IHE Rapid Assessment Level 2

THE ACTIM™ PARTUS VERSUS THE TLI$_{IQ}$® SYSTEM AS RAPID RESPONSE TESTS TO AID IN DIAGNOSING PRETERM LABOUR IN SYMPTOMATIC WOMEN

February 2008

Prepared by Paula Corabian

INSTITUTE OF HEALTH ECONOMICS
ALBERTA CANADA

Connecting People and Ideas for Better Health

ISSUE RA2-2008-01

Rapid Assessments, Level 2, are brief reports, prepared on an urgent basis, which draw on limited reviews and analysis of relevant literature and on expert opinion and regulatory status where appropriate. They are not subject to an external review process. (To view the IHE product line, please refer to the back cover.)

This rapid assessment addressed a request to assess the published research evidence on how the Actim™ Partus test compares to the TLi$_{IQ}$® System in terms of diagnostic accuracy, clinical utility, and costs when added to preterm labour management in symptomatic women with intact membranes.

Production of this document has been made possible by a financial contribution from Alberta Health and Wellness. The views expressed herein do not necessarily represent the official policy of Alberta Health and Wellness.

Reproduction of this document for non-commercial purposes is permitted provided appropriate credit is given to IHE.

Publications can be requested from:

IHE
1200, 10405 Jasper Avenue
Edmonton AB Canada T5J 3N4
Tel: (780) 448-4881
Fax: (780) 448-0018
E-mail: info@ihe.ca

or download from IHE's website:
http://www.ihe.ca

ISBN: 978-1-897443-29-3 (on-line)

TABLE OF CONTENTS

TABLES:

THE ACTIM™ PARTUS VERSUS THE TLi$_{IQ}$® SYSTEM AS RAPID RESPONSE TESTS TO AID IN DIAGNOSING PRETERM LABOUR IN SYMPTOMATIC WOMEN

REQUEST

This response addressed a request for information from Alberta Health and Wellness. The objective is to assess the current published research literature that directly compares the diagnostic performance, effectiveness, and costs (added value) of using two rapid response diagnostic tests available in Canada (the Actim™ Partus test and the TLi$_{IQ}$® System). The intended use of these laboratory tests is to aid in diagnosing spontaneous preterm labour (PTL) in symptomatic women presenting for care with intact membranes.

The specific aim is to answer the following questions:

- Is the Actim™ Partus test more accurate than the TLi$_{IQ}$® System for diagnosing true PTL in symptomatic women presenting for care with intact membranes? Which of these rapid response diagnostic tests provide results that most reliably identify women at high risk for imminent preterm birth (PTB) or preterm delivery (PTD) and/or those who are at low risk for imminent PTD/PTB?
- Are there any risks and complications to the mother or fetus from performing the Actim™ Partus test itself?
- Does the use of the Actim™ Partus test affect gestational age at delivery and/or reduce maternal stress or anxiety and the need for the removal from home support of the symptomatic woman presenting for care with intact membranes?
- Does adding the Actim™ Partus test 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, and the use of therapeutic interventions in symptomatic women presenting for care with intact membranes?
- Does using the Actim™ Partus test affect the overall cost of PTL management in symptomatic women presenting for care with intact membranes?
- How does the Actim™ Partus test compare to the TLi$_{IQ}$® System in terms of cost per test and economic utility if added to PTL management in symptomatic women presenting for care with intact membranes?

BACKGROUND

The medical, psychological, and economic burdens of suspected spontaneous preterm labour (PTL) that leads to preterm delivery (PTD) or preterm birth (PTB) are substantial for both the family and the healthcare system.[1-14] Therefore, the accurate diagnosis of PTL and prediction of PTB/PTD in symptomatic women presenting for care at rural or urban clinical settings is an ongoing and important goal for healthcare givers, to enable targeting of effective treatments and avoidance of unnecessary interventions. Recently, there has been increasing interest in identifying risk assessment markers that would aid in refining the clinical estimate of the

probability that PTL in symptomatic women will eventually result in PTD/PTB. Among the most studied to date has been the fetal fibronectin (fFN).

The use of a rapid response test (the $TLi_{IQ}^{®}$ System) to detect and measure fFN levels in cervicovaginal secretions when PTL is suspected has been shown useful in ruling out risk for imminent PTB/PTD in symptomatic women.[1] However, there are limitations associated with this test because a variety of factors can confound the interpretation of its results. The use of the $TLi_{IQ}^{®}$ System, which is the only modality for fFN detection currently available in Canada for this indication, also has the shortcoming of its expense.

A less expensive test without the limitations of the $TLi_{IQ}^{®}$ System would be advantageous in the clinical setting of suspected PTL in symptomatic women with intact membranes for patients, their caregivers, and the healthcare system. The Actim™ Partus test, designed to detect phosphorylated insulin-like growth factor binding protein-1 (*ph*IGFBP-1) in cervicovaginal secretions, has been reported as having the potential to meet these criteria.[15-20]

The aim of this assessment is to summarize the results from the published research that compared the diagnostic accuracy, clinical effectiveness (in terms of patient and resource usage outcomes), and costs of the Actim™ Partus test and the $TLi_{IQ}^{®}$ System when these tests are used to aid in diagnosing PTL and predicting the risk for imminent PTB/PTD in symptomatic women presenting for care with intact membranes.

CLINICAL PROBLEM: SUSPECTED PTL

Spontaneous preterm labour (PTL) is defined as the demonstrated progressive change of the cervix with uterine contractions between 20 and 37 completed weeks of gestation.[2-11,21] The diagnosis of PTL is complicated by its multi-factorial etiology and its pathogenesis is not well understood, although several theories exist regarding the early initiation of labour.[2,5,10,11,13,22-30] Recognized risk factors include a history of previous PTD/PTB, multiple gestations, infection such as chlamydia, gonorrhea and bacterial vaginosis (only in women with prior PTB), and inflammation during pregnancy, as well as maternal stress. Ethnic race, smoking, young/late maternal age, low socio-economic status, and various diseases during pregnancy (such as heart disease, gestational cholestasis, periodontal disease) also contribute to risk for PTL.

PTL in women with intact membranes is responsible for up to 50% of PTB/PTD,[22,28] which is a leading cause of neonatal mortality and morbidity in developed nations.[4,5,10,14,21,23,25,26,30-34]

In Canada, PTB accounts for 75% of preventable perinatal deaths in Canada.[2,3,21,31,33,35] Babies born prematurely have increased risk for neurodevelopmental problems such as cerebral palsy, respiratory, cardiac, ophthalmic, hearing, and other long-term health problems. The associated annual cost to the Canadian healthcare system was estimated in 2005 at $13.3 billion.[2]

In Alberta, almost 9% of live births were preterm in 2004, exceeding the rate of 8.6% estimated for 2002.[33,35] 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 preterm births occurred in women who never had an episode of threatened PTL and another 293 PTBs occurred in women who had a diagnosis of PTL delayed by therapy. Thus, 2,386 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 (≥ 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.[2-4,6-10,14,27,36] Clinical symptoms suggestive of PTL include uterine contractions, low abdominal pain, low backache, pelvic pressure, increased vaginal discharge, and bleeding or spotting.[2,4,13,14,19,23,25,28,32,36] 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 symptomatic women presenting for care is to identify true PTL during an early stage, before progression to PTD/PTB is imminent.[2-10,13,14,19,23,28,29,34] PTL is diagnosed by clinical history (assessment of obstetric history and demographic factors), clinical signs and symptoms, and physical examination. The clinical signs and symptoms, in combination with physical examination, are often sufficient to make a diagnosis of PTL in symptomatic women. Initial cervical dilation of ≥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.[2-9] During this time, bed rest and possible treatment, depending upon the symptoms and results of the physical exam, are prescribed.

Early detection of PTL is difficult because initial symptoms and signs are often mild and may occur in normal pregnancies.[2,5,9,11,13,14,22,25,28,29,32,36] Clinical diagnosis is often unreliable, resulting in over-diagnosis of PTL. 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.[2] 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.

PTL diagnosis is more challenging when women present with contractions without cervical change.[2,4,19,28,32,36] When the cervix is dilated <3 cm, the diagnosis of true PTL (resulting in imminent PTD/PTB) is more difficult to establish. As false positive PTL diagnoses result in unnecessary and potentially hazardous therapy, various other diagnostic and predictive markers have been explored. Because the morbidity of babies born after 34-35 weeks of gestation has diminished,[5,10,11,14,25,29,30,36,37] most efforts have focused on developing rapid response tests to aid in diagnosing early PTL and identifying risk for imminent PTB/PTD before this gestational age.

RAPID RESPONSE BIOCHEMISTRY TESTING TO AID IN DIAGNOSING PTL

Over the past decade, detection of various biochemical markers have been primarily investigated as potential diagnostic markers for PTL and predictive markers for imminent PTB/PTD in symptomatic women presenting for care before 35 weeks of gestation.[5,10-19,25,28,29,34,36,38-40] Among these, the detection of fFN and *ph*IGFBP-1 in cervicovaginal secretions have the

potential to become clinically useful rapid response tests to aid in diagnosing PTL for symptomatic women with intact membranes.

Rapid response test for fFN detection

Fetal Fibronectin (fFN) is a glycoprotein produced by many cell types, including those of the fetal amnion (membrane).[1,12,13,25,30] 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 in the cervicovaginal secretions during the first 16 to 22 weeks of gestation, then they fall to very low levels, and rise again as the pregnancy approaches term. Since 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, its presence at high levels during this period may indicate disruption of the utero-placental interface. 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.

In North America, fFN has been detected and measured in the cervicovaginal secretions by using three modalities, all manufactured by Adeza Biomedical Corporation in Sunnyvale, California (Adeza Biomedical, personal communication, November 2007). The name of Adeza Biomedical is rapidly disappearing in the marketplace as this company was integrated into Cytyc Corporation (Sunnyvale, California) in April 2007. In October, 2007 Cytyc Corporation was purchased by Hologic Inc. (Bedford, Massachusetts) (www.hologic.com). Currently, all product literature and directional inserts are changing over from Adeza to Cytyc to Hologic.

The initial modality for fFN testing was a quantitative (numeric result) solid-phase enzyme-linked immunosorbent assay (ELISA), which uses a monoclonal antibody specific for fFN (Adeza Biomedical, personal communication, November 2007).[41] However, the ELISA method was discontinued in 2001 in North America because it was found not to be practical for routine rapid testing deemed critical for diagnosing PTL in symptomatic patients.

ELISA has been replaced with two qualitative modalities (positive or negative result) for rapid fFN detection (Adeza Biomedical, personal communication, November 2007): the QuikCheck fFN® test and the TLi$_{IQ}$® System. All three modalities have the same principle and detection limit, and use the same monoclonal antibody for detection of fFN. All clinical data on the use of fFN detection to aid in diagnosing PTL for symptomatic women published since 2001 has been with either the QuikCheck fFN® test or the TLi$_{IQ}$® System.

QuikCheck fFN® test

The QuikCheck fFN® test is a visual read, dipstick method (Adeza Biomedical, personal communication).[37,42,43] This is a manually read bedside test strip, which takes approximately 10 minutes to have the final patient result available. A negative result indicating the absence of fFN will appear as one line. A positive result indicating the presence of fFN will appear as two lines. Lines may vary in appearance from very faint to very dark. If no lines appear or if the control line does not appear, the test must be repeated. The *Quik*Check fFN® test must be run within 15 minutes of sampling, and samples cannot be stored for later testing.

Although the cost per determination with the QuikCheck fFN® test is low ($35 CAD), this method does not provide a reproducible and recordable result (Adeza Biomedical, personal communication, November 2007). This 10-minute dipstick method does not provide full quality control (QC) of the device and a hard copy (a print out) of the patient result with QC information. The QuikCheck fFN® test is associated with interpretive errors because of the visual reading of the test result. For these reasons, the QuikCheck fFN® test is not marketed in Canada and the United States, and the TLi_{IQ}® System, an automated test with a reproducible and recordable result, is the only modality available to aid in diagnosing PTL in symptomatic women.

TLi_{IQ}® System

The TLi_{IQ}® System is simple to perform, and there is little risk to the mother and fetus from performing the test itself following the procedure recommended by the manufacturer (Adeza Biomedical, personal communication, November 2007).[1]

It is a lateral-flow, solid-phase immunosorbent assay device.[41,44,45] A vaginal swab is used to collect the specimen from the posterior fornix of the vagina. The swab must be lightly rotated for 10 seconds to absorb the cervicovaginal secretion. After the specimen is obtained, the sample at room temperature is added to a solid cassette device (patient specimen cassette), which is placed into an automated analyzer (the TLi_{IQ}® instrument, which is a hardware device with printer). After 20 minutes of reaction time, the intensities of the test line and control line are interpreted with the analyzer.

The hardware device reads the patient specimen cassette in 23 minutes and interprets the results based upon unique test characteristics that must be met (which are pre-programmed in the hardware device) (Adeza Biomedical, personal communication, November 2007). Upon completion, the device automatically prints and displays the patient result as positive or negative. Full quality control (QC) is built into both the patient specimen cassette and the hardware devices and the QC information is also printed. All patient and QC information is stored for future recall and printable results.

Total test time takes approximately 25 minutes from specimen arrival at the testing site – either a central laboratory or a labour and delivery unit (L&D) – to the print out of the test result (Adeza Biomedical, personal communication, November 2007). This time includes data entry of the woman's name and operator's identification into the device and verification of acceptable QC for both patient test cassette and hardware device. The total time from specimen collection to reporting the results to the clinician can be accomplished within 25 to 30 minutes if the rapid fFN assay is performed on site.

The sample can be tested immediately or held at room temperature for 8 hours to 3 days at between 2 and 8C before testing, or for up to 3 months if the sample is frozen.[45]

The TLi_{IQ}® System can be set up in a central or hospital laboratory or at the bedside (as a point-of-care test), and measurements can be performed either by the laboratory, a physician, or a nurse practitioner (Adeza Biomedical, personal communication, November 2007).

Currently, training consists of either a personal visit to the testing site or a teleconference with a company representative at no cost (Adeza Biomedical, personal communication, November 2007). Included with each system is a self-instruction 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 (while operating the hardware and the test system) has been done.

Cost

The cost for a $TLi_{IQ}^{®}$ System is approximately $2,400 CAD, including the printer and the QC device (Adeza Biomedical, personal communication, November, 2007). The approximate cost per determination for each $TLi_{IQ}^{®}$ System test is $100 CAD (per test).

