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## ORIGINAL ARTICLE

# Diagnosis of Premature Rupture of Membranes by Assessment of Urea and Creatinine in Vaginal Washing Fluid

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## ABSTRACT

**Background:** Premature rupture of membranes means fetal rupture of membranes before labor starts. Patients with history of fluid leakage throughout pregnancy should be carefully evaluated for fear of negative impacts on outcomes of pregnancy. By speculum examination it is sometimes simple to detect PROM by observing amniotic fluid accumulated in the vagina or outflow of fluid through the cervix.

**Objectives:** This study was conducted for evaluation of diagnostic value of urea and creatinine levels in vaginal wash in patients with PROM.

**Patiets and methods:** The study was conducted at Zagazig University Hospitals. 114 pregnant women were included in this study, divided into two groups: 57 pregnant women with PROM and 57 pregnant women without history of leakage of vaginal fluid.

**Results:** There is statistically significant difference between both groups considering AFI. There are statistically significant difference between the two groups regarding vaginal wash urea and creatinine. The best cutoff value of vaginal wash urea in prediction of PROM is  $\geq 6.85$  with AUC of 0.958, sensitivity of 98.2%, specificity of 70.2%, PPV of 76.7%, NPV of 97.6% and accuracy of 93%. The best cutoff value of vaginal wash creatinine in prediction of PROM is  $\geq 0.465$  with AUC of 0.992, sensitivity of 100%, specificity of 80.7%, PPV of 83.8%, NPV of 100% and accuracy of 90.4%. In our study, combined use of vaginal wash urea and creatinine in prediction of PROM had sensitivity of 98.3%, specificity of 91.2%, PPV of 91.8%, NPV of 98.1% and accuracy of 94.7%.

**Conclusion:** Urea and creatinine assay is cheaper, faster and more valid (has higher sensitivity and specificity) than other vaginal fluid markers as  $\alpha$ -fetoprotein, human chorionic gonadotropin and fetal fibronectin to establish accurate assessment of PROM.

**Key Words:** fetal membrane, premature membranes rupture, creatinine, urea

## INTRODUCTION

**P**remature membrane rupture (PROM) relates to the rupture of fetal membranes before labor starts. If it happens before week 37 of pregnancy, premature rupture of membrane is called (PPROM)<sup>(1)</sup>.

A lengthy period between PROM and delivery may lead in maternal and neonatal morbidity regarding preterm pregnancies.. This involves chorioamnionitis, fetal and

neonatal sepsis, prematurity of the fetus, abruption of the placental, prolapse of the umbilical cord, cesarean sections, and increased risk of maternal and neonatal death<sup>(2)</sup>.

Accurate and early diagnosis let clinicians design more interventions to optimize neonatal and maternal outcomes and decreasing dangerous complications<sup>(3)</sup>.

If the membrane rupture is too small or hard to see clearly the amniotic fluid leakage, PROM cannot be easily assessed, that can cause difficulty diagnosing and not to performe essential interventions<sup>(4)</sup>.

Few methods for diagnosing PPROM are present. Fern & nitrazine are the two commonly used tests. even though tests are rapid and easy, they have false positive and negative results, for example through blood, cervical mucus or semen technical or contamination errors, that means it is not reliable<sup>(5)</sup>.

Ultrasound assessment with amniotic fluid assurance is certainly not a decent test since it can't separate PROM from different reasons for oligohydramnios. In spite of the fact that the amnio- dye or tampon test considered the standard test for exact analysis, it includes instillation of dye and amniocentesis; subsequently, it is a forceful test and has a danger of abruption placental, abortion, bleeding, disease, and uterine perforation<sup>(3)</sup>.

Amnisure PROM test is another easy new test which is fast, and negligibly invasive, has high specificity and sensitivity. This test distinguishes minimal amounts PAMG-1 (of placental alpha-microglobulin-1), that is bounteous in amniotic fluid. Even though, Amnisure is not accessible in numerous centers and costly<sup>(6)</sup>.

Thus, a non-invasive, inexpensive, and simple method is required for detection of PPROM. Many markers were studied as fetal fibronectin, alpha-fetoprotein, insulin growth factor binding protein 1 urea, creatinine,  $\beta$ -hCG, and prolactin. creatinine and Urea are excreted by glomerular filtration. those markers are accessible also in amniotic fluid and have been investigated for diagnosing PPROM<sup>(7)</sup>.

**Osman and Elghazaly<sup>(8)</sup>** assessed and looked at the exactness of urea and creatinine in vaginal liquid washing for analysis of PROM and to decide cut off levels. They demonstrated that vaginal liquid washing urea and creatinine levels in vaginal liquid washing were exceptionally exact, straightforward tests for conclusion of PROM.

