

# IHE Report

## Using Fetal Fibronectin to Diagnose Pre-term Labour

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**IHE**

INSTITUTE OF  
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# ■ THE ROLE OF RAPID FETAL FIBRONECTIN ASSAY IN THE MANAGEMENT OF SPONTANEOUS PRETERM LABOUR

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### **Conflict of Interest**

Conflict of interest is considered to be financial interest, either direct or indirect, that would be affected by the research contained in this report, or creation of a situation where an author's and/or external reviewer's judgment could be unduly influenced by a secondary interest such as personal advancement.

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## EXECUTIVE SUMMARY

### Background

Women with symptoms and signs suggestive of spontaneous preterm labour (PTL) may be at high risk of preterm delivery (PTD) or preterm birth (PTB), which remains a challenging problem in modern obstetrics. Recently, there has been interest in identifying risk assessment markers that would help in refining the clinical estimate of the probability that PTL in symptomatic women will eventually result in PTD/PTB. Among the most studied and promising markers to date has been fetal fibronectin (fFN) as measured in cervicovaginal secretions when PTL is suspected.

### Objectives

To evaluate the added value of using the Rapid fFN for the TLi™ System (referred to here as the rapid fFN assay) to diagnose PTL in symptomatic women, which is the only fFN detection modality currently available in Canada and the United States for this indication.

### Results

The reviewed evidence confirms the earlier findings that the principal usefulness of the rapid fFN assay when used to diagnose PTL and predict PTB/PTD in symptomatic women lies in its high negative predictive value:

- In a meta-analysis of observational studies, a negative fFN test result was associated with a significantly decreased overall likelihood ratio for PTB at less than 34 weeks and less than 37 weeks of gestation. The fFN test was found to be most accurate in predicting PTB within 7 to 10 days of testing in symptomatic women, before advanced cervical dilation.
- In three randomized controlled trials (RCTs), 97% of women between 23 and 34 weeks of gestation (most with singleton pregnancies and cervical dilation of <3 cm) who presented for care with preterm contractions and subsequently had a negative rapid fFN assay result did not deliver within 7 days. Moreover, up to 98% of women with fFN negative results did not deliver within the next 14 days.

According to the reviewed evidence, the positive predictive value of the rapid fFN assay is a poor predictor of subsequent risk of PTB/PTD in symptomatic women with PTL.

There is little published evidence of acceptable quality that supports the potential of the rapid fFN assay to change PTL management in symptomatic women and result in improved patient outcomes and reduced unnecessary usage of healthcare resources:

- According to one non-randomized Canadian study, knowledge of a negative rapid fFN assay result may help to avoid over-diagnosis of PTL and use of unnecessary interventions (such as maternal transfer and use of medical interventions) and to reduce hospital admission rate, length of stay for evaluation and treatment, and the associated costs.
- However, the results reported by the reviewed three RCTs suggest that the benefits listed above may be negligible, raising the question of whether the use of the rapid fFN assay offers significant clinical and economic benefit beyond that observed with good clinical assessment and judgment.

## Conclusions

The absence of fFN in the cervicovaginal secretion of tested women with signs and symptoms of PTL has been shown to be a powerful predictor of the absence of progressive delivery within the next 1 to 2 weeks. The clinical importance of a positive test result remains unclear.

Knowledge of a negative rapid fFN assay result may supplement clinical judgment to diagnose PTL and predict low imminent risk of PTB/PTD in the short term with more accuracy than clinical criteria alone. However, the hypothesis that its use will inevitably improve patient outcomes and reduce healthcare resource usage and the associated costs remains to be proven. The challenge remains in the initial and ongoing education of the clinical and laboratory staff regarding the rapid fFN assay.

As the rapid fFN assay becomes widely available in Canada, institutional guidelines for testing and regular audits of its use will assist in defining its appropriate use and interpretation of the results.

## Methodology

Selected to formulate the evidence base for this systematic review were RCTs and systematic reviews reporting on the safety, diagnostic accuracy, and efficacy/effectiveness of using the rapid fFN assay as a tool for diagnosing PTL in symptomatic women. All research studies were identified by conducting a systematic search of the medical literature published in English or French between January 1995 and April 2007. Searches of The Cochrane Library, CRD databases (NHS EED, HTA, DARE), PubMed, EMBASE, CINAHL, the Web of Science, and the websites of various health technology assessment agencies, research registers, evidence-based resources, and practice guidelines sites were conducted.

The included research studies were assessed independently by two assessors for various methodological aspects using the appraisal tools developed by the Critical Appraisal Skills Programme in the United Kingdom. The evidence itself was not graded, but it was described as a potential source of bias that should be taken into account when interpreting the reported results.

## ■ ABBREVIATIONS/GLOSSARY

### **Abbreviations**

ACOG – American College of Obstetricians and Gynecologists

APHP – Alberta Perinatal Health Program

BCRCP – British Columbia Reproductive Care Program

CASP – Critical Appraisal Skills Programme

CI – confidence interval

CI<sub>95</sub> – 95% confidence interval

d – day(s)

DA – Danger Assessment

DV – Domestic violence

DVSI – Domestic Violence Screening Instrument

DVSR – Domestic Violence Supplementary Report

EGA – estimated gestational age

ELISA – enzyme-linked immunosorbent assay

FDA – U.S. Food and Drug Administration

fFN – fetal fibronectin

h – hour(s)

H-10 – Historical part of HCR-20

HCR-20 – Historical Clinical Risk-20

HTA – health technology assessment

ICC – Intra-class correlation coefficient

ICSI – Institute for Clinical Systems Improvement

IHE – Institute of Health Economics

K-SID – Kingston Screening Instrument for Domestic Violence

L&D – Labour and Delivery Unit

LMPG – Laboratory Medicine Practice Guidelines

LOHS – length of hospital stay

LR – likelihood ratio

LSI-R – Level of Service Inventory - Revised

N – sample size

NCCHTA – National Coordinating Centre for Health Technology Assessment

NPV – negative predictive value

ODARA – Ontario Domestic Assault Risk Assessment

PCL-R – Psychopathy Checklist-Revised

POCT – point-of-care testing

PPV – positive predictive value

PTB – preterm birth

PTD – preterm delivery

PTL – preterm labour

QC – quality control

RCT – randomized controlled trial

RDS – respiratory distress syndrome

ROC curve – Receiver operating characteristic curve

SARA – Spousal Assault Risk Assessment

SEM – Standard error of measurement

SOGC – Society of Obstetricians and Gynaecologists of Canada

TVUS – transvaginal ultrasound

UK – United Kingdom

USA – United States of America

VE – vaginal examination

VRAG – Violence Risk Appraisal Guide

vs. – versus

wk – week(s)

y – year(s)



## Glossary

### Sources

Online Medical Dictionary (accessed at <http://cancerweb.ncl.ac.uk/omd>)

Medical Dictionary Online (accessed at <http://www.online-medical-dictionary.org>)

**Amnion** – The extraembryonic membrane, which contains the embryo and amniotic fluid.

**Blastocyst** – In mammalian development, cleavage produces a thin-walled hollow sphere, whose wall is the trophoblast, with the embryo proper being represented by a mass of cells at one side. The blastocyst is formed before implantation and is equivalent to the blastula.

**Blastula** – The mammalian embryo in the post-morula stage in which a fluid-filled cavity, enclosed primarily by trophoblast, contains an inner cell mass, which becomes the embryonic disc.

**Cerclage, Cervical** – The surgical closure of the incompetent cervix uteri with suture material.

**Chorion** – The outermost extraembryonic membrane

**Decidua** – The inner layer of the wall of the uterus, which envelops the embryo, forms a part of the placenta, and is discharged with it.

**Effacement** – The thinning of the cervix, which occurs before and while it dilates.

**Foetus/fetus** – The unborn offspring of any viviparous mammals, in the postembryonic period, after the major structures have been outlined.

**Glycoprotein** – Conjugated protein-carbohydrate compounds including mucins, mucoid, and amyloid glycoproteins.

**Iatrogenic** – Induced inadvertently by the medical treatment or procedures or activity of a physician. Originally applied to disorders induced in the patient by autosuggestion based on the physician's examination, manner, or discussion, the term is now applied to any adverse condition in a patient occurring as the result of treatment by a physician or surgeon, especially to infections acquired by the patient during the course of treatment.

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## ■ INTRODUCTION

This report addresses a request for information from Alberta Health and Wellness on the evidence regarding the utility of adding the diagnostic test for rapid detection of fetal fibronectin (fFN) in the management of spontaneous preterm labour (PTL) in women who present for health care with symptoms and signs of PTL.

The diagnosis of suspected PTL that may lead to preterm delivery (PTD) or preterm birth (PTB) is an important healthcare issue worldwide.<sup>1-16</sup> The medical, psychological, and economic burdens of suspected PTL that leads to PTD/PTB are substantial for both family and the healthcare system. However, the healthcare providers' ability to accurately assign risk of PTD/PTB among symptomatic women is limited, as early detection of PTL continues to be a diagnostic challenge.<sup>2-7,10-15,17-20</sup> Recently, there has been increasing interest in identifying risk assessment markers that would help in refining the clinical estimate of the probability that PTL in symptomatic women will eventually result in PTD/PTB. Among the most studied and promising markers to date has been fFN as measured in cervicovaginal secretions when PTL is suspected.

The use of fFN measurement as a diagnostic tool for early detection of suspected PTL has been facilitated by the development of an fFN assay test by Adeza Biomedical Corporation.<sup>1,3-7,10-13,15,17,18</sup> In Canada and the United States, the fFN test has been performed by using an enzyme-linked immunosorbent assay (trade name: ELISA) or a system for rapid detection of fFN (trade name: Rapid fFN for the TLi™ System).

## ■ SCOPE OF THE REPORT

This report is a systematic review and critical appraisal of the published research literature concerning the added value of using the Rapid fFN for the TLi™ System (referred to here as the rapid fFN assay) to diagnose PTL in symptomatic women, which is the only modality for fFN detection currently available in Canada and the United States for this indication (Adeza, personal communication, January 2007).

The specific aim of this review was to answer the following questions, which were developed a priori by the reviewers (PC and CH):

- What is the accuracy of the rapid fFN assay for diagnosing PTL in symptomatic women? Does a rapid fFN assay result reliably identify women at high risk for PTD/PTB and/or those who are at low risk for PTD/PTB?
- Does the use of the rapid fFN assay affect gestational age at delivery and/or reduce maternal stress or anxiety and the need for the removal of the woman from home support?

- Does adding the rapid fFN assay to the management of PTL affect resource usage outcomes in terms of rates of maternal transfers and hospital admissions, assessment time, length of hospital stay (LOHS), and the use of therapeutic interventions in symptomatic women?
- Are there any risks and complications to the mother or fetus from performing the rapid fFN assay itself?

To answer these questions, the methodological approach for this study (which was developed a priori by the same two reviewers, PC and CH) included a systematic review and critical appraisal of the primary and secondary research studies reporting on:

- Population – all pregnant women (all ages; with multiple or single gestations) with symptoms and signs of PTL presenting for health care at inpatient or outpatient settings.
- Intervention – use of rapid fFN assay (all modalities).
- Comparator – use of other diagnostic tools (clinical risk assessment and/or other diagnostic tests) or no diagnostic testing.
- Outcome – diagnostic accuracy; patient and resource usage outcomes (including impact on PTB/PTD rates; maternal transport/transfer rates by air and/or road ambulance; hospital admission rates, including duration; length of assessment time; use of therapeutic interventions; prevention of over-treatment; diagnostic decisions; use of other diagnostic interventions; LOHS; maternal anxiety/stress; and need for woman's removal from her home support); and risks and complications to mother and/or fetus associated with performing the rapid fFN assay itself.

This review does not cover the use of the rapid fFN assay (alone or in conjunction with other diagnostic tests) for other categories of pregnant women, such as asymptomatic women, or for other indications, such as prediction of post-term delivery.

More details on the methodology used for this systematic review are provided in Appendix A and Appendix B. Appendix A provides an overview of the literature search strategy and Appendix B summarizes the methodological approaches used for screening and reviewing the retrieved literature, and for data extraction from and methodological quality assessment of the selected studies.

## ■ CLINICAL PROBLEM: SUSPECTED PRETERM LABOUR

Approximately 50% of PTL cases are thought to be idiopathic or spontaneous.<sup>21-24</sup> Spontaneous PTL is defined as the demonstrated progressive change of the cervix with uterine contractions between 20 and 37 completed

weeks of gestation.<sup>2,9-13,15,16</sup> The pathogenesis of PTL is not well understood, although several theories exist regarding the initiation of labour.<sup>21,22,24-28</sup> Risk factors include ethnic race, smoking, young maternal age, late maternal age, multiple pregnancy, low socio-economic status, and a history of previous PTD/PTB.<sup>2,9-15,20-25,29-31</sup> Infection such as chlamydia, gonorrhea, and bacterial vaginosis (only in women with prior PTB), as well as stress, also contribute to risk for PTL.

Women with symptoms and signs suggestive of PTL may be at high risk for PTD (defined as delivery before 37 weeks of gestation), which remains a challenging problem in modern obstetrics.<sup>8,9,11,13-16,24,32</sup> PTD has been associated with 60% to 80% of deaths in infants without congenital anomalies, accounts for up to 75% of neonatal morbidity, and contributes to long-term neurodevelopmental problems, pulmonary dysfunction, and visual impairment in newborns. The PTD/PTB rate has been increasing in many industrialized countries.

In Canada, the PTB rate (per 100 live births) has increased from 6.3 in 1981 to 6.6 in 1991 and to 7.5 in 2002.<sup>2,8,9</sup> Rates vary across the country, ranging from 5.8 in Prince Edward Island to 10.4 in Nunavut. Reasons for variation are not clear, but important contributing factors include younger maternal age in some regions, older maternal age, smoking, multiple pregnancy, and history of previous PTL.

PTB accounts for 75% of preventable perinatal deaths in Canada.<sup>2</sup> Long-term morbidity includes cerebral palsy, deafness, and blindness. Babies born prematurely have increased risk for neurodevelopmental problems such as cerebral palsy and respiratory, cardiac, ophthalmic, and other long-term health problems. The associated annual cost to the Canadian healthcare system is estimated at \$13.3-billion.<sup>2</sup>

The PTB rate in Alberta is higher than the national rate and has increased over time. The PTB rate was 8.9 in 2003, exceeding the rate of 8.6 estimated for 2002.<sup>32</sup> In 2004, almost 9% of live births were preterm.<sup>33</sup> In the fiscal year 2004-2005, a total of 1,247 women were diagnosed with threatened PTL in either an outpatient or inpatient setting in Alberta. This number represents about 3% of the approximately 41,000 births annually. In addition, 846 PTBs occurred in women who never had an episode of threatened PTL and another 293 who had a diagnosis of PTL delayed by therapy. Thus, 2,396 women may have presented to the system with symptoms of PTL, representing 5.9% of all births in 2004. Of the women with threatened PTL, 73% gave birth at term ( $\geq 37$  weeks).

## Diagnosis and management of PTL

Although the hallmarks of PTL are uterine activity and cervical change, uniformly accepted standards for diagnosing PTL do not exist.<sup>2,11,12,16</sup> Clinical symptoms suggestive of PTL include uterine contractions, low abdominal pain, low backache, pelvic pressure, increased vaginal discharge, and bleeding or spotting.<sup>2,3,10-13,15,22</sup> Contractions are more or less regular, may be painful or painless, and are distinguished from the contractions of term labour only by their persistence. Signs of PTL include cervical effacement and dilation.

The goal of clinical management for women presenting with symptoms and signs suggesting PTL is to identify PTL during an early stage, before progression to PTD/PTB is imminent.<sup>2,10-17,22,34</sup> PTL is diagnosed by clinical history (assessment of obstetric history and demographic factors) and physical examination.<sup>2,10-15,17,34</sup> The clinical signs and symptoms, in combination with physical examination, are often sufficient to make a diagnosis of PTL in symptomatic women.<sup>2-7,11,12,35</sup> Initial cervical dilation of  $\geq 3$  cm and at least 80% cervical effacement are strongly associated with PTD within 24 hours to 7 days. These women are assigned a diagnosis of PTL and aggressively treated to delay delivery, if possible, or prepared for delivery.

If the physical examination (which usually begins with digital examination of the cervix) does not immediately confirm a diagnosis of progressive PTL, the symptomatic woman is hospitalized for an initial period of observation to determine if the symptoms will subside or progress.<sup>2,10-12,16</sup> During this time, bedrest and possible treatment in the form of antibiotics or tocolytic drugs, depending upon the symptoms and results of the physical exam, are prescribed.

However, a clinical diagnosis is often unreliable and results in over-diagnosis of PTL.<sup>2,10-13,15,21,35,36</sup> The early signs and symptoms are not followed in all cases by PTD/PTB in the absence of therapeutic interventions, and as few as 1 in 20 PTL cases result in PTD within the next 14 days.<sup>2</sup> As early signs and symptoms are non-specific and can occur in term pregnancies, false positive diagnoses on strictly clinical criteria run as high as 50% and true PTL may be missed in 15% to 20% of cases.<sup>2</sup>

Often women present with contractions without cervical change, making the diagnosis more challenging.<sup>2,10-13,15,16,35,36</sup> When the cervix is dilated  $< 3$  cm, the diagnosis of true PTL (resulting in imminent PTD/PTB) is more difficult to establish.

Various methods of diagnosing PTL have been used.<sup>2,19,21,22,24,29,30,34,37-40</sup> These methods include risk factor scoring systems (based on medical history,

lifestyle behaviour, and demographic factors), assessment of the cervical changes by ultrasound examination, home uterine activity monitoring, tests for genital tract inflammation and vaginal infection, and detection of various biochemical markers (such as estriol, fFN, and various cytokines and interleukin) in cervicovaginal secretions, blood, and saliva. Among these markers, fFN received the most thorough and extensive evaluations published in the peer-reviewed literature over the last 10 years in different groups of obstetric patients.

## ■ DETECTION OF FETAL FIBRONECTIN

Fetal fibronectin (fFN) is a glycoprotein produced by many cell types, including those of the fetal amnion (membrane) ([www.fullterm.net](http://www.fullterm.net)).<sup>3,10,14,15,18,19,34,36-39,41</sup> It is found in high concentrations in amniotic fluid and throughout the membrane structure (between the chorion and decidua). Although its specific function remains unknown, it is believed that fFN may have a role in implantation and placental-uterine attachment.

In normal pregnancies, fFN levels are high during the first 16 to 22 weeks of gestation, then they fall to very low levels, and rise again as the pregnancy approaches term.<sup>3,10,14,15,18,34,36-39,41</sup> However, fFN is not normally detectable (at high levels) in cervicovaginal secretions between the 22nd and 37th week of gestation, and in particular before the 35th week of gestation. The presence of fFN at high levels during this period may indicate disruption of the utero-placental interface.

It is not clear what causes cervicovaginal fFN levels to increase prematurely in women at risk of PTD ([www.fullterm.net](http://www.fullterm.net)).<sup>3,10,13,14,36,41</sup> The release of fFN is likely attributable to various processes associated with choriodecidual separation and the onset of labour, regardless of whether the stimulus is infectious or mechanical. fFN can be detected and measured in the cervicovaginal secretions by a laboratory test that uses a specific monoclonal (FDC-6) antibody.

### **Methods for fFN testing**

Adeza Biomedical Corporation (Sunnyvale, California) manufactured the fFN assays that were used in the clinical studies published to date (Adeza Biomedical, personal communication, January 2007; [www.fullterm.net](http://www.fullterm.net)).<sup>3,5,6,18,36</sup> As of April 2007, Adeza Biomedical Corporation was integrated into Cytac Corporation (Sunnyvale, California) and is now a wholly owned subsidiary of Cytac Corporation ([www.cytac.com](http://www.cytac.com)).

Historically, the fFN test was available in two formats: a quantitative (numeric result) solid-phase enzyme-linked immunosorbent assay (ELISA) and a qualitative (positive or negative result) membrane immunosorbent assay.<sup>3,5,6,18,36</sup> Most of the available clinical data on the use of fFN for the diagnosis of PTL are based on the ELISA.