Regulatory status

In Canada**,** the $TLi_{IQ}^{®}$ System has been approved for marketing by Health Canada since 1999 (Adeza Biomedical, personal communication, January, 2008). The test is currently licensed as an aid to rapidly assess: the risk of PTD within 7 and 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 cms) sampled between 24 weeks 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 weeks and 30 weeks, 6 days of gestation in women with a singleton pregnancy (http://www.hc-sc.gc.ca/dhp-mps/md-im/licen/mdlic_e.html).[1]

The $TLi_{IQ}^{®}$ System is also approved by the Food and Drug Administration (FDA) in the United States.[1]

Clinical use of the $TLi_{IQ}^{®}$ System

The current clinical use of the $TLi_{IQ}^{®}$ System remains defined by its strong negative predictive value (NPV) as the clinical importance of a positive test result remains unclear.[1] According to results reported by over 100 primary and secondary research studies published during the last decade (Adeza Biomedical, personal communication, December 2007), its high (strong) NPV, in conjunction with clinical assessment, is a potent predictor of low imminent risk for PTB/PTD in symptomatic women (between 24 and 34 weeks, 6 days gestation, with intact membranes and minimal dilatation of <3cm) within the next 7 to 10 days from testing.[1]

Evidence from observational studies, meta-analyses of observational studies, and economic studies conducted after 2001 suggested that adding the $TLi_{IQ}^{®}$ System could lead to practice change in the PTL management, prevent unnecessary transportation of symptomatic women, and avoid unnecessary admissions to hospitals and the use of unnecessary and potentially harmful therapeutic interventions.[1] However, the hypothesis that the addition of this test to PTL management will inevitably improve outcomes for the woman and infant and reduce healthcare resource usage and the associated costs remains unproven. The results reported by randomised controlled trials (RCTs) published to date raise the question of whether its use offers significant benefit beyond that observed with good clinical assessment and judgment. The precise role of this test in clinical practice remains to be defined.

Limitations

There are some limitations associated with the use of the $TLi_{IQ}^{®}$ System due to several factors that can confound the interpretation of its results.[45] Specimens should be collected prior to digital examinations and not within 24 hours after cervical manipulation. Manipulation of the cervix may cause artificial release of fFN and lead to false positive results. Assay interference

from semen has not been ruled out, and specimens should not be collected less than 24 hours after intercourse. However, even if a woman reports having had intercourse in the previous 24 hours, a negative test result is considered valid (Adeza Biomedical, personal communication, December 2007).[45]

Patients with suspected or known placental abruption, placenta previa, or moderate or gross vaginal bleeding should not be tested.[45] In addition, the test has the shortcoming of its expense.

A rapid response test designed to detect phosphorylated insulin-like growth factor binding protein-1 (*ph*IGFBP-1) in cervicovaginal secretions has been advocated as a cheaper alternative to the TLi$_{IQ}$® System, without its limitations.

Rapid response test for phIGFBP-1 detection

Insulin-like growth factor binding protein-1 (IGFBP-1) is a subgroup of proteins of the insulin-like growth system, which has a function in the control mechanism of fetal and placental growth and development.[15-17,25] IGFBP-1 is synthesized and secreted by the human liver and maternal decidua, and its concentration in the maternal circulation increases during pregnancy. The phosphorylation status of IGFBP-1 varies in different body fluids and tissues. The non-phosphorylated isoform of IGFBP-1 predominates in the amniotic fluid, which contains little of the phosphorylated isoforms except the highly phosphorylated isoform of IGFBP-1. Human decidual cells secrete predominantly the phosphorylated isoforms of IGFBP-1, including the highly phosphorylated one. The detection of amniotic fluid isoforms of IGFBP-1 in cervical and vaginal samples is diagnostic for the rupture of fetal membranes.

As a result of isolating a highly phosphorylated isoform of IGFBP-1 (*ph*IGFBP-1) that is absent from amniotic fluid but released from the decidua to the cervical canal, a decidual versus an amniotic fluid origin of IGFB-1 can be determined using unique antibodies.[15-18,25,37,46,47] The level of *ph*IGFBP-1 rises as the cervix matures, and it can be detected in cervical secretions during the cervical ripening probably due to the detachment of fetal membranes from the decidua. The measurement of *ph*IGFBP-1 from cervical secretions can be used to estimate the ripeness of the cervix. The process of labour is hypothesized to disrupt the chorio-decidual interface (by contractions or as a normal process in the term uterus), releasing *ph*IGFBP-1 into the cervical secretions. The identification of *ph*IGFBP-1 would thus be indicative of the occurrence of the labour process and predictive of PTD.

Developments in biomedical engineering have allowed the development of a commercial bedside kit (the Actim™ Partus test) for the qualitative detection of *ph*IGFBP-1 (positive or negative results) above the level of 10 µg/L (www.medixbiochemica.com).[15-17,25,46]

The Actim™ Partus test

The Actim™ Partus test (manufactured and marketed exclusively by Medix Biochemica, Finland) is an immunochromatographic dipstick test based on monoclonal antibodies (which are also exclusively developed and produced by Medix Biochemica, Finland) (www.medixbiochemica.com).[15-17,37,46,47] Somagen Diagnostics (Edmonton, Alberta) is the only distributor of the Actim™ Partus test in Canada (Somagen Diagnostics and Medix Biochemica, personal communication, December 2007) (www.somagen.com).

Medix Biochemica markets the Actim™ Partus test as a fast point-of-care (bedside) test kit to estimate the maturity of the cervix during pregnancy, which can aid in the diagnosis of PTL (www.medixbiochemica.com). According to the manufacturer, the test is most useful for symptomatic women with gestational age between 22 and 34 weeks presenting with intact membranes, and it is not reasonable to use it to estimate the risk of PTB/PTD when the gestational age is over 36 weeks (Somagen Diagnostics and Medix Biochemica, personal communication, December 2007). The test is simple to perform and there is no risk to the mother and fetus from performing the test itself following the procedure recommended by the manufacturer (Somagen Diagnostics and Medix Biochemica, personal communication, December 2007).

During a speculum exam, cervical secretion/fluid is collected from the endocervix with a Polyester swab provided in the test kit/package (www.medixbiochemica.com).[48] The test requires at least 150 µl of sample (extracted cervical fluid) to perform correctly (for proper function of the dipstick). The sample collection should be performed before the digital exam, since the digital exam may remove the liquid present in the cervix (Somagen Diagnostics and Medix Biochemica, personal communication, December 2007).

After the swab has absorbed the sample, it should be inserted and swirled vigorously for 10 seconds in an extraction solution in which the dipstick can be dipped after the swab is discarded (www.medixbiochemica.com).[48] The dipstick is kept in the extraction solution until the liquid front reaches the result window/area. Then the dipstick is removed from the extraction solution (as soon as the liquid front becomes visible in the result window) and let to develop for 5 minutes in horizontal position. Total time, from sample collection to the availability of the results, is no more than 10 minutes (Somagen Diagnostics and Medix Biochemica, personal communication, January 2008).

The result is interpreted by counting the number of lines in the result window (www.medixbiochemica.com).[48] A positive result can be interpreted as soon as two blue lines (a control line and a test line) become visible in the result window. However, a negative test must be confirmed at 5 minutes. If only the control line has appeared after 5 minutes, the test result is negative. Appearance of a control line confirms the correct performance of the test. If a control line does not appear, the test is invalid and should be repeated using another dipstick. According to the manufacturer, no attention should be paid to the relative intensities of the control and test lines.

The manufacturer recommends testing the sample immediately (www.medixbiochemica.com).[48] However, if necessary, the sample can also be stored for up to 4 hours before testing. The kit can be stored at +2°C to +8°C, but the components need to reach room temperature before testing. The tests can be stored for 2 months also at room temperature (+18°C to +30°C), provided that the expiry date is not exceeded.

Measurements with the Actim™ Partus test can be performed in the laboratory or at the bedside (as a point-of-care test) in both rural and urban healthcare settings, and can be done either by the laboratory technician, a physician, or a nurse (Somagen Diagnostics and Medix Biochemica, personal communication, December 2007). A nurse or physician can perform the sample collection and a laboratory technician or a nurse can perform the test. Somagen Diagnostics has a territory manager, regional sales manager, and a product specialist available for appropriate

and comprehensive end user training (which can consist of technical and clinical components, if required).

Cost

According to the manufacturer, everything required for performing the Actim™ Partus test is included in an individually packaged kit (www.medixbiochemica.com) (Somagen, personal communication, December 2007). The cost is $35 CAD per test kit. The Actim™ Partus test is sold in boxes of 10 individual kits. The product has a good shelf life of 1 year with no additional capital equipment required to read the test.

Regulatory status

The Actim™ Partus test has been approved for marketing by Health Canada since 2002 (Somagen and Medix Biochemica, personal communication, December 2007). The test is currently licensed in Canada as a one step dipstick test (Class III test) for detecting the presence of phosphorylated IGFBP-1 in cervical secretions to predict PTD or susceptibility to deliver at term when fetal membranes are intact (Health Canada, personal communication, November 2007).

The Actim™ Partus test is not currently available in the United States (www.accessdata.fda.gov; www.medixbiochemica.com).

Clinical use of the Actim™ Partus test

Available clinical data regarding the validity of *ph*IGFBP-1 as a marker for PTL and the efficacy of the Actim™ Partus test to aid in diagnosing PTL and predicting PTB/PTD in symptomatic women is limited to ten peer-reviewed articles published over the last decade (Somagen and Medix Biochemica, personal communication, December, 2007). These are observational studies (most of them with small sample sizes) in which the *ph*IGFBP-1 specimens were obtained from symptomatic women presenting for care with regular uterine contractions and intact membranes and then tested.

Results obtained from four of these studies, which were published after 2001,[15-18] suggested that the Actim™ Partus test has the potential to become a clinically useful tool for ruling out true PTL in symptomatic women with intact membranes. These studies have shown that the absence of *ph*IGFBP-1 in cervical secretions of symptomatic women (between 20 and 36 weeks of gestation, most with singleton pregnancies) presenting with preterm contractions and intact membranes may be a reassuring sign that the likelihood of imminent PTB/PTD is low before 35 weeks of gestation and within 7 days from testing. They reported that a negative *ph*IGFBP-1 test result might rule out imminent PTB/PTD in up to 94% of this population of symptomatic women.

However, the validity and reliability of these results[15-18] is limited by the small sample sizes of these observational studies as well as the variability of their designs, eligibility criteria, and study protocol. None of these studies assessed whether clinicians can use the Actim™ Partus test results in conjunction with clinical assessment to improve clinical practice and patient and resource usage outcomes.

Limitations

The Actim™ Partus test has some limitations. Because *ph*IGFBP-1 is also found in human serum, bloody samples may give positive reactions. [15-18,25,37,47] Therefore, according to the manufacturer, samples for the Actim™ Partus test should be blood-free to avoid false positive results (www.medixbiochemica.com).[48]

Before an Actim™ Partus test is performed, the manufacturer recommends an examination to ensure that the fetal membranes are intact, because with ruptured fetal membranes the test will also give a positive result (www.medixbiochemica.com).[48] The level of IGFBP-1 in amniotic fluid is so elevated that, in case of leakage of amniotic fluid, the Actim™ Partus test will give a positive result. The choice to test for ruptured membranes depends on clinical presentation, and intact membranes can be confirmed with a Ferning or nitrazine test (Somagen and Medix Biochemica, personal communication, December, 2007). The Actim™ PROM test is a new test developed and marketed, also by Medix Biochemica, to detect premature rupture of membranes. However, the Actim™ Partus test does not need to be run in conjunction with the Actim™ PROM test to confirm intact membranes.

Urine or seminal fluid in the sample do not interfere with performance of the test (www.medixbiochemica.com).[48] Therefore, it has been suggested that recent intercourse does not limit the use of the Actim™ Partus among symptomatic women with intact membranes.[15-17,37,46,47] However, there is no direct scientific evidence on the effect of prior intercourse on the results of the test (Somagen and Medix Biochemica, personal communication, December, 2007).

CHARACTERISTICS OF THE ACTIM™ PARTUS TEST AND THE $TLi_{IQ}^{®}$ SYSTEM

The following table summarizes the characteristics of the Actim™ Partus test and the $TLi_{IQ}^{®}$ System:

Table 1: Characteristics of the Actim™ Partus test and the TLi$_{IQ}$® System

Characteristics	Actim™ Partus test	TLi$_{IQ}$® System
Biological role	Decidual cells synthesize. When delivery is approaching, fetal membranes detach and small amounts of *ph*IGFB-1 leak into cervix.	Adhesive molecule, confined to the extracellular matrix defining the junction of maternal and fetal units within the uterus.
Safety	There is no risk to the woman or fetus from performing the test itself following the procedure recommended by manufacturer.	There is no risk to the woman or fetus from performing the test itself following the procedure recommended by the manufacturer.
Intended use	Labeled as a qualitative test for estimation of cervical ripeness. Intended to predict PTD or susceptibility to delivery at term when membranes are intact (confirmed by first performing a test to detect PROM). Suitable for gestational age of 22-36 wk.	Intended to assist in determination of risk of PTD in women having signs and symptoms of PTL, at 24 to 35 wk of gestation, **and** risk of PTD in asymptomatic women at 22 to 31 wk as part of routine care.
Contraindications	Excessive blood may cause false positives or invalid results. Other contraindications include gestational age <22 wk and PROM.	Excessive blood may cause false positives or invalid results, sexual intercourse, or digital exam within previous 24 hours may yield false positive results.
Clinical use	Knowledge of a negative test result, may supplement clinical judgment to predict "false" PTL and low risk of imminent PTB/PTD in symptomatic women (between 22 and 36 wk, with intact membranes) within next 7 days from testing.	Knowledge of a negative test result, may supplement clinical judgment to predict "false" PTL and low risk of imminent PTB/PTD in symptomatic women (24 and 34 wk, 6 days of gestation, with intact membranes and dilatation <3 cm) within next 7 to 10 days from testing.
Publications on clinical use	Ten peer-reviewed publications spanning a decade, reporting results of observational studies.	Over 100 peer-reviewed publications spanning a decade, reporting results of systematic reviews, meta analyses, RCTs, and observational studies.
Specimen collection	Speculum exam, specific swab, and collection tube (supplied). Collect specimen from the endocervix before digital exam.	Speculum exam, specific swab, and collection tube (supplied). Collect specimen from the posterior fornix of the vagina before digital exam. Discard specimen if >3 cm dilated.
Specimen stability	Once collected <4 hours at RT.	Once collected, 8 hours at RT, 3 days +2-+8℃.
Storage	Store the test kit at +2-+8℃. The test kit and test packs can be stored for 2 mo at RT.	Store the patient test cassette at RT, 18 mo dating, individually sealed.
Time within which test results are available	Five minutes after cervical collection.	Twenty-five to 30 minutes from specimen collection to reporting test result.
Place and requirements for test performance and result interpretation	Can be performed in laboratory or at bedside, in rural and urban settings, by a physician, nurse, or laboratory technician. No reader device is required.	Can be performed in laboratory or at the bedside (Level 3 hospitals, small rural hospitals, and small clinics in remote areas) by physicians, nurses, or laboratory technicians. Reader device required.
Training and licensing requirements	Comprehensive technical training (consist of technical and clinical components if required) is available from the Canadian distributor (Somagen Diagnostics)	Included with each system is a training DVD, covering setting up the TLi$_{IQ}$® instrument, full QC, and how to run a test sample. On-site and phone install training is available.
Costs	$35 CAD per test kit. Sold in boxes of 10 individual kits.	Approximately $2,400 (CAD) per system; approximately $100 (CAD) per test.
Regulatory status	Health Canada cleared. Not FDA cleared	Health Canada and FDA cleared.

