

Cervico-Vaginal Fibronectin in Prediction of Preterm Delivery**Servikovajinal Fibronektinin Preterm Doğum Öngörüsündeki Yeri**¹ Salim SEZER¹ Baki ERDEM² Alpaslan KABAN <https://orcid.org/0000-0003-1287-4306> <https://orcid.org/0000-0003-1287-4306> <https://orcid.org/0000-0002-3623-7240>¹ Kanuni Eğitim Araştırma Hastanesi, İstanbul, Türkiye² İstanbul Eğitim ve Araştırma Hastanesi, İstanbul, Türkiye**ÖZ****Amaç:** Preterm doğumun öngörüsünde vajinal sıvıdaki artmış fibronektin düzeylerinin rolünü değerlendirmek**Gereç ve Yöntemler:** Servikovajinal yıkama sıvısında fibronektin düzeyleri 24-34. haftalar arasında olan 73 ardışık gebede ölçüldü. Fibronektin düzeyinin preterm doğum için prediktif özelliklere sahip olup olmadığı analiz edildi.**Bulgular:** 73 gebe kadından 19'u (% 26) preterm ve 54'ü (% 74) miadında doğum yaptı. Erken doğumu öngörmek için, cut-off değerleri ROC (Receive Operating Characteristic Curve) eğrileri ve karşılık gelen değerler kullanılarak belirlendi. Fibronektin için cut-off değeri 61.5 ng / mL olarak belirlendi ve duyarlılık, özgüllük, pozitif kestirim değeri (PPV) ve negatif kestirim değeri (NPV) sırasıyla % 100, % 92,6, % 82,6 ve % 100 olarak bulundu.**Sonuç:** 24-34. haftalardaki gebe kadınlarda serviko-vajinal sıvıdaki fibronektin, preterm doğumu öngörmeye kullanılabilir.**Anahtar Kelimeler:** Erken doğum, fibronektin, prediksyon**ABSTRACT****Aim:** To evaluate the roles of increased levels of fibronectin in vaginal fluid for prediction of preterm delivery**Material and Methods:** Fibronectin levels of cervicovaginal fluid were measured in 73 consecutive pregnant women aged 24-34 weeks of gestation. It was analyzed whether the level of fibronectin had predictive properties for preterm delivery.**Results:** Of the 73 pregnant women, 19 delivered preterm (26%) and 54 delivered at term (74%). For predicting preterm birth, cut-off values were determined using ROC (Receiver Operating Characteristic Curve) curves and corresponding values. The cut-off value of fibronectin was determined to be 61.5 ng / mL and the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were 100%, 92.6%, 82.6% and 100%, respectively.**Conclusion:** The study supports the fibronectin in the vaginal fluid can be used to predict preterm delivery in pregnant women at 24-34 weeks of gestation.**Keywords:** Preterm delivery, fibronectin, prediction**INTRODUCTION**

Term pregnancy is defined as a delivery from 37 completed weeks to less than 42 completed weeks (259–293 days) of gestation (1). Preterm delivery is the birth that occurred before the completion of the 37th gestational week. The ratio of preterm birth is different in reports, it can be up to 15% (2–4). The incidence of preterm delivery has increased in recent years (5).

One of the main causes of neonatal morbidity and mortality is preterm delivery. The risk of mortality and serious acute morbidities such as respiratory distress syndrome, necrotizing enterocolitis and intraventricular hemorrhage are related to preterm birth. According to a report, preterm birth and low birth weight accounted for about 17% of infant deaths. Maternal age of fewer than 17 years or more than 35 years, being underweight, having an overweight pre-pregnancy body mass index and short stature are the some of risk factors for preterm birth according to epidemiologic studies (6,7).

Many biochemical markers are being investigated for predicting premature birth. Alpha-fetoprotein (AFP), creatinine, urea, β -human chorionic gonadotropin, interleukin-6, prolactin, fibronectin and cervical length measurement are some of these. But there was no strong consensus on these markers (8).

In this study, the relationship between fibronectin levels of cervicovaginal fluid and preterm delivery was investigated.

MATERIAL AND METHODS*Patients selection*

This study was carried out at 24-34-week-old pregnant women who applied for routine antenatal follow-up between November 1, 2008 and March 31, 2009. Patients with vaginal bleeding, membranous rupture, pregnancies with > 3 cm of the cervical span, mandatory birth due to fetal or maternal reasons were excluded. The history of pregnancies was taken, the last menstrual period (LMP) was recorded and the week of pregnancy was calculated.

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Gestational weeks of pregnant women who do not know the LMP were calculated according to the first trimester ultrasonographic scan. The first trimester ultrasonographic was used to determine the gestational week if there was a significant difference (more than 7days) between the LMP and the first trimester ultrasonography. The patients did not undergone first trimester ultrasonographic scan and did not know LMP were excluded from the study.

Collection of materials

After the anamnesis was taken, the pregnant women were taken to the gynecological chair. The disposable speculum was used to evaluate the vagina and cervix. A 3 cc irrigation fluid (saline) previously received with a sterile syringe was squeezed to the cervix and vaginal fornix. The irrigation fluid accumulating in the speculum pouch at the posterior of the vagina was removed by aspiration with the syringe and the speculum was removed. The irrigation fluid collected from the posterior fornix was centrifuged for 10 minutes at 2000 rpm in a centrifuge. This fluid was maintained in deep freezing (-40 ° C) for fetal fibronectin level measurement.

A total of 80 pregnant women were enrolled. After the study was completed, the pregnancy outcome of the 5 women were not reached, 2 women were excluded from the study due to centrifugation and breakage of glass during storage. As a result, statistical analysis were obtained from 73 pregnant women.

