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■ Original Article

Phosphorylated Insulin-Like Growth Factor Binding Protein-1 and Transvaginal Ultrasonographic Cervical Length in Predicting Spontaneous Preterm Delivery in Susceptible Asymptomatic Patients

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ABSTRACT

Context: Asymptomatic cervical changes may portend and thus predict preterm labour. In addition, chorio-decidual disruption (releasing phIGFBP-1 amongst other markers into the cervical secretions) also occurs prior to preterm delivery. Despite these known facts, the search for the standardize protocol for the prediction of preterm delivery remain an area of divided opinion. ***Aim:*** This study therefore aims at determining whether phIGFBP-1 and transvaginal cervical length assessment, alone or in combination, are effective and applicable in the prediction of preterm delivery in our environment. **Settings and Design:** An analytical prospective cohort study. **Methods and Material:** One hundred and twenty three asymptomatic antenatal clients at risk for preterm delivery were recruited from 22weeks gestation, their sociodemographic characteristics and reproductive profile were obtained and the cervical length estimation was effected using transvaginal ultrasound. At 30weeks gestation, phosphorylated insulin-like growth factor-binding protein-1 (phIGFBP-1) was assessed from cervical secretions and all information entered into a proforma. Patients were followed up till delivery and gestational age at delivery were noted. The ability of the tests, singly and in combination, to correctly predict preterm delivery in asymptomatic susceptible patients was determined. **Statistical Analysis used:** Statistical analyses was carried out using the Statistical Package for Social Sciences (SPSS) version 22. Analysis was done using chi-square and students t-test to check associations for categorical variables and comparisons of means respectively, with significance set at $p<0.05$. **Results:** Eighty-four clients were used for the final analysis. The incidence of preterm

delivery was 193/1000 constituting 19.3%. The most common risk factor for preterm delivery was maternal age less than 18 or greater than 35. A history suggestive of bacterial vaginosis was the significant risk factor. The mean Cervical length at 22-24 weeks in this study was 33.71±9.61mm. Majority of women with a positive phIGFBP-1 (82.1%) had term deliveries just as the majority of women with short cervices = 25mm, with a relative risk of 0.8 and 0.83 respectively. Both tests failed to significantly predict the occurrence of preterm delivery. The sensitivity, specificity, positive predictive value, and negative predictive values for cervical length and phIGFBP-1 are 18.8%, 77.6%, 16.7%, 80% and 62.5%, 31.3%, 17.9%, 77.8% (p values >0.05). The measure of agreement of both tests using the kappa statistic was 0.071. **Conclusion:** Cervical length measurement at 22-24weeks and use of phIGFBP-1 at 30weeks failed to predict spontaneous preterm delivery in susceptible asymptomatic women in this study.

Keywords: phosphorylated insulin-like growth factor binding protein, cervical length, preterm birth, prediction.

Introduction

Preterm birth is one of the recurrent challenges of modern obstetric practice. A substantial morbidity accompanies preterm delivery as well as iatrogenic morbidity associated with prolonged neonatal intensive care. Long-term neurological and neuro-developmental challenges such as cerebral palsy are not unusual. Apart from the human cost, the financial cost of providing inpatient care for preterm babies and providing support in cases of lifelong handicap is great.[1] In the study area, preterm and low birth weight babies account for more than half of new born deaths.[2] The National Demographic and Health Survey, 2013 reports that the neonatal mortality rate (NMR) for babies categorized by mothers as small or very small was more than twice that for babies classified as average or larger.[2] Reasons for preterm birth have multiple, often interacting, antecedents and contributing factors. This complexity has greatly confounded efforts to prevent and manage this complication. Since most cases of preterm delivery cannot be prevented, predicting it will help to create preparedness for its critical management. Assessing the probability of preterm delivery is still a clinical challenge.

Insulin-like growth factor-binding protein-1 (IGFBP-1) is a subgroup of proteins of the insulin-like growth system, which has a function in the control mechanism of fetal and placental growth and development.[3] IGFBP-1 is synthesized and secreted by the human liver and maternal decidua and its concentration in the maternal circulation increase during pregnancy. The phosphorylation status of IGFBP-1 varies in different body fluids and tissues. The non-phosphorylated isoform of IGFBP-1 predominates in the amniotic fluid. The level of phosphorylated IGFBP-1 (*ph*IGFBP-1) rises as the cervix matures and it can be detected in cervical secretions during cervical ripening probably due to the detachment of fetal membranes from the decidua. The measurement of *ph*IGFBP-1 from cervical secretions can be used to estimate the ripeness of the cervix. The process of labour is hypothesized to disrupt the chorio-decidual interface (by contractions or as a normal process in the term uterus), releasing *ph*IGFBP-1 into the cervical secretions. The identification of *ph*IGFBP-1 would thus be indicative of tissue damage of the choriodecidual interface due to the occurrence of the labour process and hence predictive of PTD. Developments in biomedical engineering have allowed the development of a commercial bedside kit (the Actim™ Partus test) for the qualitative detection of *ph*IGFBP-1 (positive or negative results) above the level of 10 ìg/L.[12] Studies showed that the ActimTM Partus cervicovaginal test to detect phosphorylated insulin-like growth factor-

binding protein-1 (*ph*IGFBP-1) might improve the accuracy of predicting preterm delivery.

