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ORIGINAL ARTICLE

Phosphorylated insulin-like growth factor binding protein-1 and cervical measurement in women with threatening preterm birth

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Abstract

Objective. To assess the efficacy of the cervical phosphorylated insulin-like growth factor binding protein-1 (pIGFBP-1) in combination with cervical length measurement for the prediction of preterm delivery. *Design.* Observational prospective study. *Setting.* University Hospital, Spain. *Sample.* A total of 276 women between 24 and 34 weeks gestational age complaining of uterine contractions and intact membranes. *Methods.* Transvaginal scan to assess cervical length and cervical swabs for pIGFBP-1 detection. *Main outcome measures.* Prevalence of preterm delivery within 48 hours and 7 days, delivery at < 32, < 34 weeks, admission-to-delivery interval by cervical length and the presence of pIGFBP-1. *Results.* The prevalence of preterm delivery at < 34 weeks was 14.1% (39/276) and 7.6% (21/276) at < 32 weeks. Cervical pIGFBP-1 was positive in 38.7% (107/276), whereas cervical length < 15 mm was present in 7.2% (20/276) and was > 30 mm for 64.8% (179/276) of the women. The presence of a positive pIGFBP-1 appeared useful for prediction of delivery before 32 (likelihood ratio (LR) = 2.21, confidence interval (CI): 1.63–3.00) and 34 weeks (LR = 1.76, CI: 1.25–2.41), respectively. Receiver operating characteristic curves were significant for cervical length and pIGFBP-1 for prediction of delivery at < 34 weeks, < 32 weeks, < 48 hours and < 7 days. Combining pIGFBP-1 and cervical length had a median interval that was shorter when both were positive as compared to only one positive or both negative, but the CIs overlapped. *Conclusions.* Both cervical length measurement and pIGFBP-1 are useful for prediction of spontaneous preterm delivery. A pIGFBP-1 positive result associated with cervical length does not improve preterm delivery prediction rates.

Key words: *Insulin-like growth factor binding protein, cervical length, preterm delivery*

Introduction

Preterm delivery is a major challenge in contemporary obstetrics as it is responsible for significant neonatal morbidity and mortality. Estimated preterm birth rates in most countries of Europe vary, most often from 5% to 8% (1). Since 80% of preterm deliveries occur at beyond 34 weeks gestation, the outcome for these babies is generally good. However, babies born at gestations between 24 and 32 weeks are at significant risk of complications related to prematurity. Strategies are needed for accurately predicting those women at high risk of preterm delivery, in order to improve the management of these pregnancies and to avoid unnecessary admissions, hospital transfers and treatments such as steroids and tocolytic therapy.

Insulin-like growth factor binding protein-1 (IGFBP-1) is part of the insulin growth factor (IGF) system. There are several IGFBP-1 isoforms that differ in their ability to modulate IGF function. Phosphorylated IGFBP-1 (pIGFBP-1) variants, as well as the unmodified peptide, have been identified in amniotic fluid, fetal serum, decidua and the conditioned medium from a number of cell types. During pregnancy, IGFs and their binding proteins are important for the growth and differentiation of both maternal and fetal tissues. From early development, nearly all fetal tissues produce these peptides and express their specific receptors (2,3).

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Phosphorylation of IGFBP-1 varies with different biological fluids or tissues. Decidual cells produce pIGFBP-1, regardless of the phosphorylation state of IGFBP-1 in amniotic fluid, fetal plasma and maternal plasma. At the beginning of labor, when fetal membranes begin to detach from the parietal decidua, small quantities of pIGFBP-1 may enter cervical secretions (4). Cervical identification of pIGFBP-1 has been proposed as a valuable tool for predicting preterm delivery in symptomatic women (5,6). The objective of this study was to evaluate the use of cervical pIGFBP-1 in the prediction of preterm delivery, and to assess its association with cervical length as measured by transvaginal scan, as a predictive diagnostic test.

