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Clinical Policy Bulletin:
Non-Invasive Fetal Membranes Rupture Test

Revised April 2014

Number: 0757

Policy

Aetna considers non-invasive fetal membranes rupture tests (e.g., AmniSure ROM and the ROM Plus Fetal Membranes Rupture Test) experimental and investigational for detecting preterm rupture of membranes (ROM) and all other indications because of insufficient evidence of its clinical effectiveness over standard diagnostic methods for detecting ROM.

Background

Premature rupture of membranes (PROM) is defined as rupture of membranes before the onset of labor. Membrane rupture that occurs before 37 weeks of gestation is referred to as preterm PROM (PPROM). Premature rupture of membranes complicates approximately 8% of pregnancies and is generally followed by the prompt onset of spontaneous labor and delivery. 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. Preterm PROM complicates only 2% of pregnancies but is associated with 40% of preterm deliveries and can result in significant neonatal morbidity and mortality. The 3 causes of neonatal death associated with PPROM are prematurity, sepsis and pulmonary hypoplasia (RCOG, 2006; ACOG, 2007).
Several risk factors for PPROM have been identified, including intra-amniotic infection, low socioeconomic status, low body mass index, second and third-trimester bleeding, nutritional deficiencies of copper and ascorbic acid, connective tissue disorders (e.g., Ehlers-Danlos syndrome), cigarette smoking, cervical conization or cerclage, pulmonary disease during the pregnancy, uterine over-distention, as well as amniocentesis. The risk of recurrence for PPROM is between 16% and 32%. 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 or symptomatic contractions in the current pregnancy. In addition, PROM can occur without any identifiable risk factor.

According to the American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin *Premature Rupture of Membranes* (2007), and the Royal College of Obstetricians and Gynaecologists (RCOG) Guideline *Preterm Pre labour Rupture of Membranes* (2006), 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. Digital cervical examinations are avoided due to the increase risk of infection and they add little additional information to the speculum examination (unless the patient is in active labor or imminent delivery is planned). Diagnostic methods using nitrazine paper and determination of ferning (arborization) have sensitivities approaching 90%. The pH of vaginal secretions is generally 4.5 to 6.0, whereas amniotic fluid usually has a pH of 7.1 to 7.3; however, false-positive results may occur as the result of contamination with blood or semen, alkaline antiseptics, or bacterial vaginosis and false-negative results can occur with prolonged leakage and minimal residual fluid. In unusual cases in which the diagnosis remains unclear after physical examination, ultrasonography may be helpful. When ultrasonography is inconclusive, transabdominal instillation of indigo carmine dye followed by observation for passage of blue fluid from the vagina will confirm ROM unequivocally. 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; Medina and Hill, 2006; ACOG, 2007).

The AmniSure ROM (Rupture of Membranes) test received Food and Drug Administration 510(k) marketing clearance in 2003 and is a rapid, non-instrumented qualitative immunochromatographic test for in-vitro detection of amniotic fluid in vaginal secretion of pregnant women. AmniSure detects PAMG-1 (placental alpha-1 microglobulin) protein marker of the amniotic fluid in vaginal secretions and is intended to aid in the detection of ROM in pregnant women greater than 34 weeks gestation with signs, symptoms or complaints suggestive of ROM.

A comparison study of AmniSure versus standard diagnostic methods for detection of ROM in 203 pregnant women suspected of ROM reported that the AmniSure test was highly accurate (sensitivity = 98.9%, specificity = 100%, and negative predictive value [NPV] = 99.1%) in diagnosing ROM (Cousins et al, 2005). Test performance was calculated by comparing AmniSure results against clinical history, nitrazine and fern results, presence of pooling, ultrasound (US) evidence of oligohydramnios, and findings from repeated examinations.
A study of 184 pregnant women suspected of ROM reported the sensitivity, specificity, positive predictive value (PPV) and NPV of the AmniSure device were 98.7 %, 87.5 %, 98.1 %, and 91.3 %, respectively (Lee et al, 2007). Rupture of membranes was diagnosed if fluid was seen leaking from the cervical os or if 2 of the following 3 conditions were present: (i) pooling of fluid, (ii) positive nitrazine test, or (iii) ferning. Rupture of membranes was diagnosed definitively on review of the medical records after delivery. The investigators stated that the cause of fals- positive results in 3 patients was unknown, and that the possibility of small leak that sealed over could not be excluded.

