ORIGINAL ARTICLE

# Detection of PROM with Vaginal Fluid Creatinine Levels: A Prospective Case–Control Study

Anubha Kataria[1], Rajiv K Saxena[2], Sweta Choudhary[3], Krithika Krishna[4]

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## Abstract

**Aim and background:** It is imperative to achieve precise diagnosis of prelabor rupture of membranes (PROM) and preterm prelabor rupture of membranes (PPROM) by recognizing specific amniotic fluid indicators in vaginal environment. The study included assessment of creatinine levels in vaginal fluid along with determining its cut-off value to diagnose PROM/PPROM.

**Methods:** Sixty women with singleton pregnancy of 28 weeks or more period of gestation, were enrolled in the study to be categorized in two equal groups of 30 each. Study group comprised of patients having confirmed PROM and control group included pregnant women with intact membranes. Vaginal fluid samples were collected in a sterile syringe in study patients. In controls, 5 mL of normal (0.9%) saline was instilled into vaginal cavity, and 3 mL of vaginal fluid was collected to be sent for creatinine estimation.

**Results:** The mean value of levels of creatinine in vaginal fluid in study groups was (1.15 ± 0.55 mg/dL) and control groups was (0.15 ± 0.16 mg/dL) showing a significant difference ($p < 0.001$). The value of creatinine in vaginal fluid to detect PROM/PPROM was 0.7 mg/dL, with sensitivity of 86.67% and specificity of 100%. The positive predictive value (PPV) was 100% and negative predictive value (NPV) was 88.24% with an accuracy of 93.33%.

**Conclusion:** Creatinine estimation in vaginal fluid is an easy, reliable, as well as readily available method to diagnose PROM/PPROM.

**Clinical significance:** Accurate diagnosis of PROM/PPROM, using an easily available and reliable method is important to guide the clinical management in high-risk pregnancy.

**Keywords:** Amniotic fluid index, Chorioamnionitis, Prelabor rupture of membrane, Preterm prelabor rupture of membrane, Vaginal fluid creatinine.

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## Introduction

Prelabor rupture of membranes (PROM) denotes rupture of membranes (ROM) before labor begins, and it complicates 8–10% pregnancies beyond 37 weeks. In 3% pregnancies, membranes may rupture earlier than 37 weeks, called premature prelabor rupture of membranes (PPROM).[1,2]

Prelabor rupture of membranes is associated with obstetric complications like oligohydramnios, prematurity, chorioamnionitis, perioperative morbidity, perinatal infections, septicemia, cord prolapse, increased chances of operative interference, and placental decollement.[3] The preterm neonates also are at a high risk of developing serious complications like respiratory distress, pulmonary hypoplasia, pneumonia, necrotizing enterocolitis, meningitis, intraventricular hemorrhage and periventricular leukomalacia.[4]

Diagnosis of ROM relies mainly on history and clinical examination findings. On examination, fluid accumulation observed on speculum in the posterior vaginal fornix, leads to a presumptive clinical diagnosis of ROM. However, it may also have false-negative rate between 12 and 30% for PROM. Other conventional tests used to confirm ROM include 'Nitrazine test' where pH indicator paper containing nitrazine dye changes color from yellow to blue, due to basic nature of the amniotic fluid. Another test involves microscopic examination of vaginal fluid to see amniotic fluid crystallization on a dry glass slide in a fern like pattern, with both false-negative (13–30%) and false-positive (5–30%) results. The accuracy of nitrazine test is lower when urine, blood, or meconium contaminates the amniotic fluid. An ultrasound examination demonstrating oligohydramnios is also not a specific indicator of ROM due to the possibility of low amniotic fluid index (AFI) in other obstetric complications or fetal syndromes.[5,6] Invasive test, like the intra-amniotic injection of dye is not recommended due to high risk of fetomaternal complications.[7]

Newer test 'Amnisure' is noninvasive and simple to perform with good specificity and sensitivity rates. This test spots Placental Alpha Microglobulin – 1 in cervicovaginal secretions.[8] Certain other biomarkers like human chorionic gonadotropin (hCG), fetal fibronectin (fFN), prolactin, alpha fetoprotein (AFP), amniotic fluid interleukin-8 (IL-8), monoclonal or polyclonal antibody immunoassay tests, insulin-like growth factor binding protein-1 (IGFBP-1), and placental protein 14 (PP14) have been tested for detection of amniotic fluid in suspected ROM. The rationale is based on the etiopathogenesis of ROM which involves processes like collagen disruption, cellular death in the membranes under the

