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FETAL FIBRONECTIN AND PHOSPHORILATED INSULIN- LIKE GROWTH FACTOR BINDING PROTEIN-1 AS PREDICTORS OF SPONTANEUS PRETERM DELIVERY

Marija Hadži-Lega[1], Ana Daneva Markova[1], Milan Stefanović[2], Vlatko Girevski[1]

The aim of the paper was to assess the combined use of cervical length, fetal fibronectin and cervical phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) in the prediction of preterm delivery in symptomatic women in the following 14 days.

Cervical length was prospectively measured in 58 consecutive singleton pregnancies with intact membranes and regular contractions at 24–36 weeks; fetal fibronectin and phIGFBP-1 were also assessed. Demographic data was evaluated (history of previous preterm delivery, history of spontaneous abortion, parity, BMI, maternal age, Islamic or Orthodox religion).

Values of all variables were evaluated (demographic data, cervical length and values of phIGFBP1 and fetal fibronectin) alone and in combination with cervical length of ≤ 15mm and more than 15 mm. PhIGFPB was positive in 30 patients (22 of them gave birth in 14 days). In women with cervical length less than 15 mm phIGFBP-1, it was positive in 9 pregnant women who were delivered in 14 days. In women with cervical length less than 25 mm phIGFBP-1 was positive in 26 patients (2 of them gave birth in 14 days). In patients with cervical length more than 25 mm phIGFBP-1 was positive in 4 patients (2 of them gave birth in 14 days). Using logistic regression we confirmed that with OR 0.117 and CI 95% (0.046-0.295) and $p<0.01$ odds for preterm birth among patients with negative test results, phIGFBP-1 was by 0.117 lower than the odds for preterm birth among patients with positive test results. Using the same test, we confirmed that with OR=14,722 (CI 95% 5.27-41.1), ($p<0.01$) cervical length less than 25 mm was a good predictor of preterm delivery in symptomatic patients.

Probability for delivery in the following 14 days in patients with positive phIGFBP-1 and cervical length≤15 mm is 0.88 or probability for not delivering in those patients is 0.12. Eighty-eight percents of patients with positive phIGFBP-1 and cervical length ≤15 mm will give birth in the following 14 days.

In symptomatic women phIGFBP-1 may significantly improve the risk assessment for preterm delivery with cervical length and help to plan subsequent pregnancy management. *Acta Medica Medianae 2014;53(3):11-18.*

Key words: *preterm labor, transvaginal ultrasound, phIGFBP-1, fetal fibronectin, sensitivity*

Ss. Cyril and Methodius University in Skopje, Medical Faculty, Clinic of Obstetrics & Gynecology, Republic of Macedonia[1]
University of Niš, Medical Faculty, Departments of Obstetrics & Gynecology, Niš, Republic of Serbia[2]

Contact: Marija Hadži-Lega
Department of Obstetrics and Gynecology
State University Hospital of Skopje
Skopje, Macedonia
E-mail: marijahadzilega@yahoo.com

Introduction

Prevention of preterm delivery is the major obstetrical challenge. This is not only due to assisted conception as increased preterm delivery rates have been demonstrated also among spontaneous pregnancies. The pathophysiology is complex and multifactorial. It was established that intrauterine infections account for approximately one third of preterm delivery cases (1-3). According to a new hypothesis, these infections are not always ascending but may be caused by pathogens present in the endometrium before conception (4). This very important suggestion may explain why cytokines in cervical fluid are associated with preterm delivery (5). A number of large databases including biological material are now available for future studies on pathophysiology (6).

Threatened preterm labor occurs in approximately 2% of pregnancies (1). However, 80% of these pregnancies will proceed to term. Standard practice is to perform examinations (usually ultrasound), administer steroids and acute tocolytics, and to hospitalize such patients.

Preterm birth may also result in low-birth weight infants, and surviving low-birth weight

infants are likely to sustain neurological sequel and development disorders such as cerebral palsy, mental retardation, and visual and auditory disorders (1,2). Research has been conducted on the clarification of causes of preterm delivery and for its prevention, and various conditions including maternal age, smoking, history of preterm delivery; cervical length and bacterial vaginitis have been reported as risk factors of preterm birth (3–9). However, threatened preterm delivery and preterm delivery requiring treatment at high-level medical facilities are increasing in Macedonia. In these circumstances, to learn about unknown factors related to preterm delivery, we carried out a study including patients diagnosed with threatened preterm delivery admitted to the Department of high risk pregnancy at University Clinic of Obstetrics and Gynecology Skopje, which is a tertiary medical organization.

