AFRICAN JOURNAL OF FETOMATERNAL MEDICINE

Original Article

Cervico-Vaginal Foetal Fibronectin for Predicting Preterm Birth in Women with Preterm Contraction: A Cross-sectional Study at a Nigerian Maternity.

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Abstract

Introduction: Preterm birth contributes substantially to perinatal morbidity, mortality and long-term neuromorbidity among survivors. Its prediction, using foetal fibronectin, may reduce the associated mortality and morbidity. Cervico-vaginal foetal fibronectin (fFN) appears promising, but limited evidence is available on its applicability in low-income countries, with high burden of preterm birth, like Nigeria. This study evaluates the predictability of cervico-vaginal foetal fibronectin (fFN) for preterm birth. **Materials and method:** A cross-sectional study conducted at the Lagos Island Maternity Hospital; Nigeria evaluated foetal fibronectin in cervico-vaginal secretions of pregnant women. Participants presented with symptoms and/or signs of preterm birth between 28 weeks and 35 weeks' gestation. Foetal fibronectin was estimated using a Fetal fibronectin testing kit manufactured by Nantong Egens Biotechnology Co., Ltd China©rapid. Women were offered standard obstetric care as per institutional protocols and followed up till birth. **Results:** Thirty-three (18.4%) of 179 women had a positive fetal fibronectin result. At 7 days after testing, foetal fibronectin predicted preterm birth with sensitivity, specificity, positive and negative predictive value of 93.3%, 88.4%, 42.4% and 99.3% respectively. Foetal fibronectin predicted preterm birth before 37 weeks with sensitivity, specificity, positive and negative predictive value of 71.1%, 95.8%, 81.8%, and 92.5% respectively. Sixty-five per cent (116/179) of women had corticosteroids, while 73.2% had tocolysis. **Conclusion:** The cross-sectional study indicates fetal fetoprotein predicts preterm birth at 7 days with high sensitivity and negative predictive value. The routine use of fibronectin to predict preterm birth in low -income countries may improve the quality of care for women with symptoms of spontaneous preterm labour and perinatal morbidity and mortality in these settings.

Keywords: Tocolysis, Antenatal Corticosteroids, Delivery, Preterm Birth, Surfactant,

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Introduction

Preterm birth is the delivery of a fetus before 37 completed weeks of gestation. The global incidence was estimated by WHO[3] as 9.6% of all births with the highest rates occurring in Africa (11.9%) and North America (10.6%).[3] The frequency of preterm births is increasing worldwide,[4] presumably due to an increase in multiple births, older age at childbearing as well as the use of assisted reproductive technologies (ART) and other fertility treatments.[4-7]

Preterm birth is a common cause of neonatal mortality and severe morbidities mainly due to associated low birth weight and deficiency of lung sulfactant.[1, 2, 8] Children born prematurely have higher rates of cerebral palsy, sensory deficits, learning disabilities and respiratory illnesses compared with children born at term.[9] These severe morbidities can cause significant psychological, sociological and financial burden on the parents or the carers.[10]

Traditional approaches to predicting preterm birth was to identify risk factors, detect persistent uterine contractions, and look for progressive cervical dilatation and effacement.[10] However, about 10% of spontaneous early preterm births are associated with a history of prior preterm labour, and the symptoms and signs that ensue are often vague and non-specific.[11, 12]

A significant percentage of women with preterm contractions will not progress into established preterm birth hence, the use of clinical features is associated with over-diagnosis, unnecessary admission and unwarranted interventions with tocolysis and corticosteroids. Conversely, delayed diagnosis of preterm birth negates prompt treatment and deprives women and their neonates of early interventions. Hence, a simple investigational tool that reliably and accurately predicts progression to established preterm birth is critical to improve health outcomes of neonates delivered preterm

In recent years, fetal fibronectin has been used to predict preterm birth. Fetal fibronectin, a glycoprotein is produced in fetal tissues of amniotic fluid, placental tissue, and the extracellular substance of decidua basalis.[11-15] At 22 weeks of gestation and beyond, FFN cannot be detected from vaginal secretions because of the close approximation of the chorion and decidual, which obliterates the extra-amniotic space. .[2, 10-13] Detection of FFN in vaginal secretions from 22 weeks' gestation, but before 37 completed weeks may therefore imply pathological disruption of the extra-amniotic space and may help predict true preterm birth.[13]

