ABSTRACT

Background: The incidence of preterm birth is increasing worldwide. Preterm birth is a common cause of neonatal morbidity and mortality commonly associated with low-birth weight and deficiency of lung surfactants in the newborn. Children who were born preterm have higher rates of cerebral palsy, neurodevelopmental anomalies, learning disabilities, and respiratory illnesses compared with children born at term with attendant psychosocial and financial burden on the parents or carers. These problems may be minimized via the use of a preterm birth prediction test such as the maternal cervicovaginal fetal fibronectin test (FFT) to determine those women in genuine preterm labor and at a higher risk for preterm birth. Effective treatment can then be focused on this group of women to reduce the incidence of preterm birth. However, the FFT in preterm birth prediction is underutilized in Nigeria.

Aim: To determine the role of cervicovaginal fetal fibronectin testing as a predictor of spontaneous preterm birth in symptomatic pregnant women in a local setting.

Setting: This study was conducted at the obstetrics unit of the Department of Obstetrics and Gynaecology at the Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC), Ile-Ife, Osun state, Nigeria. The OAUTHC comprises two obstetrics units – Ife Hospital Unit (IHU) and Wesley Guild Hospital Unit at Ilesha (WGH).

Design: Cross-sectional, descriptive study.

Methods: In this study, 182 booked and unbooked singleton antenatal mothers between 28 weeks and 36 weeks 6 days gestation who had symptoms suggestive of preterm labor were recruited. An interviewer administered questionnaire was filled for each subject and a sterile speculum vaginal examination was then performed to obtain a specimen of the subject’s cervicovaginal secretion using a sterile cotton swab. A qualitative FFT was done on each sample collected, then recruited mothers were monitored till delivery and further data obtained.

Outcome Measures: The main outcome measures were the sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) of FFT in predicting spontaneous preterm birth in symptomatic pregnant women.

Results: A total of 182 women presenting with symptoms suggestive of preterm labor were recruited: 171 (93.96%) women delivered at term, whereas 11 (6.04%) women had preterm birth with a calculated preterm birth rate of 7.33 per 1000 deliveries during the study period. Also, 7 (3.85%)
women had a positive FFT, while 175 (96.15%) women had a negative test. FFT had a sensitivity, specificity, PPV, and NPV of 9.09%, 96.49%, 14.29%, and 94.29%, respectively; a LR+ and LR- of 2.59 (95% confidence interval, CI, 0.34–19.68) and 0.94 (95% CI, 0.78–1.14) respectively; a relative risk of 2.59 (95% CI, 0.341–19.675); a calculated accuracy of 91.21% (95% CI, 86.12%–94.89%); and an area under the receiver operating characteristic curve of 0.60.

**Conclusion:** The high NPV of fetal fibronectin sampling in a population of pregnant women with symptoms supports less intervention for patients with negative results.

**Key words:** Fetal fibronectin; pregnant women; preterm birth; preterm labor.

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**Introduction**

Preterm birth is defined as the delivery of a baby before 37 completed weeks of pregnancy.[1] It is a leading cause of perinatal morbidity and mortality globally.[2] Preterm birth has an increasing incidence worldwide[2-4] and factors such as assisted reproductive techniques and multiple gestation contribute to this increase.[4,5] The majority of preterm births the world over occur in the developing regions of sub-Saharan Africa and south Asia. These regions also happen to account for a greater percentage of global live births.[2]

Preterm birth represents the second most common direct etiological factor for under-5 mortality. It also contributes significantly to severe infant morbidities. Surviving preterm babies may suffer morbidities, such as apnea of prematurity, anemia of prematurity, necrotizing enterocolitis, retinopathy of prematurity, pulmonary hypoplasia, respiratory distress syndrome, intraventricular hemorrhage, intraparenchymal hemorrhage, periventricular leukomalacia, neurodevelopmental, and cognitive anomalies among others.[6,7] The management of these morbidities presents a psychosocial and economic burden on both the carers and the community as a whole.[7,8] The prediction of genuine preterm labor with its prompt treatment will therefore go a long way in reducing the incidence of preterm birth and improve the rates of infant morbidity and mortality associated with spontaneous preterm birth.