The detection of phIGFBP-1-1 and fetal fibronectin with the cervical secretions of women presenting with preterm labor has been shown to be associated with an increased risk of preterm delivery (7-9).

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 phosphorylated forms (phIGFBP-1-1). 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-1-1 can be differentiated by the use of specific monoclonal antibodies (10). Consequently, the presence of IGFBP-1 can be used to detect preterm rupture of membranes (PROM) (10), while the presence of phIGFBP-1-1 in cervical secretions reflects decidual activation (7). Recently, cervicovaginal concentrations of phIGFBP-1-1 have been shown in correlation with the risk of preterm delivery (11-21). Disruption to the choriodecidual interface results in elevated levels in cervical secretions. Potentially contaminating body fluids with fFN - such as semen and urine contain only trace quantities ofphIGFBP-1 (10). A commercial bed side test kit is available to detect phIGFBP-1 and fetal fibronectin of the cervical secretions of women presenting with threatened preterm labor. The Actim Partus test (Medix Biochemica, Kauniainen, Finland) is an immunochromatographic dipstick test based on monochrome antibodies for phIGFBP-1. The test is similar to a urine pregnancy test and does not require technical expertise. The cost per test is approximately one quarter that of fFN.

Available research suggested that a negative phIGFBP-1 test would rule out imminent delivery in ~90 to 95% of patients (9,16-22). The negative predictive value (NPV) of phIGFBP-1 was therefore felt to be comparable to fFN, although there was little evidence directly comparing the two tests in the same population (21).

The purpose of the present study was to evaluate the combination of cervical length measurement and cervicovaginal phIGFBP-1-1 and fetal fibronectin in the prediction of preterm delivery within 14 days in symptomatic patients.

Methods

Population study

Fifty-eight pregnant women were eligible to join the study at the University Clinic for Gynecology and Obstetrics, Skopje, and were admitted to Department of high risk pregnancy unit with symptoms of preterm labor (symptoms of uterine activity judged by the assessing physician to be indicative of preterm labor) at 24 to 36 weeks gestation. They were recruited in period of 6 months from September 2013 till March 2014. They had the symptoms or complaints suggestive of preterm labor including uterine contractions, intermittent lower abdo-minal pain and pelvic pressure. Recruited patients had intact amniotic membranes determined by speculum examination and minimal cervical dilatation (≤ 3cm). Women were excluded if they had ruptured membranes, antepartum hemorrhage, active labor, cervical cerclage in place and suspected chorioamnionitis (defined by fever, abdominal pain, leukocytosis).

Women who gave their written informed consent were treated according to usual hospital protocol, with addition of vaginal swabs taken for phIGFBP-1-1 and fetal fibronectin. 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 (23).

In these women, a commercially available immunochromatography- based rapid strip test (Actim Partus Test; Medix Biochemica, Kauniainen, Finland) was used to detect phIGFBP-1-1 in cervical secretions. After sterile speculum introduction prior to ultrasound or digital examination, 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 specimen extraction solution (bovine albumin and protease inhibitors in 0.5ml phosphate solution) and the sample extracted by shaking for 10s. An immunochromatography dipstick was placed in the solution for five minutes before analyzing the result. The minimum detectable concentration was 10μg/ml, although a concentration of 30μg/ml was required for 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 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. 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.

After collection of the cervical sample, a transvaginal ultrasound measurement was performed using 6.5 MHz transvaginal probe according to the Fetal Medicine Foundation Criteria (24-27). The mean of three measurements was used. A digital examination of the cervix was then performed and cervical status documented according to the modified Bishop score. A 30-minute cardiotocogram was performed and uterine contractions recorded. Urine analysis was performed in all cases to exclude urinary tract infection. Tocolysis with beta mimmetics was used according to clinical protocols and steroids were administrated as appropriate.

Outcome variable was the occurrence of preterm delivery within 14 days from the day of hospital admission.

Statistical analysis

IBM SPSS Statistics 20 was used for analysis. Test for logistic regression (binary) and receiver operating characteristic curves (ROC) were used. P values of 0.05 were considered significant.