[1]Department of Obstetrics and Gynaecology, Dr. B.R. Ambedkar Medical College Hospital, Bengaluru, Karnataka, India

[2–4]Department of Obstetrics and Gynecology, The Oxford Medical College, Hospital and Research Centre, Bengaluru, Karnataka, India

**Corresponding Author:** Anubha Kataria, Department of Obstetrics and Gynaecology, Dr. B.R. Ambedkar Medical College Hospital, Bengaluru, Karnataka, India, Phone: +91 8722083509, e-mail: anubhakataria@gmail.com

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influence of proinflammatory mediators. This may lead to higher concentration of the above-mentioned markers in the amniotic fluid. However, these methods are not being routinely used due to their high cost and complexity, and nonavailability and are still in the realm of a research setting.[9]

Undiagnosed PROM may adversely affect maternal and neonatal outcomes. 'Over-diagnosis' may also lead to unnecessary interventions and iatrogenic obstetric and neonatal complications. These include preterm birth, anxiety, inconvenience due to frequent visits to the hospital, unnecessary investigations, and high healthcare cost.[10]

The ROM detection becomes difficult when patients do not present with classical symptoms or signs suggestive of frank leaking or sudden gush of fluid from vagina. Some patients may have profuse or intermittent leakage, bleeding, or simply have a history of suspicious leaking (20–25%).[7,11,12] A test that is accurate, reliable, non-invasive, cost-effective, convenient, rapid, and easily available is desirable.

Amniotic liquor, maternal serum as well as maternal urine contain large amounts of creatinine. In amniotic fluid, mean value of creatinine is 0.6 mg/dL, until 20 weeks of pregnancy, which is equivalent to maternal serum concentration. Amniotic fluid creatinine levels then rise with gestational age, and beyond 32 weeks of gestation, amniotic fluid creatinine has 2–4-fold higher concentration than in maternal blood. Creatinine level is 1.75 mg/dL at or beyond 37 weeks.[13,14] Hence, creatinine in vaginal fluid is a significant marker for conclusion of ROM.

Another consideration is the low cost of vaginal fluid creatinine test. While creatinine estimation is done free of cost in most government hospitals all over India, it will cost anywhere from INR 100 to 250 in private laboratories. In our medical institute, the cost of each test is INR 50, which is much cheaper than any of the newer tests available for ROM. The test is a simple calorimetric test, and easily available in most of the laboratories in India.

We carried out the study to assess the validity of creatinine in vaginal fluid for ROM diagnosis.

## Methods

We carried out a hospital-based time bound prospective comparative study in the Department of Obstetrics and Gynecology, at The Oxford Medical College, Hospital and Research Centre, Bengaluru, India, over a duration of 6 months from June 2022 to November 2022.

Using a non-probability (purposive) sampling method, we included 60 patients admitted to our hospital labor room in this study. We included all women with single fetus at more than 28 weeks in the study. However, patients with pre-eclampsia, renal or hepatic disease, anomalous fetus, intrauterine fetal demise, meconium, or blood-stained liquor were excluded from the study.

Based on findings by Tigga and Malik standard deviation for creatinine level in the study was taken as 0.06 mg/dL.[15] The sample size for our study was calculated as follows:

$$n = \frac{(Z_\alpha + Z_\beta)^2 \times \sigma^2}{d^2}$$

The following values were used to calculate the sample size: $d = 2.9$; $\alpha = 0.05$; $Z_\alpha = 1.96$; $\beta = 0.80$; $Z_\beta = 0.84$; *SD* or $\sigma = 0.06$.

$n = (1.96 + 0.84)^2 \times (0.06)^2/(0.032)^2 = 29$

Our study had two groups: 'Study group' – comprising of clinically confirmed ROM and a 'Control group' – comprising of pregnant women with intact membranes on clinical examination.

Sample size for the study group was calculated as 29. Hence, 30 women were enrolled in each group. All participants consented to participate in the study.

History was taken in detail with leading questions related to ROM. After a thorough examination, patients underwent transabdominal sonography to determine gestational age, fetal viability, and AFI. In control group patients, instillation of 5 mL of sterile saline into the vagina was done with a syringe, and 3 mL of the same fluid was then collected and sent to laboratory for evaluation of creatinine level. In study group participants, ROM was confirmed by visualizing pool of fluid in vagina on examination with sterile speculum. In these patients, 3 mL of liquor leaking through os was directly collected in a syringe. The sample was centrifuged (10 min at 1500 rpm) before sending to the laboratory for creatinine value estimation.

Creatinine levels were estimated using Jaffe chemical calorimetric method. Patients were followed up further for mode of delivery, maternal and neonatal outcomes including any intranatal, postnatal, or neonatal complications.

