

Fetal fibronectin and cervical length measurement in women with preterm labor

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Abstract

Aim: Preterm birth still remains a major cause of perinatal morbidity and mortality and its rate has not declined over the last two decades despite the improvement in perinatal management. The aim of our study was to assess the use of fetal fibronectin (fFN) testing and cervical length (CL) measurement to predict preterm delivery.

Methods: This was a prospective study including all patients admitted between November 2009 and June 2011 to the University Obstetric-Gynecologic Hospital "Mbretëresha Geraldinë" in Tirana, with the diagnosis of increased preterm uterine contractility and intact membranes between 22 and 34 weeks of gestation (N=254).

Results: Among 245 women with complete data, the mean gestational age at recruitment was 29.4±2.5 weeks. Six women (9.6%) delivered within two weeks of assessment and 14 (22.5%) women delivered before 34 weeks. A positive fFN test resulted in a sensitivity of 83%, a specificity of 84%, a positive predictive value of 36%, and a negative predictive value of 98% for delivery within two weeks. For CL <25 mm, these figures were: 50%, 52%, 10%, and 91%, respectively.

Conclusion: In our study conducted in the capital city of Albania, fFN screening provided the best predictive capacity for preterm delivery. Cervical ultrasound after fFN triage appears to be an acceptable option, depending on the resources available.

Keywords: cervical length, fetal fibronectin, preterm delivery, ultrasonography.

Introduction

Preterm birth remains a major cause of perinatal morbidity and mortality (1) and its rate has not declined over the last two decades despite the improvement in perinatal management (2).

Assessing the probability of preterm delivery is still a clinical challenge and is important to reduce the clinical interventions (tocolysis, corticosteroid administration, and transfer to a tertiary care facility) which are risky and expensive. Several studies have shown that a diagnosis of preterm labor based on digital examination was not as reliable as the diagnosis based on tests such as detection of fetal fibronectin in cervicovaginal secretions and ultrasound measurement of cervical length (3). Fetal fibronectin, an extracellular matrix glycoprotein localized at the maternal-fetal interface of the amniotic membranes between the chorion and the decidua, is found at very low levels in cervicovaginal secretions under normal conditions. Levels of >50 ng/mL at or after 22 weeks of gestation have been associated with an increased risk of spontaneous preterm birth (3-6). A recent meta-analysis has shown that births before 37 weeks significantly decreased in patients whose management was based on knowledge of fFN results compared with controls whose fFN results were unknown (7).

Transvaginal CL measurement is the other validated test to predict preterm birth in women with threatened preterm labor, as well as in asymptomatic high-risk and low-risk women (3,8-14). A CL measurement of 25 mm or less is generally considered as an excellent indicator of an increased risk of preterm delivery, particularly among women with preterm labor. Several studies have reported that fFN screening and CL measurement provide similar results in predicting the risk of preterm delivery (15-20). However, it remains unclear whether combined fFN and CL measurements improve the prediction of preterm delivery and the means of such a combination (3). Availability of one of the two tests may be an issue in some facilities because the ultrasound expertise for CL measurement may not be always available in small centers. On the other hand, the additional cost of fFN testing may be difficult to justify in centers where CL measurement is readily available. Therefore, the use of CL or fFN as the first-line test might be a more rational option, limiting the

use of a second test to selected cases in a contingent approach.

Nevertheless, the evidence regarding preterm delivery issues among Albanian women is scant. In this context, the aim of our study was to determine the performance of FN testing and ultrasound CL measurement for the prediction of preterm delivery in patients with preterm labor in Albania.

Methods

This was a prospective cohort study of patients admitted between November 2009 and June 2011 to the Obstetric-Gynecologic University Hospital "Mbretëresha Geraldinë" in Tirana, with the diagnosis of increased preterm uterine contractility and intact membranes between 24 and 34 weeks. Preterm labor was defined by the presence of regular uterine contractions, lasting at least 30 seconds and occurring at least four times in 30 minutes, and significant cervical changes on digital examination. Women were excluded if they had a confirmed or suspected rupture of membranes, cervical dilatation >3 cm, cervical cerclage, vaginal bleeding, placenta previa, placental abruption, severe intrauterine growth restriction, preeclampsia, or medically indicated preterm delivery before 34 weeks. The study investigations were carried out either on admission or within 24 hours of admission if a digital examination had been performed in the 24 hours before the patient's inclusion in the study. Each subject was first examined with a vaginal speculum. A Dacron swab was rotated in the posterior fornix of the vagina and sent to the laboratory. The presence or absence of fFN was measured by a qualitative test (Fibronectin collection kit, Adeza Biomedical), and results were expressed as positive or negative. A concentration of 50 ng/mL in the vaginal fluid was indicative of a positive test. The outcome of the pregnancy was recorded in a database with other relevant information. The outcomes of interest were delivery within two weeks of admission to the study and delivery before 34 weeks. Predictive values and likelihood ratios with their respective 95% confidence intervals were first calculated for each test considered separately and subsequently for different combinations of both markers. Predictive values were compared using the McNemar test. All analyses were performed with SPSS software, version 16.0.

Results

Two hundred fifty four women were included in the study. The outcome of pregnancy could not be determined for five women who had been discharged and delivered in another centre. Among the 249 remaining women, two had an fFN assessment but no CL measurement, and further two women had CL measured but no evaluation of fFN. These cases were excluded from further analysis.

