Comparison of Vaginal Fluid Creatinine for the Diagnosis of Premature Rupture of Membranes (PROM)

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Abstract

Background : Premature rupture of membranes (PROM) is a common obstetric complication, contributing significantly to maternal and neonatal morbidity and mortality. Timely and accurate diagnosis is critical to guide appropriate management and reduce adverse outcomes. Traditional diagnostic methods such as the nitrazine test, fern test, and pooling are limited by their subjectivity and susceptibility to false results. Therefore, the search for a reliable, rapid, and cost-effective diagnostic marker continues. Creatinine, a constituent of amniotic fluid, is present in higher concentrations than in vaginal secretions. Measurement of vaginal fluid creatinine has emerged as a promising alternative for confirming PROM due to its biochemical specificity and ease of testing.

Objective :This study evaluates vaginalfluidcreatininelevel inconfirmedcaseofPROMand women without PROM, sensitivityandspecificityofvaginalfluidcreatinine indiagnosisofPROMAnd maternalandfetaloutcome in womeeen with PROM.

Materials and Methods: A Cross-sectional analytical study was conducted from january 2023 to March 2025 at Dept. of Obstetrics and Gynecology, Dr. BRAM Hospital, Raipur (C.G),involving128 pregnant women (64 PROM, 64 controls) between 28-40 weeks gestation. Creatinine levels in vaginal fluid were measured using the Jaffe method.

Result: Thestudyevaluatedvaginalfluidcreatinineasadiagnostictoolfor PROMand determinedacut-offvalueof> 0.3mg/dL,yieldingasensitivityof89.1%anda specificityof87.5%.

Conclusion:Vaginal fluid creatinine is a simple,rapid,cost effective and non-invasive test that may aid in the timely and accurate diagnosis of PROM,specially in low resources settings.

Keywords:PROM, vaginal fluid creatinine, diagnosis, Jaffe method, obstetrics

1. Introduction

Premature rupture of membranes (PROMs) constitutes one of the most important dilemmas which are difficult to diagnose in obstetric practice. Premature rupture of membranes (PROM) is **defined** as the spontaneous rupture of fetal membranes before the onset of labor.[1] When this occurs before 37 week of gestation, it is referred to as preterm premature rupture of membranes (PPROM)[1]. PROM occur in 10% of all term pregnancies and about 2-4% of preterm pregnancies, it's complicates approximately **8–10%** of all pregnancies, while PPROM occurs in about **3%** of pregnancies and is associated with significant maternal, fetal, and neonatal risks, including chorioamnionitis, umbilical cord prolapse, preterm birth, and neonatal sepsis (American College of Obstetricians and Gynecologists [ACOG], 2020).[2]

PROM is associated with a wide range of maternal and neonatal complications, including chorioamnionitis, umbilical cord prolapse, preterm labor, neonatal sepsis, and increased rates of cesarean section, thereby making its accurate and timely diagnosis critical.

Traditionally, PROM has been diagnosed using clinical methods such as sterile speculum examination, the nitrazine test, and the ferning test. However, these tests have certain limitations. The nitrazine test is prone to false positives due to contamination with blood, semen, or urine, while the ferning test can be subjective and heavily dependent on the skill of the examiner. Although advanced biochemical tests like insulin-like growth factor binding protein-1 (IGFBP-1) and placental alpha microglobulin-1 (PAMG-1) offer greater diagnostic accuracy, their high cost and limited availability restrict routine use in many clinical settings.

Vaginal fluid creatinine estimation has emerged as a promising, inexpensive, and easily accessible alternative diagnostic marker. Creatinine is present in high concentrations in amniotic fluid due to its fetal renal origin, particularly in the second and third trimesters when fetal urine is the main contributor to amniotic fluid. Its detection in vaginal fluid can therefore serve as a reliable indicator of membrane rupture.