### Statistical Analysis

The quantitative variables were analyzed with independent *t*-test and described as mean value and standard deviation. To analyze the categorical variables, Chi-square test was used and variables were described as number and percentage. The SPSS (version 18) was used for statistical calculation. Receiver operating characteristics (ROC) curve was plotted to get cut-off values of creatinine levels in vaginal fluid to predict PROM. The sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) were determined using 2 × 2 contingency table. Statistical significance was taken as $p < 0.05$.

## Results

Demographic data for both groups has been given in Table 1. No statistically significant difference was observed in demographic data among the two groups.

The comparison between creatinine values in vaginal fluid between both groups is shown in Table 1. The mean value of creatinine in study patients was 1.15 ± 0.55 mg/dL and controls was 0.15 ± 0.16 mg/dL. Mean value of creatinine in ROM patients was significantly higher ($p < 0.001$). The area under ROC was 0.947 (Fig. 1), with >0.7 mg/dL as the value of creatinine in vaginal fluid for ROM diagnosis. This cut-off value showed high sensitivity (86.67%) and specificity (100%). The PPV was 100% and NPV was 88.24% with an accuracy of 93.33%.

In our study group, the mean AFI value (11.62 ± 2.48 cm) was significantly lower than mean AFI value (13.67 ± 4.42 cm) in control group ($p = 0.03$) (Table 1).

Table 2 shows mean creatinine value in vaginal fluid with gestational age and duration of leaking in study group. Pearson correlation between gestational age and vaginal fluid creatinine values was 0.285 in study patients and 0.066 among controls, which was statistically not significant. Pearson correlation between duration of leaking and vaginal fluid creatinine values in study group was found to be negative (–0.804), which was statistically significant.

The patients were followed up for fetomaternal outcomes (Table 3). Both study and control groups had 9 ($n = 30$) vaginal

**Table 1:** Demographic features, vaginal fluid creatinine values and AFI values in both groups

| *Parameters* | *Study (n = 30)* | *Control (n = 30)* | *p-value* |
|---|---|---|---|
| Demographic features | | | |
| Age (years) | | | |
| <25 | 13 (43.3%) | 12 (40%) | 0.927 |
| 26–30 | 13 (43.3%) | 13 (43.3%) | |
| >30 | 4 (13.3%) | 5 (16.7%) | |
| Mean | 26.03 ± 4.47 | 26.20 ± 4.86 | 0.890 |
| Parity | | | |
| Primigravida | 17 (56.7%) | 12 (40%) | 0.196 |
| Multigravida | 13 (43.3%) | 18 (60%) | |
| Gestational age (weeks) | | | |
| 34–37 | 6 (20%) | 8 (26.7%) | 0.542 |
| 38–42 | 24 (80%) | 22 (73.3%) | |
| Mean | 38.53 ± 1.25 | 38.27 ± 1.41 | 0.442 |
| Vaginal fluid creatinine value (mg/dL) | | | |
| Mean | 1.15 ± 0.55 | 0.15 ± 0.16 | <0.001 |
| AFI (cm) | | | |
| Mean | 11.62 ± 2.48 | 13.67 ± 4.42 | 0.031 |

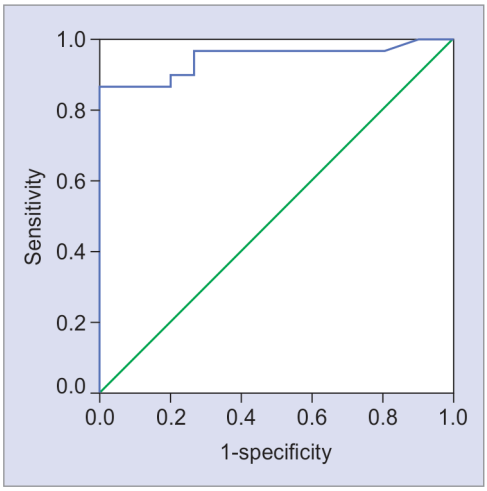


**Fig. 1:** ROC Curve analysis for determination of optimum cut-off values of vaginal fluid creatinine for detection of PROM

deliveries and 21 ($n = 30$) cesarean deliveries. The outcome in terms of mode of delivery was similar in the two groups. The mean birth weight of neonates in study group (2.96 ± 0.40 kg) was more as compared with the control group (2.78 ± 0.29 kg), with significant difference ($p = 0.04$). The neonatal intensive care unit (NICU) admissions in both groups showed no significant difference ($p = 0.24$). Patients in study group with ROM showed a higher number of fetal complications (46.7%) than in control group (36.7%), but this difference did not have statistical significance ($p = 0.38$).