The ELISA method was licensed in North America in 1995 and has been used for batch testing since then, but recently it was discontinued as it was not practical for routine rapid testing, which is a requirement for diagnosing PTL in symptomatic women (Adeza Biomedical, personal communication, January 2007).<sup>5,6,18,42</sup> Collected specimens were required to be transported to a central laboratory, licensed by the manufacturer, for analysis. Results were usually available within 4 to 48 hours after specimen collection.

The membrane assay is a point-of-care or bedside version of the fFN assay and uses a system for rapid detection of fFN (Rapid fFN for the TLi™ System, which recently changed to FullTerm™ (Adeza Biomedical, personal communication, January 2007), ([www.fullterm.net](http://www.fullterm.net)).

## ■ THE RAPID fFN ASSAY

The rapid version of the fFN test is a lateral-flow, solid-phase immunosorbent assay device designed to qualitatively detect fFN in cervicovaginal specimens collected with the Adeza Biomedical Specimen Collection Kit (Adeza Biomedical, personal communication, January 2007), ([www.fullterm.net](http://www.fullterm.net)). A vaginal swab (sterile Dacron applicator along with a speculum) is used to collect the specimen. Specimens are mixed in a collecting tube containing a liquid buffer. A portion of the liquid buffer contained in the specimen collection tube is then transferred with a pipette device to the lateral-flow, individual patient cassette placed inside the TLi IQ instrument (which is a hardware reader).

From the time the sample is collected and received at the testing site (which can be a central or hospital laboratory, or a Labour and Delivery Unit (L&D)), the assay takes approximately 30 minutes, including data entry of the woman's name, operator's identification, and verification of acceptable quality control (QC) into the TLi™ system (Adeza Biomedical, personal communication, January 2007). At the end of this time, the TLi™ system automatically prints and displays the result as positive or negative (an fFN level of  $\geq 50$  ng/mL is a positive result and an fFN level of  $< 50$  ng/mL is a negative result), along with patient identification information and full QC results on each patient specimen. The total time from specimen collection to reporting the results to the clinician should take a maximum of two hours if the rapid fFN assay is performed on site.

A TLi™ IQ instrument currently replaces the original unit called the TLi™ analyzer (Adeza Biomedical, personal communication, January 2007). This instrument has the same appearance and mechanical components as the original unit, but it uses a software upgrade. The software changes were made to meet QC requirements and simplify the QC process. The TLi™ IQ instrument eliminates the need for performing liquid calibration, as

the hardware self-verifies on a routine basis (Adeza Biomedical, personal communication, January 2007).<sup>43</sup> If the QC of the IQ instrument fails or the reagent QC fails, the instrument notifies the operator with error codes.

The measurements done with the TLI™ IQ instrument can be and have been performed in a central or hospital laboratory, as well as by the bedside in an L&D (Adeza Biomedical, personal communication, January 2007). The TLI™ IQ instrument is recommended to be located as close as possible to the site where the symptomatic woman is tested for expedited patient results.

## Indications and contraindications

The use of the fFN test for early detection of PTL has attracted interest because of its reported high negative predictive value (NPV) (Adeza Biomedical, personal communication, January 2007), ([www.fntest.com](http://www.fntest.com)).<sup>3,5-7,10,11,14,15,18,34,36,37,41</sup> For women with symptoms and signs of PTL without advanced cervical dilation, a negative cervicovaginal fFN result identifies those at risk for PTD/PTB of less than 1% within the next 1 to 2 weeks.<sup>3,5-7,10,11,14,15,18,34,36,37,41</sup>

The manufacturer recommends that the rapid fFN assay be performed to aid in the assessment of PTD risk within 14 days from the time of collection in women between 24 and 35 weeks of gestation with symptoms of PTL, intact amniotic membranes, and minimal cervical dilation (<3cm) (Adeza Biomedical, personal communication, January 200), ([www.fullterm.net](http://www.fullterm.net)).<sup>41</sup> The manufacturer also endorses the use of fFN testing, along with clinical information, at a routine prenatal visit between 22 and 31 weeks in a singleton gestation (low-risk pregnancy) to assess the risk of PTD.

The use of the rapid fFN assay is not recommended for symptomatic women who present with one or more of the following symptoms ([www.fullterm.net](http://www.fullterm.net)):<sup>5,6,30,44</sup>

- advanced cervical dilation ( $\geq 3$  cm);
- rupture of amniotic membranes;
- cervical cerclage; and/or
- moderate or gross vaginal bleeding.

## Safety

According to the manufacturer, there is no more risk to the woman from performing the rapid fFN assay than there is from performing a Pap smear test (Adeza Biomedical, personal communication, January 2007). The Institute for Clinical Systems Improvement (ICSI) stated that the fFN test itself “is performed on an outpatient bases, therefore it is little risk to the woman associated with performing the procedure.”<sup>34</sup> According to the ECRI Institute, the fFN assay does not directly cause harm to women.<sup>6</sup>

Harm to the mother and/or the fetus can be caused by treatments that may follow a false positive fFN test result.<sup>5,6,34,45</sup> The added psychological stress for the woman and the use of additional resources to monitor a predicted development of PTL are also undesirable outcomes. Another risk associated with the use of the rapid fFN test is the withholding of appropriate interventions because of false negative test results.

Clinicians considering the use of the rapid fFN assay are cautioned that any modifications to the assay protocol as described by the manufacturer may yield erroneous results ([www.fullterm.net](http://www.fullterm.net)).<sup>5,6,30</sup>

- Only the Adeza Biomedical Specimen Collection Kit is accepted for use with this assay.
- Specimens are to be taken only from the posterior fornix of the vagina or the ectocervical region of the external cervical os, since other locations have not been studied.
- The swab must be lightly rotated for 10 seconds to absorb the cervicovaginal secretion. The tube is kept at room temperature in transit to the laboratory for testing if the fFN testing is to occur within 8 hours of sample collection. Specimens that are not tested within 8 hours of collection must be stored refrigerated at 2° to 8°C and assayed within 3 days of collection or frozen and assayed within 3 months.
- The safety and effectiveness of using a cut-off other than 50 ng/mL fFN has not been established.
- Tests results may not be interpreted visually and must be based on the use of the TLi™ IQ System.
- Lubricants and creams (such as those used in a speculum exam) may interfere with the assay results, and only water should be used with a speculum examination when a fFN specimen is collected.
- Because semen may contain a sufficient amount of fFN to result in a positive fFN test, specimens should not be taken within 24 hours of intercourse.
- Manipulation of the cervix may cause artificial release of fFN; hence fFN specimens should be collected prior to digital examinations and not within 24 hours after cervical manipulation.

Results should always be used in conjunction with clinical evaluation and other diagnostic procedures, such as cervical examination, cervical microbiological culture, assessment of uterine activity, and evaluation of other risk factors ([www.ffntest.com](http://www.ffntest.com)).<sup>5,6,30,44</sup> Because fFN is present in high amounts in amniotic fluid, the test is intended only in women in whom intact membranes have been confirmed. Results from specimens containing trace amounts of blood should be interpreted with caution. Also, results should be interpreted with caution in cases where gestational age has not been confirmed.

## Regulatory status

In Canada, the Rapid fFN for the TLI<sup>TM</sup> System is licensed as an aid to rapidly assess the risk of PTD within 7 to 14 days from the time of cervicovaginal sample collection in pregnant women with signs and symptoms of early PTL, intact membranes and minimal dilatation (<3 cm) sampled between 24 and 34 weeks, 6 days gestation, and the risk of PTD in <34 weeks, 6 days when a cervicovaginal sample is obtained during a routine prenatal visit between 22 and 30 weeks, 6 days of gestation in women with a singleton pregnancy<sup>46</sup> (Adeza Biomedical, personal communication, January 2007), ([http://www.hc-sc.gc.ca/dhp-mps/md-im/licen/mdlic\\_e.html](http://www.hc-sc.gc.ca/dhp-mps/md-im/licen/mdlic_e.html)).

A search of the US Food and Drug Administration (FDA) Premarket Approval Database<sup>47</sup> revealed that the Rapid fFN for the TLI<sup>TM</sup> System is cleared to be used as an aid in assessing the risk of PTD in  $\leq 7$  or  $\leq 14$  days from the time of cervicovaginal sample collection in pregnant women with signs and symptoms of early PTL, intact amniotic membranes, and minimal cervical dilatation (<3 cm), sampled between 24 weeks, 0 days and 34 weeks, 6 days of gestation. The tests are further indicated for use in conjunction with other clinical information as an aid to rapidly assess the risk of PTD in  $\leq 34$  weeks, 6 days when a cervicovaginal sample is obtained during a routine prenatal visit between 22 weeks, 0 days and 30 weeks, 6 days of gestation in women with a singleton pregnancy.

Supplemental approval was received recently from the FDA and Health Canada for the Rapid fFN for TLI<sup>TM</sup> System using the IQ instrument (Adeza Biomedical, personal communication, January 2007).<sup>47</sup>

## Coverage

Currently, the performance of the rapid fFN assay is not reimbursed anywhere in Canada for diagnosing suspected PTL and predicting PTD in symptomatic women (Adeza Biomedical, personal communication, January 2007).<sup>33</sup>

Medical policies of various insurance plans in the United States<sup>48-55</sup> cover the use of the fFN assay in accord with the recommendations issued by the American College of Obstetricians and Gynecologists (ACOG).<sup>42</sup>

## ■ Guidelines and Consensus Documents

The National Academy of Clinical Biochemistry of the American Association for Clinical Chemistry has developed Laboratory Medicine Practice Guidelines (LMPG), which are consensus-based guidelines for the laboratory evaluation and monitoring of patients with specified disorders, published online ([www.aacc.org/AACC/members/nacb/LMPG](http://www.aacc.org/AACC/members/nacb/LMPG)). A recently released LMPG examined the clinical utility of point-of-care testing (POCT) ([www.aacc.org/AACC/members/nacb/LMPG/OnlineGuide/PublishedGuidelines/poct](http://www.aacc.org/AACC/members/nacb/LMPG/OnlineGuide/PublishedGuidelines/poct)).<sup>56</sup> This LMPG

systematically reviewed the existing scientific evidence relating POCT to patient outcome, graded the reviewed literature, and made recommendations regarding the optimal utilization of POCT devices in patient care. One of the evaluated tests was the rapid fFN assay when used to predict PTD/PTB.

The LMPG found studies showing that the major strength of the rapid fFN assay when used for this indication is its high NPV and recommended a negative result in symptomatic women as a reliable guide to place women at low imminent risk of PTD/PTB within 7 days of testing.<sup>56</sup> However, there was insufficient evidence to compare clinical outcomes (such as the number of hospital admissions, length of stay, use of tocolytic medications, cost, neonatal morbidity/mortality, and maternal morbidity from side effects of intervention therapy) between the rapid fFN assay and the ELISA format. Also, the LMPG found no studies that directly compared the rapid fFN assay with any other method to predict PTD/PTB and concluded that additional well-designed outcomes-based studies are needed to determine the true efficacy of the rapid fFN assay as a POCT device for this indication.

On the basis of limited or inconsistent scientific evidence, the ACOG<sup>42,57,58</sup> recommends fFN testing only for symptomatic women with high-risk pregnancies, where PTL is suspected and the following criteria are met: intact amniotic membranes, minimum cervical dilation (<3 cm), and sampling performed no earlier than 24 weeks, 0 days and no later than 34 weeks, 6 days of gestation. If the fFN test is to be clinically useful, the results must be available from a laboratory in a timely manner so that they can be used in making decisions regarding the clinical care of the pregnant woman. The test's clinical usefulness may rest primarily with its ability to identify women who are least likely to deliver prematurely (those with a negative result), thereby avoiding unnecessary interventions.

ICSI recently issued guidelines on PTB prevention.<sup>59</sup> From the findings reported by a health technology assessment (HTA) study,<sup>34</sup> ICSI guidelines recommend that for women with singletons who present with signs or symptoms of possible PTL, a thorough medical evaluation should include checking the cervix and collecting a specimen for possible presence of fFN if cervical dilation appears to be <3 cm. If fFN is negative, the woman can expect pregnancy prolongation for the next 7 to 14 days without the need for intervention.

In 2001, 12 international leading experts from 10 countries met and convened under the auspices of the International Preterm Labour Council to establish consensus on clinical recommendations and guidelines regarding the diagnosis, management, and treatment of PTL.<sup>60</sup> The consensus was supported by evidence from literature published during the last 15 years, which was graded using the United Kingdom National Health Service Executive classification system, endorsed by the Royal College of Obstetricians and Gynaecologists.

The Council concluded that fFN testing may be used for the diagnosis of PTL in symptomatic women as an adjuvant to clinical parameters (when clinical diagnosis is doubtful) to rule out PTB and prevent unnecessary interventions, but without further research should not be recommended for routine use.

More recently, international guidelines were developed in collaboration with the European Association of Perinatal Medicine-Study Group on “Preterm Birth”.<sup>16</sup> According to these guidelines, fFN testing may be considered to complement the clinical assessment, and tocolytic therapy should be withheld if the fFN testing or the transvaginal ultrasound scan indicates a low risk of PTB.

The fFN test is not recommended as a screening test for asymptomatic women, regardless of risk status.<sup>34,42,56-61</sup> The clinical importance of a positive test result remains unclear.

## ■ EFFICACY/EFFECTIVENESS AND SAFETY

For the purpose of this review, the value of adding the rapid fFN assay in the management of PTL in symptomatic women was evaluated by selecting primary and secondary research studies that reported on its efficacy/effectiveness in terms of impact on PTB/PTD rates, maternal transfer rates, hospital admission rates, length of assessment time, LOHS, treatment decisions, maternal anxiety and stress, and the need for removal from the woman’s home support. Also considered were primary and secondary research studies reporting on risks and complications to the mother and/or fetus from performing the test itself.

To formulate the evidence base for this review, only randomized controlled trials (RCTs) were selected as primary research studies. The hypothesis that the additional information provided by the rapid fFN assay results can be translated into better clinical practice (improved patient and resource usage outcomes) can be best tested in RCTs.<sup>6,7,73</sup> Also, for the purpose of this review, published reports of systematic reviews that, by virtue of design and quality of reporting,<sup>66,67,93</sup> were most likely to provide high levels of evidence were considered for data extraction.

The following commentary summarizes the reviewed evidence, presented according to the level of evidence (RCTs and systematic reviews). Information on upcoming research on this topic is also provided.

### **Randomized controlled trials (RCTs)**

No RCTs that compared the use of the rapid fFN assay with the use of clinical risk assessment alone or combined with other tests used to diagnose PTL in symptomatic women were located through this review’s literature search. Also,

the literature search did not reveal any RCTs that compared the use of the rapid fFN assay with the use of other diagnostic tests or with other modalities of fFN testing (such as ELISA).

The literature search revealed four RCTs that evaluated the impact of using the rapid fFN assay as an aid tool in the management of PTL in symptomatic women.<sup>62-65</sup> Of these, only three<sup>62-64</sup> were selected for this review (Table 1). The RCT by Nguyen<sup>65</sup> is available only in abstract form and was excluded from this review, as it is not possible to fully assess the adequacy of the reported evidence.

**Table 1: Summary of reviewed RCTs**

RCT	Characteristics
Grobman et al. (2004) <sup>62</sup>  Supported by a grant from Adeza Biomedical	<p><b>Objective:</b> to evaluate the impact of availability of rapid fFN assay results on physician behaviour and resource use.</p> <p><b>Sample:</b> 100 women (examined at L&amp;D; EGA of 24 to 34 wk; singleton; contractions, intact membranes, &lt;3 cm cervical dilatation; no vaginal bleeding, no VE or intercourse during last 24 h; received no hospital observation, admission, treatment).</p> <p><b>Compared:</b> Total cost and PTL management for women whose attending physicians were aware of fFN results vs. those for women whose attending physicians were not aware of fFN results.</p>
Lowe et al. (2004) <sup>63</sup>  Supported by Process Improvement grant, University of Iowa, USA	<p><b>Objective:</b> to investigate the effect of rapid fFN assay on LOHS and use of PTL interventions.</p> <p><b>Sample:</b> 97 women (examined at L&amp;D or transferred and receiving medication; EGA of 23 to 34 wk; singleton and twin; contractions and/or cervical change; intact membranes; ≤3cm cervical dilatation for primiparous and ≤4 cm for multiparous; no vaginal bleeding or cerclage; no digital examination, TVUS, or intercourse during last 24 h).</p> <p><b>Compared:</b> PTL management for women with an fFN test vs. those with no fFN test.</p>
Plaut et al. (2003) <sup>64</sup>  Supported by a grant from Adeza Biomedical	<p><b>Objective:</b> whether knowledge of rapid fFN assay results affects treatment decisions during evaluation and treatment of possible PTL.</p> <p><b>Sample:</b> 100 women (arrived at hospital with symptoms that suggested PTL; intact membranes; EGA of 24 to 34 wk and 6 d; singleton and twin; &lt;3 cm cervical dilation; no cervical manipulation–intercourse, VE, or TVUS–during last 24 h; no gross bleeding or cerclage; no previous fFN test within 2 wk).</p> <p><b>Compared:</b> PTL management in women whose fFN test results were known by treating physicians vs. those whose fFN test results were not known by treating physicians.</p>

cm – centimetre; d – day(s); EGA – estimated gestational age; fFN – fetal fibronectin; h – hour(s); L&D – Labour and Delivery Unit; LOHS – length of hospital stay (days during hospital admission); PTL – preterm labour; RCT – randomized controlled trial; TVUS – transvaginal ultrasound; USA – United States of America; VE – vaginal examination; vs. – versus; wk – week(s)



## Description of the reviewed RCTs

Details of the reviewed RCTs are summarized in Table C1, Appendix C.

All reviewed RCTs<sup>62-64</sup> were conducted in the United States, and two<sup>62,64</sup> were funded by Adeza Biomedical. Two RCTs<sup>62,63</sup> were single-centre trials performed in university hospitals and one RCT<sup>64</sup> was a multicentre trial performed in three community hospitals. The RCTs evaluated whether knowledge of results from a rapid fFN assay affects PTL management decisions (usage of various healthcare resources during the evaluation and treatment of possible PTL)<sup>62-64</sup> and healthcare costs.<sup>62</sup>

The reviewed RCTs used different inclusion and exclusion criteria. In two RCTs,<sup>62,64</sup> all women eligible for a rapid fFN assay were tested and randomly allocated to a study group where the attending/treating physician knew the test results or to a control group where the physicians were unaware of the test results (Table 1). In the RCT by Lowe et al.,<sup>63</sup> women were randomly assigned to PTL management with a rapid fFN assay performed and to PTL management without a rapid fFN assay performed.

All RCTs included symptomatic women who presented at a labour and delivery unit (L&D) for health care. One RCT included women who came with primary complaints of uterine contractions and cervical dilation of  $\leq 3$  cm and who had not received prior treatment.<sup>62</sup> Another RCT<sup>63</sup> included women with uterine contractions and/or cervical change who were examined at the L&D or those who had transferred there and were already receiving tocolytics. Inclusion criteria allowed cervical dilation of 3 to 4 cm for multiparous women in this RCT.<sup>42</sup> Plaut et al.<sup>64</sup> included women who arrived at the L&D with symptoms of PTL and had  $\leq 3$  cm cervical dilation, but did not mention specific criteria defining a PTL diagnosis or information regarding previous treatment.

One RCT<sup>62</sup> included only singleton gestations, whereas the inclusion criteria for the other two RCTs<sup>63,64</sup> allowed a few twin gestations in each study group. The mean estimated gestational age (EGA) at testing ranged between 29 and 30.4 weeks.<sup>62-64</sup> The mean EGA at delivery reported by two RCTs<sup>62,64</sup> ranged between 37.7 and 38.3 weeks. Lowe et al.<sup>63</sup> reported median values of the EGA at delivery, which ranged between 37.4 and 38.2 weeks. Although the ascertainment of gestational age in an unbiased way is very important in determining the outcome status, only Lowe et al.<sup>63</sup> described the method used to estimate the gestational age at testing and at delivery.

