

Current Perspectives on the Use of Fetal Fibronectin Testing in Preterm Labor Diagnosis and Management

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Preterm birth, defined as birth before 37 weeks of gestation, is a significant public health issue.^{1,2} Despite advances in obstetric care, approximately 1 in 10 infants is born preterm.² About 30% of preterm births are medically indicated or due to maternal or fetal diagnoses, such as preeclampsia and intrauterine fetal growth restriction.³ The remaining 70% are spontaneous preterm births, which are attributed to preterm premature rupture of membranes or spontaneous onset of preterm labor (PTL). Regardless of the cause of preterm birth, complications related to preterm delivery are responsible for more than one-third of infant mortality observed each year in the United States.² In addition to that significant neonatal death rate, the total annual medical cost associated with preterm birth within the United States, as shown by study results sponsored by the National Academy of Medicine, is estimated to be in excess of \$16.9 billion, or more than \$33,000 per preterm infant.⁴ In contrast, the average medical cost associated with a term birth is approximately \$3300 per live birth.⁵

Preterm birth is associated with a wide array of serious health problems and developmental disabilities, including respiratory issues, gastrointestinal complications, central nervous system problems, and long-term cognitive, motor, and behavioral delays.^{2,4} The rate of spontaneous preterm birth has decreased consistently over the past decade; however, in 2015, a slight increase in the number of infants born before 37 weeks of pregnancy was noted in the United States, indicating that preterm birth continues to be a major public health issue, substantiating the need for prevention and intervention.²

Identifying women with symptoms of PTL, who are at high risk for spontaneous preterm birth and most likely to benefit from treatment, provides an opportunity to utilize appropriate interventions to minimize the potential impact of preterm delivery. At the same time, accurately identifying women who present with symptoms of PTL, but who are at low risk for spontaneous preterm birth, can help reduce overtreatment and misuse of healthcare resources, along with the potential harm that may come with both. The importance of accurate spontaneous preterm birth risk assessment cannot be

ABSTRACT

One in 10 infants in the United States is delivered preterm (ie, before the 37th week of pregnancy), contributing to the significant burden on the national healthcare system. Nevertheless, a lack of agreement continues among obstetric professional societies on guidelines for standardization of the approach to the diagnosis and management of patients with symptoms of preterm labor (PTL). This disparity in consensus has likely resulted in poor identification of women at an increased risk for preterm birth (PTB). This paper presents an overview of several clinical guidelines and recommendations from a variety of studies regarding the use of fetal fibronectin (fFN) testing and transvaginal ultrasound (TVU) cervical length measurement, 2 tools that are used to assess the risk of spontaneous PTB (sPTB) in women with symptoms of PTL. We identify areas of commonality and discord within these publications. Although inconsistencies exist among the published guidelines, algorithms, and studies on how to diagnose and treat women with symptoms of PTL, each of them supports the use of fFN in conjunction with TVU for assessing the risk of sPTB. In addition, we review a case study from a regional hospital system with results demonstrating the benefits to patients and process outcomes when PTL assessment protocols are standardized, incorporating both fFN and TVU test results. In the absence of consensus on this topic, healthcare providers, administrators, and payers must navigate conflicting recommendations and identify areas of agreement for this evaluation within their own local settings.

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overstated. This paper examines several clinical guidelines, algorithms, and additional evidence from published studies regarding the assessment of women with symptoms of PTL and summarizes these recommendations in order to identify commonality on how to best utilize available tools for risk assessment of spontaneous preterm birth.

Unmet Need in Assessing Risk for Spontaneous Preterm Birth

Identifying which women are truly at risk for imminent spontaneous preterm birth is an immediate challenge that confronts any clinician evaluating women with symptoms of PTL. Numerous tools and methods are available to evaluate women with signs of PTL including: observation of clinical symptoms such as cramping, vaginal bleeding, and the frequency of uterine contractions; physical examination to assess cervical dilation; fetal monitoring and tocometry; assessment of cervical length by transvaginal ultrasound (TVU); and laboratory testing to detect the presence of fetal fibronectin (fFN). Despite the availability of these tools, accurately assessing risk for spontaneous preterm birth remains difficult.