This study was undertaken to evaluate the diagnostic utility of vaginal fluid creatinine in suspected cases of PROM and to correlate its findings with maternal and perinatal outcomes, aiming to provide an efficient, cost-effective, and accessible tool for clinical use.

2.Objectives

2.1 Primary objective:-To determine and compare vaginal fluid creatinine levels in women with and without PROM.and to assess the sensitivity and specificity of vaginal fluid creatinine in diagnosing PROM.

2.2 Secondary objective: To analyze maternal and fetal outcomes associated with PROM.

3.Materials and Methods

StudyDesign:Cross-sectionalanalyticalstudy.
Location: Dept. of Obstetrics and Gynecology, Dr. BRAM Hospital, Raipur (C.G).
Duration:1year
Subjects: 128 pregnant women (64 PROM, 64 controls) between 28-40 weeks gestation.

Inclusion Criteria:

Singleton pregnancy
gestational age 28–40 weeks
Willing to participate

Exclusion Criteria:

Multiple gestation, vaginal bleeding, anomalies, infections, or recent vaginal drug use. Detailedhistoryincludingpersonalhistory asname,age,occupation,addressand addictions.Historyofpresentpregnancyincludingaconstantvaginalfluid leakageor asensationofwetnesswithinthevaginaortheperineum,directabdominaltrauma, lowerabdominalpain,andanypainlessfreshbleeding.Menstrualhistoryaslast menstrualperiodtocalculateexpecteddateofdeliveryandgestationalage.Obstetric historyincludingparity,modeofpreviousdelivery,previoushistoryofpretermlabor orPPROM.Pasthistoryforanycomorbidities,bloodtransfusions,allergytodrugs,and surgeries. Familyhistoryfordisorders(hypertension,diabetesmellitus),consanguinity, congenitalfetalmalformations.

3.1 Methodology:

Detailed patient histories were recorded, including obstetric and medical backgrounds. All participants underwent general and obstetric examination, including sterile speculum examination to collect vaginal fluid.

A 5 ml sterile saline wash was introduced into the posterior vaginal fornix, and 3 ml of the pooled fluid was aspirated and sent for biochemical analysis. Vaginal fluid creatinine was measured using the RATE JAFFE method, where creatinine reacts with alkaline picrate forming a red complex read at 520 nm and 560 nm.

The sensitivity and specificity of vaginal fluid creatinine in diagnosing PROM were evaluated and maternal-fetal outcomes were analyzed.

4. Results

Table1:Distribution of AgeGroup, Gestational Age and Mode of Delivery AmongPROMandNon-PROMPatients.

Parameter	PROM Group(n=64)	Non-PROM Group(n=64)	P value
Age Group			
<20 Year	18(28.1%)	8(12.5%)	0.037
20-25 Year	16(25.0%)	22(34.4%)	0.156
25-30 Year	14(21.9%)	20(31.3%)	0.294
30-35 year	16(25.00%)	14(21.9%)	0.693
Gestational Age(Week)			
<37 Week(Preterm)	33(52%)	10(15.6%)	0.004
37-40 Week(Term)	25(39.1%)	42(65.6%)	
>40 Week(Post Term)	6(9.3%)	12(18.8%)	
Mode of delivery			0.034
C-Section	40(62.5%)	28(43.8%)	
Vaginal Delivery	24(37.5%)	36(56.2%)	

Age Distribution

The incidence of PROM was significantly higher in women aged <20 years (28.1%). The most affected age groups among PROM cases were <20 and 30–35 years (25%). In contrast, the non-PROM group showed the highest numbers in the 20–30 age range. The difference in age distribution was statistically significant (p = 0.037).

Gestational Age

Preterm delivery (<37 weeks) was significantly more common in the PROM group (52%) compared to the non-PROM group (15.6%). PROM cases also had fewer term and post-term deliveries (p = 0.004), reinforcing the link between PROM and preterm labor.

