ORIGINAL RESEARCH

Diagnostic role of vaginal fluid creatinine inprematurе rupture of membranes: A hospital based prospective study

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Received: 24 May, 2023 Accepted: 19 July, 2023

ABSTRACT

Background: Premature rupture of membranes (PROM) is a significant cause of perinatal morbidity and mortality, necessitating early diagnosis and intervention. Current diagnostic methods for PROM have limitations, highlighting the need for a reliable biomarker. Creatinine, present in vaginal secretions, may indicate PROM due to its ability to pass from the maternal bloodstream to the amniotic fluid. This study aimed to investigate the correlation between creatinine levels in vaginal secretions and PROM, contributing to the development of a non-invasive diagnostic approach and improved management strategies for better outcomes.

Methods: A prospective observational study was conducted over two years, enrolling 129 pregnant women with premature rupture of membranes (PROM) in the third trimester (Group A) and establishing a control group (Group B) of pregnant women without complications. Sample size was calculated to ensure statistical significance. Vaginal secretions were collected using sterile techniques, and creatinine levels were quantitatively analyzed using a biochemical assay. Statistical analysis, including descriptive statistics and appropriate tests, was performed using SPSS version 20.0. Ethical considerations were upheld, ensuring participant privacy and confidentiality.

Results: The mean age of participants in present study was 27.38 ± 4.12 years in Group A (with PROM) and 28.24 ± 4.28 years in Group B (without PROM).In present study, there were 57 primiparous women, accounting for 44.2% of Group A (with PROM), and 52 primiparous women, making up 39.1% of Group B (without PROM).In present study, the mean gestational age in weeks for Group A (with PROM) was 32.20 ± 3.24 weeks, while for Group B (without PROM) it was 32.67 ± 3.48 weeks.In present study, the mean creatinine levels in mg/dL for Group A (with PROM) were 1.89 ± 0.63 mg/dL, while for Group B (without PROM) they were 0.57 ± 0.25 mg/dL.In our study, the area under the curve (AUC) was 0.906 (95% CI: 0.866-0.943), indicating excellent diagnostic accuracy of creatinine in vaginal wash to diagnose PROM.

Conclusion: In conclusion, the present study provides valuable insights into the association between various variables, including age, parity, gestational age, foetal presentation, cervical dilation, and biomarkers such as creatinine and amniotic fluid index, with the occurrence of PROM.

Keywords: Premature rupture of membranes, creatinine, amniotic fluid index, vaginal wash, pregnancy

INTRODUCTION

Premature rupture of membranes (PROM), defined as the rupture of the amniotic sac before the onset of labor, occurs in approximately 3% of pregnancies and represents a leading cause of perinatal morbidity and mortality worldwide [1]. The condition poses a myriad of complications, including intrauterine infections, placental abruption, and preterm birth, thereby necessitating early diagnosis and prompt intervention to minimize adverse outcomes [2]. Currently, the diagnosis of PROM relies on clinical presentation and various tests, such as visualization of amniotic fluid pooling in the vaginal cavity through speculum examination, pH testing of vaginal secretions, and nitrazine testing. However, these diagnostic methods lack the desired accuracy and can sometimes yield inconclusive results [3]. As a result, there is a pressing need for a novel and reliable biomarker that can assist in the early detection of PROM, aiding clinicians in making timely and informed decisions.

Creatinine, a metabolic waste product of creatine, is predominantly produced in skeletal muscles and

excreted through the kidneys. Under normal circumstances, creatinine levels are primarily measured in blood or urine to assess renal function [4,5,6]. Recently, emerging evidence has suggested that creatinine might also be present in vaginal secretions of pregnant women due to its ability to traverse from the maternal bloodstream to the amniotic fluid through passive diffusion and active transport mechanisms [7,8]. Hence, it is plausible that the rupture of fetal membranes might lead to increased creatinine levels in vaginal secretions, potentially serving as a valuable marker for PROM diagnosis. This study aimed to investigate the presence and quantification of creatinine in vaginal secretions of women experiencing PROM in the third trimester. By elucidating the potential correlation between creatinine levels and the rupture of fetal membranes, we seek to contribute vital information towards the development of a non-invasive, accurate, and timely diagnostic approach for PROM. Moreover, establishing the reliability of creatinine as a biomarker could pave the way for more effective management strategies, ultimately leading to improved maternal and fetal outcomes.

