Progesterone for the prevention of preterm birth in twin pregnancy (STOPPIT): a randomised, double-blind, placebo-controlled study and meta-analysis


CRD summary
This review assessed the effectiveness of progesterone on the occurrence of delivery or intrauterine death before 34 weeks of gestation in women with twin pregnancy, concluding that progesterone was not effective. Despite the relatively limited literature search and poor reporting of some aspects of the review, the authors’ conclusions appear to reflect the evidence and are probably reliable.

Authors’ objectives
To assess the effectiveness of progesterone gel on the occurrence of delivery or intrauterine death before 34 weeks of gestation in women with twin pregnancy.

Searching
PubMed and the Cochrane Central Register of Controlled Trials were searched for published studies (search dates were not reported). Search terms were reported.

Study selection
Randomised controlled trials (RCTs) comparing the use of a progestogen (including progesterone, 17-hydroxyprogesterone caproate) with a placebo for the prevention of preterm birth in women with twin pregnancy were eligible for inclusion. Eligible women were in their second or third trimester. The primary outcome of interest was the incidence of delivery or intrauterine foetal death before 34 weeks’ gestation. Trials of progestogens given to women with symptoms of preterm labour, or in which data were only available in abstract form, were excluded from the review.

Where reported, progesterone gel (90mg) or placebo gel was administered daily by vagina starting at 24 weeks, while 17-hydroxyprogesterone caproate (250mg) was administered intramuscularly from 16 and 20 weeks to 35 weeks. RCTs included the outcome of interest, or spontaneous preterm delivery before 34 or 37 weeks’ gestation. Secondary outcomes were also reported for one trial, including maternal outcomes (for example, gestation at delivery, method of delivery, vaginal breech), safety outcomes (such as duration of hospital stay), neonatal outcomes (neonatal unit admission and duration of neonatal unit care), and maternal satisfaction (as reported by questionnaire).

Two reviewers screened papers for relevance, but it was unclear how discrepancies were resolved.

Assessment of study quality
Two reviewers assessed the quality of studies using the Jadad quality assessment scale, which includes items on randomisation, blinding and use of intention to treat analysis. It was unclear how discrepancies were resolved.

Data extraction
Two reviewers extracted data on spontaneous preterm delivery before 34 or 37 weeks’ gestation, to calculate the odds ratios and confidence intervals (CIs). Where data were not available, relevant authors were contacted for further information. It was unclear how discrepancies were resolved.

Methods of synthesis
Meta-analysis was conducted to combine odds ratios and their respective 95% CIs. Statistical heterogeneity was assessed using the I² test.

Results of the review
Two RCTs identified from the literature search, and one RCT conducted by the review authors, were included in the review (n=1,173 women). Trial sample sizes ranged from 24 to 655 women. The two identified RCTs were reported to
be of the highest quality according to the Jadad scale. The characteristics of the authors' own RCT suggested that this was also of high quality.

The pooled odds ratio for the three RCTs showed no effect of progesterone in preterm delivery or intrauterine death before 34 weeks' gestation (odds ratio 1.16, 95% CI: 0.89, 1.51). There was no evidence of statistical heterogeneity ($I^2=0\%$).

**Authors' conclusions**  
Progesterone, administered vaginally, did not prevent preterm birth in women with twin pregnancy.

**CRD commentary**  
The review question was clear and was supported by appropriate inclusion criteria. However, the literature search was limited to two databases and limited to published studies, which means that potentially relevant articles may have been missed. The authors reported some detail on the review process to reduce reviewer error and bias. There may also have been some selection bias, as the authors included their own RCT in the review. A reliable scale (Jadad) was used to assess validity on the studies identified from the literature search; the studies were of the highest quality. There was no evidence of statistical heterogeneity, so pooling of the results seemed appropriate. However, patient and study details for the included studies were very limited. It was unclear whether clinical and methodological heterogeneity may have been present. Despite the relatively limited literature search and poor reporting of some aspects of the review, the authors' conclusions appear to reflect the evidence and are probably reliable.

**Implications of the review for practice and research**  
**Practice:** The authors stated that progestogens are not effective in women with twin pregnancy for the prevention of preterm delivery.

**Research:** The authors stated that further research is warranted to assess the biological mechanism by which preterm delivery occurs in twin and singleton pregnancy. The authors also noted six ongoing trials, which would need a large effect size with an odds ratio of 0.65 or less to change the conclusions of this meta-analysis.

**Funding**  

**Bibliographic details**  

**Additional Data URL**  

**Other publications of related interest**  

This additional published commentary may also be of interest.

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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.