Diagnostic research in perspective: examples of retrieval, synthesis and analysis
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Accuracy of cervicovaginal fetal fibronectin test in predicting risk of spontaneous preterm birth: systematic review

Honest Honest, Lucas M. Bachmann, Janesh K. Gupta, Jos Kleijnen, Khalid S. Khan

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Abstract

Objective: To determine the accuracy with which cervico-vaginal fetal fibronectin test predicts spontaneous preterm birth in asymptomatic and symptomatic pregnant women.

Design: Systematic quantitative review of test accuracy studies.


Study Selection and Data Extraction: Two reviewers independently selected and extracted data on study characteristics, quality and accuracy. Accuracy data were used to form 2x2 contingency tables with spontaneous preterm birth before 34 and 37 weeks' gestation and birth within 7-10 days of testing (only for symptomatic pregnant women) as reference standards.

Data Synthesis: Data were pooled to produce summary receiver operating characteristic (ROC) curves and summary likelihood ratios for positive (LR+) and negative (LR-) test results.

Results: There were 64 primary articles consisting of 28 accuracy studies in asymptomatic women and 40 accuracy studies in symptomatic women, including a total of 22,390 women. Among asymptomatic women, the best summary LR+ was 4.01 (95% confidence interval 2.93 to 5.49) for predicting birth before 34 weeks' gestation, with corresponding summary LR- of 0.78 (0.72 to 0.84). Among symptomatic women, the best summary LR+ was 5.42 (4.36 to 6.74) for predicting birth within 7-10 days of testing, with corresponding summary LR- of 0.25 (0.20 to 0.31).

Conclusion: Cervico-vaginal fetal fibronectin test is most accurate in predicting spontaneous preterm birth within 7-10 days of testing among women symptomatic of threatened preterm birth before advanced cervical dilatation. These results enable clinicians to make a more rational approach to decision-making regarding in-patient admission, administration of antenatal steroids and in-utero transfer in such a situation.
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Introduction
Spontaneous preterm birth occurs in 7-11% of pregnancies before 37 weeks’ gestation and in 3-4% of pregnancies before 34 weeks’ gestation. Majority of neonatal deaths of normally formed infants occurs 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. Advances in perinatal healthcare have not altered the incidence of spontaneous preterm birth but effective management to reduce the associated complications exists. For example, the landmark Cochrane review (which is part of the Cochrane logo) showed that the use antenatal steroids significantly reduced morbidity and mortality. Timely institution of such therapy in clinical practice depends on accurate prediction of spontaneous preterm birth.

Many tests have been purported to be predictive of spontaneous preterm birth including cervicovaginal fetal fibronectin testing. 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, and thought to be released into the cervico-vaginal milieu through mechanical or inflammatory-mediated damage to the membranes or placenta before birth. Swabs taken from either the ectocervix or posterior vaginal fornix, using an enzyme-linked immunosorbent assay containing FDC-6 monoclonal antibody, to detect fetal fibronectin may be used to predict spontaneous preterm birth. However, in clinical use, factors such as contamination of the sample with maternal blood, sampling within 24 hours following intercourse and pre-eclampsia may reduce test accuracy and give false positives results.

In asymptomatic pregnant women, if fetal fibronectin could be used to identify a high-risk group, antenatal care may be optimised (e.g. by instituting closer antenatal surveillance) with view to see the pregnancy past 34 weeks’ gestation, which is now an established milestone in perinatal outcome. On the other hand, if fetal fibronectin could predict imminent spontaneous preterm birth among women symptomatic of threatened spontaneous preterm birth, but before advance cervical dilatation, antenatal steroids, tocolytics and in-utero transfer (to optimise neonatal care) may be used accordingly. Antenatal steroids have maximal effectiveness among spontaneous preterm birth within 2-7 days after administration, and tocolytics are known to effectively delay birth for at least 2 days. Therefore, amongst symptomatic women, the main outcome of interest
was in predicting spontaneous preterm birth within 7-10 days of testing because this knowledge is likely to influence subsequent management.

Many primary studies claim that cervico-vaginal fetal fibronectin test is accurate in predicting spontaneous preterm birth in a clinical setting. However, these studies have not generally been conducted with large enough sample size to provide precise accuracy estimates. In addition, existing systematic reviews have been restricted to a few database searches, their study selection has often been limited by language, and they have often ignored study quality assessment. These factors are known to introduce potential for bias. Against this background, we conducted a comprehensive and rigorous systematic review to obtain reliable estimates of fibronectin test accuracy. Our review focussed on two clinical groups of pregnant women, asymptomatic and symptomatic. We defined asymptomatic population as pregnant women without uterine tightenings/contractions, and symptomatic population as pregnant women with uterine tightenings/contractions and cervical dilatation of less than 2-3 cm.

Methods
Our review was carried out with a prospective protocol using widely recommended methodology.

