

Fetal Fibronectin: The Benefits of a High Negative Predictive Value in Management of Preterm Labor

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Introduction

Of women who present with preterm contractions, only 10% of deliveries are preterm,¹ highlighting the imprecise nature of correlating symptoms with true preterm labor (PTL).² This dilemma results in unnecessary hospitalizations and interventions, contributing to a drain on resources within the health care system and possibly overexposing patients to treatments such as antenatal corticosteroids and tocolytics. Thus, an important challenge when attempting to reduce the spontaneous preterm birth (PTB) rate is to differentiate patients who are in PTL from those in false labor.³

Many strategies for diagnosis of PTL based on clinical factors alone have led to disappointing results, and the clinical diagnosis of PTL has up to a 50% false-positive rate.^{3,4} This may be due in part to the somewhat subjective nature of clinical assessment. A significant advance in the work up of women with symptoms of PTL is the inclusion of objective tools, such as transvaginal ultrasound (TVUS) to measure cervical length (CL) and diagnostic testing for fetal fibronectin (fFN) as a component of standardized protocols.

fFN, a glycoprotein component of the extracellular matrix of the decidua basalis near the intervillous space,^{5,6} is typically absent from cervicovaginal fluid between 22 and

34 weeks of gestation; thus, its presence is considered a possible marker of pathologic disruption of the maternal-fetal interface and its absence is reassuring that PTL is not imminent.⁷ Rupture of membranes, moderate or gross vaginal bleeding and cervical dilatation greater than 3 cm are contraindications for the test. It is also important to collect the specimen with a swab for fFN testing prior to any cervical manipulation (digital cervical exam, TVUS, etc.). A specimen swab can be discarded without cost if subsequent clinical or TVUS findings are not appropriate for fFN utilization.

While the positive predictive value (PPV) of fFN is low, the negative predictive value (NPV) of fFN is high (99.5% for delivery within 7 days and 99.2% for delivery within 14 days) in women with symptoms of PTL.⁸ Therefore the clinical value of fFN is in identifying those women who are at minimal risk of imminent PTB and providing reassurance that the patient does not require any interventions or hospital admission. Studies suggest that women with preterm contractions and a negative fFN test result can be expectantly managed and spared corticosteroids, tocolytics, the stress and negative financial impact of ongoing hospitalization, or transfer to a facility capable of caring for a preterm infant.^{9,10} Inclusion of fFN testing in the evaluation of PTL facilitates efficient triage of patients and allocation of resources to those in true PTL.³

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An additional tool for assessing PTL is CL, measured by TVUS, for evaluating cervical changes beyond those determined from a digital exam, such as shortening and funneling of the cervix.¹¹ While CL is inversely related to the likelihood of delivery within 7 days,¹² the cutoff value associated with imminent PTB varies widely among studies.¹³ This results in a “gray area” in which inclusion of an additional objective measurement such as fFN as part of a standardized PTL assessment can help clarify patient management. Additionally, accurate CL values require careful imaging by a highly trained technician skilled in the use of specialized equipment, which may not be available to all providers.¹⁴

The PPV of either fFN or CL is low for either test alone, and as such, the American Congress of Obstetricians and Gynecologists (ACOG) recommends that a positive fFN test or a short CL should not be used alone as a predictor of PTB¹⁵. However, studies have demonstrated that combining fFN and CL results can yield an improved PPV up to 45.4% for delivery within 7 days.¹⁶ In a direct comparison of frequency of PTB within 7 days for women with CL 1.5-2.9 cm (TVUS alone) compared with women with CL 1.5-2.9 cm plus a positive fFN result (TVUS + fFN), combining the two tests yielded a 4-fold increase in frequency of PTB within 7 days compared to TVUS alone.¹³

Due to the high NPV associated with fFN and the improved PPV when combining fFN with CL by TVUS, we have incorporated these tools into a standardized protocol at our institutions for managing patients with suspected PTL.