℃ – Celsius degrees; FDA – Food and Drugs Administration in the United States; mo – month(s); NPV – negative predictive value; QC – quality control; *ph*IGFBP-1 – phosphorylated insulin-like growth factor binding protein-1; PROM – premature rupture of membranes; PTB – preterm birth; PTD – preterm delivery; PTL – preterm labour; RCT – randomised controlled trial; RT – room temperature; wk – week(s)

GUIDELINES AND PATIENT TEST PROTOCOLS

Published clinical practice guidelines on the diagnosis and management of PTL and assessment of risk for imminent PTB/PTD recommend only the use of fFN testing to complement clinical assessment for diagnosing PTL in symptomatic women (when clinical diagnosis is doubtful, to identify women at low risk for imminent PTB/PTD).[2-4,6-9]

Patient test protocols and guidelines for using the $TLi_{IQ}^{®}$ System to aid in diagnosing suspected PTL in symptomatic women have been developed by several reproductive care and perinatal programs in Canada, including the British Columbia Reproductive Care Program, the Alberta Perinatal Health Program, the Child Health Network of Toronto, the Kingston/Ottawa Perinatal Program, and the Nova Scotia Perinatal Program (Adeza Biomedical, personal communication, November 2007) (http://rcp.nshealth.ca/rcp_3347.html).[3,49]

No guidelines or patient test protocols specifically developed on the use of the Actim™ Partus test to aid in diagnosing suspected PTL in symptomatic women were identified by the literature search conducted for this rapid review.

AVAILABLE EVIDENCE

The literature search conducted for this rapid review revealed no published full text peer-reviewed studies that directly compared the Actim™ Partus test to the $TLi_{IQ}^{®}$ System for diagnosing PTL in symptomatic women with intact membranes. However, it revealed three abstracts reporting results from Canadian studies that directly compared the Actim™ Partus test to rapid fFN testing with the $TLi_{IQ}^{®}$ System for diagnosing PTL in symptomatic women with intact membranes (using the same patient population and the same protocol*)*. For the purpose of this report, the information contained in two of these abstracts is summarized in the section "Canadian experience".

The following commentary summarizes the results obtained from two primary research studies that directly compared the Actim™ Partus test to the QuikCheck fFN® test for diagnosing PTL in symptomatic women with intact membranes. Details of these studies are also summarized in Table C1, Appendix C. Because of the tight timelines, the methodological quality of these studies was not critically appraised, and no attempt was made to assess the validity of their findings. Information on upcoming research on this topic is also provided in this section of the report.

Comparative studies: The Actim™ Partus test versus the QuikCheck fFN® test

Ting et al.[47] compared the effectiveness of the Actim™ Partus test to the QuikCheck fFN® test in predicting PTD (Adeza Biomedical, personal communication, December 2007). One hundred and eight symptomatic women with singleton pregnancies between 24 to 34 weeks of gestation presenting with intact membranes were recruited for this study. The fFN and *ph*IGFBP-1 specimens were obtained before digital exam and tested at the L&D/antenatal ward in a tertiary healthcare setting by the same specialist in obstetrics and gynecology, who also interpreted the fFN/ *ph*IGFBP-1 test results. Results for each of the two tests were available in 10-15 minutes. However, managing obstetricians and patients were blinded to the Actim™ Partus and the QuikCheck fFN® tests results. Tocolysis and steroid therapy were administered to all the recruited patients. Outcome data were collected after delivery.

Ting et al.[47] evaluated the efficacy of each test in terms of gestational age at delivery and the admission-to-delivery interval and reported similar results in 94 women included for analysis (14 women were excluded because they did not meet the selection criteria or had incomplete data). Among those with negative *ph*IGFBP-1 and fFN results, the median (±standard deviation [SD]) gestational age at delivery was 37.4 weeks (±2.8 weeks) and 37.4 weeks (±2.1 weeks), respectively. Among those with positive *ph*IGFBP-1 and fFN results, the median (±SD) gestational age at delivery was 32.9 weeks (±4.0 weeks) and 34.2 weeks (±4.2 weeks), respectively (P <0.001 for both *ph*IGFBP-1 and fFN). A positive result with either test was associated with a significantly reduced admission-to-delivery interval.

The median admission-to-delivery interval was 2.8 weeks shorter in the group with positive *ph*IGFBP-1 results compared to those with a negative *ph*IGFBP-1 result (2.3 weeks compared with 5.1 weeks) (P <0.001).[47] The median admission-to-delivery interval was 1.8 weeks shorter in the group with positive fFN results as compared with the group with negative fFN results (3.3 weeks compared with 5.1 weeks) (P = 0.002).

Ting et al.[47] also reported on the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for both tests in the prediction of delivery within 48 hours, 7 days, and 14 days. The 48-hour time interval was chosen because it is considered "*the crucial period for the completion of corticosteroid therapy*." Although both tests had high NPVs for delivery within 48 hours, 7 days, and 14 days, the Actim™ Partus test had slightly higher values than the QuikCheck fFN® test (100%, 92%, 92%; and 97%, 89%, 89%, respectively).

The investigators performed a Kappa analysis to ascertain the measure of agreement between the two tests.[47] The Kappa was 0.75, with P = 0. This means 75% of the time the two tests are in agreement with each other and it is statistically significant.

Based on their results, the investigators concluded: "*Both pIGFBP-1 and fetal fibronectin tests are effective adjuvant bedside test kits for the prediction of preterm delivery in patients presenting with signs or symptoms of preterm labour. pIGFBP-1 has the higher NPV of 1.00 in predicting risk of delivery within 48 hours*."[47]

Eroglu et al.[37] conducted a study to determine predictive values of detecting fFN and phIGFBP-1 in cervicovaginal secretions and ultrasonographic measurement of cervical length for PTD (<35 weeks of gestation) in patients with uterine contractions. Their study included 51 symptomatic women between 24 and 35 weeks of gestation (with singleton pregnancies) presenting for care with history of uterine contractions, and 90 controls (asymptomatic women who delivered in the same setting). Symptomatic women were admitted at the antenatal ward of a tertiary healthcare centre after clinical documentation of the contraction pattern, regardless of the cervical dilatation. Cervicovaginal samples were collected before digital exam and analysed for presence of fetal fibronectin and phIGFBP-1 using the QuikCheck fFN® test and the Actim™ Partus test, respectively. Then cervical length was measured by transvaginal sonography.

NPVs of QuikCheck fFN® test and the Actim™ Partus test for delivery before 35 weeks of gestations were 91.9% and 92.3%, while NPVs of these tests for PTD within 7 days from tests were 97.3% and 97.4%.[37] PPVs were 50% and 58.3% for delivery before 35 weeks of gestation, and 35.7% and 41.7% for PTD within 7 days from testing. For delivery before 35 weeks of gestation, negative likelihood ratio value (LR-) was higher for fFN test than for *ph*IGFBP-1 test (0.69 versus 0.34), with similar confidence intervals. For PTD within 7 days from testing, the

two tests had same values (0.21 and 0.20) within the same 95% confidence intervals. Likelihood ratio values for positive *ph*IGFBP-1 test results were higher than those for positive fFN test results, but with slightly larger confidence intervals (5.74 versus 4.10 for delivery before 35 weeks of gestation and 5.36 versus 4.17 for PTD within 7 days from testing).

Same perinatal results were reported for the two tests: three cases of respiratory distress syndrome in the groups with negative results compared to six cases in the groups with positive results; and five newborns in the groups with negative results attended the Neonatal Intensive care unit compared to eight newborns in the groups with positive results.[37] No cases of neonatal sepsis or perinatal mortality were reported for any groups.

Based on their results, the investigators concluded: "*Fetal fibronectin and phIGFBP-1 tests have approximately equivalent ability to predict delivery <35 weeks' gestation. An ultrasonographic cervical length measurement >20 mm or a negative fetal fibronectin/phIGFBP-1 test obtained from patients with uterine contractions at 24-35 weeks' gestation may avoid over-diagnosis.*"

ONGOING RESEARCH

Ross et al.[50] (http://www.obgyn.ucalgary.ca/projects/premi.htm**,** accessed on November 21, 2007)[46] are currently recruiting symptomatic women attending the Foothills Medical Centre and Peter Lougheed Centre (Calgary Health Region, Alberta) for a prospective cohort study on the use of Actim™ Partus test versus that of the $TLi_{IQ}^{®}$ System. Eligible women will be asked to have the Actim™ Partus test in addition to rapid fFN testing with the $TLi_{IQ}^{®}$ System. All women will be followed-up until after the birth of their baby when they (and their baby) are discharged home.

The main objective is to determine the sensitivity, specificity, PPV, and NPV of the Actim™ Partus test in predicting PTD (<37 weeks gestation) in symptomatic women who present between 24 and 34 weeks, 6 days of gestation without cervical changes.[46,50] The study also aims to compare the sensitivity, specificity, PPV, and NPV of the Actim™ Partus test to those of the $TLi_{IQ}^{®}$ System in predicting PTD in these women.

Selection of women will follow the algorithm that has been developed for use of the $TLi_{IQ}^{®}$ System in Calgary, and will ensure that women are included only if there is real diagnostic uncertainty.[46] A maternity nurse and physician will assess any symptomatic woman as per usual hospital protocol. Patients will undergo a sterile speculum examination, and swabs for both the $TLi_{IQ}^{®}$ System and the Actim™ Partus test specimens will be taken from cervical secretions in the posterior vaginal fornix and external cervical *os* respectively. A digital examination will then be performed and the results recorded in terms of cervical dilation and effacement. Laboratory personnel will read the fFN as per the current standard.

For the purposes of the study, the specimens for the Actim™ Partus test will be prepared by swirling the Dacron swab in labelled tube of extraction medium.[46] Specimens will be frozen immediately for later collection by a research nurse, who will transport the samples from the L&D to the Department of Obstetrics and Gynaecology for reading. The results of the *ph*IGFBP-1 test will therefore be unknown to the clinical or nursing staff involved in the care of the patient (to the L&D staff). The results of the test will be read and recorded by a research nurse not involved in patient care.

All study data will be extracted from patient charts: women's characteristics, co-morbidities of pregnancy, fFN test results, gestational age at the time of recruitment, and outcome of pregnancy.[46,50] The study sample size is 360. As of September 2007, 225 women were recruited (http://www.obgyn.ucalgary.ca/projects/premi.htm**,** accessed on November 21, 2007). It is expected that recruitment will be completed by February 2008.[50]

Victoria General Hospital in Victoria, British Columbia, has undertaken a study similar to the study that is currently ongoing in Calgary, comparing the use of the Actim™ Partus test versus the use of the TLi$_{IQ}$® System to aid in diagnosing PTL for symptomatic women (Somagen and Medix Biochemica, personal communication, December 2007), (Adeza Biomedical, personal communication, December 2007). This study is currently ongoing.

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.ncchta.org/project/1486.asp). 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. The reviewers aim to identify what further research is needed and what recommendations can be made to improve practice.

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 and is currently in the editorial review stage. The final report will be published by June 2008 (http://www.ncchta.org/project/1486.asp). The team involved in the project is based at the University of Birmingham.

CANADIAN EXPERIENCE

Based on their characteristics, both the Actim™ Partus test and the TLi$_{IQ}$® System may be helpful in rural areas and remote parts of Canada as rapid response tests to aid in diagnosing PTL in symptomatic women presenting for care with intact membranes. Currently, they are actively marketed in Canada for this indication.

The use of the TLi$_{IQ}$® System in Canada

The TLi$_{IQ}$® System is the only modality for rapid fFN detection used in Canada to aid in diagnosing PTL for symptomatic women (Adeza Biomedical, personal communication, November 2007).[1] The first TLi$_{IQ}$® System was installed in 2001, and currently there are almost 300 units in Canada, available in most provinces and territories. Clinical settings using the TLi$_{IQ}$® System range from Level 3 healthcare setting, where the clinical laboratory or obstetrics and gynecology residents in the L&D perform the test, to small rural hospitals and small clinics in Nunavut and Yukon, where registered nurses, nurse practitioners, or midwives perform the test.

Several Canadian studies[1,2,51-58] evaluated the clinical application of the TLi$_{IQ}$® System in the management of PTL for symptomatic women presenting for care with intact membranes. These studies reported that knowledge of a negative test result to complement clinical diagnosis had a significant impact on the evaluation of risk for PTB/PTD, especially in Level 1 and Level 2 healthcare 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 and therapeutic interventions such as administration of antibiotics and steroids, and indirect costs associated with displacement of the mother from her family and community. However, these studies have methodological weaknesses.[1]

The use of the Actim™ Partus test in Canada

Currently the promotion of the Actim™ Partus test to Canadian healthcare settings is still in its early stages (Somagen and Medix Biochemica, personal communication, December 2007).

To date, there is no published Canadian study on the clinical and/or economic impact of adding the Actim™ Partus test to PTL management in symptomatic women presenting for care with intact membranes. According to Somagen Diagnostics, two large Canadian healthcare centres, Foothills Hospital in Calgary and Victoria General Hospital in Victoria, are currently testing the use of the Actim™ Partus test for clinical utility and economic justification for possible implementation (Somagen Diagnostics and Medix Biochemica, personal communication, December 2007).

Canadian research studies

The literature search conducted for this rapid review located three abstracts reporting results from three Canadian studies, directly comparing the use of the Actim™ Partus test versus that of the TLi$_{IQ}$® System to aid in diagnosing PTL and predicting PTB/PTD in the same group of symptomatic women presenting for care with intact membranes.[59-61] The evidence obtained from these studies was reported in slide and poster presentations at the Society of Obstetricians and Gynaecologists of Canada (SOGC) annual meetings (in 2005, 2006, and 2007) (Adeza Biomedical, personal communication, December 2007; Somagen Diagnostics and Medix Biochemica, personal communication, December 2007). None of these studies was published in a peer-reviewed journal.