Identification of studies
Our electronic searches targeted all diagnostic procedures among studies on prediction of spontaneous preterm birth. Studies were identified from various sources. We searched general bibliographic databases: 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). The electronic search strategy used to develop the database is described in detail elsewhere. For completeness, we contacted individual experts with an interest in this field 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
The study selection criteria were i) asymptomatic or symptomatic population of pregnant women, ii) cervico-vaginal fetal fibronectin testing before 37 weeks' gestation, iii) known gestation at spontaneous birth, and iv) observational cohort design. Studies were selected in a two-stage process. First, the electronic searches were scrutinised by two reviewers independently (HH and LMB) and full manuscripts of all citations that were likely to meet the predefined selection criteria were obtained. Second, final inclusion or exclusion decisions were made on examination of these manuscripts. In cases of duplicate publication, the most recent and complete versions were selected. There were no language restrictions but studies with case-control design were excluded. The assessment of English, French, Spanish language manuscripts was performed independently by two reviewers (HH and LMB), German language manuscripts by one reviewer (LMB) and other language manuscripts by people who had command of the language to allow data extraction from the manuscripts. Any disagreements about inclusion/exclusion were resolved by consensus or arbitration by a third reviewer (KSK).

Information was extracted from each selected article on study characteristics, quality and accuracy results. Study characteristics consisted of women's risk classifications, test characteristics and reference standards of the test. In studies where multiple tests were performed, we considered any positive result in a serial testing as a positive result overall. Accuracy data were used to construct 2 x 2 tables of test result and spontaneous preterm birth, which served as the reference standard. Data were extracted from studies on asymptomatic and symptomatic women for information on spontaneous preterm birth before 34 and 37 weeks' gestation. In addition, for symptomatic women, data on spontaneous preterm birth within 7-10 days of testing were also extracted. The data extraction form was piloted and tested for repeatability on the first eight manuscripts that we obtained.20-27 Overall, the observer agreement regarding the various components of data extraction form was 90-100%; with kappa values ranges from 0.9 to 1.0.

Methodological quality assessment
All manuscripts meeting the selection criteria were assessed for their methodological quality. We defined quality as the confidence that the study design, conduct and analysis minimised bias in the estimation of test accuracy. Current empirical evidence relates bias to items: case-control study designs, lack of blinding of carer to test results, non-consecutive patient enrolment, non-prospective data collection, inadequate test description, use of different reference tests, partial verification, lack of description of either the population or the reference test.28 The latter 4 items
are, however, not relevant to our review because they refer to delivery of neonates (preterm or term births). Therefore, 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.29

Data synthesis
Data were synthesised separately for studies on asymptomatic and symptomatic women with spontaneous preterm birth before 34 and 37 weeks’ gestation. For symptomatic women, data were also synthesized for spontaneous preterm birth within 7-10 days of testing. Heterogeneity of diagnostic odds ratios was assessed graphically (using forest plots and Galbraith plots) and statistically (using chi-squared test) to aid in decisions on how to proceed with quantitative synthesis.30 For each outcome within the two populations, there was either graphical or statistically significant heterogeneity. Possible sources of heterogeneity were explored by meta-regression analysis using various independent explanatory variables defined a priori. These variables were: risk classifications (high or low as defined by the authors), multiple gestation (included or excluded), type of recruitment (consecutive or others), digital exam before testing (yes or no), sexual intercourse within 24 hours preceding testing (yes or no), bleeding before testing (yes or no), methods of testing (laboratory or bedside), serial testing (yes or no), gestation at testing for asymptomatic women (before or after 24 weeks), blinding of test results (yes or no), study design (prospective or retrospective), and publication language (English or other). Where a variable presence was not explicitly stated, it was treated as “no” in the meta-regression analysis. As our meta-regression analysis failed to explain the observed heterogeneity we proceeded with meta-analysis using random effects model.31 Consequently, the pooled results should be interpreted with caution. To aid in interpretation we examined the accuracy estimate of the highest quality studies included in our review.

Summary receiver operating characteristic (ROC) curves were used as measures of accuracy for all included studies regardless of their thresholds. Summary likelihood ratios (LR) were used as measures of accuracy for studies using 50 ng/ml as their thresholds. Area under summary ROC curve provided 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.32 Summary LRs indicated by how much a given test result will raise or lower the probability of having spontaneous preterm birth. Using summary LRs, we determined post-test probabilities by Bayes’ theorem as follows: post-test probability = LR x pre-test probability/[1-
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pre-test probability x (1-LR)]. In this way, LRs are more clinically meaningful than sensitivities or specificities, for which meta-analysis are generally not recommended.\textsuperscript{37} To detect publication and related bias, we undertook funnel plot (diagnostic odds ratio vs. reciprocal of its standard error) analysis.\textsuperscript{38} All statistical analyses were performed using SPSS v. 10 and Stata 7.0 statistical packages.

