



CIGNA MEDICAL COVERAGE POLICY

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

Subject Tests for the Evaluation of Preterm Labor and Premature Rupture of Membranes

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 Parenteral Tocolytic Therapy
 Recurrent Pregnancy Loss: Diagnosis and Treatment
 Ultrasound in Pregnancy (including 3D and 4D Ultrasound)

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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 EITHER of the following for the screening of PTL because each is considered experimental, investigational or unproven:

- salivary estriol testing
- fFN or bacterial vaginosis (BV) testing

CIGNA does not cover placental alpha-microglobulin-1 (PAMG-1) testing (e.g., Amnisure® ROM) for the evaluation of premature rupture of membranes because it is considered experimental, investigational or unproven.

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 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.

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 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 PTD to receive appropriate treatment and decrease unwarranted interventions in women who will deliver at term (American College of Obstetricians and Gynecologists [ACOG], 2001).

PTL Evaluation

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).

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 PTD, 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.

fFN 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).

Salivary Estriol 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 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.

BV 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 PTD.

PROM Evaluation

Premature rupture of membranes (PROM) is rupture of membranes occurring prior to the onset of labor. Preterm PROM (PPROM) is defined a membrane rupture that occurs before 37 weeks of gestation. Intra-amniotic infection has been shown to be commonly associated with PPRM, especially if the rupture occurs at earlier gestational ages. Risk factors for PROM include previous preterm birth (especially if the cause was

PROM), short cervical length (less than 25 mm) during the second trimester, and PTL or symptomatic contractions in the current pregnancy. PROM can also occur without any identifiable risk factor.

Most cases of PROM can be diagnosed based on the patient's history and physical examination. Sterile speculum examination allows for visual inspection of fluid and provides an opportunity to assess for cervicitis and umbilical cord or fetal prolapse, cervical dilation and effacement, and to obtain cultures as appropriate. Digital cervical examinations add little additional information to the speculum examination and are avoided due to the increase risk of infection. Diagnostic methods using nitrazine paper and determination of ferning (arborization) have sensitivities approaching 90 %. The pH of vaginal secretions is generally 4.5-6.0, while amniotic fluid usually has a pH of 7.1-7.3. False-positive results may occur with this diagnostic method as a result of contamination with blood or semen, alkaline antiseptics, or bacterial vaginosis and false-negative results can occur with prolonged leakage and minimal residual fluid. In unusual cases in which the diagnosis remains unclear after physical examination, ultrasonography may be useful. When the clinical history or physical examination is unclear, membrane rupture can be diagnosed unequivocally with ultrasonographically guided transabdominal instillation of indigo carmine dye, followed by observation for passage of blue fluid from the vagina (ACOG, 2007).

At term, PROM complicates approximately 8 % of pregnancies and is generally followed by the onset of spontaneous labor and delivery. The most significant maternal risk of term PROM is intrauterine infection. Fetal risks associated with term PROM include umbilical cord compression and ascending infection. PPRM complicates only 2 % of pregnancies but is associated with 40 % of preterm deliveries and can result in significant neonatal morbidity and mortality (ACOG, 2007). An accurate diagnosis of PROM facilitates optimal clinical assessment and expectant management. Placental alpha-1 microglobulin (PAMG-1) is being investigated as a marker for the detection of PROM. PAMG is found in high levels in amniotic fluid and low levels in cervicovaginal discharge when fetal membranes are intact.

U.S. Food and Drug Administration (FDA): On January 9, 2009, the Amnisure® ROM (rupture of fetal membrane) test was granted 510(k) approval by the FDA because it is considered to be substantially equivalent to another device already on the market. Under the FDA 510(k) approval process, the manufacturer is not required to supply to the FDA evidence of the effectiveness of the Amnisure prior to marketing. The 510(k) summary stated that the Amnisure is substantially equivalent to the AmnioTest™. According the FDA, The Amnisure® ROM test is a rapid, non-instrumented, qualitative immunochromatographic test for the in vitro detection of amniotic fluid in vaginal secretion of pregnant women. Amnisure detects PAMG-1 protein marker of the amniotic fluid in vaginal secretions. The test is for use by health care professionals to aid in the detection of ROM when patients report signs, symptoms or complaints suggestive of ROM.

