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Accuracy of cervico vaginal fetal fibronectin test in predicting risk of spontaneous preterm birth

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Abstract

Preterm delivery is the leading cause of neonatal mortality. One of the best predictors to assess the risk of preterm labour (PTB) is by measuring fetal fibronectin (fFN) in cervico vaginal secretion after 26 weeks of pregnancy. The aim is to evaluate the diagnostic accuracy of qualitative cervico vaginal fFN in symptomatic women and asymptomatic high risk women during antenatal care. Prospective study which was conducted in Basrah Maternity and Child Hospital. It included 106 pregnant women at gestational age more than 26 weeks who had uterine contraction with or without pervious risk factors for PTB. Cervico vaginal fluid sampling was undertaken from all women included in the study after the age of 26 weeks of gestation and qualitative fFN assessment was done with 50ng/ml is the cut off point for positivity. As regard qualitative fFN assessment for predicting of PTB sensitivity, specificity, PPV, NPV, were 71%, 87%, 40.50%, 94% respectively in symptomatic women. While in asymptomatic women with previous high risk had 26% sensitivity, 84% specificity, 32% PPV, and 87% NPV. Qualitative assessment of fFN in cervico vaginal fluid is good predictive marker in detecting of PTB.

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Introduction

Preterm labour is defined as regular contractions of the uterus starting before 37 weeks of pregnancy that result in cervical effacement and dilatation. Globally, about 15 million babies are born preterm each year. The incidence of preterm birth varies significantly across the globe (American College of Obstetricians and Gynecologists, 2016).

Approximately 30-35% of preterm birth PTB are iatrogenic due to medical or obstetric complications, 40-45% are related to spontaneous preterm labour, and 25-30% to preterm rupture of membrane. Spontaneous pre-term birth is most commonly caused by pre-term labour in caucasians, and preterm prelabour rupture of membrane in black women indicating the existence of potentially different causative mechanism (Offiah *et al.,* 2012).

Fetal fibronectin is a glycoprotein variant of fibronectin family present in amniotic fluid, placenta and the extracelluar substance of the decidua (Bennett, 2018). Its synthesis and release is increased by the mechanical and inflammatory events which occur prior to the onset of labour (Bennett, 2018). Fibronectin is often described as "leaking" from disruption to the fetal membranes and decidua in the lower pole of the uterus associated with early biochemical events of parturition.

However, it is also an inflammatory response gene, and therefore concentrations of fibronectin in vaginal fluid can be considered to also be marker of inflammation (which may be pathological or a normal part of the onset of labour at term) (Bennett, 2018).

Fetal fibronectin may normally be detected in vaginal secretions at levels in excess of 50ng/ml. However, it is now being increasingly used to predict risk in women who are asymptomatic but at risk for other reasons, in particular cervical shortening (Foster and Shennan, 2014; Kuhrt *et al.,* 2016).

Since fFT is present in amniotic fluid and placental tissue, mechanical or inflammatory-mediated damage to the membranes before PTB might result in its release into the cervix and vagina (Honest *et al*., 2002).

The presence of cervico vaginal fFT in the second and third trimesters of pregnancy identifies a subgroup of women who are at high risk for PTB. This phenomenon may reflect the separation of the chorion from the decidual layer of the uterus, with the release of intact or degraded chorionic components of the extracellular matrix into cervical and vaginal secretions (Lockwood *et al*., 1991). Thus, early detection of PTB is difficult because initial symptoms are often mild and may occur in normal pregnancies.

Even an interesting works, mostly in USA, have been carried out among different population (Lockwood *et al*., 1991; Honest *et al*., 2002; Imas, 2003; Hezelgrave *et al*., 2015; American College of Obstetrics and Gynecologists, 2016; Bennett, 2018) but unfortunately, there is no work which has been done among women in our region. Thus, it is of value to know its accuracy, sensitivity and specificity in predicting spontaneous PTB in women with or without symptoms. It is expecting to use the results of this study to predict and diagnose PTB. In addition, the usual treatment in clinical practice depends on accurate prediction of spontaneous PTB.