METHODS and MATERIALS

Study Design and Participants

A prospective observational study was conducted to investigate the presence of creatinine in vaginal secretions of women with premature rupture of membranes (PROM) in the third trimester for two years (January 2021 to December 2022). The study was conducted at tertiary care hospital in North India, and ethical approval was obtained from the Institutional Review Board (IRB). Written informed consent was obtained from all participants prior to their inclusion in the study. A total of 129 pregnant (singleton) women diagnosed with PROM in the third trimester (gestational age ≥ 28-40 weeks) were enrolled as Group A and a control study group (Group B) was established consisting of pregnant women who did not present with any specific complaints or complications. The study implemented specific exclusion criteria to ensure the integrity of the research findings. Antenatal women were excluded from the study if they exhibited meconium-stained liquor/bloodstained liquor upon examination, had a sonographically confirmed anomalous fetus, were in active labor with uterine contractions, had used vaginal pessaries within 24 hours prior to the examination, or had confirmed intrauterine fetal demise as determined by ultrasonography, women with a history of renal disease, vaginal infections, or any medical condition that could potentially affect creatinine levels. These exclusion criteria were implemented to maintain the validity and reliability of the study results.

Sample Size Calculation: The sample size calculation for the study was determined based on a reported prevalence of premature rupture of membranes (PROM) of 10%. A precision level of 5% (0.05) was set, and the Z value corresponding to a 95% confidence level was determined to be 1.96 [9]. These parameters were used to calculate the appropriate sample size for the study, ensuring an adequate representation of the population and a sufficient level of statistical significance.A sample size of 250 (group A: 125 and group B: 125) was determined to provide sufficient statistical power to detect significant differences in creatinine levels between the study groups.

Data collection: Following a comprehensive evaluation of the participants included in the study, which involved gathering a detailed history and conducting a general examination, an obstetric examination was performed to assess the gestational age (GA) of the women. Additionally, the presentation of the fetus and fetal heart rate were carefully assessed during the examination.Each participant underwent a sterile speculum examination, and subsequently, the women were categorized into two distinct groups (group A and group B).Women who were identified as having ruptured membranes were included in the group A based on confirmation through per speculum examination, which involved observing a frank leak of fluid through the cervix or the presence of fluid pooling in the posterior fornix. Group B included women did not report any complaints or symptoms related to vaginal leakage or discharge. A baseline assessment of the amniotic fluid index (AFI) was also conducted.

Sample Collection: Vaginal secretion samples were collected from each participant. Prior to sample collection, participants were instructed to maintain strict hygiene practices, including washing hands thoroughly and using sterile gloves. In group A, a sterile speculum was inserted into the vagina to visualize the cervix, and approximately 3 mL of the fluid from these women was aspirated using a 5 mL syringe. In group B, a sterile speculum was inserted into the vagina to visualize the cervix, and a volume of 3 mL of sterile water was injected into the posterior fornix using a 5 mL syringe, and subsequently, the same volume was aspirated back.Each syringe was immediately transferred to a sterile test tube and labeled with a unique participant identifier. Care was taken to avoid contamination during the collection process. Subsequently, all women in both group A were monitored and followed up until the time of delivery or for a duration of 1 week from the collection of the samples, whichever was later.

Creatinine Analysis: The analysis of creatinine in vaginal secretions was performed using a quantitative biochemical assay. The creatinine concentration in each sample was determined using JAFFE'S (KINETIC)S method, by spectrophotometer 5010 supplied byRANDOX laboratories ltd. UK The assay kit was validated according to manufacturer instructions, and quality control measures were implemented to ensure accurate and reliable

results.Prior to analysis, the vaginal secretion samples were vortexed to ensure homogeneity. A predetermined volume of each sample was taken, and the assay procedure was carried out following the manufacturer's instructions. The absorbance or fluorescence readings were recorded using a spectrophotometer at wave length 520 nm.Standard curves were generated using known concentrations of creatinine provided in the assay kit. The concentration of creatinine in each sample was determined by comparing the absorbance values to the standard curve. All measurements were performed in duplicate, and the average values were reported.

Statistical Analysis: Statistical analysis was performed using SPSS version 20.0. Descriptive statistics, such as frequency, percentage (%), mean, standard deviation (SD), were calculated to summarize the characteristics of the study participants and the creatinine levels in vaginal secretions.To assess the significance of the differences in creatinine levels between groups (e.g., PROM vs. non-PROM), appropriate statistical tests, such as the chi-square test, or student t-test, were employed based on the distribution of the data. The Receiver operating characteristic (ROC) curve analysis was done for obtaining the optimal cut off of serum creatinine for the prediction of premature rupture of membranes (PROM).A p-value of less than 0.05 was considered statistically significant.

Ethical Considerations: The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.The privacy and confidentiality of the participants were strictly maintained throughout the study. Any identifiable information was anonymized and stored securely.