All studies[59-61] used the established protocols that are in place for rapid fFN testing for both the Actim™ Partus test and the TLi$_{IQ}$® System (Somagen and Medix Biochemica, personal communication, December 2007; Adeza Biomedical, personal communication, December 2007). They reported data on the diagnostic accuracy of these tests. However, no data on their clinical utility and/or economic impact when added to PTL management for the study population were reported by these studies.

The following commentary summarizes the information available from two abstracts.[59,60] The information provided in the abstract for the third study[61] was not summarized because it was published in French.

Turnell et al.[59,62] (Adeza Biomedical, personal communication, December 2007) directly compared the use of the Actim™ Partus test versus the TLi$_{IQ}$® System in 100 consecutive symptomatic women (between 24 and 35 weeks of gestation, most with singleton pregnancies) presenting for care at the Royal Alexandra Hospital, Edmonton, Alberta, with idiopathic PTL,

intact membranes, cervix <3 cm dilated, and no history of digital exam or sexual intercourse within the previous 24 hours. Excluded were women with bleeding, suspected intrauterine growth restriction (IUGR), non-reassuring maternal and fetal status, intercourse in the previous 24 hours, pelvic examination in the previous 24 hours, or suspected ruptured membranes.

The primary objective of the study was to determine whether the Actim™ Partus test is as effective as the TLi$_{IQ}$® System in diagnosing PTL.[59,62] The secondary objectives were to determine whether the introduction of either test into the labour assessment would result in a change in physician decision-making for the diagnosis of suspected PTL and a substantial cost savings for the Capital Health Authority. Another secondary objective was to determine whether the Actim™ Partus test would have a selective cost advantage over the TLi$_{IQ}$® System.

All women received the usual workup and assessment and were treated according to the standard of care at the time of the study.[59] Paired Dacron swabs were collected from the endocervical canal and then submitted to the laboratory for performance of the TLi$_{IQ}$® System or the Actim™ Partus tests. All physicians were blinded to the results of the Actim™ Partus test, which were recorded and then correlated with the results of the TLi$_{IQ}$® System (Adeza Biomedical, personal communication, December 2007).[59,62] All physicians were provided with results of the TLi$_{IQ}$® System and allowed to make their management decisions as they deemed appropriate. Time from testing to delivery was collected for all patients.

Out of 100 women, 75 had negative Actim™ Partus test results and 82 had negative TLi$_{IQ}$® System test results.[59] Thirteen of the 82 women with negative TLi$_{IQ}$® System test results had positive Actim™ Partus test results, while 6 out of 75 women with negative Actim™ Partus test results were found to have a positive TLi$_{IQ}$® System test result. A Pearson correlation coefficient was 0.451 ($P<0.01$). In 12 women who had positive results with both the TLi$_{IQ}$® System and the Actim™ Partus test, three delivered within 14 days of testing. One woman for each of the following combination of results delivered within 14 days: negative TLi$_{IQ}$® System/positive Actim™ Partus or positive TLi$_{IQ}$® System/negative Actim™ Partus.

Based on their results, the investigators concluded that, depending on local resources, the use of Actim™ Partus or TLi$_{IQ}$® System tests "*may be used as reasonable alternatives for the detection and diagnosis of preterm labour*."

Fortin et al.[60] compared the performance of the Actim™ Partus test, the TLi$_{IQ}$® System, and cervical length to predict PTD at the Département d'Obstétrique Gynécologie, Centre Hospitalier Universitaire Sainte-Justine, Université de Montréal, Montreal, Quebec. They recruited 71 women with PTL between 24 and 34 weeks of gestation. For most patients, samples for fFN and *ph*IGFBP-1 were obtained and tested 24 hours after admission for threatened PTL (Audibert, personal communication, December 2007). Samples for fFN and *ph*IGFBP-1 were obtained and tested in all women at the time of cervical length measurement.

In the study by Fortin et al.,[60] the TLi$_{IQ}$® System was performed in the laboratory by a technician, who was not aware of the clinical situation (Audibert, personal communication, December 2007). The results on fFN and cervical length measurements were available to the clinician and mentioned in the hospital chart. The Actim™ Partus test was performed by a research assistant, and the result was not mentioned on the hospital chart; the result was also not available to the treating physician.

Preliminary results for 61 women with complete outcomes reported that six women (10%) delivered within 2 weeks and 15 (25%) before 34 weeks.[60] The reported sensitivity, specificity, PPV, and NPV for delivery within 2 weeks were 100%, 78%, 21%, and 100%, respectively, for the TLi$_{IQ}$® System, and 0%, 92%, 0%, and 92% for IGFBP-1 for the Actim™ Partus test.[60] The reported sensitivity, specificity, PPV, and NPV for delivery before 34 weeks were 100%, 80%, 29%, and 100% for the TLi$_{IQ}$® System, and 0%, 92%, 0%, and 90% for IGFBP-1 for the Actim™ Partus test.[60]

Based on these preliminary results of this study, the investigators concluded "*IGFBP-1 was a very poor predictor of PTD and of the two tests fFN provided the best prediction for delivery within 2 weeks, and delivery before 34 weeks*."[60] Results of the final analysis, which now includes six more women with complete outcomes, should soon be submitted to the Journal of Obstetrics and Gynaecology Canada for publication (Audibert, personal communication, December 2007).

Expert opinion

Advice was obtained from a Canadian specialist in clinical biochemistry who has experience in performing both the Actim™ Partus test and the TLi$_{IQ}$® System for diagnosing suspected PTL in symptomatic women. The following commentary summarizes the advice received.

In general, point-of-care testing (POCT) can be reliable, provided that the testing program follows guidelines for accreditation of POCT (such as those from the laboratory accreditation program at the College of Physicians and Surgeons of Alberta). These guidelines assure proper method evaluation, operator training, quality control assessment, and proficiency testing.

The research evidence is supportive of a role for the TLi$_{IQ}$® System to rule out "true" PTL in symptomatic women when the test result is negative. This test, which has a good safety record, is the only adjunct test used currently in Alberta, and is usually carried out in the laboratory.

The Canadian experience with the Actim™ Partus test versus the TLi$_{IQ}$® System to aid in diagnosing PTL in symptomatic women with intact membranes, as gained through the ongoing/completed comparative studies conducted across Canada, increased the clinical awareness of both tests. There is little difference between the two tests in terms of risks and complications due to performing the test itself, although the specimen is collected from slightly different targets in the vaginal tract.

However, when compared to the TLi$_{IQ}$® System in the same population and using the same protocol, the performance of the Actim™ Partus test is associated with more false positive results, which can lead to usage of unnecessary interventions and increased healthcare costs.

The attractive feature of the Actim™ Partus test is that it is a visual read test and does not require a reader device. However, the test is hard to read if the positive line is not a strong positive line. Borderline results are usually interpreted as positive to be on the safer side. Reading the colour production on the strip can sometimes be challenging.

The Actim™ Partus test lends itself to testing outside laboratory. However, there is a concern regarding the performance of the test by non-laboratory staff, since the interpretation of its results is quite subjective. In current practice, when interpretation rather than just a number is reported, usually a laboratory professional is involved directly or with interpretive comments

based on a reported result. The use of the reader device with the TLi$_{IQ}$® System takes the subjectivity away from the reading.

The ability and possibility of using the Actim™ Partus test/TLi$_{IQ}$® System in rural and urban setting depends on the transportation system. The specimen sample for the Actim™ Partus test can be stored for 4 hours at room temperature, and then it must be frozen. The specimen sample for the TLi$_{IQ}$® System can be stored for 8 hours at the room temperature, and then must be refrigerated.

Calibration and quality control is required for the TLi$_{IQ}$® System, and quality control is required for the Actim™ Partus test. The fFN testing with the TLi$_{IQ}$® System takes about 20 minutes to perform. The Actim™ Partus test results are available in about 5 minutes. Good, reasonably simple, and reliable training is available for both tests.

DISCUSSION

Any tool that can reliably diagnose "true" PTL and predict whether a symptomatic woman presenting for healthcare is at high risk for imminent 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. Appropriate management strategies can save healthcare resources and avoid unnecessary interventions and social disruptions. Two rapid response biochemistry tests are currently available in Canada as potential diagnostic tools for PTL, the Actim™ Partus test and the TLi$_{IQ}$® System.

Both tests are relatively safe, simple to perform, and can be run by clinicians, nurses, or laboratory technicians in both urban and rural settings (Table 1). Based on these characteristics, either test has the potential to reduce unnecessary treatment and healthcare utilization by more accurately identifying symptomatic women who are not in "true" PTL. Potential advantages of the Actim™ Partus test over the TLi$_{IQ}$® System include: availability of results in less time (5 minutes versus 25 to 30 minutes); lower cost per test ($35 versus $100); and independence from reader device.

However, based on the available evidence, no definitive conclusions could be drawn on whether the Actim™ Partus test has clear advantages over the TLi$_{IQ}$® System in terms of diagnostic performance and clinical and economic impact when added to PTL management in symptomatic women presenting for care with intact membranes. There is insufficient evidence to determine which of these tests is most accurate in ruling out women at high risk for imminent PTB/PTD. There is a lack of evidence on the clinical utility and economic impact of the Actim™ Partus test. None of the available published studies directly compared the Actim™ Partus test to the TLi$_{IQ}$® System in terms of improved patient outcomes and reduced resource usage and the associated costs. The role of these tests may be more clearly defined by upcoming research.

Diagnostic performance

Although the diagnostic performance of the Actim™ Partus test has been investigated in several primary research studies, there is a lack of large well-designed studies on its use as an aid in diagnosing PTL in symptomatic women presenting for care with intact membranes. None of the

studies were randomised controlled trials comparing clinical diagnosis to clinical diagnosis plus diagnostic information obtained from the Actim™ Partus test.

The studies by Ting et al.[47] and by Eroglu et al.[37] evaluated the use of the Actim™ Partus test compared to the QuikCheck fFN® test, which is a dipstick visual read method, similar in design to the dipstick Actim™ Partus test (Adeza Biomedical, personal communication, November 2007). The results reported by these studies showed an approximate equivalent ability of the two tests to predict PTD before 35 weeks of gestation, and within 48 hours, 7 days, and 14 days from testing in symptomatic women (24 to 35 weeks of gestation, with singleton pregnancies) presenting for care with regular uterine contractions and intact membranes.

However, in the published articles reporting the results obtained from these studies,[37,47] it is not clear: if all women who had positive *ph*IGFBP-1 test results also had positive fFN test results; if the same women who had positive/negative *ph*IGFBP-1 also had positive/negative fFN result; or how many of the women who had positive/negative *ph*IGFBP-1 test results also had positive/negative fFN test results. Neither is it clearly reported if any invalid tests results were obtained during the testing process to determine whether the performance of the QuikCheck fFN®/Actim™ Partus test was associated with interpretive errors because of the visual reading of the test results.

According to the results of the literature search conducted for this rapid review, the only comparative studies which are evaluating/evaluated the use of the Actim™ Partus test versus that of the TLi_{IQ}® System as rapid response tests to aid in diagnosing PTL and predicting the risk for PTB/PTD in symptomatic women presenting for care with intact membranes are five Canadian ongoing/completed studies (Somagen Diagnostic and Medix Biochemica, personal communication, December 2007; Adeza Biomedical, personal communication, December 2007).[50,59-61] The results of the three completed Canadian studies were reported in slide and poster presentations at SOGC annual meetings during the last 3 years. None of these studies was published in a peer-reviewed journal.

The results reported in the abstracts of two completed Canadian studies[59,60] and expert opinion indicate differences in the diagnostic accuracy between the Actim™ Partus test and the TLi_{IQ}® System. More positive results were obtained with the Actim™ Partus test than with the TLi_{IQ}® System for symptomatic women (between 24 and 35 weeks of gestation) who did not deliver within the next 7 to 14 days from testing. According to the evidence available for the two completed Canadian studies,[59,60,62] it appears that the TLi_{IQ}® System provided the best prediction for delivery within two weeks.

Side effects, risks, or complications from performing the test itself

None of the studies[37,47,59,60] identified by the literature search conducted for this rapid review reported whether there were any side effects, risks, or complications for the woman and fetus from performing the QuikCheck fFN®/TLi_{IQ}® System/Actim™ Partus test itself.

According to their manufacturers, there is little risk to the woman and fetus from performing the TLi_{IQ}® System/Actim™ Partus test itself (Adeza Biomedical, personal communication, December 2007; Somagen Diagnostics and Medix Biochemica, personal communication, December 2007).

However, harm to the woman and/or the fetus can be caused by treatments that may follow a false positive test result. The added psychological stress for the woman and the use of unnecessary interventions and additional resources to monitor a predicted development of PTL are also undesirable outcomes. According to the Canadian Institute for Health information,[63] in 2002-2003 the total average cost per patient admitted to an acute care hospital for false labour was $1,400 (CAD). Another risk associated with the use of either of these tests is the withholding of appropriate interventions because of false negative test results.

Clinicians considering the use of either of these tests are cautioned that any modifications to the assay protocol as described by the manufacturer may yield erroneous results.[45,48]

Clinical and economic impact

The questions regarding whether adding the Actim™ Partus test to the PTL management would change clinical practice and affect patient outcome, resource usage, and the associated costs remain unanswered.

None of the studies directly comparing the Actim™ Partus test to either the QuikCheck fFN® test or the TLi$_{IQ}$® System[37,47,59-61] reported data on the clinical and economic impact of adding either test to PTL management in symptomatic women presenting for care with intact membranes (Adeza Biomedical, personal communication, December 2007; Somagen Diagnostics and Medix Biochemica, personal communication, December 2007).

The clinical usefulness of the Actim™ Partus test or the TLi$_{IQ}$® System rests primarily with their ability to identify symptomatic women (between 24 and 35 weeks of gestation, with singleton pregnancies, and cervical dilation <3 cm) presenting for care with intact membranes and no vaginal bleeding who are least likely to deliver prematurely (based on their high NPV), thereby avoiding unnecessary interventions and the associated adverse effects and costs.[4,5,7,9-11,29,34,36,38]

The high NPV of the TLi$_{IQ}$® System was confirmed in recently published RCTs, which evaluated the use of the TLI$_{IQ}$® System as an adjunct diagnostic tool in the management of PTL in symptomatic women.[1] However, it is yet to be determined whether its use offers significant benefit beyond that observed with good clinical assessment and judgment.

The use of the Actim™ Partus test has not been evaluated in RCTs and/or non-randomised studies to determine whether clinicians can use the additional information provided by the test results to improve clinical practice and patient outcomes, and reduce resource usage and the associated costs.

