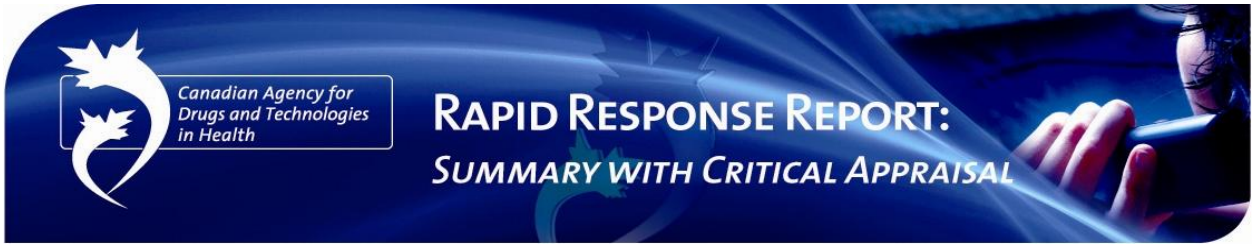

TITLE: AmniSure versus Fern Testing to Assess the Rupture of Fetal Membranes in Pregnant Women: A Review of the Comparative Accuracy, Cost-Effectiveness, and Guidelines

DATE: 04 April 2012

CONTEXT AND POLICY ISSUES

Prelabor rupture of the fetal membranes is a complication in five to 10 percent of all pregnancies, and without timely detection is associated with increased perinatal morbidity.[1,2] Accurate diagnosis of membrane rupture is important. False negatives can mean rupture goes undetected potentially leading to serious complications while false positives, particularly in cases of suspected preterm rupture can lead to unnecessary obstetric intervention including induction of labor.[3]

Conventional techniques for diagnosing membrane rupture include speculum examination, nitrazine testing to detect pH changes in vaginal discharge, and fern testing.[3,4] Fern testing involves the detection of a characteristic tree-like pattern resulting from amniotic fluid crystallization.[4]

Because of the intrusiveness and uncertainty of speculum examination[1,3] and modest diagnostic reliability of other tests, particularly in the presence of urine, semen, or blood,[1,3,4] there is a need for other detection methods. One such method is AmniSure, which is an immunoassay for placental alpha microglobulin-1 (PAMG-1). PAMG-1 is abundant in amniotic fluid, but is found in negligible amounts in vaginal secretions without membrane rupture.[3,4] It is also not present in urine or semen, and at low levels in maternal blood, reducing the risk of inaccurate results in the presence of other fluids.[3,4]

The purpose of this review is to compare the comparative diagnostic accuracy and cost-effectiveness of AmniSure compared with fern testing for detection of rupture of the fetal membrane. Evidence-based guidelines for the use of AmniSure will also be reviewed.

RESEARCH QUESTIONS

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?

KEY MESSAGE

Evidence suggests that AmniSure is an accurate method for detecting rupture of fetal membranes, but studies examining performance compared with fern testing are limited in number. No cost-effectiveness evidence or evidence-based guidelines were identified.

METHODS

Literature Search Strategy

This report makes use of a literature search conducted for a previous CADTH report. The original literature search was conducted in March 2010 on key resources including 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. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, controlled clinical trials, economic studies and guidelines. Where possible, retrieval was limited to the human population. The initial search was also limited to English language documents published between January 1, 2005 and March, 2010. For the current report, database searches were rerun on March 8, 2012 to capture any articles published since the initial search date. No methodological filters were applied to limit retrieval by study type. The search of major health technology agencies was also updated to include documents published since March 2010.

The previous CADTH report can be found at http://www.cadth.ca/media/pdf/htis-L1/J0396%20AmniSure%20final.pdf.

Selection Criteria and Methods

One reviewer screened citations retrieved from the literature search based on titles and abstracts, and selected potentially relevant articles for full-text review. A second reviewer considered full-text articles for inclusion according to the selection criteria presented in Table 1.

Table 1: Selection Criteria

Population	Pregnant women suspected of having fetal membrane rupture
Intervention	AmniSure (placental alpha-microglobulin-1 immunoassay)
Comparator	Fern test for membrane rupture
Outcomes	Diagnostic accuracy, cost-effectiveness, guidelines and recommendations regarding test use
Study Designs	Health technology assessments (HTAs), systematic reviews and meta-analyses, randomized controlled trials (RCTs), non-randomized studies, economic evaluations, evidence-based guidelines

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria in Table 1, if they were published prior to 2005, were duplicate publications of the same study, were included in a selected systematic review, were non-comparative studies, or were narrative reviews. Guidelines were excluded if they did not report methods.