RESULTS

In present study 129 patients were included in the group A and 133 patients were included in the group B. The Table 1., provides a comparison of various variables between two groups: Group A, consisting of participants with premature rupture of membranes (PROM), and Group B, comprising participants without PROM. The variables examined include mean age, age group distribution, parity, mean gestational age, gestational age categories, and previous birth types. Although no statistically significant differences were observed in mean age (p=0.098), age group distribution (p=0.509), or parity (p=0.403) between the two groups, there was a slightly higher percentage of normal vaginal deliveries in Group A (69.4%) compared to Group B (55.6%), with a p-value of 0.077. The mean gestational age and distribution across gestational age categories did not differ significantly between the groups (p>0.05). Overall, these findings suggest that the baseline variables between two groups were comparable.

Table: 1 Baseline characteristics of the patients in the two groups.

Variables	Frequency	%	Frequency	%	P value
	Group A (n=129) (With PROM)		Group B (n=133) (Without PROM)		
Mean age (in years)	27.38±4.12		28.24±4.28		0.098
Age group					
<20 years	23	17.8	17	12.8	0.509
20-30 years	72	55.8	77	57.9	
>30 years	34	26.4	39	29.3	
Parity					
Primiparous	57	44.2	52	39.1	0.403
Multiparous	72	55.8	81	60.9	
Mean gestation age (in weeks)	32.20±3.24		32.67±3.48		0.259
Gestational age					
<28 weeks	23	17.8	21	15.8	0.666
28-32 weeks	52	40.3	49	36.8	
>32 weeks	54	41.9	63	47.4	
Previous birth					
Normal vaginal delivery	50	69.4	45	55.6	0.077
Caesarean section	22	30.6	36	44.4	

In terms of foetal presentation, there were no significant differences observed between the groups. The majority of participants in both groups had a cephalic presentation, with Group A having 89.9% and Group B having 86.5% cephalic presentations. Similarly, the distribution of breech presentations did not differ significantly between the groups.Regarding cervical dilation, the frequencies and percentages across different levels of dilation were comparable between the groups, with no statistically significant differences observed. The most common cervical dilation was 1 cm in both Group A (44.2%) and Group B (45.1%).The mean creatinine levels were significantly higher in Group A (1.89 mg/dL with a standard deviation of 0.63) compared to Group B (0.57 mg/dL with a standard deviation of 0.25), with a p-value of less than 0.0001. This suggests that creatinine levels

in vaginal secretions may be a potential marker for PROM.Furthermore, the mean amniotic fluid index was significantly lower in Group A (92.21 mm with a standard deviation of 36.02) compared to Group B (108.19 mm with a standard deviation of 31.58), with a p-value of 0.0002 (Table 2).

Table: 2 Clinical and laboratory parameters in the two groups.

Variables	Frequency	%	Frequency	%	P value
	Group A (With PROM)		Group B (Without PROM)		
Foetal presentation					
Transverse	3	2.3	5	3.8	0.658
Cephalic	116	89.9	115	86.5	
Breech	10	7.8	13	9.7	
Cervical dilation					
1 cm	57	44.2	60	45.1	0.910
2 cm	41	31.8	44	33.1	
3 cm	31	24.0	29	21.8	
Mean creatinine levels (in mg/dL)	1.89±0.63		0.57±0.25		< 0.0001
Mean amniotic fluid index (in mm)	92.21±36.02		108.19±31.58		0.0002

The ROC curve analysis yielded significant results for the prediction of premature rupture of membranes (PROM) using serum creatinine levels. The optimal cut-off value determined from the ROC curve was 0.632, providing a threshold for distinguishing between positive and negative cases. The sensitivity of the test was 94.2%, indicating the proportion of true positive results correctly identified by the test. The specificity was 98%, representing the proportion of true negative results correctly identified. The positive predictive value (PPV) was 98%, reflecting the probability that a positive test result accurately predicts the presence of PROM. The negative predictive value (NPV) was 94.1%, representing the probability that a negative test result accurately predicts the absence of PROM. The area under the curve (AUC) was 0.906 (95% CI: 0.866-0.943), indicating excellent diagnostic accuracy. The statistical analysis revealed a highly significant p-value of less than 0.0001, further supporting the reliability and significance of the results (Table 3 and Figure 1). These findings highlight the potential of serum creatinine as a valuable biomarker for PROM prediction, potentially aiding in early diagnosis and effective management strategies for pregnant women

