Progestational agents to prevent preterm birth: a meta-analysis of randomized controlled trials
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CRD summary
This well-conducted review assessed progestational agents for the prevention of pre-term birth. The authors concluded that progestational agents can reduce the incidence of pre-term birth and low birth weight newborns. No difference was found in hospitalisation for threatened pre-term birth or perinatal mortality. Although the exact quality of the included studies was unknown, the conclusion is likely to be reliable.

Authors' objectives
To determine the efficacy of progestational agents for the prevention of pre-term birth in those with increased risk.

Searching
MEDLINE, EMBASE and the Cochrane Library were searched from 1966 to 2004 for articles published in any language; the search terms were reported. The reference lists of retrieved articles, relevant text books and existing reviews were checked. Abstracts from national and international meetings were searched and investigators were contacted for unpublished studies.

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

Specific interventions included in the review
Studies that compared progestational agents with placebo were eligible for inclusion. Most of the included studies evaluated 17alpha-hydroxyprogesterone caproate; others evaluated medroxyprogesterone acetate or progesterone.

Participants included in the review
Studies of women at elevated risk of pre-term birth were eligible for inclusion. The reasons for elevated risk included a history of pre-term birth and multiple spontaneous abortions.

Outcomes assessed in the review
Studies that reported delivery before 37 weeks, threatened pre-term labour, a birth weight of less than 2,500 g, perinatal mortality, or respiratory stress syndrome were eligible for inclusion. The primary outcomes assessed were pre-term delivery (less than 37 weeks) and perinatal mortality.

How were decisions on the relevance of primary studies made?
It was unclear how the reviewers determined the eligibility of studies, although disagreements over inclusion were resolved by consensus.

Assessment of study quality
Methodological quality was assessed using published guidance; specific criteria were not reported. Two reviewers independently assessed the validity of the included studies. The reviewers were blinded to study authors and institutions.

Data extraction
Two reviewers independently extracted the data from each included study, and any disagreements were resolved by
consensus. Data on the occurrence of each outcome of interest were extracted and used to derive an odds ratio (OR) with 95% confidence intervals (CIs).

**Methods of synthesis**

How were the studies combined?
The results from individual studies were combined using a fixed-effect model (Mantel-Haenszel) in the absence of statistical heterogeneity, or a random-effects model (DerSimonian and Laird) in the presence of statistical heterogeneity. A pooled OR with 95% CIs was calculated for each outcome of interest, both for progestational agents combined and for 17alpha-hydroxyprogesterone separately. The number-needed-to-treat (NNT) to prevent the occurrence of each outcome was also calculated. Publication bias was assessed using Egger's test and by visual inspection of funnel plots.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Mantel-Haenszel test and by qualitative visual inspection of L’Abbe plots. Sensitivity analyses were performed to assess the influence of individual studies on the overall results. Regression techniques were used to explore year of publication, country of study, and type and dosage of progesterone used.

**Results of the review**

Ten RCTs (n=1,339) were included in the review.

Pre-term delivery (8 studies).
Progestational agents (17alpha-hydroxyprogesterone caproate and other forms of progesterone) were associated with a significantly reduced likelihood of pre-term birth compared with placebo (OR 0.45, 95% CI: 0.25, 0.80). The NNT to prevent one premature delivery was 10 (95% CI: 6, 24). The results were similar for studies of 17alpha-hydroxyprogesterone caproate only. There was evidence of statistical heterogeneity, hence a random-effects model was used. There was no evidence of publication bias and sensitivity analyses did not influence the results. The results of the meta-regression suggested that year, country, and type and dosage of progestational agents were not associated with the occurrence of pre-term birth.

Low birth weight (6 studies).
17alpha-hydroxyprogesterone caproate was associated with a significantly reduced likelihood of low birth weight compared with placebo (OR 0.50, 95% CI: 0.36, 0.71). The NNT to prevent one low birth weight was 12 (95% CI: 7, 43). No evidence of statistical heterogeneity was found, hence a fixed-effect model was used. There was no evidence of publication bias and sensitivity analyses did not influence the results.

Threatened premature labour (5 studies).
No statistically significant difference was found between progestational agents and placebo in the likelihood of hospital admission for threatened pre-term labour (OR 0.68, 95% CI: 0.35, 1.34). There was evidence of statistical heterogeneity, hence a random-effects model was used. There was no evidence of publication bias and sensitivity analyses did not influence the results.

Perinatal mortality (5 studies provided outcomes).
No statistically significant difference was found between progestational agents and placebo in the likelihood of perinatal mortality (OR 0.69, 95% CI: 0.38, 1.26). No evidence of statistical heterogeneity was found, hence a fixed-effect model was used. The results were similar for studies of 17alpha-hydroxyprogesterone caproate only. There was no evidence of publication bias and sensitivity analyses did not influence the results. The results of the meta-regression suggested that year, country, and type and dosage of progestational agents were not associated with the rate of perinatal mortality.
Respiratory distress syndrome (3 studies).

No statistically significant difference was found between progestational agents and placebo in the incidence of respiratory distress syndrome (OR 0.83, 95% CI: 0.25, 2.76). There was evidence of statistical heterogeneity, hence a random-effects model was used.

Authors' conclusions
Progestational agents and 17alpha-hydroxyprogesterone caproate reduced the incidence of pre-term birth and low birth weight newborns.

CRD commentary
The review addressed a clear research question and the inclusion criteria appeared appropriate. Several sources were searched for relevant studies and attempts were made to identify unpublished studies. Publication bias was formally assessed and attempts were made to limit language bias. Methods were used to minimise reviewer error and bias in all stages of the review process. Methodological quality was assessed using published criteria, although exact details of the tool and results were not given; this means that it is difficult to comment on the reliability of the results of individual studies included in the review. The methods used to combine the studies seemed appropriate and differences between the studies were explored. Overall, this appears to be a well-conducted review, although reporting the results of the quality assessment would have strengthened the authors' conclusion.

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

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