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Plasma Fibronectin Concentrations for Prognosis of Preterm Delivery: A Cross-Sectional Study in Wasit City, Iraq

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Abstract

Preterm delivery is the most prevalent cause of fetus mortality and has considerable social and psychological effects for the family as well as the society. Sometimes, the reasons of preterm delivery are unknown. The influential factors, their prediction and prevention are not profoundly realized. Recognizing women who are at risk of preterm delivery is the first effective step in preventing preterm birth. We aimed to determine the diagnostic value of plasma concentration of fibronectin in diagnosing preterm delivery.This is a cross-sectional study which was carried out in the labor facilities in local hospital in Wasit.Therefore, if screening for fibronectin levels using the Enzyme-Linked Immunosorbent Assay (ELISA) test can be carried out in the last trimester of pregnancy, there is a high possibility that Preterm delivery can be prevented.A total 90 blood samples were collected by phlebotomists from patients inPretermand Full-termlabor. We carried our study on 90 pregnant women, divided into two groups. First group delivered preterm 45 and other group 45 at full term.

It was found that patients with preterm delivery had significantly a higher fibronectin concentration than those with full-term delivery (P-value< 0.001).The mean ± SD for preterm pregnancy patients was 77.58±9.06 while it was 50.16±5.38 for full-term. Based on ROC diagram, the best cutoff point of fibronectin concentration that appeared to differentiate those women who delivered earlier than others is found to be equal to or above 62.42 with a significant P-value less than 0.001. The AUC: Area Under Curve; CI: Confidence Intervals, sensitivity, specificity, positive predicting value, and negative predicting value for this test were 0.999, 0.995-1.000, 97.8%,100%,100%, 97.8%, respectively. It was concluded that Fibronectin plasma level in women with preterm delivery was significantly higher than those with term delivery.

Keywords: Fibronectin, Plasma fibronectin, Preterm delivery,

Introduction

Plasma fibronectin is an extracellular matrix glycoprotein. This glycoprotein micro molecule with an approximately heavy molecule weight (1). Fetal fibronectin in biologic fluids is produced by amniocytes and by cytotrophoblast. It is present throughout gestation in all pregnancies. It is not subject to genetic polymorphism. There are very high levels in amniotic fluid (100 µg/mL) in the second trimester and 30 µg/mL at term (2).

It is localized at the maternal- fetal interface of the amniotic membranes, between chorion and decidua, where it is concentrated in this area between decidua and trophoblast. Here it acts as a 'glue' between the pregnancy and the uterus(3).This glycoprotein is present in the amniotic fluid and can enter the maternal plasma through placental circulation. Therefore, the

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presence of this glycoprotein in vaginal secretions can be a sign of rupture of the fetal membranes and the risk of premature birth (4). Concentration of fetal fibronectin protein found in blood is 1/5th that found in amniotic fluid; it is not present in urine. In normal conditions, this glycoprotein remains in this area between chorion and decidua, and very low levels are found in cervicovaginal secretions after 22 weeks (<50 ng/mL). Levels above this value (≥50 ng/mL) at or after 22 weeks in the cervicovaginal secretions have been associated with an increased risk of spontaneous preterm birth(3). Results from an fFN evaluation may allow clinicians to better identify patients at risk and guide patient management. A recent systematic review revealed that the standard clinical practice of diagnosing PTL by documenting uterine contractions and cervical change has poor positive predictive value. The authors further concluded that a newer approach of considering both fFN and cervical length screening results could lead to more accurate assessment of the risk for preterm delivery(5).

