Fetal fibronectin test for predicting preterm labour

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The Medical Services Advisory Committee (MSAC) is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

This report was prepared by the Medical Services Advisory Committee with the assistance of Dr Liesl Birinyi-Strachan, Mr Marc Bevan, Ms Antje Smala, and Ms Jolie Hutchinson from M-TAG Pty Ltd, a unit of IMS Health. The report was edited by Ms Ann Jones of M-TAG. The report was endorsed by the Minister for Health and Ageing on 5 February 2007.

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Fetal fibronectin testing is used to predict preterm labour in women suspected of having the condition and in those who are asymptomatic but at high risk of delivery before term.

The test is a two-step procedure. The first step requires obtaining a cervicovaginal sample from a patient during a standard speculum examination. The second involves processing the sample to detect the presence or absence of $\geq$ 50 ng/mL of fetal fibronectin. The presence or absence of fetal fibronectin is used to predict the risk of preterm labour.

Fetal fibronectin testing is not currently funded under the Medicare Benefits Schedule.

Medical Services Advisory Committee—role and approach

The Medical Services Advisory Committee (MSAC) was established by the Australian Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures and under what circumstances public funding should be supported.

A rigorous assessment of evidence is thus the basis of decision making when funding is sought under Medicare. A team from the Medical Technology Assessment Group (M-TAG) Pty Ltd, a unit of IMS Health, was engaged to conduct a systematic review and economic evaluation of fetal fibronectin testing for predicting preterm labour. An advisory panel with expertise in this area then evaluated the evidence and provided advice to MSAC.

MSAC's assessment of fetal fibronectin test for predicting preterm labour

Clinical need

Preterm birth is regarded as delivery of any infant before 37 weeks gestation. In 2003, preterm births made up 7.1 per cent of all deliveries in Australia. Infants delivered prematurely (before 34 weeks gestation) have had insufficient time *in utero* to fully develop and may be born with life-threatening medical conditions. To prevent and delay preterm birth, many women in suspected preterm labour, or at high risk of preterm delivery, are hospitalised and treated; others are advised bed rest at home for significant proportions of their pregnancies.

Management of preterm birth requires substantial resources. Preterm birth was associated with 29,829 patient days in hospital (average length of stay 5.2 days) in 2003–2004.

Management of false labour also requires substantial resources; false labour was associated with 21,609 patient days in hospital (average length of stay 2.0 days) in 2003–2004. There is also concern about potential adverse events associated with unnecessary use of corticosteroids and tocolytics in the management of patients who are not at immediate risk of preterm delivery.

Safety

An extensive literature search did not identify any safety data relating to fetal fibronectin testing. Minimal risks to patients are anticipated because the cervicovaginal sample required for fetal fibronectin testing is obtained with a swab as part of a standard speculum examination.

Effectiveness

Diagnostic accuracy

The limited, applicable diagnostic accuracy evidence for women in suspected preterm labour indicates that a negative result from either pathology-based or point-of-care fetal fibronectin tests has moderate diagnostic value in identifying patients who are not at immediate risk of preterm delivery.

The diagnostic accuracy evidence was insufficient to allow conclusive recommendations to be formulated about the diagnostic precision of pathology-based or point-of-care fetal fibronectin testing in asymptomatic pregnant women at high risk of preterm delivery.

Patient management

The limited data available relating to patient management means that the value of fetal fibronectin testing in clinical decision-making in Australia remains uncertain.

Treatment effectiveness

The intent of the fetal fibronectin diagnostic test in this population is to reduce unnecessary hospitalisation and treatment of women in false labour. Therapeutic effectiveness was therefore not examined for patients in suspected preterm labour as part of this assessment. It is considered unlikely that fetal fibronectin testing would identify additional patients who would receive treatments for management of preterm birth. Fetal fibronectin testing is unlikely to substantially decrease the effectiveness of therapies currently used in the management of preterm labour.

Treatment effectiveness was not examined in asymptomatic patients at high risk of preterm delivery because diagnostic accuracy and patient management evidence was insufficient for analysis.

Economic analyses

The financial impact of fetal fibronectin testing of women in suspected preterm labour is estimated to cost Medicare Australia between $1.66 million and $3.04 million per year. The estimated savings for other healthcare funders is between $12 million and $16 million per year.

There is some uncertainty about the potential savings that could be generated as a result of providing fetal fibronectin testing for women in suspected preterm labour. Savings would be lower in instances where women who test negative for fetal fibronectin are hospitalised. Hospitalisation costs relating to women admitted before fetal fibronectin testing is performed are not avoided altogether but may be reduced as a consequence of shorter stays. The presented economic analyses do not include potential savings from a societal perspective, such as child care costs for other children; the savings associated with fetal fibronectin testing could therefore potentially be underestimated in this assessment.

This assessment found that there was insufficient evidence concerning diagnostic accuracy and patient management benefits to warrant conducting an economic analysis of asymptomatic patients at high risk of preterm delivery.

Recommendation

MSAC assessed the evidence for the use of fetal fibronectin testing in women who are at high risk of preterm labour to predict their risk of preterm delivery and the evidence pertaining to the use of fetal fibronectin testing for predicting preterm labour in women:

- who present with symptoms suggestive of preterm labour
- whose pregnancies are singleton or twin gestations
- who are at stages of pregnancy from 24 to 33 weeks 6 days gestation
- who present with intact amniotic membranes
- whose cervical dilatation is less than 3 cm.

MSAC determined that the test is safe but effectiveness has not been demonstrated.

MSAC does not support public funding for this test at this time.

– The Minister for Health and Ageing accepted this recommendation on 5 February 2007 –

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of fetal fibronectin testing—a predictive test to assess risk of preterm delivery. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are at **Appendix A**. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for fetal fibronectin testing for predicting preterm labour in women where it is suspected, and for asymptomatic women at high risk of preterm delivery.

Background

Fetal fibronectin

Fetal fibronectin is a glycoprotein normally present in the cervicovaginal secretions of pregnant women up to 22 weeks gestation. Fetal fibronectin is believed to be the major component of the chorio-decidual interface—the union between fetal and maternal tissues. The presence of fetal fibronectin during the later stages of pregnancy is thought to indicate a disruption of the chorio-decidual interface caused by mechanical or inflammatory mediated injury. Chorio-decidual disruption and the presence of fetal fibronectin between 24 and 34 weeks gestation may be related to the initiation of labour (British Columbia Reproductive Care Program 2005, Honest et al 2002).

The procedure

Fetal fibronectin testing for predicting preterm labour is a two-step procedure that can be included in the clinical examination of women who are suspected of preterm labour and for asymptomatic women at high risk of preterm delivery. The first step in fetal fibronectin testing requires obtaining a cervicovaginal sample from the patient during a standard speculum examination. The sample must be obtained before a patient undergoes vaginal digital examination. The sample would not be processed if evidence of either ruptured cervical membranes or cervical dilation ≥3 cm were detected during clinical examination.
The second step involves processing the sample to detect the presence or absence of ≥50 ng/mL of fetal fibronectin. The presence or absence of fetal fibronectin is interpreted to predict the risk of preterm labour.

Fetal fibronectin testing could potentially be used as either a pathology-based test or a point-of-care test. Both pathology-based and point-of-care tests were assessed.

Fetal fibronectin samples are presently processed using one of two available tests. Both methods have been assessed. The Adeza Biomedical TLI(IQ)™ system processes samples using a rapid fetal fibronectin cassette—a lateral flow, solid phase immunochromotographic assay using FDC-6 monoclonal antibodies. Test results are presented as a print out. This cassette is used in the TLI(IQ)™ analyser. The TLI(IQ)™ system is calibrated daily using the TLI QCETTE quality control device.

The Adeza Quikcheck fFN™ processes samples using fetal fibronectin test strips— a solid-phase immunogold assay using FDC-6 monoclonal antibodies. Positive specimens are indicated by two visible lines on the test strip. Negative specimens are indicated by the presence of one visible line.

Intended purpose

The fetal fibronectin test is intended to assess risk of preterm delivery in pregnant women who are suspected of preterm labour, or who are asymptomatic, but at high risk of preterm delivery.

It is proposed that fetal fibronectin detection can predict preterm delivery in less than 7 or less than 14 days of testing, in the respective risk groups of pregnant women. The benefit of this test for women presenting in suspected preterm labour is to identify those **not** at immediate risk and to reduce unnecessary use of therapies such as tocolytics and corticosteroids. Both these drug groups have been implicated with adverse events. This test could possibly contribute to decreases in unnecessary admissions to hospitals and transfers to tertiary care facilities. A direct benefit for women from rural and remote regions could be had if unwarranted transfers to regional health care facilities for preterm delivery surveillance was reduced or eliminated should fetal fibronectin testing become more widely available.

The detection of fetal fibronectin in asymptomatic women at high risk of preterm delivery may indicate appropriate timing for interventions, such as corticosteroids, to avoid complications often associated with neonatal prematurity.

Clinical need

Births before 37 weeks gestation are regarded as preterm. Infants born at 34 weeks gestation and earlier often have life-threatening medical conditions. Preterm births have been associated with a number of maternal medical factors such as multiple gestation, previous preterm labour, cervical sutures and uterine abnormalities. To prevent and delay preterm birth, many women in suspected preterm labour, or at high risk of preterm delivery, are hospitalised and treated; others are advised bed rest at home for significant proportions of their pregnancies.

There were 17,893 preterm births (7.1% of all births) in Australia during 2003 (Laws & Sullivan, 2005). Data from the Australian Institute of Health and Welfare (AIHW) indicates that in 2003–2004 preterm birth related to 5728 separations and 29,829 patient days in hospital. The average length of stay was 5.2 days (AIHW 2006).

Preterm infants constituted 78.2 per cent of all level 3 neonatal intensive care unit admissions during 2003. Infants with gestational ages less than 32 weeks represented 46.8 per cent of all level 3 neonatal intensive care unit admissions. In Australia, 412 perinatal deaths (16.6% of all perinatal deaths) were attributed to spontaneous preterm delivery (reported data excluded NSW, ACT, and NT) (Laws & Sullivan, 2005) during 2003.

Hospital admissions relating to false labour contribute substantial resource demands that are additional to preterm birth resource allocations. The most recent AIHW data (2003–2004) indicates that false labour before 37 weeks gestation related to 10,815 separations and 21,609 patient days in hospital. The average length of stay was 2.0 days (AIHW 2006b).

Potential adverse events resulting from use of corticosteroids and tocolytics for patients who are not at immediate risk of preterm delivery is also cause for concern.

Current treatment

According to the National Health and Medical Research Council (NHMRC, 1999) preterm birth guidelines (now rescinded), many pregnant women are hospitalised for long periods, or advised to restrict their activities, to minimise risk of preterm birth.

Pregnant women experiencing symptoms suggestive of preterm labour are usually treated using tocolytic and corticosteroid drugs up to 33 weeks, 6 days gestation. Corticosteroids assist lung development in unborn infants, and are used to reduce the risk of infant death, respiratory distress syndrome and intraventricular haemorrhage. Tocolytic drug therapy is used to induce short-term suppression of uterine contractions, usually to maximise corticosteroid treatment, or to facilitate patient transfer to a tertiary care facility (British Columbia Reproductive Care Program 2005; Victorian Perinatal Emergency Referral Service 2005).

Asymptomatic pregnant women at high risk of preterm delivery are generally monitored closely. There are currently no clear guidelines for the treatment of these patients.

Existing diagnostic procedures

Clinical assessment

Clinical assessment of women in suspected preterm labour or asymptomatic women at high risk of preterm deliveries requires attending healthcare professionals to take detailed clinical histories and to identify symptoms associated with preterm labour. Patients may be physically examined on the basis of the clinical history and/or symptoms. Physical examination involves assessing the presence of cervical effacement or cervical dilation by visual inspection of the cervix. The presence of vaginal bleeding or premature rupture of membranes can be identified at this examination. Cervical swabs can also be taken to detect any bacterial infections. A digital exam may be conducted if the cervix cannot be visualised adequately. These factors, in association with clinical history and/or symptoms such as uterine contractions, form the current clinical practice applied to determine patient management (Victorian Perinatal Emergency Referral Service 2005).

Fetal fibronectin testing would be used as an additional test to assess risk of preterm delivery. This assessment therefore considers the relative value of fetal fibronectin to current clinical practice.

Cervical ultrasound

Cervical ultrasound examination involves producing a sonogram of the cervix and allows measurement of the internal cervical os, the cervical canal and the external cervical os (Schmitz 2006). In this way, cervical length can be estimated and used as a predictor of the risk of preterm delivery. There are currently no Australian guidelines that indicate an acceptable cut-off value for ultrasound-measured cervical length to predict preterm birth.

Fetal fibronectin testing could potentially be used as either a replacement or incremental test in asymptomatic pregnant women at high risk of preterm delivery relative to cervical ultrasound (when cervical ultrasound is available). For that reason, both the replacement and incremental relative values of fetal fibronectin to cervical ultrasound were assessed.

Marketing status of the technology

There are currently two fetal fibronectin tests—the Adeza QuikCheck fFN™, which replaced a previous test, the Fetal Fibronectin Membrane Immunoassay; and the Adeza Biomedical TLI(IQ)™ System—available in Australia for predicting preterm labour. The tests are produced by Adeza Biomedical Pty Ltd and listed with the Therapeutic Goods Administration (TGA) on the Australian Registry of Therapeutic Goods under listing number AUST-L 63516. These test systems are approved for marketing in Australia, the United States of America, and Canada.

Current reimbursement arrangement

There is currently no reimbursement arrangement with the Medicare Benefits Scheme for preterm labour fetal fibronectin tests.

Approach to assessment

Research questions and clinical pathways

Pregnant women in suspected preterm labour

The PPICO criteria (target population, prior tests, index test, comparator, outcomes) developed *a priori* for the evaluation of fetal fibronectin testing for pregnant women in suspected preterm labour are given in **Table 1**.

Table 1 PPICO criteria for the use of fetal fibronectin testing in pregnant women in suspected preterm labour

Population	Prior tests	Index test	Comparator	Outcomes
Pregnant women with singleton or twin gestations presenting to a health care provider or hospital with signs and symptoms of suspected preterm labour, with intact amniotic membranes and minimal cervical dilation (< 3 cm), from 24 to 33 weeks, 6 days gestation	Clinical history Physical examination[a]	Fetal fibronectin	Current clinical practice	Change in clinical outcomes Change in clinical management Diagnostic accuracy

[a] The sample for the fetal fibronectin test must be obtained before digital vaginal examination.

The research question for this indication, based on these criteria, was as follows.

To what extent is the fetal fibronectin test for predicting preterm labour:

- safe,
- effective (including diagnostic performance and the impact of diagnosis on changes in clinical management and changes in clinical outcomes), and
- cost-effective

in the assessment of preterm delivery risk in pregnant women with singleton or twin gestations presenting to a health care provider or hospital with signs and symptoms of suspected preterm labour, with intact amniotic membranes and minimal cervical dilation (< 3 cm) from 24 to 33 weeks, 6 days gestation relative to current clinical practice?

The clinical pathway for the evaluation of pregnant women in suspected preterm labour is shown in **Figure 1**. This flowchart displays the clinical management pathway to the point of patient diagnosis.

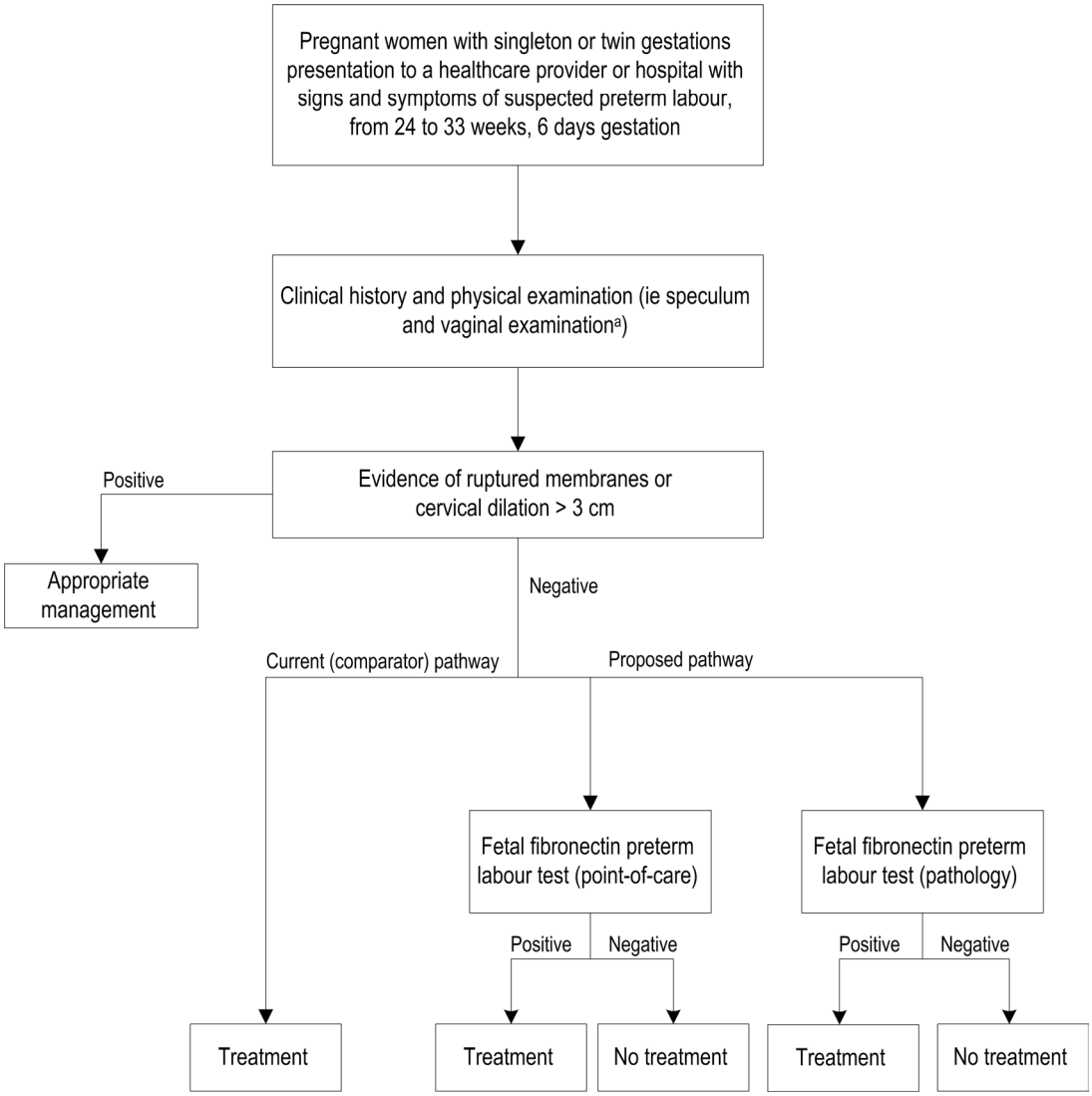

Figure 1 **Proposed pathway for fetal fibronectin test use in assessing risk of preterm delivery among women in suspected preterm labour**

[a] The sample for the fetal fibronectin test must be obtained before digital vaginal examination

Asymptomatic pregnant women with high risk of preterm delivery

The PPICO criteria developed *a priori* for the evaluation of fetal fibronectin testing in asymptomatic pregnant women with high risk of preterm delivery are given in **Table 2**.

Table 2 PPICO criteria for the use of the fetal fibronectin testing in asymptomatic pregnant women with high risk of preterm delivery

Population	Prior tests	Index test	Comparator	Outcomes
Pregnant women at high risk of preterm delivery managed in consultation with an obstetrician, with singleton gestations, who at routine visits are asymptomatic for preterm labour, but have high risk of preterm delivery as determined by commonly used clinical criteria, with intact amniotic membranes and minimal cervical dilation (< 3 cm), from 24 to 31 weeks, 6 days gestation	Clinical history Physical examination[a]	Fetal fibronectin (+/– cervical ultrasound)	Cervical ultrasound (where available) Current clinical practice	Change in clinical outcomes Change in clinical management Diagnostic accuracy

[a] The sample for the fetal fibronectin test must be obtained before digital vaginal examination.

The research question for this indication, based on these criteria, was as follows.

To what extent is the fetal fibronectin test for predicting preterm labour (with or without cervical ultrasound):

- safe,
- effective (including diagnostic performance and the impact of diagnosis on changes in clinical management and changes in clinical outcomes), and
- cost-effective

in the assessment of preterm delivery risk in pregnant women at high risk of preterm delivery managed in consultation with an obstetrician, with singleton gestations, who at a routine visit are asymptomatic for preterm labour, but have high risk of preterm delivery as determined by commonly used clinical criteria, with intact amniotic membranes and minimal cervical dilation (< 3 cm), from 24 to 31 weeks, 6 days gestation relative to cervical ultrasound or current clinical practice?

The clinical pathway for the evaluation of asymptomatic women at high risk of preterm delivery is shown in **Figure 2**. This flowchart displays the clinical management pathway to the point of patient diagnosis.

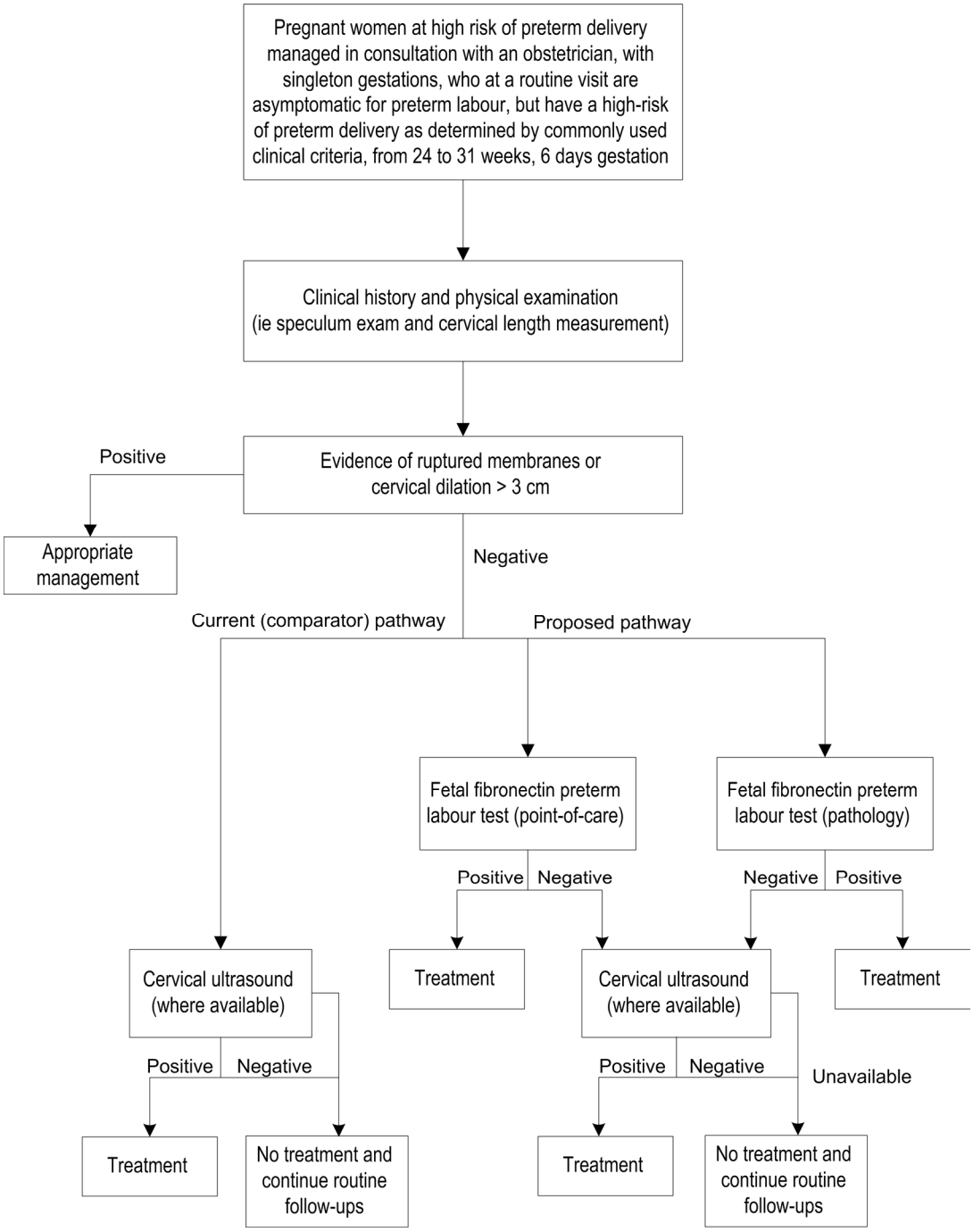

Figure 2 **Proposed pathway for fetal fibronectin test use in the risk assessment of preterm delivery in asymptomatic pregnant women at high risk of preterm delivery**

Assessment framework

Types of evidence

A systematic review of the medical literature was undertaken to identify relevant studies that examined the value of fetal fibronectin testing for predicting preterm labour. Direct evidence regarding the impact of fetal fibronectin testing on health outcomes was sought. The literature search was not limited by outcomes or comparators. In the absence of studies providing direct evidence, indirect evidence regarding the impact of the fetal fibronectin testing on clinical management and diagnostic accuracy was assessed. This indirect evidence was then combined with the evaluation of treatment effectiveness to assess the impact of the fetal fibronectin testing on health outcomes.

Review of the literature

The medical literature was searched to identify all relevant studies and reviews published up to mid-2006. Searches were conducted in the primary databases indicated in **Table 3**.

Search strategy

Primary databases

Table 3 Electronic databases searched in the fetal fibronectin test for predicting preterm labour review

Database	Period covered/date searched
Medline	1966 to June week 1, 2006
EMBASE	1980 to 2006, week 23
PreMedline	To 14 June 2006
Cochrane Library	Issue 2, 2006 (15 June 2006)

The search terms included the following (as determined from the PPICO criteria):

- fibronectins, fetal fibronectin, oncofetal fibronectin, fdc-6, TLI(IQ) system, Quikcheck test
- premature labour, premature birth, premature delivery, premature childbirth, premature parturition, preterm labour, preterm birth, preterm delivery, preterm childbirth, preterm parturition, pregnancy trimester.

Complete details of the literature searches performed using the primary databases are presented in **Appendix H**. The list of secondary databases searched is also presented in **Appendix H**.

Additional searches were conducted to source quality of life, epidemiological and economic information, as required.

Citation lists

The citation lists of identified systematic reviews were searched to identify any additional studies.

Selection criteria

Pregnant women in suspected preterm labour

Table 4 Selection criteria for studies of pregnant women in suspected preterm labour

Research question: To what extent is the fetal fibronectin test for predicting preterm labour safe, effective and cost-effective in the assessment of preterm delivery risk in pregnant women with singleton or twin gestations presenting to a health care provider or hospital with signs and symptoms of suspected preterm labour, with intact amniotic membranes and minimal cervical dilation (< 3 cm) from 24 to 33 weeks, 6 days gestation relative to current clinical practice

Selection criteria	Inclusion	Exclusion
Study design		
All studies	Studies with ≥ 10 patients[a]	Non-systematic reviews, letters and opinion pieces, non-human or *in vitro* studies
Accuracy studies	Studies investigating the diagnostic accuracy of fetal fibronectin	Unblinded diagnostic accuracy studies
Management studies	Studies evaluating the management of patients with **and** without the availability of fetal fibronectin testing	Studies comparing the management of fetal fibronectin positive patients to fetal fibronectin negative patients
Population	Pregnant women with signs and symptoms of suspected preterm labour	
Prior tests	Not specified for inclusion or exclusion criteria	
Index test	Use of the fetal fibronectin preterm labour tests as approved by the TGA	Use of the tests to detect other events than risk of preterm delivery Use of test before 24 weeks gestation Use of test after 34 weeks gestation
Comparator	Current clinical practice	
Reference standard		
Accuracy studies	Clinical follow-up until birth	
Outcomes		
Accuracy studies	Diagnostic performance	Studies not reporting diagnostic accuracy outcomes for at least one of the following: birth within seven days of testing, birth within 14 days of testing, birth before 34 weeks gestation, birth before 37 weeks gestation Studies not using the > 50 ng/mL cut off
Management studies	Effect on clinical management	

Abbreviation: TGA, Therapeutic Goods Administration

[a] Studies < 10 patients were included for the assessment of adverse events and safety data.

Asymptomatic pregnant women at high risk of preterm delivery

Table 5 Selection criteria for studies of asymptomatic pregnant women at high risk of preterm delivery

Research question: To what extent is the fetal fibronectin test for predicting preterm labour (+/– cervical ultrasound) safe, effective and cost-effective in the assessment of preterm delivery risk in pregnant women at high risk of preterm delivery managed in consultation with an obstetrician, with singleton gestations, who at a routine visit are asymptomatic for preterm labour, but have high risk of preterm delivery as determined by commonly used clinical criteria, with intact amniotic membranes and minimal cervical dilation (< 3 cm), from 24 to 31 weeks, 6 days gestation relative to cervical ultrasound or current clinical practice

Selection criteria	Inclusion	Exclusion
Study design		
All studies	Studies with ≥ 10 patients[a]	Non-systematic reviews, letters and opinion pieces, non-human or *in vitro* studies
Health outcomes studies	Studies comparing health outcomes with and without the use of fetal fibronectin	
Accuracy studies	Studies investigating the diagnostic accuracy of fetal fibronectin	Unblinded diagnostic accuracy studies[b]
Management studies	Studies evaluating the management of patients with **and** without the availability of fetal fibronectin testing	Studies comparing the management of fetal fibronectin positive patients to fetal fibronectin negative patients
Population	Asymptomatic pregnant women at high risk of preterm delivery	Patient population only consisting of asymptomatic pregnant women with multiple gestation Asymptomatic pregnant women with a low, medium or unclear risk of preterm delivery
Prior tests	Not specified for inclusion or exclusion criteria	
Index test	Use of fetal fibronectin preterm labour tests as approved by the TGA with or without the use of cervical ultrasound	Use of the tests to detect other events than risk of preterm delivery Use of test before 24 weeks gestation Use of test after 34 weeks gestation
Comparator	Current clinical practice Cervical ultrasound	
Reference standard		
Accuracy studies	Clinical follow-up until birth	
Outcomes		
Health outcomes studies	Effect on health outcomes	
Accuracy studies	Diagnostic performance	Studies not reporting diagnostic accuracy outcomes for at least one of the following: birth within seven days of testing, birth within 14 days of testing, birth before 34 weeks gestation, birth before 37 weeks gestation Studies not using the > 50 ng/mL cut off
Management studies	Effect on clinical management	

Abbreviation: TGA, Therapeutic Goods Administration

[a] Studies < 10 patients were included for the assessment of adverse events and safety data.

[b] Due to the paucity of evidence this criterion was not applied to the studies assessing the diagnostic accuracy of point-of-care fetal fibronectin testing in asymptomatic women at high risk of preterm delivery.

Search results

A total of 557 non-duplicate citations relating to fetal fibronectin testing were identified: these included 41 diagnostic accuracy and 10 management studies. The QUOROM flow chart (**Figure 3**) summarises exclusion of studies from the safety and effectiveness review of fetal fibronectin testing for predicting preterm labour.

Data extraction

Data extraction was performed with the aid of a *pro forma* based on key parameters: trial characteristics, study population characteristics, tests used and outcomes reported. This follows the procedure for data collection outlined in the *Cochrane Reviewers' Handbook* (Higgins et al 2005).

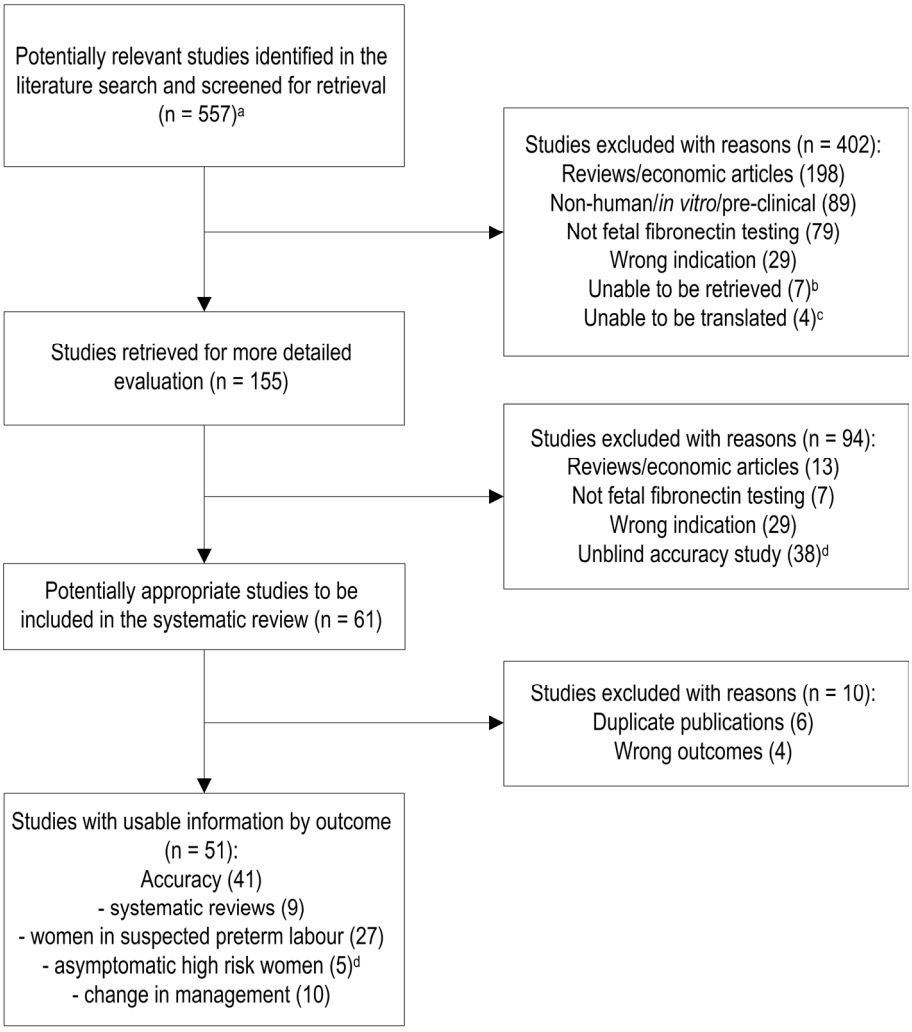

Figure 3 QUOROM flow chart used to identify and select studies for the literature review of fetal fibronectin testing

Adapted from Moher et al (1999).
[a] 530 citations identified in primary databases, 15 citations identified in secondary databases and 12 citations identified in reference lists of included systematic reviews.
[b] Four abstracts of potential diagnostic accuracy studies, two potential diagnostic accuracy studies and one systematic review were identified but could not be retrieved.
[c] Four potential diagnostic accuracy studies published in Polish could not be translated.
[d] Due to the paucity of evidence this criterion was not applied to the studies assessing the diagnostic accuracy of point-of-care fetal fibronectin testing in asymptomatic women at high risk of preterm delivery.

Statistical methods

Methodological considerations

Direct evidence of the value of fetal fibronectin testing relative to current clinical practice, when used in the relevant patient group, is required to justify reimbursement under Medicare. Ideally, this should be in the form of studies reporting effects on patient-centred health outcomes. Alternatively, evidence establishing greater diagnostic accuracy than shown for the comparator, confirmation of change in management, and substantiation that treatment will affect health outcomes, is required.