Results

Literature identification and study quality

Figure 1 summarises the process of literature identification and selection. In total, 64 primary articles met the selection criteria. They consisted of 28 accuracy studies in asymptomatic women and 40 studies in symptomatic women, including a total of 22,390 women. Table 1 summarises each study’s salient features according to whether the population was asymptomatic or symptomatic, and their risk classifications. The methodological quality is summarised in Figure 2. Thirteen (19\%) studies, 7 among asymptomatic\textsuperscript{39-45} and 6 among symptomatic women,\textsuperscript{46-51} fulfilled all four criteria for good quality. All studies except three (which accounted for 0.28\% of the total 22,390 women in our review),\textsuperscript{52-54} used thresholds of 50 ng/ml for an abnormal test result.\textsuperscript{8}
Figure 1: Study selection process for systematic review of cervico-vaginal fetal fibronectin test.

Total citations identified from electronic searches to capture primary articles on all tests for predicting preterm birth: n = 30,061

Citations excluded after screening titles and/or abstracts: n = 29,972

Primary articles on cervico-vaginal fetal fibronectin test accuracy retrieved for detailed evaluation: n = 116

from electronic search n = 89
from reference lists n = 26
contact with manufacturer n = 2 (from company’s website www.adeza.com)

Articles excluded with reasons:\n
Not test accuracy study: n = 15
Duplicate publications or more complete data sets are available: n = 9
Lack of data to construct 2x2 table: n = 5
Lack of original data i.e. reviews, letter: n = 22
Unobtainable: n = 2
Total excluded n = 53

Primary articles included in systematic review: n = 64 (see Table 1 for further details)

No. of studies included in these articles = 68*

Studies on asymptomatic women = 28
Low risk = 8 studies
High risk = 9 studies
Risk not categorized = 11 studies

Studies on symptomatic women = 40
Low risk = 5 studies
High risk = 4 studies
Risk not categorized = 31 studies

