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The combination of short cervical length and phIGFBP-1 in the prediction of preterm delivery in symptomatic women

Luana Danti, Federico Prefumo, Andrea Lojacono, Silvia Corini, Alberto Testori, & Tiziana Frusca

Maternal–Fetal Medicine Unit, Department of Obstetrics and Gynaecology, University of Brescia, Italy

Objective. **To assess the combined use of cervical length and cervical phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) in the prediction of preterm delivery in symptomatic women.** ***Methods.*** **Cervical length was prospectively measured in 102 consecutive singleton pregnancies with intact membranes and regular contractions at 24–32 weeks, and phIGFBP-1 was assessed in those with a cervix≤30 mm.** ***Results.*** **Among women with a cervix >30 mm (*n* = 42), none delivered < 34 weeks or within 7 days. Among women with a cervical length ≤ 30 mm (*n* = 60), eight delivered < 34 weeks, four of which within 7 days. A positive phIGFBP-1 conferred a significantly increased risk of delivery before 34 weeks in women with a cervix ≤ 30 mm (likelihood ratio 2.32, 95% confidence interval 1.15–4.67), and a significantly increased risk of delivering within 7 days in the subgroup of women with a cervical length of 20–30 mm (likelihood ratio 3.64, 95% confidence interval 2.20–6.01).** ***Conclusions*****. In symptomatic women with a cervical length > 30 mm the risk of preterm delivery is very low. In women with a cervix ≤30 mm, adding phIGFBP-1 assessment may improve the risk assessment for preterm delivery, and help to plan subsequent pregnancy management.**

Keywords: *Preterm labor, transvaginal ultrasound, sensitivity, specificity, predictive value, likelihood ratio*

Introduction

Only a minority of the women presenting with threatened preterm delivery will actually deliver preterm [1]. Given the side effects of tocolysis and the costs of hospital admission, a proper and correct diagnosis of impending preterm delivery is crucial. In the last years, there have been attempts to identify, among women presenting with uterine contractions, the subgroup with the highest risk of delivering preterm. There is a wealth of literature suggesting that cervical length measured by ultrasound and fetal fibronectin have the potential to improve the prediction of preterm delivery [2–4].

Insulin-like growth factor binding protein-1 (IGFBP-1) is a 28-kDa hydrophobic protein which is non-glycosylated and binds and regulates the function of insulin-like growth factors. Amniotic fluid contains little of the phosphorylated isoforms of IGFBP-1, while tissues produce mainly the phosphorylated forms (phIGFBP-1). IGFBP-1 levels in amniotic fluid are 100–1000 times higher than in serum and are essentially undetectable in other body fluids. The phosphorylated IGFBP-1 isoforms are predominantly secreted by human decidual cells. IGFBP-1 and phIGFBP-1 can be differentiated by the use of specific monoclonal antibodies [5]. Consequently, the presence of IGFBP-1 can be used to detect preterm rupture of membranes (PROM) [5], while the presence of phIGFBP-1 in cervical secretions reflects decidual activation [6]. Recently, cervicovaginal concentrations of phIGFBP-1 have been shown to correlate with the risk of preterm delivery [7–19].

The purpose of the present study was to evaluate the combination of cervical length measurement and cervicovaginal phIGFBP-1 in the prediction of preterm delivery within 7 days or before 34 weeks in symptomatic women.

Methods

Between December 2004 and December 2006, according to our departmental protocol, in all singleton pregnancies between 24+0 and 32+6 weeks presenting to our Unit with the complaint of uterine contractions, a cardiotocogram was performed. In case of documented uterine contractions (at least 4 in 20 min), women were asked to empty their bladders and were placed in dorsal lithotomy position. An ultrasound probe was inserted into the vagina, with ultrasound gel applied only between the probe and the probe cover, and not on the external surface of the probe cover. The probe was placed in the anterior fornix, and the cervical length was measured as previously described [20].

