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# Study to Evaluate the Efficacy of the Test Detecting IGFBP-1 in the Diagnosis of Premature Rupture of Membranes

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**Abstract:** ***Premature rupture of membranes is a common obstetric concern linked with infection, preterm birth, and fetal risk when diagnosis is delayed or uncertain. This cross-sectional study assessed the diagnostic accuracy of the Actim PROM test, based on insulin-like growth factor binding protein-1, among 60 pregnant women with watery vaginal discharge at BJ Medical College and Civil Hospital, Ahmedabad. Thirty women had clinically confirmed ruptured membranes, while 30 had intact membranes. Actim PROM showed 26 true positive, 29 true negative, 4 false negative, and 1 false positive result. The test showed 86.6% sensitivity, 96.6% specificity, 96.2% positive predictive value, 87.8% negative predictive value, and 91.6% overall accuracy. The results support Actim PROM as a rapid, simple, and useful non-invasive test for diagnosing PROM and guiding timely obstetric care.***

**Keywords:** premature rupture of membranes, Actim PROM, IGFBP-1, pregnancy diagnosis, obstetric care

## 1. Introduction

Premature rupture of membranes (PROM) refers to the rupture of the fetal membranes before the onset of labour, occurring in about 8-10% of term pregnancies (ACOG, 2017)[1]. When this rupture happens before 37 weeks of gestation before the onset of labour, it is known as preterm premature rupture of membranes[1].

Preterm PROM complicates 2-4% of singleton pregnancies and 7-20% of twin pregnancies[2]. PROM contributes to roughly one-third of preterm births and accounts for 18-20% of prenatal deaths, with an increased risk of ascending infection[2]. Histological studies of term membrane rupture sites reveal connective tissue thickening, cytotrophoblast and decidual thinning, and amnion-chorion disruption near the internal cervical os, making them prone to rupture[2]. These changes are driven by the release of phospholipase, prostaglandin E2, cytokines, elastases, matrix metalloproteinases, and other proteases that occur due to physiological or pathological stimuli. While similar processes are seen in preterm PROM, underlying causes likely differ[2].

Given this high incidence of PROM and preterm PROM and its associated complications like preterm labour, infection, chorioamnionitis, abruption, cord prolapse etc. early identification and timely intervention are essential to minimize maternal and fetal morbidity.

Several risk factors for spontaneous PROM have been identified.

**Risk factors for premature rupture of membranes[2]**

**Maternal factors:**

1) PROM in prior pregnancy (16-32% as compared with 4% in women with a prior uncomplicated term delivery).
2) Antepartum vaginal bleeding
3) Chronic steroid therapy
4) 4. Collagen vascular disorders eg: Ehler danlos syndrome, systemic lupus erythematosus
5) Preterm labor
6) Cigarette smoking
7) Abdominal trauma
8) Illicit drugs
9) Anemia
10) Low body mass index
11) Nutritional deficiencies
12) Low socioeconomic status

**Uteroplacental factors**

1) Uterine anomalies
2) Placental abruption
3) Advanced cervical dilatation
4) Prior cervical colonisation
5) Cervical shortening
6) Uterine overdistension
7) Intraamniotic infection
8) Multiple bimanual vaginal examinations

**Fetal Factors:** multiple pregnancy

**Differential Diagnosis**

The differential diagnosis includes urinary incontinence (leakage of urine); increased vaginal discharge, such as normal physiologic discharge or bacterial vaginosis; and cervical mucus(show), indicating the onset of labor[2].

**Diagnosis**

PROM presents a challenging diagnostic issue, as it can be difficult to definitively confirm or rule out ruptured membranes[3]. PROM can lead to both maternal and fetal complications, potentially resulting in morbidity and mortality. Adopting an aggressive interventional approach carries the risk of introducing infection and potential failure of induction if conditions are unfavourable. Conversely, a more passive, observational approach may lead to extended hospital stays. Prolonged PROM increases the risk of

oligohydramnios and cord compression, with a small chance of missing cord prolapse. Additionally, there is evidence that the risk of ascending infection rises over time[3].