Φ See Appendix 1 for complete reference list of excluded studies. *Total number of studies exceeded 64 because some primary articles provided data on more than one study.
<table>
<thead>
<tr>
<th>Study</th>
<th>Language</th>
<th>Quality of study</th>
<th>Population</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Gestation Of Testing (weeks)</th>
<th>Type of Test &amp; Frequency</th>
<th>Swab site</th>
<th>Cut-off level (ng/ml)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic: High Risk</td>
<td>English</td>
<td>Blind Prospective Test described</td>
<td>147</td>
<td>Twins.</td>
<td>Cerclage.</td>
<td>22-24, 26, 28, 30</td>
<td>Elisa Multiple 2 weekly</td>
<td>Formix</td>
<td>50</td>
<td>&lt;32 weeks</td>
</tr>
<tr>
<td>Goldingburg 1996</td>
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<td>English</td>
<td>Blind Prospective Test described</td>
<td>85</td>
<td>Iatrogenic membrane. Multiple gestation, or singletants with previous history of spontaneous preterm birth, uterine anomaly, recurrent 2nd trimester miscarriage.</td>
<td>Cerclage, threatened preterm labor, vaginal bleeding, serious maternal and fetal condition</td>
<td>22-32</td>
<td>Elisa Multiple 1-2 Weekly</td>
<td>Eucorvix</td>
<td>50</td>
<td>&lt;34 weeks</td>
</tr>
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<td>English</td>
<td>Blind Prospective Test described</td>
<td>68</td>
<td>Multiple gestation.</td>
<td>None stated.</td>
<td>24-36</td>
<td>Bedside Multiple Weekly</td>
<td>Formix</td>
<td>50</td>
<td>&lt;37 weeks</td>
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<td>English</td>
<td>Blind Prospective Test described</td>
<td>40</td>
<td>Iatrogenic membrane, previous history of spontaneous preterm birth, multiple gestation.</td>
<td>None stated.</td>
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<td>Elisa Multiple 2 weekly</td>
<td>Formix</td>
<td>50</td>
<td>&lt;37 weeks</td>
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<tr>
<td>Nageotte 1994</td>
<td>English</td>
<td>Blind Prospective Test described</td>
<td>87</td>
<td>Iatrogenic membrane, previous history of spontaneous preterm birth, cerclage, or multiple gestation.</td>
<td>Candida infection.</td>
<td>24-34</td>
<td>Elisa Multiple Weekly</td>
<td>Eucorvix</td>
<td>50</td>
<td>&lt;37 weeks</td>
</tr>
<tr>
<td>Oliveira 1998a</td>
<td>English</td>
<td>Blind Prospective Test described</td>
<td>52</td>
<td>Twins. Unilateral cervix and cervical length &gt;1cm.</td>
<td>Vaginal Bleeding. Intrauterine pressure delivery. Disagreement between 2 observers to the results of the test.</td>
<td>24-34</td>
<td>Bedside Multiple 2 weekly</td>
<td>Not stated</td>
<td>50</td>
<td>&lt;34 weeks</td>
</tr>
<tr>
<td>Kwon 1995 (Abstract)</td>
<td>English</td>
<td>Blind Test described</td>
<td>26</td>
<td>Previous history of spontaneous preterm birth, premature labour, preterm pregnancy rupture of membrane, and stillbirth.</td>
<td>None stated.</td>
<td>&gt;24</td>
<td>Elisa Multiple Weekly</td>
<td>Cervix</td>
<td>50</td>
<td>&lt;36 weeks</td>
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<tr>
<td>Nageotte 1992 (Abstract)</td>
<td>English</td>
<td>Test described</td>
<td>102</td>
<td>Multiple gestation. Uterine anomaly. Previous history of spontaneous preterm birth and cervical incompetence.</td>
<td>None stated.</td>
<td>&gt;20</td>
<td>Elisa Multiple 2 weekly</td>
<td>Formix</td>
<td>50</td>
<td>&lt;34 weeks</td>
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<tr>
<td>Asymptomatic: Low Risk</td>
<td>English</td>
<td>Blind Prospective Test described</td>
<td>155</td>
<td>All asymptomatic women in antenatal clinic with known gestation.</td>
<td>Vaginal Bleeding.</td>
<td>24-33</td>
<td>Elisa Single</td>
<td>Endocorvix</td>
<td>50</td>
<td>&lt;37 weeks</td>
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<td>Fearce 1997</td>
<td></td>
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<tr>
<td>Hoffmann 1995</td>
<td>English</td>
<td>Blind Prospective Test described</td>
<td>133</td>
<td>Low risk singleton pregnancies.</td>
<td>Placenta previa. Vaginal Bleeding. Cervical dilatation&gt;4cm or cervical effacement. Threatened preterm labor &lt;26 weeks, Unknown date.</td>
<td>26-36</td>
<td>Elisa Multiple 2 weekly</td>
<td>Eucorvix</td>
<td>50</td>
<td>&lt;37 weeks</td>
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<td>English</td>
<td>Blind Prospective Test described</td>
<td>234</td>
<td>Singleton pregnancies without previous history of spontaneous preterm birth labor or birth.</td>
<td>Vaginal Bleeding, Pre-eclampsia.</td>
<td>28</td>
<td>Elisa Single</td>
<td>Forenx</td>
<td>50</td>
<td>&lt;34 weeks</td>
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**Note:** The table details the characteristics of studies on test accuracy of cervico-vaginal fetal fibronectin in predicting spontaneous preterm birth, including study details, population size, inclusion and exclusion criteria, gestation of testing, type of test and frequency, swab site, cut-off level, and outcome.
<table>
<thead>
<tr>
<th>Study</th>
<th>Language</th>
<th>Design</th>
<th>Study Type</th>
<th>Sample Size</th>
<th>Intervention &amp; Methods</th>
<th>Outcomes</th>
<th>Duration</th>
<th>Location</th>
<th>Notes</th>
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<td>Spanish</td>
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<td>Prospective</td>
<td>263</td>
<td>Low risk singletons Intact membrane.</td>
<td>Collage</td>
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<td>E102</td>
<td>Ferris 50</td>
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<td>Greenhagen 1996</td>
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<td>Blind</td>
<td>Prospective</td>
<td>108</td>
<td>Low risk singletons pregnancies Intact membrane.</td>
<td>Previous history of spontaneous preterm labor or birth, Vaginal bleeding, Fetal anomaly.</td>
<td>24-34</td>
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<td>Di Stefano 1999</td>
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<td>Singleton pregnancies Intact membrane.</td>
<td>Previous history of spontaneous preterm labor or birth, Vaginal bleeding, Fetal anomaly. Cervical cerclage.</td>
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<td>Test described</td>
<td>18</td>
<td>Low risk primigravida.</td>
<td>Ceasars 24-48 hours, Recent usage of vaginal pessary</td>
<td>28-32</td>
<td>E102</td>
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<td>Zanetti 2000</td>
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<td>Blind</td>
<td>Test described</td>
<td>20</td>
<td>Asymptomatic pregnant women Intact membrane.</td>
<td>Cervix</td>
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<td>Collage, Fetal anomalies or death, Vaginal bleeding. Recently treated bacterial vaginitis.</td>
<td>20-24</td>
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<td>Consecutive</td>
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<td>Singleton pregnancies of women attending an inner city antenatal clinic.</td>
<td>Fetal abnormalities.</td>
<td>22-24</td>
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<td>Prospective</td>
<td>438</td>
<td>Singleton pregnancies without medical or obstetrical complications.</td>
<td>None stated.</td>
<td>26-28</td>
<td>E102</td>
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<td>Blind</td>
<td>Prospective</td>
<td>2524</td>
<td>Singleton pregnancies.</td>
<td>Placenta previa, Fetal anomalies.</td>
<td>22, 24, 28, 30</td>
<td>E102</td>
<td>Ferris 50</td>
