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Detection of fetal fibronectin in twin pregnancies in relation to gestational age

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ABSTRACT

Context: The presence of fetal fibronectin in the cervix or vagina has been investigated as a possible marker for the risk of preterm birth. Fetal fibronectin in cervical fluid can provide direct evidence of pathologic changes at the interface of fetal and maternal tissues.

Objective: To evaluate the presence of fetal fibronectin as a predictor of premature delivery in twin pregnancies in relation to gestational age.

Design: Accuracy study.

Setting: University referral unit.

Participants: 52 pregnant women with twin pregnancies and gestational age of between 24 and 34 weeks.

Main measurements: Sensivity, specificity, predictive values and relative risk ratios of the correlation between fetal fibronectin and preterm birth before 34 and 37 weeks using an immediate-reading membrane test on cervicovaginal secretions obtained from participants.

Result: The sensitivity varied between 66.7% and 85.7%, whereas the specificity was from 58.3% to 81.8% according to gestational age at the time of sampling. The relative risk of spontaneous preterm birth after a positive fetal fibronectin test, as compared with a negative fetal fibronectin test, rose from 2.8 at 24-26 weeks to 4.1 at 27-30 weeks. Analyses of the risk of delivery before 34 weeks were not statistically significant.

Conclusion: Fetal fibronectin in the cervicovaginal secretions of patients with twin pregnancies is a useful tool for the early identification of twin pregnancies likely to deliver before 37 weeks. However, the clinical value of the fibronectin test is limited because of low indices for prediction of delivery before 34 weeks. The best period for performing the fetal fibronectin test in twin pregnancies to predict preterm delivery is between 27 and 30 weeks.

Key words: Twins. Fetal fibronectin. Preterm delivery.

INTRODUCTION

Prematurity is the leading cause of perinatal morbidity and mortality.¹ Despite the availability of tocolytic drugs, aggressive surveillance techniques, and other treatment and prevention strategies, no change has been observed in premature delivery rate since the 1950s.² It is well known that twins have significantly higher perinatal mortality than singletons, with a rate 4 to 10 times greater in twins than in singletons being reported.^{3,4} The high perinatal mortality is associated with the increased rate of preterm delivery. Various approaches have been proposed in order to reduce the prematurity rate in twin pregnancies, such as prophylactic cervical cerclage, monitoring of uterine activity, long term tocolysis and bed rest. However, most published studies^{5,9} have not been able to demonstrate effective methods that significantly decrease the rate of preterm deliveries in twin pregnancies. Over the last seven years, the presence of fetal fibronectin in the cervix or vagina has been investigated as a possible marker for the risk of preterm birth. Fetal fibronectin in cervical fluid can provide direct evidence of pathologic changes at the interface of fetal and maternal tissues. Thus, fetal fibronectin as a screening test could assist the clinician in the identification of twin pregnancies at high risk for preterm birth.

The purpose of this study was to evaluate the efficacy of fetal fibronectin test in predicting preterm delivery in twin pregnancies in relation to gestational age at the time of sampling.

METHODS

The study was done at Hospital Maternidade "Leonor Mendes de Barros" and Hospital São Paulo (Universidade Federal de São Paulo) between June 1994 and August 1996. After informed consent was obtained from all patients, gestational age was established using the date of the last menstrual period and was confirmed by early ultrasonography.

Fifty-nine women were prospectively enrolled in the study and none were lost during it. Five of them were excluded because of medical complications that necessitated preterm delivery: severe pre-eclampsia (3 cases), eclampsia (1 case) and fetal distress (1 case). Two patients who delivered at term after using tocolytic agents to inhibit preterm labor were also excluded. Conversely, nine patients who underwent tocolysis unsuccessfully were included in the study. Thus, 52 patients remained for analysis.

Samples of cervicovaginal secretions were collected every two weeks between 24 and 34 weeks of gestation. The presence of fetal fibronectin was determined qualitatively using a bedside membrane immunoassay. No attempt was made to control patient treatment and management during prenatal care based on fetal fibronectin test results. The fetal fibronectin results were not communicated to the obstetric team and therefore did not influence subsequent patient management. Preterm birth was defined as delivery before 37 weeks of gestation.