In 1991, Lockwood et al. showed that mechanical or inflammatory-mediated damage to the membranes releases fibronectin into the cervicovaginal fluid since then, fFN in the cervicovaginal fluid has been used to evaluate the risk of PTB. Many studies have examined the effectiveness of fFN with CL measurement in the prediction of preterm birth, showing varied results (6).Fetal fibronectin can be distinguished from its other family members by the presence of a unique region known as the III-CS domain (7). Fetal fibronectin is elevated in cervicovaginal secretion during the first 24 weeks of pregnancy but diminishes between 24 and 34 weeks in normal pregnancies (8). A positive fetal fibronectin test enhances the ability of the clinician to predict preterm delivery either in an asymptomatic pregnant population or a population of pregnant women presenting with equivocal symptoms (5).

fibronectin test is a standard methodfor predicting preterm delivery, which iscarried out through the vaginal or blood plasma.Nonetheless, blood sampling is more accepted.Moreover, no studies have been conducted oncomparing vaginal and plasma fibronectin levelsto determine which test has a higher predictivevalue and can help predict preterm deliverysooner(4). However, a limited number of studies have been conducted on the relationship between plasma fibronectin and preterm delivery and none have used the enzyme-linked immune-sorbent assay (ELISA) in order to assess the plasma fibronectin concentration for predicting preterm delivery (1).

Detection of fetal fibronectin in cervicovaginal secretions between 24 and 34 completed weeks gestation is reported to be associated with preterm delivery in symptomatic and asymptomatic pregnant women (4).fFN should not be detectible between 22 and 35 weeks of pregnancy. Elevated levels during this period reflect a disturbance at the junction between the amniotic sac and the lining of the uterus. Elevated fFN in vaginal fluids during these weeks of pregnancy has been associated with an increased risk of preterm labor and delivery. Many pregnant women experience symptoms that suggest preterm labor. (9). Testing for presence or leakage of fetal fibronectin (fFN) during the 24th–34th weeks of pregnancy in symptomatic women may provide information that allows clinicians to rule out patients at a low risk for delivery within the following 14 days (5). For fetal fibronectin test, most samples are taken through the vaginal route when the process of preterm delivery begins. Because fibronectin concentration increases earlier in maternal plasma compared with vaginal discharges, Zygmunt proposed that high Plasma fibronectin levels could be effective in the prognosis of preterm delivery. Plasma fibronectin concentration follows an ascending trend in

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high-risk pregnancies. Assessment of Plasma fibronectin concentration is a simple, non-invasive, and accurate method for investigation of endothelial function (10). Increased plasma fibronectin concentration may result from its secretion from damaged endothelial cells occurring in placentas of women experiencing preterm delivery. Moreover, vascular endothelium, inflammation factors, and many of their mediators have a leading role in producing and releasing the changes in plasma fibronectin levels (11) Researchers have confirmed the effect of vascular lesions and failed physiological conversion of maternal spiral arteries on preterm delivery .Fibronectin plasma level in women with preterm delivery was significantly higher than those with term delivery (1).

Considering that vascular damages and inflammatory factors influence the fibronectin plasma levels, it is logical to relate the onset of preterm delivery to increased plasma levels. Studies have revealed that the amount of plasma fibronectin has a descending trend during pregnancy and it increases often weeks and months before the occurrence of pregnancy complications such aspreterm, preeclampsia, and intrauterine growth restriction (IUGR),(12).

Materials and Methods

This is a cross-sectional study which was carried out in the labor facilities in local hospital in Wasit. A total 90 blood samples were collected by phlebotomists from patients inPretermand Full-termlabor, during the period from 31th July to 31th of December of 2023 that admitted to Al-Zahra Teaching Hospital, Al Kut Hospital, Fairooz Hospital and private clinics in Wasit province.. A venous blood sample was collected, serum separated, and kept at μ70°C. All the samples were assessed for fibronectin concentrations using 96- well enzyme-linked immunosorbent assay (ELISA) kits.

Inclusion criteria according to definition of Preterm labor isdelivering a baby prior to the end of the 37th week of pregnancy, which is the primary cause of newborn mortality and according to definition of full term (control) Babies born between 39 weeks and 40 weeks and 6 days.Exclusion criteria (abortion case, IUD-intra uterine death, still death) abortion is described as a consequence, rather than an act or a choice. It is the "death of the fetus, sometimes with passage of products of conception (fetus and placenta), before 20 weeks gestation.