A cervical length ≤30 mm at transvaginal ultrasound examination was considered an indication for admission [2]. In these women, a commercially available immunochromatography-based rapid strip test (Actim Partus Test; Medix Biochemica, Kauniainen, Finland) was used to detect phIGFBP-1 in cervical secretions. After sterile speculum introduction, a sample of cervical fluid was collected from the external os with a dacron swab provided in the test package. After collection, the swab was immediately transferred to a tube containing an extraction solution, and shaken in the tube for 10 s. The swab was then withdrawn and a reagent strip was placed into the tube. The bottom end of the strip was kept in the solution until the liquid front entered the reaction area. After 20 s the strip was removed and placed in a horizontal position. A positive result (corresponding to a phIGFBP-1 concentration >10 μg/l) appeared in 5 min as two blue lines on the strip, and a negative result as a single blue line. After successful phIGFBP-1 testing, a vaginal examination was

Correspondence: Federico Prefumo Dipartimento di Ostetricia e Ginecologia, Università di Brescia, Piazzale Spedali Civili 1, 25123 Brescia, Italy. Tel: +39-030-3995340. Fax: +39-030-3995034. E-mail: federico.prefumo@libero.it

performed. Exclusion criteria were: vaginal bleeding; ruptured membranes; cervical dilatation ≥3 cm; cervical cerclage; known uterine abnormalities; fetal abnormalities; and other pregnancy complications (placenta praevia, abruptio placentae, fetal growth restriction, and pre-eclampsia). All women gave their written informed consent, and the study was approved by the local Ethical Committee. The managing clinician was aware of cervical length measurements, but blinded to phIGFBP-1 results. The decision to use corticosteroids and tocolysis, as well as maternal and fetal outcomes were recorded in the clinical notes, and reviewed by an observer blinded to phIGFBP-1 results.

Enrolled women were arbitrarily divided in two further groups according to their cervical length measurement: 20–30 mm and less than 20 mm. Variables are described as median (interquartile range) or as percentages. For inter-group comparisons, the Mann–Whitney test, χ^2 test, and Fisher's exact test were used, as appropriate. Positive and negative likelihood ratio, sensitivity, specificity, positive and negative predictive values of cervical length measurement, and phIGFBP-1 for delivery within 7 days from assessment and for delivery before 34 completed weeks of gestation were calculated. The results of cervical length measurement and phIGFBP-1 were compared using a 2×2 frequency table and Cohen's κ coefficient [21]. Survival tables were generated, and the log rank test for Kaplan–Meier curves applied. Based on the data by Lembet et al. [10], we assumed that a positive phIGFBP-1 test would have at least 90% sensitivity for preterm delivery within 7 days in symptomatic women. Assuming that at least 15% of symptomatic women with a cervical length ≤30 mm would deliver within 7 days [22], we calculated that 58 women would need to be enrolled to estimate sensitivity and specificity with a 95% confidence interval no larger than 20% [23]. As from previous local unpublished data women with cervical length ≤30 mm were 60% of all women with threatened preterm labor, we planned to enroll 97 women for this study. All calculations were performed using the SPSS statistical package (release 16, SPSS Inc., Chicago, IL).

Results

Out of 102 women with threatened preterm labor observed during the study period, 42 presented with a cervical length>30 mm, and 60 with a cervical length ≤30 mm. The demographic and clinical characteristics of the two groups are shown in Table I. Among women with a cervical length>30 mm, none delivered before 34 weeks, and only two delivered preterm at 36+4 and 36+5 weeks, respectively, 41 and 37 days after the evaluation.

