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Predicting Preterm delivery by Measuring plasma Fibronectin Concentration

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Abstract

Preterm delivery is the most prevalent cause of fetus mortality and has considerable social and psychological effects for the family as well as the society. Sometimes, the reasons of preterm delivery are unknown. The influential factors, their prediction and prevention are not profoundly realized. Recognizing women who are at risk of preterm delivery is the first effective step in preventing preterm birth. We aimed to determine the diagnostic value of plasma concentration of fibronectin in diagnosing preterm delivery. This case-control study was conducted on79 pregnant primigravida women who were in their 24-34 weeks of gestation. The women were selected by simple sampling and divided into three groups. Medical, demographic, and midwifery data were studied along with the measurements of fibronectin plasma level. Data were analyzed using SPSS software. Kruskal-Wallis and Mann-Whitney tests and the ROC diagram were used as appropriated. $P<0.05$ was considered as statistically significant. The mean (±SD) plasma fibronectin level was 1320 (±547) Mg/ml in the women with pretermdelivery and708 (±301) ng/mlin those with term delivery($P<0.001$). Based on ROC diagram, the best cut-off point for fibronectin concentration in predicting pretermdelivery was determined as 700.The sensitivity, specificity, positive predicting value, and negative predicting value for this test were 100%,61.1%,54.3%, and 100%, respectively. Fibronectin plasma level in women with preterm delivery was significantly higher than those with term delivery. Considering the high sensitivity of the cut-off point, this test could be regarded as a screening test for diagnosing pretermdelivery due to its accuracy and ease.

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Introduction

Pretermdelivery is a medical complication and an insoluble health care issue [1]. Pretermdelivery is defined as delivery before 37 completed weeks of gestation and/or less than 259 days from the mother's last menstruation [2,3,4] with anestimated prevalence of 10% worldwide [5,6,7]. Preterm birth is one of the main causes of complications such as mental disabilities, deafness, low IQ, gastrointestinal and cardiovascular disorders, even during adolescence [8, 9, 10, 11, 12]. Taking care of preterm or low-weight infants imposes asocial burden on the families as well as the healthcare system. During the first year of life, $1900 is spent for each term infant (37-40weeks) with a normal weight, $15000 for a preterminfant (< 37 weeks) weighing≤ 2500 grams, and $32000 for a preterm infant weighing<1500 grams [10, 11].

Since the reasons of preterm pregnancy are still unknown [13,14] and because of its diverse risk factors, diagnosis of the women who are at risk of preterm delivery could be the first step in preventing this complication [15]. In fact, timely diagnosis of such patients is of utmost importance; so that the usual treatments can be performed just for those who are in True labor [16].

The vast variety of diagnostic tools in this field includes cervixeffacementand dilatation evaluation, cervix activity monitoring by dynamometers, cervix ultra sonography along with diagnosing the gestational age, evaluating cervical length using abdominalsonography or preferably vaginal sonography, salivaryestriol, and fetalfibronectin. Nonetheless, none of the mentioned tools were effective in predicting pretermdelivery. Consequently, biological markers are also used in order to estimate the risk of preterm delivery in high risk women.

One of the effective factors in predicting preterm delivery is plasmafibronectin levels. This glycoprotein micro molecule with an approximately heavy molecule weight plays an important role as molecular-biological glue in adhering the chorion to menstruation desidue and leads to the consistency of pregnancy sac in the endometrium during pregnancy [17, 18]. Moreover, vascular endothelium, inflammation factors, and many of their mediators have a leading role in producing and releasing the changes in plasma fibronectin levels [19, 20].

Researchers have confirmed the effect of vascular lesions and failed physiological conversion of maternal spiral arteries on pretermdelivery [21]. Fibronectin also plays a critical role in the onset and progression of the delivery process [22].

Considering that vascular damages and inflammatory factors influence the fibronectin plasma levels, it is logical to relate the onset of preterm delivery to increased plasma levels. Studies have revealed that the amount of plasma fibronectin has a descending trend during pregnancy and it increases often weeks and months before the occurrence of pregnancy complications such aspreterm, preeclampsia, andintrauterine growth restriction (IUGR) [23]. However, a limited number of studies have been conducted on the relationship between plasma fibronectin and pretermdelivery and none have used the enzyme-linked immune-sorbent assay (ELISA) in order to assess the plasma fibronectin concentration for predicting preterm delivery.

We aimed to determine the diagnostic value of plasma concentration of fibronectin in diagnosing preterm delivery and to compare the fibronectin plasma levels in preterm and immature delivery among primigravida women with or without the risk of preterm delivery. We hope to use the results of this study along with other findings in this field to tangibly and reliably predict and diagnose pretermdelivery.

Subjects and Methods

In this case-control study, 90 primigravida women were randomly selected using simple sampling method. The sample size was calculated to be 30 in each group assuming a confidence interval of 95% and a power of 80%. The women were admitted to the prenatology and labor wards or had referred to clinics in Shiraz, southern Iran, during 2010. The participants were categorized into three groups of 30.