Serumsample Collection

A fresh venous blood specimen was aspirated from peripheral veins of the upper limb by a sterile syringe and each blood specimen was directly transferred to a sterile tube, allow the blood to clot by leaving it undisturbed at room temperature. This usually takes 10-20 minutes. Remove the clot by centrifuging at 2,000-3,000 rpm for 20 minutes. Aliquot into small tubes and store at -80°C until be used.

Serology byELISA

This ELISA kit uses Sandwich-ELISA as the method. The Microelisastripplate provided in this kit has been pre-coated with an antibody specific to pFN. Standards or samples are added to the appropriate Microelisastripplate wells and combined to the specific antibody. Then a Horseradish Peroxidase (HRP)- conjugated antibody specific for pFN is added to each Microelisastripplatewell and incubated. Free components are washed away. The TMB substrate solution is added to each well. Only those wells that contain pFN and HRP conjugated pFN antibody will appear blue in color and then turn yellow after the addition of the stop solution. The optical density (OD) is measured spectrophotometrically at a

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wavelength of 450 nm. The OD value is proportional to the concentration of pFN. You can calculate the concentration of pFN in the samples by comparing the OD of the samples to the standard curve.

Statistical analysis

Data were entered in Excel and then transformed into the software program Statistical Package for Social Sciences (SPSS) version 26. Descriptive statistics was used to describe both categorical and numerical variables. Means and standard deviations were used for continuous variables while frequencies and percentages were used for categorical. Normality tests were conducted. A point biserial correlation was applied to assess the correlation between fibronectin concentration and the time of delivery. Binary logistic regression was used to detect if fibronectin can be considered as a predictor of the time of delivery.Receiver Operator Characteristic (ROC) curve analysis was used to detect sensitivity, specificity, Area Under Curve (AUC), and cutoff value (13).

Results

The results of this study were dependent on the analysis of collected data related to 90 female patients at the time of their delivery. The sample consisted of 40 patients who gave birth at term (control) and the remaining 40 were preterm. The medical, obstetrical, and gynecological history of the participants are shown in Table 1. Most of the sample (96.7%) didn't mention any chronic diseases while the remaining 3 patients (3.3%) were with diabetes mellitus. Nearly two-thirds of the sample (62.2%) didn't use any medications at the time of data collection. Around half of the sample (53.3%) had gravida equal to or less than 3 while only 6 women were more than 6. About 56 women out of 90 never had any history of abortion. There were 19 (21.1%) with a history of one abortion in their lives. The majority (81.1%) never had any history of previous preterm labour. Among those with previous history, 12 women had one preterm labor which represented 13.3% of the total sample and only one patient had previous 6-preterm delivery. Exactly more than 50% of the samples (50%) were suffering from vaginal discharge at the time of the study.

Table(1): Frequency distribution of medical, gynecological, and obstetrical history of the 90 participant women

Variables		**Frequency**	**Percentage**
Chronic disorders	Yes	3	3.3
	No	87	96.7
Current medication	Yes	34	37.8
	No	56	62.2
Gravida	≤3	48	53.3
	4 - 6	36	40.0
	≥7	6	6.7
Abortion	No	56	62.2
	1	19	21.1
	2	9	10.0
	3	3	3.3
	4	2	2.2

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	5	1	1.1
Previous preterm labor	No	73	81.1
	Yes	17	18.9
	1	12	13.3
	2	4	4.4
	6	1	1.1
Vaginal discharge	Yes	45	50.0
	No	45	50.0

Table 2: The difference between study groups in fibronectin concentration

Type of sample	N	Mean	Standard deviation	P-value
Patient (preterm)	45	77.58	9.06	<0.001
Control (full-term)	45	50.16	5.38	

It was found that patients with preterm delivery had significantly higher fibronectin concentration than those with full-term delivery (P-value< 0.001).The mean ± SD for preterm pregnancy patients was 77.58±9.06 while it was 50.16±5.38 for full-term as seen in table 6.

