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Article

Fetal fibronectin as a screening test for premature delivery in multiple pregnancies

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Abstract

Objective: To evaluate fetal fibronectin as a screening test for premature delivery in asymptomatic women with multiple pregnancies. *Method:* In the mid-second trimester, the concentrations of fetal fibronectin in the cervical and vaginal secretions of 68 patients with multiple gestations were sampled weekly by monoclonal antibody immunoassay in order to predict preterm labor. *Results:* The results for the prediction of preterm labor differ according to whether we consider a single positive result (fetal fibronectin >50 ng/ml) as predictive of preterm labor or whether we only consider at least two consecutive positive results as predictive of preterm labor. The fetal fibronectin test had a sensitivity for preterm birth before 37 weeks of 90.9% and 86.6%, respectively, with a specificity of 68.5% vs. 78.9% and positive and negative values of 73.1% vs. 76.4% and 88.8% vs. 88.2%, respectively. Similar results were obtained for preterm birth before 34 weeks. *Conclusion:* In a condition such as multiple pregnancy which is already at risk for premature delivery the possibility of raising the specificity of the test with virtually no decrease in sensitivity guarantees better recognition of patients likely to develop premature labor. This possibility can be achieved simply by considering two positive consecutive samples as predictive of preterm labor.

Keywords: Fetal fibronectin; Preterm delivery; Multiple pregnancy

1. Introduction

In multiple pregnancies there is an increased incidence of polyhydramnios, gestosis, anemia and preterm delivery. The main complication in these cases is preterm delivery, since it represents a life-threatening situation for the twins.

It has been calculated that the mean duration of twin pregnancies is 37 weeks. In other words, about half of these pregnancies are delivered before 37 weeks. Moreover the risk linked with prematurity is increased by the low birth weight of the twins in comparison with that of single fetuses of the same gestational age [1].

Premature birth, defined as delivery before 37 complete weeks of gestation, is the leading cause of

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perinatal mortality and short- and long-term fetal morbidity. Most of the morbidity and mortality attributed to preterm birth occur in births before 34 weeks of gestation [1].

Various strategies have been used to lower this incidence including risk screening during the perinatal period, patient education, monitoring of uterine activity, long-term tocolysis, perinatal home nursing care and early prenatal care. However obstetric management could be more effective if women at risk for this condition could be identified by the early use of a biochemical marker.

Recently some authors [2–4], in a multicenter cross- sectional study of symptomatic women with suspected preterm labor, demonstrated that detection of fetal fibronectin in cervical and vaginal secretions identified pregnant women at high risk for preterm delivery. These authors postulated that because fetal fibronectin is a component of the extracellular matrix of the fetal membranes and is normally present in amniotic fluid and placental tissue, its appearance in the cervix and vagina is suggestive of mechanical or inflammation-mediated damage to the membranes.

The objective of this study was to evaluate fetal fibronectin as a screening test for premature delivery in multiple pregnancies.

2. Materials and methods

We evaluated the presence of fetal fibronectin in the cervical and vaginal secretions of 68 consecutive asymptomatic women with multiple gestations (two or more fetuses) presenting at our centers. Six of the 68 pregnancies were triplets (8.8%).

Documentation of the intact membranes and undilated cervix was performed at the start of the study. Gestational age was calculated on the basis of the last menstrual period and early vaginal ultrasonography. Informed consent was obtained from each patient at recruitment.

The study started in the mid-second trimester (24 weeks). Cervical and vaginal secretions, both from the posterior vaginal fornix and from the external cervical ostium, were sampled weekly using a sterile speculum. The samples were collected using sterile dacron swabs and analyzed immediately for the presence of fetal fibronectin.

The presence of fetal fibronectin was determined qualitatively using a commercial kit based on a monoclonal antibody specifically recognizing fetal fibronectin (Fetal Fibronectin Membrane Immunoassay; Adeza Biomedical, Sunnyvale, USA) [5,6]. A sample was defined as positive if its absorbance was greater than that of the positive control (50 ng/ml).