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<td>English</td>
<td>Blind</td>
<td>Prospective</td>
<td>1850</td>
<td>Singleton pregnancies of women who are randomized to treatment for Tachysoson vaginal or Bacterial vaginitis.</td>
<td>None stated.</td>
<td>8-22</td>
<td>E102</td>
<td>Ferris 50</td>
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<td>8-22</td>
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<td>Ison 1993</td>
<td>English</td>
<td>Blind</td>
<td>Prospective</td>
<td>54</td>
<td>Intact membrane and amniotic cervix.</td>
<td>Candida infection, fetal anomalies, Vaginal bleeding, Placenta previa, and threatened preterm labor.</td>
<td>26-29</td>
<td>E102</td>
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<td>Blind</td>
<td>Prospective</td>
<td>73</td>
<td>Intact membrane.</td>
<td>Fetal anomalies, Placenta previa, gestational or urinary infection, use of antibiotics in the preceding 7 days.</td>
<td>&lt;37</td>
<td>E102</td>
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<td>Blind</td>
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<td>E102</td>
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<td>Vaughan 1998</td>
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<td>E102</td>
<td>Ferris 50</td>
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<td>Prospective</td>
<td>105</td>
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<td>Psychiatric condition, coitus &gt;24 hours.</td>
<td>26-34</td>
<td>E102</td>
<td>Ferris 50</td>
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<tr>
<td>Mongolia 1993</td>
<td>French</td>
<td>Blind</td>
<td>Prospective</td>
<td>105</td>
<td>Intact membrane, twin, cervical changes, uterine distention, cerclage.</td>
<td>Psychiatric condition, coitus &gt;24 hours.</td>
<td>26-34</td>
<td>E102</td>
<td>Ferris 50</td>
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<td>Delivery Mode</td>
<td>Treatment</td>
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<td>Year</td>
<td>Language</td>
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<td>Duration</td>
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</tr>
<tr>
<td>Sunday</td>
<td>1996</td>
<td>English</td>
<td>Blind</td>
<td>Singleton pregnancies. Intact membrane. Cervical dilation &lt; 4 cm.</td>
<td>Bedside</td>
<td>&lt;7 days</td>
<td>None</td>
<td></td>
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<tr>
<td>Burns</td>
<td>1995</td>
<td>English</td>
<td>Blind</td>
<td>Symptomatic women in their first pregnancy. Intact membrane. Cervical dilation &lt; 3 cm and changing, no contra-indications to tocolytics</td>
<td>Elvis</td>
<td>&lt;37 weeks</td>
<td>None</td>
<td></td>
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<tr>
<td>Geffings</td>
<td>1997</td>
<td>English</td>
<td>Consecutive</td>
<td>Singleton pregnancies with intact membrane.</td>
<td>Elvis</td>
<td>&lt;34 weeks</td>
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<td></td>
</tr>
<tr>
<td>INNS</td>
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<td>English</td>
<td>Blind</td>
<td>Singleton pregnancies. Intact membrane. Cervical dilation &lt; 4 cm.</td>
<td>Bedside</td>
<td>&lt;7 days</td>
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<tr>
<td>Longer</td>
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<td>Blind</td>
<td>Singleton pregnancies. Intact membrane. Cervical dilation &lt; 2 cm.</td>
<td>Elvis</td>
<td>&lt;37 weeks</td>
<td>None</td>
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<td>Loo</td>
<td>1997</td>
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<td>Elvis</td>
<td>&lt;37 weeks</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parker</td>
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<td>English</td>
<td>Blind</td>
<td>Singleton pregnancies. Intact membrane. Cervical dilation &lt; 2 cm.</td>
<td>Elvis</td>
<td>&lt;37 weeks</td>
<td>None</td>
<td></td>
<td></td>
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<tr>
<td>Study</td>
<td>Language</td>
<td>Type</td>
<td>No.</td>
<td>Diagnosis and Procedures</td>
<td>Duration</td>
<td>Test Used</td>
<td>Median Days</td>
<td>Notes</td>
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<td>-------------</td>
<td>----------------</td>
<td></td>
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<tr>
<td>Peaceman 1997</td>
<td>English</td>
<td>Prospective, Test described</td>
<td>125</td>
<td>Singleton, twin pregnancies and 1 stage, intact membrane. Cervical dilatation &gt; 3 cm.</td>
<td>26-34</td>
<td>Elisa</td>
<td>Single</td>
<td>&lt;7 days, &lt;18 days, &lt;37 weeks</td>
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</tr>
<tr>
<td>Rizzo 1986</td>
<td>English</td>
<td>Blind, Prospective, Test described</td>
<td>108</td>
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<td>24-34</td>
<td>Elisa</td>
<td>Single</td>
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<td></td>
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<tr>
<td>Rizzo 1997</td>
<td>English</td>
<td>Blind, Prospective, Test described</td>
<td>100</td>
<td>Singleton pregnancies, intact membrane. Cervical dilatation &gt; 3 cm.</td>
<td>24-36</td>
<td>Bedside</td>
<td>Single</td>
<td>60 vagina &lt;37 weeks</td>
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<td>24-34</td>
<td>Elisa</td>
<td>Single</td>
<td>&lt;37 weeks</td>
<td></td>
</tr>
<tr>
<td>Wernzehn 1997</td>
<td>English</td>
<td>Blind, Prospective, Test described</td>
<td>101</td>
<td>Twin pregnancies, intact membrane. Coitus &lt; 24 hours. Vaginal bleeding.</td>
<td>26-34</td>
<td>Elisa</td>
<td>Multiple 2 weekly</td>
<td>50 &lt;34 weeks, &lt;37 weeks</td>
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<tr>
<td>Chalhounian 1998</td>
<td>English</td>
<td>Retrospective, Test described</td>
<td>50</td>
<td>Singleton pregnancies, intact membrane. Cervical dilatation &gt; 2 cm.</td>
<td>&lt;34</td>
<td>Bedside</td>
<td>Single</td>
<td>50 &lt;34 weeks</td>
<td></td>
</tr>
<tr>
<td>Gilis 2000</td>
<td>English</td>
<td>Prospective, Test described</td>
<td>150</td>
<td>Intact membrane. Vaginal bleeding. Coitus &lt; 24 hours. Recent digital vaginal examination.</td>
<td>24-34</td>
<td>Bedside</td>
<td>Single</td>
<td>50 &lt;7 days, &lt;36 weeks</td>
<td></td>
</tr>
<tr>
<td>Cox 1995 (Abstract)</td>
<td>English</td>
<td>Test described</td>
<td>175</td>
<td>Intact membrane. Cervical dilatation &gt; 3 cm.</td>
<td>24-31</td>
<td>Elisa</td>
<td>Single</td>
<td>50 &lt;37 weeks</td>
<td></td>
</tr>
<tr>
<td>Martin 1998</td>
<td>French</td>
<td>Retrospective, Test described</td>
<td>96</td>
<td>Intact membrane. Vaginal bleeding. Coitus &lt; 24 hours.</td>
<td>24-34</td>
<td>Elisa</td>
<td>Single</td>
<td>50 &lt;37 weeks</td>
<td></td>
</tr>
<tr>
<td>Painest 1997</td>
<td>French</td>
<td>Test described</td>
<td>73</td>
<td>Symptomatic women with cervical changes and requiring tocolytics.</td>
<td>28-35</td>
<td>Bedside</td>
<td>Single</td>
<td>50 &lt;37 weeks</td>
<td></td>
</tr>
<tr>
<td>Vosmazghi 1994</td>
<td>French</td>
<td>Test described</td>
<td>86</td>
<td>Singleton and twin pregnancies. Coitus &lt; 24 hours. Vaginal bleeding.</td>
<td>27</td>
<td>Elisa</td>
<td>Single Multiple</td>
<td>50 &lt;37 weeks</td>
<td></td>
</tr>
<tr>
<td>Lopez 2000</td>
<td>English</td>
<td>Retrospective</td>
<td>85</td>
<td>Singleton pregnancies, intact membrane. Cervical dilatation &gt; 3 cm.</td>
<td>24-35</td>
<td>Elisa</td>
<td>Single &amp; multiple</td>
<td>Not stated, Not stated</td>
<td></td>
</tr>
</tbody>
</table>

