CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

Subject **Tests for the Evaluation of Preterm Labor**

Effective Date 7/15/2009
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INSTRUCTIONS FOR USE

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Coverage Policy

CIGNA covers the following testing for preterm labor (PTL) as medically necessary for pregnant women with signs or symptoms of PTL:

- transvaginal ultrasonography (TVU) of the cervix
- fetal fibronectin (fFN) testing when ALL of the following criteria are met:
  - intact amniotic membranes
  - less than 3 centimeters (cm) of cervical dilatation
  - sampling occurs at a gestational age of at least 24 weeks, but less than 34 weeks

CIGNA does not cover the following because they are considered experimental, investigational or unproven:

- salivary estriol testing
- fFN or bacterial vaginosis (BV) testing as screening methods for PTL

General Background

Preterm delivery (PTD) is defined as the birth of an infant at less than 37 weeks of gestation. From 7–14% of live births are preterm and account for 85% of all neonatal deaths in the United States. The major

risks of PTD to the infant are death, respiratory distress syndrome (RDS), hypothermia, hypoglycemia, necrotizing enterocolitis, jaundice, infection, and retinopathy of prematurity. Preterm labor (PTL) is defined as regular contractions associated with cervical change before the completion of 37 weeks of gestation. It is the major cause of PTD. The ability to predict whether a woman is at risk of PTD is valuable, as it allows the opportunity to administer maternal corticosteroid therapy, which decreases infant morbidity and mortality. Detecting PTL also allows for the use of maternal tocolytic therapy, which may prolong pregnancy for up to 48 hours in some women, during which time corticosteroids can be administered. Because these therapies may also have unwanted maternal and fetal side effects, the use of these therapies should be limited to women with true PTL at high risk for spontaneous preterm birth.

Although the cause is often unknown, there are a variety of risk factors associated with PTL. Maternal characteristics associated with increased risk of PTL include low socioeconomic status, nonwhite race, maternal age less than 18 or over 40 years, low pre-pregnancy weight, smoking, and alcohol and/or substance abuse. Maternal medical history associated with high risk of PTL includes a previous history of PTD and a previous history of a second-trimester abortion. Existing medical conditions in the pregnant woman also increase the risk of PTL. These conditions include an increased uterine volume, uterine anomalies, trauma and infection.

Symptoms of PTL include an increase in vaginal discharge, vaginal bleeding, cramping, pelvic pressure and low back pain. A diagnosis of PTL can only be confirmed by progressive dilation of the cervix; however, there are biological and clinical markers which indicate a predisposition toward PTL. In 2001, the American College of Obstetricians and Gynecologists (ACOG) issued practice guidelines stating that screening for risk of PTL by means other than historic risk factors is not beneficial in the general obstetric population. In the at-risk population, an accurate diagnostic test for PTL would allow women who are truly at risk for PTD to receive appropriate treatment and decrease unwarranted interventions in women who will deliver at term.

Cervical Ultrasound
Cervical length is an established predictor of PTD. The length of the cervix is inversely proportional to the risk of PTD. The reliability and validity of transvaginal ultrasound (TVU) in pregnancy have been demonstrated in a number of studies. A review by Berghella et al. (2005) states that transabdominal ultrasound should not be used to assess the cervix during pregnancy, as fetal parts can obscure the cervix, and the longer distance between the probe and the cervix does not allow for optimal visualization. TVU is a standardized and reproducible test and has become the gold standard for evaluating the cervix in clinical settings, including women with PTL (Berghella, et al., 2005).

Literature Review: In an evaluation of the published evidence, the Agency for Healthcare Research and Quality (AHRQ) (2000) identified strong evidence for the effectiveness of cervical ultrasound as a diagnostic tool for assessing the risk of preterm birth in women with symptoms of PTL. The test was found to consistently identify women at low risk of preterm birth which would enable women at low risk to avoid unnecessary treatments.

An Institute for Clinical Systems Improvement (ICSI) technology assessment of the use of ultrasound to measure cervical length for the prediction of PTL stated that the clinical benefit of cervical length measurements may rest in the benefit of a negative or normal result (i.e., >25 mm) which would prevent unnecessary interventions in women who have signs and/or symptoms of PTL. Negative predictive values have ranged from 77–96%, and positive predictive values have ranged from 27–100% for a 25 mm cutoff between 18–28 weeks' gestation. It was further stated that ultrasound measurement of cervical length is not recommended before 14 weeks' gestation or after 35 weeks' gestation. Ultrasound measurement of cervical length is also not recommended as a screening test for PTL in the general obstetric population (ICSI, 2003).