**Table 2:** Gestational age and duration of PROM correlation with vaginal fluid creatinine values

| *Vaginal fluid creatinine (mean values) (mg/dL)* | | |
|---|---|---|
| *Gestational Age (weeks)* | *Study (n = 30)* | *Control (n = 30)* |
| 34–37 | 0.55 ± 0.46 | 0.12 ± 0.11 |
| 38–42 | 1.30 ± 0.46 | 0.20 ± 0.23 |
| Pearson correlation | 0.285 | 0.066 |
| *p*-value | 0.127 | 0.729 |
| *Duration of PROM [study (n = 30)]* | | |
| *Duration of leak (hours)* | *Vaginal fluid creatinine (mg/dL)* | |
| <12 hours | 1.55 ± 0.30 | |
| >12 hours | 0.66 ± 0.34 | |
| Pearson correlation | −0.804 | |
| *p*-value | <0.001 | |

**Table 3:** Neonatal outcomes and fetal complications

| *Outcomes* | *Study (n = 30)* | *Control (n = 30)* | *p-value* |
|---|---|---|---|
| Mode of delivery | | | |
| Vaginal delivery | 9 (30%) | 9 (30%) | 1 |
| LSCS | 21 (70%) | 21 (70%) | |
| Gender | | | |
| Male | 17 (56.7%) | 16 (53.3%) | 1 |
| Female | 13 (43.3%) | 14 (46.7%) | |
| Birthweight | | | |
| Mean (kg) | 2.96 ± 0.40 | 2.78 ± 0.29 | 0.042 |
| NICU admission | | | |
| Yes | 10 (33.3%) | 6 (20.0%) | 0.243 |
| No | 20 (66.7%) | 24 (80.0%) | |
| Fetal complications | | | |
| Fetal distress | 10 (33.3%) | 4 (13.3%) | 0.378 |
| Meconium-stained liquor | 3 (10%) | 2 (6.67%) | |
| Fetal growth restriction | 0 | 4 (13.3%) | |
| Death | 1 (3.33%) | 1 (3.33%) | |
| Total | 14 (46.7%) | 11 (36.7%) | |

## Discussion

In our study, we found statistically higher levels of creatinine ($p < 0.001$) among study patients (1.15 + 0.55 mg/dL) as compared with controls (0.15 + 0.16 mg/dL). The diagnostic value of 0.7 mg/dL of vaginal fluid creatinine for ROM, had sensitivity of 86.67% and specificity of 100%. The PPV was 100% and NPV was 88.24%, with an accuracy of 93.33%.

Gaied et al. conducted a prospective study from 2013 to 2015 on 90 women within 28–42 weeks.[16] Study had three groups of 30 each: confirmed ROM, suspected ROM, and a control group with no ROM. The study showed a significant difference in mean creatinine levels among three groups ($p < 0.001$). The mean creatinine value

in confirmed ROM group was 0.64 ± 0.018 mg/dL, suspected ROM group was 0.28 ± 0.013 mg/dL, and controls was 0.14 ± 0.006 mg/dL. They reported cut-off value of vaginal creatinine as 0.52 mg/dL as a diagnostic marker for ROM, with sensitivity of 98%, specificity of 45%, the PPV was 40%, and NPV was 100% with an accuracy of 60%.[16]

In another cross-sectional, hospital-based study of 90 pregnant women, Pani et al., reported a creatinine value of 0.2 mg/dL in vaginal fluid for the ROM detection, with sensitivity as well as specificity of 100%.[17] Another prospective study of 100 antenatal women, by Begum et al., reported mean value of creatinine as 0.67 ± 0.3 mg/dL in vaginal fluid among ROM group and 0.16 ± 0.09 mg/dL among controls ($p < 0.001$).[5] The value of creatinine in vaginal fluid in the study was 0.3 mg/dL for diagnosis of ROM. This result showed sensitivity of 90% and specificity of 93.83%, the PPV was 97.83%, while the NPV was 90.74%, with an accuracy of 94%.[5] Ghasemi et al. conducted a study in 2013 with 160 pregnant women in Iran.[18] Mean creatinine values in vaginal fluid were 0.86 ± 0.68 mg/dL in ROM and 0.20 ± 0.16 mg/dL in control group ($p < 0.001$). The value of creatinine to diagnose ROM was 0.25 mg/dL, with sensitivity of 74.6%, specificity of 85%, PPV of 83% and NPV of 77.2%.[18] Tigga and Malik found that creatinine values in vaginal fluid were significantly elevated in cases with confirmed ROM.[15] Mean value of creatinine in confirmed ROM and control group was 0.26 ± 0.066 mg/dL and 0.09 ± 0.0414 mg/dL, respectively, with sensitivity as 100% and specificity as 92%. The PPV and NPV were 92.59 and 100%, respectively, with an accuracy of 96%.[17] Comparable findings were recorded by Abhilash et al. with a value of >0.34 mg/dL of creatinine in vaginal fluid for ROM detection showing sensitivity of 100% and specificity of 100%; whereas PPV and NPV were 96% and 100%, respectively.[19]

