HOLOGIC®

A Practical Guide for Preterm Labor Protocol Implementation

RapidfFN® for the TLi$_{IQ}$® System

Foreword

We see patients every day on labor and delivery triage with symptoms of preterm labor. Most of these patients will not progress and ultimately deliver at term. Although strides have been made in supportive care for babies born at <37 weeks' gestation, there is still a great need for better implementation of available tools to evaluate which patients with symptoms of preterm labor are most likely to deliver imminently and which can be discharged home and are likely to deliver at term.

Currently, practitioners have few tools to assess the risk of a patient delivering preterm. The Rapid fFN test (Hologic, Inc., Marlborough, MA, USA), which determines the presence of fetal fibronectin in cervicovaginal secretions for women with symptoms of preterm labor between gestational ages of 24 weeks, 0 days and 36 weeks, 6 days, has been in use for over 20 years for evaluating preterm birth risk. Since its approval, the Rapid fFN test has been shown in numerous peer-reviewed studies to reduce unnecessary admissions, maternal transfers, and length of stay and has been used to guide the appropriate timing of antenatal corticosteroids. Our goal as clinicians is to provide the best in care through the practice of evidence-based medicine. This includes using all the tools available to evaluate a patient with symptoms of preterm labor and decide the best treatment plan for her and her baby.

Inside the pages of this monograph are the experiences and opinions of recognized experts in the field of obstetrics and maternal-fetal medicine, along with in-depth reviews of the most up-to-date literature related to preterm labor assessment. The physician and nurse authors of these articles are paid consultants of Hologic, Inc., and editorial and financial support was provided to the authors by Hologic in connection with the development of their articles.

I hope you will take the time to read the information provided and incorporate these findings into your practice. We at Hologic are committed to our partnership with you, the women's healthcare provider, to ensure that you have the most well-established technologies and data to feel comfortable counseling and treating your patients with symptoms of preterm labor.

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The Need for Integrating Fetal Fibronectin Testing Into Standardized Preterm Labor Assessment

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Key Points

- Demographic or clinical risk factors are insufficient to predict the likelihood of preterm labor; thus, physicians should use physical and biochemical diagnostic tests.
- Transvaginal cervical length measurements and the results of a fetal fibronectin test are powerful predictive metrics that can be used to direct antenatal care.
- Standardized algorithms for the assessment and treatment of preterm labor should be created and universally implemented to improve neonatal outcomes.

Introduction

In the age of modern obstetrics, obstetricians have been plagued by 2 specific, high-risk disorders: preeclampsia and preterm labor (PTL). Although a large body of literature has been published on these topics, we are far from a clinical "cure" for either. The best we can do is temporize until we are no longer able and then hope the neonatal intensive care unit is able to provide any additional support required.

Although neonatal medicine has made great advancements and many centers are able to push the limits of viability to include fetuses who are ≥23 weeks' gestational age and >500 g with varying degrees of success,[1] the emotional, medical, and financial challenges could be better curtailed if there were more advanced planning and intervention. Prolongation of pregnancy by a month, a few weeks, days, and even hours can potentially make a difference in the neonatal outcome. Conversely, the use of overly aggressive treatment approaches arising from the inability to accurately diagnose PTL is not the best approach. Is there a way to identify women at the highest risk for PTL and hone a treatment plan for those cases? Is there testing that can complement our clinical evaluation? If we standardize the approach within and across institutions, we may begin to answer these questions and have an even larger and more global positive impact on neonatal outcomes.

Problem #1: Risk Factors Are Not Reliable Indicators

The first thing we notice in our patient's obstetric history are any risk factors for PTL, including African American race, age younger than 18 years or older than 35 years, low socioeconomic status, increased maternal stress, prior spontaneous preterm birth, multiple gestation, uterine anomaly, early vaginal bleeding, low pre-pregnancy weight, and/or behavioral tendencies (tobacco, substance use), among others (**Table 1**).[2] The problem is that approximately two-thirds of patients with traditional risk factors do not deliver preterm.[3] Additionally, half of patients who deliver preterm have no risk factors.[4] This underscores the concern that even the best clinicians will be unable to follow the appropriate patients in anticipation of a preterm delivery.

Table 1. Risk Factors for Preterm Labor[2]

Demographic Factors
• African American ethnicity
• Maternal age <18 or >35 years old
• Low socioeconomic status
• Maternal stress
• Behavioral patterns (i.e., tobacco or substance use)
Clinical Factors
• History of spontaneous preterm birth
• Multiple gestation
• Cervical insufficiency or Müllerian anomalies
• Vaginal bleeding
• Anemia
• Obesity or low body weight pre-pregnancy
• Infection

Risk factors adapted from the National Institute of Child Health and Human Development (NICHD).[2]

Problem #2: Clinical Assessment Is Not Sufficient for Predicting PTL

Traditional risk factors are not necessarily reliable for predicting which patients are likely to deliver preterm, so we should be prepared to act quickly once patients with symptoms of PTL arrive in triage or the emergency department. Historically, we would

use our clinical assessment combined with data from our patient's history (e.g., recent trauma, infection), physical examination (signs/symptoms of intra-amniotic infection or abruption and interval cervical change), monitoring (uterine contractions, fetal heart rate), and laboratory findings (complete blood count) to determine the level of clinical concern. If the patient is stable, she would be discharged. If she were to have any clinical concerns, she would be admitted and treated with antenatal therapy. Treatment with magnesium sulfate, betamethasone, and sometimes even antibiotics can be used,[5] but it is important to remember that such treatment may also expose the patient to unnecessary risks, including the potential for magnesium toxicity,[6] premature use of steroids for fetal lung maturity (as we no longer advocate repetitive dosing), and antibiotic resistance.[7] Additionally, the financial implications of prolonged hospital stays[8] may be too burdensome.

Problem #3: Other Methods of Evaluation Are Underused

What other tools do we have to assess true versus false PTL? Much has been written in the recent literature evaluating 2 specific modalities: a physical assessment using transvaginal cervical length and a biochemical assessment using fetal fibronectin (fFN).[9] Cervical length has been shown to be directly correlative; the longer the cervix, the less likely the patient will deliver preterm.[10] Ideally, the normal cervix should measure ≥2.5 cm, although some studies have associated cervical lengths as short as 1.5 cm with an intermediate risk of preterm delivery.[11] fFN is a glycoprotein that is found in very low levels in the cervicovaginal secretions after week 22 of gestation.[12] Unlike most tests in which we assess the positive predictive value of the result and answer the question, "What is the likelihood of X to occur if the test is positive?", the brilliance of the approach for Rapid fFN testing is that we evaluate the negative predictive value (NPV) and answer the question, "What is the likelihood that this patient will NOT deliver within the next two weeks if the test is negative?" Because the NPV for Rapid fFN is approximately 99%[13], the results allow healthcare providers to feel reassured that their symptomatic patients are unlikely to deliver within the next 7 days.[14] Moreover, a patient who is discharged on the basis of a negative Rapid fFN result can feel confident about being managed as an outpatient, remaining in a comfortable environment with her loved ones. She will also—at least temporarily—avoid exposure to mistimed steroids (that may need to be given at a later time) and to potentially harmful effects from tocolytic therapy. Finally, the ability to confidently discharge patients home may have many benefits in terms of reduced demands on physician time and healthcare resources, thus providing potential cost savings.

Recent data show that the use of either cervical length measurements or fFN increases predictive accuracy relative to clinical assessment alone.[9] Importantly, there is an additive benefit when cervical length and fFN are used together,[15] especially in patients whose cervical length is in the "gray" zone – not long enough to be reassuring and not short enough to cause worry that delivery is imminent. When women have normal cervical length and a negative Rapid fFN result, 98% will deliver at ≥35 weeks.[16] However, even a patient with a short cervical length and a positive Rapid fFN result will deliver at 37 weeks or later nearly 50% of the time.[9] The additive benefit of cervical length measurement and Rapid fFN testing offers the highest specificity and NPV, 96.8% and 98.9%, respectively, when used to predict short-term risk (i.e., delivery within 7 days), making it especially useful for determining acute intervention such as steroid therapy.[9] The number of patients needed to treat to prevent 1 case of respiratory distress syndrome is only 17 when fFN is positive, but it increases to 509 in instances of a negative fFN (**Figure 1**).[17] This further emphasizes the need for better predictive accuracy to more appropriately intervene with magnesium sulfate, tocolytic therapy, steroids, or patient transfer to a more advanced hospital.

Current data indicate that only 23% of women receive steroids in an optimal time frame (defined as exposure to antenatal corticosteroid [ACS] between 24 hours and 7 days before delivery), 34% receive them suboptimally, and 52% have questionably appropriate exposure to ACS in that they are exposed to ACS but deliver >35 weeks gestation,[18] suggesting that steroids are often administered unnecessarily. When fetuses receive steroids 15 to 21 days before delivery, they have a composite outcome morbidity rate (chronic lung disease, intraventricular hemorrhage, necrotizing enterocolitis, proven sepsis, and periventricular leukomalacia) almost 7 times greater than those receiving steroid therapy within the 0 to 7 days before delivery.[19] As we get essentially 1 chance to treat our patient, shouldn't we make it count?

