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Tests for Amniotic Protein to Detect Rupture of Membranes (ROM) in Pregnancy

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Related Policies (if applicable)
None

Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

Tests for amniotic protein to detect rupture of membranes (ROM) in pregnancy **are considered experimental, investigational and/or unproven** for any indication. Tests include, but are not limited to:

1. Insulin-like growth factor binding protein (IGFBP-1) (e.g., Actim® PROM);
2. Placental alpha microglobulin-1 (PAMG-1) (e.g., AmniSure® ROM; PartoSure™);
3. Placental protein 12 (PP12)/insulin-like growth factor binding protein (IGFBP-1) combined with alpha fetoprotein (AFP) (e.g., ROM Plus® Fetal Membrane Rupture Test).

Policy Guidelines

None.

Description

Premature rupture of membranes (PROM) refers to an individual who is beyond 37 weeks' gestation and has presented with rupture of membranes (ROM) prior to the onset of labor. Preterm premature rupture of membranes (P-PROM) is ROM prior to 37 weeks' gestation. Spontaneous preterm rupture of the membranes (SPROM) is ROM after or with the onset of labor occurring prior to 37 weeks. Prolonged ROM is any ROM that persists for more than 24 hours prior to the onset of labor. (1)

Preterm premature rupture of membranes occurs in 2-3% of pregnancies and is responsible for, or associated with, approximately 30 to 40 percent of preterm births. It is, in fact, the single most common identifiable factor associated with preterm delivery. When it occurs, most women spontaneously go into labor within 24 hours. Treatment may consist of hospitalization for observation, prophylactic antibiotics, and corticosteroids (24-34 weeks gestation) to accelerate fetal lung maturity in individuals at risk of premature preterm delivery. Individuals who do not spontaneously go into labor shortly after ROM may opt to have labor induced after considering the risks of premature birth versus the risks of delay between ROM and delivery. The primary complication associated with ROM is infection in the mother and/or neonate, and the time between ROM and delivery is strongly associated with increasing risk of infection. Other complications associated with ROM include placental abruption, fetal distress, fetal restriction deformities, pulmonary hypoplasia, and fetal/neonate death. (1)

Most cases of PROM can be diagnosed based on the patient's history and physical examination. Conventional methods for diagnosing ROM include the following (several methods are often used together):

- Visual examination using a speculum to access the cervix, vaginal cavity, and pooling of vaginal fluid in the vagina;
- Nitrazine testing to detect pH changes in vaginal fluid;
- Ferning (detecting "fern like" patterns of amniotic fluid crystallization in dried samples of vaginal secretions); and
- Ultrasound of the abdomen. (1, 2)

More recently, noninvasive immunoassay rapid tests are being investigated as an alternative to conventional methods to diagnose ROM.

<u>Insulin-like Growth Factor Binding Protein (IGFBP-1) (e.g., Actim® PROM)</u>
IGFBP-1 is a qualitative, immunochromatographic method for detecting fetal membrane rupture by detecting only that insulin-like growth-factor-binding protein 1 (IGFBP-1) that is free of insulin-like growth factors 1 and 2 (IGF-1 and IGF-2). The method is based on the fact that the concentration of free IGFBP-1 in the blood serum is about 10 times lower than that of the IGFBP-1 bound to IGF-1 and IGF-2, while the amniotic fluid has more than 1000 times the concentration of free IGFBP-1 than the blood serum. Therefore, even a small amount of amniotic liquid in the vaginal secretion sample, is evidence of ROM. (3, 4)

<u>Placental Alpha Microglobulin-1 (PAMG-1) (e.g., AmniSure® ROM Test, PartoSure™)</u>

PAMG-1 has been investigated as a marker for the detection of PROM. PAMG-1 is a protein that is present only in amniotic fluid, and generally only in vaginal secretions after ROM in a pregnant woman but can be found in low levels in cervicovaginal discharge when fetal membranes are intact. (5)

Alpha-fetoprotein (AFP) Combined with Placental Protein 12 (PP12/insulin-like Growth Factor Binding Protein (IGFBP-1) (e.g., ROM Plus® Fetal Membrane Rupture Test)
AFP combined with PP12/IGFBP-1 is evaluated by using a rapid, qualitative immunochromatographic test which detects alpha-fetoprotein (AFP) and placental protein 12 (PP12, or insulin growth factor binding protein-1) found in amniotic fluid. Per the FDA, this test may report positive results in patients with intact membranes, therefore, decision to induce labor should not be based solely on the ROM Plus test results. (6)

Regulatory Status
On January 5, 2007, the Actim® PROM test obtained 510(k) clearance from the U.S. Food and Drug Administration (FDA) as substantially equivalent to the AmniSure® ROM test. The FDA approval stated that Actim® PROM test is a visually interpreted, qualitative immunoassay rapid test for detection of amniotic fluid in cervicovaginal secretions during pregnancy. The Actim® PROM test detects IGFBP-1, a major protein in amniotic fluid and a marker of the presence of amniotic fluid in a vaginal sample. (3) In January 2014, the FDA expanded the intended use to pregnant women who are ≥ 29-weeks' gestational age, and to use with vaginal swab samples collected without the use of a speculum in addition to the current sample type, swabs collected with the use of a speculum. (3, 7) FDA Product Codes: OAM, JJX.