PAMG-1 immunoassay Literature Review: Studies evaluating the safety and effectiveness of PAMG-1 testing to detect PROM includes cohort, observational, and uncontrolled comparative trials. A prospective cohort study (n=199) by Birkenmaier et al. (2011) evaluated the performance of the PAMG-1 immunoassay (AmniSure®) in cervicovaginal secretions of patients with uncertain ROM. Evaluation of patients included clinical assessment, examination for cervical leakage, Nitrazine test and measurement of the amniotic fluid index by ultrasound and Amnisure. ROM occurrence was based on review of the medical records after delivery. Amnisure had a sensitivity of 94.4%; specificity of 98.6%; positive predictive value (PPV), 96.2%; negative predictive value (NPV), 98.0%. Clinical assessment showed a sensitivity of 72.2%; specificity of 97.8%; PPV of 92.9%; NPV of 90.6%. Amnisure testing was reported to be more sensitive for diagnosing ROM ($p=0.00596$) compared to clinical assessment, independent of the examiners experience.

Tagore et al. (2010) compared insulin-like growth factor binding protein-1 (IGFBP-1), PAMG-1 and nitrazine testing to diagnose PROM. PAMG-1 was performed in 100 women with a sensitivity of 92.7%, specificity of 100%, PPV of 100% and NPV of 95.2%. IGFBP-1 was performed in 94 women with a sensitivity of 87.5%, specificity of 94.4%, PPV of 92.1% and NPV of 91.1%. In 98 women in whom nitrazine test was performed, the sensitivity was 85%, specificity was 39.7%, PPV was 49.3% and NPV was 79.3%.

A prospective observational study (n=189) Lee et al. 2007 compared the accuracy of an immunoassay to measure levels of PAM-1 in cervicovaginal secretions with that of conventional clinical assessment for the diagnosis of ROM. PAMG-1 immunoassay was found to confirm ROM initial presentation with a sensitivity of 98.7%, specificity of 87.5%, PPV of 98.1%, and NPV of 91.3%. PAMG-1 immunoassay was reported better than

both the conventional clinical assessment and the nitrazine test alone in confirming the diagnosis of rupture of membranes.

Cousins et al. (2005) conducted a comparative study (n=203) of AmniSure versus standard diagnostic methods for detection of ROM in women suspected of ROM. The AmniSure test was found to have a sensitivity of 98.9%, specificity of 100%, and NPV of 99.1% in diagnosing ROM (Cousins et al, 2005). Test performance was assessed by comparing AmniSure results to clinical history, nitrazine and fern results, presence of pooling, ultrasound evidence of oligohydramnios, and findings from repeated examinations.

Although study results indicate that PAMG-1 testing with Amnisure is accurate when compared to standard testing methods for PROM. However, study populations have included a wide range of gestational ages and clinical presentations. Clinical utility has not been established as no published studies have compared health outcomes in cases where treatment decisions were based on AmniSure testing versus standard testing methods.

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.

Although the available studies in the published peer-reviewed medical literature suggests that the accuracy of placental alpha-1 microglobulin (PAMG-1) immunoassay testing for the detection of premature rupture of membranes may be superior to current standard testing methods, controlled clinical trials are needed to

demonstrate improved clinical utility over these methods and the impact on health outcomes. Therefore there is insufficient evidence to support the use of PAMG-1 testing at this time.

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:

CPT* Codes	Description
84112	Placental alpha microglobulin-1 (PAMG-1), cervicovaginal secretion, qualitative

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

ICD-9-CM Diagnosis Codes	Description
658.10	Premature rupture of membranes; unspecified as to episode of care
658.13	Premature rupture of membranes; antepartum condition

*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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