Original Article

Qualitative cervicovaginal fluid β-hCG versus cervicovaginal fluid fetal fibronectin assessment in prediction of preterm labor in asymptomatic high risk women

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ABSTRACT

Context: Preterm births occur in 11% of all births worldwide, but account for more than 85% of perinatal morbidity and mortality. One of the best predictors to assess the risk of preterm labor (PTL) is by measuring fetal fibronectin (fFN) in cervicovaginal secretions (CVS). In addition, measurement of cervicovaginal fluid fFN is a good negative predictor of spontaneous PTL in both symptomatic and asymptomatic high-risk women after 22 weeks of pregnancy.

Aim: We aimed to evaluate the diagnostic accuracy of qualitative cervicovaginal beta-human chorionic gonadotropin (β-hCG) versus qualitative fFN for prediction of PTL in asymptomatic high-risk women during antenatal care.

Settings and Design: This prospective observational study was undertaken at Egypt, Zagazig University Hospitals. In all, 220 with singleton pregnancies and having risk factors for spontaneous preterm birth were included in this study.

Materials and Methods: Cervicovaginal fluid sampling was undertaken at 24 weeks gestational age for qualitative β-hCG and qualitative fFN assessment. Women were categorized into two arms: women who delivered preterm and women who delivered at term.

Statistical Analysis Used: Data were presented as mean, ±standard deviation, number, and percentage. Chi-square test (χ^2) was used for comparison between groups with regard to qualitative variables; validity of the test is done using sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

Results: As regarding qualitative β-hCG assessment for prediction of PTL, sensitivity, specificity, PPV, and NPV were 72%, 85%, 41%, and 95.5%, respectively. As regarding qualitative fFN assessment for prediction of PTL in the same studied group, sensitivity, specificity, PPV, and NPV were 73%, 87%, 38%, and 96%, respectively.

Conclusion: Our study showed that qualitative β-hCG assessment in cervicovaginal fluid can be used as an alternative method to qualitative fFN assessment as it is a valid test, more available, and not expensive in prediction of PTL in asymptomatic high-risk patients.

Key words: β-hCG; fetal fibronectin; preterm labor.

Introduction

Preterm labor (PTL) refers to the onset of labor after fetal viability but before completing 37 weeks of pregnancy. The diagnostic criteria of threatened PTL are onset of

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frequent uterine contractions (at least four contractions per 20 minutes) and cervical changes in the form of effacement and dilatation, that is, 80% cervical effacement and at least 2 cm dilatation (or cervical length <1 cm). Preterm births occur in 11% of all births worldwide, but account for more than 85% of perinatal morbidity and mortality.[1] Fetal mortality and morbidities such as neurological problems, retinopathy of prematurity, hyaline membrane disease, and necrotizing enterocolitis are common sequels of preterm delivery.[2-4]

Fetal amnion is the main source of fibronectin which is a glycoprotein found in high concentration in the liquor amnii and fetal membrane. One of the best predictors to assess the risk of PTL is by measuring the fetal fibronectin (fFN) in the cervicovaginal secretions (CVS).[5] Mechanical or inflammatory-mediated disruption of the uteroplacental interface before birth leads to the release of fFN in CVS.[6] It is absent during 24–37 weeks of pregnancy. Its presence in the CVF is a sign of PTL within 7 days.[7]

Measurement of cervicovaginal fluid fFN is a good negative predictor of spontaneous PTL in both symptomatic[8] and asymptomatic high-risk women after 22 weeks of pregnancy.[9] They found that in symptomatic patients between 24 and 34 weeks of pregnancy, measurement of fFN provides a high negative predictive value (NPV) for continuing pregnancy beyond 7 days after testing and for prolonging gestation beyond 34 weeks.[10,11]

In addition to fFN, beta-human chorionic gonadotropin (β-hCG) was also studied for its relation with PTD. Various studies showed an increased concentration of the marker during spontaneous preterm birth. Monitoring of β-hCG level in CVF as a marker for PTD can be a useful predictor in symptomatic women.[12] Gurbuz *et al*. showed that increased concentration of β-hCG in CVF was found in women with PTD, and in contrast to fFN, this test has the benefits of low cost and wide availability.[13]

