AFRICAN JOURNAL OF FETOMATERNAL MEDICINE

Original Article

Comparison of Cervicovaginal Fluid Beta Human Chorionic Gonadotropin and Fetal Fibronectin in the Prediction of Preterm Delivery

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Abstract

Background: Preterm birth is among the leading causes of perinatal morbidity and mortality globally and it's reported to be on the increase. Identifying a reliable marker that best suggests those who may have preterm delivery would allow for adequate preparations that may limit the morbidity / mortality associated with preterm birth. To date, the search for such a predictor is an area of ongoing research. However, many substances have been tried. **Objective:** To compare the validity of cervicovaginal fluid beta human chorionic gonadotrophin (β-hCG) and fetal fibronectin (fFN) in the prediction of preterm delivery among at risk women. **Materials and Methods:** This was a longitudinal cohort study involving two hundred pregnant women between the gestational ages of 24-36 weeks. Cervicovaginal fluid samples were obtained from the posterior vaginal fornix for quantitative assessment of β-hCG and fFN respectively. The patients were recruited using purposive sampling method. After counselling and obtaining an informed consent from the patient, a sterile Cusco speculum was passed into the vagina and samples collected from the posterior vagina fornix using swab sticks. Two samples were collected from the same individual, each sample was tested for beta human chorionic gonadotrophin and fetal Fibronectin. The women were followed up till delivery. **Results:** One hundred and ninety-two participants were analyzed. Eight were lost to follow-up. Ninety-eight (51%) had positive β-hCG and 94(49%) had negative β-hCG while 47(24.5%) had positive fibronectin and 145 (74.5%) had negative results. Thirty-five (56.5%) of preterm and 63(48.5%) of term had positive β-hCG **(**> 77.8mlU/ml) while 15(24.2%) of preterm and 32(24.6%) of term had positive fibronectin (>50ng/mL). Both were not statistically significant with p- value of 0.3 and 0.949 respectively. The mean cervicovaginal β-hCG level (mIU/ ml) in preterm group was 106.6±66.8 and term group was 83.5±50.1. There was statistically significant difference between preterm and term in β-hCG values, which implies that β-hCG preterm average is higher than term with (P value- 0.018). However, the mean cervicovaginal fibronectin level (ng/mL) in preterm group was 44.04 ± 56.1 and term group was 40.1±59.5. There was no statistically significant association of raised fibronectin with preterm (P value 0.696). Quantitative cervicovaginal β-hCG test had sensitivity 56.5%, specificity 51.5%, positive predictive value 35.7%, negative predictive value 71.3% and diagnostic accuracy of 53.1% at a cut-off value of > 77.8mlU/ml in the prediction of preterm delivery. On the other hand, quantitative cervicovaginal fibronectin test had sensitivity 24.2%, specificity 75.4%, positive predictive value 31.9%, negative predictive value 67.6% and diagnostic accuracy of 58.9% at cut-off value of 50ng/mL for prediction of preterm delivery. The area under the curve shows that the two markers have similar ability in predicting PTL. In the diagram below, fibronectin has a predicting value with area under curve of 0.498 which is comparable to 0.542 of β-hCG in predicting PTL. **Conclusion:** Cervicovaginal β-hCG can be used as an alternative in place of fibronectin in the prediction of preterm delivery in asymptomatic high-risk woman.

Keyword: Fibronectin, β- Human Chorionic Gonadotropin, preterm delivery

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Introduction

Globally, prematurity is the leading cause of death in children under the age of 5 years and in almost all countries with reliable data, preterm birth rates are increasing.[1] Preterm babies are defined as those born alive before 37 weeks of pregnancy are completed.[1]

Every year, an estimated 15 million babies are born preterm (before 37 completed weeks of gestation), and this number is rising. Preterm birth complications are the leading cause of death among children under 5 years of age, responsible for approximately 1 million deaths in 2015[2] and three-quarters of these deaths could be prevented with current, cost-effective interventions. The World Health Organization (WHO) estimated 9.6% of all births worldwide to be preterm[3] and worldwide, death of preterm babies constitutes 28% of the 4 million annuals newborn deaths with 99% of these deaths occurring in developing countries[4.] However, factors that were linked to preterm birth include medical conditions of the mother or foetus, genetic influences, environmental exposures, infertility treatments, behavioural and socio-economic factors as well as iatrogenic prematurity[5]. Approximately 70% of preterm deliveries occur spontaneously (45% because of preterm labour and 25% from preterm premature rupture of membranes) while interventions for maternal or fetal problems account for the remaining 30%[6]. Malaria and infectious diseases are particularly important in Africa[7-9]. More than 60% of preterm births occur in Africa and South Asia, preterm birth is truly a global problem[1]. In the lower-income countries, on average, 12% of babies are born too early compared with 9% in higher-income countries[1]. Nigeria is placed third, from the top, among the ten countries with the highest number of preterm births with 773,600.

