Regence

Medical Policy Manual Laboratory, Policy No. 57

Placental Rapid Immunoassay for Detection of Fetal Membrane Rupture

Effective: February 1, 2024

Next Review: December 2024
Last Review: December 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Placental rapid immunoassays are immunochromatographic tests for the detection of amniotic fluid in the vaginal secretions of pregnant women.

MEDICAL POLICY CRITERIA

Placental rapid immunoassays, including but not limited to the AmniSure® ROM, ROM Plus®, and Actim® PROM tests, for the diagnosis of premature rupture of membranes, are considered **investigational**.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

None

BACKGROUND

The fetus lies in sac with an inner layer of amnion and out covering of chorion. The sac, also

called the bag of waters, is filled with amniotic fluid. Most commonly, the membranes of the sac ruptures during labor; however, the membranes can rupture at any time during a pregnancy.[1] When membranes ruptures prematurely it is called premature rupture of membranes (PROM), and refers to the rupture of the amniotic and chorionic membranes before the onset of labor. At term or near term, PROM may result in normal labor. In contract, preterm PROM (PPROM) refers to the rupture of fetal membranes before labor and before 37 weeks gestation, and is associated with significantly increased risk of fetal morbidity and mortality.[2]

When the membrane of the sac ruptures, fluid may gush or dribble away, making it difficult to determine whether or not the membranes are ruptured or intact. Usually, the diagnosis of PROM or PPROM can be established by medical history, physical examination (including sterile speculum examination), and/or by standard clinical tests (i.e. Nitrazine test, ferning, assessment of pooling, smear combustion).

In cases when medical history and findings from physical examination and clinical tests are equivocal, ultrasonography to look for evidence of oligohydramnios (deficiency of amniotic fluid) may be helpful. A suspected diagnosis can be confirmed with indigo carmine amnio-dye testing. However, this invasive test carries potential risks and is not routinely performed.

RAPID IN VITRO TESTS FOR PROM

Qualitative immunochromatographic rapid tests can detect amniotic proteins as markers of amniotic fluid in the cervicovaginal secretions of pregnant women, indicating rupture of fetal membranes. These proteins include placental alpha-1 microglobulin-1 (PAMG-1), placental protein 12 (PP12), alpha-fetoprotein (AFP), and insulin-like growth factor binding protein 1 (IGFBP-1). The tests are marketed for use by health care professionals to aid in the detection of rupture of membrane (ROM) in pregnant women reporting signs, symptoms, or complaints suggestive of ROM.

REGULATORY STATUS

The following tests have received 510(k) clearance from the U.S. Food and Drug Administration (FDA):

- The AmniSure® ROM Test (AmniSure International, LLC) detects the placental alpha microglobulin-1 (PAMG-1) protein marker of the amniotic fluid.
- The ROM Plus® Test (Clinical Innovations, LLC) detects alpha-fetoprotein (AFP) and placental protein 12 (PP12).
- The Actim® PROM Test (Medix Biochemica) detects insulin growth factor binding protein-1 (IGFBP-1)

In 2018, the FDA issued a letter to healthcare providers regarding improper use of tests to diagnose ROM. This letter stated:[3]

“The FDA is reminding health care providers that tests to detect rupture of the amniotic membranes should not be used without other clinical assessments to make critical patient management decisions. Health care providers using rupture of membranes (ROM) tests should be aware of test limitations listed within manufacturer instructions. The following limitations are typically stated in ROM device labeling:

- A negative result does not assure the absence of membrane rupture.
- False negatives may result if the amniotic sac has resealed, or the position of the fetus has obstructed the rupture.
- The presence of blood, meconium, anti-fungal creams or suppositories, baby powder, baby oil, or the use of lubricant with a vaginal exam may interfere with the device.
- The test may not be accurate if sample collection and testing occurs after the timeframe recommended by the manufacturer."