Because the test results are qualitative and based on the observation of colored spot, the researcher and two independent observers compared the color reaction of each test with a standard chart supplied with each kit, showing an example of the reaction intensity to define the test as positive or negative. After recording the results found by each observer, the samples were excluded from the study in cases of discordant opinions. Cervicovaginal samples with visible blood at swab were also excluded.

Statistical Methods. Correlation between the time of delivery and fetal fibronectin test result was performed by means of sensitivity, specificity and predictive values. The data was analyzed using relative risk ratios.

RESULTS

Twenty-eight (53.8%) delivered before 37 weeks. A total of 270 samples were collected from these patients during the study. The average number of samples obtained per patient was 5.2. Twenty three samples were excluded, because of discordant results between the observers (13 cases) or presence of blood at swab (10 cases). Therefore, we analyzed 247 samples for the prediction of preterm delivery.

Table 1 presents the sensitivity, specificity, positive and negative predictive value for spontaneous preterm delivery in relation to gestational age at the time of sampling. The periods of gestational age considered were 24 to 26, 27 to 30 and 31 to 34 weeks of gestation. Twenty-one women out of a total of 43 delivered preterm when the test was performed at 24 to 26 weeks of gestation. Twenty-eight out of a total of 52 delivered preterm when the test was performed at 27 to 30 weeks of gestation. Twenty-six preterm births occurred out of a total of 50 women who underwent the test at 31 to 34 weeks. The sensitivity varied between 66.7% and 85.7%, the specificity rose from 58.3% to 81.8%, whereas positive and negative predictive values were equivalent in those three periods. Table 1 also shows that the relative risk (RR) for preterm birth was greater at 27 to 30 weeks than at 24 to 26 weeks and 31 to 34 weeks.

Because preterm birth before than 34 weeks is associated with the worst perinatal outcomes, we determined the value of the fetal fibronectin test in the prediction of spontaneous delivery before 34 weeks in those three different time periods. Nine patients out of a total of 43 delivered before 34 weeks when the test was performed at 24 to 26 weeks of gestation. Ten women out of a total of 52 delivered before 34 weeks when the test was performed at 27 to 30 weeks of gestation. Six preterm births occurred out of a total of 50 women who underwent the test at 31 to 34 weeks. In Table

2, it can be seen that the sensitivity and negative predictive values of the fetal fibronectin test at 27 to 30 weeks were better at predicting delivery before 34 weeks when compared with the other two intervals. However, the relative risk was not statistically significant.

DISCUSSION

The major cause of increased perinatal mortality in twin pregnancies is preterm delivery.¹⁰ The availability of a rapid search for the presence of cervical fetal fibronectin could improve our ability to efficiently identify patients at risk for preterm delivery. The rapid result membrane test was comparable to the standard fetal fibronectin in cervical vaginal secretions, in accordance with Bittar et al.¹¹

Goldenberg et al¹² studied how various patterns of fetal fibronectin testing were related to spontaneous preterm birth in singleton pregnancies, and reported that the last test result seems to be the best predictor of subsequent spontaneous preterm delivery. In twin

pregnancies, however, it seems that the 27 to 30-week sampling period is the most appropriate moment to evaluate the risk of preterm delivery in twin gestations because the number of false positives in this interval is less than in the other two.

Nageotte et al¹³ evaluated the predictive efficacy of weekly cervicovaginal fetal fibronectin determinations between 20 and 37 weeks in 102 asymptomatic singleton pregnancies. They reported that fetal fibronectin had high sensitivity (90.6%) but low specificity (44.3%) for prediction of preterm delivery. According to these authors, their large number of false-positive results may reflect degrees of chorionic-decidual cell activation insufficient for achieving preterm delivery.¹³ Tolino et al¹⁴ found high sensitivity (90.9%) and low specificity (68.5%) in 68 patients with multiple gestations who underwent weekly sampling of cervical and vaginal secretions.

