

Diagnosis of Premature Rupture of Fetal Membranes by Identification of Vaginal Fluid Urea and Creatinine

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ABSTRACT:

BACKGROUND:

Premature rupture of fetal membrane is one of the most common and controversial problem facing the obstetric clinician. Its Correct diagnosis has great importance because failure of diagnosis can lead to unwanted obstetric complications or over diagnosis can lead to unnecessary intervention.

OBJECTIVE:

To evaluate the reliability of vaginal fluid urea and creatinine for the diagnosis of premature rupture of membrane.

PATIENTS AND METHODS:

This study had been conducted in AL-Yarmouk Teaching Hospital, Department of Obstetrics and Gynecology. In this study, 105 pregnant women presented between 24-41 weeks of gestation were included, three groups were considered in this cohort, thirty five pregnant women with confirmed premature rupture of membrane (group A), thirty five pregnant women with suspected premature rupture of membranes (group B), and thirty five healthy pregnant women considered as control group (group C).

All patients underwent speculum examination for amniotic fluid pooling, nitrazine paper test, measurement of urea and creatinine in vaginal wash fluid sample, ultrasonographic examination for gestational age determination and amniotic fluid index calculation, and then the patients were followed up until delivery.

RESULT:

There was significant differences in the mean vaginal wash fluid urea and creatinine concentrations among the three groups ($P < 0.001$), being higher in group A than the other two groups. The gestational age at delivery and time interval between sampling and delivery was significantly shorter among patients in group A than group B and group C.

CONCLUSION:

Vaginal wash fluid urea and creatinine determination for the diagnosis of premature rupture of membrane in our study reported a comparable result in the sensitivity and specificity to other worldwide results.

KEY WORDS: premature rupture of membrane, vaginal urea and creatinine.

INTRODUCTION:

Premature rupture of membrane (PROM) is a common obstetrical problem, and the assessment of the women with a possible membrane rupture is a management issue faced in every day practice. When PROM occurs, the fetus loses the relative isolation and protection afforded within the amniotic cavity(1). It is associated with significant maternal and neonatal risks, and management strategies that are often diverse and

controversial(2). It is generally accepted that PROM occurs in 10% of all pregnancies, with majority of cases occurring after 37 weeks gestation. Preterm premature rupture of membrane (PPROM) complicates approximately 3% of pregnancies and leads to one third of preterm birth(3).

The diagnosis of PROM is based on history, examination(speculum examination) and investigations(1). Specific tests have been developed for use when the diagnosis of PROM cannot be determined by speculum examination alone. These tests include measurement of vaginal pH by Nitrazine test, alpha fetoprotein,

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Insulin-like growth factor binding protein, fetal fibronectin, Diamine oxidase and human chorionic gonadotrophin^(6,8,9,10,11)

Urea and creatinine concentration in amniotic fluid increased gradually between 20 to 32 weeks of gestation and more rapidly thereafter, when they were 2 to 4 times higher than in maternal serum.⁽¹²⁾ Throughout studies that had been conducted to assess the renal maturation of the fetus using the concentration of urea and creatinine in amniotic fluid, it was found that in the first half of pregnancy (below 20 wk) a mean creatinine concentration of 53 $\mu\text{mol/l}$ in the amniotic fluid, similar to that found in maternal serum and for urea the mean concentration about 3.8 mmol/l, while in the second half of pregnancy the mean creatinine concentration reach 120 $\mu\text{mol/l}$ at 34 wk and 177 $\mu\text{mol/l}$ at 37 week of gestation, for urea it reach 4.8 mmol/l at 34 week of gestation to 5.8 mmol/l at 37 week of gestation⁽¹⁸⁾. The increasing profile of urea and creatinine throughout normal pregnancy is due to glomerular filtration and maturation of tubular function, these levels of concentration confirmed renal maturation⁽¹³⁾.

AIM OF THE STUDY:

To evaluate the reliability of vaginal fluid urea and creatinine measurement in the diagnosis of premature rupture of membranes.

PATIENTS AND METHODS:

This study was conducted on 105 pregnant women admitted to the obstetric and gynecology department at Al-Yarmouk teaching hospital over a period of one year starting from April 2008 through April 2009.

Seventy pregnant women admitted with the complaint of vaginal fluid leakage between 24-41 weeks of gestation. The other 35 pregnant women without any complaint and complications came for regular antenatal visit were taken as control group.

Pregnant women presented with any amount of vaginal bleeding (either spontaneous or traumatic due to speculum examination), presence of regular uterine contractions, presence of multiple pregnancy, prenatal complications, Fetal anomalies, or history of intercourse within the last 48 hours all were excluded from the study.

