Original Article

ACCURACY OF PHOSPHORYLATED INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN-1 IN PREDICTING PRETERM LABOUR

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Summary

Preterm birth is the most common cause of perinatal morbidity and mortality worldwide. The routine method for predicting premature birth is the measurement of the cervical length. However, to make a better and more precise prognosis, the cervicovaginal fluid (CVF) was widely inspected through many studies. Its content is used nowadays as a diagnostic method for different conditions. One of the clinical biomarkers used to predict preterm labour in the CVF is the phosphorylated insulin-like growth factor binding protein-1 (pIGFBP-1). This study aimed to evaluate the accuracy of pIGFBP-1 as a predictor of preterm labour when used with cervical biometrics.

A prospective, cross-sectional study was conducted on pregnant patients, divided into groups: Group A included participants at risk for premature labour, and Group B - women with an uncomplicated pregnancy. All patients underwent a test for pIGFBP-1, followed by a transvaginal measurement of the cervical length.

A total of 32 patients were recruited for the study. Their pregnancy outcomes were followed up. In the group of symptomatic patients, the results were positive in 8 patients, and despite the intensive tocolytic therapy given, 5 of them gave preterm birth within 14 days. There were two patients with a cervical length of less than 10 mm. They both had positive results for pIGFBP-1 and gave spontaneous preterm birth within a few hours. The predictive value of pIGFBP-1 in cases with negative results was high.

The leading cause for fetal morbidity and mortality in the twenty-first century remains premature delivery. Many investigations are currently carried out, aiming to facilitate preterm labor prediction and quickly estimate a pregnant woman's ability to carry to time. The patients at highest risk are detected by measuring the cervical length. Newly searched clinical biomarkers such as fetal fibronectin found in the CVF might help predict preterm birth in time.

Keywords: preterm labour, cervicovaginal fluid, pIGFBP-1, cervical length, premature delivery

Introduction

Preterm birth is the most common cause of perinatal morbidity and mortality worldwide. In 2014, 14 835 606 babies were born before the 37th complete gestation week, i.e., approximately 10.6% of all live births [1]. Despite all the efforts to decrease the rate of premature labour, the results are not satisfactory.

According to the WHO Global Preterm Birth Estimates, the percentages of premature labour are slightly increasing irrespective of the screening programs that are promoted worldwide [1].

The etiology of preterm labour is extensively studied, and part of it has been elucidated. There are many risk factors known, and, in some cases, more than one persists. Some factors are well studied and documented, such as infections, cervical insufficiency, vascular or placental dysfunction, while others are not fully understood. The main factor from history is a previous preterm delivery.

Whatever the cause is, the terminal pathway that unlocks the entire process of premature labour is the same: the membranes are activated, the uterine contractility is increased, and cervical dilation and effacement are started.

The main method for predicting premature labour is measuring the cervical length. One of the most used nomograms is the one by Monsoura [2]. During every examination, there are five criteria to be looked for: cervical length, measured on the line passing through the cervical canal that is hypoechogenic compared to the cervical walls, the diameter of the internal opening of the cervical canal, the width of the cervix around the internal opening of the cervix, the width of the front uterine wall where the lower uterine segment is located, the angle between the cervix, and the posterior uterine wall. The following ultrasound findings are specific for patients with cervix insufficiency, who are more likely to give premature birth: cervical length less than 25 mm, obtuse posterior angle – more than 90º, and a diameter of the internal opening of the cervix more than 6 mm.

The cervicovaginal fluid (CVF) was widely inspected in many studies [3,4,5,6]. The most commonly used clinical biomarker test in predicting preterm labour in the CVF is fetal fibronectin (fFN), which is also officially approved by the FDA. Another biomarker with potential future use in everyday practice is the phosphorylated insulin growth factor binding protein 1.

Phosphorylated insulin growth factor binding protein-1 (pIGFBP-1) is a protein produced by the decidua. Once the membranes are activated, and the process of labour has started, small parts of the decidua drop down to the cervix and can be abnormally found in the CVF.

Non-phosphorylated and phosphorylated IGFBP-1 has been detected and tested during pregnancy. Non-phosphorylated IGFBP-1 (npIGFBP-1) is thought to be found in high concentrations in the amniotic fluid, so its presence in cervical vaginal secretion may indicate a premature rupture of the amniotic sac. The role of phosphorylated IGFBP-1 (pIGFBP-1) as a predictor of preterm birth has been studied and is assumed to predict cervical maturation.

Many studies on the adequacy of pIGFBP-1 for predicting premature labour have reported a sensitivity ranging from between 80 to 90 % and a comparable specificity of 75 – 90 % for a 10% screen-positive rate. The results were highly prognostic in symptomatic patients, indicating the onset of preterm birth within an interval of 7 to 14 days after the test was performed. Other authors have also reported that IGFBP-1 has a high prognostic value in symptomatic patients, predicting preterm birth within 7 to 14 days [7,8].

Materials and Methods

A prospective, cross-sectional study was conducted on pregnant patients divided into two groups: Group A included 20 participants at risk of premature labour and Group B - 12 women with an uncomplicated pregnancy. All these 32 patients were admitted to the Clinic of Obstetrics and Gynecology at the University Hospital – Pleven, Bulgaria, where they underwent a pIGFBP-1 test and ultrasound measurement of the uterine cervix. After informed consent from the patients, their demographic data was collected using a questionnaire designed for the study's needs. The Medical University Pleven, Bulgaria, funded the study, and the full study protocol was approved by the Ethics Committee.