In normal pregnancy, the level of fetal fibronectin drops to < 50ng/ml after 22 weeks making it undetectable between 22 to 37 weeks of gestation.[16-18]When elevated (>50ng/ml), in cervicovaginal secretion from 22 to less than 37 weeks, fetal fibronectin can be considered an indicator of preterm birth in women with symptoms.[16-18]

The American College of Obstetricians and Gynecologists (ACOG)[19] and the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)[20] have recommended the use of FFN to predict true preterm birth in women at risk. Yet, there is no effective way to predict preterm birth in sub-Saharan Africa, including Nigeria despite the high incidence of preterm birth and the overwhelming implications, including early neonatal death and long-term morbidities. The objective of this study was to evaluate the predictive role of cervico-vaginal fetal fibronectin in true preterm birth in women with spontaneous preterm contractions at the Lagos Island Maternity Hospital, Lagos state. Nigeria

Material And Methods

This was a cross-sectional study conducted from 1st July 2014 to 31st August 2015 at the Department of Obstetrics and Gynaecology of Lagos Island Maternity Hospital, Lagos state, Nigeria. Ethical approval (P/MED/LIMH/421/043) was obtained on the 13th January, 2014 from the Institutional Research Board of the Lagos Island Maternity Hospital, Lagos State, Nigeria. All patient were duly counselled before enrollment, and they were informed of the right to withdraw from the study at any time if they so wish.

Pregnant women with singleton pregnancy at gestational ages between 28 and 35 weeks who presented with symptoms or signs of preterm birth were studied. Gestational ages were calculated from the first day of the last normal menstrual period and confirmed by ultrasonography measurements in the first or second trimester.

Threatened preterm labour was defined as at least one palpable contraction lasting at least 20 seconds. Participants were recruited in the study if there was (1) no rupture of membranes; (2) absence of vaginal bleeding; (3) no indications for iatrogenic preterm birth (signs of fetal compromise, hypertensive disorders of pregnancy, chorioamnionitis, Congenital fetal anomaly); (4) absence of signs or symptoms of urinary tract infection; (5) cervical dilatation of < 3 cm and (6) absence of cervical cerclage.

- Rapid Foetal fibronectin testing kit manufactured by Nantong Egens Biotechnology Co., Ltd©, China was used for specimen collection from the posterior fornix of the vagina during a speculum examination. The swab was placed into a tube containing the extraction buffer and mixed vigorously for 10-15seconds, after specimen collection. The buffered cervico-vaginal specimen was qualitatively tested for fetal fibronectin by dispensing it into the sample application well of the Rapid FFN Cassette and the result was read according to the instructions provided by the manufacturer. Vaginal samples were collected before performance of any procedures that might disrupt the cervix, such as digital cervical examination, vaginal ultrasound, or sampling for microbiologic culture of cervical secretions. The test result was concealed from the women and standard care was rendered to all participants according to institutional policies without prejudice to their fibronectin results.

Baseline socio-demographic characteristics of each participant were obtained at recruitment using a purpose-designed proforma. Presenting symptoms and cervical status at presentation were recorded. Additional information recorded was digital examinations, sexual intercourse, or transvaginal ultrasound scan within the 24 hours preceding swab collection. The primary outcomes were the gestational age and the latency interval between

fFN testing and delivery. The data was analyzed using IBM-SPSS 22.0.

		Disease		
		Yes	No	
Test Results	Positive	True positive A	False positive B	Positive predictive value = A / A+B
	Negative	C False negative	D True negative	Negative predictive value = D / C+D
		Sensitivity = A / A+C	Specificity = D / B+D	

The sensitivity, specificity, negative and positive predictive values of the fetal fibronectin kit was generated using a 2 x 2 table (depicted below) with a 95% confidence interval.

Results

Two hundred and two women with spontaneous preterm contraction were recruited into the study. Twenty-three (23) women were excluded from the study and 13 women were lost to follow-up. Ten women had iatrogenic birth for pregnancy complications such as hypertensive disorders of pregnancy (3), antepartum hemorrhage (2), non-reassuring fetal status (4 and intra-uterine fetal death (1). Data of 179 women were analyzed for the study.

