Antibiotic treatment of bacterial vaginosis in pregnancy: a meta-analysis

CRD summary
This review assessed antibiotic treatment for bacterial vaginosis in pregnant women. The authors concluded that the screening of women with a previous pre-term delivery is justified, and that oral antibiotics given for a longer time reduced pre-term delivery. The data for antibiotic treatment of longer duration were derived from only two trials, thus casting some doubt on the reliability of the conclusions.

Authors’ objectives
To assess the effects on pre-term labour of antibiotic treatment for bacterial vaginosis (BV) in pregnant women.

Searching
MEDLINE (from 1966) EMBASE (from 1988) and the Science Citation Index Expanded (from 1997) were searched in June 2001 for studies published in English; the search terms were stated. The reference lists in identified studies were also checked.

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

Specific interventions included in the review
Studies that compared antibiotics with placebo were eligible for inclusion. The antibiotics used in the included studies were intravenous clindamycin followed by oral clindamycin, vaginal clindamycin, oral metronidazole, and oral metronidazole plus oral erythromycin.

Participants included in the review
Studies of pregnant women with BV and intact amniotic membranes at less than 37 weeks' gestation were eligible for inclusion. BV could be diagnosed clinically or using Gram staining, but diagnoses based on positive cultures of BV-associated microflora alone were insufficient. The studies included high-risk women (with at least one previous pre-term delivery) and low-risk women (without a previous pre-term delivery). All but one study were in women without pre-term labour; one study was on women with pre-term labour. All of the included studies excluded women with multiple pregnancies. Other exclusion criteria for the studies were also described in the paper. The mean gestational age at study entry ranged from 12.4 to 30.7 weeks (estimated from inclusion criteria for all but one study). In 6 studies the women were also screened for other micro-organisms or infections.

Outcomes assessed in the review
Studies that assessed any of the following outcomes were eligible for inclusion: pre-term delivery using any definition; perinatal or neonatal death; and any information about neonatal morbidity. The review assessed delivery before 37 weeks and before 32 and 34 weeks.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected studies, compared results and reached consensus.

Assessment of study quality
The studies were assessed for the adequacy of allocation concealment, baseline similarity of the treatment groups, the number of patients excluded after randomisation and the reasons for their exclusion, completeness of outcome assessment, and assessment of patient compliance. The authors did not state who performed the validity assessment.
Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data
extraction. The extracted data included: the number of patients; the inclusion criteria for patients; gestational age; the
criteria used to diagnose BV; the antibiotic regimen; the number of patients with true-positive, true-negative, false-
positive and false-negative results (calculated from the results where not reported); and outcomes. Gestational age was
estimated from the inclusion criteria for studies that did not report actual values for the participants. For each study, the
odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each outcome.

Where reports included overlapping populations, only the most complete dataset was used.

Methods of synthesis
How were the studies combined?
The studies were combined using a meta-analysis. Pooled ORs and 95% CIs were calculated using a fixed-effect model
in the absence of statistical heterogeneity and a random-effects model when heterogeneity was present.

Data from studies that reported zero events in both treatment groups were excluded from the analyses.

How were differences between studies investigated?
Clinical homogeneity among the studies was assessed by comparing the following criteria among studies: patient
inclusion and exclusion criteria; mean gestational age at randomisation; diagnostic criteria for BV; treatment regimens;
treatment of patients with concomitant genitourinary infections; and definitions of outcomes among studies.

Statistical heterogeneity was assessed using the chi-squared statistic. Subgroup analyses were used to explore the effect
of the following characteristics on delivery at less than 37 weeks for patients without pre-term labour: patient
inclusion and exclusion criteria (high- or low-risk patients); gestational age at the start of treatment (before or after 20 weeks);
route of administration of antibiotic treatment (oral treatment for at most 2 days, oral treatment for at least 7 days, or
vaginal treatment). A subgroup analysis was also conducted according to the definition of pre-term delivery (less than
34 or less than 32 weeks). The one study of women with pre-term labour was analysed separately.

Results of the review
Ten RCTs (3,969 patients) were included.

Nine of the 10 RCTs reported that the treatment groups were similar at baseline, and nine described an assessment of
compliance. Two RCTs excluded patients after randomisation. The results were presented for between 85.1 and 100%
of the patients randomised.

Women without pre-term labour; pre-term delivery defined as delivery before 37 weeks.

The meta-analysis found no statistically significant difference between antibiotics and placebo in pre-term delivery for
all patients combined or for high-risk patients. Using a random-effects model, the OR was 0.83 (95% CI: 0.57, 1.21)
for all patients and 0.50 (95% CI: 0.22, 1.12) for high-risk patients (4 RCTs, 582 high-risk patients). Significant
heterogeneity was detected for both meta-analyses (P<0.02 for both).

The meta-analysis found that oral antibiotics given for at least 7 days significantly reduced pre-term delivery compared
with placebo (the abstract stated that these results apply to high-risk women, but table III did not specify the group).
The OR (2 RCTS, 338 women) was 0.42 (95% CI: 0.27, 0.67). No significant heterogeneity was detected (P=0.38). For
low-risk women, the meta-analysis found no statistically significant difference between antibiotics and placebo in pre-
term delivery. The OR (3 RCTs, 2,530 women) was 1.25 (95% CI: 0.86, 1.81). No significant heterogeneity was
detected (P=0.74).

Women with pre-term labour (1 RCTs, 25 women).

One small RCT found no statistically significant difference between antibiotics and placebo in pre-term delivery before
37 weeks. The OR was 0.31 (95% CI: 0.03, 3.24).
The results for other subgroup analyses were reported in the paper.

**Authors' conclusions**
The authors concluded that the evidence justifies the screening of high-risk women who have had a previous pre-term delivery for BV and their treatment with oral antibiotics for a longer time period. They also concluded that further research is required.

**CRD commentary**
The review question was clear in terms of the study design, intervention, participants and outcomes. Several relevant sources were searched and the search terms were stated. No attempts were made to minimise language or publication bias. Two reviewers independently selected the studies, which reduces the potential for bias and errors. The methods used to assess validity and extract the data were not described, thus it is not known whether any efforts were made to reduce errors and bias. Validity was assessed using specified established criteria and the results were reported.

The data were combined appropriately in a meta-analysis and statistical heterogeneity was assessed. Having found significant heterogeneity, the authors explored potential reasons for this and discussed its implications. The finding of significant heterogeneity for the meta-analysis of high-risk women suggests that the evidence cannot be adequately summarised using a meta-analysis. The conclusion regarding the effect of longer duration of oral antibiotic treatment in high-risk women was based on only two studies, and is therefore based on limited evidence.

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

**Practice:** The authors stated that screen-and-treat strategies for women at high risk of pre-term delivery can be justified. They also stated that no resources should be allocated to implementation of screen-and-treat strategies in low-risk women.

**Research:** The authors stated that more studies are required in high-risk patients without pre-term labour and in patients with pre-term labour. They also stated that studies should assess the effectiveness of oral antibiotics given for a longer duration early in pregnancy in high-risk women, and evaluate the results using more restrictive definitions for pre-term delivery (less than 34 or less than 32 weeks). In addition, no further research on screen-and-treat strategies in low-risk women should be conducted.

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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.