Results

The main demographic characteristics of the study population are shown in Table 1. Mean maternal age was 30,1. Mean gestational age was 31.55 at recruitment. Mean height was 164.34. Mean weight was 74.05. Mean BMI was 27.54. Out of 58 examinees, there were nine examinees with a history of previous preterm delivery. We also evaluated the number of previous spontaneous abortions, parity and smoking status, Islamic or Orthodox religion in patients with threatened preterm labor.

Values of all variables which were evaluated (demographic data, cervical length and values of phIGFBP and fetal fibronectin in combination with cervical length of ≤ 15mm and more than 15 mm) are shown in Table 2. phIGFPB was positive in 30 patients (22 of them gave birth in 14 days). In women with cervical length less than 15 mm, phIGFBP was positive in 9 pregnant women who gave birth within the next 14 days. Among women with cervical length less than 25 mm, phIGFBP was positive in 26 patients (20 of them were delivered within 14 days). In patients with cervical length more than 25mm, phIGFBP was positive in 4 patients (2 of them gave birth in 14 days).

Using a logistic regression we confirmed that with OR 0.117 and CI 95% (0.046-0.295) and p<0.01 odds for preterm birth among patients with negative test results, phIGFBP was by 0.117 lower than the odds for preterm birth among patients with positive test results. Using the same test, we confirmed that with OR=14,722 (CI 95% 5.27-41.1), p=0.009 (p<0.01) cervical length less than 25 mm was a good predictor of preterm delivery in symptomatic patients. Using statistical analysis we calculated a prediction for preterm delivery in the following 14 days, by a combination of cervical length and phIGFBP. Formula for prediction if delivery will occur in the next 14 days using cervical length <15 mm and positive phIGFBP is calculated in the following manner:

In (odds of preterm birth) = 0.186+0.829 x (actimpartus) + 1.437x (cervical length <15 mm) = 2.08

P (preterm birth) = $1/(1+e^{-(\ln(\text{odds of preterm birth})}) = 1/(1+e^{-2,08})$ =1/1+0.1249=1/1.1249=0.88.

(e –basis of the natural logarithm ($ln = log_e$), e = 2718281828459… = 2.718)

Table 1. Demographic characteristics of study population (n=58)

	Mean ±SD (range)
Maternal age (years)	30,12 ± 4.82 (20-40)
Gestation age at examination	31,55 ± 3.95 (22-36)
BMI	27.54 ± 4.93 (18,7-43,8)
Parity	n (%)
Nuliparous	13 (22,41)
Multiparous	45 (77,59)
Previous preterm delivery	10 (17,24)
Smoker	11 (18,96)

Table 2. Prevalence and rate of cervical length, pIGFBP-1 at study entry and delivery according to the outcome (n=58)

	n	%
Cervical length ≤15	14	24,1
Cervical length 15-25	23	39,6
Cervical length >25	21	36,2
pIGFBP-1 (+)	30	51,7
Delivery in <7 days	24	41,6
Delivery in 7-14 days	11	18.9

pIGFBP-1, phosphorylated insulin growth factor binding protein-1

It means that probability of delivery in the following 14 days in patients with positive phIGFBP and cervical length ≤15 mm is 0.88 or probability for not giving birth 0.12. Eighty-eight percents of patients with positive phIGFBP and cervical length ≤15 mm will give birth in the following 14 days.

Formula for prediction of delivery in the following 14 days by combination of cervical length <25 mm and positive phIGFBP 1 is calculated as:

In (odds of preterm birth) = -0.754 + 0.593x (acimpartus) + 1.399x (cervical length <25 mm) = 1.238

P(preterm birth) = $1/(1+e^{-(\ln(\text{odds of preterm birth}))}) = 1/(1+e^{-1.238}) = 0.775$

It means that probability for delivery in the following 14 days with patients with positive phIGFBP-1 and cervical length < 25 mm is 0.76 or probability for not deliveringwith thatpatients is 0.24. Thus, 76% of thepatients with positive phIGFBP-1 and cervical length < 25 mm will deliver in the following 14 days.

By logistic regression we evaluated the prediction of delivery in the next 14 days by history of previous preterm delivery. P was not significant (p=0.2) and the model worked with 62% accuracy; therefore, only the history of previous preterm delivery was a good predictor of preterm delivery in the following 14 days. We also evaluated the history of previous spontaneous abortions, parity, smoking, BMI, vaginal ph and none of them separately is a good predictor for delivery in the next 14 days (p is not significant). The addition of a positive phIGFBP to cervical length ≤15 or 25 mm improves the accuracy of the predictive value of isolated cervical length.

