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The relationship of preterm birth with fetal fibronectin level in cervicovaginal fluid and cervical lenght in ultrasonography

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Abstract

Objective: In this study, the compatibility between fetal fibronectin determination and the use of cervical length measured by transvaginal ultrasonography of patients who were at risk of preterm birth in the examination performed at 24-34 weeks of gestation, and patients with an increased risk of preterm birth according to the result were defined.

Method: 40 patients who applied to Mustafa Kemal University Training and Research Hospital Gynecology and Obstetrics outpatient clinic between May 2021 and May 2022 were included in the study. Fibronectin results were evaluated using the liquid ELISA method taken from the vaginal secretion by a swap. Cervical lengths were evaluated as 25 mm and below, between 25-30 mm and 30 mm and above in statistical data.

Results: For fFN-positive patients, the preterm delivery rate of patients with a cervical length of 25 mm and less was determined as 100%, while the rate of preterm birth was determined as 77.8% for patients with a cervical length between 25 mm and 30 mm. In addition, the preterm labor rate of fFN-positive patients with a cervical length of 30 mm and above was determined as 78.57%.

Conclusion: All patients with a cervical length of 25 mm or less have a positive fFN test, and a strong correlation can be established between these two values. Accordingly, fFN positivity was found to have a higher sensitivity in determining the probability of preterm delivery compared to the cervical length ratio.

Keywords: Preterm Labor, Fetal Fibronectin, Cervical Length

INTRODUCTION

All the acts of birth which happen before 37. week of pregnancy is called preterm birth and it is one of the most important reasons of neonatal morbidity and mortality. Although the border (line) between preterm birth and abortion differs in many sources, births that occur after the 20th gestational week are called preterm births (1). Recently, the use of many new techniques has come to the fore to determine the risk of preterm labor. Some of these techniques are cervical length measurement with ultrasonography and determination of fetal fibronectin in cervicovaginal secretions (2).

In normal conditions the fetal fibronectin is not found in cervicovaginal fluid of pregnants between 24 and 34 weeks of pregnancy. It exists of high concentration in cervicovaginal fluid before 20. week of pregnancy. The presence of fetal fibronectin in the cervicovaginal fluids of pregnant women at 24 to 34 weeks with intact amniotic membranes has been shown in many studies (3).

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It was shown a relationship between early birth and cervical length in patients with a threat of preterm birth in many studies. In a study in UK, cervical length measurement helped distinguish between true and false labor in pregnant women with intact membranes at risk of preterm birth. In this study, the incidence of preterm birth within seven days was 8% in the entire study population; While it was 0.6% in cases with a cervical length of 25 mm and above, it was found to be 37% in cases with a cervical length less than 25 mm (4).

In our study, it was aimed to evaluate the compatibility between fetal fibronectin determination and the use of cervical length measured with the help of transvaginal ultrasonography in pregnant women with preterm birth risk, and to evaluate the increased risk of preterm birth according to the result.

METHOD

This study was performed between the dates of May 2021-May 2022. Ethics committee approval was obtained for the study from the Clinical Research Ethics Committee of Hatay Mustafa Kemal University with the decision number 29/06/2021-106. Informed consent form, which was accepted by the ethics committee, was obtained from the volunteers included in the study at the beginning of the study.

In the study, the criterion sampling size, which is one of the simple random sampling methods, was utilized and the data were obtained from the patients who presented to the outpatient clinic between May 2021 and May 2022. Forty pregnant women who has early birth risk (the existence of contraction 3 or more in 20 minutes, cervical dilatation with less than 3 cm and cervical effacement with a rate of 80%) diagnosed in their 24 – 34. week of pregnancy were included to this study prospectively. The concordance between fetal fibronectin determination in the fluid to be taken from the vaginal secretion with the help of a swab and the use of cervical length measured with the help of transvaginal ultrasonography, and according to the result of this, patients with increased risk of preterm birth were defined. Pregnant women with diabetes and hypertension, pregnant women with diagnosed fetal anomaly, pregnant women with a history of preterm birth ,pregnant women with mullerian anomaly, pregnant women younger than 18 years old, patients who had undergone cervical excisional procedure and cervical conization were excluded in the study. The study included patients who presented to the outpatient clinic and had a pregnancy defined preterm birth.

