Non-Invasive Tests for the Detection of Fetal Membrane Rupture

Policy Number: 2.04.505  Last Review: 1/2017
Origination: 12/2009  Next Review: 1/2018

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for non-invasive tests for the detection of fetal membrane rupture. This is considered investigational.

When Policy Topic is covered
Not Applicable

When Policy Topic is not covered
The use of non-invasive tests for the detection of fetal membrane rupture is considered investigational.

Considerations
This document addresses testing for suspected rupture of membranes (ROM) with test kits, including, but not limited to the AmniSure® ROM test, which detects placental alpha-1 microglobulin (PAMG-1), a protein marker of amniotic fluid in vaginal secretions; the ROM Plus® Fetal Membrane Rupture test, which tests both placental protein 12 (PP12) and alpha-fetoprotein (AFP); and the Actim® PROM test, which tests for insulin-like growth factor binding protein 1 (IGFBP-1).

Description of Procedure or Service
Premature rupture of membranes (PROM) complicates approximately 8% of pregnancies and is generally followed by the prompt onset of spontaneous labor and delivery. 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 preterm labor (PTL) or symptomatic contractions in the current pregnancy. PROM can also occur without any identifiable risk factor. The most significant maternal risk of term PROM is intra-uterine infection, a risk that increases with the duration of membrane rupture. Fetal risks associated with term PROM include umbilical cord compression and ascending infection. Membrane rupture that occurs before 37 weeks of gestation is referred to as preterm PROM (PPROM). PPROM complicates only 2% of pregnancies but is associated with 40% of preterm deliveries and can result in significant neonatal morbidity and
mortality. The three causes of neonatal death associated with PPROM are prematurity, sepsis and pulmonary hypoplasia. In the absence of clinical history or confirmatory physical exam, PROM can be definitively diagnosed with ultrasonographically-guided transabdominal instillation of indigo carmine dye, followed by observation for passage of blue fluid from the vagina (ACOG, 2007; RCOG, 2006).

**Rationale**

Placental alpha-1 microglobulin (PAMG-1) has been investigated as a marker for the detection of premature rupture of membranes (PROM). PAMG-1 can also be found in high levels in amniotic fluid and low levels in cervicovaginal discharge when fetal membranes are intact. The AmniSure ROM (Rupture of Membranes) test (AmniSure® International, LLC, Cambridge, MA) is a rapid, non-instrumented, qualitative immunochromatographic test for in-vitro detection of amniotic fluid in the vaginal secretions of pregnant women. On February 3, 2004 the AmniSure one-step Fetal Membranes Rupture (ROM) test obtained clearance from the U.S. Food and Drug Administration (FDA). This initial clearance was for the in vitro detection of amniotic fluid in vaginal secretions 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 rupture of membranes (ROM) in pregnant women at > 34 weeks gestation when patients report signs, symptoms or complaints suggestive of ROM (FDA, 2004).

The clinical performance of AmniSure was determined by one study involving two sites in which individuals between 34-41 weeks of gestation, without active vaginal bleeding from any source and placenta previa, were evaluated by clinical assessment control and the AmniSure device. The clinical assessment control was considered positive if two out of three tests (nitrazine, ferning, and pooling) were positive. Statistical analysis was available on 159 women with the positive and negative agreements between AmniSure and the control as follows:

- Positive agreement = 97.2% (69/71), 95% CI = (90.2%, 99.7%);
- Negative agreement = 97.6% (81/83), 95% CI = (91.6%, 99.7%).

The AmniSure Fetal Membranes Rupture Test was found to be similar to the predicate device in intended use (that is, detection of rupture of membranes in pregnant women). According to the original FDA clearance:

The devices differ in technological characteristics; however, the methodology of the AmniSure device is well-established and raises no concerns with safety or effectiveness. Furthermore, the AmniSure device was found to be in greater than 97% agreement with the standard clinical procedures used to detect rupture of membranes. Therefore, a substantial equivalence determination was granted for the AmniSure Fetal Membranes Rupture Test.

On January 9, 2009 the FDA-cleared indication for use was modified to remove the specification that the device is for use in women at greater than 34 weeks gestation. The updated FDA labeling is as follows:
The Amnisure ROM (rupture of fetal membrane) Test is a rapid, non-instrumented, qualitative immunochromatographic test for the in vitro detection of amniotic fluid in vaginal secretions 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 (FDA, 2009).

The evidence basis for this change in FDA labeling was provided as follows:
1. The expected values were determined in literature studies and from research performed by the sponsor;
2. Concentration of PAMG-1 in cervical and vaginal secretions of pregnant women without complications was measured and ranged from 0.05 to 0.22 ng/mL;
3. PAMG-1 concentrations in the amniotic fluid fall into 2,000-25,000 ng/mL range.

Pooled data from the 3 studies for less than 34 weeks gestational age showed:
98% agreement with current methods among positive results (95% confidence intervals 91.6% to 99.9%) and 96% agreement with current methods among negative results (95% confidence intervals 86.3 to 98.9).

Pooled data from 3 studies for greater than or equal to 34 weeks showed:
99% agreement with current methods among both positive and negative results (95% confidence intervals of 96.76 to 99.84% and 95.42 to 99.95% for positive and negative results, respectively) (FDA, 2009).

To date, the available published studies that have evaluated the safety and effectiveness of PAMG-1 testing to detect PROM have been limited. In 2005, Cousins conducted a comparative study (n=203) of AmniSure versus standard diagnostic methods for detection of ROM in women suspected of PROM. The AmniSure test was found to have a sensitivity of 98.9%, specificity of 100%, and negative predictive value (NPV) of 99.1% in diagnosing ROM. 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 (Cousins, 2005).

