

# Preterm delivery: predictive value of cervico-vaginal fetal fibronectin

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## Summary

**Objective:** This study aimed to evaluate the risk of preterm delivery in the asymptomatic obstetric population of L'Aquila by means of fetal fibronectin immunoassay in cervicovaginal secretions.

**Methods:** In this prospective study, 60 asymptomatic pregnant women at low-risk for preterm delivery were followed-up.

Fetal fibronectin cervical swabs from the endocervix and posterior vaginal fornix were obtained every second week from 24 to 36 weeks of gestation. Fetal fibronectin concentrations were measured by an enzyme-linked immunosorbent assay with a cutoff level set at 50 ng/ml.

**Results:** Twelve patients (20%) had at least one positive fetal fibronectin test result. Six women in our study group (10%) were delivered spontaneously <37 weeks; 4 of these (66%) had at least one positive fetal fibronectin test result (positive predictive value: 33%; sensitivity: 66%) and 3 of these women (75%) had a positive test result between 24 and 26 weeks. The remaining 8 patients with at least one positive fetal fibronectin test were delivered at term or post-term.

Forty-eight women always had negative tests and 46 (95.8%) of these were delivered at term (specificity 82%), whereas 2 (4.2%) were delivered prematurely.

The negative predictive value of fetal fibronectin as a predictor of term delivery in this low-risk population is 95% with odds ratio=11.5 (95% confidence interval 1.44 to 110.4), relative risk=8 (95% confidence interval 1.38 to 59.2) and Fisher Exact Test  $p < 0.024$ .

**Conclusion:** In a population of asymptomatic patients at low risk for prematurity, the occurrence of a positive cervical or vaginal fetal fibronectin test result defines a subgroup at increased risk for preterm delivery, mostly at low gestational age.

**Key words:** Preterm delivery; Fetal fibronectin.

## Introduction

Preterm birth before the 37th week of gestation is responsible for 75% of perinatal mortality and morbidity [1, 2]. The incidence of preterm birth is reported to be between 6 to 10% [3-6].

The most important risk factors involved in the etio-pathogenesis of preterm delivery are shown in Table I [5-7].

In the last five years, attention has been focused on some potential biochemical markers of early diagnosis of preterm delivery risk: assay of interleukine-6 in amniotic fluid, plasmatic collagenase, elastase and, recently, fetal cervical-vaginal fibronectin [2-17], which belongs to a family of ubiquitous proteins of high molecular weight, present in plasma and extra-cellular matrix, which play a fundamental role in several biological processes (cellular adhesion, motility, tissue repairing, coagulation, etc.) [7]. There are more than 20 isoforms of fibronectin, of which the most important are plasmatic fibronectin, synthesised by epithelial cells, cellular fibronectin, constituent of extra-cellular matrix (both are present in maternal blood and can reach high concentrations in the preclinical phase of preeclampsia), and oncofetal fibronectin, detectable in the amniotic fluid in trophoblast-placenta and in some neoplasms [13].

This fibronectin is secreted by trophoblasts and, although its exact role is unknown, it is believed to favor

adhesion of trophoblastic tissue to maternal decidua during placentation [6, 7].

In fact, several histochemical studies showed the presence of this protein at high concentrations in the interface corion-decidua [14].

Until the 20-22nd week of gestation, and at the end of gestation itself, onco-fetal fibronectin is also found in cervical-vaginal secretions at concentration of >50 ng/ml [7, 14]. Between these two periods it is detectable only in 4% of women who will deliver at term, and exceptionally in cases with rupture of membranes [6, 7].

The disappearance of fibronectin in cervical-vaginal secretions corresponds, most likely, to the moment of fusion between corion and capsular decidua with parietal decidua. Its reappearance, at the end of gestation, would be due to mechanical modifications able to make membranes slide on decidua, with the initial loss of its role of biological glue in preparation for the delivery [6, 7].

The hypothesis that explains why fibronectin could be useful in identifying women at risk of preterm delivery is correlated to the possibility of the disruption of the interface corion-decidua, which precedes preterm delivery, with subsequent release of fetal fibronectin in the cervical canal and vagina.

It was thus hypothesized that damage to fetal membranes could imply a release of fibronectin in the cervix and vagina, therefore representing a biochemical marker of preterm delivery [7].

The separation of the corion from the uterine wall could then depend on mechanical or inflammatory causes [6].

Table 1. — *Risk factors of preterm delivery.*


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– Unfavorable previous obstetric history (previous preterm deliveries and abortions)
– Uterine malformations
– Cervical incompetence
– Multiparity
– Important infections
– Abnormalities in amniotic fluid
– Low socio-economic status
– Cigarette smoke

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It has been recognized that the majority of very early deliveries is due to an ascending infection.

Bacterial products and host defences cause a mobilization of phospholipids, an increased synthesis of prostaglandins and leukotrienes, a macrophage activation with cytokine release and leukocyte activation, with release of collagenase, elastase and plasmin and with following corion proteolysis and fetal fibronectin passage into the cervix and the vagina [5-7].

