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Cervical phosphorylated insulin-like growth factor binding protein-1 for the prediction of preterm delivery in symptomatic cases with intact membranes

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Abstract

Aim: This prospective, observational study was an attempt to evaluate whether a positive cervical phosphorylated insulin-like growth factor binding protein-1 admission test in women with signs and symptoms of preterm labor (PTL) may be useful in the prediction of women who will deliver prematurely.

Methods: Pregnant women with confirmed gestational age between 24 and 37 weeks' gestation with <3 cm cervical dilatation and intact membranes were included in the study. Prior to digital examination, a sterile speculum examination was performed using a dacron swab rotated in the external cervical os for 15 s. The test was based on immunochromatographic qualitative analysis of cervical phosphorylated insulin-like growth factor binding protein-1. Test (+) and (–) cases were evaluated in terms of maternal demographic characteristics and neonatal outcomes.

Results: A total of 68 cases were enrolled in the study. There were no statistically significant differences between test (+) and (–) groups, in terms of maternal characteristics or adverse neonatal outcomes. However, cases with + test had high Bishop scores on admission ($P = 0.01$) and gestational age at delivery ($P = 0.003$). For deliveries within 7 days of admission, the strongest predictors were test positivity (RR:24,%95CI:2.8–204, $P < 0.0001$) and Bishop score (RR:1.3, %95CI: 1.0–1.6, $P = 0.03$). For deliveries <34 weeks' gestation, the test had a sensitivity, specificity, positive predictive values, negative predictive values, +likelihood ratios and –likelihood ratios of 70%, 74%, 48%, 88, 2.8 and 0.39, respectively.

Conclusion: Among women with signs and symptoms of PTL, the high negative predictive value of this test to predict the PTL <34 weeks' gestation as well as within 7 days of delivery may be of value in the reassurance of patients, avoiding unnecessary medical interventions.

Key words: cervicovaginal phIGFBP-1, prediction, preterm delivery, preterm labor.

Introduction

Spontaneous preterm birth continues to be a leading cause of neonatal morbidity and mortality in most parts of the world.[1] There have been many efforts to decrease its incidence, including the identification of maternal factors, tocolytics, bed rest and home uterine activity monitoring. However, all of these efforts are hampered by the absence of a reliable screening method as to identify the women at risk of preterm delivery.[2] At present, there is no standard clinical management in this population. A correct diagnosis is crucial because early detection may confer a prompt referral of pregnant women with signs and symptoms of early preterm labor to a tertiary perinatal center for corticosteroid treatment.[3,4] Several biochemical or biophysical

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tests have been implemented to predict the time of delivery in an accurate way.[5–8] Recent studies have focused on cervicovaginal phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1).[9–13]

IGFBP-1 is one of the major proteins of the decidualized endometrium. Its concentration in the amniotic fluid is 100 to 1000 times higher than that in the serum.[14] Amniotic fluid contains the nonphosphorylated form and the lesser phosphorylated form whereas decidua is abundant in phIGFBP-1.[15] The highly phosphorylated isoform of IGFBP-1 can be detected in cervicovaginal secretions before the onset of labor due to the detachment of fetal membranes from the decidua. Cervicovaginal detection of phIGFBP-1 has been proposed as a reliable predictor of impending preterm delivery in women with signs and symptoms suggestive of preterm labor.[16,17]

The aim of this prospective cohort study was to assess the efficacy of phIGFBP-1 at first admission of symptomatic women with intact membranes for the prediction of impending preterm delivery.

Materials and Methods

Approval for this study was obtained from the Institutional Ethical Board and all of the authors conformed to the Declaration of Helsinki during the study period. Originally, the study subjects were part of a fibronectin study for preterm labor assessment that included a total of 121 pregnant women. From this cohort, 68 symptomatic pregnant women, with a gestational age of 24–37 weeks calculated from the first day of the last menstrual period and confirmed by ultrasonography, with <3 cm cervical dilatation and intact membranes provided informed consent for enrollment in this study. The study was carried out at the Perinatology Unit at Eskisehir Osmangazi University School of Medicine, between January 2004 and June 2006. The diagnosis of preterm labor on clinical grounds included the following: (i) contractions that are painful, palpable, last longer than 30 s and occur at least four times per 20 min; (ii) evidence of a change in the position, consistency, length and/or dilatation of the cervix.[18] Symptoms suggestive of preterm labor included regular uterine contractions (>10/h), low back pain, minimal vaginal bleeding and increased vaginal discharge. Cases were excluded if they had cervical cerclage, massive vaginal bleeding, had been on tocolysis at admission, or had had cervical manipulation such as vaginal douche, intercourse or digital examination within the previous 24 h, had pre-eclampsia, multiple pregnancy, diabetes mellitus, hyperthyroidism or asthma. Levels of cervicovaginal IGFBP-1 are not affected by recent intercourse, vaginal infections or bleedings but the pregnant women were also from the fibronectin study cohort and we had to limit the sample size of the IGFBP-1 assessment so we conformed all of the above-mentioned requirements for fibronectin sampling. (The data from the fibronectic study is currently being prepared for publication.)