The Actim™ Partus test has some limitations. Because phIGFBP-1 is also found in human serum, bloody samples may give positive reactions. [3] Before an Actim™ Partus test is performed, the manufacturer recommends an examination to ensure that the fetal membranes are intact, because with ruptured fetal membranes the test will also give a positive result.[4] The level of IGFBP-1 in amniotic fluid is so elevated, that, in case of leakage of amniotic fluid, the Actim™ Partus test will give a positive result. Urine or seminal fluid in the sample does not interfere with performance of the test.[4] Therefore, it has been suggested that recent intercourse does not limit the use of the Actim™ Partus among women with intact membranes.[3,5] However, there is no direct scientific evidence of the effect of prior intercourse on the results of the test. There are also limited data on its role in predicting preterm delivery in asymptomatic patients at risk. The rapid response test designed to detect phosphorylated insulin-like growth factor-binding protein-1 (*ph*IGFBP-1) in cervicovaginal secretions, has been advocated as a cheaper alternative to the fetal fibronectin estimation, without its limitations.

When performed by trained operators, cervical length estimation using transvaginal sonography is safe, objective, acceptable to patients, highly reproducible, and more predictive than transabdominal sonographic screening.[6] Unlike the transabdominal approach, transvaginal cervical sonography is not affected by maternal obesity, cervix position, or shadowing from the fetal presenting part. Cervical length (CL) during pregnancy can range from 25 to 70mm and ultrasound width of the cervical canal ranges from 2 to 4mm.[7] There is agreement that the best time to examine patients with this method to estimate their preterm birth risk is between 18 and 24 gestational weeks.[8] Several studies reported that the measurement of cervical length in the first trimester is not predictive of preterm delivery.[8]

The length of the cervix may be useful in predicting the risk of premature delivery, with a shorter cervix predicting a higher risk.[7] A CL measurement of 25 mm or less is generally considered a reliable indicator of an increased risk of preterm delivery, particularly among women with preterm labour.

Comparing both cervical length and *ph*IGFBP-1, Rahkonen et al.[9] reported that short cervix (<25mm), positive *ph*IGFBP-1 test, combination of both, and clinician's judgment were all associated with preterm delivery < or = 34 weeks or within 14 days in a total of 246 women between 22 and 34 weeks of gestation. They showed that the rapid *ph*IGFBP-1-test has a high negative predictive value for preterm delivery, comparable to that of ultrasonographic cervical length measurement.[9] Paternoster et al. assessed *ph*IGFBP-1 in cervical secretions and the sonographic measurement of cervical length in 210 symptomatic patients. They found that 26mm was the best cut-off value for cervical length in terms of predicting preterm delivery.[10] Bittar et al. found that measuring cervical length at 2224 weeks' gestation and *ph*IGFBP-1 at 30 weeks' gestation improved the prediction of preterm delivery over either method used alone.[11] None of these studies were done in black Africans.

The ability to predict preterm delivery will go a long way in preparedness, prevention or minimization of its complications. Some authors found that the combination of cervical assessment at 2224 weeks and phosphorylated insulin-like growth factor binding protein-1 (*ph*IGFBP-1) testing at 30 weeks of gestation is useful for the prediction of preterm birth.[11]

Presently in most developing societies, there appears to be no standard protocol for the prediction of preterm delivery. This study therefore aims at determining the effectiveness of cervical *ph*IGFBP-1 and transvaginal ultrasonographic cervical length assessment in predicting preterm delivery in asymptomatic at risk patients.

Specific objectives include determining the socio-demographic characteristics incidence of preterm delivery, usefulness of cervical length and *ph*IGFBP-1, singly and in combination, in predicting preterm delivery before 37 completed weeks, and possibly propose a risk scoring system for predicting preterm delivery based on the findings.

Subjects And Methods

- **Study Setting**

  The study was carried out at the Ahmadu Bello University Teaching Hospital's [ABUTH] antenatal clinic, obstetrics and labour ward. ABUTH is located in Kaduna State of Northern Nigeria, the largest West African country. The permanent site, located in Shika, Giwa local government area of Kaduna State, is about 20km from the Zaria City gate. It serves as a referral centre for other hospitals in Kaduna and neighbouring states. The target population were clients at the antenatal clinic, which holds every day from Monday to Friday with the booking clinic for new clients holding every Wednesday. A team of doctors, composed of resident doctors and consultants assisted by nurses and supporting staff, run the clinic. Approximately fifty new clients are booked weekly while about 200 clients are seen weekly for follow up visits.

- **Study Design**

  An analytical prospective (longitudinal) cohort study was carried out. In this cohort study, the presence of the exposure of interest (short cervix and positive phIGFBP-1) was determined by the tests conducted.

- **Study Population**

  Consenting antenatal clients, during booking or follow up visits, who were between 22 and 24 weeks gestation with at least one risk factor for preterm delivery were recruited into the study between June to December, 2016. Accurate gestational dating was calculated on the basis of the last menstrual period and by first and early second trimester (up to 20 weeks) ultrasound examinations. Where there is a discrepancy of more than 10 days in estimated gestational ages, the ultrasound estimation was used.