PROM is primarily a clinical diagnosis, often indicated by a history of watery vaginal discharge and confirmed through a sterile speculum examination[4]. The traditional, minimally invasive gold standard for diagnosing rupture of membranes (ROM) involves identifying three clinical signs during a sterile speculum exam[2]:

1) Visible pooling of clear fluid in the posterior fornix of the vagina or fluid leakage from the cervical os.
2) An alkaline pH of the cervicovaginal discharge, typically assessed by the nitrazine test, where yellow nitrazine paper turns blue.
3) Microscopic ferning observed in the cervicovaginal discharge after it dries.

The lack of a non-invasive gold standard for diagnosing rupture of fetal membranes has led to the development of several tests based on alternative biochemical markers. These vaginal markers include prolactin, alpha-fetoprotein (AFP), fetal fibronectin, and insulin-like growth factor binding protein-1 (IGFBP-1)[5].

IGFBP-1 is a major protein found in the human decidua and amniotic fluid. In amniotic fluid, it exists as non-phosphorylated and less phosphorylated isoforms, whereas in decidua and maternal serum, highly and less phosphorylated isoforms (phIGFBP-1) predominate. The detection of IGFBP-1 in cervicovaginal secretions can suggest ROM when the clinical diagnosis is unclear. An immunochromatographic strip test has been developed to detect amniotic fluid in the vagina using a monoclonal antibody to IGFBP-1, which identifies the non- and less phosphorylated isoforms present in amniotic fluid, but not the highly phosphorylated IGFBP-1[6].

## 2. Aim and Objectives

To assess the accuracy of the use of insulin-like growth factor binding protein-1 in the prediction of premature rupture of membranes.

## 3. Materials and Methods

**Study Design**:

- Study Type: Observational, cross-sectional study
- Study Site: Department of obstetrics and gynaecology, BJ medical college and civil hospital, Ahmedabad.
- Study Duration: May 2024 to October 2024

**Sample Size:**

The Study included 60 pregnant women with 24 to 42 weeks of gestation complaining of watery discharge. In our study, 60 patients were divided into two groups. In one group, 30 patients with ruptured membranes and liquor draining from the vagina were taken and in the other group, 30 patients with intact membranes and no draining of liquor from the vagina were taken.

**Inclusion and exclusion criteria:**

Participants were included if they had a gestational age between 24 to 42 weeks, a single intrauterine pregnancy, and complaints of watery vaginal discharge. Exclusion criteria were vaginal bleeding (spontaneous or caused by speculum examination), a history of infection (e.g., vaginitis or cervicitis), recent vaginal washing with antiseptics, vaginal intercourse within the previous 48 hours, fetal distress, multiple pregnancies, clinical or investigative evidence of chorioamnionitis (e.g., elevated CRP or abnormal CBC), placenta previa, or the presence of established labour pains.

**Criteria for Using Actim PROM:**

- For cases: Women with clinical evidence of PROM.
- For control: women who are not in labour.