We then evaluated reliability by a different method, considering first a positive result obtained on one single occasion, and then a positive result obtained on at least two consecutive occasions. The reliability of this assay in predicting preterm labor was evaluated by means of the classic parameters of sensitivity, specificity and predictive values.

Categoric clinical data were evaluated by relative risk ratios and the χ^2-test; $P < 0.01$ was considered to be statistically significant.

3. Results

Sixty-eight pregnant women with multiple pregnancies were examined. Thirty-three (48.5%) delivered before 37 weeks and 35 (51.5%) delivered after 37 weeks of gestation. No patient was delivered before 37 weeks for reasons other than preterm labor or preterm rupture of the membranes. There were no statistical differences in maternal age, parity or history of prior preterm birth between the women delivered before or after 37 weeks.

The results of our study differ according to whether we considered a positive result obtained from a single sample or one obtained from at least two consecutive samples.

If we take the first case (i.e. a single positive sample), the sensitivity of fetal fibronectin was 90.9%, the specificity was 68.5%, the positive predictive value was 73.1% and the negative predictive value was 88.8% for the prediction of delivery before 37 weeks (Table 1). The relative risk of preterm delivery for one positive fetal fibronectin result was 6.57 (95% C.I. 4.80–77.59, χ^2-test 22.67, $P < 0.000001$).

If we take a positive result from at least two con-

Table 1
Reliability of fetal fibronectin in predicting delivery before 37 weeks from a single positive sample

Multiple pregnancy	Fetal fibronectin positive	Fetal fibronectin negative	Total
Delivery			
<37 weeks	30	3	33
>37 weeks	11	24	35
Total	41	27	68

Sensitivity 90.9%, specificity 68.5%, positive predictive value 73.1%, negative predictive value 88.8%, relative risk 6.57 (95% C.I. 4.80–77.59), χ^2-test 22.67, $P < 0.000001$.

Table 3
Reliability of fetal fibronectin in predicting delivery before 34 weeks from a single positive sample

Multiple pregnancy	Fetal fibronectin positive	Fetal fibronectin negative	Total
Delivery			
<34 weeks	14	1	15
>34 weeks	18	35	53
Total	32	36	68

Sensitivity 93.3%, specificity 66.0%, positive predictive value 37.8%, negative predictive value 96.7%, relative risk 27.22 (95% C.I. 3.23–151.39), χ^2-test 14.24, $P < 0.0001$.

secutive samples, the sensitivity of fetal fibronectin was 86.6%, but the specificity increased to 78.9%, with a positive and a negative predictive value of 76.4% and 88.2%, respectively, for the prediction of delivery before 37 weeks (Table 2). The relative risk of a preterm delivery was 6.52 (95% C.I. 5.71–115.67, χ^2-test 26.3, $P < 0.000001$).

The reliability of this test in true preterm births, i.e. those delivered before 34 weeks, showed similar results (Tables 3 and 4).

When using a single positive sample for diagnosis, the mean time of diagnosis (± S.D.) was 25.7 ± 1.8 weeks. When using two consecutive positive samples for diagnosis, the mean time was 27.1 ± 2.1 weeks. In either case the mean time of diagnosis was sufficient to begin an intervention program in those patients shown to be at high risk. Our data show a clear difference, although not significant, between the mean interval from obtaining a positive result to delivery (Table 5).

4. Discussion

The significant increase in perinatal mortality and morbidity in multiple gestations in comparison with single gestations depends on the higher incidence of preterm birth. Indeed 50% of twins are preterm and those born before 34 weeks have a still higher risk of complications.

In the last 20 years a number of protocols have been proposed for the prevention of preterm labor, such as bed rest, prophylactic cerclage and the prophylactic administration of β-mimetics and progestatives [7].

