Vaginal Fluid Urea and Creatinine for Diagnosis of Premature Rupture of Membranes

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Abstract: Objectives: To detect the accuracy of vaginal fluid urea and creatinine for diagnosis of premature rupture of membranes (PROM). **Patients and methods:** The current diagnostic accuracy test was conducted at Ain Shams University Maternity Hospital during the period between June 2011 to December 2011. Included women were divided into two groups: Group I: (cases) included fifty pregnant women with PROM. Group II: (controls) included fifty pregnant women without PROM. Women with multiple pregnancies, preterm labour, fetal distress, vaginal bleeding, congenital fetal malformations, and/or serum creatinine level more than 0.9mg/dl were excluded from this study. All women were subjected to transabdominal ultrasound and sterile Cusco speculum examination to diagnose PROM and 5ml of sterile saline solution was injected into the posterior vaginal fornix using a sterile syringe. Three ml of the injected saline was aspirated using the same syringe and sent immediately to the laboratory. Each specimen was centrifuged at 50 revolutions/ second and the supernatant fluid was separated. Measurements of both urea and creatinine were performed by enzymatic urease method and Rate Jaffe method respectively to determine their exact levels. A total of 100 pregnant women were included in the study. The included women were divided into 2 groups according to presence or absence of PROM Group I: (cases) included fifty pregnant women with PROM. Group II: (controls) included fifty women pregnant without PROM. **Results**: There was no statistical significant difference between both groups regarding maternal age, parity and gestational age at time of sampling (P>0.05). There was a statistical significant difference between the 2 groups regarding vaginal fluid urea and creatinine levels (P <0.001) as the mean vaginal fluid urea and creatinine levels was (40.3±9mg/dl and 1.45±0.26 mg/dl in group I versus 7.8±2.8 mg/dl and0.42±0.20mg/dl in group II, respectively.In the current study; the sensitivity & the specificity of vaginal fluid urea to diagnose PROM were 99% & 99% respectively, while its positive predictive value (PPV), negative predictive value (NPV) and over all accuracy were 98%, 97% and 96% respectively, with a cut-off value of 12 mg/dl. While the sensitivity & the specificity of vaginal fluid creatinine to diagnose PROM were 98% & 97% respectively, while its positive predictive value (PPV), negative predictive value (NPV) and over all accuracy were 96%, 98% and 97% respectively, with a cut-off value of 1 mg/dl. **Conclusion:** Detection of vaginal fluid urea and creatinine to diagnose PROM is a sample, reliable and rapid test with high sensitivity, specificity, PPV, NPV and over all accuracy.

1. Introduction

Spontaneous rupture of membranes (ROM) represents one of components of labour and delivery, While, premature rupture of membranes (PROM) refers to rupture of the fetal membranes prior to the onset of labour whatever the gestational age [1]. The term "prelabour" should be used rather than "premature" or "preterm" because the latter two relate neither to gestational age nor to the weight of the fetus or neonate. The membrane rupture itself should be characterized as preterm or term [2]. The fetal membranes serve as a barrier to ascending infection. Once the membranes rupture, both the mother and fetus are at risk of infection and of other complications [1]. The major cause of perinatal morbidity and mortality associated with preterm PROM is prematurity. Morbidities related to prematurity include respiratory distress syndrome,

necrotizing enterocolitis, inter-ventricular hemorrhage, cerebral palsy, and sepsis [3]. A study by Kafali and Öksüzler has shown that either urea or creatinine determination in vaginal fluid for the diagnosis of PROM is a reliable, simple and rapid test. The sensitivity, specificity, positive predictivity, and negative predictivity were all 100% in detecting PROM by evaluation of vaginal fluid urea and creatinine concentration with a cut-off value of 12 and 0.6 mg/dl, respectively. Analysis of creatinine and urea in amniotic fluid permits an evaluation of renal maturation and functionality throughout pregnancy [4].The aim of the present work was to detect the accuracy of vaginal fluid urea and creatinine for diagnosis of PROM.

