal progesterone suppositories, oral progesterone and intramuscular progesterone pellets. The studies were published between 1953 and 2003.

Participants included in the review
Studies of women with risk factors for pre-term birth were eligible for inclusion in the review. Studies were not included if they only enrolled women with multiple pregnancies.

Outcomes assessed in the review
Inclusion criteria were not explicitly specified for the outcomes, but it was clear that the review focused on pre-term delivery. The review assessed delivery before 37 weeks, delivery before 34 weeks, respiratory distress syndrome and adverse events.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The studies were assessed for adequacy of randomisation, allocation concealment, blinding, the reporting of withdrawals and follow-up rates, and were given a score out of 5 using Moher's criteria. The authors did not state how the validity assessment was performed.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Odds ratios (ORs) appear to have been obtained from individual studies. The authors stated that information about individual studies is available on request.

Methods of synthesis
How were the studies combined?
Pooled ORs with 95% confidence intervals (CIs) were calculated using fixed-effect and random-effects models. The
potential for publication bias was assessed using a funnel plot and Egger's asymmetry test.

**How were differences between studies investigated?**
Statistical heterogeneity was examined using forest plots and assessed using the chi-squared statistic. Cumulative meta-analyses were performed to examine the effect of time period of study (and when the treatment effect reached a statistically significant level) and decreasing study quality. A L’Abbe plot (event rate in treated versus control group) was used to examine the variability in the risk of delivery before 37 weeks with baseline risk.

**Results of the review**
Nine RCTs (n=5,806) were included.

Three studies obtained a maximum score of 5 for quality; four scored 2 and two only scored 1. Seven RCTs were double-blinded. All described withdrawals. The follow-up rates ranged from 54 to 100%.

Progestational agents were associated with a significant reduction in delivery before 37 weeks (OR 0.42, 95% CI: 0.31, 0.57; based on 8 studies) and before 34 weeks (OR 0.51, 95% CI: 0.34, 0.77; based on 3 studies) and in respiratory distress syndrome (OR 0.55, 95% CI: 0.31, 0.96; based on 2 studies). No significant heterogeneity was found for any of these analyses.

The reduction in the risk of delivery before 37 weeks with progestational agents exceeded statistical significance (p<0.05) in 1975 (OR 0.30, 95% CI: 0.12, 0.76, p<0.01; based on 4 studies). It was also statistically significant when the analysis was limited to the 3 higher quality studies (OR 0.47, 95% CI: 0.33, 0.66; n=1,441). The addition of poorer quality studies only improved the precision of the results.

The L’Abbe scatter plot showed that benefits from progestational agents were consistent across a range of baseline risks (control group rates) for delivery before 37 weeks.

The authors stated that the included RCTs showed no evidence of harms (no data were presented).

**Authors’ conclusions**
Progestational agents should be given to women at high risk of pre-term delivery.

**CRD commentary**
The review question was clear with respect to the participants, intervention, outcomes and study design. Several relevant sources were searched, but it was not clear whether unpublished studies were eligible or if any language restrictions were applied. The potential for publication bias was assessed and no evidence of it was found. The methods used to select the studies, assess validity and extract the data were not described, so it is not known whether any efforts were made to reduce reviewer error and bias. Study quality was assessed using defined criteria and the results of the assessment were reported.

There was little information in the paper about the interventions and participants; this hinders an assessment of the comparability of the studies and the populations the results may apply to. However, the authors did state that further information is available on request. The studies appear to have been appropriately combined in meta-analyses and the influence of study quality was assessed. No safety data were presented for the included studies, so it could not be ascertained if adverse effects were systematically sought or not. The authors stated that 9 studies were included in the review, but only data from eight were included; the reason for the inclusion of a ninth study that apparently provided no data was not reported. The authors’ conclusions appear to reflect the data, but the lack of reporting of review methods and the lack of details in the paper about the participants and interventions mean it is not possible to assess the reliability of these conclusions and their general applicability.

**Implications of the review for practice and research**
Practice: The authors stated that progestational agents should be given to women at high risk of pre-term delivery. They recommended the following regimens: intramuscular 17- hydroxyprogesterone caproate, 250 mg weekly, starting from
the 16th to 20th week of pregnancy until 36 weeks or delivery; vaginal progesterone suppositories, 100 mg every night.

Research: The authors stated the need for further research examining factors that increase the risk of premature delivery in multiple pregnancies that are not influenced by progestational agents.

**Bibliographic details**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Female; Infant, Newborn; Obstetric Labor, Premature /prevention & control; Pregnancy: Premature Birth /prevention & control; Progesterone /therapeutic use; Progestins /therapeutic use; Randomized Controlled Trials as Topic; Respiratory Distress Syndrome, Newborn /prevention & control

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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.