Those who gave birth at 37 or more gestational weeks were considered term pregnant and those who gave birth before the 37th gestational week were accepted as preterm. Of the 73 pregnant women, 19 delivered preterm and 54 delivered at term. In the study, the results of these two groups were compared.

Cervicovaginal fetal fibronectin was studied in the ELx800 (Bio-Tek Instruments, INC.) ELISA reader using the enzyme-linked immunosorbent assay (ELISA) method using a rabbit polyclonal antibody (Biomedical Technologies Inc. USA).

Statistical analysis

Mann-Whitney U test was used in the comparisons between independent groups. The Chi-Square test was used to compare expected and observed values. Statistics were made with the SPSS program.

The study was planned as a specialization thesis. Institutional ethics committee approval and informed consent form from each patient were received.

RESULTS

There was no significant difference between the two groups in the median values of pregnancy age during the examination ($P = 0.477$). The mean birth age was determined as 242 ± 11 days at preterm delivery and 275 ± 7 days at term delivery. Birth weight was measured as 2371 ± 292 at preterm delivery and 3302 ± 430 gr at term delivery and statistically significant ($P < 0.0001$) (Table 1).

Table1. Data of groups preterm and term

| Characteristics | Preterm (N=19) | Term (N=54) | P value |
|--|-------------------|----------------|---------|
| Fibronectin, (ng/mL), median (95%CI) | 85 (70-130) | 20.5 (9.25-37) | < 0.001 |
| Gestational age during examination, median (95%CI) | 32 (30–33) | 32 (28-33) | 0.477 |
| Age of birth, (days) mean±SD | 242 ± 11 | 275 ± 7 | < 0.001 |
| Birth weight, (gr) mean±SD | 2371 ± 292 | 3302 ± 430 | < 0.001 |

The cut-off value of the fibronectin was determined using ROC (Receiver Operating Characteristic Curve) curves and corresponding fibronectin values and the cut-off value was determined to be 61.5 ng / mL. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy rate were 100%, 92.6%, 82.6%, 100% and 94.5%, respectively. The fibronectin values of any pregnant who gave birth as preterm were not observed below the cut-off value, so 100% value of NPV was obtained (table2, figure 1).

Table 2. Predictive values of fibronectin when the cut-off value of fibronectin was 61.5 ng/ml

| Test result | Preterm birth (N=19) | Term birth (N=54) | Total |
|-----------------|-------------------------|----------------------|-------|
| Fibronectin (+) | 82.6% (19) | 17.4% (4) | 23 |
| Fibronectin (-) | 0.0% (0) | 100% (50) | 50 |
| Total | 19 | 54 | 73 |

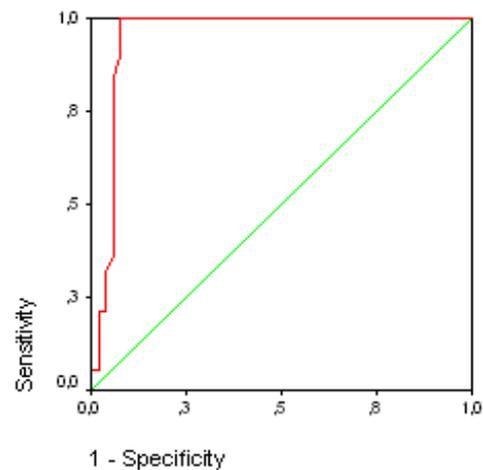


Figure 1. ROC curve of fibronectin (The area under the ROC curve is 0.95)

DISCUSSION

Premature birth is a major cause of morbidity and mortality. Increasing pre-term birth rates in recent years has also increased interest in this topic (9). The markers of preterm labor are still being investigated. In current literature, many parameters such as AFP, creatinine, urea, β -human chorionic gonadotropin, interleukin-6, ferritin, placental alpha microglobulin-1, matrix metalloproteinase-8, Intercellular adhesion molecule-1 (ICAM-1), glucose, prolactin, fibronectin and cervical length measurement have been evaluated (10–21). In this study, we evaluated the importance of fibronectin levels in cervicovaginal lavage to predict preterm delivery.

Fibronectin is a ubiquitous glycoprotein found most abundantly in the extracellular matrix of regenerating, healing and embryonic tissue (22). In a meta-analysis, cervicovaginal fetal fibronectin is an effective short-term marker of preterm delivery, especially in women with symptoms of preterm labor. Because results appear to be heterogeneous in different studies, caution should be taken when they are applied to a specific population (23). In a recent meta-analysis, Lucaroni et al. reported that cervical fibronectin was the biomarker that showed the highest strength of association with the occurrence of preterm birth (24). Alice et al. reported in their study that at 24 to 30 weeks, 50 ng of fetal fibronectin per milliliter, appears to be a reasonable cut-off point for predicting spontaneous preterm birth at <35 weeks' gestation (25). In the present study, when the fibronectin shear value was taken as 61.5 ng / mL,

none of the preterm delivery pregnant had a fibronectin value less than this value, so the NPV value was 100%.

In a systematic review by Deshpande et al., authors found that sensitivity and specificity 69.1 and 84.4 percent, respectively, for positive fibronectin value in delivery <34 weeks of gestation (26).

In another study, positive predictive values of fibronectin thresholds of 10, 50, 200, and 500 ng/mL for preterm birth <34 weeks of gestation were 19, 32, 61, and 75 percent, respectively (27). In the present study, we used the fibronectin test using a 61.5 ng/mL threshold. The positive predictive value of the fibronectin for this value was 82.6%.

In conclusion, this study showed that the increase in fibronectin levels in cervicovaginal fluid correlated with preterm delivery. However, it is necessary to investigate whether the fibronectin test as a routine

screening test in early pregnancy is suitable for cost-effectiveness.

Conflict of interest

There is no conflict of interest.

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