Patient demographic information was abstracted from the charts at recruitment in one study.<sup>62</sup> The source is not clearly stated in the other two studies.<sup>63,64</sup> Two RCTs<sup>62,63</sup> provided information on previous PTB/PTD and maternal age (mean values ranged between 26.7 and 29 years). All studies provided information on parity, but only one RCT<sup>62</sup> provided information regarding race.



In all studies, the fFN specimen collection was performed as per the manufacturer's recommendations, the analysis of the fFN specimen was performed in the hospital laboratory, and the attending/treating physician made all treatment decisions (with or without knowledge of rapid fFN assay results).<sup>62-64</sup> No information was provided on the physicians' or residents' training and experience in collecting fFN specimens. None of the reviewed studies provided information on the laboratory personnel's training and experience in using the TLi™ analyzer to perform the fFN specimen analysis.

In one RCT,<sup>62</sup> the investigators clearly stated that their facility did not introduce the rapid fFN assay into clinical practice and the test had not been used in the L&D before the study. In two RCTs,<sup>62,64</sup> during the study, the test was available only within the study protocol. The results were communicated to the attending/treating physician by residents<sup>62</sup> or directly by laboratory personnel.<sup>64</sup>

Various educational interventions were used in two RCTs<sup>62,64</sup> to inform the attending/treating physicians about the rapid fFN assay and its characteristics. In the RCT by Plaut et al.,<sup>64</sup> the women were cared for by physicians or certified nurse-midwives of a staff-model health maintenance organization and previous standardized educational materials had been distributed to them in conferences (written materials and posters). In the RCT by Grobman et al.,<sup>62</sup> prior to the study, a letter explaining the characteristics of the test was sent to the attending physicians (who were not familiar with using the rapid fFN assay in practice). Also, when fFN test results were provided to physicians, they were reminded of the meaning of the results in terms of expected delivery time through a standardized reminder.

Lowe et al.<sup>63</sup> stated that the facility was introducing the rapid fFN assay into clinical practice at the time of the study. However, it is not clear whether the test had been used in the L&D before the study or whether, during the study, it was available only within the study protocol. Neither is it clear who communicated the results to the treating physicians or whether any educational interventions were used to inform them about the rapid fFN assay and its characteristics.

### **Methodological quality of the reviewed RCTs**

Details of the criteria used to assess the methodological quality of the included RCTs are outlined in Appendices B and C, and the information provided in Table C2 (Appendix C) shows the extent to which these criteria were met in each study.

All reviewed RCTs<sup>62-64</sup> were prospective trials using parallel design and they stated the randomization methods used (Table2).

**Table 2: Methodological quality of reviewed RCTs**

RCT	Methodology
Grobman et al. (2004) <sup>62</sup>	<p><b>Randomization:</b> Computer-generated random assignment performed after collection of fFN specimen. Assignments placed in sequentially numbered opaque envelopes (kept in L&amp;D).</p> <p><b>Blinding:</b> Laboratory personnel blinded to patient characteristics and outcomes; the attending physician was apprised of patient's history, physical examination, and randomized group assignment; no information on whether patients were blinded to results.</p> <p><b>Comments:</b> RCT powered to detect a 20% reduction in total healthcare-related costs in the fFN group; no information provided on how EGA at testing/delivery was determined; no statements on side effects and complications; CI not reported for outcomes of interest; no information on laboratory personnel's training/experience in rapid fFN testing.</p>
Lowe et al. (2004) <sup>63</sup>	<p><b>Randomization:</b> Achieved through a computer-generated table in blocks of 10. Separate randomization tables used for gestations of &lt;28 wk and ≥28 wk. Results concealed by using opaque, sealed envelopes, numbered sequentially.</p> <p><b>Blinding:</b> Physicians and patients were not blinded to the randomization results.</p> <p><b>Comments:</b> RCT powered to detect a reduction in the length of stay of at least 1.3 d; no power for GA subgroup analysis; no statements on side effects and complications; CI not reported for all outcomes of interest; no test to ensure that assumptions of Cox proportional hazard model were met; no information on laboratory personnel's training/experience in rapid fFN testing; not clear whether any educational interventions were provided to physicians.</p>
Plaut et al. (2003) <sup>64</sup>	<p><b>Randomization:</b> Performed in laboratory by means of sequentially numbered opaque envelopes that matched numbered patient enrolment forms in L&amp;D. Inside the envelopes were instructions to either notify the physician of the test result or notify the physician that the patient had been assigned to the control group ("not known" group).</p> <p><b>Blinding:</b> No information on blinding was provided (it appears to be a non-blinded study). Laboratory personnel who performed the fFN test had been trained "intensively" not to release results inadvertently in the "not known" group.</p> <p><b>Comments:</b> RCT powered for primary outcome of transport to tertiary care centres (n = 500) but stopped prematurely for lack of enrolment; analyzed and reported on secondary outcomes, focusing on LOHS; PTL not clearly defined (no specific criteria for a PTL diagnosis); no information provided on how EGA at testing and delivery was determined; no statements on side effects and complications; CI not reported for all outcomes of interest; because of low enrolment, possibility of type II error for measured outcomes is not excluded; no information on laboratory personnel's training/experience in rapid fFN testing.</p>

CI – confidence interval; d – day(s); EGA – estimated gestational age; fFN – fetal fibronectin; GA – gestational age; L&D – Labour and Delivery Unit; LOHS – length of hospital stay; n = number of patients; PTL – preterm labour; RCT – randomized controlled trial; wk – week(s)

Two RCTs used adequate methods of randomization (computer-generated random assignment<sup>62</sup> and computer-generated table in blocks of 10<sup>63</sup>). The results of randomization in these RCTs were concealed through the use of sequentially numbered opaque envelopes. Randomization occurred in the L&D before fFN testing<sup>63</sup> and after fFN testing.<sup>62</sup> Lowe et al.<sup>63</sup> stratified randomization by the EGA and used separate randomization tables for gestations of <28 weeks and ≥28 weeks. This RCT is the only one to stratify by EGA, but there was no power for the EGA subgroup analysis.

In the RCT by Plaut et al.,<sup>64</sup> randomization was done in the laboratory by means of sequentially numbered opaque envelopes that matched numbered patient enrolment forms on labour and delivery.

Physicians and patients were not blinded in any of the reviewed RCTs. The laboratory personnel who performed the analysis of the fFN specimen were blinded to patient characteristics and outcomes in the RCT by Grobman et al.<sup>62</sup> Laboratory personnel who performed the analysis of the fFN specimens in the RCT by Plaut et al.<sup>64</sup> had been trained “intensively” not to release test results inadvertently in the “not known” group.

The reviewed RCTs were powered for different primary endpoints (Table 2), reported on various patient and healthcare resource usage outcomes, and used various outcome measures (Table C1, Appendix C). The sample sizes were relatively small in all reviewed RCTs and might not have been large enough to detect all differences in measured outcomes between groups.

The use of inpatient and outpatient healthcare resources subsequent to enrolment was ascertained through the use of medical records, hospital billing data, and patient interviews in one RCT.<sup>62</sup> The source is not clearly stated in the other two studies.<sup>63,64</sup>

Although assessing the diagnostic performance of the rapid fFN assay was not the primary objective of the reviewed studies, they all calculated positive predictive value (PPV) and NPV using as endpoints PTD within 7 days and/or within 14 days (Table C1, Appendix C).

No rapid fFN assay protocol was developed and implemented as part of the trial in any of the reviewed RCTs.

The reviewed RCTs did not consider all outcomes of interest, because none reported on side effects, risk, or complications from performing the test itself.

Although the reviewed RCTs met most of the quality assessment criteria (Table C2, Appendix C), the above-mentioned methodological issues made it difficult to appraise their reported results with confidence. However, this is the best quality published research on the topic and some of the reported results

can be used to gain insight into the value of adding the rapid fFN assay in the management of PTL in symptomatic women in terms of impact on patients and resource usage outcomes.

### **Findings reported by the reviewed RCTs**

**Grobman et al.**<sup>62</sup> evaluated whether the availability of the rapid fFN assay results changed physician behaviour, resource use, and resultant healthcare costs in a university hospital with 24-hour resident coverage and a strict protocol for PTL management. After obtaining the fFN specimen, enrolled women were assigned randomly into a group in which results of the fFN test were available and a group in which results of the fFN test were not available. The primary endpoint was the total costs incurred as a consequence of preterm contractions, determined by combining both the direct medical and non-medical costs that were related to obstetric care after the hospital admission for preterm contractions.

The women in both groups had comparable socio-economic backgrounds and were similar with respect to maternal age, parity, race, cervical examination at admission, and EGA at testing and delivery ( $P > 0.5$ ).<sup>62</sup> The pregnancy outcomes were not significantly different ( $P > 0.5$ ). Similar proportions of women were not working before study enrolment ( $P > 0.5$ ) or had positive fFN test results and preterm deliveries. Of eight women with a positive fFN result, one delivered within 1 week from testing and five delivered before 37 weeks of gestation (PPV of 12.5% and 62.5%, respectively). Of 91 women with negative test results, three delivered within 1 week from testing and 17 delivered before 37 weeks (NPV of 96.7% and 81.3%, respectively).

The investigators could not find any evidence that the availability of the rapid fFN assay results caused physicians to change their behaviour.<sup>62</sup> Women who did not have rapid fFN assay results available were no different than those women who did with respect to initial length of observation in L&D (median 4 hours vs. 3 hours), hospital admission at time of study entry (28% vs. 26%), use of tocolytic agents (18% vs. 16%), cessation of work (27% vs. 26%), or total healthcare-related costs ( $7.6 \pm 1.2$  vs.  $7.5 \pm 1.1$ ; data are presented as log mean  $\pm$  standard deviation). Women in both groups spent a similar number of days (median of 2 days) in hospital at the time of study entry ( $P = 0.83$ ).

After study entry, there were five hospital admissions (10%) for preterm contractions in the study group and four hospital admissions (8%) in the control group ( $P = 0.78$ ).<sup>62</sup> LOHS during these admissions was not significantly different ( $P = 0.62$ ). After women were discharged from hospital following the initial evaluation, the incidence of hospital readmissions for preterm contractions was similar in both groups: six women from the study group (12%) and 12 women from the control group (24%) ( $P = 0.1$ ).

Subgroup analyses suggested that the results were not influenced by any particular factors such as a certain cervical dilation at first pelvic examination,

existence of physicians' learning curve, or type of health care (public versus private) received by the participants. However, the study was not powered for these analyses and therefore one cannot rule out that the rapid fFN assay would have been more useful under these particular circumstances.

At delivery or at 36 to 37 weeks of gestation (whichever occurred first), all women were contacted either while in hospital or by phone calls to their homes to survey them in relation to the contribution of their hospital admission to the associated indirect costs (including lost income from time off work and need to hire additional home assistance) and other non-economic consequences (including loss of leisure time).<sup>62</sup> Eighty-five women completed the post-partum survey (44 women from the group with fFN results available and 41 women from the group with fFN results not available). The proportion of women who were not working prior to the study was similar in both groups (15/44 and 18/41,  $P > 0.5$ ).

In both groups, most women who were working before study enrolment missed some work after their initial PTD evaluation (27/29 vs. 22/23,  $P > 0.5$ ) and more than one quarter in each group never returned to work (7/27 vs. 6/22,  $P > 0.5\%$ ).<sup>62</sup> Most women in both groups felt it necessary to avoid typical leisure activity (31/44 vs. 30/41,  $P > 0.5$ ) and to arrange for increased help at home (33/44 vs. 30/41,  $P > 0.5$ ). There was no difference in the number of women who needed to pay for this increased help ( $P > 0.5$ ).

Women who participated in the RCT by **Grobman et al.**<sup>62</sup> were also asked several questions about their emotional state subsequent to their release from hospital after initial preterm contraction evaluation to determine whether knowledge of fFN test results helped to reduce their anxiety related to preterm contractions. Responses from 80 participants showed that women who had fFN results available were as likely to feel nervous, to frequently think about their contractions, and to feel satisfied with their medical care as were those for whom the fFN test results were not available.

**Lowe et al.**<sup>63</sup> investigated the impact of using the rapid fFN assay on the LOHS and the use of PTL interventions in a tertiary care centre. The facility was introducing the rapid fFN assay into clinical practice at the time of the study. Although many different residents performed the tests, all women were treated similarly. Symptomatic women seen in the L&D were assigned randomly to have a rapid fFN assay or to PTL management without rapid fFN assay. The inclusion criteria allowed eight twin gestations ( $n = 3$  in "no fFN" group;  $n = 5$  in "fFN" group) and included greater cervical dilation than the other reviewed RCTs (for multiparous women).

There were no differences between groups in demographic or obstetric characteristics.<sup>63</sup> The investigators found no differences between groups in terms of median EGA at delivery, hours spent in L&D, number of women admitted to antepartum service, length of stay in the antepartum ward, or

medical interventions (use of corticosteroids, antibiotics, or magnesium sulfate).<sup>63</sup> When the subgroups of women at <28 weeks of gestation and ≥28 weeks of gestation were also analyzed, no significant difference was found.

According to **Lowe et al.**,<sup>63</sup> one reason for the lack of differences in the use of medical therapies or length of stay might have been the difficulty of implementing the fFN testing because of the various presentations of PTL at the tertiary care centre. Another reason could have been the sample size, which was calculated to allow detection of almost 50% reduction in length of stay and might not have detected smaller differences.

The study included women who had already been started on tocolytics or other therapies before entry, but it did not report on the proportion of these women in each arm, and it was therefore difficult to interpret the results on drug use.<sup>63</sup>

The investigators performed a subgroup analysis, using the Cox proportional hazard regression, to assess the effect of the rapid fFN assay on the time to discharge from L&D while controlling for previous PTB, cervical dilation, and gestational age (<28 or ≥28 weeks) between groups.<sup>63</sup> The results showed that those women who had the test results available to their physicians had a shorter length of stay in the L&D (hazard ratio of being discharged, 1.7; 95% confidence interval (CI<sub>95</sub>) 1.1 to 2.7;  $P = 0.017$ ) than did those women who did not have the fFN test (estimate of “not discharged” distribution was based on the Cox proportional hazard regression for those women with no previous PTB, with cervical dilation, and at ≥28 weeks of gestation).<sup>63</sup> However, the investigators did not report on whether they performed any test to determine that the assumptions of the Cox proportional hazard model that was used were met.

Of the 46 women who were assigned to receive the rapid fFN assay, 35 had negative results and 11 had positive results.<sup>63</sup> When the results for women with a negative fFN test were compared with those for women with a positive fFN test, a statistically significant difference was found in admissions to the antepartum ward (25.7% versus 63.6%;  $P = 0.032$ ) and the length of stay on the antepartum service (median 0, interquartile range, 0 to 1 day versus median 1, interquartile range 0 to 3 days;  $P = 0.008$ ). There was no statistically significant difference between groups in the time spent in L&D (median 9 hours, interquartile range 3 to 36 hours versus median 8 hours, interquartile range 4 to 36 hours;  $P = 0.806$ ).

**Lowe et al.**<sup>63</sup> reported that the PPV and NPV for PTD within 7 days were 18% and 97%.<sup>63</sup> For PTD within 14 days, the PPV and NPV were 27% and 81%. However, the confidence intervals for the performance of the rapid fFN assay reported in this study are wide (Table C1, Appendix C).

**Plaut et al.**<sup>64</sup> wanted to determine whether knowledge of results affects treatment decisions during the evaluation and treatment of possible PTL performed in three community hospitals (members of a staff-model health maintenance organization). All symptomatic women enrolled in this study had the rapid fFN assay and then they were randomly assigned to either have results available or not available. The inclusion criteria allowed six twin gestations in each group. The primary objective was to look at the number of maternal transports to tertiary care centres in each group. A power calculation suggested that 500 women needed to be enrolled to show a significant difference in transport rates between the two groups. However, the study was terminated because of low enrolment (approximately 20% of the calculated sample size). Results were reported only for secondary outcomes of interest, with a focus on LOHS for evaluation and treatment.

Of 108 collected fFN swabs, there were 10 positive test results and 98 negative test results.<sup>64</sup> The overall prevalence of delivery within 2 weeks was 2.8% (three women). Four of the positive results were known (two women received aggressive therapy and one of them delivered within 14 days). There were six positive test results in the group in which the results were not known (two women received aggressive therapy but none delivered within 14 days). Of the 98 negative results, 47 were known (six women received aggressive therapy and one delivered within 14 days). Of 51 negative results in the group where the result was not known, four women received aggressive tocolysis (one delivered within 14 days).

The PPV and NPV of the rapid fFN assay were 10% and 98%, respectively, for the prediction of PTD within 14 days.<sup>64</sup> For women who had negative results, the LOHS (including observation periods and any admissions) was not significantly shorter when the result was known (6.8 hours) than when it was not known (8.1 hours,  $P = 0.35$ ). However, when physicians knew the fFN status of women with a negative result who were observed for >6 hours (17% of all women), the mean LOHS was significantly shortened from 37.8 hours to 22.7 hours (40%,  $P = 0.04$ ).

The investigators also looked at the decision to use tocolysis and its predictive values for delivery within 14 days.<sup>64</sup> Aggressive tocolytic therapy was given to 16 women. The decision on whether to use it had an NPV of 100% ( $CI_{95}$  96% to 100%), a PPV of 21% ( $CI_{95}$  3% to 72%), and a sensitivity of 100% ( $CI_{95}$  44% to 100%) for delivery within 14 days. Of the women who were not given aggressive tocolytic therapy, none delivered within 14 days. Results were unchanged when they were analyzed only for women for whom the fFN results were not known.



## Systematic reviews

No systematic reviews conducted to assess the added value of using the rapid fFN assay in the management of suspected PTL and predicting PTD/PTB in symptomatic women were located through the present review's literature search.

The literature search identified 13 citations of published systematic reviews and HTA studies that potentially met the inclusion criteria of the review (as outlined in Appendix A). Full text articles were retrieved for only 11 of them.<sup>1,5-7,34,68-74</sup> On closer examination of the full text articles, none of these studies met the inclusion criteria of the review. Most of the retrieved studies were excluded and the reasons are documented in Table B1 (Appendix B).

For the purpose of this report, only one systematic review<sup>68</sup> was selected for data extraction. This review was the most recently published systematic review on the topic and the largest meta-analysis on the diagnostic accuracy of fFN testing in symptomatic women. Honest et al.<sup>68</sup> included in their meta-analysis the studies that were reviewed by the other authors of the retrieved systematic reviews.<sup>6,7,73</sup> Details of the selected systematic review and the results of the critical appraisal of this study's methodological quality are provided in Appendix D (Tables D1, D2, and D3).

### Description of the selected systematic review

**Honest et al.**<sup>68</sup> conducted a systematic quantitative review of test accuracy studies to determine the diagnostic performance of a cervicovaginal fFN test in predicting PTB in women with or without symptoms of PTL (Table D1 and Table D2). The review included women tested for cervicovaginal fFN prior to 37 weeks of gestation. No inclusion criteria relating to the reference standard were specified. Spontaneous PTB served as the reference standard, and the reviewers assessed birth at 34 weeks and 37 weeks of gestation, as well as PTB within 7 to 10 days of being tested.

The systematic review conducted by **Honest et al.**<sup>68</sup> included 64 observational studies (prospective and retrospective cohort studies), of which 40 reported on fFN testing in symptomatic women and 28 reported on fFN testing in asymptomatic women. All but three of the included studies used a threshold value of 50 ng/mL to indicate an abnormal result and one study did not indicate the cut-off level. Separate meta analyses on the diagnostic accuracy of fFN testing (combining results on ELISA and the rapid fFN assay) in symptomatic and asymptomatic women were conducted.

The outcome measures were not specified a priori by **Honest et al.**<sup>68</sup> The reviewers used 2 x 2 tables to calculate measures of test accuracy. Summary likelihood ratios (LRs) for positive and negative fFN test results were calculated



for those studies with a threshold value of 50 ng/mL. Summary receiver operating characteristic curves were used as measures of accuracy for all included studies.