In 2004, the FDA granted AmniSure® ROM Test 510(k) approval. According to the FDA, AmniSure® ROM Test is a qualitative immunoassay intended to aide in the detection of rupture of membrane (ROM) in pregnant women >34 weeks gestation when the patient reports signs, symptoms, or complaints suggestive of ROM. FDA Product Codes: NQM, JJX. (5)

On November 23, 2011, the FDA granted ROM Plus® Fetal Membrane Rupture Test 510(k) approval. According to the FDA, the ROM Plus® fetal membranes rupture test is 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 by detecting AFP and PP12. Notably, the FDA offers the following warning as a special condition for use: "The test may report positive results in patients with intact membranes, thereforethe decision to induce labor should not be based solely on the ROM Plus test results. FDA Product Codes: NQM, JJX. (6)

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 to rapidly assess the risk of spontaneous preterm delivery in ≤7 days from the time of the cervicovaginal sample collection in pregnant women with signs and symptoms of early preterm labor (PTL), 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 Product Code: QBB. (8)

In 2018, the FDA issue a warning urging healthcare providers to not use ROM tests alone to make critical patient management decisions. The FDA stated they are concerned that misuse, relying solely on ROM tests without using other assessments (over reliance), and inaccurate interpretation of lab test results of ROM tests could result in an increased risk of fetal harm or death. (9)

Currently, Amnioquick® Duo has not been granted U.S. FDA 510(k) approval. The test is a rapid *in vitro* test to evaluate IGFBP-1 and AFP (alpha fetoprotein). (10)

NOTE: This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Rationale

This policy is based on professional guidelines and position statements related to products used to test premature rupture of membranes (PROM) in pregnancy.

This policy addresses amniotic protein tests to detect rupture of membranes (ROM) in pregnancy and include the following tests:

- Insulin-like growth factor binding protein (IGFBP-1) (e.g., Actim® PROM);
- Placental alpha microglobulin-1 (PAMG-1) (e.g., AmniSure® ROM; PartoSure™);
- Placental protein 12 (PP12)/insulin-like growth factor binding protein (IGFBP-1) combined with alpha fetoprotein (AFP) (e.g., ROM Plus® Fetal Membrane Rupture Test).

Practice Guidelines and Position Statements

National Institute for Clinical Excellence (NICE)

In 2022, NICE updated their prior 2015 guideline for preterm labour and birth which includes the following guidelines related to diagnosing preterm prelabour rupture of membranes (P-PROM) (11):

- 1.3.1 In a woman reporting symptoms suggestive of P-PROM, offer a speculum examination to look for pooling of amniotic fluid and: if pooling of amniotic fluid is observed, do not perform any diagnostic test but offer care consistent with the woman having P-PROM. If pooling of amniotic fluid is not observed, perform an insulin-like growth factor binding protein-1 test or placental alpha-microglobulin-1 test of vaginal fluid. [2015, amended 2019]
- 1.3.2 If the results of the insulin-like growth factor binding protein-1 or placental alphamicroglobulin-1 test are positive, do not use the test results alone to decide what care to offer the woman, but also take into account her clinical condition, medical and pregnancy history and gestational age, and either: offer care consistent with the woman having P-PROM or re-evaluate the woman's diagnostic status at a later time point. [2015]

- 1.3.3 If the results of the insulin-like growth factor binding protein-1 or placental alphamicroglobulin-1 test are negative and no amniotic fluid is observed: do not offer antenatal prophylactic antibiotics explain to the woman that it is unlikely she has P-PROM, but that she should return for reassessment if there are any further symptoms suggestive of P-PROM or preterm labour. [2015, amended 2022)
- 1.3.4 Do not use nitrazine to diagnose P-PROM. [2015]
- 1.3.5 Do not perform diagnostic tests for P-PROM if labour becomes established in a woman reporting symptoms suggestive of P-PROM. [2015]

The 2018 NICE guidelines related to biomarker tests to diagnose preterm labour in women with intact membranes provides the following recommendations (12):