Evidence of an effect on management change is a key component where an additional diagnostic test is to be used in the clinical pathway. The most appropriate design for investigation of effects on management change is a pre-test, post-test case series study. Where a pre-test management plan is not reported, study outcomes are likely to be biased and do not truly represent change in patient management.

An ideal comparative accuracy study design for diagnostic tests permits performance of each test as a consecutive series in a population with a defined clinical presentation. The study should be an independent, blinded comparison with a valid reference standard (NHMRC 2005).

Diagnostic performance

The accuracy evaluation of new diagnostic tests involves comparing the new test with its comparators and the reference standard—the best available proxy for the true condition status. The new diagnostic test and its comparators can be independently compared with the reference standard to assess sensitivity, specificity, accuracy, diagnostic odds ratio (DOR) and likelihood ratios.

Sensitivity is defined as the proportion of all patients with a specified condition whose results are positive. Specificity is the proportion of all patients without the specified condition who test negative. Test accuracy is represented by the proportion of patients who are correctly identified as positive or negative by the test. The DOR is an expression of the odds of positive test results in patients with the specified condition, compared with those who do not have the condition. A DOR of 100 provides convincing evidence of the test's ability to discriminate the presence of absence of the condition.

The likelihood ratio of a positive test is the probability that a person with, as opposed to without, the condition would have a positive test result. The likelihood ratio of a negative test is the probability that a negative result will be found for a person with, as opposed to without, the condition. A positive ratio of greater than 10 and a negative ratio less than 0.1 provide convincing diagnostic evidence. A positive likelihood ratio of greater than 5 and a negative likelihood ratio of less than 0.2 provide strong diagnostic evidence (Medical Services Advisory Committee, 2005). Bayes' theorem indicates that the post-test odds of a condition are equal to the pre-test odds of the condition multiplied by the likelihood ratio. The post-test probability of a condition can be determined for any given pre-test probability using this approach.

SROC methodology

The summary receiver operating characteristic (SROC) approach (Moses et al 1993) is used to compare overall diagnostic accuracy of different tests—or the extent to which accuracy depends on study characteristics. The methodology follows Irwig et al (1995) whereby the logits of true positive rate (TPR) and false positive rate (FPR) are calculated, their difference (D = logit TPR – logit FPR) and sum (S = logit TPR + logit FPR) are also calculated. A regression model is fitted to the straight lines where D is the outcome and S is the explanatory variable. The model can be fitted with or without weights (inverse variance, variance of the diagnostic log odds ratio D = logit TPR – logit FPR). The axes have the following interpretations: the difference in the logits is the log of the diagnostic odds ratio, and the sum of the logits is a marker of diagnostic threshold. The summary ROC curve is produced by applying regression coefficients to ROC dimensions.

Investigating sources of heterogeneity

The Littenberg-Moses regression method is extended to examine the impact on accuracy of potential confounders by adding a covariate to the regression equation.
The exponential of each of these terms estimates multiplicative increases in diagnostic odds ratios for each factor.

Heterogeneity in threshold

The SROC approach can also be extended to examine effect on diagnostic threshold, in particular differences in thresholds between potential covariates or study characteristics. S is a measure of the threshold for classifying a test as positive, which has a value of 0 when sensitivity equals specificity. The value of S becomes positive when a threshold is used that increases sensitivity (decreases specificity) and becomes negative when a threshold is used that decreased sensitivity (increases specificity).

Diagnostic summary measures

Forest plots of the likelihood ratios and SROC curves are presented using the graphical output of the Meta-disc® program. Graphical output was customised for this assessment.

During the calculation of summary diagnostic measures; studies with zero values were re-calculated with inclusion of 0.5 to each of the diagnostic outcomes—true positive, false positive, true negative, false, negative.

Appraisal of the evidence

Appraisal of the evidence was conducted at three stages:

Stage 1: Appraisal of the applicability and quality of individual studies included in the review

Stage 2: Appraisal of the precision, size and clinical importance of the primary outcomes used to determine the safety and effectiveness of the test

Stage 3: Integration of this evidence in order to draw conclusions about the net clinical benefit of the index test in the context of Australian clinical practice.

Appraisal of the quality and applicability of individual studies

The quality and applicability of the included studies was assessed according to pre-specified criteria according to the study design (**Appendix G**).

Ranking the evidence

Studies evaluating the direct impact of the test or treatment on patient outcomes were ranked according to the study design, using the levels of evidence designated by the National Health and Medical Research Council (NHMRC) (**Table 6**).

Table 6 NHMRC levels of evidence for studies of effectiveness

Level of evidence	Study design
I	Evidence obtained from a systematic review of level II studies
II	Evidence obtained from properly designed randomised controlled trials
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies with concurrent controls: non-randomised experimental trials, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies without concurrent controls: historical control studies, two or more single-arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test/post-test outcomes

Source: NHMRC, 2005

Studies of diagnostic accuracy were ranked according to the NHMRC levels of evidence for diagnoses are shown in **Table 7**.

Table 7 NHMRC levels of evidence for diagnosis

Level of evidence	Study design
I	Evidence obtained from a systematic review of level II studies
II	Evidence obtained from studies of test accuracy with: an independent blinded comparison with a valid reference standard, among consecutive patients with a defined clinical presentation
III-1	Evidence obtained from studies of test accuracy with: an independent blinded comparison with a valid reference standard, among non-consecutive patients with a defined clinical presentation
III-2	Evidence obtained from studies of test accuracy with: a comparison with reference standard that does not meet the criteria required for level II or III-1 evidence
III-3	Evidence obtained from diagnostic case-control studies
IV	Evidence obtained from studies of diagnostic yield (no reference standard)

Source: NHMRC, 2005

Studies were also graded according to the pre-specified quality and applicability criteria, as shown in **Table 8**.

Table 8 Grading system used to rank included studies

Validity criteria	Description	Grading system
Appropriate comparison	Did the study evaluate a direct comparison of the index test strategy versus the comparator test strategy?	C1 direct comparison CX other comparison
Applicable population	Did the study evaluate the index test in a population that is representative of the subject characteristics (age and sex) and clinical setting (disease prevalence, disease severity, referral filter and sequence of tests) for the clinical indication of interest?	P1 applicable P2 limited P3 different population
Quality of study	Was the study designed to avoid bias? High quality = no potential for bias based on pre-defined key quality criteria Medium quality = some potential for bias in areas other than those pre-specified as key criteria Poor quality = poor reference standard and/or potential for bias based on key pre-specified criteria	Q1 high quality Q2 medium quality Q3 poor reference standard poor quality or insufficient information

Expert advice

An advisory panel with expertise in perinatal care was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for advisory panels, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations and consumer bodies for nominees. Membership of the advisory panel is provided at **Appendix B**.

Results of assessment

Is it safe?

An extensive literature search did not identify any safety data pertaining to fetal fibronectin testing. Potential risks to patients are however expected to be minimal, because the cervicovaginal sample required for fetal fibronectin testing is obtained with a swab as part of a standard speculum examination.

Is it effective?

Summary

The summary diagnostic measures indicate that a negative fetal fibronectin (fFN) test result from either pathology-based or point-of-care testing of women in suspected preterm labour has moderate diagnostic value to identify patients not at immediate risk of preterm delivery. The limited quality and applicability of the included studies to Australian clinical practice should be considered when interpreting the summary results.

Lack of evidence meant that informed conclusions could not be made about the diagnostic accuracy of pathology-based or point-of-care fFN testing in asymptomatic pregnant women at high risk of preterm delivery.

Based on the limited patient management data available, the value of fFN testing in clinical decision-making in Australia remains uncertain.

Evidence of treatment effectiveness was not examined for patients in suspected preterm labour because the intended purpose of the diagnostic test in this population is to reduce unnecessary treatment of women with false labour. It is unlikely that the introduction of fFN testing would identify new patients to receive treatment for preterm labour. It is therefore unlikely that the introduction of fFN testing would substantially decrease the effectiveness of currently used treatments for the management of preterm labour.

Treatment effectiveness was not examined in asymptomatic patients with a high risk of preterm delivery because of insufficient evidence in relation to diagnostic accuracy and change in patient management.

Direct evidence

Does it improve health outcomes?

The literature search identified two studies that reported health outcomes of fetal fibronectin testing for patients in suspected preterm labour (Grobman et al 2004; Plaut et al 2003). Neither study was included as direct evidence because they were designed to assess patient management and had limited applicability to the Australian setting.

Linked evidence

Diagnostic accuracy studies

The literature search for studies concerning diagnostic accuracy of fetal fibronectin testing identified 41 studies that were eligible for review. These studies included nine systematic reviews and 32 primary studies.

Systematic reviews

The evaluation of fetal fibronectin testing's diagnostic accuracy for preterm birth in suspected and/or asymptomatic high risk pregnant women considered evidence presented in nine systematic reviews. The characteristics of these reviews are described in **Appendix C**. A tenth systematic review identified in the literature search could not be retrieved (Hayes 2000).

Assignment of quality criteria confirmed that two systematic reviews (AHRQ 2000, Honest et al 2002) were classified as high quality. A systematic review by Chien et al (1997) was found to provide medium quality—the scope and description of the literature search was limited. The remaining six systematic reviews were considered to be low quality—they had limitations in scope and inadequate methodologies (Faron et al 1998, ICSI 2000, Lamont et al 2003, Leitich et al 1999, Leitich et al 2003, Revah et al 1998). A breakdown of the quality of the systematic reviews is outlined in **Appendix C**.

The AHRQ report (2000) did not present a statistical analysis of the results. Review of individual studies' results presented in the AHRQ (2000) report indicated that fetal fibronectin had a good negative predictive value for diagnosing preterm delivery for women in suspected preterm labour.

Honest et al (2002) presented a meta-analysis of the diagnostic accuracy of fetal fibronectin testing as both summary likelihood ratios (LR) and summary receiver operating characteristic (SROC) curves. The fetal fibronectin test was found to be moderately effective in the diagnosis of preterm delivery within 7–10 days for women in suspected preterm labour (LR+ 5.4, LR– 0.3). The test accuracy was less effective in the diagnosis of preterm delivery before 34 weeks (LR+ 3.6, LR– 0.3) or 37 weeks (LR+ 3.3, LR– 0.5) gestation among women in suspected preterm labour. Honest and colleagues (2002) were unable to explain detected heterogeneity using meta-regression. Analysis revealed a number of data extraction errors that may have affected the conclusion of the meta-analysis.

Chien et al (1997) examined the diagnostic accuracy of fetal fibronectin using summary likelihood ratios in their review, which was classified as medium quality. This meta-analysis found the fetal fibronectin test to be moderately effective in diagnosing preterm delivery within seven days (LR+ 5.0, LR– 0.2). The test was less effective in diagnosing preterm delivery before 34 weeks (LR+ 2.6, LR– 0.2) or 37 weeks (LR+ 4.6, LR– 0.5) gestation among women in suspected preterm labour. The authors also reported likelihood ratios for asymptomatic high risk patients to diagnose preterm delivery before 34 weeks (LR+ 2.4, LR– 0.6) or 37 weeks (LR+ 2.0, LR– 0.4) gestation. Chien and colleagues (1997) applied meta-regression analysis but were unable to explain detected heterogeneity.

The systematic reviews contained sub-optimal diagnostic accuracy quality (lower than level II evidence, NHMRC 2005). This may limit the validity of conclusions made in relation to the current research questions.

Summaries of reported relevant results from the systematic reviews are presented in **Appendix C**. Results for biological markers, other than fetal fibronectin, and for low-risk or unsorted asymptomatic women, were not summarised. Three systematic reviews did not present meta-analyses of included studies results (AHRQ 2000, ICSI 2000, Lamont et al 2003).

Primary studies

There were 32 primary studies identified among the 41 eligible for review that examined the diagnostic accuracy of fetal fibronectin testing. Summaries of study designs and outcomes, population and test characteristics, and an assessment of study quality and applicability for all diagnostic accuracy studies used in the assessment are presented in **Appendix C**. The confounding factors reported in the included diagnostic accuracy studies are also summarised. Separate examinations of diagnostic accuracy were made for pregnant women in suspected preterm labour and asymptomatic pregnant women at high risk of preterm delivery.

Pregnant women in suspected preterm labour

Evaluation of the diagnostic performance of fetal fibronectin testing relative to current clinical practice among patients in suspected preterm labour was identified in 27 studies. Diagnostic accuracy of pathology-based fetal fibronectin testing was evaluated in 21 studies; another six studies evaluated the diagnostic accuracy of point-of-care fetal fibronectin testing.

Pathology testing

Study characteristics

There were 21 studies identified that investigated the diagnostic accuracy of fetal fibronectin pathology testing of pregnant women in suspected preterm labour. Of these, studies by Grandi et al (1996) and Tekesin et al (2005) were classified as high quality and limited applicability. The characteristics of these studies are presented in **Table 9**. Both studies applied blinded prospective designs and enrolled consecutive patient cohorts. The studies included patients on the basis of uterine contraction with or without cervical changes. Applicability of these studies was limited by inclusion of patients tested after 34 weeks gestation—a period outside the targeted population's timeframe. Grandi et al (1996) used a test that has been superseded. Results are likely to have limited applicability in the Australian setting.

Table 9 Characteristics of the best available evidence for the use of pathology-based fetal fibronectin testing for pregnant women in suspected preterm labour

Author (year) Country	Study design	Patients (N)	Test characteristics	Study quality[a]
Grandi (1996) Argentina	Prospective, consecutive patient enrolment Blinded comparison to reference standard Sep 1995–Dec 1995	Singleton gestation patients with uterine contractions Intact membranes and cervical dilation < 3 cm Gestational age 24–36 weeks (26)	Sample from the cervix using an ELISA (single test)	Level II P2, Q1 *Applicability*: Unknown/obsolete fibronectin test Timeframe of testing
Tekesin (2005) Germany	Prospective, consecutive patient enrolment Blinded comparison to reference standard Nov 2001–Jan 2004	Singleton gestation patients with uterine contractions Intact membranes and cervical dilation < 3 cm Gestational age 24–35 weeks (170)	Sample from the cervix using the TLI(IQ)™ system (single test)	Level II P2, Q1 *Applicability*: Timeframe of testing

[a] According to criteria outlined in **Table 7**, **Table 8** and **Appendix G**

Of the other 19 studies identified, all were regarded as medium quality and of limited applicability. Characteristics of these studies are reported in **Table 10**. Only one of these studies was found to use a currently available test: most used superseded fetal fibronectin tests, or the test type was insufficiently described to permit comparison. Differences in testing timeframes, presenting symptoms and degree of cervical dilation may affect the applicability of the results to the targeted population.

Studies by Morrison et al (1993) and Rinehart et al (2001) included patients with diagnoses of false labour in women presenting with symptoms of preterm labour. The effect of applicability of these studies to the target population is unknown.

Studies by Rizzo et al (1996, 1997) present overlapping patient groups. This assessment refers to statistical analyses of the summary diagnostic measures from the 1997 study. Exception occurs where significant differences were found when compared with results from the 1996 study. Analyses for each study are presented in this instance.

Table 10 Characteristics of included studies providing evidence for the use of pathology-based fetal fibronectin testing among pregnant women in suspected preterm labour

Author (year) Country	Study design	Patients (N)	Test characteristics	Study quality[a]
Bartnicki (1996) Germany	Prospective, non-consecutive patient enrolment Blinded comparison to reference standard	Unspecified gestation patients with TPL symptoms Intact membranes and cervical dilation < 2 cm Gestational age 22–35 weeks (112)	Sample from the posterior fornix using the Fetal Fibronectin Enzyme Immunoassay™ (single test)	Level III-1 P2, Q2 *Applicability*: Unknown/obsolete fibronectin test Cervical dilation < 2 cm Timeframe of testing *Quality*: Non-consecutive enrolment
Burrus (1995) USA	Prospective, non-consecutive patient enrolment Blinded comparison to reference standard Feb 1994–Oct 1994	Unspecified gestation patients with uterine contractions Intact membranes and cervical dilation < 3 cm Gestational age 22–35 weeks (45)	Sample from the cervix using an ELISA (single test)	Level III-1 P2, Q2 *Applicability*: Unknown/obsolete fibronectin test Timeframe of testing *Quality*: Non-consecutive enrolment
Iams (1995) USA	Prospective, non-consecutive patient enrolment Blinded comparison to reference standard	Unspecified gestation patients with TPL symptoms Intact membranes and cervical dilation < 3 cm Gestational age 24–34 weeks (192)	Sample from the exocervix or posterior fornix using an ELISA (single test)	Level III-1 P2, Q2 *Applicability*: Unknown/obsolete fibronectin test *Quality*: Non-consecutive enrolment
Inglis (1994)[b] USA	Prospective, non-consecutive patient enrolment Blinded comparison to reference standard	Singleton gestation patients with TPL diagnoses Intact membranes Gestational age < 37 weeks (38)	Sample from the endocervix or posterior fornix using an ELISA (single test)	Level III-1 P2, Q2 *Applicability*: Unknown/obsolete fibronectin test Unclear cervical dilation Unclear testing timeframe *Quality*: Non-consecutive enrolment
Irion (1995) Switzerland	Prospective, non-consecutive patient enrolment Blinded comparison to reference standard	Unspecified gestation patients with uterine contractions Intact membrane and cervical dilation < 2 cm Gestational age 24–36 weeks (64)	Sample from the endocervix using an ELISA (single test)	Level III-1 P2, Q2 *Applicability*: Unknown/obsolete fibronectin test Cervical dilation < 2 cm Timeframe of testing *Quality*: Non-consecutive enrolment
Langer (1997) France	Prospective, non-consecutive patient enrolment Blinded comparison to reference standard Feb 1994–May 1995	Unspecified gestation patients with uterine contractions Intact membrane and cervical dilation < 2 cm Gestational age 24–34 weeks (61)	Sample from the endocervix or exocervix using an ELISA (single test)	Level III-1 P2, Q2 *Applicability*: Unknown/obsolete fibronectin test Cervical dilation < 2 cm *Quality*: Non-consecutive enrolment

Author (year) Country	Study design	Patients (N)	Test characteristics	Study quality[a]
La Shay (2000) USA	Prospective, non-consecutive patient enrolment Blinded comparison to reference standard	Singleton gestation patients with uterine contractions Intact membranes and cervical dilation < 3 cm Gestational age 24–34 weeks (118)	Sample from the endocervix or posterior fornix using the Fetal Fibronectin Enzyme Immunoassay™ (single test)	Level III-1 P2, Q2 *Applicability*: Unknown/obsolete fibronectin test *Quality*: Non-consecutive enrolment
Lockwood (1991) USA	Prospective, non-consecutive patient enrolment Blinded comparison to reference standard	Unspecified gestation patients with uterine contractions Intact membranes Gestational age < 37 weeks (117)	Sample from the cervix or posterior fornix using the ROM-check™ (single test)	Level III-1 P2, Q2 *Applicability*: Unknown/obsolete fibronectin test Unclear cervical dilation Unclear testing timeframe *Quality*: Non-consecutive enrolment
Malak (1996)[c] UK	Prospective, non-consecutive patient enrolment Blinded comparison to reference standard	Singleton gestation patients with TPL symptoms Intact membranes and cervical dilation < 2 cm Gestational age 24–34 weeks (112)	Sample from the exocervix or posterior fornix using an ELISA (single test)	Level III-1 P2, Q2 *Applicability*: Unknown/obsolete fibronectin test Cervical dilation < 2 cm *Quality*: Non-consecutive enrolment
Morrison (1993)[d] USA	Prospective, non-consecutive patient enrolment Blinded comparison to reference standard	Singleton gestation patients with uterine contractions Intact membranes and cervical dilation < 1 cm Gestational age 24–36 weeks (28)	Sample from the exocervix using an ELISA (single test)	Level III-1 P2, Q2 *Applicability*: Unknown/obsolete fibronectin test Cervical dilation < 1 cm Timeframe of testing *Quality*: Non-consecutive enrolment
Peaceman (1997) USA	Prospective, non-consecutive patient enrolment Blinded comparison to reference standard	Singleton, twin or triplet gestation patients with TPL symptoms Intact membranes and cervical dilation < 3 cm Gestational age 24–35 weeks (763)	Sample from the posterior fornix using an ELISA (single test)	Level III-1 P2, Q2 *Applicability*: Unknown/obsolete fibronectin test Timeframe of testing *Quality*: Non-consecutive enrolment
Rinehart (2001)[d] USA	Prospective, non-consecutive patient enrolment Blinded comparison to reference standard Mar 1998–Jun 1999	Singleton or twin gestation patients with TPL symptoms Intact membranes and cervical dilation < 2 cm Gestational age 24–34 weeks (235)	Unclear	Level III-1 P2, Q2 *Applicability*: Unknown/obsolete fibronectin test Cervical dilation < 2 cm *Quality*: Non-consecutive enrolment
Rizzo (1996)[e] Italy	Prospective, non-consecutive patient enrolment Blinded comparison to reference standard Jan 1993–Sep 1995	Singleton gestation patients with uterine contractions Intact membranes and cervical dilation < 3 cm Gestational age 24–36 weeks (108)	Sample from the exocervix or the posterior fornix using an ELISA (single test)	Level III-1 P2, Q2 *Applicability*: Unknown/obsolete fibronectin test Timeframe of testing *Quality*: Non-consecutive enrolment

Author (year) Country	Study design	Patients (N)	Test characteristics	Study quality[a]
Rizzo (1997)[e] Italy	Prospective, non-consecutive patient enrolment Blinded comparison to reference standard Jan 1994–Sep 1996	Singleton gestation patients with uterine contractions Intact membranes and cervical dilation < 3 cm Gestational age 24–36 weeks (106)	Sample from the exocervix or the posterior fornix using an ELISA (single test)	Level III-1 P2, Q2 *Applicability*: Unknown/obsolete fibronectin test Timeframe of testing *Quality*: Non-consecutive enrolment
Rozenberg (1996)[b] France	Prospective, non-consecutive patient enrolment Blinded comparison to reference standard Oct 1993–Mar 1994	Unspecified gestation patients with uterine contractions Intact membranes Gestational age 24–34 weeks (56)	Sample from the posterior fornix using the Fetal Fibronectin Enzyme Immunoassay™ (single test)	Level III-1 P2, Q2 *Applicability*: Unknown/obsolete fibronectin test Unclear cervical dilation *Quality*: Non-consecutive enrolment
Rozenberg (1997) France	Prospective, non-consecutive patient enrolment Blinded comparison to reference standard Sep 1994–Jun 1995	Singleton gestation patients with uterine contractions Intact membranes and cervical dilation < 2 cm Gestational age 24–34 weeks (76)	Sample from the posterior fornix using the Fetal Fibronectin Enzyme Immunoassay™ (single test)	Level III-1 P2, Q2 *Applicability*: Unknown/obsolete fibronectin test Cervical dilation < 2 cm *Quality*: Non-consecutive enrolment
Schmitz (2006) France	Prospective, non-consecutive patient enrolment Blinded comparison to reference standard Jan 1997–May 2000	Singleton gestation patients with uterine contractions Intact membranes and cervical dilation < 3 cm Gestational age 18–35 weeks (359)	Sample from the posterior fornix using a ELISA (single test)	Level III-1 P2, Q2 *Applicability*: Unknown/obsolete fibronectin test Timeframe of testing *Quality*: Non-consecutive enrolment
Skoll (2006) Canada	Prospective, non-consecutive patient enrolment Blinded comparison to reference standard	Singleton, twin or triplet gestation patients with TPL diagnoses Intact membranes Gestational age 24–34 weeks (149)	Sample from the posterior fornix using the TLI(IQ)™ system (single test)	Level III-1 P2, Q2 *Applicability*: Unclear cervical dilation *Quality*: Non-consecutive enrolment
Zamora (2000) Venezuela	Prospective, non-consecutive patient enrolment Double blind	Unspecified gestation patients with uterine contractions Intact membranes Gestational age 28–36 weeks (22)	Sample from the exocervix using an ELISA (single test)	Level III-1 P2, Q2 *Applicability*: Unknown/obsolete fibronectin test Timeframe of testing Unclear cervical dilation *Quality*: Non-consecutive enrolment

Abbreviations: ELISA, enzyme-linked immunosorbent assay; NR, not reported; TPL, threatened preterm labour

[a] According to criteria outlined in **Table 7**, **Table 8** and **Appendix G**

[b] Subgroup of patients with symptoms of suspected preterm labour.

[c] Subgroup of patients enrolled between 24–34 weeks gestation.

[d] Enrolled patients with diagnoses of false labour.

[e] Rizzo et al (1996) and Rizzo et al (1997) had overlapping patient cohorts.

Note: In this current review threatened preterm labour is termed suspected preterm labour.

A summary of the sensitivity, specificity, predictive values and diagnostic accuracy for each of these studies is presented in **Appendix C**.

The high quality study by Tekesin et al (2005) examined the outcome of births within seven days of testing. The authors reported prevalence of 7 per cent and diagnostic accuracy of 77 per cent (PPV 20%, NPV 98%, Sn 82%, Sp 77%). When the outcomes of births within 14 days of fetal fibronectin testing were examined, the prevalence increased to 9 per cent and the diagnostic accuracy rose to 80 per cent (PPV 30%, NPV 98%, Sn 88%, Sp 79%). When assessing the outcome of preterm birth before 37 weeks gestation, both prevalence and diagnostic accuracy increased to 27 per cent and 83 per cent respectively (PPV 67%, NPV 89%, Sn 69%, Sp 88%).

The high quality study by Grandi et al (1996) examined the effect of fetal fibronectin testing in birth outcomes before 37 weeks gestation. The authors reported prevalence of 31 per cent and diagnostic accuracy of 50 per cent (PPV 31%, NPV 69%, Sn 50%, Sp 50%).

Summary statistics [1]

A summary of the diagnostic accuracy of pathology based fetal fibronectin testing is displayed as summary receiver operating characteristic (SROC) curves for outcomes of preterm delivery within seven days of testing, and within 14 days of testing (**Appendix C**). The area under curve (AUC) was similar for preterm delivery within seven days of testing and preterm delivery within 14 days of testing (0.88, 0.90 unweighted AUC respectively). The test threshold for the outcome of preterm birth within seven days of testing was heterogenous. This indicates that other summary diagnostic measures for outcomes of preterm births within seven days of testing should be interpreted cautiously.

A summary diagnostic odds ratio (DOR) was calculated for the pathology based fetal fibronectin test studies. The pooled DOR for the assessment of preterm delivery risk within seven days of testing was 17.77 (95% CI: [11.49, 27.49]); and for the assessment of preterm delivery risk within 14 days of testing the summary DOR was 19.81 (95% CI: [11.94, 32.86]).

Forest plots are presented for the positive and negative likelihood ratios of preterm delivery outcomes within seven days of pathology-based fetal fibronectin testing. Using a fixed-effects model, the summary likelihood ratio for a positive result was 4.44 (95% CI: [3.87, 5.10]) (**Figure 4**). A similar model was applied to calculate a summary likelihood ratio for a negative result: 0.26 (95% CI: [0.19, 0.36]) (**Figure 5**).

[1] Additional analyses for predicting preterm birth before 37 weeks gestation are presented in **Appendix C**. The data set was too small to achieve reliable calculations of summary diagnostic measures for outcomes of preterm deliveries before 34 weeks gestation.

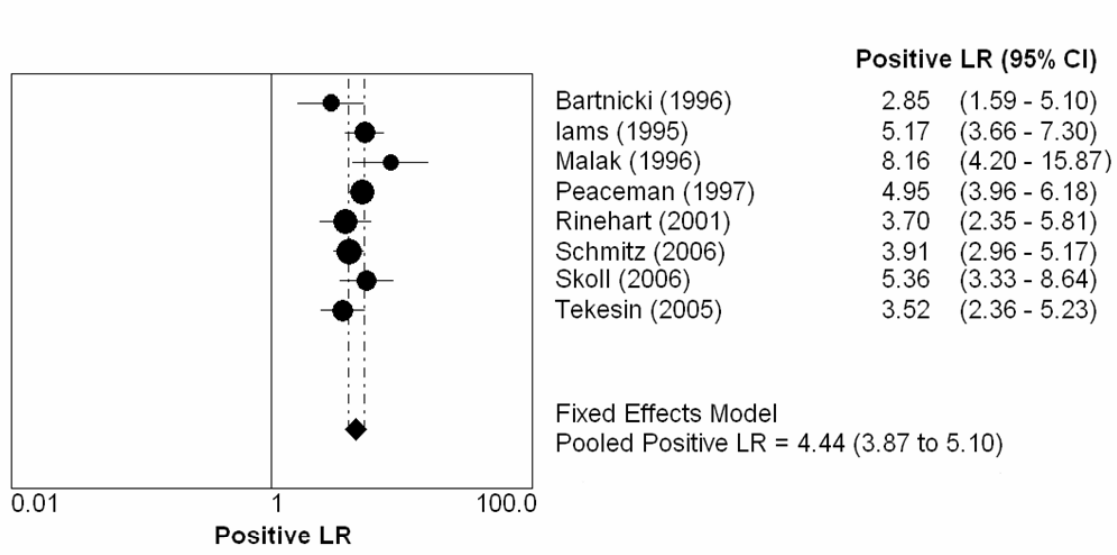

Figure 4 **Summary positive likelihood ratios (fixed effects) for the diagnostic accuracy of pathology-based fetal fibronectin testing among women in suspected preterm labour for assessment of preterm delivery risk within seven days of testing**

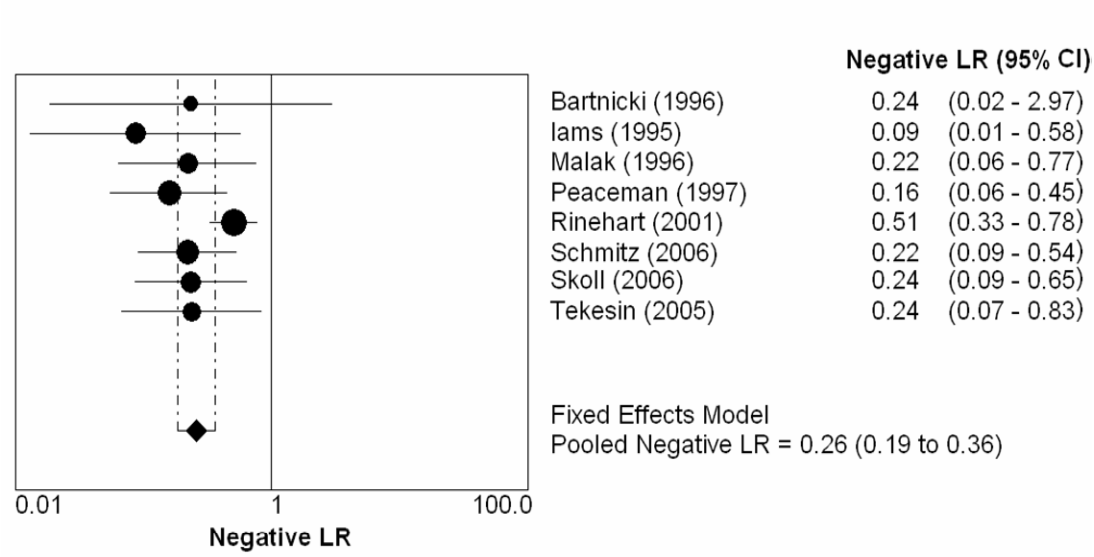

Figure 5 **Summary negative likelihood ratios (fixed effects) for the diagnostic accuracy of pathology-based fetal fibronectin testing among women in suspected preterm labour for assessment of preterm delivery risk within seven days of testing**

Forest plots are also presented for positive and negative likelihood ratios for preterm delivery outcome within 14 days of fetal fibronectin pathology-based testing (**Figure 6** and **Figure 7**, respectively). The summary likelihood ratios were 4.66 (95% CI: [3.94, 5.52]) for a positive result and 0.24 (95% CI: [0.16, 0.36]) for a negative result.

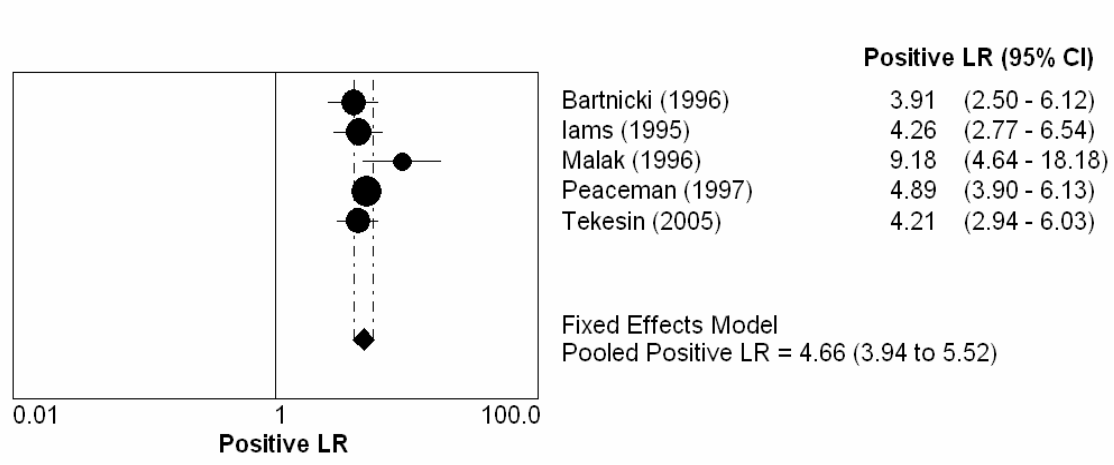

Figure 6 **Summary positive likelihood ratios for the diagnostic accuracy of pathology-based fetal fibronectin testing for assessment of preterm delivery risk within 14 days of testing**

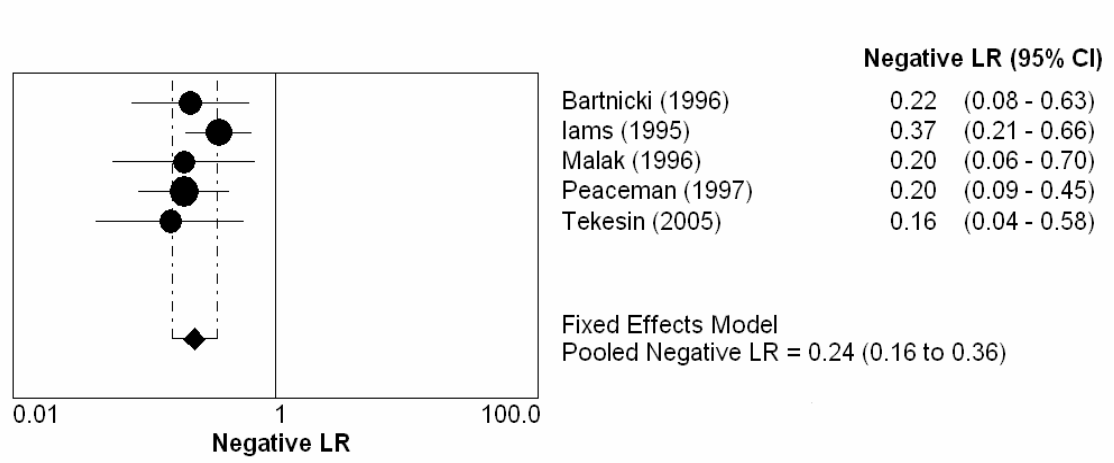

Figure 7 **Summary negative likelihood ratios for the diagnostic accuracy of pathology-based fetal fibronectin testing for assessment of preterm delivery risk within 14 days of testing**

The Littenberg-Moses regression method was applied to evaluate characteristics of gestational age, cervical dilation and presenting symptoms of the diagnostic accuracy of pathology-based fetal fibronectin testing for delivery within seven days of testing. These characteristics were unable to explain the heterogeneity found in the data sets.

