Fetal fibronectin as a short-term predictor of preterm birth in symptomatic patients: a meta-analysis

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CRD summary
This review concluded that the cervical foetal fibronectin test had limited accuracy in predicting preterm birth within seven days of sampling in symptomatic pregnant women. This conclusion reflected the data presented, although it was possible that relevant studies were missed by the search strategy.

Authors’ objectives
To assess the accuracy of cervicovaginal fibronectin as a short-term predictor of preterm birth in symptomatic patients.

Searching
MEDLINE, EMBASE, Current Contents and The Cochrane Library were searched (1966 to April 2008) without language restrictions. Search terms (which included methodological terms for test accuracy studies) were reported. Abstracts from relevant scientific meetings since 1981 were handsearched for unpublished studies. Bibliographies of systematic reviews and text book chapters were screened for additional references. Experts in the field and manufacturers of the foetal fibronectin test were consulted.

Study selection
Diagnostic cohort studies of patients with signs and symptoms of preterm labour who underwent cervicovaginal foetal fibronectin testing before 37 weeks gestation and that described the assay used were eligible for inclusion. Participants in included studies had to have known gestational ages after spontaneous labour and delivery (reference standard); a positive reference standard was defined as preterm delivery within seven days of testing.

Half of the included studies used a quantitative enzyme-linked immunoassays (ELISA) for foetal fibronectin; a positive test (predictive of preterm birth) was defined as foetal fibronectin of at least 50ng/mL. Other included studies used rapid bedside foetal fibronectin tests (TLiQ) or membrane immunoassay. Gestational age at sampling was similar across most studies and ranged from 18 to 36 weeks overall. Seventeen of 32 included studies included only singleton pregnancies, 10 studies made no specification and five studies included both singleton and multiple pregnancies (four studies did not provide separate data and one study reported separate data).

Studies were assessed for inclusion in the review by two reviewers. Disagreements were resolved by consensus with a third reviewer.

Assessment of study quality
Methodological quality of included studies was assessed with a modified version of the QUADAS tool. Twelve criteria were assessed and these covered aspects of patient spectrum, reference standard, verification bias, review bias, clinical review bias, incorporation bias, test execution, study withdrawals and indeterminate results. Study quality was defined as high when at least nine criteria were met.

Methodological quality was assessed independently by two reviewers.

Data extraction
Data were extracted to populate 2x2 contingency tables of foetal fibronectin and spontaneous preterm birth. Where a 2x2 table contained zero values, 0.5 was added to all cells in that table. Estimates of sensitivity and specificity with 95% confidence intervals (CIs) were calculated for each study.

Data were assessed independently by two reviewers.
Methods of synthesis

Pooled estimates of the overall sensitivity and specificity, with 95% CIs, for any foetal fibronectin assay were determined from a summary receiver operating characteristic (SROC) curve, fitted using a bivariate random-effects model. Pooled estimates included data for both singleton and multiple pregnancies, except one study for which separate data were provided; only data on singleton pregnancies from this study were included in the analysis. Post-test probabilities were calculated from pooled estimates of likelihood ratios and pre-test odds of delivery within seven days of testing (7.7%).

Between-study heterogeneity was assessed using Cochrane Q and $I^2$ tests.

Subgroup analyses were conducted for different types of foetal fibronectin test and cut-off values.

The effect of study characteristics (multifoetal gestation, method of testing (ELISA versus others), blinding of test results, high quality studies vs. others, prevalence of delivery within seven days, USA studies versus others, studies published before 2002 versus others and language of publication) on test accuracy was assessed using a series of univariate regression models. Data were considered insufficient to support multivariate regression modelling.

Publication bias was assessed using a funnel plot.

Results of the review

Thirty-two studies (5,355 participants) were included in the review. Twenty-four studies were considered high quality (met at least nine out of 12 quality assessment criteria). The commonest methodological weaknesses were lack of reporting of withdrawals and not reporting the time interval between foetal fibronectin sampling and delivery within seven days (reference standard).

Prevalence of preterm delivery within seven days of testing ranged from 1.8% to 29.7%.

Overall pooled estimate of sensitivity was 76.1% (95% CI 69.1% to 81.9%, $I^2$=47%) and the pooled estimate of specificity was 81.9% (95% CI 78.9% to 84.5%, $I^2$=83%). Pooled positive LR was 4.20 (95% CI 3.53 to 4.99). Pooled negative likelihood ratio was 0.29 (95% CI 0.22 to 0.38).

Subgroup analyses gave similar results for different types of foetal fibronectin test.

Regression analyses indicated that test accuracy was affected by prevalence of delivery within seven days of testing and that blinding and publication before 2002 were each associated with increased estimates of accuracy.

Funnel plot analysis showed no evidence of publication bias.

Authors' conclusions

The cervical foetal fibronectin test had limited accuracy in predicting preterm birth within seven days of sampling in symptomatic pregnant women.

CRD commentary

The review presented clearly defined inclusion criteria and searched a range of sources for relevant studies. The lack of language restrictions and the search of conference proceedings limited the likelihood of language and publication biases. However, use of methodological terms for test accuracy studies has been shown to significantly reduce the sensitivity of searches and may have resulted in omission of relevant studies. Measures were taken throughout the review process to reduce potential for error and/or bias. Appropriate meta-analytic methods were applied and between-study heterogeneity was explored, within the limits of the available data.

The authors’ conclusions reflected the data presented, although it was possible that relevant studies were missed by the search strategy.
Implications of the review for practice and research

**Practice:** The authors stated that foetal fibronectin appeared to have limited value as a short-term predictor of preterm birth in symptomatic patients.

**Research:** The authors stated that further research was needed to develop improved biomarkers and to assess the potential of combining multiple biomarkers for the prediction of preterm birth. They suggested that studies could be undertaken to assess the predictive value of foetal fibronectin as a continuous variable (rather than dichotomised at a specified threshold, as was the case for all studies in the review).

**Funding**
Not stated.

**Bibliographic details**

**PubMedID**
19701045

**DOI**
10.1097/AOG.0b013e3181b47217

**Original Paper URL**
http://journals.lww.com/greenjournal/Abstract/2009/09000/Fetal_Fibronectin_as_a_Short_Term_Predictor_of.22.aspx

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Biomarkers /metabolism; Chorion /metabolism; Decidua /metabolism; Female; Fibronectins /metabolism; Humans; Predictive Value of Tests; Pregnancy; Premature Birth /etiology /metabolism; Reproducibility of Results; Vaginal Smears

**AccessionNumber**
12009109063

**Date bibliographic record published**
07/07/2010

**Date abstract record published**
10/11/2010

**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.