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Information for Health Care Providers

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Fetal Fibronectin Enzyme Immunoassay and Rapid fFN® for the TLiQ® System

A TEST TO AID IN THE ASSESSMENT OF PRETERM DELIVERY RISK

This brochure was prepared by Hologic, Inc. to familiarize you with the clinical interpretation of the Fetal Fibronectin Enzyme Immunoassay or Rapid fFN for the TLiQ® System. In conjunction with other clinical information, testing for the presence of fetal fibronectin in cervicovaginal secretions of women with suspected preterm labor and women undergoing routine prenatal care will help you and your patients gain valuable information about their pregnancies, including assessment of risk of preterm delivery. Additional copies of this brochure are available by calling 1-800-442-9892.

INTENDED USE

The Fetal Fibronectin Enzyme Immunoassay and Rapid fFN for the TLiQ System are devices to be used as an aid in assessing the risk of preterm delivery in ≤ 7 or ≤ 14 days from the time of cervicovaginal sample collection in pregnant women with signs and symptoms of early preterm labor, intact amniotic membranes, and minimal cervical dilatation (< 3 cm), sampled between 24 weeks, 0 days and 34 weeks, 6 days gestation.

The negative predictive values of the Fetal Fibronectin Enzyme Immunoassay of 99.5% and 99.2%, for delivery in ≤ 7 and ≤ 14 days, respectively, make it highly likely that delivery will not occur in these time frames. In addition, although the positive predictive values were found to be 12.7% and 16.7% for delivery in ≤ 7 and ≤ 14 days, respectively, this represents an approximate 4-fold increase over the reliability of predicting delivery given no test information.

These devices are further indicated for use in conjunction with other clinical information as an aid in assessing the risk of preterm delivery in ≤ 34 weeks, 6 days, when a cervicovaginal sample is obtained during a routine prenatal visit between 22 weeks, 0 days and 30 weeks, 6 days of gestation in women with a singleton gestation. The negative predictive value of the Fetal Fibronectin Enzyme Immunoassay ranges from 96.4% to 97.9% making it highly likely that delivery will not occur in these time frames. The positive predictive value ranges from 13.3% to 31.7% for delivery in ≤ 34 weeks, 6 days and represents an approximate 4- to 7-fold increase in risk over the reliability of predicting delivery given no test information.

The clinical utility of a real time fetal fibronectin test result that is rapidly available using Rapid fFN represents a significant and critically needed improvement in the ability to manage preterm labor that may result in preterm delivery.

PRETERM DELIVERY: THE CLINICAL DILEMMA

Of the approximately 4,000,000 deliveries that occur annually in the United States, about 400,000 are premature. Preterm delivery, defined by the American College of Obstetricians and Gynecologists as delivery prior to the 37th week of gestation, is responsible for the majority of non-chromosomal perinatal morbidity and mortality (1–4). Symptoms of threatened preterm delivery include uterine contractions, change of vaginal discharge, vaginal bleeding, backache, abdominal discomfort, pelvic pressure, and cramping. Diagnostic modalities for identification of threatened preterm delivery include uterine activity monitoring and performance of a digital cervical examination, which allows estimation of cervical dimensions. These methods have been shown to be limited, as minimal cervical dilatation (< 3 centimeters) and uterine activity occur normally and are not necessarily diagnostic of imminent preterm delivery (5,12,14). While several serum biochemical markers have been evaluated, none have been widely accepted for practical clinical use (6,7). Cervicovaginal fetal fibronectin, measured using enzyme-linked immunosorbent assay or Rapid fFN, has gained increased acceptance for practical clinical use.

FETAL FIBRONECTIN: PRESENCE AT THE MATERNAL-FETAL INTERFACE

Fetal fibronectin, an isoform of fibronectin, is a major component of the extracellular matrix of the membranes of the amniotic sac. Fetal fibronectin can be distinguished from other members of the fibronectin family by the presence of a unique region, known as the III-CS domain. Scientists have developed a monoclonal antibody, called FDC-6, which specifically recognizes the III-CS domain of fetal fibronectin (8-10).

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Immunohistochemical studies of placentae show that fetal fibronectin is confined to the extracellular matrix of the interface between the maternal and fetal units within the uterus; this interface is also known as the choriodecidual junction (5,11). These studies suggest that fetal fibronectin is a product of extravillous chorionic trophoblasts which cover the periphery of the amniotic sac and attach to the maternal decidua of the uterus. Because of fetal fibronectin's unique localization adjacent to the placenta and amniotic sac, a number of clinical trials have been conducted to study the association of cervicovaginal fetal fibronectin expression to risk of preterm delivery.

Fetal fibronectin can be detected in cervicovaginal secretions of women throughout pregnancy by use of a monoclonal antibody-based immunoassay. Fetal fibronectin is elevated in cervicovaginal secretions during the first 24 weeks of pregnancy but diminishes between 24 and 34 weeks in normal pregnancies. The significance of its presence in the vagina during the first 24 weeks of pregnancy is not understood. However, it may simply reflect the normal growth of the extravillous trophoblast population and the placenta. Detection of fFN in cervicovaginal secretions between 24 and 34 completed weeks gestation is reported to be associated with preterm delivery in symptomatic (5, 12-16) and asymptomatic pregnant women (17-20).

SUMMARY: FETAL FIBRONECTIN AS A CLINICAL TOOL

Two prospective clinical studies have been conducted to demonstrate the safety and effectiveness of the Fetal Fibronectin Enzyme Immunoassay as a risk factor for preterm delivery.

In the first trial, it was determined that expression of fetal fibronectin in vaginal secretions can be used to assess the risk of preterm delivery in ≤ 7 or ≤ 14 days of specimen collection (as described in Intended Use) among symptomatic pregnant women with signs and symptoms of preterm labor. In this same trial, which included 763 women evaluated at 10 clinical sites, it was also determined that expression of fetal fibronectin is also related to other clinical features, including delivery in ≤ 36 completed weeks (preterm delivery) and neonatal well-being. A positive fetal fibronectin test result suggests elevated risk of early delivery with its attendant neonatal consequences. In contrast, a negative fetal fibronectin test result is strongly associated with prolonged gestation and term delivery. Symptomatic women with a negative fetal fibronectin test result have less than a 1% chance of delivering in ≤ 7 or ≤ 14 days from the time of specimen collection. Thus, in the absence of other clinical evidence, a negative fetal fibronectin test result indicates a reduced risk of preterm delivery. This should be considered in light of other information in making patient management decisions.

