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Medical Policy

BlueCross BlueShield of Kansas
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Title: Fetal Fibronectin

Professional
Original Effective Date: July 29, 2002
Revision Date(s): November 10, 2005; April 18, 2007; October 25, 2013; July 21, 2015; August 5, 2015; November 9, 2016
Current Effective Date: November 9, 2016
Archived Date: February 18, 2021

Institutional
Original Effective Date: April 1, 2006
Revision Date(s): April 18, 2007; October 25, 2013; July 21, 2015; August 5, 2015; November 9, 2016
Current Effective Date: November 9, 2016
Archived Date: February 18, 2021

State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact Blue Cross and Blue Shield of Kansas Customer Service.

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

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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 individuals 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

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individuals who are experiencing symptoms of PTL, asymptomatic individuals at increased risk of PTL, and asymptomatic individuals as part of routine pregnancy care.

Background

Fetal fibronectin (FFN) is a high-molecular-weight glycoprotein that can be isolated from fetal connective tissue, placenta, and amniotic fluid. FFN 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 elevated 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 FFN test became available, permitting results within 20 minutes of testing. This assay produces qualitative results, reported as positive, negative, or indeterminate. Generally, an 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 typically hospitalized for an initial period to observe whether symptoms subside or progress. During this time, bed rest and possible treatment in the form of intravenous (IV) hydration; antibiotics; or tocolytic drugs, depending on the symptoms and results of the physical exam, are prescribed. In many cases, the symptoms of PTL 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 probable. 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

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- 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 FFN test (Adeza Fetal Fibronectin Enzyme Immunoassay, Adeza Biomedical, Sunnyvale, CA) was approved by the U.S. Food and Drug Administration (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 (less than 3 cm) sampled between 24 weeks and less than 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 less than 31 weeks.

POLICY

A. The use of fetal fibronectin (FFN) assays may be considered **medically necessary** for use in individuals
   1. with singleton or twin gestations, and
   2. with intact membranes, and
   3. cervical dilation less than 3 cm, and
   4. who are experiencing symptoms suggestive of preterm labor between 24 and less than 35 weeks' gestation

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This population represents individuals who are most likely to be hospitalized and treated in an attempt to prevent preterm birth.

B. All other applications of the FFN assay are considered **experimental / investigational**, including, but not limited to, the following:
   1. As part of routine pregnancy monitoring in *asymptomatic* individuals with singleton gestation and no risk factors for preterm birth
   2. As part of clinical monitoring of *asymptomatic* individuals 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
   3. As part of clinical monitoring in individuals with triplet or higher-order gestations, intact membranes, cervical dilation less than 3 cm, and who are experiencing symptoms suggestive of preterm labor
   4. As a test to identify individuals at term being considered for induction who are likely to deliver within 24–48 hours and therefore, do not require induction

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RATIONALE

The most recent literature search was for the period July 2010 through July 2011.

Women with symptoms of preterm labor

Are elevated fetal fibronectin (FFN) levels predictive of preterm birth?

Evidence for this question consists of a large number of observational studies and several systematic reviews that have evaluated the performance characteristics and predictive value of FFN for pre-term birth.

The policy for this indication was originally based on a 1997 TEC Assessment. (1) Observational studies in women with symptoms suggestive of preterm labor (PTL), identified by the Assessment, reported 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 (NPV) 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 NPV of this test provides evidence that only approximately 1% of these women will deliver within a 2-week interval. Because of the relatively low PPV of the assay, positive results of an FFN assay have more limited clinical impact. The TEC 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.

Several meta-analyses have been published since the TEC Assessment; 2 of these reviewed studies on diagnostic accuracy. In 2009, Sanchez-Ramos and colleagues conducted a meta-analysis of studies on the diagnostic accuracy of FFN for predicting preterm birth within 7 days of testing in women with signs or symptoms of PTL. (2) It is worth noting that this outcome differs from delivery within 14 days, which was the outcome used in the TEC Assessment. They identified 32 observational studies; of these 17 stated that they were limited to singleton pregnancies, 5 stated that they included both singleton and multiple pregnancies, and the remaining 10 studies were silent on this issue. Separate analyses were not conducted for single and multiple pregnancies. In a pooled analysis of data from all 32 studies (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 FFN test; after 2002, the rapid test was more commonly used. 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 2 types of fetal fibronectin tests, and no other studies comparing test types were identified.