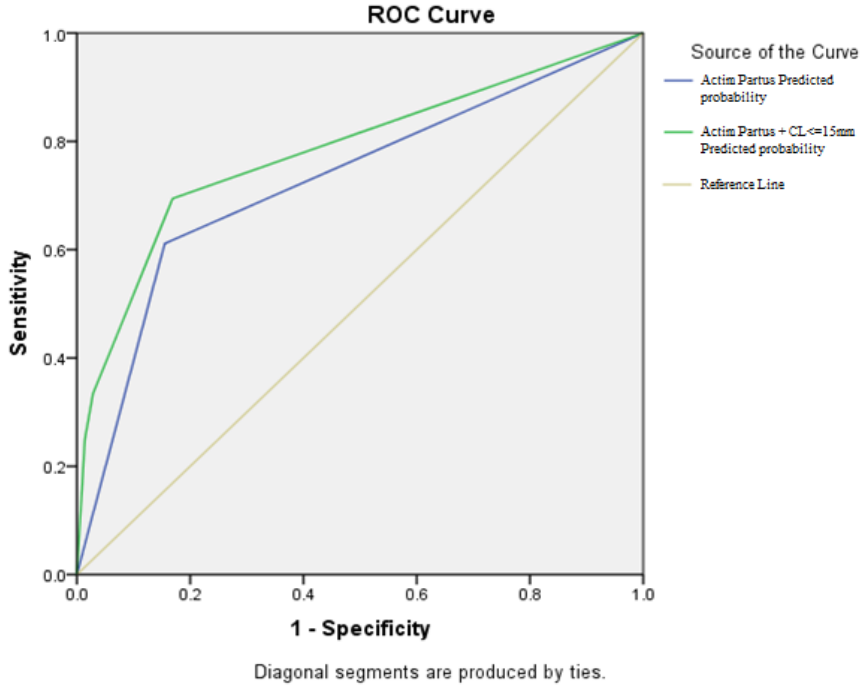

Figure 1. ROC curves for the performance of combinations in Actim partus test, length of cervix CL ≤ 15 mm as predictors of preterm birth

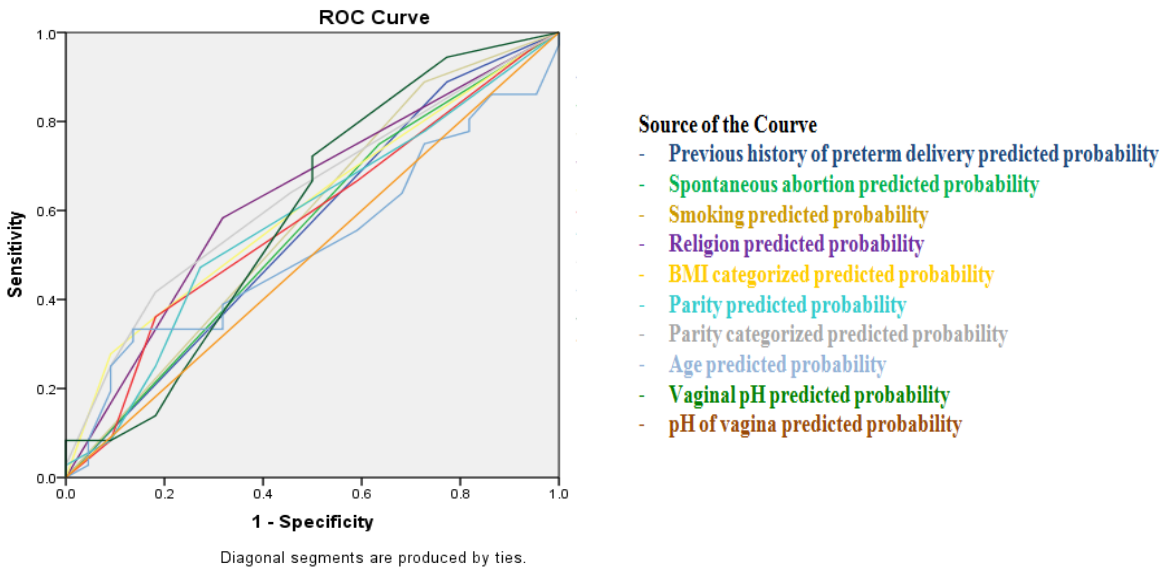

Figure 2. ROC curves for the performance of other variables tested the ability of prediction of preterm labor

