Fetal Fibronectin Enzyme Immunoassay

Medical Policy

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Medicine

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Description

Assessment of fetal fibronectin (FFN) is proposed for use in the diagnosis and management of preterm labor (PTL) and in the management of women at term being considered for induction. A rapid test is available that can provide results within 20 minutes. FFN testing has been considered for several categories of patients including women who are experiencing symptoms of preterm labor, asymptomatic women at increased risk of pre-term labor and asymptomatic women as part of routine pregnancy care.

Fetal fibronectin (FFN) is a high-molecular-weight glycoprotein that can be isolated from fetal connective tissue, placenta, and amniotic fluid. Fetal fibronectin can be measured in cervicovaginal secretions early in pregnancy and at term, but is rarely detectable between 21 and 37 weeks' gestation in normal pregnancies that are delivered at term. However, FFN may also be detected between 21 and 37 weeks in association with preterm delivery. It has been hypothesized that elevation of FFN signals the separation of the placental uterine junction, and thus FFN may be a useful marker in predicting which women will experience spontaneous labor within a short period of time. In 1998, a rapid fetal fibronectin test became available, permitting results within 20 minutes of testing. This assay produces qualitative results, reported as positive, negative, or indeterminate. Generally, a FFN level of 50 ng/mL or higher is considered a positive test.

The clinical importance of FFN measurement relates to the diagnosis and management of preterm labor (PTL). Clinical symptoms of PTL are nonspecific and include vaginal spotting or bleeding, increased or changed vaginal discharge, intermittent abdominal cramping, backache, and inappropriate uterine contractions. Signs of PTL include cervical effacement and dilation, or a shortened cervix, as assessed by transvaginal ultrasound. When symptoms of PTL develop and the physical exam does not immediately confirm a diagnosis of progressive PTL, the patient is usually hospitalized for an initial period of observation to determine if the symptoms subside or progress. During this time, bed rest and possible treatment in the form of IV hydration, antibiotics, or tocolytic drugs, depending on the symptoms and results of the physical exam, are prescribed. In many cases, the symptoms of preterm labor subside during the period of observation and prophylactic treatment. However, if the signs and symptoms of PTL are
sufficiently advanced or suspicious, delivery within 7 days may be highly likely. In these cases, particularly if gestation is 34 weeks or less, corticosteroid treatment for the induction of fetal lung maturity is indicated.

However, accurate diagnosis of PTL is extremely difficult; current methods of assessing risk result in overdiagnosis of PTL. FFN has been investigated as a method to more accurately diagnose PTL and thus eliminate unnecessary hospitalizations, tocolytic therapy, and corticosteroid treatment in women who do not truly have PTL. The use of FFN has been studied in several different categories of patients:

- Women of average risk who are experiencing symptoms suggestive of preterm labor;
- Women with multiple gestations or other high-risk factors for preterm birth who are experiencing symptoms of preterm labor;
- Asymptomatic women with no risk factors for preterm birth; FFN is used in these patients as a screening test at certain intervals during pregnancy;
- Asymptomatic women with multiple gestations or other high-risk characteristics of preterm birth; FFN is used in these patients as a screening test at certain intervals during pregnancy;
- Women at term being considered for induction who are likely to deliver within 24–48 hours and therefore do not require induction.

**Regulatory Status**

In 1998, a rapid qualitative fetal fibronectin test (Adeza Fetal Fibronectin Enzyme Immunoassay, Adeza Biomedical) was approved by the FDA through the premarket approval process. The test is indicated:

1. As an aid to rapidly assess the risk of preterm delivery in less than 7 or less than 14 days from the time of sample collection in pregnant women with signs and symptoms of early preterm labor, intact amniotic membranes, and minimal cervical dilation (< 3 cm) sampled between 24 weeks and <35 weeks gestation;

2. For use in conjunction with other clinical information to rapidly assess the risk of preterm delivery before 35 weeks in women with singleton pregnancies undergoing a routine prenatal examination between 22 weeks and <31 weeks.

**Policy**

The use of FFN assays may be considered **medically necessary** for use in women with singleton or twin gestations, with intact membranes, cervical dilation <3 cm, and who are experiencing symptoms suggestive of preterm labor between 24 and <35 weeks’ gestation. This population represents women who are most likely to be hospitalized and treated in an attempt to prevent preterm birth.

