Anthem

Medical Policy

Subject: Rupture of Membranes Testing in Pregnancy
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Description/Scope

This document addresses testing for suspected rupture of membranes (ROM) with test kits, such as 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).

Position Statement

Not Medically Necessary:

Evaluation of cervicovaginal fluid for specific amniotic fluid protein(s), (for example, placental alpha microglobulin-1 [PAMG-1], placental protein 12 [PP12], alpha-fetoprotein), is considered **not medically necessary** for all indications, including detection of preterm rupture of membranes.

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% confidence interval [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 imnmunochromatographic 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).

On January 9, 2014, the Actim PROM test obtained an updated 510(k) clearance from the FDA for indications to include use of the device in pregnant women ≥ 29 weeks gestational age and to allow use of the device with vaginal swabs collected without use of a speculum, in addition to the current sample type swabs collected with the use of a speculum. No changes to the test itself had been made by the manufacturer (FDA, 2014).

On April 11, 2018, the FDA cleared the PartoSure™ test (Qiagen, Inc., Germantown, MD), subject to post-approval study results. The PartoSure is another test kit approved for the detection of PAMG-1 in cervicovaginal secretions. The test is indicated:

> As an aid to rapidly assess the risk of spontaneous preterm delivery in ≤ 7 days from the time of cervicovaginal sample collection in pregnant women with signs and symptoms of early preterm labor, intact amniotic membranes and minimal cervical dilatation (< 3 cm), sampled between 24 weeks, 0 days and 34 weeks, 6 days gestation in women with a singleton gestation (FDA, 2018).

The FDA labeling for the PartoSure test kit includes test limitations including, but not limited to:

- The PartoSure result should not be interpreted as absolute evidence for the presence or absence of a process that will result in delivery ≤ 7 days from specimen collection.
- The PartoSure test result should always be used in conjunction with information available from the clinical evaluation of the patient and other diagnostic procedures, such as cervical examination, assessment of uterine activity, and evaluation of other risk factors.
- Results should be interpreted with caution when a specimen is obtained from a patient with unconfirmed gestational age.
- PartoSure test results are qualitative and not quantitative. No quantitative interpretation should be made based on the strength of the test or control lines.
- This test should only be used in patients with signs and symptoms of preterm labor.
- At this time, information is insufficient to rule out interference by cervical digital examination; therefore, specimens should be collected prior to digital examinations (FDA, 2018).

The American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin No. 217 entitled, Prelabor Rupture of Membranes was updated in 2020 with no change in position as follows:

> Several commercially available tests for amniotic proteins are currently on the market, with reported high sensitivity for PROM. However, false-positive test result rates of 19–30% have been reported in patients with clinically intact membranes and symptoms of labor. These tests are appealing in light of the requirements of regulatory bodies related to Clinical Laboratory Improvement Amendments of 1988 quality standards on the point-of-care methods of clinical assessment such as Nitrazine and fern testing. The studies evaluating these protein tests are problematic because most of them use conventional clinical assessment (pooling, ferning, pH) as controls or gold standards for the diagnosis of rupture of membranes, calling into question their utility in equivocal cases. Additionally, the U.S. Food and Drug Administration released a letter to health care providers in response to adverse events related to their use, including 13 fetal deaths and multiple reports of health complications in pregnant women. The U.S. Food and Drug Administration letter reminded health care providers that these tests should not be used without other clinical assessments because of concerns about “misuse, overreliance, and inaccurate interpretation of lab test results from rupture of membranes tests used to detect rupture of membranes in pregnant women. These can lead to serious adverse events, including fetal

death, infection, and other health complications in pregnant women." At most these test kits should be considered selectively relative to standard methods of diagnosis (ACOG, 2020).

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 weak. The use of this type of testing has not been widely accepted for detection of premature rupture of membranes and has not been demonstrated to have significant positive impact on clinical outcomes for pregnant individuals and neonates in comparison to the established methods of PROM detection.

Background/Overview

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).

Definitions

Fern test: This term refers to microscopic crystallization of amniotic fluid on drying which is used as one measure of the presence of PROM.