EVIDENCE SUMMARY

Validation of any new diagnostic technique involves three steps:

- Demonstration of its technical feasibility, including assessment of its reproducibility and precision. For comparison among studies, a common standardized protocol is necessary.
- An understanding of normal and abnormal values as studied in different clinical situations. For accurate interpretation of study results, sensitivities, specificities, and positive and negative predictive values compared to a gold standard must be known.
- The clinical utility of a diagnostic technique is related to how the results of the test can be used to guide patient management resulting in an improvement in net health outcomes. The clinical utility of both positive and negative tests must be assessed. Relevant outcomes of a negative test (i.e., suspected pathology is not present) may be avoidance of more invasive diagnostic tests or avoidance of an ineffective therapy. Relevant outcomes of a positive test (i.e., suspected outcome is present) may also include avoidance of a more invasive test plus the institution of specific, effective therapy.

SYSTEMATIC REVIEWS

A 2014 systematic review (SR) evaluated the published data through April 2013 for accuracy of two amniotic fluid-specific biomarker tests, insulin-like growth factor binding protein-1 (IGFBP-1; Actim® PROM) and PAMG-1 (AmniSure®).[4] Of the 17 studies that met inclusion criteria, 10 were for Actim PROM IGFBP-1 (n=1,066), four were for AmniSure PAMG-1 testing (n=1,081), and three additional studies included both biomarker tests. Pooled analysis included only those women with suspected ROM who had later confirmation of the diagnosis. The analysis found significantly higher specificity and positive predictive value (PPV) for AmniSure compared to Actim® PROM. Limitations included heterogeneity of the design and protocols of included studies, clinical characteristics of included patients, and the gold standard used for confirming the diagnosis. In addition, women with bleeding were excluded from most of the included studies, making it unclear whether the findings were representative of the broader population of women presenting with suspected PROM. Further, clinical utility was not studied. It remains unclear whether the use of these tests resulted in improved health outcomes.

NONRANDOMIZED STUDIES

Since the 2014 SR summarized above, several studies have been published that compare the sensitivity and specificity of PAMG-1 tests with conventional clinical diagnostic methods and with tests for other markers such as fetal fibronectin and IGFBP-1.[5-13] No studies were identified that compared the health outcomes of treatment management with and without this testing.

Additionally, several studies have been published that examine the use IGFBP-1 testing compared with conventional diagnostic methods (i.e. ferning, Nitrazine test, visualization of

fluid, and transabdominal ultrasound to measure amniotic fluid).[14, 15] No studies were identified that compared the health outcomes of treatment management with and without testing.

PRACTICE GUIDELINE SUMMARY

Currently, no published evidence-based clinical practice guidelines recommend the use of rapid in vitro tests for the detection of ruptured fetal membranes.

AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS

The American College of Obstetricians and Gynecologists (ACOG) practice bulletin on premature rupture of membranes was updated in 2020.[16] The bulletin notes false-positive test result rates are reported to be 19- 30% in women with intact membranes and symptoms of labor. ACOG cautions that “at most these test kits should be considered selectively relative to standard methods of diagnosis.”

U.S. DEPARTMENT OF VETERANS AFFAIRS AND DEPARTMENT OF DEFENSE

The 2023 evidence-based U.S. Department of Veteran Affairs and Department of Defense (VA/DoD) clinical practice guideline on management of pregnancy is silent on the use of either the AmniSure or ROM Plus tests.[17]

SUMMARY

There is not enough research to show that placental rapid immunoassays can improve health outcomes for patients suspected of having premature rupture of fetal membranes. These tests include but are not limited to the AmniSure® ROM, ROM Plus, and Actim® PROM tests. No clinical guidelines based on research recommend placental rapid immunoassays to detect rupture of fetal membranes. Therefore, placental rapid immunoassays, including but not limited to, the AmniSure® ROM, ROM Plus, and Actim® PROM tests, are considered investigational.