We believe that the fetal fibronectin test has great potential for improving the clinician's ability to select patients for preventive approaches and tocolytic drug therapy and for reducing the number

Table 1 - Predictive values for spontaneous preterm delivery before 37 weeks in accordance with the gestational age at the time of the fetal fibronectin test

Gestational age	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	Relative Risk (95% CI)
24 to 26	66.7% (43.1 to 84.5)	81.8% (59.0 to 94.0)	77.8% (51.9 to 92.6)	72.0% (50.4 to 87.1)	2.8 (1.4 to 5.5)
27 to 30	85.7% (66.4 to 95.3)	70.8% (48.8 to 86.6)	77.4% (58.5 to 89.7)	80.9% (57.4 to 93.7)	4.1 (1.7 to 10)
31 to 34	84.6% (64.3 to 95.0)	58.3% (36.9 to 77.2)	68.8% (49.9 to 83.3)	77.8% (51.9 to 92.6)	3.1 (1.3 to 7.6)

CI = Confidence interval

Table 2 - Predictive values for spontaneous preterm delivery before 34 weeks in accordance with the gestational age at the time of the fetal fibronectin test

Gestational age	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	Relative Risk (95% CI)
24 to 26	55.6% (22.7 to 84.7)	61.8% (43.6 to 77.3)	27.8% (10.7 to 53.6)	84.0% (63.1 to 94.7)	1.7 (0.5 to 5.6)
27 to 30	80.0% (44.2 to 96.5)	45.2% (30.2 to 61.2)	25.8% (12.5 to 44.9)	90.5% (68.2 to 98.3)	2.7 (0.6 to 11.5)
31 to 34	66.7% (30.9 to 91.0)	36.6% (22.6 to 53.1)	18.8% (7.9 to 37.0)	83.3% (57.7 to 95.6)	1.1 (0.3 to 4.0)

CI = Confidence interval

of women who unnecessarily receive treatment for a perceived threat of preterm labor. However, despite the high sensitivity and negative predictive value towards delivery before 34 weeks, the period when the majority of perinatal mortality is likely to occur, the analysis of the data showed that the relative risk of a positive fetal fibronectin test is not statistically significant when compared with the negative test. Therefore, we found no evidence to support the idea that the fetal fibronectin test could reduce the perinatal mortality in twin pregnancies.

In conclusion, the fetal fibronectin test seems to be a useful tool in clinical practice for early identification of twin pregnancies likely to develop preterm labor. However, the clinical value of the fibronectin test is limited because of low indices for prediction of delivery before 34 weeks. The best period for performing the fetal fibronectin test in twin pregnancies for prediction of preterm delivery is between 27 and 30 weeks.

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RESUMO

Objetivo: Avaliar a presença da fibronectina fetal como fator de predição do parto prematuro na prenhez gemelar de acordo com a idade gestacional. **Tipo de Estudo:** Estudo de acurácia. **Local:** Centro de Referência Universitário. **Participantes:** 52 gestantes com prenhez gemelares foram submetidas ao teste de imunoensaio de membrana entre 24 e 34 semanas para verificar a correlação entre a presença de fibronectina fetal na secreção cérvico-vaginal e o risco de parto prematuro antes de 34 e 37 semanas de gestação. **Variáveis estudadas:** Sensibilidade, especificidade, valores preditivos e risco relativo da correlação entre a presença de fibronectina fetal na secreção cérvico-vaginal e o risco de parto prematuro antes de 34 e 37 semanas de gestação. **Resultado:** A sensibilidade variou entre 66,7% e 85,7%, enquanto a especificidade foi de 58,3% a 81,8% de acordo com a idade gestacional em que o exame foi realizado. O risco relativo para o parto prematuro espontâneo após um teste positivo comparado ao teste negativo variou de 2,8 entre 24-26 semanas a 4,1 entre 27-30 semanas. Os dados analisados para predição do parto antes de 34 semanas não mostraram resultados estatisticamente significantes. **Conclusão:** O teste da fibronectina fetal é útil para identificação precoce das gemelígestas com risco elevado para o parto prematuro antes de 37 semanas. Contudo, o valor clínico do teste é limitado devido aos baixos valores de predição para ocorrência do parto antes de 34 semanas. O melhor período para a realização do teste para predição do parto prematuro é entre 27 e 30 semanas de gestação.