2. Patients and methods

The current diagnostic accuracy test was conducted at Ain Shams University Maternity

Hospital during the period between June 2011 to December 2011. Included women were divided into two groups: Group I : (cases) included fifty pregnant women with PROM. Group II: (controls) included fifty pregnant women without PROM. A written informed consent was obtained from all women after approval of study protocol by ethical and research committee of council of Obstetrics and Gynecology Department, Ain Shams University. Women with multiple pregnancies, preterm labour, fetal distress, vaginal bleeding, congenital fetal malformations, and/or seum creatinine level more than 0.9mg/dl were excluded from this study. All women were subjected to transabdominal ultrasound and sterile Cusco speculum examination to diagnose PROM. PROM was diagnosed based on sudden gush of watery vaginal fluid, passing of watery fluid from external cervical os during sterile Cusco speculum examination, an alkaline pH of the cervicovaginal discharge, which change yellow nitrazine paper to blue (nitrazine test); and/or ferning of the cervicovaginal discharge on drying using microscopy (ferning test) [1,5]. 5ml of sterile saline solution was injected into the posterior vaginal fornix using a sterile syringe. 3 ml of the injected saline was aspirated using the same syringe and sent immediately to the laboratory. Each specimen was centrifuged at 50 revolutions/ second and the supernatant fluid was separated. Measurements of both urea and creatinine were performed by enzymatic urease method and Rate Jaffe method(Roche Integra 700 ®[Roche Diagnostics],Germany) respectively to determine their exact levels.

Statistical analysis

Data were analyzed using SPSS® for Windows®, version 13.0 (SPSS, Inc, USA). Description of quantitative (numerical) variables was performed in the form of mean, standard deviation (SD) and range. Description of qualitative (categorical) data was performed in the form of number of cases and percent. Analysis of numerical variables was performed by using independent student's t-test. Analysis of categorical data was performed by using Chi-squared test. Diagnostic accuracy was assessed using the following terms: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and overall accuracy.ROC (receiver operator characteristic) curve was used to find out the best cut off value of certain variable). Sensitivity: ability of the test to detect positive cases and calculated as true positive cases/true positive cases + false negative cases. Specificity: ability of the test to exclude negative cases and calculated as true negative cases/true negative cases + false positive cases.

PPV is the percentage of true positive cases to all positive (proportion of all individuals with positive tests, who have the disease). NPV is the percentage of true negative cases to all negative (the proportion of all individuals with negative tests, who are non-diseased. While over all Accuracy means true negative +true positive / all cases.

A difference with P value <0.05 was considered statistically significant.

3. Results

A total of 100 pregnant women were included in the study. The included women were divided into 2 groups according to presence or absence of PROM Group I: (cases) included fifty pregnant women with PROM. Group II: (controls) included fifty pregnant women without PROM. There was no statistical significant difference between both groups regarding maternal age, parity and gestational age at time of sampling (P>0.05) table1. There was a statistical significant difference between the 2 groups regarding vaginal fluid urea and creatinine levels (P <0.001) table 2. In the current study; the sensitivity & the specificity of vaginal fluid urea to diagnose PROM were 99% & 99% respectively, while its positive predictive value (PPV), negative predictive value (NPV) and over all accuracy were 98%, 97%and 96%respectively, with a cut-off value of 12 mg/dl. While the sensitivity & the specificity of vaginal fluid creatinine to diagnose PROM were 98% & 97% respectively, while its positive predictive value (PPV), negative predictive value(NPV) and over all accuracy were 96%,98%and 97% respectively, with a cut-off value of 1 mg/dl. Figure (1) shows the Receiver operator characteristic (ROC) curve for vaginal fluid urea and creatinine as predictors of PROM.

Table (1): Comparison between both groups regarding maternal age, parity and gestational age at time of sampling*.

	Group I	Group II	P **
Age(years)	26.2+2	26.2+4	>0.05 (NS)
Parity	2±1	1±0.6	>0.05 (NS)
Gestational age (weeks)	32.4±2.9	31.4±3.1	>0.05 (NS)

*Values are expressed as mean± standard deviation
** Analysis using Independent Student's *t*-Test
NS non-significant

Table (2): Comparison between both studied groups as regard vaginal urea and creatinine levels*

	Group I	Group II	P**
Urea(mg/dl)	40.3±9	7.8±2.8	<0.001(S)
Creatinine(mg/dl)	1.45±0.26	0.42±0.20	<0.001(S)