Therefore, the release of this protein in the cervical-vaginal secretion, from the 24th week of amenorrhea, seems to allow the identification of a population at high risk of preterm delivery.

Moreover, the presence in fetal fibronectin of an epitope IIICS allowed the development of a monoclonal antibody, FCD-6 [7, 14].

The aim of this work was to evaluate the risk of preterm delivery by a serial onco-fetal fibronectin assay in asymptomatic patients of the obstetric population of L'Aquila.

## Materials and Methods

Sixty women, undertaking routine prenatal examination at the Department of Obstetrics and Gynecology at the University of L'Aquila, were recruited for this study between April and June, 1998.

The average age of patients was 28.9 years, ranging from 24 to 36 years.

Informed consent was obtained from all the women.

Table II shows risk factors that we considered sufficiently important to exclude women bearing them from trial.

A cervical dacron swab was obtained every two weeks from each patient between 24 and 36 weeks of gestation or until the delivery, by placing the swab either on the esocervix or on the vaginal posterior fornix for 10 to 15 seconds. Each swab was then inserted in a polypropylene tube containing 750 ng/ml of assay buffer, filtered and stored at +4 °C until assay.

A quantitative test of onco-fetal fibronectin was performed with the enzyme-linked immunosorbent assay (ELISA) using commercially available kits (Azeda Biomedical). According to the manufacturer instructions, samples were considered positive if the fetal fibronectin concentration was >50 ng/ml.

Statistical testing was conducted with Fisher's Exact Test (when cell frequency <5) for categorical variables. In all cases statistical significance was accepted when  $p < 0.05$ .

## Results

Of the entire study population, 12 women (20%) were positive at least once in the fetal fibronectin test (Table III), while the remaining part of the study population was persistently negative (48 patients, equal to 80%).

Of the women who had spontaneous preterm delivery (10% of the study population), 4 (66%) were positive at the fetal fibronectin test (and were delivered within two weeks), and 2 (33%) negative.

The positive predictive value was 33%, with a sensitivity for women who had a preterm delivery of 4/6 (66%).

The remaining 8 women who had a positive fibronectin test result were delivered at term or even post-term (2 patients: 25%).

In the remaining part of the study population (48 patients who had a negative fibronectin test result), 2 women had a preterm delivery (4%) and 46 (95.8%) were delivered at term (negative predictive value of 46/48, 95%, with a specificity of 46/54, 82%).

The fact that our analysis showed a higher percentage of positive test results around the 36th week of gestation suggests that the gestational period is a decisive factor for a fibronectin assay.

The finding of a positive value in the early gestational period was more significant in relation to the risk of a preterm delivery.

In fact, 3 out of 4 women who were positive in the fibronectin determination between the 24th and the 26th week of gestation had a preterm delivery.

The positive predictive value is 33%, and the negative predictive value is 95% (relative risk=8 [95% confidence interval 1.38 to 59.2], odds ratio=11.5 [95% confidence interval 1.44 to 110.4]).

Table 2. — *Exclusion criteria adopted in recruitment of patients.*


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– History of preterm delivery or labor in a previous or in the actual pregnancy
– History of preterm rupture of membrane
– Bleeding
– Known congenital abnormalities
– Multiple pregnancies
– Maternal or fetal complications during the examination and/or during gestation
– Genital infection
– Cervical cerclage

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Table 3. — *Fetal fibronectin as a delivery predictor before 37 weeks of gestation (bi-weekly sampling).*


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	fFN* positive	fFN negative	Total
Delivery <37 weeks	4	2	6
Delivery >37 weeks	8	46	54
Total	12	48	60

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\*fFN: fetal fibronectin cervicovaginal

## Discussion

The data collected in our investigation suggested the following observations:

1) For a test to be considered highly diagnostic, extreme sensibility, specificity and predictivity are required. In a recent study, reported values have been respectively, 60, 95 and 85%, in patients at high-risk of preterm delivery, either asymptomatic or symptomatic [7].

In our study sensibility (66%) and specificity (82%) are comparable with those reported in the literature, while positive predictability (33%) in asymptomatic patients at low-risk of preterm delivery is much lower.

A positive predictive value of 33% definitely implies a high percentage of false positives (67%).

2) Although our study population is very small, we can nevertheless assess, according to the literature, that concentrations of cervical and/or vaginal fibronectin higher than 50 ng/ml can be considered an index of higher risk of preterm delivery. As a matter of fact women with at least one positive fetal fibronectin test experienced a greater prevalence of spontaneous preterm birth than women whose tests were all negative ( $p=0.024$ ). Women with at least one positive fetal fibronectin result were 8 times (95% confidence interval 1.38 to 59.2) more likely to experience spontaneous preterm birth than were women with negative test results.

3) More specifically, according to our experience, an early positive fibronectin test has greater predictive value.

In fact, as shown in our study, 75% of patients who had a positive test result between the 24th and 26th week of gestation had a preterm delivery.

4) A twofold cervical and/or vaginal swab could probably be part of routine investigations during pregnancy.

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