Original Research Paper

Volume - 10 | Issue - 12 | December - 2020 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Obstetrics & Gynaecology

DIAGNOSIS OF PREMATURE RUPTURE OF MEMBRANES BY ASSESSMENT OF UREA AND CREATININE IN VAGINAL WASHING FLUID

Basu D*	Assistant Professor, Department Of Gynaecology And Obstetrics, NRS Medical College, Kolkata. *Corresponding Author
Ghosh S	Junior Resident, Department Of Gynaecology And Obstetrics, NRS Medical College, Kolkata.
Das C	Professor And Head Of The Department, Department Of Gynaecology And Obstetrics, NRS Medical College, Kolkata

ABSTRACT **BACKGROUND:** Spontaneous rupture of membranes (ROM) is a component of labor process stage I and delivery. Premature ROM (PROM) refers to rupture of the fetal membranes prior to the onset of labor irrespective of gestational age. **OBJECTIVE:** The purpose of this study was to evaluate the importance of vaginal washing fluid urea and creatinine for the diagnosis of PROM. **MATERIALS AND METHODS:** A total of 120 pregnant women were recruited and they underwent different examinations including amniotic fluid pooling, nitrazine paper test, fern test, , vaginal washing fluid urea and creatinine sampling. 80 pregnant women were included between 20 and 40 weeks of gestation with complaint of vaginal fluid leakage. Patients who had positive pooling, nitrazine paper test and fern test were considered as confirmed PROM group (group I). On the other side, patients with pooling (-) and/or nitrazine paper test (-) and/or fern test (-) were taken as suspected unconfirmed PROM cases (group II). Another group comprising of 40 pregnant women between 20 and 40 weeks of gestation without any complaint or complication were recruited as group III. Urea and creatinine of vaginal wash fluid were measured for all 120 pregnant women and their reliability in diagnosing PROM evaluated. Cut-off value was determined by receiver operating characteristic (ROC) curve. **RESULTS:** Vaginal fluid concentrations of urea and creatinine were significantly different between the three groups ($p<0.001$). **CONCLUSION:** This study demonstrated that urea and creatinine in vaginal wash fluid have better diagnostic power than conventional diagnostic methods.

KEYWORDS : Premature Rupture Of Membranes, Creatinine, Urea, Vaginal Washing Fluid

INTRODUCTION

Premature rupture of membranes (PROM) refers to rupture of the fetal membranes prior to the onset of labor (1-4). PROM has previously been reported to occur in 8-19.53% of term pregnancies and 2-25% of all pregnancies (3,4). Compared to normal group, the average hospitalization period of term and preterm newborns with PROM were prolonged 20% and 25.1% respectively.

PROM is a clinical diagnosis. Confirmation of diagnosis of PROM depends on documentation of: 1) leakage of clear fluid from the cervical os, 2) alkaline pH of the cervico-vaginal discharge, demonstrated by change in colour of nitrazine paper from yellow to blue in contact with the discharge; 3) microscopic ferning of the cervico-vaginal discharge (3,4).

Inspection of fluid leakage from cervix has been clinical method for definite diagnosis of PROM, but it is associated with 12-30% false negative results. Nitrazine test and Fern test may also give false positive or negative results due to possible contamination by alkaline urine, semen, blood, meconium, vaginitis, cervicitis and using antibiotics(4). Several studies have focused on finding different biochemical agents with high concentration in amniotic fluid like Prolactin, alpha-fetoprotein (AFP),fetal fibronectin (fFN), beta-subunit of human gonadotropin (β-HCG). (4)

Recently urea and creatinine in cervicovaginal discharge have gain importance in predicting PROM fairly accurately (6,7). Urea is produced in the metabolism of nitrogen-containing compounds in the urine. Creatinine is a product of creatinine phosphate in muscles and is mainly filtered from blood by kidneys .Urea and creatinine of fetal urine are important sources of amniotic fluid in second half of pregnancy (7) and that is why vaginal fluid creatinine and urea may be helpful in diagnosis of PROM.