Fetal Fibronectin (fFN)
fFN, a high molecular weight glycoprotein found in the cervicovaginal secretions, has been investigated as a marker for PTL when the results are used in conjunction with the results from standard clinical tests. The detection of fFN at levels greater than 50 nannograms (ng) per milliliter (mL) between 22–35 weeks of gestation is considered abnormal. The data indicate that a negative test has a maximal negative predictive value of approximately 96% for not delivering within the next two weeks, while the positive predictive value of the test is 15–20%. The Fetal Fibronectin Enzyme Immunoassay Kit, an enzyme-linked immunosorbent assay (ELISA), and the Fetal Fibronectin Rapid System, a rapid-reacting membrane immunoassay, manufactured by Adeza Biomedical Corporation (Sunnyvale, CA), detect fFN in the cervicovaginal secretions (Adeza Biomedical Corporation, 2002). Both tests have Premarket Approval (PMA) from the U.S. Food and Drug Administration

(FDA). These tests were developed to facilitate the early diagnosis of PTL and accurate prediction of PTD, thereby enhancing obstetrical decision-making. Both tests can be performed in any Clinical Laboratory Improvement Amendments (CLIA)-approved laboratory. The ELISA test results are available within 4–48 hours, while the rapid test results are available within 1–3 hours (Hayes, 2000; Ramsey and Andrews, 2003).

Literature Review:
Kurtzman et al. (2008) performed a secondary analysis of prospectively collected data for asymptomatic, high-risk women (n=563) with singleton pregnancies. Women with a history of preterm delivery (PTD) underwent quantitative fFN screening at 24 weeks gestation. The association between quantitative fFN concentrations collected at 24 weeks and subsequent gestational age at delivery was analyzed. At 24 weeks, 497 patients (88%) had an fFN level of 0 ng/mL. The remaining patients (n=66) were grouped according to fFN levels as follows:

- fFN 1-49 ng/mL (n=41)
- fFN 50-199 ng/mL (n=17)
- fFN ≥ 200 ng/mL (n=8)

As the fFN concentrations increased, spontaneous preterm delivery rates progressively increased. Compared with the fFN 0 ng/mL group, the relative risk for spontaneous PTD < 34 weeks increased in each group: 2.42 (fFN, 1-49 ng/mL; 95% CI, 0.76-5.66), 4.68 (fFN, 50-199 ng/mL; 95% CI, 1.28-10.95), and 9.94 (fFN, □ 200 ng/mL; 95% CI, 2.90-19.67). It was noted that the small number of women with markedly elevated fFN levels (> 200 ng/mL) was a clear limitation of the study. The study is also limited by its retrospective design.

In 2008, the Institute of Health Economics (IHE) conducted a systemic review of the evidence on the rapid fFN assay used for the management of spontaneous PTL in symptomatic women. The IHE reviewed evidence from other systematic reviews, RCTs, nonrandomized studies, guidelines and consensus statements. The report summarized that "the current clinical use of the rapid fFN assay to diagnose PTL and predict PTB/PTD for symptomatic women who present for health care remains defined by its strong NPV. Knowledge of a negative rapid fFN assay result may supplement clinical judgment to predict "false" PTL followed by absence of PTD/PTB in the short term with more accuracy than clinical criteria alone, but this does not appear to necessarily translate into better clinical outcomes. The clinical importance of a positive test result remains unclear" (IHE, 2008).

Other systematic reviews have evaluated the utility fFN testing. Krupa et al. (2006) stated that measurement of fFN together with evaluation of cervical length by TVU may provide an acceptable level of accuracy in predicting preterm birth. Honest et al. (2002) found Cervicovaginal fFN testing to be most accurate in predicting spontaneous preterm birth within 7–10 days of testing among women with symptoms of threatened preterm birth before advanced cervical dilatation.

Randomized and nonrandomized studies (Schmitz, et al., (2006; Gomez, et al., 2005; Lowe, et al., 2004) support the use of fFN detection in symptomatic women. An ICSI technology assessment published in 2000 reported fFN sensitivity values of 36–83%, specificity values of 70–96%, a PPV range of 45–78% and an NPV range of 76–100% in symptomatic women with intact amniotic membranes. The ICSI Technology Assessment committee concluded that fFN is not recommended as a screening test for asymptomatic patients, regardless of risk status (ICSI, 2000).