The percentage of women admitted with a diagnosis of PTL who end up delivering at term varies widely between studies (15%-70%) and has been shown to vary by gestational age at presentation.⁶⁻⁹ For example, a systematic review found that among women diagnosed with PTL based on clinically observed criteria, more than 70% of these patients ultimately gave birth at term, illustrating that “the classic criteria for the diagnosis of PTL—regular uterine contractions with concomitant cervical change” has limited predictive value.⁹ Another study found that fewer than 10% of women who were given a clinical diagnosis of PTL gave birth within 7 days.¹⁰ Clearly, there is a demonstrated need to supplement the classic clinical examination with additional information to improve the assessment of risk for spontaneous preterm birth in this group of patients.

Although many women presenting with PTL symptoms deliver at term, it is critical to identify the subset of patients who are at greatest risk of preterm delivery. By identifying this high-risk cohort, patients may then be admitted for observation or transferred to a facility with an appropriate-level neonatal intensive care unit, and interventions to prevent spontaneous preterm birth may focus on those who are at greatest risk of delivering preterm. A recent study utilizing administrative claims data demonstrated that more than three-quarters of patients (75.9%) presenting either through an emergency department (ED) or labor and delivery (LD) setting at less than 37 weeks' gestation with symptoms of PTL were discharged; of those patients, 1 in 5 (20.1%) went on to deliver within the next 3 days.^{11,12} This analysis of real-world data suggests that patients at imminent risk of spontaneous preterm birth are not being effectively identified or properly managed, indicating a significant need to improve triage and assessment practices.

Despite the availability of a variety of diagnostic tools, it is unclear whether clinicians should use these tools in combination, sequentially, or independently.^{1,13-18} The lack of consensus on how to systematically assess risk for spontaneous preterm birth results in potentially inappropriate triage of women with symptoms of PTL, contributes to wide practice variation, and highlights the need for a standardized assessment protocol to ensure that all of the available diagnostic and assessment tools are used appropriately—to ensure that patients at low risk of spontaneous preterm birth are not being unnecessarily treated and that patients at high risk are being identified and treated properly.

Review of Clinical Guidelines, Algorithms, and Expert Opinion on the Use of fFN Testing to Assess Risk of Spontaneous Preterm Birth

In order to understand recommendations for assessing risk for spontaneous preterm birth in patients with symptoms of PTL, we reviewed several published guidelines from major obstetric societies, a variety of algorithms from published studies, and expert opinions available online, all of which detail the evaluation and management of these patients. In conducting this review, we found that there is agreement regarding the value of fFN testing, particularly when performed in conjunction with TVU for women with an equivocal cervical length (which varies by study).^{1,13-19}

fFN is an extracellular matrix glycoprotein that is produced by fetal cells and can be detected in cervicovaginal fluid (CVF).²⁰⁻²² Generally, fFN is detectable from early in gestation until early in the second trimester; it then decreases to undetectable levels in a pregnancy that is at low risk for preterm birth.²³⁻²⁵ The presence of fFN in CVF during or after the second trimester may indicate a disruption of the decidual-chorionic interface of the amniotic membrane and is associated with a significant increased risk of spontaneous preterm birth.^{20,21,26}

fFN testing is indicated by the FDA for use in risk assessment of spontaneous preterm birth within ≤ 7 or ≤ 14 days following cervicovaginal sample collection in patients with symptoms of PTL who are between 24 and 34 weeks of gestation with intact membranes and minimal cervical dilation (< 3 cm).²⁷ A lack of agreement, however, exists among professional organizations, published algorithms, and expert opinion as to the specific clinical characteristics of women for whom fFN testing should be used (Table).¹⁶

Over the past 2 decades, the American Congress of Obstetricians and Gynecologists (ACOG) has provided varied and somewhat conflicting guidance on the assessment of women presenting with symptoms of PTL. In its most recent practice bulletin (171; summarized in the Table), ACOG focuses primarily on the treatment and management of patients at risk of delivery within 7 days, rather than the identification of patients at risk for preterm delivery, and advises against using short cervical length or fFN testing alone in

TABLE. Guidelines, Algorithms, and Evidence-Based Expert Opinion for fFN testing and PTL Assessment