Guvenal *et al*. reported that cervicovaginal β-hCG >28 mIU/mL had the ability to predict preterm delivery between 24 and 36 weeks gestation with a sensitivity, specificity, positive predictive value (PPV), and NPV of 87, 65, 28, and 97%, respectively, in women with threatened PTL. The kits used for "pregnancy test" in urine can detect β-hCG levels of >25 mIU/mL, and so those kits could detect the β-hCG level which predicts preterm delivery according to a previously mentioned study.[14]

The aim of our study is to evaluate the diagnostic accuracy of qualitative assessment of cervicovaginal fFN versus qualitative assessment of cervicovaginal β-hCG for prediction of PTL in asymptomatic high-risk women during antenatal care.

Materials and Methods

This prospective observational study was performed from May 2015 to September 2017 at Zagazig University Hospitals. This study was approved by the Research Ethical Committee of Zagazig University Hospitals. Written informed consent was obtained from all participants. In all, 220 women with singleton pregnancies and risk factors for spontaneous preterm birth were included in this study. Cervicovaginal fluid sampling was undertaken for qualitative assessment of β-hCG and fFN at 24 weeks of gestation.

Inclusion criteria

There were past history of one or more spontaneous PTL or preterm premature rupture of membranes, previous spontaneous second-trimester miscarriage, previous cervical surgery, or an accidental finding of a cervical length of 25 mm or less in the current pregnancy.

Exclusion criteria

Prior sexual intercourse (within 24 h), or suspected or confirmed rupture of membranes, or who had visible vaginal bleeding on the swab were excluded. Early obstetric ultrasound (11–14 weeks of gestation) was performed to confirm the gestational age. Baseline demographic data, obstetric history, and risk factors were tabulated and analyzed. For qualitative assay of both β-hCG and fFN, vaginal specimens were collected by the following method.

Specimen collection

The anterior cervical lip was grasped with sponge forceps after introducing sterile Cusco speculum into the vagina. Before doing any cervical manipulations or introducing any vaginal material, sampling was performed. The Hologic specimen collection kit was used to collect 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 approximately 10 s to absorb cervicovaginal 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. Two specimen collection devices per patient were obtained, one for each assay. Specimen transport tubes were labeled with the patient's name and any other identifying information required.

Qualitative assessment of β-hCG

It was performed as a bedside test. The swab was then inserted in a tube containing 0.75 mL of sterile normal saline

for dilution.[4] From this sample, three drops were used for a bedside β-hCG test using ACON–HCG one-step pregnancy test strip (Rapid Diagnostic Pvt. Ltd, India), with a detection cut-off value of 25 mIU/mL.

Qualitative assessment of fFN

It was done using quick check fFN test; it is a 10-min, one-step, visual test. The test strip was removed from the foil pouch and its lower end (indicated by the arrows) was inserted into the tube containing the extraction buffer for 10 min. A positive sample containing fFN will result in two lines in test strip and a negative sample will result in one control line in test strip.[11,12,15] All women were then followed up till delivery. Women were categorized into two arms: women who delivered preterm (before 37 completed weeks of gestation) and women who delivered at term (at or after 37 completed weeks of gestation). Cases with iatrogenic PTL were excluded from the study and were calculated among women who did not complete follow-up. We included only women with spontaneous PTL.

Sample size calculation

The sample size was calculated using Open Epi according to the following PPV of β-hCG assay mentioned in Abbott *et al.* (2015) which was 24% and that of fFN assay mentioned in Ibrahim *et al.* (2013) which was 79%. Therefore, at power of study 80% and confidence interval (CI) 95%, the sample size was calculated to be 220 cases.

Statistical analysis

The collected data were statistically analyzed using Statistical Package for Social Sciences (SPSS), version 20. Data were presented as mean, ± standard deviation, number, and percentage. Chi-square test (χ^2) was used for comparison between groups with regard to qualitative variables; validity of the test is done using sensitivity, specificity, PPV, and NPV.