Another meta-analysis, published in 2010 by Conde-Agudelo and Romero, was limited to multiple pregnancies. (3) The authors identified 4 prospective observational studies evaluating the diagnostic accuracy of FFN for predicting spontaneous preterm birth in symptomatic pregnant women with twin pregnancies. (3) Sample sizes of the studies ranged from 38 to 87 women. All 4 studies examined single testing at 20-35 weeks' gestation, and all considered an FFN of at least 50 ng/mL to be a positive test. In a pooled analysis of 3 studies (total n=168) that reported on delivery within 7 days of testing, the pooled sensitivity was 85% (95% CI: 51-98), and pooled specificity was 78% (95% CI: 66-90). For delivery within 14 days, a pooled analysis of 2 studies (n=125) found a pooled sensitivity of 64% and pooled specificity of 76% (95% CI: 62-89). Diagnostic accuracy was lower for other outcomes, including preterm birth before 34 weeks and preterm birth before 37 weeks. Sensitivity and specificity for delivery within 7 days were similar to estimates in the Sanchez-Ramos et al. meta-analysis. (2)

Does the use of FFN reduce the rate of pre-term births and/or reduce resource utilization for women with suspected pre-term labor (PTL)?

Numerous comparative studies, both comparative cohort studies and randomized controlled trials (RCTs), have examined the impact of FFN testing on hospital admissions and other measures of healthcare utilization. A smaller number of studies have evaluated the impact of FFN on the rate of preterm births.

A 2008 Cochrane review summarized the literature on the impact of FFN testing on health outcomes in women with signs or symptoms of PTL between 22 and 34 weeks' gestation. (4) Thirteen RCTs 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 (RR) was 0.54 (95% CI: 0.34-0.87). However, other outcomes for which there were sufficient data, including preterm birth at less than 34, 32, or 28 weeks, birthweight less than 2,500 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%); RR: 1.01 (95% CI: 0.78-1.30).

Among the studies included in the Cochrane review was one published in 2003 by Plaut and colleagues. (5) They reported on a study that randomized women with symptoms of PTL to management either directed or not directed by the results of an FFN test. In this study, the length of hospitalization was shorter when physicians knew the results of a negative test. The

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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 PTL. (6) All women underwent an FFN test, but the results were only known in 1 group of women. The women who did not have the FFN 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 healthcare-related costs. A third trial in the Cochrane review, published in 2007 by Ness and colleagues, was similar in design to the Grobman et al. study. (7) One-hundred women with symptoms of PTL received FFN testing, as well sonographic testing of cervical length, and were randomly assigned 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 2 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 PTL was significantly higher in the knowledge group (19.6%) than in the blinded group (4.1%).

A 2010 systematic review by Dutta and Norman identified 10 studies on the impact of FFN testing on healthcare utilization in women with singleton pregnancies and symptoms of PTL. (8) This analysis excluded patients with additional risk factors such as placenta previa, spontaneous rupture of membranes, etc. Four out of the 10 studies reported a statistically significant decrease in the number of hospital admissions and length of stay when women were tested for FFN compared to no testing. The other 6 studies found significant differences in these outcomes in women with a positive FFN test compared to a negative FFN test.

There are limited data specifically addressing the use of FFN in symptomatic patients with additional high-risk factors for preterm birth e.g. triplet or higher-order multiples; these high-risk patients are presumably already undergoing standard aggressive management of symptoms, and there are a lack of data suggesting that the results of FFN assessment would alter management.

Asymptomatic women at high risk for premature labor
Are elevated FFN levels predictive of preterm birth in this population?