Table 3: Correlation and regression analysis for fibronectin and the time of delivery

R	P-value	P-value	Odds ratio	95% CI
0.881	<0.001	0.025	2.283	1.108-4.705

In this table, the correlation coefficient (R=0.881) means that there is a significant (P-value < 0.001) strong positive correlation between fibronectin and the time of delivery (preterm and full-term groups).

In binary logistic regression, the fibronectin (independent variable) was shown as a significant (P-value =0.025) predictor for the time of delivery (dependent variable) among the study group. The Odds ratio=2.283 means that the occurrence of preterm labor is double for each unit increasing in the fibronectin concentration.

Table 4: Receiver Operator Characteristic (ROC) curve analysis for sensitivity, specificity, Area Under Curve (AUC), and fibronectin concentration cutoff value between preterm and full-term labor women

Predictor	AUC	95% CI	Cutoff point	P-value	SN	SP	PPV	NPV
Fibronectin concentration	0.999	0.995-1.000	62.42	< 0.001	97.8%	100%	100%	97.8%

AUC: Area Under Curve; CI: Confidence Intervals; SN: Sensitivity; SP: Specificity; PPV: Positive Predictive Value; NPV: Negative Predictive Value.

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The cutoff point of fibronectin concentration that appeared to differentiate those women who delivered earlier than others is found to be equal to or above 62.42 with a significant P-value less than 0.001.