* Elisa = Enzyme-linked immunosorbent assay
‡ If quality item (i.e. clinician blinded to the result, consecutive population enrolments, prospective or retrospective study design or description of the test) is not stated, it was either not reported or was not explicitly clear.
*** Asymptomatic population defined as pregnant women without uterine tightening or contractions.
† Risk classifications, if stated, were based on either clinical or historical factors as defined by the study's author(s), e.g. history of previous spontaneous preterm birth, history of recurrent miscarriages, multiple gestations, etc.
Fibronectin test in asymptomatic women

The accuracy of the test was studied using bedside (n=3) or laboratory (n=26) methods, either on a single occasion (n=13) or by serial testing (n=16) at various gestations (Table 1). In these studies, fibronectin was used as a screening tool in low risk pregnancy (n=8) or as a selective screening tool in high-risk pregnancy (n=9) (Table 1). Most studies were carried out during the second or early third trimester of the pregnancy. Meta-regression analysis showed that test accuracy was not dependent on method of testing, serial testing, risk classifications or gestation at testing. Cervico-vaginal fetal fibronectin test showed different accuracy estimates in predicting spontaneous preterm birth for the various gestations of interest as shown in Figure 3 and Figure 4. The effect of these on changes in probabilities of spontaneous preterm birth is shown in Figure 4. Exploration of study quality as a source of heterogeneity did not reveal statistically significant differences in accuracy estimates of studies with high and low quality features. The accuracy estimates of studies that fulfilled all four of the quality criteria were generally consistent with the pooled results. For example, the median likelihood ratios for predicting spontaneous preterm birth before 34 weeks’ gestation among the five highest quality studies were 3.99 (inter-quartile range 1.73 to 10.18) for a positive test result and 0.38 (inter-quartile range 0.10 to 0.69) for a negative test result.