Source	Cervical Dilatation	Contraction Frequency	Effacement	Cervical Length	fFN Test With TVU ^a
Professional Society Guidance					
ACOG Practice Bulletin 171 ¹ (2016)	No guidance	No guidance	No guidance	No guidance	"The positive predictive value of a positive fetal fibronectin test result or a short cervix alone is poor and should not be used exclusively to direct management in the setting of acute symptoms"
ACOG Practice Bulletin 130 ²⁸ (2012)	No guidance	No guidance	No guidance	No guidance	Does not recommend fFN use for screening in asymptomatic women
SMFM ¹⁹	No guidance	No guidance	No guidance	20-29 mm	"fFN seems to be most helpful for women with a 'borderline' TVU CL of 20 to 29 mm"
Expert Opinion					
Lockwood 2017 ¹⁶ (UpToDate)	<3 cm	≥4 in 20 min or ≥8 in 60 min	No guidance	20-30 mm	Yes
Published Algorithms					
Rose 2010 ¹³	<2 cm	≥4 /hr	<80%	16-29 mm	Yes
Ness 2007 ¹⁴	≤3 cm	≥6 /hr	<100%	20-29 mm	Yes
Iams 2003 (clinical + sonography data equivocal) ¹⁵	≤2 cm	Regular contractions ^b	<80%	20-30 mm	Yes
Iams 2003 (clinical + sonography data in conflict) ¹⁵	<3 cm and has changed	Regular contractions ^b	<80%	<35 mm	Yes

ACOG indicates American Congress of Obstetricians and Gynecologists; CL, cervical length; fFN, fetal fibronectin; PTL, preterm labor; SMFM, Society for Maternal Fetal Medicine; TVU, transvaginal ultrasound.

^afFN testing recommended for reported cervical length

^bStates contraction frequency alone is insufficient to establish a diagnosis of PTL

the management of patients with symptoms of PTL.¹ However, in an earlier practice bulletin, from 2003, ACOG stated, "fFN testing may be useful in women with symptoms of PTL to identify those with negative values and a reduced risk of preterm birth, thereby avoiding unnecessary interventions."²⁸ Interestingly, Practice Bulletin 130, "Prediction and Prevention of Preterm Birth," recommends against the use of fFN testing in asymptomatic women, but never addresses its use in women with symptoms of PTL.²⁹ In contrast, the Society for Maternal Fetal Medicine (SMFM)¹⁹ supports fFN use in conjunction with TVU, stating, "fFN seems to be most helpful for women with a 'borderline' TVU CL (cervical length) of 20 to 29 mm." The recommendation from SMFM appears consistent with many other algorithms available in published studies on the topic (Table).

Recently, experts published an evidence-based standardized protocol for diagnosis of PTL.¹⁶ The algorithm (Figure¹⁶) recommends that fFN be used in women with a cervical length between 20 and 30 mm and cervical dilatation <3 cm, similar to an algorithm published by Ness et al in 2007.¹⁴ In addition to this protocol available online, other decision algorithms for the diagnosis and management of patients with symptoms of PTL exist.¹³⁻¹⁷ The diagnosis of PTL and subsequent treatment decisions in these algorithms are based on a combination of factors; they include gestational age, presence of uterine contractions, whether membranes are intact, cervical

dilatation, fFN testing status, and TVU measured cervical length (Figure).¹⁶ Given that no single marker has both high negative and positive predictive values for spontaneous preterm birth, the algorithms rely on multiple factors to guide treatment decisions.

Similar to the professional society recommendations, all of the algorithms examined here are consistent in their recommendations on the use of fFN testing in conjunction with TVU and with other clinical signs of PTL. The various algorithms differ in the specific parameters for using fFN in assessing risk for spontaneous preterm birth, and this variance primarily revolves around the cervical length measurement determined to indicate the need for fFN testing¹³⁻¹⁷ (Table). For example, the algorithm published by Rose et al recommends using fFN for women with a cervical length between 16 and 29 mm and cervical dilatation of ≤2 cm.¹³ In contrast, the Ohio State Algorithm by Iams et al recommends the use of fFN testing when the clinical and sonography data are equivocal (<2 cm dilatation and 20-30 mm cervical length) or in contrast (<3 cm dilatation, having changed by digital exam, and 35 mm cervical length measurement). Although the algorithms differ in the specific clinical characteristics of women who are candidates for fFN testing, they maintain a commonality regarding the utility of a standardized protocol-based approach, supporting the use of fFN testing coupled with TVU as the best diagnostic manner to evaluate a woman's

