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RESEARCH ARTICLE

Comparison of Detection Methods for Premature Rupture of Membranes: IGFBP-1 Immunoassay Test vs. Nitrazine Test

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Abstract

Objective*: This study aimed to compare the diagnostic accuracy of the Insulin-like Growth Factor Binding Protein-1 (IGFBP-1) immunoassay test with the conventional Nitrazine test in detecting Premature Rupture of Membranes (PROM).*

Method*: A diagnostic cross-sectional study was conducted as part of a multicenter study in 19 centers. It involved 40 pregnant women (20 with PROM and 20 without PROM) between 28–36 weeks of gestation at Dr. M. Djamil Hospital, Padang. The IGFBP-1 immunoassay (Actim PROM) and Nitrazine tests were performed using posterior vaginal fornix swabs. PROM diagnosis was confirmed by speculum examination. Data analysis included ROC curves, Youden's Index, and AUC using SPSS v27.*

Result*: The IGFBP-1 immunoassay yielded 100% sensitivity and 100% positivity in PROM cases. The Nitrazine test showed 75% sensitivity with 4 false negatives. IGFBP-1 provided more accurate results, was unaffected by vaginal bleeding or infections, but was more costly and required immediate handling.*

Conclusion*: IGFBP-1 immunoassay demonstrates superior sensitivity and specificity compared to the Nitrazine test for PROM diagnosis. It is particularly advantageous in cases with unclear symptoms or contamination, supporting its use as a more reliable diagnostic tool in obstetric care.*

Keywords: *Premature rupture of membranes; IGFBP-1 immunoassay; Nitrazine test; Diagnostic accuracy; Amniotic fluid detection*

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INTRODUCTION

Premature Rupture of Membranes (PROM) refers to the rupture of the amniotic sac before labour begins. Labor is marked by symptoms such as the discharge of mucus mixed with blood, increasing frequency and intensity of contractions. PROM is characterized by the release of clear, painless fluid from the vagina.[1] When the amniotic sac ruptures before 37 weeks of gestation, it is referred to as preterm premature rupture of membranes (PPROM). PPROM is a serious condition, particularly in low- and middle-income countries, where it significantly contributes to maternal and neonatal morbidity and mortality rates.[2]

According to the World Health Organization (WHO), the global prevalence of PROM ranges from 5% to 15% of all pregnancies, influenced by factors such as healthcare service availability and quality, screening, prevention, and individual risk factors. These include maternal age, parity, education level, abortion history, prior PROM, prior caesarean section, urinary tract infections, vaginal infections, abdominal trauma, and hydramnios. According to Herbert et al., the incidence of PROM in the United States is 12.1%, while in Canada it is 4.3%. In Africa, the incidence varies widely by country, with reports of 1.3% to 3.3% in Nigeria, 2.4% to 4.7% in Egypt, 13.8% in Uganda, 14.6% in Jimma, 23.5% in Harar, and 9.2% in Ethiopia.[3,4,5]

PROM contributes to 40% of preterm births, which are one of the three leading causes of neonatal death. It is also responsible for 21.4% of morbidity and 18-20% of perinatal mortality in both developed and developing countries.[6]

The incidence of PROM varies across Asia. Research from various Asian countries shows a prevalence ranging from 1.2% to 18.7% of all deliveries. Zuang et al. found a 18.7% incidence of PROM in a multi-centre cohort study of 43,543 women in China, with 16.26% experiencing PROM at 37 weeks of gestation and 2.5% experiencing preterm PROM. Risk factors for PROM in Asia include extreme maternal age, high or low parity, low education level, urinary tract or vaginal infections, history of abortion or previous PROM, and fetal malpresentation. Perinatal mortality rates due to PROM vary across Asian countries, from 9 per 1,000 live births in India to 40 per 1,000 live births in Pakistan. These differences highlight the complexity of PROM and the need for proper prevention and management strategies to reduce risks for both mothers and infants.[7]

In Indonesia, the incidence of PROM ranges from 4.5% to 6% of all pregnancies. The incidence in different hospitals in Indonesia varies, with 11.22% of patients at Cipto Mangunkusumo Hospital, 5.1% at Kariadi Hospital, 5.3% at Sardjito Hospital, 7.9% at Cilegon Regional Hospital, and 5.05% at Hasan Sadikin Hospital. A study by Hafni et al. in West Sumatra found that the incidence of PROM at RSUP Dr. M. Djamil Padang was 8.1%.[8] These findings are higher than the global systematic review and meta-analysis from 2020, which found a prevalence of 4.33%.[9] PROM can complicate term pregnancies in about 8% of cases, and preterm PROM can complicate delivery in 1% of cases.[10,11,12]

