The effect of second-trimester antibiotic therapy on the rate of preterm birth

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CRD summary
The authors concluded that macrolides and clindamycin administered in the second trimester of pregnancy significantly reduce the pre-term delivery rate in high-risk women, whereas metronidazole used alone is associated with an increased pre-term delivery rate. Given the poor reporting of the review methods and failure to assess study quality or adequately address differences between the studies, these conclusions may not be reliable.

Authors' objectives
To assess the effect of second-trimester antibiotics (macrolides, clindamycin and metronidazole) on the risk of pre-term birth.

Searching
MEDLINE, PubMed, EMBASE, the Cochrane Database of Systematic Reviews, the Cochrane CENTRAL Register and the Cochrane Pregnancy and Childbirth Group's Specialised Register were searched for articles published between 1965 and March 2006; the search terms were provided. The reference lists of retrieved articles were checked. Articles published only as abstracts were excluded.

Study selection
Randomised controlled trials (RCTs) in which women received macrolides, clindamycin or metronidazole during the second trimester of pregnancy (12 to 28 weeks' gestation), in order to prevent pre-term delivery, were eligible. Control groups were required to receive placebo or no treatment. The primary outcome was the rate of pre-term delivery (prior to 37 weeks' gestation), while the secondary outcome was mean gestational age at delivery. Trials were required to include at least 30 women and to follow up at least 95% of participants. Studies of women with premature rupture of membranes or pre-term labour were excluded.

All women in the included studies had increased risk of pre-term delivery. Risk factors included cervico-vaginal foetal fibronectin positivity, urogenital infection, history of pre-term delivery, weight under 50 kg before pregnancy, and periodontitis. Antibiotics were administered at varying doses and frequencies, either orally or vaginally, for up to 6 weeks. Erythromycin was the sole macrolide used. Erythromycin and metronidazole were used in combination in several studies, whereas clindamycin was used alone in all cases. The controls received no treatment, placebo or vitamin C. Some studies reported rates of late miscarriage as well as pre-term delivery.

Two reviewers independently selected studies for inclusion, with any disagreements resolved by consensus or by discussion with a third person.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
For binary data, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from the numbers of events in the control and intervention groups of each study. Continuous data were reported as means or as mean differences, with 95% CIs or standard deviations.

The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
Data were pooled in a meta-analysis using a fixed-effect model to obtain pooled ORs or weighted mean differences for each type of intervention. Subgroup analyses were conducted to assess the effect of route of antibiotic administration.
Results of the review
Fourteen RCTs (n=7,545) were included in the review.

There were 3 RCTs (n=1,827) of macrolides. The pre-term birth rate was significantly lower in the group receiving erythromycin with (2 RCTs) or without (1 RCT) metronidazole (OR 0.72, 95% CI: 0.56, 0.93, p=0.01). Findings for mean gestational age at delivery (1 RCT) were not statistically significant.

There were 5 RCTs (n=1,528) of clindamycin. The pre-term birth rate was significantly lower in the group receiving clindamycin (OR 0.68, 95% CI: 0.49, 0.95, p=0.02; 5 RCTs), as was the gestational age at delivery (38.8 versus 38.0 weeks, p=0.04; 1 RCT).

There were 8 RCTs (n=5,529) of metronidazole. No significant difference was found between the groups for any outcome when metronidazole with (2 RCTs) or without (6 RCTs) erythromycin was compared with controls. When RCTs of metronidazole alone were pooled, there was a significantly higher rate of pre-term delivery in the intervention group (OR 1.31, 95% CI: 1.08, 1.58, p=0.005; 6 RCTs).

The results of subgroup analyses were also reported.

Authors' conclusions
Macrolides and clindamycin administered in the second trimester of pregnancy significantly reduce the pre-term delivery rate in high-risk women, whereas metronidazole used alone is associated with an increased pre-term delivery rate.

CRD commentary
The review objectives and inclusion criteria were clear. Relevant sources were searched but, as inclusion was restricted to studies published in full, the review was prone to publication bias; this bias was not formally assessed. It was not stated whether the search was restricted by language. Steps were taken to minimise error and bias in the review process by having more than one reviewer involved at the study selection stage, but it is unclear whether this also applied to the data extraction. Study validity does not appear to have been systematically assessed, and the lack of information in this area makes it difficult to determine the reliability of the evidence presented. Although clinical heterogeneity between the studies was discussed in the text, there was no mention of a formal assessment of statistical heterogeneity. The forest plots for clindamycin and metronidazole indicate visible and statistically significant heterogeneity, which suggests that it might not have been appropriate to pool these data. In view of the poor reporting of the review methods and failure to assess study quality or adequately address heterogeneity, the authors' conclusions may not be reliable.

Implications of the review for practice and research
Practice: The authors stated that metronidazole should be avoided during the second trimester of pregnancy in women at high risk of pre-term delivery.

Research: The authors stated that more research is required to determine what treatment regimen should be used to reduce the risk of pre-term birth and who should be the target population.

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