The Value of Standardization

The ACOG Committee on Patient Safety and Quality Improvement has officially called for development of clinical guidelines and standardization of practice to improve patient outcomes. They note that checklists and protocols improve outcomes and strongly encourage their use.¹⁵ Similarly, the American College of Nurse-Midwives (ACNM) issued the following position statement: “Evidence-based methods of identifying women at risk for premature labor, including ongoing risk assessment at each visit, screening women with PTL contractions using fFN testing, and screening using CL measurement techniques should be accessible in all practice settings.”¹⁷ Finally, the Association of Women’s Health, Obstetric and Neonatal Nurses (AWHONN) issued a call to action for quality patient care in labor and delivery for structured systems to help optimize communication about and response to rapid changes in patient status. Among the strategies they list are checklists and standard order sets.¹⁸

An evidence-based protocol evaluated by Rose and colleagues and used at the Mayo Clinic (see *Figure 1*) offers an opportunity for a standardized evaluation for women with symptomatic PTL.⁹ The protocol prescribes a triage evaluation whereby fFN is collected (but not immediately processed) from women presenting with >4 contractions/hr and without evidence of Preterm premature rupture of the membranes (PPROM) or placental abruption. Following specimen collection for fFN testing, a digital exam is performed, and women with cervical dilatation ≥ 3 cm are admitted for interventions such as antenatal corticosteroids, prophylactic antibiotics and possible tocolytics. For women found to have cervical dilatation <3 cm, transvaginal CL assessment is performed. Women found to have a CL ≤ 1.5 cm are considered at increased risk for PTB and admitted for intervention. Women with

a transvaginal CL of ≥ 3 cm are discharged to home for expectant management. fFN is used to triage women with cervical dilatation of <3 cm and CL by TVUS between 1.6 and 2.9 cm. Women who test positive for fFN are observed and given steroids, but other interventions are withheld pending further cervical change. Women who test negative for fFN are discharged home. When this protocol was utilized in a prescribed manner, the authors found a 56% reduction in hospital admissions and associated expenses without “compromise of patient care”.⁹

For obstetrical facilities that do not have 24/7 access to providers skilled at performing transvaginal CL measurement, we recommend considering a protocol that relies on a negative fFN result alone for discharging patients and a positive fFN result for further observation and clinical assessment to determine if interventions are warranted (*Figure 2*).¹⁹

Evidence Regarding Use of fFN Alone for Diagnosis of Preterm Labor

A meta-analysis published in 2016 by Berghella and colleagues²⁰ called into question the usefulness of fFN in assessment of PTL. The authors included 6 studies for a total of 546 singleton gestations with symptoms of PTL, and concluded that women tested with fFN had a similar incidence of PTB compared with control patients who were not tested with fFN, with comparable incidences between groups at various time points of gestation. No differences were found in the number of women who delivered within 7 days, the mean gestational age at delivery, the rate of maternal hospitalization, the use of tocolysis and antenatal steroids, the mean duration of the triage evaluation, and neonatal outcomes that included respiratory distress syndrome and admission to the neonatal intensive care unit. Management that incorporated fFN screening resulted in higher hospitalization charges. The authors concluded that fFN testing in singleton gestations with symptoms of PTL was not associated with an improvement in perinatal outcomes and was associated with higher costs.²⁰

While the meta-analysis suggested that fFN alone is not an effective screening tool, it did not address the overall utility of fFN in PTL assessment for the following reasons:

- Trials that utilized CL measurements for decision-making were excluded. As noted, the cost savings and efficiency of fFN is higher when used in conjunction with TVUS.^{9,13,21-23}
- Treatment was at the discretion of the providers, who were not consistently aware of or required to consider the results of fFN testing.²⁴
- The meta-analysis did not evaluate the association of clinical interventions, including the use of steroids and tocolytics, with the results of diagnostic fFN testing or perinatal outcomes.
- The finding that fFN testing increased cost by \$153 reflects only one study²⁵ which compared the cost of the test (\$153) versus observation, and failed to consider the cost of unnecessary hospital admissions or interventions.

Studies Included in the Meta-Analysis

The 6 studies that were included in the meta-analysis are further described and are summarized in Table 2.

