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MATERNO-FETAL MEDICINE

Biochemical markers predicting pre-term delivery in symptomatic patients: phosphorylated insulin-like growth factor binding protein-1 and fetal fibronectin

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Abstract
Purpose The aim of this study was to evaluate the efficacy of the phosphorylated insulin-like growth factor-binding protein (phIGFBP-1) and of the fetal fibronectin test (fFN) in predicting pre-term delivery in symptomatic women.
Methods We included 210 symptomatic women at 24–34 weeks' gestation, who underwent the phIGFBP-1 and fFN test. We analyzed the prevalence of pre-term delivery in these patients within 7 days upon admission, before the 34th and the 37th weeks' gestation.
Results The 3.8% of women delivered within 7 days upon the admission, the 7.6% before 34 weeks and the 16.2% before 37 weeks' gestation. The phIGFBP-1 and fFN test had a high specificity and a high negative predictive value in predicting pre-term delivery within 7 days, before 34 and before 37 weeks' gestation. The logistic regression of phIGFBP-1 was statistically significant in predicting pre-term delivery with an odds ratio of 10.08 <34 weeks' gestation. The multivariate analysis showed that the phIGFBP test had a higher OR <34 weeks' gestation ($p < 0.001$) and that the two variables were independent and useful in combination to predict pre-term delivery (<37 weeks' gestation).
Conclusion The phIGFBP-1 test may be better that the fFN test in predicting pre-term delivery before 34 weeks' gestation.

Keywords Phosphorylated insulin-like growth factor binding protein-1 test · Fetal fibronectin test · Biochemical markers · Spontaneous pre-term delivery

Abbreviations

fFN	Fetal fibronectin
phIGFBP-1	Phosphorylated insulin-like growth factor-binding protein
NS	Non-significant
PPV	Positive predictive value
NPV	Negative predictive value

Introduction

Pre-term deliveries occur before the 37 weeks' gestation, and account for 5–7% of deliveries in Europe and 11% in the United States [1, 2]. There is considerable interest in biochemical markers capable of differentiating patients at a truly high risk of pre-term delivery from those requiring no treatment. A test was introduced that is designed to screen

The use of the phosphorylated insulin-like growth factor-binding protein test may be more advantageous than fetal fibronectin test in predicting pre-term delivery in symptomatic patients.

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cervico-vaginal secretions for the presence of fetal fibronectin (fFN), an isoform of a high-molecular-weight glycoprotein, is produced by fetal membranes, found in the basement membrane near the choriodecidual interface, and may indicate the mechanical or inflammatory-mediated detachment of the membranes from the decidua [3–5]. Its presence in cervical-vaginal secretions between 20 and 34 weeks' gestation is a strong predictor of pre-term delivery in both asymptomatic and high-risk women, and many studies have provided evidence that a positive fFN test is a predictor of pre-term delivery in patients presenting with pre-term uterine contractions [6, 7]. Another biochemical assays for the prediction of pre-term delivery is one rapid test for determining the presence of phosphorylated insulin-like growth factor-binding protein (phIGFBP-1) in endocervical secretions [8–16]. phIGFBP-1 is mainly secreted by maternal decidual cells, and may be an indicator of tissue damage of the choriodecidual interface [9, 11]. In the early stages of labor, the fetal membrane begins to detach from the decidua and a small amount of phIGFBP-1 may be found in cervical secretions. phIGFBP-1 may be found in cervical secretions [9–16]. Kekki et al. [13] have reported that a phIGFBP-1 concentration of at least 10 μg/L in a cervical swab sample indicates a tenfold greater risk of pre-term delivery.

The aim of this study was to evaluate the efficacy of the phIGFBP-1 test in predicting pre-term delivery in symptomatic women.