  Clients with at least one or more risk factors for preterm delivery (previous history of spontaneous preterm delivery, multifetal pregnancy, tobacco smoking, alcohol ingestion, vaginal bleeding in early pregnancy (6-13 weeks), two or more voluntary terminations of pregnancy using dilatation and curettage, short interpregnancy interval, invitro fertilization, history suggestive of bacterial vaginosis in index pregnancy, and various diseases in pregnancy such as heart disease, gestational cholestasis, and periodontal disease) were included into the study. While women with vaginal bleeding or contractions presently, ruptured membranes, previous cervical surgeries; gestational age less than 22 weeks gestation were excluded from being recruited. Also, women that had active interventions prior to the commencement of study, such as rescue cerclage were excluded. When such interventions occurred during the course of the study, the patients were excluded from further analysis.

- **Data Collection Methods**

  Consenting clients that meet the inclusion criteria and who do not have any exclusion criteria were recruited consecutively into the study. Written informed consent was obtained (see appendix I). Patient characteristics, including sociodemographic data and previous obstetric and medical history, were obtained from the patients using the study proforma (see appendix II). Research assistants (comprising of nurses and house officers) worked hand in hand with the researcher to obtain this information after being trained.

  For each consenting subject at 22 to 24weeks gestation, a transvaginal ultrasound was performed by the researcher with the patient in dorsal position after she has emptied her bladder voluntarily. All the sonography was performed by the researcher after being trained by the co- supervising consultant. The TVU end-firing probe of the machine (Mindray DC-8 2011, China) was covered in ultrasonic gel and covered with the male condom. The probe was then inserted into the vagina and placed in the anterior fornix, and the cervical length was measured using standard protocol.

The cervical canal was first identified, and a longitudinal view was obtained bearing in mind the cervical canal often does not lay in the maternal sagittal axis. The vaginal probe was placed in the anterior fornix without pressure. The widest viewing angle of the ultrasound was used. Cervical length (CL) was defined as the distance between the internal and external os along the endocervical canal. In cases where the cervical canal was curved, the CL was measured by a straight line between internal and external os or by the sum of two straight lines that essentially follow the curve if the deviation is greater than 5mm. The actual cervical length measured was recorded in milimetres. For the purpose of this study, a short cervix was one that measured 25millimetres or less. As such, those with short cervices formed the experimental group and those with normal cervical lengths formed the control.

The patients were then followed up and at 30weeks gestation, each subject was examined by the researcher with a sterile vaginal speculum. Ensuring there is no blood and liquor, cervical secretion/fluid is collected from the external cervical os with a Polyester swab provided in the Actim Partus test kit/package. The swab was left in the cervical os for 10-15 seconds to allow it to absorb the cervical secretion (the timing ensures that enough cervical fluid was collected into the swab).

The sample collection was performed before any indicated digital exam or transvaginal ultrasound, since these may remove the liquid present in the cervix.

After the swab has absorbed the sample, it was inserted and swirled vigorously for 10-15 seconds in the extraction solution (containing sodium phosphate, sodium chloride, Ethylene Diamine Tetraacetic Acid, Tween-20, bovine serum albumin, aprotinin and proclin 300). The swab was then removed from the extraction solution and discarded. The dipstick was then dipped into the extraction solution and left inside until the liquid front reached the result window/area. The dipstick was then removed from the extraction solution as soon as the liquid front becomes visible in the result window (this takes about 20seconds) and allowed to develop within 5 minutes in horizontal position.

The result was interpreted by counting the number of lines in the result window. A positive result occurred as soon as two blue lines (a control line and a test line) become visible in the result window. However, a negative test was confirmed at 5 minutes. When only the control line had appeared after 5 minutes, the test result was negative. Appearance of a control line confirmed the correct performance of the test. If a control line did not appear, the test was invalid and was repeated using another dipstick. According to the manufacturer's guideline, no attention was paid to the relative intensities of the control and test lines. Also, no attention was paid to lines appearing after 5minutes.

According to the manufacturer's recommendation, the samples were tested immediately. Though the samples can be stored for up to 4 hours at room temperature (250C) before testing, they were all tested immediately, results documented and samples discarded. The kit was stored at +2°C to +8°C in the refrigerator, but the components were allowed to reach room temperature before testing.

Those with positive tests formed the experimental group while those with negative tests form the control.

Pregnant women were followed up till delivery and the gestational age at delivery documented. Those with iatrogenic preterm delivery were excluded from further analysis. Respondents who did not deliver in this institution were called on their phone numbers and pertinent information was obtained.