Critical Appraisal of Individual Studies

Critical appraisal of selected studies was performed based on study design. Studies of diagnostic accuracy were assessed for quality using the QUADAS tool.[5] Randomized controlled trials and non-randomized studies were assessed for quality using the Downs and Black checklist.[6] Instead of calculating numeric scores, the strengths and limitations of each study were described. No HTAs, systematic reviews, economic evaluations or evidence-based guidelines were identified for critical appraisal.

SUMMARY OF EVIDENCE

Quantity of Research Available

The original and updated search identified a total of 313 citations for review. Upon screening of titles and abstracts, 306 were excluded, and 7 were retrieved for full-text screening. No additional references were identified in the grey literature. Of the 7 selected articles, 3 did not meet the inclusion criteria. Four publications were selected for inclusion. The PRISMA flowchart in Appendix 1 details the process of study selection.

Four prospective observational studies of diagnostic accuracy of AmniSure compared with fern testing were identified.[7-10] No health technology assessments, systematic reviews and meta-analyses, randomized controlled trials, economic evaluations, or evidence-based guidelines were selected for inclusion.

Additional references of potential interest are provided in Appendix 2.

Summary of Study Characteristics

A detailed description of individual study characteristics is provided in Appendix 3.

Study design

All included studies[7-10] were prospective observational studies designed to determine the diagnostic accuracy of AmniSure compared with conventional clinical criteria for assessing fetal membrane rupture. Studies were conducted in Thailand,[7] Kuwait,[8] South Korea,[9] and the United States of America.[10] Patients in the included studies were recruited between 2005 and 2009.[7-9] One study, published in 2005, did not state the observation period.[10]

Population

One study[8] included pregnant women who had reached term (37 weeks gestation) undergoing induction of labor due to premature rupture of membrane. Three studies included both women with term and preterm pregnancies, with symptoms or signs of rupture of membrane.[7,9,10] One

study included a control group of pregnant women undergoing induction of labor for reasons unrelated to membrane rupture.[8] All studies excluded patients with vaginal bleeding.

Index and reference tests

In all studies, the index test used was AmniSure (placental alpha-microglobulin-1 immunoassay). Three included studies[7,9,10] used a set of conventional clinical criteria as a reference test. One study[8] individually compared AmniSure to fern testing and nitrazine testing. In studies using multiple clinical criteria as the reference standard, these criteria included leaking amniotic fluid on speculum examination[7,9] or combinations of fern tests,[7,9,10] nitrazine tests,[7,9,10] visual pooling of fluid,[9,10] and positive nile blue test.[7] In all studies, final diagnosis was confirmed after delivery, based on review of patient clinical history.

Outcomes

All included studies[7-10] reported the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the diagnostic tests

Summary of Critical Appraisal

A summary of critical appraisal of individual studies can be found in Appendix 4.

All included studies explicitly described the inclusion and exclusion criteria.[7-10] Both index and reference tests were performed in a short time period, minimizing risk of change in clinical condition between tests.[7-10] In all studies, both tests were applied to all participants, with details of the index test described in enough detail to permit replication. In all cases the index test or reference test was compared with a final diagnosis based on review of patient medical history, however the criteria for that diagnosis was not explicitly stated in three studies.[7,9,10] In one study where the elements informing final diagnosis were clearly stated, they were dependent on reference test results (fern testing) among other clinical criteria described in Appendix 3.[8] Given that the reference tests were based on conventional clinical criteria, it is unlikely that in the remaining studies[7,9,10] final diagnosis was made independent of their results. Two studies[7,9] stated that final diagnosis was made without knowledge of AmniSure test results. One study[10] indicated that reference and index test results were interpreted independently from each other. In one study[9], obstetric care providers were blinded to AmniSure test results.

Summary of Findings

Detailed findings from each individual study can be found in Appendix 5.

One study directly compared AmniSure with the fern test.[8] Compared with fern testing, AmniSure had higher sensitivity, specificity, positive predictive value, negative predictive value and accuracy. The statistical significance of these findings was not reported.

Two studies[7,9] found that AmniSure had statistically significantly higher sensitivity for the diagnosis of ruptured membrane compared with a set of conventional clinical criteria, including fern testing. Conventional clinical criteria for detecting rupture of membrane had higher specificity than AmniSure in two studies,[7,9] but this difference was not statistically significant in one of them.[9] Negative predictive value was higher for AmniSure in two studies.[7,9] The positive predictive value was not statistically significantly different between AmniSure and conventional

clinical criteria in two studies.[7,9] One study[7] found no difference in accuracy between AmniSure and conventional criteria.