The aim of this study was to evaluate the reliability of vaginal washing fluid urea and creatinine for diagnosis of PROM .

MATERIALS AND METHODS

This diagnostic analytical study, has been performed between April 2018 and May, 2019 in Antenatal ward and labour room of NRS Medical College & Hospital,Kolkata,India.

Inclusion Criteria:

Pregnant women with singleton pregnancy and gestational age between 20-40 weeks were studied.

Exclusion Criteria:

Subjects with , regular uterine contractions (i.e labour contractions), meconium in amniotic fluid, visible blood in vaginal secretion, history of coitus in the past night, use of vaginal drugs, presence of fetal anomalies, intrauterine fetal death were excluded.

Total 120 women were included in the present study.

Demographic and obstetric characteristics, results of speculum examination, fern test, nitrazine test, urea and creatinine were documented . Urea concentration was measured by enzymatic photometry or urease, and creatinine concentration was determined by Jaffee synthetic chemical calorimetric.

Gestational age was determined based on the first day of last menstruation period in reliable cases, or one ultrasound in less than 14 weeks or two ultrasound documents between 14 and 24 weeks of pregnancy. Pregnant women were examined in lithotomy position, leakage of fluid was inspected by sterile speculum and results were registered as positive, negative or suspicious. Vaginal secretions were immediately transferred on nitrazine paper.

PH above 6.5 was considered positive. A sample of cervicovaginal secretion was taken and put on slides. The slides were examined after drying by microscope for ferning pattern. Patients who had positive pooling, nitrazine paper test and fern test were considered as confirmed PROM group (group A). On the other side, patients with complaints of leakage but pooling (-) and/or nitrazine paper test (-) and/or fern test (-) were taken as suspected PROM cases (group B).

From 120 patients, 40 patients who fulfilled the criteria were included in group 1 and the remaining 40 patients were included in group 2, another 40 pregnant women who were admitted to antenatal ward and labour room and who fulfill the inclusion criterias , with 20-40 weeks of gestational age without any complaint or complication and with pooling (-), nitrazine paper test (-) and fern test (-) were taken as control group (group C).

For collection of vaginal wash fluid urea and creatinine 5 ml of sterile normal saline was injected into the posterior fornix of vagina and then was aspirated by the same syringe and was sent to the laboratory. All speculum examinations were performed by the same obstetrician and

all samples were studied in central laboratory of NRS Medical College & Hospital ; same technique used for measuring the values.

Statistical analysis

Statistical analysis was performed. Results have been expressed as frequency, mean and standard deviation. Chi^2 and one-way . P<0.05 was considered statistically significant.

RESULTS

Demographic data for each group are presented at table 1 and table 2. The parameters (age, gestational age, gravid and parity) were compared with between groups . There were no statistically significant differences between groups (p>0.05).

Table I : Association between Age in Years and PROM

Age in Years	Group-A	Group-B	Group-C	TOTAL
≤20	11	8	9	28
Row %	39.3	28.6	32.1	100.0
Col %	27.5	20.0	22.5	23.3
21-25	13	14	11	38
Row %	34.2	36.8	28.9	100.0
Col %	32.5	35.0	27.5	31.7
26-30	13	14	19	46
Row %	28.3	30.4	41.3	100.0
Col %	32.5	35.0	47.5	38.3
31-35	3	4	1	8
Row %	37.5	50.0	12.5	100.0
Col %	7.5	10.0	2.5	6.7
TOTAL	40	40	40	120
Row %	33.3	33.3	33.3	100.0
Col %	100.0	100.0	100.0	100.0

Chi-square value: 3.9662; **p-value:**0.6812

In Group-A, 11(27.5%) patients were ≤20 years old, 13(32.5%) patients were 21-25 years old, 13(32.5%) patients were 26-30 years old and 3(7.5%) patients were 31-35 years old. In Group-B, 8(20.0%) patients were ≤20 years old, 14(35.0%) patients were 21-25 years old, 14(35.0%) patients were 26-30 years old and 4(10.0%) patients were 31-35 years old. In Group-C, 9(22.5%) patients were ≤20 years old, 11(27.5%) patients were 21-25 years old, 19(47.5%) patients were 26-30 years old and 1(2.5%) patient was 31-35 years old.