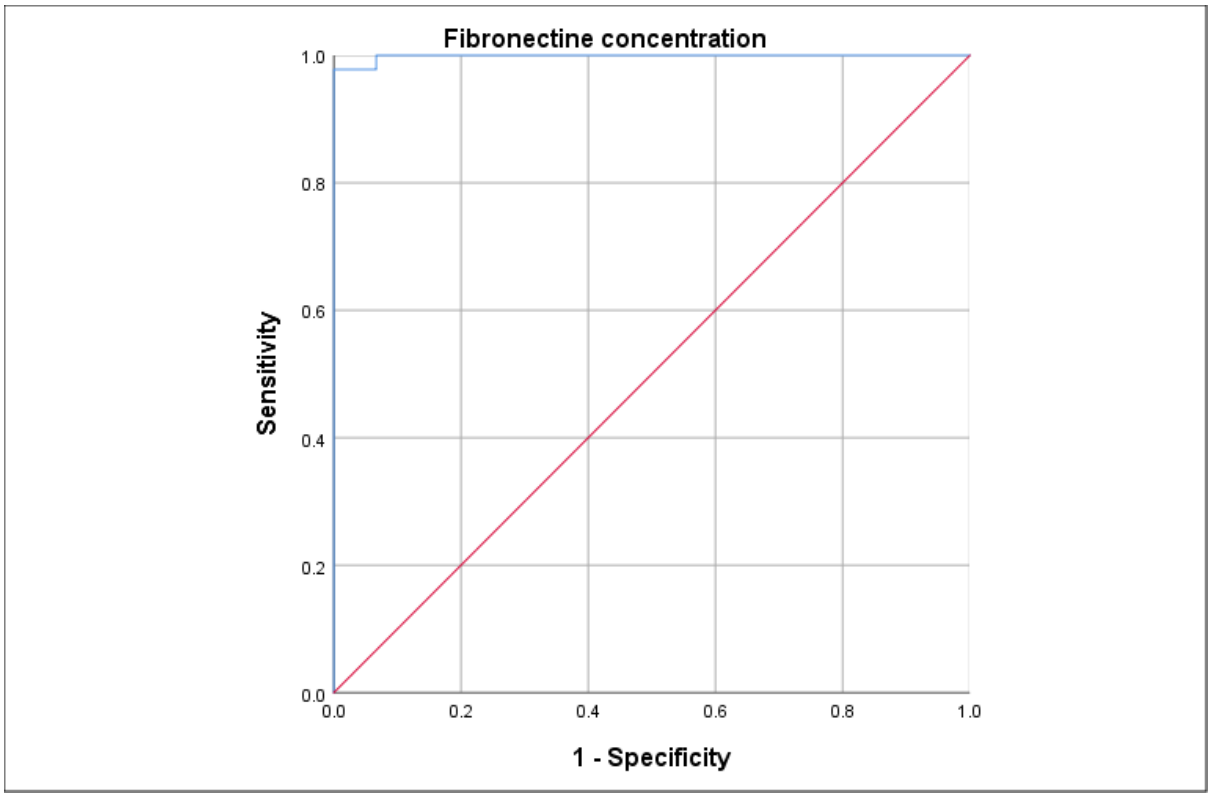

Figure1: ROC analysis for fibronectin concentration cutoff point.

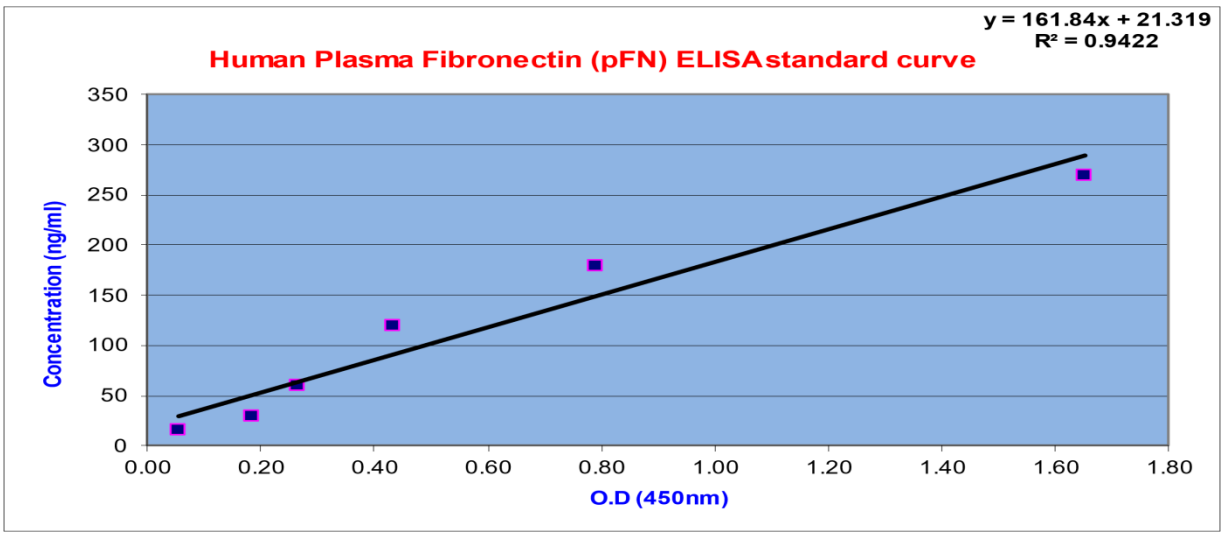

Figure 2: Human plasma Fibronectin(pFN) ELISA Standard curve

Known concentrations of Human pFN Standard and its corresponding reading OD is plotted on the log scale (x-axis) and the log scale (y-axis) respectively. The concentration of Human pFN in sample is determined by plotting the sample's O.D. on the Y-axis. The original concentration is calculated by multiplying the dilution factor.

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Discussion

Fibronectin is a glycoprotein produced by the chorionic and acts as a glue between the placenta and the decidua. It is normally secreted in the vagina and the cervix within 16-20 week of gestation, but it is rarely found in the vaginal secretions after the 21st week. It increases again in the vaginal secretions before delivery. Hence, the early presence of fibronectin in vaginal and cervical discharges can predict preterm delivery(13).

It was found that patients with preterm delivery had significantly higher fibronectin concentration than those with full-term delivery (P-value< 0.001).The mean ± SD for preterm pregnancy patients was 77.58±9.06 while it was 50.16±5.38 for full-term as seen in table 6.