In the 40 observational studies reporting on fFN testing in symptomatic women, the diagnostic accuracy of the test in predicting PTB for the various gestational ages of interest was evaluated using bedside or laboratory methods (either on a single occasion or serially), and the reported values varied considerably.<sup>68</sup> However, a meta-regression analysis showed that the accuracy of the test did not depend on the method of fFN testing, how often the test was done, or the risk classification of the symptomatic women.

**Honest et al.**<sup>68</sup> did not report results separately on the use of the rapid fFN assay for diagnosing PTL and predicting risk of PTB/PTD in symptomatic women.

### **Methodological quality of the selected systematic review**

The study conducted by **Honest et al.**<sup>68</sup> is a well-conducted systematic review (see Tables D2 and D3). The objectives of the review were clearly stated, the literature search was comprehensive, there were no language restrictions, and attempts were made to uncover unpublished data. Although the selection criteria have not been clearly reported in the reviewed published report,<sup>68</sup> additional details of the included studies and inclusion and exclusion data extraction tables were available from the British Medical Journal website.

Although two reviewers selected the studies for inclusion in a systematic way, the quality assessment and data extraction processes were not described in the report. The reviewers assessed the quality of all the included studies. A study was considered to be of good quality if it used a prospective design, consecutive enrolment, adequate test description (to allow replication by others), and blinding of the test result from clinicians managing the women. However, the authors did not state how the included studies were assessed for validity, or how many of the reviewers performed the validity assessment.

The authors did not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. However, the authors stated that the data extraction form was piloted for repeatability on the first eight studies.

There was considerable discussion in this review regarding possible biases related to the quality of the included studies. The reviewers carried out tests for heterogeneity and biases through meta-regression and graphical means.

The review's conclusions appear to follow from the results, and the conclusion that further research is needed is an appropriate statement.

**Honest et al.**<sup>68</sup> did not consider all outcomes of interest. They did not evaluate or report on the efficacy/effectiveness of using fFN testing in terms of impact on maternal transfer rates, hospital admission rates, length of assessment time, LOHS, treatment decisions, maternal anxiety and stress, and need for removal of the woman from her home support. Neither did they report on the risks and complications to the mother or fetus from performing the test itself.

### **Findings reported by the selected systematic review**

**Honest et al.**<sup>68</sup> confirmed the results of previously conducted systematic reviews that the accuracy of the fFN testing in predicting PTB outcomes in symptomatic women varied (see Table D1). The test was found to be most accurate in predicting PTB within 7 to 10 days after testing among women with symptoms of PTL but no advanced cervical dilatation. For predicting PTB within 7 to 10 days, the reviewers estimated a pooled LR for positive results of 5.42 (CI<sub>95</sub>: 4.36, 6.74) and a pooled LR for negative results of 0.25 (CI<sub>95</sub>: 0.20, 0.31).

The results reported by **Honest et al.**<sup>68</sup> were further explained and discussed by Khan in a paper that was published subsequently.<sup>75</sup> According to this paper, there were 17 studies that reported the accuracy of the fFN test in the prediction of PTB within 1 week. Among individual studies, the test had different accuracy estimates. However, the statistical analysis for heterogeneity showed that any differences between test accuracy values were minor and they were not related to the method of testing, serial testing, or women's risk classifications.

When the methodological quality of the included observational studies was examined as a source of heterogeneity, the reviewers found no significant differences in the estimated values of test accuracy in studies with high and low methodological quality features.<sup>68,75</sup> The median LR values for predicting PTB within 7 to 10 days of testing among the four highest quality studies were 6.16 (CI<sub>95</sub>% 4.53, 7.33) for a positive result and 0.32 (CI<sub>95</sub>: 0.01, 0.45) for a negative result. Funnel plot analysis showed no evidence of asymmetry that would indicate presence of publication or related bias for the main outcomes.<sup>68,75</sup>

The reviewers addressed the use of estimated LR values with respect to fFN testing by illustrating the impact with an example of decision making about the use of steroids in symptomatic women at 31 weeks of gestation.<sup>68</sup> They calculated the number of women who would need to be treated with steroids at 31 weeks of gestation to prevent one case of neonatal respiratory distress syndrome (RDS) using the estimated pooled LR values for predicting PTD before 37 weeks of gestation. For women with symptoms of PTL but no fFN test results, 109 women would need to be treated to prevent one case of RDS. For those with negative fFN test results, 509 symptomatic women would need to be treated to prevent one case of RDS. Among those with positive fFN test results, 17 symptomatic women would require treatment to prevent one case of RDS.

According to **Honest et al.**,<sup>68</sup> this approach will allow clinicians to make explicit decisions on the basis of more realistic probabilities generated by fFN testing, and provides a framework for the use of diagnostic evidence in therapeutic decision making in symptomatic women. The “results enable clinicians to make a more rational approach to decision making regarding inpatient admission, administration of antenatal steroids, and in utero transfer in women with threatened spontaneous preterm birth.” However, the reviewers recommended, “future research should focus on undertaking high quality primary studies of test accuracy to improve our ability to predict spontaneous preterm birth.”

## **Ongoing Research**

The National Coordinating Centre for Health Technology Assessment (NCCHTA) in the United Kingdom (UK) is currently conducting an evidence synthesis project entitled Screening to Prevent Pre-Term Birth – Systematic Reviews of Accuracy and Effectiveness Literature with Economic Modelling (<http://www.hta.ac.uk/project.asp?PjtId=1486>). The objectives are to:

(1) examine all of the research available to find out how accurate various available tests are at identifying pregnant women (symptomatic and asymptomatic) who may be at risk of giving birth prematurely; (2) investigate how effective various treatments and medications are at stopping premature labour; and (3) explore the cost-effectiveness of these tests and treatments or medications for women at risk of delivering their babies prematurely. From these objectives, the reviewers aim to identify what further research is needed and what recommendations can be made to improve practice.

The NCCHTA systematic review aims to determine the added value of predictive and diagnostic tests in symptomatic and asymptomatic women deemed to be at risk for different reasons, taking into account systematic reviews of diagnostic tests that have already been published (<http://www.hta.ac.uk/project.asp?PjtId=1486>; Swinburne, University of Birmingham, personal communication, September 2005). The predictive and diagnostic tests of interest include risk scores, identification of bacterial vaginosis, detection of fetal breathing movements, ultrasound examination, cervical transvaginal sonography, cervicovaginal fibronectin test, and first-trimester midstream urine culture.

The customer for this project is the National Screening Committee in the UK (Swinburne, University of Birmingham, personal communication, September 2005). The project, started in October 2005, is currently in the editorial review stage, and the final report will be published by December 2007 (<http://www.hta.ac.uk/project.asp?PjtId=1486>). The team involved in the project is based at the University of Birmingham.

## ■ CANADIAN EXPERIENCE WITH THE RAPID fFN ASSAY

The rapid fFN assay using the TLI™ IQ instrument is the only fFN testing system ever used in Canada to diagnose PTL in symptomatic women (Adeza Biomedical, personal communication, January 2007). The first TLI™ IQ unit was installed in 2001 and currently there are more than 200 IQ units in Canada, with the addition of 2 to 5 systems per month. The device comes with a 15-minute training DVD, which covers setting up the TLI™ IQ instrument, full QC, and how to run a test sample. Although on-site training is preferred if possible, phone install training has been done in remote areas of Canada.

Encouragement for greater access to the rapid fFN assay is occurring across Canada (Adeza Biomedical, personal communication, January 2007).<sup>2,33</sup> Hospitals and specialized bodies and facilities supporting the use of the rapid fFN assay are currently attempting to approach or have already approached their provincial governments and regional health authorities to obtain funding or payment for this procedure. In March 2005, the British Columbia Perinatal Program established guidelines for rapid fFN testing (Adeza Biomedical, personal communication, January 2007). In December 2006, the Department of Health in Nova Scotia funded a two-year clinical trial of fFN testing within all hospitals in the province.

In Alberta, the rapid fFN assay was introduced in the Calgary Health Region in 2002 as a pilot study.<sup>33</sup> Based on the outcomes from the pilot study, rapid fFN testing has been implemented fully and currently it is routinely used in community hospitals and tertiary care centres in this region. A qualified medical laboratory technologist, who received training on the operation, maintenance, and QC for the test, performs the rapid fFN assay.<sup>46</sup> Proficiency testing is reported to the College of Physicians and Surgeons of Alberta.

The Capital Health Region of Alberta has also conducted a pilot study (from June 15, 2004 through February 15, 2005) in a tertiary care centre<sup>33,76</sup> and found that the use of the rapid fFN assay resulted in a decrease in the LOHS without adverse impact on premature delivery. Currently, the rapid fFN assay is used in four hospitals in Edmonton (Adeza Biomedical Corporation, personal communication, January 2007), (Dr. Rhada Chari, personal communication, July 2007).

In 2006, Alberta Health and Wellness recommended that the rapid fFN assay be made available to Alberta women through each health region no later than April 1, 2008. As a result of this recommendation, the Alberta Perinatal Health Program (APHP) and the Tripartite Partnership (including the Capital Health and Calgary Health regions and the Alberta Medical Association) issued a document intended to assist healthcare teams regarding the introduction of fetal fibronectin testing, which was published in March 2007.<sup>77</sup>

## Canadian research studies

Several studies<sup>76,78-84</sup> were recently conducted in Level 1 healthcare centres (providing care for healthy mothers and babies, or those with few complications)<sup>33</sup> Level 2 healthcare centres (housing more advanced capacity and equipment for perinatal care)<sup>33</sup> and Level 3 healthcare centres (housing the most specialized perinatal care staff and equipment)<sup>33</sup> in Nova Scotia, Quebec, Manitoba, Alberta, and British Columbia. The clinical application of the TLi™ IQ system in the management of PTL in symptomatic women was reported to have a significant impact on the evaluation of risk for PTB/PTD, especially in Level 1 and Level 2 centres, which lack the resources for intensive care of the preterm newborn. The impact was reported in terms of reducing the rate and high costs of transfer associated with transport, unnecessary hospitalization, interventions such as antibiotics and steroids, and indirect costs associated with displacement of the mother from her family and community. No negative neonatal outcomes were reported.

For the purpose of this report, only one of the Canadian studies was selected for data extraction. It was a non-randomized controlled study<sup>79</sup> published in full text in a peer reviewed journal. The following commentary summarizes the evidence reported by this study.<sup>79</sup> The highlights of this study<sup>79</sup> are provided in Appendix E (Table E1).

**Abenham et al.**<sup>79</sup> examined how the availability of the rapid fFN assay affected the utilization of hospital resources at a teaching hospital in Montreal. The investigators compared the rates, duration, and costs of hospitalization for a prospective cohort of women who presented with signs and symptoms of PTL after the rapid fFN assay became available (N = 116), and a historical baseline cohort (N = 116) who presented with PTL before fFN testing was available. The study included singleton pregnancies presenting between 24 and 34 weeks of gestation. The women in each study group presented during a designated 20-week period. The post-fFN study period did not begin until 6 months after its introduction to allow for a learning period by clinicians in terms of the use and interpretation of the test.

During the study period when the rapid fFN assay was available, 51 tests were performed and only 35 were valid (of which 91% had a negative result).<sup>79</sup> The availability of the rapid fFN assay was associated with more unnecessary testing and more subjects undergoing additional evaluation (46% in the study population vs. 32% in the baseline population). The assay was also associated with significant reductions in admission rates for PTL (from 24.1% to 12.1%), mean length of stay in hospital (from 5.2 days to 0.6 days), and overall costs (from \$102,660 to \$26,169) without an increase in PTB rates. The utilization of the rapid fFN assay accurately predicted women who were not likely to deliver prematurely.

However, this study<sup>79</sup> utilized historical controls for comparison, which might have resulted in selection bias. Little information is provided about the selection

of the historical cohort other than the fact that the controls were identified through a systematic review of the hospital records, as was the cohort for the period when the rapid fFN assay was available. A change in physician practice patterns over time may also have influenced the assessed outcomes.

Another important observation about this study is that not all women in the post-fFN period actually had a rapid fFN assay and the remaining women were diagnosed and admitted or discharged on the basis of clinical criteria.<sup>79</sup> It is also important to note that 12 of the rapid fFN assays (25%) were “inappropriate” (although half of these were for twin gestations, which were excluded). The investigators noted the need for continued monitoring and the importance of education around the appropriate use of the rapid fFN assay.

**A cost analysis** was undertaken in Alberta in 2005 to determine whether adding the rapid fFN assay in the PTL management of symptomatic women would have a net positive effect on health system costs and whether the costs avoided in unnecessary transportation and hospitalization outweigh the incremental costs.<sup>33</sup> In this province, most women with threatened PTL are transferred from Level 1 to Level 2 or 3 centres for health care because of the greater capacity of these hospitals to respond to perinatal complications and to provide specialized neonatal care. Transfer from Level 1 or 2 hospitals to either Level 2 or 3 hospitals is accomplished through Alberta’s air and ground ambulance system.

The results obtained through this **cost analysis** suggested a potential for cost savings to the provincial health system if the rapid fFN assay is universally introduced.<sup>33</sup> However, the net savings would be greatest if the test is introduced in Level 2 and 3 hospitals only, primarily resulting from reduced LOHS. If the test is also introduced to Level 1 hospitals, then the net savings to the system are reduced considerably. The cost savings would not offset costs associated with introducing the test in Level 1 hospitals, even when air and ground ambulance transfer costs are considered. A net loss for Level 1 hospitals was largely explained by the need for hospitals delivering fewer than 1,000 babies per year to purchase or rent the fFN test hardware.

## **Canadian Guidelines**

**The British Columbia Reproductive Care Program (BCRCP)**<sup>17</sup> is presently advocating that peripheral centres gain access to the rapid fFN assay as an “important laboratory adjunct” and is making efforts to see that “peripheral laboratory sites will be compensated for adding this testing scheme to their diagnostic armamentarium.”<sup>17</sup> The anticipated benefits include the following:

- Decrease in hospital admissions, LOHS, and assessment time for suspicious PTL in community-based hospitals throughout the province.
- Decrease in hospital admissions, length of stay, assessment time, and air and road ambulance transports from rural areas into Level 3 facilities in Victoria and Vancouver.

- More appropriate identification of women who need corticosteroid and tocolytic treatment.
- Decrease in the use of tocolytics in women who are not at risk for PTD.
- Reduced stress and anxiety for the pregnant mother and her family as a result of reassurance and absence of unnecessary transfer out of her home community.

According to **BCRCP guidelines**,<sup>17</sup> women eligible for rapid fFN testing would include those meeting the following criteria:

- 24 to 35 weeks completed gestation;
- threatened PTL (defined by regular uterine contractions >6 per hour and/or pelvic pressure);
- intact amniotic membranes;
- $\leq 3$  cm cervical dilatation; and
- established fetal well-being.

A positive result in association with PTL symptoms and cervical change would suggest a high enough risk for PTD “that the woman should be treated and transferred to an appropriate facility to care for a neonate of the expected gestational age.”<sup>17</sup> If the woman is in an urban tertiary centre, then management plans, including consideration of tocolytics, administration of corticosteroids, etc., may be undertaken.”

If the rapid fFN assay result is negative, consideration should be given to having the symptomatic woman stay in her community “and treatment with tocolytic therapy and corticosteroids would not be justified.”<sup>17</sup> Women should be educated regarding PTL symptoms and need for early follow up. Because the NPV of the fFN test decreases with time, re-evaluation should be considered if the woman continues to have symptoms suggestive of PTL. Re-evaluation should occur 5 to 7 days after the first symptomatic episode, provided that the cervix is <3 cm dilated.

For monitoring purposes, the **BCRCP guidelines**<sup>17</sup> recommend that for those centres in British Columbia using the rapid fFN assay, a case review of all women presenting with PTL should occur to determine the cost-benefit for the facility/region.

According to the educational materials and guidelines published by APHP in March 2007<sup>77</sup> the indications for the rapid fFN assay include:

- gestational age between 24 weeks, 0 days and 34 weeks, 6 days;
- signs of threatened PTL: uterine contractions ( $\geq 6$  per hour, with or without pain; the contractions occur for more than 1 hour) and persistent pelvic pressure that does not subside with rest; and
- persistent dull low back pain.



Contraindications for the rapid fFN include:<sup>77</sup>

- gestational age <24 weeks, 0 days;
- gestational age >34 weeks, 6 days;
- maternal or fetal risks that compromise mother or fetus (such as trauma, severe gestational hypertension, severe intrauterine growth restriction);
- ruptured membranes;
- cervix  $\geq 3$  cm dilated;
- placenta previa or abruptio placenta;
- active vaginal bleeding; and/or
- cancer of the reproductive tract.

According to the APHP document,<sup>77</sup> if the rapid fFN assay result is negative (<50 ng/mL of fFN is detected), there is a greater than 95% probability that the symptomatic woman will not give birth within the next 14 days, and consideration should be given to:

- reassure the woman;
- treat bacterial vaginosis if present;
- educate the woman regarding signs and symptoms of PTL and regarding avoidance of activities that aggravate her PTL signs and symptoms;
- discharge the woman home after test results are reviewed with the managing physician; and
- advise the woman to make an appointment with her physician for follow up.

If the rapid fFN assay result is positive (>50 ng/mL of fFN is detected), the woman should be advised regarding the results and treated for PTL as per hospital/health region policy or guidelines.<sup>77</sup>

According to the **Society of Obstetricians and Gynaecologists of Canada (SOGC)**, in the case of women over 32 weeks of gestation, the rapid fFN assay result, cervical assessment, and clinical observation of contractions would all influence the decision about the use of tocolysis, steroids, and antibiotics.<sup>2</sup> A positive rapid fFN assay result alone necessitates admission.

In Level 1 centres, management of PTL for symptomatic women with positive rapid fFN assay includes transport if the woman has other signs and symptoms of active labour.<sup>2</sup> Also, women at <33 weeks of gestation, with no other signs of active labour, need to be transported. With a negative result, management includes close follow up in the home community and possible transfer of the woman by air for further assessment. According to the **SOGC**, if the symptoms resolve and the fFN test result is negative, then the pregnancy is managed in a more routine fashion at the health centre in the woman's home community until 36 weeks of gestation, with timely transfer for delivery.

The availability of the rapid fFN assay in Level 2 centres allows for more certainty in the decision to transfer a symptomatic woman to a tertiary centre



when the result is positive.<sup>2</sup> A negative result confers more confidence in postponing transfer, because there exists a 99% certainty that delivery will not occur in the next 14 days.

Although Level 3 centres in Canada do not face the issue of maternal transfer decisions, the addition of the rapid fFN testing in the management of PTL for symptomatic women allows for reduced admission rates, length of stay, assessment time, and use of tocolytic agents, antibiotics, and corticosteroids when results are negative.<sup>2</sup> According to the **SOGC**, in these centres, fFN results in determining PTL risk are comparable to those from vaginal ultrasound.

## ■ DISCUSSION

Any tool that can reliably diagnose true PTL and predict whether a symptomatic woman presenting for health care is at high risk for PTB/PTD would be valuable in enabling the choice of the most appropriate interventions for prolonging gestation. Such a test would also be important in identifying those women who are not in “true” PTL, and who are unlikely to benefit from such interventions and could therefore be spared the associated side effects and complications. This outcome can save healthcare resources by transporting women who are in need for inpatient admissions for PTL and can avoid unnecessary work and social disruptions. The rapid fFN assay was developed to be such a diagnostic test.

According to the reviewed literature on the use of rapid fFN assay for this indication, there is little risk to the mother and fetus from performing the procedure itself. Another advantage is the simplicity of conducting the test. Based on these advantages and its strong (high) NPV reported by previous primary and secondary research studies, the test has the potential to reduce unnecessary treatment and healthcare utilization by more accurately identifying symptomatic women who are not in true PTL. This review’s findings confirm earlier findings that the NPV of the rapid fFN assay, in conjunction with clinical assessment, is a potent predictor of low imminent risk for PTB/PTD in symptomatic women. However, the precise role of the rapid fFN assay in clinical practice remains to be defined.