All other applications of the FFN assay are considered investigational, including, but not limited to, the following:

- As part of routine pregnancy monitoring in **asymptomatic** women with singleton gestation and no risk factors for preterm birth;
• As part of clinical monitoring of **asymptomatic** women at high risk for preterm birth, including but not limited to those with multiple gestations, history of preterm birth, uterine malformation, cervical incompetence, or history of 2 or more spontaneous second trimester abortions;

• As part of clinical monitoring in women with triplet or higher-order gestations, intact membranes, cervical dilation <3cm, and who are experiencing symptoms suggestive of preterm labor;

• As a test to identify women at term being considered for induction who are likely to deliver within 24–48 hours and therefore, do not require induction.

### Policy Guidelines

CPT code 82731 (fetal fibronectin, cervicovaginal secretions, semi-quantitative) may be used to describe the fetal fibronectin ELISA tests performed exclusively at reference laboratories. The rapid fetal fibronectin test produces qualitative results (i.e., positive, negative, or indeterminate) and therefore, CPT code 82731 does not describe the rapid test.

### Rationale

The policy was created in 1997 and updated in 2005. In 2010, it returned to active review and was updated with a literature search using the MEDLINE database for the period March 2005 through July 2010.

**Fetal fibronectin measurement in women with symptoms of preterm labor.**

The policy was based on a 1997 TEC Assessment, which noted that there were no published intervention trials in which the results of the FFN assay are used in patient management, and all published studies of the predictive value of the FFN assay in relation to preterm birth were observational. (1) Observational studies in women with symptoms suggestive of pre-term labor report that the positive predictive value (PPV) of the FFN assay for preterm birth ranged from 0.45 to 0.81, while the negative predictive value for preterm birth within 14 days of the test was 0.95 to 0.99. Calculated sensitivities for the observational studies range from 41% to 100% and specificities ranged from 70% to 96%. The TEC Assessment concluded that a negative FFN result in symptomatic women can be used to prompt discontinuation of hospitalization and treatment, since the consistently high negative predictive value of this test provides evidence that only approximately 1% of these women will deliver within a 2-week interval. Because of the relatively low positive predictive value of the assay, positive results of an FFN assay have more limited clinical impact. The 1997 Assessment concluded that positive results may support the need for continued hospitalization and preventive measures, including tocolytic therapy, corticosteroid treatment, or patient transfer to a tertiary care center with a neonatal intensive care unit.

The conclusion of the TEC assessment was supported by a 1999 study by Joffe et al. who reported on a prospective study that examined the impact of the use of FFN on the rate of hospitalization for PTL compared to a baseline period before the FFN assay was implemented. (2) All patients presenting with symptoms suggestive of preterm labor underwent an FFN assay; results were reported within 24–48 hours. It is not clear whether the patients were hospitalized in the interval between testing and FFN results. In those with negative results, tocolysis was
discontinued and activity restrictions were lifted. In those with positive results, betamethasone was initiated with the use of oral tocolysis at the discretion of the physician. Compared to the prior year, which served as a baseline, during the study year there were fewer admissions for PTL, fewer PTL admissions per patient, and fewer prescriptions written for tocolytic agents. In addition, the length of stay per admitted patients was decreased. There were no differences in neonatal outcomes.

More recently, Sanchez-Ramos and colleagues conducted a meta-analysis of studies on the diagnostic accuracy of fetal fibronectin for predicting preterm birth within 7 days of testing in women with signs or symptoms of preterm labor (3) (It is worth noting that this outcome differs from delivery within 14 days which was the outcome used in the TEC Assessment.) In a pooled analysis of data from 32 cohort studies which had a total of 5,355 patients, the pooled estimate of sensitivity was 76.1% (95% confidence interval [CI] =69.1% to 81.9%) and the pooled estimate of specificity was 81.9% (95% CI = 78.9% to 84.5%). The authors conducted a meta-regression analysis to evaluate the impact of different study characteristics on diagnostic accuracy. They found that year of publication was a statistically significant factor, with older studies having findings of higher accuracy than more recent studies (studies in the meta-analysis were published between 1995 and 2008). The authors posited that this may be due to the switch from the membrane immunoassay to the rapid fetal fibronectin test; after 2002, the rapid test was used more commonly. This implies that the rapid test may be less accurate than the membrane test. However, the study did not actually compare the diagnostic accuracy of the two types of fetal fibronectin tests and no other studies comparing test types were identified.