Problem #4: There Is No Standardization

In the interest of optimizing patient care and maximizing outcomes with the least morbidity and mortality, we strive to treat as many patients who are truly high risk while avoiding unnecessary intervention in those who are not as high risk—an approach that applies in all areas of medicine, not just obstetrics

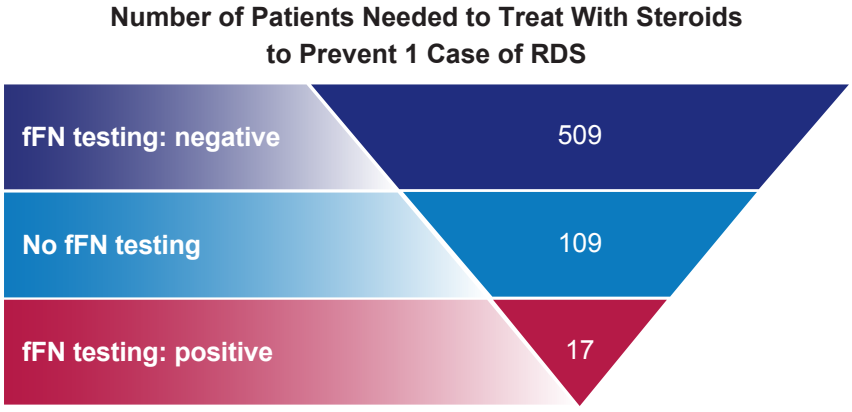

Figure 1. Number needed to treat with antenatal steroids at 31 weeks' gestation to prevent 1 case of neonatal respiratory distress syndrome associated with spontaneous preterm birth within 7–10 days of testing.[17] fFN=fetal fibronectin; RDS=respiratory distress syndrome.

and gynecology. Universal protocols across institutions and practices that manage similar clinical populations should lead to better overall outcomes. In a recent Committee Opinion, the American College of Obstetricians and Gynecologists (ACOG) stated that "protocols and checklists should be recognized as a guide to the management of a clinical situation or process of care that will apply to most patients" and "obstetrician gynecologists should be engaged in the process of developing guidelines and presenting data to help foster stakeholder buy-in and create consensus, thus improving adherence to guidelines and protocols."[20] Standardization of the management of PTL will allow better identification of high-risk patients who present to triage. Hospitals across all levels of care can then admit and manage women with the greatest risk for PTL, initiate timely and appropriate interventions, optimize maternal and fetal safety, effectively transport those in need to a higher level of fetal/neonatal acuity, and avoid unnecessary antenatal treatment. Although newer and larger studies are needed, the results we have from the past 5 to 10 years show that adopting a triage protocol that incorporates fFN testing with a zero tolerance policy for deviation from protocol decreases hospital admissions by 56%,[8] healthcare expenditures by nearly $40,000,[8] and average hospital stay from 5.2 to 0.6 days.[21] One of these same studies postulated that universal adoption of this protocol would save $560 million annually across the country.[8]

Closing Remarks

The climate of medicine is continuously changing. The latitude to manage patients based on a "gut feeling" without an evidence-based foundation is no longer accepted or acceptable. One can look at the glass as half empty and believe that professional recommendations hamstring one's ability to practice the "art of medicine." Alternatively, we can look at this as a way to fulfill our Hippocratic oath to "respect the hard-won scientific gains of those physicians in whose steps I walk" and "apply, for the benefit of the sick, all measures [that] are required, avoiding those twin traps of overtreatment and therapeutic nihilism."[22] It seems certain that PTL is still the leading cause of neonatal morbidity and mortality with a heterogeneous and complex etiology not amenable to a single diagnostic test. Along with other assessments, fFN can help manage decisions for symptomatic patients. It seems reasonable to achieve virtually 100% compliance with a reasonable and standardized triage protocol/algorithm.

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The Inconsistencies and Limitations of Cervical Length for Preterm Labor Assessment

Perinatal Associates of New Mexico is the largest provider of perinatal care in the state of New Mexico. With subspecialty training in maternal-fetal medicine, our practice cares for pregnant women with a variety of medical, surgical, and obstetric complications. With specific training in ultrasound for prenatal diagnosis, detection of fetal growth abnormalities, and cervical length evaluation, each patient seen in our office receives high-quality care. We hold ourselves to the highest standards in ultrasound performance, investing significant time and effort in annual renewal of our practice accreditation in ultrasound. Understanding the limitations of ultrasound, we also routinely implement fetal fibronectin testing to most accurately assess the risk of spontaneous preterm birth in patients with symptoms of labor.

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Key Points

- **Standardized protocols and techniques exist for obtaining quality transvaginal ultrasound (TVUS) images of the cervix and measuring the cervical length.**
- **Proper technical training on TVUS imaging and cervical length measurements is essential for use in clinical practice.**
- **A combination of tools, including fetal fibronectin testing and TVUS cervical length imaging, may accurately estimate the risk of preterm birth and direct the choice of subsequent maternal and fetal management.**

Overview of Preterm Labor Assessment

Preterm labor (PTL) is one of the most common reasons pregnant women are evaluated in the hospital. Nevertheless, correctly identifying women with preterm uterine contractions who will truly deliver preterm is an imprecise science.[1,2] Importantly, prior research demonstrates that of patients evaluated with symptoms of PTL, more than 50% will ultimately deliver at term.[3] Accurately triaging pregnant women at high risk for spontaneous preterm birth (sPTB) allows clinicians to provide these specific patients with interventions known to improve neonatal outcomes. Such interventions may include antenatal corticosteroids to reduce respiratory distress syndrome and other neonatal comorbidities, magnesium sulfate as a tocolytic with the goal of fetal neuroprotection, antibiotics for group B streptococcal prophylaxis, and maternal transfer to facilities with the appropriate level of neonatal intensive care.[1] Proper identification of women with symptoms of PTL who are considered at low risk to deliver preterm also benefits clinicians and patients, allowing them to avoid unnecessary maternal hospital admissions and costly medical interventions.[4] Traditionally, clinical signs and symptoms have been the cornerstone of PTL assessment, but they have proven to be nonspecific, subjective, and poorly predictive of sPTB.[1,2] Aside from clinical signs and symptoms, biochemical markers such as fetal fibronectin (fFN) and anatomic markers such as cervical length, as determined by transvaginal ultrasound (TVUS), have been used to enhance our ability to characterize the risk of sPTB in both asymptomatic and symptomatic patients.[5-7]

Utility of Transvaginal Cervical Length in Determining the Risk of Preterm Birth

One of the initial steps of labor is cervical effacement or shortening. Generally, the earlier cervical shortening occurs and the greater the degree of cervical shortening, the higher the risk of sPTB. TVUS provides the clinician with an objective evaluation of this physiologic change in pregnancy; thus, measurement of the cervical length has become an important clinical tool to identify women at risk of sPTB.[8] Typically, the cervical length is stable from 14 to 28 weeks' gestation,[9] with a mean measurement of approximately 35 and 34 mm at 24 and 28 weeks, respectively.[8] After 28 weeks, the cervical length gradually decreases.[9]

Understanding the normal distribution of cervical lengths across gestation, a cervical length of <25 mm is widely accepted as shortened relative to the 5th and 10th percentile of all cervical lengths.[8,10] Women with high-risk pregnancies and a cervical length <25 mm are at a higher risk of sPTB.[11] Furthermore, in a large cohort of pregnant women (N=2915, with both high- and low-risk pregnancies), the relative risk of preterm delivery with a cervical length of ≤22 mm at 24 weeks was 9.49 (95% CI, 5.95–15.15).[8] Based on much of these early data, substantive research has been performed to determine the utility of TVUS to measure the cervical length in patients with and without a history of sPTB.

For patients with symptoms of PTL, clinical evaluation, cervical length as measured by TVUS, and fFN testing have been proposed as diagnostic tools for evaluation of risk of preterm delivery. Clinically, it is important for physicians to have a tool with which to rule out PTL, and a negative

fFN test result, with a reported negative predictive value of 99.5% for delivery in ≤7 days, is a valuable predictive metric for ruling out patients in suspected PTL.[12] A substantial body of research supports the use of either fFN testing or cervical length evaluation by TVUS to predict and improve a variety of maternal and neonatal outcomes for patients who are symptomatic.[13-15] However, some have argued that the predictive accuracy of cervical length or fFN testing for sPTB in patients with symptoms of PTL is limited when either is used alone.[16-18] With this basis, the American College of Obstetrics and Gynecology states that a short cervix or positive fFN test result should not be used alone for management of patients with symptoms of PTL because of their poor positive predictive values.[1] Interestingly though, a large prospective cohort from the Netherlands demonstrated that cervical length measured by TVUS and fFN testing work best when used together, particularly when the cervical length is between 15 and 30 mm. The study detailed the potential for a substantial reduction in referrals and transfers to perinatal centers if fFN testing was used in conjunction with cervical length as compared with cervical length alone.[19]

Practical Considerations and the Importance of Training of Personnel for Performing Transvaginal Cervical Length Measurements

The diagnostic value of cervical length measurement depends on the quality of images collected, necessitating proper training and credentialing of individuals who perform the procedure.[20] Anatomic and technical challenges with the use of TVUS for cervical length measurement have been reported in early studies.[21,22] As such, the Society for Maternal and Fetal Medicine and the Perinatal Quality Foundation developed the Cervical Length Education and Review (CLEAR) program to help standardize the measurement of cervical length (**Table 1**).[23] Criteria include, but are not limited to, optimized field of view, correct imaging plane, proper placement of calipers, and consideration of cervical mobility.[23] Additionally, TVUS should be performed after emptying the maternal bladder because a full bladder may affect focal myometrial contraction development and image adequacy.[23,24] Despite the efforts of the CLEAR program and the Perinatal Quality Foundation, both of which have made imaging standards and online training available, 15% of study participants did not submit cervical images that met acceptable quality criteria in a recent voluntary study.[25] In an earlier study, more than 25% of images did not meet quality criteria.[26] This documented lack of adherence to recommended imaging guidelines by individuals performing TVUS cervical length measurements is a source of possible error in cervical length assessment in the actual clinical setting and may ultimately affect patient management.[26]