The literature search did not locate any primary or secondary research studies that directly compared the use of the rapid fFN assay with any other method used to diagnose PTL and predict PTB/PTD in symptomatic women. No studies located by this literature search were designed to directly compare the rapid fFN assay with the ELISA. Validation of the rapid fFN assay as a new method appears to be limited to studies that looked at its diagnostic accuracy values for predicting PTB/PTD and then compared the results with prior published values obtained with the ELISA.

## **Diagnostic performance of the rapid fFN assay**

The reviewed meta-analysis<sup>68</sup> addressed the question of the diagnostic performance of the rapid fFN assay. A negative fFN test result was associated with a significantly decreased overall LR for PTB at less than 34 weeks and less than 37 weeks of gestation. The fFN test was found to be most accurate in predicting PTB within 7 to 10 days of testing in symptomatic women without advanced cervical dilation. The primary source of evidence was from observational studies. In most studies, the clinical staff was blinded to the test results and managed the suspected PTL cases according to standard protocols. These studies, however, did not report on whether the clinicians and women could use the additional information provided by the test to improve patient outcomes and clinical practice.

The reviewed RCTs<sup>62-64</sup> confirm the findings from the observational studies reviewed by Honest et al.<sup>63,64</sup> that the main usefulness of the rapid fFN assay when used to diagnose PTL and predict PTB/PTD in symptomatic women lies in its high NPV. In these studies, 97% of women who presented for care with preterm contractions at 23 to 34 weeks of gestation (most of them with singleton pregnancies and cervical dilation of <3 cm) and subsequently had a negative rapid fFN assay result did not deliver within 7 days after the test result.<sup>62,63</sup> Moreover, up to 98.0% of the women with negative rapid fFN assay results did not deliver within the next 14 days.<sup>63,64</sup>

Most of the research data on the diagnostic performance of the rapid fFN assay for PTL in symptomatic women was obtained from studies conducted in the United States. The populations in these studies may be significantly different from those in Canadian studies, particularly in terms of genital infection rates,<sup>78</sup> and these differences may affect the diagnostic performance of the test. However, Skoll et al.<sup>78</sup> recently reported that the rapid fFN test performed equally well in ruling out PTL in Canadian populations. These authors conducted a prospective, blinded clinical evaluation of the rapid fFN assay in 149 symptomatic women (between 24 and 34 weeks of gestation, most of them with singleton pregnancies) presenting at two Canadian tertiary care centres. In this population, a negative rapid fFN assay result was associated with a 97.4% likelihood of not delivering within 7 days after testing and with a 91.4% chance of delivering after 34 weeks.

## **Added value of using the rapid fFN assay**

The diagnostic performance of the rapid fFN assay for PTL in symptomatic women suggests that the test has the potential to become a useful tool for reducing the use of interventions and the number of transfers and hospital admissions for symptomatic women who are not at imminent risk for PTD/PTB. However, the evidence on whether the rapid fFN assay fulfills its potential role as a beneficial modifier of clinical care for these symptomatic women is mixed.

Both the randomized and non-randomized clinical trials published to date and reporting on the impact of adding the rapid fFN assay in the management of symptomatic women have methodological flaws. Generally, there is little good published evidence supporting the potential of the rapid fFN assay to change the management of PTL, improve outcomes for the women and their infants, and reduce usage of healthcare resources.

### **Evidence from RCTs**

The results reported by one RCT<sup>62</sup> suggest that it is difficult to engender changes in physician behaviour and that the introduction of the test might not result in improved efficiencies. Grobman et al.<sup>62</sup> found no difference in time spent in the L&D for initial evaluation, frequency of use of tocolysis or corticosteroids, number of admissions, or readmission post-discharge. Although this study was conducted over approximately 12 months, a subgroup analysis did not reveal the existence of a learning curve. However, it is possible that, if the test were used for a longer period, physicians might have become more comfortable with its characteristics and changed their clinical responses.

The results reported by Lowe et al.<sup>63</sup> suggest that the use of the rapid fFN assay does not affect the gestational age at delivery, frequency of use of medical interventions, length of stay in the L&D, or rate of inpatient admissions. Within the group of women tested with the rapid fFN assay, a “negative fFN test was associated with fewer admissions to the antepartum ward and a shorter length of stay”. However, this subgroup analysis was conducted on a retrospective basis.

In the RCT by Plaut et al.,<sup>64</sup> knowledge of the rapid fFN assay results was noted to improve care only in those women with an LOHS greater than 6 hours, and only by an LOHS decrease of 2 hours. The clinical and financial impact of a decrease in LOHS of 2 hours may not support the cost of testing. This study, however, suffered from low enrolment, and the possibility of not finding a difference for the other parameters of improved care such as maternal transport and use of tocolysis is highly possible.

The reviewed RCTs<sup>62-64</sup> did not incorporate explicit protocols for PTL management based on using positive and negative rapid fFN assay results or implement effective educational interventions. This absence may explain the reported limited impact of fFN testing in terms of change in clinical practice. Some of the investigators argued that they attempted to mimic the real world.<sup>63,64</sup>

Various educational interventions were used in two RCTs<sup>62,64</sup> to inform the attending/treating physicians about the test, but no information was gathered to assess whether the clinicians correctly understood and interpreted the test results. However, no evaluation of the effectiveness of the educational interventions that were used was conducted. It was not clear whether the clinicians in these studies

were already doing a very good job in correctly diagnosing PTL and thus there was no room for improvement, or whether the educational interventions that were used failed to adequately inform the clinicians on how to use the fFN test results in supplementing their clinical judgment.

The reviewed RCTs<sup>62-64</sup> did not directly address how changes in admission practices affected overall patient outcomes. Neither did they evaluate the woman's role in the treatment decision-making process.

PTL management for symptomatic women is not limited to hospitalization and administration of medical therapy. In most cases women are given instructions to reduce work hours and to increase bedrest. None of the reviewed RCTs evaluated the effect of using the rapid fFN assay on bedrest recommendations. The survey results reported by Grobman et al.<sup>62</sup> showed that the availability of rapid fFN assay results did not significantly alter the frequency of work cessation. Also, no significant difference was found between groups in terms of the number of women who felt the need to avoid typical leisure activity and arrange for increased help at home after their initial evaluation.

Neither did the reviewed RCTs directly address the impact of using rapid fFN assay on maternal stress and anxiety. The survey by Grobman et al.,<sup>62</sup> however, reported that knowledge about the test results did not help to reduce women's anxiety related to preterm contractions and there was no significant difference between groups in the women's emotional state subsequent to their release from hospital after initial PTD evaluations.

### **Evidence from non-randomized studies**

Several non-randomized studies and economic studies, conducted recently in the United States, Canada, Australia, and New Zealand<sup>2,79,85-89</sup> suggested that adding the rapid fFN assay can lead to practice change in the management of PTL and save healthcare resources. The results reported by several Canadian studies<sup>2,79</sup> suggest that knowledge of a negative fFN result may help to avoid over-diagnosis of PTL and use of unnecessary interventions (such as maternal transfer and use of medical interventions), and reduce hospital admission rate, length of stay for evaluation and treatment, and the associated costs. The studies did not report negative neonatal outcomes with the incorporation of the rapid fFN testing as an aid in diagnosing suspected PTL.

However, these studies<sup>2,79,85-89</sup> have methodological weaknesses that limit their findings' usefulness in determining the actual value of the test. Their findings were limited, in part, by the retrospective design, the use of historical control groups (if any) for comparison, and selective literature-based cost-efficacy analyses. The use of historical controls may have resulted in patient selection bias. Change in physicians' practice patterns because of factors other than the introduction of the fFN test might have influenced the outcomes.

## Recommended use of the rapid fFN assay

Guidelines and consensus statements issued on PTL management and assessment of risk factors for PTB/PTD recommend the use of fFN testing for diagnosing PTL in symptomatic women when clinical diagnosis is doubtful.<sup>2,16,17,34,42,56-61</sup> Some investigators suggest that using the rapid fFN assay, particularly once clinical criteria is met, would suggest admission is most useful.<sup>64,79,86</sup> For women for whom the clinical criteria rules out imminent risk of PTB/PTD, there is little benefit. However, there may be a particular benefit for those women at high risk, such as those who would be admitted on clinical criteria. Other investigators suggested using fFN testing when the clinical and ultrasonography data are equivocal or in conflict (such as women who present with mild symptoms and few contractions but whose cervical examination reveals advanced effacement).<sup>87</sup>

According to the reviewed evidence, the PPV of the rapid fFN assay is a poor predictor of subsequent risk of PTB/PTD in symptomatic women with PTL.<sup>16,57-64</sup> Therefore, it is recommended not to use a positive rapid fFN assay result as the primary guide for decisions related to the prevention of PTB/PTD. However, when a diagnostic test with a low PPV is introduced, there is always a concern that clinicians will over interpret a positive test result. If clinicians do not fully understand this limitation of the test, they may place too much weight on a positive test result and be more inclined to administer interventions to women who test positive than they would have been on the basis of clinical criteria only.

## Policy considerations

Although the rapid fFN assay is currently available in most Canadian provinces, no province has yet implemented a provincial policy for routine application of the test and its performance is not reimbursed anywhere in Canada.<sup>33</sup> Several jurisdictions are moving towards province-wide access to this test, although its clinical efficacy/effectiveness in terms of patient and resource usage outcomes has not yet been established by well-designed RCTs, as required by current standards for evidence-based health care.

Because the rapid fFN assay is a new diagnostic test and does not replace an existing laboratory test, its introduction into clinical practice presents resource, training, and quality assurance implications for physicians, laboratory personnel, and healthcare administrators.<sup>33</sup> Depending on the decision to place the fFN unit in a hospital laboratory or at the bedside (as a point-of-care test), all affected healthcare providers need to work together to determine optimal processes for transportation of specimens and timely reporting of the results, which is critical for patient care decision making.

Initial and ongoing education of the clinical and laboratory staff and regular audits of the clinical practice are necessary to ensure optimal use of the rapid

fFN assay, because a variety of factors can confound the interpretation of its results. For a successful use of this test, education of the clinical personnel is essential, so that the contraindications to fFN specimen collection are rigorously observed and the fFN samples are collected according to the recommendations from the manufacturer.

There is a need for establishing clear protocols and implementing a standardized clinical pathway for the use of the rapid fFN assay results in managing PTL in symptomatic women, if the value of this tool is to be realized optimally. Test implementation may lead to an increase, rather than a decrease, in the use of interventions for preventing PTB/PTD and PTL, if clinicians are not willing to change their current practice of care on the basis of its results.

## **Future predictors of PTD/PTB**

An improved understanding of the pathophysiology of PTD/PTB has led to the development of new tests to predict PTD/PTB in symptomatic women.<sup>6,21-25,27-30,74,90-92</sup> Many biochemical tests have been investigated recently, including those testing for the concentration of interleukin-6 in the cervix, corticotropin-releasing hormone in maternal blood, lactoferrin in the cervix, intercellular adhesion molecule-1 in the choriodecidua, and beta-human chorionic gonadotropin in cervicovaginal secretion. None of these biochemical tests have reached any firm place in clinical practice. Use of multiple markers holds promise for implementing interventions to prevent PTD/PTB.

## **Limitations**

The present review has several limitations. The literature review was confined to published reports of RCTs and systematic reviews that were written in English or French and were publicly available (free of charge). Only full text articles were included because abstracts provide insufficient details to allow an accurate, unbiased assessment and comparison of the study results. The authors of the abstract-only publications were not contacted for full details of their studies.

The selected RCTs were assessed using a quality tool, with the expectation that this would aid in identifying the studies that should be given more weight in the overall synthesis. However, the findings of the selected studies were not directly comparable, as their authors took different approaches and none of them met all the criteria used to judge their methodological quality. Although the original aim of quality assessment became redundant because of these factors, it still had value in highlighting the study design and execution flaws.

The present review only summarizes the recommendations from reports of relevant clinical practice guidelines and consensus documents and does not appraise their scientific foundations. The working groups for the documents that did not provide information on the methodological approaches used were not contacted to determine if the recommendations were based on research evidence.

Qualitative research literature, which talks about the benefits and limitations of using the rapid fFN assay to diagnose PTL from physicians' and women's perspectives, was not included.

The extent of publication bias was not assessed.

## ■ CONCLUSIONS

The current clinical use of the rapid fFN assay to diagnose PTL and predict PTB/PTD for symptomatic women who present for health care remains defined by its strong NPV. The absence of fFN in the cervicovaginal secretion of tested women has been shown to be a powerful predictor of the absence of progressive PTD/PTB within the next 7 to 10 days. It appears the challenge remains in the initial and ongoing education of the clinical and laboratory staff regarding this diagnostic test. The test results must be rapidly available and the clinicians must be willing to act on a negative test result by not initiating traditional interventions. The clinical importance of a positive test result remains unclear.

Knowledge of a negative rapid fFN assay result may supplement clinical judgment to predict "false" PTL followed by absence of PTD/PTB in the short term with more accuracy than clinical criteria alone, but this does not appear to necessarily translate into better clinical outcomes. The hypothesis that this use of the rapid fFN assay will inevitably improve outcomes for the woman and infant and reduce healthcare resource usage and the associated costs remains unproven.

The RCTs published to date suggest that these benefits may be negligible. Their reported results raise the question of whether the use of the rapid fFN assay offers significant benefit beyond that observed with good clinical assessment and judgment.

The rapid fFN assay seems to provide useful information when there is uncertainty about whether to transport a symptomatic woman for PTL from a Level 1 or Level 2 healthcare centre to a Level 2 or Level 3 healthcare centre. Because good evidence, reported by published RCTs, considers only the impact of the rapid fFN assay available in Level 2 and Level 3 hospitals where admission (or transfer) for care would occur, further well-designed research is warranted to study the clinical and economic impact of using the test in Level 1 hospitals.

As the rapid fFN assay becomes widely available in Canada, institutional guidelines for appropriate patient selection and testing, as well as regular audits of its use, are needed. These measures will help to define appropriate use and interpretation of the test results in a clinically meaningful way.

# ■ APPENDIX A: METHODOLOGY

## Search Strategy

A comprehensive and systematic literature search was conducted by a Research Librarian with the Alberta Heritage Foundation for Medical Research on October 6 to 11, 2005, and updated on April 19, 2007 (see Table A1). In addition to major electronic databases, relevant library collections, websites of practice guidelines, regulatory agencies, evidence-based resources, and other health technology assessment (HTA) related agency resources were searched. Internet search engines were also used to locate grey literature. Searches of the medical literature published between January 1995 and April 2007 were conducted without language restriction. Searches were limited to human studies only. In terms of publication type, searches were limited to reviews, guidelines, and clinical trials. These limits were applied in databases where such functions were available.

Medical Subject Headings (MeSH) terms relevant to this topic are fibronectins and premature labour.

**Table A1: Search strategy**

<sup>†</sup>See below for limits

Database	Platform	Edition or date searched	Search Terms <sup>††</sup>
Core Databases			
The Cochrane Library	<a href="http://www.thecochrane-library.com">http://www.thecochrane-library.com</a>	Issue 2 2007 Searched April 19, 2007	1. All Fields: (fetal or foetal) and (fibronectin or fibronectins)  or  2. Record Title: ((preterm or premature) and (birth or delivery or labor or labour)) and  Abstract: test or testing or tests or marker or markers or predictor* or predicting or predict or prediction or predicts or diagnosis or diagnostic or diagnose or identifying or identifies or identify or managing or management or detection or detect or screening
CRD Databases (DARE, HTA, & NHS EED)	<a href="http://nhscred.york.ac.uk">http://nhscred.york.ac.uk</a>	Searched April 19, 2007	(fetal or foetal) and fibronectin  or  (marker or predict or diagnosis or diagnostic or diagnose or identifies or identify or detect) and (preterm[TI] or premature[TI]) and (birth[TI] or delivery[TI] or labor[TI] or labour[TI])



**Table A1: Search strategy (continued)**

Database	Platform	Edition or date searched	Search Terms <sup>††</sup>
<b>Core Databases (continued)</b>			
PubMed	http://www.pubmed.gov	Searched April 19, 2007	<ol style="list-style-type: none"> <li>1. ((fetal or foetal) and (fibronectin or fibronectins))</li> <li>2. ((Test or testing or tests or marker or markers or predictor* or predicting or predict or prediction or predicts or diagnosis or diagnostic or diagnose or identifying or identifies or identify or managing or management or detection or detect or screening) and (preterm[TI] or premature[TI]) and (birth[TI] or parturition[TI] or delivery[TI] or labor[TI] or labour[TI]))</li> <li>3. (in process[sb] or publisher[sb])</li> <li>4. Limit 1 by: Clinical Trial or Meta-Analysis or Review or Practice Guideline</li> <li>5. Limit 2 by: Meta-Analysis or Review or Practice Guideline</li> <li>6. ((1 and 3) or 4) or ((2 and 3) or 5)</li> </ol>
Web of Science	Licensed Resource (ISI Interface)	Searched April 19, 2007	<ol style="list-style-type: none"> <li>1. TS=((fetal or foetal) SAME fibronectin*)</li> <li>2. TI=((premature or preterm) and (birth or labour or labor or delivery)) and TI=(test* or detect* or predict* or marker* or diagnos* or risk* or screen* or identif*)</li> <li>3. TS=(randomized controlled trial or RCT or placebo or ((singl* or doubl* or trebl* or tripl*) SAME (blind* or mask*))) or (clinical SAME trial))</li> <li>4. TS=(review or meta-analysis or critical appraisal or technology assessment)</li> <li>5. TS=((practice or clinical) SAME guideline*)</li> <li>6. (1 and (3 or 4 or 5)) or (2 and (4 or 5))</li> </ol>
CINAHL	Licensed Resource (EBSCO Interface)	Searched April 19, 2007	<ol style="list-style-type: none"> <li>1. (fetal or foetal) and fibronectin*</li> <li>2. limit 1 to (clinical trial or practice guidelines or research or "review" or "systematic review")</li> <li>3. ((premature or preterm) and (birth or labour or labor or delivery))TITLE and (test* or detect* or predict* or marker* or diagnos* or risk* or screen* or identify* or manag*)TITLE</li> <li>4. limit 3 to (practice guidelines or "review" or "systematic review")</li> <li>5. 2 or 4</li> </ol>

**Table A1: Search strategy (continued)**

Database	Platform	Edition or date searched	Search Terms <sup>††</sup>
<b>Core Databases (continued)</b>			
BIOSIS previews	Licensed Resource (ISI Interface)	Searched April 19, 2007	<p>1. TS=((fetal or foetal) SAME fibronectin*)</p> <p>2. TI=((premature or preterm) and (birth or labour or labor or delivery)) and TI=(test* or detect* or predict* or marker* or diagnos* or risk* or screen* or identif*)</p> <p>3. TS=(randomized controlled trial or RCT or placebo or ((singl* or doubl* or trebl* or tripl*) SAME (blind* or mask*)) or (clinical SAME trial))</p> <p>4. TS=(review or meta-analysis or critical appraisal or technology assessment)</p> <p>5. TS=((practice or clinical) SAME guideline*)</p> <p>6. (1 and (3 or 4 or 5)) or (2 and (4 or 5))</p>
EMBASE	Licensed Resource (OVID Interface)	Searched April 19, 2007	<p>1. (fetal or foetal) adj2 fibronectin).mp.</p> <p>2. ((premature or preterm) and (birth or labour or labor or delivery))[TI] and (test\$ or detect\$ or predict\$ or marker\$ or diagnos\$ or risk\$ or screen\$ or identif\$ or manag\$)[TI]</p> <p>Limits</p> <p>3. Randomized Controlled Trial/</p> <p>4. exp Randomization/</p> <p>5. Double Blind Procedure/</p> <p>6. Single Blind Procedure/</p> <p>7. Clinical Trial/</p> <p>8. (clin\$ adj25 trial\$).mp.</p> <p>9. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).mp.</p> <p>10. exp Placebo/</p> <p>11. (placebo\$ or random\$).mp.</p> <p>12. RCT.mp.</p> <p>13. or/3-12</p> <p>14. meta-analysis.pt.</p> <p>15. (meta-anal\$ or metaanal\$).mp.</p> <p>16. (((quantitativ\$ adj3 review\$1) or quantitativ\$) adj3 overview\$).mp.</p> <p>17. (((systematic adj3 review\$1) or systematic) adj3 overview\$1).mp.</p> <p>18. (((methodologic adj3 review\$1) or methodologic) adj3 overview\$).mp.</p> <p>19. (integrat\$ adj5 research).mp.</p>