In a separate clinical trial, it was determined that expression of fetal fibronectin in either a cervical or vaginal specimen obtained from asymptomatic pregnant women at approximately 24 weeks of gestation identifies a portion of pregnant women who ultimately deliver in ≤ 34 weeks, 6 days of gestation. In this population of 2929 asymptomatic pregnant women, a positive cervical fetal fibronectin test result at 24 weeks gestation was associated with an approximate 9-fold increase in the risk of delivery in ≤ 34 weeks, 6 days of gestation. The prevalence of delivery ≤ 34 weeks, 6 days of gestation was 4.4%, thus, the positive predictive value of 31.7% for the cervical specimen represents an approximate 7-fold increase over the reliability of predicting delivery given no fetal fibronectin test information. More important, cervicovaginal expression of fetal fibronectin at approximately 24 weeks gestation is associated with a nearly 60-fold increase in the probability of early preterm delivery, i.e., delivery < 28 weeks of gestation, when neonatal outcome may be severely compromised. In addition, cervicovaginal expression of fetal fibronectin between 22 weeks, 0 days and 30 weeks, 6 days is associated with a 4- to 10-fold increase in the risk of delivery ≤ 34 weeks, 6 days of gestation. The results of this study further demonstrate that the Fetal Fibronectin Enzyme Immunoassay should be used in conjunction with all other available clinical information to most accurately identify risk of preterm delivery ≤ 34 weeks, 6 days of gestation among asymptomatic pregnant patients evaluated between 22 weeks, 0 days and 30 weeks, 6 days.

A third prospective study of 587 cervicovaginal specimens from both symptomatic and asymptomatic pregnant women demonstrated equivalency between Rapid fFN and the fFN Enzyme Immunoassay. Both tests were in agreement 94.9% of the time (Kappa coefficient = 0.81, 95% confidence interval [0.75, 0.88] Table 1).

Table 1

Agreement Between fFN Enzyme Immunoassay and Rapid fFN for the TLi® System (n=587) Among Symptomatic and Asymptomatic Women

	fFN Enzyme Immunoassay (+)	fFN Enzyme Immunoassay (-)	
Rapid fFN (+)	77	17	94
Rapid fFN (-)	13	480	493
	90	497	587

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FETAL FIBRONECTIN: CLINICAL TRIAL RESULTS

Assessment of Risk for Symptomatic Patients

A prospective study of 763 pregnancies was conducted at 10 clinical sites in the United States to assess the association of vaginal expression of fetal fibronectin to preterm delivery. The Fetal Fibronectin Enzyme Immunoassay was used to assess risk of preterm delivery for symptomatic pregnant women meeting the following clinical criteria:

- Present for unscheduled obstetrical care
- Have signs and symptoms of threatened preterm delivery limited to:
  - Uterine contractions (with or without pain)
  - Intermittent lower abdominal pain, dull backache, pelvic pressure
  - Vaginal bleeding during the second or third trimester
  - Menstrual-like intestinal cramping (with or without diarrhea)
  - Change in vaginal discharge (amount, color, or consistency)
  - Vague sense of discomfort characterized as “not feeling right”
- Have a gestational age between 24 weeks, 0 days and 34 weeks, 6 days
- Have intact amniotic membranes
- Have minimal cervical dilatation (< 3 centimeters)

Relationship of Fetal Fibronectin to Delivery Endpoints

The safety and effectiveness of the Fetal Fibronectin Enzyme Immunoassay was evaluated in a population of 763 pregnant patients with signs and symptoms commonly associated with threatened preterm delivery. The relationship of the Fetal Fibronectin Enzyme Immunoassay test result to the primary endpoint of delivery in ≤ 7 and ≤ 14 days is shown in Table 2. For delivery ≤ 7 days, the sensitivity, specificity, and positive and negative predictive values of the Fetal Fibronectin Enzyme Immunoassay were 86.4%, 82.3%, 12.7%, and 99.5%, respectively. For delivery ≤ 14 days, the sensitivity, specificity, and positive and negative predictive values of the Fetal Fibronectin Enzyme Immunoassay were 83.3%, 82.9%, 16.7%, and 99.2%, respectively.

Table 2
Sensitivity, Specificity, and Positive and Negative Predictive Values of Fetal Fibronectin for Delivery ≤ 7 and ≤ 14 Days among Symptomatic Women (n=763)[a]

Delivery	n (%)	Sensitivity (95% CI)	Specificity (95% CI)	Pred Val + (95% CI)	Pred Val - (95% CI)
≤ 7 Days	22 (2.9%)	86.4% (66.4, 95.3)	82.3% (79.4, 84.9)	12.7% (4.2, 33.7)	99.5% (98.7, 99.8)
≤ 14 Days	30 (3.9%)	83.3% (66.3, 93.7)	82.9% (80.0, 85.4)	16.7% (7.3, 33.7)	99.2% (98.3, 99.6)

[a]Proportion of deliveries at each endpoint are calculated using 763 as the denominator

Additional Clinical Data for Symptomatic Patients

The Fetal Fibronectin Enzyme Immunoassay test result was also related to other clinical features, including delivery in ≤ 36 completed weeks of gestation (preterm delivery) and neonatal well-being. The sensitivity, specificity, and positive and negative predictive values of the Fetal Fibronectin Enzyme Immunoassay were 41.3%, 86.2%, 44.7%, and 84.5%, respectively, for delivery ≤ 36 completed weeks (162 or 21.2% of the 763 subjects delivered ≤ 36 completed weeks).

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The relationship of the fetal fibronectin test result to neonatal well-being is shown in Table 3.