Symptomatic treatment included i.v. ritodrine hydrochloride or magnesium sulphate. Ritodrine hydrochloride was given as an i.v. infusion of 50–100 μg/min in 5% dextrose solution in water and was increased by 50 μg/min every 20 min until adequate tocolysis was achieved or up to a maximum dose of 350 μg/min. Magnesium sulfate was given as a bolus dose of 4 g in 100 mL saline solution, followed by a maintenance dose of 2 g/h as an intravenous infusion. A total i.m. dose of 24 mg betamethasone was given 12 mg twice daily to enhance fetal lung maturation. Mode of delivery was dependent on obstetric indications.

Sterile speculum examination was performed to check for signs of infection and to take cervical Dacron swab samples for an immunochromatographic quantitative assay of phIGFBP-1 (Actim Partus Test, Medix Biochemica, Kauniainen, Finland). Cervical secretions were collected using two sterile Dacron swabs, one for the detection of phIGFBP-1 and one to exclude rupture of membrane (actim PROM Test, Medix Biomedica, Kauniainen, Finland). They were then kept in the cervix for 15 s. Each swab was placed in a separate tube containing 0.5 mL of extraction buffer containing sodium phosphate, sodium chloride, EDTA, Tween-20. The swab was mixed in the tube for 20 s. The swabs were then withdrawn, and the lower end of the dipstick of each rapid bedside test was inserted into buffer for 20 to 40 s. Thereafter, the dipsticks were removed and placed on a surface in a horizontal position. A positive result was indicated by the presence of two lines, whereas a negative result was indicated by the presence of a single control line. When there were no visible lines, which was observed in two cases, a new sample was not taken. These patients were assigned as test positive. Test (+) and (–) cases were evaluated in terms of maternal demographic characteristics and neonatal outcomes.

Results were blinded to managing obstetricians during the study. Decision on tocolytic and steroid use after specimen collection were made by managing physicians. Test (+) and (–) cases were evaluated in terms of maternal demographic characteristics such as

age, body mass index (BMI), number of parity, previous history of preterm delivery (PTD), smoking habits, number of pregnancies from assisted reproductive techniques (ART), Bishop scores at admission, gestational age at delivery, mode of delivery, use of tocolytics, steroids, presence of histological chorioamnionitis, neonatal outcomes such as birthweight, Apgar scores, days at neonatal intensive care unit (NICU), newborn sepsis, neonatal death, and delivery before 34 weeks' gestation as well as within 7 and 14 days of admission. History of previous PTD was defined as patients that had had at least one prior delivery before 37 weeks' gestation. Cases with gestational age between 34 to 37 weeks gestation were not included in the calculation of preterm delivery <34 weeks' gestation. The histological chorioamnionitis was defined by the criteria of Salafia *et al.*[19]

Primary outcomes of the present study were the deliveries less than 34 weeks of gestation and deliveries within 7 days of admission. Assuming the preterm birth rate of 7% in the low risk group (negative test) and 30% in the high-risk group (positive test) we calculated that 66 cases would be necessary to yield a significant association between phIGFBP-1 and primary outcomes with the power set at 80% and α value of 0.05. Statistical analysis was performed using SPSS 10.0 (SPSS 10.0 Inc, Chicago, IL, USA) statistical package program. Results are presented as the mean ± standard deviation. Patient demographic characteristics were analyzed using the Student's *t*-test, the χ^2 or Fisher's exact test, where appropriate. A univariate analysis was performed using a logistic regression model to evaluate the association of various confounding variables and cervicovaginal phIGFBP-1 with the outcome of pregnancy. Kaplan-Meier curves were compared with the Wilcoxon log-rank test. In order to deal with the uncertainty in estimation, we generated 95% confidence intervals (CI) for post-test probabilities around the point estimate.