Materials and methods

This prospective study involved 210 Caucasian women with uterine contractions who received prenatal care between January 2006 and December 2006 in our departments of obstetrics in Padua and Milan. All the patients signed an informed consent form approved by the local Health Sciences in Human Subjects Committee. The inclusion criteria were a singleton pregnancy at 24–34 weeks' gestation, with documented uterine contractions (at least 10 per hour) and intact membranes. The exclusion criteria were >2 cm dilatation of the cervix, having undergone a cervical examination or sexual intercourse less than 24 h previously, vaginal bleeding, placenta previa, multiple gestations, fetal abnormalities and uterine anomalies. Gestational age was based on menstrual data confirmed by an early first-trimester ultrasound scan; the other recorded data included demographic information, pre-term labor management and delivery outcomes. All the women were admitted to hospital and received an intravenous infusion with ritodrine; fetal lung maturation was accelerated by administering 24 mg of betamethasone (12 mg intramuscularly on two consecutive days) to the women with fetuses at less than 34 weeks' gestation. Immediately upon admission, vaginal fFN samples were collected by rolling a dacron swab on the posterior fornix for 10 s. In accordance with the manufacturer's instructions (Adeza Biomedical Corporation), the samples containing an fFN concentration of more than 50 ng/mL were considered as positive. The fFN concentrations were measured within 30 days of collection by means of an enzyme-linked immunosorbent assay (ELISA) using the specific FDC-6 monoclonal antiboby. A rapid cervical sample for phIGFBP-1 determination (Actim Partus Test, Medix Biochemica, Kauniainen, Finland) was taken by means of a polyester-tipped swab during a speculum examination of the cervix, and extracted with specimen-extraction solution. The lower end of the swab was inserted into the external cervical orifice and left in place for about 10 s, after which it was placed in a test tube containing 0.5 mL of buffer solution. The dipstick was dipped into the samples and left for 15 s to allow the liquid front to enter the results area. After removing the dipstick from the solution and holding it for 5 min in a horizontal position, the test was interpreted as being positive, negative or invalid, respectively, when two, one or no blue lines appeared in the result area. The test is based on immunochromatography and has a detection limit of 10 μg/L. The clinicians were informed of the test results, but no changes were made in the treatment of the positive or negative patients.

Statistical analysis

Student's *t* test was used to compare the average values of the continuous variables, with the values being expressed as the mean ± SD. Pearson's Chi-square test or Fisher's exact test was used to analyze the categorical variables, whose values are expressed as percentages. Univariate logistic regression analysis was performed to assess the capability of the fFN and the phIGFBP-1 test to predict pre-term birth. A multivariate logistic regression model was then developed using the forward stepwise method and 95% confidence levels in order to analyze the significant predictive variables in combination.

Results

Two hundred and ten symptomatic women with singleton pregnancies were included in the study. The average maternal age of the patients delivering pre-term was 30.7 ± 5.1 years, and that of the patients delivering at term was 30.4 ± 5.6 years (non-significant: NS); their average body mass index was 22.72 ± 3.7 and 23.36 ± 3.99 kg/m^2, respectively (NS). The mean gestational age at sampling was 28.7 gestational weeks. We analyzed the prevalence of

pre-term delivery in these patients within 7 days upon admission, before the 34th and the 37th weeks' gestation.

The prevalence of pre-term delivery in symptomatic patients was: 3.8% within 7 days, 7.6% before 34 weeks' gestation and 16.2% before 37 weeks' gestation. Among the patients who were both phIGFBP-1 and fFN test positive, median gestational age at delivery was 32.3 weeks' gestation. Of those in whom delivery took place within 7 days, phIGFBP-1 test was positive in 10.8% ($p = 0.034$) and fFN test in 9.1% (NS) instead phIGFBP-1 test was positive in 24.3% ($p < 0.0001$) and fFN test in 22.7% ($p = 0.009$) before 34 weeks' gestation (Table 1). A positive phIGFBP-1 (48.6%) and fFN (45.4%) tests were significant predictors of delivery before 37 weeks' gestation ($p < 0.0001$) (Table 1).

Table 2 shows the percentage of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of phIGFBP-1 and fFN tests. We have shown the high NPP of phIGFBP-1 test: 97.7% within 7 days, 97.1% before 34 weeks' gestation and 90.8% before 37 weeks' gestation (Table 2).