Table 3
Neonatal Well-Being Among Symptomatic Women Stratified by Fetal Fibronectin Test Result[a]

		fFN +	fFN -	p-value[b]
Total Subjects	**n (%)**	150 (19.7%)	613 (80.3%)	—
Infant Weight (grams)	**Avg** **SD** **n** **Range**	2804.0 776.2 154 625–4280	3242.8 582.7 636 835–5800	0.0001
Infant Weight (grams) n (%)	 **<1500** **<2500**	 11 (7.1%) 57 (37.0%)	 6 (0.9%) 69 (10.8%)	 0.00005 <0.00001
Perinatal Morbidity Respiratory Distress	**n (%)**	18 (11.7%)	22 (3.5%)	0.0001
NICU Admission	**n (%)**	44 (28.6%)	68 (10.7%)	<0.000001
Neonatal Hospital Days		5.9±11.1	2.9±7.1	0.01

The number of subjects, distribution of positive fetal fibronectin test results, sensitivity, and predictive value of a positive test for delivery in ≤ 7 days from specimen collection for symptomatic pregnant women < 32 weeks and ≥ 32 weeks is shown in Table 4. The proportion of positive tests and the sensitivity of the Fetal Fibronectin Enzyme Immunoassay are the same for women before and after 32 weeks. The number of symptomatic women seeking care increases gradually with advancing gestational age as does the number of deliveries.

Table 4
Distribution of Symptomatic Subjects and Fetal Fibronectin Test Results Before and After 32 Weeks Gestation[a]

EGAS[a] (Weeks)	Subjects N	fFN +[b] n (%)	Sensitivity (%) (fFN+/Del ≤7 Days)	Pred Val + (%) (Del ≤7 Days/fFN+)
< 32 Weeks	483	91 (18.8%)	8/9 (88.9%)	8/91 (8.8%)
≥ 32 Weeks	280	59 (21.0%)	11/13 (84.6%)	11/59 (18.6%)
TOTAL	763	150 (19.7%)	19/22 (86.4%)	19/150 (12.7%)

[a]Estimated Gestational Age at Specimen Collection
[b]fFN + = positive Fetal Fibronectin Enzyme Immunoassay test result

The ability of other clinical factors to assess risk of preterm delivery were also evaluated in this prospective trial and compared to the Fetal Fibronectin Enzyme Immunoassay. The sensitivity, specificity, positive predictive values, and negative predictive values and their 95% confidence intervals for delivery in ≤ 7 days for the Fetal Fibronectin Enzyme Immunoassay, cervical dilatation, uterine activity, vaginal bleeding, and ascending genital tract infection (bacterial vaginosis) are provided in Table 5.

Table 5
Sensitivity, Specificity, and Positive and Negative Predictive Values for Risk Factors Among Symptomatic Women

Risk Factor	n	Positive Test Defined[a]	Sensitivity (95% CI)[b]	Specificity (95% CI)	Pred Val + (95% CI)	Pred Val - (95% CI)
fFN Enzyme Immunoassay	763	≥ 0.05 µg/mL	86.4% (66.4%, 95.3%)	82.3% (79.4%, 84.9%)	12.7% (4.2%, 33.7%)	99.5% (98.7%, 99.8%)
Uterine Activity	750	≥ 4 cntx/hr	54.5% (34.5%, 73.1%)	75.3% (72.0%, 78.3%)	6.3% (1.4%, 24.3%)	98.2% (96.9%, 98.9%)
Cervical Dilatation	757	> 1 cm	38.1% (20.6%, 59.4%)	88.3% (85.8%, 90.4%)	8.5% (2.1%, 27.9%)	98.0% (96.7%, 98.8%)
Vaginal Bleeding	759	Any Bleeding	40.9% (23.0%, 61.6%)	85.2% (82.4%, 87.6%)	7.6% (1.9%, 26.3%)	98.0% (96.7%, 98.7%)
Ascend Gen Tract Inf	763	Bacterial Vaginosis	9.1% (2.5%, 27.8%)	84.1% (81.2%, 86.5%)	1.7% (0.1%, 17.6%)	97.3% (95.9%, 98.2%)

[a]Cutoff used to define a positive test result for determining sensitivity, etc.
[b]95% Confidence Interval (Lower Limit, Upper Limit)

Assessment of Risk for Asymptomatic Patients

The safety and effectiveness of the Fetal Fibronectin Enzyme Immunoassay as a risk factor for preterm delivery in ≤ 34 weeks, 6 days of gestation was evaluated in a prospective study of 2929 singleton pregnancies at 10 clinical sites in the United States. A cervical and vaginal specimen were obtained from asymptomatic pregnant women receiving routine prenatal care between 22 weeks, 0 days and 30 weeks, 6 days of gestation.

Relationship of Fetal Fibronectin Expression to Delivery Endpoints

The primary endpoint of this study was spontaneous preterm delivery ≤ 34 weeks, 6 days of gestation. Secondary endpoints included delivery < 28 weeks, ascending genital tract infection, and neonatal outcome. Of the 2929 women in this study, 127 (4.4%) delivered ≤ 34 weeks, 6 days of gestation and 19 (0.7%) delivered < 28 weeks of gestation. Of the 2915 cervical and 2922 vaginal specimens obtained between 22 weeks, 0 days and 24 weeks, 6 days gestation, 82 (2.8%) and 101 (3.5%), respectively, were positive for fetal fibronectin. The association of the Fetal Fibronectin Enzyme Immunoassay test result to delivery in < 28 and ≤ 34 weeks, 6 days of gestation for the vaginal and cervical specimens collected at the 24 week visit is shown in Table 6a. Similarly, at the 26 week visit, 2431 cervical and 2435 vaginal specimens were obtained, and 82 (3.4%) and 84 (3.4%), respectively, were positive for fetal fibronectin. The association of the Fetal Fibronectin Enzyme Immunoassay test result to delivery in ≤ 34 weeks, 6 days of gestation is shown in Table 6b. At the 28 week visit, 2308 cervical and 2312 vaginal specimens were obtained. A total of 60 (2.6%) and 72 (3.1%) were positive at the cervical and vaginal regions, respectively. The association of the Fetal Fibronectin Enzyme Immunoassay test result at the 28 week visit to delivery in ≤ 34 weeks, 6 days of gestation is shown in Table 6c. Results of Fetal Fibronectin testing at the 30 week visit showed that of the 2422 cervical and 2425 vaginal specimens obtained, 79 (3.3%) and 82 (3.4%), respectively, were positive for fetal fibronectin. The association of the Fetal Fibronectin Enzyme Immunoassay test result at the 30 week visit to delivery in ≤ 34 weeks, 6 days is shown in Table 6d. The presence of fetal fibronectin in either a cervical or vaginal specimen between 22 weeks, 0 days and 30 weeks, 6 days gestation identifies a sub-population of women at very high risk for delivery ≤ 34 weeks, including many who deliver < 28 weeks of gestation, when neonatal outcome may be severely compromised.