Indigo carmine test: This test involves amniocentesis and instillation of dye into the amniotic cavity. Leakage of blue-stained fluid into the vagina within 20 to 30 minutes, as evidenced by staining of a tampon, is regarded as a definitive diagnosis of PROM or PPROM. This invasive test is currently considered the "Gold Standard" diagnostic for detection of PROM.

Nitrazine test: This test is designed only to confirm an alkaline pH in the cervicovaginal secretions (the pH of the vaginal secretions is generally 4.5–6.0, whereas amniotic fluid usually has a pH of 7.1–7.3), and is the most common test used to diagnose PROM.

Pooling test: This test involves direct visualization of clear fluid in the posterior fornix of the vagina or leakage of fluid from the cervical os which is considered a diagnostic option for detection of PROM.

Premature rupture of membranes (PROM): Rupture of membranes that occurs before the onset of labor.

Preterm premature rupture of membranes (PPROM): Rupture of membranes that occurs before 37 weeks of gestation.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Not Medically Necessary:

CPT	
84112	Evaluation of cervicovaginal fluid for specific amniotic fluid protein(s) (eg, placental alpha microglobulin-1 [PAMG-1], placental protein 12 [PP12], alpha-fetoprotein), qualitative, each specimen
ICD-10 Diagnosis	
	All diagnoses

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Peer Reviewed Publications:

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membranes. Rev Obstet Gynecol. 2008; 1(1):11-22.
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Government Agency, Medical Society, and Other Authoritative Publications:

1. American Congress of Obstetricians and Gynecologists (ACOG) Committee on Practice Bulletins-Obstetrics. ACOG Practice Bulletin No. 217: Prelabor Rupture of Membranes. Clinical Management Guidelines for Obstetrician-Gynecologists. Updated 2020. Obstet Gynecol. 2020;135(3):e80-e97. For additional information visit the web site at: http://www.acog.org/. Accessed on June 28, 2023.
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Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
	12/06/2023	Revised References section.
Reviewed	08/10/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Coding section with 10/01/2023 CPT changes, removed 0066U deleted as of 10/01/2023.
Reviewed	08/11/2022	MPTAC review. Updated References section.
Revised	05/12/2022	MPTAC review. Revised position statement from INV and NMN to NMN. Updated Coding, References and Websites sections.
Reviewed	08/12/2021	MPTAC review. The References and Websites sections were updated.
Reviewed	08/13/2020	MPTAC review. The Rationale and References sections were updated.
Reviewed	08/22/2019	MPTAC review. The Rationale and References sections were updated.
Revised	11/08/2018	MPTAC review. Acronyms were removed from the title and position statement. The Rationale, References and Index sections were updated.
	09/20/2018	Updated Coding section with 10/01/2018 CPT changes; added 0066U.
Reviewed	01/25/2018	MPTAC review. The document header wording was updated from “Current Effective Date” to “Publish Date.” References were updated.
Reviewed	02/02/2017	MPTAC review. References were updated.
Reviewed	02/04/2016	MPTAC review. Updated References section. Removed ICD-9 codes from Coding section.
Reviewed	02/05/2015	MPTAC review. Updated References section.
Revised	02/13/2014	MPTAC review. No change to stance which was expanded to include other test kits for detection of suspected premature ROM. Information was added to the Rationale about the ROM Plus Fetal Membranes Rupture Test and the Actim PROM test, both of which are also considered investigational and not medically necessary. The Rationale and References were updated.
	01/01/2014	Updated Coding section with 01/01/2014 CPT descriptor changes.
New	05/09/2013	MPTAC review. Initial document development.

Applicable to Commercial HMO members in California: When a medical policy states a procedure or treatment is investigational, PMGs should not approve or deny the request. Instead, please fax the request to Anthem Blue Cross Grievance and Appeals at fax # 818-234-2767 or 818-234-3824. For questions, call G&A at 1-800-365-0609 and ask to speak with the Investigational Review Nurse.

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member’s contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.