Figure 2: Methodological quality of studies included in the systematic review. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.
Fibronectin test in symptomatic women

The accuracy of the test was studied using bedside (n=11) or laboratory (n=30) methods, either on a single occasion (n=35) or serially (n=5) (Table 1). Meta-regression analysis showed that test accuracy was not dependent on method of testing, serial testing, or risk classifications. As with fetal fibronectin test in asymptomatic women, the test showed different accuracy estimates in predicting spontaneous preterm birth for the various gestation of interest shown in figure 3 and figure 4. The effect of these on changes in probabilities of spontaneous preterm birth is shown in Figure 4. Exploration of study quality as a source of heterogeneity did not reveal statistically significant differences in accuracy estimates of studies with high and low quality features. The accuracy estimates of studies that fulfilled all four of the quality criteria were generally consistent with the pooled results. For example, the median likelihood ratios for predicting for predicting spontaneous preterm birth within 7-10 days of testing among the four highest quality studies were 6.16 (inter-quartile range 4.53 to 7.33) for a positive test result and 0.32 (inter-quartile range 0.01 to 0.45) for a negative test result. Funnel plot analysis did not show any evidence of asymmetry to indicate presence of publication or related bias for the main outcomes.

Figure 3: Summary Receiver Operating Characteristic (ROC) curves and areas (95% CI) for cervico-vaginal fetal fibronectin test in predicting spontaneous preterm birth in asymptomatic and symptomatic women.
Chapter 4

Figure 4: Pooled estimates of likelihood ratios (LRs) for cervico-vaginal fetal fibronectin test and their impact on predictive probabilities of spontaneous preterm birth in asymptomatic and symptomatic women.

### Table 4.1

<table>
<thead>
<tr>
<th>Population/Birth Outcome (no. of studies)</th>
<th>Summary Likelihood ratios (LRs)</th>
<th>Post-test Probabilities (% (95% CI))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weighted Pre-test Probability</td>
<td>Test Negative</td>
</tr>
<tr>
<td></td>
<td>Median (%)</td>
<td>Test Positive</td>
</tr>
<tr>
<td></td>
<td>Weighted Pre-test Probability</td>
<td>Test Negative</td>
</tr>
<tr>
<td></td>
<td>Median (%)</td>
<td>Test Positive</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;34 weeks (n=12)</td>
<td>4.2</td>
<td>0.78 (0.72-0.84)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.01 (3.95-5.49)</td>
</tr>
<tr>
<td>&lt;37 weeks (n=25)</td>
<td>12.2</td>
<td>0.52 (0.44-0.62)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.94 (2.47-3.50)</td>
</tr>
<tr>
<td>Symptomatic women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7-10 days (n=14)</td>
<td>3.0</td>
<td>0.25 (0.20-0.31)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.42 (4.36-7.76)</td>
</tr>
<tr>
<td>&lt;34 weeks (n=8)</td>
<td>15.7</td>
<td>0.32 (0.16-0.66)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.64 (2.32-6.77)</td>
</tr>
<tr>
<td>&lt;37 weeks (n=17)</td>
<td>21.2</td>
<td>0.48 (0.41-0.56)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.27 (2.74-3.92)</td>
</tr>
</tbody>
</table>

### Discussion

Our results show that the cervico-vaginal fetal fibronectin test exhibits a range of accuracy in predicting various spontaneous preterm birth outcomes. The test is most accurate in predicting spontaneous preterm birth within 7-10 days of testing among women symptomatic of threatened preterm birth before advanced cervical dilatation.

Quality of our review

The strength of our inferences depends on the rigour of our methodology. In contrast to the previous four systematic reviews,12-15 we have identified 64 studies (at least twice as many studies as the largest previous review14) because we did not limit our search to a single database13,15 nor did we apply language restrictions.13 Cognisant that meta-analysis of test accuracy studies 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.15 Methodological issues that may overestimate accuracy such as case-control design, absence of test descriptions, and different reference tests,28 were not applicable to the studies we reviewed. Our quality assessment, however, were affected by poverty of reporting in some instances. Moreover, quality was not a significant factor explaining differences between their results. Assessment of heterogeneity and exploration for reasons behind heterogeneity were planned a priori. In the presence of unexplained heterogeneity, we proceeded with caution, pooling data with random effects model, which produces a

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wider confidence interval. However, due to the large number of studies in our review the accuracy estimates were generally more precise compared to previous reviews.

