UREA AND CREATININE LEVELS IN VAGINAL FLUID- A RELIABLE MARKER FOR PRELABOUR RUPTURE OF MEMBRANES

Kshama Kedar¹, Jayant Patil², Suvarna Nimkar³

¹Associate Professor, Department of Obstetrics and Gynaecology, Indira Gandhi Government Medical College, Nagpur, Maharashtra.

²Resident, Department of Obstetrics and Gynaecology, Indira Gandhi Government Medical College, Nagpur, Maharashtra.

³Assistant Professor, Department of Obstetrics and Gynaecology, Indira Gandhi Government Medical College, Nagpur, Maharashtra.

ABSTRACT

BACKGROUND

Prelabour rupture of membranes is known to have adverse effect on pregnant women with unfavourable foetal outcome. Failure to identify membrane rupture can result in failure to implement obstetric measures, while false diagnosis can lead to inappropriate interventions. Different tests are described, but there has been no gold standard test for diagnosing PROM.

Thus, to find out the test which is rapid, bedside, inexpensive and accurate led to the study for detection of levels of creatinine and urea in the vaginal fluid for diagnosis of PROM.

MATERIALS AND METHODS

This is a prospective case control study done over a time period of 2 years in a tertiary care institute. Total 160 pregnant women were divided into study and control groups, each of 80. Vaginal fluid washing was collected, urea and the creatinine estimation was done by (GLDH) Kinetic Method and Jaffe's Method respectively.

RESULTS

Creatinine at a threshold value of 0.668 mg/dL had a sensitivity, specificity, PPV, NPV and accuracy of 100%, 91.25%, 91.95%, 100% and 95.62% respectively. In the diagnosis of PROM for a threshold value of 9.906 mg/dL for urea, the sensitivity, specificity, PPV, NPV and accuracy were 100%, 92.5%, 93.02%, 100% and 96.25% respectively in the detection of PROM.

CONCLUSION

We found that determination of urea and creatinine in vaginal fluid is a reliable marker for diagnosing PROM. This is a simple, practical, cost-effective and easily accessible test if incorporated routinely in the low resource setting. This test has the potential of becoming the gold standard test for the diagnosis of PROM.

KEY WORDS

Prelabour Rupture of Membranes, Vaginal Fluid Urea and Creatinine Levels, Diagnosis of PROM.

HOW TO CITE THIS ARTICLE: Kedar K, Patil J, Nimkar S. Urea and creatinine levels in vaginal fluid- a reliable marker for prelabour rupture of membranes. J. Evolution Med. Dent. Sci. 2018;7(20):2456-2459, DOI: 10.14260/jemds/2018/553

BACKGROUND

Of the many problems complicating pregnancy, one of utmost importance is the Premature Rupture of Membranes (PROM). Premature Rupture of Membranes (PROM) refers to the rupture of amniotic membranes prior to the onset of labour regardless of gestational age, while preterm premature rupture of membranes (PPROM) means rupture of amniotic membranes before 37 weeks of gestational age.¹ It complicates 8% of term pregnancies (≥ 37 weeks), while Preterm Premature Rupture of Membranes (PPROM) complicates 2 - 4% of singleton and 7 - 20% of twin pregnancies. On an average 20 - 40% of preterm births are a result of PPRM and it accounts for 18 - 20% of perinatal deaths in developed countries and much more in the developing countries.²

PROM increases the risk of chorioamnionitis upto 15% and foetal infection risk upto 5%. Foetal infection risk increases upto 20% in those with chorioamnionitis. Also, the hospital stay of neonates with premature rupture of membranes increases by 20 - 25% with the cost of hospitalisation increasing upto 60%. There is also a risk of 1% endometritis in term and post-term period.³

Latency from membrane rupture to delivery is brief and is inversely proportional to gestational age with 93% of cases with PPRM delivering in a week.⁴ With PROM thus there are increased risk of preterm deliveries, caesarean sections and low birth weight babies, neonatal complications like respiratory distress syndrome, necrotising enterocolitis, inter-ventricular haemorrhage, cerebral palsy, septicaemia, neonatal deaths and perinatal mortality.⁵ Serious complications in conservative management occurring early are retained placenta and postpartum haemorrhage (PPH) necessitating dilatation and curettage (12%), maternal sepsis (0.8%) and maternal death (0.14%).⁶

