Vaginal progesterone vs cervical cerclage for the prevention of preterm birth in women with a sonographic short cervix, previous preterm birth, and singleton gestation: a systematic review and indirect comparison metaanalysis


CRD summary
The review concluded that both vaginal progesterone and cerclage significantly reduced the risk of pre-term birth in women with a sonographic short cervix in the mid trimester, singleton gestation and previous pre-term birth. Indirect comparisons indicated equal efficacy. The former conclusions appear reliable, but the latter is more uncertain due to lack of precision.

Authors' objectives
To compare vaginal progesterone with cerclage for the prevention of pre-term birth in asymptomatic, singleton gestation, women with a short cervix and a previous spontaneous pre-term birth.

Searching
MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), ISI Web of Science and LILACS were searched from inception to October 2012. Several clinical trials registries and Google Scholar were also searched; search terms were reported. Other sources included conference proceedings, contact with experts in the field, and reference lists (of relevant studies, reviews and books). There were no language restrictions.

Study selection
Eligible studies were randomised controlled trials (RCTs) that compared vaginal progesterone versus placebo/no treatment or cerclage versus no cerclage for the prevention of pre-term birth. The women had to be asymptomatic with a sonographic short cervix (cervical length less than 25 mm) and in the mid trimester of a singleton pregnancy, and must have had a previous spontaneous pre-term birth at less than 37 weeks of gestation. Quasi-randomised studies were excluded.

Most of the included studies examined the interventions in women with a sonographic short cervix. The degree of pre-term birth assessed varied across trials, from ≤32 weeks to <37 weeks. Most trials performed cervical length screening at less than 25 weeks gestation. Progesterone doses, modes of administration, and timings of administration varied across studies. All but one of the cerclage trials used the McDonald procedure. Adverse events were recorded in many studies.

Two reviewers independently selected studies for inclusion, with disagreements resolved by discussion.

Assessment of study quality
The Cochrane risk of bias tool was used to evaluate bias in the following areas: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias.

Two reviewers independently assessed risk of bias, with disagreements resolved by discussion.

Data extraction
Intention-to-treat data from two previous individual patient data meta-analyses (see Other publications of related interest field) were extracted in order to calculate risk ratios.

Two reviewers extracted data, with disagreements resolved by discussion.

Methods of synthesis
Both pair-wise direct comparisons, and indirect comparisons were performed. For the direct comparisons, a fixed-effect model was used if there was no evidence of substantial statistical heterogeneity (which was assessed using $I^2$ in
The indirect comparisons were performed according to the methods outlined by Bucher et al. (1997). Placebo/no cerclage was used as the common comparator.

Sensitivity analyses examined the effect of excluding patients who received cerclage in the progesterone trials, and patients who received progesterone in the cerclage trials. An analysis was also planned which excluded studies at high risk of bias.

**Results of the review**

Nine RCTs were included (662 women). Sample sizes ranged from six to 301 women. Four studies were of vaginal progesterone versus placebo (158 women) and five studies evaluated cerclage vs no cerclage (504 women). All studies were judged to have a low risk of bias. None of the studies that assessed cerclage had blinding of participants or healthcare providers.

**Direct comparisons:** Both vaginal progesterone and cerclage were associated with significant reductions in the risk of pre-term birth at less than 32 weeks of gestation (RR 0.47, 95% CI 0.24 to 0.91, four RCTs for vaginal progesterone compared with placebo; RR 0.66, 95% CI 0.48 to 0.91, five RCTs for cerclage compared with no cerclage) and composite perinatal morbidity and mortality (RR 0.43, 95% CI 0.20 to 0.94, four RCTs for vaginal progesterone; RR 0.64, 95% CI 0.45 to 0.91, five RCTs for cerclage).

**Indirect comparisons:** There were no significant differences between vaginal progesterone and cerclage for any outcome measures (RR 0.71, 95% CI 0.34 to 1.49 for risk of pre-term birth at less than 32 weeks; RR 0.67, 95% CI 0.29 to 1.57 for risk of composite perinatal morbidity and mortality). Findings were similar in sensitivity analyses in which patients who received co-interventions were excluded.

There was no evidence of statistically significant heterogeneity. Funnel plots suggested no evidence of publication bias.

**Authors’ conclusions**

Both vaginal progesterone and cerclage significantly reduced the risk of pre-term birth in women with a sonographic short cervix in the mid trimester, singleton gestation and previous pre-term birth. Indirect comparisons indicated that both were equally efficacious. Selection of the optimal treatment needs to consider adverse events, cost and patient/clinician preferences.

**CRD commentary**

The review addressed a clear question and was supported by reproducible eligibility criteria. Efforts to identify studies were undertaken using numerous different methods, although it appeared that all the included studies had been identified in the two previous (individual patient data) meta-analyses which were used by the authors in this review. Suitable methods (such as independent duplicate processes) were used to reduce the risk of reviewer error and bias throughout the review.

Risk of bias was adequately assessed with all studies judged to be at a low risk of bias. The trials were generally small; over half of them recruited fewer than 50 participants. The authors justified use of placebo/no cerclage as the common comparator in the indirect meta analyses by citing similar rates of pre-term birth and adverse perinatal outcomes in the respective control groups (this also allayed concerns, to some extent, about the lack of participant blinding in cerclage studies). Some uncertainty remained about how appropriate this method was, particularly given the small sample sizes of most included studies. However, appropriate methods were used to pool data and to assess and investigate heterogeneity.

The authors’ conclusions fairly reflect the evidence on the effectiveness of the respective treatments, but the lack of precision (wide confidence intervals) suggests their conclusions about treatment equivalence should be interpreted with more uncertainty.

**Implications of the review for practice and research**

**Research:** The authors estimated that any future trial which directly compared progesterone with cerclage would need to
recruit around 800 patients.

Practice: The authors stated that, given similar efficacy, therapeutic decision-making could be informed by reports about adverse events and cost-effectiveness of the interventions, as well as the patient and physician's preferences. They added that the current recommendation that patients with a short cervix and a history of pre-term birth should be treated with cervical cerclage must be revisited in light of the results of their study. Medical treatment with vaginal progesterone could decrease the risks associated with anaesthesia and a surgical procedure; therefore, it is important to disclose the availability of a non-surgical therapeutic choice to patients with a history of pre-term birth and a short cervix.

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