The summary diagnostic measures indicated that a negative pathology-based fetal fibronectin test result for predicting preterm labour in women where it is suspected provides moderate diagnostic value to assess preterm delivery risk within seven or 14 days of testing. The limited applicability of the included studies to Australian clinical practice should be considered when interpreting the summary results.

Point-of-care testing

Study characteristics

Coleman et al (1998) and Volumenie et al (2001) investigated the diagnostic accuracy of fetal fibronectin testing at the point-of-care among women in suspected preterm labour. These studies were classified as high quality; their characteristics are presented in **Table 11**. These were blinded prospective studies using consecutively enrolled patient cohorts. Neither study used a currently available fetal fibronectin test. The patient population reported in the Coleman et al (1998) study corresponded with this assessment's target population. Volumenie et al (2001) recruited patients outside the target timeframe (between 24–34 weeks gestation) and recruited patients whose cervical dilation (< 4 cm) differed from the target population (< 3 cm). The differences in test and patient characteristics may affect the applicability of these studies.

Table 11 Characteristics of the best available evidence for the use of point-of-care fetal fibronectin testing for women in suspected preterm labour

Author (year) Country	Study design	Patients (N)	Test characteristics	Study quality[a]
Coleman (1998) New Zealand	Prospective, consecutive patient enrolment Blinded comparison to reference standard May 1996–June 1997	Singleton or twin gestation patients with uterine contractions or threatened preterm labour diagnoses Intact membranes and cervical dilation < 3 cm Gestational age 24–34 weeks (121)	Sample from posterior fornix using a prototype of the Quikcheck™ assay (single test)	Level II P2, Q1 *Applicability:* Unknown/obsolete fibronectin test
Volumenie (2001) France	Prospective, consecutive patient enrolment Blinded comparison to reference standard Jan 1998–Dec 1998	Patients with singleton gestation with uterine contractions Intact membranes and cervical dilation < 4 cm Gestational age 24–36 weeks (130)	Sample from the cervix using the ROM-check™ membrane immunoassay (single test)	Level II P2, Q1 *Applicability:* Unknown/obsolete fibronectin test Cervical dilation < 4 cm Timeframe of testing

[a] According to criteria outlined in **Table 7**, **Table 8** and **Appendix G.**
Note: In this current review threatened preterm labour is termed suspected preterm labour.

Coleman et al (1998) expressed concern about the effect of inter-observer variation on the interpretation of point-of-care test results. Inter-observer variation could potentially affect the diagnostic accuracy of the point-of-care test and this should be taken into account when interpreting the diagnostic accuracy of point-of-care fetal fibronectin testing.

Coleman et al (1998) reported prevalence of 12 per cent and diagnostic accuracy of 82 per cent (PPV 37%, NPV 95%, Sn 67%, Sp 84%) for preterm birth within seven days of fetal fibronectin testing. Exclusion of patients with medically indicated preterm birth from analyses caused the prevalence rate to drop to 10 per cent; sensitivity, NPV and diagnostic accuracy increased to 83, 98 and 84 per cent respectively.

Coleman et al (1998) also reported outcomes of preterm birth before 34 weeks gestation. The authors reported prevalence of 16 per cent and diagnostic accuracy of 79 per cent (PPV 37%, NPV 90%, Sn 53%, Sp 83%) for point-of-care fetal fibronectin testing. Volumenie et al (2001) also reported outcomes of preterm birth before 37 weeks

gestation. They reported prevalence of 27 per cent and diagnostic accuracy of 49 per cent (PPV 19%, NPV 69%, Sn 28%, Sp 57%) for point-of-care fetal fibronectin testing.

Another four studies categorised as medium quality and/or limited applicability were also identified. Characteristics of these studies are described in **Table 12**. None of these studies used a point-of-care fetal fibronectin test that is currently available. They therefore have limited applicability in the current Australian setting.

Parker et al (1995) recruited patients on the basis of a broad range of preterm labour symptoms. The remaining three studies in the medium quality and/or limited applicability category recruited patients on the basis of uterine contractions with or without cervical changes. All of these studies included patients tested outside the timeframe indicated for the target population. Two of the studies included patient groups with cervical dilations that differed from the target population. The study by Senden et al (1996) included patients who were < 4 cm dilated; Parker et al (1995) included patients who were < 2 cm dilated. The testing timeframe and degree of cervical dilation may both affect applicability of results to the targeted population.

Table 12 Characteristics of included studies providing evidence for the use of point-of-care fetal fibronectin testing for women in suspected preterm labour

Author (year) Country	Study design	Patients (N)	Test characteristics	Study quality[a]
Benattar (1997) France	Prospective, non-consecutive patient enrolment Blinded comparison to reference standard	Patients with singleton or twin gestations and uterine contractions Intact membranes and cervical dilation < 3 cm Gestational age 24–36 weeks (124)	Sample from exocervix or posterior fornix using a solid immunogold assay (single test)	Level III-1 P2, Q2 *Applicability:* Unknown/obsolete fibronectin test Timeframe of testing *Quality:* Non-consecutive enrolment
Parker (1995) Australia	Prospective, non-consecutive patient enrolment Blinded comparison to reference standard Apr 1994–Dec 1994	Patients with singleton gestations patients and threatened preterm labour diagnoses Intact membranes and cervical dilation < 2 cm Gestational age 20–34 weeks (36)	Sample from the exocervix or posterior fornix using the Fetal Fibronectin Membrane Immunoassay™ (single test)	Level III-1 P2, Q2 *Applicability:* Unknown/obsolete fibronectin test Cervical dilation < 2 cm Timeframe of testing *Quality:* Non-consecutive enrolment
Senden (1996) Scotland	Prospective, non-consecutive patient enrolment Blinded comparison to reference standard	Patients with singleton gestations and uterine contractions Intact membranes and cervical dilation < 4 cm Gestational age 25–35 weeks (25)	Sample from the posterior fornix using the Fetal Fibronectin Membrane Immunoassay™ (single test)	Level III-1 P2, Q2 *Applicability:* Unknown/obsolete fibronectin test Cervical dilation < 4 cm Timeframe of testing *Quality:* Non-consecutive enrolment
Tsoi (2006) UK and South Africa	Prospective, non-consecutive patient enrolment Blinded comparison to reference standard Feb 2002–June 2003	Patients with singleton gestations and uterine contractions Intact membranes and cervical dilation < 3 cm Gestational age 24–36 weeks (195)	Sample from the endocervix or posterior fornix using the Fetal Fibronectin Membrane Immunoassay™ (single test)	Level III-1 P2, Q2 *Applicability:* Unknown/obsolete fibronectin test Timeframe of testing *Quality:* Non-consecutive enrolment

[a] According to criteria outlined in **Table 7**, **Table 8** and **Appendix G.**
Note: In this current review threatened preterm labour is termed suspected preterm labour.

A summary of the sensitivity, specificity, predictive values and diagnostic accuracy of each study is presented in **Appendix C**.

Summary statistics [2]

A summary of the diagnostic accuracy of point-of-care fetal fibronectin testing is presented as summary receiver-operating characteristic (SROC) curves for the outcome of preterm delivery within seven days of testing (**Appendix C**). The area under the curve (AUC) was 0.91 for the unweighted SROC curve, and 0.88 for the weighted (inverse variance) SROC curve. A perfect test is indicated by AUC equal to 1 (MSAC, 2005). Neither SROC curve detected heterogeneity in the test threshold.

The Littenberg-Moses regression method was used to examine the impact of cervical dilation, gestational age and presenting symptoms of the diagnostic accuracy of fetal fibronectin. None of these factors were found to have a significant effect on diagnostic accuracy.

Because heterogeneity was not detected by SROC curves, a summary diagnostic odds ratio (DOR) was also calculated. The summary DOR was 22.22 (95% CI: [9.20, 53.65]). According to the guidelines for the assessment of diagnostic technologies (MSAC, 2005) the magnitude of DOR > 1 reflects the strength of the technology to diagnose a condition.

Forest plots are presented for the positive and negative likelihood ratios for the outcome of preterm delivery with seven days of point-of-care fetal fibronectin testing. Results from both the random and fixed effect models are presented since the positive likelihood ratio data set was heterogenous. The summary likelihood ratios for a positive result were 3.56 (95% CI: [2.90, 4.36]) for a fixed effect model (**Figure 8**), and 4.64 (95% CI: [2.29, 9.40]) for a random effect model (**Figure 9**). The summary likelihood ratio for a negative result was 0.21 (95% CI: [0.11, 0.40]) using a fixed effects model (**Figure 10**). The guidelines for the assessment of diagnostic technologies (MSAC 2005) indicate that a positive likelihood ratio > 5 and a negative likelihood ratio < 0.2 provide strong diagnostic evidence for the value of a test.

[2] The data set was too small to reliably calculate summary diagnostic measures for the outcomes of preterm delivery within 14 days of testing, preterm delivery before 34 weeks gestation and preterm delivery before 37 weeks gestation.

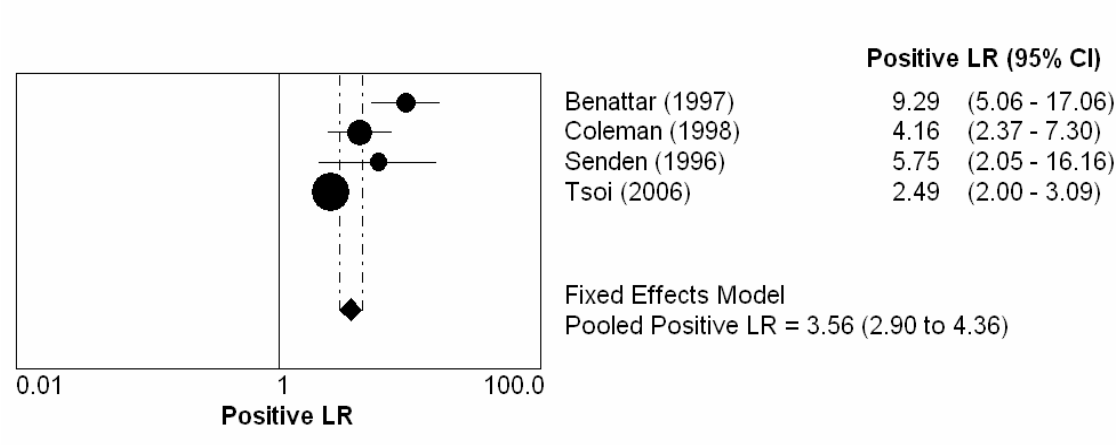

Figure 8 **Summary positive likelihood ratios (fixed effects) for the diagnostic accuracy of point-of-care fetal fibronectin testing among women in suspected preterm labour for assessment of preterm delivery risk within seven days of testing**

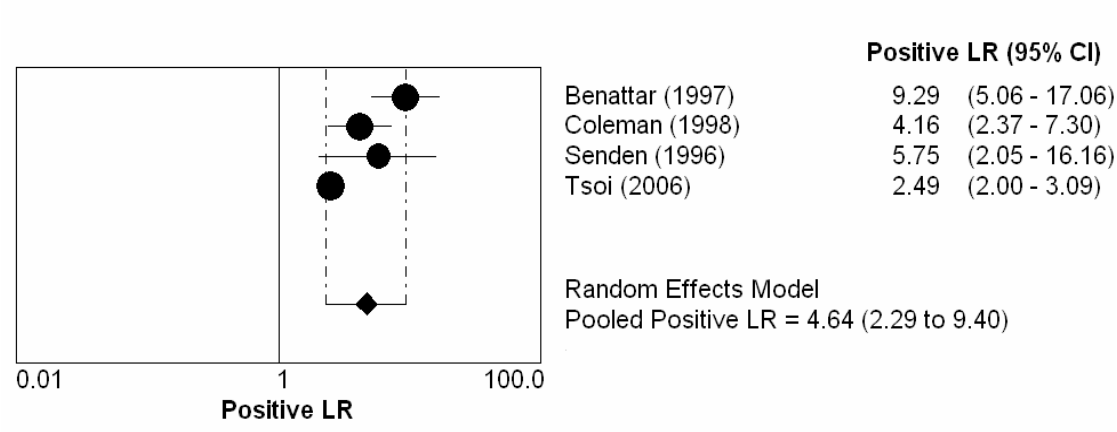

Figure 9 **Summary positive likelihood ratios (random effects) for the diagnostic accuracy of point-of-care fetal fibronectin testing among women in suspected preterm labour for assessment of preterm delivery risk within seven days of testing**

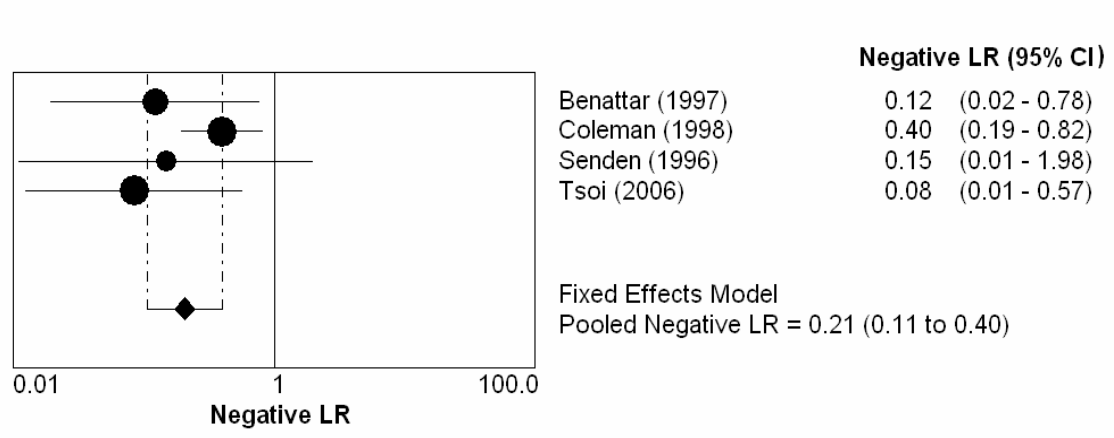

Figure 10 **Summary negative likelihood ratios (fixed effects) for the diagnostic accuracy of point-of-care fetal fibronectin testing among women in suspected preterm labour for assessment of preterm delivery risk within seven days of testing**

The summary diagnostic measures indicated that negative point-of-care fetal fibronectin test results to predict preterm labour in women where it is suspected, provides moderate diagnostic value to assess risk of preterm delivery within seven days of testing. The quality and applicability of the included studies should be considered when interpreting the summary values.

Asymptomatic pregnant women at high risk of preterm delivery

The literature review identified five studies that provided diagnostic performance of fetal fibronectin testing relative to current clinical practice in asymptomatic pregnant women at high risk of preterm delivery. Of these, two studies evaluated the diagnostic accuracy of point-of-care fetal fibronectin testing; and three evaluated the diagnostic accuracy of pathology-based fetal fibronectin testing. There were no studies that provided information about the incremental or replacement diagnostic value of fetal fibronectin testing relative to cervical ultrasound in asymptomatic pregnant women at high risk of preterm delivery.

Pathology testing

Literature searching identified three studies that were classified as medium quality and limited applicability which investigated the diagnostic accuracy of fetal fibronectin pathology-based testing without cervical ultrasound in asymptomatic pregnant women at high risk of preterm delivery (Leeson et al 1996, Nageotte et al 1994, Morrison et al 1996). Characteristics of these studies are presented in **Table 13**. The studies applied designs that were blinded and prospective with non-consecutively enrolled patient cohorts. The risk factors in these studies are appropriate to the target population with the exception that they included a small number of multiple gestations in the patient groups.

The applicability of these studies is limited by the use of fetal fibronectin tests not currently available in Australia. The studies by Leeson et al (1996) and Nageotte et al (1994) included patients tested after 33 weeks gestation, which is outside of the timeframe for this assessment's target population.

Table 13 Characteristics of included studies providing evidence for the use of pathology-based fetal fibronectin testing among asymptomatic pregnant women at high risk of preterm delivery

Author (year) Country	Study design	Patients (N)	Test characteristics	Study quality[a]
Leeson (1996) UK	Prospective, non-consecutive patient enrolment Blinded comparison to reference standard Jul 1992–Feb 1994	Patients with singleton or multiple gestations and history of prior spontaneous preterm birth, uterine malformation or cervical sutures Gestational age 24–34 weeks (42)	Sample from the posterior fornix using the Fetal Fibronectin Membrane Immunoassay™ (2 week intervals)	Level III-1 P2, Q2 *Applicability:* Unknown/obsolete fibronectin test Timeframe of testing *Quality:* Non-consecutive enrolment
Morrison (1996) USA	Prospective, non-consecutive patient enrolment Blinded comparison to reference standard	Patients with singleton or multiple gestations, with history of prior spontaneous preterm birth, uterine malformation or history of second trimester abortions Gestational age 26–28 weeks (85)	Sample from the exocervix using an enzyme-linked immunoassay (single test)	Level III-1 P2, Q2 *Applicability:* Unknown/obsolete fibronectin test *Quality:* Non-consecutive enrolment
Nageotte (1994) USA	Prospective, non-consecutive patient enrolment Blinded comparison to reference standard	Patients with singleton, twin or triplet gestations and history of prior spontaneous preterm birth, uterine malformation or cervical sutures Gestational age 24–34 weeks (87)	Sample from the exocervix or posterior fornix using the Fetal Fibronectin Membrane Immunoassay™ (1 week intervals)	Level III-1 P2, Q2 *Applicability:* Unknown/obsolete fibronectin test Timeframe of testing *Quality:* Non-consecutive enrolment

[a] According to criteria outlined in **Table 7**, **Table 8** and **Appendix G**.

A summary of the sensitivity, specificity, predictive values and diagnostic accuracy for each of these studies is presented in **Appendix C**.

Summary diagnostic measures of pathology-based fetal fibronectin testing accuracy in asymptomatic women at high risk of preterm delivery could not be calculated reliably because of the small body of medium quality and limited applicability studies. Therefore, no conclusions were made about the diagnostic accuracy of pathology fetal fibronectin testing with or without cervical ultrasound.

Point-of-care testing

Studies by Bittar et al (1996) and Paternoster et al (2000); categorised as low quality and limited applicability, investigated the diagnostic accuracy of fetal fibronectin point-of-care testing without cervical ultrasound in asymptomatic pregnant women at high risk of preterm delivery. The characteristics of these studies are presented in **Table 14**.

Bittar et al (1996) enrolled patients on the basis of histories of previous preterm births, presence of a cervical cerclage or uterine malformation. Paternoster et al (2000) enrolled patients with a much wider range of risk factors, including pre-eclampsia, placenta previa and gestational hypertension. The effect these risk factors may have on determining preterm delivery among high risk asymptomatic patients was unclear.

The applicability of these studies is limited by their use of fetal fibronectin tests not currently available in Australia. Bittar et al (1996) included patients tested outside the timeframe for the target population. Results reported by Paternoster et al (2000) have limited applicability due to imprecise reporting of sampling intervals for fetal fibronectin testing.

Table 14 Characteristics of included studies for the use of point-of-care fetal fibronectin testing among asymptomatic pregnant women at high risk of preterm delivery

Author (year) Country	Study design	Patients (N)	Test characteristics	Study quality[a]
Bittar (1996) Brazil	Prospective, non-consecutive patient enrolment Unblinded Jan 1994–Jan 1995	Singleton gestation patients with a previous preterm birth, cervical cerclage, or uterine malformation Gestational age 24–34 weeks (102)	Sample from exocervix using an solid immunogold assay (2 week intervals)	Level III-2 P2, Q3 *Applicability*: Unknown/obsolete fibronectin test Timeframe of testing *Quality*: Non-consecutive enrolment Unblinded
Paternoster (2000) Italy	Non-consecutive patient enrolment Unblinded	Singleton or multiple gestation patients with a previous preterm birth, cervical cerclage, uterine malformation, history of second trimester abortions, placenta previa, gestational hypertension, intrauterine growth restriction, polydramnios, pre-eclampsia Gestational age 24–34 weeks (120)	Sample from the vagina using the Fetal Fibronectin Membrane Immunoassay™	Level III-2 P2, Q3 *Applicability*: Unknown/obsolete fibronectin test Unknown sampling interval *Quality*: Non-consecutive enrolment Unblinded

[a] According to criteria outlined in **Table 7**, **Table 8** and **Appendix G**.

A summary of the sensitivity, specificity, predictive values and diagnostic accuracy for each of these studies is presented in **Appendix C**.

Summary diagnostic measures of the accuracy of point-of-care fetal fibronectin testing of asymptomatic women at high risk of preterm delivery could not be calculated reliably because of the small body of poor quality and limited applicability studies. Therefore, no conclusions were made about the diagnostic accuracy of point-of-care fetal fibronectin testing with or without cervical ultrasound.

Patient management

Randomised controlled trials

The literature review identified four randomised controlled trials (RCTs) that reported the effects of fetal fibronectin testing to predict preterm labour on patient management (Grobman et al 2004, Lowe et al 2004, Nguyen et al 2002, Plaut et al 2003). All studies were conducted in North American settings, and did not apply to the Australian setting.

The low levels of treatment reported in the current clinical practice arms of these trials are a major deficit area. This contrasts directly with Australian standard care under which almost all symptomatic patients are treated (advisory panel advice). The trial characteristics and primary findings of these RCTs are presented in **Appendix D**.

Non-randomised studies

There were six studies identified that provided limited information about change in patient management following fetal fibronectin testing (Abenheim et al 2005, Foxman et al 2004, Joffe et al 1999, Musaad et al 2005, Parry et al 2006, Watson et al 1998). All six studies included patients with suspected preterm labour symptoms. No studies were identified that examined the effect of fetal fibronectin testing on patient management in asymptomatic women at high risk of preterm delivery.

Quality and applicability

The study by Foxman et al (2004) included a physician survey that examined reasons for requesting fetal fibronectin tests, and sought information about therapies considered before fetal fibronectin tests were ordered. This study applied non-consecutive patient enrolment; and gestational age at testing was outside the target population's timeframe. Analysis was based on a small subgroup of patients for whom both clinical data and survey results were available. Patient population and fetal fibronectin test characteristics reporting was inadequate and extrapolation between reported results and diagnostic accuracy results were imprecise. The study was excluded from this review.

The remaining five studies were historical case controls that provided very limited patient management evidence. These studies were included because more robust evidence was scant.

Little insight into the potential change in management following the introduction of fetal fibronectin testing is provided by Abenheim et al (2005) and Joffe et al (1999). This is chiefly because the patient population analysed included patients normally considered ineligible for fetal fibronectin testing. Inadequate patient characteristics reporting by Parry et al (2006) meant that applicability to the target population could not be evaluated with certainty.

Consequently, the studies by Abenheim et al (2005), Joffe et al (1999), Parry et al (2006) and Foxman et al (2004) were not included in this review. Results of these studies are summarised in **Appendix D**.

Studies by Musaad et al (2005) and Watson et al (1998) were conducted in New Zealand and Australian settings respectively. Although they were categorised as lower quality studies (historical case control), they had the highest applicability among the identified patient management studies. These studies each compared management of patients in suspected preterm labour at a time when fetal fibronectin testing was available, to a stage immediately before the test's introduction. Study characteristics are provided in **Table 15**.

Musaad et al (2005) used the currently available TLI(IQ)^{TM} system in a New Zealand patient population who correspond with the target population (intact membranes, cervical dilation < 3 cm, gestational age 24–34 weeks). The prevalence of preterm birth before 37 weeks gestation (30–40%) is similar to the study populations described in the diagnostic accuracy section. A hospital protocol was introduced concomitantly with fetal

fibronectin testing for this study. The protocol stipulated that patients who were fetal fibronectin positive were to be admitted to hospital and treated with nifedipine (tocolytic), antibiotics and corticosteroids. Patients with negative results were discharged and scheduled for follow-up within one week. Implementation of this protocol would have influenced patient management so results should be interpreted cautiously.

Watson et al (1998) conducted their study in Australia and used the Fetal Fibronectin Membrane Immunoassay™—a test that is no longer available in this country. This study recruited a patient population that corresponded with the target population—intact membranes, cervical dilation < 3 cm, gestational age 25–34 weeks. The prevalence of preterm birth varied from 44 per cent among historical controls, to 18 per cent following introduction of fetal fibronectin testing. The difference, however, was not significant. A protocol to manage preterm labour was introduced in conjunction with fetal fibronectin testing in this study. According to this protocol, patients who were fetal fibronectin positive were treated with tocolytics (Indocid suppository or salbutamol infusion), corticosteroids (betamethasone), vitamin K and narcotic analgesia (as needed). Fetal fibronectin negative patients were treated with corticosteroids, vitamin K and narcotic analgesia (as needed). The results of this study must be understood within the context of the protocol introduction.

Table 15 Characteristics of studies included in the assessment of fetal fibronectin testing on patient management

Author (year) Country	Study design	Patients (N)	Test characteristics
Musaad (2005) New Zealand	Historical case-control	Patients with singleton or twin gestations and symptoms of threatened preterm labour Intact membranes and cervical dilation < 3 cm Gestational age 24–34 weeks Prevalence of preterm birth (< 37 weeks): Cases 40% (30) Controls 30% (30)	Sample from the exocervix or posterior fornix using the TLI(IQ)™ system (single test)
Watson (1998) Australia	Historical case-control Case recruitment: July 1996–June 1997	Patients with unspecified gestations and symptoms of threatened preterm labour Intact membranes and cervical dilation < 3 cm Gestational age 25–34 weeks Prevalence of preterm birth (< 37 weeks): Cases 17.6% (17) Controls 43.8% (32)	Sample from the exocervix or posterior fornix using the Fetal Fibronectin Membrane Immunoassay™ (single test)

Note: In this current review threatened preterm labour is termed suspected preterm labour.

Changes in patient management resulting from the introduction of fetal fibronectin testing reported by Musaad et al (2005) and Watson et al (1998) are provided in **Table 16**.

Musaad et al (2005) noted a reduction of 40 per cent and 60 per cent respectively for tocolytics and corticosteroid usage when fetal fibronectin was introduced. Watson et al (1998) noted a 70 per cent reduction in use of tocolytics. Musaad et al (2005) reported a non-significant reduction in the average length of hospital stay (approximately 0.7 days) consistent with the introduction of fetal fibronectin testing. No significant differences in *in utero* transfers were reported consistent with introduction of fetal fibronectin testing

(Musaad et al 2005). It is noted that the average length of stay for fetal fibronectin positive patients reported by Musaad et al (2005) was shorter than before the introduction of fetal fibronectin testing. It is not clear whether this effect was caused by the small sample size or a change in suspected preterm labour patient management.

Watson et al (1998) reported that 94 per cent of patients were treated with tocolytics and corticosteroids in the period before fetal fibronectin testing became available. This is comparable with treatment received by fetal fibronectin positive patients. It was reported that two patients in the study, one who refused treatment, and another whose baby was a footling breech presentation, skewed the result.

Table 16 Results of included studies in the assessment of fetal fibronectin testing on patient management

Author (year)	Preterm birth definition	Study arm	Tocolytic usage n/N (%)	Corticosteroid usage n/N (%)	Mean length of stay (days)	Transfers n/N%
Musaad (2005)	Unclear	Historical control	22/30 (73.3)	29/30 (96.7)	2.7 ± 2.3	1/30 (3.3)
		fFN positive	8/8 (100.0)	8/8 (100)	2.5 ± 1.6	1/8 (12.5)
		fFN negative	2/22 (9.1)	3/22 (13.6)	1.77 ± 1.34	0/22 (0.0)
Watson (1998)	Included medically indicated birth	Historical control	30/32 (93.8)	30/32 (93.8)	–	–
		fFN positive	3/3 (100.0)	3/3 (100.0)	–	–
		fFN negative	1/14 (7.1)	14/14(100.0)	–	–

Abbreviation: fFN, fetal fibronectin

These studies provide applicable, if limited, quality evidence demonstrating changes in patient management from introduction of fetal fibronectin testing. These quality issues mean that the degree of change in patient management, and any resulting value associated with fetal fibronectin testing in clinical decision making, remain uncertain.

Treatment effectiveness

Treatment effectiveness evidence relating to patients in suspected preterm labour was not examined. The fetal fibronectin diagnostic test is intended to reduce unnecessary treatment, not to identify new cases, in this population. Current Australian clinical practice is to treat almost all patients who present with symptoms of preterm labour (expert opinion from the advisory panel). It is therefore unlikely that use of this test would detect additional patients who would otherwise remain untreated. Introducing fetal fibronectin testing would be unlikely to substantially decrease the effectiveness of treatments currently used to manage preterm labour. There is evidence that existing therapies are sufficient to effectively manage preterm labour.

Insufficient diagnostic accuracy and changes in patient management evidence concerning asymptomatic patients at high risk of preterm delivery meant that treatment effectiveness was not examined for this group.

What are the economic considerations?

Summary

The financial impact of fetal fibronectin testing for women in suspected preterm labour for Medicare Australia is estimated at between $1.66 million and $3.04 million per year. The total costs for Medicare Australia would depend on the combination of point-of-care and pathology testing performed in practice.

The estimated savings for other healthcare funders managing patients in suspected preterm labour are between $12 million and $16 million per year. This saving would be driven by reduction in hospital admissions for women with true negative fetal fibronectin test results.

Some uncertainty remains about potential savings associated with fetal fibronectin testing for women in suspected preterm labour—savings would be reduced where some women who test negative for fetal fibronectin were admitted to hospital. In situations where women were admitted before fetal fibronectin testing was performed, hospitalisation costs would not be avoided, but could be reduced as a consequence of shorter stays.

The presented economic analyses do not represent potential savings from a societal perspective, such as child care costs for siblings. Cost savings resulting from fetal fibronectin testing could potentially be underestimated.

There was insufficient diagnostic accuracy and patient management evidence to conduct economic analyses relating to asymptomatic patients at high risk of preterm delivery.

Review of the literature identified five studies conducted in the Australian setting that focused on the socio-economic costs associated with infants born before full term, resource utilisation and use of fetal fibronectin testing for preterm labour (Giles et al 2000; Gill 2001; Ni Chuileannain et al 1998; Parker et al 1995; Watson et al 1998). Studies comparing fFN testing with historical case-control groups are scant. No study describing the economic impact of fetal fibronectin testing or its cost-effectiveness in Australia was identified.

Gill (2001) assessed the socio-economic impact of preterm delivery in Australia, focussing on costs associated with infants born before full term. In 1998, hospital expenditure for neonatal care in NSW was reported at $145 million. This figure does not

include costs of treating false or preterm labour or indirect costs for post-neonatal treatment of extremely low birth weight infants or their mothers.

The description of resource utilisation associated with fetal fibronectin testing in Australia was based on a blinded prospective study by Parker et al (1995). This study included 36 women in suspected preterm labour before 34 weeks gestation in a tertiary referral hospital. A third (33%, 12/36) of patients was transferred from metropolitan or country hospitals to secure access tertiary neonatal care facilities, if necessary. Almost a third (31%, 11/36) of the 36 women tested positive, and the remainder (69%, 25/36) tested negative for fetal fibronectin. Steroids were administered to all women who tested positive for fetal fibronectin (100%, n = 11), and to 80 per cent (n = 20) of women who tested negative. Tocolytics were administered to 73 per cent (n = 8) versus 32 per cent (n = 8), respectively. The difference in use of tocolytics was found to be significant ($p = 0.03$). The study does not indicate existence of a historical control group.

Ni Chuileannain et al (1998) reported results of a subsequent unblinded study performed in the same centre as Parker et al (1995). This retrospective audit examined fetal fibronectin testing in 70 women with singleton gestations and preterm labour symptoms before 34 weeks gestation. The study's aims were to establish confirmation of the results reported by Parker et al (1995) and to assess if knowledge of the test results influenced patient management. The study does not indicate existence of a historical control group.

Ni Chuileannain et al (1998) reported that 20 women tested positive for fetal fibronectin and 50 tested negative. A significant proportion of the study population (40%) was transferred from other hospitals; 25 per cent of these women returned positive fetal fibronectin test results and 75 per cent tested negative. Corticosteroids were administered to all women who tested positive for fetal fibronectin, and to 29 per cent who tested negative. Women who had glucocorticoid treatment initiated before referral and fetal fibronectin testing were excluded from this analysis. Based on fetal fibronectin test results, tocolytic treatment that was running on arrival at the hospital was ceased for two women who tested positive (2/4), and for two other women who tested negative (2/8). Overall, tocolytic treatment was administered more often for women who tested positive for fetal fibronectin than for women who tested negative (35% vs 12%).

Antenatal hospital stays were reported to be markedly, but not significantly, shorter for women who tested negative for fetal fibronectin than for women whose results were positive (mean: 45 vs 70 hours, median: 36 vs 48 hours) (Ni Chuileannain et al 1998). Women who tested positive for fetal fibronectin and delivered on admission were not included in the calculation. Of women who tested negative for fetal fibronectin, 44 per cent were discharged from hospital within 24 hours, whereas 15 per cent of those who tested positive were discharged within 24 hours. The authors concluded that clinicians aligned treatment decisions to fetal fibronectin test outcomes.

The strong negative predictive value of fetal fibronectin testing that guides treatment of women with preterm labour was examined in a small comparative study by Watson et al (1998). Results showed that 20 per cent (n = 8) of the fetal fibronectin group received tocolytics, compared with 100 per cent (n = 32) of the historical control group. This difference was found to be significant ($p < 0.0001$).

Giles et al (2000) conducted a study reporting socio-economic costs for infants born before full term in an Australian setting. The study included an audit performed between June 1996 and January 1998 that assessed the effect and associated costs of fetal

fibronectin testing on the number of admissions to a NSW tertiary hospital. In all nine hospitals and referral units included in the audit, routine fetal fibronectin testing was performed for women (n = 151) admitted for preterm labour between 24 and 34 completed weeks gestation. Of all women who tested positive for fetal fibronectin at referral units, 88 per cent (n = 29/33) were referred to the tertiary care hospital, compared with only 10 per cent (n = 7/65) of women who tested negative for fetal fibronectin. Transport cost savings were calculated to be $30,297 that would have been otherwise expended if the remaining 58 women required transfers to the tertiary care facility. (The distances between the tertiary centre and referring units were between 15 and 814 km). Details of cost calculations and underlying unit cost data were not provided.

Giles et al (2000) found that the standard treatment protocol for preterm labour was a 24-hour admission for tocolysis and corticosteroids administration. This included an admission averaging seven days to the antenatal ward before transfer to the referring unit. A further cost saving of $153,120 could have been made by avoiding admission of 58 women who were transferred to the primary referral hospital. The average length of stay was 9.9 days for fetal fibronectin positive patients vs 2.3 days for fetal fibronectin negative patients. Shorter hospital stays were calculated at $2970 per patient.
Cost calculation details were not provided. Transfers from the nine rural hospitals to the primary referral hospital were reported to be reduced by 51 per cent between the time figures were established in 1996 and re-measurement in 1998.

Health economic analyses relating to fetal fibronectin testing for management of preterm labour were identified for Canada (Mozurkewich et al 2000; Abenheim et al 2005), Mexico (Garcia et al 2004), New Zealand (Musaad et al 2005) and the USA (Joffe et al 1999; Sullivan et al 2001) (**Appendix E**). These studies are considered to have limited applicability to the Australian setting—treatment patterns and reimbursement frameworks differ and resulting economic assessments may be inaccurate.

