



Fetal Fibronectin Test Performance in Patients at Low Risk for Preterm Delivery

Sumithra Jeganathan^{1*}, Alexander G. Shilkrut¹, Aleksandr M. Fuks², Sari J. Kaminsky¹

Abstract

Objectives: Spontaneous preterm birth is a leading cause of neonatal death. Fetal fibronectin (fFN) testing in cervical secretions between 22-34.6 weeks of gestation is used to predict non-delivery within the next 7 days in patients with symptoms of preterm labor. The objective of this study is to analyze fFN test performance in a group of patients with low risk for preterm delivery that presented with preterm labor symptoms, and to evaluate how the results of fFN testing influenced management decisions.

Materials and Methods: Patients after preterm delivery (gestational age 24.0-36.6 weeks) and patients who underwent fFN testing in Metropolitan Hospital, NYC Health+Hospitals, New York, NY, from January 1, 2015 to December 31, 2015 were identified and reviewed. Patients with positive fFN test results (fFN+; >50 ng/dL) were compared to patients with negative fFN test results (fFN-).

Results: Among 77 patients identified, 66 (86%) were fFN- and 11 (14%) fFN+; 15 patients (78%) who delivered preterm were not tested with fFN. Preterm birth rate during the study period was 1.9%. There was no difference in maternal or neonatal characteristics between the two groups. Among fFN-, 4 patients (6%) delivered preterm, while among fFN+, none delivered preterm. In both groups, none delivered within 7 days of testing. Compared to fFN-, fFN+ had higher rates of admissions (36% vs 0%; $P < 0.001$) and steroid administration (82% vs 0%; $P < 0.001$).

Conclusions: In this retrospective analysis, use of fFN testing as an initial screening test for patients with symptoms of preterm labor in this low risk population did not result in improved clinical outcomes and was associated with a higher rates of hospital admissions and steroid administration.

Keywords: Fetal fibronectin, Preterm labor, Preterm labor symptoms

Introduction

Spontaneous preterm birth is one of the leading causes of neonatal death with approximately one million preterm newborns dying every year.¹ Symptoms of preterm birth are usually vague and nonspecific, and it is often a challenging task for clinician to identify which patients will deliver preterm.² Antenatal corticosteroids can be administered to decrease respiratory complications and improve survival rates to those at risk of preterm labor.³ Preferably, corticosteroid should be given within 7 days of delivery.² Tocolytics can be used to delay onset of preterm labor for 48 hours to allow administration of corticosteroids, but beyond that, they have showed minimal benefit to the reduction of neonatal morbidity and mortality.⁴ Admissions and transfers to a higher level of care centers for suspected preterm labor are often associated with inconvenience, loss of productivity and significant cost, hence it is important to develop clinical tests that would allow to identify reliably patients at risk for preterm labor.

Fetal fibronectin (fFN) is an extracellular matrix protein present at the decidual-chorionic interface that when

disrupted leaks into vagina, where it can be identified in the vaginal secretions. fFN test detects the presence of fFN in cervical secretions between 22-34.6 weeks gestation and is reported as positive when fFN concentration in the vaginal secretions is greater than >50 ng/mL.⁵

The initial reports of fFN use were enthusiastic.⁶ They showed that negative fFN test result (<50 ng/mL) can predict, with high accuracy, that women with preterm labor symptoms will not deliver in the next 7 days, which can potentially help to avoid unnecessary interventions.⁷

However, the management of women with positive fFN results (>50 ng/dL) is still controversial and ranges from observation, admissions with corticosteroid administration, tocolysis and antibiotics in various combinations.⁸

A recent systematic review of six randomized clinical trials showed that fFN testing did not improve clinical outcomes or significantly reduce rates of hospitalizations and interventions, while increasing hospitalization costs.⁹

The objective of this study is to analyze fFN testing in a low risk unselected group of patients who presented with symptoms of



Key Messages

- ▶ Fetal fibronectin testing in a low risk patients resulted in increased intervention.
- ▶ Fetal fibronectin testing in patients with symptoms of preterm labor in this low risk population did not result in improved clinical outcomes.

preterm labor, and to evaluate how the results of fFN influenced management decisions.

Materials and Methods

This retrospective case review study was conducted in Metropolitan Hospital, NYC Health+Hospitals in New York City, NY. Charts of all patients who had fFN test performed from January 1, 2015 to December 31, 2015 were identified and reviewed. Cases were identified by reviewing laboratory records during the study time period. Patients were tested in a triage area of Labor and Delivery Unit when they presented with symptoms of threatening preterm labor.

A list of patients who delivered preterm (between 24.0 and 36.6 weeks gestational age) during the study period was also collected from delivery database.