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Table 6a
Association of the Cervical and Vaginal Fetal Fibronectin Test Result at the 24 Week Visit[a] to Delivery < 28 and ≤ 34 Weeks, 6 Days of Gestation (n=2929)

Outcome	Del (n)[b]	Sensitivity % (95% CI)[c]	Specificity % (95% CI)	Pred Val + % (95% CI)	Pred Val - % (95% CI)	Relative Risk (95% CI)
Cervical (n=2915)[d]						
<28 Weeks	19	63.2% (41.0, 80.9)	97.6% (96.9, 98.1)	14.6% (4.9, 36.2)	99.8% (99.5, 99.9)	59.2 (23.9, 146.5)
≤34 Weeks	127	20.5% (14.9, 28.3)	98.0% (97.4, 98.5)	31.7% (24.2, 40.2)	96.4% (95.6, 97.0)	8.9 (6.1, 12.9)
Vaginal (n=2922)[e]						
<28 Weeks	19	63.2% (41.0, 80.9)	96.9% (96.2, 97.5)	11.9% (3.5, 33.1)	99.7% (99.4, 99.8)	47.9 (19.2, 119.0)
≤34 Weeks	127	18.9% (13.0, 26.5)	97.2% (96.6, 97.8)	23.8% (17.2, 31.9)	96.3% (95.5, 97.0)	6.5 (4.4, 9.7)

[a]24 week visit refers to the gestational age range of 22 weeks, 0 days – 24 weeks, 6 days among asymptomatic women
[b]Delivery ≤ 34 Weeks, 6 Days of Gestation
[c]95% Confidence Interval (Lower Limit, Upper Limit)
[d]n= 82 Positive Cervical fFN Enzyme Immunoassay test results at the 24 week visit
[e]n= 101 Positive Vaginal fFN Enzyme Immunoassay test results at the 24 week visit

Table 6b
Association of the Cervical and Vaginal Fetal Fibronectin Test Result at the 26 Week Visit[a] to Delivery ≤ 34 Weeks, 6 Days of Gestation (n=2435)

Outcome	Del (n)[b]	Sensitivity % (95% CI)[c]	Specificity % (95% CI)	Pred Val + % (95% CI)	Pred Val - % (95% CI)	Relative Risk (95% CI)
Cervical (n=2431)[d]						
≤34 Weeks	90	20.0% (13.5, 29.9)	97.3% (96.5, 97.8)	22.0% (14.6, 31.6)	96.9% (95.6, 97.1)	7.2 (4.5, 11.4)
Vaginal (n=2435)[e]						
≤34 Weeks	91	18.7% (11.9, 27.9)	97.1% (96.3, 97.7)	20.2% (13.2, 29.6)	96.9% (96.1, 97.5)	6.4 (4.0, 10.4)

[a]26 Week Visit refers to the gestational age range of 25 weeks, 0 days – 26 weeks, 6 days among asymptomatic women
[b]Delivery ≤ 34 Weeks, 6 Days of Gestation
[c]95% Confidence Interval (Lower Limit, Upper Limit)
[d]n= 82 Positive Cervical fFN Enzyme Immunoassay test results at the 26 week visit
[e]n= 84 Positive Vaginal fFN Enzyme Immunoassay test results at the 26 week visit

Table 6c
Association of the Cervical and Vaginal Fetal Fibronectin Test Result at the 28 Week Visit[a] to Delivery ≤ 34 Weeks, 6 Days of Gestation (n=2312)

Outcome	Del (n)[b]	Sensitivity % (95% CI)[c]	Specificity % (95% CI)	Pred Val + % (95% CI)	Pred Val - % (95% CI)	Relative Risk (95% CI)
Cervical (n=2308)[d]						
≤34 Weeks	76	10.5% (5.4, 19.4)	97.7% (96.9, 98.2)	13.3% (7.4, 22.7)	97.0% (92.3, 97.6)	4.4 (2.2, 8.8)
Vaginal (n=2312)[e]						
≤34 Weeks	75	17.3% (10.4, 27.4)	97.4% (96.6, 97.9)	18.1% (13.3, 32.8)	97.2% (97.2, 98.4)	6.5 (3.8, 11.3)

[a]28 Week Visit refers to the gestational age range of 27 weeks, 0 days – 28 weeks, 6 days among asymptomatic women
[b]Delivery ≤ 34 Weeks, 6 Days of Gestation
[c]95% Confidence Interval (Lower Limit, Upper Limit)
[d]n= 60 Positive Cervical fFN Enzyme Immunoassay test results at the 28 week visit
[e]n= 72 Positive Vaginal fFN Enzyme Immunoassay test results at the 28 week visit

Table 6d
Association of the Cervical and Vaginal Fetal Fibronectin Test Result at the 30 Week Visit[a] to Delivery ≤ 34 Weeks, 6 Days of Gestation (n=2425)

Outcome	Del (n)[b]	Sensitivity % (95% CI)[c]	Specificity % (95% CI)	Pred Val + % (95% CI)	Pred Val - % (95% CI)	Relative Risk (95% CI)
Cervical (n=2422)[d]						
≤34 Weeks	66	25.8% (16.8, 37.5)	97.4% (96.6, 97.9)	21.5% (13.3, 32.8)	97.9% (97.2, 98.4)	10.3 (6.2, 17.0)
Vaginal (n=2425)[e]						
≤34 Weeks	66	16.7% (10.1, 26.2)	97.0% (96.2, 97.6)	13.4% (7.4, 22.4)	97.7% (97.0, 98.2)	5.7 (3.1, 10.5)

[a]30 Week Visit refers to the gestational age range of 29 weeks, 0 days – 30 weeks, 6 days among asymptomatic women
[b]Delivery < 34 Weeks, 6 Days of Gestation
[c]95% Confidence Interval (Lower Limit, Upper Limit)
[d]n= 79 Positive Cervical fFN Enzyme Immunoassay test results at the 30 week visit
[e]n= 82 Positive Vaginal fFN Enzyme Immunoassay test results at the 30 week visit

Additional Clinical Data for Asymptomatic Patients

The association of the cervical Fetal Fibronectin Enzyme Immunoassay test result to delivery in ≤ 34 weeks, 6 days of gestation was compared to other risk factors evaluated at the 24 week visit. Other risk factors evaluated included patient self-perception of uterine activity in the previous two weeks, cervical dilatation ≥ 1 centimeter, history of second trimester vaginal bleeding, bacterial vaginosis, and history of at least one previous preterm delivery ≤ 34 weeks, 6 days of gestation. The association of these risk factors to delivery ≤ 34 weeks, 6 days of gestation is shown in Table 7. With the exception of bacterial vaginosis, each of these risk factors is significantly associated with delivery ≤ 34 weeks, 6 days of gestation.