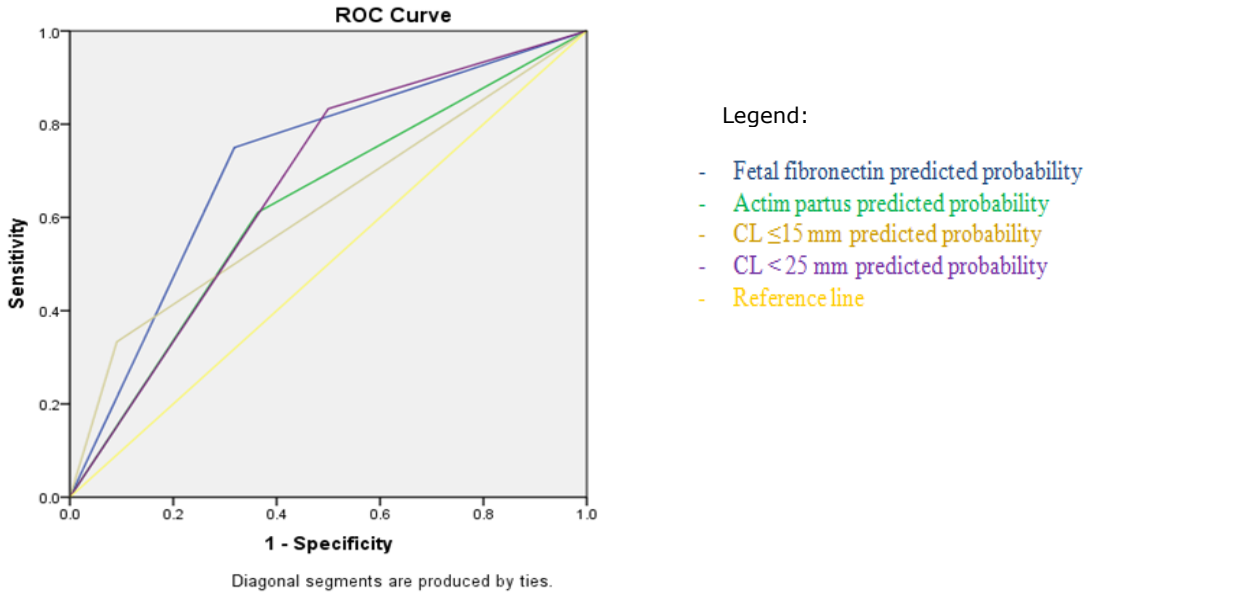

Figure 3. ROC curves for performance of fetal fibronectin, Actim partus test, length of cervix CL ≤ 15 mm and length of cervix CL <25 mm as individual predictors of preterm birth