**Table A1: Search strategy (continued)**

Database	Platform	Edition or date searched	Search Terms <sup>††</sup>
<b>Core Databases (continued)</b>			
EMBASE (continued)			<p>20. (quantitativ\$ adj3 synthes\$).mp.</p> <p>21. or/14-20</p> <p>22. review.pt. or (review\$ or overview\$).mp.</p> <p>23. (medline or medlars or pubmed or index medicus or embase or cochrane).mp.</p> <p>24. (scisearch or web of science or psycinfo or psychinfo or cinahl or cinhal).mp.</p> <p>25. (excerpta medica or psychlit or psychlit or current contents or science citation index or sciences citation index).mp.</p> <p>26. (hand search\$ or manual search\$).mp.</p> <p>27. (((electronic adj3 database\$) or bibliographic) adj3 database\$) or periodical index\$).mp.</p> <p>28. (pooling or pooled or mantel haenszel).mp.</p> <p>29. (peto or der simonian or dersimonian or fixed effect\$).mp.</p> <p>30. ((combine\$ or combining) adj5 (data or trial or trials or studies or study or result or results)).mp.</p> <p>31. or/23-30</p> <p>32. 22 and 31</p> <p>33. (hta\$ or health technology assessment\$ or biomedical technology assessment\$).mp.</p> <p>34. technology assessment, biomedical/ or biomedical technology assessment/</p> <p>35. critical appraisal.mp.</p> <p>36. or/33-35</p> <p>37. 21 or 32 or 36</p> <p>38. exp Practice Guideline/</p> <p>39. (1 and (13 or 37 or 38)) or (2 and (37 or 38))</p>
<b>Books and Theses</b>			
NEOS (Central Alberta Library Consortium)	<a href="http://www.library.ualberta.ca/catalogue">http://www.library.ualberta.ca/catalogue</a>	Searched April 19, 2007	fetal fibronectin; fibronectins; Title: (premature or preterm) and (birth or labour or labor or delivery)

**Table A1: Search strategy** (continued)

Database	Platform	Edition or date searched	Search Terms <sup>††</sup>
<b>Books and Theses</b> (continued)			
AMICUS	<a href="http://www.nlc-bnc.ca/amicus">http://www.nlc-bnc.ca/amicus</a>	Searched April 19, 2007	Subject Keyword or Title Keyword: fetal and fibronectin;  Title Keyword: preterm delivery or preterm birth or preterm labour;  Title Keyword: preterm labor or premature labor or premature labour;  Title Keyword: premature delivery or premature birth
LocatorPlus (US National Library of Medicine)	<a href="http://locatorplus.gov">http://locatorplus.gov</a>	Searched April 19, 2007	"fetal fibronectin"  (preterm or premature)[in Title] and (labor or labour or delivery or birth)[in Title] and (1995 or 1996 or 1997 or 1998 or 1999 or 2000 or 2001 or 2002 or 2003 or 2004 or 2005 or 2006 or 2007)[in Publisher: Date]
Theses Canada Portal	<a href="http://www.nlc-bnc.ca/thesescanada">http://www.nlc-bnc.ca/thesescanada</a>	Searched April 19, 2007	Search the full text of electronic theses: "fetal fibronectin"
ProQuest Dissertations & Theses Full Text	Licensed Resource (ProQuest Interface)	Searched April 19, 2007	Citation and Abstract: fetal fibronectin  Document Title: ((preterm or premature) and (birth or delivery or labour or labor)) and (test* or detect* or predict* or marker* or diagnos* or risk* or screen* or identif*)
<b>Guidelines</b>			
AMA Clinical Practice Guidelines	<a href="http://www.topalbertadoctors.org/TOPTOP/CPG/CPGTopics.htm">http://www.topalbertadoctors.org/TOPTOP/CPG/CPGTopics.htm</a>	Searched April 19, 2007	Browsed for relevant guidelines
CMA Infobase	<a href="http://mdm.ca/cpgsnew/cpgs/index.asp">http://mdm.ca/cpgsnew/cpgs/index.asp</a>	Searched April 19, 2007	fetal fibronectin; foetal fibronectin; preterm birth; preterm delivery; preterm labor; preterm labour; premature birth; premature labor; premature labour; premature delivery
National Guideline Clearinghouse	<a href="http://www.ngc.gov">http://www.ngc.gov</a>	Searched April 19, 2007	fetal fibronectin; foetal fibronectin
Canadian Task Force on Preventive Health Care	<a href="http://www.ctfphc.org">http://www.ctfphc.org</a>	Searched April 19, 2007	Browsed the topic section: Prenatal and Perinatal Preventive Care

**Table A1: Search strategy (continued)**

Database	Platform	Edition or date searched	Search Terms <sup>††</sup>
<b>Clinical Trials</b>			
ClinicalTrials.gov (US)	<a href="http://clinicaltrials.gov/">http://clinicaltrials.gov/</a>	Searched April 19, 2007	fetal fibronectin; foetal fibronectin
CenterWatch Clinical Trials Listing Service	<a href="http://www.centerwatch.com/">http://www.centerwatch.com/</a>	Searched April 19, 2007	Browsed Obstetrics/ Gynecology and Pediatrics/ Neonatology
CENTRAL (Cochrane Library)	Licensed Resource (Wiley Interface)	Searched April 19, 2007	(fetal or foetal) and fibronectin
National Research Register	<a href="http://www.update-software.com/national/">http://www.update-software.com/national/</a>	Searched April 19, 2007	fetal next fibronectin; foetal next fibronectin
<b>Coverage/Regulatory/Licensing</b>			
Alberta Health and Wellness	<a href="http://www.health.gov.ab.ca">http://www.health.gov.ab.ca</a>	Searched April 19, 2007	Must contain in the body the words: fetal fibronectin; Must contain in the body the words: foetal fibronectin;
Medical Devices Active Licence Listing	<a href="http://www.mdall.ca">http://www.mdall.ca</a>	Searched April 19, 2007	Devicename: tli system Company Name: Adeza
US Food and Drug Administration (General site search)	<a href="http://www.fda.gov">http://www.fda.gov</a>	Searched April 19, 2007	Adeza "fetal fibronectin"
US Food and Drug Administration Premarket Approval Database	<a href="http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm">http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm</a>	Searched April 19, 2007	Applicant Name: Adeza
US Medicare Coverage Database	<a href="http://www.cms.hhs.gov/mcd/search.asp">http://www.cms.hhs.gov/mcd/search.asp</a>	Searched April 19, 2007	Both Local and National Coverage, All States, Entire Document: fetal fibronectin

**Table A1: Search strategy** (continued)

Database	Platform	Edition or date searched	Search Terms <sup>††</sup>
<b>Coverage/Regulatory/Licensing</b> (continued)			
Aetna Clinical Policy Bulletins	<a href="http://www.aetna.com/about/cov_det_policies.html">http://www.aetna.com/about/cov_det_policies.html</a>	Searched April 19, 2007	"fetal fibronectin"
BlueCross BlueShield	<a href="http://www.bluecares.com">http://www.bluecares.com</a>	Searched April 19, 2007	Browsed Diagnostic and Monitoring Tests category and Obstetrics Gynecology Urology category
<b>Evidence-Based Medicine Resources</b>			
ACP Journal Club (Ovid)	<a href="http://www.acpjournals.org">http://www.acpjournals.org</a>	Searched April 19, 2007	"fetal fibronectin"; "foetal fibronectin"
ATTRACT	<a href="http://www.attract.wales.nhs.uk">http://www.attract.wales.nhs.uk</a>	Searched April 19, 2007	Fibronectin
Bandolier	<a href="http://www.jr2.ox.ac.uk/bandolier/">http://www.jr2.ox.ac.uk/bandolier/</a>	Searched April 19, 2007	Fibronectin
BestBETs	<a href="http://www.bestbets.org">http://www.bestbets.org</a>	Searched April 19, 2007	Fibronectin
Clinical Evidence	Licensed Resource	Searched April 19, 2007	Fibronectin
TRIP database	<a href="http://www.tripdatabase.com">http://www.tripdatabase.com</a>	Searched April 19, 2007	Title and Text: "fetal fibronectin"; Title and Text: "foetal fibronectin";
<b>HTA Resources</b>			
AETMIS	<a href="http://www.aetmis.gouv.qc.ca">http://www.aetmis.gouv.qc.ca</a>	Searched April 19, 2007	Fibronectin
CADTH	<a href="http://www.cadth.ca/index.php/en/hta/reports-publications/search">http://www.cadth.ca/index.php/en/hta/reports-publications/search</a>	Searched April 19, 2007	Fibronectin; preterm; premature
ICES	<a href="http://www.ices.on.ca">http://www.ices.on.ca</a>	Searched April 19, 2007	Fibronectin

**Table A1: Search strategy** (continued)

Database	Platform	Edition or date searched	Search Terms <sup>††</sup>
<b>HTA Resources</b> (continued)			
HTA at McGill	<a href="http://www.mcgill.ca/tau">http://www.mcgill.ca/tau</a>	Searched April 19, 2007	Browsed list of reports and works in progress
Medical Advisory Secretariat	<a href="http://www.health.gov.on.ca/english/providers/program/mas/mas_mn.html">http://www.health.gov.on.ca/english/providers/program/mas/mas_mn.html</a>	Searched April 19, 2007	Browsed list of technology assessments
ECRI	<a href="http://www.ecri.org">http://www.ecri.org</a>	Searched April 19, 2007	Fibronectin
CCE	<a href="http://www.med.monash.edu.au/healthservices/cce/">http://www.med.monash.edu.au/healthservices/cce/</a>	Searched April 19, 2007	fetal fibronectin; foetal fibronectin
Health Quality Council, Saskatchewan	<a href="http://www.hqc.sk.ca/portal.jsp?Tnp y1RKzAkMsCVz+LX1gQTBIzBf0QfLQkUwK4QBZaJsd3xH8TRx63ozOVcA+lmY4">http://www.hqc.sk.ca/portal.jsp?Tnp y1RKzAkMsCVz+LX1gQTBIzBf0QfLQkUwK4QBZaJsd3xH8TRx63ozOVcA+lmY4</a>	Searched April 19, 2007	Browsed publication list
MHRA (UK)	<a href="http://www.mhra.gov.uk">http://www.mhra.gov.uk</a>	Searched April 19, 2007	Advanced full text search: fibronectin
NICE (UK)	<a href="http://www.nice.org.uk/">http://www.nice.org.uk/</a>	Searched April 19, 2007	Fibronectin
NZHTA	<a href="http://nzhta.chmeds.ac.nz">http://nzhta.chmeds.ac.nz</a>	Searched April 19, 2007	Browsed publications page
NCCHTA	<a href="http://www.ncchta.org/">http://www.ncchta.org/</a>	Searched April 19, 2007	Fibronectin; labour; birth; delivery
University HealthSystem Consortium <sup>**</sup>	<a href="http://www.uhc.edu">http://www.uhc.edu</a>	Searched April 19, 2007	Browsed the "Publications in Print" section of the website

**Table A1: Search strategy** (continued)

Database	Platform	Edition or date searched	Search Terms <sup>††</sup>
Search Engine			
Google	http://www.google.ca	Searched April 19, 2007	"fetal fibronectin" filetype:pdf; "fetal fibronectin" -filetype:pdf; Adeza "fetal fibronectin";

Note: <sup>†</sup>Limits: Searches were limited to human studies only; publication type: limited to reviews, guidelines, and clinical trials. These limits are applied in databases where such functions are available.

<sup>††</sup> "\*, "\$", and "?" are truncation characters that retrieve all possible suffix variations of the root word; e.g., surg\* retrieves surgery, surgical, surgeon, etc. Semi-colons separate searches that were entered separately.

Further relevant articles were found by examination of the references listed in the retrieved papers.

The manufacturer of the rapid fFN assay available on the market in North America was contacted for information on regulatory status, availability, and coverage in Canada and the United States. The manufacturer was also contacted for information regarding ongoing or completed primary research studies conducted in Canada on the value of adding the rapid fFN assay in diagnosing suspected PTL in symptomatic women.

Health Canada, Therapeutic Products Directorate was contacted to request information on the regulatory status of the rapid fFN testing device in Canada. Also requested was information on whether data on risks and complications to mother and/or fetus from performing the rapid fFN assay itself were taken into consideration when the device was licensed.



## ■ Appendix B: Screening and Reviewing the Literature

One reviewer (PC) conducted the initial study selection, which was based on the study titles and abstracts only. The inclusion or exclusion of studies was determined on the basis of a list of inclusion and exclusion criteria developed a priori by two reviewers (PC and CH) for this study. Always erring on the side of caution, as only limited information is provided in abstracts, the reviewers selected studies for retrieval if they seemed to meet the inclusion criteria listed below. The retrieval was limited to published studies written in English or French.

Copies of the full text of potentially eligible studies were then retrieved and assessed for eligibility by one reviewer (PC) using the same selection criteria. In some cases, when the full text of the article was retrieved, closer examination revealed that it did not meet the inclusion criteria specified by the review protocol. Consequently, these papers were not used to formulate the evidence base for the systematic review and they are listed in Table B1. However, where appropriate, relevant information contained in the excluded papers was used to inform the sections of the report and to expand the review discussion.

### **Inclusion criteria**

Studies were included in the review if:

- they had a published report that was publicly available (free of charge);
- they included pregnant women (all ages; single or multiple gestation) with symptoms and signs of spontaneous preterm labour (PTL) presenting for health care at an inpatient or outpatient setting (urban or rural);
- they reported on the use of the rapid fetal fibronectin (fFN) assay in diagnosing PTL in symptomatic women;
- they compared the rapid fFN assay with clinical risk assessment, other diagnostic tests used for this indication (such as transvaginal/endovaginal ultrasonography, and/or other fFN testing modality), or no testing;
- they measured efficacy/effectiveness and safety of using the rapid fFN assay in terms of at least one of the following outcomes:
  - rates of spontaneous preterm delivery (PTD) or preterm birth (PTB);
  - ambulance transport/transfer rates (air and/or road);
  - hospital admission rates (including duration);
  - length of assessment time;
  - use of interventions to prevent PTL or PTB/PTD (including use of tocolytics);
  - impact on treatment decisions (prevention of over-treatment);
  - use of other diagnostic tests;

- length of hospital stay;
- maternal anxiety and stress;
- need for removal from the woman's home support; and/or
- risks and complications to the woman and fetus from performing the test itself.

Only full text articles were included because abstracts do not provide adequate detail on patient selection, allocation, study design, outcome, and measurement methods to allow an accurate, unbiased assessment, and comparison of the study results. In the case of duplicate publications, the most recent and complete version was included.

The authors of the abstract-only publications were not contacted for full details of their studies.

### **Type of studies**

Considered for inclusion were all published reports of:

- randomized controlled trials (RCTs) reporting on the safety and efficacy/effectiveness of rapid fFN assay for diagnosing suspected PTL in women with symptoms and signs of PTL; and/or
- systematic reviews of primary research reporting on the safety and efficacy/effectiveness of using rapid fFN assay for diagnosing suspected PTL in women with symptoms and signs of PTL.

**Using criteria from Cook et al.,<sup>93</sup>** a review was considered to be systematic if it met the following criteria:

- focused clinical question;
- explicit search strategy;
- use of explicit, reproducible, and uniformly applied criteria for article selection;
- critical appraisal of the included studies;
- qualitative or quantitative data synthesis.

### **Guidelines and consensus documents**

The section on Guidelines and Consensus Documents summarizes recommendations from reports of relevant clinical practice guidelines, position papers, and consensus statements issued on the definition and/or diagnosis of PTL and/or on the use of rapid fFN assay as a diagnostic tool for this indication.

### **Background information**

Where appropriate, relevant published material, in the form of overview materials, clinical reviews, letters, conference materials, commentaries, discussion papers, editorials, and abstracts, was included as background information for the various sections of the report.

Exclusion criteria

Excluded were published reports of studies that:

- evaluated various modalities of fFN testing modalities for diagnosing suspected PTL in symptomatic women and did not report separately on the safety and efficacy of the rapid fFN assay when used for this indication;
- involved both symptomatic and asymptomatic women and did not separately report on the use of the rapid fFN assay in symptomatic women;
- included women who experienced premature rupture of membranes and/or medically indicated PTL and/or asymptomatic women with multiple gestations and did not separately report on these subjects;
- focused on the use of the rapid fFN assay as a screening tool, involving only asymptomatic women; or
- focused on the use of the rapid fFN assay for other indications (such as a predictive tool for post-term delivery).

Published reports of non-RCTs or other types of primary research studies (such as cohort studies, case series, and case reports), editorials, letters, and technical reports were excluded. However, information contained in non-RCTs or comparative studies conducted in Canada was used to inform the section on Canadian research studies.

Also excluded from data extraction were published reports of narrative and descriptive reviews, which summarized the research on the topic but lacked an explicit description of a systematic approach to the identification and interpretation of evidence.

Table B1: Excluded studies

Study	Reason for exclusion
<b>Agency for Healthcare Research and Quality (AHRQ) (2000)<sup>94</sup></b> Management of preterm labor Evidence Report/Technology Assessment (produced by Berkman et al for the AHRQ)	<p>This study met all the criteria for a systematic review. However, 12 of the 14 observational studies included in it were also reviewed by another systematic review,<sup>68</sup> which conducted the largest meta-analysis on the topic. Honest et al.<sup>68</sup> excluded the other two studies (a case-control study with historical controls, which did not report enough data to construct 2 x 2 tables; and a prospective cohort study, which was a duplicate publication of a more recent and complete version included by Honest et al.<sup>68</sup>).</p> <p>The reviewed version does not report separate results on the diagnostic accuracy of the rapid fFN testing modality.</p>

**Table B1: Excluded studies** (continued)

Study	Reason for exclusion
<p><b>Australia and New Zealand Horizon Scanning Network (2004)<sup>1</sup></b></p> <p>A rapid foetal fibronectin assay as a predictive test for women suspected of being in pre-term labor</p> <p>Horizon scanning prioritising summary (by Linda Mundy from the Adelaide Health Technology Assessment)</p>	<p>This study did not meet all criteria for a systematic review. It summarizes the results published by two randomized controlled trials on the use of rapid fFN testing.</p>
<p><b>Chien et al. (1997)<sup>73</sup></b></p> <p>The diagnostic accuracy of cervicovaginal fetal fibronectin in predicting preterm delivery: an overview</p> <p>Systematic review</p>	<p>This study met all criteria for a systematic review. However, the meta-analysis conducted on the use of fFN testing in symptomatic women was restricted to nine observational studies, which were also included in one more recently published systematic review<sup>68</sup> that conducted the largest meta-analysis on the topic.</p> <p>The reviewed version of this systematic review does not report separate results on the use of the rapid fFN testing modality.</p>
<p><b>Faron et al. (1998)<sup>70</sup></b></p> <p>Prediction of preterm delivery by fetal fibronectin: a meta-analysis</p> <p>Systematic review</p>	<p>This study did not meet all criteria for a systematic review.</p> <p>One of its inclusion criteria was that the studies report on the measurement of the cervicovaginal fFN by a "kit using a previously described enzyme-linked immunoabsorbant assay."</p>
<p><b>HAYES, Inc. (2000)<sup>95</sup></b></p> <p>Fetal fibronectin test</p> <p>Health Technology Assessment report (produced by Hayes, Inc.)</p>	<p>The published report of this health technology assessment study was not publicly available.</p> <p>This evaluated both ELISA and the rapid fFN testing and did not report separate results for each method (Hayes, Inc., personal communication, October 20, 2005).</p>
<p><b>Health Technology Assessment Information Service (HTAIS) of ECRI (2000)<sup>6</sup></b></p> <p>Fetal fibronectin assay for prediction of preterm birth and neonatal morbidity</p> <p>Custom Health Technology Assessment Report (produced by ECRI)</p>	<p>This study met all the criteria for a systematic review. However, all observational studies included in it to pool data on diagnostic accuracy of fFN testing in symptomatic women were also reviewed in a more recently published study,<sup>68</sup> which also met the criteria for a systematic review and conducted the largest meta-analysis on the topic.</p> <p>The reviewed version does not report separate results on the diagnostic accuracy of the rapid fFN testing modality.</p>
<p><b>Institute for Clinical Systems Improvement (ICSI) (2000)<sup>34</sup></b></p> <p>Fetal fibronectin for the prediction of preterm labor</p> <p>Technology Assessment Report (produced by ICSI)</p>	<p>This study did not meet all criteria for a systematic review.</p> <p>All the studies included in it were also reviewed in a more recently published systematic review,<sup>68</sup> which conducted the largest meta-analysis on the topic.</p>

**Table B1: Excluded studies** (continued)

Study	Reason for exclusion
<b>Krupa et al. (2006)<sup>74</sup></b> Predictors of preterm birth Systematic review	This study did not meet all criteria for a systematic review. It included studies that evaluated both ELISA and the rapid fFN testing and did not report separate results for each method.
<b>Leitch et al. (1998)<sup>72</sup></b> Cervicovaginal fetal fibronectin as a marker for preterm delivery: a meta-analysis Systematic review	This study did not meet all criteria for a systematic review. All 15 observational studies included in this review were also reviewed by a more recently published systematic review, <sup>68</sup> which conducted the largest meta-analysis on the topic.
<b>Leitch and Kaider (2003)<sup>69</sup></b> Fetal fibronectin – how useful is it in the prediction of preterm birth? Systematic review	This study is an update of a previous study (Leitch et al. <sup>72</sup> ), which was excluded from this review because it did not meet all criteria for a systematic review (see above). The same reasons for exclusion apply for this study. It pooled results from 21 observational studies on symptomatic women (some examined ELISA and others a solid-phase immunogold assay), which are not cited in the reviewed version.
<b>Nguyen (2002)<sup>65</sup></b> The cost-effectiveness of fetal fibronectin testing in suspected preterm labor: a randomized trial Randomized controlled trial	This study was available only in abstract form.
<b>Revah et al. (1998)<sup>71</sup></b> Fetal fibronectin as a predictor of preterm birth: an overview Systematic review	This study did not meet all criteria for a systematic review. Thirteen of the 15 observational studies examining the use of fFN testing in symptomatic women were also reviewed in a more recently published systematic review, <sup>68</sup> which conducted the largest meta-analysis on the topic.
<b>Technology Evaluation Center (TEC) Program (1997)<sup>5</sup></b> Fetal fibronectin enzyme immunoassay TEC Assessment (for Blue Cross and Blue Shield Association)	This study did not meet all criteria for a systematic review. All 12 observational studies on the use of fFN testing included in this review were also reviewed by a more recently published systematic review, <sup>68</sup> which conducted the largest meta-analysis on the topic.

