

Accuracy of cervicovaginal fetal fibronectin test in predicting risk of spontaneous preterm birth: systematic review

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Abstract

Objective To determine the accuracy with which a cervicovaginal fetal fibronectin test predicts spontaneous preterm birth in women with or without symptoms of preterm labour.

Design Systematic quantitative review of studies of test accuracy.

Data sources Medline, Embase, PASCAL, Biosis, Cochrane Library, Medion, National Research Register, SCISEARCH, conference papers, manual searching of bibliographies of known primary and review articles, and contact with experts and manufacturer.

Study selection Two reviewers independently selected and extracted data on study characteristics, quality, and accuracy.

Data extraction Accuracy data were used to form 2×2 contingency tables with spontaneous preterm birth before 34 and 37 weeks' gestation and birth within 7-10 days of testing (for symptomatic pregnant women) as reference standards. Data were pooled to produce summary receiver operating characteristic curves and summary likelihood ratios for positive and negative test results.

Data synthesis 64 primary articles were identified, consisting of 28 studies in asymptomatic women and 40 in symptomatic women, with a total of 26 876 women. Among asymptomatic women the best summary likelihood ratio for positive results was 4.01 (95% confidence interval 2.93 to 5.49) for predicting birth before 34 weeks' gestation, with corresponding summary likelihood ratio for negative results of 0.78 (0.72 to 0.84). Among symptomatic women the best summary likelihood ratio for positive results was 5.42 (4.36 to 6.74) for predicting birth within 7-10 days of testing, with corresponding ratio for negative results of 0.25 (0.20 to 0.31).

Conclusion Cervicovaginal fetal fibronectin test is most accurate in predicting spontaneous preterm birth within 7-10 days of testing among women with symptoms of threatened preterm birth before advanced cervical dilatation.

Introduction

Spontaneous preterm birth occurs in 7-11% of pregnancies before 37 weeks' gestation^{1 2} and in 3-4% of pregnancies before 34 weeks' gestation.³ Most neonatal deaths of normally formed infants occur when they are born before 34 weeks' gestation. Many of the surviving preterm infants, especially those from the earlier gestations, suffer serious morbidity such as bronchopulmonary dysplasia, intraventricular haemorrhage, retrolental fibroplasia, neurodevelopmental problems, and cognitive difficulties.^{4 5} Advances in perinatal health care have not altered the incidence of

spontaneous preterm birth, but there is effective management to reduce the associated complications.⁶

Fetal fibronectin is a glycoprotein found in amniotic fluid, placental tissue, and the extracellular substance of the decidua basalis next to the placental intervillous space. It is thought to be released through mechanical or inflammatory mediated damage to the membranes or placenta before birth.⁷ Swabs can be taken from the ectocervix or posterior vaginal fornix, and an enzyme linked immunosorbent assay (ELISA) can be used to detect fetal fibronectin. The results may indicate the likelihood of spontaneous preterm birth.⁸ In clinical use, however, factors such as contamination of the sample with maternal blood, sampling within 24 hours after intercourse, and pre-eclampsia may reduce the accuracy of the test and give false positive results.

We conducted a systematic review to obtain reliable estimates of accuracy.

Methods

We used a prospective protocol with widely recommended methods.^{9 10}

Identification of studies

Our electronic searches targeted all diagnostic procedures among studies on prediction of spontaneous preterm birth.¹¹ We searched Medline (1966-2000), Embase (1980-2000), PASCAL (1973-2001), and BIOSIS (1969-2001). We also searched specialist computer databases: the Cochrane Library (2000:4), MEDION (1974-2000) (a database of diagnostic test reviews set up by Dutch and Belgian researchers), National Research Register (2000:4), SCISEARCH (1974-2001), and conference papers (1973-2000). We contacted individual experts and the manufacturer of fetal fibronectin test to uncover grey literature. We also checked reference lists of known reviews and primary articles to identify cited articles not captured by electronic searches.

Study selection and data extraction procedures

Our selection criteria were studies in asymptomatic or symptomatic pregnant women, cervicovaginal fetal fibronectin testing before 37 weeks' gestation, known gestation at spontaneous birth, and observational cohort design. We had no language restrictions, but we excluded case-control studies.