Pregnant women with symptoms suggestive of preterm labor are conventionally accorded in-patient care and treated with corticosteroids to hasten lung maturity, tocolytics to delay birth so the fetus will have adequate corticosteroid exposure, and in-utero transfer to a perinatal center for optimal neonatal care should preterm birth occur.[9] But studies have shown that only about 20% of pregnant women with symptoms suggestive of preterm labor will eventually have a preterm birth.[10] This means that about 80% of these women with threatened preterm labor will not progress to preterm birth and may not require drug treatment. However, the antenatal prediction of those symptomatic pregnant women with genuine preterm labor is challenging.

Several methods have been employed in attempts to predict genuine preterm labor but the use of maternal cervicovaginal fetal fibronectin in preterm birth prediction has been promising.[11,12] Fetal fibronectin is an extracellular matrix glycoprotein produced by amniocytes and cytotrophoblasts. It is present mainly in the choriodecidual interface which is the union between the fetal and maternal tissues.[13-17] Normally, fetal fibronectin is present in cervicovaginal secretions of pregnant women but its concentration significantly reduces to undetectable levels after 22 weeks of gestation due to the close approximation of the choriodecidual interface around this time, thereby effectively sealing off the extra-amniotic space. Therefore, detection of fetal fibronectin in cervicovaginal secretions after 22 weeks but before term may indicate a disruption of the choriodecidual interface, which will help to recognize genuine preterm labor and therefore facilitate the prediction of preterm birth.[13-17]

Although, various authorities have advocated the use of fetal fibronectin in preterm birth prediction,[11,12] it has been largely underutilized in Nigeria. This may not be unrelated to the gap in knowledge occasioned by the dearth of local studies concerning cervicovaginal fetal fibronectin and preterm birth in Nigeria.

This study, therefore, aims to assess the effectiveness of utilizing maternal cervicovaginal fetal fibronectin test (FFT) in women with symptoms suggestive of preterm labor in the prediction of preterm birth.

**Methods**

**Study population**

The study was carried out among booked and unbooked pregnant women presenting with symptoms (uterine contractions) suggestive of preterm labor between 28 weeks and 36 weeks 6 days of gestation at the obstetric emergency units and the antenatal clinics of both arms of the hospital.
Study design
This is a cross-sectional, descriptive study.

Patient recruitment
All patients who met the inclusion criteria below were recruited until the sample size target was met.

Inclusion criteria
1. Patients willing to give informed consent
2. Gestational age should be between 28 weeks and 36 weeks 6 days
3. There should be at least one (1) palpable uterine contraction
4. Cervical dilatation should be ≤2 cm
5. Fetal membranes should be intact
6. There should be no indication for preterm delivery (presence of any medical or obstetric indication for the preterm delivery)
7. There should be neither sexual intercourse, digital cervical examination, transvaginal ultrasonography, nor vaginal suppository use in the prior 24 h of presentation.

Exclusion criteria
1. Indicated preterm birth
2. Cervical dilation ≥3 cm
3. Rupture of fetal membranes
4. Vaginal bleeding
5. Sexual intercourse, digital cervical examination, transvaginal ultrasonography, douching, and vaginal suppository use in the prior 24 h of presentation.

Sample size determination
The sample size was determined based on a prevalence of preterm birth of 118 per 1,000 deliveries according to a study conducted among a target population in Nigeria by Olugbenga et al.,[20] using the statistical formula for estimating sample size for single proportion.[21,22] Using a fall-out rate of 10%, a minimum sample size of 178 was obtained and a total of 182 subjects were included in the final analysis for this study.

Baseline data collection
Following recruitment of patients at admission to the antenatal ward, the study protocol was explained to the patient and a written consent obtained using the subject information and consent sheets. An interviewer-administered questionnaire was then filled for each subject, to document relevant data related to sociodemographic characteristics and symptomatology of the preterm labor.

The managing physicians were blinded to the results of the FFN test to ensure that decisions regarding admission, use of tocolytics and antenatal steroid therapy were made on clinical grounds by each physician, without recourse to the result of the cervicovaginal fetal fibronectin status. At the time of delivery, further data collected include gestational age at delivery, birth weight, and APGAR score.

