Experimental
&
Clinical Article

Value of Pre-Induction Cervical Fetal Fibronectin (FFN) Assessment as A Predictor of Succesful Vaginal Birth in Nulliparas Undergoing Labor Induction

Hüseyin Mete TANIR, Kamil Turgay ŞENER, Zafer YILDIZ

Eskişehir, Turkey

OBJECTIVE: To determine the value of pre-induction assessment of cervical FFN in the prediction of succesful vaginal birth within 24 hours post-sampling.
STUDY DESIGN: This was a prospective observational trial of nulliparous women undergoing labor induction. Inclusion criterias were: gestational age between 36 to 42 weeks, singleton cephalic presentation of the fetus, intact membrane and Bishop score <6. Pre-induction cervical ripening was performed by using 25 microgr intravaginal misoprostol (PGE1), repeated every four hours, up to a maximum dose of three doses. Induction was subsequently continued by oxytocin and amniotomy. Prior to cervical ripening, FFN samples were collected by using steril speculum and analyzed by standard quantitative immunoassay.
RESULTS: A total number of 43 women met the inclusion criterias, of which 51.1% delivered vaginally within 24 hours of labor induction. There was no statistically significant difference in the rates of vaginal delivery betwen women with positive (84%) and negative (72.0%) FFN results (p=0.54), although more FFN positive cases were vaginally delivered. Sensitivity, specificity, positive and negative predictive values of FFN in predicting successful vaginal birth within 24 hours of labor induction were:0.44,0.67,0.83 and 0.24, respectively. There were no differences in any of the neonatal outcomes between FFN negative and positive groups. Indications of cesarean section did not differ among two groups.
CONCLUSION: In nulliparas undergoing pre-induction cervical ripening, positive FFN test prior to labor induction did not predict successful vaginal birth within 24 hours.

Key Words: Labor induction, Cervical fibronectin, Vaginal delivery, Prediction

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Introduction

Labor induction at term is commonly seen in approximately 20% of all deliveries.[1] In nulliparous women, induction of labor is has been associated with operative deliveries.[2] Hence, pre-induction determination of cervical conditions is crucial to accurately predict the duration and outcome of labor. The traditional method of predicting pre-induction favorability of cervix is Bishop score. However, the assessment is subjective and and result in poor predictive value for the outcome of labor induction. Secondly, studies on the evaluation of cervix by transvaginal ultrasonography, including both the measurement of cervical lenght and morphologic changes in the cervix like funneling have yielded inconclusive results. However, in the last decade, numerous studies have addressed the importance of decidual membrane proteins produced by fetal and decidual tissues.[3,4] FFN is an extracellular matrix protein present in the amniotic fluid and the fetal membranes at the chorio-decidual interface. It is not present in the cervicovaginal fluid from 22-37 weeks. When the labor is imminent, FFN enters into cervical and vaginal secretions. FFN has been proposed as a new tool for cervical asssessment before labor induction.[5,6]

This prospective cohort study was conducted in an aim to determine the role of pre-induction FFN in cervicovaginal secretions to predict the duration and outcome of labor in nulliparous women with unfavorable cervix.

Material and Method

Forty-three consecutive nulliparous women at 37-42 weeks' gestation were included in the current investigation at the Hospital of Eskisehir Osmangazi University, Eskisehir, Turkey. The indications for the induction were were postdate pregnancy (n=7), hypertension (n=10), intrauterine growth restriction (n=4), macrosomia (n=7), postterm pregnancy (n=5) and other medical or fetal problems necessitating delivery (n=10). Exclusion criterias were vaginal bleeding, non-vertex presentation, uterin scar due to previous cesarean section or myomectomy, placenta previa, multiple gestation, allergy or

Department of Obstetrics and Gynecology, Perinatology Unit, Osmangazi University Faculty of Medicine, Eskişehir

Address of Correspondence: H. Mete Tanır
Osmangazi University Faculty of Medicine
Department of Obstetrics and Gynecology
Meşelik, Eskişehir
mtanir@superonline.com

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ashtma inresponse to prostaglandins, abnormal non-stress test before the induction, and premature rupture of membranes. All women were informed about the intent of the current investigation and gave written informed consent. The study was approved by hospitals ethics committee.