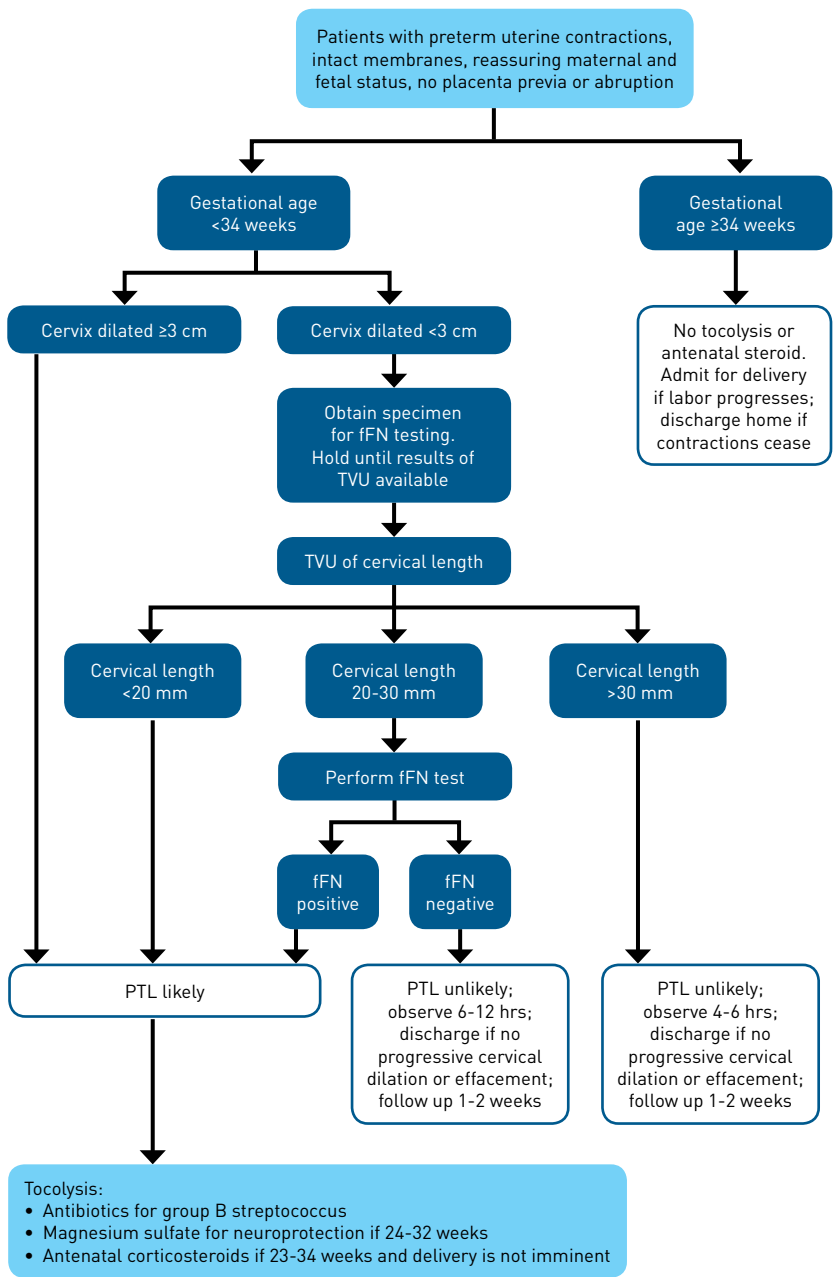
risk of spontaneous preterm birth when she presents with symptoms of PTL.