Nigeria is one of ten countries that contribute two-thirds of all newborn deaths worldwide [10]. Neonatal deaths account for 33% of under-five mortality in Nigeria, and prematurity is a leading cause, constituting 32% of all neonatal deaths, and of the survivors, 10%–15% have significant handicaps[11,12]. The common complications encountered in these group of patients include severe morbidities such as respiratory distress syndrome, intraventricular hemorrhage, bronchopulmonary dysplasia, and necrotizing enterocolitis are far more common in preterm than in term infants[12,13]. Therefore, WHO has developed new guidelines with recommendations for improving outcomes of preterm birth, this set of key interventions can improve the chances of survival and health outcomes for preterm infants. The guidelines include interventions provided to the mother – for example corticosteroid injections before birth, antibiotics when she has ruptured her membranes before the onset of labour, and magnesium sulphate to prevent future neurological impairment of the child, as well as interventions for the newborn baby – for example, thermal care, feeding support, kangaroo mother care, safe oxygen use, and other treatments to help babies breathe more easily[1]. Also, WHO is currently coordinating two clinical trials, called the WHO ACTION Trials (Antenatal Corticosteroids for Improving Outcomes in preterm Newborns) for women at risk of preterm birth and immediate kangaroo mother care (KMC) multi-country trial (compared with the current recommendations of initiating KMC when baby is stable) in Ghana, India, Malawi, Nigeria, and the United Republic of Tanzania[1].

The prevention of prematurity may be the most important intervention to reduce the burden facing maternal and child health-care providers. Efforts at risk identification, accurate and early diagnosis, and proper interventions hold the most promise for the prevention of preterm delivery. Several strategies have been developed, which include identification of women who are high risk for preterm labor and delivery, so that appropriate intervention strategies could be instituted early before significant cervical changes occur, to ensure the success of the prevention strategies.[12,14,15] Various biomarkers to determine or predict preterm birth in women at risk have been studied. The most promising of the predictive methods is the combination of fibronectin and cervical length. But this has its own drawbacks, especially in low-resource countries where the cost of the fibronectin and its availability constitute a problem in these settings. Beta human chorionic gonadotropin was studied for its relationship with preterm delivery. The various studies showed an increase concentration of this marker during spontaneous preterm birth. Monitoring of beta human chorionic gonadotrophin level in cervicovaginal fluid as a marker for preterm delivery can be a useful predictor in symptomatic women. Gurbuz et al showed that increased concentration of beta-human chorionic gonadotropin in cervicovaginal fluid was found in women with preterm delivery and in contrast to fibronectin, this test has the benefit of low cost and wide availability.[16] Therefore, this study seeks to determine if beta human chorionic gonadotropin (β-hCG) concentration in cervicovaginal secretions of pregnant women can be compared with fibronectin in the prediction of preterm delivery in women at risk of preterm birth in low resource settings.

Methodology

This was a longitudinal cohort study involving two hundred pregnant women between the gestational ages of 24-36weeks gestation. The study population comprised of women who presented at antenatal clinic, labour ward and maternity ward of the University of Abuja Teaching Hospital, Abuja from

December 2021 to August 2022. Participants were recruited and screened for eligibility to be enrolled into the study. Cervicovaginal fluid samples were obtained from the posterior vaginal fornix for quantitative assessment of β-hCG and fFN respectively. The patients were recruited using purposive sampling method. After counselling and obtaining an informed consent from the patient, a sterile Cusco speculum was passed into the vagina and samples collected from the posterior vagina fornix using swab sticks. Two samples were collected from the same individual, each sample was tested for beta human chorionic gonadotrophin and fetal fibronectin, here the case is β-hCG (Test A) while the control was fibronectin (Test B). Fibronectin as the standard was compared with β-hCG in the analysis to determine the validity of beta human chorionic gonadotrophin (β-hCG) as compared to fetal fibronectin (fFN). The women were followed up to delivery. Four registrars were recruited, one from each team, to serve as research assistants for the study. A training session was held with the research assistants to educate them on the study protocol and their respective roles. In each team, one registrar was responsible for recruitment of patients according to laydown eligibility criteria and obtained informed consent. The principal investigator with the research assistants from each team recruited and collected records of participants. She was also responsible for recruiting participants in her own team. The sample was taken once and then patients were followed up to delivery in the labour ward. Data was presented as frequencies, means and standard deviations. The level of statistical significance was set at P-value less than 0.05. The results were presented as tables and figures.