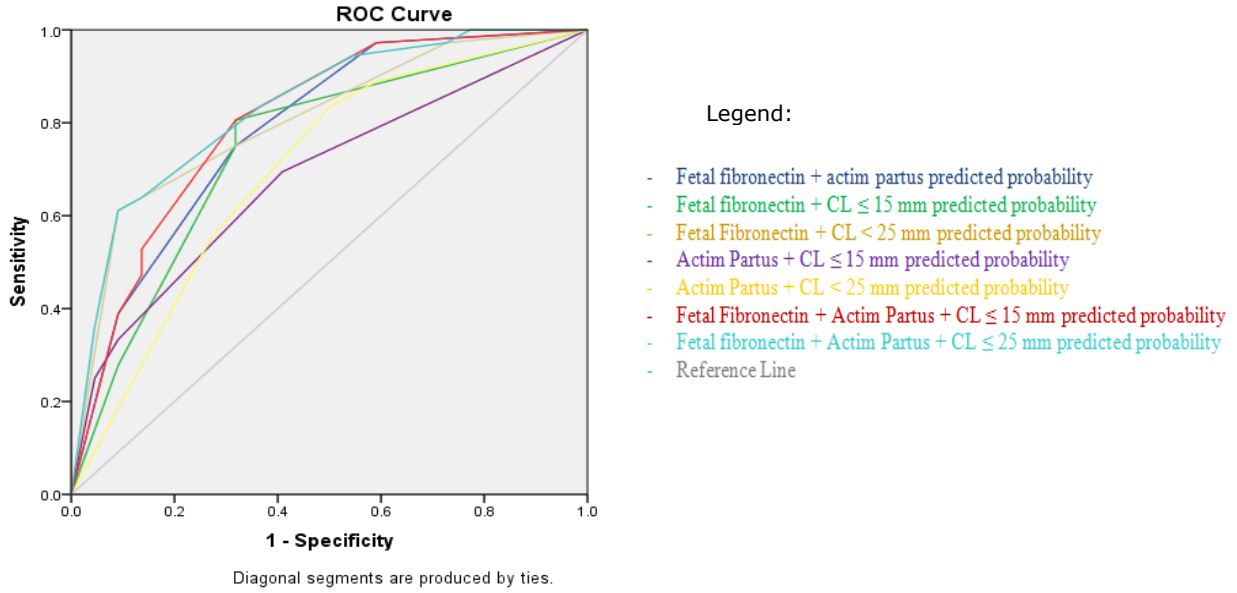

Figure 4. ROC curves for the performance of combinations of fetal fibronectin, Actim partus test, length of cervix CL ≤ 15 mm and length of cervix CL <25 mm as predictors of preterm delivery

ROC curves for using cervical length to predict delivery in the following 14 days showed a cervical length of ≤25 mm by presenting the area under the curve (AUC), with the value of 0.667(0.517-0.817, p<0.050). ROC curves were significant for cervical length ≤25 mm in prediction of delivery in the next 14 days. ROC curves for using positive phIGFBP to predict delivery in the following 14 days showed a positive phIGFBP as presenting the area under the curve (AUC), whose value was 0.624(0.474-0.773, p>0.05). ROC curves were not significant for positive phI GFBP alone as a predictor for delivery in the next 14 days. ROC curves for using cervical length ≤15 mm and ≤25 mm in combination with positive phIGFBP-1 showed the following values - 0.683(0.545-0.821, p<0.05) and 0.698(0.554-0.843, p,0.05). Therefore, both the combinations of cervical length ≤15 mm and cervical length ≤25 mm with positive phIGFBP-1 are good prediction models of delivery in the next 14 days (Figure 1).

ROC curves for other variables which were evaluated for prediction of delivery in the following 14 days (history of preterm delivery, history of spontaneous abortion, parity, BMI, ph of vagina, Islamic or Orthodox religion) showed that the area under the curve (AUC) was between 0.5 to 0.6, with p>0.05. They are not good predictors for delivery in the next 14 days (Figure 2).

Discussion

Despite advances in obstetric care, preterm delivery remains a major cause of neonatal morbidity and mortality. With women presenting an acute risk of preterm delivery, tocolysis,

steroids and in utero transfer to a center with neonatal intensive care are recommended (28). This involves unnecessary treatment and complex management in a relevant number of symptomatic women who eventually will not deliver prematurely. 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 (29). 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 (29). However, given the clinical significance of the risk of a false negative diagnosis, i.e. the risk of not appropriately treating a pregnancy which will be completed 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 (4,30-34). 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 (29). As well as fibronectin, phIGFBP-1 is commercially available as a bed-side test, and is approximately by 50% cheaper.

Some recent studies have evaluated a combination of cervical length and phIGFBP-1 in the prediction of preterm delivery in symptomatic women. Eroglu et al. (17) 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 authors (9,13), but appreciably higher than reported by some other authors (8,18) and the one 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. (20) studied 210 women with a singleton pregnancy with documented uterine contractions and intact membranes between 24 and 34 weeks' gestation. They found that a cervical length of d <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. (21) examined 246 symptomatic women between 22 and 34 weeks of gestation, among which 10 (4.1%) gave birth before 34 weeks. They found that a short cervix (<25 mm), a positive phIGFBP-1 test, and a combination of both were associated in 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 14 days from presentation. We confirmed that the majority of pregnant women presenting with threatened preterm labor potentially undergoes unnecessary treatment and a few of them will be delivered within 14 days (only 36). PhIGFBP alone is not a good predictor for delivery in the next 14 days, however, a combination of cervical length (≤15 mm,≤25mm) with phIGFBP is a good predictor. It means that probability for giving birth in the following 14 days in patients with positive phIGFBP and cervical length≤15 mm is 0.88 or probability for not giving birth in those patients is 0.12. Eighty-eight percents of patients with positive phIGFBP and cervical length ≤15 mm will be delivered in the following14 days.