Unlike laboratory testing, TVUS is not subject to significant regulatory scrutiny by the US Food and Drug Administration under the current system of medical care and government oversight. This lack of oversight allows for a broad availability of TVUS, but also permits a significant amount of variability in performance of cervical length assessment, which undoubtedly affects patient care. Incorrect measurement of the cervical length could lead to excessive and unnecessary treatment for poorly measured shortened cervical lengths or could result in inadequate treatment of patients who truly have a short cervical length and are at great risk for preterm birth. Therefore, it is good practice to consider results of multiple diagnostic tests to determine the risk of preterm birth most accurately. Along with TVUS cervical length measurements, the measurement of fFN provides clinicians with an additional clinically validated and objective test to predict preterm birth.[27-29] Clinical evidence has demonstrated that the combination of cervical length measurement and fFN test results improves the likelihood of identifying symptomatic women at low risk for sPTB.[14,19,30]

Table 1. Cervical Length Education and Review Criteria for Image Acquisition and Quality

Cervical Length Education and Review (CLEAR)*
1. Measurements are taken from transvaginal images, not transabdominal.
2. The cervix occupies approximately 75% of the image.
3. Anterior and posterior cervix widths are equal.
4. The maternal bladder is empty.
5. The internal cervical os is visible.
6. The external cervical os is visible.
7. The entire length of the endocervical canal, extending between the internal and external os, is visible.
8. Calipers are placed correctly at the internal and external os and extend along the endocervical canal.
9. Cervix mobility is evaluated by applying fundal pressure to document funneling that may shorten the cervical length.

Comments

- If the cervix is curved, take 2 or more linear measurements and add them to obtain cervical length.
- Obtain 3 measurements fitting all criteria and use the shortest best measurement.
- Total exam time is 3–5 minutes.

*Adapted from Perinatal Quality Foundation. Cervix measurement criteria: measurement of the cervix. Perinatal Quality Foundation. Available at: https://clear.perinatalquality.org/Docs/image_criteria.pdf.

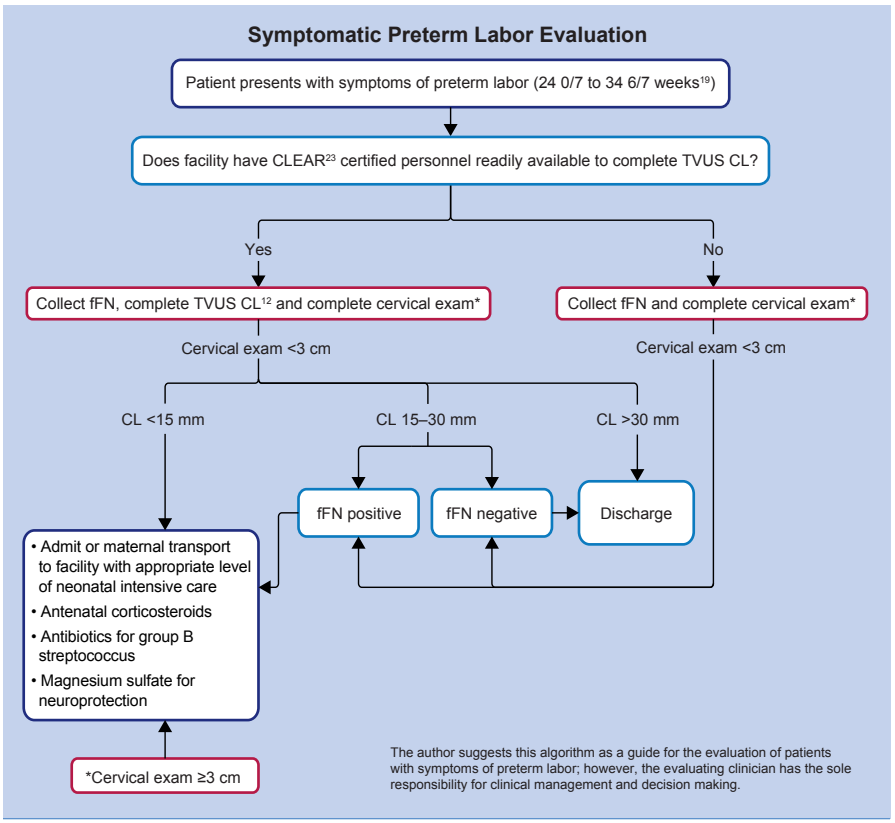

Figure 1. Algorithm for diagnosis and management of preterm labor. CL=cervical length; CLEAR=Cervical Length Education and Review program; fFN=fetal fibronectin; TVUS=transvaginal ultrasound.[12,19,23]

A "Gray Zone" for Cervical Length Measurements and Impact on Fetal Fibronectin Testing

Accurate measurement of cervical length becomes increasingly important considering the various definitions for a short cervical length in practice. DeFranco et al analyzed 9 clinical studies that investigated the combined use of cervical length and fFN testing to predict the outcomes of suspected preterm labor.[14] The criteria for short cervical length varied significantly, ranging from <15 to 31 mm across all studies, yet all definitions of a short cervix were combined to generate performance characteristics.[14] Currently available assessment algorithms for preterm labor also display inconsistent criteria for short cervical length.[4] For example, in one algorithm, it is recommended that patients with cervical lengths between 20 and 30 mm should be evaluated using fFN.[4] Other algorithms use wider ranges of cervical lengths to guide fFN testing, including cervical length measurements as short as 15 mm[19,31] (**Figure 1**) and 16 mm. Thus, these discrepant research definitions for the use of fFN in the assessment of patients with cervical lengths between 15 and 30 mm (ie, the "gray zone") do not provide any reliable direction for practicing clinicians. Ultimately, confusing research criteria and a lack of societal support creates inconsistent preterm labor evaluation pathways. This lack of society guidelines may diminish the use of fFN testing because providers may be uncertain when it is appropriate to use this test. Most recently, this phenomenon has been illustrated in an analysis of a national multipayer claims database. Among patients with symptoms of preterm labor, 12% had fFN testing completed before delivery. In this cohort, 75.9% were discharged home. Surprisingly, 20.1% of those discharged home delivered within 3 days from discharge. Of the group who delivered within 3 days after discharge, only 4.2% received fFN testing. The results of this study by Blackwell et al clearly demonstrate that the role of fFN testing in preterm labor management has not been universally adopted across the United States and highlights the need to address this disparity in patient care to improve patient outcomes (**Figure 2**).[32]

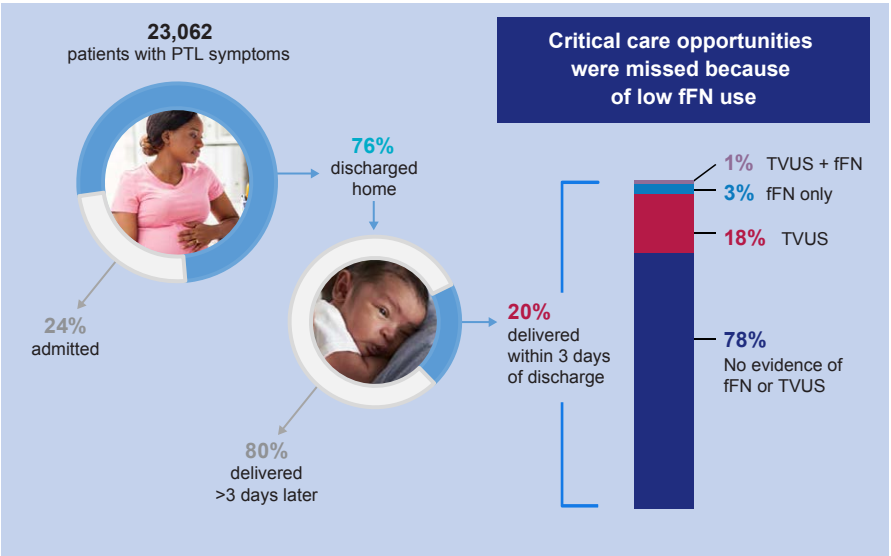

Figure 2. fFN testing is greatly underused in the clinical setting, suggesting substantial room for improvement in patient outcomes with more universal adoption of fFN testing in the management of PTL. fFN=fetal fibronectin; PTL=preterm labor; TVUS=transvaginal ultrasound cervical length measurement. Adapted from Blackwell SC, Sullivan EM, Petrilla AA, et al. Utilization of fetal fibronectin testing and pregnancy outcomes among women with symptoms of preterm labor. *ClinicoEconomics and Outcomes Research.* 2017;9:585-594 (Dove Medical Press Limited).

Conclusion

The clinician has a variety of tools to choose among when evaluating pregnant women with symptoms of PTL. Each of these tools has inherent benefits and limitations and varies in its predictive value for sPTB. Given the significant variation in measurements of cervical length using TVUS, this tool should be used only by individuals with specific training who can demonstrate their technical aptitude to proficiently acquire proper images. Ideally, images should undergo routine quality review. If TVUS or appropriately trained providers are not available at an institution evaluating women with symptoms of PTL, fFN testing can provide objective and reliable results.

Furthermore, when TVUS and properly trained providers are available, TVUS cervical length measurements and fFN testing should be used together (**Figure 1**) to provide the most accurate assessment of risk of sPTB in patients presenting with symptoms of PTL.