Specimen collection
For women who met the inclusion criteria, specimen was obtained from the posterior vaginal fornix during a sterile speculum vaginal examination using the sterile swab provided in the rapid fetal fibronectin test kit (a product of the Nantong Egens Biotechnology company Ltd, China). The swab was applied to the posterior vaginal fornix for about 5 to 10 seconds to absorb the cervicovaginal secretions and then withdrawn carefully and placed in the extraction buffer tube. A digital vaginal examination was then done immediately after specimen collection to ascertain the cervical dilatation.

The buffer tube was then shaken manually for about 10 to 15 seconds and the swab was thereafter removed and discarded. The subject’s identification number on the questionnaire was then appended on the specimen tube. The sample was then dispensed into the applicator well of the cassette and left to stand for 15 minutes.

During this period, the sample flows across a nitrocellulose membrane and an antifetal fibronectin antibody in the membrane flows with the sample. This antifetal fibronectin antibody, which is mouse obtained, forms an antigen-antibody complex with the fetal fibronectin in the sample, and this complex crosses a zone on its flow path containing a second antifetal fibronectin antibody. A reaction between the flowing antigen-antibody complex and the immobilized antibody forms a visible line. The sample flow then continues and crosses a second zone containing immobilized antimouse antibody, which then reacts with the unbound mouse derived antifetal fibronectin conjugate and forms a second visible line, serving as an assay control.

Precautions taken before obtaining the specimen were centered on excluding factors that may interfere with the interpretation of results. These factors include sexual intercourse, digital cervical examination, transvaginal ultrasonography, douching, and vaginal suppository use in the prior 24 h of presentation.[23]

Interpretation of results
The rapid fetal fibronectin test was positive if two lines were observed, whereas the test was negative if only the control line appears. It is invalid if no lines appeared or the control line was absent. The test result was concealed from the women and the attending physician. Management was at the discretion of the attending physician.
Consent
Informed and written consent was obtained from all the subjects who participated in this study. This study confined to the standards of declarations of Helsinki.

Statistical analysis
All statistical analyses were performed using IBM-SPSS® version 22.0 (IBM Corp., Armonk, NY, USA, 2011). Numerical parametric variables were presented as mean ± standard deviation (SD), numeric nonparametric variables were presented as median and interquartile range, whereas categorical variables were presented as frequencies and percentages (%). Chi-square or Fisher’s exact tests were used for categorical outcomes. Student’s t-test was used for comparison between groups for variables which were normally distributed, while Mann–Whitney U-test was used for skewed data. A two-sided P value <0.05 was considered significant.

The diagnostic accuracy of qualitative cervicovaginal FFT in predicting preterm birth was determined using sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV). Furthermore, the predictive power was assessed utilizing the area under the receiver operating characteristic (ROC) curve, likelihood ratios (LR), accuracy and diagnostic odds ratio (DOR).

Results
A total of 182 women were included in the final statistical analysis of this study. The mean maternal ages of the subject groups who had preterm and term deliveries were 32.27 years ± 5.55 SD and 30.89 years ± 5.05 SD, respectively, whereas the combined mean maternal age for both groups was 30.98 years ± 5.089 SD with an age range of 18–42 years as shown on Table 1. A greater proportion (38.50%) of the subjects were traders; all (100%) of the subjects were married; a greater proportion (73.60%) of the subjects was booked and majority (91.80%) of the subjects were ethnic Yoruba’s [Table 2].

The mean parities of the subject groups who had preterm and term deliveries were 1.55 ± 0.93 and 1.20 ± 1.15, respectively, whereas the combined mean parity for both groups was 1.23 ± 1.14 with a range of 0–5 as shown on Tables 1 and 3. The mean body mass indices (BMI) of the subject groups who had preterm and term deliveries were 26.98 ± 3.29 kg/m² and 28.28 ± 5.57 kg/m², respectively, whereas the combined mean BMI for both groups was 28.20 ± 5.46 kg/m² with a range of 19.30–48.50 kg/m² as shown on Tables 1 and 3.