Results

Twenty cases were lost during follow-up, and therefore 200 cases were included in the final analysis. Table 1 shows demographic data of the studied group. There is a highly significant ($P < 0.00001$) difference between women with preterm and term delivery as regards qualitative assessment of cervicovaginal β-hCG as shown in Table 2. In addition, there is a highly significant ($P < 0.00001$) difference between women with preterm and term delivery as regards qualitative assessment of cervicovaginal fFN as shown in Table 3. Table 4 shows validity of qualitative assessment of cervicovaginal β-hCG (sensitivity 73.68%, specificity 87.85%, PPV 38.89%, NPV 96.95%, accuracy 86.5%) and fFN (sensitivity 72%, specificity 85.71%, PPV 41.86%, NPV 95.54%, accuracy 84%) in predicting PTL in asymptomatic high-risk women.

Table 1: Demographic data of the studied group

Demographic data	Value
Age (years)	
M±SD	25.2±4.1
BMI (kg/m^2)	25.4±5.1
Parity	
No. of deliveries (median)	2 (1-2)
GA at delivery (weeks)	
M±SD	36.8±2.9
Risk factors	
Previous preterm labor	(37%)
Previous 2nd trimester miscarriage (16-24 weeks)	(20%)
Previous PROM	(38%)
Previous cervical surgery	10 (5%)

SD, Standard deviation; BMI, Body mass index; GA, Gestational age; PROM, Premature rupture of membrane

Discussion

PTL is a major cause of neonatal morbidity and mortality all over the world. There are various biomarkers that can identify patients with high risk of PTL. Therefore, those patients could be followed up and an effective management can be performed.[16,17]

Early diagnosis of asymptomatic women with high risk of PTL could help prevent it and gives the chance to enhance fetal lung maturity. If pregnant women are diagnosed as low risk for PTL, this could reduce the length of hospital stay and antenatal visits.

As regarding β-hCG assessment for prediction of PTL in the studied group, sensitivity, specificity, PPV, NPV, and accuracy were 73.68%, 87.85%, 38.89%, 96.95%, 86.5%, respectively.

Bernstein *et al*. evaluated β-hCG assessment in patients who had a risk of preterm delivery using a cut-off value >50 mIU/mL. The predictive values were sensitivity 50%, specificity 87%, PPV 33%, and NPV 93%.[16] A cut-off value 28 mIU/mL was used by Guvenal *et al*. between 24 and 36 weeks of pregnancy and reported sensitivity 87%, specificity 65%, PPV 28%, and NPV 97% for predicting preterm delivery.[14] A cut-off value of 77.8 mIU/mL was used by Garshasbi *et al*. and showed a sensitivity of 87%, specificity 97%, PPV 88.5%, and NPV 98% for predicting preterm delivery.[17] β-hCG value of >14 mIU/mL was the optimal cut-off value for predicting PTL <34 weeks with sensitivity 83.3%, specificity 85.5%, PPV 33.3%, and NPV 98.3%.[18] The lower cut-off value of β-hCG assessment in this study as compared to a study by Bernstein *et al*. (>50 mIU/mL) and Garshasbi *et al*. (>77.8 mIU/mL) may be explained by the difference in the inclusion criteria of the study populations, earlier period of gestation, and a relatively low rate of PTL <34 weeks (8%) in this study.[16,18] Adhikari *et al*. showed

Table 2: Qualitative assessment of cervicovaginal β-hCG in women with preterm and term delivery

Cervicovaginal β-hCG assessment	Women who delivered preterm ($n=19$)	Women who delivered at term ($n=181$)	*P*
Positive	14 (73.7%)	22 (12.1%)	<0.00001
Negative	5 (26.3%)	159 (87.9%)	

β-hCG, Beta-human chorionic gonadotropin

Table 3: Qualitative assessment of cervicovaginal fFN in women with preterm and term delivery