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Algorithms for Preterm Labor Assessment and Care

Ochsner Medical Center provides women with the highest quality of care and is ranked among the top 5% in the United States for women's health. Ochsner is proud to be the only Level 4 Labor and Delivery unit in the state of Louisiana supporting approximately 3400 births per year. Preterm birth is a major issue in our state. According to the most recent March of Dimes report card, Louisiana is 1 of 4 states with an "F" rating for preterm births. We have an average preterm birth rate of 12.6%, with the rate among black women being 50% higher than the rate among all other women. The safety of mothers and babies is paramount at Ochsner, and the talented group of dedicated professionals on staff works tirelessly to improve all aspects of perinatal treatment. In 2015, Ochsner had no early elective deliveries, a low primary cesarean delivery rate, and a low episiotomy rate.

Rajiv Gala, MD

Ochsner Baptist –
A Campus of Ochsner Medical Center
New Orleans, LA

Key Points

- The March of Dimes Preterm Labor Assessment Toolkit is no longer available, creating an unmet need for a standardized preterm labor algorithm.
- The predictive value of fetal fibronectin (fFN) tests, clinical symptoms, and transvaginal ultrasound cervical length measurements for assessment of preterm labor is highest when 2 or more criteria are combined.
- Use of fFN testing is directed by clinical criteria and/or cervical length measurements and helps dictate patient care in uncertain circumstances.

The Need for Standardized Preterm Labor Assessment and Care Pathways

Current technologies, such as fetal fibronectin (fFN)[1-3] and transvaginal ultrasound (TVUS) cervical length (CL) measurements,[3] have shown value in predicting preterm birth and guiding preterm labor management. For example, a systematic review of the literature demonstrated that combined fFN and CL as measured by TVUS can provide a predictive metric of higher value than either fFN or CL alone.[4,5] However, professional organizations such as the March of Dimes and the American College of Obstetricians and Gynecologists (ACOG) either lack current recommendations or do not provide strong guidance on standardized preterm labor assessment. ACOG has suggested that additional randomized clinical trials are needed to confirm the predictive utility of fFN and TVUS CL measurements[6]; in the meantime, the need remains for access to preterm labor algorithms that use the most current information to direct patient care.

Currently Available Clinical Algorithms for Preterm Labor Assessment and Care

With the Preterm Labor Assessment Toolkit no longer available from the March of Dimes, there is a need for standardized protocols that can be adopted by institutions that currently lack a procedure. Here, 4 evidence-based care pathways developed by the Mayo Clinic,[5] Ochsner Medical Center,[5] Dr. Michael Ruma, MD, MPH, of the Perinatal Associates of New Mexico, and a Southeastern hospital system are described. These algorithms delineate care to optimize management of women presenting with symptoms of preterm labor at ≤35 weeks' gestation. Focus within these protocols is on the use of fFN tests in combination with clinical criteria and/or TVUS CL measurements to guide patient care.

Algorithm Characteristics

When a woman who is ≤34 weeks pregnant presents with symptoms including uterine contractions, lower abdominal pain, cramping, or other relevant signs and symptoms, physicians should initiate patient care pathways. A generalized flow diagram that combines elements of all 4 care pathways is provided in **Figure 1**. Major components of each pathway are summarized in **Table 1** (for the individual algorithms, see **Appendix**). The first step in each care pathway is a cervical examination/sterile speculum examination (SSE) to determine cervical dilation, assess any rupture of membranes, and collect fFN samples; fFN specimens are stable for up to 8 hours at room temperature,[7] and there is no cost incurred for collection of untested samples. fFN collection by SSE must be performed before complete cervical examination to reduce the chance of false-positive results. When membranes are intact and the cervix is dilated <3 cm, the care pathways begin to differentiate based on the availability of technologies at a given facility. As an example, the Mayo Clinic algorithm recommends that TVUS and CL measurements be performed and used to guide the decision to evaluate fFN samples.[8] For facilities without access to TVUS, other algorithms (Ochsner and Southeastern) recommend evaluation of patient symptoms and cervical examination results to direct the use of fFN tests.[5]

Scenarios for Evaluating fFN Samples

Transvaginal ultrasound CL measurements and cervical dilation

help determine whether fFN samples collected initially will be processed. In the case of TVUS CL measurements ≥3 cm, the Mayo Clinic[5] and Perinatal Associates of New Mexico algorithms direct practitioners not to send fFN for evaluation, and patients are discharged. In patients with CL ≤1.5 cm (Mayo Clinic,[5] Perinatal Associates of New Mexico), fFN is not evaluated, and patients are considered for admission and antenatal treatments.

In patients with intermediate TVUS CL measurements, defined as <3 cm but >1.5 cm (Mayo Clinic,[5] Perinatal Associates of New Mexico), fFN samples are sent for evaluation to determine the appropriate clinical approach. Thus, a woman with intermediate TVUS CL and a positive fFN result is admitted and treated with antenatal therapies, whereas a woman with intermediate CL and a negative fFN result either remains in the hospital for further observation or is discharged.

As noted previously, the Ochsner and Southeastern algorithms recommend using clinical symptoms and cervical dilation as guides for use of fFN when TVUS is not available for measurement of CL. The clinical scenarios whereby fFN is not evaluated are when cervical dilation is absent or cervical dilation is <1 cm with resolving clinical symptoms, for which discharge is recommended; or when dilation is ≥3 cm, for which the patient is admitted.[5]

Consistent with the approach to intermediate TVUS CL measurements used in the algorithms from the Mayo Clinic and the Perinatal Associates of New Mexico, fFN testing is recommended by both the Ochsner and Southeastern algorithms when cervical dilation is at an intermediate measurement (either <3 cm[5] or >1 cm) and when clinical symptoms are persistent. For women with intermediate cervical dilation and a positive fFN test, both algorithms recommend admission to the hospital and initiation of antenatal therapy, whereas women with negative fFN results may be discharged from the hospital with preterm labor education.[5]

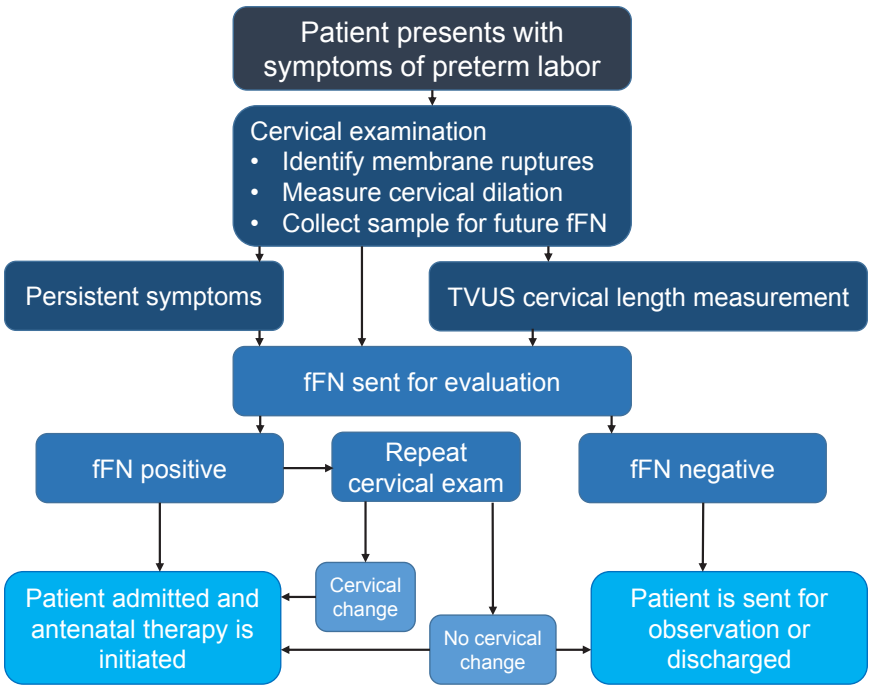

Figure 1. Generalized pathway based on 4 patient care algorithms. FN=fetal fibronectin; TVUS=transvaginal ultrasound.

Table 1. Summary of Key Pathway Characteristics*

Pathway	Cervical Exam Directs fFN	TVUS Directs fFN
Ochsner[5]	✓	X
Mayo Clinic[5]	X	✓
Ruma	✓/X	✓/X
Southeastern	✓	X

fFN=fetal fibronectin; TVUS=transvaginal ultrasound.

*All fFN specimens are obtained before cervical examination and/or TVUS; the decision to send the specimen to the laboratory for analysis is based on physical examination or TVUS results.

Conclusion

Standardization of preterm labor assessment and care can improve outcomes and is strongly recommended by ACOG; the American College of Nurse-Midwives; the Association of Women's Health, Obstetric and Neonatal Nurses; and the Society for Maternal-Fetal Medicine.[9-12] Despite the current lack of standardized protocols from ACOG and the March of Dimes, the 4 algorithms summarized here are regularly used in clinical practice; these pathways combine clinical symptoms, TVUS CL measurements, and fFN test results to guide patient care, providing much-needed guidance until standardized protocols are approved. In particular, fFN can be used in combination with either TVUS or clinical criteria/symptoms to assess the risk of preterm birth and appropriately manage care of women with preterm labor. Furthermore, fFN results can guide decisions for patient admission or discharge in cases of intermediate cervical examination or TVUS CL measurement results.

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Standardizing Preterm Labor Assessment at a Resource-Limited Regional Hospital

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The Upper Peninsula Health System-Marquette, a regional level-3 hospital with a neonatal intensive care unit and ~700 births per year, is staffed by clinicians covering a wide variety of specialties, such as family practice and board certified OB/GYN providers. The hospital is also a maternal transfer facility receiving patients from the entire Upper Peninsula region of Michigan.

