

Is routine sampling of fetal fibronectin justified?

This test does help identify women likely to deliver early. To warrant universal use, however, a screening test should meet 5 conditions—including availability of an effective intervention.

Routine fetal fibronectin sampling to identify women at risk for preterm delivery seems justified, studies suggest. Closer scrutiny, however, reveals the absence of an element crucial to successful screening: an effective intervention.

This article reviews the landmark studies of fetal fibronectin testing, as well as findings of a recent multicenter double-blind, placebo-controlled trial of antibiotic therapy.

Approximately two thirds of preterm births are “spontaneous,” associated with preterm premature rupture of the membranes (PPROM) or preterm labor. The remainder have been linked to a variety of other maternal and fetal conditions, such as preeclampsia remote from term, and fetal growth restriction.

Because most studies have focused on identifying women at risk of spontaneous

preterm birth, our discussion is limited to this group.

Requirements for routine screening

A screening test is not meant to be diagnostic. Persons with positive findings require more conclusive testing, followed by treatment or another intervention.¹

A screening program must meet specific criteria before widespread implementation can be recommended:

1. The screened condition poses a significant burden.
2. The test is sensitive and specific.
3. It is inexpensive and easy to perform.
4. It is safe and acceptable to patients.
5. Effective treatment is available for patients who test positive.

Cervicovaginal fibronectin is elevated in women who deliver preterm

Fetal fibronectin is a glycoprotein produced by many cell types, including those of the fetal amnion. Indeed, high concentrations of

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KEY POINTS

- Spontaneous preterm birth is associated with elevated cervicovaginal fetal fibronectin levels, especially in women who deliver at an early gestational age.
- A recent study suggests that antibiotic therapy in women with a positive fetal fibronectin screening test does not reduce the incidence of spontaneous preterm birth or improve neonatal outcomes.
- Fetal fibronectin cannot be recommended as a screening test for preterm birth.

the protein are found in amniotic fluid and maternal plasma.²

Fetal fibronectin acts as an intracellular adhesive; it “glues” the blastocyst to the uterine endometrium. In addition, the glycoprotein is secreted throughout pregnancy, bonding the placenta to the uterus until parturition.

Normally, cervicovaginal secretions contain increased amounts of fetal fibronectin at the beginning of gestation and 1 to 2 weeks before the onset of labor at term. However, in women who deliver preterm, these levels are elevated as early as the second trimester. This observation led early investigators to postulate that fibronectin sampling might be a suitable screening test for increased risk of spontaneous preterm delivery.

Possible causes. It is not clear precisely what causes cervicovaginal fetal fibronectin levels to increase prematurely in women at risk of preterm delivery.

One possibility might be infection: A large percentage of preterm births are associated with subclinical infection and bacterial colonization of the fetal membranes; inflammation associated with such infection may lead to disruption of the extracellular matrix, causing release of fetal fibronectin into the cervix and vagina.

Landmark studies confirm predictive role

In 1991, Lockwood et al² published one of the first studies to find a predictive association between fetal fibronectin levels and preterm delivery. In 144 women with uncomplicated pregnancies, cervicovaginal concentrations of fetal fibronectin were rarely greater than 50 ng/mL between 21 and 37 weeks of gestation. In contrast, high levels were detected in 95% of 65 patients with PPROM and in 50% of 117 patients with preterm uterine contractions and intact membranes. The 3 groups were well matched for age, race, gravidity, and parity. An elevated fetal fibronectin level identified

60 women who delivered before term with a sensitivity of 81.7% and specificity of 82.5%.

From 1996 to 1998, Goldenberg et al³⁻⁵ published several reports on a large multicenter observational study of 2,929 women. In contrast to the Lockwood study, these women were asymptomatic—there was no indication that any would deliver prematurely.

Sensitivity was greater for earlier than for later preterm delivery; thus, a positive test would be more useful for identifying women who would deliver before 28 weeks.

Cervicovaginal fetal fibronectin was measured every 2 weeks between weeks 22 to 24 and 30; a test was considered positive if the concentration was 50 ng/mL or greater. The primary outcome was spontaneous delivery associated with PPROM or preterm labor before 35 weeks. The investigators found a significant association between abnormal fetal fibronectin levels and preterm birth (TABLE 1).

Specificity and negative predictive values were much greater than sensitivity and positive predictive values, suggesting that a negative test might be more informative clinically than a positive one. Additionally, sensitivity for earlier preterm delivery (24 to 26 weeks) was greater than for later preterm delivery (28 to 30 weeks); thus, a positive fetal fibronectin test would be more useful for identifying women who would deliver before 28 weeks' gestation.

Because the Goldenberg study was a large multicenter trial that included women across a broad spectrum of age, race, and socioeconomic status, its results could be applied to all US women. Indeed, this study provided a compelling incentive to use fetal fibronectin sampling as a screening test for risk of preterm delivery.