Association of Age in Years with PROM not found to be statistically significant (p=0.6812).

Table 2: Association between GRAVIDA and PROM

GRAVIDAE	Group-A	Group-B	Group-C	TOTAL
Multi Gravida	20	23	22	65
Row %	30.8	35.4	33.8	100.0
Col %	50.0	57.5	55.0	54.2
Primi Gravida	20	17	18	55
Row %	36.4	30.9	32.7	100.0
Col %	50.0	42.5	45.0	45.8
TOTAL	40	40	40	120
Row %	33.3	33.3	33.3	100.0
Col %	100.0	100.0	100.0	100.0

Chi-square Value: .4699; **p-value:**0.7906

In Group-A, 20(50.0%) patients had Multi Gravida and 20(50.0%) patients had Primi Gravida. In Group-B, 23(57.5%) patients had Multi Gravida and 17(42.5%) patients had Primi Gravida. In Group-C, 22(55.0%) patients had Multi Gravida and 18(45.0%) patients had Primi Gravida.

Association of Gravidae with PROM was not statistically significant (p=0.7906).

Table 3: Distribution of mean AGE, G/AGE, UREA and Creatinine with PROM

		Number	Mean	SD	Minimum	Maximum	Median	p-value
Age	Group-A	40	23.6250	3.8142	18.0000	31.0000	23.0000	0.5300
	Group-B	40	24.5250	4.0824	19.0000	34.0000	23.5000	
	Group-C	40	24.4000	3.6711	19.0000	33.0000	25.0000	
Gestational Age	Group-A	40	30.3750	5.6554	20.0000	38.0000	31.0000	0.7500
	Group-B	40	30.3000	5.7744	18.0000	38.0000	31.0000	
	Group-C	40	29.4750	6.2017	20.0000	38.0000	29.0000	
UREA	Group-A	40	35.5000	5.5239	22.2000	43.1000	37.5500	<0.0001
	Group-B	40	18.5000	4.1957	8.9000	25.2000	19.4500	
	Group-C	40	13.8950	4.1172	8.7000	28.8000	12.2000	
Createnine	Group-A	40	4.5700	1.3629	1.9000	7.5000	4.8500	<0.0001
	Group-B	40	.9925	.2805	0.5000	1.7000	0.9000	
	Group-C	40	.1825	.0984	0.1000	0.4000	0.1500	

In Group-A, the mean Age (mean± s.d.) of patients was 23.6250 ± 3.8142 years. In Group-B, the mean Age (mean± s.d.) of patients was 24.5250 ± 4.0824 years. In Group-C, the mean Age (mean± s.d.) of patients was 24.4000 ± 3.6711 years. Difference of mean Age between three groups was not statistically significant (p=0.5300).

In Group-A, the mean Gestational Age (mean± s.d.) of patients was 30.3750 ± 5.6554. In Group-B, the mean Gestational Age (mean± s.d.) of patients was 30.3000 ± 5.7744. In Group-C, the mean Gestational Age (mean± s.d.) of patients was 29.4750 ± 6.2017.

Difference of mean Gestational Age between three groups was not statistically significant (p=0.7500).

0.13 mg/dl was set as a cut-off value for creatinine and it is found that a cut-off value of 12.0 mg/dl is optimal for urea.

In Group-A, the mean UREA (mean± s.d.) of patients was 35.5000 ± 5.5239. In Group-B, the mean UREA (mean± s.d.) of patients was 18.5000 ± 4.1957. In Group-C, the mean UREA (mean± s.d.) of patients was 13.8950 ± 4.1172.