All included patients underwent a sterile speculum examination (under aseptic technique

without use of antiseptic solution). Amniotic fluid pooling with or without Valsalva maneuver was noted. The nitrazine paper test was applied.

Thirty five pregnant women with confirmed PROM, which was evidenced by positive pooling of amniotic fluid with or without Valsalva maneuver and positive nitrazine paper test were taken as group A.

Thirty five pregnant women with suspected PROM, who were pooling (+ve) and nitrazine test (-ve) or pooling (-ve) and nitrazine test (+ve) were taken as group B.

Group C includes 35 apparently healthy pregnant women without any complaint came for regular antenatal visit were taken as a control group.

Then vaginal washing fluid urea and creatinine sampling was done for all groups as follows: 5ml of sterile saline solution was injected into posterior vaginal fornix and 3ml of it was aspirated with the same syringe and sent immediately to the laboratory, where the sample was centrifugated and the supernatant taken for quantitative measurement of urea and creatinine by the usual colorimetric method.

All patients sent for ultrasound examination for assessment of gestational age and calculation of amniotic fluid index. The gestational age determined by accurate last menstrual period and early ultrasound.

All patients were followed till delivery and gestational age at delivery time was recorded.

Statistical analysis: After that statistical analysis of the data was carried out using the available statistical package of SPSS-15 (statistical packages for social sciences version 15). Data were presented in simple measures of frequency, percentage, mean, standard deviation, and range (minimum – maximum values). The significance of difference of different means was tested using analysis of variance (ANOVA) for more than two groups and using independent student-t-test for difference between two means while different percentages were tested using chi-square test (χ^2 -test). Statistical significance was considered whenever the P value was less than 0.05.

Receiver operating characteristic curve analysis was used to establish the optimal cut-off concentration for vaginal washing fluid urea and creatinine levels. Sensitivity and specificity were calculated using 2x2 table.

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RESULTS:

The three studied groups were comparable age, and the P value was 0.394, 0.194. and 0.596, regarding the maternal age, parity, and gestational age as showing in table (1).

Table 1: Comparison between the three groups regarding maternal age , parity, and gestational age.

	Group A PROM(+) NO.35	Group B PROM (±) NO.35	Group C Control NO.35	P-value
Maternal age(years) mean±SD	28.26±7.44	27.26±6.66	27.26±6.16	0.394
Parity Mean±SD	2.20±2.06	2.06±2.15	1.69±1.64	0.194
Gestational age(weeks) Mean±SD	34.91±4.85	33.51±5.06	34.14±5.53	0.596

The comparison between the three groups as regards to the mean level of urea and creatinine of vaginal fluid showed high significant difference (P=0.0001), and as it has been showed in table(2), there was corresponding difference in the amniotic fluid index as measured by ultrasound.

Table 2: Comparison between the three groups as regards to the mean level of urea and creatinine of vaginal fluid, and amniotic fluid index(AFI).

	Group A NO.35	Group B NO.35	Group C NO.35	P value
AFI(cm) Mean±SD	9.24±2.5	9.81±3.12	11.16±2.04	0.013
Vaginal fluid urea(mmol/l) Mean±SD	3.62±1.07	2.35±1.54	0.68±0.52	0.0001
Vaginal fluid creatinine(μmol/l) Mean±SD	101.44±36.35	64.62±34.12	26.34±10.84	0.0001

The cut-off value as determined by ROC curve was 1.77mmol/l for vaginal urea, and 52.7μmol/l for vaginal creatinine, table(3) shows that the specificity and sensitivity of both values are 100%, 97% respectively with P value less than 0.001.

Table 3: Best cut-off value, specificity, and sensitivity of vaginal urea and creatinine to diagnose PROM.

Test	Cut-off value	specificity	sensitivity	P value
Vaginal urea	1.77mmol	100%	97%	<0.001
Vaginal creatinine	52.7μmol	100%	97%	<0.001

Ninety seven percent of group A (confirmed) had vaginal level of urea and creatinine above the cut-off value, and 100% of the control group were below that level, while the suspected group had two location, where 68% above the cut- off value, and 32% below that level, table(4). Those who are above cut-off value from group B had low amniotic fluid index and short latency period (time from the date of examination to the delivery).

Table 4: Distribution of all groups according to the cut-off value of vaginal fluid urea and creatinine.