Material and methods

This prospective study investigated 276 women with a singleton pregnancy between 24 and 34 weeks of gestation (calculated from ultrasound verified first day of the last menstrual period), with intact membranes but threatened preterm labor, who were admitted to the University Hospital La Fe in Valencia, Spain, from June 2004 to July 2008. Sequential recruitment resulted in 325 women with consultation causes of abdominal pain of whom 49 were subsequent to enrollment excluded from final analysis because of lack of outcome data, principally because of delivery at other hospitals. Outcome data for final analysis were thus available for 276 women. The main symptoms were abdominal pain (n = 163; 59%), contractions (n = 69; 25%), vaginal bleeding (n = 20; 7%), leaking of fluid (n = 8; 3%), lumbar pain (n = 8; 3%) and other (n = 8; 3%). All the women gave informed signed consent. Exclusion criteria were: premature rupture of membranes (PROMs) detected clinically by nitrazine test or by IGFBP-1 bed-side test, moderate to intense vaginal bleeding, pregnancies ending in preterm delivery because of placental abruption, fetal distress leading to induction of labor or cord prolapse, active labor (cervix 100% effaced, > 3 cm dilation), fetal anomalies or the presence of a cerclage suture. Approval was obtained from the Hospital Universitario La Fe Ethics Committee.

For pIGFBP-1 determination, cervical fluid was collected with a Dacron swab (Actim Partus Test, Medix Biochemica, Kauniainen, Finland) from the external cervical os, prior to ultrasound assessment or digital examination. After collection, the swab was immediately transferred to a specimen extraction solution (bovine albumin and protease inhibitors in 0.5 ml phosphate solution) and the sample extracted by shaking for 10 seconds. An immunochromatography dipstick was placed in the solution for five minutes before analyzing the result. The minimum detectable concentration was 10 μg/ml, although a concentration of 30 μg/ml was required for a positive result, which appeared as two blue lines on the test dipstick. A negative result appeared as a single blue line. As vaginal bleeding and amniotic fluid leak could produce false positive results, patients with these conditions were excluded from the study. Urine or seminal liquid did not interfere with the test result.

After collection of the cervical sample, a transvaginal ultrasound measurement of cervical length was performed using a 6.5 MHz transvaginal probe Sonoline (Siemens, München, Germany) according to the Fetal Medicine Foundation criteria (7). The mean of three measurements was used and the presence of funneling recorded. A digital examination of the cervix was then performed and cervical status documented according to the modified Bishop score (dilation, effacement, consistency, position and station). A 30-minute cardiotocogram was performed and uterine contractions recorded. Uterine contractions were considered significant if there were more than three in a 30-minute period. Urine analysis was performed in all cases to exclude urinary tract infection. Tocolysis with nifedipine or atosiban was used in all cases of established preterm labor according to clinical protocols and steroids (betamethasone 12 mg intramuscularly in two doses) were administered as appropriate.

Outcome variables were the occurrence of preterm delivery within 48 hours, in the first 7 days, delivery at < 32, < 34 weeks and the admission-to-delivery interval by cervical length and the presence of pIGFBP-1.

Statistical analysis

SPSS 13.0 Statistics Package (SPSS Inc., Chicago IL, 2004) was used for analysis. The chi-squared test, Student's *t*-test, Spearman's correlation, log rank test for Kaplan–Meier curves and receiver operating characteristic (ROC) curves were used. *P*-values of 0.05 were considered significant. All tests were two-tailed. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and positive and negative likelihood ratio (LR) and confidence intervals (CIs) for cervical length and pIGFBP-1 were calculated. The LR for a given test result indicates how much the result will raise or lower the probability of disease. It was calculated according to the Centre for Evidence-Based Medicine (8).

Results

The main demographic characteristics of the study population are shown in Table I. Mean maternal age

Table I. Demographic characteristics of study population (n = 276).