The logistic regression of phIGFBP-1 was statistically significant in predicting pre-term delivery ($p < 0.0001$), with an odds ratios (OR) of 5.12 within 7 days ($p = 0.026$), an OR of 10.08 before 34 weeks' gestation ($p < 0.0001$) and an OR of 9.29 before 37 weeks' gestation ($p < 0.0001$) (Table 3a).

Table 1 Percentage of positive results (%) of phIGFBP-1 and fFN test in predicting pre-term delivery within 7 days upon admission, before 34 (<34) and before 37 (<37) g. w. weeks' gestation

Delivery	phIGFBP-1 test (%)	*p*	fFN test (%)	*p*
7 days	10.81	0.034	9.09	NS
<34 g. w.	24.32	<0.0001	22.73	0.009
<37 g. w.	48.65	<0.0001	45.45	<0.0001

Table 2 Sensitivity, specificity, PPV and NPV of phIGFBP-1 and fFN in predicting pre-term delivery within 7 days upon admission, before 34 (<34) and before 37 (<37) g. w. weeks' gestation

Parameter	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
phIGFBP-1 test				
7 days	50	83.7	10.8	97.7
<34 g. w.	64.3	85.7	24.3	97.1
<37 g. w.	52.9	89.2	48.7	90.8
fFN test				
7 days	50	80.2	9.1	97.6
<34 g. w.	62.5	82.5	22.7	96.4
<37 g. w.	50	85.9	45.5	88
phIGFBP-1 + fFN tests				
<37 g. w.	50	95.2	71.4	88.8

The ability of the fFN test in predicting pre-term delivery in 7 days was not statistically significant at Fisher's exact test (Table 3a). Instead the logistic regression of fFN test was statistically significant with an OR of 7.84 before 34 weeks' gestation ($p = 0.009$) and 6.08 before 37 weeks' gestation ($p < 0.0001$) (Table 3a). The multivariate analysis of the phIGFBP-1 and fFN test showed that the phIGFBP test had a higher odds ratio (OR 23.61) in predicting pre-term delivery before 34 weeks' gestation ($p < 0.001$). The combination of phIGFBP-1 ($p < 0.001$) and fFN ($p = 0.02$) was therefore statistically significant only before 37 weeks' gestation (Table 3b). The multivariate analysis showed that the two variables were independent and therefore, useful in combination to predict pre-term delivery. Confounding factors such as the number of previous pregnancies and deliveries, smoking situation, education and tobacco use were tested, but were not included in the final logistic model.

Conclusion

Recent attempts to predict pre-term birth have included the use of biochemical markers such as phIGFBP-1 and fFN test. Many studies have shown that a positive fFN test predicts pre-term delivery in patients presenting with pre-term uterine contractions [6, 7]. Lockwood et al. [6] were the first to find the high NPV of the fFN test in relation to pre-term delivery, and the results of our own study show that this is true in relation to pre-term delivery within 7 days (97.6%), <34 (96.4%) and <37 weeks' gestation (88%). We compared the effectiveness of fFN test in predicting pre-term delivery with that of phIGFBP-1 because previous studies have shown that the latter is also capable of predicting the risk of pre-term delivery, albeit to different extents: Kekki et al. [13] found that its sensitivity, specificity, PPV, and NPV are respectively 89, 94, 94 and 89% instead Akercan et al. [9] reported corresponding figures of 78, 87, 73 and 90%. Akercan et al. also analyzed its accuracy in predicting pre-term delivery in 36 patients with premature membrane rupture, finding it rapid, 100% sensitive and 92% specific, with a PPV and NPV of respectively 84 and 100% [14]. Lembet et al. compared its predictive capacity in 36 symptomatic and 18 asymptomatic women, and found its sensitivity and specificity were respectively 89.5 and 94.1%, and its PPV and NPV respectively 94.4 and 88.9% [11]. Furthermore, our data relating to a larger number of symptomatic pregnant women patients than in our previous study [10] confirmed the high NPV of the phIGFBP-1 test. The phIGFBP-1 test was positive in 10.81% of the women who delivered within 7 days, and the fFN test was positive in 9%. As the percentage of women with a positive fFN test who gave birth