Several complications associated with PROM include fetal distress, systemic infection, and bleeding in the brain ventricles, leading to high-risk deliveries and high mortality rates.[9] PROM contributes to 40% of preterm births, which are a leading cause of neonatal death. Additionally,

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PROM is responsible for 21.4% of morbidity and 18-20% of perinatal deaths in both developed and developing countries.[6,13]

Common symptoms in pregnant women suspected of having PROM include the discharge of fluid from the vagina or the sensation of water leaking, suspected to be amniotic fluid. Diagnosis can be challenging, especially when the rupture is small, which often complicates the prognosis for both the mother and the fetus. Therefore, many diagnostic tools have been developed to address this issue. The gold standard for non-invasive diagnostics must have high specificity and sensitivity, be applicable at all stages of pregnancy, and detect even low concentrations. One such test is immunoassay-based, including Insulin-like Growth Factor Binding Protein 1 (IGFBP-1), Placental Alpha Microglobulin-1 (PAMG-1), Alpha-fetoprotein (AFP), and Placental Protein 12 and Alpha-fetoprotein (ROM Plus). Conventional tests include Nitrazine, vaginal pH measurement, and the fern test.[14]

Accurate diagnosis of PROM remains a clinical challenge in obstetrics. While there is no standard non-invasive diagnostic test currently available, PROM diagnosis is made based on patient history, identification of amniotic fluid collection from the cervical canal during a sterile speculum examination, Nitrazine testing, and the fern pattern observed under a microscope. Evaluation of Nitrazine testing has been associated with a 5% rate of false positive or false negative results.[15] A non-invasive gold standard for PROM diagnosis is still lacking, leading to the development of several alternative biochemical marker tests. These include vaginal prolactin, Alpha-fetoprotein (AFP), fetal fibronectin, IGFBP-1, PAMG-1, and ROM Plus.[16]

The identification of symptoms such as unclear fluid discharge from the birth canal, followed by speculum examination revealing fluid from the cervix, may still lead to an uncertain diagnosis, requiring further diagnostic tests. Confirming the diagnosis in unclear cases presents a significant challenge in current obstetric practice. An accurate diagnosis is necessary to reduce maternal and fetal complications. Optimal tests must be specific for amniotic fluid and unaffected by contamination from other bodily substances. Various tests with varying qualities have been developed to assess the integrity of the membranes, including cytology, biochemistry, calorimetry, and ultrasound techniques. Inaccuracies in testing may lead to unnecessary interventions, while poor sensitivity may result in missed diagnoses, increasing the risk of morbidity and mortality for both mother and fetus. Conventional tests like the fern and Nitrazine tests show high rates of false positives and negatives in women with vaginal infections or the presence of semen in the vaginal canal.[15]

In the last two decades, non-invasive tests using simple dipsticks have been developed. These tests detect specific proteins found in amniotic fluid with high sensitivity and specificity. Currently available tests include Alpha-fetoprotein (AFP), fetal fibronectin, IGFBP-1, PAMG-1, and ROM Plus.[17]

IGFBP-1 is a protein synthesized in the decidua and placenta. IGFBP-1 concentrations are 100-1,000 times higher in amniotic fluid than in maternal serum, making it easily detectable in amniotic fluid throughout pregnancy, not easily contaminated, and unaffected by bleeding.

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Similarly, PAMG-1 has the advantage of being unaffected by semen or bleeding.[15]

Based on existing theories and research, the researcher is interested in comparing the accuracy of the rapid immunoassay IGFBP-1 with conventional Nitrazine testing. While many non-invasive tests have been developed, there has been little comparison to actual clinical results. This study aims to compare the detection of PROM using the IGFBP-1 immunoassay versus the Nitrazine test. Additionally, the researcher has not found any studies examining the relationship between these tests and unclear clinical symptoms in Indonesia. Both IGFBP-1 and Nitrazine tests can be used interchangeably in suspected cases of PROM. However, IGFBP-1 offers higher sensitivity in doubtful cases of PROM, especially when there are complications such as bleeding. IGFBP-1 has the advantage of being unaffected by blood contamination or gestational age.