- **Sample Size Calculation for independent cohort studies**

The estimated sample size (n) was determined using the formula below

$$n = \frac{[Z\alpha\sqrt{\left(1+\frac{1}{m}\right)\,P_0(1-P_0)} + Z_\beta\sqrt{\frac{P_1(1-P_1)}{m}} + P_2\,(1-P_2)]^2}{(P_1-P_2)^2}$$

$$P_0 = \frac{P_1 + mP_2}{m+1}$$

Where:

n = minimum sample size per comparison Group

Zα = Z-score corresponding to 95% level of significance i.e. 1.645

Zβ = Z-score corresponding to 80% statistical power of study i.e. 0.840

m = the number of control subjects per experimental subject

P_1 = is the probability of preterm delivery in controls (taken as prevalence of preterm delivery which is 11.7%)[4]

P_2 = is the probability of preterm delivery in experimental subjects which is 52.6%[7]

NB: m was taken as 1 with a presumed equal number of control to experimental subjects. Considering attrition, the minimum sample size per comparison group will be 17 patients.

NB: Four comparison groups (positive and negative phIGFBP-1, and short and long cervices) will be used and there will be at least 17 patients per group. Recruitment of patients thus continued until there were at least 17 patients per group.

Data Analyses

Data was analyzed using Statistical Package for Social Sciences (SPSS) version 22. Chi square test was used to determine relationships between variables and alpha level of significance will be set at 0.05.

The primary outcome measure was spontaneous preterm delivery before 37 completed weeks of gestation. The secondary outcome variables that were analyzed included percentage of asymptomatic women at risk for preterm delivery that eventually deliver preterm, proportion of women with positive *ph*IGFBP-1 that deliver preterm, proportion of women with negative *ph*IGFBP-1 that deliver preterm, proportion of women with positive *ph*IGFBP-1 that deliver at term, proportion of women with negative *ph*IGFBP-1 that deliver at term, proportion of women with a normal cervical length that deliver preterm, proportion of women with a normal cervical length that deliver at term, proportion of women with a short cervical length that deliver preterm and proportion of women with a short cervical length that deliver at term. Results are displayed using tables and charts.

For the purpose of this study, the cut-off for obesity will be weight = 90kg or body mass index (BMI) of $\geq$30kg/m^2. Preterm delivery will be defined as that occurring between 28 weeks to 37 weeks 6 days. Spontaneous preterm delivery was defined as preterm delivery after the spontaneous onset of contractions or preterm premature rupture of membranes, regardless of whether the delivery was vaginal, caesarean section, or, in the case of premature membrane rupture, induced.

Ethical Consideration

Ethical clearance was obtained from the Health Research Ethics Committee of ABUTH (ABUTH/HREC/N08/2013). A written consent was also obtained from the clients. Clients that do not consent to participate in the study still received due care and attention at the clinic. Both tests used in this study are standard obstetric investigations considered safe in pregnancy with no associated risks to both mother and baby. Clients that participated in this study benefited by having free investigations. In addition, clients benefited by early intervention when abnormalities were

detected. Strict confidentiality was maintained by coding of proformas using serial numbers, locking up of all materials after use, and non-use of identifiers during dissemination of findings.

Those who started bleeding vaginally or had preterm premature rupture of membranes or preterm contractions were managed as per existing protocol in our hospital and where these occurred prior to 30 weeks gestation, they were excluded from *ph*IGFBP-1 detection and further analysis.

Results

A total of 123 women were recruited into the study over the study period. Thirty-one women were lost to follow up and another eight (8) had indicated preterm delivery mostly from severe preeclampsia (and one case of polyhydramnios). Data from a total of 84 women were therefore analyzed.

Table 1: Socio-Demographic and Obstetric Characteristics of Participants

Socio-Demographic Characteristics	Frequency	Percentage
Age Group (years)		
15-19	5	6.0
20-24	15	17.9
25-29	22	26.2
30-34	24	28.6
35-39	17	20.2
≥40	1	1.2
Ethnicity		
Hausa	55	65.5
Igbo	7	8.3
Yoruba	6	7.1
Others	16	19.0
Occupation		
House wife	39	46.4
Students	15	17.9
Traders	12	14.3
Civil servant	4	4.8
Artisan	3	3.6
Health worker	1	1.2
Others	10	11.9
Total number of Pregnancy		
1-4	55	65.5
≥ 5	29	34.5
Estimated Gestational Age		
22 weeks	56	66.7
23 weeks	18	21.4
24 weeks	10	11.9
Total number of parity		
Nulliparous	26	31.0
1-4	42	50.0
≥ 5	16	19.0

The age of participants ranged between 16 to 42 years with a mean age of 28.74 ± 5.868 years. Majority were Hausa housewives. Of the study participants, 31% were nulliparous, and 50% with parity less than 4. Most (66.7%) were recruited at 22weeks gestation.