Materials and methods

Subjects

A prospective study was conducted in Basrah Maternity and Child Hospital from April 2017 till October 2018. This study was approved by the research ethical community. 106 women with singleton pregnancy, with gestational age between 26 – 36 weeks. They had symptom of PTB which include history of uterine contractions and no history of vaginal bleeding, vaginal discharge or cervical dilatation. Asymptomatic pregnant women with risk factors like previous PTB, premature rupture of membrane, mid trimester abortion, previous cervical surgery like Manchester operation and history of accident finding of cervical length of less than 25 mm by ultrasound in the present pregnancy.

Exclusion Criteria

- Premature preterm rupture of membrane at the present pregnancy
- Vaginal bleeding

- Multiple pregnancy
- History of intercourse 24 hours before vaginal sampling

Samples collection and processing

All the studied women were examined for vital signs as well as uterine consistency, uterine contraction and obstetric examination.

1) Vaginal Sampling and preparation

The Hologic specimen collection kit was used to collect vaginal specimens for this assay.

The polyester tipped swab provided in the specimen collection kit should be inserted into the vagina and lightly rotated across the posterior fornix for approximately10s to absorb cervico vaginal secretions.

After obtaining the specimen, the swab was carefully removed from the vagina and was placed into a tube of buffer provided with specimen collection kit. One specimen collection devices per patient were obtained.

Specimen transport tubes were labeled with the patient's name and any other identifying information required.

2) Preparation of the fibronectin instrumentation

A) Press of NO.3 of the instrument
B) Press of enter on the instrument
C) Introduce the blue caset then press on enter, wait until the pass ward appear on the printer of the instrument, now the instrument is ready for work.

3) Preparation of caset of result

A) Press on the test patient then enter.
B) Press the name and code number of the patient on the instrument then enter.
C) Put the caset then press enter.
D) Put the sample on the caset quickly by pipette, aspiration of 0.1 ml then press enter.
Appositive sample was > 50ng/ml

All the studied pregnant women were undertaken ultrasound examination for assessment of fetal age, fetal presentation and all were undertaken urine examination and complete blood test and after samples collection all the pregnant women were followed during the rest of pregnancy and timing of delivery and mode of delivery were recorded beside neonatal condition was recorded.

Statistical Analysis

The statistically analysis for the collected data were done by using Statistical Package for the Social Sciences (SPSS) data were presented as mean ± SD, number and%. Chi-square test (X^2) was used for comparison between groups with regard to qualitative assessment. Validity of the test is done using sensitivity, specificity and positive predictive value, and negative predictive value.

Results

A total of 106 cases of pregnant women were included in the study. The mean age for the studied women was 31±5 years, 14% of them were primgravida, and 86% were muliparus women (Table 1). 14% of the studied women had history of previous preterm delivery and 4.7% had history of mid trimester miscarriage.

The positivity test for fFN in the studied group in regard to gestational age was 100% among women with preterm delivery in comparison to 4% women who delivered at term (Table 2). The relationship was highly significant ($p<0.001$). No case of negative fFN in the preterm group while (96%) of the term group were negative fFN.

It was noticed that 4 women out of 15 primigravida were positive for fFN (26.6%) (Table 3), while 8 (8.7%) of multiparous women were positive for fFN. It was also showed that 83 (91.3%) of case of multipara women had negative fFN test in comparison to 11 (73.4%) of primigravida women.

The validity of qualitative assessment of cervico vaginal fFN was shown in Table (4). There were 71% sensitivity, 87% specificity, 40.5% PPV, 94% NPV in predicting PTB in symptomatic women. While in asymptomatic women with pervious high risk had 26% sensitivity, 84% specificity, 32% PPV, and 87% NPV (Table 4).

Table 1. Demographic data of the studied women.

