Fetal fibronectin as a predictor of preterm birth: an overview

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Authors' objectives
To determine the clinical utility of foetal fibronectin in cervicovaginal fluid as a predictor of pre-term birth in patients with and without uterine contractions.

Searching
MEDLINE was searched from January 1976 to December 1997 for articles published in English using the following keywords: 'fibronectin', 'fetal fibronectin', 'oncofetal fibronectin', 'preterm', 'PROM', 'preterm birth' and 'preterm labour'.

Study selection
Study designs of evaluations included in the review
Prospective studies where care givers were blinded to the fibronectin test results, were eligible for inclusion.

Specific interventions included in the review
No inclusion criteria relating to the index test were specified. Studies evaluating the foetal fibronectin test were included. Twenty-two studies used a quantitative enzyme-linked immunosorbent assay (ELISA) to test for the presence of fibronectin. The foetal fibronectin assay was considered positive if the value was greater than 50 ng/mL. Two studies used a Fetal Fibronectin Membrane Immunoassay kit, which includes an immunogold assay that forms a visual spot on a measuring device if the foetal fibronectin sample is greater than 50 ng/mL. Swabs were taken from either the cervix (6 studies), the vagina (8 studies) or both (10 studies). When sampling was from both the cervix and vagina, the tests were considered positive if the sample from either the vagina or cervix was positive in nine studies and if both samples were positive in one study.

Reference standard test against which the new test was compared
No inclusion criteria relating to a reference standard test were specified. The foetal fibronectin test was evaluated against delivery 7 to 28 days post-test, and against any pre-term delivery.

Participants included in the review
Studies of women who were at less than 37 weeks' gestation were eligible for inclusion. Within the included studies, the gestational age at initial sampling ranged from 20 to less than 37 weeks. Women presenting with uterine contractions were considered 'symptomatic', while women at low or high risk of premature labour but without uterine contractions were considered 'asymptomatic'. All of the studies were restricted to women with intact membranes. The maternal age was not stated in most studies but, where reported, the mean value ranged from 22 to 31 years.

Outcomes assessed in the review
No inclusion criteria relating to the outcome measures were specified. The outcome measures used in the review were the foetal fibronectin test characteristics, i.e. sensitivity, specificity, positive predictive value and negative predictive value. Studies were excluded if the test characteristics were not reported or could not be calculated on a per patient basis.

How were decisions on the relevance of primary studies made?
Two authors independently reviewed all the articles, and any discrepancies were resolved by consensus.

Assessment of study quality
The authors did not state that they assessed validity.
Data extraction
Two authors independently extracted the data, and any discrepancies were resolved by consensus.

Methods of synthesis
How were the studies combined?
The data were analysed descriptively. Summary values (95% confidence intervals, CIs) were calculated for the test characteristics of symptomatic and asymptomatic women where possible.

How were differences between studies investigated?
No statistical test for heterogeneity was conducted.

Results of the review
Twenty-five articles, reporting on 24 studies involving 6,779 women, were included in the review. Sixteen articles reporting on 15 studies evaluated only symptomatic women (n=2,699), while 8 studies included only asymptomatic women (n=3,969). Three studies that evaluated asymptomatic women included women at high risk for premature labour (n=215), and 5 studies involved principally women at low risk of premature labour (n=3,754). One study evaluated both symptomatic (n=38) and asymptomatic women (n=73) at low risk of premature labour.

For symptomatic women, the sensitivity for delivery within 7 to 10 days of sampling was 98% (95% CI: 95, 100), and the specificity was 83% (95% CI: 82, 85). For delivery within 14 days, the sensitivity was 82% (95% CI: 74, 90) and the specificity was 85% (95% CI: 83, 87). For delivery within 21 days, the sensitivity was 73% (95% CI: 67, 80) and the specificity was 90% (95% CI: 87, 92). For delivery at less than 34 weeks' gestation, the sensitivity was 87% (95% CI: 81, 94) and the specificity was 85% (95% CI: 81, 89). For any pre-term delivery (less than 37 weeks), the sensitivity was 54% (95% CI: 51, 58) and the specificity was 87% (95% CI: 85, 88).

For asymptomatic women, there were few studies that evaluated sensitivity and specificity for delivery within 7 to 28 days. The sensitivity for delivery at less than 34 weeks' gestation was 43% (95% CI: 36, 50), and the specificity was 89% (95% CI: 88, 90). For any pre-term delivery (less than 37 weeks), the sensitivity was 64% (95% CI: 57, 71) and the specificity was 86% (95% CI 84, 88).

The best site for sampling foetal fibronectin was evaluated in three studies. Two studies found cervical foetal fibronectin to be more sensitive than vaginal fibronectin.

Authors' conclusions
A meta-analysis of the published literature indicates that foetal fibronectin is able to determine, among symptomatic women, those who will not deliver within 7 to 10 days. Patients with a negative foetal fibronectin test result may be safely observed at home and may avoid treatment with antibiotics, tocolytics, and corticosteroids. Further research should confirm the accuracy of the rapid tests and should focus on evaluations of interventions among those who test positive. In contrast, the foetal fibronectin ELISA does not differentiate well among asymptomatic patients, those who will deliver pre-term from those who will not. Therefore, sampling for foetal fibronectin should not be undertaken in this population, as a positive result may cause unnecessary anxiety or result in unnecessary or harmful interventions, and a negative result may be falsely reassuring.

CRD commentary
The review used a clearly stated objective and some relevant inclusion criteria were specified. The reference standard used to evaluate the index test was appropriate. The methodology used to conduct the review, such as the number of authors involved in the data extraction, was clearly reported. MEDLINE was the only electronic database used and the search was restricted to English language publications, which means that some important information may have been missed. No attempt was made to look for unpublished studies and the presence of publication bias cannot be ruled out.

The validity of the individual studies was not investigated, and the influence of potential sources of bias arising from
the quality of the primary studies was not discussed. The possible heterogeneity of the included studies was not formally investigated or discussed. The methods used to generate summary values for the test characteristics were not described, and it is therefore not possible to fully assess their appropriateness. However, the simple pooling of sensitivity and specificity values from individual studies to produce a summary estimate is rarely appropriate and, in the absence of any assessment of heterogeneity, cannot be justified.

The authors' conclusions are based upon the summary estimates of sensitivity and specificity discussed above, and as such should be treated with some caution.

**Implications of the review for practice and research**
Practice: The authors state that symptomatic patients with a negative foetal fibronectin test result may be safely observed at home and may avoid treatment with antibiotics, tocolytics and corticosteroids. They further state that sampling for foetal fibronectin should not be undertaken in asymptomatic patients.

Research: The authors note that further research is necessary to determine the effectiveness and cost-effectiveness of approaches to the screening of asymptomatic women.

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