Review of Recent Studies on fFN Testing to Assess Risk of Preterm Birth

While multiple guidelines recommend the use of fFN testing under certain conditions, there remains a true lack of clear direction regarding when to use fFN testing in the diagnosis of PTL. This discrepancy may be due in part to the available medical literature presenting conflicting results regarding the utility of fFN testing.^{21,30-32} A detailed review of these studies reveals that the disparate results are largely due to inconsistent application of fFN testing, lack of adherence to standard protocols for management based on fFN results, and inappropriate use of the test to positively identify women at risk of spontaneous preterm birth. fFN testing is most valuable as a tool to help identify which women are at low risk for spontaneous preterm birth among those that present with symptoms of PTL. Unfortunately, much of the recent literature seeks to expand the use of fFN testing to identify which women will ultimately deliver preterm (at less than 37 weeks' gestation) as a primary outcome, an outcome the fFN test was not designed to assess under its FDA indications.^{14,20,21,26,27,33-36} Thus, the lack of strict adherence to diagnostic and treatment protocols, as well as the expansion of the use of fFN beyond its core assessment strength, has resulted in literature-based evidence that has confounded our understanding of the proper role of fFN testing. This likely has diminished use of this diagnostic tool in clinical settings.

Several randomized trials, and a recent meta-analysis collating them, report that fFN testing had a limited impact on reducing the spontaneous preterm birth rate, a major outcome of interest.^{31,32,37-39} Nonetheless, although the result of the meta-analysis was not statistically significant, the relative risk for spontaneous preterm birth at <37 weeks of gestation was 0.72 (95% CI, 0.52-1.01) when the fFN test was randomly used to assess patients with symptoms of PTL. This relative risk determination demonstrates a directionality toward favoring fFN testing, even for an outcome that is not its original indication, nor the primary strength of the

FIGURE. Up-To-Date Algorithm for Diagnosis and Management of PTL¹⁶



fFN indicates fetal fibronectin; PTL, preterm labor; TVU, transvaginal ultrasound. Adapted from reference 16.

fFN test. Ideally, this phenomenon, where use of fFN may lead to a reduction in spontaneous preterm birth, would be further borne out in additional randomized controlled studies. In addition, several studies included in the meta-analysis lacked clearly defined protocols for treatment of women who were identified as high risk and left treatment options to physician discretion in all

Case Study: Using a Standardized Algorithm for Preterm Labor Evaluation⁴⁴

The discord among national guidelines has resulted in confusion as to the best manner in which to utilize screening tools that are available to assess the risk of sPTB in patients with symptoms of PTL. Nevertheless, ACOG promotes practice standardization and the use of clinical guidelines¹ as a powerful method to improve patient outcomes, with numerous studies supporting this approach in patient care.^{13,41,42} Based on evidence in the literature that treatment algorithms can improve patient outcomes, researchers at the Upper Peninsula Health System in Marquette, Michigan (UPHS-M), implemented a standardized PTL evaluation algorithm based on a previously published March of Dimes Preterm Labor Assessment Toolkit (PLAT), with the hope of improving patient outcomes and process flow.⁴⁴

Pregnant women presenting to UPHS-M between November 2015 and November 2016 were evaluated and managed solely using the March of Dimes PLAT algorithm. Patients with intact membranes and cervical dilation <2 cm underwent testing for fFN; if patients tested positive for fFN and the TVUS finding was <25 mm, patients were triaged for further assessment. Otherwise, patients were discharged as long as they were clinically stable.

Compared with a cohort of patients seen at UPHS-M between January 2013 and October 2015 prior to implementation of the PLAT algorithm, the implementation of the standardized PTL evaluation protocol significantly reduced triage time (2.2-hour decrease; $P < .013$); among nontransfer patients, maternal hospital admissions decreased by 55% during the study.

This study's results illustrates the importance of the use of a standardized algorithm using both fFN testing and TVUS in the evaluation of patients with symptoms of PTL. When the PTL evaluation protocol was followed, improvements were not only noted in the efficiency of triage of these patients, but also in a decreased rate of unnecessary maternal hospital admissions to UPHS-M.

groups (fFN positive, fFN negative, and fFN result blinded), which may confound any of the results presented in these studies and the final results reported in the meta-analysis.³²

The lack of guidance for clinicians treating patients with symptoms of PTL could easily contribute to the variability in the outcomes in these studies. A recent study examining the use of fFN to triage women with symptoms of PTL found that "practitioners either ignored the fFN result[s] or did not clearly understand them."³⁸ The inherent advantage of using a standardized decision algorithm in any scenario is that it eliminates variability in management at the end of each arm in the evaluation and management pathways. Implementation of a standardized decision algorithm in future studies, in which clinician management is directed by the results of fFN testing in combination with TVU cervical length, could potentially minimize this variability and more accurately determine whether fFN testing leads to reduced rates of spontaneous preterm birth or other major outcomes of interest, such as improved neonatal outcomes.