Results

Initially, 200 participants were recruited but only one hundred and ninety-two were analyzed according to inclusion criteria for the study at gestational age between 24 to 36 weeks. Eight were lost to follow up. The mean age was 32.06 ± 4.91 and the mean gestational age was 30.73 ± 3.33. Of the 192 participants, 138 had tertiary education followed by those that had secondary education. Majority of the participants were skilled 60.8%, followed by unskilled 20.8% then housewife 18.2%. One hundred and seventy-four women were married and eighteen were single.

By parity, majority of the women were multipara, 138 (71.9%) and primipara were 54 (28.1%). One hundred and thirty-six had spontaneous vaginal delivery while 56 had caesarean section. Of these, 26 had premature rupture of membrane while 166 had no rupture of membrane.

Based on gestational age, 62(32.3%) were preterm and 130 were term (67.7%). Of the preterm, 9(14.5%) were between gestational age of 24 - 33^{+6} while 53(85.5%) were 34- 36^{+6} as showed in Table 1.

Table 1: Demonstrates demographic characteristics of study population.

Variables	Frequency (%)
Education	
No formal education	10(5.2)
Secondary	42(21.9)
Tertiary	138(71.9)
Occupation	
Housewife	35(18.2%)
Unskilled	40(20.8%)
Skilled	117(60.9%)
Marital status	
Married	174(90.6)
Single	18(9.4)
Parity	
Primipara	54(28.1)
Multipara	138(71.9)
Mode Of Delivery	
SVD	136(70.8)
C/S	56(29.2)
PPROM	
Yes	26(13.6)
No	166(86.4)
Gestational Age at Delivery	
Preterm	62 (32.3)
Term	130 (67.7)
Type of Preterm	
24-33 $^{+6}$	9 (14.5)
34-36 $^{+6}$	53 (85.5)

Table 2: Distribution of cases according to cervicovaginal β-hCG and Fibronectin cut-off value

VARIABLE	FREQUENCY (%)
B-HCG	
Positive	98 (51)
Negative	94 (49)
FIBRONECTIN	
Positive	47 (24.5)
Negative	145 (75.5)

Table 3: Distribution of cases according to cervicovaginal β-hCG cut-off value and gestation age at delivery.

Delivery	Cervicovaginal Beta human chorionic gonadotrophin		Chi	P-value
	Positive (>77.8mIU/ml)	Negative (<77.8mIU/ml)		
Preterm	35(56.5)	27(43.5)	1.07	0.3
Term	63(48.5)	67(51.5)		

Table 4: Distribution of cases according to cervicovaginal Fibronectin cut-off value and gestation age at delivery

Delivery	Cervicovaginal fetal fibronectin		Chi	P-value
	Positive (>50ng/mL)	Negative (<50ng/mL)		
			0.004	0.949
Preterm	15(24.2)	47(75.8)		
Term	32(24.6)	98(75.4)		

Table 5: Mean cervicovaginal β-hCG (mIU/ml) and fFN level in preterm and term group.

	Preterm		Term			
	Mean ± SD	Min-Max	Mean±SD	Min-Max	t	p
β-Hcg	106.6±66.8	44-321	83.5±50.1	2-217	2.39	0.018
Fibronectin	44.04±56.1	0-155	40.1±59.5	1-301.7	0.392	0.696

Table 6: Comparison of Cervicovaginal β-hCG and fFN

	Sensitivity	specificity	PPV	NPV	Accuracy	p value
β-hCG	56.5	51.5	35.7	71.3	53.1	
Fibronectin	24.2	75.4	31.9	67.6	58.9	**0.252**

Table 2 shows the distribution of cases according to cervicovaginal β-hCG and Fibronectin cut-off value. Ninty-eight (51%) had positive β-hCG and 94(49%) had negative β-hCG while 47(24.5%) had positive fibronectin and 147(74.5%) had negative results.

Distribution of cases according to cervicovaginal cut-off value and gestation age at delivery, 35(56.5%) of preterm and 63(48.5%) of term had positive β-hCG **(**> 77.8mlU/ml) while 15(24.2%) of preterm and 32(24.6%) of term had positive fibronectin **(**>50ng/mL). Both were not statistically significant with p- value of 0.3 and 0.949 respectively as shown in Tables 3 and 4.