We extracted study characteristics, quality, and accuracy of results from each selected article. We extracted data for asymptomatic and symptomatic women on spontaneous preterm birth before 34 and 37 weeks' gestation. We defined asymptomatic women as those without uterine tightenings or contractions and symptomatic women as those with uterine tightenings or contractions and cervical dilatation of <2-3 cm.

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A list of excluded references and a table summarising the included studies appear on bmj.com as *webextras*

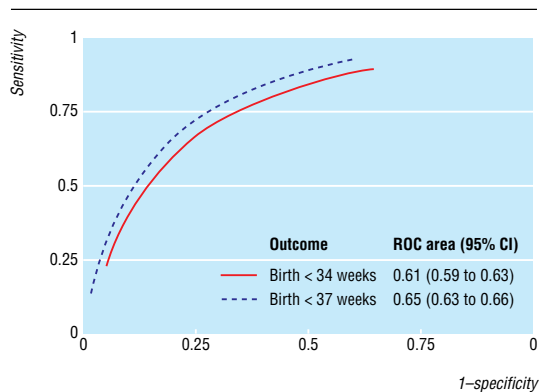


Fig 1 Summary receiver operating characteristic (ROC) curves for cervicovaginal fetal fibronectin test in predicting spontaneous preterm birth in asymptomatic women

Assessment of study quality

We considered a study to be of good quality if it used a prospective design, consecutive enrolment, adequate test description (to allow replication by others), and blinding of the test result from clinicians managing the patients.¹²

Data synthesis

We synthesised data separately for studies on asymptomatic and symptomatic women with spontaneous preterm birth before 34 and 37 weeks' gestation. For symptomatic women we also synthesised data for spontaneous preterm birth within 7-10 days of testing. We used random effects models.

We used summary receiver operating characteristic (ROC) curves as measures of accuracy for all included studies regardless of their thresholds. The area under the curve provides an average measure of accuracy from the combined studies (especially when there are different test thresholds) and a convenient way of comparing accuracy of the test for different outcomes. We used summary likelihood ratios as measures of accuracy for studies using 50 ng/ml as the threshold. These ratios indicate by how much a given test result will raise or lower the probability¹³ of having a spontaneous preterm birth. Using summary ratios we determined probabilities after the test by Bayes' theorem.¹³ In this way, ratios are more clinically meaningful than sensitivities or specificities, for which meta-analysis are generally not recommended.

Results

Literature identification and study quality

Twenty eight accuracy studies in asymptomatic women and 40 studies in symptomatic women met the selection criteria, with a total of 26 876 women (see the webextra table with the long version on bmj.com for study details). Thirteen (19%) studies, seven among asymptomatic¹⁴⁻²⁰ and six among symptomatic women,²¹⁻²⁶ fulfilled all four criteria for good quality. All studies except three²⁷⁻²⁹ (which accounted for 0.28% of the 22 390 women in our review) used thresholds of 50 ng/ml to indicate an abnormal test result.⁸

Fibronectin test in asymptomatic women

In women without symptoms three studies examined the accuracy of the test using bedside methods and 26 used laboratory methods. Thirteen studies examined single testing and 16 looked at serial testing. Eight studies examined the use of fibronectin as a screening tool in low risk pregnancy and nine as a selective screening tool in high risk pregnancy. Most studies were carried out during the second trimester or early in the third trimester. Meta-regression analysis showed the accuracy of the test did not depend on the method of testing, how often the test was done, classification of risk, or gestation at testing.

The estimates of the accuracy of the test in predicting spontaneous preterm birth for the various gestations of interest varied considerably. Figure 1 shows the summary receiver operating characteristic curve for asymptomatic women. Figure 2 shows the pooled estimates of likelihood ratios. See the full version of the paper on bmj.com for detailed forest plots from individual studies.

We found no significant differences in estimates of accuracy in studies with high and low quality features.