Cervicovaginal fFN assessment	Women who delivered preterm ($n=25$)	Women who delivered at term ($n=175$)	*P*
Positive	18 (72%)	25 (14%)	<0.00001
Negative	7 (28%)	150 (86%)	

fFN, fetal fibronectin

Table 4: Validity of qualitative assessment of cervicovaginal β-hCG and fFN in predicting preterm labor

	Sensitivity	Specificity	PPV	NPV	Accuracy
Cervicovaginal β-hCG	73.68%	87.85%	38.89%	96.95%	86.5%
Cervicovaginal fFN	72%	85.71%	41.86%	95.54%	84%

β-hCG, Beta-human chorionic gonadotropin; fFN, Fetal fibronectin; PPV, Positive predictive value; NPV, Negative predictive value

that hCG value of >14 mIU/mL was the ideal cut-off value for predicting PTL <34 weeks with sensitivity 83.3%, specificity 85.5%, PPV 33.3%, and NPV 98.3%. Qualitative assessment of cervicovaginal fluid β-hCG at 26–36 weeks of gestation was valuable in the prediction of PTL in asymptomatic high-risk women. Using a cut-off value of 25 mIU/mL, the sensitivity was 68.3%, specificity 96.1%, PPV 76.9%, NPV 94.3%, and diagnostic accuracy 91.8% to predict PTL.[19]

Regarding fFN assay for prediction of PTL in the same studied group, sensitivity, specificity, PPV, NPV, and accuracy were 72%, 85.71%, 41.86%, 95.54%, and 84%, respectively.[20] Goldenberg *et al*. demonstrated that screening asymptomatic women for the presence of cervicovaginal fFN at 24 weeks 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 (<50 ng/mL).[21] 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.[22] The association between the presence of fFN and PTL in asymptomatic women was evaluated in a meta-analysis by Honest *et al*. The likelihood ratio was 4.0 (95% CI: 2.9, 5.5) for positive result of predicting PTL before 34 weeks of pregnancy.[7] 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 500 ng/mL or greater, respectively). A threshold of 50–199 ng/mL had sensitivity 46.5%, specificity 88.7%, PPV 23.7%, and NPV 95.6%.[23] 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 to a single fFN test.[24]

Conclusion

β-hCG assessment in cervicovaginal secretion can be used as an alternative to fFN assessment as it is simple, available, and not expensive, and the validity of qualitative cervicovaginal β-hCG in high-risk patients for predicting PTL is nearly similar to that of cervicovaginal fFN assessment. The utility of β-hCG in our hospital is easily applicable, with early diagnosis and early interference which minimizes the rate of PTL in our locality.

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Conflicts of interest

There are no conflicts of interest.

References

1. Beck S, Wojdyla D, Say L, Betran A, Merialdi M, Requejo JH, *et al*. The worldwide incidence of preterm birth: A systematic review of maternal mortality and morbidity. Bull World Health Organ 2010;88:31-8.
2. McGowan JE, Alderdice FA, Holmes VA, Johnston L. Early childhood development of late-preterm infants: A systematic review. Pediatrics 2011;127:1111-24.
3. Woythaler MA, McCormick MC, Smith VC. Late preterm infants have worse 24-month neurodevelopmental outcomes than term infants. Pediatrics 2011;127:e622-9.
4. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet 2008;371:75-84.
5. Kim A, Lee ES, Shin JC, Kim HY. Identification of biomarkers for preterm delivery in mid-trimester amniotic fluid. Placenta 2013;34:873-8.
6. Vis JY, Wilms FF, Oudijk MA, Porath MM, Scheepers HC, Bloemenkamp KW, *et al*. Cost-effectiveness of fibronectin testing in a

