Cigna Medical Coverage Policy

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

Effective Date: 2/15/2013
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Home Uterine Activity Monitoring (HUAM)
Recurrent Pregnancy Loss: Diagnosis and Treatment
Ultrasound in Pregnancy (including 3D and 4D Ultrasound)

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Coverage Policy

Cigna does not cover EITHER of the following for the evaluation of preterm labor (PTL) because each is considered experimental, investigational or unproven.

- salivary estriol testing
- 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.

Cigna does not cover EITHER of the following for the evaluation of pregnant women at high risk for preterm delivery because each is considered experimental, investigational or unproven for this indication (this list may not be all inclusive):

- inflammatory biomarker testing, including but not limited to cytokines (e.g., interleukin-6, interleukin-8), maternal matrix metalloproteinase-9, and C-reactive protein
- hormone-related biomarker testing including but not limited to human chorionic gonadotrophin and phosphorylated insulin-like growth factor binding protein-1

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).

Preterm Labor Evaluation

**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 a randomized controlled trial (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%, positive predictive value (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% negative predictive value (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.

**Bacterial Vaginosis 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.

Premature Rupture of Membranes (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 PPROM, 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. PPROM 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: 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%. Amniture 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 Amniture 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.

**Preterm Delivery Prediction**

**Inflammatory and Hormone-Related Biomarkers:** It is suggested in the medical literature that intra uterine infection and inflammation play a role in spontaneous preterm deliveries. Elevated concentrations of inflammatory biomarkers such as interleukin-6 (IL-6), C-reactive protein (CRP), and matrix metalloproteinase-9 (MMP-9) have been associated with an increased risk for preterm birth and/or newborn morbidity. Hormone-related biomarker (e.g., human chorionic gonadotrophin and phosphorylated insulin-like growth factor binding protein-1) are also being investigated as predictors of preterm delivery. Simple, rapid, noninvasive, and safe tests of markers of asymmetric intrauterine infection that are associated with adverse neonatal outcomes could be useful in development of strategies for risk stratification and prediction of morbidity among women with or without symptoms of labor (Sorokin, et al., 2010).

**Literature Review:** Studies have been conducted evaluating the safety, effectiveness, and clinical utility of these biomarkers have been conducted and include observational studies and systematic reviews. Conde-Agudelo et al. (2011) performed a systematic review of observational studies (n=72 studies/89786 women) to evaluate the accuracy of novel biomarkers to predict spontaneous preterm birth in women with singleton pregnancies and no symptoms of preterm labor. For serum levels of biomarkers including interleukins-2, -6 and -10, and C-reactive protein, the pooled sensitivities and specificities ranged from 3%-49% and 51%-97% respectively. Positive and negative likelihood ratios predicting preterm birth before 32, 34, and 37 weeks of gestation were between 0.4 and 4.5 (median, 1.1), and between 0.6 and 1.3 (median, 1.0), respectively.
cervicovaginal levels of interleukins-6 and -8, the pooled sensitivities, specificities, varied from 24%-44% and 75%-93% (median, 83%), with positive and negative LRrs from 1.1 to 4.0, and 0.6 to 1.0 respectively. For amniotic fluid levels of biomarkers including interleukin-6, MMP-8, and C-reactive protein, the pooled sensitivities, specificities, and positive and negative LRrs ranged from 12%-86%, from 43%-99%, from 0.9-40.0, and from 0.2- 1.1, respectively.

In summary, moderate predictive accuracy was found for 4/30 biomarkers (IL-6 and angiogenin, in amniotic fluid; human chorionic gonadotrophin and phosphorylated insulin-like growth factor binding protein-1, in cervicovaginal fluid). The remaining biomarkers had low predictive accuracy. None of the biomarkers evaluated in this review meet the criteria to be considered a clinically useful test to predict spontaneous preterm birth (Conde-Agudelo, et al., 2011).