One study[10] found that AmniSure had high sensitivity (98.9%), specificity (100.0%), positive predictive value (100.0%) and negative predictive value (99.1%), but did not report the performance of the conventional clinical criteria used as a reference test, or the variability of these results.

No evidence was identified regarding cost-effectiveness of AmniSure or evidence-based guidelines for its use.

Limitations

One study was identified comparing AmniSure to the fern test alone. 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. This study exclusively included term pregnancies and may not be generalizable to pre-term 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. All studies excluded patients with vaginal bleeding or other complications which may limit generalizability of their findings. No evidence-based guidelines or cost-effectiveness analyses were identified.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

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.

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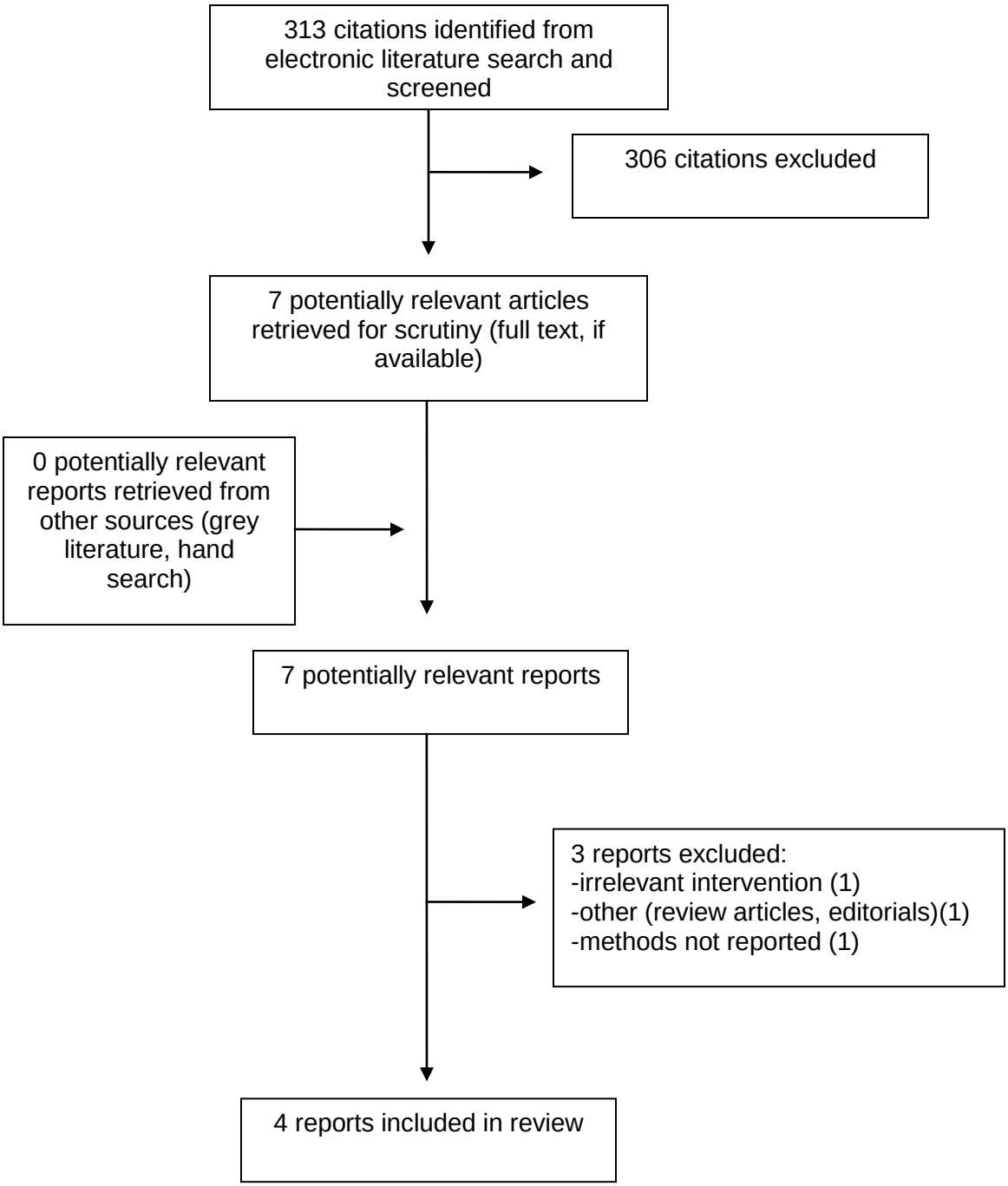
Appendix 1: Selection of Included Studies



