Prediction of preterm birth with different biochemical markers and cervical length

Hadži-Lega M.[1], Daneva Markova A.[1], Stefanovic M.[2], Girevski V.,[1] Sterjovska-Aleksovska A.[3]

[1] University Clinic of Obstetrics & Gynecology, Medical Faculty, Ss. Cyril and Methodius University, Skopje, R. Macedonia

[2] Departments of Obstetrics & Gynecology, Medical Faculty Nis, R. Serbia

[3] Faculty of Medical Sciences, University Goce Delcev, Stip, R. Macedonia

Introduction

Preterm labor and delivery is a multifactorial entity that has serious medical, health-related, economical and personal implications. Its worldwide incidence ranges from around 5%-15%, depending on the population. Over half of the preterm deliveries are spontaneous. The worldwide rates of preterm birth have increased in the past couple of decades in spite of the efforts to alleviate the problems associated with preterm delivery and the medical advances made. Preterm deliveries and associated complications account for over 75% of the neonatal mortality rates and for around half of the neurological sequalle in newborn children.

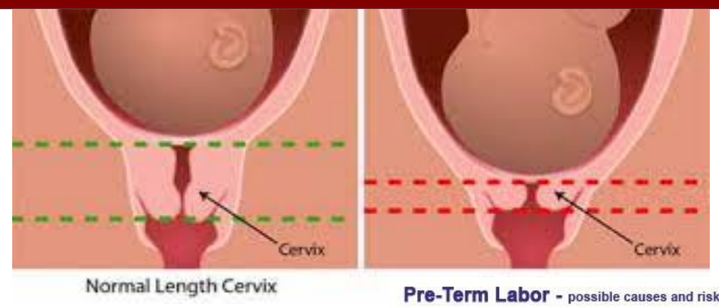
Aim

The primary aim of the thesis was to evaluate the most important biochemical markers (fFN, ph-IGFBP-1, IL-6, IL-2R, TNF-α), ultrasonographically measured cervical length, as well as different combinations of markers in the prediction of preterm birth within 14 days of testing in women with symptoms of preterm labor. The study also evaluated the maternal risk fatctors, the demographic and socio-economic characteristics of pregnant women at risk of preterm labor in Macedonia. We also made an effort to describe the most successfull prediction model that foresees preterm labor within 14 days of testing in symptomatic pregnant women.

Materials and methods

The study was conducted as a prospective study at the University Clinic of Gynecology and Obstetrics, University "Ss. Cyril and Methodius" in Skopje Macedonia. The study included 58 women with singleton pregnancies with a menstrual age between 24 and 36+6 gestational weeks, admitted at the Clinic with a diagnosis of preterm labor defined as uterine contractions and/or changes in the consistency of the cervix (shortening, dilatation and ripening), as well as a control group of 49 pregnant women with signleton pregnancies with a menstrual age between 22 and 36+6 gestational weeks that did not have symptoms of preterm labor. After obtaining informed consent fot participation form every patient, we took a detailed history, performed tocography and did a speculum exam to obtain test specimens for fFN, ph-IGFBP-1, IL-6, IL-2R, TNF-α and did blood draws to determine the adequate serum concentrations of the respective markers. We also took vaginal and cervical specimens and urine for microbiological cultures, determined the vaginal pH and measured the cervical length with transvaginal ultrasound.

The obtained data was digitized, and all statistical tests were performed using SPSS version 13.0. We used descriptive statistical analysis to display the following parameters: mean, standard deviation, coefficient of variation, interval of varioation. The categorical variables were tested using Chi square and Fischer exact tests, and the quantitative variables were analyzed with the independent sample test and Mann-Whiteney's U test. to determine the corelation between the variables we used Spearman Rank Orded Correlation test and Pearson's coefficient of linear correlation. We used binary logistic regression to determine the predicitve role of the analyzed parameters in the prediction of preterm labor.



Normal Length Cervix

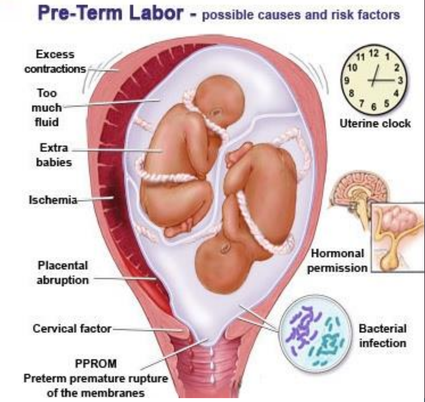


Table 1 Prediction of preterm birth with biochemical markers and cervical length

Combination of predictors	Area Under the Curve (AUC) 95% CI	P (preterm birth)
Actimpartus and Fetal fibronectin	0,799 95% CI (0,677-0,921)	0,94
Cervical length and Fetalfibronectin	0,784 95% CI (0,663-0,906)	0,526
Actimpartusand Cervical length	0,705 95% CI (0,566-0,843)	0,613
Actimpartus, Fetalfibronectinand Cervical length	0,830 95% CI (0,718-0,941)	0,69
Cervicallenghtand IL-6 in cervix	0,751 95% CI (0,624-0,878)	0,57
Fetalfibronectinand IL-6 in cervix	0,759 95% CI (0,610-0,908)	0,867
Fetalfibronectin, ActimpartuswIL-6 in cervix	0,823 95% CI (0,697-0,948)	0,774
Fetalfibronectin, Actimpartus andIL-6 in cervix and cervical lenght	0,850 95% CI (0,741-0,960)	0,9396
Fetalfibronectin, Actimpartus, IL-6 in cervix, cervical lenghtand CRP	0,867 95% CI (0,769-0,966)	0,9853
Fetalfibronectin, Actimpartus, IL-6 in cervix, cervical lenght,CRPand IL-2 in serum	0,912 95% CI (0,837-0,987)	0,995