As discussed elsewhere, results from fetal fibronectin tests do not change delivery outcomes, eliminating need for cost-effectiveness or cost-benefit assessments.
A cost minimisation analysis for the current clinical pathway versus the proposed pathway for fetal fibronectin testing is presented because evidence supports change in patient management pathways when the fetal fibronectin test is applied.

Patient management cost

Test costs

The Adeza Biomedical TLI(IQ)^{TM} sample cassette test cost was quoted at $180 and does not include additional costs for calibration, control tests and labour. A separate calculation of costs to Medicare is also presented.

Fetal fibronectin test costs were calculated separately for provision as pathology-based (**Table 17**) or point-of-care tests (**Table 18**). It was assumed that the Adeza QuikCheck fFN^{TM} system would be used when provided as point-of-care test, and the Adeza Biomedical TLI(IQ)^{TM} system used when test samples were sent to a pathology laboratory for analysis. Medicare Australia does not generally fund biochemical testing outside accredited pathology laboratories. **Table 17** provides an estimate of test costs should fetal fibronectin testing be listed on the MBS.

Table 17 Fetal fibronectin test costs (when performed as pathology-based test)

	Resource	Unit cost	Source	Comment
Reagent costs				
A	Cassette kits (26)	$4680 / 26 = $180	Applicant	
B	Calibration kit (1)	($160)	Applicant	Re-usable, unlimited use, therefore no costs per test considered
C	Control kit (1) *)	$150 / (12*26) = $0.48	Applicant / own research	Each pack of cassettes (26 tests) needs to be tested. The control kit allows 12 x tests
D	fFN specimen collection kit (8)	$0	Applicant	
E	Label roll for printer (400)	$60 / 400 = $0.15	Applicant	
F	Total reagent cost	$180.63	F = A + C + D + E	
Labour costs				
G	Scientist to run control for each batch	$0.08	Calculated	Once per batch (1/26) * 4 minutes * $30.25/hr
H	Scientist to run calibration once a day (assumption)	$0.50	Calculated	Once per test * 1 minute * $30.25/hr
I	Scientist to process sample	$1.01	Calculated	Once per test * 2 minutes * $30.25/hr
J	Pathologist to advise	$1.89	Calculated	Once per test * 1 minute * $113.34/hr
K	Total labour cost	$3.48	K = G + H + I + J	
L	**Total test costs (pathology testing)**	$184.11	L = F + K	
M	**85% Medicare fee (pathology testing)**	**$215.41**	M = L * 1.17	17% margin added
N	**100% Medicare fee (pathology testing)**	**$253.43**	N=(M * 100%) / 85%	

Notes: Hospital scientist, 4th year, NSW Award, MicroPay job code 05.003.14: $999.60 pw +15% = $1149.54 / 38 hours a week = $30.25 per hour; APP: App 205,000 pa / (40 hours per week * 52 weeks) = $113.34 per hour.
Ref: http://www.health.nsw.gov.au/policies/ib/2006/pdf/IB2006_023.pdf and http://www.health.nsw.gov.au/jobs/empcond/awards/HREA/hospital-scientists.pdf
Reference: Salary for APP provided by advisory panel.

Table 18 Fetal fibronectin test costs (when performed as point-of-care test)

	Resource	Unit cost	Source	Comment
Reagent costs				
A	QuikCheck fFN (10)	$950 / 10 = $95	Applicant	
Labour costs				
B	Labour to process sample etc	$5.67	Calculated	Once per test * 3 minutes * $113.34/hr
C	**Total test costs (point-of-care testing)**	$100.67	C = A + B	
D	**85% Medicare fee (point-of-care testing)**	**$117.78**	D = C[a] 1.17	17% margin added
E	**100% Medicare fee (point-of-care testing)**	**$138.57**	E = (D[a] 100%) / 85%	

[a] 25 tests = $2212 as by July 2006; APP: App 205,000 pa / (40 hours per week * 52 weeks) = $113.34 per hour.

Fetal fibronectin tests performed using the Adeza Biomedical TLI(IQ)™ system, which requires an analyser as additional equipment, increases overall test costs. The costs for the analyser, consisting of a processing unit and printer ($5000) are not included in the presented cost calculation—an average number of tests performed using the equipment, and the number of years the equipment is in service, are required for a detailed breakdown of costs. These rates may differ between labs. Equipment costs are not covered by Medicare.[3]

Other costs

Hospital costs were calculated based on the most recently available public hospitals data (Round 8 of the National Hospital Cost Data Collection, 2003–2004). Previous hospital clinical profiles data indicate a very broad profile of major principal diagnoses for DRGs O60A Vaginal Delivery +Cscc and O60B Vaginal Delivery–Cscc—preterm delivery was the most frequent principal diagnosis in both. These DRGs were therefore considered when estimating hospital costs associated with preterm delivery. DRG O64A False Labour < 37 Wk/+Cscc was considered in relation to hospital admissions costs relating to false labour.

Drug treatment expenses are included in the DRG costs and were not considered separately.

Emergency attendance and transport fees charged by the Metropolitan Ambulance Service Victoria ($793.97) were used as a representative transport cost—the amounts reported by Giles (2000) were considered to be outdated. It was assumed that transport would be initiated by a hospital and not by a GP or patient. Costs would escalate when air ambulance transfer was required, but in the absence of detailed data for transport, was not considered.

Table 19 provides cost details for other medical and pharmaceutical services.

[3] Where one sample is processed per day (365 per year), the discounted equipment costs would be $4 per test, where two tests are processed per day (730 per year), the discounted equipment costs would be $2 per test (four year depreciation time, straight line depreciation, financing of $5160 (processing unit plus printer plus calibration kit) at 8.3 per cent over four years, no maintenance costs), discounted at 5 per cent per annum.

Table 19 Resources and unit costs (other than test costs)

Resource	Unit cost	Bearer	Source	Comment
Medical services				
Threatened premature labour (clinical history, vaginal examination)	$19.10 $17.90	MBS Patient	MBS 16502 or MBS 16508 HIC statistics	Average cost per episode, weighted by number of provided services
Hospital services				
Hospitalisation for false labour < 37 weeks/+Cscc	$1628	Govt	DRGO64A National Hospital Cost Data Collection (Round 8, 2003–2004 v 5.0)	Average cost per episode Public hospitals only
Hospitalisation for preterm labour (Vaginal delivery +/–Cscc)	$3809	Govt	DRGO60A[a] DRGO60B[a] National Hospital Cost Data Collection (Round 8, 2003–2004 v 5.0)	Average cost per episode, weighted by number of separations Public hospitals only
Diagnostic and investigational services				
Cervical ultrasound	–	MBS		No MBS item number available
Allied health services				
Inter-hospital patient transfer	$793.97	Govt[b]	Metropolitan Ambulance Service Victoria (2006)	Emergency attendance and transport fee (ground transport)

[a] The clinical profiles of previous hospital data collections show a very broad profile of different major principal diagnoses for both the DRGs (O60A and O60B). However, preterm delivery was the most frequent principal diagnosis in both DRGs.
[b] Inter-hospital patient transfer costs are paid by the hospital initiating the transfer. Any cost of transfer to the initial hospital is borne by the patient or a third party insurer.
Abbreviation: MBS, Medicare Benefits Schedule

Management costs for women in suspected preterm labour

Costs are defined as price (unit costs) multiplied by the number of consumed units; it was therefore necessary to consider service provision frequency to derive costs.

Medical services

It was assumed that all women in suspected preterm labour contacted their GP or obstetrician before attending hospital. This assumption differs from clinical practice, but the error in costs resulting from this approach is smaller than it would be if assumed that all women would directly attend hospitals.

Hospitalisation

Nearly all women in Australia who are suspected of preterm labour are admitted to hospital (advisory panel advice). While this is standard care, only a small proportion of all women admitted to hospital deliver preterm. The remaining women are admitted to hospital in false labour; however, it is possible that preterm delivery may occur at later stages of gestation. It was necessary to estimate the number of women admitted to hospital for both conditions because costs for inpatient treatment for false labour differ from preterm delivery costs.

The following scenarios were considered to calculate patient management costs:

- When fetal fibronectin testing is not performed, all women presenting with symptoms of preterm labour are admitted to hospital.

- When the fetal fibronectin test is applied, the decision not to admit women to hospital is based on a negative test result (false negative + true negative). All other women who test positive are admitted to hospital, for either false labour (false positive test result) or for preterm delivery (true positive test result). Women who are not admitted to hospital in the first instance, but who have false negative test results, are considered as being admitted to hospital for preterm delivery.

The scenarios are also described in **Table 20**.

Table 20 Fetal fibronectin test results and hospital admissions

Women presenting with preterm labour	Pregnancy outcome (Action)	
Test result	**Preterm delivery**	**No preterm delivery**
Positive	True positive (Admitted for preterm delivery)	False positive (Admitted for false labour)
Negative	False negative (Not admitted / admitted for preterm delivery)	True negative (Not admitted, follow up as outpatient)

Based on the evidence presented in the diagnostic accuracy assessment, the prevalence of delivering within seven days after presenting in suspected preterm labour is 6.0 per cent and 10.1 per cent for pathology-based and point-of-care testing, respectively. This prevalence also represents the proportion of women obtaining true positive and false negative test results. Because fetal fibronectin testing does not alter pregnancy outcomes, the prevalence figures from all studies were averaged to establish an overall prevalence rate which was applied to the management of patients with and without fetal fibronectin testing (8.1%). The results for this scenario are shown in **Table 21**.

Table 21 Distribution of hospital admissions with and without fetal fibronectin testing

	Patient management		
	With fFN test (< 7 days)		Without fFN test
	Point-of-care	Pathology	
All women	100%	100%	100%
Prevalence of preterm delivery within 7 days (admission to hospital for preterm delivery)[a]	10.1%	6.0%	8.1%
True negative (no admission to hospital)	66.1%	78.1%	N/A
Remaining proportion (admission to hospital for false labour)	23.8%	15.9%	91.9%

[a] Fetal fibronectin testing does not alter pregnancy outcomes, therefore the prevalence figures from all studies were averaged to establish an overall prevalence rate.
Abbreviation: fFN, fetal fibronectin

Transportation

Data relating to the probability of being transported to hospital for preterm labour are scant. A small case-control study by Musaad (2005) reported transport probabilities of 3.3% (1/30 patients) whether or not the fetal fibronectin test was used (see **Table 16**). Study limitations mean that these results should be interpreted cautiously.

Total management costs per patient

Table 22 summarises patient management costs for the proposed service (fetal fibronectin test) and the comparator (current) pathway.

Overall, the fetal fibronectin test is associated with cost savings, regardless of whether the test is performed as a point-of-care test or in a pathology setting. The cost savings are driven by the significant reduction in hospital costs that offset costs of conducting fetal fibronectin testing.

Table 22 Patient management costs for suspected preterm labour (per episode)

Resource item	Unit cost	Number of units (Proportion of patients)		Total cost		Incremental costs of proposed service
		Proposed service	Comparator	Proposed service	Comparator	
Costs borne by MBS						
Threatened premature labour (consultation)	$19.10	1	1	$19.10	$19.10	$0
Fetal fibronectin test (point-of-care testing)	$138.57	1	0	$138.57	$0	$138.57
Fetal fibronectin test (pathology testing)	$253.43	1	0	$253.43	$0	$253.43
Total costs borne by MBS (point-of-care testing)						$138.57
Total costs borne by MBS (pathology-based testing)						$253.43
Costs borne by state government agencies						
Hospitalisation for false labour (point-of-care testing)	$1628	0.231 (23.1%)	0.919 (91.9%)	$376.07	$1496.13	$–1120.06
Hospitalisation for false labour (pathology testing)	$1628	0.159 (15.9%)	0.919 (91.9%)	$258.85	$1496.13	$–1237.28
Hospitalisation for preterm delivery (point-of-care testing)	$3809	0.101 (10.1 %)	0.081 (8.1%)	$411.37	$308.53	$76.18
Hospitalisation for preterm delivery (pathology testing)	$3809	0.06 (6.0%)	0.081 (8.1%)	$228.56	$308.53	$–79.99
Transport to other hospital	$794	0.033 (3.3%)	0.033 (3.3%)	$26.20	$26.20	$0
Total costs borne by state government agencies (point-of-care testing)						$–1043.88
Total costs borne by state government agencies (pathology-based testing)						$–1317.27
Costs borne by patients						
Threatened premature labour (consultation)	$17.90	1	1	$17.90	$17.90	$0
Total costs borne by patients						$0
Total incremental costs (point-of-care testing)						**$–905.32**
Total incremental costs (pathology-based testing)						**$–1063.84**

Asymptomatic pregnant women at high risk of preterm delivery

Lack of clinical assessment data meant that conclusions could not be made for asymptomatic pregnant women at high risk of preterm delivery. An additional epidemiological and economic literature search did not locate relevant population-based preterm labour and delivery occurrence data for the population in focus. Therefore, economic assessment for this patient group is not provided.

Resource allocation

Costs of procedures and outpatient treatment have been allocated to Medicare Australia. Other costs associated with treatment such as reagents, hospital admissions and transport, are borne by other healthcare sectors including public and private hospitals. Fetal fibronectin test funding provokes a significant decrease in overall patient management costs for state governments. **Table 23** provides a breakdown of future service costs for fetal fibronectin in the healthcare system should the test be listed by the MBS.

Table 23 Allocation of direct costs among healthcare funders should fetal fibronectin testing be listed by the MBS

Procedure	Medicare Australia costs	State government costs	Patient costs
Current management	$19.10	$1821.89	$17.90
fFN testing (point-of-care)	$157.67	$778.00	$17.90
fFN testing (pathology)	$272.53	$504.62	$17.90

Financial implications of a positive recommendation

Medicare Australia

Since Medicare Australia would meet the costs of outpatient consultations and the fetal fibronectin test, the financial impact calculation is based on the estimated number of those services.

The three year forecast of outpatient consultations relating to preterm labour is presented in **Figure 11**. The MBS items:

- 16502 Polyhydramnios, unstable lie, multiple pregnancy, pregnancy complicated by diabetes or anaemia, threatened premature labour treated by bed rest only or oral medication, requiring admission to hospital each attendance that is not a routine antenatal attendance, to a maximum of 1 visit per day

and

- 16508 (Pregnancy complicated by acute intercurrent infection, intrauterine growth retardation, threatened premature labour with ruptured membranes or threatened premature labour treated by intravenous therapy, requiring admission to hospital – each attendance that is not a routine antenatal attendance, to a maximum of 1 visit per day)

were summed to generate the total number of outpatient consultations for preterm labour. The best fit with historical data was achieved when an exponential smoothing

method was applied—a steady state forecast of 11,981 consultations per year (95% CI: [10979, 12983]).

It was assumed that fetal fibronectin tests (either point-of-care or pathology-based) are performed for each consultation for false labour. This uptake rate is likely to be an overestimation because the test would not be provided to all women. Exclusions would apply for:

- women presenting with evidence of ruptured membranes or cervical dilation > 3 cm
- gestational age or contraindications.

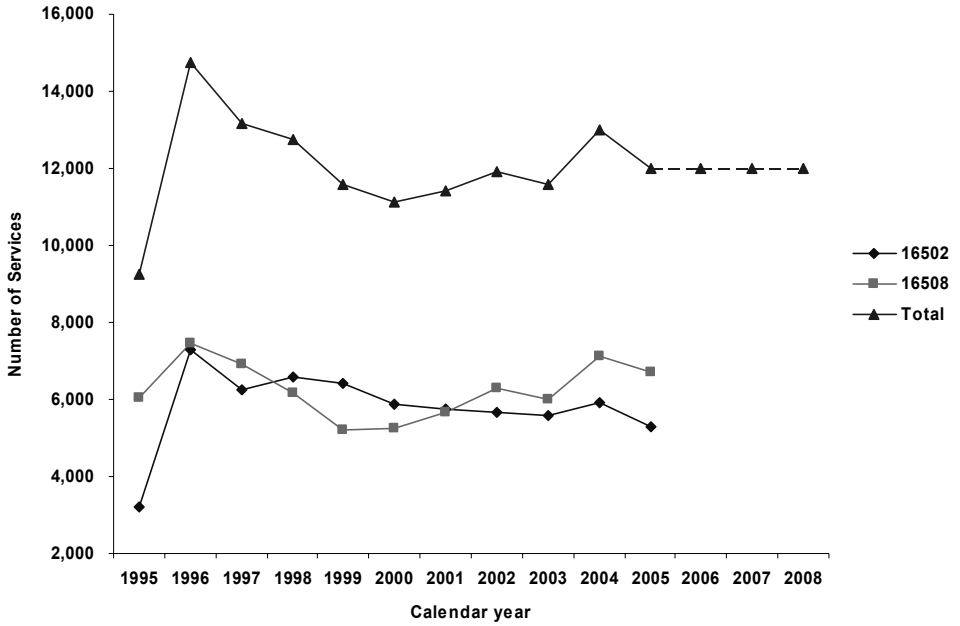

Figure 11 2006–2008 forecast of services provided by Medicare for preterm labour

Reference: Medicare Australia Stats online, www.medicareaustralia.com.au

The aggregated financial impact of increased funding for the fetal fibronectin test for Medicare Australia is shown in **Table 24** and **Table 25**.

Table 24 Aggregated financial impact of fetal fibronectin test funding to Medicare Australia, pathology-based testing

		Year 1	Year 2	Year 3	Reference
A	Number of consultations	11,981	11,981	11,981	**Figure 11**
B	Cost per consultation	$19.10	$19.10	$19.10	**Table 19**
C	Current annual costs	$ 228,800	$228,800	$228,800	= A * B
D	Number of fFN tests—based on consultations for preterm labour	11,981	11,981	11,981	= A
E	Cost per fFN test (pathology-based testing)	$253.43	$253.43	$253.43	**Table 17**
F	Annual costs fFN test (pathology-based testing)	$3,036,323	$3,036,323	$3,036,323	= D * E
G	Future annual costs (pathology-based testing)	$3,265,124	$3,265,124	$3,265,124	= C+F
H	Incremental costs (pathology-based testing)	$3,036,323	$3,036,323	$3,036,323	= G–C

Table 25 Aggregated financial impact of fetal fibronectin test funding to Medicare Australia, point-of-care testing

		Year 1	Year 2	Year 3	Reference
A	Number of consultations	11,981	11,981	11,981	**Figure 11**
B	Cost per consultation	$19.10	$19.10	$19.10	**Table 19**
C	Current annual costs	$ 228,800	$228,800	$228,800	= A * B
D	Number of fFN tests—based on consultations for preterm labour	11,981	11,981	11,981	= A
E	Cost per fFN test (point-of-care)	$138.57	$138.57	$138.57	**Table 18**
F	Annual costs fFN test (point-of-care)	$1,660,192	$1,660,192	$1,660,192	= D * E
G	Future annual costs (point-of-care)	$1,888,992	$1,888,992	$1,888,992	= C+F
H	Incremental costs (point-of-care)	$1,660,192	$1,660,192	$1,660,192	= G–C

Assuming that the fetal fibronectin test would reach 100 per cent uptake and was funded both as point-of-care and pathology tests, the financial impact for Medicare Australia would be in the range of $1.66 million to $3.04 million per year. The total costs for Medicare Australia, depending on the mix of point-of-care and pathology-based testing, are provided in **Figure 12**.

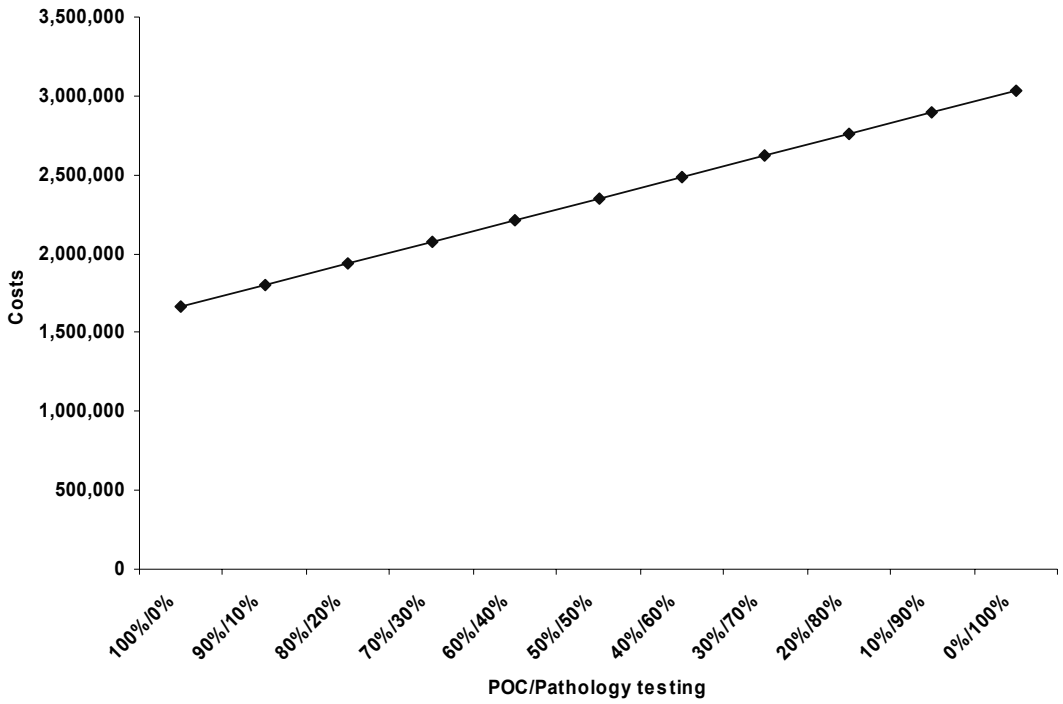

Figure 12 Budget impact for Medicare Australia, by point-of-care and pathology-based testing (100% uptake rate)

Assuming a purely hypothetical uptake rate of 80 per cent, the costs for Medicare Australia would be between $1.33 million and $2.43 million per year.

Hospitalisation savings

Because the fetal fibronectin test does not change pregnancy outcomes, the financial impact estimate is based entirely on the number of admissions for false labour, and how this rate would change should fetal fibronectin testing be funded.

The number of admissions for false labour is shown in **Table 26** (National Hospital Cost Data Collections). AR-DRG version 4.2 provided only one DRG for false labour (DRG O64Z), which did not distinguish by gestational age. However, the proportion of preterm false labour episodes can be estimated when considering the most recent data from round 8 of the National Hospital Cost Data Collection, using AR-DRG version 5.0, which splits false labour episodes by gestational age—DRG O64A False labour < 37 Wk/+Ccc and O64B False labour ≥ 37 Wk –Ccc. These data indicate an equal split between DRGs (O64A = 9451 episodes, O64B = 9403 episodes). Thus, half of all separations were previously considered preterm episodes for false labour.

Table 26 Separations and DRG costs for false labour

DRG code	Number of separations (sector) (average cost per DRG)						
	1997–1998	1998–1999	1999–2000	2000–2001	2001–2002	2002–2003	2003–2004
O64Z False labour (AR-DRG v4.2)	8811 (public) ($712)	14229 (public) ($971)	18671 (public) ($957)	17,257 (public) ($988)	17,581 (public) ($957)	19,433 (public) ($1097)	18,890 (public) ($1158)
	1254 (private) ($634)	1572 (private) ($1227)	1973 (private) ($717)	2470 (private) ($3134)	3556 (private) ($1449)	2707 (private) ($913)	Not available[a]
Considered as preterm false labour episodes (50%)	5033	7901	10,322	9864	10,569	11,070	10,799[b]

Source: National Hospital Cost Data Collections

[a] Data from the National Hospital Cost Data Collection (round 8, 2003–2004) are currently available for public but not for private hospitals.

[b] Last observation in 2002-2003 for private hospitals was considered for calculation.

A logarithmic function ($y = 3023.6*\ln(x) + 5682.8$, $r = 0.903$) appropriately describes the historic pattern of false labour episodes and was used to forecast the number of false labour episodes for the next three years (see **Figure 13**). It is important to note that the projected increase aligns with an increase expected for the overall number of preterm births when analysing data of the National Perinatal Statistics Unit (NPSU) (data not shown).

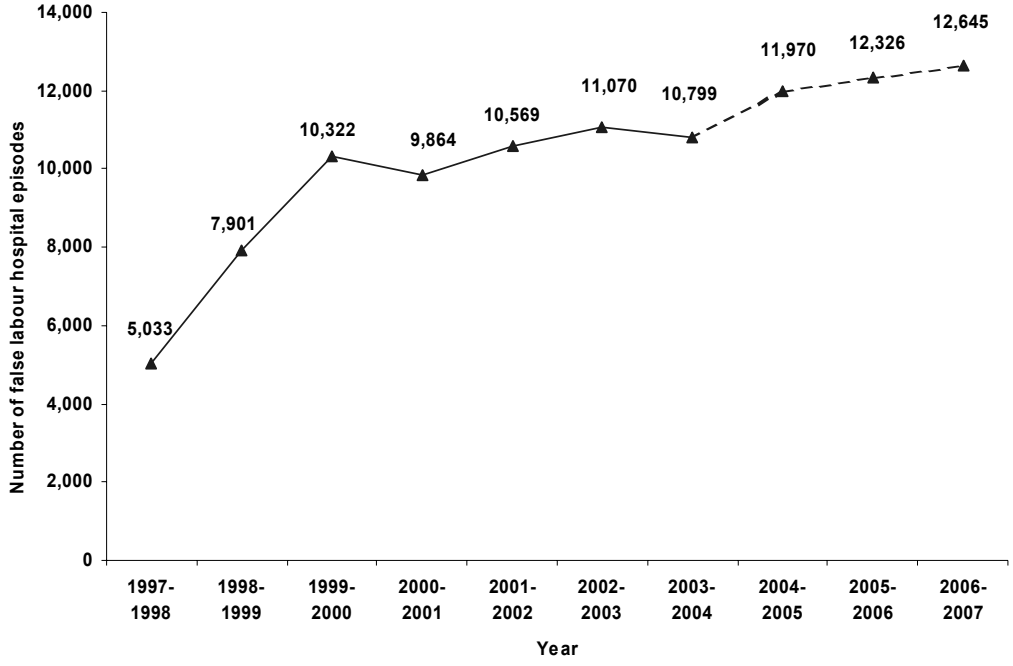

Figure 13 Historical and forecasted number of false labour hospital episodes

The medical and financial benefit of fetal fibronectin testing lies in identifying women who are not at risk of preterm delivery and do not require admission for false labour. The expected reduction in false labour consultations was based on the proportion of true negative test results for seven days after testing, assuming that these women were not admitted to hospital. This approach does not take into account that these women may have preterm deliveries later in their pregnancies.

The aggregated financial impact of increased fetal fibronectin testing funding for other healthcare funders is shown in **Table 27** and **Table 28**.

Table 27 Aggregated financial impact of fetal fibronectin test funding among other healthcare funders, pathology-based testing

		Year 1	Year 2	Year 3	Reference
A	Expected number of false labour admissions to hospital	11,970	12,326	12,645	**Figure 13**
B	Cost per false labour admission to hospital	$1628	$1628	$1628	**Table 19**
C	Current annual costs	$19,487,160	$20,066,728	$20,586,060	= A * B
D	True negative test results (not admitted to hospital) (pathology)	78.1%	78.1%	78.1%	**Table 21**
E	Remaining annual number of false labour episodes (pathology)	2621	2699	2769	= A * (1–D)
F	Future annual costs (pathology)	$4,267,688	$4,394,613	$4,508,347	= E * B
G	Incremental costs (pathology)	$–15,219,472	$–15,672,115	$–16,077,713	= F–C

Table 28 Aggregated financial impact of fetal fibronectin test funding for other healthcare funders, point-of-care testing

		Year 1	Year 2	Year 3	Reference
A	Expected number of false labour admissions to hospital	11,970	12,326	12,645	**Figure 13**
B	Cost per false labour admission to hospital	$1628	$1628	$1628	**Table 19**
C	Current annual costs	$19,487,160	$20,066,728	$20,586,060	= A * B
D	True negative test results (not admitted to hospital) (point-of-care)	66.1%	66.1%	66.1%	**Table 21**
E	Remaining annual number of false labour episodes (point-of-care)	4058	4179	4287	= A * (1–D)
F	Future annual costs (point-of-care)	$6,606,147	$6,802,621	$6,978,674	= E * B
G	Incremental costs (point-of-care)	$–12,881,013	$–13,264,107	$–13,607,386	= F–C

The savings for other healthcare funders are estimated at between $15 million and $16 million per year. These savings are driven by avoiding admissions to hospital for women with true negative fetal fibronectin test results. Again, it should be noted that if a mixture of point-of-care and pathology testing is to be funded, the resulting incremental savings are between $12 million and $16 million per year. These savings should be considered as overestimates if some women testing fetal fibronectin negative are admitted to hospital. Also women admitted to hospitals before fetal fibronectin testing may have shorter hospital stays and consequently lower costs. These scenarios, however, could not be evaluated using the current evidence.

The economic analyses presented do not include potential savings from a societal perspective (eg child care costs for other children); and thus, savings associated with fetal fibronectin testing could also be potentially underestimated.

Conclusions

Safety

An extensive literature search did not identify any safety data; however, risks to mothers and their babies are expected to be minimal, because the fetal fibronectin test sample is obtained with a cervicovaginal swab as part of a standard speculum examination.

Effectiveness

Diagnostic accuracy

The summary diagnostic measures indicate that a negative fetal fibronectin test result from either pathology-based or point-of-care testing provides moderate diagnostic value to identify patients not at immediate risk of preterm delivery. The limited quality and applicability of the included studies to Australian clinical practice should be considered when interpreting the results.

Due to both the quality and applicability of the diagnostic studies in asymptomatic pregnant women at high risk of preterm delivery it was inappropriate to make conclusions about the diagnostic accuracy of pathology-based or point-of-care fetal fibronectin testing.

Patient management

Based on the limited data available relating to patient management, the value of fetal fibronectin testing in clinical decision-making in Australia remains uncertain.

Treatment effectiveness

Treatment effectiveness was not examined for patients suspected of preterm labour. The fetal fibronectin diagnostic test is intended to reduce unnecessary treatment of women in false labour. It is unlikely that any new patients would receive treatment who would not otherwise if fetal fibronectin testing was introduced. It is unlikely that the introduction of fetal fibronectin testing would substantially decrease the effectiveness of treatments currently used to manage preterm labour. Treatment effectiveness was not examined in asymptomatic patients at high risk of preterm delivery because there was insufficient evidence of diagnostic accuracy and patient management.

Economic analyses

The financial impact for Medicare Australia of fetal fibronectin testing for women in suspected preterm labour is estimated at between $1.66 million and $3.04 million per year. The estimated savings for other healthcare funders is between $12 million and $16 million per year.

Some uncertainty remains about the potential savings associated with use of fetal fibronectin testing for women in suspected preterm labour. Savings would be lower if some women who test negative for fetal fibronectin were admitted to hospital. If women were admitted to hospitals before fetal fibronectin testing is performed, hospitalisation costs would not be avoided, but may be reduced as a consequence of shorter stays. Savings associated with fetal fibronectin testing could be potentially underestimated in the economic analyses presented; potential savings from the societal perspective are not included.

There was insufficient diagnostic accuracy and patient management evidence to support economic analysis of asymptomatic women at high risk of preterm delivery.

Recommendation

MSAC assessed the evidence for the use of fetal fibronectin testing in women who are at high risk of preterm labour to predict their risk of preterm delivery and the evidence pertaining to the use of fetal fibronectin testing for predicting preterm labour in women:

- who present with symptoms suggestive of preterm labour
- whose pregnancies are singleton or twin gestations
- who are at stages of pregnancy from 24 to 33 weeks 6 days gestation
- who present with intact amniotic membranes
- whose cervical dilatation is less than 3 cm.

MSAC determined that the test is safe but effectiveness has not been demonstrated.

MSAC does not support public funding for this test at this time.

– The Minister for Health and Ageing accepted this recommendation on 5 February 2007 –

Appendix A MSAC terms of reference and membership

MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness
- advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to AHMAC.

The membership of MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	Expertise or affiliation
Dr Stephen Blamey (Chair)	general surgery
Associate Professor John Atherton	cardiology
Professor Syd Bell	pathology
Dr Michael Cleary	emergency medicine
Dr Paul Craft	clinical epidemiology and oncology
Ms Catherine Farrell	Department of Health and Ageing representative
Dr Kwun Fong	thoracic medicine
Dr David Gillespie	gastroenterology
Dr Debra Graves	medical administrator
Professor Jane Hall	health economics
Professor John Horvath	Chief Medical Officer, Department of Health and Ageing
Dr Terri Jackson	health economics
Professor Brendon Kearney	health administration and planning
Associate Professor Frederick Khafagi	nuclear medicine
Dr Ray Kirk	health research
Associate Professor Donald Perry-Keene	endocrinology
Dr Ewa Piejko	general practice
Ms Sheila Rimmer	consumer health issues
Professor Ken Thomson	radiology
Dr Mary Turner	Australian Health Ministers' Advisory Council representative
Dr Douglas Travis	urology
Dr David Wood	orthopaedic surgery

Appendix B Advisory panel

Advisory panel for MSAC application 1103

Dr Ewa Piejko (Chair) MBBS, FRACGP General Practitioner Newport, Victoria	Member of MSAC
Professor Lesley Barclay AO PhD BA MEd RN RM FRCNA Distinguished Fellow ACMI Professor; Health Services Development, Co-Director of the Graduate School for Health Practice Darwin, NT	Nominated by the Royal College of Nursing
Professor Syd Bell MBBS, MD, FRCPA Area Director, Microbiology, South East Sydney Area Health Services Randwick, NSW	Member of MSAC
Dr Fiona Cullinane MD, MRCOG, MRCPI, FRANZCOG Consultant Obstetrician Royal Women's Hospital Carlton, Victoria	Nominated by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists
Dr Steven Kan MBBS, FRACGP General Practitioner Balcatta, WA	Nominated by the Royal Australian College of General Practitioners
Ms Diane Walsh BA DipEd Independent Consumer Representative Rapid Creek, NT	Nominated by the Consumers' Health Forum

Evaluators for MSAC application 1103

Dr Liesl Birinyi-Strachan BSc(Hons) PhD	M-TAG Pty Ltd, A unit of IMS Health
Mr Marc Bevan BSc(Hons)	M-TAG Pty Ltd, A unit of IMS Health
Ms Jolie Hutchinson BSc(Hons)	M-TAG Pty Ltd, A unit of IMS Health
Ms Antje Smala BAgEng(Hons) BEng(Hons)	M-TAG Pty Ltd, A unit of IMS Health

Appendix C Supplementary diagnostic accuracy data

Systematic reviews

Table 29 and **Table 30** present the characteristics and results extracted from included systematic reviews assessing the diagnostic accuracy of fetal fibronectin testing for predicting preterm labour.

