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137 Harley Street, London, W1G 6BG, UK

Tel: +44 (0) 207 034 3070

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Prediction of preterm birth with different biochemical markers and cervical length

Hadži-Lega M, Daneva-Markova A, Stefanovic M, Girevski V, Sterjovska-Aleksovska A

University Clinic of Obstetrics & Gynecology, Medical Faculty, Skopje, R. Macedonia, Departments of Obstetrics & Gynecology, Medical Faculty, Nis, R. Serbia, Faculty of Medical Sciences, University Goce Delcev, Stip, R. Macedonia

Objective

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 sequels in newborn children. 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 factors, 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 successful prediction model that foresees preterm labor within 14 days of testing in symptomatic pregnant women.

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 singleton pregnancies with a menstrual age between 22 and 36+6 gestational weeks that did not have symptoms of preterm labor. After obtaining informed consent for participation from 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 variation. 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-Whitney's U test. To determine the correlation between the variables we used Spearman Rank Order Correlation test and Pearson's coefficient of linear correlation. We used binary logistic regression to determine the predictive role of the analyzed parameters in the prediction of preterm labor.

Results

The average age of the included patients in this study was 30.15 \pm 4.8, ranging from 20 to 40 years. Our data did not point out significant association between the age of the patient, her nutritional status evaluated through BMI, her religious beliefs and history of previous abortions and/or miscarriages and an increased risk of preterm labor and delivery. We documented 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. According to our data, determining the serum concentrations of IL-6 had no diagnostic use in the prediction of preterm labor and delivery. We also found significant differences 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 slightly less optimally 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 than 21.5mm, levels of IL-6 higher than 1305 pg/mL in the cervico-vaginal secretion, 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 than 21.5 mm, levels of IL-6 higher than 1305 pg/mL in the cervico-vaginal secretion, serum levels of CRP higher than 6.1mg/L which was excellent at identifying the patients that were to deliver within 14 days of admittance. However, the study is only the beginning 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 unnecessary interventions in the low-risk group, as well as achieve the benefits from such intervention in the high-risk groups of patients.