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.

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 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)

**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.

**SCIENTIFIC EVIDENCE**

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 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®).[3] Of the 17 studies that met inclusion criteria, 10 were for Actim PROM IGFBP-1 (N=1066), four were for AmniSure PAMG-1 testing (N=1081), and three additional studies included both biomarker tests. Pooled analysis included only those women with suspected ROM who had later confirmation of the diagnosis. This analysis found significantly higher specificity and positive predictive value (PPV) for AmniSure compared to Actim PROM. Limitations of this systematic review included heterogeneity of the design and protocols of included studies, the 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 and, therefore, it remains unclear whether the use of these tests resulted in improved health outcomes.

Nonrandomized Studies

Since the 2014 systematic review 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.[4-8] 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).[9,10] No studies were identified that compared the health outcomes of treatment management with and without testing.

Clinical Practice Guidelines

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[2] on premature rupture of membranes was updated in 2013, replacing the prior 2007 version[11] which was silent on rapid tests for markers of ROM.

Institute for Clinical Systems Improvement[12]

The 2013 Institute for Clinical Systems Improvement (ICSI) clinical practice guideline on management of labor lists AmniSure as an option for detection of amniotic fluid, in addition to ferning, pooling, and the Nitrazine test.

U.S. Department of Veteran Affairs, and Department of Defense Department of Defense[13]
The 2009 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.

**Summary**

There is not enough research to know if or how well placental rapid immunoassays, including but not limited to, the AmniSure® ROM, ROM Plus, and Actim® PROM tests works to detect rupture of fetal membranes. This does not mean that it does not work, but more research is needed to know. 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**

8. Abdelazim, IA, Abdelrazak, KM, Al-Kadi, M, Yehia, AH, Abdulkareem, AF. 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 Sep;290(3):457-64. PMID: 24715211


CROSS REFERENCES

None

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