METHODS

This study is a diagnostic test research that forms part of a multicenter study conducted in 19 centers, utilizing a cross-sectional design and consecutive sampling. The research was carried out at the Emergency Obstetric and Neonatal Service (PONEK) of Dr. M. Djamil General Hospital in Padang from January 2024 until the required sample size was met. The target population included all pregnant women presenting at the hospital during this time period.

The study focused on pregnant women between 28–36 weeks of gestation who experienced vaginal fluid discharge, suspecting premature rupture of membranes (PROM). Inclusion criteria included the gestational age and clinical symptoms, while exclusion criteria ruled out pregnancies with fetal congenital anomalies, maternal undernutrition, intrauterine growth restriction (IUGR), antepartum hemorrhage due to placenta previa, multiple gestations, and maternal illnesses such as peripartum cardiomyopathy and severe preeclampsia. The sample size was calculated to compare the sensitivity and specificity between IGFBP-1 immunoassay and nitrazine test, with a final target of 40 subjects per center (20 PROM cases and 20 non-PROM).

The independent variables in this study were the IGFBP-1 immunoassay test and the nitrazine test, and the dependent variable was PROM diagnosis confirmed through speculum examination. Operational definitions were established for PROM, nitrazine test, and IGFBP-1 test, including their instruments, procedures, outcome interpretations, and measurement scales. The research used primary data collected through interviews and observations, including maternal age and test results.

The data collection procedure involved informed consent followed by two separate vaginal swabs from the posterior fornix, one for the nitrazine test and the other for the IGFBP-1 test. The same procedure was applied to a control group. Research instruments included patient medical records, ultrasound, sterile speculums and swabs, litmus paper, and the Actim PROM kit for IGFBP-1 testing. The primary material used in the study was amniotic fluid.

Data processing involved editing, coding, tabulating, and analyzing data. Descriptive analysis included statistical summaries such as percentages, means, standard deviations, medians, and ranges. Analytical testing involved the Kolmogorov-Smirnov test for normality and Youden's Index,

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ROC curve, and AUC to evaluate diagnostic accuracy. The research aimed to compare the diagnostic performance (sensitivity, specificity, PPV, and NPV) of both tests using SPSS version 27.0.1, with statistical significance set at $p < 0.05$.

RESULT AND DISCUSSION

1. Characteristics of Research Subjects

Table 1 displays the characteristics of the research subjects. The mean age of the mothers who were subjects in this study was 27.95 ± 6.52 years. This finding is consistent with several previous studies. Two studies conducted in India, Biradar's research involving 126 pregnant women with premature rupture of membranes (PROM) found the highest percentage in the age range of 21-25 years (42%), followed by 26-30 years (32%), 31-35 years (14%), and 18-20 years (12%). Meanwhile, Patil et al., who studied 100 pregnant women, found a mean age of 22 ± 7.6 years.37,38 Other studies conducted in Ethiopia by Tsegaye et al. reported a mean age of 28.9 ± 1.12 years, with the majority aged 18-35 years (91.7%), and Jena et al. found a mean age of 27.5 ± 3.5 years.39,40 A study in Indonesia by Aryati et al., specifically in Surabaya, reported a mean age of 28.70 ± 5.14 years.[18]

2. Results of the IGFBP-1 Immunoassay Test in PROM Patients

Table 2 shows the results of the IGFBP-1 immunoassay test in PROM patients. This study showed that the Immunoassay IGFBP-1 test was positive in 100% of the 20 patients with PROM, and negative in 0%. Aryati's study on PROM patients in Surabaya showed positive results in 84.8% and negative results in 15.2%.41 Chalurkar et al., in their study of 74 PROM cases, found 67 positive and 7 negative results.[19]

Insulin-like growth factor binding protein 1 (IGFBP-1) is synthesized by the decidua and fetal liver and is a major protein in amniotic fluid detectable during pregnancy that regulates cell growth and metabolism.26,42 IGFBP-1 concentrations in amniotic fluid are 100 to 10,000 times higher than in serum.41 IGFBP-1 is useful for diagnosing PROM through a dipstick diagnostic device.42