Salivary Estriol
Estriol levels have been shown to increase significantly 2–4 weeks before the onset of spontaneous labor. Estriol assessment has historically been accomplished through serial blood or 24-hour urine collections, the latter devised to allow for correction of diurnal hormone variations. Salivary estriol testing was developed because of the cumbersome nature of these tests. The FDA issued a PMA for SalEst™ (Adeza Biomedical Corporation, Sunnyvale, CA) in 1998. Salivary estriol has been identified as a predictor primarily of late preterm birth. Late preterm birth has low rates of neonatal morbidity and mortality and thus the test is rarely used in clinical practice (Ramsey and Andrews, 2003).

Literature Review: A Hayes review of the evidence identified only two published clinical studies investigating the use of salivary estriol as a predictor of PTL or PTD. Both studies compared the diagnostic performance of salivary estriol testing to that of the Creasy system, which is based on demographic profile and medical and behavioral risk factors. The results of these studies suggested that salivary estriol testing is more accurate in

predicting which women will experience PTL. However, neither diagnostic method has high sensitivity and specificity. Using two consecutive positive SalEst tests as criteria for prediction, the SalEst tests had 44% sensitivity, 92% specificity, 19% positive predictive value (PPV), and 98% negative predictive value (NPV). The test characteristics for the Creasy scoring system were 48% sensitivity, 75% specificity, 7% PPV, and 97% NPV. In addition, the available studies have not demonstrated that improved prediction of PTL and delivery permits earlier or more effective treatment designed to delay or prevent preterm birth. Further studies are needed to determine if the diagnostic information provided by the SalEst test improves patient outcomes such as length of gestation or incidence of preterm birth (Hayes, 2005).

Bacterial Vaginosis (BV)
BV is characterized by an overgrowth of a mixture of anaerobic bacteria and mycoplasmas that replace the normal vaginal lactobacilli. BV is a common disorder, occurring in up to 20% of women during pregnancy. Most of these cases will be asymptomatic. BV may resolve spontaneously, although women with BV in early pregnancy are likely to have persistent infection later in pregnancy. BV is associated with an increased risk for spontaneous PTD (Leitich, et al., 2003). Therefore, BV testing is recommended for women who are symptomatic for infection and will benefit from appropriate antibiotic treatment. However, there is insufficient evidence to support the use of screening asymptomatic women for BV as a means of preventing PTD.

Literature Review: In a Cochrane review, Swadpanich et al. (2008) assessed the effectiveness and complications of antenatal lower genital tract infection screening and treatment programs in reducing preterm birth and subsequent morbidity. Only one study by Kiss et al. (2004) met the inclusion criteria of evaluating methods of antenatal lower genital tract infection screening compared with no screening. As previously stated, the primary outcome measure in this study was PTD at less than 37 weeks. The intervention group (n=2058) had significantly lower rates of preterm birth than the control group (3% vs. 5%). The reviewers “found evidence that infection screening and treatment programs in pregnant women may reduce PTB and preterm low birthweight.” It was noted that future studies should include evaluation of gestational ages at screening tests and the effects of different types of infection screening programs (Swadpanich, et al., 2008).

According to the ICSI guideline for the Management of Labor, the assessment and treatment of a patient with PTL may include screening high-risk women for BV with a history of at least one PTD. The guideline states that treatment of BV infection in pregnant women at high risk for PTD with a traditional seven-day course of therapy early in pregnancy appears to reduce PTD. The evidence evaluating the treatment of low-risk pregnant women with asymptomatic BV is limited by use of inadequate therapy in the available studies (ICSI, 2007).

A Cochrane review by McDonald et al. (2005) indicates that there was no difference in the risk of PTD for any treatment versus no treatment or placebo. However, there is some evidence that treatment of BV in women with a history of PTD reduces the occurrence of preterm rupture of membranes and low birthweight. Based on these outcomes, the authors suggest that there may be some benefit in screening for BV and treatment with oral antibiotics in women who have experienced a previous preterm birth. However, the evidence does not demonstrate that the use of antibiotics for BV reduces preterm birth. There is also no evidence for outcomes for the neonate that includes survival, severe health effects and/or long-term hospitalization. A 2007 update of this Cochrane review again found little evidence that screening and treating all pregnant women with asymptomatic BV will prevent preterm birth and its consequences (McDonald, et al., 2007).