The socio-demographic characteristics of the women are as in Table 1A. The mean age of enrolled patient was 29.1 ± 5.79 years and most (35.8%) of the women were nullipara. The gestational age at enrolled patients is depicted in table 1B: The mean gestational age at recruitment and maternal age was 31.9 ± 1.89 weeks

Thirty-three (18.4%) women had a positive FFN result, while 146 women had negative results. Among women who had positive fetal fibronectin test, five (15.1%) women gave birth within 24 hours of testing. None of the women with a negative fibronectin test had preterm birth. The sensitivity of fibronectin to predict preterm birth was 100% within 24 hours. The specificity, positive predictive value and negative predictive value was 83.9%, 15.2% and 100 %, respectively.

At 7 days of fFN testing, 15 (8.4%) women (14 FFN positive and 1FFN negative) gave birth. The sensitivity of fibronectin to predict preterm birth within 7 days of test was 93.3%, with specificity, positive predictive value and negative predictive value of 88.4%, 42.4% and 99.3%, respectively.

The prediction of preterm birth within 14 days of FFN testing and before 37 weeks' gestation are shown in Table 2 while the validity of fetal fibronectin test is shown on Table 3.

One hundred and forty women had hospital admission for risk of preterm birth. The mean duration of admission was 4.9 days and 4.7 days for the FFN positive and negative patients respectively, while the latency period between

Table I. Socio-Demograghic Characteristics of Women with Spontaneous Preterm Contractions at The Lagos Island Maternity Hospital, Lagos State

Characteristics	Frequency		
	FFN* positive (n= 33)	FFN negative (n=146)	Total (n=179)
Age (years)	29.0 ± 6.88	29.1 ± 5.54	29.1 ± 5.79
Nulliparous	7	57	64
Primipara	15	39	54
Multipara	11	50	61
G.A* at recruitment (weeks)	31.6 ± 1.87	32.0 ± 1.90	31.9 ± 1.89

Table IB. Gestational age at enrollment of study participants at the Lagos Island Maternity Hospital, Lagos State

Characteristics	Frequency		
	FFN* positive (n= 33)	FFN negative (n=146)	Total (n=179)
G.A* at recruitment (weeks)	31.6 ± 1.87	32.0 ± 1.90	31.9 ± 1.89

*FFN = fibronectin *G. A = Gestational age

Table II. Fibronectin Test Results and Delivery Outcomes of Pregnant Women with Symptoms and/or Signs of Preterm Labour At LIMH

Delivery outcomes	FFN positive (n=33)		FFN negative (n=146)		Total (n=179)	
	frequency	%	frequency	%	frequency	%
Latency interval between admission testing and delivery						
< 24 hours	5	15.2	0	0	5	2.8
> 24 Hours to ≤ 7days	9	27.3	1	0.7	10	5.6
> 7 Days to ≤ 14days	8	24.2	4	2.7	12	6.7
> 14 Days	11	33.3	141	96.6	152	84.9
Total	33	100	146	100	179	100
Latency interval (Cumulative) between admission testing and delivery						
< 24 Hours	5	15.2	0	0	5	2.8
≤ 7 days	14	42.4	1	0.7	15	8.4
≤ 14 days	22	66.7	5	3.4	27	15.1
≤ 37 Weeks	27	15.1	11	6.2	38	21.2

Delivery outcomes = Selected intervals of delivery from testing

Table III: The Validity of Foetal Fibronectin Test (95% Confidence Intervals)

Latency period / Statistics	< 24 Hours	< 7 Days	< 14 Days
Sensitivity (%)	100.0 CI 46.3 to 100.0	93.3 CI 66.0 to 99.7	81.5 CI 61.3 to 93.0
Specificity (%)	83.9 CI 77.4 to 88.9	88.4 CI 82.3 to 92.7	92.8 CI 87.1 to 96.2
The probability that a fFN test result is a true positive (PPV) or true negative (NPV) are			
PPV (%)	15.2 CI 5.7 to 32.7	42.4 CI 26.0 to 60.6	66.7 CI 48.1 to 81.5
NPV (%)	100.0 CI 96.8 to 100.0	99.3 CI 95.7 to 100.0	96.6 CI 91.8 to 98.7
likelihood Ratios:			
PLR	6.2 CI 4.4 to 8.7	8.1 CI 5.2 to 12.6	11.3 CI 6.2 to 20.5
NLR	0.0	0.08 CI 0.0 to 0.5	0.2 CI 0.1 to 0.4