Difference of mean UREA between three groups was statistically significant (p<0.0001).

In Group-A, the mean Createnine (mean± s.d.) of patients was 4.5700 ± 1.3629. In Group-B, the mean Createnine (mean± s.d.) of patients was .9925 ± .2805. In Group-C, the mean Createnine (mean± s.d.) of patients was .1825 ± .0984.

Difference of mean Createnine between three groups was statistically significant (p<0.0001).

DISCUSSION

Diagnosis of PROM is critical to plan treatment and for a favourable perinatal outcome and avoid complications such as chorioamnionitis and neonatal sepsis (2). But in most of the cases diagnosis is made according to the complaints made by the pregnant women and clinical examinations and traditional methods (4) though clinical complaint is not reliable.

In this present study 40 patients from 80 pregnant women who complained of fluid leakage found to be having confirmed PROM, while PROM could not be confirmed in 40 using usual diagnostic techniques.

Simple, rapid yet reliable tests for the diagnosis of PROM are needed and several biochemical markers have been studied previously.

Among studies related to PROM and vaginal washing fluid urea and creatinine one was conducted by Li Hy et al (8) to determine vaginal fluid hCG, AFP and creatinine measurements to confirm PROM. In that study 10 control patients and 10 confirmed PROM cases were included and the results showed that the sensitivity, specificity, positive predictive value, negative predictive value and accuracy of creatinine were 90%, 100%, 100%, 90.9%, and 95% (8). That study

showed creatinine in vaginal fluid washings as useful marker for diagnosing PROM. It was more expensive than the present study.

In another study by Gurbuz et al (18) study group consisted of 54 women in their third trimester of pregnancy with PROM confirmed by inspection of vaginal pooling of fluid and the control group made of 34 pregnant women with intact membranes. A cut-off value of 0.12 mg/dl was set for Creatinine and its sensitivity, specificity, positive predictive value, negative predictive value and accuracy in diagnosing PROM calculated. That study concluded that vaginal fluid creatinine measurement is not only cheaper and quicker but has higher sensitivity and specificity in confirming the diagnosis of PROM.

In the study by Kafali and Oksuzler (9) vaginal fluid urea was used for PROM diagnosis and 47 patients were included with confirmed PROM, 36 patients with suspected but unconfirmed PROM and 56 pregnant women included without any complaint . "The sensitivity, specificity, positive predictivity and negative predictivity were all 100% in detecting PROM by evaluation of vaginal fluid urea and creatinine concentration with cut-off values of 12 and 0.6 mg/dl respectively"(9).

The fourth study related to vaginal washing fluid urea and creatinine levels was conducted by Kariman et al (12). In that study 84 pregnant women in two groups, 42 confirmed PROM and 42 controls were included. The mean level of vaginal fluid urea and creatinine in the PROM group was higher than the control and statistically significant.

The other study was carried out by Mohamed and Mostafa (2011). The sensitivity, specificity, positive predictivity and negative predictivity were 100% in differentiating PROM by measuring of vaginal wash fluid urea and creatinine concentration with cut-off values of 13.2 mg/dl and 0.31 mg/dl respectively (13). In the present study, we determined a cut-off value of 0.13 mg/dl for creatinine. We have found that power diagnostic including sensitivity, specificity, positive predictive value, negative predictive value and accuracy of vaginal fluid creatinine was 100%. The optimal cut-off value for urea (12 mg/dl) gave a sensitivity level of 90%, at a specificity of 70.0%, positive predictive values of 83.0%, and negative predictive values of 87.5% and accuracy level of 85%.

In this study, three tests including direct speculum examination, fern test and nitrazine test were used for diagnosing PROM. Moreover strength of this study is investigating patients in three groups (confirmed PROM, suspected but unconfirmed and control group).