Okun et al. (2005) conducted a systematic review of the literature to determine whether antibiotic treatment for BV or trichomonas vaginalis during pregnancy decreases the risk of preterm birth and associated adverse outcomes. Fourteen randomized controlled clinical trials were conducted in which antibiotics versus no treatment or placebo were compared in women who were not in labor and who were in the second or third trimester of pregnancy. The researchers found that while treatment reduced the risk of persistent infection, the incidence of PTL was not reduced; in women with trichomonas vaginalis treated with metronidazole, the incidence of preterm birth was increased. According to these reviewers, “there is inadequate evidence to justify a policy of screening and antibiotic treatment of high-risk women with BV to reduce the risk of preterm birth.”

In a multicenter randomized controlled trial (RCT), Kiss et al. (2004) screened over 4000 asymptomatic women for BV during a routine evaluation early in the second trimester. The caregivers for the intervention group received the results of the testing and instituted treatment. The caregivers for the control group were not given any test results. The primary outcome measure was PTD at less than 37 weeks. The intervention group had significantly lower rates of preterm birth than the control group (3% vs. 5%). It is possible the results were

influenced by physician knowledge of patients with a risk factor for PTL, leading to a different level of care for those with a positive result. It is unclear if factors specific to the country in which it was conducted preclude the application of these study results to patients in the United States.

Professional Societies/Organizations
The U.S. Preventive Services Task Force (USPSTF) guideline on screening for BV in pregnancy concluded that the evidence is insufficient to recommend for or against routinely screening high-risk pregnant women for BV. The USPSTF recommended against routinely screening average-risk asymptomatic pregnant women for BV. It was stated that study results were conflicting and that although the magnitude of benefit exceeded risk in several studies, the single largest study evaluated reported no benefit among high-risk pregnant women (USPSTF, 2001). In a 2008 update to this guideline, the USPSTF restated that pregnant women at low risk for PTD should not be screened for BV and maintained that the current evidence is insufficient to assess the balance of benefits and harms of screening for BV in pregnant women at high risk for PTD (USPSTF, 2008).

According to American College of Obstetricians and Gynecologists (ACOG) (2003), TVU for the determination of cervical length, fFN testing, or a combination of both may be useful in determining women at high risk for PTL. However, their clinical usefulness may rest primarily with their negative predictive value, given the lack of proven treatment options to prevent preterm birth. Fetal fibronectin testing may be useful in women with symptoms of PTL to identify those with a negative value and decreased risk of PTL, thereby reducing unnecessary intervention.

ACOG (2001) found that there is no data to support the use of BV screening as a strategy to identify or prevent preterm birth. ACOG also recommends against the routine screening of average-risk asymptomatic pregnant women for BV.

In January 2001, ACOG stated it could not recommend salivary estriol testing due to its high false-positive rate that could lead to unnecessary prenatal care interventions. The 2003 ACOG Practice Bulletin for the management of PTL does not address the use of salivary estriol in the management of PTL.

Summary
Preterm delivery (PTD) is the most common cause of neonatal death. Tests predictive of preterm labor (PTL) may provide an advantage to patients and healthcare providers in the management of potential PTL. The combination of fetal fibronectin (fFN) and cervical ultrasound has a high negative predictive value (NPV); the information gained from these tests can help providers avoid unnecessary interventions in women with symptoms of PTL. It has not been demonstrated that fFN is efficacious as a screening tool in women at high risk of PTL. Since salivary estriol is a predictor of late preterm birth, when morbidity and mortality rates are lower, the reliability and the clinical utility of the test are questionable. Testing for bacterial vaginosis (BV) as a screening test for asymptomatic women who are at high-risk of PTL is not useful, as the available evidence does not show that treatment for BV reduces the incidence of PTD. Currently, there is insufficient evidence in the medical published peer-reviewed literature to support the use of fFN and BV as screening tests for risk of PTL. Salivary estriol testing for the evaluation of PTL is considered investigational at present.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

CPT®* Codes	Description
76817	Ultrasound, pregnant uterus, real-time with image documentation, transvaginal
82731	Fetal fibronectin, cervicovaginal secretions, semi-quantitative

ICD-9-CM Diagnosis Codes	Description

644.00	Threatened premature labor, unspecified as to episode of care
644.03	Threatened premature labor, antepartum

Experimental/Investigational/Unproven/Not Covered:

HCPCS Codes	Description
S3652	Saliva test, hormone level; to assess preterm labor risk

***Current Procedural Terminology (CPT®) ©2008 American Medical Association: Chicago, IL.**

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	7/15/2008	0099	Tests for the Evaluation of Preterm Labor
Great-West Healthcare	7/19/2007	98.298.04	Fetal Fibronectin and Salivary Estriol Testing (SalEST) for Preterm Labor