On admission to labor ward, before digital examination and labor induction, a speculum examination was performed by co-author of study (ZY). FFN in the cervicovaginal secretion was assessed using qualitative, fast reacting immunoassay test (Adeza Biomedical, Sunnyvale, CA, USA) with a positive cut-off value of 50 ng/ml. A fluid sample was collected from the posterior vaginal fornix by using a sterile Dacron polyester swab. The delivery room staff were blinded to the results of ultrasonographic assessment of cervix.

Pre-induction cervical ripening was performed by using 25 µgr intravaginal misoprostol (PGE1), repeated every four hours, up to a maximum dose of three doses. If the Bishop score was equal or greater than 5, oxytocin was started followed by amniotomy. Oxytocin was started at 2 mU/mn and increased by 2 mU/mn every 30 mn until labor was established. Patients with initial Bishop score equal or greater than 5 were induced by oxytocin followed by amniotomy. Continous electronic fetal heart rate monitoring was used for all cases.

For the purpose of the study, we defined an induction as successful only if vaginal delivery occurred by induction protocols.

Data were entered into the statistical software package programme, SPSS version 13,0 (SPSS Inc., Chicago, IL, USA). Normal data distribution was tested via histogram and Kolmogorov-Smirnov test. Results were presented as the mean±standard deviation. Data with non-parametric distribution was given as median with interquartile range (IQR). Patient demographic characteristics were analyzed by the Student *t* test; χ^2, and the Fisher's exact tests were used, where appropriate. Predictive value of FFN test was analyzed by Cox's model. A Wilcoxon log-rank test was used to compare Kaplan-Meier curves for the duration of whole labor among FFN positive and negative nulliparous women. A two-sided p value less than 0,05 was considered statistically significant.

Results

Table 1 shows the demographic and labor characteristics of nulliparous women with positive (n:25) and negative FFN (n=18) results and their labor outcome. As shown in Table 1, there were no differences in maternal demographic and neonatal characteristics between FFN (+) and (-) groups. Moreover, There was no statistically significant difference in the rates of vaginal delivery between women with positive (84%) and negative (72,0%) FFN results (p=0,54), although more FFN positive cases were vaginally delivered. Within 24 hour of labor induction, 22 (51,1%) and 33 (76,7%) nulliparous women delivered vaginally within 24 hours and 48 hours of labor induction. Sensitivity, specificity, positive and negative predictive values of FFN in predicting successful vaginal birth within 24 hours of labor induction were: 0,44, 0,67, 0,83, and 0,24, respectively. The same figures for prediciton vaginal delivery within 48 hours of induction were 0,69, 0,55, 0,85 and 0,44, respectively. Furthermore, for prediction delivery within 24 hours of induction, negative (LR-) and positive likelihood ratios (LR+) were 0,3 and 1,8 respectively. As shown in Table 1, nulliparous women with positive FFN had shorter duration of oxytocin use (fetal fibronectin-positive 565±123 minutes compared to 667±224 minutes, p<0.01) and lower maximum oxytocin dose (fetal fibronectin-positive 12 mIU/ml compared with fetal fibronectin-negative 28 mIU/ml, P=0,003). However, duration of cervical ripening with misoprostol did not differ significantly between FFN positive (490 ±120 min) and FFN negative (510±110 min) groups (p:0,54). As shown in Figure 1, there was no statistically significant difference in the percentages of FFN positive and negative nulliparous women delivered within 24 hours of admission (Log-rank Mantel Cox, χ^2:0,363, p:0547)

Table 1: Demographic and labor characteristics of nulliparous women with positive (n:25) and negative FFN (n=18) results and their labor outcome.