Appendix 2: Additional Reference of Potential Interest

Clinical practice guidelines – no methods reported

Di Renzo GC, Roura LC, Facchinetti F, Antsaklis A, Breborowicz G, Gratacos E, et al. Guidelines for the management of spontaneous preterm labor: identification of spontaneous preterm labor, diagnosis of preterm premature rupture of membranes, and preventive tools for preterm birth. J Matern Fetal Neonatal Med [Internet]. 2011 May [cited 2012 Apr 02];24(5):659-67. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3267524

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Reviews

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Appendix 3: Summary of Study Characteristics

First Author, Publication Year, Country	Study design, duration	Patient Characteristics, Sample size (N)	Index test	Reference test	Clinical Outcomes
Phupong,[7] 2012 Thailand	Prospective observational Jan. 2008 to Jan. 2009	Pregnant women with symptoms or signs of ROM (N=100) Mean maternal age: NR Mean gestational age: 36.5 ± 3.5 wk 76% preterm Exclusion: patients with active vaginal bleeding, multiple pregnancies, fetal anomalies and fetal death	AmniSure	Conventional clinical criteria: Leaking amniotic fluid on speculum examination OR two of a) positive nitrazine test, b) positive fern test, c) positive nile blue test Final diagnosis of ROM was made after delivery and review of medical records	Sensitivity, specificity, PPV, NPV, false positive rate, false negative rate
Abdelazim,[8] 2011 Kuwait	Prospective observational Jan. 2006 to Jan. 2008	Pregnant women (37 weeks gestation) undergoing induction of labor due to PROM (N=75) Mean maternal age: 27.5 ± 5.25 yr Mean gestational age: 37.4 ± 2.83 wk Control: Pregnant women (37 weeks) undergoing induction of labor without PROM, due to hypertension, diabetes or IUGR (N=75) Mean maternal age: 29.1 ± 4.34 yr Mean gestational age: 37.9 ± 2.86 wk Exclusion: Patients with multiple pregnancies, fetal distress, vaginal bleeding, preterm labor, or chorioamnionitis.	AmniSure	Fern test or nitrazine test Diagnosis of PROM was based on patient's history of sudden gush of water, pooling of amniotic fluid, positive fern test, positive nitrazine test, and confirmed by visualization of fluid passing from the cervical canal during speculum examiniation	Sensitivity, specificity, PPV, NPV, accuracy
Lee,[9] 2007 South Korea	Prospective observational	Pregnant women with symptoms or signs of ROM (N=184)	AmniSure	Conventional clinical criteria: Leaking amniotic fluid on speculum examination OR two of a) visual	Sensitivity, specificity, PPV, NPV,

First Author, Publication Year, Country	Study design, duration	Patient Characteristics, Sample size (N)	Index test	Reference test	Clinical Outcomes
	March 2005 to Feb. 2006	Mean maternal age: NR Mean gestational age: 35 ± 0.5 wk 43% preterm Exclusion: Patients with active vaginal bleeding.		pooling of fluid in the posterior fornix, b) positive fern test, c) positive nitrazine test Final determination of ROM was made after delivery and review of medical record.	false negative rate
Cousins,[10] 2005 USA	Prospective observational Dates not specified	Pregnant women (15 to 42 wk gestation) with signs or symptoms of ROM (N=203) Mean maternal age: NR Mean gestational age: NR % preterm: NR Exclusion: Patients with active vaginal bleeding or known placenta previa	AmniSure	Clinical criteria: Two of a) visual pooling of amniotic fluid, b) positive nitrazine test, c) positive fern test Final determination of PROM or PPROM was made after delivery and review of the medical record	Sensitivity, specificity, PPV, NPV

IUGR = intrauterine growth restriction; NPV = negative predictive value; NR = not reported; PPROM = preterm PROM; PPV = positive predictive value; PROM = premature rupture of membranes; ROM = rupture of membranes; USA = United States of America; wk = week; yr = year