In the first trimester, IGFBP-1 levels are typically similar in the vagina and cervix, but from the second trimester onward, IGFBP-1 levels are twice as high in the cervix compared to the vagina. Sampling inaccuracies can affect test results, so ideally swabs should be taken from the posterior vaginal fornix.41 Moreover, IGFBP-1 is degraded by vaginal proteases and is reported to be unreliable if more than 12 hours have passed since membrane rupture.[19]

The IGFBP-1 test (e.g., Actim PROM) is a rapid immunoserological test to detect amniotic fluid but has some disadvantages. First, it is relatively costly per test.36 In contrast, the Nitrazine test is a simple litmus paper test with minimal cost (no additional lab fees).[11] Second, although IGFBP-1 tests are quick (results in about 5 minutes), the procedure requires special equipment and some preparation time (e.g., posterior fornix swab and reagent buffer), whereas Nitrazine is simpler to apply directly.[20]

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Technically, IGFBP-1 protein can degrade if samples are not promptly analyzed or properly stored.[19] Thus, vaginal fluid samples must be collected and tested immediately to avoid protein degradation. Also, contamination can affect results; for example, vaginal bleeding may interfere with IGFBP-1 strip readings. Ramsauer et al. reported that about 11% of IGFBP-1 tests became non-evaluable due to blood stains on the strip.[21] Therefore, the presence of blood or other vaginal secretions can cause test errors. Although Actim PROM claims resistance to some interferences, sample handling should still be careful to minimize errors (e.g., avoid contamination from blood or antiseptics before sampling).[25]

3. Results of the Nitrazine (Litmus) Test in PROM Patients

Table 3 presents the results of the nitrazine test in PROM patients. This study showed that the Nitrazine test was positive in 16 of the 20 PROM patients (75%) and negative in 4 patients (25%). The Nitrazine test using litmus paper has long been used as a simple and rapid method to detect PROM because amniotic fluid has a basic pH (above 7.0) compared to the normally acidic vaginal fluid (pH 4.5–6.0). Olorinoye et al. studied 64 pregnant women with PROM and reported positive results in 56 cases and negative results in 8 cases.12 Nunes et al. reported a 100% positive rate for the Nitrazine test.[20]

Several clinical and technical factors can cause false negatives in Nitrazine testing. The test relies on pH differences between amniotic fluid (pH ~7) and normal vaginal fluid (pH 3.8–4.5). If the amniotic fluid volume tested is small or dried (e.g., due to long duration of membrane rupture), the pH strip may not turn blue, resulting in a false negative. Chronic PROM or prolonged leakage can reduce amniotic fluid volume, preventing activation of Nitrazine.[21]

Contamination by other substances such as residual urine or menstrual fluid (more acidic) or antiseptics may moderate the pH, so the strip shows no positive reaction.[22] Vaginal infections (vaginitis or cervicitis) may also lower vaginal pH, making it difficult for the Nitrazine strip to detect alkalinity. In summary, factors causing false negatives include:[21]

- Prolonged duration of membrane rupture: Longer PROM reduces available fluid to test.
- Normal or acidic vaginal pH: Acidic vaginal pH can neutralize amniotic alkalinity, preventing color change.
- Contamination: Exposure to urine, blood, semen, or antiseptics may interfere with the test (e.g., urine is alkaline, blood/semen can cause nonspecific reactions, acidic substances reduce reactivity).
- Subjective interpretation: Faint strip color or wet strips due to mucus can complicate reading.

Thus, the four samples with negative Nitrazine results were most likely affected by a combination of prolonged leakage duration (less residual fluid) and vaginal environment factors (low pH or other substances). Similar cases are documented, including ACOG reports that infection, mucus, or duration since membrane rupture can affect conventional test accuracy.[21]

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4. Comparison of Sensitivity and Specificity Between IGFBP-1 and Nitrazine Tests

Table 4 compares the performance of the IGFBP-1 immunoassay and nitrazine tests. Diagnostic methods have advanced and been extensively studied over the past decades. Biomarkers like IGFBP-1, found at higher concentrations in amniotic fluid than vaginal fluid, provide strong predictive value in PROM diagnosis. Several studies indicate that newer biomarker tests are more accurate and easier to process than classic tests.[21]