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 (24). 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. The patients with vaginal bleeding were excluded from the study due to possible false positive results (21).

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.

Conclusion

Finally, testing the value of the combination of phIGFBP-1 and cervical length allow us to find a prediction model based on logistic regression analysis. Again, our study population was too small to allow such an approach. However, the combined use of phIGFBP-1 and cervical length with symptomatic women might have the potential for decreasing the false positive diagnoses of impending preterm delivery, allowing therefore to reduce the biological and economic costs of inappropriate treatment.

Other demographic data (history of previous preterm delivery, history of spontaneous abortion, parity, BMI, Islamic or Orthodox religion), vaginal Ph are not good predictors of delivery in the following 14 days.

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FETALNI FIBRONEKTIN I FOSFORILOVANI INSULINU SLIČAN FAKTOR RASTA-PROTEIN 1 KAO PREDIKTORI SPONTANOG PREVREMENOG PORODAJA

Marija Hadži-Lega, Ana Daneva-Markova, Milan Stefanović, Vlatko Girevski

Cilj rada bio je da se proceni kako kombinacija dužine cerviksa, fetalnog fibronektina i cervikalnog fosforilovanog insulinu sličnog faktora rasta–protein 1 (phIGFBP-1) utiče na predviđanje prevremenog porođaja kod simptomatskih trudnica u roku od 14 dana.

Dužina cerviksa je prospektivno merena kod 58 jednoplodnih trudnoća, sa očuvanim membranama i regularnim kontrakcijama u periodu od 24. do 36. gestacijske nedelje; takođe su procenjivani i fetalni fibronektin i phIGFBP-1. Analizirani su i demografski podaci: istorija prethodnih prevremenih porođaja, istorija spontanog abortusa, paritet, BMI, starost majke, verska pripadnost – pravoslavna ili muslimanska.

Vrednosti svih varijabli bile su procenjene (demografski podaci, dužina cerviksa, kao i vrednosti phIGFBP-1 i fetalnog fibronektina) pojedinačno i u kombinaciji sa dužinom cerviksa ≤ 15 mm i iznad 15 mm. Vrednost PhIGFPB bila je pozitivna kod 30 trudnica (22 trudnice su se porodile u narednih 14 dana). Kod trudnica sa dužinom cerviksa manjom od 15 mm, vrednost phIGFBP-1 bila je pozitivna kod 9 trudnica koje su se porodile u roku od 14 dana. Kod trudnica sa dužinom cerviksa > 25 mm, vrednost phIGFBP-1 je bila pozitivna kod četiri trudnice (dve trudnice su se porodile u narednih 14 dana). Primenom logističke regresije potvrđeno je da je sa vrednostima OR 0.117 i CI 95% (0.046-0.295) i $p<0.01$ za prevremene trudnoće kod trudnica sa negativnim rezultatima testa vrednost phIGFBP-1 bila za 0.117 niža u poređenju sa izgledima za prevremeni porođaj kod trudnica sa pozitivnim rezultatima testa. Primenom istog testa potvrđeno je da je sa vrednostima OR=14,722 i CI 95% (5,27-41.104) i $p=0.009$ ($p<0.01$) cervikalna dužina ispod 25 mm bila dobar prediktor prevremenog porođaja kod simptomatskih trudnica.

Verovatnoća za porođaj u narednih 14 dana kod trudnica sa pozitivnom vrednošću phIGFBP-1 i dužinom cerviksa ≤15 mm iznosila je 0.88, odnosno 0.12 da se porođaj ne desi. Pozitivna vrednost phIGFBP-1 i dužina cerviksa ≤15 mm odredila je porođaj u roku od 14 dana kod 88% ispitanica.

Kod simptomatskih trudnica phIGFBP-1 može značajno da poboljša procenu rizika za prevremeni porođaj sa podatkom o dužini cerviksa i da pomogne u planiranju daljeg toka trudnoće. *Acta Medica Medianae 2014;53(3):11-18.*

Ključne reči: *prevremeni porođaj, transvaginalni ultra zvuk, phIGFBP-1, fetalni fibronektin, senzitivnost*