A retrospective cohort study examined the frequency and clinical significance of a positive AmniSure test in subjects with preterm labor and intact membranes by sterile speculum examination. A total of 90 subjects with preterm labor and intact membranes underwent AmniSure testing prior to amniocentesis; 64 subjects also underwent fetal fibronectin (fFN) testing. Amniotic fluid (AF) was cultured for aerobic and anaerobic bacteria and genital mycoplasmas and assayed for matrix metalloproteinase-8. AmniSure positive results occurred in 19% of study subjects (17/90). Subjects with a positive AmniSure test had significantly higher rates of adverse pregnancy and neonatal outcomes (for example, impending preterm delivery, intra-amniotic infection/inflammation, and neonatal morbidity) than those with a negative AmniSure test. A positive test was associated with significantly increased risk of intra-amniotic infection and/or inflammation, delivery within 7,
14, or 28 days and spontaneous preterm birth (at less than 35 weeks), among subjects with a negative fFN test. The authors concluded that a positive AmniSure test in subjects with preterm labor and intact membranes is a risk factor for adverse pregnancy outcome, particularly in those with a negative fFN test. However, it was noted that a positive AmniSure test in subjects without symptoms or signs of ROM should not be taken as an indicator that membranes have ruptured (Lee, 2012). Additional cohort, uncontrolled, comparative, and observational studies have demonstrated the accuracy of AmniSure ROM testing, however, no studies have shown how use of this test will impact clinical outcomes, as compared to conventional methods of PROM detection, and further research is needed (Abdelazim, 2012; Birkenmaier, 2012; Lee, 2007; Tagore, 2010).

On November 23, 2011 another ROM test, the ROM Plus® Fetal Membrane Rupture Test (Clinical Innovations, LLC, Murray, UT) obtained clearance from the FDA through the 510(k) approval process, as substantially equivalent to the predicate device, the AmniSure ROM test. The approved indications for use are as follows:

As a rapid, qualitative immunochromatographic test for the in-vitro detection of amniotic fluid in vaginal secretions of pregnant women with signs and symptoms of ROM. The test detects AFP (alpha-fetoprotein) and PPI12 (placental protein 12 or insulin growth factor binding protein) from amniotic fluid in vaginal secretions. The test is for prescription use by health care professionals to aid in the detection of rupture of membranes (ROM) in pregnant women in conjunction with other signs and symptoms (FDA, 2011).

Notably, the package insert contains the following warning as a special FDA condition for use: "The test may report positive results in patients with intact membranes and, therefore, decisions to induce labor should not be based solely on the ROM Plus test results" (FDA, 2011).

In 2007, another rapid in-vitro test, the Actim® PROM test (Alere™ Inc., Waltham, MA) obtained 510(k) clearance from the FDA as substantially equivalent to the AmniSure ROM test. The FDA approved indications are as follows:

The Actim PROM test is a visually interpreted, qualitative immunochromatographic rapid test for the detection of amniotic fluid in cervicovaginal secretions during pregnancy. The Actim PROM test detects IGFBP-1, which is a major protein in amniotic fluid and a marker of the presence of amniotic fluid in a cervicovaginal sample. The test is intended for professional use to help diagnose the rupture of fetal membranes (ROM) in pregnant women at >34 weeks gestation when patients report signs, symptoms or complaints suggestive of ROM or if such signs are otherwise observed (FDA, 2007).

According to the American Congress of Obstetricians and Gynecologists (ACOG) Practice Bulletin No. 80: Premature Rupture of Membranes:

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. 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; ACOG reaffirmed this guideline which does not address testing for PAMG-1 with AmniSure - December 2012).

The Royal College of Obstetricians and Gynecologists (RCOG), Scientific Advisory Committee Guideline on Preterm Prelabor Rupture of Membranes concurs with ACOG that:

The diagnosis of PROM is based primarily on the patient's history and physical examination. Patients often report a sudden gush of fluid or continued leakage of fluid. Sterile speculum examination provides a visual inspection of fluid and an opportunity to inspect for cervicitis and umbilical cord or fetal prolapse, cervical dilation and effacement, and to obtain cultures as appropriate. In unusual cases in which the diagnosis remains unclear after physical examination, ultrasonography may be helpful. Management of ROM hinges on knowledge of gestational age and evaluation of the relative risks of preterm birth versus intrauterine infection, abruptio placentae, and cord accident that could occur with expectant management (RCOG, 2006).

The available evidence regarding the use of rapid immunoassay test kit devices to detect PROM is inadequate to form firm conclusions regarding its safety, efficacy and how this testing will impact clinical outcomes for the pregnant woman and neonatal child, in comparison with established methods of PROM detection. According to a 2012 review article, to date, published studies have been prospective and observational with small sample size. The lack of a noninvasive test "Gold Standard" with which to compare other forms of testing for PROM, such as the AmniSure test or the ROM Plus Fetal Membrane test, confounds the evidence and emphasizes the need for larger randomized controlled trials before the clinical utility of testing for protein markers in suspected PROM can be established (van der Ham, 2012).

References:

Billing Coding/Physician Documentation Information
84112 Placental alpha microglobulin-1 (PAMG-1), cervicovaginal secretion, qualitative

Code S3628 was deleted effective 7/1/2011.
**Additional Policy Key Words**

N/A

**Policy Implementation/Update Information**

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<tr>
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<td>2/15/10</td>
<td>New policy; considered investigational, policy became effective 2/15/2010.</td>
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<td>Policy statement revised to remove specific test name (Amnisure).</td>
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