*PPV: Positive predictive value * NPV: Negative predictive value

*PLR: Positive likelihood ratio *NLR: Negative likelihood ratio

Table IV: Fetal fibronectin test and admission characteristics of pregnant women with symptoms and/or signs of preterm labour at LIMH. (95% confidence intervals)

Characteristics	FFN positive (n=33)	FFN negative (n=146)	Total (n=179)
Number of patients admitted	32	108	140
Duration on admission (mean in days)	4.9 CI 1.14 -8.66	4.7 CI 1.31 to 8.09	4.7 CI 1.23 to 8.17
Latency period (Mean in days)	8.9 CI 6.51 to 24.30	45.9 CI 13.68 to 78.12	38.8 CI 2.02 to 79.63
Mean G.A at delivery (Mean in weeks)	34.3 CI 28.56 to 40.04	38.3 CI 35.28 to 41.31	37.58 CI 32.82 to 42.02

FFN denotes fetal fibronectin; G.A denotes Gestational age; LIMH denotes Lagos Island Maternity Hospital; Latency period = duration between testing and delivery; CI = Confidence interval

Table V. FFN test results and interventions to FFN positively and negatively tested pregnant women with symptoms and/or signs of preterm labour at LIMH

Interventions	FFN positive(n=33)		FFN negative(n=146)		Total(n=179)	
	Frequency	%	Frequency	%	Frequency	%
Use of tocolytics	29	87.9	102	69.9	131	73.2
Use of corticosteroids	30	90.9	86	58.9	116	64.8
Use of antibiotics	19	57.6	60	41.1	79	44.1

fibronectin testing and birth was 45.9 days for women who had negative test as in Table 4. One hundred and thirty-one (73.2%) women had tocolysis, 116 women (64.8%) had corticosteroids, while 79 (44.1%) women had antibiotics.

Discussion

The objective of the study was to evaluate the ability of cervicovaginal fetal fibronectin to predict preterm birth in symptomatic pregnant women in a low-resource setting. The study found that fetal fibronectin predicted preterm birth at 7 days post-test, with sensitivity, specificity and negative predictive value of 93.3%, 88.4% and 99.3% respectively. In addition, fetal fibronectin predicted preterm birth before 37 weeks with sensitivity, specificity and negative predictive value of 71.1%, 95.8% and 92.5%, respectively.

Implications for practice:

There appears to be some usefulness for fetal fibronectin to predict preterm birth in symptomatic pregnant women as found in this study. However, fetal fibronectin showed a much more consistent result to predict women who would not have true preterm birth, despite being symptomatic. Fetal fibronectin had a specificity of 83.9%, 88.4% and 95.8% for preterm birth at day 1, day 7, and for before 37weeks, respectively. The negative predictive value was 100%, 99.3% and 92.5% respectively for the same time points. This implies the possibility of out-patient care for symptomatic women, with an advantage of reduced costs to the woman and the health systems.

Though few previous studies assessed the accuracy of FFN within 24 hours, this study reports that only
15.1% of women with a positive test went on to have preterm birth within 24 hours of fetal fibronectin test. A smaller study involving 25 Chinese women[21] reported sensitivity and NPV of 100% and specificity and PPV of 66.6% and 40%, respectively. Regarding the ability of fFN test to predict preterm birth within 7 days, our results are similar previous reports of other studies. In addition, women with a positive test had higher likelihood of preterm birth within 14 days of testing unlike women with a

negative test. The reported NPV for preterm birth at 14 days is similar to that of previous studies, which was 91.7 – 98%.[21, 26, 27 22-4]

There are concerns on the management of symptomatic women with a positive fFN result. This is due to the low PPV (15.2-42.4%) for preterm birth prediction within 7 days of testing. In such a circumstance, there is the need for meticulous review of the woman's obstetric and medical history, as well as a detailed risk assessment to determine the management plan. There will be the need for counseling of the women and respect for the women's choice of treatment plan.