ELISA – enzyme-linked immunosorbent assay; fFN – fetal fibronectin

## Data extraction

Details of the reviewed RCTs are summarized in Table C1 (Appendix C) and the main characteristics, findings, and conclusions from the published reports of relevant systematic reviews are summarized in Tables D1 and D2 (Appendix D). Details from the reviewed Canadian studies are summarized in Table E1 (Appendix E).

Study profile information and outcome data were extracted by one reviewer (PC) using data extraction forms developed a priori:

### For reviewed RCTs and Canadian studies (Table C1 and Table E1)

- **Study:** author(s), year of publication, setting, and study duration;
- **Study protocol and patients' characteristics:** sample size, inclusion and exclusion criteria and details of study protocol (definitions used for symptomatic women, PTL/PTD; criteria used for diagnosing PTL; method used to estimate gestational age; information on how the groups were compared), patients' characteristics (age, race, risk classification, socio-economic status, etc.), and baseline measurements (such as estimated gestation age and cervical dilation at testing);
- **Interventions and outcomes:** rapid fFN assay (description of fFN testing: device type and frequency of test; analytical method), comparator (description of the comparator used or of how patient groups were compared), other interventions (description of other diagnostic interventions used), outcome(s) (information on primary/secondary outcomes and outcome measures), and operator (information on professional background, training, and experience for professionals who performed the tests: collected the fFN specimens and analyzed the fFN specimens); and
- **Reported results of interest:** diagnostic accuracy (in terms of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the test, and likelihood ratio (LR) for positive and negative test results), clinical/patient outcomes (in terms of PTD/PTB rates, hospital admission rates, length of assessment time, length of hospital stay, treatment decisions, treatment administration, maternal transport/transfer rates; maternal anxiety or stress reduction), and safety outcomes (side effects and complications or risks and complications to the woman and/or fetus from performing the test itself).

### For systematic reviews (Tables D1 and D2)

- **Study:** author, year of publication, country;
- **Study's characteristics:** inclusion/exclusion criteria for primary research studies; evaluated intervention; comparator; outcomes and outcome measures)
- **Study's main findings and conclusions:** reported results on diagnostic accuracy (in terms of sensitivity, specificity, PPV and NPV of the test, and LRs for positive and negative test results), clinical/patient outcomes (in terms of PTD/PTB rates, hospital admission rates, length of assessment

time, length of hospital stay, treatment decisions, treatment administration, maternal transport/transfer rates, maternal anxiety or stress reduction), and safety outcomes (side effects and complications or risks and complications to the patient and/or fetus from performing the test itself), conclusions stated by the authors quoted directly from the published report; and

- **Study's objective and methods:** objective/aim/focus of the systematic review; information on search strategy, selection criteria, critical appraisal tools, and qualitative and quantitative data synthesis.

## **Methodological quality assessment**

The included systematic review and RCTs were assessed with respect to various methodological aspects using the appraisal tools developed by the Critical Appraisal Skills Programme (CASP) in the United Kingdom (<http://www.phru.nhs.uk/>; <http://www.phru.nhs.uk/casp/casp.htm>). The appraisal tools were accessed at [http://www.phru.nhs.uk/casp/critical\\_appraisal\\_tools.htm](http://www.phru.nhs.uk/casp/critical_appraisal_tools.htm).

Two reviewers (PC and CH) independently assessed the methodological quality of the included studies using the appraisal tools developed by CASP. The two reviewers discussed the appraisal tools with respect to the interpretation of the questions prior to critically appraising the studies.

Any disagreements in the critical appraisal results for each of the selected studies were resolved by discussion until consensus was reached. The degree of the difference or equivalence between the two reviewers was not measured and a statistical measure of the inter-rater agreement was not provided, as consensus was required to finalize the critical appraisal results for each of the selected studies. The reviewers were not blinded to any aspects of the published papers being evaluated.

Critical appraisal results for all included studies are presented in Table C2 (Appendix C) and Table D3 (Appendix D). The evidence itself was not graded, but it was described in terms of potential sources of bias that should be taken into account when interpreting the reported results.

## **Expert review**

External reviewers with clinical expertise in obstetrics and gynecology and health technology assessment methodologies evaluated the draft report and provided feedback. In selecting reviewers, the practice of the Institute of Health Economics is to choose experts who are well recognized and published in peer-reviewed literature, and who can offer a provincial and/or national perspective on using the rapid fFN assay to diagnose PTL and predict PTB/PTD.

In addition, the manufacturer of the Rapid fFN for TLi™ System, Adeza Biomedical Corporation, was contacted for technical information and for feedback on whether the information was correctly represented in the draft report.

## ■ Appendix C: Selected RCTs (Results and Methodology)

### **Abbreviations used in Tables C1 and C2**

°C – Celsius degrees

CI<sub>95</sub> – 95% confidence interval

cm – centimetre(s)

d – day(s)

fFN – fetal fibronectin

EGA – estimated gestational age

h – hour(s)

HA – hospital admission (at time of study entry)

HMO – health maintenance organization

L&D – Labour and Delivery Unit

LOHS – length of hospital stay (days during hospital admission)

mo – month(s)

N – number of patients

NPV – negative predictive value

NSS – not statistically significant (ly)

PPV – positive predictive value

PTB – preterm birth

PTD – preterm delivery

PTL – preterm labour

RCT – randomized controlled trial

sec. – second(s)

Sn – sensitivity

Sp – specificity

SS – statistically significant (ly)

TVUS – transvaginal ultrasound



USA – United States of America

US – ultrasound or ultrasonography

VE – vaginal examination

vs. – versus

wk – week(s)

y – year(s)

**Table C1: RCTs on the use of the rapid fFN assay**

Study	Study protocol and women's characteristics
<p>Grobman et al. (2004)*<sup>62</sup></p> <p><b>Country:</b> USA</p> <p><b>Setting:</b> university hospital</p> <p><b>Duration:</b> approximately 12 mo (not clear between what dates)</p>	<p><b>Sample size:</b> 100 women who came to L&amp;D with complaints associated with PTL (112 were offered enrolment; 12 denied)</p> <p><b>Inclusion:</b> EGA of 24 to 34 wk, singleton pregnancy, primary complaint of uterine contractions, and &gt;6 contractions/h (by external tocodynametry)</p> <p><b>Exclusion:</b> vaginal bleeding, non-intact amniotic membranes, <math>\geq 3</math> cm cervical dilatation, or a VE or sexual intercourse within 24 h; already received hospital observation, admission, or treatment for preterm contractions</p> <p><b>Protocol:</b></p> <ul style="list-style-type: none"><li>– all participants underwent evaluation by a physician (focused history, assessment of fetal heart tones and uterine contraction frequency with external monitors, and physical examination); as part of physical examination, each woman underwent a cervix examination with a speculum at which time an fFN specimen was obtained; immediately after, a digital cervical examination was performed;</li><li>– participants were assigned to <b>study group</b> (n = 50; fFN test results were communicated to attending physician) and <b>control group</b> (n = 50; fFN results were not communicated to attending physician); the fFN specimen for each woman in the study group was sent immediately for analysis; the fFN specimen for each woman in the control group was stored at -20°C (control group swabs were analyzed as a single batch);</li><li>– the fFN test had not been used in L&amp;D before study; during the study, the fFN test was available only within the study protocol;</li><li>– no information provided on how EGA was determined</li></ul> <p><b>Women' characteristics:</b> NSS differences between groups with respect to women's mean age, parity, whether they had known risks for PTB; women in each group had comparable socio-economic backgrounds; their pregnancy outcomes were also NSS different; similar proportions of women had positive fFN test results and PTD.</p> <p><b>Baseline measurements:</b> NSS difference between groups in mean cervical dilation and mean EGA</p>

\*Study supported by a grant from Adeza Biomedical

\*\*Summarized results reported on diagnostic accuracy, safety, and efficacy of rapid fFN testing in terms of impact on patient and resource usage outcomes

\*\*\* Data were reported in the reviewed RCT as median (interquartile range)

Interventions and outcomes	Reported results**
<p><b>Rapid fFN assay:</b> to obtain an fFN specimen, a Dacron swab was placed in the posterior vaginal fornix for 10 sec. to absorb cervicovaginal secretions; analysis of fFN specimen was performed with a rapid fFN cassette used with the TLi™ analyzer (Rapid fFN for the TLi™ analyzer)</p> <p><b>Comparator:</b> no availability of fFN test results (<i>rapid fFN testing was not compared with other diagnostic intervention</i>)</p> <p><b>Other interventions:</b> no other diagnostic interventions are mentioned</p> <p><b>Outcome(s):</b> primary outcome was the total costs; other outcomes: pregnancy outcomes, PTD rates, HA rates, LOHS, treatment usage, length of assessment, maternal anxiety</p> <p><b>Operator:</b> the physician collected fFN specimens as part of the physical examination; laboratory personnel of hospital laboratory performed the analysis (<i>no additional information provided</i>)</p>	<p><b>Diagnostic accuracy:</b></p> <p><b>PPV:</b> 12.5% for delivery within 1 wk; 62.5% for delivery before 37 wk</p> <p><b>NPV:</b> 96.7% for delivery within 1 wk; 81.3% for delivery before 37 wk</p> <p><b>Clinical outcomes:</b></p> <p><b>PTD:</b> 10 PTDs in study group (20%) vs. 13 PTDs in control group (6%) (<math>P = 0.45</math>)</p> <p><b>Assessment time***:</b> 3 h (2-5 h) for study patients vs. 4 h (2-5 h) for control patients (<math>P = 0.44</math>)</p> <p><b>HA:</b> 13 (26%) women in study group vs. 14 (28%) in control group (<math>P = 0.82</math>)</p> <p><b>LOHS***:</b> 2 d (1-5 d) for women in both groups (<math>P = 0.83</math>) (during admissions at study entry); 4 d (2-7 d) for study patients vs. 2 d (1-11 d) for control patients (<math>P = 0.62</math>) (during admissions after study entry)</p> <p><b>Treatment decisions:</b> tocolysis used in 8 study patients (16%) vs. 9 control patients (18%) (<math>P = 0.79</math>); corticosteroid used in 8 study patients (16%) vs. 10 control patients (20%) (<math>P = 0.60</math>)</p> <p><b>Safety:</b></p> <p>No reporting on side effects, risks, or complications from performing test itself</p>

**Table C1: RCTs on the use of the rapid fFN assay (continued)**

Study	Study protocol and women's characteristics
<p>Lowe et al. (2004)*<sup>63</sup></p> <p><b>Country:</b> USA</p> <p><b>Setting:</b> university hospital</p> <p><b>Duration:</b> August 2000 to May 2002</p>	<p><b>Sample size:</b> 110 women enrolled (examined at L&amp;D or transferred and already receiving tocolytic medication); 97 women available for study analysis</p> <p><b>Inclusion:</b> EGA of 23 to 34 wk; &gt;16 y of age; signs and symptoms of PTL (uterine contractions and/or cervical change); cervical dilatation of <math>\leq 3</math> cm for primiparous and of <math>\leq 4</math> cm for multiparous women</p> <p><b>Exclusion:</b> high order multifetal gestation (more than twins), cerclage, preterm premature rupture of membranes, and vaginal bleeding</p> <p><b>Protocol:</b></p> <ul style="list-style-type: none"><li>– EGA assigned by woman's last menstrual period and 1st or early 2nd trimester US; if last menstrual period unknown or discrepancy existed regarding dates, EGA assigned based on US;</li><li>– women assigned to <b>fFN group</b> (N = 46; PTL management with a test performed) and <b>no fFN group</b> (N = 51; PTL management without a test performed);</li><li>– rapid fFN assay performed at 24 h after sexual intercourse, digital examination, TVUS scanning, or use of creams or lubricants; results available in 1 h;</li><li>– all women treated by the same faculty practice</li></ul> <p><b>Women's characteristics:</b> NSS difference between groups with regard to age, gravidity, parity, previous PTB, referring physician, multiple gestations</p> <p><b>Baseline measurements:</b> NSS between groups in median EGA at the time of test; NSS difference between groups in cervical dilation or effacement measurements on examination</p>

\*Study supported by a Process Improvement grant sponsored by the University of Iowa, IA, USA

\*\*Summarized results reported on diagnostic accuracy, safety, and efficacy of rapid fFN testing in terms of impact on patient and resource usage outcomes

Interventions and outcomes	Reported results**
<p><b>Rapid fFN:</b> for fFN specimen collection, a Dacron swab was rolled against the posterior lip of the cervix; specimen was then placed into a buffer solution and sent to laboratory; results reported positive if the assay measured &gt;50 ng/mL and negative if &lt;50 ng/mL</p> <p><b>Comparator:</b> no rapid fFN assay performed (<i>rapid fFN assay was not compared with other diagnostic intervention</i>)</p> <p><b>Other interventions:</b> no other diagnostic interventions are mentioned</p> <p><b>Outcome(s):</b> time spent in L&amp;D; admission to antepartum unit; length of stay on antepartum ward (LOHS); treatment decisions (use of magnesium, betamethasone, and antibiotics); EGA at delivery</p> <p><b>Operator:</b> residents collected the fFN specimens; analysis of fFN specimen was performed in laboratory (<i>no additional information provided</i>)</p>	<p><b>Diagnostic accuracy</b></p> <p><b>Sn:</b> 66.7% (CI95 9.4-99.2) (delivery &lt;7 d); 75.0% (CI95 0.6-80.6) (delivery &lt;14 d); 38.5% (CI95 13.9-68.5) (delivery &lt;37 wk)</p> <p><b>Sp:</b> 79.1% (CI95 64.0-90.0) (delivery &lt;7 d); 81.0% (CI95 65.9-91.4) (delivery &lt;14 d); 81.8% (CI95 64.5-93.0) (delivery &lt;37 wk)</p> <p><b>PPV:</b> 18.2% (CI95 2.3-51.8) (delivery &lt;7 d); 27.3% (CI95 6.0-61.0) (delivery &lt;14 d); 45.5% (CI95 16.8-76.6) (delivery &lt;37 wk)</p> <p><b>NPV:</b> 97.1% (CI95 85.1-99.9) (delivery &lt;7 d); delivery &lt;14 d); 77.1% (59.9-89.6) (delivery &lt;37 wk)</p> <p><b>Clinical outcomes</b></p> <p><b>EGA at delivery:</b> NSS difference in median EGA at delivery (37.4 wk in "no fFN" group vs. 38.2 wk in "fFN" group; P = 0.258)</p> <p><b>Admissions:</b> NSS differences between groups (P = 0.265)</p> <p><b>LOHS:</b> NSS difference between groups (P = 0.224)</p> <p><b>Treatment decisions:</b> NSS differences between groups in number of women who received magnesium (P = 0.84), antibiotics (P = 683), or betamethasone (P = 545)</p> <p><b>Safety</b></p> <p>No reporting on side effects, risks, or complications from performing test itself.</p> <p>One woman delivered within 7 d of a negative fFN result. "Further safety monitoring did not reveal any other unexpected or potentially harmful effects."</p>

**Table C1: RCTs on the use of the rapid fFN assay (continued)**<sup>35,7324</sup>

Study	Study protocol and women's characteristics
<p>Plaut et al (2003)*<sup>64</sup></p> <p><b>Country:</b> USA</p> <p><b>Setting:</b> 3 community hospitals</p> <p><b>Duration:</b> samples collected between September 2000 and December 2001</p>	<p><b>Sample size:</b> 108 swabs from 100 women who arrived at hospital with PTL (consent obtained for 114; three patients excluded because they were evaluated at a clinic and not in L&amp;D, for two patients there were no data about labour and delivery, for 1 patient the specimen was too bloody and was rejected by laboratory); eight patients were entered twice (allowed if &gt;2 wk passed since initial evaluation)</p> <p><b>Inclusion:</b> EGA of 24 wk to 34 wk and 6 d; symptoms that suggested PTL</p> <p><b>Exclusion:</b> cervical manipulation (intercourse, VE, or TVUS) within previous 24 h, confirmed rupture of membranes, gross bleeding (more than bloody show), cervical dilation <math>\geq 3</math> cm, cervical cerclage, or previous fFN testing within 2 wk</p> <p><b>Protocol:</b></p> <ul style="list-style-type: none"><li>– participants were members of a staff-model HMO and were cared for by these staff physicians or certified nurse-midwives;</li><li>– during admission, as part of labour evaluation (before digital examination) an fFN specimen was obtained and immediately sent for analysis; turnaround time for test results of 1 to 2 h;</li><li>– participants assigned to <b>fFN result known group</b> (n = 51; test results communicated to physician) and <b>fFN result not known group</b> (n = 57; test results not communicated to physician);</li><li>– the fFN test was available only within the study protocol;</li><li>– no information provided on how EGA was determined</li></ul> <p><b>Women's characteristics:</b> NSS differences between groups with respect to parity, number of twin pregnancies, whether they had known risks for PTB, fFN positivity</p> <p><b>Baseline measurements:</b> NSS difference between groups in mean EGA</p>

\*Study supported by a grant from Adeza Biomedical.

\*\*Summarized results reported on diagnostic accuracy, safety, and efficacy of rapid fFN testing in terms of impact on patient and resource usage outcomes.