Demographic data	Value
Age (year) m ±SD	31 ± 5
BMI (kg/m²)	29
Parity:	
- primgravida.	15
- number of parity (1-5).	44
-more than (5).	47
Risk factors:	
-pervious preterm labour.	15
- pervious 2nd trimester miscarriages (16-24 weeks).	5
- pervious preterm prelabour rupture of membrane.	6
- pervious cervical surgery.	-ve
Age of gestation at time of labour:	
-preterm <37 weeks.	9
-term >37 weeks.	97
Women with symptom of preterm labour.	97

Table 2. Qualitative assessment of cervical fFN in this study in regard to the gestational age at time of labour.

Cervical fFN assessment	Women who delivered preterm N:9 (%)	Women who delivered at term N: 97 (%)	P – value
Positive	9 (100)	3(4)	0.001
Negative	-	94 (96)	0.001

Table 3. Qualitative assessment of cervico vaginal fFN in regard to parity in the studied group.

Cervical fFN	Primigravida N (15)	P >1 (91)
+ve	4 (26.6%)	8 (8.7%)
-ve	11 (73.4%)	83 (91.3%)

Table 4. Validity of qualitative assessment of cervico vaginal fFN.

fFN (+ve)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Symptomatic women with preterm labour	71	87	40.5	94
Asymptomatic women with pervious risk factors	26	84	32	87

Fig. 1. Fetal Fibronectin Machine.

Discussion

Preterm birth is one of the causes of neonatal morbidity and mortality in the world. There are various methods which can detected patients with high risk of PTB and the patients could be followed and effective management can be performed. Early diagnosis of asymptomatic women with high risk of PTB could help prevent it and given the chance to enhance fetal lung maturity.

It was interesting to detect fFT in the cervico vaginal secretions of patients with preterm rupture of membranes, given the high levels present in amniotic fluid. The findings of the present study strongly confirmed the significant relationships between high fFT levels and the occurrence of PTB.

If pregnant women are diagnosed as low risk for PTB, this could reduce the length of hospital stay and antenatal visit. It has been demonstrated that screening asymptomatic women for the presence of cervico vaginal fFN at 24 weeks of pregnancy had a high sensitivity in predicting more than 60% of spontaneous PTB within the following 4 weeks (sensitivity, 0.63; 95% CI: 0.4, 0.8; relative risk=59.2, 95% CI: 35.9, 97.8) compare to women with a negative fFN assessment (<50ng/ml) (Goldenberg, *et al.,* 2001).

It has been reported that high NPV and specificity for vaginal fFN in the prediction of PTB in asymptomatic high-risk women within 2 weeks of assessment (Leitich and Kaider, 2003).

In patients with intact membranes, the presence of cervico vaginal fFT made it possible to distinguish between those with irrelevant uterine contractions and those at true risk for PTB. The association between the presence of fFN and PTB in asymptomatic women was evaluated by meta-analysis. The likelihood ratio was 4.0 (95% CI: 2.9, 5.5) for positive result of predicting PTB before 34 weeks of pregnancy (Honest *et al.*, 2002).

Spontaneous preterm birth (< 34 weeks) 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 500ng/ml. or greater, respectively). A threshold of 50-199ng/ml. had sensitivity 46.5%, specificity 88.7%, PPV 23.7%, and NPV 95.6% (Abbott *et al.,* 2015).

It has been found that serial sampling and assessment of fFN in asymptomatic high-risk women for PTB 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 to a single fFN test (Roman *et al.,*

Overall, sensitivity rates appeared to be higher in women with symptoms of preterm labour than in asymptomatic women while specificity in both group is high. fFT plays a critical part both in maintaining contact between the uterus and the placenta and its membranes and in facilitating the physiologic separation of the placenta from the uterus after the fetus has been delivered.

In conclusion, fFT is a moderately sensitive, but sufficiently specific marker for preterm delivery occurring before 37 weeks. Sensitivity and specificity rate are higher if delivery within a specific period of time after fFN sampling is used as outcome. To the best of my knowledge, this study is the first to be done on the relationship of fFT and PTB among women in the community.

Fetal fibronectin is only a single marker, and combination of fFN with other risk factors such as a history of a previous preterm delivery or cervical ultrasonography may farther increase the predictive capacity of the model containing fFN alone. It can be emphasized that it is possible to identify these patients that could lead to meaningful therapeutic intervention.

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