

Research Article

Diagnostic Accuracy of IGFBP-1 (ACTIM-PROM) Versus the Nitrazine Test for Preterm Premature Rupture of Membranes

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Abstract

Objective: To evaluate the diagnostic performance of insulin-like growth factor-binding protein-1 (IGFBP-1; ACTIM PROM) compared with the nitrazine test for the diagnosis of preterm premature rupture of membranes (PPROM).

Methods: This observational analytical study included 30 pregnant women, comprising 15 women with PPRM and 15 controls. Posterior fornix fluid collected during a sterile speculum examination was analyzed using both the nitrazine test and the ACTIM PROM immunoassay.

Results: The nitrazine test demonstrated a sensitivity of 80.0%, specificity of 73.3%, and overall diagnostic accuracy of 76.6%. ACTIM PROM demonstrated a sensitivity of 93.3%, specificity of 100%, and overall diagnostic accuracy of 96.6%. ACTIM PROM showed significantly higher specificity than the nitrazine test, whereas no significant difference was observed in sensitivity.

Conclusion: ACTIM PROM demonstrated superior specificity and overall diagnostic accuracy compared with the nitrazine test and may serve as a reliable diagnostic tool for the diagnosis of PPRM.

Keywords: ACTIM PROM; diagnostic accuracy; IGFBP-1; nitrazine test; preterm premature rupture of membranes.

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INTRODUCTION

Premature Rupture of Membranes (PROM) is defined as the spontaneous rupture of the fetal membranes before the onset of labor. When membrane rupture occurs before 37 weeks of gestation, it is referred to as preterm premature rupture of membranes (PPROM).^{1,2} PPRM complicates approximately 1% of pregnancies worldwide and accounts for nearly one-third of all preterm births.³ In Indonesia, PROM occurs in approximately 4.5–7.6% of pregnancies and remains a significant contributor to maternal and neonatal morbidity and mortality.⁴

Accurate and timely diagnosis of PPRM is crucial because delayed or missed diagnosis may result in inappropriate clinical management, increasing the risks of maternal infection, preterm birth, and adverse neonatal outcomes. Despite its

clinical importance, diagnosing PPRM remains challenging because no universally accepted non-invasive reference standard is currently available. Conventional diagnostic approaches include clinical history, sterile speculum examination, microscopic ferning, and the nitrazine test. Although the nitrazine test is widely used because of its simplicity, rapidity, and low cost, its diagnostic performance is limited by false-positive and false-negative results caused by blood contamination, semen, vaginal infections, or other factors that alter vaginal pH.^{5,6}

To improve diagnostic accuracy, several biochemical markers have been evaluated, including beta-human chorionic gonadotropin (β -hCG), fetal fibronectin, placental alpha microglobulin-1 (PAMG-1), and insulin-like growth factor-binding protein-1 (IGFBP-1). ACTIM PROM is a rapid immunochromatographic

assay that detects IGFBP-1 in blood and maternal tissues and has demonstrated high diagnostic accuracy for PROM in previous clinical studies.⁷ However, evidence comparing its diagnostic performance with the nitrazine test remains limited, particularly in Indonesian clinical settings.

Therefore, this study aimed to compare the diagnostic performance of ACTIM PROM and the nitrazine test by evaluating their sensitivity, specificity, and overall diagnostic accuracy in women with suspected PPRM.

METHODS

This multicenter observational analytical study employed a cross-sectional design to compare the diagnostic performance of the insulin-like growth factor-binding protein-1 (IGFBP-1) immunoassay (ACTIM PROM) with the nitrazine test for the diagnosis of Preterm Premature Rupture of Membranes (PPROM).

The study was conducted between January and December 2017 at the Rural Health and Training Center, Poonjeri, affiliated with Chettinad Hospital and Research Institute. Eligible participants were pregnant women between 28 and 36 weeks of gestation who presented with complaints of vaginal fluid leakage and provided written informed consent. Women were considered clinically positive for PPRM if amniotic fluid was visibly leaking through the cervical os during sterile speculum examination or if two of the following three clinical findings were present: visible pooling of fluid in the posterior fornix, a positive nitrazine test, or microscopic ferning.⁸ Women with multiple pregnancies, active vaginal bleeding, congenital fetal anomalies, clinical signs of intra-amniotic infection, or insufficient vaginal fluid specimens were excluded.

A total of 30 pregnant women were enrolled, including 15 women with clinically diagnosed PPRM and 15 pregnant women with intact fetal membranes who served as the control group. Following history taking and sterile speculum examination, vaginal fluid was collected from the posterior fornix. Each specimen was evaluated using both the nitrazine test and the ACTIM PROM immunoassay for IGFBP-1. Nitrazine test results were interpreted according to the manufacturer's instructions based on pH-dependent color changes, whereas ACTIM PROM results were interpreted qualitatively as either positive or negative according to the manufacturer's protocol.

Statistical analyses were performed using IBM SPSS Statistics version 21 (IBM Corp., Armonk, NY, USA). Diagnostic performance, including sensitivity, specificity, and overall diagnostic accuracy, was calculated for each test. Differences in diagnostic performance between the two methods were analyzed using the Chi-square test. A two-sided p-value of <0.05 was considered statistically significant.

RESULTS

A total of 30 pregnant women between 28 and 36 weeks of gestation were included in this study, comprising 15 women with clinically diagnosed preterm premature rupture of membranes (PPROM) and 15 pregnant women with intact fetal membranes who served as controls.

The ACTIM PROM immunoassay correctly identified 14 of 15 women with PPRM and all 15 women in the control group, yielding one false-negative result and no false-positive results (Table 1).