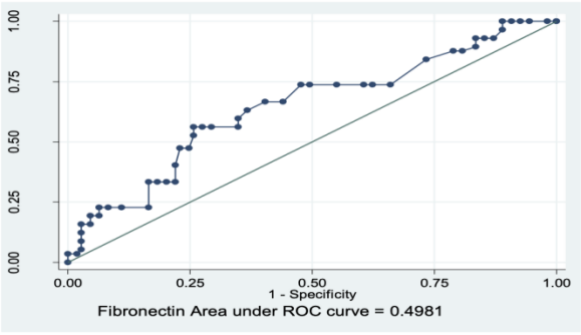

Figure 1: Receiver Operating Characteristic (ROC) Curve for Fibronectin

The mean cervicovaginal β-hCG level (mIU/ml) in preterm group was 106.6±66.8 and term group was 83.5±50.1. Cervicovaginal β-hCG level was significantly higher in preterm compared to term. There was statistically significant association of raised β-hCG with preterm (P value- 0.018). However, the Mean cervicovaginal Fibronectin level (ng/mL) in preterm group was 44.04±56.1 and term group was 40.1±59.5. There was no statistically significant association of raised Fibronectin with preterm (P value 0.696) as represented in Table 5.

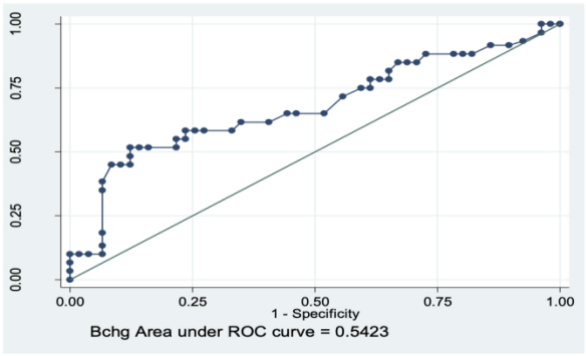

Figure 2: Receiver Operating Characteristic (ROC) Curve for B-HCG.

This study also showed that quantitative cervicovaginal β-hCG test had sensitivity 56.5%, specificity 51.5%, positive predictive value 35.7%, negative predictive value 71.3% and diagnostic accuracy of 53.1% at cut-off value of > 77.8mlU/ml for prediction of preterm delivery. On the other hand, quantitative cervicovaginal Fibronectin test had sensitivity 24.2%, specificity 75.4%, positive predictive value 31.9%, negative predictive value 67.6% and diagnostic accuracy of 58.9% at cut-off value of >50ng/mL for prediction of preterm delivery. Figures 1 and 2 represent the ROC. The area under the curve shows that the two markers have similar ability in predicting PTL. In the diagram, Fibronectin has a predicting value with area under curve of 0.498 which is comparable to 0.542 of β-hCG in predicting preterm labour.

Discussion

The World Health Organization (WHO) estimated 9.6% of all births worldwide to be preterm[3] and worldwide, death of preterm babies constitutes 28% of the 4 million annuals newborn deaths with 99% of these deaths occurring in the developing countries[4]. Preterm birth (PTB) is an obstetric complication of complex etiology associated with significant neonatal morbidity and mortality worldwide. However, to reduce the incidence of preterm birth, intervention will be most useful if targeted towards women at risk of preterm delivery. Therefore, identification of such women by risk factor assessment and prediction of preterm birth constitutes an important part of the main strategy to reduce preterm birth.

In this study, comparison of cervicovaginal fluid beta human chorionic gonadotrophin (β-hCG) and fetal fibronectin (fFN) in the prediction of preterm delivery among at risk women between 24-36 weeks gestation, the Mean cervicovaginal β-hCG level (mIU/ml) in preterm group was 106.6±66.8 and term group was 83.5±50.1. There was significantly higher level of cervicovaginal β-hCG in the preterm delivery group as compared to the term delivery group. There was significant association of raised β-hCG level with cut

off value > 77.8mlU/ml in cervicovaginal secretion for prediction of preterm delivery in this study. However, the Mean cervicovaginal Fibronectin level (ng/ mL) in preterm group was 44.04±56.1 and term group was 40.1±59.5 and there was no statistically significant association of raised Fibronectin level with cut off valve of ≥ 50ng/mL with preterm and term (P value 0.696).

This test using > 77.8mlU/ml as cut off value, β-hCG test had sensitivity 56.5%, specificity 51.5%, positive predictive value 35.7%, negative predictive value 71.3% and diagnostic accuracy of 53.1% for prediction of preterm delivery in asymptomatic high-risk women compared to Fibronectin test that had sensitivity 24.2%, specificity 75.4%, positive predictive value 31.9%, negative predictive value 67.6% and diagnostic accuracy of 58.9% at cut-off value of 50ng/mL for prediction of preterm delivery.