Table 7
Univariate Association of All Risk Factors Surveyed or Obtained at the 24 Week Visit[a] to Delivery ≤ 34 Weeks, 6 Days of Gestation Among Asymptomatic Women (n=2929)

Risk Factor	Pos Test Defined[b]	Sensitivity (95% CI)[c]	Specificity (95% CI)	Pos PV (95% CI)	Neg PV (95% CI)	Rel Risk (95% CI)
fFN Immunoassay (Cervical) n=2915	≥ 0.05 µg/mL @24 Weeks	20.5% (14.9, 28.3)	98.0% (97.4, 98.4)	31.7% (24.2, 40.2)	96.4% (95.6, 97.0)	8.9 (6.1, 12.9)
fFN Immunoassay (Vaginal) n=2922	≥ 0.05 µg/mL @24 Weeks	18.9% (13.0, 26.5)	97.2% (96.6, 97.8)	23.8% (17.2, 31.9)	96.3% (95.5, 97.0)	6.5 (4.4, 9.7)
Uterine Activity n=2929	2 Weeks Prior to 24 Weeks	31.5% (23.4, 39.6)	83.1% (81.7, 84.5)	7.8% (5.5, 10.1)	96.4% (95.7, 97.1)	2.2 (1.5, 3.1)
Cervical Dilatation n=2929	≥ 1 cm @24 Weeks	45.7% (37.0, 54.3)	81.3% (79.8, 82.7)	9.9% (7.5, 12.4)	97.1% (96.4, 97.7)	3.4 (2.4, 4.7)
Prev PTD[d] n=1704	≤ 34 Weeks	27.6% (19.3, 37.8)	88.4% (86.7, 89.8)	11.3% (6.2, 19.6)	95.8% (94.7, 96.7)	2.7 (1.7, 4.2)
Vaginal Bleeding n=2929	2nd TM Bleeding	16.5% (10.1, 23.0)	90.9% (89.9, 92.0)	7.6% (4.5, 10.0)	96.0% (95.3, 96.8)	1.9 (1.2, 3.0)
Bac Vag[e] n=2900	PH, Clue Cells @24 Weeks	29.4% (21.2, 37.0)	76.9% (75.6, 78.7)	5.5% (3.8, 7.2)	96.0% (95.2, 96.8)	1.4 (0.9, 2.0)

[a]24 Week Visit refers to the gestational age range of 22 weeks, 0 days – 24 weeks, 6 days among asymptomatic women
[b]Cutoff used to define a positive test result for determining sensitivity, etc.
[c]95% Confidence Interval (Lower Limit, Upper Limit)
[d]Prev PTD: Previous preterm delivery ≤ 34 weeks, 6 days of gestation
[e]Bac Vag: Bacterial Vaginosis at the 24 week visit

In general, these risk factors have equal or greater sensitivity and are less specific than the Fetal Fibronectin Enzyme Immunoassay test result. Use of the Fetal Fibronectin Enzyme Immunoassay in conjunction with other risk factors at approximately 24 weeks gestation identifies those women at highest risk for delivery ≤ 34 weeks, 6 days of gestation and decreases the number of false positive observations attributable to other risk factors. For example, results shown in Table 8 demonstrate that the positive predictive value of cervical dilatation ≥ 1 centimeter (9.9%) is increased by addition of the cervical Fetal Fibronectin Enzyme Immunoassay test result (40.0%). (Results for vaginal specimens are similar and are not shown here.)

Table 8
Predictive Value for the Combination of the Cervical Fetal Fibronectin Test Result with Cervical Dilatation ≥ 1 Centimeter Among Asymptomatic Women

Results at the 24 Week Visit[a]	n	Del ≤ 34 Wks (n)	Del ≤ 34 Wks (%)
All Subjects	2915	127	—
fFN+[b]	82	26	31.7%
CD ≥ 1 cm[c]	583	58	9.9%
fFN-, CD < 1 cm	2280	55	2.4%
fFN+, CD < 1 cm	52	14	26.9%
fFN-, CD ≥ 1 cm	553	46	8.3%
fFN+, CD ≥ 1 cm	30	12	40.0%

[a]24 Week Visit refers to the gestational age range of 22 weeks, 0 days – 24 weeks, 6 days among asymptomatic women
[b]fFN+: cervical fFN Enzyme Immunoassay test result positive (+)
[c]CD: cervical dilatation

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History of preterm delivery is one of the strongest risk factors for preterm delivery, yet nulliparous pregnant women account for approximately 50% of preterm deliveries in the United States. Table 9 shows the association of the Fetal Fibronectin Enzyme Immunoassay test result to delivery in ≤ 34 weeks, 6 days of gestation for nulliparous women, and parous women stratified by history of previous preterm delivery. (Results for vaginal specimens are similar and are not shown here.)