An important clinical disadvantage for both the Actim™ Partus test and the TLi$_{IQ}$® System is that neither can be performed in the following situations: premature rupture of membranes (PROM), cervical cerclage, and preeclampsia. The studies directly comparing the Actim™ Partus test to either the QuikCheck fFN® test or the TLI$_{IQ}$® System excluded women with these conditions.[37,47,50,59,60] Conclusively, none of these testing modalities is an ideal predictor of PTB/PTD.

Both the TLi$_{IQ}$® System and the Actim™ Partus test seem 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. However, all reviewed

completed studies directly comparing the Actim™ Partus test to the $TLI_{IQ}^{®}$ System were conducted in tertiary healthcare centers.

Health Canada has approved both tests to aid in diagnosing PTL and predicting PTB/PTD in symptomatic women. Canadian clinical practice guidelines recommend only the use of rapid fFN testing to complement clinical assessment for diagnosing PTL in symptomatic women (when clinical diagnosis is doubtful, to identify women at low risk for imminent PTB/PTD). Patient test protocols for using the $TLi_{IQ}^{®}$ System have been developed by several reproductive care and perinatal programs in Canada.

Further research

Further well-designed research is warranted to confirm the diagnostic performance of the Actim™ Partus test, and to evaluate the clinical and economic implications of introducing the test into clinical practice. The hypothesis that the additional information provided by the Actim™ Partus test results can be translated into better clinical practice (defined by improved patient outcomes and reduced resource usage and associated costs) can best be tested in RCTs.

Further well-designed research is also warranted to compare the clinical and economic impact of using the Actim™ Partus test as an alternative to the $TLi_{IQ}^{®}$ System in Level 1 hospitals as adjunct tools to clinical examination for diagnosing PTL in symptomatic women.

Issues raised by point-of-care testing (POCT)

Testing with the $TLi_{IQ}^{®}$ System and the Actim™ Partus test is bedside or extra-laboratory testing, also known as point-of-care testing (POCT). The Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS) recently completed an assessment that aimed to provide an appropriate definition for POCT, draw up a list of Canada approved kits and instruments, flag the major issues associated with POCT, and identify the quality-control and quality-assurance measures proposed in Canada and around the world.[64]

In the AETMIS assessment, POCT is defined as "*testing performed by qualified health professionals outside recognized and accredited public or private laboratories and outside health and social services institutions (as defined by law)*."[64] Although advocates of POCT maintain that "*it improves access to some tests, reduces turnaround time, and helps meet patients' needs more effectively*," AETMIS identified several points that merit further consideration. These include "*the risks of unnecessary tests, errors due to inadequate staff training and experience, the extra work being required of quality-control professionals*," and the cost of reagents, supplies, and quality-control material, which is higher for POCT than for tests conducted in central laboratories. Ethical issues of concern included "*providing patients with accurate information so that they can give informed consent to the test and ensuring the confidentiality of patients' test results and consultations with the prescribing health professional*."

The literature reviewed by AETMIS indicated that "*most point-of-care tests are technically effective when performed by health professionals in a proper setting*."[64] To mitigate an existing concern that POCT "*might be performed by unqualified staff*," it has been proposed that "*professional laboratory technicians take part in selecting and maintaining the test devices, training operators, and regularly verifying their competence and the accuracy of the*

documentation provided to patients (in accordance with the requirements issued by regulatory bodies)."

Even though the use of POCT is rapidly expanding, it is not yet regulated.[64] Rapid access to point-of-care tests and their results raises the issues of their appropriateness and frequency. Based on the analysis of the major issues raised by POCT and examination of the different measures in place in other provinces and countries to ensure the quality of this practice, AETMIS identified the principles and conditions that could guide how this practice should be governed in Québec.[64] POCT should be performed only when justified by the need for a rapid response and in situations requiring immediate test results, and must remain a complementary adjunct to central laboratory services. The following conditions must be met in an effort to promote high-quality test results and prevent any harm to people's health:

- POCT must be performed in a secure setting that meets strict quality standards, including education and training for test operators, periodic audits, internal and external quality controls, and a collaborative relationship with central laboratories.
- Each step in the testing procedure must be accurately recorded in the medical file and the source of errors at the different testing stages must be identified.
- The confidentiality of patients' test results and consultations with the health professionals who order the tests must be safeguarded, whether the information is being reported, stored or transmitted.
- Responsibilities must be clearly defined in policies and procedures on the use of the different tests (which must include standards, guidelines, and accreditation and certification procedures).
- The appropriateness and frequency of the tests must be evaluated.
- Manufacturers' recommendations, maintenance programs, and hygiene and waste-disposal measures must be strictly observed.
- Decisions with regard to prioritizing point-of-care tests "*must be based on a comprehensive analysis of each test, including an economic component to ensure that its benefits outweigh its disadvantages and costs.*"

Other predictors of PTD/PTB in symptomatic women

An improved understanding of the pathophysiology of PTD/PTB has led to the development of new tests to predict PTD/PTB in symptomatic women.[5,11-14,19,22-25,28,29,34,38,39] Many biochemical tests have been investigated recently, including those testing for the concentration of inflammatory markers such as interleukin-6 and tumor necrosis factor-α in cervicovaginal secretion, of corticotropin-releasing hormone in maternal blood, of lactoferrin in the cervix, of intercellular adhesion molecule-1 in the choriodecidua, and of beta-human chorionic gonadotropin in cervicovaginal secretion. Screening for microorganisms (such as bacterial vaginosis) has also been employed to predict PTB. None of these biochemical tests are standard diagnostic tools in clinical practice and currently remain as research tools.

Development of multiple marker tests for PTL and the use of molecular biology techniques (genomics and proteomics) may be the predictive methods of the future.[10-12,25,28,34,38,65] However,

the clinical value of using these methods for the diagnosis of PTL and prediction of PTB/PTD remains to be determined.

Limitations

The present review has several limitations. The literature review was confined to published reports of primary and secondary research studies that were written in English and were publicly available (free of charge). Only full text articles were included for data extraction because abstracts provide insufficient details to allow an accurate, unbiased assessment and comparison of the study results. However, for the purpose of this review, the information contained in Canadian abstract publications was summarized to inform the section "Canadian research studies".

Only one reviewer performed study selection and data extraction.

The methodological quality of the selected studies was not assessed using a quality appraisal tool, to determine the validity of their findings, and to identify the studies that should be given more weight in the overall synthesis.

The present review only summarizes the recommendations from reports of relevant clinical practice guidelines and consensus documents, and does not appraise their scientific foundations.

Qualitative research literature, which provides information about the benefits and limitations of the two rapid response technologies to diagnose PTL (from physicians' and women's perspectives), was not included.

The extent of publication bias was not assessed.

CONCLUSIONS

The Actim™ Partus test holds promise in identifying those symptomatic women who are least likely to deliver prematurely when they are between 24 and 35 weeks of gestation, with singleton pregnancy, cervical dilation <3 cm, intact membranes, and no vaginal bleeding. However, the value of the Actim™ Partus test as an alternative to the $TLi_{IQ}^{®}$ System to complement clinical examination for diagnosing PTL in symptomatic women remains unclear.

Both tests are relatively safe and simple to perform. Either test has the potential to reduce unnecessary treatment and healthcare utilization by more accurately identifying symptomatic women who are not in "true" PTL. Potential advantages of the Actim™ Partus test over the $TLi_{IQ}^{®}$ System include availability of results in less time and lower cost. However, the available evidence is insufficient to determine whether the Actim™ Partus test or the $TLi_{IQ}^{®}$ System is superior in terms of diagnostic performance and clinical and economic impact when added to PTL management.

Bringing together the investigators who conducted the three completed Canadian studies to share their findings would help to inform the decision on which test under which circumstances should be adopted as an adjunct tool to clinical examination for diagnosing PTL in symptomatic women. The two ongoing Canadian studies may help in clarifying the respective roles of these tests. Waiting for these studies' final results will add to the evidence base and aid the decision-making process.

Depending on the setting, resources, number of tests conducted, and expertise available, one test modality may be more appropriate than the other. Hence, well-designed research studies conducted in other setting besides large urban hospitals to measure resource utilization related to better outcomes for mothers and newborns would address these issues.

APPENDIX A: SEARCH STRATEGY

A comprehensive literature search was conducted by the IHE Research Librarian on November 4th and 5th, 2007. Major electronic databases used include: The Cochrane Library, CRD Databases: (NHS EED, HTA, DARE), PubMed, EMASE, CINAHL and Web of Science. In addition, relevant library collections, web sites of practice guidelines, regulatory agencies, evidence-based resources, and other HTA related agency resources (AETMIS, CADTH, ICES) were searched. Internet search engines were also used to locate grey literature.

The search strategy outlined below retrieved articles published from 2002 to 2007. The search was further limited to systematic reviews, randomised controlled trials, health technology assessments, economic evaluations, and clinical practice guidelines.

Medical Subject Headings (MeSH) terms relevant to this topic include: Premature birth; Predictive Value of Tests; Insulin-Like Growth Factor Binding Proteins; Interleukin-6; Fibronectins.

Database	Edition or date searched	Search Terms ††
Databases		
The Cochrane Library http://www.the cochranelibrary.com	Issue 4, 2007	"preterm birth or preterm labor or preterm labour or preterm deliver* or premature birth or premature labor or premature labour or premature deliver* **in** Title, Abstract or Keywords **and** diagnos* or predict* or sensitiv* or specific* **in** Title, Abstract or Keywords **and** actim™ Partus or somatomedin binding protein* or igfbp or insulin-like growth factor or interleukin-6 or corticotropin releasing hormone* or chorionic gonadotropin or lactoferrin or fetoprotein* or alkaline phosphatase or salivary estriol or fetal fibronectin or foetal fibronectin **in** Title, Abstract or Keywords, from 2002 to 2007
MEDLINE	November 2, 2007	1 obstetric labor, premature/ or premature birth 2 ((premature or preterm) adj2 (labor or labour or deliver$ or birth$)).mp 3 1 or 2 4 "Predictive Value of Tests" 5 exp Diagnosis 6 predict$.mp 7 "Sensitivity and Specificity" 8 or/4-7 9 3 and 8 10 exp Insulin-Like Growth Factor Binding Proteins 11 (Actim™ Partus or igfbp or somatomedin-binding protein$).mp 12 exp Biological Markers 13 exp Estriol 14 salivary estriol.mp 15 Corticotropin-Releasing Hormone 16 Interleukin-6 17 Alkaline Phosphatase 18 exp Chorionic Gonadotropin 19 fetal proteins/ or alpha-fetoproteins 20 Lactoferrin 21 (corticotropin releasing hormone$ or corticotropin releasing factor$ or crh).mp 22 (interleukin 6 or IL-6).mp

Database	Edition or date searched	Search Terms ††
Databases (cont'd)		
MEDLINE (cont'd)	November 2, 2007	23 alkaline phosphatase.mp 24 (human chorionic gonadotropin or hcg).mp 25 alpha fetoprotein$.mp 26 lactoferrin.mp 27 Fibronectins 28 (fetal fibronectin or foetal fibronectin or ffn).mp 29 salivary proteinase.mp 30 serum ferritin.mp 31 or/10-30 32 9 and 31 33 meta-analysis.pt 34 (meta-anal$ or metaanal$).mp 35 (quantitativ$ adj3 (review$1 or overview$1)).mp 36 (systematic adj3 (review$1 or overview$1)).mp 37 (methodologic adj3 (review$1 or overview$1)).mp 38 (integrat$ adj5 research).mp 39 (quantitativ$ adj3 synthes$).mp 40 or/33-39 41 review.pt. or (review$ or overview$).mp 42 (medline or medlars or pubmed or index medicus or embase or cochrane).mp 43 (scisearch or web of science or psycinfo or psychinfo or cinahl or cinhal or scopus).mp 44 (excerpta medica or psychlit or psyclit or current contents or science citation index or sciences citation index or biosis).mp 45 (hand search$ or manual search$).mp 46 ((((electronic adj3 database$) or bibliographic) adj3 database$) or periodical index$).mp 47 (pooling or pooled or mantel haenszel).mp 48 (peto or der simonian or dersimonian or fixed effect$).mp 49 ((combine$ or combining) adj5 (data or trial or trials or studies or study or result or results)).mp 50 or/42-49 51 41 and 50 52 40 or 51 53 (hta$ or health technology assessment$ or biomedical technology assessment$).mp 54 technology assessment, biomedical/ or biomedical technology assessment 55 53 or 54 56 52 or 55 57 randomized controlled trial.pt 58 clinical trial.pt 59 randomi?ed.ti,ab 60 placebo.ti,ab 61 randomly.ti,ab 62 trial.ti,ab 63 or/57-62 64 animals 65 humans 66 64 not (64 and 65) 67 63 not 66 68 practice guideline.pt

Database	Edition or date searched	Search Terms ††
Databases (cont'd)		
MEDLINE (cont'd)	November 2, 2007	69 comparative stud$.mp 70 "Costs and Cost Analysis" 71 Cost-Benefit Analysis 72 "cost of illness" 73 (economic evaluat$ or economic analys$ or economic study or economic studies or economic assess$ or economic consequence$).mp 74 ((cost-benefit or benefit-cost or cost effectiv$ or cost utility) adj2 (analys$ or evaluat$ or assess$ or study or studies)).mp 75 (cost minimization or cost minimisation or cost consequence$ or cost offset$).mp 76 ((cost or costs) adj2 analys$).mp 77 ("cost of illness" adj4 (analys$ or evaluat$ or assess$ or study or studies or framework$)).mp 78 or/70-77 79 56 or 67 or 68 or 69 or 78 80 32 and 79 81 limit 80 to yr="2002 - 2007"
CRD Databases (DARE, HTA & NHS EED)	November 5, 2007	#1 MeSH Obstetric Labor, Premature EXPLODE 1 #2 "preterm birth" OR "preterm labor" OR "preterm labour" OR "preterm delivery" OR "premature birth" OR "premature labor" OR "premature labour" OR "premature delivery" #3 #1 OR #2 #4 MeSH Predictive Value of Tests #5 MeSH Diagnosis EXPLODE 1 #6 MeSH Sensitivity and Specificity EXPLODE 1 2 3 4 5 6 7 #7 predict* #8 #4 OR #5 OR #6 OR #7 #9 #3 AND #8 #10 MeSH Insulin-Like Growth Factor Binding Proteins EXPLODE 1 #11 "actim partus" OR igfbp OR "insulin-like growth factor" OR "somatomedin-binding" #12 MeSH Biological Markers EXPLODE 1 #13 "salivary estriol" OR "salivary proteinase" OR "serum ferritin" #14 MeSH Corticotropin-Releasing Hormone #15 MeSH Interleukin-6 #16 MeSH Alkaline Phosphatase #17 MeSH Chorionic Gonadotropin EXPLODE 1 2 3 4 5 #18 MeSH fetal proteins #19 MeSH alpha-fetoproteins #20 MeSH Lactoferrin #21 "corticotropin releasing hormone" OR "corticotropin releasing hormones" OR "corticotropin releasing factor" OR crh #22 interleukin-6 OR IL-6 #23 "alkaline phosphatase" #24 "human chorionic gonadotropin" OR hcg #25 "alpha fetoprotein" OR "alpha fetoproteins" #26 lactoferrin #27 MeSH Fibronectins