Demographic features of all cases were recorded after taken identities and addresses. In order to determine the preterm birth risk, the patients were prepared in the lithotomy position, a sterile speculum examination was performed without the use of any chemicals before the digital examination, and a sterile swab from the posterior vaginal fornix was used for fetal fibronectin test. For the purpose of ensuring standardization, all measurements were done by the same physician. Sampling was done for genital secretion smear and culture. The existence of fetal fibronectin in vaginal secretions was evaluated with ELISA method.

Postpartum required information was recorded and available data were entered into IBM SPSS Statistics 28.0.1.0 software. Frequency, percentage, mean, standard deviation, median, minimum and maximum values were used in descriptive statistics. In the analysis of the data, mean/standard deviation evaluation was made and Mean±SD tests were used. Sensitivity, specificity, negative and positive predictive value of the results of the data used were calculated. P values <0.05 were considered significant. fFN positivity or negativity and cervical length 25 mm and below, between 25-30 mm and above 30 mm; The relationship in terms of demographic characteristics, clinical features and newborn characteristics was examined.

RESULTS

Age, body mass index (BMI, kg/m2), gravida, parity, number of abortions, previous weeks of preterm birth (PBW), hemoglobin (Hb) levels, fFN positive and negative patients are listed in Table 1 of 40 pregnant patients included in the study. Mean of the patients were evaluated, and the mean was also evaluated according to the cervical lengths.

There were multiple pregnancies in 11 of 40 pregnant who were included to study. When the results are also considered; all 11 pregnants had preterm birth was observed. However, when the fFN test results of these cases were examined, the test results of 8 pregnant women were positive and 3 pregnant women were found to be negative. When the cervical lengths were evaluated, the cervical length of 7 patients with fFN positive was determined as 30 mm and above, while 1 patient was determined as 25-30 mm. The cervical lengths of 3 negative pregnant women differed from each other, and 1 patient was 25-30 mm, while 2 pregnant women were 30 mm and above.

As seen in table 2, when compared the clinical features of patients showed that Bishop score was less in patients with positive test result (For fFN 1.23 ± 0.8 vs 2. 2 ± 1.8; for cervical length bishop score 25 mm and below 0.9 ± 0.05/ for the range of 25- 30 mm 0.9 ± 0.10 ve 30 mm and for above 1.02 ± 0.05). As seen in Table 2, the week of birth (DH) was significantly lower (31.3 ± 2.16 weeks for fFN positive vs 36.8 ± 2.8 weeks for negative); for cervical length 25 mm and less at birth week 33.5 ± 2.7 weeks; 32.5 ± 3.00 weeks for 25 mm-30 mm and 32.4 ± 2.5 weeks for 30 mm and above) cervical lengths were evaluated. The tocolysis time (TS) is shorter in fFN positive patients (7.1 ± 14.3 hours in positive patients, 10.1 ± 9.8 hours in negative patients).

Table 1. Comparison of features before birth in terms of fFN and cervical length

	Mean± SS* fFN			Mean± SS* Cervical Length (mm)			
	+	-	P value	n≤ 25	25< n<30	n ≥ 30	P value
Age (Year)	25.5 ± 4. 5	24.3 ± 3. 3	0.058	34.5 ± 5. 2	29.5 ± 3. 2	32.8 ± 5. 1	0.067
BMI, kg/m2	22.0 ± 5.5	26.7 ± 4. 2	0.063	28.2 ± 4. 5	27.2 ±2. 5	26.9 ± 4. 4	0.068
Gravida (n)	3.2 ± 1. 2	2.2 ± 1. 4	0.053	3.4 ± 1. 1	2.1 ± 1. 1	3.2 ± 1. 6	0.052
Parity (n)	0.59 ± 0. 8	0.89 ± 0. 1	0.06	1.02 ± 0. 9	2.02 ± 0. 7	0.88 ± 1. 3	0.064
Abortus (n)	2.7 ± 0. 5	1.8 ± 0. 7	0.019	1.3 ± 0. 6	0.7 ± 0. 4	0.98 ± 0. 4	0.041
PBW (week)	21.1± 4. 2	32.6 ± 1. 1	0.031	32.6 ± 5. 8	32.6 ± 3. 8	34.5 ± 3.0	0.059
Hb (gr/dl)	13.2 ± 2.1	15.3 ± 1. 0	0.057	13.2 ± 1. 7	11.2 ± 1. 72	12.3 ± 1. 4	0.054