Parameters	FFN positive (n=25)	FFN negative (n=18)	p value
Maternal age (years)	26,6±1,1*	27,5±1,9	0,78
Gestational age (weeks)	39,1±2,3	39,5±1,8	0,62
Number of abortions n(%)	3 (12)	2(11,1)	0,84
Body mass index (kg/m^2)	28,8±2,1	27,4±3,2	0,31
Bishop score on admission	2,3±1,3	3,1±1,4	0,53
Vaginal delivery (%) within 24 h of induction	84	72	0,54
Indication for cesarean delivery			0,42
Arrest of dilatation (n)	1	2	
Arrest of descent (n)	1	-	
Nonreassuring fetal tracing (n)	1	1	
Failed induction (n)	1	2	
Duration of oxytocin use (min)	565±123	667±224	0,03
Maximum oxytocin dose (mIU/ml)**	12 (9-13)	28 (22-30)	0,003
Duration of induction until Bishop score > 6 (min)	490±120	510±110 min	0,54
Birthweight (gram)	3272±213	3345±196	0,57
1 min Apgar score <7 1 min (n)	2	1	0,86
5 min Apgar score <7 (n)	0	0	-
Meconium passage (n)	1	1	0,23
Cord pH <7	0	0	

**mean±standard deviation, **median (interquartile range, IQR)*

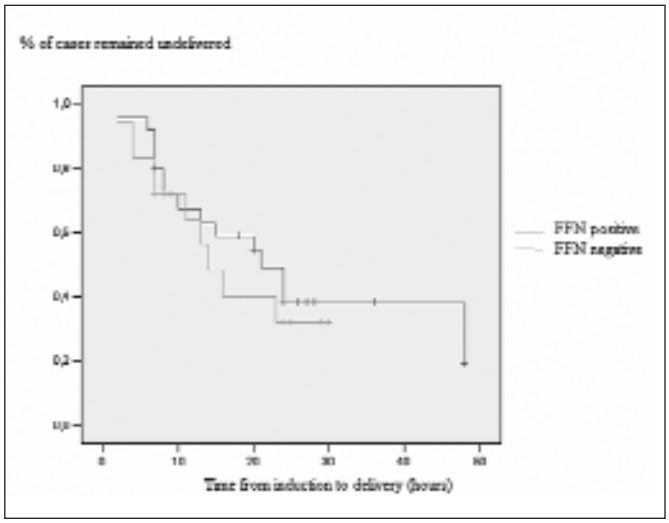

Figure 1: Percentages of FFN positive and negative nulliparous women remained undelivered (y -axis) within 24 hour of labor induction (x-axis). (log-rank, p:0,547)

Discussion

The present study demonstrated that the presence of FFN in cervicovaginal secretions prior to induction did not predict the outcome of labor of nulliparous women, although more cases with positive FFN required lower total oxytocin dose and duration.

Elective induction of labor at term in nulliparous women has been associated with increased cesarean delivery. An accurate identification of nulliparous women prone to deliver vaginally is especially important as to reduce the unscheduled cesarean deliveries caused due to failed induction. Parity, high Bishop score, shorter sonographic cervical lenght, low body mass index have been proposed as an indicator of vaginal delivery in women undergoing labor induction.[7-9] In the current study, none of them, except body mass index, were studied. However, conflicting results are frequently observed and those above-mentioned methods have not been found regarded as independent predictors of successful labor induction.[4,10] Garite et al.[11] proposed that presence of FFN in cervicovaginal secretions independently predicts which cases would have a shorter labor induction and lower cesarean delivery, even in nulliparous women with low cervical inducibility.

In a prospective, blinded recent study of Sciscione et al.[10] including 241 nulliparous women requiring labor induction, women with positive FFN had a shorter duration of cervical ripening, duration of oxytocin dose and lower maximal dose of oxytocin, similar to the results of our study. These authors used transcervical Foley catheter as pre-induction cervical ripening in cases with unfavorable cervix. However, the current study did not show any significant difference in the time interval from induction to cervical ripening, shown in Table 1, In contrast, Tam et al.[12] stated that cervicovaginal FFN had better cervical response to prostaglandins, and shorter time interval from induction to delivery induction.