The rapid fFN Hologic TLiIQ system was performed on patients with symptoms of preterm labor who presented to the triage of Labor and Delivery between 24 weeks & 0 days to 34 weeks and 0 days following manufacturer’s guidelines (Hologic, Inc 1240 Elko Drive, Sunnyvale, CA, USA).

The vaginal swab was obtained using a sterile speculum to visualize the cervix and a sterile polyester tipped

applicator used to obtain a sample from posterior fornix. Inclusion criteria consisted of no recent vaginal exam, absence of vaginal bleeding, intercourse and a cervical dilatation less than 3 cm. Patients who were excluded were the ones with ruptured membranes, multiple gestations, advanced dilation, cerclage and patients who transferred care during their pregnancy. A test was considered positive if fFN concentration was greater than 50 ng/dL.

Data was analyzed with MedCalc statistical software version 17.1 (MedCalc Software, Ostend, Belgium). Chi-square, Fischer’s exact test and ANOVA tests were used to analyze categorical values as appropriate. *P* values of <0.05 were considered statistically significant.

Results

There were 98 fFN tests performed during the study period and 21 patients were excluded from analysis. Of the patients excluded from analysis, 12 patients transferred prenatal care, 2 patients had extramural delivery, 1 patient was induced for preeclampsia, 1 patient had cerclage in situ, and 5 patients had twin gestation (Figure 1).

Ninety-three women had test performed once, 5 women had test performed twice. No patients in our study had test performed more than two times during pregnancy. We considered this cohort of patients a low risk group, as preterm labor rate during the study period at our hospital was 1.9%. Four patients (5%) had commercial insurance, 73 patients (95%) were insured by Medicaid.

The demographic and clinical characteristics of the remaining 77 patients for the analysis (divided into a group of patients with negative fFN test and a group of patients with positive fFN test) are shown in Table 1. Although median age and median fetal weight were

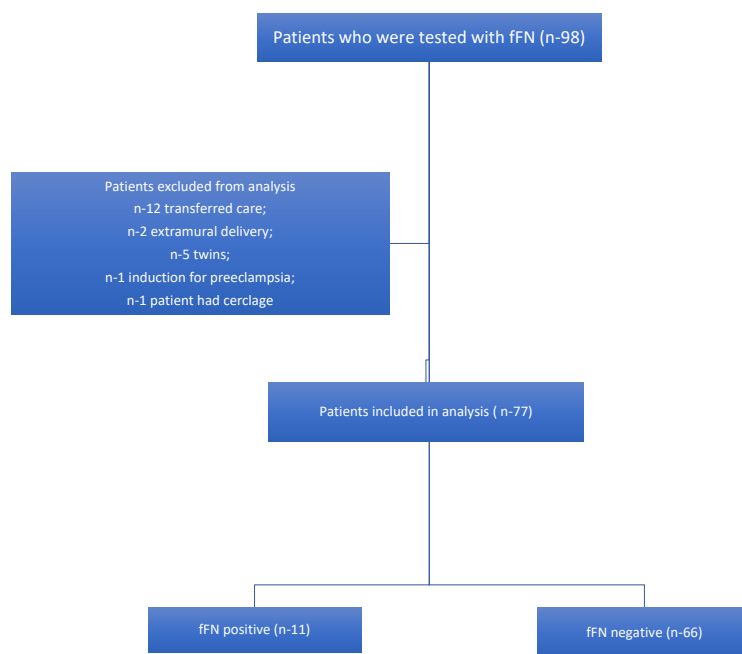


Figure 1. Patient Flow Chart.

numerically higher in patients tested negative with the fFN test, there were no statistically significant differences in demographic and clinical characteristics between the two groups of patients.

The clinical outcomes of both groups of patients presented in Table 2. There were 4 (6%) preterm deliveries in fFN negative group and no preterm deliveries in fFN positive group. No patients in either group delivered within 7 days of the test or prior to 34 weeks' gestation. Four patients (36.3%) in fFN positive group were admitted to the hospital and nine patients (81.3%) in fFN positive group received steroids for fetal lung maturity. There were no admissions or steroids administration in fFN negative group. 19 patients delivered preterm during study period. 15 patients (78%) who delivered preterm due to preterm labor or PPROM (Preterm premature rupture of the membranes) during the study period were not tested with fFN during prenatal care.

Discussion

This retrospective review of 77 patients who received fFN test during prenatal care in our clinic during 2015 showed that introduction of fFN to our clinical practice did not result in improved perinatal outcomes. There were only a small number of preterm deliveries among patients who were tested with fFN during their pregnancy. Majority of patients who actually delivered preterm secondary to preterm labor or PPROM did not have fFN testing at all during their prenatal care. None of the patients who tested fFN positive have delivered preterm.