The test for pIGFBP-1 was performed on the pregnant women studied at 18 to 22 weeks' gestation. The inclusion criterion for group A was the presence of at least one of the following symptoms: uterine contractions, abdominal pressure, and vaginal discharge. Group B were patients admitted to the clinic for routine examinations, not related to threatened preterm birth, without any symptoms, and with no change in the cervical status on examination. According to the test requirements, patients with leakage of amniotic fluid before the test were excluded from the study. So were the patients with vaginal bleeding or/and with more than 3 cm cervical dilation.

All patients had a test of pIGFBP-1 performed with Actim Partus for a rapid qualitative examination of phosphorylated insulin growth factor binding protein 1 in cervicovaginal secretion with high-sensitivity immunochromatographic test strips. In this test, the values above 10 μg/l are considered significant. At this stage, the test is only available for in vitro diagnosis. All the requirements for performing the test by the producer were observed. The test was followed by transvaginal measurement of the cervical length according to the Fetal Medicine Foundation's guidelines. The results of the pIGFBP-1 test were blinded, and tocolytic and corticosteroid therapy was administered to all the patients from Group A, according to the clinic's protocol.

Results

A total of 32 patients were recruited for the study. Their pregnancy outcomes were followed up, and there were no difficulties in obtaining information about the outcomes in patients who gave birth in another unit.

We found a link between the pIGFBP-1 expression and the occurrence of preterm birth (Cramer's V = 0.441). This gene's appearance is related to a marked increase in the prevalence of premature labor, and its negative expression is linked to an increase in the number of term births.

Assessment of the results of pIGFBP-1 appearance as a preterm birth predictor revealed a low sensitivity of 56% and a sufficient accuracy of 78%.

Binary logistic regression analysis was made to establish the indicators' connection to premature birth incidence and evaluate both individual and combined aspects of their impact. The parameters tested as possible contributing factors were the pIGFBP-1 expression, history of risk factors, complaints during pregnancy, and cervical length. The analysis results demonstrated that all four studied indicators were significantly correlated with the risk of premature birth. A cervical length of ≤ 25.6 mm had the highest association-related in those with greater values, with an about 30 times higher risk of premature birth. The positive expression of pIGFBP-1 ranked second: the risk of premature birth elevating to 8.3 times higher than those who had a negative expression. Complaints presented during pregnancy related to about 5.5 times greater risk, and prior history of risk factors was related to 2.4 times higher premature birth risk.

The data available on pIGFBP-1 expression gathered from 32 patients was insufficient to initiate a regression model, bearing in mind the combined effect of the analyzed four indicators (OR = 0.39).

Discussion

Premature delivery remains the leading cause of fetal morbidity and mortality in the twenty-first century. Many investigations are currently focused on predicting preterm labour, and the ability of a pregnant woman to carry to time is quickly determined. Patients at the highest risk are detected by measuring the cervical length. Newly studied clinical biomarkers such as fetal fibronectin and pIGFBP-1 detected in the CVF might help to predict preterm birth at a particular time ahead.

A study on more than 60 000 singleton pregnancies found a significant effect from using a combination of obstetrical history and cervical length measurement: the reported detection rate for extreme preterm birth was 80% for a 10% screen-positive rate [10]. This was later implemented in the Fetal Medicine Foundation's protocols for routine practice in antenatal care, in combination with progesterone application [9].

One of the extensive studies proposed a protocol for management of the Fetal Medicine Foundation, suggesting routine use of cervical biometrics at 16th gestation week and further follow-up, combining the patient's history and progesterone therapy, when necessary [10].

The Society of Maternal-Fetal Medicine proposed a protocol for predicting premature labour, including routine transvaginal cervical measurement in the second trimester in combination with the history of a previous pregnancy. All the practitioners following this protocol have received a special training to follow the specific guidelines [10].

The American College of Obstetricians and Gynecologists recommend cervical measurement by transvaginal ultrasound during each routine examination and, if necessary, testing for biomarkers to decide on further treatment [11].

According to current research on preterm rates and outcomes in Pleven, 139 babies were born in 2018 before the 37th week of gestation. Of these, 11.5% could not survive the severe complications and passed away; 20.1% have health problems associated with prematurity. Only 68.4% are healthy but still at risk for late complications [12]. Irrespective of these results, there is currently no adequate protocol for predicting and preventing premature births.

Of the patients we studied, 23.8% had undergone IVF procedures, 30.2% had had a previous loss of a pregnancy, and their pregnancies were more than valuable. According to the official certification programs, the number of obstetricians performing routine transvaginal measurement of the cervical length in the region is less than 5%. Yearly, nearly 2000 babies are born in this region, i.e., 2000 pregnancies cannot receive the standard level of care such as screening protocols for predicting preterm birth that is recommended by official international professional societies.

Therefore, we suggest that elements of those models be included in everyday practice. Our results are based on investigations of a small group. However, many more studies can be reported that clearly state the effectiveness of these protocols, suggesting proper scanning of pregnant women for preterm delivery prediction. We strongly believe this is the right way to change the number of preemies born every day worldwide and the health complications associated with premature birth.

Conclusion

In modern obstetrics, the problem of premature delivery cannot be considered as unmanageable. It is of huge importance to find new methods for preterm birth screening or improve on the investigations. According to most studies, the more markers are included in a protocol, the more accurate the prognosis is, the higher the specificity is, and the higher the chance for better pregnancy outcomes.

The perfect management steps for predicting preterm labour are still unknown, and there is more to be researched. The efforts should probably be directed on identifying the women about to deliver preterm and postpone the labour as long as needed for a transfer to a unit capable of providing effective preterm neonatal care. At the same time, use corticosteroids for stimulating lung maturation. For this purpose, the testing of fetal fibronectin and/ or pIGFBP-1 is highly sensitive and specific when combined with cervical biometrics. This gives us the grounds to promote and advocate for implementing these methods in routine practice to lower the preterm birth rate and all its effects on fetal morbidity and mortality.

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