Diagnosis is easy when clinical situation is obvious, but difficult when there is doubt as to whether PROM has occurred or not. It is vital to diagnose this condition accurately. Different tests have been tried, but until now there has been no gold standard test for diagnosing PROM.⁷ Traditionally, minimally invasive gold standard for diagnosis of PROM relies on clinician's ability to document three clinical signs on sterile speculum examination: 1) Visual pooling of

'Financial or Other Competing Interest': None.
Submission 06-04-2018, Peer Review 30-04-2018,
Acceptance 07-05-2018, Published 14-05-2018.

Corresponding Author:

Dr. Suvarna Nimkar,

Assistant Professor,

Department of Obstetrics and Gynaecology,

Indira Gandhi Government Medical College,

Nagpur, Maharashtra.

E-mail: suvarnanimkar@gmail.com

DOI: 10.14260/jemds/2018/553

clear fluid in the posterior fornix of the vagina or leakage of the fluid from the cervical os; 2) An alkaline pH of the cervicovaginal discharge, which is typically demonstrated by nitrazine paper and/or 3) Microscopic ferning of the cervicovaginal discharge.⁸

Failure to identify membrane rupture can result in failure to implement obstetric measures, while false diagnosis can lead to inappropriate interventions such as hospitalisation or labour induction.⁹

The need to identify markers in amniotic fluid for inexpensive, rapid, bedside and accurate detection of PROM led to the studies for detection of levels of Creatinine and Urea in the vaginal washing fluid, which initiates this study.

Aims and Objectives

1. To determine the diagnostic accuracy of vaginal washing fluid urea and creatinine levels in the detection of PROM.
2. To give suitable recommendations based on the study findings.

MATERIALS AND METHODS

This is a prospective case-control study conducted in the Department of Gynaecology and Obstetrics in collaboration with the Department of Biochemistry at a tertiary care hospital in central India over the period of 2 years. The study consisted of antenatal patients admitted to the labour room. These patients are divided into two groups namely-

Group I- The Study (Cases) Group

This group consisted of pregnant patients with the history of leaking per vagina and confirmed leak on per speculum and per vaginal examination.

Group II- The Control Group

This group consisted of healthy pregnant patients who did not either had the history of leaking per vagina or leak per speculum/ vaginal examination.

All the patients are between 28 weeks and 42 weeks of gestation. Total sample size of the study is 160. The study is approved by the ethics committee.

Inclusion Criteria

Antenatal women with singleton pregnancy, gestational age between 28 - 42 weeks without any foetal congenital renal anomaly or severe medical illness.

Exclusion Criteria

PROM in patients having multiple pregnancies, congenital foetal anomaly, history of vaginal infection, intrauterine foetal demise, meconium stained liquor and women not willing to participate in the study.

Study Methodology

After obtaining consent from pregnant female detailed history regarding leaking per vaginum and its duration along with obstetric history, menstrual history, history of past illness, immunisation history etc. was taken. Then the general examination including per abdomen examination was done. This was followed by local examination. The sample was collected during the sterile speculum examination, which was done for the observation of pooling of the amniotic fluid. During the examination, the posterior fornix was irrigated by

5 cc of Normal Saline, then 3 cc of this washing fluid was aspirated back in the same syringe and this sample was transferred in a sterile plain bulb. After proper labelling, this sample was then sent for further processing in the biochemical laboratory immediately. In case of delay, these samples were preserved in the refrigerators at 4 - 8°C. In the biochemistry laboratory, the samples were centrifuged at 50 revs/min for 10 minutes. Then the supernatant fluid was used for the estimation of urea and creatinine. The samples were processed in the ERBA XL-640 automated analyser. Urea and creatinine estimation were done by (GLDH) Kinetic Method and Jaffe's Method (Initial Rate) respectively.