Interventions and outcomes	Reported results**
<p><b>Rapid fFN:</b> during admission speculum examination, a Dacron swab was rotated in the posterior fornix for 10 sec.; analysis of fFN specimen was performed with Adeza TLi™ qualitative method (Adeza, Sunnyvale, CA)</p> <p><b>Comparator:</b> no availability of fFN test results (<i>the rapid fFN assay was not compared with other diagnostic intervention</i>)</p> <p>Other interventions: no other diagnostic interventions are mentioned</p> <p><b>Outcome(s):</b> primary outcome was transport to tertiary care centres; secondary outcomes were LOHS (including observation periods and any admissions) and treatment decisions</p> <p><b>Operator:</b> not clear who collected the fFN specimens; laboratory personnel performed the analysis of fFN specimen (<i>no additional information provided</i>)</p>	<p><b>Diagnostic accuracy:</b></p> <p><b>Sn:</b> 33% (CI95 6%-79%) (delivery &lt;14 d)</p> <p><b>Sp:</b> 91% (CI95 85%-95%) (delivery &lt;14 d)</p> <p><b>PPV:</b> 10% (CI95 1%-64%) (delivery &lt;14 d)</p> <p><b>NPV:</b> 98% (CI95 93%-99%) (delivery &lt;14 d)</p> <p><b>Clinical outcomes:</b></p> <p><b>PTD:</b> 3 women delivered within 14 d (2.8%)</p> <p><b>LOHS:</b> for women with negative fFN test, LOHS was NSS shorter when result was known (6.8 h) than when result not known (8.1 h), (P = .35); when physicians knew result for women with negative fFN test who were observed for &gt;6 h, LOHS was SS shorter (shortened 40%, to 22.7 h from 37.8 h) (P = .04).</p> <p><b>Treatment decisions:</b> aggressive tocolytic therapy given to 16 women; decision whether to use it had an NPV of 100% (CI95 96%-100%) for delivery within 14 d.</p> <p><b>Safety:</b></p> <p>No reporting on side effects, risks, or complications from performing test itself.</p>

**Table C2: Quality assessment results for the reviewed RCTs**

Study characteristic	
<b>QUESTION</b>	<b>1. Did the study ask a clearly focused question?</b> Consider if the question is 'focused' in terms of the population studied, the intervention given, and the outcomes considered.
	<b>2. Was this an RCT and was it appropriately so?</b> Consider: – why this study was carried out as an RCT – if this was the right research approach for the question being asked
<b>VALIDITY OF RESULTS</b>	<b>3. Were participants appropriately allocated to intervention and control groups?</b> Consider: – how participants were allocated to intervention and control groups. Was the process truly random? – whether the method of allocation was described. Was a method used to balance the randomization, e.g., stratification? – how the randomization schedule was generated and how a participant was allocated to a study group – if the groups were well balanced. Are any differences between the groups at entry to the trial reported? – if there were differences reported that might have explained any outcome(s) (confounding)
	<b>4. Were participants, staff, and study personnel 'blind' to participants' study group?</b> Consider: – the fact that blinding is not always possible – if every effort was made to achieve blinding – if you think it matters in this study – the fact that we are looking for 'observer bias'
	<b>5. Were all of the participants who entered the trial accounted for at its conclusion?</b> Consider: – if any intervention-group participants got a control-group option or vice versa – if all participants were followed up in each study group (was there loss to follow up?) – if all the participants' outcomes were analyzed by the groups to which they were originally allocated (intention-to-treat analysis) – what additional information you would have liked to have seen to make you feel better about this



	Grobman et al. <sup>62</sup> (2004)	Lowe et al. <sup>63</sup> (2004)	Plaut et al. <sup>64</sup> (2003)
	✓	✓	✓
	✓	✓	✓
	✓	✓	✓
	X	X	X
	✓	✓	✓

**Table C2: Quality assessment results for the reviewed RCTs (continued)**

Study characteristic	
<b>VALIDITY OF RESULTS</b> (continued)	<b>6. Were the participants in all groups followed up and data collected in the same way?</b>  Consider: <ul style="list-style-type: none"><li>– if, for example, they were reviewed at the same time intervals and if they received the same amount of attention from researchers and health workers. Any differences may introduce performance bias.</li></ul>
	<b>7. Did the study have enough participants to minimize the play of chance?</b>  Consider: <ul style="list-style-type: none"><li>– if there is a power calculation. This will estimate how many participants are needed to be reasonably sure of finding something important (if it really exists and for a given level of uncertainty about the final result).</li></ul>
	<b>8. How are the results presented and what is the main result?</b>  Consider: <ul style="list-style-type: none"><li>– if, for example, the results are presented as a proportion of people experiencing an outcome, such as risks, or as a measurement, such as mean or median differences, or as survival curves and hazards</li><li>– how large this size of result is and how meaningful it is</li><li>– how you would sum up the bottom-line result of the trial in one sentence</li></ul>
	<b>9. How precise are these results?</b>  Consider: <ul style="list-style-type: none"><li>– if the result is precise enough to make a decision</li><li>– if a confidence interval were reported, would your decision about whether or not to use this intervention be the same at the upper confidence limit as at the lower confidence limit?</li><li>– if a P value is reported where confidence intervals are unavailable</li></ul>
<b>APPLICABILITY OF RESULTS</b>	<b>10. Were all important outcomes considered so that the results can be applied?</b>  Consider: <ul style="list-style-type: none"><li>– if the people included in the trial could be different from your population in ways that would produce different results</li><li>– if your local setting differs much from that of the trial</li><li>– if you can provide the same treatment in your setting</li></ul> <p>Consider outcomes from the point of view of the individual, policy maker and professionals, family/caregivers, and wider community</p> <p>Consider:</p> <ul style="list-style-type: none"><li>– if the report discusses if any benefit reported outweighs any harm and/or cost. If this information is not reported, can it be filled in from elsewhere?</li><li>– if policy or practice should change as a result of the evidence contained in this trial</li></ul>

Key: Yes = ✓; No/partially met = X

Adapted from a tool developed by the Critical Appraisal Skills Programme (CASP), Public Health Resource Unit, Institute of Health Science, Oxford, and accessed at [http://www.phru.nhs.uk/casp/casp\\_rct\\_tool.pdf](http://www.phru.nhs.uk/casp/casp_rct_tool.pdf)

	Grobman et al. <sup>62</sup> (2004)	Lowe et al. <sup>63</sup> (2004)	Plaut et al. <sup>64</sup> (2003)
	✓	✓	✓
	✓	✓	X
	✓	X	✓
	✓	✓	✓
	X	X	X

## ■ Appendix D: Selected Systematic Reviews (Results and Methodology)

### **Abbreviations used in Tables D1, D2, and D3**

CI<sub>95</sub> – 95% confidence interval

d – day(s)

ffFN – fetal fibronectin

hour – hour(s)

LR – likelihood ratio

NNT – number needed to treat

PTB – preterm birth

PTL – preterm labour

ROC – receiver operating characteristic

UK – United Kingdom

wk – week(s)

**Table D1: Selected systematic reviews**  
(characteristics, main findings, and conclusions)

Study	Study's characteristics	Study's main findings* and conclusions**
Honest et al. (2002) <sup>68</sup> UK	<p><b>Included studies:</b> observational cohort studies (test accuracy studies)</p> <p><b>Excluded studies:</b> case control studies</p> <p><b>Participants:</b> pregnant women with or without PTL symptoms or signs tested for cervicovaginal fFN prior to 37 wk gestation (the gestation had to be known at the time of spontaneous birth)</p> <p><b>Intervention:</b> fFN test (bedside and laboratory methods of testing)</p> <p><b>Comparator(s):</b> not clearly specified (no inclusion criteria relating to the reference standard were specified; spontaneous PTB served as the reference standard for the review)</p> <p><b>Outcome(s) and outcome measures:</b> the outcome measures were not specified a priori. Assessed were spontaneous PTB at 34 wk as well as 37 wk gestation, and spontaneous PTB within 7 to 10 d of being tested. Data were pooled to produce summary ROC curves and summary LR for positive and negative test results.</p>	<p><b>Main Findings*</b></p> <ul style="list-style-type: none"> <li>– forty studies on the use of fFN testing in symptomatic women (total of 4606 symptomatic women) were selected for this systematic review;</li> <li>– only 6/40 studies in symptomatic women met all 4 criteria for good quality. When study quality was examined, no differences were found in estimates of accuracy in studies with high- and low-quality features.</li> <li>– 11 studies used bedside methods, 29 studies used laboratory methods, and one study used both; according to meta-regression analysis, accuracy of the test did not depend on the method of testing, how often the test was done, or classification of risk.</li> </ul> <p><b>In symptomatic women</b></p> <ul style="list-style-type: none"> <li>– <i>for predicting PTB within 7 to 10 d of testing (14 studies):</i> the pooled LR for positive results was 5.42 (CI<sub>95</sub>: 4.36, 6.74) and the pooled LR for negative results was 0.25 (CI<sub>95</sub>: 0.20, 0.31);</li> <li>– <i>for predicting PTB before 34 weeks' gestation (8 studies):</i> the pooled LR for positive results was 3.64 (CI<sub>95</sub>: 2.32, 5.73) and the pooled LR for negative results was 0.32 (CI<sub>95</sub>: 0.16, 0.66);</li> <li>– <i>for predicting PTB before 37 weeks' gestation (27 studies):</i> the pooled LR for positive results was 3.27 (CI<sub>95</sub>: 2.74, 3.92) and the pooled LR for negative results was 0.48 (CI<sub>95</sub>: 0.41, 0.56).</li> </ul> <p><b>Conclusions**</b></p> <p>"Cervicovaginal fetal fibronectin test is most accurate in predicting spontaneous preterm birth within 7 to 10 d of testing among women with symptoms of threatened preterm birth before advanced cervical dilatation."</p>

\* Main findings regarding the use of fFN testing in women with symptoms and signs of PTL

\*\* Conclusions stated by the author(s) and quoted directly from the published report

**Table D2: Selected systematic reviews (objective and methods)**

Study	Study's objective and methods
Honest et al. (2002) <sup>68</sup> UK	<p><b>Objective:</b> Systematic quantitative review of test accuracy studies to determine the accuracy with which a cervicovaginal fFN test predicts spontaneous PTB in women with or without symptoms of PTL.</p> <p><b>Methods:</b></p> <ul style="list-style-type: none"> <li>– MEDLINE (1966 to 2000), EMBASE (1980 to 2000), Pascal (1973 to 2001), BIOSIS Previews (1969 to 2001), The Cochrane Library (Issue 4, 2000), MEDION (1974 to 2000), the National Research Register (Issue 4, 2000), SciSearch (1974 to 2001), and conference papers (1973 to 2000) were searched (no language restriction). Search terms not stated in this publication (published elsewhere). Also examined were bibliographies of retrieved papers. Contacted were individual experts and manufacturer of fFN test for unpublished material. In case of duplicate publications, the most recent and complete version was included.</li> <li>– Considered for inclusion were observational cohort studies. Case-control studies were excluded. Studies using cervicovaginal fFN testing prior to 37 weeks' gestation as the index test were eligible for inclusion.</li> <li>– Two reviewers independently screened the search results for inclusion. A final inclusion or exclusion decision was made based on full manuscripts of relevant articles. Disagreements were resolved by consensus, or arbitration by a third reviewer.</li> <li>– Two reviewers independently extracted data on study characteristics, quality, and accuracy. Accuracy data were used to form 2x2 contingency tables with spontaneous PTB before 34 and 37 weeks' gestation and PTB within 7 to 10 d of testing (for symptomatic pregnant women) as reference standards. Data were pooled separately for asymptomatic and symptomatic women at both endpoints of 34 and 37 weeks' gestation and for symptomatic women for spontaneous PTB within 7 to 10 d of testing.</li> <li>– Data were pooled to produce summary ROC curves and summary LR for positive and negative test results. Summary ROC curves were used as measures of accuracy for all included studies, regardless of their thresholds. Summary LRs were calculated for studies with a threshold of 50 ng/mL and data were pooled using a random-effects model. Publication and related biases were assessed using a funnel plot analysis.</li> <li>– The quality of all the included studies was assessed. Quality was defined as the confidence that the study design, conduct, and analysis minimized bias in the estimation of test accuracy. A study was classed as good quality if it used a prospective design, consecutive enrolment, adequate test description, and blinding of the test result from clinicians managing the women.</li> <li>– The heterogeneity of diagnostic odds ratios was assessed graphically using forest and Galbraith plots, and statistically using the chi squared test. Possible sources of heterogeneity were explored by meta-regression using various independent explanatory variables defined a priori (e.g., risk classifications, multiple gestation, type of recruitment, digital examination before testing, sexual intercourse within 24 h preceding testing, bleeding before testing, methods of testing, serial testing, gestation at testing for asymptomatic women, blinding of test results, study design, and publication language). A subgroup analysis of the highest quality studies was also performed.</li> </ul>

**Table D3: Quality assessment results for the selected systematic review**

Study characteristic		Honest et al. <sup>68</sup> (2002)
<b>QUESTION</b>	<b>1. Did the review address a clearly focused issue?</b> Was there enough information on the population studied, the intervention given, and the outcomes considered?	✓
	<b>2. Did the authors look for the appropriate sort of papers?</b> The 'best sort of studies' would address the review's question and have an appropriate study design.	✓
<b>VALIDITY OF RESULTS</b>	<b>3. Did the reviewer(s) try to identify all the important, relevant studies included?</b> Consider: – which bibliographic databases were used; – if there was follow up from reference lists; – if there was personal contact with experts; – if reviewers searched for unpublished and published studies; – if reviewers searched for non-English language studies.	✓
	<b>4. Did the reviewer(s) assess the quality of the included studies?</b> Consider: – if a clear, predetermined strategy was used to determine which studies were included; look for: - a quality assessment checklist or scoring system; - more than one assessor	✓
	<b>5. If the results of the review have been combined, was it reasonable to do so?</b> Consider if: – the results were similar from study to study (look for tests of heterogeneity) – the results of all the included studies are clearly displayed – the results of the different studies are similar – the reasons for any variations in results are discussed	✓
	<b>6. How are results presented and what is the main result?</b> Consider: – how the results were expressed (NNT, odds ratio, relative risk, etc.) – how large the size of result is and how meaningful it is – if you are clear about the review's 'bottom line' results	✓

**Table D3: Quality assessment results for the selected systematic review (continued)**

Study characteristic		Honest et al. <sup>68</sup> (2002)
<b>VALIDITY OF RESULTS</b> (continued)	<b>7. How precise are the results?</b>  Consider if: – the results are presented with confidence intervals; – a P value is reported where confidence intervals are unavailable	✓
<b>APPLICABILITY OF RESULTS</b>	<b>8. Can the results be applied to the local population?</b>  Consider if: – the population sample covered by the review could be different from your population in ways that would produce different results; – your local setting is likely to differ much from that of the review; – you can provide the same intervention in your setting	✓
	<b>9. Were all important outcomes considered?</b>  Consider outcomes from the point of view of the individual, policy makers and professionals, family/ caregivers, and the wider community.	X
	<b>10. Should policy or practice change as a result of the evidence contained in this review?</b>  Consider if the review discusses whether any benefit reported outweighs any harm and/or cost. If this information is not reported, can it be filled in from elsewhere?	✓

Key: Yes = ✓ ; No/partially met = X

Adapted from the tool developed by the Critical Appraisal Skills Programme (CASP), Public Health Resource Unit, Institute of Health Science, Oxford, accessed at [http://www.phru.nhs.uk/casp/casp\\_s\\_review\\_tool.pdf](http://www.phru.nhs.uk/casp/casp_s_review_tool.pdf)



## ■ Appendix E: Results Reported by Published Canadian Studies

### **Abbreviations used in Table E1**

fFN – fetal fibronectin

EGA – estimated gestational age

L&D – Labour and Delivery Unit

LOHS – length of hospital stay

N – sample size

NPV – negative predictive value

NSS – no statistically significant

PPV – positive predictive value

PTB – preterm birth

PTL – preterm labour

SS – statistically significant

TVUS – transvaginal ultrasound

vs. – versus

wk – week(s)

**Table E1: Canadian studies on the use of the rapid fFN testing device<sup>24,35</sup>**

Study	Study protocol and women's characteristics
<p>Abenham et al. (2005)<sup>79</sup></p> <p><b>Setting:</b> university hospital</p> <p><b>Duration:</b> study period between May 1 and September 18, 2003; historical baseline period between February 10 and June 29, 2002</p>	<p><b>Sample size:</b> 116 women presenting to L&amp;D with signs and symptoms of PTL during study period (<b>study population</b>)</p> <p><b>Inclusion:</b> singleton pregnancy, EGA of 24 to 34 wk, signs and symptoms of PTL (uterine contractions, low back pain, pelvic pressure, or low abdominal pressure)</p> <p><b>Exclusion:</b> multiple pregnancy, ruptured membranes, vaginal bleeding, a history of recent intercourse, or recent digital examination of the cervix</p> <p><b>Protocol:</b></p> <ul style="list-style-type: none"><li>– a prospective cohort of symptomatic women presenting when the rapid fFN assay was available (N = 116, <b>study population</b>) compared with a historical cohort of symptomatic women presenting before the rapid fFN assay was available (N = 116, <b>baseline population</b>)</li><li>– subjects for both cohorts were identified by systematically assessing all birthing centre triage visits, admissions, and discharges.</li><li>– data on fFN test results during study period were obtained directly from fFN log book.</li><li>– initial clinical evaluation of threatened PTL was identical in both cohorts: a non-stress test, urine dip-stick test, and speculum examination (visual cervix evaluation and swab collection to screen for group B streptococci, mycoplasma and ureaplasma, gonorrhea, and chlamydia)</li><li>– during study period, an fFN specimen was collected as part of speculum examination of all subjects. Specimens were discarded if PTL was either clinically confirmed (cervix dilated 3 cm in presence of contractions) or clinically ruled out (cervix closed and uneffaced and no palpable or measured contractions at monitoring); fFN test results were available within 30 minutes of placing the sample in the analyzer</li></ul> <p><b>Women's characteristics:</b> no specific information provided on characteristics of interest such as age, parity, race, and socio-economic status of women included in the study</p> <p><b>Baseline measurements:</b> groups were comparable in the distribution of EGAs at presentation; <i>no information is provided on how the EGAs were determined</i></p>

\*Summarized results reported on diagnostic accuracy, safety, and efficacy of rapid fFN testing in terms of impact on patient and resource usage outcomes.

Interventions and outcomes	Reported results*
<p><b>Rapid fFN:</b> a swab for fFN was obtained from the posterior fornix over a 10-second interval <i>(no additional information provided)</i></p> <p><b>Comparator:</b> no rapid fFN assay performed <i>(rapid fFN assay was not compared with other diagnostic tools)</i></p> <p><b>Other interventions:</b> results show the effect of availability of fFN testing alone, independent of additional assessments <i>(information from TVUS measurements of cervical length was not incorporated into the evaluation of women who present in L&amp;D with preterm contractions; no other diagnostic interventions are mentioned)</i></p> <p><b>Outcome(s):</b> three categories of patient outcomes: (1) PTL (subjects who were admitted and eventually discharged undelivered), (2) PTB (subjects who delivered after admission), (3) no admission (subjects who were discharged with another diagnosis)</p> <p><b>Operator:</b> not clear where the analysis of the fFN specimen was performed and by whom</p>	<p><b>Diagnostic accuracy:</b></p> <p><b>PPV:</b> 33%</p> <p><b>NPV:</b> 100%</p> <p><b>Clinical outcomes:</b></p> <p><b>PTL:</b> admissions for PTL were SS less in study population than in baseline population (12.1% vs. 24.1%, <math>P = 0.03</math>)</p> <p><b>PTB:</b> NSS difference between study and baseline populations in the number of subjects who delivered after admission (8.8% vs. 7.8%)</p> <p><b>LOHS:</b> mean LOHS per woman with PTL declined from 5.2 d to 0.6 d (<math>P &lt; 0.0001</math>)</p> <p><b>Cost:</b> mean cost per woman with PTL declined from \$3666 to \$581 (<math>P &lt; 0.0001</math>)</p> <p><b>Safety:</b></p> <p>No reporting on side effects, risks or complications from performing test itself</p>

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