Mode of Delivery

Cesarean section was performed more frequently in PROM cases (62.5%) compared to non-PROM cases (43.8%), indicating a significant association ($p < 0.05$).

Table2:DistributionMaternalComplications and WBC count ,NeonatalOutcomeandBirthWeightinPROMvs.Non-PROM

Maternal Complication	PROM(n=64)	Non-PROM(n=64)	P-Value
Infections	4(6.25%)	0(0%)	0.005
Puerperal Sepsis	6(9.38)	1(1.56%)	0.05
Postpartum Hemorrhage	5(7.8%)	3(4.7%)	0.47
Fever	19(10.9%)	3(3.1%)	0.08
No Complication	30(46.9%)	57(85.9%)	<0.001
WBC Count			
<15,000mm^3	20(31.2%)	50(78.1%)	<0.001
15,000-20,000mm^3	24(37.5%)	10(15.6%)	
20,000-25,000mm^3	12(18.8%)	3(4.7%)	
>25,000mm^3	8(12.5%)	1(1.6%)	
Neonatal Outcome			
Healthy	44(68.8%)	55(85.9%)	0.023
NICU Admission	8(12.5%)	7(10.9%)	
Still Birth	7(10.9%)	0(0.0%)	
Death	5(7.8%)	2(3.1%)	
Birth Weight (kg)			
<1.5	6(9.4%)	1(1.6%)	
1.5-2.0	12(18.8%)	4(6.3%)	

2.0-2.5	15(23.4%)	9(14.1%)	0.003
2.5-3.0	21(32.8%)	26(40.60%)	
>3.0	10(15.6%)	24(37.5%)	

Maternal Complications

Infections (6.25%), puerperal sepsis (9.38%), and fever (10.9%) were more common in the PROM group. The PROM group also had significantly fewer women without complications (46.9% vs. 85.9%, $p < 0.001$).

WBC Count

Higher WBC counts were noted in the PROM group, with 68.75% having counts above 15,000/mm³ compared to 21.87% in the non-PROM group ($p < 0.001$), suggesting infection or inflammation.

Neonatal Outcome

PROM was associated with more stillbirths (10.9%) and neonatal deaths (7.8%). NICU admission was also higher in the PROM group (12.5% vs. 10.9%). Overall, adverse neonatal outcomes were significantly associated with PROM ($p = 0.023$).

Birth Weight

The PROM group had significantly lower mean birth weights (2.34 ± 0.52 kg) compared to the non-PROM group (2.79 ± 0.48 kg) ($p = 0.003$).

TableNo.3:DistributionofVaginalFluidCreatinineinPROMstudyparticipant

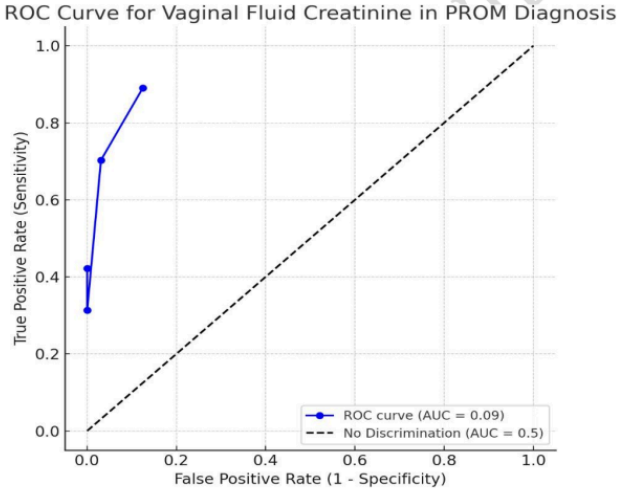
Vaginal Fluid Creatinine (mg/dL)	Non-PROM (n=64)	PROM (n=64)	Total (n=128)	Chi-Square (p-value)
0.11 – 0.20	24 (37.5%)	5 (7.8%)	29 (22.7%)	$\chi^2 = 19.47$, $p < 0.001$
0.21 – 0.30	32 (50.0%)	2 (3.1%)	34 (26.6%)	$\chi^2 = 41.18$, $p < 0.001$
0.31 – 0.40	6 (9.4%)	12 (18.8%)	18 (14.1%)	$\chi^2 = 2.34$, $p = 0.126$
0.41 – 0.50	2 (3.1%)	18 (28.1%)	20 (15.6%)	$\chi^2 = 15.25$, $p < 0.001$
0.51 – 0.60	0 (0.0%)	7 (10.9%)	7 (5.5%)	$\chi^2 = 7.79$, $p = 0.005$
> 0.60	0 (0.0%)	20 (31.3%)	20 (15.6%)	$\chi^2 = 22.98$, $p < 0.001$
Total	64 (100.0%)	64 (100.0%)	128 (100.0%)	$\chi^2 = 92.39$, $p < 0.001$