Fewer data are available on FFN testing in asymptomatic women. No meta-analyses of studies on diagnostic accuracy of FFN testing in asymptomatic women with singleton pregnancies and no additional risk factors were identified.

Several studies have evaluated use of the FFN assay in asymptomatic women with singleton pregnancies. One of the studies was an RCT and others were observational studies. The RCT was published in 2006 by Shennan and colleagues in the UK. (9) The study evaluated whether treatment with metronidazole reduced early PTL in women at increased risk of preterm birth who

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had positive FFN findings in the second trimester of pregnancy. One hundred women with positive FFN findings (at least 50 ng/mL) were randomly assigned to receive 1 week of oral metronidazole 400 mg 3 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 preterm 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 with singleton pregnancies led to an early intervention that improved outcomes.

Another study, also from the U.K. 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, while 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 a 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.

A third study from the U.K., a prospective cohort study published in 2011, evaluated the value of FFN testing and cervical length measurement, alone or combined, for predicting preterm birth in asymptomatic high-risk women with singleton pregnancies. (11) The study included 147 women who had one of the factors indicating increased risk of preterm birth: previous preterm birth, previous preterm rupture of the membranes, previous late miscarriage, extensive cervical surgery, uterine abnormalities or presence of cervical cerclage. At each prenatal care visit (2-6 week intervals) occurring between 22 weeks 0 days and 30 weeks 0 days of gestation, FFN levels were assessed, and cervical length was measured. A total of 34 of 147 (23%) of women tested positive for FFN (at least 50 ng/ml). The mean cervical length was 31 mm (95% CI: 29.4 to 33.4). Eleven of 28 women (39%) with a positive FFN test delivered before 34 weeks compared to 4 of 111 (4%) of women with a negative FFN test. Similarly, 12 of 26 (46%) women with a positive FFN test delivered before 37 weeks compared to 12 of 106 (11%) women with a negative FFN. (Eight women with induction or elective cesarean section were excluded from the 34-week analysis, and 15 were excluded from the 37-week analysis.) The authors did not report statistical significance e.g., p values for the above analyses. FFN status added value to prediction of preterm birth regardless of the cervical length. When hazard ratios were calculated, there was a statistically significant association between a positive FFN test and preterm birth rate both for

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women with a cervical length 25 mm or less (hazard ratio [HR]: 3.14, 95% CI: 1.34 to 7.38) and for those with a cervical length of more than 25 mm (HR: 2.78, 95% CI: 1.23 to 6.27). This study does not address the issue of whether intervening in women with a high FFN value would reduce the rate of preterm delivery.

There was one meta-analysis of diagnostic accuracy of FFN in asymptomatic women with multiple pregnancies—this was addressed in the Conde-Agudelo and Romero publication, described above. (3) Fifteen observational studies, with sample sizes ranging from 29 to 169, were identified. Studies included a total of 1,221 women (1,133 twins, 57 triplets, 2 quadruplets, and 29 unspecified). In a pooled analysis of data from 9 studies (n=842 women), the sensitivity of FFN for predicting preterm birth before 34 weeks was 45% (95% CI: 35-57), and the pooled specificity was 81% (95% CI: 76-86). Findings were similar for predicting spontaneous preterm birth before 37 weeks' gestation. (The outcome of delivery after 7 or 14 days was not reported for asymptomatic women.)

There is a relative lack of evidence, and no systematic reviews, on whether FFN testing in asymptomatic high-risk women reduces resource utilization or rates of preterm birth.

Asymptomatic women at average risk for premature labor
There is a lack of evidence on the diagnostic accuracy of FFN in asymptomatic women with singleton pregnancies and no risk factors for preterm birth, as well as a lack of evidence on whether FFN reduces the rate of preterm births and/or reduces resource utilization in this population of women.

Women at term being considered for induction
The 1997 TEC 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 (PTL) due to the value of a negative test result. Recent systematic reviews have found a significant impact of FFN testing in women with singleton pregnancies and symptoms of preterm labor on reduced rates of preterm birth before 37 weeks' gestation and on hospitalization rates. There is insufficient evidence that FFN testing improves the net health outcome 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.