Serum samples from 105 pregnant women participating in this study were collected. The plasma fibronectin were measured at 24-28 wk of gestation and again at 32-36 weeks of gestation. The plasma fibronectin was analyzed using ELISA method and its concentration in term and preterm deliveries was compared. The Plasma fibronectin concentrations in women with preterm delivery were higher than in those who delivered at term ($p = 0.001$). Accordingly, Plasma fibronectin concentrations were significantly higher in the second serum samples ($p = 0.01$). Plasma fibronectin concentrations was also higher in obese women and in those suffering from preeclampsia ($p = 0.12$) and gestational diabetes ($p = 0.81$). In other words, the increase in gestational age was accompanied by a significant increase in the fibronectin concentration in the preterm delivery group ($p = 0.001$)(10) .compared maternal plasma fibronectin concentration in three study groups, including women with symptoms and risk factors of preterm delivery, women 1with symptoms but without risk factors of preterm delivery, and healthy pregnant women. The results showed the mean (±SD) plasma fibronectin concentrations in case group 1, case group 2, and the control group were 1017 (535), 907 (556), and 772 (297), respectively which were not significantly different based on the Kruskal Wallis test. The mean plasma fibronectin level was significantly higher in the women with preterm delivery compared to those with term delivery $P \leq 0.001$(1). The difference between the results may be because of the kits utilized.

Increased plasma fibronectin concentration may result from its secretion from damaged endothelial cells occurring in placentas of women experiencing preterm delivery .Production and secretion of fibronectin into body fluids is accompanied by the natural growth of placental and trophoblastic villi, which increase with an increase in gestational age(15).

On the contrary, a systematic review showed the unsatisfactory results of using plasma fibronectin testing in the identification of pregnant women who required interventions. Additionally, physicians' information about vaginal fibronectin concentration was not influential in the reduction of the rate of preterm delivery and had no benefits for either the mother or the fetus(16).

Furthermore, a study demonstrated that in comparison with the overall assessment of fibronectin concentration at a particular age, longitudinal measurement of plasma fibronectin concentration at 26, 30, and 34 weeks of gestation was a better predictor of the incidence of preeclampsia (17).

study was conducted on 105 pregnant women,Serum samples were obtained fromwomen at 24-36 weeks of gestation. However, only 40 women gave permission to collect vaginal samples. Fibronectin concentration was measured using the ELISA technique. Then, plasma and vaginal fibronectin levels were compared in term and preterm deliveries.The mean

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plasma fibronectin level was 6226.43±7174.97 ng/ml among the mothers with term infants and 7724.01±1143.82 ng/ml among those with preterm infants (p=0.667). The mean fetal fibronectin level was 156.61±126.42 ng/ml among the mothers with term infants and 127.71±43.14 ng/ml among those with preterm infants (p=0.241) (4).

This difference might be due to the number of samples and the laboratory method used in plasma fibronectin evaluation. Considering the higher accuracy of the ELISA in evaluating blood variables compared with other methods such as nephelometry, if the sample size had been larger, the difference would have been significant.

those a study that examined fibronectin levels in plasma, this study found that there was no difference in fibronectin levels in the plasma of women with normal pregnancy in the first trimester to the third trimester with women who were not pregnant(18).

Astudy concludes that fibronectin levels are not specific biomarkers in detecting miscarriage in the first trimester of pregnancy. The average fibronectin level of normal pregnancy in the first trimester was 118.8 ± 18.4 ng/mL with the lowest level of 85.3 ng/mL and the highest of 154.5 ng/mL. Meanwhile, the mean fibronectin level of miscarriage was 208.2 ± 152.0 ng/mL with the lowest level of 82.8 ng/mL and the highest of 154.5 ng/mL with the lowest level of 82.8 ng/mL and the highest of 519.5 ng/mL(19).

The plasma and vaginal fibronectin concentrations in the diagnosis of preterm delivery have been presented in ROC curves. The cut-off point of plasma fibronectin level was 1750 ng/ml with a sensitivity of 80.25% and specificity of 85.17%. Additionally, the cut-off point of vaginal fibronectin level was 158.98 ng/ml with a sensitivity of 94.62% and specificity of 22.08%(4).