**Method for carrying out Actim PROM:**

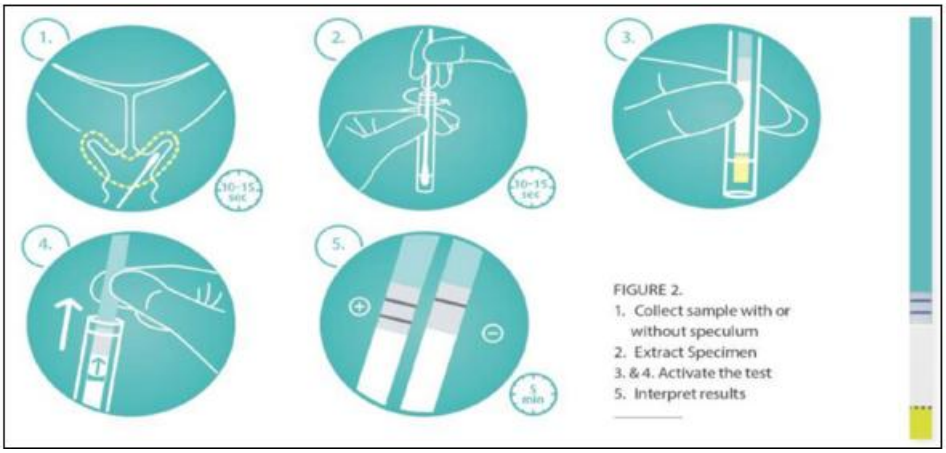


**Figure:** method for carrying out Actim Prom(7)

- A cervical swab is taken during speculum examination using the included polyester swab.
- The swab should be left at the posterior fornix for 10-15 seconds to let the specimen absorb.
- Then place the swab into extraction samples for 10-15 seconds swirling it around and removing it.
- Place the yellow part of the dipstick into the extraction solution until the liquid reaches the result area. Place the dipstick in a horizontal position.

- A Negative result should be read at 5 minutes. And a positive test can be read as soon as two blue lines- a control line and the positive line appear in the result area.

Negative Actim PROM result:

- Women found to be negative using the Actim PROM test will no longer require admission and can be safely discharged home.

Positive Actim PROM Result:

- Women who are pre-term will have targeted interventions according to the duration of pregnancy to improve perinatal morbidity and mortality (antenatal corticosteroids +/-tocolysis)
- Women who are term will be offered induction of labour.

## 4. Results

**Table 1:** Patient's demographic details:

| Table: 1 | Case | Control |
|---|---|---|
| Age | 22.5 Years | 25 Years |
| Parity | 1 | 2 |
| Gestational Age | 33 weeks +/- 5 days | 34 weeks+/- 6 days |
| BMI | 25.5 kg/m$^2$ | 26.4 kg/m$^2$ |

As regards descriptive data of the patient's characteristics: the mean age was found to be 22.5 years in the case group and 25 years in the control group; mean parity among the case group and control group was 1 and 2 respectively; the mean gestational age at premature rupture of membranes occurred was 33 weeks +/- 5 days in case group and 34 weeks +/- 6 days in control group and BMI of patients presented with premature rupture of membranes was 25.5 kg/m$^2$ and 26.4 kg/m$^2$ in case and control group respectively.

**Table 2:** Actim prom test results

| Table: 2 | Case | Control |
|---|---|---|
| Positive | 26 | 1 |
| Negative | 4 | 29 |

Table 1 shows that among 30 cases with ruptured membranes Actim Prom was True positive in 26 cases and false negative in 4 cases. Among 30 controls with intact membranes, Actim Prom was true negative in 29 cases and false positive in 1 case.

## 5. Discussion

Accurate diagnosis of PROM remains a frequent clinical problem in obstetrics[1]. PROM is a frequent diagnostic and therapeutic dilemma in obstetrics[2]. In uncertain cases, the major contaminants of amniotic fluid which have to be considered in the diagnosis or exclusion of ruptured membranes are blood, urine, cervical mucus, vaginal discharge and seminal fluid[2]. A reliable method for detecting amniotic fluid in the vagina is essential for distinguishing it from these non-specific substances[2]. Typically, the diagnosis of PROM is based on the patient's history, identification of gross pooling of amniotic fluid from the cervical canal during a sterile speculum examination, as well as microscopic examination and the Nitrazine test[3].

Accurate diagnosis of PROM is crucial, as missed diagnoses can result in serious obstetric complications like chorioamnionitis and preterm birth, while overdiagnosis may lead to unnecessary interventions, such as hospitalization[3]. The diagnostic approach is primarily clinical, with over 90% of cases confirmed through a suspicious history or ultrasound findings, followed by the observation of fluid passing from the cervix or a positive nitrazine test or vaginal pooling of fluid. Traditional tests for PROM, such as the nitrazine and ferning tests, are commonly used but have limited sensitivity and specificity[1].