Statistical Analysis

The data were entered into Microsoft Excel and was analysed using SPSS Version 20.0. The qualitative data was represented in the form of frequency and percentage. The quantitative data was represented in the form of mean and standard deviation. The association between two qualitative variables was calculated by using chi-square test and the difference between two means in both groups was calculated using unpaired t-test. A p-value less than 0.05 was considered as statistically significant.

RESULTS

Most of the participants in both cases and control groups belonged to 21 - 30 years (80.0% in cases and 88.8% in controls). There is no statistical significant difference between the two groups with regards to maternal age. Most of the participants in case group were primigravida (43.7%), while in the control group most of the participants were of second gravida status (45.0%). Both the groups are comparable with regards to gravida status. As per the LMP, 23.8% participants were preterm in the case group compared to 13.8% participants in the control group and as per the earliest ultrasound scan 26.3% participants were preterm in the case group compared to 12.5% participants of the control group. There was no statistically significant difference between the two groups with regards to GA as per LMP and scan.

Urea Conc. mg/dL	Group	N	Mean	Standard Deviation	P value
	Case	80	19.48	4.88	0.0001
	Control	80	5.97	3.01	
Creatinine Conc. (mg/dL)	Group	N	Mean	Standard deviation	P value
	Case	80	1.22	0.28	0.0001
	Control	80	0.36	0.26	

Table 1. Comparison of Concentration of Urea and Creatinine in both the Groups

Urea Threshold= 9.906 mg/dL	PROM	
	Case Group	Control Group
Positive (≥ 9.906 mg/dL)	80 (TP)	6 (FP)
Negative (< 9.906 mg/dL)	0 (FN)	74 (TN)
Creatinine Threshold= 0.668 mg/dL	Case Group	Control Group
	80 (TP)	7 (FP)
Negative (< 0.668 mg/dL)	0 (FN)	73 (TN)

Table 2. Calculation of the Threshold Value of Urea and Creatinine in the Vaginal Washing Fluid

(TP- True Positive, FP- False Positive, TN- True Negative, FN- False Negative).

Calculation of the Threshold Value of Urea in the Vaginal Washing Fluid

Standard Deviation was calculated as 4.88 and 95% confidence interval is given by 1.96 SD below the mean value. Threshold value of urea= Mean – 1.96 SD= 9.906 mg/dL and any value above this indicated PROM.

Calculation of the Threshold Value of Creatinine in the Vaginal Washing Fluid

The standard deviation was calculated as 0.283 and 95% confidence interval is given by the value of 1.96 SD= 0.555. Threshold value of creatinine= Mean – 1.96 SD= 0.668 mg/dL and any value above this indicated PROM.

Birth Weight	Group		Total
	Case (n= 80)	Control (n= 80)	
Low birth weight	32	25	57
	56.1%	43.9%	100.0%
Normal birth weight	48	55	103
	46.6%	53.4%	100.0%
Chi-square= 1.335, df= 1, p-value= 0.248 not significant			
Table 3. Association of Birth Weight between both the Groups			

Type of Delivery		Cases	Controls	Total	Significance
PTND	No.	8	10	18	Chi-square=12.48, df= 1, p=0.0004 significant
	%	10%	12.50%	11.25%	
FTND	No.	28	48	76	
	%	35%	60%	47.50%	
Total Vaginal Deliveries	No.	36	58	94	
	%	45%	72.50%	58.75%	Chi square=12.48, df=1, p=0.0004 significant
Preterm LSCS	No.	9	1	10	
	%	11.25%	1.25%	6.25%	
Term LSCS	No.	35	21	56	
	%	43.75%	26.25%	35%	
Total LSCS	No.	44	22	66	
	%	55%	27.50%	41.25%	
Table 4. Association of Type of Delivery between both the Groups					

DISCUSSION

In the current study it was observed that the mean age of case group was 24.95 ± 3.78 years, while that of the control group was 24.96 ± 3.23 years. The p-value being > 0.05 concludes no statistically significant difference with regards to maternal age in the two groups.