Table 9
Association of the Cervical Fetal Fibronectin Test Result Obtained at the 24 Week Visit[a] to Delivery ≤ 34 Weeks, 6 Days of Gestation Among Nulliparous and Parous Asymptomatic Women Stratified by History of Previous Preterm Delivery (n=2929)

	fFN+[b] n (%)	PTD[c] n (%)	Sensitivity (95% CI)[d]	Specificity (95% CI)	Pos PV (95% CI)	Neg PV (95% CI)	Rel Risk (95% CI)
Nulliparous n=1211	29 (2.4%)	40 (3.3%)	25.0% (11.6, 38.4)	98.4% (97.7, 99.1)	34.5% (17.2, 51.8)	97.5% (96.6, 98.4)	13.6 (7.4, 25.1)
Parous n=1704	53 (3.1%)	87 (5.1%)	18.4% (10.3, 26.5)	97.7% (97.0, 98.4)	30.2% (17.8, 42.5)	95.7% (94.7, 96.7)	7.1 (4.4, 11.2)
PTD[e] n=212	8 (3.8%)	24 (11.3%)	20.8% (4.6, 37.1)	98.4% (96.6, 99.9)	62.5% (29.0, 96.0)	90.7% (86.7, 94.7)	6.7 (3.4, 13.3)
No PTD n=1492	45 (3.0%)	63 (4.2%)	17.5% (8.1, 26.8)	97.6% (96.8, 98.4)	24.4% (11.9, 37.0)	96.4% (95.4, 97.4)	6.8 (3.8, 12.1)

[a]24 Week Visit refers to the gestational age range of 22 weeks, 0 days – 24 weeks, 6 days among asymptomatic women
[b]Positive cervical fFN Enzyme Immunoassay test result at the 24 week visit
[c]Preterm delivery ≤ 34 weeks, 6 days of gestation
[d]95% Confidence Interval (Lower Limit, Upper Limit)
[e]PTD: History of preterm delivery ≤ 34 weeks, 6 days of gestation

The relationship of the cervical Fetal Fibronectin Test Result to neonatal well-being is shown in Table 10. (Results for vaginal specimens are similar and are not shown here.)

Table 10
Neonatal Well-Being Stratified by the Cervical Fetal Fibronectin Test Result Obtained at the 24 Week Visit[a] Among Asymptomatic Women

		fFN +	fFN -	p-value
Total Neonates[b]	n (%)	81 (2.8%)	2829 (97.2%)	—
Infant Weight (grams)	Avg	2587	3175	0.0001
	SD	1127	617	
	n	81	2829	
	Range	220-4895	195-6390	
Infant Weight (grams)				
n (%)				
	<1500	18 (22.2%)	52 (1.8%)	0.001
	<2500	31 (38.3%)	314 (11.1%)	0.001
Perinatal Morbidity	n (%)			
Respiratory Distress		17 (21.0%)	68 (2.4%)	0.001

[a]24 Week Visit refers to the gestational age range of 22 weeks, 0 days – 24 weeks, 6 days among asymptomatic women
[b]Neonate information available for only 2913 subjects with cervical specimens at 24 week visit

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Table 10
Neonatal Well-Being Stratified by the Cervical Fetal Fibronectin Test Result Obtained at the 24 Week Visit[a] Among Asymptomatic Women

		fFN +	fFN -	p-value
Neonatal Sepsis		4 (4.9%)	13 (0.5%)	0.040
Necrotizing Enterocolitis		6 (7.4%)	7 (0.2%)	0.001
NICU Admission	n (%)	24 (29.6%)	156 (5.5%)	0.001
Perinatal Mortality	n (%)	6 (7.4%)	15 (0.5%)	0.001

[a]24 Week Visit refers to the gestational age range of 22 weeks, 0 days – 24 weeks, 6 days among asymptomatic women
[b]Neonate information available for only 2913 subjects with cervical specimens at 24 week visit

CLINICAL SIGNIFICANCE OF FETAL FIBRONECTIN

Clinical experience with the Fetal Fibronectin Enzyme Immunoassay has been limited to observational studies establishing the association between the test result and likelihood of delivery. Clinical experience with Rapid fFN has been limited to observational laboratory concordance studies. No randomized controlled studies have yet been completed to determine the therapeutic efficacy of using the Fetal Fibronectin Enzyme Immunoassay or Rapid fFN in conjunction with other clinical information for threatened preterm delivery. In the absence of such studies, it is not possible to make recommendations regarding specific treatment options.

Management of Women with a Positive Fetal Fibronectin Test Result

Symptomatic pregnant women with a positive fetal fibronectin test are at increased risk for delivery in ≤ 7 days, ≤ 14 days of specimen collection, and for preterm delivery in ≤ 36 completed weeks. Asymptomatic pregnant women with a positive fetal fibronectin test are at increased risk for delivery in ≤ 34 weeks, 6 days of gestation. Thus, a positive fetal fibronectin test enhances the ability of the clinician to predict preterm delivery in either an asymptomatic pregnant population or a population of pregnant women presenting with equivocal symptoms. In either population, identification of risk would allow for increased surveillance and improved management of patients who are otherwise clinically unremarkable. Increased surveillance and subsequent early identification of additional clinical symptoms would likely result in the earlier, efficacious management of treatable symptoms. Finally, and perhaps most important, a positive fetal fibronectin test is associated with adverse neonatal outcome, particularly respiratory distress syndrome. Thus, early identification of risk, particularly among symptomatic pregnant women, would be likely to improve delivery of corticosteroid therapy before rapid progression of labor and delivery.

Management of Women with a Negative Fetal Fibronectin Test Result

The absence of fetal fibronectin in cervicovaginal secretions after 24 weeks gestation is associated with continuation of pregnancy. Symptomatic pregnant women with a negative fetal fibronectin test result between 24 and 34 weeks, 6 days of gestation have a < 1% probability of delivering in ≤ 7 or ≤ 14 days from the time of specimen collection, and approximately a 15% chance of delivery in ≤ 36 completed weeks. Among symptomatic pregnant women, a negative test would likely lead to more judicious use of tocolytic drugs which lowers the probability of maternal and fetal toxicity associated with these medications and preserves their effectiveness for a time when they may be more critically needed. Asymptomatic pregnant women with a negative test result between 22 weeks, 0 days and 30 weeks, 6 days gestation have approximately a 2–4% chance of delivery ≤ 34 weeks, 6 days and a < 0.5% chance of delivery < 28 weeks when tested between 22 weeks, 0 days and 24 weeks, 6 days. Clearly, the majority of women with a negative fetal fibronectin test result who deliver prematurely, deliver after 34 completed weeks when serious perinatal morbidity is unlikely though possible. In addition, women, especially symptomatic patients, with a negative test result may not require severe lifestyle changes, e.g., bedrest or work restrictions, which can have significant social, economic, and emotional effects. It is critical to recognize that a negative fetal fibronectin test result does not eliminate the possibility of a preterm delivery. Symptomatic patients with a negative fetal fibronectin test are still at increased risk for prematurity, simply because they present for unscheduled care, and asymptomatic patients may develop detectable risk later in pregnancy even though the test result is negative at 24 weeks of gestation. Thus, increased patient education and continued surveillance should continue to be critical components of patient management.