The first group (case1, n=30) included pregnant women who had symptoms of pretermdelivery with one or several related risk factors including pre-eclampsia, diabetes, and premature rupture of membrane.

The second group (case2, n=30) consisted of pregnant women with pretermdelivery symptoms who did not have any of risk factors of the first group.

And the third group (control group, n=30) included healthy pregnant women without any risk factors or pretermdelivery symptoms.

We included primigravida women aged 15-45 years with agestational age of 24-34 weeks based on the mother's last menstruation and her sonography. Moreover, the first group had to have at least one of the related risk factors of pretermdelivery. Women who were unwilling to continue their participation and those who were inaccessible during the follow-up were excluded from our study. We also excluded women in the second and/or the third group who developed one of the symptoms or risk factors of preterm delivery.

Data were collected using a questionnaire including the women's demographic data, information related to pregnancy, midwifery history, the risk factors related to preterm pregnancy, type of delivery, fetus weight, post delivery conditions. The mother's last menstruation date was important for determining the exact gestational age. In order to promote accuracy, gestational age was calculated based on the first sonography of the patient which was preferably performed during the first 12 weeks of gestation and matched with the gestational age based on the mother's menstruation.

After completing the questionnaires, blood samples were withdrawn in a comfortable environment. 5cc venous blood was taken from the mother and kept in plastic tubes containing Ethylene diamante tetra acetic acid (EDTA). After coding, the samples were immediately moved to the laboratory in a cold box and centrifuged at 3000 rounds for 20 minutes. Then, all the samples were kept at -70℃ until testing.

Then, the patients were followed up by the researcher until delivery and after that by using the information in their records. In case the participants' delivery was not carried out inside the clinical centers under study, they were followed up through appointments or phone calls. Data were analyzed using SPSS software (version 19). Independent *t*, Mann-Whitney, and Kruskal-Wallis tests were used as appropriated.

Also, the Receiver Operating Ccharacteristic (ROC) diagram was used to specify the predicting value of pretermdelivery using plasma fibrobectin. $P<0.05$ was considered as statistically significant.

Results

Among the 90 pregnant women who were initially selected, 79 were eventually enrolled in our study.25 (31.6%) women had pretermdelivery and 54 (68.4%) had term delivery. No significant difference was found between the three groups regarding demographic, medical, and gestational characteristics (P=0.343, table1). Some demographic variables such as occupation and level of education, had a significant relationship with high plasma fibronectin levels and pretermdelivery (P=0.019).

Table 1: Descriptive data of serum fibronectin levels (ng/ml) in the three groups (Kruskal-Wallis test)

group	No.	Mean	SD	Median	Maximum	Minimum	Mean Rank	Chi-square	P value
1	27	1017	535	820	2450	400	45.17	2.12	0.343
2	27	907	556	800	2650	360	38.07		
3	25	772	297	720	1400	110	26.05		

The mean (±SD) plasma fibronectin concentrations in case group 1, case group 2, and the control group were 1017 (±535), 907 (±556), and 772 (±297), respectively which were not significantly different based on the Kruskal Wallis test.

The mean plasma fibronectin level was significantly higher in the women with preterm delivery compared to those with term delivery ($P \leq 0.001$, Mann-Whitney test). We found a significant relationship between birth weight and the mother's plasma fibronecin level in all the three groups. This relationship implies thatthe higher the mother's plasmafobronectin level, the lower the fetus birth weight will be ($p<0.001$).

Based on ROC diagram, the best cut-off point for fibronectin concentration in predicting preterm delivery 24-34 weeks of gestation was determined as 700. The sensitivity, specificity, positive predicting value, and negative predicting value for this test were 100%, 61.1%, 54.3%, and 100%, respectively (Figure 1).

The findings of the present study revealed a statistically significant relationship between plasma fibronectin level and preeclampsia.

This shows a significant difference between the mothers with and without preeclampsia regarding preterm delivery and high concentration of plasma fibronectin (P=0.02).