PBW: preterm birth week

Table 2. The relationship of clinical features in terms of fFN and cervical length

	Mean± SS* fFN		Mean± SS* Cervical length (mm)		
	+	-	n≤ 25	25< n <30	n ≥ 30
Bishop	1.23 ± 0.8	2.2 ± 1. 8	0.9 ± 0.05	0.9 ± 0.10	1.02 ± 0.05
Dilatation(cm)	1.8 ± 1. 2	1.4 ± 1. 0	2.1 ± 1. 2	2.0 ± 0.8	1.4 ± 1. 0
Effacement (%)	32.2± 20. 5	29.0 ± 20. 3	37.6 ± 18. 7	28. 6 ± 15. 2	26.6 ±20. 4
Tocolysis Time (hour)	7.1 ± 14. 3	10.1 ± 9. 8	6.9 ± 16. 1	7.2 ± 15,0	7.8 ± 7. 8
Birth Week	31.3 ± 2. 16	35.5 ± 3.7	33.5 ± 2.7	32.5 ± 3.00	32.4 ± 2. 5

The fFN and cervical length ratios were calculated to predict delivery before 7, 14, 21 days and before 34, 37 weeks. While fFN gave better results in terms of specificity, cervical length gave lower results in terms of sensitivity than fFN. The best results were obtained when both results were evaluated together. Details are given in Tables 3 and 4.

Table 3. Predictive value of fFN for birth before 7, 14, 21 days and before 34, 37 weeks

	≤ 7 days	≤ 14 days	≤ 21 days	≤ 34 weeks	≤ 37 weeks
Sensitivity (%)	% 76.08	% 84.2	% 75.01	% 88.3	% 81.7
Specificity (%)	% 90.00	%79.01	% 71.09	%82.8	%78.02

Sensitivity: The ability of the test to identify patients among real patients.
Specificity: The ability of the test to determine the healthy ones among the real healthy ones

Tablo 4. Predictive value of cervical length for birth before 7, 14, 21 days and before 34, 37 weeks

	≤ 7 days	≤ 14 days	≤ 21 days	≤ 34 weeks	≤ 37 weeks
Sensitivity (%)	% 66.05	% 64.03	% 65.01	% 78.8	% 71.7
Specificity (%)	% 70.00	%69.05	% 77.03	%72.3	%68.09

Sensitivity: The ability of the test to identify patients among real patients.
Specificity: The ability of the test to determine the healthy ones among the real healthy ones

The power of predicting age, BMI, multiple pregnancy, preterm birth history, Bishop score, cervical dilatation, deletion, applied tocolysis fFN positivity, and cervical length to deliver within these weeks of deliveries under ≤ 7 days, ≤ 14 days, ≤ 21 days, ≤ 34 weeks, ≤ 37 weeks examined.

In line with these data the pregnancy week of patients go to hospital and birth week were examined. Patients whose cervical lengths were measured according to their complaints were tested for pregnant women who met the fFN test criteria. In line with this test, the diagnosis of preterm birth was made by considering the gestational weeks of the patients on the day of admission to the hospital. According to the test results of 32 patients with fFN positive out of 40 patients included in the study, it was predicted in how many days preterm delivery would occur.