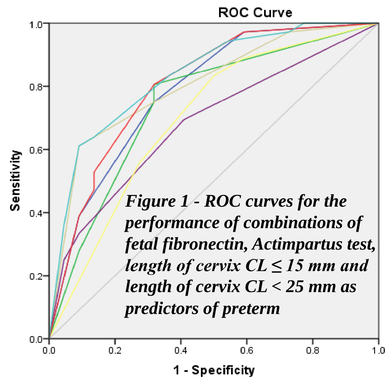


Figure 1 - ROC curves for the performance of combinations of fetal fibronectin, Actimpartus test, length of cervix CL ≤ 15 mm and length of cervix CL < 25 mm as predictors of preterm

Diagonal segments are produced by ties.

- **Fetal fibronectin + actimpartus predicted probablity**
- **Fetal fibronectin + CL ≤ 15 mm predicted probablity**
- **Fetal Fibronectin + CL < 25 mm predicted probablity**
- **ActimPartus + CL ≤ 15 mm predicted probablity**
- **ActimPartus + CL < 25 mm predicted probablity**
- **Fetal Fibronectin + ActimPartus + CL ≤ 15 mm predicted probablity**
- **Fetal fibronectin + ActimPartus + CL ≤ 25 mm predicted probability**

Table 1 shows the values of the Area Under the Curve with 95% confidence interval and the calculated values for prematurity - P (preterm birth) for different combinations of clinical and biochemical markers as predictors of preterm labor. It notes that the best predictor is combination test of Fetal fibronectin, test Actim partus, the concentration of IL-6 in cervical fluid, cervical length less than 21.5 mm, the concentration of CRP and IL-6 in serum. The likelihood of premature delivery in this case is 0.995, which shows that 99.5% of pregnant women admitted with signs and symptoms of spontaneous preterm delivery in the next 14 days will have delivery.

Both the AUC value for this combination of predictors is greatest - 0.912 95% CI (0,837-0,987), indicating that this combination of predictors classifies premature births than those whose delivery occurs at term.

Table 2 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)
n (%)	
Parity	
Nuliparous	13 (22,41)
Multiparous	45 (77,59)
Previous preterm delivery	10 (17,24)
Smoker	11 (18,96)

Results

The average age of the included patients in this study was 30.15±4.8, ranging from 20 to 40 years. Our data did not point out significant association betweeen the age of the patient, her nutritional status evaluated through BMI, her religious beliefs and history of previous abortions and/or misscarriges and an increased risk of preterm labor and delivery.

We documented a significantly higher serum concentrations of CRP in patients that delivered within 14 days of admittance, when compared with patients that remained pregnant after this period. The univariate analysis of serum concentration of CRP as a test for predicting preterm delivery gave a sensitivity of 69.4%, specificity of 72.7%, PPV 81%, NPV 59%, LR+ 2.54, LR- 0.42 and AUC of 0.756.

IL-6 concentrations in the cervico-vaginal secretion gave similar results. The univariate analysis of cervico-vaginal secretion IL-6 gave a sensitivity of 69.4%, specificity of 68.2%, PPV 78.1%, NPV 57.69%, LR+ 2.18, LR- 0.45 and AUC of 0.759. Determining the serumconcentratios of IL-6, according to our data, had no diagnostic use in the prediction of preterm labor and delivery.

We also found significant diffrences in the serum concentrations of IL-2R in patients that delivered within 14 days of admittance, when compared with patients that remained pregnant after this period. The test had a sensitivity of 69.4%, specificity of 68.2%, PPV 78.12%, NPV 57.7%, LR+ 2.18, LR- 0.45 and AUC of 0.688.

The patients that delivered within 14 days of admittance also had a significantly higher rate of phIGFBP-1 isolation in the cervico-vaginal secretion. The test was a significant predictor of preterm labor with a sensitivity of 66.7%, specificity of 63.6%, PPV 75%, NPV 54%, LR+ 1.83, LR- 0.52 and AUC of 0.652.

The fFN test in our population performed slighlty less optimaly than expected with a sensitivity of 75%, specificity of 68.2%, PPV 79% and a NPV of 62.5%.

We achieved the best rate of preterm labor prediction when combining the actim partus test, a positive fFN test, cervical length less then 21.5mm, levels of IL-6 higher than 1305 pg/mL in the cervico-vaginal sectretion, serum levels of CRP higher than 6.1mg/L which gave the combined test a sensitivity of 88.9%, specificity of 77.3%, PPV and AUC of 0.912 and a prediction rate of 99.5% in our studied population.

Conclusion

The best statistical model for predicting preterm labor in our study was to use a combination of the actim partus test, a positive fFN test, cervical length less then 21.5mm, levels of IL-6 higher than 1305 pg/mL in the cervico-vaginal sectretion, serum levels of CRP higher than 6.1mg/L which was excellent at identifying the patietns that were to deliver within 14 days of admittance. However, the study is only the begining of this type of research in our population. Further research is required in terms of the evaluation of cost-benefit of using such test to prevent subsequent uncecessary interventions in the low-risk group, as well as achieve the benefits from such intervention in the high-risk groups of patients.

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