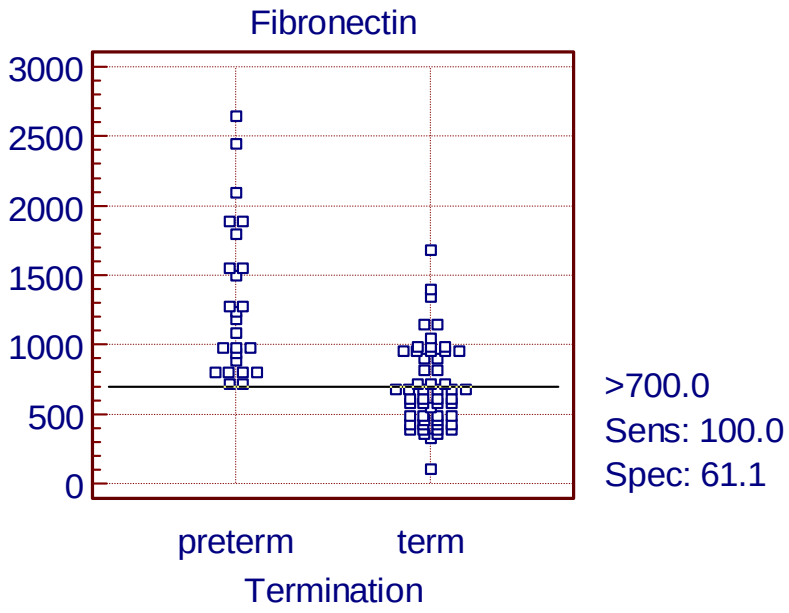

Figure 1: Optimal Cutoff Values, Sensitivity and Specificity Obtained from ROC Curve Analysis

In this study, Mann-Whitney U test was used in order to determine the relationship between preeclampsia and fibronectin and the results are presented in table2. As the table depicts, a statistically significant relationship was found between the incidence of preeclampsia and fibronectin level.

Discussion

Given the complications of preterm delivery and its role in increased prenatal mortality, it is important to identify the women at risk and implement preventive measures. So far, limited studies have been conducted on the relationship between the mother's plasma fibronectin level and pretermdelivery. However, in the mentioned studies, all the obtained predictive indexes were less than the findings of this study.

In the only similar study which was performed by Zygmunt and colleagues in 1997, the plasma fibronectin test's sensitivity, specificity, positive predicting value, and negative predicting value were reported as 50%, 95%, 50%, and 90%, respectively [24]. The preformed test in our study had a higher accuracy and diagnostic ability, because of using ELISA. We also found that plasma fibronectin had a higher sensitivity for predicting preterm delivery compared with fetal fibronectin.

Table2: The relationship between preeclampsia and fibronectin

Fibronectin / preeclampsia	Mean	SD	Mann-Whitney U	P-value
Yes	1818	486	-3.125	0.02
No	835	349		

The highest level of sensitivity, specificity, and positive and negative predicting values in simultaneous application of fetus fibronectin test and sonography were estimated as 71%, 71%, 17%, and 75%, respectively, in 2010 [25]. Nevertheless, other studies verified sensitivity and positive prediction valuesof 52.2% and 30-40%, respectively for fetus fibronectin test without sonography [26, 27]. Thus, the positive fibronectin predicting value has been quite considerable in the studies conducted on the issue. In this regard, the results of the present study showed that plasma fibronectintest had a high diagnostic power in comparison to the other methods and is capable of providing a correct estimation.

The findings of the present study strongly confirmed the significant relationship between high plasma fibronectin levels and the occurrence of the pretermdelivery. Based on the findings of this study, 25 women had preterm deliveries, while 54hadterm deliveries. Zygmunt and co-workers also found a significant relationship between fibronectin levels and the occurrence of the preterm deliveryin the case and control groups [25]. In the present study, though, the difference between the case and the control group was not statistically significant.

This difference might be due to the number of samples and the laboratory method used in plasma fibronectin evaluation. Considering the higher accuracy of the ELISA in evaluating blood variables compared with other methods such as nephelometry, if the sample size had been larger, the difference would have been significant.

One of the considerable results of the present study was the high level of fibronectin in the women with risk factors in pregnancy compared to those without any risk factors. In the first case group who had the risk factors for pretermdelivery, the average level of plasma fibronectin was higher than the second case group and the control group who did not have the risk factors; however, the difference was not statistically significant.

The study findings also confirmed the significant relationship between plasma fibronectin level and the occurrence of preeclampsia. In fact, the participants with both preeclampsia and pretermdelivery had high plasma fibronectin concentration in comparison to those without preeclampsia ($P<0.001$). These findings are consistent with several other studies [28, 29]. Aydin and co-workers found a statistically significant relationship between the occurrence of gestational blood pressure as well as preeclampsia and increased plasma levels of fibronectin. It should be noted that in Aydin's study, plasma fibronectin evaluation was performed serially and in three stages during 24-34 weeks of gestation [28]. Although the number of women with preeclampsia in this study was much smaller in comparison to that of Aydin's study, the consistency of the results in this small scope was quite considerable.

Inaccurate calculation of the gestational age and its effect on the results of the analysis: In this regard, it was attempted to use Last Normal Menstrual Period (LNMP) together with sonography. Furthermore, it was not possible to increase the power of the test due to financial limitations.

Conclusion

The present study aimed to introduce measurement of the mother's plasma fibronectin level in order to enhance the early diagnosis of preterm delivery among the pregnant women. Considering the appealing results obtained in the study, the findings are expected to be taken into account by the health and treatment authorities; so that a reliable, accurate test can be developed for screening preterm delivery and, consequently, prevent the high mortality rate resulting from prematurity.

The current study can provide appropriate strategies for performing further studies. It can also provide the basis for future studies on preterm delivery or other risk factors in pregnancy using measurement of the mother's plasma fibronectin level.

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