Results

As shown in Table 1, there were no statistically significant differences between test (+) and (–) groups, in

Table 1 Maternal and neonatal characteristics of cases with cervicovaginal phosphorylated insulin-like growth factor binding protein-1 positive and negative cases

	phosphorylated insulin-like growth factor binding protein-1 test		
	(+) ($n = 25$)	(–) ($n = 43$)	*P* value
Age (years)	28.4 ± 4.6	28.4 ± 5.3	ns
Body mass index (kg/m^2)	25.1 ± 3.5	26.9 ± 4.4	ns
Gravidity (*n*)	2.1 ± 1.3	2.2 ± 1.3	ns
Parity (*n*)	0.7 ± 0.3	0.6 ± 0.4	ns
Abortion (*n*)	1.8 ± 0.8	1.5 ± 0.5	ns
Gestational age on admission (weeks)	30.6 ± 3.5	29.6 ± 2.3	ns
Tocolytic use (*n*)	23	40	ns
Cesarean delivery (*n*)	18	20	ns
Delivery <34 weeks gestation (%)	48	11.6	0.01
Vaginal delivery (*n*)	16	14	ns
Histological chorioamnionitis (*n*)	8	8	ns
Bishop score on admission	3.3 ± 0.3	2.1 ± 0.2	0.01
Cervical dilatation on admission (cm)	2.5 ± 0.2	1.4 ± 0.3	ns
Cervical effacement on admission (%)	37.6 ± 10.1	26.6 ± 11.3	0.02
Duration of tocolysis (days)	6.1 ± 1.4	5.9 ± 2.3	ns
Gestational age at delivery (weeks)	34.3 ± 2.1	36.6 ± 2.4	0.03
Time from admission to delivery (days)	8.4 ± 1.5	20.2 ± 2.1	0.001
Apgar score (1 mn)	6.0 ± 2.2	7.1 ± 1.9	ns
Apgar score (5 mn)	8.1 ± 1.7	8.7 ± 1.4	ns
Birthweight (g)	1972 ± 372	2472 ± 747	0.04
Days at neonatal intensive care unit (days)	5.73 ± 5.8	4.45 ± 6.1	ns
Newborn sepsis (*n*)	2	3	ns
Neonatal death (*n*)	3	1	ns

ns, not significant.

Table 2 Univariate analysis of several confounding factors to determine deliveries <34 weeks' gestation

	PTD <34 weeks' gestation		
	Relative risk	%95 CI	*P* value
Age	0.83	0.81–1.2	0.13
Body mass index	0.81	0.78–1.32	0.43
Multiple pregnancy	1.20	0.68–4.78	0.23
History of PTL	5.11	1.3–19.76	0.03
+ phIGFBP-1 test	4.13	1.65–10.4	0.03
Bishop score	1.26	0.77–1.32	0.34
Cervical dilatation	1.23	0.76–2.55	0.325
Cervical effacement	1.09	0.78–1.23	0.45
Corticosteroid use	1.01	0.8–1.5	0.34
Histological chorioamnionitis	1.25	0.34–5.1	0.655

CI, confidence interval; phIGFBP-1, phosphorylated insulin-like growth factor binding protein-1; PTD, preterm delivery; PTL, preterm labor.

Table 3 Univariate analysis of confounding factors to determine the deliveries within 7 days of admission

	Delivery within 7 days of admission		
	Relative risk	%95 CI	*P*-value
Age	0.92	0.83–1.02	0.115
Body mass index	0.91	0.81–1.03	0.157
Multiple pregnancy	0.60	0.16–2.22	0.444
History of PTL	3.23	0.86–12.09	0.081
phIGFBP-1 (+)	14.6	4.30–49.99	0.001
Bishop score	1.30	1.01–1.66	0.036
Cervical dilatation	1.63	1.03–2.57	0.034
Cervical effacement	1.02	0.99–1.05	0.062
Tocolysis	0.24	0.02–2.44	0.229
Corticosteroid use	0.61	0.20–1.80	0.374
Histological chorioamnionitis	0.82	0.24–2.75	0.753