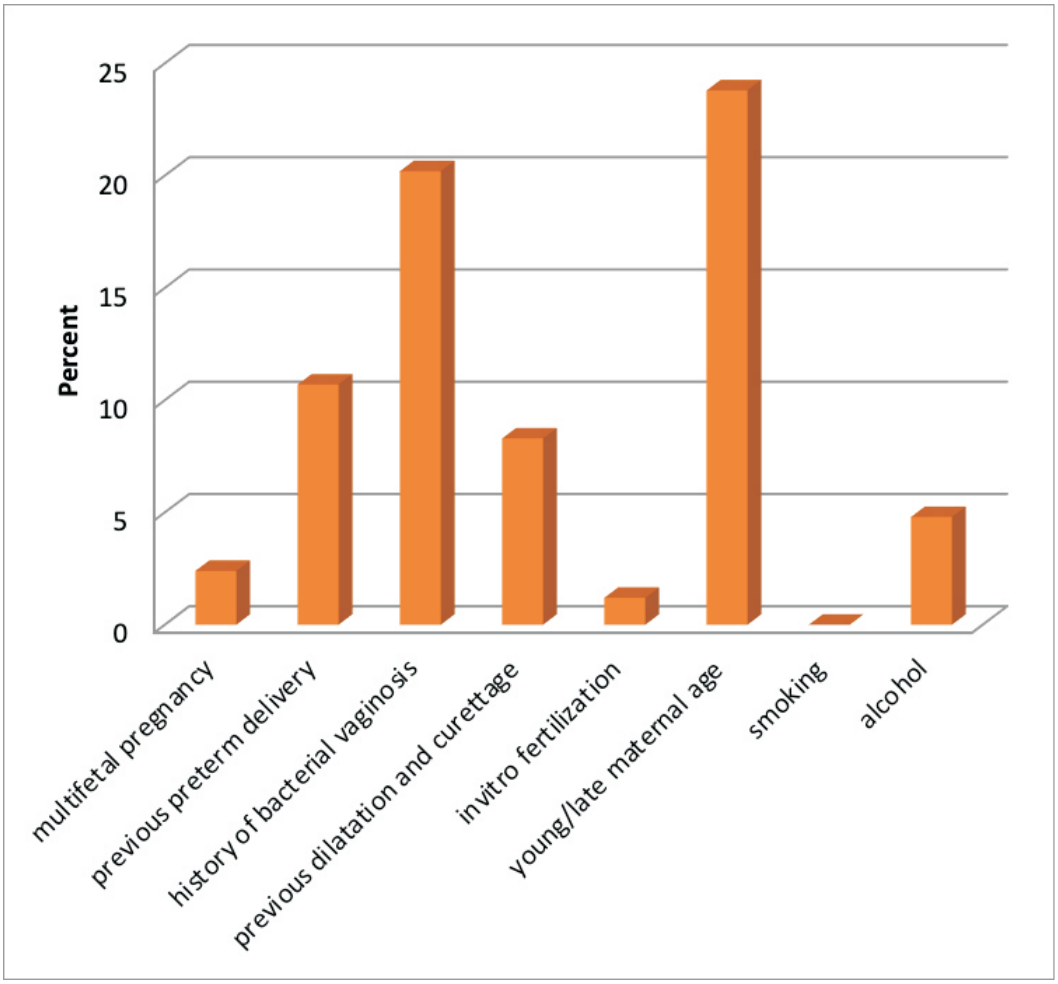


Figure 1: Risk Factors for Preterm Delivery

The commonest risk factor for preterm delivery was age less than 18 or greater than 35 as seen in 23.8% of cases. Other risk factors that were commonly encountered among participants were history suggestive of bacterial vaginosis (20.2%) and previous spontaneous preterm delivery (10.7%). There was no single patient that smoked among the participants.

However, history suggestive of bacterial vaginosis was the only risk factor that showed significant association with preterm delivery *(p=0.03)*.

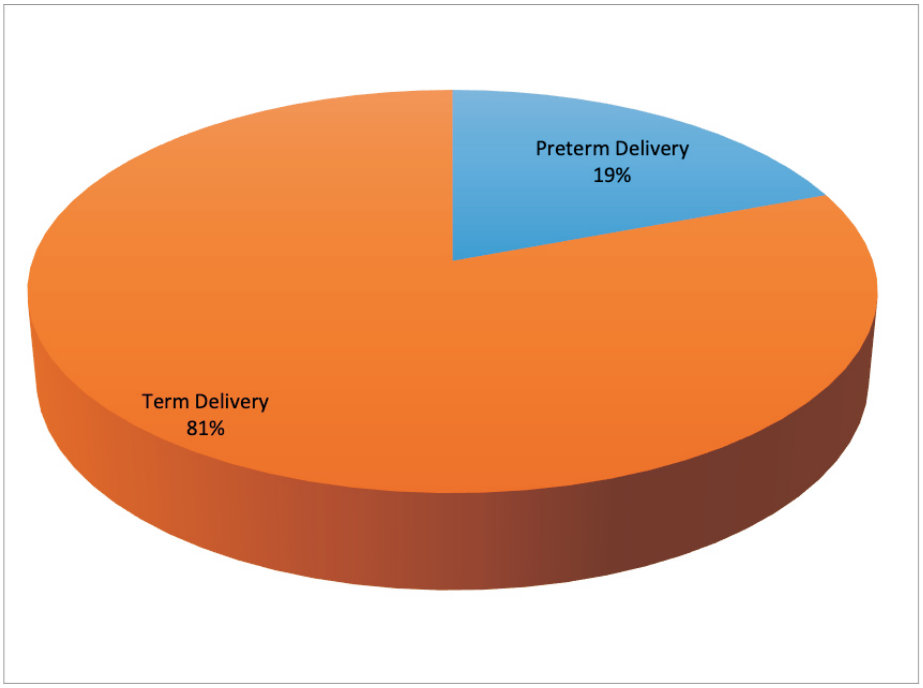


Figure 2: Incidence of Preterm Delivery

Incidence of preterm delivery among asymptomatic women at risk of preterm delivery was 193/1000 women. Most (80.7%) women with a risk factor for preterm delivery ended up having term deliveries meaning having a risk factor is not sufficient to have preterm delivery.