Additional Studies Evaluating the Cost-Effectiveness of fFN

Giles and colleagues¹⁰ sought to determine whether fFN

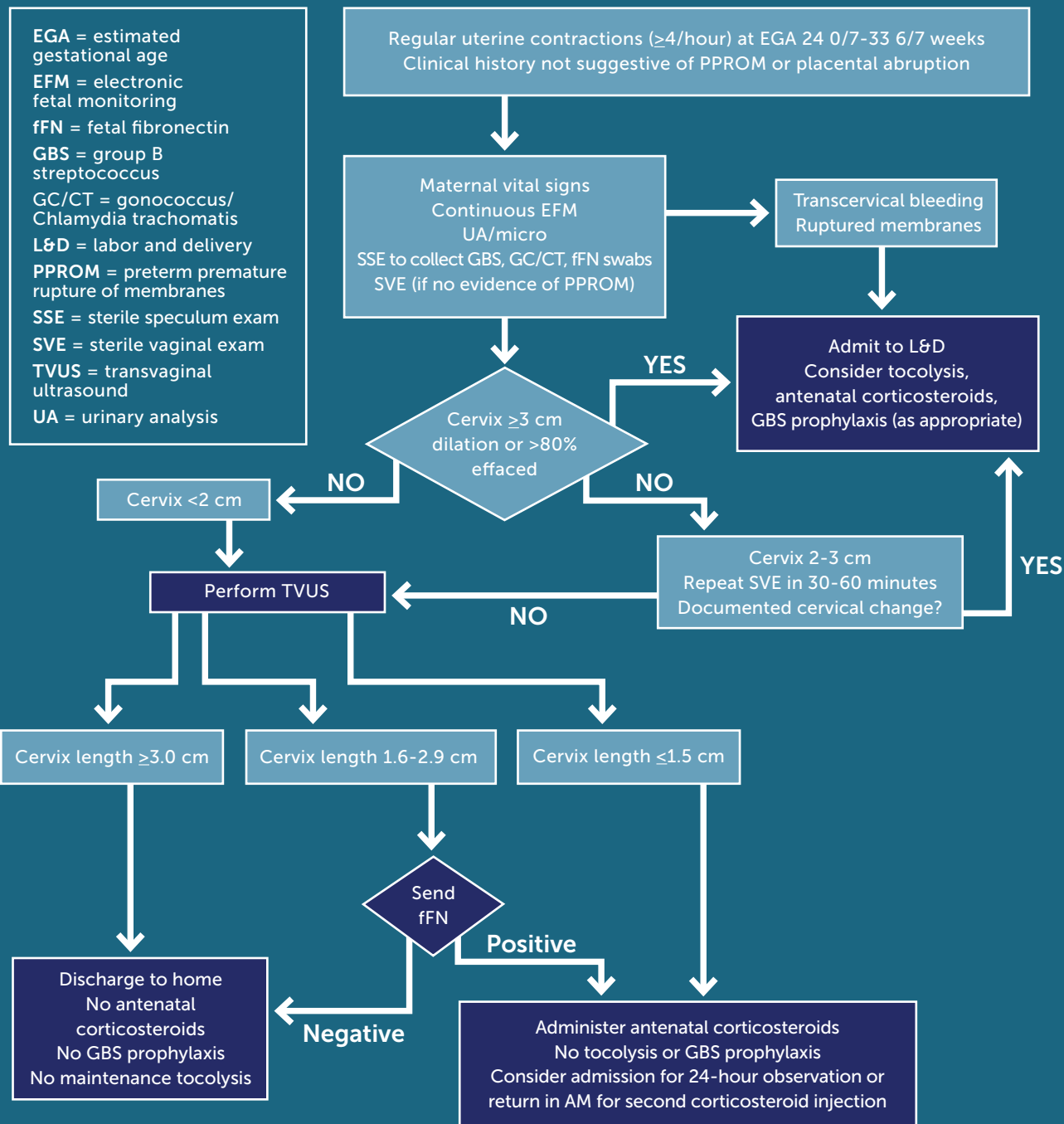


Figure 1
Protocol for Evaluation of Preterm Labor: Combined use of fFN + TVUS

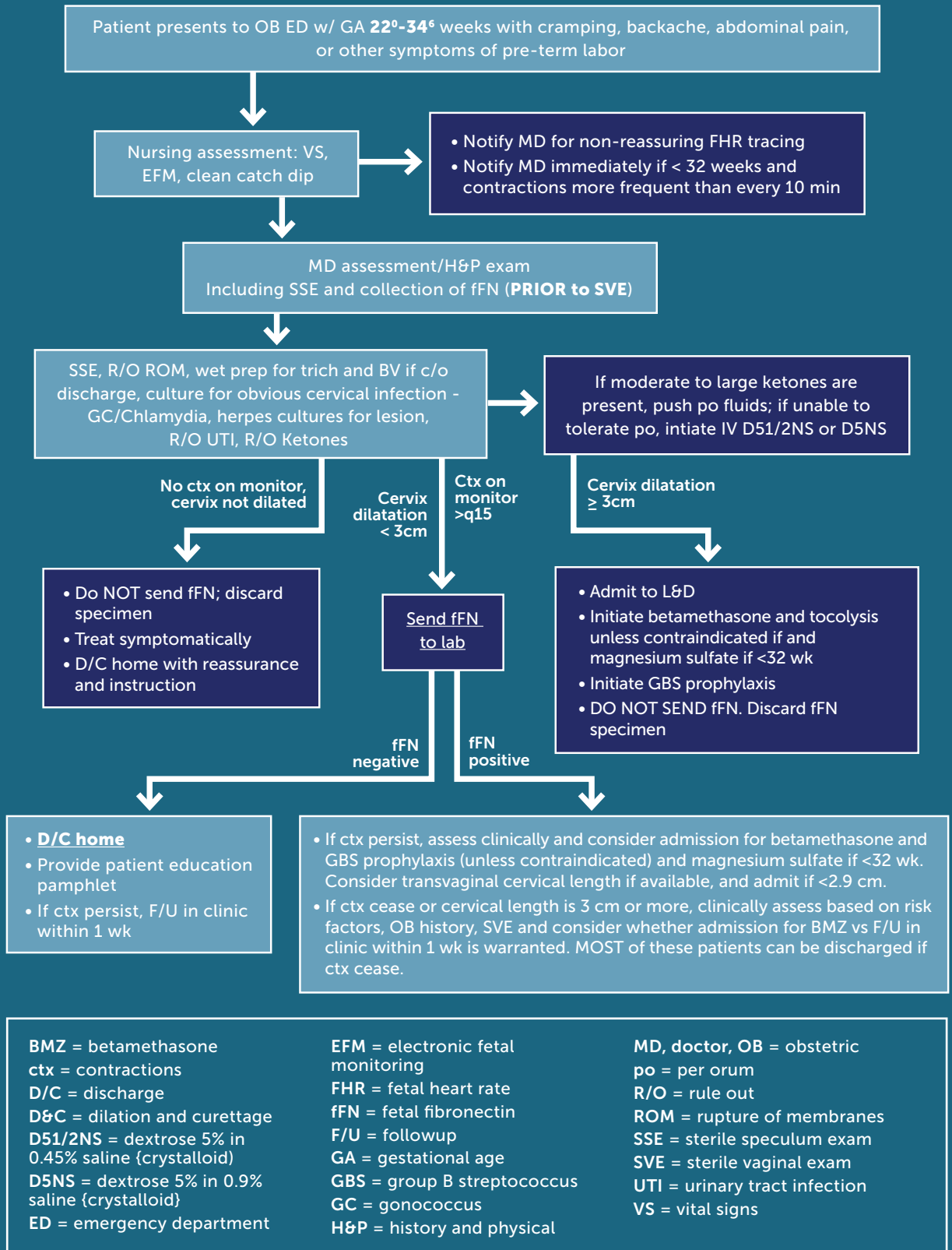
(Permission granted by Rose, Mayo Clinic)

testing impacted costs, admission, and transfer rates from referral hospitals to a tertiary obstetric hospital. An 18-month prospective audit of fFN use was conducted in 9 referral hospitals and one university maternal-fetal medicine unit (N=151 patients). Overall, 90% of patients admitted to a referral hospital with threatened PTL and who had a negative fFN were not transferred, with cost savings of \$30,297.

In a prospective cohort study, Joffe and colleagues evaluated the impact of fFN testing and reported a significant reduction in the number of admissions, number of prescriptions for tocolytics, and LOS, with an estimated cost savings of \$486,000 over the 12 month study period.³¹

As described above, Rose and colleagues conducted a 12-month retrospective observational study to look at the effect of a standardized evidence-based protocol for

SUSPECTED PRETERM LABOR 22⁰-34⁶ WEEKS



<p>BMZ = betamethasone ctx = contractions D/C = discharge D&C = dilation and curettage D51/2NS = dextrose 5% in 0.45% saline {crystalloid} D5NS = dextrose 5% in 0.9% saline {crystalloid} ED = emergency department</p>	<p>EFM = electronic fetal monitoring FHR = fetal heart rate fFN = fetal fibronectin F/U = followup GA = gestational age GBS = group B streptococcus GC = gonococcus H&P = history and physical</p>	<p>MD, doctor, OB = obstetric po = per orum R/O = rule out ROM = rupture of membranes SSE = sterile speculum exam SVE = sterile vaginal exam UTI = urinary tract infection VS = vital signs</p>
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Figure 2: Protocol for Evaluation of Preterm Labor When Access to TVUS is Limited¹⁹
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PTL evaluation on outcomes and resource use.⁹ All 201 patients underwent triage evaluation per protocol with a combination of fFN and CL measurement (*Figure 1*). The hospital admission rate was reduced by 56% compared with the previous year, in which no standardized algorithm was used for PTL assessment. This resulted in a total yearly cost savings of \$39,900.