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MECHANISMS OF RELEASE OF FETAL FIBRONECTIN

The exact mechanisms underlying the onset of labor and delivery in humans are unknown, therefore, it is impossible to conclusively describe a mechanism by which fetal fibronectin appears in cervicovaginal secretions. Immunohistochemical studies have shown that fetal fibronectin is localized in the extracellular matrix of the maternal-fetal interface also known as the choriodecidual junction. The immunolocalization of fetal fibronectin in the placenta and amniotic sac, particularly in the lower uterine segment, suggests that fetal fibronectin may be extravasated or "leaked" into the vagina. Two possible pathways may lead to the appearance of fetal fibronectin in cervicovaginal secretions. In the first pathway, the mechanical stress caused by uterine contractions and cervical change leads to choriodecidual separation, which, in turn, promotes loss of fetal fibronectin from the interface. Accumulating clinical evidence suggests the existence of a second pathway in which localized inflammation of the choriodecidual interface, resulting perhaps from occult ascending bacterial infiltration, promotes maternal host defense. If the infectious stimulus and maternal response are sufficiently powerful, the resulting inflammation could promote degradation of the choriodecidual extracellular matrix and weakening of the amniotic membranes. Such a process has been discussed in the literature and can be summarized as follows: 1) an ascending bacterial infiltration from the lower genital tract results in the recruitment of leukocytes to the decidua and membranes; 2) bacterial and leukocyte-derived proteases degrade decidual and chorionic extracellular matrix; 3) degradation of extracellular matrix proteins results in the extravasation of fetal fibronectin into the vagina and, if the degradation is severe, premature rupture of the amniotic membranes occurs; 4) the same ongoing inflammatory process promotes localized release of prostaglandins and cytokines, resulting in cervical ripening and contractions (21-26). Thus, fetal fibronectin's appearance in cervicovaginal secretions is likely attributable to various processes associated with choriodecidual separation and the onset of labor, regardless of whether the stimulus is infectious or mechanical.

WHY THE PATIENT POPULATIONS ARE RESTRICTED

The Fetal Fibronectin Enzyme Immunoassay and Rapid fFN have two clinical applications. In the first application, the test is intended to be used as an aid to assess risk of delivery for women with symptoms of preterm labor who have intact amniotic membranes and minimal cervical dilatation (< 3 centimeters). The test is not intended for use among symptomatic women who have advanced cervical dilatation (≥ 3 centimeters), rupture of amniotic membranes, cervical cerclage, or visual evidence of moderate or gross vaginal bleeding. Delivery typically occurs imminently when cervical dilatation exceeds 3 centimeters or if the amniotic membranes are ruptured. Therefore, additional diagnostic testing is usually not necessary to confirm risk for women with advanced cervical dilatation or rupture of amniotic membranes. Moderate or gross vaginal bleeding is an independent risk factor for preterm delivery and may be associated with other severe obstetrical or medical problems. Clinical attention should be focused on identification of the origin of bleeding rather than on immediate assessment of delivery risk. Currently, there is insufficient information characterizing the association of vaginal fetal fibronectin expression to delivery for women with cervical cerclage.

In the second application, the Fetal Fibronectin Enzyme Immunoassay and Rapid fFN are intended to be used in conjunction with other clinical information as an aid to assess the risk of preterm delivery ≤ 34 weeks, 6 days of gestation, when a cervicovaginal sample is obtained from asymptomatic pregnant women during a routine prenatal visit between 22 weeks, 0 days and 30 weeks, 6 days of gestation. The test is intended for use only among pregnant women with singleton gestations regardless of parity and history of previous preterm delivery ≤ 34 weeks, 6 days. The safety and effectiveness of the Fetal Fibronectin Enzyme Immunoassay or Rapid fFN have not been demonstrated for asymptomatic pregnant women who have a known risk factor for preterm delivery, e.g., multiple gestations, cervical cerclage, or placenta previa.

For both the symptomatic and asymptomatic patient populations, the Fetal Fibronectin Enzyme Immunoassay and Rapid fFN should be used in conjunction with all other clinical information to assess risk of delivery, e.g., uterine contractions, cervical dilatation, ascending genital tract infection, vaginal bleeding, obstetrical history, etc.

CAN FETAL FIBRONECTIN ALONE BE USED TO IDENTIFY RISK OF DELIVERY?

The Fetal Fibronectin Enzyme Immunoassay and Rapid fFN are objective tests that can be used as an aid in assessing the risk of preterm delivery among symptomatic and asymptomatic pregnant women. Detection of fetal fibronectin in cervicovaginal secretions should not be interpreted alone to assess risk of imminent delivery. The Fetal Fibronectin Enzyme Immunoassay and Rapid fFN should be used in conjunction with other clinical tests and information to assess overall risk of preterm delivery and assure appropriate patient management.

SPECIMEN COLLECTION

The specimen should be obtained from the posterior fornix of the vagina during a speculum examination. *The Hologic Specimen Collection Kit is the only acceptable specimen collection system which can be used to collect specimens for this assay. Only results from specimens obtained during a speculum examination are valid. Results from specimens obtained in any other manner, for example, vaginal examination, are invalid.* The polyester tipped swab provided in the Specimen Collection Kit should be inserted into the vagina and lightly

rotated across the posterior fornix for approximately 10 seconds to absorb the cervicovaginal secretions. Once the specimen is obtained, carefully remove the swab from the vagina and place it into the tube of buffer provided with the Specimen Collection Kit. Use only one Specimen Collection Device per patient. Label the Specimen Transport Tube with the patient's name and any other identifying information required.

To safely interpret the Fetal Fibronectin Enzyme Immunoassay or Rapid fFN test result, the sample must be collected before performance of any activities or procedures which might disrupt the cervix, e.g., coitus, digital cervical examination, vaginal ultrasound, microbiologic culture of cervical secretions, or pap smear. Finally, the test result is invalid if the swab is contaminated by lubricants, soaps, or disinfectants, e.g., K-Y® Jelly lubricant, Betadine® disinfectant, hexachlorophene, Monistat® cream. Soaps or disinfectants may interfere with the antibody-antigen reaction. The method of collection is also described in the directional insert for the Specimen Collection Kit.