In general, when the findings were evaluated, it was determined while 8 patients to be fFN test negative, 32 patients were fFN test positive. The evaluation of cervical length of fFN positive 32 patients; fFN test positive 3 patients' cervical length were 25 mm and below and in those patients, preterm birth occurred at 34th week of pregnancy. According to our findings patients with 25 mm – 30 mm cervical length were fFN test positive and they all gave birth before 34th week of pregnancy.

It was determined 9 patients with a cervical length 25 mm – 30 mm. Seven of these 9 patients were found to be fFN test

positive. In this group (fFN test positive 7 patients) 3 of them gave preterm birth before 34th week of their pregnancy. Other 4 patients gave birth before 37th week of pregnancy. According to these results patients who have 25 mm – 30 mm cervical length and fFN test positive, gave preterm birth all.

Tablo 5. The relationship of cervical lenght and fetal fibronectin

	Cervix Lenght		
	n≤ 25	25< n <30	n ≥ 30
FFN +	3	7	22
FFN-	0	2	6

Among 28 patients with a cervix length of 30 mm and above, 22 patients with positive fFN test were found. Eleven of these patients had preterm birth before 34th week. The other 5 patients with fFN test positive gave birth before 37th week of pregnancy.

When fFN results were evaluated in line with these data, it was determined that the predictive power of preterm birth was highly effective. Moreover, the specificity of fFN test results were higher than cervical length specificity.

DISCUSSION

In the study, it would be a more meaningful diagnostic method to evaluate fFN positivity/negativity and cervical length status together to diagnose preterm birth in patients.

Iams et al. (5) have examined fFN samples taken from 192 patients with ELISA method in their study. In the process from sample taken till birth was significantly higher in fFN (-) patients when compared with fFN (+) patients. When the results of this study were compared with the literature data in terms of time to birth and weeks of gestation at birth, it was determined that births occurred in a shorter time and earlier weeks. Including the pregnants who have up to 4 cm cervical opening is the reason of this result. Whereas the pregnants who have 2 cm and less cervical opening were included most of the studies. However, in cases with positive fibronectin results, births could be predicted in about 10 days, and patient management was reviewed within this framework.

Chuileannain et al. (6) retrospectively evaluated 70 women with regular uterine contractions, a singleton pregnancy before 34th weeks, and who underwent fFN (qualitative test kit) testing. In this study 20 pregnants were fFN positive and 50 were negative had been found. Ten births (14.3%) occurred before 34th week of pregnancy. It was determined in patients with positive test result tocolytic treatment and usage of corticosteroid was higher when compared with patients with negative test result.

In their study, Chuileannain et al. (6) presented the process from sampling till birth and this time was found to be 29.3 days in women with fFN test positive and 62.5 days in women with fFN test negative. The gestational week of birth was 34.9 weeks in women with fFN (+) and 38.2 weeks in women with fFN (-) were found.

In the study performed by Tekesin et al. (7), the week of gestation at birth and the time to birth were found to be significantly lower in women with positive fFN test.

In the study performed by Chuileannain et al. (6), it was determined that the rate of needing neonatal intensive care unit or receiving special care service was 6 times higher in newborn babies of pregnant women who were positive for fFN test compared to newborns of pregnant women with negative fFN test.

In a multicentered study which performed by Peaceman et al. (8), 725 singleton and 38 multiple pregnancies (totally 763 pregnants) were evaluated. In this study it was determined birth within 7 days, preterm birth, increased risk of neonatal morbidity and mortality.

Sakai et al. (9) have evaluated 185 pregnants with symptom of preterm labor by fFN test and preterm labor index (uterine contractions, bleeding, cervical dilatation). The patients with preterm labor index 4 and more were evaluated as positive, 3 and less were evaluated as negative. Preterm labor index is a simple method which can guess the preterm labor results with preterm birth or not. It improved the results of the combined use of the two tests in terms of predicting birth within a week. As a result, it was commented that, predicting the preterm birth, usage of two determinants instead of one would be increase of right diagnosis.