**Gezer et al.<sup>(9)</sup>** decided if urea and creatinine estimations in vaginal liquid could be utilized to analyze Preterm Premature Rupture Of Membranes PPROM and anticipate conveyance interim after PPROM. They presumed that estimation of urea and creatinine levels in vaginal liquid is a fast and solid test for diagnosing and furthermore for foreseeing conveyance interim after (PPROM)

The point of this examination to assess the symptomatic estimation of vaginal wash urea and creatinine levels in patients with PROM.

#### PATIENTS AND METHODS

This (cross-sectional) study was achieved at the Department of Obstetrics and Gynecology, Zagazig University Hospitals in the period from april 2018 to October 2018. It was based on clinical and biochemical parameters. It was performed on 114 pregnant women with symptoms of PROM with gestational age from 24 weeks onwards.

Written informed consent was obtained from all participants and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Patients were divided into 2 groups as follows:

**Group A (definite rupture of membranes):**  
It included 57 pregnant women with PROM with the following inclusion criteria:

1. Pregnancy in 3<sup>rd</sup> trimester (completed 24 weeks to completed 37 weeks).
2. Singleton pregnancy.
3. History of watery vaginal leakage.
4. Visualization of amniotic fluid leakage (sterile cusco speculum examination: positive fluid leakage).

**Group B (control Group):**

It included 57 pregnant women who came to outpatient clinic for the routine antenatal care with the following inclusion criteria:

1. Pregnancy in 3<sup>rd</sup> trimester (completed 24 weeks to completed 37 weeks).
2. Singleton pregnancy.
3. No history of vaginal fluid leakage.

**4.** Average amount of amniotic fluid index:  
AFI > 10cm.

**Exclusion criteria:**

- Meconium stained amniotic fluid.
- Blood in vaginal secretion.
- Intercourse in the previous night.
- Vaginal drugs Usage.
- Reported fetal anomalies.
- Patients in labor.
- IUFD and prenatal complication.
- Oligohydramnios.

**Methods:**

All women in this study were subjected to:

**1-** History taking.

**2-** General examination.

**3-** Abdominal examination.

**4-** Complete clinical examination (speculum examination, fern test and nitrazine test).

**5-** Transabdominal ultrasonography for fetal viability, gestational age, congenital fetal malformation, placental localization and assessment of amniotic fluid index through 4 quadrant technique.

**6-** Vaginal wash urea measurement by enzymatic urease method.

**Result Interpretation of Urease Test:**

Positive Reaction: Change to bright pink color in 15 min to 24 h.

Negative Reaction: No color change.

**7-** Vaginal wash creatinine measurement test by RATE JAFFE method : A precise volume of sample is introduced into a reaction cup containing an alkaline picrate solution. Absorbance readings are taken at both 520 nm and 560 nm. Creatinine from the sample combines with the reagent to produce a red colour complex. The observed rate measurement at 25.6 seconds after sample introduction has been shown to be a direct measure of the concentration of the creatinine in the sample.

**Statistical Analysis**

Data were entered checked and analyzed using Epi-Info version 6 and SPP for Windows version 8 (Dean, 2006).

Data were summarized using:

**The arithmetic mean:**

As an average describing the central tendency of observations:

**Mann Whitney-U test:**

It is used for comparison between the 2 groups (successful and weaning) for the not normally distributed data.

**Sensitivity:** Ability of the test to detect true positive cases =  $A/(A + C)$ .

**Specificity:** Ability of the test to detect true negative cases =  $D/(B + D)$ .

**Accuracy:** The proportion of all test result both positive and negative, that are correct =  $(A + D)/(A + B + C + D)$ .

**Predictive value**

**Student t test**

It was used when comparing two means.

For all above mentioned statistical tests done, the threshold of significance is fixed at 5% level (p-value).

The results was considered:

- Significant when the probability of error is less than 5% ( $p < 0.05$ ).
- Non-significant when the probability of error is more than 5% ( $p > 0.05$ ).
- Highly significant when the probability of error is less than 0.1% ( $p < 0.001$ ).
- The smaller the p-value obtained, the more significant are the results.