*Values are expressed as mean± standard deviation
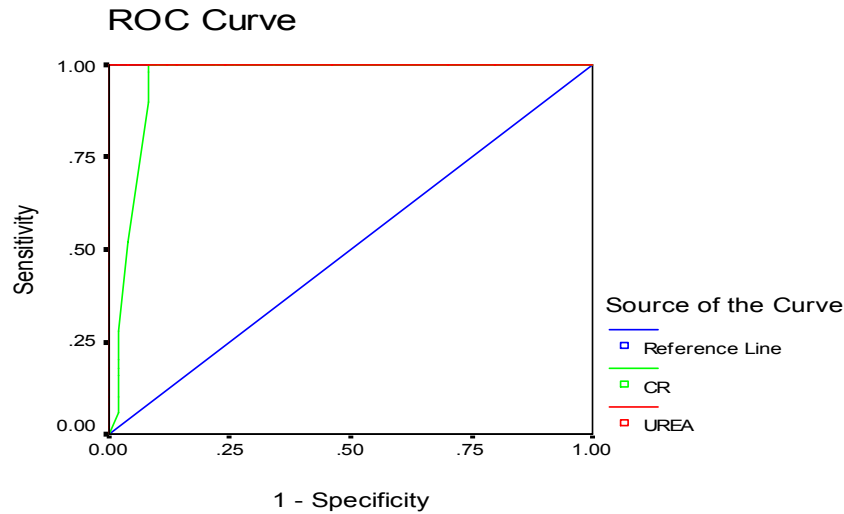** Analysis using Independent Student's *t*-Test
S significant

Figure (1) shows the Receiver operator characteristic (ROC) curve for vaginal fluid urea and creatinine as predictors of premature rupture of membranes.

4. Discussion

The results of this study showed that both vaginal fluid creatinine and urea concentrations are good predictors of PROM. The best cutoff point for vaginal fluid creatinine concentration as diagnostic of PROM was 1 mg/dl (sensitivity 98% specificity 97%). The best cutoff point for vaginal fluid urea concentration as diagnostic of PROM was 23mg/dl (sensitivity 99%-specificity 99%). It is in agreement with the study conducted by Li *et al.* who have found creatinine less expensive and easier to measure than human chorionic gonadotropin (hCG) and alpha feto protein(AFP) and appears to be more accurate than hCG [6].It also agrees with the study conducted by Gurbuz *et al.* that showed that vaginal fluid creatinine is an extremely useful marker in doubtful cases of PROM. In these cases, new methods such as AFP, Beta-hCG and fetal fibronectin were investigated. However, they have low specificity owing to overlap between the values of AFP, hCG, and fibronectin in patients with and without intact membranes the creatinine assay is cheaper and faster than other methods, and has higher sensitivity and specificity to establish accurate diagnosis. It is a possible candidate to become a gold standard test for PROM[7].

Gurbuz *et al.*, reported that the sensitivity, specificity, positive predictivity, and negative predictivity were all 100% in detecting PROM by evaluation of vaginal fluid creatinine concentration [8].

It also agrees with the study conducted by Kafali et al. who were the first who conducted study using urea to diagnose PROM.In this study a total of 139 pregnant women were recruited. Group I consisted of 47 patients with diagnosis of PROM confirmed by amniotic fluid pooling and nitrazine paper test. Group II consisted of 36 patients in whom diagnosis of PROM was suspected but unconfirmed by amniotic fluid pooling and / or nitrazine paper test. Group III consisted of 56 pregnant women without any complaint or complication. The results were evaluated with a significance level of *P*<0.01 the sensitivity, specificity, positive predictivity, and negative predictivity were all 100% in detecting PROM by evaluation of vaginal fluid urea and creatinine with a cut-off value of 12 and 0.6 mg/dl, respectively [4].

Creatinine values in the amniotic fluid that best represent fetal maturity are 1.5-2.0 mg/dl [4]. A creatinine concentration of 1.75mg/dl or more correlates significant with a gestational age of 37 weeks or more. Which confirmed renal maturation, the increasing growth profile of creatinine and urea throughout normal pregnancy is due to glomerular filtrations and maturation of tubular function [9].So it can be concluded that vaginal and creatinine determination can be used not only in the diagnosis of PROM but also used as fetal maturation test in case of preterm labour [4].

The strengths of the current study included the use of more than one criterion to diagnose PROM including symptoms,signs and investigations, Most of study results similar to those reported in other studies which makes our results are robust. Our study is limited by lack of comparison between vaginal fluid urea and creatinine and the diagnostic test that is available and widely used in Europe and has also been

approved by the Food and Drug Administration (FDA) which is AmniSure® test due to lack of financial resources as the study was funded by authors only.

Conclusion:

Detection of vaginal fluid urea and creatinine to diagnose PROM is a sample, reliable and rapid test with high sensitivity, specificity, PPV, NPV and over all accuracy.

Declaration of interest

The authors reported no conflict of interest. All of the authors had substantial contributions to conception and design, acquisition of data, analysis and interpretation of data, drafting and revising the article critically with final approval of the version to be published. The research was funded by the authors.

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