Rozenberg et al. (10) have evaluated symptomatic 76 pregnants with fFN test and cervical length in their study. Abnormal cervical length was determined as 26 mm. It was determined as preterm birth risk is 5.6% if fFN test (-) with normal cervical length; preterm birth risk is 30% if fFN test (+) with normal cervical length; preterm birth risk is 44% if fFN test (-) with short cervical length; preterm birth risk is 52% if fFN test (+) with short cervical length. With regard of these results of the study the patient is in safe if fFN test (-) with normal cervical length. However preterm birth risk would be increased if one of these parameters is abnormal. Preterm birth risk is maximum if these parameters are both abnormal. As can be seen, combining the two tests provides stronger predictive power than either alone.

In our study 11 multiple pregnancy was observed among total 40 pregnants. It has been observed that the incidence of multiple pregnancy has increased due to assisted reproductive techniques. Preterm birth is observed in 27% of pregnancies with assisted reproductive techniques (11). It was

determined that multiple pregnancies were 8,7% percentages of all preterm births. Thirty-50% of all multiple pregnancies end before 37 weeks (12). This is thought to be due to the stretching of the uterus. The prediction of preterm labor was considered in 11 patients with multiple pregnancies in our study.

In the study, when the clinical findings were compared, it was significantly higher in patients who have Bishop score, fFN test positive in both groups. When cervical dilatation and effacement were evaluated, a significant increase was found in cases with positive fFN test. No significant difference was found in those with fFN-positive tocolysis duration. Within the scope of the study, the relationship between fFN positivity/ negativity and cervical lengths of 40 pregnant women was examined, and fFN tests of pregnant women with a cervical length of 25 mm and below were determined as positive in line with this study, and delivery occurred before the 34th week in pregnant women. As a result of these findings, fFN results of patients with cervical lengths of 25 mm or less are directly proportional, there is a risk of premature birth in pregnant women and pregnant women should be observed in this process. But when the fFN test positivity and negativity were tested, there was no significant relationship was observed in pregnants who have 30 mm and above cervical length. It was observed that 78.57% of pregnant women with cervical lengths of 30 mm and above had preterm delivery.

As a result of these findings, when the relationship between fFN and cervical length is examined; For fFN positive patients, the preterm delivery rate of patients with a cervical length of 25 mm and less was determined as 100%, while the rate of preterm delivery in patients with a cervical length between 25 mm and 30 mm was determined as 77.8%. In addition, the preterm labor rate of fFN-positive patients with a cervical length of 30 mm and above was determined as 78.57%. Considering these results, while the cervical length was found to be significantly higher for fFN positive cases below 25 mm, its power in predicting preterm labor in cases between 25 mm and 30 mm and above 30 mm was found to be close to each other. When fFN results and cervical lengths are taken into account, all patients with a cervical length of 25 mm or less have a positive fFN test, and a strong correlation can be established between these two values. But the rate of patients who have fFN test positivity with normal cervical length was found to be high. In line with this result, it was determined that fFN positivity has a higher sensitivity in determining the probability of preterm birth compared to the cervical length ratio. More than 50% of twin pregnancies give birth at <37 weeks, and although ultrasonographic short cervix and fFN scanning are useful in detecting preterm birth, there is no effective method to predict preterm labor and prevent birth, since the delivery process is multifactorial in multiple pregnancies.

The small number of samples and the inclusion of multiple pregnancies in the study are limitations of the study.

Considering fetal fibronectin results and cervical lengths, all patients with cervical lengths of 25 mm and less were found to have positive fFN test, and a strong correlation was established between these two values. However, the rate of patients who have fFN test positivity with normal cervical length was found to be high. Fetal fibronectin positivity was found to have a higher sensitivity in determining the probability of preterm birth compared to the cervical length ratio.

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Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article.

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Ethical Declaration

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Informed consent was obtained from the participant and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: AA, Design: AA Supervising: AA, Financing and equipment: AA, Data collection and entry: AA,OSK , Analysis and interpretation: AA,OSK Literature search: OSK, Writing: OSK, Critical review: OSK

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