Reis et al.[13] stated that higher parity, Bishop score and previous vaginal delivery have been associated with succesful labor induction. In the same study, the presence of cervicovaginal FFN failed to predict the outcome of induced labor. Similar to the results of the current investigation, Mouw et al.[14] examined the predictive value of cervicovaginal FFN for spontaneous onset of labor in pregancies of 41 weeks gestation or more, and concluded that FFN did not predict accurately enough whether or nor the birth will take place within 3 days of sampling. In the present study, there was no difference in the rates of cesarean section within 24 hours of labor induction between FFN positive and negative groups. However, a review of the literature by Kiss et al.[15] revealed that pregnant women with negative pre-induction FFN were more likely to have higher cesarean delivery. Roman et al.[16] found that cervical FFN assment was significantly correlated with only the latent phase of labor and failed to be and independent predictive factor for successful labor induction in a prospectively followed 90 pregnant women with Bishop score <5. The same authors also concluded that FFN test was expensive and yielded a a lower predictive value than did Bishop score or ultrasound determination of cervical lenght. The present study did only evaluate the predictive value of cervicovaginal FFN. Hence, with regard to other prognosticators for labor induction, data were lacking. Secondly, we studies a small number of cases that may lead to type II error in statistical comparisons. Moreover, it would have been better to correlate all these factors with succesful labor induction as to examine the predictive values of each prognostic factor for the outcome of labor.

To conclude, given the results of the current investigation, the presence of FFN from cervicovaginal secretions in nulliparous women requiring labor induction was not predictive of a favorable response within 24 hours of labor induction.

Doğum İndüksiyonu Uygulanan Nulliparlarda Başarılı Vajinal Doğum Öngörü Testi Olarak İndüksiyon Öncesi Servikal Fetal Fibronektin (FFN) Değerlendirmesinin Yeri

Yapılan bu gözlemsel, prospektif çalışmada nullipar olgularda indüksiyon öncesi servikal sıvıda fetal FFN'nin örnekleme sonrası ilk 24 saat içinde başarılı vajinal doğumu öngörmedeki yeri araştırılmıştır.

36-42 hafta arası, Bishop skoru 6'nın altında ve membranları sağlam olan olan 43 olgu çalışmaya dahil edilmiştir. İndüksiyon: 25 mikrogram intravajinal misoprostol (PGE1), 4 saatte bir, toplam 3 doz şeklinde uygulanmıştır. Bishop skoru uygun

hal gelen olgularda oksitosin ve amniyotomi başlanmıştır. Servikal olgunlaşma öncesi, FFN örnekleri steril spekulum muayenesi sırasında Dakron swab ile toplanmış ve standard semikantitatif immunoassay yöntemi ile sonuçlar yorumlanmıştır.

Çalışmada, %51,1 olgu indüksiyon başlangıcından sonraki ilk 24 saat içinde vajinal yolla doğurtulmuştur. Pozitif (%84) ve negatif FFN (%72) sonuçları olan olgular arasında istatiksel önemde bir farka rastlanmamıştır. Testin ilk 24 saat içindeki vajinal doğumu öngörmedeki sensitivite, spesifisite, pozitif ve negatif öngörü değerleri sırasıyla, 0,44, 0,67, 0,83 ve 0,24'tür. FFN negatif ve pozitif olgular arasında yenidoğan sonuçları açısından bir farka rastlanmadı. Aynı zamanda sezaryen endikasyonları her iki grupta farklı bulunmadı.

Sonuçta, indüksiyon öncesi servikal olgunlaştırıcı ilaç kullanılan nullipar olgularda, indüksiyon öncesi servikal FFN değerlendirmesi ilk 24 saat içindeki başarılı vajinal doğumu öngörmemektedir.

Anahtar Kelimeler: Doğum indüksiyonu, Servikal fibronektin, Vajinal doğum, Öngörü

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