terms of maternal characteristics, mode of delivery and adverse neonatal outcomes. However, test (+) cases had high Bishop scores on admission (3.4 ± 1.2 vs 2.5 ± 0.3, $P = 0.03$), and a greater gestational age at delivery (33.4 ± 3.1 weeks vs 36.8 ± 2.1 weeks, $P = 0.002$) and a greater neonatal birthweight (1972 ± 372 g vs 2472 ± 772, $P = 0.04$). Of women with positive cervicovaginal phIGFBP-1, 12 cases were delivered before 34 week's gestation, whereas five cases had negative phIGFBP-1 ($P = 0.01$). Rates of preterm birth at 24–28, 28–32 and 32–33 week's gestation were 12.1%, 18.1% and 15.1%, respectively. As shown in Table 2, a univariate analysis showed that the strongest predictors of PTD <34 weeks' gestation was a history of PTL ($P = 0.03$) and the presence of cervicovaginal phIGFBP-1 ($P = 0.03$). However, for predicting deliveries within 7 days of admission, phIGFBP-1 positivity (RR: 24, %95CI: 2.8–204, $P < 0.0001$), Bishop score (RR: 1.3, 95%CI: 1.01–1.66, $P = 0.03$) and cervical dilatation on admission (RR: 1.63, 95%CI: 1.03–2.57, $P = 0.03$) were found to be statistically significant, as shown in Table 3.

As depicted in Table 4, for the prediction of deliveries <34 weeks' gestation, phIGFBP-1 test had a sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV), positive likelihood ratios (LR) and negative LR of 70%, 74%, 48%, 89, 2.8 and 0.3, respectively. For deliveries within 7 days of admission, the corresponding figures were: 93.3%, 79%, 56%, 97%, 4.5 and 0.08 respectively. Moreover, in terms of deliveries within 14 days of admission, the test yielded the corresponding figures: 68%, 80%, 61%, 74%, 2.7 and 0.43, respectively, as shown in Figure 1, Kaplan-Meier survival analysis showed that a higher percentage of women with positive phIGFBP-1 delivered within 14 days of sampling, compared to those with negative phIGFBP-1 (Mantel-Cox, log-rank: 35.4, $P = 0.0001$).

Table 4 Sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios of cervicovaginal phosphorylated insulin-like growth factor binding protein-1 for predicting the deliveries <7 days, <14 days of admission as well as <34 weeks' gestation

	Prediction of deliveries within					
	<7 days	>7 days	<14 days	>14 days	<34 weeks	>34 weeks
+ phIGFBP-1 test (*n*)	14	11	17	11	12	13
− phIGFBP-1 test (*n*)	1	42	8	32	5	38
Sensitivity % (ratio)	93.3 (14/15)		60.7 (17/28)		70.5 (12/17)	
Specificity % (ratio)	792 (42/53)		80 (32/43)		74.5 (38/51)	
PPV % (ratio)	56 (14/25)		68 (17/25)		48 (12/25)	
NPV % (ratio)	97.6 (42/43)		74.4 (32/43)		88.8 (38/43)	
LR + (%95CI)	4.4 (2.1–5.2)		2.8 (1.9–4.3)		2.8 (1.1–3.8)	
LR − (%95CI)	0.8 (0.4–0.9)		0.4 (0.1–0.6)		0.3 (0.1–0.9)	

LR, likelihood ratios; NPV, negative predictive values; PPV, positive predictive values; phIGFBP-1, phosphorylated insulin-like growth factor binding protein-1.

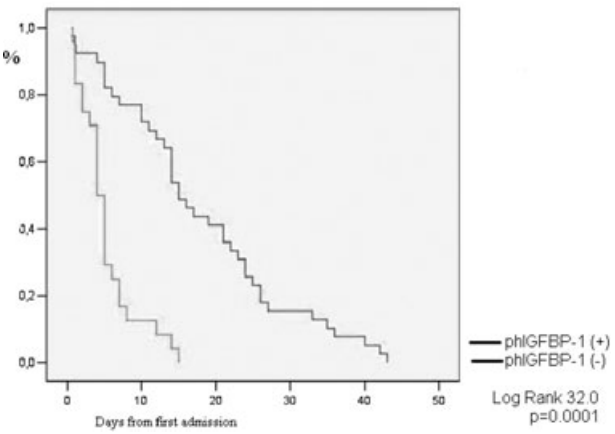

Figure 1 Percentage of cases that remained undelivered (y-axis) since the first day of admission to the clinic (x-axis) in women with positive (green) and negative (blue) cervicovaginal phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1).