Table 29 Characteristics of systematic reviews assessing the diagnostic accuracy of fetal fibronectin

Systematic review (year)	Research question	Search strategy (included studies)	Inclusion/exclusion criteria	Methodology	Comment[a]
AHRQ (2000)	What are the appropriate criteria for the diagnosis of preterm labour? How much positive or negative predictive value does the use of biologic markers add to clinical opinion in diagnosing preterm labour?	A detailed search strategy was described using Medline, EMBASE, International Pharmaceutical Abstracts, reference lists and grey literature Literature search was completed in 1999 Search terms included synonyms for premature labour combined with terms for biological markers (n = 16)	Studies with the following characteristics were included: pregnant women with signs and symptoms of preterm labour, the use of a diagnostic biological marker, and an assessment of preterm birth Articles in English, French and German included Studies were excluded for the following reasons: non-systematic review, < 40 subjects, wrong language, wrong patient group, wrong intervention, twin gestation	The literature search and data extraction were completed by independent reviewers with disagreements solved by third reviewer or discussion Results of included studies were individually summarised An assessment of the quality of included studies was undertaken Results were not meta-analysed	High quality Limited validity — included low-level diagnostic studies
Chien (1997)	To determine if cervicovaginal fetal fibronectin testing had clinical value in the prediction of preterm birth	A brief search strategy was described using Medline and reference lists Literature search was completed in 1996 Search terms included synonyms for pregnancy combined with terms for fetal fibronectin (n = 17)	Studies with the following characteristics were included: pregnant women symptomatic or asymptomatic for preterm delivery; cervicovaginal fetal fibronectin test < 37 weeks gestation; and an assessment of preterm birth No language restrictions Studies were excluded for the following reasons: non-relevant, wrong patient group, inadequate description of patient group, non-systematic review, wrong outcomes, duplicate publications	The literature search and data extraction were completed by independent reviewers with disagreements solved by third reviewer or discussion Results of included studies were individually summarised An assessment of the quality of included studies was undertaken Sources of heterogeneity were explored Results presented as pooled likelihood ratios	Medium quality — limited documentation and scope of the literature search Limited validity — included low-level diagnostic studies

Systematic review (year)	Research question	Search strategy (included studies)	Inclusion/exclusion criteria	Methodology	Comment[a]
Faron (1998)	To assess the cervicovaginal fetal fibronectin test to predict preterm delivery	A brief search strategy was described using Medline, conference proceedings and reference lists Literature search was completed in 1997 A description of the search terms was not presented (n = 29)	Studies with the following characteristics were included: prospective cohort study with women tested between 20–36 weeks gestation; fetal fibronectin analysed using the ELISA test with 50 ng/mL cut off; patients and physicians blind to test results; less than 20% of patients excluded from analysis No language restriction Studies were excluded for the following reasons: non-relevant, wrong outcomes, wrong diagnostic test, < 80% of enrolled women in final analysis, large proportion of patient tested before 20 weeks	The details of the literature search and data extraction procedures were unclear Results of included studies were individually summarised No assessment of quality was undertaken Results presented as pooled likelihood ratios Sources of heterogeneity were not explored Authors of included studies contacted for more information	Low quality — limited documentation and scope of the literature search — reporting of a number of methodology details is unclear Limited validity — included low-level diagnostic studies
Honest (2002)	To determine the accuracy with which a cervicovaginal fetal fibronectin test predicts spontaneous pre-term birth in women with or without symptoms of pre-term labour	A detailed search strategy was described[b] using Medline, EMBASE, Pascal, Biosis, Cochrane Library, Medion, National Research Register, SciSearch, conference proceedings and reference lists Literature search was completed in 2001 Search terms included terms for premature labour combined with terms for diagnostic tests that assess the risk of preterm delivery combined with diagnostic accuracy terms (n = 68)	Studies with the following characteristics were included: pregnant women, symptomatic or asymptomatic for preterm delivery; cervicovaginal fetal fibronectin test < 37 weeks gestation; known gestation at spontaneous birth; observational cohort design No language restriction Studies were excluded for the following reasons: non-relevant, wrong outcomes, non-systematic review, duplicate publication, unobtainable	The literature search and data extraction were completed by independent reviewers with disagreements solved by third reviewer or discussion Results of included studies were individually summarised An assessment of the quality of included studies was undertaken Sources of heterogeneity were explored Results presented as pooled likelihood ratios and SROC curves	High quality Limited validity — included low-level diagnostic studies

Systematic review (year)	Research question	Search strategy (included studies)	Inclusion/exclusion criteria	Methodology	Comment[a]
ICSI (2000)	To assess the diagnostic accuracy, safety and clinical value of fetal fibronectin in the risk assessment for preterm birth	No search strategy was described, Medline, PreMedline and reference lists were searched Unclear when literature search was completed A description of the search terms was not presented (n = ?)	Details of the inclusion/exclusion criteria were not reported	The details of the literature search and data extraction procedures were unclear A limited quality assessment was undertaken Results of included studies were individually summarised Results were not meta-analysed	Low quality — limited documentation and scope of the literature search — limited description of inclusion/exclusion criteria — reporting of a number of methodology details is unclear Limited validity — included low-level diagnostic studies
Lamont 2003	To prepare international clinical guidelines on the diagnosis, treatment and management of preterm labour	A brief search strategy was described using Medline, EMBASE, Biosis, Current Contents and Derwent Drug File Literature search was completed in 2001 Search terms included terms for fetal fibronectin combined with terms for cervical ultrasound (n = 6)	Details of the inclusion/exclusion criteria were not reported	The details of the literature search and data extraction procedures were unclear Results were not meta-analysed	Low quality — limited documentation of the literature search — limited description of inclusion/exclusion criteria — reporting of a number of methodology details is unclear Limited validity — included diagnostic studies of unknown quality

Systematic review (year)	Research question	Search strategy (included studies)	Inclusion/exclusion criteria	Methodology	Comment[a]
Leitich (1999)	To determine the value of cervicovaginal fetal fibronectin as a marker for preterm delivery	A brief search strategy was described using Medline and EMBASE Literature search was completed in 1997 Search terms included terms for premature labour combined with terms for fetal fibronectin (n = 27)	Studies with the following characteristics were included: original, published prospective studies of pregnant women < 37 weeks gestation with intact membranes; assessed using cervicovaginal fetal fibronectin test; and an assessment of preterm birth Articles in English were included The exclusion criteria were not reported	The details of the literature search and data extraction procedures were unclear Results of included studies were individually summarised No assessment of quality was undertaken Sources of heterogeneity were not explored Results presented as pooled sensitivity and specificity as well as pooled predictive values	Low quality — limited documentation and scope of the literature search — limited description of exclusion criteria — reporting of a number of methodology details is unclear Limited validity — included low-level diagnostic studies
Leitich (2003)	To determine the value of cervicovaginal fetal fibronectin as a marker for preterm delivery [update]	A brief search strategy was described using Medline and EMBASE Literature search was completed in 2002 Search terms included terms for premature labour combined with terms for fetal fibronectin (n = 40)	Studies with the following characteristics were included: original, published prospective studies of pregnant women < 37 weeks gestation with intact membranes; assessed using cervicovaginal fetal fibronectin test; and an assessment of preterm birth Articles in English were included The exclusion criteria were not reported	The details of the literature search and data extraction procedures were unclear No assessment of quality was undertaken Sources of heterogeneity were not explored Results presented as pooled sensitivity and specificity	Low quality — limited documentation and scope of the literature search — limited description of exclusion criteria — reporting of a number of methodology details is unclear Limited validity — included low-level diagnostic studies

Systematic review (year)	Research question	Search strategy (included studies)	Inclusion/exclusion criteria	Methodology	Comment[a]
Revah (1998)	To determine the clinical utility of fetal fibronectin as a predictor of preterm birth in patients with and without uterine contractions	A brief search strategy was described using Medline Literature search was completed in 1997 Search terms included terms for premature labour combined with terms for fetal fibronectin (n = 24)	Studies with the following characteristics were included: prospective studies of women < 37 weeks gestation with caregivers blinded to fetal fibronectin test results Articles in English were included Studies were excluded for the following reasons: non-relevant, wrong outcomes, wrong patient group, fetal fibronectin not clearly blinded, non-systematic reviews	The literature search and data extraction were completed by independent reviewers with disagreements solved by third reviewer or discussion Results of included studies were individually summarised No assessment of quality was undertaken Sources of heterogeneity were not explored Results presented as pooled sensitivity and specificity	Low quality — limited documentation and scope of the literature search — reporting of a number of methodology details is unclear Limited validity — included low-level diagnostic studies

Abbreviation: SROC, summary receiver operator characteristic

[a] Quality determined after applying the quality criteria in **Appendix G**.

[b] Literature search described in Honest et al (2003).

Table 30 **Results of systematic reviews assessing the diagnostic accuracy of fetal fibronectin**

Systematic review (year)	Summary of results
AHRQ (2000)	• Predictive values of fetal fibronectin (women in suspected preterm labour) for predicting delivery: o within seven days ranged from 13% to 44% (PPV) and 98% to 100% (NPV) o < 37 weeks ranged from 31% to 83% (PPV) and 69% to 92% (NPV)
Chien (1997)	• Summary LR of fetal fibronectin (women in suspected preterm labour) for predicting delivery: o within seven days was LR+ 5.0 (3.8, 6.4) and LR– 0.2 (0.1, 0.4) o < 34 weeks was LR+ 2.6 (1.8, 3.7) and LR– 0.2 (0.1, 0.5) o < 37 weeks was LR+ 4.6 (3.5, 6.1) and LR– 0.5 (0.4, 0.6) No explanation for heterogeneity was discovered • Summary LR of fetal fibronectin (in asymptomatic high risk women) for predicting delivery: o < 34 weeks was LR+ 2.4 (1.8, 3.2) and LR– 0.6 (0.4, 0.9) o < 37 weeks was LR+ 2.0 (1.5, 2.6) and LR– 0.4 (0.2, 0.8)
Faron (1998)	• Summary LR of a single fetal fibronectin test (women in suspected preterm labour) for predicting delivery: o < 34 weeks was LR+ 2.2 (1.6, 3.0) and LR– 0.3 (0.2, 0.6) o < 37 weeks was LR+ 3.5 (2.6, 4.6) and LR– 0.4 (0.3, 0.5) • Summary LR of multiple fetal fibronectin testing (women in suspected preterm labour) for predicting delivery: o < 34 weeks was LR+ 2.9 (2.0, 4.2) and LR– 0.3 (0.0, 3.0) o < 37 weeks was LR+ 2.7 (2.1, 3.6) and LR– 0.4 (0.2, 0.7)
Honest (2002)	• Summary LR of fetal fibronectin (women in suspected preterm labour) for predicting delivery: o within 7–10 days was LR+ 5.4 (4.4, 6.7) and LR– 0.3 (0.2, 0.3) o < 34 weeks was LR+ 3.6 (2.3, 5.7) and LR– 0.3 (0.2, 0.7) o < 37 weeks was LR+ 3.3 (2.7, 3.9) and LR– 0.5 (0.4, 0.6) No explanation for heterogeneity was discovered
ICSI (2000)	• Sensitivity and specificity of fetal fibronectin (women in suspected preterm labour) for predicting delivery at < 37 weeks ranged from 36% to 83% (Sn) and 70% to 96% (Sp) • Predictive values of fetal fibronectin (women in suspected preterm labour) for predicting delivery at < 37 weeks ranged from 45% to 78% (PPV) and 76% to 100% (NPV)
Lamont (2003)	• Fetal fibronectin has a high negative predictive value but a low positive predictive value

Systematic review (year)	Summary of results
Leitich (1999)	• Sensitivity and specificity of fetal fibronectin (women in suspected preterm labour) for predicting delivery: o within seven days was Sn 89% (80%, 97%) and Sp 86% (81%, 91%) o within 14 days was Sn 78% (70%, 86%) and Sp 86% (81%, 91%) o < 34 weeks was Sn 85% (73%, 96%) and Sp 68% (28%, 100%) o < 37 weeks was: Sn 60% (48%, 71%) and Sp 86% (82%, 89%) • Sensitivity and specificity of fetal fibronectin (in asymptomatic high risk women) for predicting delivery: o within seven days was Sn 22% (3%, 60%) and Sp 97% (96%, 97%) o within 14 days was Sn 43% (0%, 95%) and Sp 95% (92%, 99%) o < 34 weeks was Sn 69% (20%, 100%) and Sp 74% (46%, 100%) o < 37 weeks was Sn 78% (63%, 93%) and Sp 78% (63%, 93%) • Sensitivity and specificity of a single fetal fibronectin test (women in suspected preterm labour) for predicting delivery: o < 34 weeks was Sn 85% (73%, 96%) and Sp 68% (28%, 100%) o < 37 weeks was Sn 60% (48%, 71%) and Sp 86% (82%, 89%)
Leitich (2003)	• Sensitivity and specificity of fetal fibronectin (women in suspected preterm labour) for predicting delivery: o within seven days was Sn 77% (67%, 88%) and Sp 87% (84%, 91%) o within 14 days was Sn 74% (67%, 82%) and Sp 87% (83%, 92%) o < 34 weeks was Sn 63% (37%, 90%) and Sp 86% (79%, 93%) o < 37 weeks was Sn 54% (43%, 65%) and Sp 85% (81%, 89%) • Sensitivity and specificity of multiple fetal fibronectin testing (in asymptomatic high risk women) for predicting delivery: o < 34 weeks was Sn 92% (62%, 100%) and Sp 59% (47%, 71%) o < 37 weeks was Sn 78% (63%, 93%) and Sp 78% (63%, 93%)
Revah (1998)	• Sensitivity and specificity of fetal fibronectin (women in suspected preterm labour) for predicting delivery: o within seven days was Sn 98% (95%, 100%) and Sp 83% (82%, 85%) o within 14 days was Sn 82% (74%, 90%) and Sp 85% (83%, 87%) o < 34 weeks was Sn 87% (81%, 94%) and Sp 85% (81%, 89%) o < 37 weeks was Sn 54% (51%, 58%) and Sp 87% (85%, 88%) • Predictive values of fetal fibronectin (women in suspected preterm labour) for predicting delivery: o within seven days was PPV 15% (12%, 18%) and NPV 100% (99%, 100%) o within 14 days was PPV 25% (20%, 29%) and NPV 99% (99%, 100%) o < 34 weeks was PPV 39% (31%, 47%) and NPV 96% (93%, 98%) o < 37 weeks was PPV 58% (54%, 62%) and Sp 85% (84%, 87%)

Abbreviations: LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; Sn, sensitivity; Sp, specificity

Primary studies

The extracted diagnostic measures from the included primary studies are presented in **Table 31** (pathology-based fetal fibronectin testing for pregnant women in suspected preterm labour); **Table 32** (point-of-care fetal fibronectin testing for pregnant women in suspected preterm labour); **Table 33** (pathology-based fetal fibronectin testing in asymptomatic pregnant women at high risk of preterm delivery) and **Table 34** (point-of-care fetal fibronectin testing in asymptomatic pregnant women at high risk of preterm delivery).

Due to a limited amount of available evidence it was only possible to reliably calculate the summary diagnostic measures for pathology-based fetal fibronectin testing for pregnant women in suspected preterm labour (delivery within seven days of testing, delivery within 14 days of testing, delivery before 37 weeks gestation) as well as point-of-care fetal fibronectin testing for pregnant women in suspected preterm labour (delivery within seven days of testing).

The corresponding unweighted and inverse variance weighted SROC curves are presented for pathology-based fetal fibronectin testing for pregnant women in suspected preterm labour for the outcomes of preterm delivery within seven days of testing (**Figure 14**; **Figure 15**), preterm delivery with 14 days of testing (**Figure 16**; **Figure 17**) and preterm delivery before 37 weeks gestation (**Figure 18**; **Figure 19**). Heterogeneity was detected in the test threshold for the outcome of preterm delivery before 37 weeks gestation. Therefore, other summary diagnostic measures for the outcome of preterm delivery before 37 weeks gestation should be interpreted with caution. The SROC curves for point-of-care fetal fibronectin testing for pregnant women in suspected preterm labour for the outcome of preterm delivery within seven days of testing are presented in **Figure 20** (unweighted) and **Figure 21** (inverse variance weighted).

The Littenberg-Moses regression method was used to evaluate the characteristics of gestational age, cervical dilation and presenting symptoms on the diagnostic accuracy of pathology-based fetal fibronectin testing for the outcomes of delivery before 37 weeks gestation. These characteristics were unable to explain the heterogeneity within the data sets.

Forest plots are presented for the positive (**Figure 22**, **Figure 23**) and negative (**Figure 24**, **Figure 25**) likelihood ratios of pathology-based fetal fibronectin testing for the outcome of delivery before 37 weeks gestation. Both the positive and negative likelihood ratio data sets were heterogenous and therefore the results from both the random and fixed effect models are presented.

Table 31 Diagnostic accuracy of pathology fetal fibronectin testing for pregnant women in suspected preterm labour

Author (year)	Preterm birth definition	Prevalence/ N (%)	PPV (%)	NPV (%)	Sn (%)	Sp (%)	Accuracy (%)	Quality[a]
Preterm delivery within seven days of testing								
Bartnicki (1996)	Unclear	2/112 (1.8)	5.9	100.0	100.0	70.9	71.4	III-1 P2, Q2
Iams (1995)	Spontaneous birth	14/192 (7.3)	28.9	99.3	92.9	82.0	82.8	III-1 P2, Q2
Malak (1996)	Spontaneous birth	10/112 (8.9)	44.4	97.9	80.0	90.2	89.3	III-1 P2, Q2
Peaceman (1997)	Included—medically indicated birth	23/763 (3.0)	13.3	99.5	87.0	82.4	82.6	III-1 P2, Q2
Rinehart (2001)	Included—medically indicated birth	28/235 (11.9)	33.3	93.6	57.1	84.5	81.3	III-1 P2, Q2
Schmitz (2006)	Spontaneous birth	23/359 (6.4)	21.1	98.5	82.6	78.9	79.1	III-1 P2, Q2
Skoll (2006)	Unclear	15/149 (10.1)	37.5	97.4	80.0	85.1	84.6	III-1 P2, Q2
Tekesin (2005)	Spontaneous birth	11/170 (6.5)	19.6	98.4	81.8	76.7	77.1	II P2, Q1
Preterm delivery within 14 days of testing								
Bartnicki (1996)	Unclear	17/112 (15.2)	41.2	96.2	82.4	78.9	79.5	III-1 P2, Q2
Iams (1995)	Spontaneous birth	26/192 (13.5)	40.0	94.6	69.2	83.7	81.8	III-1 P2, Q2
Malak (1996)	Spontaneous birth	11/112 (9.8)	50.0	97.9	81.8	91.1	90.2	III-1 P2, Q2
Peaceman (1997)	Included—medically indicated birth	30/763 (3.9)	16.7	99.2	83.3	82.9	83.0	III-1 P2, Q2
Tekesin (2005)	Spontaneous birth	16/170 (9.4)	30.4	98.4	87.5	79.2	80.0	II P2, Q1
Preterm delivery before 34 weeks gestation								
Burrus (1995)	Unclear	26/37 (70.3)	79.3	62.5	88.5	45.5	75.7	III-1 P2, Q2
Rinehart (2001)	Included—medically indicated birth	27/235 (11.5)	35.4	94.7	63.0	85.1	82.6	III-1 P2, Q2
Tekesin (2005)	Spontaneous birth	28/170 (16.5)	43.5	93.5	71.4	81.7	80.0	II P2, Q1
Preterm delivery before 37 weeks gestation								
Bartnicki (1996)	Unclear	40/112 (35.7)	79.4	83.3	67.5	90.3	82.1	III-1 P2, Q2
Grandi (1996)	Unclear	8/26 (30.8)	30.8	69.2	50.0	50.0	50.0	II P2, Q1
Iams (1995)	Spontaneous birth	62/192 (32.3)	60.0	76.2	43.5	86.2	72.4	III-1 P2, Q2

Author (year)	Preterm birth definition	Prevalence/ N (%)	PPV (%)	NPV (%)	Sn (%)	Sp (%)	Accuracy (%)	Quality[a]
Inglis (1994)	Unclear	9/38 (23.7)	43.8	90.9	77.8	69.0	71.1	III-1 P2, Q2
Irion (1995)	Unclear	22/64 (34.4)	57.7	81.6	68.2	73.8	71.9	III-1 P2, Q2
Langer (1997)	Unclear	18/61 (29.5)	55.6	81.4	55.6	81.4	73.8	III-1 P2, Q2
La Shay (2000)	Unclear	34/118 (28.8)	58.8	76.2	29.4	91.7	73.7	III-1 P2, Q2
Lockwood (1991)	Unclear	60/117 (51.3)	83.1	81.0	81.7	82.5	82.1	III-1 P2, Q2
Malak (1996)	Spontaneous birth	22/112 (19.6)	77.8	91.5	63.6	95.6	89.3	III-1 P2, Q2
Morrison (1993)	Unclear	10/28 (35.7)	64.3	92.9	90.0	72.2	78.6	III-1 P2, Q2
Peaceman (1997)	Included—medically indicated birth	162/763 (21.2)	44.7	84.5	41.4	86.2	76.7	III-1 P2, Q2
Rinehart (2001)	Included—medically indicated birth	100/235 (42.6)	72.9	65.2	35.0	90.4	66.8	III-1 P2, Q2
Rizzo (1996)[b,c]	Unclear	47/108 (43.5)	81.4	81.5	74.5	86.9	81.5	III-1 P2, Q2
Rizzo (1997)[b]	Unclear	49/106 (46.2)	76.9	83.3	81.6	78.9	80.2	III-1 P2, Q2
Rozenberg (1996)	Unclear	20/56 (35.7)	75.0	80.0	60.0	88.9	78.6	III-1 P2, Q2
Rozenberg (1997)	Spontaneous birth	20/76 (26.3)	45.2	86.7	70.0	69.6	69.7	III-1 P2, Q2
Tekesin (2005)	Spontaneous birth	45/170 (26.5)	67.4	88.7	68.9	88.0	82.9	II P2, Q1
Zamora (2000)	Unclear	3/22 (13.6)	60.0	100.0	100.0	88.2	81.8	III-1 P2, Q2

Abbreviations: NPV, negative predictive value; PPV, positive predictive value; Sn, sensitivity; Sp, specificity

[a] According to criteria outlined in **Table 7**, **Table 8** and **Appendix G.**

[b] Rizzo et al (1996) and Rizzo et al (1997) have an overlapping patient cohort.

[c] Used vaginal sample subgroup.

Table 32 Diagnostic accuracy of point-of-care fetal fibronectin testing for pregnant women in suspected preterm labour

Author (year)	Preterm birth definition	Prevalence/ N (%)	PPV (%)	NPV (%)	Sn (%)	Sp (%)	Accuracy (%)	Quality[a]
Preterm delivery within seven days of testing								
Benattar (1997)	Unclear	9/124 (7.3)	42.1	99.0	88.9	90.4	90.3	III-1 P2, Q2
Coleman (1998)	Included—medically indicated birth	15/121 (12.4)	37.0	94.7	66.7	84.0	81.8	II P1, Q1
Senden (1996)	Included—medically indicated birth	3/25 (12.0)	50.0	100.0	100.0	86.4	88.0	III-1 P2, Q2
Tsoi (2006)	Unclear	19/195 (9.7)	21.2	99.1	94.7	61.9	65.1	III-1 P2, Q2
Preterm delivery within 14 days of testing								
Benattar (1997)	Unclear	16/124 (12.9)	57.9	95.2	68.8	92.6	89.5	III-1 P2, Q2
Preterm delivery before 34 weeks gestation								
Coleman (1998)	Included—medically indicated birth	19/121 (15.7)	37.0	90.4	52.6	83.3	78.5	II P1, Q1
Parker (1995)	Spontaneous birth	5/36 (13.9)	45.5	100.0	100.0	80.6	83.3	III-1 P2, Q2
Preterm delivery before 37 weeks gestation								
Benattar (1997)	Unclear	25/124 (20.2)	47.4	84.8	36.0	89.9	79.0	III-1 P2, Q2
Volumenie (2001)	Unclear	32/120 (26.7)	19.1	68.5	28.1	56.8	49.2	II P2, Q1

Abbreviations: NPV, negative predictive value; PPV, positive predictive value; Sn, sensitivity; Sp, specificity
[a] According to criteria outlined in **Table 7**, **Table 8** and **Appendix G.**

Table 33 Diagnostic accuracy of pathology-based fetal fibronectin testing among asymptomatic pregnant women at high risk of preterm delivery

Author (year)	Preterm birth definition	Prevalence/ N (%)	PPV (%)	NPV (%)	Sn (%)	Sp (%)	Accuracy (%)	Quality[a]
Preterm delivery with 14 days of testing (per patient)								
Leeson (1996)	Spontaneous birth	5/42 (11.9)	36.4	96.8	80.0	81.1	81.0	III-1 P2, Q2
Preterm delivery before 34 weeks gestation (per patient)								
Nageotte (1994)	Spontaneous birth	13/87 (14.9)	28.6	97.8	92.3	59.5	64.4	III-1 P2, Q2
Morrison (1996)	Unclear	14/85 (16.5)	42.9	88.7	42.9	88.7	81.2	III-1 P2, Q2
Preterm delivery before 37 weeks gestation (per patient)								
Leeson (1996)	Spontaneous birth	13/40 (32.5)	63.6	79.3	53.8	85.2	75.0	III-1 P2, Q2
Nageotte (1994)[b]	Spontaneous birth	27/87 (31.0)	51.1	92.5	88.9	61.7	70.1	III-1 P2, Q2
Preterm delivery within seven days of testing (per sample)								
Leeson (1996)	Spontaneous birth	2/168 (1.2)	12.5	100.0	100.0	91.6	91.7	III-1 P2, Q2
Preterm delivery within 14 days of testing (per sample)								
Leeson (1996)	Spontaneous birth	7/167 (4.2)	31.3	98.7	71.4	93.1	92.2	III-1 P2, Q2
Preterm delivery before 37 weeks gestation (per sample)								
Leeson (1996)	Spontaneous birth	47/159 (29.6)	50.0	72.7	17.0	92.9	70.4	III-1 P2, Q2
Nageotte (1994)[c]	Spontaneous birth	73/678 (10.8)	21.4	93.4	56.2	75.0	73.0	III-1 P2, Q2

Abbreviations: NPV, negative predictive value; PPV, positive predictive value; Sn, sensitivity; Sp, specificity

[a] According to criteria outlined in **Table 7**, **Table 8** and **Appendix G.**

[b] Results presented for fetal fibronectin sampling every two weeks.

[c] Results presented for fetal fibronectin samples from the posterior fornix.

Table 34 Diagnostic accuracy of point-of-care fetal fibronectin testing among asymptomatic pregnant women at high risk of preterm delivery

Author (year)	Preterm birth definition	Prevalence/ N (%)	PPV (%)	NPV (%)	Sn (%)	Sp (%)	Accuracy(%)	Quality[a]
Preterm delivery before 37 weeks gestation (per patient)								
Bittar (1996)	Spontaneous birth	38/102 (37.3)	84.8	85.5	73.7	92.2	85.3	III-2 P2, Q3
Preterm delivery before 37 weeks gestation (per sample)								
Paternoster (2000)	Spontaneous birth	53/161 (32.9)	42.1	89.4	90.6	38.9	55.9	III-2 P2, Q3

Abbreviations: NPV, negative predictive value; PPV, positive predictive value; Sn, sensitivity; Sp, specificity
[a] According to criteria outlined in **Table 7**, **Table 8** and **Appendix G**.

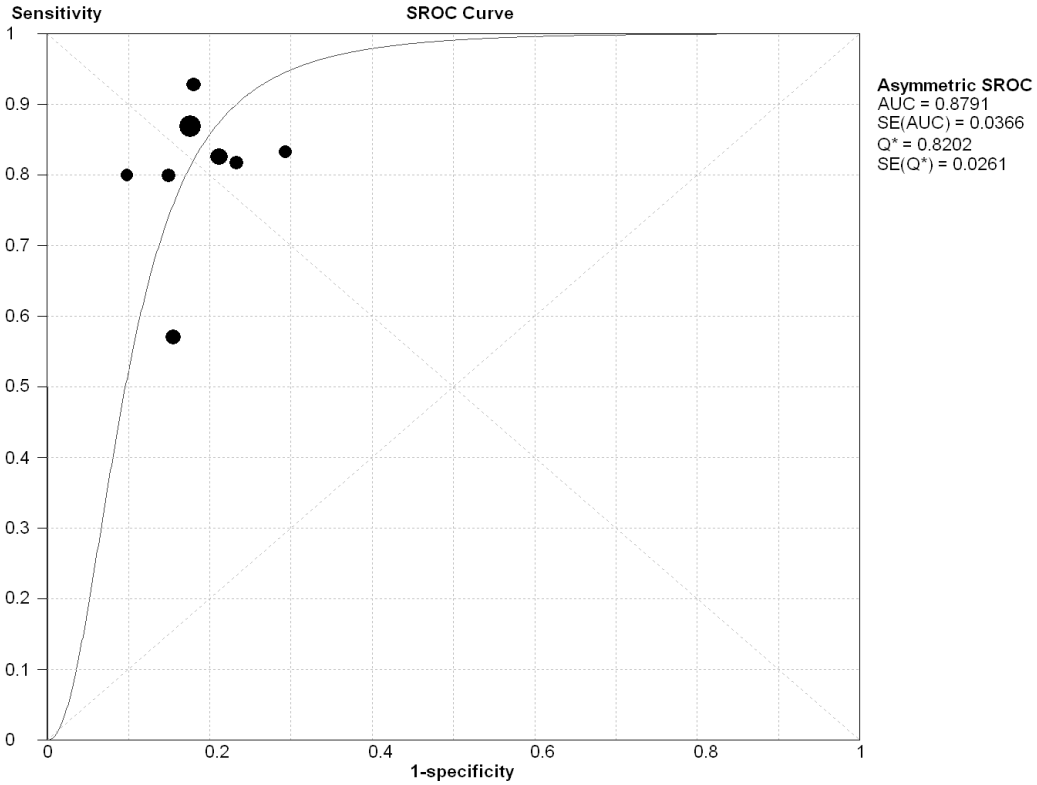

Figure 14 Unweighted SROC curve (Moses model) for the diagnostic accuracy of pathology-based fetal fibronectin testing for women in suspected preterm labour for assessment of preterm delivery risk within seven days of testing

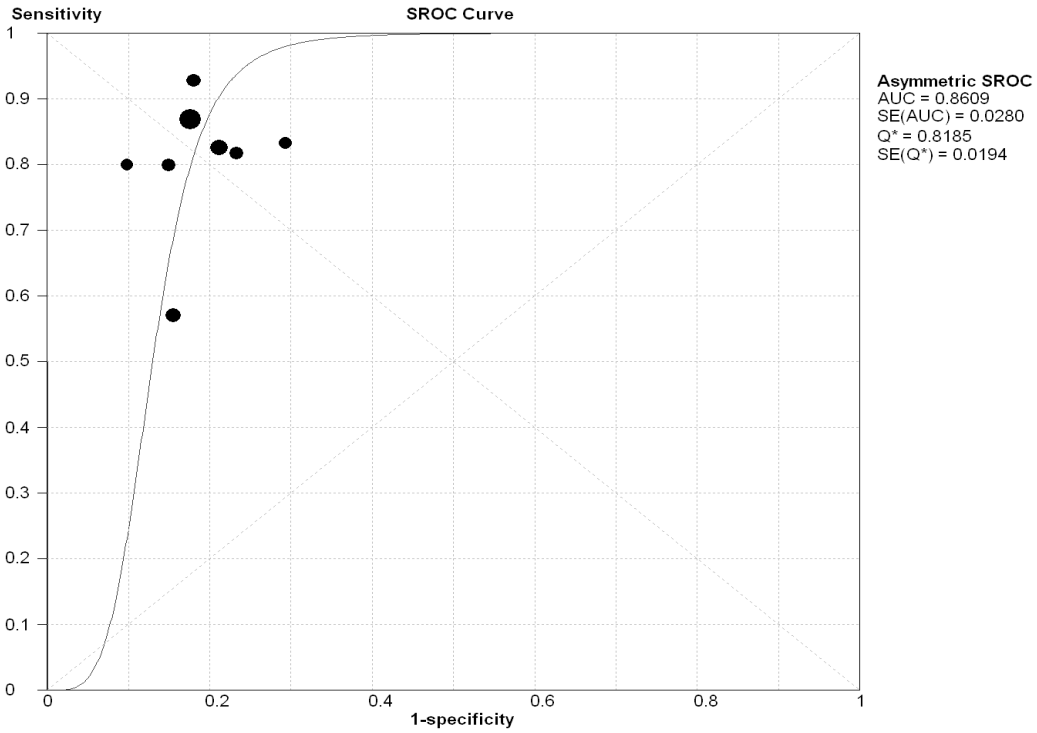

Figure 15 **Inverse variance weighted SROC curve (Moses model) for the diagnostic accuracy of pathology-based fetal fibronectin testing for women in suspected preterm labour for assessment of preterm delivery risk within seven days of testing**

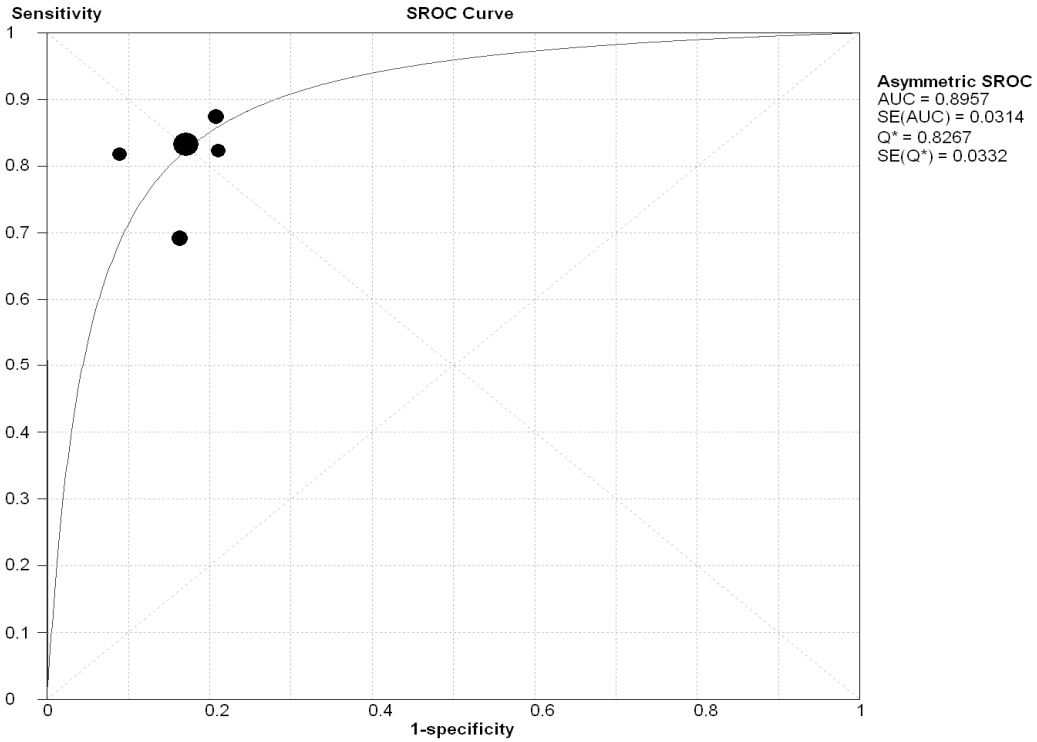

Figure 16 **Unweighted SROC curve (Moses model) for the diagnostic accuracy of pathology-based fetal fibronectin testing for women in suspected preterm labour for assessment of preterm delivery risk within 14 days of testing**