Two hundred forty five women were included in

the final analysis, including seven twin pregnancies, and 147 (60%) women were initially transferred from another centre because of preterm labor. Twenty four women (9.6%) delivered within two weeks, and 55 women (22.5%) delivered before 34 weeks.

General characteristics and pregnancy outcomes in study subjects are summarized in Table 1. The values of the different tests in predicting delivery within two weeks and before 34 weeks are presented in Table 2. Fetal fibronectine was the best single test

Table 1. General characteristics, pregnancy outcomes, and test results of the individuals under study (N=245)

Characteristics	Mean value (\pm SD) / n (%)
Maternal age in years (mean \pm SD)	27.6 \pm 6.2
Nulliparous [n (%)]	115 (46.8)
Maternal transfer [n (%)]	146 (59.7)
Gestational age at inclusion in weeks (mean \pm SD)	29.4 \pm 2.5
Gestational age at delivery in weeks (mean \pm SD)	36.5 \pm 3.2
Received tocolytics [n (%)]	174 (71.0)
Delivery within 2 weeks [n (%)]	24(9.7)
Delivery before 34 weeks [n (%)]	55 (22.6)
Delivery before 37 weeks [n (%)]	91 (37.1)
Admission to delivery interval in days (mean \pm SD)	49.9 \pm 22.8
Median cervical length in mm (range)	26.5 (0-51)
Cervical length <15 mm [n (%)]	12 (28.8)
Cervical length <25 mm [n (%)]	20 (48.4)
Cervical length <30 mm [n (%)]	16 (38.7)
Positive fFN [n (%)]	10 (22.6)

for the prediction of delivery within two weeks (with a sensitivity of 83% and a specificity of 84%), whereas CL measurement had a slightly better sensitivity than fFN (71% vs. 50%, respectively) for

predicting delivery before 34 weeks. The specificity of fFN was significantly higher than the CL measurement ($P < 0.001$). Overall, there was no significant difference between the sensitivity of fFN testing, CL measurement, and their combinations.

Table 2. Predictive values for preterm birth of cervical length, fFN

Delivery	Parameter	Sensitivity % (95% CI)	Specificity % (95% CI)	LR+ % (95% CI)	LR- % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Within 2 weeks (prev 9.7%)	fFN +	83(36-100)	84(72-92)	5.2(2.6-10.4)	0.2(0.0-1.2)	36(13-65)	98(89-100)
	CL <25 mm	50(12-88)	52(38-65)	1.0(0.4-2.4)	1.0(0.4-2.2)	10(2-26)	91(75-98)
<34 weeks (prev 22.6%)	fFN +	50(23-77)	85(72-94)	3.4(1.4-8.1)	0.6(0.3-1.0)	50(23-77)	85(72-94)
	CL <25 mm	71(42-92)	58(43-72)	1.7(1.1-2.7)	0.5(0.2-1.2)	33(17-53)	87(71-96)
<34 weeks (prev 37.1%)	fFN +	48(35-60)	92(86-99)	6.2(1.9-20.0)	0.5(0.4-0.8)	79(68-89)	75(64-86)
	CL <25 mm	74(52-90)	67(50-81)	2.2(1.3-3.7)	0.4(0.2-0.8)	57(37-74)	81(64-93)

Discussion

Findings from our study confirm that both cervicovaginal fFN testing and endovaginal CL measurement provide good prediction of delivery within two weeks or before 34 weeks in women with threatened preterm labor. In addition, we have tested two different strategies combining both tests, with the aim of improving the predictive value while decreasing the need for additional resources. For the prediction of delivery within two weeks, the best performance was provided by the fFN testing alone. However, the sensitivities did not differ significantly between the various combinations; this means that, depending on local resources, a choice can be made among these options. In facilities where vaginal ultrasound equipment and expertise are readily available (especially in tertiary care centres), CL measurement is a good test for the initial triage. When CL results are in an intermediate range, fFN testing clearly provides useful additional information to decide whether the woman with resolved preterm labour can be discharged. In facilities where vaginal ultrasound is not routinely offered, fFN testing offers an excellent option to decide if a woman with preterm labor requires treatment and referral to a tertiary facility. Regardless of the strategy employed, it is important to perform the fFN swab sampling before any other vaginal examinations (CL measurement or digital examination) as routinely recommended for fFN testing. The swab is simply discarded if the test is deemed unnecessary on the basis of CL measurement.

There is no agreement about the benefits of combining fFN testing and CL measurement in women with preterm labor. Rozenberg et al. (16)

using a one-step combination (both tests performed for every patient), found the combination of tests to have limited value, whereas several other studies reported increased predictive values when both tests were combined in various ways (15,18,20). The selective use of fFN after CL measurement, was proposed by Hincz et al. (18) and by Schmitz et al. (20). Both studies reported an improved specificity when fFN testing was limited to cases of intermediate measurement of CL (21-31mm for Hincz, and 16-30mm for Schmitz). Gomez et al. (19) found a significant improvement in the prediction of preterm delivery when fFN was tested after a CL of <30 mm. However, numerous reports have confirmed that both cervical length measurement and fFN testing had a good to excellent reproducibility (3). Depending on the type of facility and staff availability, the choice of the first-line test, fFN testing, or CL measurement, provides similar predictive values among women with threatened preterm labor.

Conclusion

We have confirmed that fFN testing in patients selected by use of cervical sonography is more specific for predicting preterm birth than cervical length measurement alone, and it is as effective as fFN testing in all women. Cervical ultrasound after fFN triage is an acceptable option, depending on the resources available.

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