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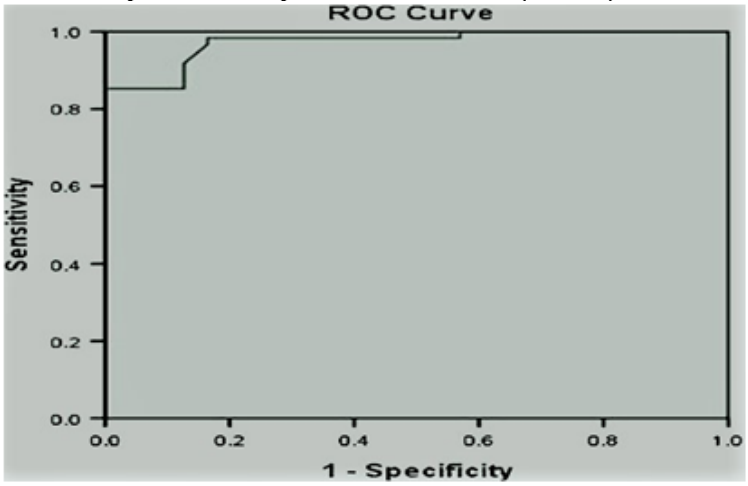
Table : 3 ROC curve analysis to determine the optimal cut-off value of serum creatinine for predicting premature rupture of membranes (PROM).

ROC curve	Cut off 0.632
Sensitivity	94.2
Specificity	98
Positive predictive value (PPV)	98
Negative predictive value (NPV)	94.1
Area under the curve (AUC)	0.906 (95% CI: 0.866-0.943)
p value	<0.0001

Figure: 1 ROC curve analysis to determine the optimal cut-off value of serum creatinine for predicting premature rupture of membranes (PROM).



DISCUSSION

The early and accurate diagnosis of premature rupture of membranes (PROM) is crucial for appropriate management and minimizing potential complications. In cases where the patient is preterm, the decision to continue or terminate the pregnancy relies on an accurate diagnosis of PROM. While history and per speculum examination are commonly used, additional tests have been described for diagnosing ruptured membranes [9]. These include the fern test, pH test, and the use of amniosense pads. Biochemical markers such as fetal fibronectin, di amine oxidase, prolactin, glucose, insulin-like growth factor binding protein, urea, and creatinine estimation have also been explored. However, currently, there is no confirmatory non-invasive diagnostic test available for PROM. The ideal test would be simple, noninvasive, rapid, and cost-effective [7,8]. The mean age of participants in present study was 27.38 ± 4.12 years in Group A (with PROM) and 28.24 ± 4.28 years in Group B (without PROM).In the study conducted by Kariman et al., the mean ages were reported as 26.25 ± 5.40 years, and 25.54 ± 4.69 years in the PROM, and healthy control groups, respectively [10]. Similarly, Ghasemi et al., observed that the average age of the study participants was 25.05 ± 6 years in the confirmed PROM group and 25.85 ±5 years in the control group, with no statistically significant difference between the two groups [11]. Sharma et al., also reported similar mean ages in both the PROM group (23.44 years) and the control group (23.30 years) [12]. In present study, there were 57 primiparous women, accounting for 44.2% of Group A (with PROM), and 52 primiparous women, making up 39.1% of Group B (without PROM). Additionally, there were 72 multiparous women, representing 55.8% of Group A, and 81 multiparous women, comprising 60.9% of Group B.Sharma et al., reported that most of the patients in their study were primiparous and well-matched in both the PROM and control groups [12].The results from the study conducted by Kedar et al., align with our findings, as they reported mean gravida status of 1.91 ± 0.83 in the case group and 2.04 ± 0.83 in the control group, with a p-value greater than 0.05 [6]. In present study, the mean gestational age in weeks for Group A (with PROM) was 32.20 ± 3.24 weeks, while for Group B (without PROM) it was 32.67 ± 3.48 weeks.The findings from our study are consistent with the studies conducted by Sharma et al., and Begum et al., [12,13]. In a similar study by Kafali et al., which evaluated vaginal wash fluid creatinine levels, the mean gestational periods were 35.6 weeks in the PROM group and 40.1 weeks in the control group [14]. Similarly, Gurbuz et al., reported mean gestational periods of 36.67 weeks in the PROM group and 35.29 weeks in the control group [15]. These results support the similarities in the mean gestational ages observed in our study.