REFERENCES

1. Posner GD, Dy, J., Black, A., Jones, G.D. *Oxorn-Foote Human Labor & Birth*. 6th ed. New York: McGraw-Hill, 2013, pp.
2. Practice bulletins No. 139: premature rupture of membranes. *Obstet Gynecol.* 2013;122:918-30. PMID: 24084566
3. FDA. FDA alerts healthcare providers, women about risks associated with improper use of rupture of membrane tests. [cited 12/14/23]. 'Available from:' https://www.fda.gov/news-events/press-announcements/fda-alerts-healthcare-providers-women-about-risks-associated-improper-use-rupture-membranes-tests.
4. Palacio M, Kuhnert M, Berger R, et al. Meta-analysis of studies on biochemical marker tests for the diagnosis of premature rupture of membranes: comparison of performance indexes. *BMC Pregnancy Childbirth.* 2014;14:183. PMID: 24884494
5. Thomasino T, Levi C, Draper M, et al. Diagnosing rupture of membranes using combination monoclonal/polyclonal immunologic protein detection. *The Journal of reproductive medicine.* 2013;58(5-6):187-94. PMID: 23763001

6. Ng BK, Lim PS, Shafiee MN, et al. Comparison between AmniSure placental alpha microglobulin-1 rapid immunoassay and standard diagnostic methods for detection of rupture of membranes. *BioMed research international.* 2013;2013:587438. PMID: 24073412
7. Abdelazim IA, Makhlouf HH. Placental alpha microglobulin-1 (AmniSure test) versus insulin-like growth factor binding protein-1 (Actim PROM test) for detection of premature rupture of fetal membranes. *The journal of obstetrics and gynaecology research.* 2013;39(6):1129-36. PMID: 23718844
8. Doret M, Cartier R, Miribel J, et al. Premature preterm rupture of the membrane diagnosis in early pregnancy: PAMG-1 and IGFBP-1 detection in amniotic fluid with biochemical tests. *Clinical biochemistry.* 2013;46(18):1816-9. PMID: 24140132
9. Abdelazim IA, Abdelrazak KM, Al-Kadi M, et al. Fetal fibronectin (Quick Check fFN test) versus placental alpha microglobulin-1 (AmniSure test) for detection of premature rupture of fetal membranes. *Arch Gynecol Obstet.* 2014;290(3):457-64. PMID: 24715211
10. Eleje GU, Ezugwu EC, Ezebialu IU, et al. Performance indices of AmnioQuick Duo+ versus placental alpha-microglobulin-1 tests for women with prolonged premature rupture of membranes. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics.* 2019;144(2):180-86. PMID: 30387138
11. Esin S, Tohma YA, Alay İ, et al. Comparison of placental α microglobulin-1 protein assay (Amnisure) with speculum examination for the diagnosis of premature preterm rupture of membranes (PPROM): a clinical evaluation. *Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology.* 2020:1-5. PMID: 32835549
12. Elçi E, Güneş Elçi G, Sayan S. Comparison of the accuracy and reliability of the AmniSure, AMNIOQUICK, and AL-SENSE tests for early diagnosis of premature rupture of membranes. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics.* 2020;149(1):93-97. PMID: 31925795
13. Sean Esplin M, Hoffman MK, Theilen L, et al. Prospective evaluation of the efficacy of immunoassays in the diagnosis of rupture of the membranes. *J Matern Fetal Neonatal Med.* 2020;33(15):2594-600. PMID: 30636471
14. Abdelazim IA. Insulin-like growth factor binding protein-1 (Actim PROM test) for detection of premature rupture of fetal membranes. *The journal of obstetrics and gynaecology research.* 2014;40(4):961-7. PMID: 24612210
15. Kallioniemi H, Rahkonen L, Heikinheimo O, et al. Usefulness of the insulin-like growth factor binding protein-1 bedside test for ruptured fetal membranes. *Acta obstetricia et gynecologica Scandinavica.* 2014;93(12):1282-9. PMID: 25146582
16. Prelabor Rupture of Membranes: ACOG Practice Bulletin, Number 217. *Obstet Gynecol.* 2020;135(3):e80-e97. PMID: 32080050
17. U.S. Department of Veteran Affairs, Veterans Health Administration, Veterans Health Administration. VA / DoD Clinical Practice Guideline. Management of Pregnancy. 2023. [cited 12/14/2023]. 'Available from:' https://www.healthquality.va.gov/guidelines/WH/up/VA-DoD-CPG-Pregnancy-Full-CPG_508.pdf.

CODES

Codes	Number	Description
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
HCPCS	None	

Date of Origin: *August 2010*