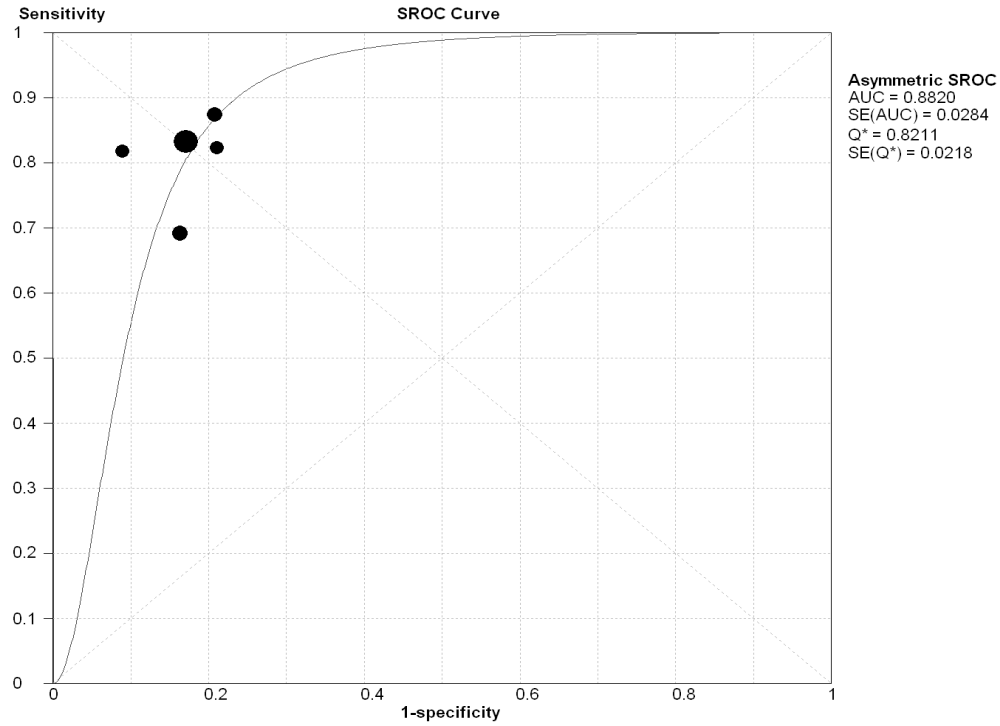

Figure 17 **Inverse variance weighted SROC curve (Moses model) for the diagnostic accuracy of pathology-based fetal fibronectin testing for women in suspected preterm labour for assessment of preterm delivery risk within 14 days of testing**

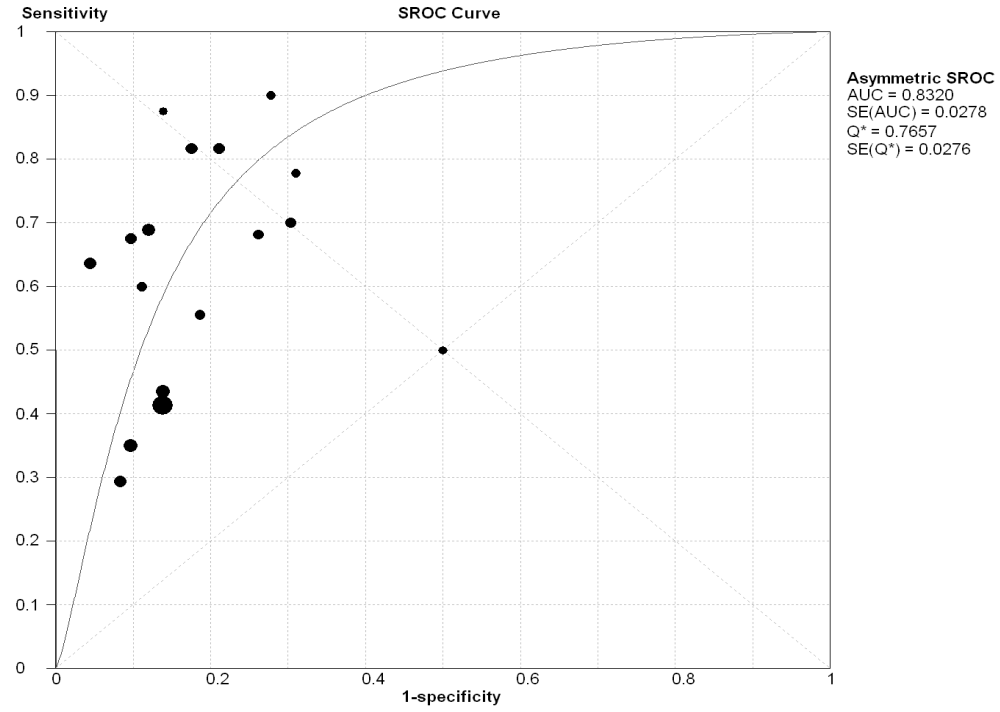

Figure 18 **Unweighted SROC curve (Moses model) for the diagnostic accuracy of pathology fetal fibronectin testing for women in suspected preterm labour for assessment of preterm delivery risk before 37 weeks gestation**

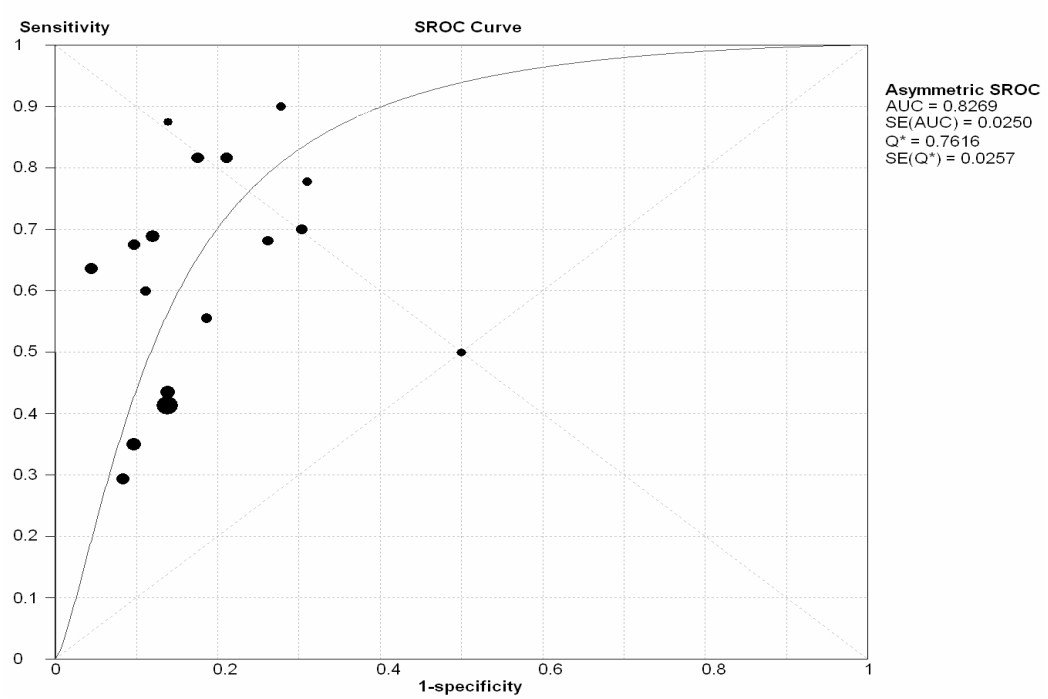

Figure 19 **Inverse variance weighted SROC curve (Moses model) for the diagnostic accuracy of pathology-based fetal fibronectin testing for women in suspected preterm labour for assessment of preterm delivery risk before 37 weeks gestation**

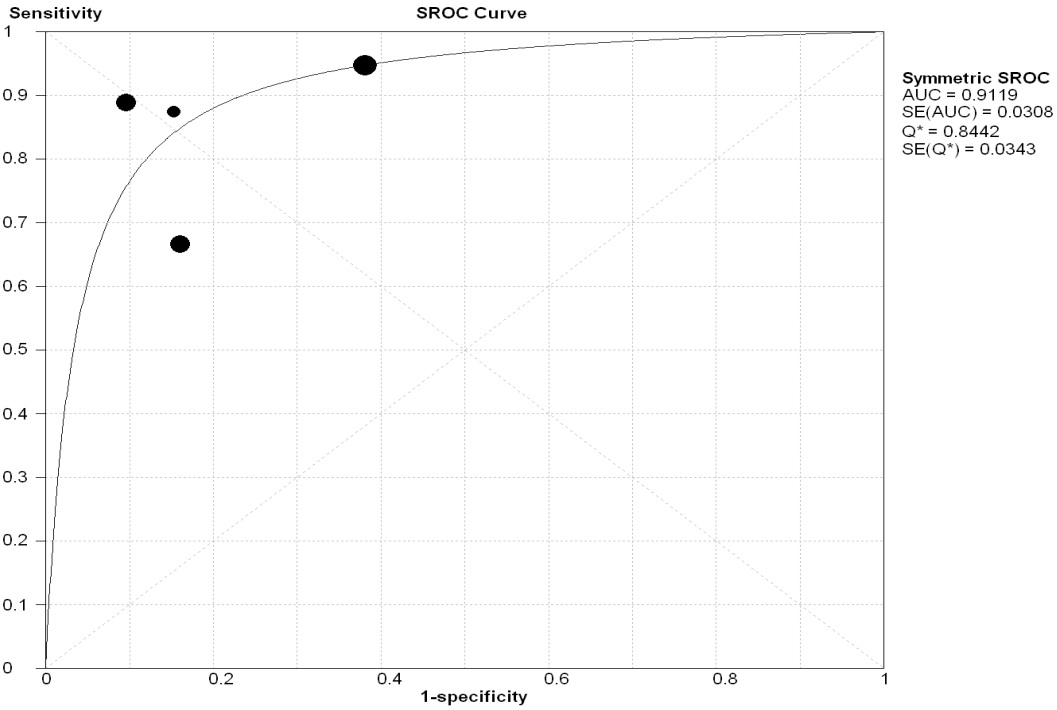

Figure 20 **Unweighted SROC curve (Moses model) for the diagnostic accuracy of point-of-care fetal fibronectin testing for women in suspected preterm labour for assessment of preterm delivery risk within seven days of testing**

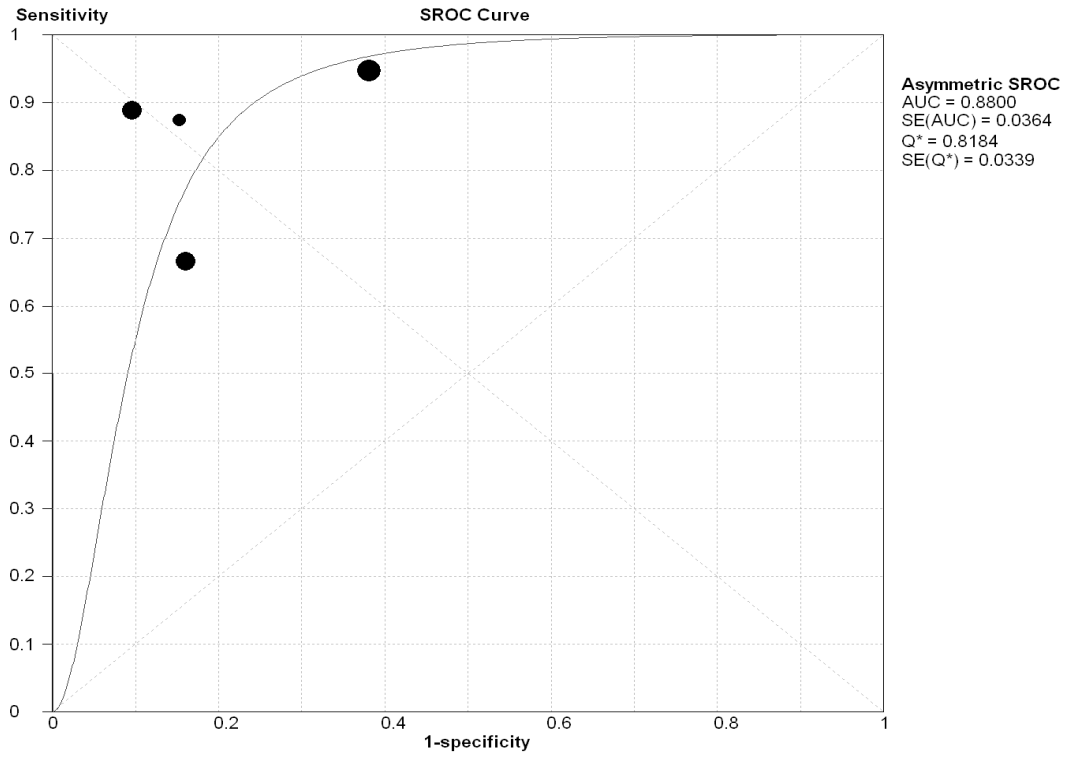

Figure 21 **Inverse variance weighted SROC curve (Moses model) for the diagnostic accuracy of point-of-care fetal fibronectin testing for women in suspected preterm labour for assessment of preterm delivery risk within seven days of testing**

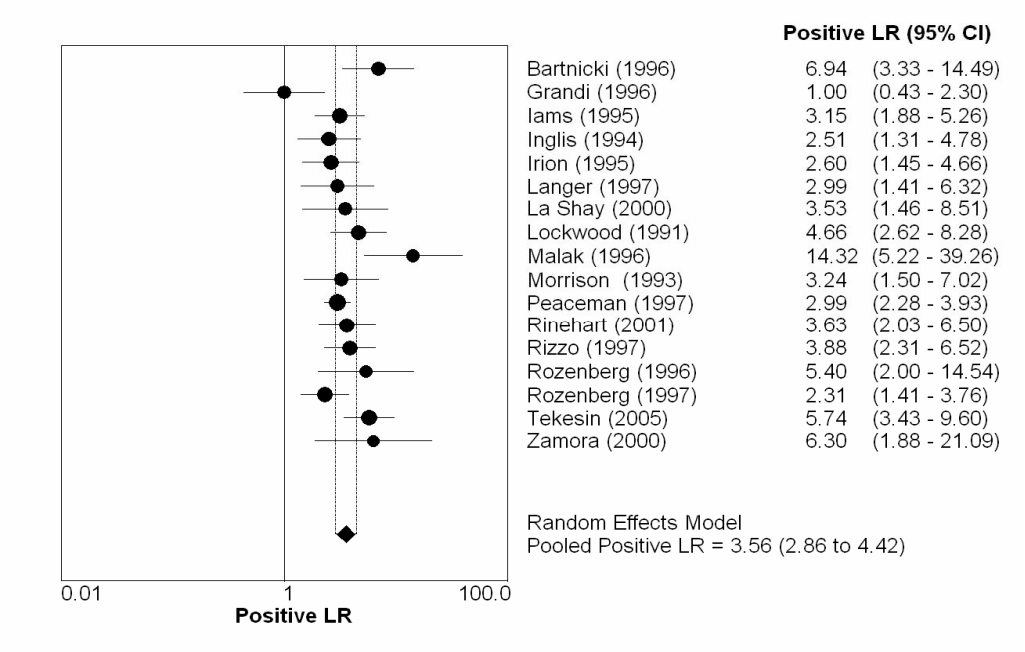

Figure 22 **Summary positive likelihood ratios (random effects) for the diagnostic accuracy of pathology-based fetal fibronectin testing for women in suspected preterm labour for assessment of preterm delivery risk before 37 weeks gestation**

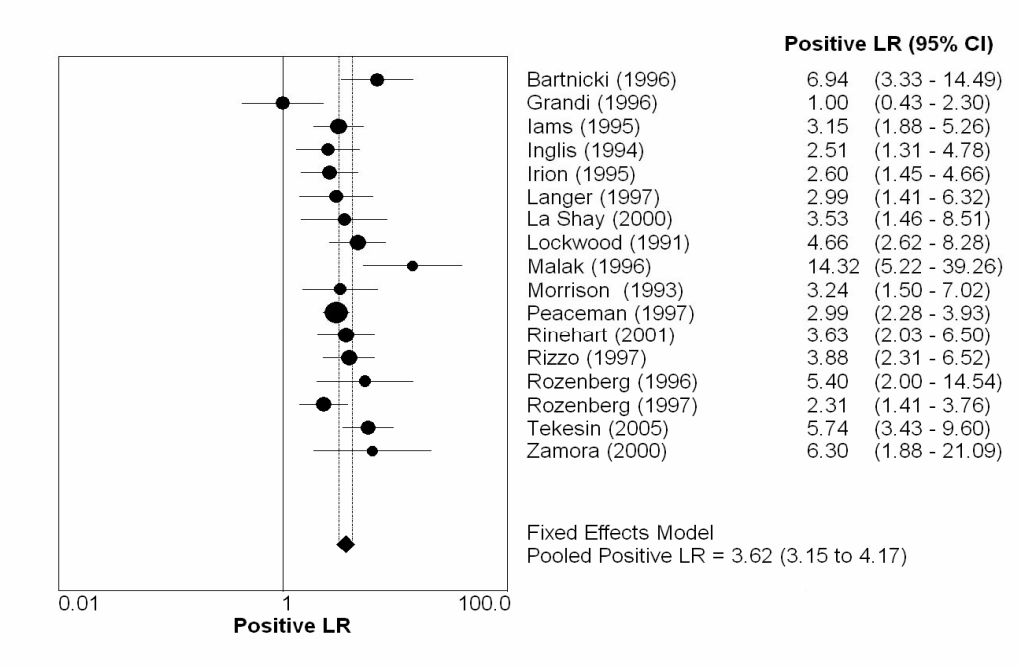

Figure 23 **Summary positive likelihood ratios (fixed effects) for the diagnostic accuracy of pathology-based fetal fibronectin testing for women in suspected preterm labour for assessment of preterm delivery risk before 37 weeks gestation**

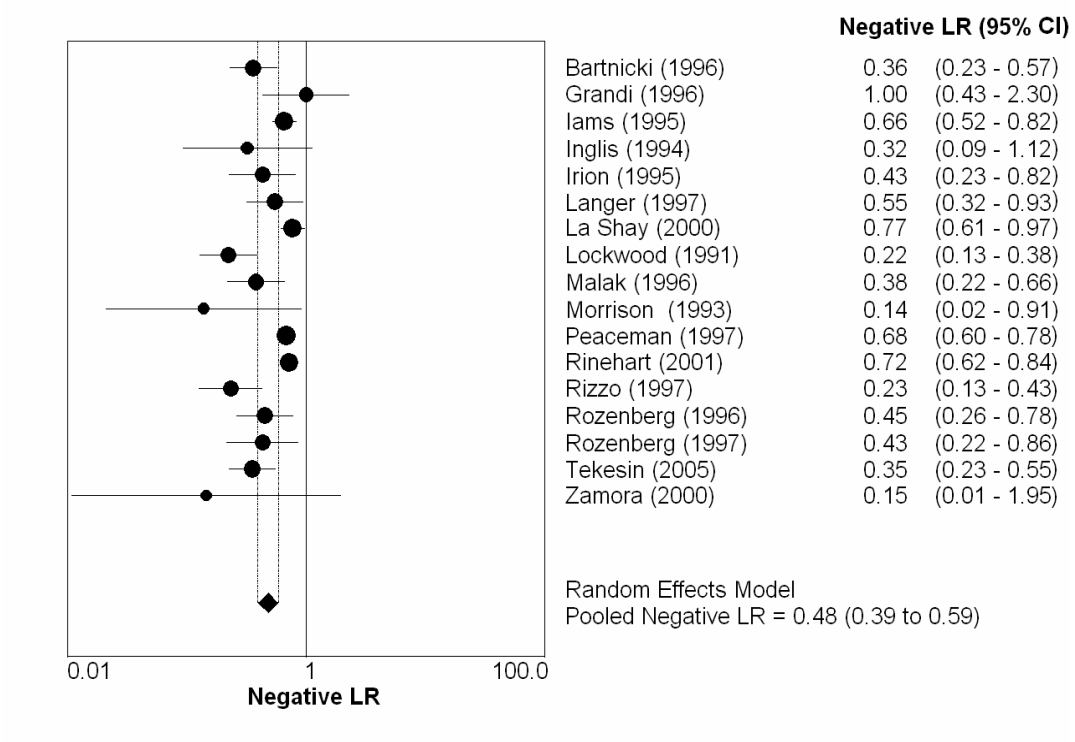

Figure 24 **Summary negative likelihood ratios (random effects) for the diagnostic accuracy of pathology-based fetal fibronectin testing for women in suspected preterm labour for assessment of preterm delivery risk before 37 weeks gestation**

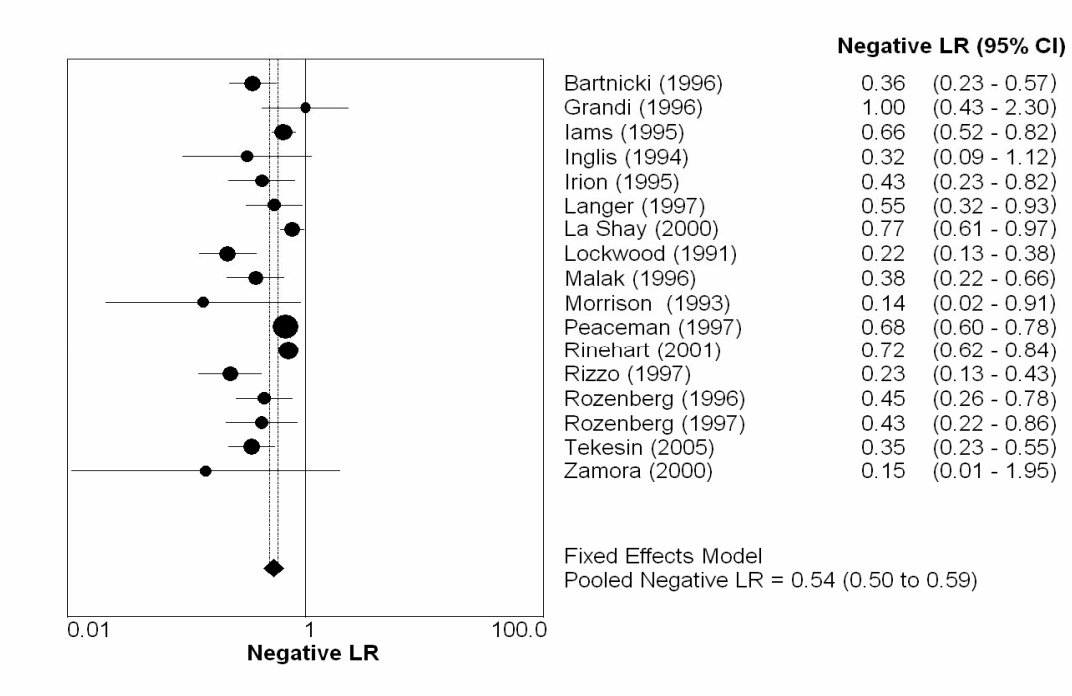

Figure 25 **Summary negative likelihood ratios (fixed effects) for the diagnostic accuracy of pathology-based fetal fibronectin testing for women in suspected preterm labour for assessment of preterm delivery risk before 37 weeks gestation**

Appendix D Supplementary patient management data

Randomised controlled trials

There were four randomised controlled trials (RCTs) identified that reported the effects of fetal fibronectin testing for predicting preterm labour on patient management (Grobman et al, 2004; Lowe et al, 2004; Nguyen et al, 2002; Plaut et al, 2003). The study details are presented in **Table 35**. All trials were conducted in the United States. The abstract only was available for the study by Nguyen et al (2002). Plaut et al (2003) conducted a multi-centre study. Only Grobman et al (2004) clearly defined the symptoms of preterm labour, and designed a study that was limited to singleton gestations. All four studies had similar exclusion criteria; the only major exception was that Grobman et al (2004), Nguyen et al (2002) and Plaut et al (2003) applied cervical manipulation within 24 hours as an exclusion criterion, whereas Lowe et al (2004) delayed testing until 24 hours after cervical manipulation.

Lowe et al (2004) reported methods applied to determine gestational age. Grobman et al (2004) and Nguyen et al (2002) reported details of current practices used to identify patients at risk of preterm delivery. All four studies reported obtaining samples from the posterior vaginal fornix. It appears likely that all samples were analysed using the Rapid Fetal Fibronectin analyser.

Table 35 Characteristics of diagnostic RCTs comparing fetal fibronectin testing to current clinical practice

Author (year)	Study design (country)	Inclusion criteria	Exclusion criteria	Determination of gestational age	Fetal fibronectin characteristics	Current clinical practice characteristics
Grobman (2004)	Single centre RCT (USA)	Patients with symptoms of preterm labour (primary complaint of uterine contractions, > 6 contraction per hour by external tocodynometry), with singleton gestations between 24–34 weeks	Vaginal bleeding, cerclage, non-intact amniotic membranes, > 3 cm cervical dilation, cervical manipulation within 24 hours, already received hospital-based observation, admission or treatment	NR	Cervicovaginal samples swabbed from the posterior vaginal fornix. Samples were analysed using the Rapid Fetal Fibronectin analyser	Standardised evaluation including a focused history, assessment of fetal heart tones, assessment of uterine contraction frequency, digital cervical examination and physical examination
Lowe (2004)	Single centre RCT (USA)	Patients with symptoms of preterm labour (uterine contractions and/or cervical change), > 16 years of age, with a singleton or multiparous gestation between 23–34 weeks. fFN testing was delayed in patients who had cervical manipulation within 24 hours	Vaginal bleeding, cerclage, non-intact amniotic membranes, > 3 cm cervical dilation for singleton gestation or > 4 cm cervical dilation for multiparous gestation, multi-fetal gestations	Determined from last menstrual period and first or early second-trimester ultrasound. In cases of discrepancy, ultrasound data were used	Cervicovaginal samples swabbed from the posterior vaginal fornix. Samples were sent to the laboratory and analysed within the hour (presumably using the Rapid Fetal Fibronectin analyser)	NR
Nguyen (2002) Abstract only	Single centre RCT (USA)	Patients with symptoms of preterm labour with gestations between 24–35 weeks	Abdominal trauma, non-intact amniotic membranes, > 3 cm cervical dilation, vaginal bleeding, non-reassuring fetal heart tracing, history of tocolysis in current pregnancy, recent digital examination or intercourse	NR	Cervicovaginal samples swabbed from the posterior vaginal fornix. Samples were analysed using the Rapid Fetal Fibronectin analyser	Serial digital examinations
Plaut (2003)	Multi-centre RCT (USA)	Patients with symptoms of preterm labour, with singleton or multiparous gestations between 24–34 weeks	Vaginal bleeding, cerclage, non-intact amniotic membranes, > 3 cm cervical dilation, cervical manipulation within 24 hours, previous fFN testing within two weeks	NR	Cervicovaginal samples swabbed from the posterior vaginal fornix. Samples were analysed using the Rapid Fetal Fibronectin analyser	NR

Abbreviations: fFN, fetal fibronectin; NR, not reported; RCT, randomised controlled trial

These RCTs were assessed on measures that were used to minimise any study bias (**Table 36**). Grobman et al (2004) and Lowe et al (2004) reported a secure randomisation procedure; however, Nguyen et al (2002) did not report randomisation methods, and Plaut et al (2003) used an inadequate procedure—participants were randomised by using sequentially numbered envelopes matched to patient enrolment forms. None of the studies blinded either patients or physicians. Because treatment was based on physician discretion in all studies, this may have affected the results. The initial number of patients randomised, but not included in the analysis in trials by Lowe et al (2004) and Plaut et al (2003) was unclear.

Table 36 Assessment of the measures to minimise bias of diagnostic randomised controlled trials comparing fetal fibronectin testing with current clinical practice

Author (year)	Randomisation	Blinding	Patient follow-up
Grobman (2004)	Randomisation was performed the use of computer-generated random assignment	Patients and physicians were not blinded	100 patients were randomised: 50 women each to the fFN group and to management without fFN All patients were included in the analysis
Lowe (2004)	Randomisation was achieved through the use of a computer-generated table in blocks of 10. Separate randomisation tables were used for gestations of < 28 weeks and ≥ 28 weeks	Patients and physicians were not blinded	110 patients were available for enrolment. 46 women were randomised to the fFN group and 51 women were randomised to management without fFN 97 (88%) of enrolled patients were randomised and included in analysis
Nguyen (2002)	NR	Patients and physicians were not blinded	77 patients were available for enrolment. 42 women were randomised to the fFN group and 35 women were randomised to management without fFN
Plaut (2003)[a]	Randomisation was performed by means of sequentially numbered envelopes that matched patient enrolment forms on labour and delivery	Patients and physicians were not blinded	114 patients were available for enrolment. 51 women were randomised to the fFN group and 57 women were randomised to management without fFN 108 (95%) of enrolled patients were randomised and included in analysis

Abbreviations: fFN, fetal fibronectin; NR, not reported

[a] Eight patients were entered into the study twice, as > 2 weeks had passed since the initial evaluation.

A summary of results from the diagnostic RCTs is provided in **Table 37**. These trials produced similar results. They indicated that there was no difference in medical resource usage in the management of preterm labour with the addition of fetal fibronectin testing in the American healthcare setting. The only exception occurred in the trial by Nguyen et al (2002) which reported a significantly increased length of stay in the triage unit for the fetal fibronectin group compared with current clinical practice (3.3 + 1.7 hours vs 2.7 + 1.7 hours, $p = 0.03$). The trial by Plaut et al (2003) reported a significant decrease in the length of stay for a subgroup of patients with known negative fetal fibronectin test results who were observed for > 6 hours, compared with current clinical practice (22.7 hours vs 37.8 hours, $p = 0.04$).

Lowe et al (2004) also identified a reduction in hospital admissions and length of stay in the known negative fetal fibronectin group compared with the known positive fetal fibronectin group (25.7% vs 63.6%, $p = 0.32$; median 0 days, range 0–1 vs median 1 day, range 0–3, $p = 0.008$; for hospital admissions and length of stay, respectively).

This trial did not however report a significant difference in hospital admissions and length of stay between the fetal fibronectin group and the current clinical practice group. This suggests that the positive fetal fibronectin group received more intensive management when test results were known.

Table 37 Results of diagnostic randomised controlled trials comparing fetal fibronectin testing with current clinical practice

Author (year)	Summary of results
Grobman (2004)	The fetal fibronectin test results did not affect medical resource usage, there was no significant difference in the use of tocolytics, corticosteroids or hospital admissions/length of stay
	The fetal fibronectin test results did not improve patient satisfaction or emotional state
	The fetal fibronectin test results did not improve the patient activity status (ie work status, level of leisure activity, need for extra assistance)
	Subgroup analysis of patients with and without cervical change did not find a significant difference in the management of patients when the fetal fibronectin results were known
	Subgroup analysis of first 50 patients and second 50 patients (ie physician learning curve) did not find a significant difference in the management of patients when the fetal fibronectin results were known
	Subgroup analysis of patients with and without private attending physicians did not find a significant difference in the management of patients when the fetal fibronectin results were known
Lowe (2004)	The fetal fibronectin test results did not affect medical resource usage, there was no significant difference in the use of tocolytics, corticosteroids, antibiotics or hospital admissions/length of stay
	Subgroup analysis of patients with gestation < 28 weeks and gestation $\geq$ 28 weeks did not find a significant difference in the management of patients when the fetal fibronectin results were known
	There was significantly fewer admissions in the fetal fibronectin negative group than the positive group (25.7% vs 63.6%, $p = 0.32$). The length of stay was also shorter in the fetal fibronectin negative group than the positive group (median 0 days, range 0–1 vs median 1 day, range 0–3, $p = 0.008$)
Nguyen (2002)	The fetal fibronectin test results did not affect medical resource usage, there was no significant difference in the use of tocolytics or hospital admissions
	The fetal fibronectin test increased the time spent in the triage unit (3.3 $\pm$ 1.7 hours vs. 2.7 $\pm$ 1.7 hours, $p = 0.03$)
Plaut (2003)	A known negative fetal fibronectin test result did not affect medical resource usage, there was no significant difference in length of stay
	A known negative fetal fibronectin test resulted in significant decrease in the length of stay for a subgroup of patients observed for > 6 hours (22.7 hours vs 37.8 hours, $p = 0.04$)

RCTs investigating effects of fetal fibronectin diagnostic testing on changes in patient management potentially offers the best available evidence for clinical utility of the test. There are however differences in the management of suspected preterm labour in the current clinical practice groups (< 50% of patients treated with tocolytics or corticosteroids) reported in these trials (**Table 38**) compared with the current Australian practice of treating nearly all patients who are in suspected preterm labour (expert opinion of the advisory panel). These differences limit the applicability of these studies for Australian settings.

Table 38 Summary of the management details reported in the current clinical practice groups in the diagnostic randomised controlled trials

Author (year)	Hospital admissions n/N (%)	Patients receiving tocolysis n/N (%)	Patients receiving corticosteroids n/N (%)
Grobman (2004)	14/50 (28)	9/50 (18)	10/50 (20)
Lowe (2004)	12/51(24)	23/51(45)	22/51(43)
Nguyen (2002)	NR	NR	NR
Plaut (2003)[a]	NR	6/57(11)[a]	–

Abbreviation: NR, not reported

[a] Aggressive therapy (this includes the use of magnesium sulphate, nifedipine, > 1 tocolytic, or any tocolytics used along with corticosteroids).

Non-randomised studies

There were four studies identified (Abenheim et al 2005; Joffe et al 1999; Foxman et al 2004; Parry et al 2006) that did not provide applicable information concerning the potential change in patient management from fetal fibronectin test results. The characteristics and results of these studies are shown in **Table 39** and Table 40, respectively.

The studies were not used in the analysis of patient management because Abenheim et al (2005) and Joffe et al (1999) presented management changes in relation to patient populations that including patients who were by definition ineligible for fetal fibronectin testing. Foxman et al (2004) and Parry et al (2006) inadequately reported participant patient characteristics making applicability to either the target or study population unclear.

Table 39 Characteristics of studies not evaluated in the assessment of fetal fibronectin testing on patient management

Author (year) Country	Study design	Patients (N)	Test characteristics
Abenheim (2005)[a] Canada	Historical case-control	Patients with singleton gestations and TPL symptoms Intact membranes and cervical dilation < 3 cm Gestational age 24–34 weeks Prevalence of preterm birth (< 37 weeks): Cases 8.6% (116) Controls 7.8% (116)	Sample from the posterior fornix using the TLI(IQ)™ system (single test)
Foxman (2004) USA	Diagnostic pre-test post-test study Jan 2002–Jun 2002	Patients with singleton gestation Gestational age 22–34 weeks (58)	Unclear
Joffe (1999)[a] USA	Historical case-control Case recruitment: Jul 1996–Jun 1997 Control recruitment: Jul 1995–Jun 1996	Patients with singleton or multiple gestations and TPL symptoms Intact membranes and cervical dilation < 3 cm Gestational age 24–35 weeks Prevalence of preterm birth (< 35 weeks): Cases 2.8% (1936) Controls 2.1% (1837)	Sample from the posterior fornix using an ELISA (single test)
Parry (2006) New Zealand	Historical case-control Case recruitment: Sep 2003–Nov 2003 Control recruitment: Jul 2002–Sep 2002	Patients with unspecified gestation with symptoms of TPL Gestational age 27–33 weeks Cases (9) Controls (11)	Unclear

Abbreviations: ELISA, enzyme-linked immunosorbent assay; NR, not reported; TPL, threatened preterm labour
[a] Data from a patient group including a patient ineligible for fetal fibronectin testing.
Note: In this current review, suspected preterm labour is termed threatened preterm labour.