Thepresentstudyevaluatedthediagnosticutilityofvaginalfluidcreatinine concentrationforidentifyingprematureruptureofmembranes(PROM). Asubstantialproportionof**non-PROMpatients(87.5%)**hadcreatininelevelsbelow **0.30mg/dL**,whereasonly**10.9%**ofPROMpatientsfellintothisrange.**50%of non-PROMpatients**hadlevelsbetween**0.21–0.30mg/dL**,comparedtojust**3.1%**of PROMcases(**p<0.001**),suggestingthatlowervaginalfluidcreatinineconcentrations arestronglyassociatedwiththeabsenceofmembranerupture. Conversely,highercreatininelevelswerepredominantlyseenin thePROMgroup. Notably,**31.3%ofPROMcases**hadcreatininevalues**greaterthan0.60mg/dL**,while nonon-PROMpatientexhibitedlevelsabove0.50mg/dL(**p<0.001**).Thissharp contrastindicatesthatelevatedvaginalcreatinineconcentrationsarehighlyspecific for PROM.Levelsinthe**0.41–0.50mg/dL**and**0.51–0.60mg/dL**rangesalsodemonstrated significantassociationswithPROM,furthersupportingthistrend(**p<0.001andp= 0.005**, respectively). Interestingly,inthe**0.31–0.40 mg/dL**range, the distribution between PROM (18.8%) andnon-PROM(9.4%)patientsdidnotreachstatisticalsignificance(**p=0.126**), possiblyindicatingadiagnostic“grayzone”wherethecreatinineconcentrationalone maynotbedefinitivefordiagnosingPROM.

TableNo.4: VaginalFluidcreatininesensitivity,specificity,PPV,NPV

Creatinine Cut-off (mg/dL)	TP (PROM)	FN (PROM)	FP (Non-PROM)	TN (Non-PROM)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
≥ 0.31	57	7	8	56	89.1%	87.5%	87.7	88.9
≥ 0.4	45	19	2	62	70.3%	96.9%	95.7	76.5
≥ 0.5	27	37	0	64	42.2%	100.0%	100.0	63.4
≥ 0.6	20	44	0	64	31.3%	100.0%	100.0	59.3

A significantly higher proportion of PROM cases had vaginal fluid creatinine levels ≥0.31 mg/dL (sensitivity: 89.1%, specificity: 87.5%, accuracy: 93%). This was statistically significant ($p < 0.001$), suggesting strong diagnostic utility. ROC curve analysis confirmed excellent diagnostic accuracy (AUC ≈ 0.92).



