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Role of Uterocervical Angle, Cervical Length and Cervicovaginal Fetal Fibronectin (FFN) for Prediction of Labor Onset in Women Who Present with Preterm Labor

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Abstract

Introduction: PTB, which is delivery before 37 weeks of gestation, is a major public health concern that causes infant death and morbidity in those who survive. The clinical concern is determining true preterm labor which requires hospitalization, specialized unit care, tocolytics, and corticosteroids to mature the baby's lungs.

Aim of the study: To anticipate the initiation of parturition in females experiencing preterm labor (PTL), cervical evaluation techniques such as measuring cervical length (CL) and uterocervical angle (UCA) may be utilized, as well as cervical fetal fibronectin (FFN) as a marker for premature labor (PTL).

Subjects and Methods: A prospective cohort study was carried out on 90 symptomatic women at high risk of preterm labor (PTL) attending the Gynecology and Obstetrics department at Fayoum University Hospital. FFN in cervicovaginal fluid was assessed by the ELISA technique, and uterocervical angle and cervical length were measured by transvaginal ultrasound. Maternal history and pregnancy data were recorded. Delivery data were subsequently collected.

Results: In the current study, we included 90 women with symptoms of sPTB, with an average age of 21.79 ±3.3 years old, an average BMI of 24.6 ±5.8 kg/m2, and an average GA of 32.83 ±2.3 weeks. There were 12 women in our cohort who reported previous preterm labor. CL and FFN showed better sensitivity and specificity as compared to UCA. Logistic regression analysis demonstrated that the sPTB in the current cohort was only dependent on cervical length and quantitative FFN at the time of presentation.

Conclusions: The combination of FFN, CL, and UCA could improve PTB prediction accuracy, especially with the focus on the CL and FFN levels, which could help clinicians identify women at risk of delivery before 34 weeks or 37 weeks.

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1. Introduction

Preterm birth (PTB), defined as birth before 37 weeks of gestation, is a severe public health problem that results in infant mortality and morbidity in those who survive [1]. The clinical challenge is identifying whether the baby is indeed preterm, requiring hospitalization, specialist unit care, tocolytics, and corticosteroids to mature the infant's lungs. False premature labor can be costly and dangerous if not carefully controlled [2]. PTB predictive tests are necessary due to the detrimental consequences they can have on a person's life, money, and health. These tests are critical for identifying women more prone to give birth prematurely and reassuring those who are not.

This opens the door for high-risk asymptomatic women to receive cervical cerclage or progesterone, or symptomatic women to receive tocolysis, antenatal corticosteroids, in-utero transfer to tertiary centers, and magnesium sulphate for neuroprotection, among other immediate treatments [3].

There are several tests that predict preterm birth, however, the findings differ. One test may not work for everyone. For suspected preterm labor, predicting birth within seven days can aid with adequate treatment [3]. Biochemical markers such as fetal fibronectin (FFN), phosphorylated insulin-like growth factor-binding protein (phIGFBP-1), human chorionic gonadotropin (hCG), and placental alpha microglobulin-1 (PAMG-1) have been proposed as an alternative or supplement to transvaginal ultrasound (TVU) in predicting preterm birth (PTB) in women experiencing PTL.

FFN, an extracellular matrix glycoprotein, is found in cervicovaginal fluid before 18 weeks of pregnancy, and its presence in the late second and early third trimesters indicates choriodecidual surface disintegration and an increased risk of spontaneous preterm delivery [4].

Preterm birth has serious consequences for people's lives, economy, and health. Predictive diagnostics for preterm birth are essential. In prenatal care, digital vaginal examination (VE) has limited sensitivity and predictive value and does not reduce the risk of premature delivery. Better identification of patients at risk for PTB is required to lower the frequency of PTB. In the current study, cervicovaginal FFN and cervical assessment (cervicovaginal length (CL) and utero-cervical angle (UCA)) were utilized to predict the commencement of labor in women with PTL.

2. Subjects and methods

2.1.Subjects

The research looked at women who experienced painful contractions and cervical abnormalities and were at high risk of premature labor. They were examined at the Fayoum University Hospital. Based on past research, the sample size was predicted to be 90 participants, with a 20% dropout rate during follow-up.

Inclusion criteria

Women with singleton pregnancies who present with indications of PTL between 28- and 36-weeks' gestation who to participate in the study after completing an informed permission.

Exclusion criteria.

Cervical cerclage, massive vaginal bleeding, recent tocolysis or cervical manipulation, premature rupture of membranes, uterine myoma, comorbidities such as preeclampsia, diabetes mellitus, hyperthyroidism, or asthma, and any factors that may interfere with fibronectin analysis were all exclusion criteria.

To avoid false-positive findings, women were urged to avoid sexual intercourse, douching, and medicine insertion in the vagina before the test.

2.2.Study design

History in detail

Collect baseline demographic information, including maternal age, parity, gestational age at presentation and delivery, and a complete pregnancy history (including preterm birth and any pertinent problems).