The average gestational age at delivery among asymptomatic susceptible women is mean 38.65 ±2.14 weeks with a range of 30 to 43 weeks.

The mean cervical length at 22-24 weeks in this study was 33.71± 9.61mm with a range of 14-61mm.

Table 2: Distribution of Time of Delivery by phIGFBP-1 Status and Cervical Length

	Time of Delivery		
	Preterm n(%)	**Term n(%)**	**Total**
***ph*IGFBP-1 status**			
Positive	10 (17.9)	46 (82.1)	56 (100.0)
Negative	6 (22.2)	21 (77.8)	27 (100.0)
Total	**16 (19.3)**	**67 (80.7)**	**83 (100.0)**
Cervical length			
Short	3 (16.7)	15 (83.3)	18 (100.0)
Normal	13 (20.0)	52 (80.0)	65 (100.0)
Total	**16 (19.3)**	**67 (80.7)**	**83 (100.0)**

X^2 (2, N=84) 0.223 p=0.637 for cervical length; X^2 (2, N=84) 0.101 p=0.751 for phIGFBP-1

Majority of women with a positive phIGFBP-1 (82.1%) had term deliveries and similarly, majority of women with short cervices = 25mm had term deliveries. The relative risk (RR) of having a preterm delivery with a positive phIGFBP-1 is 0.8 while the risk ratio of having preterm delivery with a short cervix is 0.83. in both instances, the risk ratio is close to 1 meaning there is little difference in risk of preterm delivery among women with positive or negative phIGFBP-1 and short or normal cervices.

Table 3: Validity of Cervical Length and phIGFBP-1 Status in predicting preterm delivery before 37 completed weeks

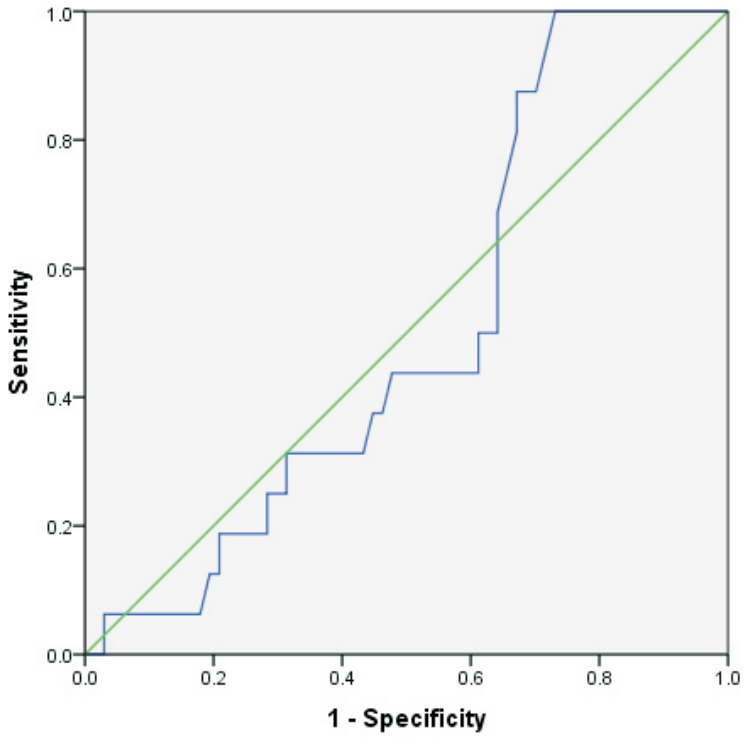
	Screening Test	
Measure of Validity	**Cervical Length % (95% Confidence Interval)**	**PhIGFBP-1 % (95% Confidence Interval)**
Sensitivity	18.8% (4.1% - 45.7%)	62.5% (35.4% - 84.8%)
Specificity	77.6% (65.8% - 86.9%)	31.3% (20.6% - 43.8%)
Positive Predictive Value	16.7% (6.2% - 37.8%)	17.9% (12.6% - 24.7%)
Negative Predictive Value	80.0% (75.4% - 84.0%)	77.8% (62.9% - 87.9%)

Cervical length measurement has a high specificity of 77.6% (which was statistically significant) meaning it has the ability to correctly identify those who will deliver at term; and a high negative predictive value meaning those with a normal cervix will truly carry pregnancies to term. Using 95% confidence interval means that we are 95% certain that in 77.6% of cases, cervical length measurement has the ability to correctly identify those who will deliver at term. The sensitivity however is low meaning that it is only in 18.8% of cases that a short cervix correctly identifies those who will deliver preterm; and also a low positive predictive value of 16.7% meaning that those with a short cervix won't necessarily have preterm delivery.