Key Points

- Collected pre- and post-implementation data for transfer rate, time in triage, admissions, and obstetric outcomes
- Observed reduced transfers, time in triage, and admissions with no adverse outcomes
- Used fetal fibronectin (fFN) and transvaginal ultrasound to streamline patient assessment in triage
- Overcame objections that, because of the low positive predictive value, fFN is not useful for guiding clinical management

Background

The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine recommend that integrated, regional, risk-appropriate obstetric centers that are equipped to provide specialized care be available to pregnant women at high risk.[1] However, not all women with symptoms of imminent preterm birth deliver immediately or benefit from a maternal transfer.[2,3] Therefore, the decision for maternal transfer for preterm labor (PTL) needs to be based on standardized, evidence-based practice. A reduction in maternal transfers and costs has been observed following the implementation of fetal fibronectin (fFN) testing for assessing the risk of PTL.[4,5] Furthermore, a systematic review indicated that fFN testing has utility in identifying women unlikely to proceed to PTL, thereby potentially avoiding unnecessary interventions and reducing healthcare resource use.[6]

The Need for Standardization of Preterm Labor Assessment

Our goal of implementing standardized care was to reduce unnecessary maternal admissions and associated costs and to improve patient outcomes. A key impetus for undertaking the initiative of standardizing PTL assessment was the great degree of variability in clinical practices across facilities transferring patients to our hospital. Examples of heterogeneities include not obtaining fFN samples, insufficient intravenous (IV) catheter size or no IV, initiation of tocolytic therapy before transfer in the absence of testing for PTL, and performance of vaginal exam before transfer, which precludes collection of a sample for fFN testing upon arrival following transfer. Such variations in clinical practice can result in suboptimal obstetric outcomes. By adopting a standardized evidence-based PTL assessment protocol, we aimed to bridge the gap in obstetric care across the region and ensure consistency of practice.

A precedent for improvements in outcomes following implementation of standardized care can be found at the Mayo Clinic (Rochester, MN), where a standardized protocol combining fFN and cervical length was used for triage of women with symptoms of PTL. Adoption of the protocol was associated with a 56% reduction in hospital admissions and consequent cost savings.[7]

Implementation of a Standardized Preterm Labor Assessment Algorithm

To effectively implement a change in clinical practice, it was crucial to identify a champion for the cause and provide evidence on which to base the need for change. The team involved in this initiative included a nurse champion, a representative from Hologic, Inc. (Marlborough, MA), and 2 clinicians (one each from obstetric gynecology and family medicine practices). We educated residents, providers, and nursing staff to emphasize the importance and benefits of standardizing protocols to achieve the goal of improving perinatal outcomes.

We followed the March of Dimes Preterm Labor Assessment Toolkit (PLAT) and tailored it to fit the needs of hospitals that have no obstetrics units. The toolkit contains an algorithm and an order set. With the assistance of the information technology department, we changed the laboratory order set so that it aligned with the PLAT recommendations, which include risk assessment via transvaginal ultrasound and fFN testing.[8] Additionally, we met

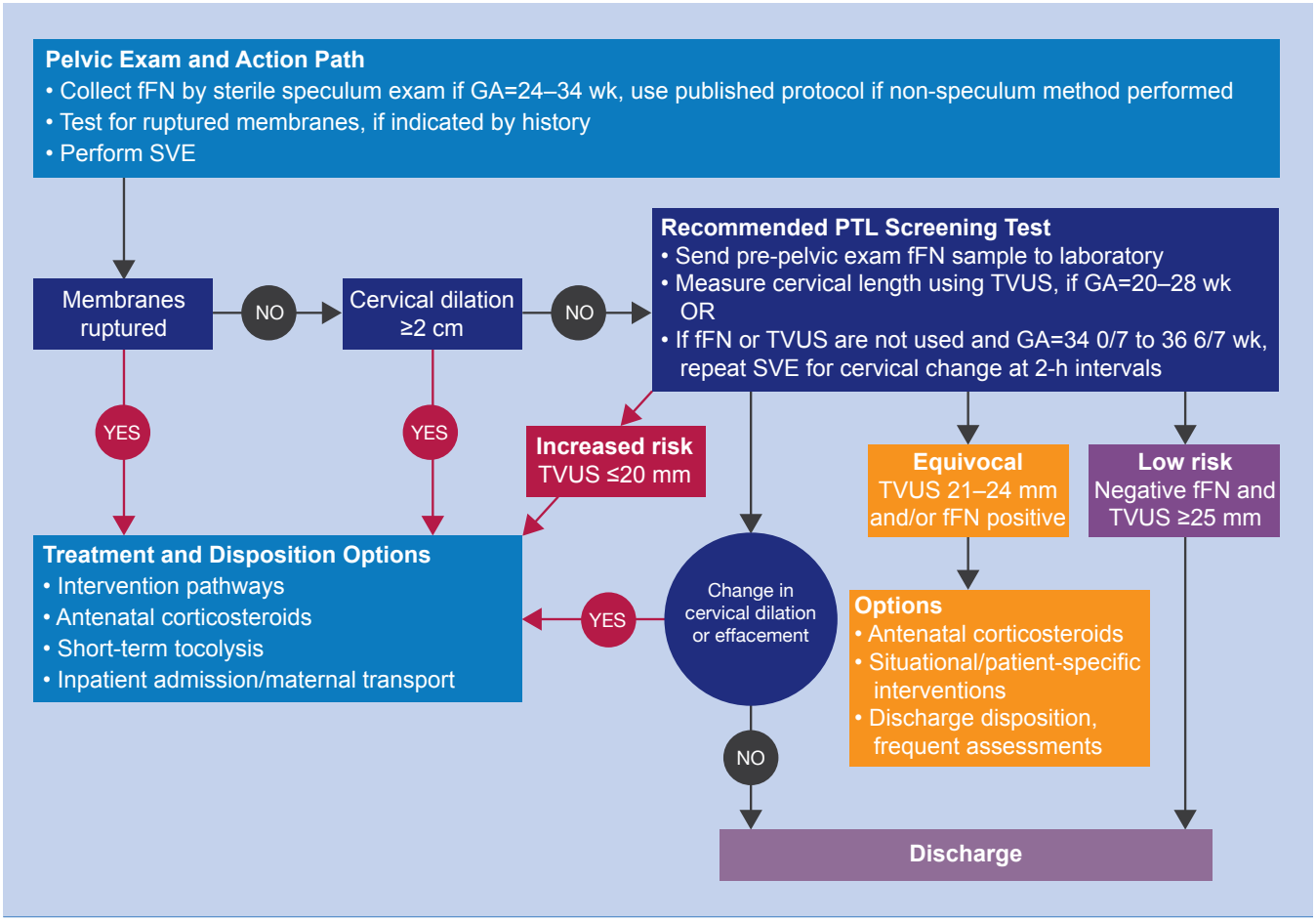

Figure 1. Preterm labor disposition decision algorithm. Adapted from the March of Dimes Preterm Labor Assessment Toolkit.[8] fFN=fetal fibronectin; GA=gestational age; PTL=preterm labor; SVE=sterile vaginal exam; TVUS=transvaginal ultrasound.

with the laboratory director and quality control personnel to ensure availability of the analyzer for a reasonable fFN test turnaround time of ~1 hour.

The protocol was available in electronic and print versions (**Figure 1**).[8]

Printed versions of the protocol were posted in provider offices and meeting rooms. Efforts to encourage adoption of the standardized protocol included lunch and dinner lectures with internal healthcare providers and in-service training for external providers. The providers and nursing staff were educated on the correct procedures for speculum exams. Additionally, specific steps in the protocol were emphasized, particularly the need to collect the fFN sample before any vaginal exam.

Although it was challenging to convince the physicians to adopt the new standardized protocol, communication of pre-implementation outcomes data from our facility were effective to demonstrate the need for improvement and drive changes to the clinical practice. The nursing champion primarily took responsibility for spearheading the efforts for standardization.

Outcomes Demonstrating Effective Implementation

To demonstrate the effectiveness of using a standardized protocol, we compared pre- and post-implementation patient data using preset criteria, including codes for threatened PTL and gestational age 24 to 36.6 weeks. Pair-wise comparisons of time to discharge from triage, maternal admission rate, and time to delivery from evaluation were performed using Tukey's multiple comparison test.

Data from 90 pregnant women admitted to the hospital before implementation of the standardized protocol were compared with a cohort of 91 women post-implementation. Eleven women in the pre-implementation group and 0 in the post-implementation group delivered preterm. Following implementation of the protocol, the average time in triage decreased by nearly half, from 4.5 hours to 2.6 hours, resulting in a savings of ~$340,000 in triage costs. Compared with pre-implementation, maternal hospital admissions were reduced by 78% (9 vs 2 patients, excluding transfer patients). This was associated with a savings of ~$150,000 in admissions costs.

Results also demonstrated an increase in the number of speculum exams after implementation of standardized PTL assessment. Sample collections for fFN testing and cervical length measurements nearly doubled (**Figure 2**). Additionally, implementation of the standardized protocol reduced variation in practice and allowed physicians to defer interventions to only those in true preterm labor, thus decreasing the overall use of tocolytics.