Ramasamy and Vijayaraghavan divided 300 pregnant women into three equal groups ($n = 100$) as cases with ROM, cases with suspected ROM and controls.[20] The value of creatinine in ROM diagnosis was recorded as >0.3 mg/dL with sensitivity of 98.36%, specificity of 100%, PPV of 100%, and NPV of 97.14%.[20] Table 4 displays cut-off values of creatinine in vaginal fluid reported in various Indian studies along with their sensitivity, specificity, PPV, and NPV values.

Mean AFI value in our study was statistically lower ($p = 0.031$) in ROM group (11.62 ± 2.48 cm) as compared with the control group (13.67 ± 4.42 cm). Pani et al., reported mean AFI in confirmed cases, suspected cases and controls as 4.6 ± 1.2 cm, 4.3 ± 1.6 cm and 10 ± 1.7 cm, respectively, thereby showing lower AFI values in confirmed and suspected ROM cases.[17] However, AFI levels may not be a reliable indicator of ROM due to intermittent leakage or even cessation of leakage due to the descent of the presenting part. Begum et al. published that AFI was statistically low among controls in comparison to ROM group. Mean values of AFI in the control and ROM groups were 8.41 ± 2.91 cm and 9.56 ± 2.61 cm, respectively ($p = 0.04$).[5]

The present study did not show significant correlation of creatinine value with gestational age in either group ($p = 0.127$, 0.729). The 2023 study by Deshpande et al. included 140 women with ROM and 140 women with no leak.[21] They too reported no correlation between creatinine values in vaginal fluid and gestational age.

Our study found a negative correlation between the level of creatinine and duration of vaginal leaking, with a coefficient of −0.804 ($p < 0.001$). This implies that vaginal fluid creatinine levels were comparatively lower in patients with longer duration of leak. This was probably because creatinine was 'washed-off' over the prolonged duration of leaking, and the vaginal washings yielded lower values. Tigga and Malik studied 50 women with PROM, duration of PROM was >24 hours in 12 women and <24 hours in 38 women.[15] The level of vaginal fluid creatinine showed a negative correlation with the duration of leak (correlation coefficient – 0.627) which was statistically highly significant ($p < 0.001$).[15]

We recorded a significant difference in mean birth weights among both groups.[22,23]

However, other neonatal outcomes and fetal complications were comparable in both groups in our study.

## Conclusion

Rupture of membranes continues to be a threat to maternal and neonatal outcome due to its difficult diagnosis in cases without classical symptoms or signs. Multiple modalities have been introduced for diagnosis of ROM. However, many of these methods are cost-ineffective and/or unavailable especially in low resource settings. Creatinine level estimation in vaginal fluid is a reliable, easily available, cost-effective method which is also simple to perform. Hence, it may be used effectively to diagnose ROM and manage patients accordingly.

### Ethical Approval

This study was given approval by the ethics committee of the institute.

**Table 4:** Vaginal fluid creatinine cut-off values in Indian studies

| *Authors* | *Study population* | *Cut-off mg/dL* | *Sensitivity* | *Specificity* | *PPV* | *NPV* |
|---|---|---|---|---|---|---|
| Madhavi and Himavarshini[3] | 100 | >0.3 | 99.89% | 100.0% | 100% | 97.70% |
| Begum et al.[5] | 100 | >0.3 | 90% | 93.83% | 97.8% | 90.74% |
| Pani et al.[17] | 90 | >0.2 | 100% | 100% | 98.3% | 98.3% |
| Tigga and Malik[15] | 100 | >0.16 | 100% | 92% | 92.59% | 100% |
| Abhilash et al.[19] | 100 | >0.34 | 100% | 100% | 100% | 96% |
| Ramasamy and Vijayaraghavan[20] | 300 | >0.3 | 98.36% | 100% | 100% | 97.14% |
| Deshpande et al.[21] | 280 | >0.6 | 96.1% | 100% | 100% | 96.3% |
| Present study (2022) | 60 | >0.7 | 86.67% | 100% | 100% | 88.24% |

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