In the group of women with a cervical length ≤30 mm, 21 delivered preterm, and 8 before 34 completed weeks of gestation. phIGFBP-1 was positive in 19 women (32%) and negative in 41 (68%). Table II shows the demographic and clinical characteristics of women with a cervical length ≤30 mm according to phIGFBP-1 test results. Cases with a positive phIGFBP-1 had a significantly shorter length of gestation, assessment to delivery interval, lower birth weight, and higher rate of delivery<37 weeks, with a trend for a higher proportion of cases delivered<34 weeks. Cervical length was 20–30 mm in 41 cases, and less 20 than mm in 19 women. Results of phIGFBP-1 and cervical assessment are compared in Table III. Disagreement between the two tests was observed in 24 cases (40%), with a Cohen's κ coefficient of 0.08 (95% confidence interval, −0.21 to 0.36).

Figure 1 shows the assessment to delivery interval curves according to phIGFBP-1 results in cases with cervical length of 20–30 mm (panel A) and in those with cervical length <20 mm (panel B). The difference between the curves was statistically significant in the 20–30 mm group ($p = 0.03$) but not in the <20 mm group ($p = 0.25$). The positive and negative likelihood ratio, sensitivity, specificity, positive, and negative predictive values of cervical length measurement and phIGFBP-1 for different pregnancy outcomes in women with a cervical length ≤30 mm are shown in Tables IV and V. A positive phIGFBP-1 confers a significantly increased risk of delivery before 34 weeks independent of cervical length, and a significantly increased risk of delivering within 7 days in the subgroup with a cervical length of 20–30 mm.

Discussion

In a consecutive series of women with threatened preterm labor, we demonstrated that assessment of cervical length identifies a higher risk for preterm birth within 7 days, and before 34 weeks of gestation. The combination of phIGFBP-1 and cervical length might provide a better identification of women in labor.

In women presenting an acute risk of preterm delivery, tocolysis, steroids, and *in utero* transfer to a center with neonatal intensive care are recommended [24]. This involves unnecessary treatment and complex management in a relevant number of symptomatic

Table I. Demographic and clinical characteristics of women with a cervical length ≤30 mm ($n = 60$) and>30 mm ($n = 42$).

	Cervical length ≤30 mm	Cervical length>30 mm	*p*
Maternal age (years)	31 (28–34)	34 (30–37)	0.009
Nulliparous	38 (63%)	26 (62%)	0.88
Gestational age at assessment (weeks)	30.0 (28.7–31.4)	28.9 (26.6–30.9)	0.15
Cervical length (mm)	23 (18–27)	37 (34–40)	<0.001
Corticosteroids	28 (47%)	4 (10%)	<0.001
Tocolysis	22 (37%)	5 (12%)	0.005
Gestational age at delivery (weeks)	38.0 (36.3–39.3)	39.6 (38.6–40.0)	<0.001
Delivery <37 weeks	21 (35%)	2 (5%)	<0.001
Delivery <34 weeks	8 (13%)	0 (0%)	0.02
Delivery within 7 days	4 (7%)	0 (0%)	0.23
Assessment to delivery interval (days)	55 (34–74)	76 (56–87)	<0.001
Male fetus	36 (60%)	19 (45%)	0.14
Birth weight (g)	2960 (2458–3388)	3145 (2855–3572)	0.02
Admission to NICU	15 (25%)	1 (2%)	0.002

Values are given as median (interquartile range) or number (%).

Table II. Demographic and clinical characteristics of women with a cervical length ≤30 mm according to phIGFBP-1 test results.

	Positive phIGFBP-1 (n = 19)	Negative phIGFBP-1 (n=41)	p
Maternal age (years)	26 (29–33)	32 (29–35)	0.16
Nulliparous	13 (68%)	25 (61%)	0.58
Gestational age at assessment (weeks)	30.0 (28.7–32.3)	29.9 (28.4–31.3)	0.53
Cervical length (mm)	22 (15–26)	24 (19–27)	0.27
Corticosteroids	14 (74%)	14 (34%)	0.004
Tocolysis	11 (58%)	11 (27%)	0.02
Gestational age at delivery (weeks)	36.3 (34.0–38.3)	38.3 (37.1–39.5)	0.005
Delivery <37 weeks	12 (63%)	9 (22%)	0.002
Delivery <34 weeks	5 (26%)	3 (7%)	0.11
Delivery within 7 days	2 (11%)	2 (5%)	0.75
Assessment to delivery interval (days)	39 (21–65)	59 (43–76)	0.02
Male fetus	11 (58%)	25 (61%)	0.82
Birth weight (g)	2450 (2230–3200)	3130 (2595–3420)	0.04
Admission to NICU	7 (37%)	8 (20%)	0.15

Table III. Comparison between phIGFBP-1 and cervical length assessment in 60 symptomatic women with a cervical length≤30 mm.