triage in women with threatened preterm labor: Alleviation of pregnancy outcome by suspending tocolysis in early labor (APOSTEL-I trial). BMC Pregnancy Childbirth 2009;9:38.
7. Honest H, Bachmann LM, Gupta JK, Kleijnen J, Khan KS. Accuracy of cervicovaginal fetal fibronectin test in predicting risk of spontaneous preterm birth: Systematic review. BMJ 2002;325:301.
8. Deshpande S, van Asselt A, Tomini F, Armstrong N, Allen A, Noake C, *et al*. Rapid fetal fibronectin testing to predict preterm birth in women with symptoms of premature labour: A systematic review and cost analysis. Health Technol Assess 2013;17:1-138.
9. Shennan A, Crawshaw S, Briley A, Hawken J, Seed P, Jones G, *et al*. A randomised controlled trial of metronidazole for the prevention of preterm birth in women positive for cervicovaginal fetal fibronectin: The PREMET Study. BJOG 2006;113:65-74.
10. Skoll A, St Louis P, Amiri N, Delisle M, Lalji S: The evaluation of the fetal fibronectin test for prediction of preterm delivery in symptomatic patients. J Obstet Gynaecol Can 2006;28:206-13.
11. Díaz J, Chedraui P, Hidalgo L, Medina M. The clinical utility of fetal fibronectin in the prediction of pre-term birth in a low socio-economic setting hospital in Ecuador. J Matern Fetal Med 2009;22:89-93.
12. Sanchez-Ramos L, Mentel C, Bertholf R, Kaunitz AM, Delke I, Loge C. Human chorionic gonadotropin in cervicovaginal secretions as a predictor of preterm delivery. Int J Gynaecol Obstet 2003;83:151-7.
13. Gurbuz A, Karateke A, Ozturkmen M. and Kabaca C. Human chorionic gonadotropin assay in cervical secretions for accurate diagnosis of preterm labor. Int J Gynaecol Obstet 2004;85:132-8.
14. Guvenal T, Kantas E, Erselcan T, Culhaoglu Y, Cetin A. Beta-human chorionic gonadotropin and prolactin assays in cervicovaginal secretions as a predictor of preterm delivery. Int J Gynaecol Obstet 2001;75:229-34.
15. Schmitz T, Maillard F, Bessard-Bacquaert S, Kayem G, Fulla Y, Cabrol D, *et al*. Selective use of fetal fibronectin detection after cervical length measurement to predict spontaneous preterm delivery in women with preterm labor. Am J Obstet Gynecol 2006;194:138-43.
16. Bernstein P, Stern R, Lin N, Furgiuele J, Karmen A, Comerford-Freda M, *et al*. β-Human chorionic gonadotropin in cervicovaginal secretions as a predictor of preterm delivery. Am J Obstet Gynecol 1998;179:870-3.
17. Chan R. Biochemical markers of spontaneous preterm birth in asymptomatic women. Biomed Res Int 2014;2014:164081.
18. Garshasbi A, Ghazanfari T, Faghih Zadeh S. Beta□human chorionic gonadotropin in cervicovaginal secretions and preterm delivery. Int J Gynaecol Obstet 2004;86:358-64.
19. Adhikari K, Bagga R, Suri V, Arora S, Masih S. Cervicovaginal HCG and cervical length for prediction of preterm delivery in asymptomatic women at high risk for preterm delivery. Arch Gynecol Obstet 2009;280:565-72.
20. Ibrahim MI, Harb HM, Ellaithy MI, Awad EM. Diagnostic validity of cervicovaginal human chorionic gonadotrophin at 26–36 weeks of gestation as a biochemical predictor of preterm birth. J Obstet Gynaecol Res 2013;39:1121-8.
21. Goldenberg RL, Iams JD, Mercer BM, Meis PJ, Moawad A, Das A, *et al*. The Preterm Prediction Study: toward a multiple-marker test for spontaneous preterm birth. Am J Obstet Gynecol 2001;185:643-51.
22. Leitich H, Kaider A. Fetalfibronectin – How useful is it in the prediction of preterm birth? BJOG 2003;110:66-70.
23. Abbott D, Hezelgrave N, Seed P, Norman J, David A, Bennett P, *et al*. Quantitative fetal fibronectin to predict preterm birth in asymptomatic women at high risk. Obstet Gynecol 2015;125:1168-76.
24. Roman AS, Koklanaris N, Paidas MJ, Mulholland J, Levitz M, Rebarber A. "Blind" vaginal fetalfibronectin as a predictor of spontaneous preterm delivery. Obstet Gynecol 2005;105:285-9.