Discussion

Based on the results of the present study, the detection of phIGFBP-1 in cervicovaginal secretions of pregnant women with signs and symptoms suggestive of preterm labor may confer a high-risk of preterm delivery. Nearly half of the women with premature contractions enrolled in the present study subsequently delivered before 34 weeks' gestation. This finding is consistent with previous studies showing that a bedside phIGFBP-1 test may be of value in predicting premature delivery in women with premature contractions.[20,21]

The present study showed that phIGFBP-1 had a sensitivity, specificity, PPV, NPV, positive LR and negative LR of 70%, 74%, 48%, 89%, 2.8 and 0.39 respectively for predicting deliveries at less than 34 weeks' gestation. For predicting deliveries within 7 days of admission, the corresponding figures were: 93%, 79%, 56%, 97%, 4.5 and 0.08, respectively. With regard to the prediction of preterm deliveries within 7 days of admission, Lembet *et al.*[20] reported that sensitivity, specificity, positive and negative predictive values of the rapid phIGFBP-1 test for preterm delivery were 93.8%, 85%, 83.3% and 94.1%, respectively. Our figures were quite comparable to the results of the latter study. These figures were quite high, compared to those of the present study. Akercan *et al.*[22] stated that the same above-mentioned figures in the prediction of deliveries before 37 weeks' gestation were 78%, 87%, 73% and 90%, respectively. In a prospective study of 77 pregnant women with gestational ages of 24–36 weeks, the latter study also combined the measurement of transvaginal cervical length.

The authors concluded that there was an association between cervical length and gestational age at delivery in patients with a positive phIGFBP-1 test ($r = 0.55$). As a result, all of these studies including the present study highly confer a high risk of preterm delivery. The high negative predictive value of this test may aid the clinician to avoid unnecessary and potentially hazardous medications.

Given the results of the present study, the sensitivity, specificity, positive and negative predictive values of cervicovaginal phIGFBP-1 for the prediction of deliveries within 14 days of submission were 68%, 80%, 61%, 74%, 2.7 and 0.43, respectively. According to those results, the sensitivity and negative predictive value of the test were better in predicting the deliveries within 7 days of admission, compared to those within 14 days

as shown in Table 4. The value of the tests lies in their negative predictive value, especially for delivery within seven days.

Paternoster *et al.*,[23] through a prospective study including low-risk, symptomatic and asymptomatic pregnant women concluded that the sensitivity, specificity, negative and positive predictive values of this test in the prediction of preterm delivery before 37 weeks' gestation were similar to above-mentioned studies. However, in asymptomatic women, the figures were 22.2%, 91.8%, 11.8%, and 96%, respectively. Based on the result of the latter study with low sensitivity and positive predictive values, there is still room for large studies that include asymptomatic low-risk pregnant women before 37 weeks' gestation. However, for symptomatic cases, the absence of phIGFBP-1 can be a reassuring sign that the likelihood of preterm birth is low. In addition, its presence in cervicovaginal secretions yields a high detection rate of preterm delivery.[9,24]

With regard to the high-risk, asymptomatic group, there is only one study that includes asymptomatic pregnant women with a previous history of at least one preterm birth.[23] The latter study incorporated cervical length measurement in a longitudinal study design and suggested that cervical length assessment at 22–24 weeks together with phIGFBP-1 as a secondary screening test improved the detection of preterm delivery upon either method used alone.

According to the present study, neonatal morbidities like infections did not differ among symptomatic pregnant women with positive and negative phIGFBP-1 tests. In the present study, women with positive phIGFBP-1 were no more likely to have histological evidence of placental inflammation noted at birth than women with negative phIGFBP-1 results. Among symptomatic women, several biomarkers like phIGBFBP-1 confer rapid and reliable information. The value of multi-marker tests, however, especially inflammatory markers and cervical length measurements, need to be assessed through studies of a large data set in both symptomatic and asymptomatic women.[5]

The major limitation of the present study was the sample size. Hence, it is necessary to repeat this study a with large sample size and with different exclusion criteria and weeks of gestation. The cause of preterm labor is multifactorial. Therefore, it is conceivable that, in the future, powerful markers will definitely change the physicians' directions towards evidence-based clinical approaches for high-risk pregnant women so as to provide the best options for screening and therapeutic interventions.

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