Fibronectin test in symptomatic women

In women with symptoms 11 studies examined the accuracy of the test using bedside methods and 30 used laboratory methods. Thirty five examined occasion testing, and five looked at serial testing. Meta-regression analysis showed that the accuracy of the test did not depend on the method of testing, how often the test was done, or classification of risk. As for asymptomatic women, the accuracy of the in predicting spontaneous preterm birth for the various gestations of interest varied considerably. Figure 3 shows the

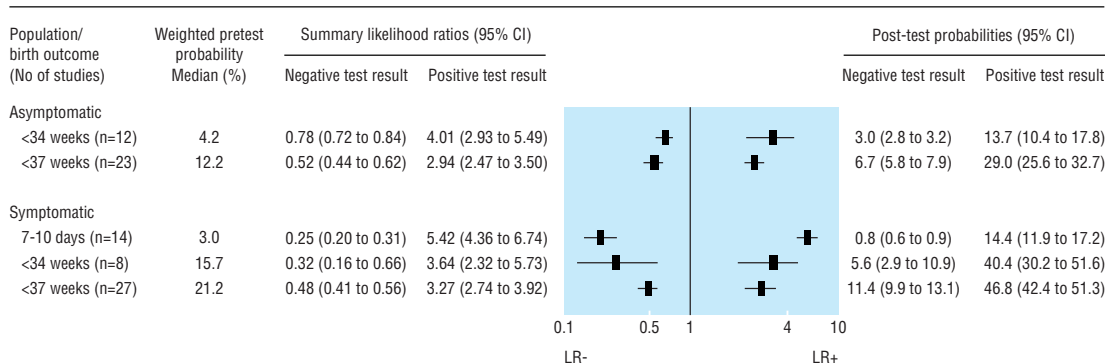


Fig 2 Pooled estimates of likelihood ratios for cervicovaginal fetal fibronectin test and their impact on predictive probabilities of spontaneous preterm birth in asymptomatic and symptomatic women

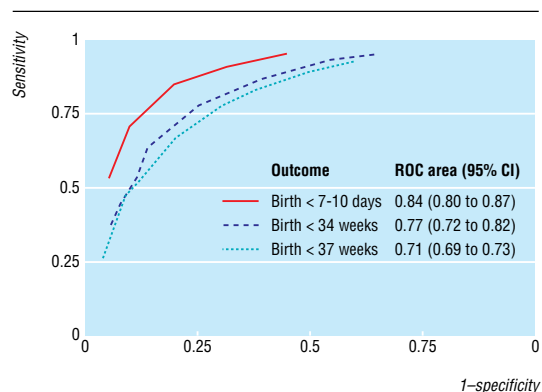


Fig 3 Summary receiver operating characteristic (ROC) curves and areas for cervicovaginal fetal fibronectin test in predicting spontaneous preterm birth symptomatic women

summary receiver operating characteristic curve for symptomatic women. See the full version of the paper on bmj.com for detailed forest plots from individual studies. The pooled estimate of the likelihood ratios can be found in figure 2.

When we examined study quality as a source of heterogeneity we found no significant differences in estimates of accuracy in studies with high and low quality features. Funnel plot analysis did not indicate presence of publication or related bias for the main outcomes.

Discussion

Our results show that the accuracy of the cervicovaginal fetal fibronectin in predicting various spontaneous preterm birth outcomes varies. The test is most accurate in predicting spontaneous preterm birth within 7-10 days after testing among women with symptoms of threatened preterm birth before advanced cervical dilatation.

Quality of our review

In contrast with the previous four systematic reviews³⁰⁻³³ we identified 64 studies (at least twice as many studies as the largest previous review³²). Because meta-analysis of studies that examine test accuracy are fraught with difficulty due to poor methodological quality of the primary studies, we scrutinised the selected studies for their quality, an assessment undertaken in only one previous review.³³ Methodological issues that may overestimate accuracy such as case-control design, absence of test descriptions, and different reference tests,³⁴ were not applicable to the studies we reviewed. Our assessments of quality were affected by poor reporting in some instances, though quality did not significantly explain differences between their results. Assessment and exploration for reasons behind heterogeneity were planned a priori. In the presence of unexplained heterogeneity we pooled data with a random effects model, which produces a wider confidence interval. However, because of the large number of studies the estimates of accuracy were generally more precise compared with previous reviews.

