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Novel markers for the diagnosis of premature rupture of membrane in pregnancy: urea, creatinine and prolactin of vaginal fluid

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Abstract

Objective: To evaluate the effectiveness of urea, creatinine and prolactin of vaginal fluid in the diagnosis premature rupture of membranes (PROM).

Materials and Methods: In this prospective study, 200 pregnant women with gestational age of 28 to 36 weeks 6 Days were included in our study and divided into two equal groups: study group comprised of 100 women with history of leaking per vaginam and documented PROM 100 women with intact membrane made the control group. All women underwent per speculum examination and five ml of normal saline was poured into the vagina and the sample was collected after a few minutes, and sent to the laboratory for examination for various markers.

Results: The vaginal washing concentration of urea, creatinine and prolactin was significantly different in the two groups ($p < 0.001$). The sensitivity, specificity, positive and negative predictive values of urea in detecting PROM were 79.5%, 82.3%, 81.6%, and 80.2%, respectively. Creatinine had 74.4% sensitivity, 84.8% specificity, and 82.8% and 77.0% positive and negative predictive values for detecting PROM. Prolactin had 87.7% sensitivity, 92.2% specificity, and 90.2% positive and 88.2% negative predictive values for detecting PROM, thus, was the best in predicting PROM.

Conclusion: Prolactin has more diagnostic value than urea and creatinine in detecting PROM, and can be used in suspected cases.

Keywords: Premature rupture of membranes, urea, creatinine, prolactin, vaginal fluid

Introduction

Premature rupture of membranes (PROM) refers to fetal membranes' rupture before the onset of labor. If it occurs before 37 weeks of pregnancy, it is called premature preterm rupture of membrane (PPROM) (1). PROM affects 3 to 18.5% of all pregnancies. In term or preterm pregnancies, a long duration between PROM and delivery can result in maternal and neonatal morbidity. This includes intrauterine infections (Chorioamnionitis), neonatal and fetal sepsis, fetal prematurity, placental abruption, umbilical cord prolapse, cesarean delivery, postpartum endometritis [1-6].

Any patient with a history of painless leakage of vaginal fluid during pregnancy or a small amount of amniotic fluid in ultrasound should be evaluated carefully because of the adverse effects on pregnancy outcomes. Early and accurate diagnosis allows clinicians to design some interventions for optimizing maternal and neonatal outcomes and decrease serious complications [7]. PROM is detected by speculum examination with the observation of amniotic fluid in the vaginal fornix (pooling test) or liquid outflow from cervix on vulsalva maneuver [8]. However, when the membrane rupture is small or it is impossible to clearly see amniotic fluid leakage, PROM cannot be detected easily, which might lead to failure in diagnosis and non-performance of necessary interventions [9, 10]. There are a few methods for PROM diagnosis. Fern and Nitrazine are two traditional, commonly used tests. Although they are easy and rapid tests, both have high false positive and negative results, for example through blood, semen or cervical mucus contamination or technical errors, which means they are not completely reliable [8-13].

Ultrasound examination measure amniotic fluid in uterus. If fluid levels are low PROM is likely but it is not a good test because it cannot differentiate PROM from other causes of oligohydramnios [7]. Although the Indigo carmine amnio-dye or tampon test is a standard test for accurate diagnosis, it involves amniocentesis and instillation of dye; therefore, it is an

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it is an aggressive test and has a risk of placental abruption, miscarriage, bleeding, infection, and iatrogenic uterine perforation so it is rarely done [7]. The Amnisure ROM test is another new test that is easy, fast, and minimally invasive, with high sensitivity and specificity. This test identifies trace amounts of placental alpha-microglobulin-1 (PAMG-1), which is abundant in amniotic fluid [14, 15]. However, Amnisure it is not available in many centers and it is expensive.

For this reason, a non-invasive, simple, and inexpensive method of detecting PPRM is required. Several markers have been studied such as alpha-fetoprotein, fetal fibronectin, creatinine, insulin growth factor binding protein 1, urea, prolactin, and β -hCG(5,7,13-18). β -hCG is a glycoprotein that is secreted in the placenta from syncytiotrophoblasts. Prolactin is a single-chain polypeptide that is secreted during pregnancy from the mother's and fetus's pituitary and decidua. Urea and creatinine are both excreted through glomerular filtration. These markers are also available in amniotic fluid and have been examined for finding PROM in some studies [5, 16-18]. The present study evaluated the value of urea, creatinine and prolactin of vaginal fluid in the diagnosis of PROM in pregnancy. Urea and creatinine of *et al* urine are the most important sources of amniotic fluid in second half of pregnancy. Thus we can say that vaginal fluid creatinine and urea may be helpful in diagnosis of PROM.

Materials and Methods

Between April 2016 and March 2018, 240 pregnant women with gestational age of 28 to 40 weeks were enrolled in the study. All participants were explained the procedure and informed consent was received. The study was approved by the Institutional Ethics Committee.