	Mean ± SD (range)
Maternal age (years)	29.4 ± 5.9 (15–46)
Gestational age at examination (weeks)	29.9 ± 2.8 (23–34)
Gestational age at delivery (weeks)	37.4 ± 3.4 (23–42)
Interval examination-delivery (days)	51.5 ± 28.5 (0–140)
	n (%)
Parity	
Nulliparous	161 (58.3)
Multiparous	115 (41.6)
Previous preterm delivery	26 (9.4)
Smoker	65 (23.5)
Reproductive treatment (IVF, ICSI)	10 (3.6)

Note: IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection; SD, standard deviation.

was 29.4 ± 5.9 years. Mean gestational age was 30 ± 3 weeks at recruitment and 37 ± 3 weeks at delivery. Of the women, 58.3% were nulliparous, and the prevalence of previous preterm delivery before 37 weeks was 9.4% (n = 26). In 77.2% (n = 213), tocolysis was given because of persistent uterine contractions for at least one hour and steroids were administered up to 34 weeks in 72.5% (n = 200). The prevalence of preterm delivery was 14.1% (n = 39) before 34 weeks and 7.6% (n = 21) before 32 weeks. The rate of spontaneous delivery was 6.9% (n = 19) within 48 hours and 9.4% (n = 26) within 7 days. Median cervical length was 32 mm (range 3–58 mm). The frequency of a cervical length < 15 mm was 7.2% (n = 20) and < 30 mm was 35.1% (n = 97). The prevalence of a positive pIGFBP-1 result was 38.7% (n = 107) (Table II). The average length of admission was 8.7 days for women with a positive pIGFBP-1 and 5.5 days for women with a negative pIGFBP-1 ($p < 0.001$, CI: 5.0–1.3).

Table II. Prevalence and rate of cervical length, pIGFBP-1 at study entry and delivery according to the outcome (n = 276).

	n	%
Cervical length < 15 mm	20	7.2
Cervical length < 30 mm	97	35.1
pIGFBP-1 (+)	107	38.7
Delivery within 48 hours	19	6.8
Delivery within in 7 days	26	9.4
Delivery ≤ 32 weeks	21	7.6
Delivery < 34 weeks	39	14.1

Note: pIGFBP-1, phosphorylated insulin-like growth factor binding protein-1.

pIGFBP-1 was positive in 32.5% (56/172) of women with a cervical length ≥ 30 mm and in 50.5% (49/97) of women with a cervical length < 30 mm ($p < 0.005$). Moreover, the rate of a positive pIGFBP-1 was 35.8% (89/249) among women with a cervical length ≥ 15 mm and 80% (16/20) for those with a cervical length < 15 mm ($p < 0.001$). Using the cut-off of < 15 mm, there was agreement between cervical length and positive pIGFBP-1 results (kappa: 0.15, $p < 0.001$). There was an inverse correlation between the modified Bishop score and cervical length measured by transvaginal scan ($p < 0.001$). Both variables correlated with the interval between examination and delivery ($p < 0.001$), which was 43.7 ± 31.7 days in women with a positive result vs. 56.8 ± 25.3 days in women with a negative pIGFBP-1 result ($p < 0.001$). The predictive values of pIGFBP-1 to adequately detect preterm delivery before 34 and 32 weeks, and within the first 48 hours and the first 7 days after assessment are shown in Table III. The presence of a positive pIGFBP-1 appeared useful for prediction of delivery before 32 (LR = 2.21, CI: 1.63–3.00) and 34 weeks (LR = 1.76, CI: 1.25–2.41), respectively. Only a small increase in the diagnostic probability (LR+ of around 2) was observed.

ROC curves for the optimal cut-off point for using cervical length to predict delivery before 34 showed a cervical length value of ≤ 20.5 mm as giving an area under the curve (AUC) of 0.76 (0.67–0.84, $p < 0.001$), and values of 88% for sensitivity and 54% for specificity. ROC curves were significant for cervical length and pIGFBP-1 for prediction of delivery at < 34 weeks, < 32 weeks, < 48 hours and < 7 days. In all instances, cervical length had a higher AUC than pIGFBP-1 for the same delivery time prediction, although the CIs overlapped. For prediction of delivery < 32 weeks, the value for cervical length AUC with a 95% CI was 0.84 (0.75–0.93, $p < 0.001$) and for pIGFBP-1, it was 0.7 (0.59–0.82, $p < 0.005$) (Figure 1).