Table 1. Result of ACTIM-PROM Testing

ACTIM-PROM	Amniotic Fluid Condition		Total
	Case	Control	
Positive	14	0	14
Negative	1	15	16
Total	15	15	30

The nitrazine test correctly identified 12 of 15 women with PPRM and 11 of 15 women with intact membranes, resulting in three false-negative and four false-positive results (Table 2).

Table 2. Result of Nitrazine Testing

Nitrazine Test	Amniotic Fluid Condition		Total
	Case	Control	
Positive	12	4	16
Negative	3	11	14
Total	15	15	30

The diagnostic performance of both tests is summarized in Tables 3 and 4. ACTIM PROM demonstrated higher overall diagnostic performance than the nitrazine test, with a sensitivity of 93.33%, specificity of 100%, and overall diagnostic accuracy of 96.66%. In comparison, the nitrazine test demonstrated a sensitivity of 80.00%, specificity of 73.33%, and overall diagnostic accuracy of 76.66%.

Although the difference in sensitivity between the two tests was not statistically significant ($p=0.283$), ACTIM PROM demonstrated significantly higher specificity than the nitrazine test ($p=0.032$).

Table 3. Comparison of the Sensitivity of ACTIM-PROM and the Nitrazine Test

Diagnostic test	Sensitivity			P-value
	Negative	Positive	(%)	
ACTIM-PROM	1	14	93.33	0.283
Nitrazine	3	12	80	

Table 4. Comparison of Specificity of ACTIM-PROM and the Nitrazine Test

Diagnostic test	Specificity			P-value
	Negative	Positive	(%)	
ACTIM-PROM	15	0	100	0.032*
Nitrazine	11	4	73.33	

* $p < 0.05$

DISCUSSION

Principal Findings

This study demonstrated that ACTIM PROM outperformed the conventional nitrazine test in diagnosing preterm premature rupture of membranes (PPROM). ACTIM PROM demonstrated higher sensitivity, specificity, and overall diagnostic accuracy than the nitrazine test, with a statistically significant difference observed for specificity but not for sensitivity. Although the difference in sensitivity was not statistically significant, ACTIM PROM showed significantly higher specificity, indicating better ability to correctly identify women without PPRM.

The diagnostic performance of the nitrazine test observed in this study was comparable to that reported in previous studies. Sensitivity of 87.5% and specificity of 100%, whereas accuracy of 93.6%, sensitivity of 94.1%, and specificity of 90.5%.^{9,10} These findings suggest that the nitrazine test remains a useful diagnostic tool; however, its diagnostic performance may be affected by several clinical conditions.

The lower specificity of the nitrazine test may be attributable to its dependence on vaginal pH. Because amniotic fluid is alkaline (pH 7.1–7.3), nitrazine paper changes color in its presence. However, blood contamination, semen, alkaline antiseptics, bacterial vaginosis, and other factors that increase vaginal pH may produce false-positive results, whereas prolonged or chronic membrane rupture may lead to false-negative results.¹¹ Nitrazine test is an indirect, pH-based

method rather than an amniotic fluid-specific assay. Its diagnostic performance therefore depends on sufficient leakage and adequate sampling of amniotic fluid within the vagina, while the overlap and variability of cervicovaginal pH limit its ability to specifically identify membrane rupture.¹² These limitations may explain the lower specificity observed in the present study.

The superior diagnostic performance of ACTIM PROM is consistent with previous investigations evaluating insulin-like growth factor-binding protein-1 (IGFBP-1) as a biomarker of membrane rupture. Previous study has reported sensitivity of 87.5%, specificity of 94.4%, PPV of 92.1% and NPV of 91.1%.¹³ Further demonstrated excellent diagnostic performance, with sensitivity and specificity of 97.5% and 97.4% with PPV and NPV of 95% and 94.8% respectively without speculum examination and sensitivity and specificity of 95.7% and 90.0% with PPV and NPV of 97.5% and 97.4% respectively, following speculum examination.¹⁴

ACTIM PROM detects insulin-like growth factor-binding protein-1 (IGFBP-1), a protein synthesized primarily by decidual cells and the fetal liver that is abundant in amniotic fluid but normally absent from vaginal secretions. Consequently, detection of IGFBP-1 in cervicovaginal fluid strongly suggests membrane rupture. This biological characteristic may explain the higher diagnostic accuracy observed with ACTIM PROM compared with the pH-based nitrazine test.¹⁵

Strengths and Limitations

This study has several limitations. First, the relatively small sample size may have limited the statistical power to detect differences in diagnostic performance, particularly sensitivity, between ACTIM PROM and the nitrazine test. Second, although the study was conducted at multiple centers, the study population was limited to three hospitals within a single region, which may limit the generalizability of the findings. Third, only ACTIM PROM and the nitrazine test were evaluated, without comparison with other commercially available biomarkers, such as placental alpha-microglobulin-1 (PAMG-1) or fetal fibronectin. Therefore, larger multicenter studies comparing multiple diagnostic modalities are warranted to validate these findings.

CONCLUSION

ACTIM PROM demonstrated higher specificity and diagnostic accuracy than the nitrazine test for the diagnosis of preterm premature rupture of membranes (PPROM). Although the difference in sensitivity between the two tests was not statistically significant, the significantly higher specificity of ACTIM PROM indicates a lower likelihood of false-positive results. These findings suggest that ACTIM PROM is a reliable diagnostic method and may provide greater diagnostic value than the conventional nitrazine test in women with suspected PPRM.

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