Table 4: Agreement of Cervical Length and phIGFBP-1 Status

	phIGFBP-1 Status				
Cervical Length	**Positive**	**Negative**	**Total**	**Kappa Statistic**	**P-value**
Short	14	4	18		
Normal	43	23	66	0.071	0.309
Total	57	27	84		

The above table shows the measure of agreement of both tests in predicting preterm delivery in susceptible asymptomatic patients. A kappa statistic of 0.071 (which is less than 0.2) means there is poor agreement between the cervical length measurement and the result of the bedside phIGFBP-1 test.



Area: 0.507;p-value: 0.931

Figure 3: Receiver Operatin Characteristics Curve (ROC) for Evaluating the Diagnostic Ability of Cervical length in diagnosing Preterm Delivery

Receiver - operating characteristics (ROC) curves was constructed and the area under the curve (AUC) was used to compare the predictive value of cervical length at 22-24 weeks, in predicting spontaneous preterm delivery. Here, the true positive rates (sensitivity) were plotted in function of the false positive rate (100% specificity) for the cutoff point of cervical length. The AUC obtained was 0.507. This showed that in asymptomatic patients at risk of preterm delivery, cervical length measurement is not important in predicting occurrence of preterm delivery.

Discussion

The mean age of 28.7years among study participants showed that most women were young. They were also mainly Hausa housewives, which is not unexpected considering the study was conducted in northwestern Nigeria where most women are not occupationally empowered.[2]

From this study, incidence of preterm delivery is 193/1000 (or 19.3%). This finding is lower than the 23.8% documented in a previous study[12] and higher than the quoted average of 5-13%.[13] The mean cervical length at 22-24 weeks in this study was 33.7mm which is longer than the 27mm obtained in a similar study[12] but similar to the findings of 38mm and 35mm by Heath[14] and Iams.[7]

Common risk factors for preterm delivery in this study included young or late maternal age, history suggestive of bacterial vaginosis, and previous preterm delivery. Of these, only history suggestive of bacterial vaginosis was found to be statistically significant in preterm birth prediction. This finding has been corroborated in a previous study[15] where up to a nine-fold increase has been reported.

The major findings in this study show that the

use of cervical length at 22-24 weeks and phIGFBP at 30 weeks, singly or in combination, do not significantly predict the occurrence of preterm delivery in asymptomatic patients at risk in our environment. This finding conflicts with other documented studies using phIGFBP-1 and cervical length.[12]

Although prior preterm birth is the most important risk factor for a subsequent preterm delivery, this study showed that majority of such patients will end up delivering at term. This has been shown in previous studies.[12,16]

For cervical length, with a risk ratio of having a preterm delivery in patients with a short cervix is 0.83, which is close to 1 suggests that there is little difference in risk of preterm delivery among women with short or normal cervices. Previous studies[17,19] have shown that cervical length is inversely related to the risk of preterm delivery in asymptomatic women but none of these studies were done among native African blacks. The ROC curve, which is mostly to the right in this study, with AUC of 0.507, also further showed that in asymptomatic patients at risk of preterm delivery, cervical length measurement is not important in predicting occurrence of preterm delivery.

The poor sensitivities and low positive predictive values observed in this study (because preterm births were infrequent) were also reported in similar studies.[20] Routine screening using cervical length as a predictor of preterm delivery is not recommended in low risk populations.[21]

Previous studies[22-24] have shown that transvaginal ultrasonographic cervical length measurement has been found to be effective in predicting preterm delivery in asymptomatic high risk groups such as uterine anomalies, excisional cervical procedures such as cone biopsy, and multiple dilatation and evacuation procedures greater than 13 weeks. None of these high-risk groups were assessed in this study. This is probably the reason why a statistically insignificant relationship was obtained between short cervix and preterm delivery. Similarly, the 2013 Cochrane Review for Cervical Assessment by Ultrasound for Preventing Preterm Delivery finds that cervical length measurement using transvaginal ultrasound is one of the best predictors of preterm delivery in all populations so far. They concluded that there is currently insufficient evidence to recommend routine screening of asymptomatic or symptomatic pregnant women with transvaginal ultrasound for cervical length without a specific intervention.[35]

Therefore, routine use of ultrasound for cervical length measurement remains controversial in asymptomatic women and the American College of Obstetricians and Gynecologists (ACOG) does not explicitly recommend this form of screening.[26]

Results from this study showed that there was no significant association between a positive phIGFBP-1 and the occurrence of preterm delivery (risk ratio of 0.8). many statistical tests were applied to check for any significance. This is similar to the finding of Kekki et al in 2001[27] where no single asymptomatic woman with a positive phIGFBP-1 using quantitative assay delivered preterm whereas 41% of the symptomatic women delivered preterm. These may mean that this biomarker may be better for the prediction of preterm delivery in symptomatic women. Phosphorylated IGFBP-1 has been tested in many symptomatic women[27-30] but few studies have tested its significance in asymptomatic women.[11,27]

In checking the measure of agreement of both short cervical length of 25mm or less and positive phIGFBP-1 in predicting preterm delivery in susceptible asymptomatic women, the kappa statistic of 0.071 obtained in this study reveals that cervical length measurement is not important in predicting occurrence of preterm delivery. This was conflicting with the finding in a previous similar study.[11] Prediction of a risk scoring system could not be done because most parameters found were not statistically significant. Research has focused on combined risk scoring systems that use multiple serum markers, ultrasound, and maternal but these have not been fully validated in large-scale studies.[7,21,31-32]

The major limitation of this study is that being a cohort study, some patients recruited were lost to follow up; as such, dynamic cohorts were used. It will also have been more appropriate to do the

phIGFBP-1 testing at 4-weekly intervals in order to determine the most appropriate gestational age for testing. This however was limited by cost.