These results are identical with the study results of Tavana Z et al (2010),¹⁰ who observed the mean ages to be 25.2 ± 5.7 , 25.4 ± 5.6 and 26.7 ± 5.5 years in the confirmed PROM, suspected PROM and the healthy control group respectively. Similarly, Kariman N et al (2013)⁸ in their study also found the mean ages to be 26.25 ± 5.40 , 25.46 ± 6.0 and 25.54 ± 4.69 in the confirmed PROM, suspected PROM and the healthy control group respectively and Ghasemi M et al (2016)¹¹ found the mean ages of the study participants to be 25.0 ± 5.6 and 25.8 ± 5.5 years in the confirmed PROM and

the control group respectively with no statistically significant difference in between the two groups.

The observed mean gravida status of the case group and the control group was 1.91 ± 0.83 and 2.04 ± 0.83 respectively and the p-value was observed to be > 0.05 . Thus, there was no statistically significant difference in the two groups and the two groups under study were identical. Also, it was noted that most of the participants in the case group were primigravida (43.7%), while in the control group most of the participants were of second gravida status. Similar results were found in the study of Tavana Z et al (2010),¹⁰ Kariman N et al (2013)⁸ and Begum J et al (2017).¹²

The mean gestational age in the case group was 37.48 ± 2.03 weeks and in the control group was 38.28 ± 1.68 weeks as per calculations from the dates of last menstrual period. Thus, it was observed that there was no statistically significant difference between the groups.

The distribution of study participants as per gestational age as per the earliest scan shows the mean gestational age of 37.16 ± 2.25 weeks and 38.13 ± 1.67 weeks in the case and the control group respectively. Thus, it was seen that no statistically significant difference was present in the two study groups. Thus, the mean gestational ages in both the study groups are identical. Conversely, we can say that there was no statistically significant difference in the case and the control group with regards to gestational age. Similar results were found by Kariman N et al (2013),⁸ Tigli A et al (2014)¹³ and Begum J et al (2017)¹² in their studies.

In the study by Tavana Z et al (2010),¹⁰ the mean gestational ages are lower than those observed in our study. But similar to our study, there is no statistically significant difference with regards to the gestational age between the study groups.

In present study, the mean concentration of urea was found to be 19.48 ± 4.88 and 5.97 ± 3.01 mg/dL in the case and the control group respectively. This shows a statistically significant difference in the value of urea in the two groups. The threshold value of 9.906 mg/dL was worked out. It showed a sensitivity of 100%, specificity of 92.5%, PPV of 93.02%, NPV of 100% and an accuracy of 96.25% in diagnosing PROM.

Also, it was observed that the mean concentration of creatinine was 1.22 ± 0.28 mg/dL in the case group and 0.36 ± 0.26 mg/dL in the control group. Thus, there is a statistically significant difference in the two groups regarding the creatinine concentration. The cut-off value for creatinine worked out to be 0.668 mg/dL which showed 100% sensitivity, 91.25% specificity, PPV of 91.95%, NPV of 100% and accuracy of 95.62% for the detection of PROM.

The difference in the values of urea and creatinine concentration in the different studies might be due to the different inclusion criteria for the study participants, a difference in the gestational ages, different dilutions used in sample collection and the different biochemical procedures used for estimation of urea and creatinine.

In this study, we observed that 56.1% of the babies delivered in the confirmed case group were low birth weight (LBW) compared to 43.9% in the control group. Thus, more LBW babies were delivered in the case group as compared to the control group, but this difference was not statistically significant.

It is observed that preterm vaginal deliveries occurred in 10% of participants in the case group as compared to 12.5% participants in the control group, whereas full-term vaginal deliveries were seen in 35% participants of the case group as compared to 60% participants in the control group. Preterm lower segment caesarean section (LSCS) was performed in 11.25% of the participants of the case group compared to 1.25% participants of the control group, whereas 43.75% of study subjects in the case group had undergone term LSCS to terminate the pregnancy compared to 26.25% study subjects in the control group. Thus, we observed that 55% participants in case group underwent LSCS compared to 27.5% of the control group. This is a statistically significant difference in the two study groups with regards to the type of delivery.