PRINCIPLE OF THE FETAL FIBRONECTIN ENZYME IMMUNOASSAY

The Fetal Fibronectin Enzyme Immunoassay is a solid-phase enzyme-linked immunosorbent assay (ELISA). During the assay, cervicovaginal samples are incubated in microtiter wells coated with FDC-6, a monoclonal antibody specific for fetal fibronectin (5). The resulting antibody-antigen complex is washed to remove non-specifically bound material and then reacted with an enzyme-labeled antibody directed against human fibronectin. Following formation of the antigen-antibody "sandwich," the microtiter well is washed to remove unbound labeled antibody and then incubated with an enzyme substrate. The presence or absence of fetal fibronectin in the specimen is determined spectrophotometrically at a wavelength of 550 nanometers.

PRINCIPLE OF RAPID FFN FOR THE TLiQ® SYSTEM

The Rapid fFN Cassette is a lateral flow, solid-phase immunochromatographic assay. During the assay, cervicovaginal samples flow from an absorbent pad across a nitrocellulose membrane via capillary action through a reaction zone containing murine monoclonal anti-fetal fibronectin antibody conjugated to blue microspheres (conjugate). The conjugate, embedded in the membrane, is mobilized by the flow of the sample. The sample then flows through a zone containing goat polyclonal anti-human fibronectin antibody which captures the fibronectin-conjugate complexes. The remaining sample flows through a zone containing polyclonal goat anti-mouse IgG antibody which captures unbound conjugate, resulting in a control line. After 20 minutes of reaction time, the intensities of the test line and control line are interpreted with the TLiQ Analyzer.

The TLiQ Analyzer uses optical reflectance technology to create a digitized format of a reacted Rapid fFN Cassette. The data are analyzed using multiple parameters, including a comparison of sample data to calibration data. The TLiQ Analyzer provides one of three possible test results: Positive, Negative, or Invalid.

The method of operation of the TLiQ Analyzer includes: 1) inserting the Rapid fFN Cassette into the TLiQ Analyzer; 2) initializing the TLiQ Analyzer using the instrument keypad; 3) collecting the reflectance data using the TLiQ Analyzer software; 4) converting the raw data into a reportable result using the TLiQ Analyzer software.

Each package of Rapid fFN Cassettes is labeled with a "calibration code" unique to each cassette lot. The calibration code is established by the manufacturer and specifies the reference calibration value. The reference calibration value represents the signal intensity associated with 0.050 µg/mL fFN.

The analysis software converts the raw data from the TLiQ Analyzer into one of three possible test results: positive, negative, or invalid. The raw data are converted to a test result by determining the intensity of the signal derived from a patient sample, and ascertaining whether the signal intensity from the patient sample is greater than, equal to, or less than, the signal intensity specified by the reference calibration value.

The result is reported as positive if the signal intensity derived from the patient sample is greater than or equal to that specified by the reference calibration value. The result is reported as negative if the signal intensity derived from the patient sample is less than that specified by the reference calibration value. The result is reported as invalid if the test does not meet internal quality controls.
Internal controls are part of the TLiQ System and are performed automatically with every test. These internal controls check for 1) a threshold level of signal at the procedural control position, 2) proper sample flow across the Rapid fFN Cassette, 3) absence of conjugate aggregation (Cassette: Pass/Fail), and 4) proper function of analyzer hardware (Analyzer: Pass/Fail).

DEFINITION OF A POSITIVE OR A NEGATIVE TEST

The Fetal Fibronectin Enzyme Immunoassay

Patient specimens having an absorbance greater than or equal to the absorbance of the Positive Reference Calibrator (containing 0.050 µg/mL fFN) are defined as positive for the presence of fetal fibronectin. Patient specimens having an absorbance less than the absorbance of the Positive Reference Calibrator are defined as negative for the presence of fetal fibronectin.

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Patient specimens having a signal intensity greater than or equal to the signal intensity specified by the reference calibration value (0.050 µg/mL fFN) will be displayed as "Positive" on the TLiQ Analyzer. Patient specimens having a signal intensity less than the signal intensity specified by the reference calibration value (0.050 µg/mL fFN) will be displayed as "Negative" on the TLiQ Analyzer.

LIMITATIONS

The Fetal Fibronectin Enzyme Immunoassay or Rapid fFN result should not be interpreted as absolute evidence for the presence or absence of a process that will result in delivery in ≤ 7 days from specimen collection for symptomatic women or ≤ 34 weeks, 6 days of gestation for asymptomatic women. A positive Fetal Fibronectin Enzyme Immunoassay or Rapid fFN result may be observed for patients who have experienced cervical disruption caused by, but not limited to, events such as sexual intercourse, digital cervical examination, or vaginal probe ultrasound. The Fetal Fibronectin Enzyme Immunoassay or Rapid fFN result should always be used in conjunction with information available from the clinical evaluation of the patient and other diagnostic procedures such as cervical examination, cervical microbiological culture, assessment of uterine activity, and evaluation of other risk factors.

- Modification of the assay protocol described herein may yield erroneous results.
- The assay has been optimized with specimens taken from either the posterior fornix of the vagina or the ectocervical region of the external cervical os. Samples obtained from other locations should not be used.
- The safety and effectiveness of using a cutoff other than 0.050 µg/mL fFN has not been established.
- Assay interference from the following components has not been ruled out: douches, white blood cells, red blood cells, bacteria, and bilirubin.
- The presence of infections has not been ruled out as a confounding factor to risk of preterm delivery.
- At this time, information is insufficient regarding the association of cervicovaginal expression of fetal fibronectin and delivery in asymptomatic pregnant women with HIV/AIDS.
- Results should be interpreted with caution when a specimen is obtained from a patient with unconfirmed gestational age.
- Test results are difficult to interpret if the specimen contains semen or if the specimen was collected less than 24 hours after coitus. Two studies were conducted establishing that intercourse and the presence of semen may lead to a positive test result. In the first study, fetal fibronectin was detected in 23% of post-coital vaginal specimens obtained from 22 non-pregnant women. In the second study, fetal fibronectin was detected in 21 of 41 sperm samples obtained from healthy male volunteers. These results suggest that sperm (or semen) may contain a sufficient concentration of fetal fibronectin to result in a positive fetal fibronectin test result. However, even when a patient reports having had intercourse in the previous 24 hours, a negative fetal fibronectin test result is valid.

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