Database	Edition or date searched	Search Terms ††
Databases (cont'd)		
CRD Databases (DARE, HTA & NHS EED) (cont'd)	November 5, 2007	#28 "fetal fibronectin" OR "foetal fibronectin" OR ffn #29 #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 #30 #14 AND #33 RESTRICT YR 2002 2007
EMBASE –Ovid platform (Licenced resource)	November 2, 2007	1 "immature and premature labor"/ or premature labor/ or prematurity 2 ((premature or preterm) adj2 (labor or labour or delivery or birth$)).mp 3 1 or 2 4 "prediction and forecasting"/ or prediction 5 predict$.mp 6 exp DIAGNOSIS 7 "sensitivity and specificity" 8 or/4-7 9 3 and 8 10 Biological Marker 11 somatomedin binding protein/ or somatomedin binding protein 6 12 insulin-like growth factor binding protein$.mp 13 (Actim™ Partus or igfbp or somatomedin-binding protein$).mp 14 salivary estriol.mp 15 Corticotropin Releasing Factor 16 (corticotropin releasing hormone$ or corticotropin releasing factor$ or crh).mp 17 Interleukin 6 18 (interleukin 6 or IL-6).mp 19 Alkaline Phosphatase 20 alkaline phosphatase.mp 21 Chorionic Gonadotropin 22 (human chorionic gonadotropin or hcg).mp 23 ALPHA FETOPROTEIN/ or FETOPROTEIN 24 alpha fetoprotein$.mp 25 Lactoferrin 26 lactoferrin.mp 27 Fibronectin 28 (fetal fibronectin or foetal fibronectin or ffn).mp 29 salivary proteinase.mp. 30 Ferritin Blood Level 31 serum ferritin.mp 32 or/10-31 33 9 and 32 34 meta-analysis.pt 35 (meta-anal$ or metaanal$).mp 36 (quantitativ$ adj3 (review$1 or overview$1)).mp 37 (systematic adj3 (review$1 or overview$1)).mp 38 (methodologic adj3 (review$1 or overview$1)).mp. 39 (integrat$ adj5 research).mp. 40 (quantitativ$ adj3 synthes$).mp. 41 or/34-40 42 review.pt. or (review$ or overview$).mp

Database	Edition or date searched	Search Terms ††
Databases (cont'd)		
EMBASE –Ovid platform (Licenced resource) (cont'd)	November 2, 2007	43 (medline or medlars or pubmed or index medicus or embase or cochrane).mp 44 (scisearch or web of science or psycinfo or psychinfo or cinahl or cinhal or scopus).mp 45 (excerpta medica or psychlit or psyclit or current contents or science citation index or sciences citation index or biosis).mp 46 (hand search$ or manual search$).mp 47 ((((electronic adj3 database$) or bibliographic) adj3 database$) or periodical index$).mp 48 (pooling or pooled or mantel haenszel).mp 49 (peto or der simonian or dersimonian or fixed effect$).mp. 50 ((combine$ or combining) adj5 (data or trial or trials or studies or study or result or results)).mp 51 or/43-50 52 42 and 51 53 41 or 52 54 (hta$ or health technology assessment$ or biomedical technology assessment$).mp 55 technology assessment, biomedical/ or biomedical technology assessment 56 54 or 55 57 53 or 56 58 exp clinical trial 59 randomi?ed.ti,ab 60 placebo.ti,ab 61 randomly.ti,ab 62 trial.ti,ab 63 or/58-62 64 animal 65 human 66 64 not (64 and 65) 67 63 not 66 68 exp practice guideline 69 economic evaluation/ or "cost benefit analysis"/ or "cost effectiveness analysis"/ or "cost minimization analysis"/ or "cost utility analysis" 70 "cost of illness" 71 (economic evaluat$ or economic analys$ or economic study or economic studies or economic assess$ or economic consequence$).mp 72 ((cost-benefit or benefit-cost or cost effectiv$ or cost utili$) adj2 (analys$ or evaluat$ or assess$ or study or studies)).mp 73 (cost minimization or cost minimisation or cost consequence$ or cost offset$).mp 74 ((cost or costs) adj2 analys$).mp 75 ("cost of illness" adj4 (analys$ or evaluat$ or assess$ or study or studies or framework$)).mp. 76 or/69-75 77 comparative stud$.mp. 78 comparative study/ 79 77 or 78 80 57 or 67 or 68 or 76 or 79 81 33 and 80 82 limit 81 to yr="2002 - 2007"

Database	Edition or date searched	Search Terms ††
Databases (cont'd)		
Web of Science – ISI platform (Licensed resource)	November 5, 2007	(preterm birth or preterm labor or preterm labour or preterm deliver* or premature birth or premature labor or premature labour or premature deliver*) AND (predict* or diagnos*) AND ("insulin-like growth factor" or "actim partus" or igfbp OR "somatomedin-binding" or "salivary estriol" or "corticotropin releasing hormone" or interleukin-6 or "alkaline phosphatase" or "chorionic gonadotropin" or "fetoprotein" or "fetoproteins" or lactoferrin or "fetal fibronectin" or "foetal fibronectin") DocType=All document types; Language=All languages; Databases=SCI-EXPANDED, SSCI, A&HCI; Timespan=2002-2007
Library Catalogue		
NEOS (Central Alberta Library Consortium)	November 5, 2007	"preterm birth$ or preterm labor or preterm labour or preterm deliver$ or premature birth$ or premature labor or premature labour or premature deliver$" AND Any field "predict$ or diagnos$" AND "actim™ Partus or igfbp or insulin-like growth or somatomedin-binding or biological marker$ or salivary estriol or corticotropin-releasing or interleukin-6 or alkaline phosphatase of chorionic gonadotropin or fetoprotein$ or lactoferrin or fibronectin" 2002-2007
Guidelines		
AMA Clinical Practice Guidelines http://www.topalbertadoctors.org/TOP/CPG	November 5, 2007	Browsed list of guidelines. No results found.
CMA Infobase http://mdm.ca/cpgsnew/cpgs/index.asp	November 5, 2007	Premature; Preterm
National Guideline Clearinghouse http://www.ngc.gov	November 5, 2007	("preterm labor" or "preterm birth" or "preterm delivery" or "premature birth" or "premature labor" or "premature delivery") AND (predict or prediction or predictive or diagnosis or diagnostic) **AND** (actim or insulin-like or igfbp or somatomedin); ("biological marker" or "biological markers"); (interleukin or estriol or corticotropin); (phosphatase or gonadotropin or fetoprotein*); (lactoferrin or fibronectin)
Clinical Trials		
ClinicalTrials.gov (US) http://clinicaltrials.gov/	November 5, 2007	Preterm birth AND predict*; preterm birth AND diagnosis; actim partus; insulin-like or igfbp or somatomedin); preterm birth AND biological marker; interleukin or estriol or corticotropin; phosphatase or gonadotropin or fetoprotein; lactoferrin or fibronectin; preterm birth and ffn
CenterWatch Clinical Trials Listing Service http://www.centerwatch.com/	November 5, 2007	Preterm; Premature delivery; premature birth; premature labor; premature labour; fibronectin; interleukin-6; chorionic gonadotropin No results found.

Database	Edition or date searched	Search Terms ††
Clinical Trials (cont'd)		
metaRegister of Controlled Trials (mRCT) http://www.controlled-trials.com/mrct/	November 5, 2007	preterm birth; premature birth; preterm labour; premature labour AND (predict* or diagnos*); insulin-like; igfbp; somatomedin; biological marker; interleukin; estriol; corticotrophin; phosphatise; gonadotropin; fetoprotein; lactoferrin; fibronectin
National Research Register http://www.nrr.nhs.uk/search.htm	November 5, 2007	Preterm birth; preterm labour; preterm delivery; premature birth; premature labour; premature delivery; AND (predict* or diagnos*)
HTA resources		
AETMIS http://www.aetmis.gouv.qc.ca	November 5, 2007	Preterm; premature; fibronectin; interleukin; gonadotropin; corticotropin No results found.
CADTH http://www.cadth.ca/	November 5, 2007	Preterm; premature; fibronectin; interleukin; gonadotropin; corticotropin No results found.
Institute for Clinical and Evaluative Sciences (ICES), Ontario http://www.ices.on. ca/	November 5, 2007	Preterm; premature birth; premature labour; premature delivery No results found
Health Technology Assessment Unit At McGill http://www.mcgill.ca/tau/	November 5, 2007	Browsed lists of reports 2002-2007. No results found.
Medical Advisory Secretariat http://www.health.gov.on.ca/english/providers/program/mas/mas_mn.html	November 5, 2007	"preterm birth"; "preterm labour"; "preterm delivery"' "premature birth"; "premature labour"; "premature delivery" No results found.
CCE http://www.med.monash.edu.au/healthservices/cce/	November 5, 2007	Browsed list of evidence reports. No results found.
ECRI http://www.ecri.org (Licenced Resource)	November 5, 2007	("preterm birth" or "preterm labour" or "preterm labor" or "preterm delivery") AND (prediction or predictive or predict or diagnosis or diagnostic); ("premature birth" or "premature labour" or "premature labor" or "premature delivery") AND (prediction or predictive or predict or diagnosis or diagnostic)
Health Quality Council, Saskatchewan http://www.hqc.sk.ca	November 5, 2007	"preterm birth"; "preterm labour"; "preterm delivery"' "premature birth"; "premature labour"; "premature delivery" No results found.

Database	Edition or date searched	Search Terms ††
HTA Resources (cont'd)		
NHS Health Technology Assessment programme http://www.ncchta. org	November 6, 2007	Preterm; pre-term birth; premature birth; fibronectin; interleukin; gonadotropin; corticotrophin
NZHTA http://nzhta.chmeds.ac. nz/publications. htm	November 6, 2007	Browsed list of publications No relevant results found.
NICE (UK) http://www.nice.org.u k/	November 6, 2007	Preterm; pre-term; premature Browsed guidance lists. No relevant results found.
Search Engines		
Google http://www.google. com	November 6, 2007	predict OR prediction OR predictive OR diagnosis OR diagnoses OR diagnostic "preterm birth"
Copernic (Basic, 17 engines enabled) http://www.copernic.c om	November 6, 2007	"preterm birth" AND (predict OR prediction OR predictive OR diagnosis OR diagnostic)

Note:

†† "*", "# ", and "?" are truncation characters that retrieve all possible suffix variations of the root word e.g. surg* retrieves surgery, surgical, surgeon, etc.

; are used to separate search terms that were searched separately

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

Canadian specialists in perinatology, obstetrics and gynaecology, and clinical biochemistry were contacted for expert opinion on the current status of using the Actim™ Partus test as a tool for diagnosing suspected preterm labour (PTL) in symptomatic women. The Canadian specialists were also contacted for information regarding ongoing or completed primary research studies directly comparing the value of adding the Actim™ Partus test to that of adding the TLi$_{IQ}$® System in diagnosing suspected PTL in symptomatic women. At the time this report was completed, advice was received from one specialist in clinical biochemistry.

The Canadian distributor of the Actim™ Partus test (Somagen Diagnostics, Edmonton, Alberta) and the Canadian representative of the TLi$_{IQ}$® System's manufacturer (Adeza Biomedical) were contacted for information on their regulatory status, availability, cost, and coverage of these tests in Canada. They were also contacted for information regarding ongoing or completed primary research studies directly comparing the value of adding these tests in diagnosing suspected PTL in symptomatic women.

Health Canada, Therapeutic Products Directorate was contacted for information on regulatory status of the Actim™ Partus test in Canada. Also requested was information on whether data on risks and complications to woman and/or fetus due to performing the test 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 selection was determined on the basis of a list of inclusion and exclusion criteria developed *a priori* for this study. Studies were selected for retrieval if they seemed to meet the inclusion criteria listed below. The retrieval was limited to published studies written in English. Where appropriate, relevant information contained in English summaries of HTA reports not written in English was used to expand this review's discussion.

Copies of the full text of potentially eligible studies were then retrieved and assessed for eligibility by the same reviewer (PC) using the same selection criteria. Closer examination of the retrieved full text articles revealed that some did not meet the inclusion criteria specified by the review protocol. Consequently, these papers were not used to formulate the evidence base for this 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's discussion.

Inclusion criteria

A study was **included in the review if** it was published and publicly available (free of charge).

Selected for data extraction were studies reporting on:

Population – all pregnant women (all ages), with multiple or single gestations presenting for healthcare with symptoms and signs of PTL and intact membranes at inpatient or outpatient settings (rural and/or urban).

Intervention – use of the Actim™ Partus as an adjunct rapid response diagnostic test for PTL.

Comparator – use of the $TLi_{IQ}^{®}$ System as an adjunct rapid response diagnostic test for PTL.

Outcome – diagnostic accuracy (sensitivity, specificity, positive and negative predictive values, and/or likelihood ratios for positive and negative results); clinical outcomes (patient and resource usage outcomes in terms of impact on gestation age at delivery, maternal anxiety/stress, and need for woman's removal from her home support; rates of spontaneous PTB/PTD, maternal transfers and hospital admissions; and impact on assessment time, length of hospital stay, use of other diagnostic tests, and use of therapeutic interventions); risks and complications to mother and/or fetus associated with performing the rapid diagnostic test itself; and costs associated with adding the test for PTL management.

Only full, peer-reviewed articles were included because abstracts do not provide adequate detail on the study's methodology and findings.

In the case of duplicate publications, the most recent and complete version was included.

Type of studies

Considered for inclusion were all published reports of:

- primary research studies that directly compared the use of the Actim™ Partus test to the use of the $TLi_{IQ}^{®}$ System to diagnose PTL for symptomatic women with intact membranes, and reported on these tests' efficacy/effectiveness (in terms of their

diagnostic accuracy, and patient and resource usage outcomes), safety and associated costs when compared to each other as adjunct tests to clinical examination; and/or

- secondary research studies (systematic reviews, health technology assessment studies, and economic analyses) reporting on the safety, efficacy/effectiveness, and/or costs and cost-effectiveness of using the Actim™ Partus test versus the $TLi_{IQ}^{®}$ System to diagnose PTL for symptomatic women with intact membranes.

Using criteria from Cook et al.,[66] **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; and
- qualitative or quantitative data synthesis.