Only 11 (6.04%) of the 182 study participants had preterm birth (PTB) within 6 months of recruitment in the two units of our study center with a total annual birth of about 3000. This gives a calculated preterm birth rate of 7.33 per 1000

Table 1: Background characteristics of study respondents

| Variable       | Mean±SD       | Median   | Interquartile range | Range         |
|----------------|---------------|----------|---------------------|---------------|
| Age (years)    | 30.98±5.08    | 31       | 28-34               | 18-42         |
| Parity         | 1.23±1.14     | 1        | 0-2                 | 0-5           |
| BMI (kg/m²)    | 26.20±5.46    | 27       | 24.60-31.30         | 19.30-48.50   |

Table 2: Background characteristics of study respondents

| Variable       | Frequency (182) | Percentage (100%) |
|----------------|-----------------|-------------------|
| Marital status |                 |                   |
| Single         | 0               | 0.00%             |
| Married        | 182             | 100.00%           |
| Booking status |                 |                   |
| Booked         | 134             | 73.80%            |
| Unbooked       | 48              | 26.40%            |
| Occupation     |                 |                   |
| Professional   | 58              | 31.90%            |
| Artisan        | 27              | 14.80%            |
| Trader         | 70              | 38.50%            |
| Housewife      | 27              | 14.80%            |

Table 3: Comparison of maternal characteristics between preterm and term delivery

| Variable       | Mean±standard deviation | P     |
|----------------|-------------------------|-------|
|                | Preterm (n=11)          | Term (n=171) |
| Age (years)    | 32.27±5.55              | 30.89±5.05     | 0.73    |
| Parity         | 1.55±0.93               | 1.20±1.15     | 0.46    |
| BMI (kg/m²)    | 26.98±3.29              | 28.28±5.57     | 0.14    |
| Married        | 11 (6.04%)              | 171 (93.96%)  | 0.63    |
| Single         | 0 (0.00%)               | 0 (0.00%)     | 0.94    |
| Booking status |                         |            |
| Booked         | 8 (72.73%)              | 126 (73.68%)  | 0.93    |
| Unbooked       | 3 (27.27%)              | 45 (26.32%)   |         |
| Occupation     |                         |            |
| Professional   | 4 (36.36%)              | 54 (31.58%)   | 0.96    |
| Artisan        | 2 (18.19%)              | 25 (14.62%)   |         |
| Trader         | 4 (36.36%)              | 66 (38.60%)   |         |
| Housewife      | 1 (9.09%)               | 26 (15.20%)   |         |
| Ethnicity      |                         |            |
| Yoruba         | 10 (90.91%)             | 157 (91.81%)  |         |
| Igbo           | 1 (9.09%)               | 13 (7.60%)    |         |
| Hausa          | 0 (0.00%)               | 1 (0.59%)     |         |
| Prior preterm birth |                   |            |
| Present        | 0 (0.00%)               | 1 (0.59%)     | 0.80    |
| Absent         | 11 (100.00%)            | 170 (99.41%)  |         |
| PIH            |                         |            |
| Present        | 0 (0.00%)               | 5 (2.92%)     | 0.57    |
| Absent         | 11 (100.00%)            | 166 (97.08%)  |         |
deliveries. Also, 70 women (38.46%) delivered by caesarean section, whereas 112 women (61.54%) delivered vaginally [Table 4].

A greater proportion (73.68%) of patients that delivered at term was booked and this is comparable to the proportion (72.7%) of those who delivered preterm and were booked. All patients (100%) with prior history of preterm birth and associated pregnancy-induced hypertension (PIH) delivered at term. Also, there were no significant differences between women who delivered at term and women who had PTB regarding maternal age, BMI, parity, occupation, ethnicity, mode of delivery, and mode of patient care as shown on Tables 3 and 4.

Greater proportions of women with preterm (90.91%) and term (96.49%) births had negative FFT compared with 9.09% and 3.51% respectively in women who tested positive to fetal fibronectin (P > 0.05), as shown on Table 5. The diagnostic performance of qualitative FFN test in predicting preterm delivery showed a sensitivity and specificity of 9.09% and 96.49% respectively; a PPV and NPV of 14.29% and 94.29% respectively; a positive likelihood ratio (LR+) and negative likelihood ratio (LR-) of 2.59 (95% confidence interval, CI, 0.34–19.68) and 0.94 (95% CI, 0.78–1.14) respectively; a relative risk (RR) of 2.59 (95% CI, 0.34–19.675); a calculated accuracy of 91.21% (95% CI, 86.12%–94.89%); and an area under the ROC of 0.60 as shown on Table 6.