Other studies⁶⁻⁸ corroborated the landmark

TABLE 1

**Fetal fibronectin as a predictor of spontaneous preterm delivery:
Detection at 22-24 weeks' gestation**

TIMING OF SPONTANEOUS PRETERM DELIVERY	SENSITIVITY (%)	SPECIFICITY (%)	POSITIVE PREDICTIVE VALUE (%)	NEGATIVE PREDICTIVE VALUE (%)
<32 weeks	50	94	13	99.9
<35 weeks	32	95	21	97
<37 weeks	19	95	29	91

Data from Goldenberg et al.^{3,5}

Some experts argue that a negative fibronectin test is useful in identifying those at low risk of delivery, thereby avoiding tocolysis and hospitalization.

Lockwood and Goldenberg studies, providing an affirmative answer to the question "Can we screen for preterm delivery?"

Does fibronectin sampling meet the standard for screening?

Significant burden. There is no question that preterm birth represents a significant burden.^{9,10} For one, it is common. Recent data indicate that approximately 10% of deliveries in the United States occur before 37 weeks of gestation, which translates to more than 400,000 preterm births annually. Of these, 2% to 3% occur before 32 weeks' gestation.

Preterm infants are at a greatly increased risk of serious complications (eg, respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage) and death.¹¹ In fact, preterm delivery is perhaps the most common cause of neonatal death.

Good marks for accuracy, cost, ease of use, safety, acceptability. As noted, a positive result is strongly associated with preterm birth. Further, this noninvasive test poses little to no threat to women, is simple for the cli-

nician to perform, is economical, and is well received by patients.

Availability of effective treatment. Of the 5 conditions a widely used screening test must possess, this is the only one in which fetal fibronectin sampling is lacking. No effective interventions exist to decrease preterm birth in women with positive tests.

Antibiotic therapy fails to reduce preterm births

In May 2003, Andrews et al¹² published the results of a multicenter, double-blind, placebo-controlled trial in which asymptomatic women with fetal fibronectin levels over 50 ng/mL (6.6% of the 16,317 women screened) received antibiotic therapy.

The final study population included 347 women given a 10-day course of metronidazole (250 mg 3 times daily) plus erythromycin (250 mg once daily) and 356 women taking placebo. The 2 groups were well matched for age, ethnicity, marital status, education, average gestational age, and incidence of bacterial vaginosis.

Treatment did not reduce the rate of spontaneous preterm birth. No differences were seen in the incidence of delivery before 32, 35, or 37 weeks, or in birth weight (TABLE 2). Nor was there improvement in any health parameters in the infants delivered by women in the antibiotic group.

Was the study flawed?

One could argue that the Andrews study had some limitations. First, it is possible that the sample size was too small to detect differences between the treatment groups. Second, screening was performed at a mean gestational age of 23 weeks (range, 21 to 26 weeks), which may not have been early enough. Third, patient compliance was poor (only about 50% of the antibiotic group took all of their medication);

thus, treatment efficacy may have been inadequately assessed. In addition, the 10-day treatment regimen may have been too brief.

Could other agents yield better results?

It is possible that metronidazole and erythromycin were not the appropriate antibiotics for treating the subclinical infection associated with preterm delivery. In fact, an entirely different class of agents may be needed.

Is inflammation a factor? If inflammation rather than subclinical infection is the primary precipitant of fetal fibronectin release into the cervix and vagina prior to preterm labor, antiinflammatory therapy may have a role in its prevention.

Clinical experience

We do not use fetal fibronectin as a screening test in asymptomatic women since there is no established intervention. There is more debate about whether it can be used as a diagnostic test. Some experts argue that, in patients with “threatened” preterm labor, a negative fetal fibronectin test may be useful in identifying those at low risk of delivery, thereby avoiding tocolysis and hospitalization.

However, since this benefit has not been demonstrated in clinical trials or observational

TABLE 2**Effect of antibiotic therapy on spontaneous preterm delivery**

OUTCOMES	METRONIDAZOLE / ERYTHROMYCIN	PLACEBO	RELATIVE RISK (95% CI)
Spontaneous preterm delivery			
<32 weeks	4.3%	2.2%	1.94 (0.83-4.52)
<35 weeks	6.9%	7.5%	0.92 (0.54-1.56)
<37 weeks	14.4%	12.4%	1.17 (0.80-1.70)
Birth weight			
<1,500 g	3.5%	3.2%	1.12 (0.50-2.50)
<2,500 g	12.7%	14.3%	0.88 (0.60-1.29)
CI = confidence interval Data from Andrews et al. ¹²			

studies, it should not alter our practice. Until it has been proven, we will continue to manage women with symptoms of preterm labor without the use of fetal fibronectin. ■

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