The lack of a non-invasive gold standard test for diagnosing rupture of membranes has driven the search for alternative biochemical markers such as vaginal prolactin (PRL), alpha-fetoprotein (AFP), fetal fibronectin, growth hormone (GH), insulin-like growth factor binding protein-1(IGFBP-1), interleukin-6 (IL-6), human placental lactogen (HPL), or combinations of these[8].

During pregnancy, IGFBP-1 is produced in the decidua and found in high concentrations in amniotic fluid and maternal serum. IGFBPs bind strongly to insulin-like growth factors (IGFs), preventing IGFs from attaching to their receptors. Matrix metalloproteinases (MMPs) act as IGFBP proteases, and proteolytic cleavage of IGFBPs by specific MMPs has been documented[2].

This study was a cross-sectional study to determine if the measurement of levels of insulin growth factor binding protein-1(IGFBP- 1) (Actim- PROM) in vaginal fluid were useful for the diagnosis of premature rupture of membranes. In our study of 60 patients, clinically ruptured membranes and cases with liquor draining were observed in 30 patients. Among them, Actim PROM was true positive in 26 cases and false negative in 4 cases. In the remaining 30 patients with intact membranes, Actim PROM was true negative in 29 cases and false positive in 1 case.

The sensitivity and specificity of Actim PROM in diagnosing PROM in this study were 86.6% and 96.6%, respectively. The positive predictive value and negative predictive value of Actim PROM were 96.2% and 87.8%, respectively. The diagnostic accuracy of Actim PROM was 91.6%.

| Studies | Sensitivity | Specificity | Positive predictive value | Negative predictive value | Diagnostic accuracy |
|---|---|---|---|---|---|
| Present study | 86.60% | 96.60% | 96.20% | 87.80% | 91.60% |
| Salah Bakr et. Al.(1) | 89.70% | 86.90% | 76.50% | 94.60% | 87.80% |
| Ramsauer B et. Al.(9) | 73.90% | 77.80% | - | - | - |
| Marcellin L et. Al.(10) | 97.50% | 97.40% | 97.50% | 97.40% | - |
| Erdemoglu E et. Al.(11) | 97% | 97% | - | - | 97% |
| B Martinez et. Al. (12) | 86% | 74% | 73% | 87% | - |

These findings are similar to those of the study conducted by Salah Bakr et al., in which sensitivity and specificity were 89.7% and 86.9%, respectively, and the positive predictive value and negative predictive value were 76.5% and 94.6%, respectively. In contrast, studies conducted by Marcella et al. and Erdemoglu E et al. reported a sensitivity of 97% in both studies. The diagnostic accuracy in our study was 91.6%, which is close to the findings of Ahmed et al., where diagnostic accuracy was 87.8%, but slightly lower than the 97% diagnostic accuracy reported by Erdemoglu E et. Al.

## 6. Conclusion

One-step cervicovaginal IGFBP-1(Actim prom) dipstick was a rapid reliable, non-invasive, easy and accurate diagnostic test for PPROM. Dipstick was easily and rapidly available in all settings without any need for complex laboratory equipment.

## 7. Limitations of the Study

The study had some limitations that could impact how its findings apply to a broader population. With only 60 participants, the small sample size makes it harder to draw conclusions that apply to larger groups. Since it was a cross-sectional study, there wasn't any follow-up over time to check for false negatives or positives. The fact that it was done at a single institution also means the results might not reflect a wide range of clinical settings or patient populations. Additionally, the strict exclusion criteria- like recent vaginal bleeding, infections, or antiseptic washes—might leave outpatients whose conditions could make diagnosing PROM more complex.

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