Results from this study cannot be conclusively used to modify practice in our environment. This is because it was a single study with small sample size and some methodological limitations including single point testing. Since both cervical length at 22-24 weeks and phIGFBP-1 testing at 30 weeks did not significantly predict the occurrence of preterm delivery in susceptible women, it is recommended as a routine test in these women.

The finding of history suggestive of bacterial vaginosis as a significant risk factor for preterm delivery should stimulate obstetricians to look out for, and treat this condition since it can be diagnosed in the side lab.

It is also recommended that findings of studies done in other parts of the world should not always be extrapolated to women in our environment because there may be some differences due to genetic predisposition and lifestyle. The findings from this study further corroborates this fact that our women may be different.

Further research is definitely needed on the use of phIGFBP-1 among our women because this being a first study will not be sufficient to draw conclusions and generalize findings. Studies on the validity of cervical length measurement, with and without fundal pressure, cervical gland area, internal os diameter et cetera can be conducted in a multicenter randomized trial with a large sample size in order to draw conclusions that may change practice.

Conclusion

Cervical length measurement at 22-24weeks and use of phIGFBP-1 at 30weeks did not predict spontaneous preterm delivery in susceptible asymptomatic women in our environment.

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Conflict of Interest: Nil

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Appendix I

Consent Form

(ABUTH-HREC N08-2013)

I am Dr. Aisha Mustapha, A resident doctor in Obstetrics and Gynaecology Department, carrying out a study on ***"Phosphorylated Insulin-Like Growth Factor-Binding Protein-1 and Transvaginal Ultrasonographic Cervical Length Predicting Spontaneous Preterm Delivery in Susceptible Asymptomatic Patients."***

The study will involve putting you in a dorsal position (while lying on your back, your hips and knee joints are flexed), and then inserting an appropriate size sterile disposable plastic speculum into the vagina in order to obtain a swab. At a subsequent visit, a vaginal ultrasound scanning will be done using a special probe, covered with a single-use protective sheath. The two tests will not injure you or your baby in any way whatsoever.

I humbly request your consent to participate in this study. You have the right to withdraw from the study at any point before or during the procedures without compromising the quality of care you deserve. Kindly indicate your acceptance below. Thank you.

Please Turn Over

* The information above has been adequately explained to me. I have had opportunity to ask questions and I have been answered satisfactorily. I voluntarily accept to participate in this study and understand that I have the right to withdraw from the study at any time, without compromising the quality of care I deserve.

Thumbprint: _____

Date: _____

This client has voluntarily entered into this study following an informed consent.
Signature of person obtaining consent: _____

Signature of witness: _____

Appendix II

Study Proforma

Phosphorylated Insulin-Like Growth Factor Binding Protein-1 and Transvaginal Ultrasonographic Cervical Length Predicting Spontaneous Preterm Delivery in Susceptible Asymptomatic Women.

Code: _____

Age in years (as at last birthday): _____

Tribe: _____

Occupation: _____

Marital status: _____

Highest education: _____

Phone number: _____

Address: _____ Gravidity: _____

a) Number of deliveries: _____

b) Number of spontaneous miscarriages: _____

c) Number of induced abortions: _____

Parity: _____

Last Childbirth: _____

Last Menstrual Period: _____

Expected Date of Delivery: _____

Estimated Gestational Age: _____

Date of entry into study: _____

Weight (kg): _____

Height (m): _____

Risk factors for preterm delivery. There can be multiple risk factors

- Tobacco Smoking [ ]
- Ingestion of Alcohol [ ]
- Multifetal pregnancy [ ]
- Previous spontaneous preterm delivery [ ]
- History suggestive of Bacterial vaginosis [ ]
- In-vitro fertilization [ ]
- Previous dilatation and curettage [ ]
- Young/late maternal age <18 OR >35years [ ]
- Various diseases during pregnancy (such as heart disease, gestational cholestasis, periodontal disease) [ ]
- Vaginal bleeding in early pregnancy 6-13weeks [ ]
- Short inter-pregnancy interval [ ]
- Short stature [ ]

Gestational age at previous preterm delivery (IF ANY): _____

Cervical length (in millimetres) at 22-24 weeks: _____

Result of pIGFBP-1 test at 30 weeks

- Positive [ ]
- Negative [ ]

Gestational age at delivery (IN WEEKS): _____

Type of delivery: _____

- Spontaneous [ ]

Induced (STATE INDICATION): _____