Sorokin et al. (2010) conducted an observational study (n=475) to determine if the maternal serum concentration of IL-6, CRP, and MMP-9 in asymptomatic women at risk for preterm birth, was associated with an increased risk for preterm birth and/or neonatal morbidity. Maternal serum samples collected from patients enrolled in a multicenter randomized controlled trial of single versus weekly corticosteroids. Concentrations of IL-6, CRP, and MMP-9 were subsequently determined using enzyme-linked immunosassays. Maternal serum concentrations of IL-6 and CRP, but not MMP-9, above the 90th percentile at the time of randomization were associated with preterm birth less than 32 weeks.

Wei et al. (2010) conducted a systematic review of observational studies (n=17 studies/6270 participants) that reported the association between inflammatory cytokines and spontaneous preterm birth as an outcome in asymptomatic women. Spontaneous preterm birth was reported to be strongly associated with increased levels of IL-6 in mid-trimester cervicovaginal fluid (OR 3.05, 95% CI 2.00-4.67) and amniotic fluid (OR 4.52, 95% CI 2.67-7.65), but there was no association in plasma specimen (OR 1.5, 95% CI 0.7-3.0). Spontaneous preterm birth was also found to be strongly associated with increased CRP levels in midtrimester amniotic fluid (OR 7.85, 95% CI 3.88-15.87), but the association was weak in plasma specimen (OR 1.53, 95% CI 1.22-1.90). There were insufficient data for a meta-analysis of other inflammatory cytokines.

Although available study results are promising, there is currently insufficient evidence to support the use of inflammatory and hormone-related biomarkers as predictors of preterm birth in women with intact membranes who are not in labor.

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).

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 a paucity of studies assessing the effectiveness of salivary estriol testing. The reliability and the clinical utility of the test are questionable. The test is a predictor of late preterm birth when morbidity and mortality rates are lower. 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 or BV testing for the evaluation of risk for 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.

The evidence in the published peer-reviewed medical literature indicates that there is an association between elevated levels of some inflammatory and hormone-related biomarkers. However, the clinical utility of these biomarkers has not been demonstrated. In addition, patient-selection criteria have not been clearly established. Additional well-designed clinical trials are needed to further define the role of this testing in pregnancy management.

### Coding/Billing Information

**Note:**
1. This list of codes may not be all-inclusive.
2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

#### Experimental/Investigational/Unproven/Not Covered:

**Salivary Estriol Testing and Bacterial Vaginosis (BV) Testing**

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<th>Description</th>
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<td>87480</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); Candida species, direct probe technique</td>
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<td>87510</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); Gardnerella vaginalis, direct probe technique</td>
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<tr>
<td>87512</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); Gardnerella vaginalis, quantification</td>
</tr>
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<td>87660</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); Trichomonas vaginalis, direct probe technique</td>
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<tr>
<td>82677</td>
<td>Estriol</td>
</tr>
<tr>
<td>87799†</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA), not otherwise specified; quantification, each organism</td>
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*Note: Experimental/Investigational/Unproven/Not Covered when used to report testing for bacterial vaginosis for the evaluation of preterm labor.*

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<td>S3652</td>
<td>Saliva test, hormone level; to assess preterm labor risk</td>
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<th>ICD-9-CM Diagnosis Codes</th>
<th>Description</th>
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<tr>
<td>644.00</td>
<td>Threatened premature labor, unspecified as to episode of care</td>
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<tr>
<td>644.03</td>
<td>Threatened premature labor, antepartum</td>
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**Placental Alpha-Microglobulin-1 (PAMG-1) Testing (e.g., Amnisure® ROM)**

#### Experimental/Investigational/Unproven/Not Covered:

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<tr>
<td>84112</td>
<td>Placental alpha microglobulin-1 (PAMG-1), cervicovaginal secretion, qualitative</td>
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### ICD-9-CM Diagnosis Codes

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<td>658.13</td>
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### Biomarker Testing

**Experimental/Investigational/Unproven/Not Covered:**

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<td>83518</td>
<td>Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; qualitative or semiquantitative, single step method (eg, reagent strip)</td>
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<td>Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, by radioimmunoassay (eg, RIA)</td>
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<td>Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified</td>
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<td>87799</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA), not otherwise specified; quantification, each organism</td>
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### References


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