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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.

Practice 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.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

82731 Fetal fibronectin, cervicovaginal secretions, semi-quantitative

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

ICD-9 Diagnoses

644.03 Threatened premature labor, antepartum condition or complication
644.13 Other threatened labor, antepartum condition or complication
644.21 Early onset of delivery, delivered, with or without mention of antepartum condition

ICD-10 Diagnoses (Effective October 1, 2015)

O47.02 False labor before 37 completed weeks of gestation, second trimester
O47.03 False labor before 37 completed weeks of gestation, third trimester
O60.02 Preterm labor without delivery, second trimester

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O60.03	Preterm labor without delivery, third trimester
O60.12x1	Preterm labor second trimester with preterm delivery second trimester, fetus 1
O60.12x2	Preterm labor second trimester with preterm delivery second trimester, fetus 2
O60.12x3	Preterm labor second trimester with preterm delivery second trimester, fetus 3
O60.12x4	Preterm labor second trimester with preterm delivery second trimester, fetus 4
O60.12x5	Preterm labor second trimester with preterm delivery second trimester, fetus 5
O60.12x9	Preterm labor second trimester with preterm delivery second trimester, other fetus
O60.14x1	Preterm labor third trimester with preterm delivery third trimester, fetus 1
O60.14x2	Preterm labor third trimester with preterm delivery third trimester, fetus 2
O60.14x3	Preterm labor third trimester with preterm delivery third trimester, fetus 3
O60.14x4	Preterm labor third trimester with preterm delivery third trimester, fetus 4
O60.14x5	Preterm labor third trimester with preterm delivery third trimester, fetus 5
O60.14x9	Preterm labor third trimester with preterm delivery third trimester, other fetus

REVISIONS

11-10- 2006	In "Policy" section, #3, added "or twin gestations".
04-18- 2007 effective 05-01-2007	In "Coding" Diagnosis section, added 640.03, 644.13, and 644.21 (added 5th digit to current codes) per Medical Director.
10-25-2013	Published 09-25-2013 for an effective date of 10-25-2013 for professional and institutional.
	Description section updated
	In Policy section: ▪ Policy language was updated to current language from: "Fetal Fibronectin Enzyme immunoassay testing is considered medically necessary when ALL the following criteria is met AND when performed at a laboratory-offering test results that are available with 24-hour sampling. 1. Patient has signs or symptoms of pre-term labor (inappropriate uterine contractions for gestational age, such as greater than 4 per hour, intermittent abdominal cramping, pelvic pressure, or backache; increase or change in vaginal discharge; or, vaginal spotting or bleeding), 2. Patient is between 24 and 34 weeks of completed gestation, 3. Single or twin gestations 4. Minimal cervical dilation (less than 3cm) AND 5. Intact amniotic membranes" ▪ The policy language update does not represent a change in policy intent.
	Rationale section added
	In Coding section: ▪ Added coding instructions following the CPT code. ▪ Updated nomenclature for ICD-9 codes: 644.03, 644.13

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	▪ Removed ICD-9 codes: 644.00, 644.10, 644.20 ▪ Added ICD-10 codes
	References updated
07-21-2015	Policy published 07-14-2015 for an effective date of 07-21-2015.
	In Policy section: ▪ Clarified Item A by adding "and" after A 1 and A 2 to indicate all criteria applied. This does not change the intent of how the policy has been interpreted.
	All other sections reviewed with no changes.
08-05-2015	In Revision section: ▪ Corrected 07-21-2015 Revision from "Policy published 07-14-2015 for an effective date of 08-13-2015." to "Policy published 07-14-2015 for an effective date of 07-21-2015."
11-09-2016	Description section updated
	In Policy section: ▪ In Items A, B1, B2, B3, and B4 revised "women" to "individuals"
	References updated
02-18-2021	Policy archived

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Additional References

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