Though our study excluded multiple gestations, the results we reported were similar to those of studies that involved multiple gestations, with close similarity of the negative predictive values. Amanda and et. al., [25] and Cheung et. al.,[21] found sensitivity, specificity, PPV and NPV of 80%, 85.1%, 37.5%, 97.4% and 100%, 70.1%, 50%, 100% respectively, while Lowe et al[24] found sensitivity, specificity, PPV and NPV of 66.7%, 79.1%, 18.2%, and 97.1%.

The relationship between the latency period and the sensitivity/specificity in this study shows clearly that the sensitivity of fetal fibronectin test in predicting true preterm labour decreases as latency period increases. Sensitivity reduces from 100% to 93.3% and then to 81.5% for latency period of less than 24 hours, less than 7 days and less than 14 days respectively. This is unlike the specificity of the foetal fibronectin, which increased as latency period increased.

Thirty-two (22.9%) of 140 women admitted into the ward had positive fFN test result and 10.7% (15/140) had preterm birth within 7 days of admission. This included a woman with a negative fFN test. The mean duration of stay on admission in the FFN negative patients was 4.7 days.

The cost of having a qualitative fFN test of $5 (1,750 Naira) was cost beneficial to the patient compared to the average cost of admission which at the study center (LIMH) was $53 (₦18,500). This cost excludes other cost of medications (analgesics, steroids, and antibiotics) which were routinely administered to the admitted in this study.

Steroids have been clearly shown to reduce perinatal morbidity and mortality when administered to women who have preterm birth prior to 34 weeks' gestation.[28-32] This has made the administration of corticosteroids to women with symptomatic preterm labour standard of care in anticipation of preterm birth. However, this includes women who may not have preterm birth. In a systematic review, Honest et al[10] evaluated the use of steroids in symptomatic women at 31 weeks' gestation and the occurrence of respiratory distress syndrome (RDS). They found that among patients with positive FFN test results, 17 symptomatic women would require treatment to prevent one case of RDS while for those with negative FFN test results, 509 symptomatic women would need to be treated to prevent one case of RDS. In this study 116 patients (64.8%) of total 179 patients had steroids administered among which 86 (48%) of them who had a negative FFN test result. The fact that a negative FFN result confers a 99.3% chance of not experiencing preterm birth within the next seven days permits the withholding of antenatal corticosteroids. Such fetuses would have been spared the yet unknown adverse effects that may be associated with antenatal corticosteroid therapy. Therefore, the use of fFN would reduce the need for corticosteroid administration in women symptomatic preterm labour.

The strength of the study is the ability to use fetal fibronection qualitative test in a low-income setting with high prevalence of preterm birth. The results which can reliably predict that a symptomatic woman with negative test, would not experience preterm birth is another strength as it would reduce health care costs. Despite the strength, a limitation of this study is the use of a qualitative test in detecting fetal fibronectin in cervico-vaginal secretions. A quantitative assessment of cervico-vaginal fetal fibronectin will be more useful, allowing for quantification of the fetal fibronectin concentration. However, it is not readily accessible and would also be more expensive, preventing its use in routine clinical practice. Considering that the qualitative testing is not in routine clinical use in Nigeria as at yet however, it is expected that the qualitative testing done in this study will still influence clinical practice.

Conclusion

The study shows more of the clinical relevance of FFN test in its ability to predict women with symptomatic preterm labour who would not experience preterm birth. The use of fFN may significantly improve the quality of care by reducing hospital admission, unwarranted obstetric interventions and cost without unduly increasingperinatal morbidity and mortality, especially in a resource-constrained country like Nigeria.

Funding Information: The research team did not receive any external fund-ing for this project. It was entirely funded by the team.

Consent for Publication: Not applicable

Competing interests: All the authors have no competing interest to declare

Abbreviations

fFN – Foetal fibronectin; NPV – Negative predictive value; PPV – Positive predictive value; LIMH – Lagos Island Maternity Hospital

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