The current study is contradictory to the study by Effat DM et al (2012),¹⁴ who found no statistically significant difference in the type of delivery between the case, suspect and the control group. In their study vaginal deliveries were conducted in 72%, 76% and 60% of participants of the case, the suspect and the control group respectively.

Corresponding 28%, 24% and 40% participants in the three groups underwent LSCS for the termination of pregnancy.

CONCLUSION

We found that determination of urea and creatinine is a reliable method for diagnosis of PROM, thus can be used as an adjunctive test in confirming PROM. Both the urea and the creatinine have equal sensitivity and specificity in diagnosing PROM. This test is simple, practical, cost-effective and easily accessible test if incorporated routinely for the detection of PROM in the low resource community. Overall, this test has the potential of becoming the gold standard test for the diagnosis of PROM.

REFERENCES

- [1] DeFranco E, Atkins K, Heyl PS. Preterm labor, premature rupture of membranes and cervical insufficiency. Evans, Arthur T, eds. Manual of Obstetrics. 7th edn. Lippincott Williams & Wilkins 2007;8:135-50.
- [2] Spinillo A, Montanari L, Sanpaolo P, et al. Fetal growth and infant neurodevelopmental outcome after preterm premature rupture of membranes. *Obstet Gynecol* 2004;103(6):1286-93.
- [3] Benedetto C, Tibaldi C, Marozio L, et al. Cervicovaginal infections during pregnancy: epidemiological and microbiological aspects. *J Matern Neonatal Med* 2004;16(Suppl 2):9-12.
- [4] Mercer B, Arheart KL. Antimicrobial therapy in expectant management of preterm premature rupture of membranes. *Lancet* 1995;346(8985):1271-9.
- [5] ACOG Committee on Practice Bulletins-Obstetrics. ACOG Practice Bulletin No. 80: premature rupture of membranes. Clinical management guidelines for obstetrician-gynecologists. *Obstet Gynecol* 2007;109(4):1007-19.
- [6] Mercer BM, Moretti ML, Prevost RR, et al. Erythromycin therapy in preterm premature rupture of membranes: a prospective, randomized trial of 220 patients. *Am J Obstet Gynecol* 1992;166(3):794-802.
- [7] Kafali H, Oksuzler C. Vaginal fluid Urea & Creatinine in diagnosis of premature rupture of membranes. *Arch Gynaecol Obstet* 2007;275(3):157-60.
- [8] Kariman N, Afrakhte M, Hedayati M, et al. Diagnosis of premature rupture of membranes by assessment of urea and creatinine in vaginal washing fluid. *Iran Journal of Reproductive Medicine* 2013;11(2):93-100.
- [9] Medina TM, Hill DA. Preterm premature rupture of membranes: diagnosis and management. *Am Fam Physician* 2006;73(4):659-64.
- [10] Tavana Z, Hamed B, Zolghadri J, et al. The evaluation of diagnostic role of vaginal fluid urea, creatinine and I-HCG level for detection of premature rupture of membrane. *The Internet Journal of Gynecology and Obstetrics* 2010;15(1):1-6.
- [11] Ghasemi M, Jaami R, Alleyassin A, et al. The value of urea, creatinine, prolactin and beta sub-unit of human chorionic gonadotropin of vaginal fluid in the diagnosis of premature preterm rupture of membranes in pregnancy. *Turk J Obstet Gynecol* 2016;13(2):62-6.
- [12] Begum J, Samal SK, Ghose S, et al. Vaginal fluid urea and creatinine in the diagnosis of premature rupture of membranes in resource limited community settings. *J Fam Reprod Health* 2017;11(1):43-9.
- [13] Tigli A, Kurt S, Kopuz A. The roles of beta-human chorionic gonadotropin, creatinine and urea in vaginal washing fluid in the diagnosis of premature rupture of membranes. *Perinatal Journal* 2014;22(3):133-7.
- [14] Effat DM, Elkafrawy MAS, Elbagory E. The role of vaginal fluid creatinine versus human chorionic gonadotropin in diagnosis of premature rupture of membranes. *AAMJ* 2012;10(3):299-316.