**RESULTS**

There was non significant difference between both groups regarding age, BMI and Gestational age; Table (1)

There was non significant difference between both groups regarding amniotic fluid index; Table (2)

There are statistically significant difference between the two groups regarding vaginal wash urea and creatinine; Table (3)

The best cutoff of vaginal wash urea in prediction of PROM is  $\geq 6.8$  with AUC 0.937, sensitivity 93.3, specificity 79.2, PPV 94.4, NPV 76, +LR 4.49, -LR 0.08 and accuracy 90.4% ( $P < 0.05$ ); Table (4)

The best cutoff vaginal wash creatinine in prediction of PROM is  $\geq 0.465$  with AUC 0.999, sensitivity 100, specificity 95.8, PPV 98.9, NPV 100, +LR 23.8, -LR 0 and accuracy 99.1% ( $P < 0.05$ ); Table (5)

Combined usage of vaginal wash urea and creatinine in predicting of PROM had sensitivity of 100%, specificity 79.2%, PPV

94.7%, NPV 100%, +LR 95.6% 4.81, -LR 0 and accuracy; Table (4), Table (5)

**Table (1) comparison of age and BMI among studied groups:**

	PROM (57)	Non-PROM (57)	T	p
<b>Age:</b>				
Mean ± SD	<b>27.44 ± 6.97</b>	<b>28.65 ± 7.69</b>	<b>-0.881</b>	<b>0.380</b>
<b>BMI:</b>				
Mean ± SD	<b>24.53 ± 5.56</b>	<b>25.67 ± 6.12</b>	<b>-1.041</b>	<b>0.3</b>
<b>Gestational age:(weeks)</b>				
Range	<b>24 - 36</b>	<b>24 - 34</b>	<b>0.614</b>	<b>0.540</b>
Mean ± SD	<b>31.6 ± 3.67</b>	<b>31.19 ± 3.34</b>		

**Table (2) comparison of amniotic fluid index among studied groups:**

	PROM (57)	Non-PROM (57)	T	p
<b>AFI:</b>				
Mean ± SD	<b>7.02 ± 1.64</b>	<b>13.39 ± 2.34</b>	<b>-19.512</b>	<b>0.380</b>

**Table (3) comparison of Vaginal fluid urea and creatinine level (ml/dl)among studied groups**

	PROM	Suspected PROM	T	p
	Mean ± SD	Mean ± SD		
<b>Urea</b>	<b>13.45± 3.48</b>	<b>6.52± 1.89</b>	<b>13.219</b>	<b>&lt;0.001**</b>
<b>Creatinine</b>	<b>1.78± 0.55</b>	<b>0.36± 0.13</b>	<b>MW (-9.099)</b>	<b>&lt;0.001**</b>

t independent sample t test

MW mannwhitney test

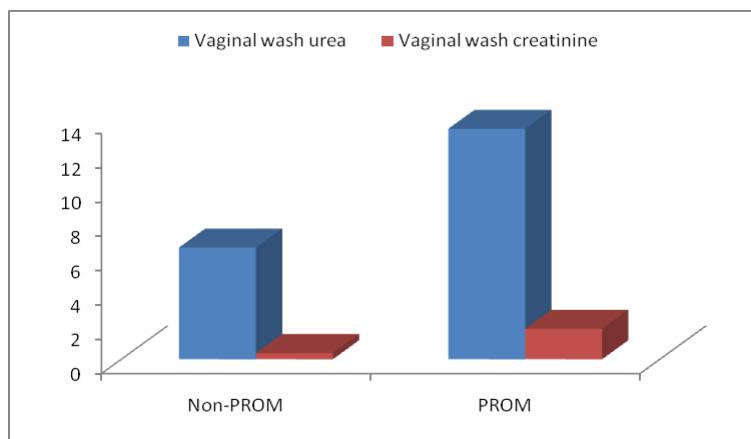
p≤ 0.001 is highly significant

**Table (4) performance of vaginal wash urea and performance of vaginal wash creatinie in prediction of PROM among study cases:**

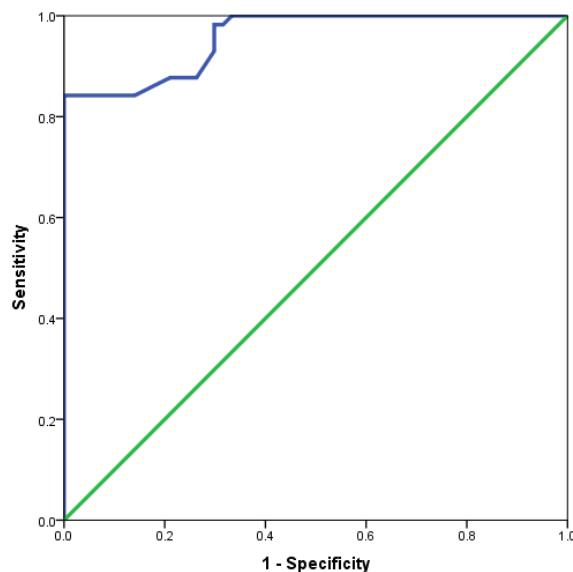
	Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	P
urea	<b>6.85</b>	<b>0.958</b>	<b>98.2</b>	<b>70.2</b>	<b>76.7</b>	<b>97.6</b>	<b>93</b>	<b>&lt;0.001**</b>
creatinine	<b>0.465</b>	<b>0.994</b>	<b>100</b>	<b>80.7</b>	<b>83.8</b>	<b>100</b>	<b>90.4</b>	<b>&lt;0.001**</b>