Objective signs of impending preterm delivery such as cervical modifications and uterine contrac-

Table 2
Reliability of fetal fibronectin in predicting delivery before 37 weeks from two consecutive positive samples

Multiple pregnancy	Fetal fibronectin positive	Fetal fibronectin negative	Total
Delivery			
<37 weeks	26	4	30
>37 weeks	8	30	38
Total	34	34	68

Sensitivity 86.6%, specificity 78.9%, positive predictive value 76.4%, negative predictive value 88.2%, relative risk 6.52 (95% C.I. 5.71–115.67), χ^2-test 26.3, $P < 0.000001$.

Table 4
Reliability of fetal fibronectin in predicting delivery before 34 weeks from two consecutive positive samples

Multiple pregnancy	Fetal fibronectin positive	Fetal fibronectin negative	Total
Delivery			
<34 weeks	10	1	11
>34 weeks	13	44	57
Total	23	45	68

Sensitivity 90.9%, specificity 77.1%, positive predictive value 38.4%, negative predictive value 97.6%, relative risk 33.84 (95% C.I. 3.75–188.23), χ^2-test 16.18, $P < 0.0005$.

Table 5
Comparison of the positive sample-delivery interval between the two groups

	Single positive sample	Two consecutive positive samples	
No. of patients	32	27	
Sample-delivery interval (days)	54 ± 37	43 ± 39	$P < 0.05$

tions have shown a sensitivity and specificity of less than 45%. Vaginal pH has a higher sensitivity but its specificity is very poor [4–8]. Less reliable indicators are obstetric anamnesis, demographic factors and obstetric risk factors [4,9].

The first evaluation of the effectiveness of fetal fibronectin content in cervical and vaginal secretions in predicting preterm delivery was performed by Lockwood et al. [4]. They studied 117 pregnant women between 24 and 37 weeks' gestation with uterine contractions or precocious cervical modifications, comparing fetal fibronectin levels with gestational age at the time of onset of labor [4]. They were able to demonstrate the clinical effectiveness of fetal fibronectin in predicting preterm delivery in symptomatic patients.

Morrison et al. [10] evaluated fetal fibronectin vaginal and cervical levels in 28 pregnant women between 24 and 34 weeks' gestation with regular uterine contractions (>10/h), with unruptured membranes and a cervical dilatation ≤1 cm. Cervical fetal fibronectin levels >50 ng/ml identified patients with preterm labor who subsequently had a preterm delivery, with a sensitivity of 90%, a specificity of 72%, a positive predictive value of 64% and a negative predictive value of 93%.

In the present study a single positive test for the presence of fetal fibronectin in the cervical and vaginal secretions of women with multiple gestations was predictive of preterm delivery before 37 weeks' gestation with a sensitivity of 90.9% and a specificity of 68.5%. If at least two positive consecutive samples were considered diagnostic, the sensitivity was 86.6% and the specificity was 78.9%. This means that in a condition that is already at risk for premature delivery such as multiple pregnancy the specificity of the test can be raised with virtually no decrease in sensitivity, guaranteeing a better recognition of patients likely to go into premature labor.

Our results show that serial determinations of cervical and vaginal fetal fibronectin levels are predictive of preterm delivery in an asymptomatic risk group such as women with multiple pregnancies.

The presence of fetal fibronectin in cervical and vaginal secretions in the second or third trimester may identify women with multiple gestations who are still asymptomatic but at high risk for preterm labor. Identification of these patients could lead to an early therapeutic approach such as bed rest, administration of tocolytic agents, patient education, perinatal monitoring with tocodynamometry and home nursing care, all of which may preclude early onset of labor [11,12].

Additional work needs to be carried out to confirm these results and to determine whether fetal fibronectin is present in cervical and vaginal secretions before uterine contractions become apparent. In addition, future studies may better evaluate the time interval between a positive test and the beginning of preterm labor. In this way the test could also be useful for calculating induction of labor.

From our data we can conclude that in multiple pregnancies a biochemical marker such as fetal fibronectin could be considered a useful tool in clinical practice for the early identification of patients likely to develop preterm labor.

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