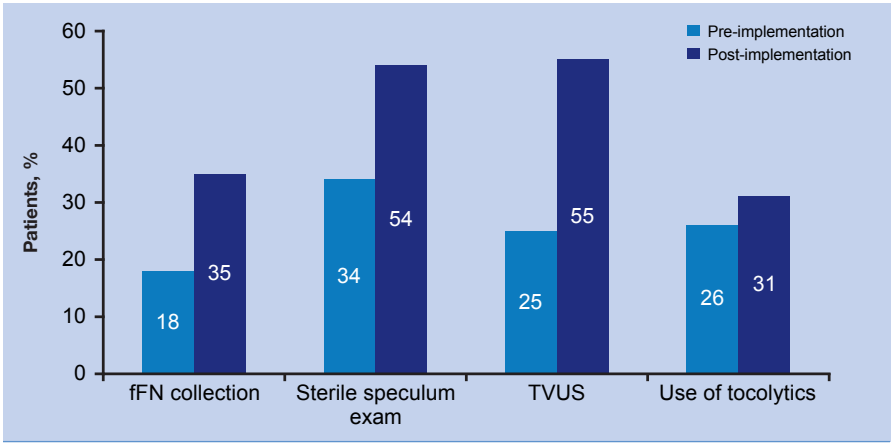

Figure 2. Improved outcomes following implementation of standardized PTL assessment. fFN=fetal fibronectin; PTL=preterm labor; TVUS=transvaginal ultrasound.

Summary

In a resource-limited hospital, through the concerted efforts of a nursing champion, a representative of Hologic, and clinicians, we were able to effectively implement a standardized protocol for PTL assessment, which translated into improved obstetric outcomes and cost savings for our facility. Adoption of an evidence-based standardized protocol led to a reduction in triage times and unnecessary interventions for women not truly in PTL. Our experience can serve as an example to other hospitals wanting to undertake standardization of their PTL assessment as a quality improvement initiative with the added benefit of also driving cost savings.

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Implementing a Standardized Preterm Labor Assessment Protocol: Effective Collaboration Within a Multidisciplinary Team at WellStar

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WellStar Kennestone Regional Medical Center (Marietta, GA) is a large, suburban hospital that performs ~6000 deliveries per year and has a level 3 neonatal intensive care unit. Patient safety is the key goal, along with striving to identify and implement evidence-based clinical practice to improve patient outcomes.

Key Points

- Used a standardized, evidence-based protocol for preterm labor assessment (real-world implementation, including timeline and milestones) and created lab orders that integrated fetal fibronectin testing
- Identified key leaders within the physician and nursing staff for implementation
  - Physician champion helped address variances in clinical practice and communicate the need for standardized assessment
  - Clinical nurse specialist spearheaded the performance improvement project and motivated the team
- Collected metrics pre- and post-implementation to show value (eg cost savings, decreased time in triage, decreased admissions)
- Overcame objections surrounding the complexity of implementing a standardized assessment in a large hospital setting

The Challenge of Accurately Identifying Preterm Labor

Accurate identification of women at increased risk of imminent preterm birth continues to be a challenge that is further compounded by wide variation in clinical practices employed to evaluate and manage preterm labor (PTL).[1] The March of Dimes Foundation emphasizes the need to standardize PTL assessment to improve maternal-fetal outcomes and, until recently, has made available the Preterm Labor Assessment Toolkit (PLAT), a step-by-step guide to help healthcare providers and hospitals facilitate implementation of a standardized protocol for identifying women in PTL.[2] The most recent iteration of the March of Dimes PLAT is currently under revision; however, the components of the toolkit are similar to widely used algorithms and order sets used at hospital systems across the United States and rely on standardization of PTL assessment using a combination of fetal fibronectin (fFN) and transvaginal ultrasound (TVUS). The American College of Obstetricians and Gynecologists (ACOG) strongly encourages the standardization of practice to improve outcomes and advises that protocols and checklists can reduce patient harm.[3] Furthermore, ACOG recommends that the development of protocols be a collaborative, inclusive, and multidisciplinary process. By providing clear guidelines for triage, implementing standardized nursing protocols, and updating organizational policies, healthcare systems have the opportunity to reduce patient harm and improve maternal health outcomes.

The WellStar Experience in Standardizing PTL Assessment

Described here is an experience in using the March of Dimes PLAT to implement a standardized evidennce-based protocol for PTL assessment. This system-wide initiative stemmed from the need to improve maternal outcomes, reduce the rate of preterm birth, and curtail unnecessary healthcare expenditures. In 2015, the Atlanta, Georgia, area received an F grade for preterm birth rate (≥11.5%) in the March of Dimes report card.[4] As an institution committed to providing a high standard of care, WellStar welcomed the opportunity to implement standardized PTL assessment as part of an evidence-based approach to clinical practice.

WellStar implemented a shorter version of the March of Dimes algorithm, which was embedded into the institutional policy, thereby also aligning with the Joint Commission requirement that the protocol be embedded into the policy and readily available.

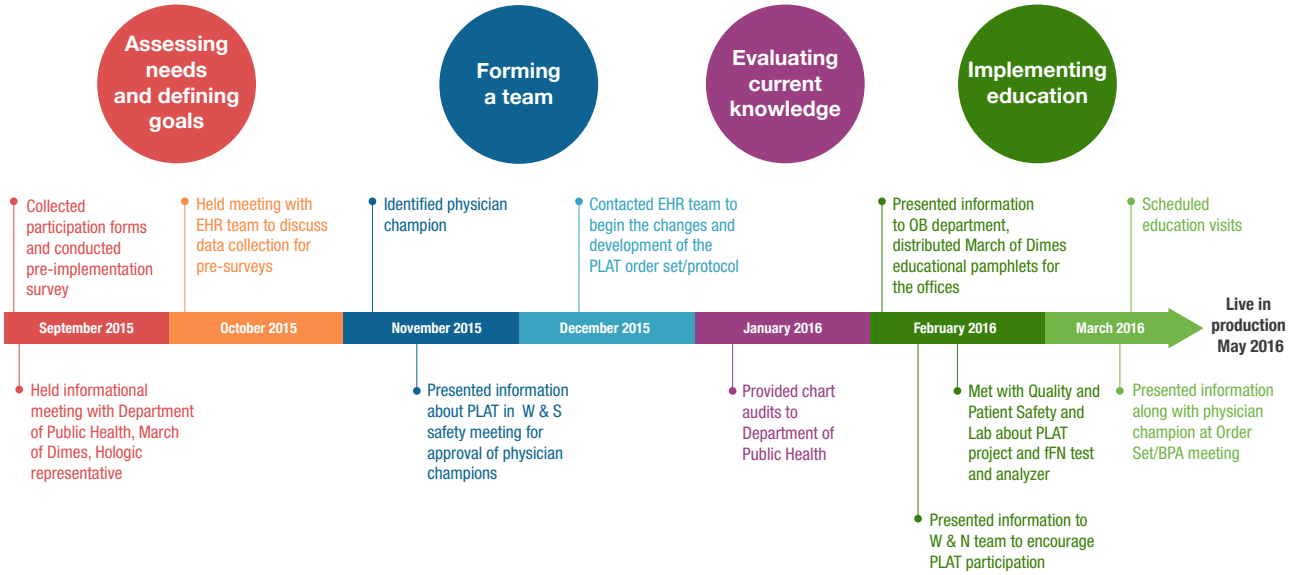

Figure 1. Timeline for PLAT implementation championed by the clinical nurse specialist. BPA=best practice advisory; EHR=electronic health record; OB=obstetrics; PLAT=March of Dimes Preterm Labor Assessment Toolkit; W & N=Women's and Newborn Committee, W & S=Women's Quality and Safety Committee

Initiating a system-wide change in clinical practice for a large healthcare facility can be challenging. Both preparation and implementation need to be collaborative, involving participants from multidisciplinary teams for successful implementation. The multistep process involved in preparing for standardization of PTL assessment began with a needs assessment to identify the scope of the problem and define goals. A schematic timeline for implementation is shown in **Figure 1**.

The process involved a multidisciplinary team that included a physician champion, a clinical nurse specialist, triage nurses, the Department of Public Health, and a representative from Hologic, Inc. (Marlborough, MA). Because credible data drive behavior change, we collected data on triage times, disposition times, wait times, PTL rates, and costs before beginning implementation of a standardized PTL assessment process. These data were provided to the team to underscore the need for improvement, explain outcome goals, and facilitate a change in clinical practice. A physician champion committed to improving health outcomes was identified. In addition to communication with other hospital staff, the physician champion assisted with developing the PTL assessment order set. A laboratory panel was created, which consisted of fFN, urine culture, culture for Group B streptococci with susceptibility, and microscopic urinalysis (**Figure 2**). The PTL assessment protocol was available in an electronic format and was also posted in the triage areas.