The sensitivity for β-hCG is higher than Fibronectin but the diagnostic accuracy of fetal Fibronectin on the other hand was higher than that of β-hCG in the prediction of preterm birth. So also, the specificity for Fibronectin is higher than that of β-hCG. The findings from this study were not comparable to the study done by Guvenal et al who found significant association of cervicovaginal β-hCG level in preterm labour group with cut off value of 27.1 mIU/ml having sensitivity, specificity, positive and negative predictive value of 87.5%, 65.4%, 28% and 97% respectively. Similar study done by Gharshasbi et al with higher cut off value of 77.8mIU/ml had sensitivity, specificity, positive and negative predictive value of 87.5%, 97%, 88.5, 98% respectively[17].

In this present study though there was significant rise in the beta HCG in the preterm group than the term group, the sensitivity, specificity, positive predictive valve, and negative predictive value was lower when compared to the above findings. So also, in a study done by Bernstein et al who demonstrated at a cervicovaginal fluid β-hCG cut off value >50 mIU/ml before 34- weeks' gestation had sensitivity, specificity, positive and negative predictive value of 50%, 87%, 33% 93% respectively[18] with specificity and negative predictive value higher than the present study.

Similarly, Abasalizadeh et al found lower sensitivity (45.5%), higher specificity (91.2%) and higher negative predictive value (95.4%) at cut off level of 45mIU/ml for cervicovaginal β-hCG for prediction of preterm delivery [19]. The above study is comparable to this present study with higher sensitivity (56.5%) and negative predictive value (71.3%) respectively.

However, regarding fFN assay for prediction of PTL, in this present study, the sensitivity, specificity, PPV, NPV, and accuracy were 24.2%, 75.4%, 31.9%, 67.6% and 58.9% respectively. These values were lower than the studies done by Goldenberg et al. demonstrated that screening asymptomatic women for the presence of cervicovaginal fFN at 24weeks of pregnancy had a high sensitivity in predicting more than 60% of spontaneous PTL within the following 4 weeks (sensitivity, 0.63; 95% CI: 0.4, 0.8; relative risk = 59.2, 95% CI: 35.9, 97.8) compared to women with a negative fFN assessment (<50ng/mL)[20].

Also, Roman et al. reported high NPV and specificity for vaginal fFN in the prediction of PTL in asymptomatic high-risk women within 2 weeks of assessment[21], which is like the present study that has higher NPV and specificity respectively. Honest et al. evaluated the association between the presence of fFN and PTL in asymptomatic women in a meta-analysis. They found out that there was a likelihood ratio of 4.0 (95% CI: 2.9, 5.5) for positive result for predicting PTL before 34 weeks of pregnancy[137]. Spontaneous preterm birth (<34weeks) increased from 2.7%, 11.0%, 14.9%, 33.9%, and 47.6% with increasing concentration of fFN (less than 10, 10–49, 50–199, 200–499, and 500 ng/mL or greater, respectively). At a threshold of 50–199 ng/mL, the sensitivity 46.5%, specificity 88.7%, PPV 23.7%, and NPV of 95.6% were noted[23].

A study by Leitich and Kaider found that serial sampling and assessment of fFN in asymptomatic high-risk women for PTL increased the sensitivity for delivery at less than 34 weeks of pregnancy to 92%, compared with 23% with a single fFN measurement. This meta-analysis confirmed that highest prediction using fFN testing is observed among high-risk patients and it also showed that serial fFN testing is the best compared to a single fFN test[24]. This test has variable sensitivity, specificity, positive and negative predictive value in various studies. The differences in results across the studies may have been due to dissimilarities in case selection, as some studies selected both asymptomatic and symptomatic women, different timings of sample collection and diversities in the study population.

Conclusion

From the above study, there was no statistically significant difference between β-hCG and fFN therefore β-hCG assessment in cervicovaginal secretion can be compared and used as an alternative to fFN assessment as it is low cost, widely available, has a simple procedure and sample collection method, for the prediction of preterm delivery in asymptomatic at-risk women.

Recommendation

More studies should be done in our setting using serial sampling and assessment of β-hCG and fFN in asymptomatic high-risk women with risk factor for preterm delivery as against single sampling method that was done in this study.

Large studies probably a randomized control trial will be needed in clearly defining the comparison between β-hCG and fFN.

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