Chen and Dudenhansen (2008) compared 2 rapid strip tests for the detection of amniotic fluid, based on the detection of insulin-like growth factor-binding protein-1 (IGFBP-1) and of PAMG-1. Samples of amniotic fluid were taken in 20 pregnant women between 31 3/7 and 41 2/7 gestational weeks at elective cesarean section before delivery of the newborn. These samples were diluted with 0.9 % saline solution in a dilution series down to concentrations of 1:320. Immunoassay strip tests were then compared in their ability to detect remaining concentrations of amniotic fluid. In 5 cases, both test methods showed the same results. In all remaining 15 cases, the test based on PAMG-1 proved to be superior by detecting amniotic fluid at least at one descending concentration below the test based on IGFBP-1. Thus, the rapid strip test based on PAMG-1 seems to be a more sensitive bedside test compared with the test based on IGFBP-1 for the detection of amniotic fluid.

These studies indicated that the AmniSure is a promising method of detection of PPROM. However, controlled clinical studies are needed to determine the clinical effectiveness of the AmniSure ROM test over standard diagnostic methods for ROM.

Commenting on the studies on AmniSure by Cousins et al (2005) as well as Lee et al (2007), Duff (2009) stated "[t]hese results are promising, but require further confirmation before a recommendation for routine use of this device can be made". Caughey et al (2008) stated that "[i]n time, such noninvasive tests [as the AmniSure] may replace the need for traditional clinical assessment and amnio-dye testing for the diagnosis of PROM".

Lee and colleagues (2009) stated that the AmniSure test is approved for the diagnosis of PROM. Yet, a fraction of patients with a positive test have intact membranes by sterile speculum examination. The objective of this study was to determine the clinical significance of this finding. The study population consisted of 4 groups of nulliparous women at term: (i) not in labor without clinical evidence of ROM (n = 125); (ii) in labor without clinical ROM with a negative AmniSure test (n = 56); (iii) in labor without clinical ROM with a positive AmniSure test (n = 25); and (iv) in labor with clinical ROM (n = 30). The AmniSure test was performed in cases without clinical ROM (groups i, ii and iii). The AmniSure test was positive more frequently in women in labor with intact membranes than in patients not in labor at term without ROM (30.9 % (25/81 women) versus 4.8 % (6/125 women); p < 0.001). In addition, patients in labor without clinical ROM with a positive Amnisure test had a significantly shorter admission-to-delivery interval than those in labor without clinical ROM with a negative Amnisure test (p < 0.05). The authors concluded that a positive AmniSure test is present in about 1/3 nulliparous
women at term presenting in labor with intact membranes; and patients with a positive AmniSure test had a shorter admission-to-delivery interval than those with a negative test.

A review of Amnisure by the Canadian Agency for Drugs and Technologies in Health (CADTH) identified 6 controlled clinical trials and 1 evidence-based guideline regarding the diagnostic accuracy and use of the AmniSure and other similar tests for determining whether premature rupture of fetal membranes has occurred in a pregnancy (HTIS, 2010). No economic evaluations were identified regarding the cost-effectiveness of the AmniSure and other similar tests. CADTH identified no relevant health technology assessments, systematic reviews, meta-analyses, or randomized controlled trials.

