



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

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Home Uterine Activity Monitoring (HUAM)
 Parenteral Tocolytic Therapy
 Recurrent Pregnancy Loss: Diagnosis and Treatment
 Ultrasound in Pregnancy (including 3D and 4D Ultrasound)

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2010 CIGNA

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 EITHER of the following because each is 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. 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 PTB. The ability to predict whether a woman is at risk of PTB 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.

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 PTB and a previous history of a second-trimester abortion. Existing medical conditions in the pregnant woman which also increase the risk of PTL include 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. Screening for risk of PTL by means other than historic risk factors is not beneficial in the general obstetric population. However, in the at-risk population, an accurate diagnostic test for PTL would allow women who are truly at risk for PTB to receive appropriate treatment and decrease unwarranted interventions in women who will deliver at term (American College of Obstetricians and Gynecologists [ACOG], 2001).

Cervical Ultrasound

Cervical length is an established predictor of PTB. The length of the cervix is inversely proportional to the risk of PTB. 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).

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 nanograms (ng) per milliliter (mL) between 22–35 weeks of gestation is considered abnormal. In general, the sensitivity of fetal fibronectin increases in symptomatic women, women with a cervical length of less than 2.5 mm, women with a history of prior preterm delivery, and women with bacterial vaginosis. The negative predictive value (NPV) in women with preterm contractions ranges from 69% to 92% before 37 weeks gestation, while the positive predictive value (PPV) of the test is 15–20%. A negative fetal fibronectin has a 95% likelihood that delivery will not occur within 14 days of sampling (Gibbs, et al., 2008). fFN testing was developed to facilitate the early diagnosis of PTL and accurate prediction of PTB, thereby enhancing obstetrical decision-making.

U.S. Food and Drug Administration (FDA): 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). Both tests can be performed in any Clinical Laboratory Improvement Amendments (CLIA)-approved laboratory.

Literature Review: The use of fFN detection in women who are symptomatic for PTL is supported by a number of randomized and nonrandomized studies (Tanir, et al., 2008; Schmitz, et al., 2006; Gomez, et al., 2005; Lowe, et al., 2004), as well as meta-analyses and systematic reviews (Sanchez-Ramos, et al., 2009; Honest, et al., 2009; Institute of Health Economics [IHE], 2008; Smith, et al., 2007; Krupa, et al., 2006; Honest, et al., 2002). 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 have been reported (2006; Gomez, et al., 2005; Lowe, et al., 2004; Honest, et al., 2002). The use of fFN screening for asymptomatic women has not been supported by the evidence in the published peer-reviewed medical literature.

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: The available evidence investigating the use of salivary estriol includes an RCT (n=601) by Heine et al. (1999) that compared the accuracy of salivary estriol testing to that of the Creasy score for predicting PTL followed by PTB. Serial salivary estriol testing was found to correctly predict the appropriate outcome more often than the Creasy score, 91% versus 75%, respectively. Salivary estriol testing had a sensitivity of 44%, specificity of 92%, PPV of 19%, and an NPV of 98%, using two consecutive positive tests as criteria for prediction. Corresponding values for the Creasy system were 48% sensitivity, 75% specificity, 7% PPV, and 97% NPV (Heine, et al., (2000). While these study results suggest that salivary estriol testing may predict outcomes more accurately than the Creasy scoring system, the impact of salivary estriol testing on treatment decision making or patient outcomes has not been demonstrated. Additional studies are needed to establish the role of this testing method in the management of PTL and PTB.

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 PTB (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 PTB.

Literature Review: Studies in the published peer-reviewed medical literature evaluating the use of BV screening for women who are asymptomatic for PTL have yielded conflicting results. A Cochrane review by Swadpanich et al. (2008) assessed the effectiveness and complications of antenatal lower genital tract infection screening and treatment programs in reducing PTB and subsequent morbidity. Some evidence was found to suggest that in general infection screening and treatment programs in pregnant women may reduce PTB and preterm low birthweight. This review was based on the results of one randomized controlled trial (RCT), Kiss et al. (2004). A Cochrane review by McDonald et al. (2007) found little evidence that screening and treating all pregnant women with asymptomatic BV will prevent preterm birth and its consequences (McDonald, et al., 2007).

The Institute for Clinical Systems Improvement (ICSI) reported that 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, 2009).

A systematic review (n=14 RCTs) by Okun et al. (2005) found that while treatment reduced the risk of persistent infection with BV or trichomonas vaginalis, the incidence of PTL was not reduced; in women with trichomonas vaginalis treated with metronidazole, the incidence of preterm birth was increased.

There is insufficient evidence to support the use of screening asymptomatic women for BV as a means of preventing PTB.

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

There is sufficient evidence in the published peer-review scientific literature to support the use of fetal fibronectin (fFN) testing and transvaginal ultrasonography (TVU) for women who have symptoms of preterm labor (PTL). The combination of 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 method 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 published peer-reviewed medical literature to support the use of salivary estriol testing for the evaluation of PTL, and fFN or BV as screening tests for risk of PTL.

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[®]) © 2010 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

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Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA's subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.