- 1.1 There is currently insufficient evidence to recommend the routine adoption of Actim Partus and PartoSure to help diagnose preterm labour in women with intact membranes when transvaginal ultrasound measurement of cervical length is not available or not acceptable.
- 1.2 There is currently insufficient evidence to recommend the routine adoption of the Rapid fetal fibronectin 10Q Cassette Kit (using thresholds other than 50 nanograms/millilitre [ng/ml] to guide clinical management) to help diagnose preterm labour in women with intact membranes when transvaginal ultrasound measurement of cervical length is not available or not acceptable. Recommendations on qualitative fetal fibronectin testing with a fixed threshold of 50 ng/ml are not affected by this diagnostics guidance.
- 1.3 Further research is needed on the accuracy of the tests and their effect on clinical outcomes. Centres using the tests to help diagnose preterm labour in women with intact membranes are encouraged to take part in studies to address the research considerations. Data is needed on:
    - The impact of gestational age on the accuracy of the test(s);
    - How the test(s) affects clinical decision-making;
    - The effect of the test(s) on outcomes for mother and baby.

<u>American College of Obstetrics and Gynecologists (ACOG)</u>

The ACOG guidance on prelabor rupture of membranes (PROM) was updated in 2018 (reaffirmed in 2020). (13) The bulletin notes that diagnosis of ROM should be confirmed by clinical assessment with direct visualization of amniotic fluid, a simple pH test of vaginal fluid, or arborization (ferning) of dried vaginal fluid which is identified under a microscope. ACOG noted that 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. ACOG noted that 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 previously 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. FDA 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.

Canadian Agency for Drugs and Technologies in Health (CADTH)

On April 4, 2012, the Health Technology Inquiry Service of CADTH published an updated Summary with critical appraisal report titled "AmniSure versus Fern Testing to Assess the Rupture of Fetal Membranes in Pregnant Women: A Review of the Comparative Accuracy, Cost-Effectiveness, and Guidelines." (14) The purpose was to evaluate the comparative diagnostic accuracy and cost-effectiveness of AmniSure® compared to fern testing for detection of rupture of the fetal membrane. Evidence-based guidelines for the use of AmniSure® were also reviewed. The literature search included PubMed, The Cochrane Library (2010, Issue 3), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, and Canadian and major international health technology agencies, as well as a focused Internet search. The CADTH research questions were:

1. "What is the comparative accuracy of the AmniSure test versus the fern test for the assessment of rupture of the fetal membrane?"
2. "What is the cost-effectiveness of the AmniSure test versus the fern test for the assessment of rupture of the fetal membrane?"
3. "What are the evidence-based guidelines regarding the use of the AmniSure and fern tests for the assessment of rupture of fetal membranes in pregnant women?"

The CADTH assessment concluded the following: "AmniSure was found to have high sensitivity and predictive accuracy for rupture of fetal membranes, however the lack of direct comparison to individual tests and limited statistical reporting prevent drawing conclusions about comparative effectiveness. Performance results suggest that AmniSure may be a useful tool for detecting membrane rupture, but no evidence related to cost-effectiveness was identified. Evidence-based guidelines for the use of AmniSure in clinical practice are lacking."

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	84112, 84999
HCPCS Codes	None

*Current Procedural Terminology (CPT®) ©2025 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
06/15/2026	Document updated. Coverage unchanged. Added reference 12.
01/01/2026	Document updated. Coverage unchanged. No new references; others updated and/or removed.
02/15/2025	Reviewed. No changes.
03/15/2024	Document updated with literature review. Coverage unchanged. Added references 10, 34 and 35; others updated/some removed.
03/15/2023	Reviewed. No changes.
05/15/2022	Document updated with literature review. Coverage unchanged. Added references 2, 3, 5, 10, 25, 35; others updated, and some removed.
02/15/2021	Reviewed. No changes.
02/15/2020	Document updated with literature review. The following change was made to Coverage: Added PartoSure™ as an example of a placental alpha microglobulin-1 (PAMG-1) test. Added references 1, 2, 7, 12-29, 31-38.

02/15/2017	Document updated with literature review. Coverage unchanged. Rationale and References reorganized.
02/15/2016	Reviewed. No changes.
08/15/2015	New medical document. Tests for amniotic protein to detect rupture of membranes (ROM) in pregnancy are considered experimental, investigational and/or unproven, for any indication. Tests include, but are not limited to: 1) Placental alpha microglobulin-1 (PAMG-1) (e.g., AmniSure® ROM); 2) Placental protein 12 (PP12)/insulin-like growth factor binding protein (IGFBP-1) combined with alpha fetoprotein (AFP) (e.g., ROM Plus® Fetal Membrane Rupture Test); 3) Insulin-like growth factor binding protein (IGFBP-1) (e.g., Actim® ROM).