In a prospective cohort study, Neil and Wallace (2010) evaluated the clinical utility of Amnisure. A total of 184 women presenting with a history of PROM to a tertiary maternity hospital were included in this study. Before and after Amnisure, the attending clinician assessed and recorded membrane status (PROM or intact), his/her level of confidence in this diagnosis, and the intended management plan. There was clinician uncertainty regarding the diagnosis of PROM in 83 (47 %) women. Amnisure significantly increased clinician confidence and led to a change of intended management in 23 (13 %) women. In 33 women presenting with possible preterm PROM, 7 thought to have PROM before Amnisure had a negative test, leading to a change of management in these women. The authors concluded that Amnisure is clinically useful when the clinician is uncertain about the diagnosis; but not useful when the clinician is confident about the diagnosis.

Pollet-Villard et al (2011) compared 2 biochemical tests of PROM in-vitro: (i) Actim PROM (Medix Biochemica, Kauniainen, Finland), which detects IGFBP-1, and (ii) AmniSure (AmniSure International LLC, Cambridge, MA), which detects PAMG-1. Samples of amniotic fluid were collected during caesarean section in 41 patients. A dilution series was prepared and both tests were performed twice at each dilution. Sensitivity, detection limit, response time, and reproducibility of both tests were compared. Both tests' sensitivity was 100 % at dilution 1:10 and 1:20. AmniSure sensitivity was higher at dilution 1:40 and 1:80 (p < 0.05). In 29 of 40 cases, AmniSure had a lower detection limit than Actim PROM. AmniSure response times were shorter and reproducibility was higher than Actim PROM (p < 0.05). The authors concluded that AmniSure had a lower detection limit of amniotic fluid than Actim PROM, with a shorter response time, a higher sensitivity, and a better reproducibility.

In a case-control prospective study, Marcellin et al (2011) compared the performance of 2 rapid tests for the diagnosis of PROM based on the detection of IGFBP-1 and PAMG-1 in cervico-vaginal secretions. Pregnant women between 24 and 41 (6/7) weeks' of gestation, consulting for profuse amniotic fluid loss (group 1) or for other reasons without any rupture of membrane (group 2) were included in the study. Successively, AmniSure test (PAMG-1) without speculum, and then Actim Prom test (IGFBP-1) during speculum examination were performed during the same visit. A total of 80 subjects (40 in each group) were included between 25 (1/7) to 41 (1/7) weeks of gestation. AmniSure diagnostic test demonstrated a sensitivity and specificity of 95 % (82.4 to 99.4) and 94.8 % (79.3 to 98), respectively and a PPV and NPV of 95 % (84.7 to 100) and 94.8 % (87.9 to
100), respectively. Actim Prom test demonstrated a sensitivity and specificity of 97.5 % (85.7 to 100) and 97.4 % (82.4 to 99.4), respectively and a PPV and NPV of 97.5 % (88.5 to 100) and 97.4 % (92.5 to 100), respectively. The authors concluded that both tests have similar performance to diagnose PROM.

Birkenmaier et al (2012) evaluated the performance of the PAMG-1 immunoassay (AmniSure) in cervico-vaginal secretions in patients with uncertain ROM and investigated the influence of the examiners experience. This prospective cohort study was performed in pregnant women (17 to 42 weeks of gestation) with signs of possible ROM. Evaluation included clinical assessment, examination for cervical leakage, nitrazine test as well as measurement of the amniotic fluid index by US and Amnisure. Occurrence of ROM was based on review of the medical records after delivery. A total of 199 women were included in this study. Amnisure had a sensitivity of 94.4 %; specificity of 98.6 %; PPV of 96.2 %; NPV of 98.0 %. Clinical assessment showed a sensitivity of 72.2 %; specificity of 97.8 %; PPV of 92.9 %; NPV of 90.6 %. Amnisure was more sensitive for diagnosing ROM (p = 0.00596) compared to clinical assessment, independent of the examiners experience. Furthermore, the sole use of Amnisure reduced costs by 58.4 % compared to clinical assessment. The authors concluded that Amnisure was more sensitive compared to clinical assessment, independent of the examiners experience and gestational age.