When comparing the predictive value for the mean interval to delivery time of the cervical length < 15 mm with the cervical length < 30 mm with a positive pIGFBP-1, a cervical length < 15 mm was the best predictor for short interval to delivery (Table IV). Combining a positive pIGFBP-1 result and a cervical length of either < 15 or < 30 mm did not improve the predictive value over the isolated estimation of cervical length (Figure 2). The addition of a positive pIGFBP-1 result to cervical length < 15 or 30 mm did not improve the accuracy of the predictive value of isolated cervical length.

Discussion

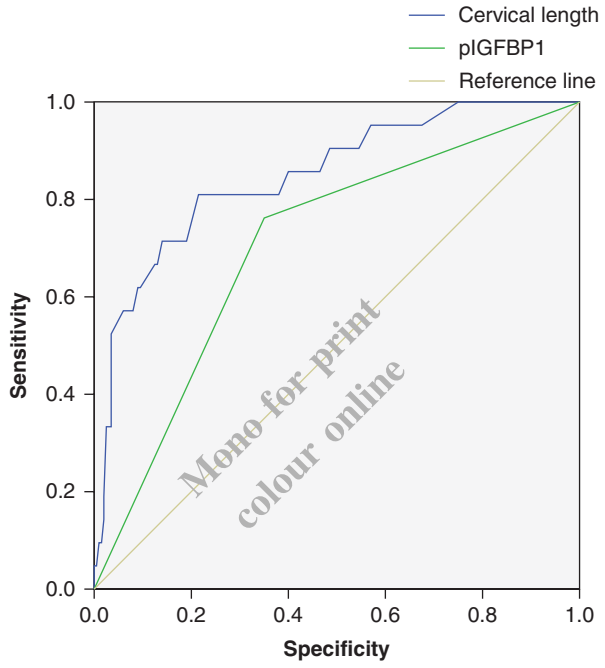
Despite advances in obstetric care, preterm delivery remains a major cause of neonatal morbidity and

Table III. Diagnostic accuracy of pIGFBP-1 for delivery at < 48 hours, < 7 days, < 32 weeks and < 34 weeks.

	Delivery < 48 hours	Delivery < 7 days	Delivery < 32 weeks	Delivery < 34 weeks
Sensitivity	73.7	73.1	76.2	59
Specificity	64.9	66.2	65.5	66
PPV	16.1	21.8	18.4	23.4
NPV	96.4	95	96.4	88.6
LR+ (CI)	2.1 (1.52–2.91)	2.16 (1.60–2.92)	2.21 (1.63–3.00)	1.76 (1.25–2.41)
LR– (CI)	0.41 (0.19–0.87)	0.41 (0.21–0.78)	0.36 (0.17–0.79)	0.62 (0.41–0.93)

Note: pIGFBP-1, phosphorylated insulin-like growth factor binding protein-1; PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio; CI, confidence interval.

mortality. No biological marker that allows accurate identification of high-risk patients has yet been identified, although various diagnostic tools have been devised. The best test for identifying preterm delivery risk should be both sensitive and highly specific, avoiding unnecessary admissions, administration of corticosteroids, tocolysis and transfer to a tertiary unit. Three tests have been introduced over the last years into routine obstetric care: fetal fibronectin, cervical pIGFBP-1 and cervical length measured by transvaginal ultrasound (9). In a systematic review of symptomatic women, the mean sensitivity and specificity of fetal fibronectin to predict delivery within seven days after testing were 77% and 87%, respectively (10), which are slightly higher than the values we obtained for pIGFBP-1. The cut-off point of 50 ng/ml fetal fibronectin in cervico-vaginal secretions is the most accurate for predicting spontaneous preterm delivery (11). Many studies have shown an association between ultrasonographic cervical length and preterm delivery (12,13).



	AUC (95% CI)	*p*
Cervical length	0.849 (0.759-0.939)	0.000
pIGFBP-1	0.706 (0.593-0819)	0.002

Figure 1. ROC curve: cervical length and positive pIGFBP-1 for delivery at < 32 weeks. Note: AUC, area under the curve; pIGFBP-1, phosphorylated insulin-like growth factor binding protein-1; ROC, receiver operating characteristic.