van Baaren and colleagues evaluated the cost-effectiveness of combining CL measurement and fFN for symptomatic women between 24 and 34 weeks gestation.³² They concluded that fFN testing saved between €2.4 and 7.6 million per year compared with treating all symptomatic patients, resulting in a cost savings of €3,919 per patient.

Conclusion

In summary, the available evidence verifies the cost savings and utility of a diagnostic protocol which includes fFN for identifying patients who have symptoms of PTL but are likely experiencing false labor. The test is easy to administer, non-invasive, and has no related side effects. The NPV of fFN is high, with a negative test associated with a <1% chance of giving birth within the next two weeks. The test itself is objective, and its benefits with respect to costs and decreased healthcare utilization are well-documented. A standardized, evidence-based protocol for evaluation of symptomatic PTL should ideally include CL and fFN to avoid unnecessary interventions for patients unlikely to progress to active PTL (*Figure 1*). However, in the absence of reliable access to TVUS, an alternative algorithm can be used in which a negative fFN test alone can provide reassurance against imminent delivery (*Figure 2*). Thus, objective evaluation of patients with symptoms of PTL can help direct critical resources to those patients most likely to need them.

Author Biographies

Dr. Brigid McCue is the Lead Ob/Gyn Hospitalist at Ochsner Baptist Hospital, specializing in the care of the hospitalized woman on the labor floor, emergency department, and in-patient floors. She earned a Doctor of Medicine degree and a Doctor of Philosophy in Immunology degree from Albert Einstein School of Medicine. Dr. McCue went on to complete an Ob/Gyn Residency at Brown University, and she is board certified in Obstetrics and Gynecology. Dr. McCue is the immediate past-president of the Society of Ob/Gyn Hospitalists, treasurer of the New England Ob/Gyn Society.

Dr. Vanessa Torbenson is an Ob/Gyn Hospitalist currently practicing at the Mayo Clinic where she also serves as an associate program director for the residency program. She earned a Doctor of Medicine degree from the University of Chicago Pritzker School of Medicine and completed her residency at Western Pennsylvania Hospital. Dr. Torbenson is board certified in Obstetrics and Gynecology and serves as the Chair of the Simulation Committee for the Society of Ob/Gyn Hospitalists.

Table 2 Studies Included in Meta-Analysis

Lowe et al. ²⁶	<ul style="list-style-type: none"> Investigated the effect of fFN on length of stay (LOS) and use of PTL interventions in a tertiary care center. Randomized, non-blinded comparison of symptomatic women who were tested with fFN (n=46) versus women who were not (n=51). Concluded that a negative fFN test was associated with fewer hospital admissions and a shorter LOS.
Grobman et al. ²⁸	<ul style="list-style-type: none"> Compared whether the knowledge of fFN results affected treatment and costs. Powered to find a 20% reduction in total health care-related costs. Found no differences between groups; however, physicians were not obligated to use the fFN results to provide care for patients.
Nguyen et al. ²⁵	<ul style="list-style-type: none"> Evaluated cost for fFN testing versus observation only. As expected, testing was more expensive (\$153 per test), although the study did not consider the costs of hospital stay, delivery, or other outcomes.
Plaut et al. ²⁹	<ul style="list-style-type: none"> Use of fFN resulted in no difference in LOS; however, if the patient had been observed for at least 6 hours and the physician knew that the fFN results were negative, LOS was shortened by 40%. Treatment was at the discretion of the physician and was not determined by fFN results.
Lee et al. ²⁴	<ul style="list-style-type: none"> Evaluated length of stay in triage, admission rate, and number of births before 34 or 37 weeks for symptomatic women between 24 and 34 weeks gestation. Diagnosis was made by digital cervical exam only or cervical exam plus fFN. Physicians were required to discharge the patient if the fFN was negative. Detected no differences in outcomes; however, to demonstrate significance, the fFN test would have needed to reduce triage time by 50% to 1.4 hours, a reduction that was highly unlikely given that the test itself requires one hour to conduct.

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