In a prospective observational study, Phupong and Sonthirathi (2012) compared the efficacy of PAMG-1 rapid immunoassay with conventional standard methods for the diagnosis of ROM. Patients with symptoms or signs of PROM were included in this study. Conventional standard methods were performed to establish the diagnosis and were compared with PAMG-1 immunoassay results. Rupture of membrane was diagnosed if visualization of fluid leaking from the cervical os or 2 of the following 3 conditions were present: positive nitrazine test, ferning test, and Nile blue test. The diagnosis of ROM was confirmed by reviewing the medical records after delivery. A total of 100 patients (gestational age 36.5 +/- 3.5 weeks, range of 22 to 41 weeks of gestation) were recruited into the study. Seventy-six percent were preterm and 24 % were at term. PAMG-1 immunoassay had a sensitivity of 97.2 %, specificity of 69 %, PPV of 90.8 %, NPV of 90.9 % and an accuracy of 89 %. In contrast, conventional combined standard methods had a sensitivity of 88.7 %, specificity of 96.6 %, PPV of 98.4 %, NPV of 77.8 %, and accuracy of 91 % for the diagnosis of ROM. The authors concluded that PAMG-1 immunoassay is a rapid method for the diagnosis of ROM and it has a higher sensitivity than conventional standard methods for the diagnosis of ROM.

In a comparative prospective study, Abdelazim and colleagues (2012) examined the accuracy of the PAMG-1 test (AmniSure) for the diagnose PROM. A total of 150 pregnant women after 37 weeks gestation were included in this study for induction of labor and divided into 2 groups according to the presence or absence of PROM; 75 patients with PROM were included in group I and 75 patients without PROM were included in group II as controls. Patients with multiple pregnancies or fetal distress or vaginal bleeding or preterm labor or chorioamnionitis were excluded from this study. Trans-abdominal US was done to detect the gestational age and the amniotic fluid index (AFI less than or equal to 5 cm in PROM) followed by sterile speculum examination to detect amniotic fluid pooling from the cervical canal and for the collection of samples. The sensitivity and the specificity of
PAMG-1 to diagnose PROM were 97.33 % and 98.67 %, respectively, compared with 84 % sensitivity and 78.67 % specificity for Ferning test and 86.67 % sensitivity and 81.33 % specificity for nitrazine test. The PPV and NPV of PAMG-1 were 98.64 % and 97.37 %, respectively, compared with 79.74 % PPV and 83.1 % NPV for Ferning test and 82.28 % PPV and 85.91 % NPV for nitrazine test. PAMG-1 was more accurate (98 %) for detection of PROM than Ferning (81.33 %) or nitrazine (84.0 %) tests.

In a retrospective cohort study, Mi Lee and associates (2012) examined the frequency and clinical significance of a positive Amnisure test in patients with preterm labor and intact membranes by sterile speculum examination. A total of 90 patients with preterm labor and intact membranes underwent Amnisure tests prior to amniocentesis (less than 72 hrs); most patients (n = 64) also underwent fetal fibronectin (fFN) tests. Amniotic fluid (AF) was cultured for aerobic/anaerobic bacteria and genital mycoplasmas and assayed for matrix metalloproteinase-8. The prevalence of a positive Amnisure test was 19 % (17/90). Patients with a positive Amnisure test had significantly higher rates of adverse pregnancy and neonatal outcomes (e.g., impeding 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 (less than 35 weeks) among patients with a negative fFN test. The authors concluded that a positive Amnisure test in patients with preterm labor and intact membranes is a risk factor for adverse pregnancy outcome, particularly in patients with a negative fFN test. Moreover, a positive Amnisure test in patients without symptoms or signs of ROM should not be taken as an indicator that membranes have ruptured.

An evidence review of methods to diagnose rupture of membranes by Caramore and Dresang (2011) concluded that, where diagnosis is essential and conventional testing proves equivocal, amniocentesis with injection of indigo carmine dye is the most definitive test. The authors stated that the most widely available of the newer biochemical assays, the PAMG-1 assay, appears to offer improved accuracy compared with conventional methods, but the clinical significance of a positive test, particularly in the setting of labor, is unclear.