Clinical application
The clinical impact of the accuracy estimates we produced depends on how the resultant changes in probabilities due to fibronectin testing alter therapeutic effectiveness in decision-making. We demonstrate this impact with an example of decision making about the use of antenatal steroids in symptomatic pregnant women with threatened preterm birth at 31 weeks' gestation as shown in Table 2. The absolute effect of antenatal steroids depends on the risk of spontaneous preterm birth following presentation. The higher the risk, the lower the number of patients needed to be treated (NNT) to prevent one case of RDS 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. As shown in Table 2, if steroids were to be used for all symptomatic women at this gestation without fibronectin testing then 109 women would need to be treated with antenatal steroids to prevent 1 case of RDS. For a positive test result, the NNT would be 20, a figure considerably lower than that without testing. On the other hand, for a negative test result, the NNT would be 509.
Table 2: Cervico-vaginal fetal fibronectin testing among symptomatic women and the 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.

<table>
<thead>
<tr>
<th>Fibronectin test result at 31 weeks' gestation</th>
<th>Probability of spontaneous preterm birth within 7-10 days of testing (%)</th>
<th>Risk of RDS at 32 weeks' gestation&lt;sup&gt;56,57&lt;/sup&gt;</th>
<th>Rate of RDS&lt;sup&gt;+&lt;/sup&gt; at 32 weeks' gestation (%)</th>
<th>NNT&lt;sup&gt;++&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>No testing</td>
<td>4.5&lt;sup&gt;+&lt;/sup&gt;</td>
<td>0.53</td>
<td>2.0</td>
<td>109</td>
</tr>
<tr>
<td>Test positive</td>
<td>20.6&lt;sup&gt;+&lt;/sup&gt;</td>
<td>0.53</td>
<td>11.0</td>
<td>20</td>
</tr>
<tr>
<td>Test negative</td>
<td>1.0&lt;sup&gt;+&lt;/sup&gt;</td>
<td>0.53</td>
<td>0.4</td>
<td>509</td>
</tr>
</tbody>
</table>

<sup>#</sup> Pre-test probability of spontaneous preterm birth within 7-10 days of testing for symptomatic pregnant women presenting at 31 weeks' gestation.<sup>22,24,39;53;58-65</sup>

% Information on the calculation of probabilities using likelihood ratios shown in Figure 4:

- Pre-test probability of spontaneous preterm birth within 7-10 days (i.e. no testing) for women presenting at 31 weeks' gestation = 4.5%
- This value is converted to pre-test odds = 4.5/(100-4.5) = 0.047
- Post-test odds for spontaneous preterm birth among women with a positive test = pre-test odds x LR+ = 0.047 x 5.45 = 0.26
- This is then converted to post-test probability = 0.26/(0.26+1) = 0.206 = 20.6%
- (A similar calculation may be carried out for the negative test result using LR- found in Figure 4)

<sup>†</sup> The rate of RDS is calculated as follows:
- Probability of spontaneous preterm birth for a positive fibronectin test result at 32 weeks (31 weeks + 7-10 days) = 20.6%
- The risk of RDS at this gestation = 0.53<sup>++</sup>
- Therefore, the probability of a neonate suffering from RDS in woman who tested positive = 20.6 x 0.53 = 11%
- (A similar calculation may be carried out for the negative test result)

<sup>##</sup> An example calculation of NNT to prevent 1 case of RDS among women who tested positive:

- Rate of RDS at 32 weeks' gestation = 11%
- This value is converted to odds of RDS without treatment = 11/(100-11) = 0.12
- Odds of treatment benefit = 0.12 x 0.53 = 0.064 (where 0.53 = odds ratio [OR] for treatment benefit of antenatal steroids, obtained from Cochrane review<sup>6</sup>, which coincidentally, is the same figure as the risk for RDS at 32 weeks' gestation)
- This is then converted to the rate of RDS following antenatal steroid treatment = 0.064/(1-0.064) = 0.059
- Rate difference of RDS between treatment and without antenatal steroid treatment = 0.11-0.059 = 0.051
- NNT = 1/0.051 = 20
- This means that with a positive fibronectin test, 17 symptomatic pregnant women who presented at 31 weeks' gestation need to be treated with antenatal steroids to prevent 1 case of RDS
- (A similar calculation may be carried out for the negative test result)

This approach will allow clinicians to make explicit decisions based on 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 in-patient admission, administration of antenatal steroids and in-utero transfer in symptomatic women presenting with threatened spontaneous preterm birth. Future research should focus on undertaking high quality primary studies of test accuracy to improve our ability to predict spontaneous preterm birth.
Acknowledgements
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References


Accuracy of cervicovaginal fetal fibronectin in predicting spontaneous preterm birth


Accuracy of cervicovaginal fetal fibronectin in predicting spontaneous preterm birth


Appendix 1: Reference list of excluded studies.

Not test accuracy study:


Duplicate publications or more complete data sets are available:


Lack of data to construct 2x2 table:


31. Lack of original data (e.g. reviews, letter, editorial, etc):


Accuracy of cervicovaginal fetal fibronectin in predicting spontaneous preterm birth


Unobtainable:


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