Test		Group A		Group B		Group C	
		NO.	%	NO.	%	NO.	%
Vaginal fluid urea	Positive>1.77mmom/l	34	97	24	68	0	0
	Negative<1.77mmol/l	1	3	11	32	35	100
Vaginal fluid creatinine	Positive>52.7µmol/l	34	97	24	68	0	0
	Negative<52.7µmol/l	1	3	11	32	35	100

The distribution of group A according to the gestational age showed that the level of vaginal fluid urea and creatinine are increased with the gestational age(all above the cut-off value).There was significant difference between each groups regarding the time interval between sampling and delivery, it was found that in groupA, most of the patients(85%) delivered within 48hours, while in group C most of the patients delivered at term. In group B, some patients had short interval to delivery and other had long interval, the shortest time had been seen in those with the highest level of vaginal fluid urea and creatinine.

DISCUSSION:

PROM is important obstetrical problem and the correct diagnosis has great importance because failure of diagnosis can lead to unwanted obstetric complications like chorioamnionitis , preterm birth ; on the other hand over diagnosis can lead to unnecessary interventions like hospitalization or induction of labour. The approach to the diagnosis of membrane rupture is clinical , with over 90% of cases being confirmed based on the presence of a suspicious history or ultrasonographic finding followed by documentation of fluid passing from the cervix or the presence of nitrazine / ferning positive vaginal pool of fluid⁽¹⁴⁾. In this study we measure the level of urea and creatinine in vaginal washing fluid and we found the level of both in cases with confirmed diagnosis of PROM are (urea 1.5 – 6.0 mmol/l and creatinine 44.20 200.0 µmol/l) which where significantly higher than those of control group (urea 0.02 -1.55 mmol/l and creatinine 10.00 – 45.50 µmol/l). The result of this study is consistent with that of Kafali H who measure both urea and creatinine in vaginal washing fluid and found that the levels in patients with confirmed PROM (urea 1.80 -8.1 mmol/l and creatinine 50-220 µmol/l) were significantly higher than in control group (urea 0.018 – 1.5 mmol/l and for creatinine 1.76 -39.78 µ mol/l)⁽¹⁵⁾.In this study we found that measurement of urea and creatinine

in vaginal washing fluid is accurate in diagnosis of PROM with sensitivity 97% and specificity 100% for both. This result in agreement with that of the Kafali H in which the sensitivity and specificity were 100% for urea and creatinine measurement in diagnosis of PROM⁽¹⁵⁾. Also Gurbuz et al. study reported that the sensitivity and specificity of creatinine measurement in vaginal washing fluid for diagnosis of PROM were 100%⁽¹⁶⁾.

In the current study we determined cut-off point of urea (1.77 mmol/l) and of creatinine (52.70 µmol/l) in the vaginal washing fluid according to receiver operating characteristic curve. This finding is comparable to study of Kafali H who determined cutoff point of urea (1.99 mmol/l) and of creatinine (53.04 µmol/l)⁽¹⁵⁾.

In group B where the diagnosis of PROM was suspected , it was found that 24 cases of 35 total cases have short latency period (less than 1 week), half of those patients have low AFI but all have high level of urea and creatinine in vaginal washing fluid ,while the remaining 11 cases have long latency period and have normal (some cases low) AFI and similar level of urea and creatinine to that of control group. In group A where the diagnosis of PROM was confirmed by positive speculum examination and nitrazine test, the latency period was shorter than that of control group and those who delivered within 48 hours they had low AFI and high level of urea and creatinine in vaginal washing fluid. It was found that all patients in group A who had PROM at advanced gestational age had higher level of urea and creatinine than those of gestational age less than 30 weeks and this result attributed to renal maturity and its ability to secrete more urea and creatinine in fetal urine , but almost always the levels of urea and creatinine were more than cut-off value.

This result is consistent with that of Tyden et al, who found that the analysis of urea and creatinine in amniotic fluid permits an evaluation of renal maturation and functionality throughout pregnancy,

also many studies had been reported that pregnant women in the early gestational age have a mean creatinine concentration of 0.6 mg/dl (53.0 μ mol/l) in the amniotic fluid, similar to that found in maternal serum then it increase gradually between 20 and 32 weeks of gestation and more rapidly thereafter, when they were two to four times higher than maternal serum⁽¹⁷⁾.

It was found that urea and creatinine measurement in vaginal washing fluid are not expensive and easy and this result is consistent with that of Li Hy et al and Kafali H, who found that urea and creatinine are less expensive and easier to measure than HCG and AFP and appear to be more accurate than HCG⁽¹⁵⁾.

In 2008, the FDA had approved a bedside test for the diagnosis of PROM. It is an immunoassay test which can be done without speculum examination and it depends on the detection of PAMG-1, 34 KDa placental glycoprotein. It is highly specific and sensitive (99%)⁽¹⁸⁾. **CONCLUSION:** Vaginal wash fluid urea and creatinine determination for the diagnosis of premature rupture of membrane in our study reported a comparable result in the sensitivity and specificity to other worldwide results.

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