The clinical nurse specialist spearheaded the process by providing updates, education, data, and results to the team. To encourage participation, staff education and departmental presentations by a clinical nurse specialist and an educator were scheduled. Additionally, educational pamphlets for both patients and providers were distributed to clinicians for their offices. A representative from Hologic provided patient education brochures and presented guidance about practical and logistic aspects of the fFN test. For instance, the staff found it helpful to know that the sample

PLAT – Preterm Labor Assessment

☑ (PLAT) Preterm Labor Assessment Panel
Urinalysis w/microscopic, automated
Once First occurrence Today at 1911
Antepartum, Sign & Hold

And
Urine Culture, Clean Catch
STAT First occurrence Today at 1911
Antepartum, Sign & Hold

And
POC AmniSure
STAT, Once First occurrence Today at 1911
Antepartum, Sign & Hold

And
Culture, Group B Strep w/susceptibility
STAT First occurrence Today at 1911
Antepartum, Sign & Hold

And
Fetal Fibronectin
Once First occurrence Today at 1911
Obtain before vaginal exam **Obtain if patient is between 24.0 and 34.0 weeks' gestation without vaginal bleeding, ROM, or intercourse in the last 24 hours**, Antepartum, Sign & Hold

Figure 2. PLAT laboratory test order set. The 5 tests listed are pre-selected. PLAT=March of Dimes Preterm Labor Assessment Toolkit.

collection kits are free and that, once collected, a sample can be stored at room temperature for 8 hours to allow for completion of other diagnostic tests, such as TVUS.[5]

Postimplementation Outcomes

Outcomes data after the implementation of standardized PTL assessment were collected to evaluate the effectiveness of the protocol. Implementation of a standardized protocol decreased disposition time by 20 to 40 minutes per patient in the triage areas. It also translated into effective disposition decisions, with timely and appropriate administration of antenatal corticosteroids and tocolytics per ACOG guidelines. The rate of fFN testing increased from 51.7% pre-implementation to 94.5% post-implementation. Successful implementation of standardized PTL assessment resulted in cost savings of $264,637 to the WellStar Kennestone Regional Medical Center, attributable to the reduction in admissions for false labor, avoidance of unnecessary interventions, and decreased requirements for nursing care hours. Finally, based on recent March of Dimes statistics, successful implementation of a standardized protocol correlated with an improvement in premature birth rate for the county (Cobb County) from grade F to C.[6]

Challenges

WellStar faced a number of challenges when preparing for and implementing the standardized PTL assessment protocol. Given the large size of our facility, there was a need to employ multiple channels of communication to disseminate information on the new standardized process across multidisciplinary teams. Additionally, wide variation in clinical practice is an area of vulnerability for a large hospital. Having a dedicated physician champion to communicate the rationale and the goals of the standardization process was pivotal. Of note, 1 challenge that WellStar faced with collection of outcomes data was use of the triage sign-in book to collect data on triage times manually. Recent improvements in the system-wide use of electronic records will enable more efficient data collection in the future.

Summary

Adoption of a standardized, evidence-based protocol for PTL assessment facilitates management of PTL by evidence-based approaches to clinical decision making. A multidisciplinary team approach, including the involvement of physician or nurse champion, has been crucial in enabling the implementation of evidence-based standardized PTL assessment at WellStar. Successful implementation resulted in improved PTL outcomes and reduced healthcare costs. The process and protocol followed at WellStar can serve as a model for other healthcare systems in standardization of their PTL clinical management pathways.

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Appendix

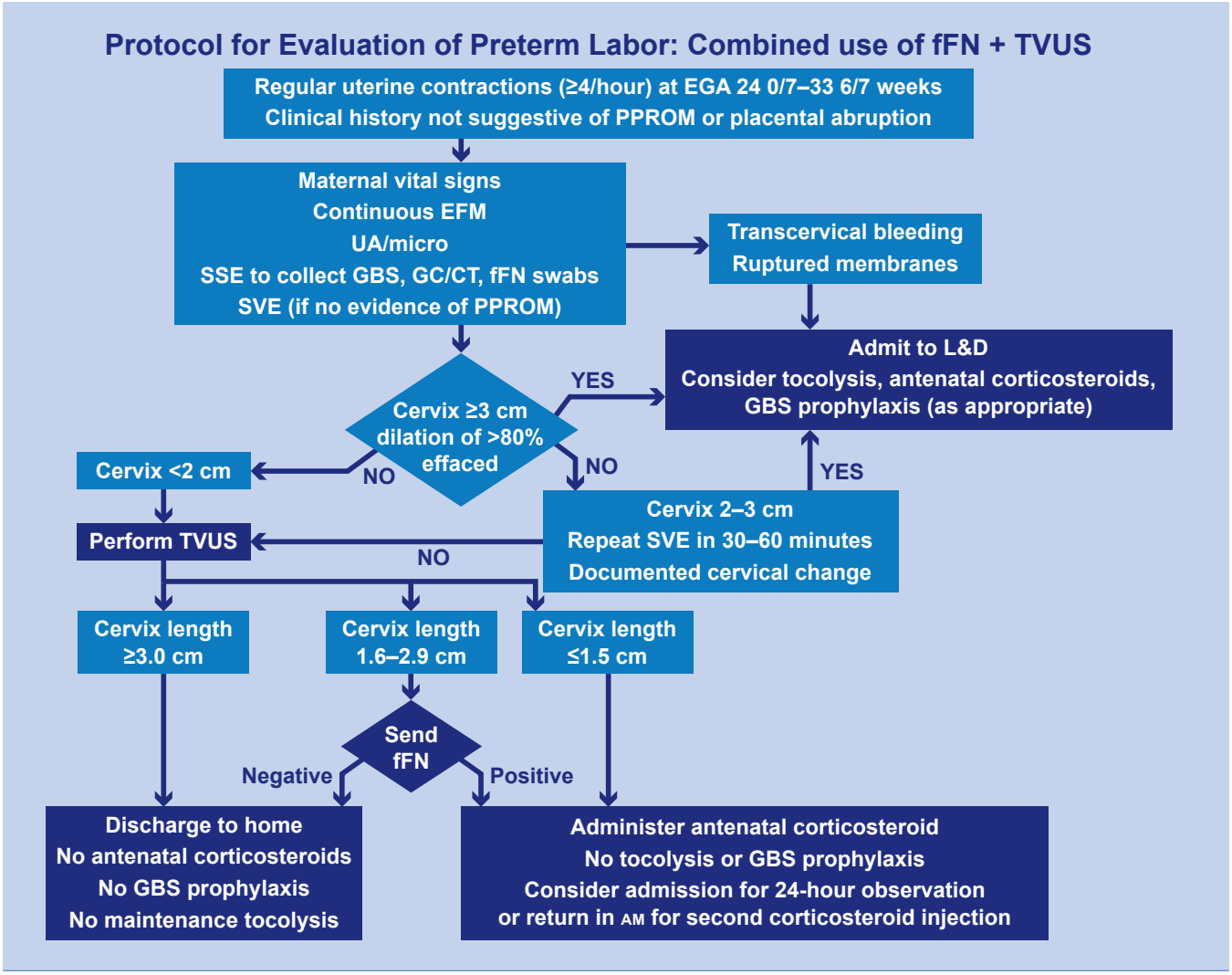

Figure 1. Mayo Clinic Algorithm.
EGA=estimated gestational age; EFM=electronic fetal monitoring; fFN=fetal fibronectin; GBS=group B streptococcus; GC/CT=gonococcus/*Chlamydia trachomatis*; L&D=labor and delivery; PPROM=preterm premature rupture of the membranes; SSE=sterile speculum exam; SVE=sterile vaginal exam; TVUS=transvaginal ultrasound; UA=urinary analysis.
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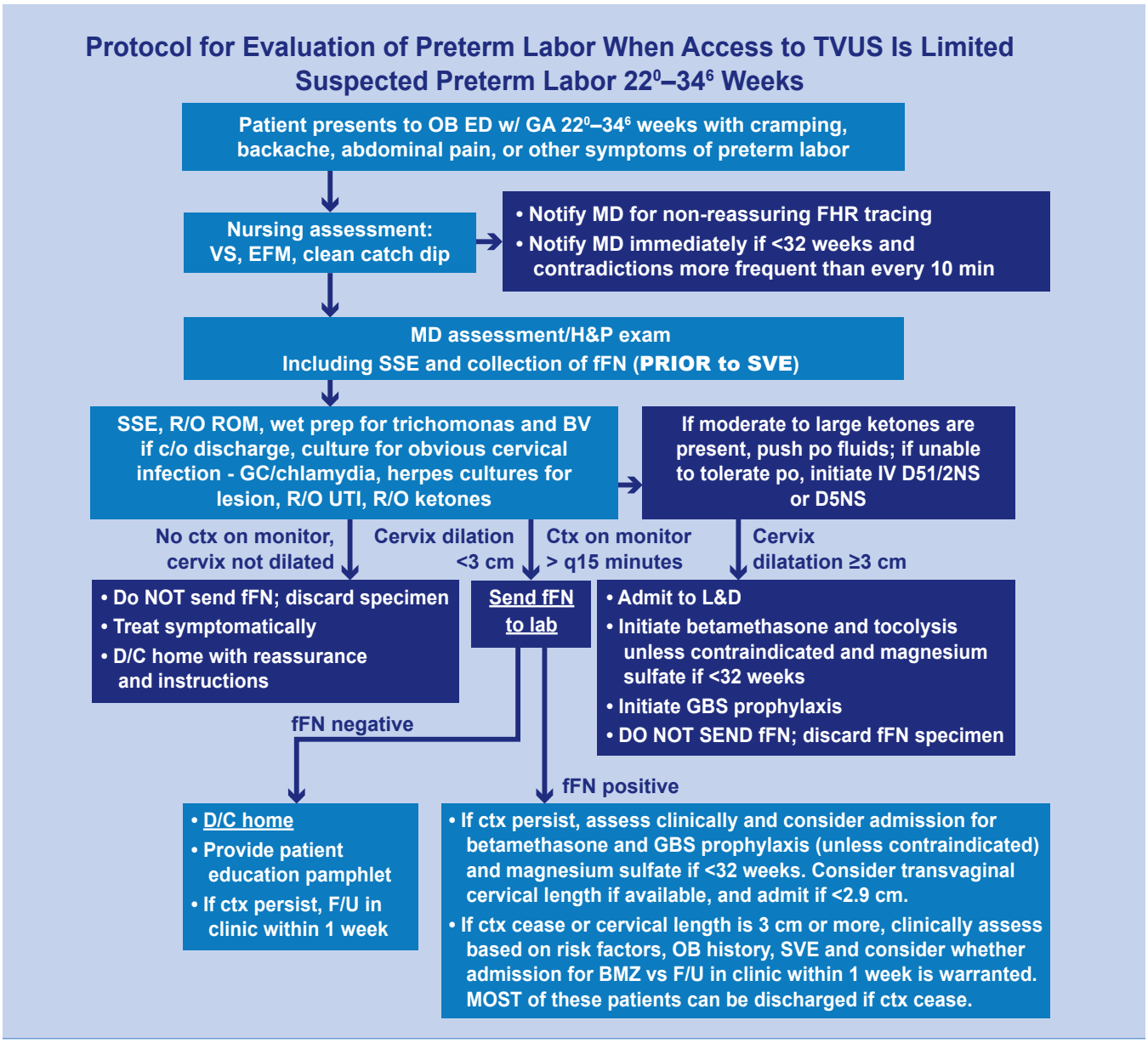