Negative fFN test result in patients with symptoms of preterm labor allowed for confidently discharging patients home, but it is balanced against the cost of the test (approximately \$200) and the cost of the follow up for positive result that often prompts additional action and associated costs.¹⁰

As with any introduction of a new technology into

Table 1. Demographic and Clinical Characteristics of Patients Tested With the fFN Test

Characteristics	Negative fFN test n = 66 (86%)	Positive fFN test n = 11 (14%)	P Value
Median age, (min-max)	29 (16–41)	25 (14–35)	0.19 ^b
Ethnicity, n (%)			
Black	15 (22.7)	3 (27.2)	
Caucasian	1 (1.5)	0 (0)	
Hispanic	49 (72.1)	7 (63.6)	
Other ^a	1(1.5)	1 (9)	
Parity, median (min-max)	1 (0–6)	1 (0–3)	0.13 ^b
Body mass index, median (min-max)	30.1 (21–52)	33.0 (24–44)	0.70 ^b
History of SPTB	4 (6)	1 (9)	0.55 ^c
Delivery mode, n (%)			0.26 ^d
Cesarean	16(24.2)	1 (9)	
NSVD	51 (75.8)	10 (91)	
Median fetal weight, gram (min-max)	3245 (2295-4490)	2933 (1010–3880)	0.37 ^b
GA fFN	31 (24–34.4)	31.2 (24.6–33.5)	0.46 ^b

fFN, fetal fibronectin; GA, Gestational age; NSVD, normal spontaneous vaginal delivery; SPTB, spontaneous preterm birth.

^a Other includes Indian, Arab

^b This P value was determined using one-way analysis of variance (ANOVA).

^c This P value was determined using Fisher's exact test.

^d This P value was determined using χ^2 test.

Table 2. Clinical Outcomes of Patients Tested With the FFN Test

Characteristics	Negative FFN n = 66 (86%)	Positive FFN n = 11 (14%)	P value
Median gestational delivery age, weeks, (min-max)	39.5 (34.5 - 41.0)	38.6 (37 - 41.4)	0.89 ^a
Preterm delivery, n (%)	4 (6)	0 (0)	
Delivery before 34 weeks, n (%)	0 (0)	0 (0)	
Delivery within 7 days of fFN test, n (%)	0 (0)	0 (0)	
Admitted to the hospital	0 (0)	4 (36.3)	<0.001 ^b
Administered betamethasone	0 (0)	9 (81.8)	<0.001 ^b

FN, fetal fibronectin.

^a This P value was determined using one-way analysis of variance (ANOVA).

^b This P value was determined using Fisher's exact test.

clinical practice, there is a learning curve for clinicians utilizing the new product, as they try to achieve consensus on who and when the new product should be used.

Once fFN test was introduced in clinical practice a few decades ago, it was designed to help triage difficult cases of threatened preterm labor, potentially avoiding costly admissions.¹¹ Clinicians were advised that patients with negative result are at very low risk for preterm delivery in the following week, and there was no clear guidance on what to do with positive ones, except the notion that patients with positive fFN are at somewhat higher risk for preterm delivery.

Once the test is available, in the absence of clear guidelines, there is a possibility of testing all patients with vague symptoms of preterm labor. In clinical practice, pretest probability of disease often is either not available, cannot be estimated, or not used to guide clinical practice, but it is pretest probability that will guide the value of positive and negative test results.

False positives results can occur due to the presence of blood, sexual intercourse within 24 hours or digital cervical examination.¹²⁻¹⁴

Physicians are also faced with medicolegal pressures to act on positive test results, which frequently leads to admissions, administration of steroids, antibiotics, more frequent follow ups, with costs of follow ups reaching thousands of dollars for each positive test.¹⁵

We cannot estimate from the design of our study whether individual patients would be admitted or discharged if fFN was not available, but our data shows little difference between fFN positive and fFN negative groups in regard to gestational age at delivery or fetal weight. The study has also showed that significantly larger proportion of patients with positive fFN received steroids and were admitted for observation. There were no patients who delivered within 7 days of positive fFN test, so all patients who received steroids, were given it outside of ideal administration window. There is no definite risk of single dose of corticosteroids for the fetus administered for lung maturity, but the risks of multiple doses of corticosteroids are well documented in the literature.¹⁶

A 2013 systematic review of five randomized trials and 15 test accuracy studies on fFN testing on symptomatic women, reported sensitivity of delivery <37 weeks gestation of 60.8% and specificity of 82.3%. Similar sensitivities and specificities were reported for delivery within one week of testing and delivery prior to 34 weeks' gestation.⁷

Applying fFN test to our population with probability of preterm delivery of 1.9% will give us excellent negative predictive value of 99%, but dismal positive predictive value of 6%.