Urea is present in amniotic fluid, maternal blood and urine. "In the first half of pregnancy creatinine concentrations are similar in maternal serum and in amniotic fluid" (10). Oliveira et al have observed significant correlations between gestational age and amniotic fluid creatinine ($r>0.85$, $p<0.01$) (14).

CONCLUSION

In conclusion, our study showed that measurement of vaginal wash fluid urea and creatinine is a simple and quite reliable test for diagnosis of PROM.

ACKNOWLEDGMENTS

The authors are grateful to all pregnant women who were included in the study for their excellent cooperation, and to the Head of the Department,Dept. of gynaecology and Obstetrics, NRS Medical College,Kolkata for her guidance.

CONFLICT OF INTEREST

The authors declare that there is not any conflict of interest.

REFERENCES

1. Cunningham F, Gant F, Leveno J. Williams Obstetrics. 23nd Ed. New York: McGraw-Hill; 2010.
2. Rupture of Membranes. Washington, DC: American College of Obstetricians and Gynecologists; 1998. (ACOG Practice Bulletin No. 1)
3. Caughey AB, Robinson JN, Norwitz ER. Contemporary diagnosis and management of preterm premature rupture of membranes. Rev Obstet Gynecol. 2008;1:11–22. [PMC free article] [PubMed]
4. ParkJ S, Lee Si E, Norwitz ER. Non-invasive Testing for Rupture of the Fetal Membranes. US Obstet Gynecol. 2007:13–16.
5. Kim Y, park Y, kwon H. Vaginal fluid ß-Human chorionic gonadotropin level in the diagnosis of premature rupture of membranes. Acta Obstet Gynecol Scand. 2005;84:802–805. [PubMed]
6. Hannah ME, Hodnett ED, Willan A, Foster GA, Di Cecco R, Helewa M The Term PROM Study Group, authors, authors. The Term PROM Study Group, authors. Prelabor rupture of the membranes at term: expectant management at home or in hospital? Obstet Gynecol. 2000;96:533–538. [PubMed]
7. Healy AJ, Veille JC, Sciscione A, McNutt LA, Dexter SC. The timing of elective Delivery in preterm premature rupture of the membranes: a survey of members of the Society of Maternal-Fetal Medicine. Am J Obstet Gynecol. 2004;190:1479–1481. [PubMed]
8. Li HY, Chang TS. Vaginal fluid creatinine, human chorionic gonadotropin and Alpha-fetoprotein levels for detecting premature rupture of membranes. Zhonghua Yi Xue Za Zhi (Taipei) 2000;63:686–690.[PubMed]
9. Kafali H, Oksuzler C. Vaginal fluid urea and creatinine in diagnosis of premature rupture of membranes. Arch Gynecol Obstet. 2007;275:157–160. [PubMed]
10. Delanghe J, De Slypere JP, De Buyzere M, Robbrecht J, Wieme R, Vermeulen A. Normal reference values for creatine, creatinine, and carnitine are lower in vegetarians. Clin Chem. 1989;35:1802–1803.[PubMed]
11. Gurbuz A, Karateke A, Kabaca C. Vaginal fluid creatinine in premature rupture of membranes. Int J Gynecol Obstet. 2004;86:270–271. [PubMed]
12. Kariamn N, Toloui H, Azarhoush R, Alavi Majd H, Jan-nesari Sh. Diagnostic values of urea and creatinin values of cervicovaginal discharges in determining of premature rupture of membranes. Pajouhesh Dar Pezeshki. 2010;33:222–227.
13. Mohamed A, Mostafa W. The Value of Measurement of Vaginal Fluid Urea, Creatinine & Beta HCG in the Diagnosis of Premature Rupture of Membranes. KAJOG. 2011;2:41–47.
14. Oliveira FR, Barros EG, Magalhães JA. Biochemical profile of amniotic fluid for the assessment of fetal and renal development. Braz J Med Biol Res. 2000;35:215–222. [PubMed]