Table 40 Results of studies not evaluated in the assessment of fetal fibronectin testing on patient management

Author (year)	Preterm birth definition	Protocol introduction	Study arm	Tocolytic use n/N (%)	Corticosteroid use n/N (%)	Hospital admissions n/N (%)	Mean length of stay (days)	Transfers n/N%
Abenheim[a] (2005)	Unclear	No	Control	–	–	37/116 (31.9)	5.2 ± 11.5	–
			Case	–	–	24/116 (20.7)	0.6 ± 1.4	–
Foxman (2004)	Unclear	Unclear	Pre-test	–	–	33/58 (56.9)	–	–
			Post-test	–	–	3/58 (5.2)	–	–
Joffe (1999)[a]	Included medically indicated birth	Yes	Control	184/1837 (10.0)	21/1837 (1.1)	516/1837 (28.1)	2.0 ± 1.7	–
			Case	153/1936 (7.9)	43/1936 (2.2)	329/1936 (17.0)	1.6 ± 1.4	–
Parry (2006)	Unclear	No	Control	9/11 (81.8)	9/11 (81.8)	–	3.8	–
			Case	5/9 (55.6)	5/9 (55.6)	–	2.5	–

[a] Data included a patient ineligible for fetal fibronectin testing.

Appendix E Supplementary economic data

There were six studies identified that did not provide applicable information concerning the economic analysis of fetal fibronectin testing. The characteristics and results of these studies are shown in **Table 41.**

Table 41 Economic analyses of fetal fibronectin testing

Reference	Country	Indication	Study design / population / brief results
Abenhaim et al (2005)	Canada	Resource utilisation and costing	Historical case control study Singleton pregnant women between 24 and 34 weeks of gestation and presented with signs and symptoms of preterm labour in a tertiary care hospital's birthing centre, 2002–2003 Management costs with (n = 116) vs without fFN test (n = 116), fFN test applied in 41% of study group Hospital admission rate: 12.1% vs 24.1% Duration of hospital stay: 0.6 ± 1.4 vs 5.2 ± 11.5 days Costs per test: CAD$ 141 ± 232 (AUD 141 ± 249)[a] Mean cost per admission: CAD$ 441 ± 5275 vs CAD$ 3666 ± 8159 (AUD 473 ± 5663 vs AUD 3935 ± 8759) Mean total cost per hospitalised patient: CAD$ 581 ± 976 vs CAD$ 3666 ± 8159 (AUD 624 ± 1048 vs AUD 3935 ± 8759) Mean total cost per patient presented with signs and symptoms of preterm labour: CAD$ 226 vs CAD$ 885 (AUD 243 vs 950) *Note: This publication does not explicitly state that costs were reported in CAD$. Because the study reports costs in Canada, it was assumed that CAD$ cost data were cited.*
Alonso et al (2004)[b]	Mexico	Resource utilisation and costing	Prospective longitudinal comparative study Singleton pregnant women between 24 and 34 weeks of gestation who presented at hospital with signs and symptoms of preterm labour, 2001–2002 Treatment of fFN negative (n = 304) vs positive women (n = 158). Women who tested positive were treated according to existing treatment protocol, if negative they were discharged within 24 hours if not contraindicated for other medical reasons Duration of hospital stay: 1.2 ± 0.5 vs 4.3 ± 0.9 days (fFN negative vs fFN positive) Mean hospital costs per patient including care for preterm neonates and mothers: MXN7522 (fFN negative) vs MXN22,660 (fFN positive) (AUD950 vs AUD2861)
Joffe et al (1999)	USA	Resource utilisation and costing	Historical case control study Singleton and multiple gestations between 24 and 34.9 weeks presented at a tertiary care hospital with signs and symptoms of preterm labour, 1995–1997 With fFN test (n = 1989) vs without fFN test (n = 1831) Hospital admission rate: 17.0% vs 28.1% Admission frequency per patient: 1.6 ± 1.1 vs 1.8 ± 1.3 times Duration of hospital stay: 1.6 ± 1.4 vs 2.0 ± 1.seven days Charges per patient: US$1354 ± 1458 vs US$1715 ± 1640 (AUD 2184 ± 2352 vs 2766 ± 2645)

Reference	Country	Indication	Study design / population / brief results
Mozurkewich et al (2000)	Canada	Cost-effectiveness analysis	Decision tree modelling of nine different management strategies for preterm labour, with varying approaches of applying fFN test, cervical length measurement, tocolytic and corticosteroid treatment Based on literature data, 1999 $ Cost-effectiveness as cost per RDS avoided and cost per death prevented compared with next most effective strategy: - Treat all with corticosteroids as outpatients, no tocolysis: CAD 167,000 per avoided RDS (AUD 170,565) - Cervical length plus corticosteroids: CAD 233,000 per avoided RDS (AUD 237,974); CAD 850,000 per avoided death (AUD 868,146) - Treat all with corticosteroids; tocolytics administered only for women with abnormal cervical length: CAD600,000 per avoided RDS (AUD 612,809), CAD6 million per avoided death (AUD 6.128 million) All other strategies dominated (more expensive and less effective) or with extended dominance (higher ICER than the next most effective strategy) *Note: This publication does not explicitly state that costs were reported in CAD. Because the study reports costs in Canada, it was assumed that CAD cost data were cited.*
Musaad et al (2005)	New Zealand	Resource utilisation and costing	Historical case control study Women with singleton and twin gestations between 24 and < 34 weeks presented at a hospital with signs and symptoms of preterm labour, year not stated—probably 2003; no exclusion of women who had sexual intercourse within 24 hours before fFN test With fFN test (n = 30) vs without fFN test (n = 30) Median duration of hospital stay: 1 (if fFN negative) vs 2 days Cost per patient: NZD 918 vs NZD943 (AUD 840 vs AUD 863) The authors stated that the cost savings were lower than expected, probably due to continued application of obstetric ultrasound for fFN negative women
Sullivan et al (2001)	USA	Resource utilisation and costing	Decision tree modelling of hospital treatment costs for preterm labour Three different management approaches: 1) fFN testing in all women presenting with threatened preterm labour 2) fFN testing in those who are admitted based on traditional criteria (following clinical examination) 3) no fFN test Hospital cost perspective Broad variation of preterm labour prevalence and admission rates fFN testing after decision of hospital admission based on traditional criteria may reduce the costs from hospital point of view

Abbreviations: AUD, Australian dollar; CAD, Canadian dollar (exchange rate at July 1, 2004, Mozurkewich et al at July 01, 1999); fFN test, fetal fibronectin test; ICER, incremental cost-effectiveness ratio; MXN, Mexican New Peso (exchange rate as by June 30, 2004); NZD, New Zealand dollar (exchange rate as by July 01, 2005; RDS, respiratory distress syndrome; SD, standard deviation; US$, US Dollar (exchange rate at July 1, 1998).

[a] Including costs for inappropriate or invalid tests, cost per test were CAD135 (AUD145).

[b] English translation of original article provided by Applicant.

Appendix F Studies included in the review

Diagnostic accuracy

Table 42 presents the characteristics and results extracted from included systematic reviews assessing the diagnostic accuracy of fetal fibronectin testing for predicting preterm labour.

Table 43 presents the characteristics and results extracted from included primary studies assessing the diagnostic accuracy of fetal fibronectin testing for predicting preterm labour.

Table 42 Characteristics and results of systematic reviews assessing the diagnostic accuracy of fetal fibronectin

Systematic review	Research question	Search strategy inclusion/exclusion criteria (included studies)	Methodology	Results	Comment[a]
AHRQ (2000)	What are the appropriate criteria for the diagnosis of preterm labour? How much positive or negative predictive value does the use of biologic markers add to clinical opinion in diagnosing preterm labour?	A detailed search strategy was described using Medline, EMBASE, International Pharmaceutical Abstracts, reference lists and grey literature Literature search was completed in 1999 Search terms included terms for premature labour combined with terms for biological markers Inclusion criteria: pregnant women with signs and symptoms of preterm labour, the use of a diagnostic biological marker, and an assessment of preterm birth Articles in English, French and German articles included Exclusion criteria: non-systematic review, < 40 subjects, wrong language, wrong patient group, wrong intervention, twin gestation (n = 16)	The literature search and data extraction were completed by independent reviewers; disagreements resolved by third reviewer or discussion Results of included studies were individually summarised An assessment of the quality of included studies was undertaken Results were not meta-analysed	Predictive values of fetal fibronectin (women in suspected preterm labour) for predicting delivery: within seven days ranged from 13% to 44% (PPV) and 98% to 100% (NPV) < 37 weeks ranged from 31% to 83% (PPV) and 69% to 92% (NPV)	High quality Limited validity - included low-level diagnostic studies
Chien (1997)	To determine whether cervicovaginal fetal fibronectin testing was had clinical value in predicting preterm birth	A brief search strategy was described using Medline and reference lists Literature search was completed in 1996 Search terms included terms for pregnancy combined with terms for fetal fibronectin Inclusion criteria: pregnant women symptomatic or asymptomatic for preterm delivery; cervicovaginal fetal fibronectin test < 37 weeks gestation; assessment of preterm birth No language restrictions Exclusion criteria: non-relevant, wrong patient group, inadequate description of patient group, non-systematic review, wrong outcomes, duplicate publications (n = 17)	The literature search and data extraction were completed by independent reviewers; disagreements resolved by third reviewer or discussion Results of included studies were individually summarised An assessment of the quality of included studies was undertaken Sources of heterogeneity were explored Results presented as pooled likelihood ratios	Summary LR of fetal fibronectin (women in suspected preterm labour) for predicting delivery: - within seven days was LR+ 5.0 (3.8, 6.4) and LR– 0.2 (0.1, 0.4) - < 34 weeks was LR+ 2.6 (1.8, 3.7) and LR– 0.2 (0.1, 0.5) - < 37 weeks was LR+ 4.6 (3.5, 6.1) and LR– 0.5 (0.4, 0.6) No explanation for heterogeneity was discovered Summary LR of fetal fibronectin (asymptomatic high risk women) for predicting delivery: - < 34 weeks was LR+ 2.4 (1.8, 3.2) and LR- 0.6 (0.4, 0.9) - < 37 weeks was LR+ 2.0 (1.5, 2.6) and LR- 0.4 (0.2, 0.8)	Medium quality - limited documentation and scope of the literature search Limited validity - included low-level diagnostic studies

Systematic review	Research question	Search strategy inclusion/exclusion criteria (included studies)	Methodology	Results	Comment[a]
Faron (1998)	To assess the cervicovaginal fetal fibronectin test to predict preterm delivery	A brief search strategy was described using Medline, conference proceedings and reference lists Literature search was completed in 1997 A description of the search terms was not presented Inclusion criteria: prospective cohort studies with women tested between 20–36 weeks gestation; fetal fibronectin analysed using the ELISA test with 50 ng/mL cut off; patients and physicians blind to test results; less than 20% of patients excluded from analysis No language restriction Exclusion criteria: non-relevant, wrong outcomes, wrong diagnostic test, < 80% of enrolled women in final analysis, large proportion of patient tested before 20 weeks (n = 29)	The details of the literature search and data extraction procedures were unclear Results of included studies were individually summarised No assessment of quality was undertaken Results presented as pooled likelihood ratios Sources of heterogeneity were not explored Authors of included studies contacted for more information	Summary LR of a single fetal fibronectin test (of women in suspected preterm labour) for predicting delivery: - < 34 weeks was LR+ 2.2 (1.6, 3.0) and LR– 0.3 (0.2, 0.6) - < 37 weeks was LR+ 3.5 (2.6, 4.6) and LR– 0.4 (0.3, 0.5) Summary LR of multiple fetal fibronectin testing (of women in suspected preterm labour) for predicting delivery: - < 34 weeks was LR+ 2.9 (2.0, 4.2) and LR– 0.3 (0.0, 3.0) - < 37 weeks was LR+ 2.7 (2.1, 3.6) and LR– 0.4 (0.2, 0.7)	Low quality - limited documentation and scope of the literature search - reporting of a number of methodology details is unclear Limited validity - included low-level diagnostic studies
Honest (2002)	To determine the accuracy with which a cervicovaginal fetal fibronectin test predicts spontaneous pre-term birth in women with or without symptoms of pre-term labour.	A detailed search strategy was described[b] using Medline, EMBASE, Pascal, Biosis, Cochrane Library, Medion, National Research Register, Scisearch, conference proceedings and reference lists Literature search was completed in 2001 Search terms included terms for premature labour combined with terms for diagnostic tests that assess the risk of preterm delivery combined with diagnostic accuracy terms Inclusion criteria: pregnant women, symptomatic or asymptomatic for preterm delivery; cervicovaginal fetal fibronectin test < 37 weeks gestation; known gestation at spontaneous birth; observational cohort design No language restriction Exclusion criteria: non-relevant, wrong outcomes, non-systematic review, duplicate publication, unobtainable (n = 68)	The literature search and data extraction were completed by independent reviewers; disagreements resolved by third reviewer or discussion Results of included studies were individually summarised An assessment of the quality of included studies was undertaken Sources of heterogeneity were explored Results presented as pooled likelihood ratios and SROC curves	Summary LR of fetal fibronectin (women in suspected preterm labour) for predicting delivery: - within 7–10 days was LR+ 5.4 (4.4, 6.7) and LR– 0.3 (0.2, 0.3) - 34 weeks was LR+ 3.6 (2.3, 5.7) and LR– 0.3 (0.2, 0.7) - 37 weeks was LR+ 3.3 (2.7, 3.9) and LR– 0.5 (0.4, 0.6) No explanation for heterogeneity was discovered	High quality Limited validity - included low-level diagnostic studies

Systematic review	Research question	Search strategy inclusion/exclusion criteria (included studies)	Methodology	Results	Comment[a]
ICSI (2000)	To assess the diagnostic accuracy, safety and clinical value of fetal fibronectin in the risk assessment for preterm birth	No search strategy was described, Medline, PreMedline and reference lists were searched Unclear when literature search was completed A description of the search terms was not presented Details of the inclusion/exclusion criteria were not reported (n = ?)	The details of the literature search and data extraction procedures were unclear A limited quality assessment was undertaken Results of included studies were individually summarised Results were not meta-analysed	Sensitivity and specificity of fetal fibronectin (women in suspected preterm labour) for predicting delivery < 37 weeks ranged from 36% to 83% (Sn) and 70% to 96% (Sp) Predictive values of fetal fibronectin (women in suspected preterm labour) for predicting delivery < 37 weeks ranged from 45% to 78% (PPV) and 76% to 100% (NPV)	Low quality - limited documentation and scope of the literature search - limited description of inclusion/exclusion criteria - reporting of a number of methodology details is unclear Limited validity - included low-level diagnostic studies
Lamont 2003	To prepare international clinical guidelines on the diagnosis, treatment and management of preterm labour	A brief search strategy was described using Medline, EMBASE, Biosis, Current Contents, Derwent Drug File Literature search was completed in 2001 Search terms included terms for fetal fibronectin combined with terms for cervical ultrasound Details of the inclusion/exclusion criteria were not reported (n = 6)	The details of the literature search and data extraction procedures were unclear Results were not meta-analysed	Fetal fibronectin has a high negative predictive value but a low positive predictive value	Low quality - limited documentation of the literature search - limited description of inclusion/exclusion criteria - reporting of a number of methodology details is unclear Limited validity - included diagnostic studies of unknown quality

Systematic review	Research question	Search strategy inclusion/exclusion criteria (included studies)	Methodology	Results	Comment[a]
Leitich (1999)	To determine the value of cervicovaginal fetal fibronectin as a marker for preterm delivery	A brief search strategy was described using Medline and EMBASE Literature search was completed in 1997 Search terms included terms for premature labour combined with terms for fetal fibronectin Inclusion criteria: original, published prospective studies of pregnant women < 37 weeks gestation with intact membranes; assessed using a cervicovaginal fetal fibronectin test; assessment of preterm birth Articles in English were included Exclusion criteria: not reported (n = 27)	The details of the literature search and data extraction procedures were unclear Results of included studies were individually summarised No assessment of quality was undertaken Sources of heterogeneity were not explored Results presented as pooled sensitivity and specificity as well as pooled predictive values	Sensitivity and specificity of fetal fibronectin (of women in suspected preterm labour) for predicting delivery: - within seven days was Sn 89% (80%, 97%) and Sp 86% (81%, 91%) - within 14 days was Sn 78% (70%, 86%) and Sp 86% (81%, 91%) - < 34 weeks was Sn 85% (73%, 96%) and Sp 68% (28%, 100%) - < 37 weeks was: Sn 60% (48%, 71%) and Sp 86% (82%, 89%) Sensitivity and specificity of fetal fibronectin (in asymptomatic high risk women) for predicting delivery: - within seven days was Sn 22% (3%, 60%) and Sp 97% (96%, 97%) - within 14 days was Sn 43% (0%, 95%) and Sp 95% (92%, 99%) - < 34 weeks was Sn 69% (20%, 100%) and Sp 74% (46%, 100%) - < 37 weeks was Sn 78% (63%, 93%) and Sp 78% (63%, 93%) Sensitivity and specificity of a single fetal fibronectin test (of women in suspected preterm labour) for predicting delivery: - < 34 weeks was Sn 85% (73%, 96%) and Sp 68% (28%, 100%) - > 37 weeks was Sn 60% (48%, 71%) and Sp 86% (82%, 89%)	Low quality - limited documentation and scope of the literature search - limited description of exclusion criteria - reporting of a number of methodology details is unclear Limited validity - included low-level diagnostic studies

Systematic review	Research question	Search strategy inclusion/exclusion criteria (included studies)	Methodology	Results	Comment[a]
Leitich (2003)	To determine the value of cervicovaginal fetal fibronectin as a marker for preterm delivery [update]	A brief search strategy was described using Medline and EMBASE Literature search was completed in 2002 Search terms included terms for premature labour combined with terms for fetal fibronectin Inclusion criteria: original, published prospective studies of pregnant women < 37 weeks gestation with intact membranes; assessed using a cervicovaginal fetal fibronectin test; assessment of preterm birth Articles in English were included Exclusion criteria: not reported (n = 40)	The details of the literature search and data extraction procedures were unclear No assessment of quality was undertaken Sources of heterogeneity were not explored Results presented as pooled sensitivity and specificity	Sensitivity and specificity of fetal fibronectin (women in suspected preterm labour) for predicting delivery: - within seven days was Sn 77% (67%, 88%) and Sp 87% (84%, 91%) - within 14 days was Sn 74% (67%, 82%) and Sp 87% (83%, 92%) - < 34 weeks was Sn 63% (37%, 90%) and Sp 86% (79%, 93%) - < 37 weeks was Sn 54% (43%, 65%) and Sp 85% (81%, 89%) Sensitivity and specificity of multiple fetal fibronectin testing (in asymptomatic high risk women) for predicting delivery: - < 34 weeks was Sn 92% (62%, 100%) and Sp 59% (47%, 71%) - < 37 weeks was Sn 78% (63%, 93%) and Sp 78% (63%, 93%)	Low quality - limited documentation and scope of the literature search - limited description of exclusion criteria - reporting of a number of methodology details is unclear Limited validity - included low-level diagnostic studies

Systematic review	Research question	Search strategy inclusion/exclusion criteria (included studies)	Methodology	Results	Comment[a]
Revah (1998)	To determine the clinical utility of fetal fibronectin as a predictor of preterm birth in patients with and without uterine contractions	A brief search strategy was described using Medline Literature search was completed in 1997 Search terms included terms for premature labour combined with terms for fetal fibronectin Inclusion criteria: prospective studies of women less than 37 weeks gestation with caregivers blinded to fetal fibronectin test results Articles in English were included Exclusion criteria: non-relevant, wrong outcomes, wrong patient group, fetal fibronectin not clearly blinded, non-systematic reviews (n = 24)	The literature search and data extraction were completed by independent reviewers; disagreements resolved by third reviewer or discussion Results of included studies were individually summarised No assessment of quality was undertaken Sources of heterogeneity were not explored Results presented as pooled sensitivity and specificity	Sensitivity and specificity of fetal fibronectin (of women in suspected preterm labour) for predicting delivery: - within seven days was Sn 98% (95%, 100%) and Sp 83% (82%, 85%) - within 14 days was Sn 82% (74%, 90%) and Sp 85% (83%, 87%) - < 34 weeks was Sn 87% (81%, 94%) and Sp 85% (81%, 89%) - < 37 weeks was Sn 54% (51%, 58%) and Sp 87% (85%, 88%) Predictive values of fetal fibronectin (of women in suspected preterm labour) for predicting delivery: - within seven days was PPV 15% (12%, 18%) and NPV 100% (99%, 100%) - within 14 days was PPV 25% (20%, 29%) and NPV 99% (99%, 100%) - < 34 weeks was PPV 39% (31%, 47%) and NPV 96% (93%, 98%) - < 37 weeks was PPV 58% (54%, 62%) and Sp 85% (84%, 87%)	Low quality - limited documentation and scope of the literature search - reporting of a number of methodology details is unclear Limited validity - included low-level diagnostic studies

Abbreviations: LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; Sn, sensitivity; Sp, specificity; SROC, summary receiver operator characteristic

[a] Quality determined after applying the quality criteria in **Appendix G**.

[b] Literature search described by Honest et al (2003).

Table 43 Characteristics and results of primary studies assessing the diagnostic accuracy of fetal fibronectin

Author (year), country, study design	Population (N)	Index test, birth definition	Study outcomes	Study quality[a]
Bartnicki (1996) Germany Prospective, non-consecutive patient enrolment Blinded comparison to reference standard	Patients with unspecified gestation and symptoms of TPL Intact membranes and cervical dilation < 2 cm Gestational age 22–35 weeks (112) Confounding factors: NR	Sample from the posterior fornix using the Fetal Fibronectin Enzyme Immunoassay™ (single test) Unclear birth definition	Preterm delivery within seven days of testing: – Prevalence 2/112 (1.8), PPV 5.9, NPV 100.0, Sn 100.0, Sp 70.9, Acc 71.4 Preterm delivery within 14 days of testing: – Prevalence 17/112 (15.2), PPV 41.2, NPV 96.2, Sn 82.4, Sp 78.9, Acc 79.5 Preterm delivery before 34 weeks gestation: – Prevalence 40/112 (35.7), PPV 79.4, NPV 83.3, Sn 67.5, Sp 90.3, Acc 82.1	Level III-1 P2, Q2 *Applicability*: Previous fibronectin test Cervical dilation < 2 cm Timeframe of testing *Quality*: Non-consecutive enrolment
Benattar (1997) France Prospective, non-consecutive patient enrolment Blinded comparison to reference standard	Patients with singleton or twin gestation and uterine contractions Intact membranes and cervical dilation < 3 cm Gestational age 24–36 weeks (124) Confounding factors: No recent sexual intercourse, no vaginal bleeding	Sample from exocervix or posterior fornix using an solid immunogold assay (single test) Unclear birth definition	Preterm delivery within seven days of testing: – Prevalence 9/124 (7.3), PPV 42.1, NPV 99.0, Sn 88.9, Sp 90.4, Acc 90.3 Preterm delivery within 14 days of testing: – Prevalence 16/124 (12.9), PPV 57.9, NPV 95.2, Sn 68.8, Sp 92.6, Acc 89.5 Preterm delivery before 37 weeks gestation: – Prevalence 25/124 (20.2), PPV 47.4, NPV 84.8, Sn 36.0, Sp 89.9, Acc 79.0	Level III-1 P2, Q2 *Applicability*: Previous fibronectin test Timeframe of testing *Quality*: Non-consecutive enrolment
Bittar (1996) Brazil Prospective, non-consecutive patient enrolment Unblinded Jan 1994–Jan 1995	Patients with singleton gestation who had a previous preterm birth, cervical cerclage, or uterine malformation Gestational age 24–34 weeks (102) Confounding factors: No recent sexual intercourse, no vaginal bleeding	Sample from exocervix using an solid immunogold assay (2 week intervals) Spontaneous birth	Preterm delivery before 37 weeks gestation: – Prevalence 38/102 (37.3), PPV 84.8, NPV 85.5, Sn 73.7, Sp 92.2, Acc 85.3	Level III-2 P2, Q3 *Applicability*: Previous fibronectin test Timeframe of testing *Quality*: Non-consecutive enrolment Unblinded

Author (year), country, study design	Population (N)	Index test, birth definition	Study outcomes	Study quality[a]
Burrus (1995) USA Prospective, non-consecutive patient enrolment Blinded comparison to reference standard Feb 1994–Oct 1994	Patients with unspecified gestation and uterine contractions Intact membranes and cervical dilation < 3 cm Gestational age 22–35 weeks (45) Confounding factors: NR	Sample from the cervix using an ELISA (single test) Unclear birth definition	Preterm delivery before 34 weeks gestation: - Prevalence 26/37 (70.3), PPV 79.3, NPV 62.5, Sn 88.5, Sp 45.5, Acc 75.7	Level III-1 P2, Q2 *Applicability*: Previous fibronectin test Timeframe of testing *Quality:* Non-consecutive enrolment
Coleman (1998) New Zealand Prospective, consecutive patient enrolment. Blinded comparison to reference standard May 1996–Jun 1997	Patients with singleton or twin gestations with uterine contractions or diagnosis of TPL Intact membranes and cervical dilation < 3 cm Gestational age 24–34 weeks (121) Confounding factors: Recent sexual intercourse, slight vaginal bleeding, no major vaginal bleeding	Sample from posterior fornix using the QUIKCHECK™ assay (single test) Included medically indicated birth	Preterm delivery within seven days of testing: - Prevalence 15/121 (12.4), PPV 37.0, NPV 94.7, Sn 66.7, Sp 84.0, Acc 81.8 Preterm delivery before 34 weeks gestation: - Prevalence 19/121 (15.7), PPV 37.0, NPV 90.4, Sn 52.6, Sp 83.3, Acc 78.5	Level II P2, Q1 *Applicability*: Previous fibronectin test
Grandi (1996) Argentina Prospective, consecutive patient enrolment Blinded comparison to reference standard Sep 1995–Dec 1995	Patients with singleton gestation with uterine contractions Intact membranes and cervical dilation < 3 cm Gestational age 24–36 weeks (26) Confounding factors: No recent sexual intercourse	Sample from the cervix using an ELISA (single test) Unclear birth definition	Preterm delivery before 37 weeks gestation: - Prevalence 8/26 (30.8), PPV 30.8, NPV 69.2, Sn 50.0, Sp 50.0, Acc 50.0	Level II P2, Q1 *Applicability*: Previous fibronectin test Timeframe of testing

Author (year), country, study design	Population (N)	Index test, birth definition	Study outcomes	Study quality[a]
Iams (1995) USA Prospective, non-consecutive patient enrolment Blinded comparison to reference standard	Patients with unspecified gestation with symptoms of TPL Intact membranes and cervical dilation < 3 cm Gestational age 24–34 weeks (192) Confounding factors: Vaginal bleeding	Sample from the exocervix or posterior fornix using an ELISA (single test) Spontaneous birth	Preterm delivery within seven days of testing: – Prevalence 14/192 (7.3), PPV 28.9, NPV 99.3, Sn 92.9, Sp 82.0, Acc 82.8 Preterm delivery within 14 days of testing: – Prevalence 26/192 (13.5), PPV 40.0, NPV 94.6, Sn 69.2, Sp 83.7, Acc 81.8 Preterm delivery before 37 weeks gestation: – Prevalence 62/192 (32.3), PPV 60.0, NPV 76.2, Sn 43.5, Sp 86.2, Acc 72.4	Level III-1 P2, Q2 *Applicability*: Previous fibronectin test *Quality*: Non-consecutive enrolment
Inglis (1994) USA Prospective, non-consecutive patient enrolment Blinded comparison to reference standard	Patients with singleton gestations and diagnoses of TPL Intact membranes Gestational age < 37 weeks (38) Confounding factors: NR	Sample from the endocervix or posterior fornix using an ELISA (single test) Unclear birth definition	Preterm delivery before 37 weeks gestation: – Prevalence 9/38 (23.7), PPV 43.8, NPV 90.9, Sn 77.8, Sp 69.0, Acc 71.1	Level III-1 P2, Q2 *Applicability*: Previous fibronectin test Unclear cervical dilation Unclear testing timeframe *Quality*: Non-consecutive enrolment
Irion (1995) Switzerland Prospective, non-consecutive patient enrolment Blinded comparison to reference standard	Patients with unspecified gestation with uterine contractions Intact membrane and cervical dilation < 2 cm Gestational age 24–36 weeks (64) Confounding factors: No recent sexual intercourse, no vaginal bleeding	Sample from the endocervix using an ELISA (single test) Unclear birth definition	Preterm delivery before 37 weeks gestation: – Prevalence 22/64 (34.4), PPV 57.7, NPV 81.6, Sn 68.2, Sp 73.8, Acc 71.9	Level III-1 P2, Q2 *Applicability*: Previous fibronectin test Cervical dilation < 2 cm Timeframe of testing *Quality*: Non-consecutive enrolment

Author (year), country, study design	Population (N)	Index test, birth definition	Study outcomes	Study quality[a]
Langer (1997) France Prospective, non-consecutive patient enrolment Blinded comparison to reference standard Feb 1994–May 1995	Patients with unspecified gestation with uterine contractions Intact membrane and cervical dilation < 2 cm Gestational age 24–34 weeks (61) Confounding factors: No recent sexual intercourse, no vaginal bleeding	Sample from the endocervix or exocervix using an ELISA (single test) Unclear birth definition	Preterm delivery before 37 weeks gestation: – Prevalence 18/61 (29.5), PPV 55.6, NPV 81.4, Sn 55.6, Sp 81.4, Acc 73.8	Level III-1 P2, Q2 *Applicability*: Previous fibronectin test Cervical dilation < 2 cm *Quality*: Non-consecutive enrolment
La Shay (2000) USA Prospective, non-consecutive patient enrolment Blinded comparison to reference standard	Patients with singleton gestation and uterine contractions Intact membranes and cervical dilation < 3 cm Gestational age 24–34 weeks (118) Confounding factors: No recent sexual intercourse, no obvious bleeding, no recent cervical manipulation	Sample from the endocervix or posterior fornix using the Fetal Fibronectin Enzyme Immunoassay™ (single test) Unclear birth definition	Preterm delivery before 37 weeks gestation: – Prevalence 34/118 (28.8), PPV 58.8, NPV 76.2, Sn 29.4, Sp 91.7, Acc 73.7	Level III-1 P2, Q2 *Applicability*: Previous fibronectin test *Quality*: Non-consecutive enrolment

Author (year), country, study design	Population (N)	Index test, birth definition	Study outcomes	Study quality[a]
Leeson (1996) UK Prospective, non-consecutive patient enrolment Blinded comparison to reference standard Jul 1992–Feb 1994	Patients with singleton or multiple gestations and prior spontaneous preterm births, uterine malformations or cervical sutures Gestational age 24–34 weeks (42) Confounding factors: No recent sexual intercourse, no major vaginal bleeding, slight vaginal bleeding	Sample from the posterior fornix using the Fetal Fibronectin Membrane Immunoassay™ (2 week intervals) Spontaneous birth	Preterm delivery within seven days of testing (per sample): – Prevalence 2/168 (1.2), PPV 12.5, NPV 100.0, Sn 100.0, Sp 91.6, Acc 91.7 Preterm delivery within 14 days of testing (per sample): – Prevalence 7/167 (4.2), PPV 31.3, NPV 98.7, Sn 71.4, Sp 93.1, Acc 92.2 Preterm delivery within 14 days of testing: – Prevalence 5/42 (11.9), PPV 36.4, NPV 96.8, Sn 80.0, Sp 81.1, Acc 81.0 Preterm delivery before 37 weeks gestation (per sample): – Prevalence 47/159 (29.6), PPV 50.0, NPV 72.7, Sn 17.0, Sp 92.9, Acc 70.4 Preterm delivery before 37 weeks gestation: – Prevalence 13/40 (32.5), PPV 63.6, NPV 79.3, Sn 53.8, Sp 85.2, Acc 75.0	Level III-1 P2, Q2 *Applicability*: Previous fibronectin test Timeframe of testing *Quality*: Non-consecutive enrolment
Lockwood (1991) USA Prospective, non-consecutive patient enrolment Blinded comparison to reference standard	Patients with unspecified gestation and uterine contractions Intact membranes Gestational age < 37 weeks (117) Confounding factors: No recent sexual intercourse, vaginal bleeding	Sample from the cervix or posterior fornix using the ROM-check™ (single test) Unclear birth definition	Preterm delivery before 37 weeks gestation: – Prevalence 60/117 (51.3), PPV 83.1, NPV 81.0, Sn 81.7, Sp 82.5, Acc 82.1	Level III-1 P2, Q2 *Applicability*: Previous fibronectin test Unclear cervical dilation Unclear testing timeframe *Quality*: Non-consecutive enrolment

Author (year), country, study design	Population (N)	Index test, birth definition	Study outcomes	Study quality[a]
Malak (1996) UK Prospective, non-consecutive patient enrolment Blinded comparison to reference standard	Patients with singleton gestations and symptoms of TPL Intact membranes and cervical dilation < 2 cm Gestational age 24–34 weeks (112) Confounding factors: No recent sexual intercourse, no vaginal bleeding	Sample from the exocervix or posterior fornix using an ELISA (single test) Spontaneous birth	Preterm delivery within seven days of testing: – Prevalence 10/112 (8.9), PPV 44.4, NPV 97.9, Sn 80.0, Sp 90.2, Acc 89.3 Preterm delivery within 14 days of testing: – Prevalence 11/112 (9.8), PPV 50.0, NPV 97.9, Sn 81.8, Sp 91.1, Acc 90.2 Preterm delivery before 37 weeks gestation: – Prevalence 22/112 (19.6), PPV 77.8, NPV 91.5, Sn 63.6, Sp 95.6, Acc 89.3	Level III-1 P2, Q2 *Applicability*: Previous fibronectin test Cervical dilation < 2 cm *Quality*: Non-consecutive enrolment
Morrison (1993) USA Prospective, non-consecutive patient enrolment Blinded comparison to reference standard	Patients with singleton gestations and uterine contractions Intact membranes and cervical dilation < 1 cm Gestational age 24–36 weeks (28) Confounding factors: No recent sexual intercourse, slight vaginal bleeding, no major vaginal bleeding	Sample from the exocervix using an ELISA (single test) Unclear birth definition	Preterm delivery before 37 weeks gestation: – Prevalence 10/28 (35.7), PPV 64.3, NPV 92.9, Sn 90.0, Sp 72.2, Acc 78.6	Level III-1 P2, Q2 *Applicability*: Previous fibronectin test Cervical dilation < 1 cm Timeframe of testing *Quality*: Non-consecutive enrolment
Morrison (1996) USA Prospective, non-consecutive patient enrolment Blinded comparison to reference standard	Patients with singleton or multiple gestations and prior spontaneous preterm births, uterine malformations or history of second trimester abortions Gestational age 26–28 weeks (85) Confounding factors: No major vaginal bleeding	Sample from the exocervix using an ELISA (single test) Unclear birth definition	Preterm delivery before 34 weeks gestation: – Prevalence 14/85 (16.5), PPV 42.9, NPV 88.7, Sn 42.9, Sp 88.7, Acc 81.2	Level III-1 P2, Q2 *Applicability*: Previous fibronectin test *Quality*: Non-consecutive enrolment