In our subgroup of symptomatic patients, specificity was similar to previously reported value of 84%, negative predictive value of 93%; sensitivity and positive predictive value cannot be calculated from our sample, as none of

fFN positive patients has delivered preterm.

Berghella et al have concluded in 2016 meta-analysis that clinician's knowledge of fFN results did not reduce rates of maternal hospitalization, use of tocolytics, use of antenatal corticosteroids, but increased hospitalization cost.⁹ Our study has also showed that knowledge fFN results may have increased the number of admissions and antenatal steroid administration, as significant number of patients with positive results have received interventions, unlike the fFN- group, but none of them proceeded to have preterm delivery.

On the other hand, our study showed that majority of patients who did deliver preterm did not have fFN test done during their pregnancy, which shows us that it is difficult to determine based on clinical presentation who will or who will not deliver preterm, and many patients who do deliver preterm have minimal advance warning signs.

Several strategies have been explored to make fFN test results more predictive and cost effective.

One strategy is to use fFN as a reflex test for patients who are determined to have short cervical length in the range of 20-29 mm. This subgroup of patients would have already received higher level of surveillance, and fFN will help to triage some of the patients in this group to low risk. This strategy was outlined in Society of Maternal Fetal Medicine Preterm Birth Toolkit¹⁷ and as an app available on "App store".¹⁸

Another is a scoring system used in Europe, that takes into account patient's historical information such as history of preterm delivery, prior cervical surgery combined with quantitative fFN and cervical length for asymptomatic women and presented in the form of an app QUIPP (available for download in App Store)¹⁹ Quantitative fFN is not available in the US, so if number 50 (ng/mL) for fFN positive patients is entered, one can approximately predict the risk of preterm birth to guide management decisions (Table 3).

A third strategy, to use the test for its negative predictive value, and disregard positive results. Although scientifically, it makes sense due to low positive predictive value of fFN in low risk populations, it is clinically hard to disregard a positive test, due to medico legal pressures, as there are not many other tools available for physicians to estimate patient's risk for preterm delivery, which underscores the importance of institutional policies guiding test's utilization.

Also, a quantitative fFN may help further stratify the risk for preterm delivery. Abbott et al reported that increasing fFN thresholds to 200 and 500 ng/mL can increase positive predictive value for spontaneous preterm birth.²⁰ Radnor et al further confirmed the findings that higher quantitative levels of fFN increases positive predictive value.²¹ Instrumentation for quantitative fFN is not commercially available in the US.

But, at this point routine screening of symptomatic

Table 3. Strategies to improve Predictive Value of fFN Testing

Title	Strategy	App Link	Reference
CL+ fFN	Use fFN as a reflex test for symptomatic patients with CL 20-30 mm	https://appsto.re/us/AYOjeb.i App Store/ Android Search: SMFM Preterm Birth Toolkit	SMFM PTB Toolkit ¹⁷
CL+fFN+risk factors (QUIPP)	Use risk questionnaire in combinations with quantitative fFN or for asymptomatic patients add CL measurements.	https://itunes.apple.com/us/app/quipp/id964256400?mt=8 App Store/ Android Search: quipp	www.quipp.org ¹⁹

FN, fetal fibronectin; CL, cervical length.

patients with qualitative fFN alone does not appear to be warranted as it can increase medical costs, and provide limited benefits.²²

Our study's limitations include a short observation period, exclusion of 21 (21%) of patients from the analysis and a small sample size. The retrospective nature of the study precludes complete accurate assessment for what management strategies would be carried out if fFN was not available, and whether more or less patients would receive interventions. It was impossible to ascertain the quality of specimens collected and potential rate of false positive results.

To overcome these limitations, we would need to design prospective study to compare different strategies for fFN utilization side by side, including one where fFN is not being used at all in management decisions.

In conclusion, in our study, fFN testing in a symptomatic cohort of low risk patients has resulted in increased interventions for fFN positive patients with little difference in outcomes.

Authors' Contribution

SJ: conceptualization, methodology, data curation, investigation, writing - original draft. AGS: Conceptualization, methodology, writing - review & editing visualization. AMF: Methodology, formal analysis. SJK: Writing - review & editing, visualization, supervision.

Conflict of Interests

Authors declare they have no conflicts of interest.

Ethical Issues

The study received approval from the Institutional Review Board in New York Medical College and Metropolitan Hospital prior to the start of the data collection (IRB# L-12, 048).

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