A 2008 Cochrane review reviewed the literature on the impact of fetal fibronectin testing on health outcomes in women with signs or symptoms of preterm labor between 22 and 34 weeks' gestation. (4) Thirteen trials were identified; 7 were excluded because they were limited to women with only positive or only negative FFN tests. Another trial had limited reporting of outcomes, leaving 5 eligible trials. The analyses were based on singleton pregnancies. A pooled analysis of 3 trials found that the rate of preterm birth prior to week 37 was significantly lower when there was knowledge of the FFN level (21/135, 16%) compared to no knowledge of the FFN level ( 40/140, 29%); the risk ratio was 0.54 (95% CI =0.34-0.87). However, other outcomes for which there was sufficient data, including preterm birth at less than 34, 32 or 28 weeks, birthweight less than 2500 grams, maternal hospitalizations and tocolysis did not differ significantly between the groups with and without FFN knowledge. For example, a pooled analysis of 4 studies found a similar rate of tocolysis when there was knowledge of FFN findings (64/175, 37%) and when there was no FFN knowledge (66/175, 38%); risk ratio =1.01 (95% CI =0.78-1.30).

One of the studies included in the Cochrane review was published in 2003 by Plaut and colleagues. They reported on a study that randomized women with symptoms of preterm labor to management either directed or not directed by the results of a fetal fibronectin test. In this study, the length of hospitalization was shorter when physicians knew the results of a negative test. (5) The results of this study contrast with those of Grobman and colleagues, who, in 2004, conducted a randomized trial in women with a singleton pregnancy who were experiencing symptoms of preterm labor. (6) All women underwent a fetal fibronectin test, but the results were only known in one group of women. The women who did not have the fetal fibronectin results available were no different than those women who did with respect to initial length of labor and delivery observation, hospital admission, tocolysis, cessation of work, or total health care-related costs. A third trial in the Cochrane review, published by Ness and colleagues in 2007, was similar in design to the Grobman study. (7) One hundred women with symptoms of
preterm labor received FFN testing, as well sonographic testing of cervical length, and were randomized to a group that was told the test results (knowledge group) or a group blinded to results. The primary outcome, length of evaluation in triage, did not differ significantly in the two groups. The time from evaluation to discharge was a mean of 2.24 hours in the knowledge group and 2.49 hours in the blinded group. Among the secondary outcomes, groups did not differ in the rate of delivery within 7 days, delivery within 14 days or spontaneous preterm birth before 34 weeks. There was a significantly lower rate of delivery before 37 weeks in the group with knowledge of test results. In addition, the study found that the admission rate for pre-term labor was significantly higher in the knowledge group (19.6%) than in the blinded group (41%).

There are limited data specifically addressing the use of FFN in symptomatic patients with additional high-risk factors for preterm birth; these high-risk patients are presumably already undergoing standard aggressive management of symptoms, and there were no data to suggest that the results of FFN would alter management. Some data have since appeared regarding symptomatic patients with twin gestations. One study published in 1998 by Terrone and colleagues calculated a negative predictive value of 94% for delivery within 1 week in 43 patients with twin gestations who presented with symptoms of preterm labor. (8) Negative predictive values between 92% and 99% have been extracted from other studies with small numbers of twins. (9) Although the data are sparse, they suggest that a negative FFN assay may contribute to the decision to withhold or withdraw aggressive treatment for PTL in symptomatic women with twin gestations.

There are no data addressing the use of FFN in triplet or higher-order gestations.

Fetal fibronectin measurement in asymptomatic women

The 1997 TEC Assessment concluded that, in asymptomatic patients both with and without additional risk factors (including multiple gestations) for preterm birth, the positive predictive value of FFN findings was inadequate to identify women who require preventive treatment based upon the FFN result alone. (1)

Since the TEC Assessment, there have been no additional studies that would alter these conclusions. Although the FFN assay is a risk predictor for preterm delivery among asymptomatic women, there is no proven effective treatment for asymptomatic women at risk of preterm birth that is known to improve maternal or fetal outcomes.