In present study, the mean creatinine levels in mg/dL for Group A (with PROM) were 1.89 ± 0.63mg/dL, while for Group B (without PROM) they were 0.57 ± 0.25mg/dL.The results of our present study align with the findings of El-Garhy et al., who reported a mean value of vaginal fluid creatinine concentrations of 0.70 ± 0.88 mIU/mL in confirmed PROM cases and 0.04 ± 0.18 mIU/mL in the control group. The difference between the two groups was highly statistically significant with a p-value of less than 0.001 [16]. Similarly, Gada et al., demonstrated a considerable difference in creatinine levels between the studied groups, with a concentration of 0.64 ± 0.018 mg/dL in confirmed PROM cases and 0.14 ± 0.006 mg/dL in controls [17]. Zanjani et al., also reported a significantly higher creatinine level in the confirmed PROM group compared to the other groups, with a p-value less than 0.001 [18]. Additionally, Malchi et al., reported a significantly higher overall mean creatinine level in the case group compared to the control group [19]. These findings further support the association between elevated creatinine levels and the presence of PROM. The study conducted by Oliviera et al. reported mean

creatinine levels of 1.28 mg/dL at 27-34 weeks gestation and 1.83 mg/dL at 36-42 weeks gestation [3]. A creatinine concentration of 2 mg/dL was indicative of a gestational age of at least 37 weeks. Similarly, Kafali et al. reported a range of 1.5-2 mg/dL for amniotic fluid creatinine values indicative of fetal maturity [14]. In the study by Deshpande et al., it was suggested that a creatinine concentration of 1.75 mg/dL or higher was significantly correlated with a gestational age of 37 weeks or more, and amniotic fluid creatinine levels could serve as a marker of fetal maturity [20]. These findings support the use of creatinine concentration as an indicator of gestational age and fetal maturity [21]. In our study, the area under the curve (AUC) was 0.906 (95% CI: 0.866-0.943), indicating excellent diagnostic accuracy of creatinine in vaginal wash to diagnose PROM. Our study findings align with previous research conducted by Kafali et al., Mansooreh et al., Kafali et al., and Li et al., who also utilized vaginal fluid creatinine to detect premature rupture of membranes (PROM) [14, 22, 23, 24]. While there may be slight differences in results due to variations in study design, such as the inclusion of both vaginal fluid urea and creatinine in some studies, the overall trends are consistent. Kafali et al., determined optimal cut-off values of 0.9 mg/dL for creatinine using ROC curves [14]. Li et al., demonstrated a significant difference ($p < 0.001$) and similar sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) compared to our study [24]. Kafali et al., reported a reliable and rapid diagnostic test for PROM using creatinine levels in vaginal fluid, with 100% sensitivity, specificity, NPV, and PPV [23]. Mansooreh et al., reported high diagnostic accuracy with a sensitivity of 96.5%, specificity of 100%, PPV of 100%, and NPV of 96.8% using a cut-off value of 0.5 mg/dL [22]. Gurbuz et al., achieved excellent diagnostic accuracy with 100% sensitivity, specificity, PPV, and NPV using a cut-off value of 0.12 mg/dL [15]. In a study by El-Garhy et al., creatinine level sensitivity and specificity were 72% and 94%, respectively, with a cut-off value of 0.25 mg/dL [16].

In our study, the mean amniotic fluid index (in mm) for Group A (with PROM) was 92.21 ± 36.02 mm, while for Group B (without PROM) it was 108.19 ± 31.58 mm. The difference in mean amniotic fluid index between the two groups was statistically significant ($p = 0.0002$).In the study conducted by El-Garhy et al., the mean amniotic fluid index (AFI) was 4.30 ± 1.64 cm in the group with confirmed premature rupture of membranes (PROM) and 11.60 ± 2.60 cm in the control group. There was a highly significant difference between the two groups in terms of AFI, with a p-value less than 0.001 [16]. Similarly, in the study by Gada et al., a highly significant difference in AFI was observed between the studied groups. The mean AFI was 5.30 ± 1.54 cm in the PROM group and 11.06 ± 1.86 cm in the control group [17].

Limitations: This study has several limitations that should be acknowledged. First, the sample size is relatively small, which might affect the generalizability of the findings. Additionally, the study focused on a specific population of women with PROM in the third trimester, limiting the extrapolation of the results to other gestational ages or conditions. Further studies with larger sample sizes and diverse populations are warranted to validate the findings and assess the clinical utility of creatinine detection in vaginal secretions for PROM diagnosis.

CONCLUSION

In conclusion, the present study provides valuable insights into the association between various variables, including age, parity, gestational age, foetal presentation, cervical dilation, and biomarkers such as creatinine and amniotic fluid index, with the occurrence of PROM. The results highlight the potential utility of serum creatinine levels as a diagnostic biomarker for PROM, aiding in early detection and appropriate management strategies for pregnant women. Further research and validation studies are recommended to confirm these findings and establish the clinical significance of serum creatinine in the diagnosis of PROM.

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