More recently, pIGFBP-1 detection in cervical secretions by a rapid, bedside, one-step strip test has become an important tool for assessing risk of preterm labor (14–16). IGFBP-1 belongs to the superfamily of insulin-like binding proteins. The phosphorylation status in decidual tissues is different from the isoform in amniotic fluid and is the basis for this test. Several studies have proven the efficacy of detection of non-phosphorylated forms of IGFBP-1 in cervical fluid after suspicion of PROMs that could not be confirmed by examination (17,18). Most studies that detect the phosphorylated isoform in cervical secretions used a qualitative, immunoenzymatic bedside test with which it was possible to detect concentrations over 10 µg/l. A true positive test is obtained at concentrations over 30 µg/l (6,19–21). This test is accurate and easy to use, and the results are available within five minutes of sampling. Other authors have set cut-off points for pIGFBP-1 concentration at 6.4 µg/l, thus reducing the sensitivity and specificity rates (5).

Several studies carried out on women with regular contractions showed predictive values for pIGFBP-1, for detection of spontaneous preterm delivery before 37 weeks of sensitivity: 89–73%, specificity: 94–82%, PPV: 94–56% and NPV: 92–79% (6,16,19). Results from our study showed lower predictive values. One reason could be our criterion of < 34 weeks for preterm delivery. Considering this, the high NPV obtained for this cut-off is noteworthy. Therefore, we suggest that the applicability of pIGFBP-1 for prediction of preterm delivery is mainly its accuracy in detecting those women who are not at risk for

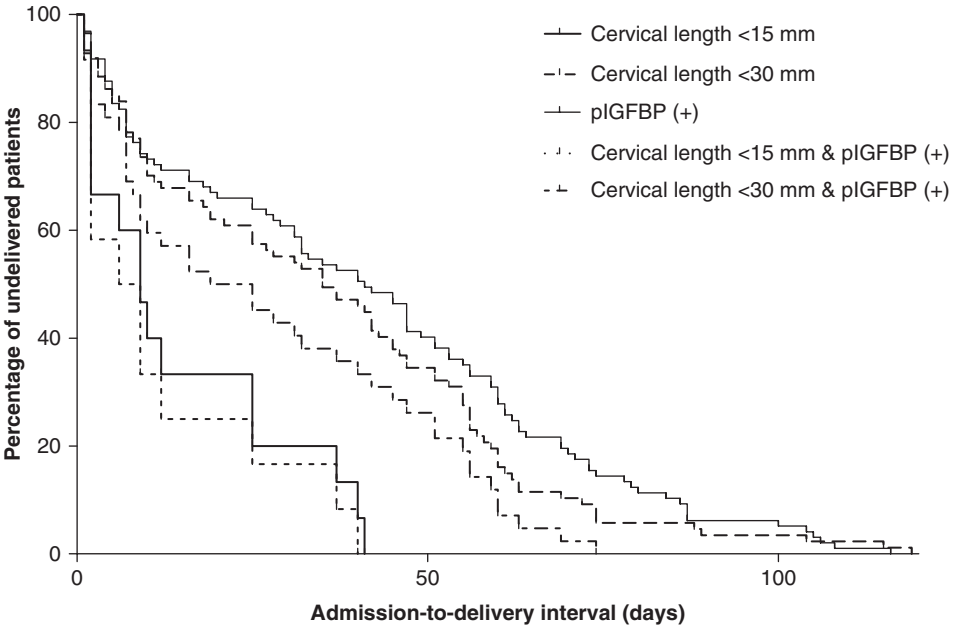


Figure 2. Admission-to-delivery interval curves according to pIGFBP and cervical length results. Note: pIGFBP-1, phosphorylated insulin-like growth factor binding protein-1.