**Discussion**

This study demonstrated a preterm delivery prevalence rate of 7.33 per 1,000 deliveries. This rate is expected to be higher than community based studies because our center is a tertiary center which attends to referrals from other primary and secondary centers. This should reduce the denominator and thus exaggerate the preterm delivery rate in teaching hospitals. But interestingly, it is far lower than the preterm delivery rate of 118 per 1,000 deliveries previously reported in Nigeria by Olugbenga et al.\[24\] This prevalence is also lower than the 50 per 1,000 deliveries reported in most developed European countries.\[21\] This difference may not be unrelated to the exclusion of indicated preterm delivery from this study. Thus, reducing the numerator and may account for the lower prevalence.

Although, with a high specificity and NPV, the overall diagnostic performance of qualitative cervicovaginal FFT in spontaneous preterm birth prediction in this study is poor. The specificity and NPV are comparable with those of Iams et al.\[24\] with a calculated specificity and NPV of 86% and 76%, respectively; and Deshpande et al.\[25\] with a pooled specificity of 82.3%. The RR of 2.9 (95% CI, 0.341–19.675) for preterm delivery in those that tested positive to fetal fibronectin compared with those who tested negative is comparable to 2.9 (95% CI, 2.2–3.7) obtained by Peaceman et al.\[26\] Also, the positive likelihood ratio (LR+) and negative likelihood ratio (LR-) of 3.1 and 0.2, respectively, obtained in this study are comparable with those obtained by Gomez et al.\[27\] with an LR+ and LR- of 3.6 and 0.5, respectively. The receiver operating characteristic curve (ROC) area of 0.60 of fetal fibronectin in preterm birth prediction obtained in this study is comparable with that of Gomez et al.\[27\] with an ROC area of 0.758. These imply a poor overall diagnostic performance of the qualitative FFN test in the prediction of preterm delivery.

The high NPV of FFT in this study implies that preterm birth prediction is informative when the result is negative and suggests that patients with a negative test may safely be observed in the outpatient setting. This gives the clinician a specific test on which a decision not to treat may be based. It also improves the clinician’s ability to select patients for drug
therapy and to reduce the number of women who receive such treatment unnecessarily.

This also means that pregnant women with symptoms suggestive of preterm labor with a negative FFT result may not require severe lifestyle changes, like bed rest and work restrictions, which can have significant social, economic, and emotional effects. It may also help avoid unnecessary hospital admissions, prolonged hospital stays, transferal to tertiary units with advanced neonatal support, and the administration of tocolysis and corticosteroids.

It is, however, critical to recognize that a negative FFT does not eliminate the possibility of preterm delivery. Symptomatic women with negative test are still at increased risk of prematurity, simply because they present for unscheduled care. Thus, increased patient education and continued surveillance should continue to be critical components of patient management.

In contrast, the low PPV and overall poor diagnostic performance of the qualitative FFT implies that preterm birth in symptomatic pregnant women who test positive for cervicovaginal fetal fibronectin can be predicted with limited accuracy and clinicians should individualize the management of this group of patients.

Fetal fibronectin testing in a Nigerian population has similar high NPV for preterm delivery to other populations worldwide.

The use of bedside qualitative fetal fibronectin testing will allow the clinicians to adapt their decisions based on the test results. Patients with true low-risk pregnancies will be reassured that the risk of preterm birth is low because the test has a high NPV. Whereas, management of those that test positive can be individualized.

Use of qualitative fetal fibronectin testing in routine clinical practice allows management and resources to be targeted more appropriately and may limit unnecessary intervention.

**Recommendations**

We propose that bedside qualitative fetal fibronectin testing be implemented as hospital policy in Nigeria and women with negative results be managed in an ambulatory fashion.

To achieve this, awareness needs to be created in Nigerian hospitals about the usefulness of the qualitative fetal fibronectin test in the prediction of spontaneous preterm birth.

The test kits also need to be made available at a greatly subsidized cost to the local hospitals. This can be accomplished through active involvement of nongovernmental organizations and the Nigerian government at the federal, state, and local levels. This will go a long way in encouraging its utilization by obstetricians in Nigeria.

Also, adherence to an agreed local management protocol especially with a negative fetal fibronectin test result is critical. Further local studies need to be done in this field, especially involving the quantitative alternative and also with larger sample sizes to give credence to the findings from this study.

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**Conflicts of interest**

There are no conflicts of interest.

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