Figure 2. Ochsner Medical Center Algorithm.
BMZ=betamethasone; BV=bacterial vaginosis; ctx=contractions; D/C=discharge; D51/2NS=dextrose 5% in 0.45% saline (crystalloid); D5NS=dextrose 5% in 0.9% saline (crystalloid); ED=emergency department; EFM=electronic fetal monitoring; FHR=fetal heart rate; fFN=fetal fibronectin; F/U=follow up; GA=gestational age; GBS=group B streptococcus; GC=gonococcus; H&P=history and physical; IV=intravenous; L&D=labor and delivery; MD=doctor; OB=obstretric; po=per os; R/O=rule out; ROM=rupture of membranes; SSE=sterile speculum exam; SVE=sterile vaginal exam; TVUS=transvaginal ultrasound; UTI=urinary tract infection; VS=vital signs.
Reprinted with permission from the Ochsner Baptist Division of Maternal Fetal Medicine.

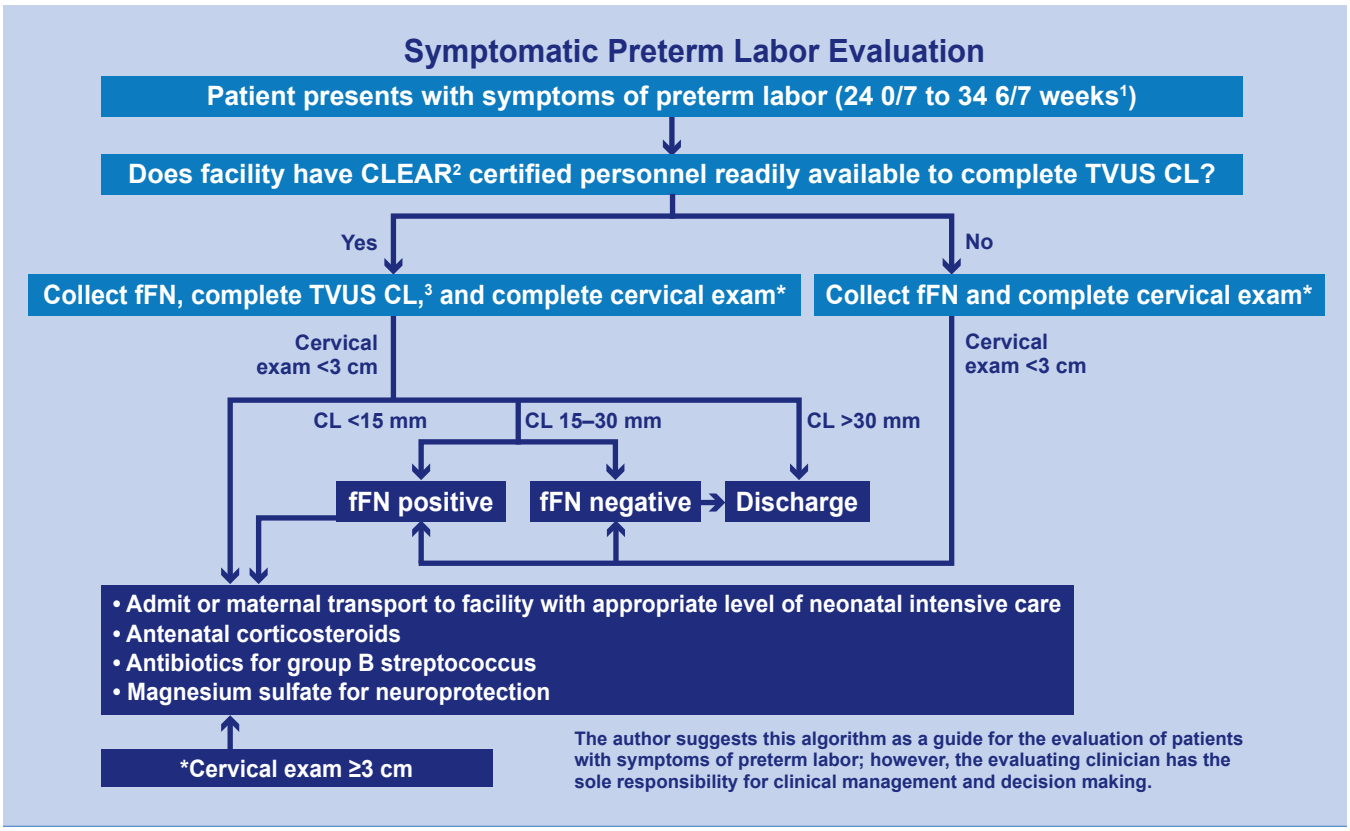

Figure 3. Michael Ruma, MD, MPH, of the Perinatal Associates of New Mexico Algorithm. CL=cervical length; CLEAR=Cervical Length Education and Review program; fFN=fetal fibronectin; TVUS=transvaginal ultrasound.

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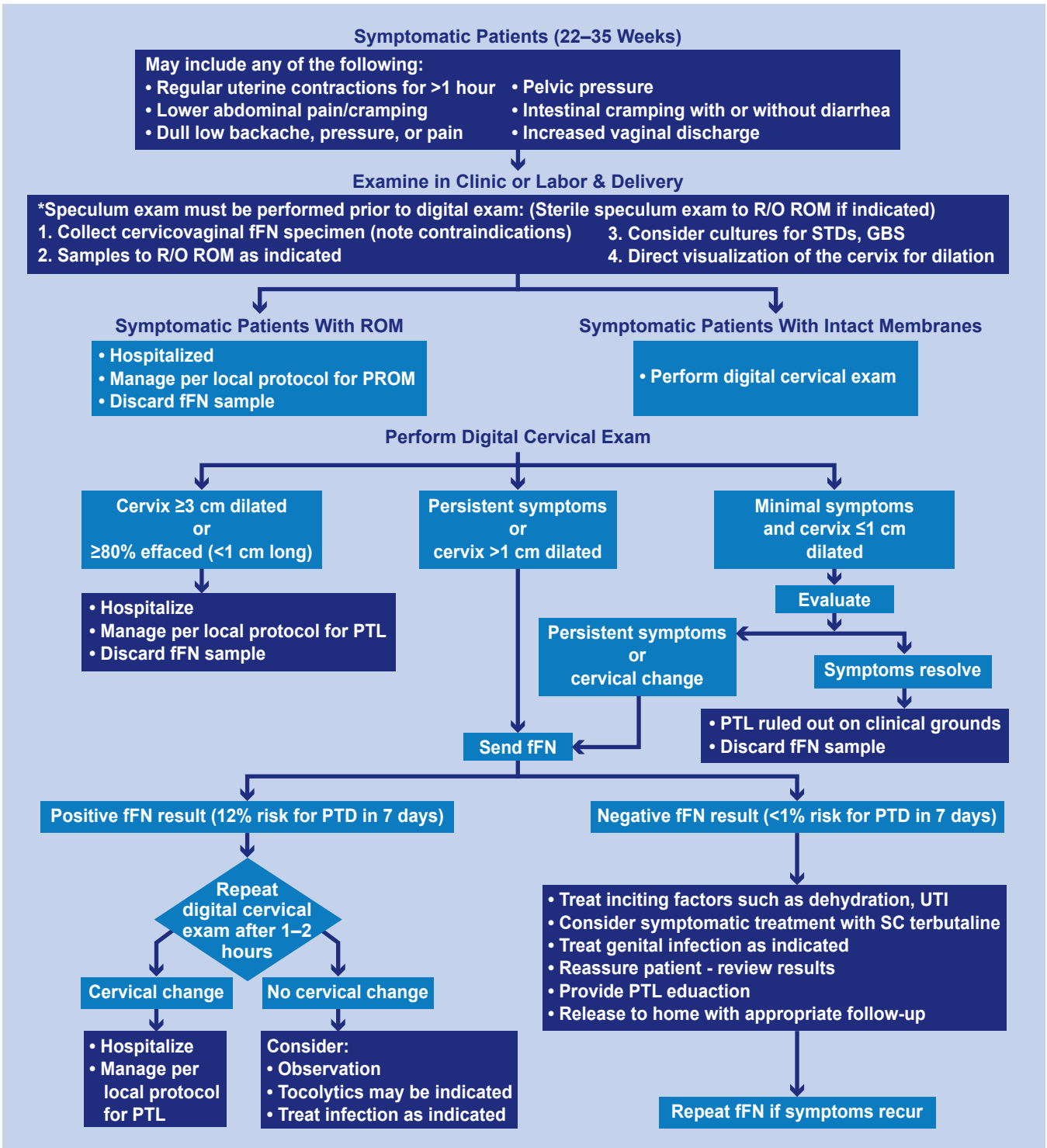

Figure 4. Southeastern Hospital System Algorithm.
fFN=fetal fibronectin; GBS=group B streptococcus; PROM=premature rupture of the membranes; PTD=preterm delivery; PTL=preterm labor; R/O=rule out; ROM=rupture of the membranes; SC=subcutaneous; STD=sexually transmitted disease; UTI=urinary tract infection.

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