Assessing Risk for Spontaneous Preterm Birth: Underutilization of fFN Testing

The lack of consensus on when to use fFN testing may impact the use of this tool, and 2 recent analyses of administrative claims data support a low utilization of fFN testing in obstetric care today.^{11,12,27} A recent retrospective claims analysis covering more than 23,000 women presenting with symptoms of PTL in LD settings across the United States found that fFN testing was performed in only 14%, while 21.5% underwent evaluation by TVU.^{11,12} The same study found that 20.1% of patients discharged from LD settings delivered within 3 days and only 4.2% of these women were evaluated by an fFN test. As described in the study by Barner et al,⁴⁰ a sizeable review of nearly 30,000 patients in the Texas Medicaid population found that of patients with 1 hospital or ED visit for symptoms of PTL, only 12% were evaluated with fFN testing.⁴⁰

Need for Standardized Protocols Incorporating fFN Testing

The aforementioned lack of clear consensus among published clinical guidelines and algorithms, as well as the heterogeneity of outcomes examined and reported in the literature, may contribute to the underutility of fFN testing as observed in real-world data. Consensus may be difficult to achieve, but consistent implementation of a standardized protocol alone has been previously demonstrated to positively influence patient care.^{14,41-43} Further support of standardization comes from a recently presented research project conducted in northern Michigan (see [Case Study](#)⁴⁴). In addition to improving outcomes for patients, implementation of standardized protocols can positively affect healthcare expenditures. For example, a study performed by Rose et al demonstrated that implementation of an evidence-based protocol for PTL assessment reduced the rate of

maternal hospital admission by 56% and resulted in an annual cost savings of \$39,900.¹³ In assessing a variety of published data, there appears to be a clear role for fFN in combination with TVU to assess, identify, and potentially appropriately intervene among patients with symptoms of PTL to determine those at high risk of spontaneous preterm birth.

Conclusions

Although the ability to diminish the progression of PTL is limited, evaluating patients with symptoms of PTL through the use of standardized protocols is critical so clinicians can deliver therapies to those patients at greatest risk of spontaneous preterm birth, thereby promoting fetal maturation and reducing the risk of adverse perinatal outcomes.^{1,35,36,45} Conversely, accurately triaging women who present with suspected PTL, but are actually at low risk for spontaneous preterm birth, may reduce the use of unnecessary interventions and the expense incurred with such treatment.^{13-16,27}

fFN testing has been shown to be effective in identifying patients at low and high risk of spontaneous preterm birth within 1 to 2 weeks in patients with symptoms of PTL.²⁷ The use of this test in standardized algorithms can reduce disposition times and hasten treatment decisions in situations where timely intervention is crucial to the unborn neonate.^{13,30,46-49} To date, there remains a lack of true consensus in our field around when fFN testing should be used in the diagnostic pathway and how it should be coupled with other tests, such as TVU cervical length measurement. This disparity creates inconsistent assessment pathways and causes confusion; it may also diminish the use of fFN testing because clinicians may be unsure when fFN testing is appropriate.

Ultimately, healthcare providers and institutions should look to areas of agreement within the data published on this topic and adopt a standardized approach to PTL assessment. Implementing standardized algorithms based on this evidence will help ensure that testing occurs at the appropriate point in the diagnostic pathway in order to optimize patient care and improve the identification and management of women at high risk of delivering preterm.^{44,50} Tools such as fFN testing, which improve outcomes and meaningfully guide decision making, should be incorporated into these clinical decision pathways. Clinicians should be encouraged to follow standardized algorithms in order to fully realize their potential to reduce the impact of PTL and spontaneous preterm birth on patients and the healthcare system. ■

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