	Cervical length		
phIGFBP-1	<20 mm	20–30 mm	Total
Positive	7	12	19
Negative	12	29	41
Total	19	41	60

women who eventually will not deliver preterm. Therefore, there is a need for assessment tools to reliably identify cases who are at highest risk of early delivery, and those who are not and can avoid treatment. Cervical length measurement by transvaginal ultrasound and assessment of fibronectin in cervical secretion are the most extensively studied prognostic factors in cases of threatened preterm delivery [25]. Cervicovaginal fibronectin is estimated to have a positive and negative likelihood ratio of 4.10 and 0.35, respectively, in the prediction of delivery within 7–10 days, while the same values for a cervical length measurement of 15 mm are 8.61 and 0.03 [25]. However, given the clinical significance of the risk of a false negative diagnosis, i.e. the risk of not appropriately treating a pregnancy which is going to deliver within a few days, there have been various attempts to combine cervical length and fibronectin assessment in a single or two-step test, with discordant results [2,26–30]. phIGFBP-1 appears to have a similar accuracy to fibronectin, with a positive and negative likelihood ratio of 3.29 and 0.20, respectively, in the prediction of delivery within 7 days, a positive and negative likelihood ratio of 2.53 and 0.32, respectively, in the prediction of delivery within 48 hours [25]. As well as fibronectin, phIGFBP-1 is commercially available as a bed-side test, and is approximately 50% cheaper.

Some recent studies evaluated a combination of cervical length and phIGFBP-1 in the prediction of preterm delivery in symptomatic women. Eroglu et al. [15] assessed 51 cases between 24 and 35 weeks of gestation. These authors reported an increase in specificity and positive predictive value by combining phIGFBP-1 with cervical length. However, the sensitivity reported for phIGFBP-1 alone (>80%) was similar to that described by the same and other groups [10,11,17], but appreciably higher than what was reported by others [8,16] and found in our series. This variability may be explained by the small absolute number of events in each study, as well by differences in case selection criteria. Paternoster et al. [18] studied 210 women with a singleton pregnancy with documented