Two subsequent studies, both from the UK, evaluated use of the FFN assay in asymptomatic women at increased risk of preterm birth. One study reported on a secondary analysis of a prospectively-created database of asymptomatic women with singleton pregnancies who had a history of pre-term delivery and were tested for FFN at 24 weeks’ gestation. (10) Data on 563 women were available. A total of 497 (88%) of women had an FFN of 0, 41 (8%) had an FFN between 1-49 ng/mL, 17 (0.3%) had an FFN between 50-199 ng/ML and 7 (0.1%) had an FFN of at least 200 ng/mL. A number of analyses were conducted comparing women with different levels of FFN and calculating the association between FFN level and risk of preterm birth before 28, 32, 34 and 37 weeks. Compared to women with an FFN of 0, those with an FFN above 50 ng/mL had significantly increased risk of spontaneous preterm delivery prior to 32, 34 and 37 weeks’ gestation. For example, 90/497 (18%) women with an FFN of 0 had preterm delivery before 37 weeks, compared to 12/25 (48%) of those with FFN above 50 ng/mL. In addition to multiple statistical comparisons, the study was limited by the small number of women with increased FFN levels which resulted in wide confidence intervals in all analyses.
The other study, by Shennan and colleagues in the U.K., evaluated whether treatment with metronidazole reduces early preterm labor in women with singleton pregnancies who have positive FFN findings in the second trimester of pregnancy. (11) One hundred women with positive FFN findings (at least 50 ng/mL) were randomized to receive a week of oral metronidazole 400 mg three times a day or placebo. There was not a statistically significant difference between groups in the primary outcome, delivery before 30 weeks. Rates were 11/53 (21%) in the metronidazole group and 5/46 (11%) in the placebo group. Among the secondary outcomes, there was a significantly higher rate of pre-term delivery before 37 weeks in the group assigned to metronidazole compared to placebo (62% vs. 39%, respectively). The trial was stopped early due to the poorer outcomes in the metronidazole groups. Thus, this study did not show that FFN assessment in asymptomatic high-risk women led to an early intervention that improved outcomes.

Fetal fibronectin testing for use in women at term being considered for induction

The 1997 Assessment concluded that the evidence is insufficient to support the use of the FFN assay to identify women at term being considered for induction who are likely to deliver within 24–48 hours and, therefore, do not require induction. (1) Although many studies show an association between FFN levels and imminent term delivery, there is no evidence that the predictive values are sufficiently high to alter management.

Summary

A 1997 TEC Assessment concluded that there was sufficient evidence to support the use of fetal fibronectin (FFN) measurement in selected women with signs or symptoms of preterm labor. This conclusion was based on the value of a negative test. A more recent Cochrane review of studies with this population of women found that knowledge of FFN level reduced the preterm birth rate before 37 weeks’ gestation, although other outcomes (including material hospitalization) were not affected by FFN knowledge. Another recent meta-analysis found significantly lower diagnostic accuracy in newer versus older studies evaluating fetal fibronectin tests; no studies comparing the accuracy of the newer rapid fetal fibronectin test to the older membrane test were identified.

There is insufficient evidence that FFN testing improves outcomes for asymptomatic women at average risk or at increased risk of preterm labor. No published evidence was identified on FFN assessment in women with triple or higher-order gestations, or in women being considered for induction.

Thus, FFN assessment may be considered medically necessary in women with singleton or twin gestations who have signs or symptoms of preterm labor since the original premise has not been disproven. However, use of FFN assessment is considered investigational for all other applications.

Technology Assessments, Guidelines and Position Statements

The American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin of October 2001 (reaffirmed 2008) reached the following recommendations regarding FFN testing: (12)

1. FFN or ultrasonography to determine cervical length may be useful in determining women at high risk for preterm labor. However, their clinical usefulness may rest primarily with their negative predictive value given the lack of proven treatment options to prevent preterm birth.
2. FFN testing may be useful in women with symptoms of preterm labor to identify those with negative values and a reduced risk of preterm birth, thereby avoiding unnecessary intervention.

**Medicare National Coverage**

No national coverage determination.

**References:**

1. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Fetal fibronectin enzyme immunoassay. TEC Assessments 1997; Volume12, Tab 16.


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