For studies in which the reporting of the study methodology and outcomes was unclear, their authors were contacted for further information. Contacted were only the authors who provided an e-mail address as contact information in the published reports of their studies.

Guidelines and patient test protocols

The section "Guidelines and patient protocols" summarizes recommendations from reports of relevant clinical practice guidelines, position papers, and consensus statements issued on the diagnosis and/or management of PTL.

This section also summarizes the information on patient test protocols that have been developed specifically for using the $TLi_{IQ}^{®}$ System or the Actim™ Partus test to aid in diagnosing suspected PTL and predicting PTB/PTD in symptomatic women.

Canadian research studies

For the purpose of this rapid review, information contained in abstracts of comparative studies conducted in Canada was summarized to inform the section "Canadian research studies". The authors of the abstract-only publications were contacted by e-mail for details of their studies.

Background information

Where appropriate, relevant published material in the form of overview materials, clinical reviews, narrative and descriptive reviews, letters, conference material, commentaries, discussion papers, editorials, and abstracts were included as background information to inform the various sections of the review.

Exclusion criteria

This review does not cover the use of the two rapid response diagnostic tests (the Actim™ Partus test or the $TLi_{IQ}^{®}$ System) alone or in conjunction with other diagnostic tests, for other categories of pregnant women such as symptomatic women with preterm pre-labour premature rupture of membranes (PROM), asymptomatic women, or for other indications (e.g., for prediction of pre-

eclampsia or postterm delivery or for selection of the most suitable PTL induction methods).

Published reports of primary and secondary research studies were **excluded from data extraction if**:

- they involved both symptomatic and asymptomatic women and did not report separately the results for the symptomatic women; or
- they included women who experienced PROM and/or medically indicated PTL and did not separately report on these subjects.

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.

Editorials, letters and technical reports were **excluded**.

Table B1: Excluded studies

Study	Reason for exclusion
Larouche A, Simard F. Mesure de la fibronectine foetale et de l'IGFBP-1 chez les femmes gravides entre 20 et 34 semaines de grossesse, symptomatiques d'un travail pre-terme. *Ann Biol Clin Que* 2006;43(3)":20	Study conducted in Canada to compare the use of the Actim™ Partus test to that of the TLi$_{IQ}$® System. It is available only in abstract form written in French.
Cararach V, Palacio M, Sandhez M, Cobo T, Figueras F, Coll O. *Comparison of cervical length and two biochemical markers to predict spontaneous preterm delivery in women admitted because of preterm labour before 34 weeks.* FIS of Spanish Ministry of Health; Abstract presented to the Department of Obstetrics and Gynecology, Hospital Clinic-IDIBAPS-University of Barcelona, Barcelona, Catalonia, Spain, 2007	Study conducted in Spain to compare the use of the Actim™ Partus test to that of the QuikCheck fFN® test. It is available only in abstract form.
Krupa FG, Faltin D, Cecatti JG, Surita FG, Souza JP. Predictors of preterm birth. *International Journal of Gynaecology & Obstetrics* 2006;94(1):5-11; Systematic review	It did not meet all of the criteria for a systematic review. It did not report on *ph*IGFBP-1 as a biochemical marker to aid in diagnosing PTL.
Vogel I. Biomarkers for the prediction of preterm delivery. *Acta Obstetricia et Gynecologica Scandinavica* 2005;84(6):516-25; Structured review	It did not meet all of the criteria for a systematic review. It did not report on *ph*IGFBP-1 as a biochemical marker to aid in diagnosing PTL.

Data extraction

Study profile information and outcome data were extracted from the selected studies by one reviewer (PC) using data extraction tabulated forms developed *a priori*:

- Study: author(s), year of publication, objective(s), setting, and duration.

- Study's and women's characteristics: sample size; inclusion and exclusion criteria; details of study protocol; women's characteristics (demographic characteristics); and baseline measurements (estimated gestational age and cervical dilation at testing).
- Interventions, outcomes: the rapid response tests used; other diagnostic interventions used; information on primary/secondary outcomes and outcome measures; and operator's information (professional background, training and experience for professionals who performed the tests: collected the specimens and/or analysed the specimens).
- Reported results of interest: diagnostic accuracy, clinical outcomes, safety, and costs.

Methodological quality assessment

No formal methodological quality assessment was conducted for the included studies because of the tight timelines.

APPENDIX C: RESULTS REPORTED BY PRIMARY RESEARCH STUDIES

Abbreviations

d - day(s)

EGA – estimated gestational age at testing

fFN – fetal fibronectin

g - grams

LR – likelihood ratio(s)

(LR+) - likelihood ratio for positive results (within 95% confidence interval)

(LR-) - likelihood ratio for positive results (within 95% confidence interval)

NICU – neonatal intensive care unit

NPV – negative predictive value

NS – not statistically significant

*ph*IGFBP-1 – phosphorylated insulin-like growth factor binding proteine-1

PPV – positive predictive value

PTB – preterm birth

PTD – preterm delivery

PTL – preterm labour

s –second(s)

Sn – sensitivity

Sp – specificity

SS – statistically significant

USA – United States of America

vs. - versus

wk – week(s)

Table C1: Primary research studies on the Actim™ Partus vs. the TLi$_{IQ}$® System for diagnosing PTL

Study	Study's and women's characteristics	Interventions and outcomes	Reported results
Ting et al. (2007)[47] **Objective(s):** to compare the clinical effectiveness of Actim™ Partus vs. the TLi$_{IQ}$® System in the prediction of PTD **Setting:** Maternal Fetal Medicine Department, Women's and Children's Hospital, Singapore **Duration:** Jan 2003 through Jan 2005 This project was funded through a Singhealth Research Grant.	**Sample:** 108 women recruited, but only 94 women had complete data for analysis **Inclusion:** women presenting with symptoms suggesting PTL between 24 wk and 34 wk, singleton gestation and intact membranes **Exclusion:** women with multiple gestation, PROM, cervical cerclage, cervical dilatation ≥3 cm, placenta previae, chorioamnionitis, intrauterine growth restriction of fetus, preeclampsia, suspected fetal asphyxia, or a major fetal anomaly **Protocol:** Before digital cervical exam, a speculum exam was performed: two dry Dacron swabs were placed at posterior fornix, adjacent to the cervix for 10s. Swabs were then removed, washed in the respective test reagent and analysed using fFN and *ph*IGFBP-1 bedside test kits. Results were qualitatively reported as either positive or negative. Managing obstetrician was blinded to results of both tests, and administered clinical care according to hospital clinical guidelines for PTL management. EGA calculated based on the last menstrual period and confirmed by first or early second trimester ultrasonography. **Women's characteristics:** NSS differences concerning maternal age, parity and gravidity between women with positive results of fFN and *ph*IGFBP-1 and those with negative results **Baseline measurements:** NSS differences concerning EGA between women with positive results of fFN and *ph*IGFBP-1 and those with negative results; SS difference in mean cervical dilatation (P <0.05)	**Intervention**: *ph*IGFBP-1 testing with Actim™ Partus test (Medix Biochemica, Finland) **Comparator:** fFN testing with QuikCheck fFN® (Adeza Biomedical, Sunnyvale, California, USA) **Other diagnostic interventions:** no other diagnostic interventions are mentioned **Outcome(s) and outcome measure(s):** gestational age at delivery, admission-to-delivery interval, mode of delivery, indication of delivery and baby status **Operator:** the fFN and phIGFBP-1 specimens were obtained and tested by specialist in obstetrics and gynecology, who also interpreted the fFN/ *ph*IGFBP-1 test results	**Diagnostic accuracy** Sn *ph*IGFBP-1: 100% (delivery within 48h), 69% (delivery <7d), 72% (delivery <14d) Sn fFN: 60% (delivery within 48h), 56% (delivery <7d), 61% (delivery <14d) Sp *ph*IGFBP-1: 74% (delivery within 48h), 78% (delivery <7d), 80% (delivery <14d) Sp fFN: 72% (delivery within 48h), 76% (delivery <7d), 78% (delivery <14d) PPV *ph*IGFBP-1: 18% (delivery within 48h), 39% (delivery <7d), 46% (delivery <14d) PPV fFN: 11% (delivery within 48h), 32% (delivery <7d), 39% (delivery <14d) NPV *ph*IGFBP-1: 100% (delivery within 48h), 92% (delivery <7d), 92% (delivery <14d) NPV fFN: 97% (delivery within 48h), 89% (delivery <7d), 89% (delivery <14d) **Clinical outcomes** Gestational age at delivery: 32.9 wk (±4.0) for positive *ph*IGFBP-1 (n = 28 women) and 37.4 wk (±1.8) for negative *ph*IGFBP-1 (n = 66 women) (P<0.001); 34.2 (±4.2) for positive fFN (n = 28 women) and 37.4 wk (±2.1) for negative fFN (n = 66 women) (P<0.001); Admission-to-delivery interval: 2.3 wk (±2.8) for positive *ph*IGFBP-1 (n = 28 women) and 5.1 wk (±3.2) for negative *ph*IGFBP-1 (n = 66 women) (P<0.001); 3.3 wk (±2.8) for positive fFN (n = 28 women) and 5.1 wk (±3.3) for negative fFN (n = 66 women) (P<0.002); **Safety:** no reporting on side effects, risks, or complications from performing the test itself **Cost:** no reporting on costs associated with adding the tests to the PTL management

Study	Study's and women's characteristics	Interventions and outcomes	Reported results
Eroglu et al. (2007)[37] **Objective(s):** to determine the predictive values of presence of fFN and *ph*IGFBP-1 in cervicovaginal secretions, and ultrasonographic measurement of cervical length for PTD<35 wk in the same patient population with regular premature uterine contractions **Setting:** Department of Obstetrics & Gynecology, Baskent University, Ankara, Turkey **Duration:** Feb 2004 to Feb 2006 Not clear who funded the study.	**Sample:** 51 symptomatic women admitted at antenatal ward, with history of regular uterine contractions (confirmed by tocodynamometry), regardless of cervical dilation **Inclusion:** women between 24 and 35 wk gestation with uterine contractions (>10/h) **Exclusion:** vaginal bleeding, confirmed rupture of membranes, multiple pregnancy, cervical dilatation ≥3 cm, placenta previa, abruptio placenta, intrauterine growth restriction, pre-eclampsia, congenital fetal abnormality, sexual intercourse within past 24h, or uterine anomalies **Protocol:** Before digital exam, specimen collection was performed: a swab was applied (10-15s) to posterior fornix for fFN testing and to external cervical os for *ph*IGFBP-1 testing. Then ultrasonographic examination was performed. Primary physician blinded for tests' results until delivery. Decision for hospitalisation made on frequency of uterine contractions or digital exam results. EGA based on last menstrual period confirmed by a 1st trimester or an early 2nd trimester ultrasonography. **Women's characteristics:** mean maternal age of 27.6 y, mean parity of 0.4, mean BMI of 22.6 kg/m^2, 3.9% with ≥2 spontaneous abortus, 3.9% with history of spontaneous PTD, 3.9% smoking, 20% with ≥12 y of education, 80% with <10 y of education **Baseline measurements:** mean EGA at enrolment of 29.5 wk; mean cervical dilation of 0.5 cm; NSS differences concerning EGA between women with positive results of fFN and *ph*IGFBP-1 and those with negative results; SS difference in mean cervical dilatation (*P* =0.008, P=0.003, respectively)	**Intervention:** *ph*IGFBP-1 testing with Actim™ Partus test (Medix, Biochemica, Finland) **Comparator:** fFN testing with QuikCheck fFN® (Adeza Biomedical, Sunnyvale, California, USA) and measurement of cervical length with transvaginal ultrasonography (Philips HDI 5000 Sono CT ultrasound machine) **Other diagnostic interventions:** low vaginal cultures for group B streptococcus and cervical cultures for gonococcus and Chlamydia **Outcome(s) and outcome measure(s):** primary outcome measure was delivery <35 wk' gestation; secondary outcome measure was delivery within 7 days from admission **Operator:** no information on who performed the tests (who collected and analysed the specimens); not clear whether the specimens were analysed in L&D or in a laboratory; no information on who interpreted the results	**Diagnostic accuracy** Sn *ph*IGFBP-1: 70% (delivery <35wk), 83.3% (delivery within 7d) Sn fFN: 70% (delivery <35wk), 83.3% (delivery within 7d) Sp *ph*IGFBP-1: 87.8% (delivery <35wk), 84.4% (delivery within 7d) Sp fFN: 82.9% (delivery <35wk), 80% (delivery within 7d) PPV *ph*IGFBP-1: 58.3% (delivery <35wk), 41.7% (delivery within 7d) PPV fFN: 50% (delivery <35wk), 97.4% (delivery within 7d) NPV *ph*IGFBP-1 1: 92.3% (delivery <35wk), 97.3% (delivery within 7d) NPV fFN: 91.9% (delivery <35wk), 83.3% (delivery within 7d) (LR+) *ph*IGFBP-1: 5.74 (2.3 – 15.8) (delivery <35wk), 5.36 (2.3 – 12.2) (delivery within 7d) (LR-) *ph*IGFBP-1: 0.34 (0.1- 0.7) (delivery <35wk), 0.20 (0.01 – 0.7) (delivery within 7d) (LR+) fFN: 4.10 (1.8 to 9.5) (delivery <35wk), 4.17 (1.9 – 8.5) (delivery within 7d) (LR-) fFN: 0.69 (0.1 – 0.8) (delivery <35wk), 0.21 (0.01 – 0.7) (delivery within 7d) **Clinical outcomes** Gestational age at birth: 32.8 wk (±3.7) for positive *ph*IGFBP-1 (n = 12 women) and 37.7 wk (±2.1) for negative *ph*IGFBP-1 (n = 39 women) (P=0.001); 33.7 wk (±4.1) for positive fFN (n =14 women) and 37.6 wk (±2.2) for negative fFN (n = 37 women) (P=0.003); Respiratory distress syndrome: 6 cases (50%) for positive *ph*IGFBP-1 (n = 12 women) and 3 cases ((7.7%) for negative *ph*IGFBP-1 (n = 39 women) (P=0.002); 6 cases (42.9%) for positive fFN (n = 14 women) and 3 cases (8.1%) for negative fFN (n = 37 women) (P=0.002); NICU: six cases (50%) for positive *ph*IGFBP-1 (n = 12 women) and three cases ((7.7%) for negative *ph*IGFBP-1 (n = 39 women) (P=0.002); six cases (42.9%) for positive fFN (n = 14 women) and three cases (8.1%) for negative fFN (n = 37 women) (P=0.002); Birthweight: 2, 255g (±847) for positive *ph*IGFBP-1 (n = 12 women) and 3,066g (±538) for negative *ph*IGFBP-1 (n = 39 women) (P=0.008); 2,395g (±856) for positive fFN (n =14 women) and 3,039g (±558) for negative fFN (n = 37 women) (P=0.018); **Safety:** no reporting on side effects, risks, or complications from performing the test itself **Cost:** no reporting on costs associated with adding the tests to the PTL management