**Table (5) performance of combined vaginal wash urea and creatinine in prediction of PROM among study cases**

	PROM	No PROM	Total
<b>Screening test positive</b>	<b>56</b>	<b>5</b>	<b>61</b>
<b>Screening test negative</b>	<b>1</b>	<b>52</b>	<b>53</b>
<b>Total</b>	<b>57</b>	<b>57</b>	<b>114</b>



**Figure (1):** Combined bar chart showing mean vaginal wash urea and creatinine



**Figure (2) ROC curve showing performance of vaginal wash urea in prediction of PROM in studied patients**

## DISCUSSION

Cameron<sup>(11)</sup> revealed the precision of urea and creatinine to decide the PROM from 90-100%. Urea assumes a significant job in the digestion of nitrogen-containing mixes in the pee. Creatinine is a separate result of creatinine phosphate in muscles and is normally delivered at a genuinely consistent rate and is fundamentally sifted through of the blood by kidneys. Urea and creatinine of fetal pee are the most significant wellsprings of amniotic liquid in second 50% of pregnancy.

This study was conducted for evaluation of the diagnostic value of vaginal wash urea and

creatinine levels in PROM patients. The study was completed at Obstetrics and Gynecology Department, Hospitals of Zagazig University. A total of 114 pregnant women were enrolled in this study, between completed 24 weeks to completed 37 weeks of gestation, divided into two groups: Fifty seven pregnant women with PROM and fifty seven pregnant women with no history of vaginal fluid leakage.

The study showed that there are non-significant differences between both groups regarding age, BMI, onset of leakage, gestational age, gravidity, parity, history of abortion, systolic and diastolic blood pressure, respiratory and

heart rates and temperature, but there is statistically significant difference between the studied groups regarding AFI.

**Kariman et al.**<sup>(12)</sup> evaluated and compared the reliability of vaginal washing fluid urea and creatinine for diagnosis of PROM. A total of 179 pregnant women were recruited. The one group consisted of 126 pregnant women between 14 and 41 weeks of gestation with the complaint of vaginal fluid leakage. Patients who had positive pooling, nitrazine paper test and fern test were considered as confirmed PROM group (group 1). On the other side, patients with pooling (-) and/or nitrazine paper test (-) and/or fern test (-) were taken as suspected unconfirmed PROM cases (group 2). The control group consisted of 53 pregnant women between 14 and 41 weeks of gestation without any complaint or complication. The parameters (age, gestational age, gravid and parity) were compared with analysis of variance between groups test.

The study showed that there is statistically a significant difference between the two groups regarding vaginal wash urea. The best cutoff value of vaginal wash urea in prediction of PROM is  $\geq 6.85$  with AUC of 0.958, sensitivity of 98.2%, specificity of 70.2%, PPV of 76.7%, NPV of 97.6% and accuracy of 93%. **The same study** also showed the mean concentration of vaginal fluid urea among groups. The mean vaginal fluid urea levels in group 1, 2 and 3 were  $13.77 \pm 5.41$  mg/dl (range 1.0-43),  $4.71 \pm 3.64$  mg/dl (range 0.2-32) and  $5.13 \pm 5.97$  mg/dl (range 0.1-23) respectively, and the differences were statistically significant ( $p < 0.001$ ). The area under the curve is 84% for urea. A cut-off value of 6.0 mg/dl is optimal for urea. According to the urea cut-off point, sensitivity of 90%, specificity of 79%, positive predictive value of 83%, negative predictive value of 87.5% and accuracy of 85% were found.

A study was carried out by **Mohamed and Mostafa**<sup>(13)</sup>. The sensitivity, specificity, positive predictivity and negative predictivity were 100% in detecting PROM by evaluation of vaginal urea and creatinine concentration

with cut-off values of 13.2 mg/dl and 0.31 mg/dl respectively.