Clinical application

The use of antenatal steroids in women with symptoms of threatened preterm birth at 31 weeks' gestation

Cervicovaginal fetal fibronectin testing among symptomatic women and number of women needed to be treated (NNT) at 31 weeks' gestation with antenatal steroids to prevent one case of neonatal respiratory distress syndrome (RDS) associated with spontaneous preterm birth within 7-10 days of testing

Test result*	Probability of spontaneous preterm birth within 7-10 days of testing (%)	Risk of RDS at 32 weeks' gestation	Rate of RDS* at 32 weeks' gestation (%)	NNT
No testing	4.5‡	0.53	2.0	109
Test positive	20.6§	0.53	11.0	17
Test negative	1.0§	0.53	0.4	509

*See full version of this paper on bmj.com for details for calculations.

serves as a useful example for the clinical application of our findings (table).⁶ The absolute effect of antenatal steroids depends on the risk of spontaneous preterm birth after presentation. The higher the risk, the lower the number of women that needed to be treated to prevent one case of respiratory distress syndrome and vice versa. The risk, and hence the therapeutic benefits, depends not only on the gestational age at presentation but also on the post-test probabilities of spontaneous preterm birth associated with fibronectin testing. If steroids were to be used for all symptomatic women at this gestation without fibronectin testing then we would need to treat 109 women with antenatal steroids to prevent one case of respiratory distress syndrome. If we treated only those women with a positive test result we would need to treat 17, a figure considerably lower than that without testing

This approach will allow clinicians to make explicit decisions on the basis of more realistic probabilities generated by fibronectin testing and provides a framework for the use of diagnostic evidence in therapeutic decision making. Specifically, our results enable clinicians to make a more rational approach to decision making regarding inpatient admission, administration of antenatal steroids, and in utero transfer in women with threatened spontaneous preterm birth. Future research should focus on undertaking high quality

What is already known on this topic

Spontaneous preterm birth is a major cause of neonatal morbidity and mortality

If spontaneous preterm birth can be predicted, effective therapeutic strategies can be used to improve neonatal outcomes

Though the cervicovaginal fetal fibronectin test has been proposed as a predictive test, estimates of its accuracy are variable

What this study adds

The cervicovaginal fetal fibronectin test is most accurate in predicting spontaneous preterm birth within 7-10 days of testing among women with symptoms of threatened preterm birth before advanced cervical dilatation

After a positive test result 17 symptomatic women at 31 weeks' gestation would need to be treated with antenatal steroids to prevent one case of respiratory distress syndrome

primary studies of test accuracy to improve our ability to predict spontaneous preterm birth.

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Competing interests: None declared.

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Corrections and clarifications

Prolonged erections produced by dihydrocodeine and sildenafil

In the penultimate paragraph of this "Drug point" by David Goldmeier and Harpal Lamba (29 June, p 1555) we wrongly edited out "we suggest that." The sentence should read: "We suggest that the acute opiate intake in our patients on sildenafil produced abnormally high cyclic guanosine monophosphate concentrations in peripheral nerve endings, which resulted in prolonged erections even after orgasm."

Obituary

In the obituary of Richard Dyer Mudd (15 June, p 1458) we wrongly spelt the name of his son in law, John McHale. It was correct in the original draft, but unfortunately, the electronic spellcheck facility suggested changing this to Michele, and we clicked on OK by mistake. Our apologies.

Exponent of "male menopause" censured by GMC

We wrongly stated at the start of this news article by Owen Dyer (13 July, p 65) that Dr Malcolm Carruthers, who was censured by the General Medical Council for serious medical misconduct, prescribed male hormones over the internet. He did not; he suggested prescriptions for GPs to fill.

10-minute consultation: Paraesthesia

In this article by Badal Pal (22 June, p 1501), a late proofreading slip led to a word being wrongly inserted into the title of the accompanying box. The title should read: "Investigations [not "Phalen's investigations"] for paraesthesia in fingers and hand."

Consumption of seafood and preterm delivery

When we scanned Yasuo Ishida's faxed letter "Method of cooking should be named" into our electronic system, two errors were introduced but not noticed (25 May, p 1279). In one case, a letter was wrongly inserted, and in the other a number dropped off. The sentence "Or [are we to] eat raw sashimi with snake?" should have read "with sake" (the Japanese fermented alcoholic drink made from rice). The correct zipcode for the author has a 7 in it (MO 63117).