Table 3 Univariate (a) and multivariate (b) analysis of the ability of phIGFBP-1 test and fFN test in predicting pre-term delivery within 7 days upon admission, and before 34 (<34) and before 37 (<37) g. w. weeks' gestation

Parameter	Delivery within 7 days		*p*	Delivery <34 g. w.		*p*	Delivery <37 g. w.		*p*
	pOdds ratio	(95% CI)		Odds ratio	(95% CI)		Odds ratio	(95% CI)	
a. Univariate analysis									
ph IGFBP-1	5.12	(1.20–21.89)	0.026	10.08	(3.34–34.82)	<0.0001	9.29	(4.05–21.3)	<0.0001
fFN	*	*	* NS	7.84	(1.67–36.66)	0.009	6.08	(2.84–13)	<0.0001
b. Multivariate analysis									
ph IGFBP-1	*	*	* NS	23.61	(3.75–148.3)	<0.001	15.71	(3.84–64.34)	<0.0001
fFN	*	*	* NS	3.97	(0.66–23.82)	NS	4.25	(1.21–14.91)	0.02

* Fisher's exact test NS

pre-term was not statistically significant, we could not make a univariate and multivariate analysis. In brief, phIGFBP-1 proved to be the better test for predicting a pre-term delivery within 7 days. In predicting a pre-term delivery at <34 weeks' gestation, it not only had a high and stable NPV, but also a high odds ratio in the multivariate analysis. The odds ratio is so high due to the fact that this predictor is significant ($p < 0.0001$). On the contrary, the fFN test that we considered in the multivariate regression model has a much lower odds ratio because of its non statistically significance. Furthermore, the combination of phIGFBP-1 and fFN test results was not significant in predicting pre-term delivery, and the fFN test did not add anything to the capacity of phIGFBP-1 to predict pre-term delivery before the 34th gestational weeks.

Considerable interest has been shown also regarding the use of sonographic measurements. The use of transvaginal sonography to visualize the cervix has shown that cervical shortening is predictive of pre-term birth [16]. In a previous study, we have compared the performance the sonographic measurement of cervical length and phIGFBP-1 test in predicting pre-term delivery in 210 symptomatic patients [16]. Our own ROC curves showed that 26 mm was the best cut-off value for cervical length in terms of predicting pre-term delivery, with a sensitivity and NPV of 86 and 97%, respectively [16]. The recent introduction of a new cervico-vaginal test to detect phIGFBP-1 may improve the accuracy of predicting pre-term delivery as we found that it had a high NPV of 91% [16]. We found that their combination had an NPV of 90%, greater specificity and a better PPV than either method alone [16]. We have shown that the cervical length and the phIGFBP-1 test are independent variables that can be used together to predict pre-term delivery and we concluded that sonographically measured cervical length of >26 mm with a negative phIGFBP-1 test in a patient with regular uterine contractions before 37 weeks' gestation seems to indicate a low risk of pre-term delivery and may therefore allow the avoidance of unnecessary interventions [16].

This is the first study comparing fFN and phIGFBP-1 tests, and it is interesting to note that phIGFBP-1 was better in predicting pre-term delivery before the 34th gestational weeks, the crucial period for lung maturation. There was no difference between the two tests in predicting pre-term delivery before 37 weeks' gestation. We believe that, by the 37 weeks' gestation (approaching delivery time), there may be changes in decidual cells and the amnio-chorial compartment; consequently, on the basis of our findings, the phIGFBP-1 test seems to be useful in predicting pre-term delivery in symptomatic patients before the 34th gestational weeks. Furthermore, it is much cheaper than the fFN test and given the decrease in the number of admissions and drugs administered, it has a better cost/benefit ratio. In addition, unlike fFN, phIGFBP-1 is unaffected by vaginal bleeding, urine, seminal plasma, vaginal examinations and vaginal ultrasounds.

In conclusion, phIGFBP-1 seems to be the best marker for predicting pre-term delivery before the 34 weeks' gestation, although further comparative studies using the same patient population and study design are needed to confirm our results.

Conflict of interest None.

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