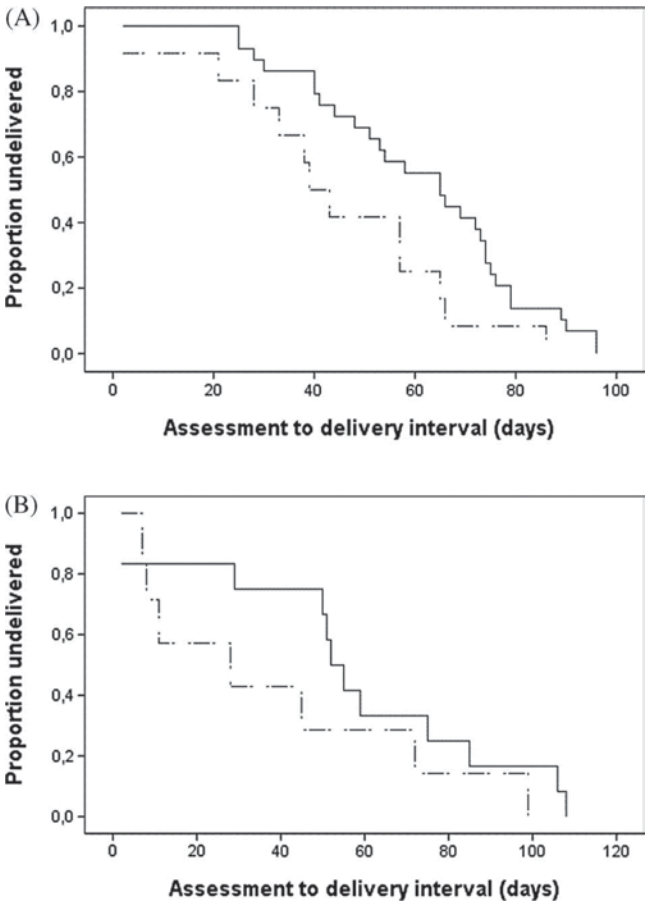

Figure 1. Assessment to delivery interval Kaplan–Meier curves according to phIGFBP-1 results in cases with cervical length of 20–30 mm (panel A) and in those with cervical length<20 mm (panel B). The difference between the curves was statistically significant in the 20–30 mm group (p=0.03) but not in the<20 mm group (p=0.25).

uterine contractions and intact membranes between 24 and 34 weeks' gestation. They found that a cervical length of<26 mm and a positive phIGFBP-1 have an odds ratio of 16 and 9 for preterm delivery before 37 weeks, respectively. Rahkonen et al. [19] examined 246 symptomatic women between 22 and 34 weeks of gestation, among which 10 (4.1%) delivered before 34 weeks. They

Table IV. Positive (LR+) and negative (LR−) likelihood ratio, sensitivity, specificity, positive predictive value and negative predictive value of phIGFBP-1 for delivery within 7 days in 60 symptomatic women with a cervical length≤30 mm.

	Cervical length≤30 mm	Cervical length 20–30 mm	Cervical length<20 mm
Delivery within 7 days (*n*)	4/60	1/41	3/19
Positive phIGFBP/delivery within 7 days (*n*)	2/4	1/1	1/3
phIGFBP-1 LR+	1.65 (0.57–4.74)	3.64 (2.20–6.01)	0.89 (0.16–4.97)
phIGFBP-1 LR−	0.72 (0.27–1.94)	0	1.07 (0.44–2.59)
Sensitivity	50% (7–93%)	100% (2–100%)	33% (1–91%)
Specificity	70% (56–81%)	73% (56–85%)	63% (35–85%)
Positive predictive value	11% (1–33%)	8% (0–38%)	14% (0–58%)
Negative predictive value	95% (83–99%)	100% (91–100%)	83% (52–98%)

Values are given with 95% confidence interval.
Results of phIGFBP-1 testing are also reported for cases with cervical length between 20 and 30 mm and<20 mm.

Table V. Positive (LR+) and negative (LR−) likelihood ratio, sensitivity, specificity, positive predictive value and negative predictive value of phIGFBP-1 for delivery before 34 weeks in 60 symptomatic women with a cervical length≤30 mm.

	Cervical length≤30 mm	Cervical length 20–30 mm	Cervical length<20 mm
Delivery before 34 weeks (*n*)	8/60	3/41	5/19
Positive phIGFBP/delivery before 34 weeks (*n*)	5/8	2/3	3/5
phIGFBP-1 LR+	2.32 (1.15–4.67)	2.53 (0.97–6.62)	2.10 (0.70–6.28)
phIGFBP-1 LR−	0.51 (0.21–1.27)	0.45 (0.09–2.27)	0.56 (0.18–1.72)
Sensitivity	63% (24–91%)	67% (9–99%)	60% (15–95%)
Specificity	73% (59–84%)	74% (57–87%)	71% (42–92%)
Positive predictive value	26% (9–51%)	17% (2–48%)	43% (10–82%)
Negative predictive value	93% (80–98%)	97% (82–100%)	83% (52–98%)

Values are given with 95% confidence interval.
Results of phIGFBP-1 testing are also reported for cases with cervical length between 20 and 30 mm and<20 mm.

found that a short cervix (<25 mm), a positive phIGFBP-1 test, and a combination of both were associated with preterm delivery ≤34 weeks or within 14 days ($p<0.01$). The negative predictive values for delivery ≤34 weeks were 97.4, 97.6, and 97.1, respectively, and within 14 days 98.7, 99.0, and 98.3, respectively.