preterm delivery. Detection of pIGFBP-1 in cervical secretions is useful for prediction of preterm delivery in symptomatic women and is most accurate at predicting delivery within seven days of the assessment (6,19). In our cohort, predictive values for delivery before 32 weeks were not different from delivery within seven days of assessment. A negative pIGFBP-1 was associated with shorter hospital admission in our study (8.73 vs. 5.52 days). This was previously addressed by Kwek et al. (6) and has a significant impact on cost and inconvenience to pregnant women and their families. In our study, LR for pIGFBP-1 slightly increases the probability of preterm delivery before 32 and 34 weeks. The LR is a powerful measure of the accuracy of a diagnostic test. It is the ratio of the probability of a given test result in patients with disease to the probability of the same test result in patients without disease. The LR for a given test result indicates how much that result will raise or lower the probability of disease. When analyzing the impact of LRs of different magnitude on the post-test probability of disease, LRs from 2 to 5 yield small increases in the post-test probability of disease, from 5 to 10 moderate increases and above 10 large increases. For ratios less than unity, the smaller the LR, the greater the decrease in probability (22).

Table IV. Mean admission-to-delivery interval (days) and 95% CI for cervical length, positive pIGFBP-1 and combined cervical length and positive pIGFBP-1.

	Mean ± SE	95% CI
Cervical length < 15 mm	13.1 ± 3.6	6–20.2
Cervical length < 30 mm	39.5 ± 3.1	33.4–45.6
pIGFBP-1	44.6 ± 3.1	38.5–50.8
Cervical length < 15 mm and pIGFBP-1	10.2 ± 3.6	3.1–17.2
Cervical length < 30 mm and pIGFBP-1	28.7 ± 3.7	21.4–35.9

Note: CI, confidence interval; pIGFBP-1, phosphorylated insulin-like growth factor binding protein-1; SE, standard error.

Other studies have evaluated the efficacy of multiple markers for the prediction of preterm delivery. In one, cervical interleukin (IL)-6, IL-8 and pIGFBP-1 were combined with cervical ultrasonography to predict preterm delivery in symptomatic women. The combination of IL-6, IL-8 and cervical ultrasonography was the best predictor, and pIGFBP-1 appeared to be more of a marker for puerperal and neonatal infectious morbidity in threatened preterm delivery cases than a preterm delivery prediction marker by itself (5). When comparing fetal fibronectin and pIGFBP-1, both tests have a high NPV for predicting risk of delivery within 48 hours, 7 or 14 days, but pIGFBP-1 has shown a higher NPV in predicting the risk of delivery within 48 hours (20), which is crucial for completion of corticosteroid therapy. The advantages of pIGFBP-1 compared to fetal fibronectin are connected to seminal plasma containing fibronectin and 93% of pregnant women having intercourse during pregnancy and a cervical dilatation > 3 cm could result in a false positive result with fetal fibronectin (15). However, vaginal hemorrhage can cause false positives for pIGFBP-1 (21).

A combination of cervical ultrasonography assessment and pIGFBP-1 in asymptomatic women with previous preterm delivery history identified preterm delivery before 34 weeks in 91.7% of women and before 37 weeks in 80% of women. Cervical length was measured between 22 and 24 weeks of gestational age, and pIGFBP-1 was most accurate when assessed at 30 weeks of gestational age in a study by Bittar et al. (21). Our study used a population with symptoms of preterm delivery. This is the first study where a combination of pIGFBP-1 and cervical length was tested in symptomatic women. The combination of cervical length below 15 or 30 mm and a positive pIGFBP-1 result did not improve the predictive value over the isolated estimation of cervical length for admission-to-delivery interval.

The main limitation of this study is the loss of 49 patients after enrollment because of delivery in local hospitals. Exclusion of these patients from analysis could have biased the results.

Cervical pIGFBP-1 provided additional information for assessing symptomatic women at high risk of preterm delivery. It is a reasonable predictive diagnostic tool for delivery before 32 and 34 weeks and within the first 48 hours and 7 days of assessment and most accurate in detecting women who were not at risk for preterm delivery, but did not improve the predictive value of transvaginal scans for cervical length.

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***Disclosure of interest*:** The authors declare no conflicts of interest.

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