AReceiverOperatingCharacteristic(ROC)curvewasplottedusingthesensitivityandspecificity valuesofvaginalfluidcreatinineatvariousdiagnosticthresholds(≥0.31, 0.4,0.5,and0.6mg/dL)forthedetectionofPrematureRuptureofMembranes (PROM).The ROC curve visuallyrepresents thediagnosticperformanceofthetestby plottingthetruepositiverate(sensitivity)againstthefalsepositiverate(1−specificity)

foreachcutoffvalue.**basedonROCanalysis,theoptimalcutoffvalueforvaginal fluidcreatinine inthediagnosis ofPROM is≥ 0.31 mg/dL.**

Thecurvedemonstratedgooddiagnosticaccuracy,withanareaunderthecurve**(AUC) ofapproximately0.92.AnAUCcloserto1.0** indicatesexcellentdiagnosticability.he highAUCinthiscasesuggeststhatvaginalfluidcreatinineisastrongmarkerforthe diagnosisofPROM.odeterminetheoptimaldiagnosticthreshold,Youden'sIndex (Sensitivity+Specificity−1)wascalculatedforeachcutoff.ThehighestYouden's Indexwasobservedatacreatininecutoffof≥0.31mg/dL,yieldinga**sensitivityof 89.1%**and**specificityof87.5%.**Thisindicatesthatthisthresholdprovidesthebest balancebetweendetectingtruePROMcasesand minimizingfalse positives.herefore, basedonROCanalysis,theoptimalcutoffvalueforvaginalfluidcreatinineinthe diagnosisofPROMis**≥0.31 mg/dL**.

5.Discussion

This study aimed to evaluate the diagnostic utility of vaginal fluid creatinine levels in distinguishing between PROM and non-PROM cases among 128 pregnant women. The study observed statistically significant associations between PROM and several factors, including maternal age <20 years, unbooked antenatal status, preterm gestational age.

Maternal age was significantly associated with PROM, particularly in women younger than 20 years and those ≥35 years. Nutritional deficiencies, genitourinary infections, and cervical immaturity may contribute to membrane rupture in these groups. These findings align with studies by Meis PJ, Cleary-Goldman J, and Singh D et al., though some studies report no association.

Preterm delivery was significantly associated with PROM, with the PROM group delivering on average at 36.78 weeks vs. 38.27 weeks in non-PROM. This aligns with Mercer BM, Parry & Strauss, and Tavana et al., highlighting PROM as a major risk factor for preterm birth.

Cesarean section rates were significantly higher in the PROM group (62.5%) due to fetal distress, infection, or failed induction. Similar trends were reported by Sharma et al. and Deshmukh et al.

PROM was also significantly associated with higher maternal WBC counts, indicating infection. This parallels Mercer, Gibbs, and Yoon's findings. Vaginal swab culture positivity was notably higher in PROM cases (46.8%), affirming risk of ascending infection.

Adverse neonatal outcomes, including low birth weight, NICU admission, and stillbirths, were significantly higher in PROM. The average birth weight was significantly lower in the PROM group (2.34 kg vs. 2.79 kg). These findings are supported by Mercer, Okeke, and Yudin. higher proportion of PROM cases had vaginal fluid creatinine levels ≥0.31 mg/dL (sensitivity: 89.1%, specificity: 87.5%, accuracy: 93%). This was statistically significant ($p < 0.001$), suggesting strong diagnostic utility. ROC curve analysis confirmed excellent diagnostic accuracy (AUC ≈ 0.92).Similar trend were reported on Zanjani et al,Kariman et al Manala et al,Ramasay et al,Singh et al.

This study reaffirms the multifactorial nature of PROM. Vaginal fluid creatinine is a reliable diagnostic tool. Early identification of risk factors, can improve maternal and neonatal outcomes.

6. Conclusion:

The vaginal fluid creatinine level was significantly higher in the PROM group compared to the non-PROM group, in the present study vaginal fluid creatinine cut off was >0.3mg/dl sensitivity and specificity were 89.1% and 87.5%. Vaginal fluid creatinine is a simple, rapid, cost-effective, and non-invasive test that may aid in the timely and accurate diagnosis of PROM, especially in low-resource settings where advanced diagnostic modalities are not readily available. Incorporating this test into clinical practice could enhance early decision-making and improve maternal and neonatal outcomes.

References

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