REFERENCES

1. Corabian P, Harstall C. *The role of the rapid fetal fibronectin assay in the management of spontaneous preterm labour*. Institute of Health Economics, editor. Edmonton AB: Institute of Health Economics; 2007.
2. Farquarhson D, Lange I, MacDonald WA, Morin L, Simard F. *SOGC Special Report: Preterm Labour*. Society of Obstetricians and Gynaecologists of Canada; 2005.
3. British Columbia Reproductive Care Program. *Preterm labour*. British Columbia Reproductive Care Program, editor. Vancouver BC: 2005; Obstetric Guideline 2A.
4. Di Renzo GC, Roura LC. Guidelines for the management of spontaneous preterm labor. *Journal of Perinatal Medicine* 2006;34(5):359-66.
5. Zimmer M. Current principles of the diagnosis and treatment of preterm delivery. *Advances in Clinical and Experimental Medicine* 2007;16(1):155-64.
6. Lamont RF. Evidence-based labour ward guidelines for the diagnosis, management and treatment of spontaneous preterm labour. *Journal of Obstetrics and Gynaecology* 2003;23(5):469-78.
7. Ressel G. ACOG issues recommendations on assessment of risk factors for preterm birth. *American Family Physician* 2002;65(3):509-10.
8. Institute for Clinical Systems Improvement (ICSI). *Management of labour*. Bloomington MN: Institute for Clinical Systems Improvement (ICSI); 2005. Available at: file://E:\De printat\Diagnostic tests\ICSI_Management of labor.htm.
9. Management of Preterm Labor. *ACOG Practice Bulletin Clinical Management Guidelines for Obstetrician-Gynecologists* 2003;101(5):1039-47.
10. Reedy NJ. Born Too Soon: The Continuing Challenge of Preterm Labor and Birth in the United States. *Journal of Midwifery and Women's Health* 2007;52(3):281-90.
11. Chandiramani M. Preterm labour: Update on prediction and prevention strategies. *Current Opinion in Obstetrics and Gynecology* 2006;18(6):618-24.
12. Vogel I. Biomarkers for the prediction of preterm delivery. *Acta Obstetricia et Gynecologica Scandinavica* 2005;84(6):516-25.
13. Krupa FG, Faltin D, Cecatti JG, Surita FG, Souza JP. Predictors of preterm birth. *International Journal of Gynaecology & Obstetrics* 2006;94(1):5-11.
14. Herbst A, Nilsson C. Diagnosis of early preterm labour. *BJOG-An International Journal of Obstetrics and Gynaecology* 2006;113:60-7.
15. Lembet A, Eroglu D, Ergin T, Kuscu E, Zeyneloglu H, Batioglu S, et al. New rapid bed-side test to predict preterm delivery: phosphorylated insulin-like growth factor binding protein-1 in cervical secretions. *Acta Obstetricia et Gynecologica Scandinavica* 2002;81(8):706-12.

16. Kwek K, Khi C, Ting HS, Yeo GS. Evaluation of a bedside test for phosphorylated insulin-like growth factor binding protein-1 in preterm labour. *Annals of the Academy of Medicine, Singapore* 2004;33(6):780-3.

17. Elizur SE, Yinon Y, Epstein GS, Seidman DS, Schiff E, Sivan E. Insulin-like growth factor binding protein-1 detection in preterm labor: evaluation of a bedside test. *American Journal of Perinatology* 2005;22(6):305-9.

18. Akercan F, Kazandi M, Sendag F, Cirpan T, Mgoyi L, Terek MC, et al. Value of cervical phosphorylated insulinlike growth factor binding protein-1 in the prediction of preterm labor. *Journal of Reproductive Medicine* 2004;49(5):368-72.

19. Leitich H. Controversies in diagnosis of preterm labour. *BJOG-An International Journal of Obstetrics and Gynaecology* 2005;112:61-3.

20. Pereira L, Gravett MG. Identification of novel protein biomarkers of preterm birth in human cervical-vaginal fluid. *Journal of Proteome Research* 2007;6(4):1269-76.

21. Health Canada. *Canadian Perinatal Health Report, 2003*. Mnister of Public Works and Government Services Canada, editor. Ottawa, ON: Minister of Public Works and Government Services Canada; 2003.

22. Haram K, Mortensen JHS, Wollen AL. Preterm delivery: an overview. *Acta Obstetricia et Gynecologica Scandinavica* 2003;82(8):687-704.

23. Logghe H, Walker JJ. Towards improved neonatal outcome: future strategies. *Seminars in Fetal Neonatal Medicine* 2004;9(6):491-8.

24. Carson RJ. Detection and prevention of premature labour. *Neurological Endocrinology Letters* 2004;25 Suppl 1:35-41.

25. Thorlacius LS, Blakney G, Krahn J, Bamforth F, Higgins TN. Biochemistry testing associated with pregnancy and the newborn period - a lot has changed since you were a baby! *Clinical Chemistry* 2006;39:519-41.

26. McParland P. Preterm labour and prematurity. *Current Obstetrics and Gynaecology* 2004;14(5):309-19.

27. Carbonne B. Is it possible to improve diagnostic and prognostic criteria of preterm labour? *European Journal of Obstetrics, Gynecology & Reproductive Biology* 2004;117 Suppl 1:S6-S9.

28. Yeast JD, Lu G. Biochemical markers for the prediction of preterm labor. *Obstetrics and Gynecology Clinics of North America* 2005;32(3):369.

29. Resnik R. Issues in the management of preterm labor. *Journal of Obstetrics and Gynaecology Research* 2005;31(5):354-8.

30. Hagberg H. Preterm birth. *Quality Improvement in Perinatal Care* 2006;1-23.

31. Reproductive Health Report Working Group. *Alberta Reproductive Health: Pregnancies and Births 2004*. Alberta Health and Wellness, editor. Edmonton, AB: Alberta Health and Wellness; 2004.

32. Wen SW, Smith G, Yang Q, Walker M. Epidemiology of preterm birth and neonatal outcome. *Seminars in Fetal Neonatal Medicine* 2004;9(6):429-35.

33. Reproductive Health Report Working Group. *Alberta Reproductive Health: Pregnancies and Births 2005 Table Update*. Alberta Health and Wellness, editor. Edmonton, AB: Alberta Health and Wellness; 2005.

34. Goldenberg RL. Biochemical markers for the prediction of preterm birth. *American Journal of Obstetrics and Gynecology* 2005;192(5 SPEC. ISS.):S36-S46.

35. Wanke MI. *Review of rapid fetal fibronectin assay in the management of suspected preferm labour: synthesis report 06-01S*. Prepared for the Alberta Health Technologies Decision Process Edmonton AB, Alberta Health and Wellness, editor, 2006.

36. Abies AZ. Preterm labor: Diagnostic and therapeutic options are not all alike. *Journal of Family Practice* 2005;54(3):245-52.

37. Eroglu D, Yanik F, Oktem M, Zeyneloglu HB, Kuscu E. Prediction of preterm delivery among women with threatened preterm labor. *Gynecologic and Obstetric Investigation* 2007;64(2):109-16.

38. Turan OM, Turan S, Funai EF, Buhimschi IA, Copel JA, Buhimschi CS. Fetal adrenal gland volume - A novel method to identify women at risk for impending preterm birth. *Obstetrics and Gynecology* 2007;109(4):855-62.

39. Love-Gregory L. Assessing the pregnant patient: A review of new potential screening tests. *Laboratory Medicine* 2006;37(6):371-4.

40. Ugwumadu A, Yanamandra N, Hay P. A randomised controlled trial of metronidazole for the prevention of preterm birth in women positive for cervicovaginal fetal fibronectin: the PREMET study. *BJOG: An International Journal of Obstetrics & Gynaecology* 2006;113(7):851-2.

41. Adeza Biomedical Corporation. *Adeza Biomedical fetal fibronectinenzyme immunoassay and rapid fFN for the TLi iq System*. Sunnyvale CA: Adeza Biochemical; 2004.

42. Groom KM, Liu E, Allenby K. The impact of fetal fibronectin testing for women with symptoms of preterm labour in routine clinical practice within a New Zealand population. *Australian & New Zealand Journal of Obstetrics & Gynaecology* 2006;46(5):440-5.

43. Adeza Biomedical Corporation. *QuikCheck fFN*. Sunnyvale CA: Adeza Biomedical Corporation; 2003.

44. Adeza Biomedical Corporation. *Adeza TLi® iq System*. Sunnyvale CA: Adeza Biomedical Corporation; 2008.

45. Adeza Biomedical Corporation. *fFN Rapid fFN cassette kit*. Sunnyvale CA: Adeza Biomedical Corporation; 2004.

46. Lange I, Cooper S, Ross S, Wood S. Pilot assessment of a rapid phIGFBP-I assay for predicting preterm labour in symptomatic patients. *Partus Study Protocol* 2005;12 Aug 2005:1-11.

47. Ting HS, Chin PS, Yeo GS, Kwek K. Comparison of bedside test kits for prediction of preterm delivery: Phosphorylated insulin-like growth factor binding protein-1 (pIGFBP-1) test and fetal fibronectin test. *Annals Academy of Medicine Singapore* 2007;36(6):399-402.

48. Medix Biochemica. *Actim™ Partus, 2002.* Finland; Medix Biochemica.

49. Education Standing Committee. *Educational materials for the introduction of fetal fibronection testing*. Alberta Perinatal Health Program, editor. Edmonton, AB: Alberta Perinatal health Program; 2007.

50. Ross S. Pilot assessment of a rapid PHIGFBP-I assay for predicting preterm labour in symptomatic patients. *Journal of Obstetrics and Gynaecology Canada* 2007;S35-S36.

51. Armson BA, Dodds L, O'Connell C, Howlett A, Dooley K, McPhee A, et al. *Fetal fibronectin testing for suspected preterm labour in Nova Scotia.* Poster presentation, Halifax, Nova Scotia.

52. Farquharson D, Lee L, a Garg A. *Clinical utilization and cost saving analysis of fetal fibronectin assay in a tertiary care institution.* Poster Presentation, University of British Columbia, New Westminster BC.

53. Holfeld S, Brydon L, Carson GD. *Tertiary hospital experience using fetal fibronectin as a predictor of preterm delivery.* Presentation.

54. Abdulhafid A, Lange IR, Anderson K, Swaby C, Goodliff L. *Does fetal fibronection (fFN) reduce hospital costs in the management of preterm labour (PTL)?* Presentation. Department of Obstetrics & Gynaecology, University of Calgary/Calgary Health Region.

5. McDonald WA. *Management of suspected preterm labour in the Baffin Region of Nunavut utilizing the fetal fibronectin assay.* Presentation to Baffin Regional Hospital, Territory of Nunavut, Canada.

56. Abenhaim HA, Morin L, Benjamin A. Does availability of fetal firbonectin testing in the management of threatened preterm labour affect the utilization of hospital resources? *Journal of Obstetrics and Gynaecology Canada* 2005;27(7):689-94.

57. Skoll A, St Louis P, Amiri N, Delisle MF, Lalji S. The evaluation of the fetal fibronectin test for prediction of preterm delivery in symptomatic patients. *Journal of Obstetrics and Gynaecology Canada* 2006;28(3):206-13.

58. Gale J. *Advances in diagnosis and management of TPTL: experiences of a level 2+ centre with fetal fibronectin (fFN).* Presentation November 19, 2005 . 2005.

59. Turnell R, Liu K, Blakney G, Chari R. A direct comparison of fetal fibronectin (fFN) and PIGFBP-1 (ACTIM PARTUS) in the diagnosis of preterm labour (PTL) *Journal of Obstetrics and Gynaecology Canada* 2005;S17.

60. Forton S, Brunet S, Simoneau J, Audibert F. Prediction of preterm delivery: comparison of insulin-like growth factor binding protein (IGFBP-1), fetal fibronection and ultrasound cervical length. *Journal of the Society of Obstetrics and Gynaecology of Canada* 2007.

61. Larouche A, Simard F. Mesure de la fibronectine foetale et de l'IGFBP-1 chez les femmes gravides entre 20 et 34 semaines de grossesse, symptomatiques d'un travail pre-terme. *Ann Biol Clin Que* 2006;43(3):20.

62. Turnell RW, Liu K, Blakney G, Chari R. A direct comparison of fetal fibronectin [fFN] and plGFBP-1 [Actim™ Partus] in the diabnosis of preterm labour [PRL]. Slide Presentation to Society of Obstetricians and Gynaecologists of Canada Annual Meeting 2005.

63. Canadian Institute for Health Information (CIHI). *Giving birth in Canada. The costs*. Canadian Institute for Health Information (CIHI), editor. Ottawa ON: Canadian Institute for Health Information (CIHI); 2006.

64. St-Hilaire C. *Point-of-care testing in the private sector*. Agence d'evaluation des technologies et des modes d'intervention en sante (AETMIS), editor. Montreal, QC: AETMIS; 2008.

65. ECRI. Proteomics may rapidly identify women at risk for premature births from inflammation and infection. Available at: *mhtml:file://F:\my work\TNs\Lab tests for PTL\articles\ECRI_Proteomics_identify PTBs* 2005 Jan 28 (accessed 2008 Jan 11).

66. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Annals of Internal Medicine* 1997;126(5):376-80.

IHE HTA Product Line

Health Technology Assessment Reports are comprehensive qualitative or quantitative literature reviews that include an appraisal of the methodological quality of the included studies, with reference to relevant provincial statistics and, sometimes, a cost or economic analysis. Turnaround time: 6 months to 1 year.

Rapid Assessments are reports in which the methodology has been modified in one or more areas to shorten the turnaround time.

- ***Level 1 (QwikNote) –*** rapid responses that provide a listing of potentially relevant information, including study abstracts and references, based on a limited search of electronic databases.
  Turnaround time: 7 to 14 working days.
- ***Level 2 (TechNote)*** – short reports, based on a limited search of electronic databases, that summarize the published literature but do not provide an in-depth analysis of the data.
  Turnaround time: 1 to 3 months.
- ***Level 3 (CompNotes)*** – literature reviews that provide a qualitative or quantitative analysis of the data but do not formally appraise the methodological quality of the included studies.
  Turnaround time: 3 to 6 months.

Information Papers are reports that provide information on HTA topics with respect to methodological, policy, or administrative issues, but do not necessarily focus on published evidence. Turnaround time: varies according to topic.