In our study, combined use of vaginal wash urea and creatinine in prediction of PROM had sensitivity of 98.3%, specificity of 91.2%, PPV of 91.8%, NPV of 98.1% and accuracy of 94.7%.

Our study showed that urea and creatinine assays are cheap and fast methods, as they take 20 minutes and have high sensitivity and specificity to establish accurate diagnosis. It is a possible candidate to become a gold standard test for PROM as it is cheaper, faster, higher sensitivity and specificity than  $\alpha$ -FP,  $\beta$ -HCG and fetal fibronectin.

**Osman and Elghazaly**<sup>(8)</sup> evaluated and compared the accuracy of urea and creatinine in vaginal fluid washing for diagnosis of PROM and to determine cut off levels. They showed that vaginal fluid washing urea and creatinine levels in vaginal fluid washing were very accurate, simple tests for diagnosis of PROM.

**Gezer et al.**<sup>(9)</sup> determined whether urea and creatinine measurements in vaginal fluid could be used to diagnose Preterm Premature Rupture Of Membranes (PPROM) and predict delivery interval after PPROM. They concluded that measurement of urea and creatinine levels in vaginal fluid is a rapid and reliable test for diagnosing and also for predicting delivery interval after PPROM.

## CONCLUSION

This study concluded that urea and creatinine assay is cheap, fast and valid (has high sensitivity and specificity) to establish accurate PROM diagnosis. In the present series, the simplicity and the availability of this test make it attractive in clinical practice. So, vaginal fluid creatinine and urea are possible candidates to become acceptable test for diagnosis of PROM.

## REFERENCES

- 1- Cunningham G, Leveno K, Bloom S, et al. William's Obstetrics, 24th Edition. New York: McGraw-Hill Education, 2014.
- 2- Tavassoli F, Ghasemi M, Mohamadzade A, Marzieh Ghasemi and Fatemeh Tavassoli . Survey of pregnancy outcome in preterm

- premature rupture of membranes with amniotic fluid index <5 and ≥5. *Oman Med J* 2010; 25: 118-23.
- 3- Park JS, Lee SE and Norwitz ER.** Non-invasive testing for rupture of the fetal membranes. *Touch Briefings: US Obstetrics and Gynecology* 2007; Issue 1: 13–6.
- 4- Ladfors L.** Pre-labor ruptures of the membranes at or near term: clinical and epidemiological studies PhD thesis, University of Gothenburg, Sweden, 1998.
- 5- Lee SE, Park JS, Horwitz ER.** Measurement of placental alpha-microglobulin-1 in cervicovaginal discharge to diagnose rupture of membranes 2007; 109(3):634-640.
- 6- Palacio M, Kuhnert M, Berger R, Larios CL and Marcellin L.** Meta analysis of studies on biochemical marker tests for the diagnosis of premature rupture of membranes: comparison of performance indeces. *BMC Pregnancy and Childbirth* 2014; 14: 183.
- 7- Ni CY, Jia WX, Yi WM, Feng LH and Yu LZ.** Practicability of using vaginal fluid markers in detecting premature rupture of membranes. *Ann Clin Biochem* 2003; 40: 542-5.
- 8- Osman OM and Elghazaly M.** Can vaginal washing fluid urea, creatinine and qualitative β-hCG diagnose suspected premature rupture of membranes? *Open Journal of Obstetrics and Gynecology* 2014; 4: 967-972.
- 9- Gezer C, EkinA, Golbasi C and Kocahakimoglu C.** Use of urea and creatinine levels in vaginal fluid for the diagnosis of preterm premature rupture of membranes and delivery interval after membrane rupture. *The Journal of Maternal-Fetal and Neonatal Medicine*, 2016.
- 10- Liu J, Feng ZC, Wu J.** The Incidence Rate of Premature Rupture of Membranes and its Influence on Fetal-neonatal Health: A Report from Mainland China. *J Trop Pediatr* 2010; 56: 36-42.
- 11- Cameron E.** Diagnosis of premature rupture of membranes: inspiration from the past and insights for the Future. *J Obstet Gynaecol Can* 2010; 32: 561-569.
- 12- Kariman N, Afrakhte M, Hedayati M, Hedayati M and Fallahian M.** Diagnosis of premature rupture of membranes by assessment of urea and creatinine in vaginal washing fluid. *Iran J Reprod Med* 2013; 11(2): 93-100.
- 13- Mohamed A, Mostafa W.** The Value of Measurement of Vaginal Fluid Urea, Creatinine and Beta HCG in the Diagnosis of Premature Rupture of Membranes. *KAJOG* 2011; 2: 41–47.

#### How to Cite

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