The hypothesis of performance differences between IGFBP-1 and Nitrazine is supported by empirical literature. Generally, studies comparing the two show that IGFBP-1 tends to have equal or slightly higher sensitivity and specificity. For example, Tagore et al. (2010) reported IGFBP-1 sensitivity at 87.5% and specificity at 94.4%, compared to Nitrazine's 85.0% sensitivity and only 39.7% specificity.[21] This dramatic difference in specificity indicates that IGFBP-1 produces fewer false positives. Abdelazim et al. (2014) found IGFBP-1 sensitivity 89.3% and specificity 82.7%, versus Nitrazine's 86.7% sensitivity and 81.3% specificity. Liang et al. (2014) reported IGFBP-1 sensitivity 93.33% and specificity 98.89%, versus Nitrazine's 93.33% and 94.44%.47 These data consistently show IGFBP-1's diagnostic performance is at least comparable and often superior, particularly in specificity. The combined results strengthen the hypothesis that sensitivity and specificity differ, favoring IGFBP-1.[23]

This study found that the IGFBP-1 immunoassay test had sensitivity 100%, specificity 100%, positive predictive value (PPV) 100%, negative predictive value (NPV) 100%, true positive 100%, false positive 0%, true negative 100%, and false negative 0%. Palacio (2014) reported IGFBP-1 sensitivity at 100%, meaning all positive cases were correctly detected.[21] Aryati et al. (2015) reported 85% sensitivity, indicating 15% false negatives.[18] Chalurkar (2017) noted 90.54%, and Abdelazim (2013) 89.3%. Nitrazine sensitivity was reported by Abdelazim (2013) as 86.7%.[19,24]

Palacio (2014) also reported IGFBP-1 specificity at 100%, meaning no false positives. Aryati et al. (2015) reported 95% specificity, with 5% false positives. Chalurkar (2017) reported 65.38%, and Abdelazim (2013) 82.7%. Nitrazine specificity was 81.3%.[19.24] Palacio (2014) found PPV for IGFBP-1 at 100%, meaning all positive results reflected true positives. Aryati et al. found PPV at 97%.45 Chalurkar reported 83.75%, Abdelazim 83.8%. Nitrazine PPV was 82.2%.[19] Palacio (2014) reported NPV for IGFBP-1 at 100%, meaning all negative results were true negatives. Aryati et al. found 78%, indicating 22% false negatives.50 Chalurkar found 65%, Abdelazim 88.6%. Nitrazine NPV was 85.9%.[19,24]

Aryati et al. (2015) reported true positives for IGFBP-1 at 84.8% and false positives 5.3%.[19] Abdelazim (2013) reported 89.3% true positives and 17.3% false positives. Nitrazine true positives were 86.7% with 19.1% false positives.[24] Aryati et al. reported true negatives IGFBP-1 at 94.7% and false negatives 15.2%.[19] Abdelazim reported 82.7% true negatives and 10.7% false negatives. Nitrazine had 81.3% true negatives and 12.7% false negatives.[24]

Diagnostic accuracy reflects the overall ability of a test to provide correct results (both positive and negative). IGFBP-1 tests have been reported to have higher accuracy than Nitrazine. Olorinoye et al. (2021) reported Nitrazine accuracy of 93.75%, while Bakr et al. (2021) found IGFBP-

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1 accuracy at 87.8%, higher than Nitrazine's 80.0%.[20,26]

5. ROC Curve Analysis

The area under the curve (AUC) for the IGFBP-1 immunoassay test was 1.00, while the nitrazine (litmus) test had an AUC of 0.825. This indicates that the IGFBP-1 immunoassay test has superior sensitivity and specificity compared to the nitrazine test in diagnosing PROM, making it a more accurate diagnostic tool in clinical settings.

CONCLUSION

Based on the study conducted at PONEK RSUP Dr. M. Djamil Padang, the average age of patients with premature rupture of membranes (PROM) was 27.95 ± 6.52 years, consistent with prior research indicating PROM mostly occurs in young reproductive age women (18-35 years). The Immunoassay IGFBP-1 test showed excellent diagnostic performance with 100% sensitivity and specificity, accurately detecting all PROM cases without false positives or negatives, proving it to be a highly reliable tool. In contrast, the Nitrazine test showed 75% sensitivity and 100% specificity, indicating it missed some PROM cases likely due to interference from external factors like infection or contaminants affecting pH interpretation. Overall, the Immunoassay IGFBP-1 test outperformed Nitrazine in accuracy, making it the recommended diagnostic method for PROM, though further studies with larger samples are needed to confirm these findings.

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