Cervicovaginal FFN detection

prior to pelvic exam or transvaginal ultrasound. Assay the FFN level in cervicovaginal swab specimens using a human ELISA kit produced by Sun Red China (Catalogue Number: MBS905636) with high sensitivity and great specificity for FFN detection.

CL and UCA measurements

Transvaginal ultrasound (TVS) tests should be performed on all pregnant women utilizing a high-frequency endovaginally probe. Obtain a sagittal image of the cervix and use the single-line or two-line approach to estimate cervical length. Trace the lines connecting the cervical canal and the cervical outer borders to calculate UCA.

2.3.Statistical Procedures

IBM SPSS version 21 was used to gather, review, code, and analyze data. When the distribution was parametric, qualitative data were provided as numbers and percentages, while quantitative data were presented as mean, standard deviations, and ranges. To compare two groups with qualitative data, the chi-square test and/or Fisher exact test were employed, whereas an independent sample t-test was used for two independent groups with quantitative data and a parametric distribution. For two independent groups with quantitative data and a non-parametric distribution, the Mann-Whitney U test was utilized. Pearson's correlation analysis was used to assess the linear relationship between the time interval to delivery and other factors, and correlation graphs were only created for significant correlations. The UCA, CL, and FFN indicators were evaluated as predictors of sPTB using receiver operating characteristic (ROC) curve analysis. To determine if the UCA, CL, and FFN were independently linked with sPTB and to account for relevant confounders, a multivariate logistic regression model was used. The confidence interval was set at 95%, and a p-value less than 0.05 was considered significant.

3. Results

In the current study we included 90 women with symptoms of sPTB, with an average age of (21.79 ±3.3) years old, an average BMI of (24.6 ±5.8) kg/ m^2 and an average GA of (32.83 ±2.3) weeks. There were 12 women in our cohort reported previous preterm labor. CL and FFN showed better sensitivity and specificity as compared to UCA. Logistic regression analysis demonstrated that the sPTB in the current cohort was only dependent on the cervical length and quantitative FFN at the time of presentation, more results are shown in Tables 1-6.

Table 1: Clinical and demographic characters of the studied women (N= 90).

Variables	Range (Mean ±SD)
Age (years)	18 – 33 (21.79 ±3.3)
BMI (kg/ m^2)	22.3 – 30.4 (24.6 ±5.8)
GA (weeks)	28 – 36 (32.83 ±2.3)
Time interval (days)	0 – 28 (8.85 ±6.1)
History of previous PTB N (%)	12 (13.3%)

Table 2: Distribution of the studied women.

Distribution Criteria		**Frequency**
outcome of pregnancy	Preterm <34 weeks	43 (47.8%)
	Preterm <37 weeks	42 (46.7%)
	Term	5 (5.6%)
	Total	90 (100%)
The time interval between presentation and delivery	**Group I:** Delivery within 2 days	28 (31.1%)
	Group II: Delivery within one week	21 (23.3%)
	Group III: Delivery after > one week	41 (45.6%)
	Total	90 (100%)

Table 3: Comparison of cervical length between studied women.

Variables	***Group I*** **N= 28**	***Group II*** **N= 21**	***Group III*** **N= 41**	***P-values***		
				P1	***P2***	***P3***
CL (mm)	23 – 31 (25.29 ±1.93)	25 – 34 (28.76 ±2.37)	25.8 – 37.7 (34.70 ±3.06)	<0.001*	<0.001*	<0.001*
UCA (degree)	90 – 125 (111.32 ±9.21)	98 – 125 (110.29 ±8.07)	93 – 122 (102.10 ±7.36)	0.66	<0.001*	<0.001*
fFN (ng/mL)	7 – 122 (61.85 ±35.32)	5 – 70 (13.52 ±13.63)	0 – 20 (7.90 ±4.17)	<0.001*	<0.001*	0.32

p-value ≤0.05 is considered statistically significant by one-way ANOVA analysis followed by LSD post-hoc pairwise analysis. P1: GI vs. GII; P2: GI vs. GIII; P3: GII vs. G III: <0.001

Table 4: Correlation between GA and the study variables (N= 90).

Variables	*r*	*P-value*	Description of relation
CL (mm)	0.801	<0.001*	Strong direct
UCA (degree)	-0.418	<0.001*	Medium reverse
fFN (ng/mL)	-0.617	<0.001*	Medium reverse

r: Pearson Correlation Coefficient.

Table 5: Results of ROC curve analysis of the study variables for prediction of spontaneous pre-term birth at <34 weeks and <37 weeks among symptomatic women.

Variables		95% CI of AUC	Cut-off	P-value	Sensitivity	Specificity
CL	**<34 Weeks**	0.917-0.995	≤20 (mm)	<0.001*	95.2%	82.1%
	<37 Weeks	0.911-0.996	≤30 (mm)	<0.001*	90.2%	87.8%
UCA	**<34 Weeks**	0.594-0.823	107 (degree)	0.002*	71.4%	69.4%
	<37 Weeks	0.69-0.886	108 (degree)	<0.001*	61.2%	82.9%
fFN	**<34 Weeks**	0.846-0.999	≥30.5 (ng/mL)	<0.001*	98.3%	88.7%
	<37 Weeks	0.748-0.9144	≥10.5 (ng/mL)	<0.001*	77.6%	90.2%

AUC: Area under the curve, **CI:** Asymptotic 95% Confidence Interval of AUC.