Our experiment appears to disagree with reported a PPV of 41% and reported NPV of 95.5% This high NPV enables the clinicians to reassure the patient and for possible discharge from the intensive care unit (20)showed sensitivity of 75.00%, specificity of 98.75%, positive predictive value of 92.31% and negative predictive value of 95.18%. The sensitivity and specificity indicates good performance.NPV of 95.18% is high in asymptomatic women in this study and it remains high in most study(21).

The plasma and vaginal fibronectin concentrations in the diagnosis of preterm delivery have been presented in ROC curves. Accordingly, the cut-off point of plasma fibronectin level was ≥4000 ng/mL with a sensitivity of 60.7% and specificity of 52.6%. Additionally, the cut-off point of vaginal fibronectin level was ≤90 ng/mL with a sensitivity of 100% and specificity of 46.9%. Thus, plasma fibronectin testing had lower sensitivity and higher specificity compared to vaginal fibronectin testing. This implies that plasma testing had lower false-positive cases and could identify a more significant number of true positive cases of preterm delivery(10).

the study with a reported sensitivity and specificity of 56% and 64.8%, respectively; where it did not improve the prediction of preterm delivery andthere was no significant increase in odds of preterm birth < 34 weeks or birth within the next 7 d (OR 2.28, 95% CI 0.84-6.17 and OR 3.61, 95% CI 0.89-14.7 respectively (22).

the study is to determine if qfFN can reliably predict term labour in asymptomatic women from rural and remote areas.There was a small-to-moderate negative correlation (r_s −0.27, P < 0.05) between time until labour and fFN. Quantitative fFN was observed to be

a significant predictor of time until labour after adjusting for confounding variables ($P < 0.001$). The fFN levels may play a role in predicting term labour in rural women(23).

The study aimed to determine whether qualitative fetal fibronectin effective in predicting delivery in term pregnancies within 5 days of the test examined 268 women with singleton pregnancies at 38 weeks + 1 day) of gestation with irregular and painful uterine contractions, intact membranes and cervical dilatation less than 2 cm. All women were admitted to hospital up to 72 h after birth. On admission, a qualitative fetal fibronectin test was performed in cervicovaginal secretions. The primary outcome measure was delivery within 5 days of presentation. Among the women who delivered within 5 days after admission, 65.2% had positive fFN assessment and 56.5% had gestational age ≥ 275 days. Logistic regression analysis demonstrated that significant contributors to the prediction of delivery within 5 days were fibronectin positivity and gestational age ≥ 275 days, with no significant contribution from parity. Qualitative fetal fibronectin test in term pregnancies are useful tests for predicting spontaneous onset of labour within 5 days. It helps women and healthcare providers to determine the optimum time for hospital admission(24).

the initiation of parturition in females experiencing preterm labor (PTL) by measuring cervical fetal fibronectin (FFN) as a marker for premature labor (PTL) included 90 women with symptoms of sPTB, There were 12 women in our cohort who reported previous preterm labor , FFN showed better sensitivity and specificity. Logistic regression analysis demonstrated that the sPTB in the current cohort was only dependent on quantitative FFN at the time of presentation.FFN could improve PTB prediction accuracy; FFN levels which could help clinicians identify women at risk of delivery before 34 weeks or 37 weeks(25).Six studies randomized 546 women with singleton gestations and threatened preterm labor (PTL) at 23 0/7 to 34 6/7 weeks. A total of 277 women were randomized to knowledge and 269 to no knowledge of FFN. No trials were identified on asymptomatic women or multiple gestations. The risk of bias of included studies was mixed. The evidence for preterm birth before 32 weeks is uncertain because the quality was found to be very low (average RR 0.79, 95%CI 0.16 to 3.96; 4 trials; 357 women; very low-quality evidence). However, management based on knowledge of FFN results may make little or no difference to preterm birth before34 weeks or maternal hospitalization (2).

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