Appendix 4: Summary of Critical Appraisal

First Author, Publication Year, Country	Strengths	Limitations
Phupong,[7] 2012 Thailand	• Selection criteria clearly described • Final diagnosis likely to correctly classify the condition • Short time period between index and reference tests • All patients received both index and reference tests • Index test described in sufficient detail to permit replication • Final diagnosis performed without knowledge of index test results	• Specific criteria for final diagnosis unclear • Unclear if final diagnosis was made independent of reference test results
Abdelazim,[8] 2011 Kuwait	• Selection criteria clearly described • Final diagnosis likely to correctly classify the condition • Short time period between tests • All patients received both index and reference tests • Index test described in sufficient detail to permit replication	• Final diagnosis dependent on reference test results • Unclear whether final diagnosis was made without knowledge of the index test results • Unclear whether reference and index test results were interpreted independently from one another
Lee,[9] 2007 South Korea	• Selection criteria clearly described • Final diagnosis likely to correctly classify the condition • Short time period between tests • All patients received both tests • Index test described in sufficient detail to permit replication • Final diagnosis performed without knowledge of index test results • Obstetric care providers blinded to index test results	• Specific criteria for final diagnosis unclear • One participant lost to follow-up, but reasons not explained • Unclear whether final diagnosis was made independent of reference test results
Cousins,[10] 2005 USA	• Selection criteria clearly described • All patients received both tests • Index and reference tests performed by different clinicians blinded to each other's results • Short time between tests • Index test described in sufficient detail to permit replication	• Specific criteria for final diagnosis unclear • Unclear if final diagnosis was made independent of reference and index test results • Results from reference test not reported

Appendix 5: Summary of Individual Study Findings

First Author, Publication Year, Country	Main Study Findings	Authors' Conclusions
Phupong,[7] 2012 Thailand	Sensitivity: AmniSure: 97.2% (95% CI 94 to 100) Conventional: 88.7% (95% CI 82.5 to 94.9) P = 0.031 Specificity: AmniSure: 69% (95% CI 59.9 to 78.1) Conventional: 96.6% (95% CI 93.1 to 100) P = 0.008 PPV: AmniSure: 90.8% (95% CI 85.1 to 96.5) Conventional: 98.4% (95% CI 95.9 to 100) P = 0.062 NPV: AmniSure: 90.9% (95% CI 85.3 to 96.5) Conventional: 77.8% (95% CI 69.7 to 86) P = 0.019 Accuracy: AmniSure: 89% (95% CI 82.9 to 95.1) Conventional: 91% (95% CI 85.4 to 96.6) P = 0.813	"PAMG-1* is a rapid method of diagnosing ROM. PAMG-1 has a higher sensitivity than the conventional standard methods for the diagnosis of ROM but has a lower specificity." (p. 229) *PAMG-1 immunoassay is the generic name for AmniSure
Abdelazim,[8] 2011 Kuwait	Sensitivity: AmniSure: 97.33% Fern test: 84.0% Specificity: AmniSure: 98.67% Fern test: 78.67% PPV: AmniSure: 98.64% Fern test: 79.74% NPV: AmniSure: 97.37% Fern test: 83.1% Accuracy: AmniSure: 98.0% Fern test: 81.33% P-values and 95% confidence intervals not reported	"Detection of the PAMG-1 in the vaginal fluid using (AmniSure® test) is an accurate method to diagnose rupture of fetal membranes with high sensitivity, specificity, negative and positive predictive values." (p.4)
Lee,[9] 2007 South Korea	Sensitivity: AmniSure: 98.7% (95% CI 95.1 to 99.8) Conventional: 87.4% (95% CI 81 to 92)	"In conclusion, the placental alpha-microglobulin-1 immunoassay is a rapid and accurate method for

First Author, Publication Year, Country	Main Study Findings	Authors' Conclusions
	P < 0.001 Specificity: AmniSure: 87.5% (95% CI 66.5 to 96.7) Conventional: 100% (95% CI 83 to 100) P = 0.25 PPV: AmniSure: 98.1% (95% CI 94.2 to 99.5) Conventional: 100% (95% CI 97 to 100) NPV: AmniSure: 91.3% (95% CI 70.5 to 98.5) Conventional: 54.5% (95% CI 39 to 69) P-values not reported, except where indicated	confirming the diagnosis of ROM. Moreover, its performance appears to be superior to conventional clinical assessment (pooling, nitrazine, ferning) and the nitrazine test alone." (p. 639-40)
Cousins,[10] 2005 USA	AmniSure: Sensitivity: 98.9% Specificity: 100.0% PPV: 100.0% NPV: 99.1% Performance metrics from the conventional clinical tests were not reported	"AmniSure is a rapid, bedside strip test that can detect rupture of fetal membranes with a high degree of predictive accuracy" (p. 320)

CI = confidence interval; NPV = negative predictive value; NR = not reported; PAMG-1 = placental alpha-microglobulin-1; PPV = positive predictive value; ROM = rupture of membrane