Our study concentrated on the most clinically relevant forms of preterm delivery, i.e. those deliveries taking place within 7 days from presentation or before 34 weeks. We confirmed that the majority of pregnant women presenting with threatened preterm labor potentially undergoes unnecessary treatment as only 21% and 8% will deliver before 37 and 34 weeks, respectively, and very few will delivery within 7 days (4%). Although our results should be interpreted with caution due to the small absolute number of cases, we confirmed that a cervical length measurement>30 mm in symtpomatic women identifies a low-risk subgroup, as all these women will deliver at or very near to term, and none will deliver before 34 weeks or within 7 days (Table I). It is unlikely that the additional costs of phIGFBP-1 assay, tocolysis, or admission for observation are justified in this subgroup.

On the contrary, the assessment of phIGFBP-1 in women with threatened preterm delivery and a cervical length ≤30 mm has a low positive predictive value but a high negative predictive value for delivery within 7 days and before 34 weeks. Therefore, the use of the test may be useful to further stratify risk in the group with cervical length 20–30 mm, where ultrasound alone has a low specificity. Negative phIGFBP-1 may identify low-risk cases that can be discharged at home. In the group with a cervix<20 mm, the combination of phIGFBP-1 increases the false negative rate, so we would still recommend admitting and treating these patients. However, since the risk of delivering before 34 weeks is still lower with a negative phIGFBP-1 test as compared to a positive one (25% *vs* 14%), in phIGFBP-1 negative cases an earlier discharge from hospital may be offered (Table V).

Attention was paid to avoid any bias in phIGFBP-1 results related to the sampling methodology. The cervical rather than vaginal approach was chosen, as it was likely to provide more robust results as recently demonstrated [31]. No ultrasound gel was used on the probe cover for the transvaginal ultrasound examination, and all digital cervical examinations were performed after sampling for phIGFBP-1, as their effect on testing results is unclear. Vaginal bleeding, which may give false positive results, was a criterion for patient exclusion [31].

In our study, we also evaluated the degree of agreement between cervical length measurement and phIGFBP-1 by calculating Cohen's κ coefficient. This coefficient can vary between −1 and 1. Negative κ values express a negative association between two test results, while the theoretical maximum value of 1 is observed with perfect agreement. If the κ value is <0.6, the agreement can be regarded as poor [21,32]. We found a very low value of κ (0.08), suggesting that cervical length and phIGFBP-1 may reflect different pathways leading to the syndrome of preterm delivery. This might explain the different performance of the two tests, and justifies attempts to combine them.

The present study has several limitations. As the original assumptions obtained from the literature on phIGFBP-1 sensitivity and prevalence of preterm labor for cervical length<30 mm overestimated the findings in our population, the final sample size was underpowered, and the calculated confidence intervals for the performance parameters of each combination of phIGFBP-1 and cervical length were wide. In this study, the managing clinician was aware of cervical length measurements, but blinded to phIGFBP-1 results. This is likely to have affected the decision to use

corticosteroids and tocolysis, and consequently have influenced the final incidence of preterm delivery in the different subgroups. Finally, testing the value of the combination of phIGFBP-1 and cervical length would more appropriately require a prediction model based on logistic regression analysis, eventually validated in a prospective series. Again, our study population was too small to allow such an approach. Therefore, our preliminary results need to be confirmed in larger clinical series. However, the combined use of phIGFBP-1 and cervical length in symptomatic women might have the potential to decrease the false positive diagnoses of impending preterm delivery, allowing therefore to reduce the biological and economic costs of inappropriate treatment.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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