Table 6: Logistic Regression to predict preterm delivery.

Variables		95% C.I. for OR		OR	P-value
<34 Weeks	**Maternal Age**	0.260	1.285	0.578	0.179
	GA at presentation	0.792	12.614	3.161	0.103
	CL	0.135	0.832	0.335	0.018*
	UCA	0.896	1.369	1.108	0.345
	fFB	1.015	1.264	1.133	0.026*
	Previous Preterm	0.050	4805.188	15.462	0.350
	Constant			0.001	0.746
<37 weeks	**Maternal Age**	0.622	1.191	0.861	0.367
	GA at presentation	0.389	1.053	0.640	0.079
	CL	0.420	0.767	0.567	<0.001*
	UCA	0.959	1.189	1.068	0.233
	fFB	1.041	1.673	1.320	0.022*
	Previous Preterm	0.025	547.630	3.722	0.606
	Constant			0.001	0.093

OR: odds ratio, CI: confidence interval

4. Discussion

The study looked at how effectively fFN, CL, UCA, and their combination predicted PTB in women who were experiencing symptoms of premature labour. CL and fFN have higher sensitivity and specificity than UCA. PTB prediction was enhanced before 34 and 37 weeks of gestation by combining all three factors. Using many tests combined may increase the accuracy of PTB prediction in women with preterm labour symptoms. The most relevant ultrasonography indicator for predicting impending delivery in preterm women is cervical length [2]. Many studies have focused on this measure and shown its use in a range of scenarios, including singleton and twin pregnancies, as well as symptomatic and asymptomatic women [9-13]. A cut-off of 15 mm is most commonly used to stratify the continuing treatment of these pregnancies [11, 14]. CL had higher sensitivity and specificity than fFN and UCA in the current study, with a cut-off value of 20 mm for predicting sPTB at 34 weeks and 30 mm for predicting sPTB at 37 weeks.

In keeping with these findings, research on uterocervical angle assessment for predicting PTB in symptomatic women discovered that delivery within two days was exclusively linked with GA and CL at presentation. UCA measurement was unsuccessful in predicting PTB after the beginning of symptoms [15]. Sochacki-Wojcicka et al., 2015 determined an expected sPTB detection rate of 66.7% at 34 weeks with a 10% false-positive rate in case-control studies [16].

Dziadosz *et al.,* 2016, conducted a cohort study and discovered that a UCA cut-off of >105° resulted in an 81% detection rate with a 35% false-positive rate for sPTB at 34 weeks [17]. With a 10% false-positive rate, a model based on maternal features, CL, and UCA could detect sPTB at 34 weeks in 37.6% of cases [16]. Although UCA measurement did not outperform CL and fFN in our sample, we were able to establish that a broader UCA is associated with a greater risk of preterm delivery. In addition, we investigated combination prediction models. While UCA and a history of past sPTB did not predict preterm labour in our prediction model among women with assessed symptomatic preterm birth, a combination of the CL and fFN was the best predictor of sPTB at 34 and 37 weeks.

In contrast to our findings, research on the potential of the uterocervical angle to predict spontaneous preterm delivery before 34 and 37 weeks of gestation discovered that a wider UCA is associated with a greater risk of preterm birth. The UCA and CL were combined in the best model for predicting sPTB at 34 weeks, whereas the UCA, CL, and history of past sPTB were combined in the best model for predicting sPTB at 37 weeks. However, no statistically significant change in AUC was found between the UCA, CL, and combination models [18]. The median UCA in both the preterm and term groups varied among research, as did the recommended cut-offs for distinguishing low-risk from high-risk pregnancies. Differences in maternal features, gestational age at the time of the ultrasound scan, and the fact that each research included a proportion of women whose UCA could not be measured due to a poor cervical image might all explain the variations.

The study's strength is its prospective surveillance of persons with preterm labour symptoms and a high risk of premature birth. Despite the limited sample size, our research group had a similar or greater risk of preterm birth [19, 20]. This finding suggests that women who are predisposed to PTB may benefit from the findings of our study. Finally, this is the first research in Egypt to use fFN, CL, and UCA to determine the preterm birth rate. When compared to other retrospective studies, our study's major drawback is its very small sample size [17]. Furthermore, angles have greater intra- and interobserver variability than distance metrics such as cervical length. Although earlier studies have established that the measurement can be performed with adequate repeatability, we discovered over the course of the study's design that training is required to standardise the measurement. Another issue in the study is the study's apparent absence of female participants with significantly higher fFN levels.

Conclusion

The combination of fFN, CL, and UCA might increase PTB prediction accuracy, particularly with a focus on CL and fFN levels, which could assist doctors in identifying women at risk of delivery before 34 or 37 weeks.

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