Author (year), country, study design	Population (N)	Index test, birth definition	Study outcomes	Study quality[a]
Nageotte (1994) USA Prospective, non-consecutive patient enrolment Blinded comparison to reference standard	Patients with singleton, twin or triplet gestations with prior spontaneous preterm births, uterine malformations or cervical sutures Gestational age 24–34 weeks (87) Confounding factors: NR	Sample from the exocervix or posterior fornix using the Fetal Fibronectin Membrane Immunoassay™ (1 week intervals) Spontaneous birth	Preterm delivery before 34 weeks gestation: – Prevalence 13/87 (14.9), PPV 28.6, NPV 97.8, Sn 92.3, Sp 59.5, Acc 64.4 Preterm delivery before 37 weeks gestation (per sample): – Prevalence 73/678 (10.8), PPV 21.4, NPV 93.4, Sn 56.2, Sp 75.0, Acc 73.0 Preterm delivery before 37 weeks gestation: – Prevalence 27/87 (31.0), PPV 51.1, NPV 92.5, Sn 88.9, Sp 61.7, Acc 70.1	Level III-1 P2, Q2 *Applicability*: Previous fibronectin test Timeframe of testing *Quality*: Non-consecutive enrolment
Parker (1995) Australia Prospective, non-consecutive patient enrolment Blinded comparison to reference standard Apr 1994–Dec 1994	Patients with singleton gestation and diagnoses of TPL Intact membranes and cervical dilation < 2 cm Gestational age 20–34 weeks (36) Confounding factors: No recent sexual intercourse	Sample from the exocervix or posterior fornix using the Fetal Fibronectin Membrane Immunoassay™ (single test) Spontaneous birth	Preterm delivery before 34 weeks gestation: – Prevalence 5/36 (13.9), PPV 45.5, NPV 100.0, Sn 100.0, Sp 80.6, Acc 83.3	Level III-1 P2, Q2 *Applicability*: Previous fibronectin test Cervical dilation < 2 cm Timeframe of testing *Quality*: Non-consecutive enrolment
Paternoster (2000) Italy Non-consecutive patient enrolment Unblinded	Patients with singleton or multiple gestations with previous preterm births, cervical cerclage, uterine malformation, history of second trimester abortions, placenta previa, gestational hypertension, intrauterine growth restriction, polydramnios, pre-eclampsia Gestational age 24–34 weeks (120) Confounding factors: NR	Sample from the vagina using the Fetal Fibronectin Membrane Immunoassay™ Spontaneous birth	Preterm delivery before 37 weeks gestation (per sample): – Prevalence 53/161(32.9), PPV 42.1, NPV 89.4, Sn 90.6, Sp 38.9, Acc 55.9	Level III-2 P2, Q3 *Applicability*: Previous fibronectin test Unknown sampling interval *Quality*: Non-consecutive enrolment Unblinded

Author (year), country, study design	Population (N)	Index test, birth definition	Study outcomes	Study quality[a]
Peaceman (1997) USA Prospective, non-consecutive patient enrolment Blinded comparison to reference standard	Patients with singleton, twin or triplet gestations and symptoms of TPL Intact membranes and cervical dilation < 3 cm Gestational age 24–35 weeks (763) Confounding factors: Vaginal bleeding	Sample from the posterior fornix using an ELISA (single test) Included medically indicated birth	Preterm delivery within seven days of testing: – Prevalence 23/763 (3.0), PPV 13.3, NPV 99.5, Sn 87.0, Sp 82.4, Acc 82.6 Preterm delivery within 14 days of testing: – Prevalence 30/763 (3.9), PPV 16.7, NPV 99.2, Sn 83.3, Sp 82.9, Acc 83.0 Preterm delivery before 37 weeks gestation: – Prevalence 162/763 (21.2), PPV 44.7, NPV 84.5, Sn 41.4, Sp 86.2, Acc 76.7	Level III-1 P2, Q2 *Applicability*: Previous fibronectin test Timeframe of testing *Quality*: Non-consecutive enrolment
Rinehart (2001) USA Prospective, non-consecutive patient enrolment Blinded comparison to reference standard Mar 1998–Jun 1999	Patients with singleton or twin gestation with symptoms of TPL Intact membranes and cervical dilation < 2 cm Gestational age 24–34 weeks (235) Confounding factors: No recent sexual intercourse, no recent cervical manipulation, no major vaginal bleeding, slight vaginal bleeding	Unclear test description Included medically indicated birth	Preterm delivery within seven days of testing: – Prevalence 28/235 (11.9), PPV 33.3, NPV 93.6, Sn 57.1, Sp 84.5, Acc 81.3 Preterm delivery before 37 weeks gestation: – Prevalence 100/235 (42.6), PPV 72.9, NPV 65.2, Sn 35.0, Sp 90.4, Acc 66.8	Level III-1 P2, Q2 *Applicability*: Unclear fibronectin test Cervical dilation < 2 cm *Quality*: Non-consecutive enrolment
Rizzo (1996) Italy Prospective, non-consecutive patient enrolment Blinded comparison to reference standard Jan 1993–Sep 1995	Patients with singleton gestations and uterine contractions Intact membranes and cervical dilation < 3 cm Gestational age 24–36 weeks (108) Confounding factors: NR	Sample from the exocervix or the posterior fornix using an ELISA (single test) Unclear birth definition	Preterm delivery before 37 weeks gestation: – Prevalence 47/108 (43.5), PPV 81.4, NPV 81.5, Sn 74.5, Sp 86.9, Acc 81.5	Level III-1 P2, Q2 *Applicability*: Previous fibronectin test Timeframe of testing *Quality*: Non-consecutive enrolment

Author (year), country, study design	Population (N)	Index test, birth definition	Study outcomes	Study quality[a]
Rizzo (1997) Italy Prospective, non-consecutive patient enrolment Blinded comparison to reference standard Jan 1994–Sep 1996	Patients with singleton gestations and uterine contractions Intact membranes and cervical dilation < 3 cm Gestational age 24–36 weeks (106) Confounding factors: NR	Sample from the exocervix or the posterior fornix using an ELISA (single test) Unclear birth definition	Preterm delivery before 37 weeks gestation: – Prevalence 49/106 (46.2), PPV 76.9, NPV 83.3, Sn 81.6, Sp 78.9, Acc 80.2	Level III-1 P2, Q2 *Applicability*: Previous fibronectin test Timeframe of testing *Quality*: Non-consecutive enrolment
Rozenberg (1996) France Prospective, non-consecutive patient enrolment Blinded comparison to reference standard Oct 1993– Mar 1994	Patients with unspecified gestation and uterine contractions Intact membranes Gestational age 24–34 weeks (56) Confounding factors: No recent sexual intercourse	Sample from the posterior fornix using the Fetal Fibronectin Enzyme Immunoassay™ (single test) Unclear birth definition	Preterm delivery before 37 weeks gestation: – Prevalence 20/56 (35.7), PPV 75.0, NPV 80.0, Sn 60.0, Sp 88.9, Acc 78.6	Level III-1 P2, Q2 *Applicability*: Previous fibronectin test Unclear cervical dilation *Quality*: Non-consecutive enrolment
Schmitz (2006) France Prospective, non-consecutive patient enrolment Blinded comparison to reference standard Jan 1997–May 2000	Patients with singleton gestations and uterine contractions Intact membranes and cervical dilation < 3 cm Gestational age 18–35 weeks (359) Confounding factors: No recent sexual intercourse, no vaginal bleeding, no recent cervical manipulation	Sample from the posterior fornix using a ELISA (single test) Spontaneous birth	Preterm delivery within seven days of testing: – Prevalence 23/359 (6.4), PPV 21.1, NPV 98.5, Sn 82.6, Sp 78.9, Acc 79.1	Level III-1 P2, Q2 *Applicability*: Previous fibronectin test Timeframe of testing *Quality*: Non-consecutive enrolment

Author (year), country, study design	Population (N)	Index test, birth definition	Study outcomes	Study quality[a]
Senden (1996) Scotland Prospective, non-consecutive patient enrolment Blinded comparison to reference standard	Patients with singleton gestations and uterine contractions Intact membranes and cervical dilation < 4 cm Gestational age 25–35 weeks (25) Confounding factors: Vaginal bleeding	Sample from the posterior fornix using the Fetal Fibronectin Membrane Immunoassay™ (single test) Included medically indicated birth	Preterm delivery within seven days of testing: – Prevalence 3/25 (12.0), PPV 50.0, NPV 100.0, Sn 100.0, Sp 86.4, Acc 88.0	Level III-1 P2, Q2 *Applicability*: Previous fibronectin test Cervical dilation < 4 cm Timeframe of testing *Quality*: Non-consecutive enrolment
Skoll (2006) Canada Prospective, non-consecutive patient enrolment Blinded comparison to reference standard	Patients with singleton, twin or triplet gestations and diagnoses of TPL Intact membranes Gestational age 24–34 weeks (149) Confounding factors: No major vaginal bleeding	Sample from the posterior fornix using the TLI(IQ)TM system (single test) Unclear birth definition	Preterm delivery within seven days of testing: – Prevalence 15/149 (10.1), PPV 37.5, NPV 97.4, Sn 80.0, Sp 85.1, Acc 84.6	Level III-1 P2, Q2 *Applicability*: Unclear cervical dilation *Quality*: Non-consecutive enrolment
Tekesin (2005) Germany Prospective, consecutive patient enrolment. Blinded comparison to reference standard Nov 2001–Jan 2004	Patients with singleton gestations and uterine contractions Intact membranes and cervical dilation < 3 cm Gestational age 24–35 weeks (170) Confounding factors: No recent sexual intercourse, no recent cervical manipulation, no vaginal bleeding	Sample from the cervix using the TLI(IQ)™ system (single test) Spontaneous birth	Preterm delivery within seven days of testing: – Prevalence 11/170 (6.5), PPV 19.6, NPV 98.4, Sn 81.8, Sp 76.7, Acc 77.1 Preterm delivery within 14 days of testing: – Prevalence 16/170 (9.4), PPV 30.4, NPV 98.4, Sn 87.5, Sp 79.2, Acc 80.0 Preterm delivery before 34 weeks gestation: – Prevalence 28/170 (16.5), PPV 43.5, NPV 93.5, Sn 71.4, Sp 81.7, Acc 80.0 Preterm delivery before 37 weeks gestation: – Prevalence 45/170 (26.5), PPV 67.4, NPV 88.7, Sn 68.9, Sp 88.0, Acc 82.9	Level II P2, Q1 *Applicability*: Timeframe of testing

Author (year), country, study design	Population (N)	Index test, birth definition	Study outcomes	Study quality[a]
Tsoi (2006) UK and South Africa Prospective, non-consecutive patient enrolment Blinded comparison to reference standard Feb 2002–Jun 2003	Patients with singleton gestations and uterine contractions Intact membranes and cervical dilation < 3 cm Gestational age 24–36 weeks (195) Confounding factors: NR	Sample from the endocervix or posterior fornix using the Fetal Fibronectin Membrane Immunoassay™ (single test) Unclear birth definition	Preterm delivery within seven days of testing: – Prevalence 19/195 (9.7), PPV 21.2, NPV 99.1, Sn 94.7, Sp 61.9, Acc 65.1	Level III-1 P2, Q2 *Applicability*: Previous fibronectin test Timeframe of testing *Quality*: Non-consecutive enrolment
Volumenie (2001) France Prospective, consecutive patient enrolment Blinded comparison to reference standard Jan 1998–Dec 1998	Patients with singleton gestations and uterine contractions Intact membranes and cervical dilation < 4 cm Gestational age 24–36 weeks (130) Confounding factors: No recent sexual intercourse, no vaginal bleeding	Sample from the cervix using the ROM-check™ membrane immunoassay (single test) Unclear birth definition	Preterm delivery before 37 weeks gestation: – Prevalence 32/120 (26.7), PPV 19.1, NPV 68.5, Sn 28.1, Sp 56.8, Acc 49.2	Level II P2, Q1 *Applicability*: Previous fibronectin test Cervical dilation < 4 cm Timeframe of testing
Zamora (2000) Venezuela Prospective, non-consecutive patient enrolment Double blind	Patients with unspecified gestations and uterine contractions Intact membranes Gestational age 28–36 weeks (22) Confounding factors: No recent sexual intercourse, no recent cervical manipulation	Sample from the exocervix using an ELISA (single test) Unclear birth definition	Preterm delivery before 37 weeks gestation: – Prevalence 3/22 (13.6), PPV 60.0, NPV 100.0, Sn 100.0, Sp 88.2, Acc 81.8	Level III-1 P2, Q2 *Applicability*: Previous fibronectin test Unclear cervical dilation *Quality*: Non-consecutive enrolment

Abbreviations: PPV, positive predictive value; NPV, negative predictive value; Sn, sensitivity, Sp, specificity; fFN, fetal fibronectin
[a] According to criteria outlined in **Table 7**, **Table 8** and **Appendix G**.

Patient management

Table 44 presents the characteristics and results extracted from included randomised controlled trials assessing the affect of fetal fibronectin testing on patient management.

Table 45 presents the characteristics and results extracted from included non-randomised controlled trials assessing the affect of fetal fibronectin testing on patient management.

Table 44 Characteristics and results of randomised controlled trials assessing the affect of fetal fibronectin testing on patient management

Author (year)/ country/ study design	Population (N)	Index test, current clinical practice (CCP)	Study outcomes	Study quality
Grobman (2004) USA Diagnostic RCT	Inclusion criteria: Patients with symptoms of preterm labour (primary symptom– uterine contractions, > 6 contraction per hour by external tocodynometry); singleton gestation between 24–34 weeks Exclusion criteria: Vaginal bleeding, cerclage, non-intact amniotic membranes, > 3 cm cervical dilation, cervical manipulation within 24 hours, already received hospital-based observation, admission or treatment Determination of gestational age: NR	Index test: Cervicovaginal samples swabbed from the posterior vaginal fornix. Samples analysed using the Rapid Fetal Fibronectin analyser CCP: Standardised evaluation including a focused history, assessment of fetal heart tones, assessment of uterine contraction frequency, digital cervical examination and a physical examination	Fetal fibronectin test results did not affect medical resource usage, there was no significant difference in the use of tocolytics, corticosteroids or hospital admissions/length of stay Fetal fibronectin test results did not improve patient satisfaction or emotional state Fetal fibronectin test results did not improve the patient activity status (ie. work status, level of leisure activity, need for extra assistance) Subgroup analysis of patients with and without cervical change did not find a significant difference in the management of patients when the fetal fibronectin results were known Subgroup analysis of first 50 patients and second 50 patients (ie. physician learning curve) did not find a significant difference in the management of patients when the fetal fibronectin results were known Subgroup analysis of patients with and without private attending physicians did not find a significant difference in the management of patients when the fetal fibronectin results were known	Randomisation was performed the use of computer-generated random assignment Patients and physicians were not blinded 100 patients were randomised. 50 women to the fFN group and 50 women to management without fFN. All patients were included in the analysis

Author (year)/ country/ study design	Population (N)	Index test, current clinical practice (CCP)	Study outcomes	Study quality
Lowe (2004) USA Diagnostic RCT	Inclusion criteria: Patients with symptoms of preterm labour (uterine contractions and/or cervical change); > 16 years of age; singleton or multiparous gestations between 23–34 weeks. (fFN testing was delayed in patients who had cervical manipulation within 24 hours) Exclusion criteria: Vaginal bleeding, cerclage, non-intact amniotic membranes, > 3 cm cervical dilation for singleton gestation or > 4 cm cervical dilation for multiparous gestation Determination of gestational age: Determined from last menstrual period and first or early second-trimester ultrasound. In the case of discrepancies ultrasound data were used	Index test: Cervicovaginal samples swabbed from the posterior vaginal fornix. Samples were sent to the laboratory and analysed within the hour (presumably Rapid Fetal Fibronectin analyser) CCP: NR	The fetal fibronectin test results did not affect medical resource usage, there was no significant difference in the use of tocolytics, corticosteroids, antibiotics or hospital admissions/length of stay Subgroup analysis of patients with gestation < 28 weeks and gestation > 28 weeks did not find a significant difference in the management of patients when the fetal fibronectin results were known There was significantly fewer admissions in the fetal fibronectin negative group than the positive group (25.7% vs 63.6%, $p = 0.32$). The length of stay was also shorter in the fetal fibronectin negative group than the positive group (median 0 days, range 0–1 vs median 1 day, range 0–3, $p = 0.008$)	Randomisation was achieved through the use of a computer-generated table in blocks of 10. Separate randomisation tables were used for gestations of < 28 weeks and > 28 weeks Patients and physicians were not blinded 110 patients were available for enrolment: 46 randomised to the fFN group; 51 randomised to management without fFN 97 (88%) of enrolled patients were randomised and included in analysis
Nguyen (2002) [Abstract only] USA Diagnostic RCT	Inclusion criteria: Patients with symptoms of preterm labour and gestation between 24–35 weeks Exclusion criteria: Abdominal trauma, non-intact amniotic membranes, > 3 cm cervical dilation, vaginal bleeding, non-reassuring fetal heart tracing, history of tocolysis in current pregnancy, recent digital examination or intercourse Determination of gestational age: NR	Index test: Cervicovaginal samples swabbed from the posterior vaginal fornix. Samples were analysed using the Rapid Fetal Fibronectin analyser CCP: Serial digital examinations	The fetal fibronectin test results did not affect medical resource usage, there was no significant difference in the use of tocolytics or hospital admissions The fetal fibronectin test increased the time spent in the triage unit (3.3 + 1.7 hours vs. 2.7 + 1.7 hours, $p = 0.03$)	Randomisation procedure not reported Patients and physicians were not blinded 77 patients were available for enrolment: 42 randomised to the fFN group; 35 randomised to management without fFN

Author (year)/ country/ study design	Population (N)	Index test, current clinical practice (CCP)	Study outcomes	Study quality
Plaut (2003) USA Diagnostic RCT	Inclusion criteria: Patients with symptoms of preterm labour, and singleton or multiparous gestations between 24–34 weeks Exclusion criteria: Vaginal bleeding, cerclage, non-intact amniotic membranes, > 3 cm cervical dilation, cervical manipulation within 24 hours, previous fFN testing within two weeks Determination of gestational age: NR	Index test: Cervicovaginal samples swabbed from the posterior vaginal fornix. Samples were analysed using the Rapid Fetal Fibronectin analyser CCP: NR	A known negative fetal fibronectin test result did not affect medical resource usage, there was no significant difference in length of stay A known negative fetal fibronectin test resulted in significant decrease in the length of stay for a subgroup of patients observed for > 6 hours (22.7 hours vs. 37.8 hours, $p = 0.04$)	Randomisation by means of sequentially numbered envelopes that matched patient enrolment forms on labour and delivery Patients and physicians were not blinded 114 patients were available for enrolment: 51 randomised to the fFN group; 57 randomised to management without fFN 108 (95%) of enrolled patients were randomised and included in analysis

Abbreviations: RCT, randomised controlled trial; CCP, current clinical practice; NR, not reported; fFN, fetal fibronectin

Table 45 Characteristics and results of non-randomised controlled trials assessing the affect of fetal fibronectin testing on patient management

Author (year) Country Study design	Population (N)	Index test, birth definition	Study outcomes	Study quality
Abenheim (2005) Canada Historical case-control	Patients with singleton gestations and symptoms of TPL Intact membranes and cervical dilation < 3 cm Gestational age 24–34 weeks Prevalence of preterm birth (< 37 weeks): Cases 8.6% (116) Controls 7.8% (116) Confounding factors: No vaginal bleeding, No recent sexual intercourse, No recent cervical manipulation	Sample from the posterior fornix using the TLI(IQ)^{TM} system (single test) Unclear birth definition No protocol introduction	Hospital admissions: Cases 24/116 (20.7) Control 37/116 (31.9) Mean length of stay (days): Cases 0.6 ± 1.4 Control 5.2 ± 11.5	P3, Q3 *Applicability*: Includes patients ineligible for fetal fibronectin testing *Quality*: Historical case-control study
Foxman (2004) USA Diagnostic pre-test post-test study Jan 2002–Jun 2002	Patients with singleton gestations Gestational age 22–34 weeks (58) Confounding factors: NR	Unclear Unclear birth definition Unclear protocol introduction	Hospital admissions: Pre-test 33/58 (56.9) Post-test 3/58 (5.2)	P3, Q2 *Applicability*: Inadequate description of patient population *Quality*: Non-consecutive enrolment
Joffe (1999) USA Historical case-control Case Recruitment: Jul 1996–Jun 1997 Control Recruitment: Jul 1995–Jun 1996	Patients with singleton or multiple gestations and symptoms of TPL Intact membranes and cervical dilation < 3 cm Gestational age 24–35 weeks Prevalence of preterm birth (< 35 weeks): Cases 2.8% (1936) Controls 2.1% (1837) Confounding factors: No vaginal bleeding or recent sexual intercourse	Sample from the posterior fornix using an ELISA (single test) Included medically indicated birth Protocol introduction	Tocolytic usage: Cases 153/1936 (7.9) Control 184/1837 (10.0), Corticosteroid usage: Cases 43/1936 (2.2) Control 21/1837 (1.1) Hospital admissions: Cases 329/1936 (17.0) Control 516/1837 (28.1) Mean length of stay (days): Cases 1.6 ± 1.4 Control 2.0 ± 1.7	P3, Q3 *Applicability*: Includes patients ineligible for fetal fibronectin testing *Quality*: Historical case-control study

Author (year) Country Study design	Population (N)	Index test, birth definition	Study outcomes	Study quality
Musaad (2005) New Zealand Historical case-control	Patients with singleton or twin gestations and symptoms of TPL Intact membranes and cervical dilation < 3 cm Gestational age 24–34 weeks Prevalence of preterm birth (< 37 weeks): Cases 40% (30) Controls 30% (30) Confounding factors: No vaginal bleeding or recent sexual intercourse	Sample from the exocervix or posterior fornix using the TLI(IQ)™ system (single test) Unclear birth definition Protocol introduction	Tocolytic usage: Cases 10/30 (33.3) Control 22/30 (73.3) Corticosteroid usage: Cases 11/30 (36.7) Control 29/30 (96.7) Mean length of stay (days): Cases 1.52 ± 1.16 Control 2.7 ± 2.3	P1, Q3 *Quality*: Historical case-control study
Parry (2006) New Zealand Historical case-control Case Recruitment: Sep 2003–Nov 2003 Control Recruitment: Jul 2002–Sep 2002	Patients with unspecified gestations and symptoms of TPL Gestational age 27–33 weeks Cases (9) Controls (11) Confounding Factors: NR	Unclear Unclear birth definition No protocol introduction	Tocolytic usage: Cases 5/9 (55.6) Control 9/11 (81.8) Corticosteroid usage: Cases 5/9 (55.6) Control 9/11 (81.8) Mean length of stay days: Cases 2.5 Control 3.8	P3, Q3 *Applicability*: Inadequate description of patient population *Quality*: Historical case-control study
Watson (1998) Australia Historical case-control Case Recruitment: Jul 1996–Jun 1997	Patients with unspecified gestations and symptoms of TPL Intact membranes and cervical dilation < 3 cm Gestational age 25–34 weeks Prevalence of preterm birth (< 37 weeks): Cases 17.6% (17) Controls 43.8% (32) Confounding factors: No vaginal bleeding, No recent sexual intercourse	Sample from the exocervix or posterior fornix using the Fetal Fibronectin Membrane Immunoassay™ (single test) Included medically indicated birth Protocol introduction	Tocolytic usage: Cases 4/17 (23.5) Control 30/32 (93.8) Corticosteroid usage: Cases 17/17 (100.0) Control 30/32 (93.8)	P1, Q3 *Quality*: Historical case-control study

Abbreviations: TPL, threatened preterm labour; NR, not reported

Appendix G Quality criteria

Study design	Quality checklist
Systematic review	Was the research question specified?
	Was the search strategy documented and adequate?
	Were the inclusion and exclusion criteria specified, appropriate and applied in an unbiased way?
	Was a quality assessment of included studies undertaken?
	Were the methods of the study appraisal reproducible?
	Were the characteristics and results of the individual studies summarised?
	Were the methods for pooling the data appropriate?
	Were sources of heterogeneity explored?
	Was a summary of the main results and precision estimates reported?
Studies evaluating effectiveness of an intervention on health outcomes	
Randomised controlled trial	Were the inclusion and exclusion criteria specified?
	Was the assignment to the treatment groups really random?
	Was the treatment allocation concealed from those responsible for recruiting subjects?
	Was there sufficient description about the distribution of prognostic factors for the treatment and control groups?
	Were the groups comparable at baseline for these factors?
	Were outcome assessors blinded to the treatment allocation?
	Were the care providers blinded?
	Were the subjects blinded?
	Were all randomised participants included in the analysis?
	Was a point estimates and measure of variability reported for the primary outcome?
Cohort study	Were subjects selected prospectively or retrospectively?
	Was the intervention reliably ascertained?
	Was there sufficient description about how the subjects were selected for the new intervention and comparison groups?
	Was there sufficient description about the distribution of prognostic factors for the new intervention and comparison groups? Were the groups comparable for these factors?
	Did the study adequately control for potential confounding factors in the design or analysis?
	Was the measurement of outcomes unbiased (ie blinded to treatment group and comparable across groups)?
	Was follow-up long enough for outcomes to occur?
	What proportion of the cohort was followed-up and were there exclusions from the analysis?
	Were drop-out rates and reasons for drop-out similar across intervention and unexposed groups?
Case-control study	Was there sufficient description about how subjects were defined and selected for the case and control groups?
	Was the disease state of the cases reliably assessed and validated?
	Were the controls randomly selected from the source of population of the cases?
	Was there sufficient description about the distribution of prognostic factors for the case and control groups? Were the groups comparable for these factors?
	Did the study adequately control for potential confounding factors in the design or analysis?
	Was the new intervention and other exposures assessed in the same way for cases and controls and

Study design	Quality checklist
	kept blinded to case/control status?
	How was the response rate defined?
	Were the non-response rates and reasons for non-response the same in both groups?
	Was an appropriate statistical analysis used?
	If matching was used, is it possible that cases and controls were matched on factors related to the intervention that would compromise the analysis due to over-matching?
Case series	Was the study based on a representative sample selected from a relevant population?
	Were the criteria for inclusion and exclusion explicit?
	Did all subjects enter the survey at a similar point in their disease progression?
	Was follow-up long enough for important events to occur?
	Were the techniques used adequately described?
	Were outcomes assessed using objective criteria or was blinding used?
	If comparisons of sub-series were made, was there sufficient description of the series and the distribution of prognostic factors?
Study of diagnostic accuracy	Was the spectrum of patients representative of the patients who will receive the test in practice?
	Were selection criteria clearly described?
	Is the reference standard likely to correctly classify the target condition?
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?
	Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?
	Did patients receive the same reference standard regardless of the index test result?
	Was the reference standard independent of the index test (ie the index test did not form part of the reference standard)?
	Was the execution of the index test described in sufficient detail to permit replication of the test?
	Was the execution of the reference standard described in sufficient detail to permit its replication?
	Were the index test results interpreted without knowledge of the results of the reference standard?
	Were the reference standard results interpreted without knowledge of the results of the index test?
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?
	Were uninterpretable/ intermediate test results reported?
	Were withdrawals from the study explained?

Appendix H Literature search strategies

Medline search strategy

The search strategy used to identify relevant studies of fetal fibronectin tests for predicting preterm labour in Medline is presented in **Table 46**.

Table 46 Fetal fibronectin test for predicting preterm labour, Medline search strategy (1966 to June Week 1, 2006)

	Keywords / search history	Results
1.	fibronectins/	16294
2.	((fetal or foetal) adj fibronectin$).ti,ab.	277
3.	((oncofetal or oncofoetal) adj fibronectin$).ti,ab.	95
4.	(ffn or onfn or fdc-6).ti,ab.	100
5.	oncofetal fibronectin.rw.	22
6.	(tli system$ or (tli adj iq) or tliiq or quikcheck).ti,ab,rw.	2
7.	86088-83-7.rn.	0
8.	or/1-7	16362
9.	exp labor, premature/	10641
10.	(preterm adj5 (birth or deliver$ or labour or labor)).ti,ab.	10123
11.	(prematur$ adj5 (birth or deliver$ or labour or labor)).ti,ab.	8195
12.	((preterm or premature$) adj5 (partu$ and childbirth)).ti,ab.	5
13.	exp pregnancy trimesters/	23298
14.	(((early or late) adj pregnancy) or trimester$).ti,ab.	34476
15.	or/9-14	64414
16.	8 and 15	384
17.	limit 16 to human	377

EMBASE search strategy

The search strategy used to identify relevant studies of fetal fibronectin tests for predicting preterm labour in EMBASE is presented in **Table 47**.

Table 47 Fetal fibronectin tests for predicting preterm labour, EMBASE search strategy (1980 to Week 23, 2006)

	Keywords / search history	Results
1.	fibronectin/	17064
2.	fetal fibronectin/	8
3.	oncofetal fibronectin/	4
4.	((fetal or foetal) adj fibronectin$).ti,ab.	260
5.	((oncofetal or oncofoetal) adj fibronectin$).ti,ab.	88
6.	(ffn or onfn or fdc-6).ti,ab.	85
7.	(tli system$ or (tli adj iq) or tliiq or quikcheck).ti,ab,tn.	3
8.	86088-83-7.rn.	17120
9.	or/1-8	17154
10.	premature labor/	9402
11.	prematurity/	23860
12.	(preterm adj5 (birth or deliver$ or labour or labor)).ti,ab.	9809
13.	(prematur$ adj5 (birth or deliver$ or labour or labor)).ti,ab.	7043
14.	((preterm or premature$) adj5 (partu$ and childbirth)).ti,ab.	5
15.	first trimester pregnancy/	7125
16.	second trimester pregnancy/	4684
17.	third trimester pregnancy/	4674
18.	(((early or late) adj pregnancy) or trimester$).ti,ab.	28822
19.	or/10-18	66520
20.	9 and 19	427
21.	limit 20 to human	399

PreMedline search strategy

The search strategy used to identify relevant studies of fetal fibronectin tests for predicting preterm labour in PreMedline is presented in **Table 48**.

Table 48 Fetal fibronectin tests for predicting preterm labour, PreMedline search strategy (14 June, 2006)

	Keywords / search history	Results
1.	((fetal or foetal) adj fibronectin$).ti,ab.	8
2.	((oncofetal or oncofoetal) adj fibronectin$).ti,ab.	0
3.	(ffn or onfn or fdc-6).ti,ab.	3
4.	oncofetal fibronectin.rw.	0
5.	(tli system$ or (tli adj iq) or tliiq or quikcheck).ti,ab,rw.	1
6.	or/1-5	8
7.	(preterm adj5 (birth or deliver$ or labour or labor)).ti,ab.	301
8.	(prematur$ adj5 (birth or deliver$ or labour or labor)).ti,ab.	163
9.	((preterm or premature$) adj5 (partu$ and childbirth)).ti,ab.	0
10.	(((early or late) adj pregnancy) or trimester$).ti,ab.	847
11.	or/7-10	1235
12.	6 and 11	6

Cochrane Library search strategy

The search strategy used to identify relevant studies of fetal fibronectin tests for predicting preterm labour in the Cochrane Library is presented in **Table 49**.

Table 49 Fetal fibronectin tests for predicting preterm labour, Cochrane Library search strategy (Issue 2, 2006)

	Keywords / search history	Results
1.	MeSH descriptor Fibronectins explode all trees in MeSH products	98
2.	(fetal, foetal) near fibronectin* in All Fields in all products	44
3.	(oncofetal, oncofoetal) near fibronectin* in All Fields in all products	1
4.	ffn or onfn or "fdc-6" or "fdc 6" in All Fields in all products	9
5.	"oncofetal fibronectin" in All Fields in all products	1
6.	"tli system*" or (tli near iq) or tliiq or quikcheck in All Fields in all products	0
7.	(#1 OR #2 OR #3 OR #4 OR #5 OR #6)	120
8.	MeSH descriptor Obstetric Labor, Premature explode all trees in MeSH products	585
9.	preterm near (birth, deliver*, labour, labor) in All Fields in all products	1293
10.	prematur* near (birth, deliver*, labour, labor) in All Fields in all products	1594
11.	(preterm, premature*) near (partu* and childbirth) in All Fields in all products	0
12.	MeSH descriptor Pregnancy Trimesters explode all trees in MeSH products	968
13.	((early, late) near pregnancy) or trimester* in All Fields in all products	2274
14.	(#8 OR #9 OR #10 OR #11 OR #12 OR #13)	4258
15.	(#7 AND #14)	41

Secondary databases

Searches of the following secondary databases/sites were also performed:

- Agencia de Evaluación de Tecnologías Sanitarias, España (Spain)
- Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS) (Quebec, Canada)
- Agence Nationale d'Accreditation et d'Evaluation en Santé (France)
- Agency for Healthcare Research and Quality (USA)
- Alberta Heritage Foundation for Medical Research (Canada)
- Austrian Institute of Technology Assessment
- British Columbia Office of Health Technology Assessment (Canada)
- Blue Cross Blue Shield Association Technology Evaluation Center (USA)
- Canadian Agency for Drugs and Technologies in Health (CADTH) (formerly Coordinating Office for Health Technology Assessment [CCOHTA])
- Catalan Agency for Health Technology Assessment (CAHTA)
- Centre for Health Program Evaluation (Monash University, Australia), Monash University Evidence Centre Reports (Australia)
- Centers for Medicare and Medicaid Services (USA)
- Centre for Reviews and Dissemination (University of York, UK)
- Current Controlled Trials metaRegister and ISRTCN register
- Danish Centre for Evaluation and Health Technology Assessment (DACEHTA)
- Department of Health Publications (UK)
- ECRI (formerly Emergency Care Research Institute) (USA)
- Finnish Office for Health Technology Assessment (FinOHTA)
- German Institute for Medical Documentation and Information (DIMDI)
- Harvard Centre for Risk Analysis: Program on the Economic Evaluation of Health Technology (USA)
- Health Council of the Netherlands
- Health Economics Research Group (Brunel University, UK)

- Health Information Research Unit (HIRU) internal database (McMaster University, Canada)
- Health Technology Advisory Committee (Minnesota Department of Health, USA)
- Health Technology Assessment International Conference Proceedings
- Health Technology Board for Scotland (UK)
- Institute for Clinical Evaluative Sciences (Canada)
- Institute for Medical Technology Assessment Erasmus MC (Netherlands)
- International Network of Agencies for Health Technology Assessment (INAHTA)(Sweden)
- International Society of Technology Assessment in Health Care (Montreal, Canada)
- Israel Centre for Technological Assessment of Health Care Services
- Medion Database (Netherlands)
- Monash University Evidence Centre Reports (Australia)
- National Guidelines Clearinghouse (USA)
- National Health and Medical Research Council Australia publication list
- National Health Service Health Technology Assessment Programme (UK)
- National Information Center on Health Services Research and Health Care Technology (HSTAT database) (USA), National Library of Medicine Health Services/Technology Assessment Text (HSTAT) (USA)
- New Zealand Health Technology Assessment
- Scottish Intercollegiate Guidelines Network (SIGN) (Scotland)
- Swedish Council on Technology Assessment in Health Care (SBU)
- Swiss Centre for Technology Assessment (TA-SWISS)
- Swiss Network for Health Technology Assessment (SNHTA).

Abbreviations

ABS	Australian Bureau of Statistics
AHMAC	Australian Health Ministers' Advisory Council
AIHW	Australian Institute of health and Welfare
AUC	area under the curve
CI	confidence interval
D	difference
DOR	diagnostic odds ratio
DRG	diagnosis related group
ELISA	enzyme-linked immunosorbent assay
fFN	fetal fibronectin
FPR	false positive rate
GP	general practitioner
LR	likelihood ratio
MBS	Medicare Benefits Schedule
MSAC	Medical Services Advisory Committee
NHMRC	National Health and Medical Research Council
NPSU	National Perinatal Statistics Unit
NPV	negative predictive value
NR	not reported
POC	point-of-care
PPICO	population, prior tests, index test, comparators, outcomes
PPV	positive predictive value
QUOROM	quality of reporting of meta-analyses
RCT	randomised controlled trial
RD	risk difference
ROC	receiver operating characteristic
S	sum
SD	standard deviation
Sn	sensitivity
Sp	specificity
SROC	summary receiver operating characteristic
TGA	Therapeutic Goods Administration
TPL	threatened preterm labour
TPR	true positive rate

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