Van der Ham, et al. (2012) evaluated the diagnostic accuracy of PAMG-1 and IGFBP-1 for rupture of the fetal membranes (ROM). The authors noted that sample sizes of recent studies are small and studies used different 'silver standard' definitions for ROM. Therefore, reported results should be interpreted with caution. The authors found that, compared to nitrazine or ferning test alone, IGFBP-1 and PAMG-1 are more accurate. However, compared to the conventional testing (combination of history, ferning, nitrazine, speculum and ultrasound) no statistical difference in accuracy was found. The authors concluded that IGFBP-1 and PAMG-1 seem to be sensitive and specific; however, evidence is lacking especially in equivocal cases and comparative studies against the real gold standard (amnio-dye) have still not been published. The authors stated that further effectiveness research is needed before tests can be applied in practice.

An assessment by the Canadian Agency for Drugs and Technologies in Health (CADTH, 2012) found that AmniSure had 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. The assessment stated that evidence-based
guidelines for the use of AmniSure in clinical practice are lacking. The assessment
stated that there is a limited quantity of evidence directly comparing AmniSure to
conventional clinical methods, which include fern testing as one of the diagnostic
criteria, for detecting rupture of fetal membranes. The assessment identified one
study comparing AmniSure to the fern test alone. This study exclusively included
term pregnancies and may not be generalizable to preterm membrane rupture.
Other identified studies made a comparison to a suite of clinical criteria which
varied between studies. These criteria included fern tests, but a positive fern test
was not necessarily required to make a diagnosis, limiting the ability to draw a
direct comparison. The assessment noted that all studies excluded patients with
vaginal bleeding or other complications which may limit generalizability of their
findings. CADTH identified no evidence-based guidelines or cost-effectiveness
analyses of Amnisure.

van der Ham et al (2011) stated that PROM is a common obstetrical problem, but
its diagnosis is frequently problematic. Lacking a gold standard, the diagnosis is
equivocal in some 10 % of cases. These researchers performed a systematic
review to assess the accuracy of several tests for the diagnosis of PROM in these
equivocal cases. They performed an electronic search in PubMed, Embase,
DARE and the Cochrane Library and reference lists for potentially missed articles.
No language restrictions were used. Only accuracy studies for diagnostic
methods for PROM in women with equivocal PROM were selected. The studies
were scored according to STARD and QUADAS guidelines. Based on the full
description of reference and index tests, an expert panel finally decided whether
the selected articles were of sufficient quality to be included. These investigators
identified 3,864 studies of which 146 full manuscripts were obtained. They
excluded 133 due to multiple reasons. The remaining 13 studies were scored by
an expert panel. Only 3 articles with a total of 155 patients fulfilled all criteria.
These articles tested 3 different methods: (i) pH measurement (64 patients), (ii)
insulin-like growth factor binding protein-1 (ILGBP-1, 83 patients) and (iii) alpha
fetoprotein (AFP, 8 patients). Sensitivity varied from 88 % (pH) to 100 % (AFP),
specificity varied from 56 % (ILGPP-1) to 100 % (AFP). Based on the limited
evidence on the accuracy of tests to diagnose ruptured membranes, the authors
concluded that the use of a particular test cannot be recommended.

The ROM Plus Fetal Membranes Rupture Test is a rapid, qualitative test for the in-
vitro detection of amniotic fluid in vaginal secretions of pregnant women. It detects
both placenta protein 12 (PP12) and alpha-fetoprotein (AFP). However, there is
insufficient evidence regarding the effectiveness of this test.

CPT Codes / HCPCS Codes / ICD-9 Codes

HCPCS codes not covered for indications listed in the CPB:
84112 Placental alpha microglobulin-1 (PAMG-1), cervicovaginal secretion, qualitative

ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):

630 - 677 Complications of pregnancy, childbirth, and the puerperium
V22.0 - V23.9 Supervision of pregnancy
V28.8 Other specified antenatal screening

The above policy is based on the following references:

Assessment HTA. Ottawa, ON: Canadian Agency for Drugs and Technologies in Health (CADTH); March 15, 2010.