All patients were divided into two groups. The PROM group comprised women with ruptured membranes and the control group included women who had just presented to our center for periodic examinations. PROM was verified by a sterile speculum examination and observation of fluid leakage in the cervix or accumulation of fluid in the posterior fornix of the vagina, or by both Nitrazine and Fern tests. Patient who had positive pooling, Nitrazine paper test and fern test were considered as confirmed PROM group and these patients were subjected to amniotic fluid urea and creatinine test.

Patients with fetal malformations, fetal growth restriction, fetal distress, placenta previa, vaginal bleeding, vaginal infection, maternal disease, hypertension, preeclampsia and other pregnancy complications were excluded.

Five ml of normal saline solution was poured by a syringe in the posterior vaginal fornix of all participants. After a few minutes the fluid was aspirated by the same syringe and was sent to the laboratory for examination. Urea concentration was measured by enzymatic photometry or urease test and creatinine concentration was determined by Jaffe synthetic chemical calorimetric method.

The statistical package for social sciences (SPSS) software version 16 (Chicago, IL, USA) was used to analyze the data. A p-value less than 0.05 was considered significant.

Results

There was no significant difference between the two groups regarding demographic characteristics (Table 1). The mean of blood urea, creatinine and prolactin were 7.1 ± 5.1 mg/dl, 0.71 ± 0.61 mg/dl and 67.2 ± 35.1 mIU/ml in the study group and 2.6 ± 1.2 mg/dl, 0.20 ± 0.14 mg/dl and 10.4 ± 4.2 mIU/ml in the control group. All the results were significant ($p < 0.001$) (Table 2).

The cut-off, sensitivity, specificity, positive and negative predictive values for detecting PROM of blood urea, creatinine and prolactin are mentioned in Table 3.

Table 1: Comparison of the demographic characteristics

Variables	Investigation Group	Control Group
Age (years old)	22.5 \pm 6.5	22.8 \pm 5.1
Gestational age	37.2 \pm 2.3	32.7 \pm 2.0
No. of pregnancies	2.1 \pm 1.7	2.1 \pm 1.4
No. of deliveries	1.3 \pm 1.4	1.42 \pm 1.5
No. of abortions	0.21 \pm 0.40	0.25 \pm 0.30

Table 2: Comparison of means of blood urea, creatinine and prolactin ($p < 0.001$)

Vaginal Fluid	Urea	Creatinine	Prolactin Markers
PROM group	7.1 \pm 5.1	0.71 \pm 0.61	67.2 \pm 35.1
Control group	2.6 \pm 1.2	0.20 \pm 0.14	10.4 \pm 4.2

Table 3: Evaluation of indicators for diagnostic PROM markers

Variable	Cut-off	Sensitivity	Specificity	PPV	NPV
Urea	3.2	79.5	82.3	81.6	80.2
Creatinine	0.22	74.4	84.8	82.8	77.0
Prolactin	15	87.7	92.2	90.2	88.2

Discussion

Timely and accurate diagnosis of PROM will prevent many adverse effects [1]. In most cases diagnosis is made according to the clinical complaints and traditional methods. However reliance on clinical assessment leads to both false-negative results. Thus we need simple, reliable and rapid test for the diagnosis of PROM. Hence, using biochemical tests and its markers in the vagina has been increased for early diagnosis of ruptured membrane. Alpha fetoprotein, insulin-like hormone, prolactin, urea, creatinine and β -hCG [5, 16-18] plus alanine transaminase and aspartate transaminase [19] have been studied. Researchers are still looking for a simple, fast, and easy way to detect membrane rupture that is accessible and non-invasive. PAMG-1 is a good choice for detecting PROM, it is not available and is expensive compared with prolactin or β -hCG. Thus, some researchers have preferred to find a more convenient diagnostic method.

In our study we found that the levels of the mentioned markers were significantly higher in the study group (with PROM) in comparison to control group (without PROM). The clinical application of prolactin, urea and creatinine in diagnosing PROM has been supported by many studies. In our study cut off value of prolactin urea and creatinine was 15, 3.2, 22 respectively with highest sensitivity and specificity of prolactin 87.7%, 92.2% respectively followed by urea and creatinine.

M Tigga, S Malik *et al.* [20] reported Prolactin to have an average diagnostic performance with a cut off value of 23.56 mg/m l with 78% sensitivity, 70.9%. 75.56% PPV, 73% NPV. In our study cut off value of prolactin was 15 mg/ml. the sensitivity, specificity, PPV, NPV was 87.7%, 92.2%, 90.2% and 88.2% respectively.

In 2004, Buyukbayrak *et al.* [3] found that prolactin with a 30 μ IU/mL cut-off point had 95% sensitivity, 87% specificity, and 87% accuracy, which is consistent with our study and reported that prolactin is a useful diagnostic test in PROM. Li Hy *et al.* [16] studied to determine the usefulness of vaginal fluid hcG, AFP, and creatinine measurement in detection of PROM. They found that creatinine in vaginal fluid washing is a useful marker for PROM diagnosis. It was less expensive and easier to measure

than hcG and AFP, and appeared to be more accurate than hcG. In our study sensitivity and specificity of creatinine is less than prolactin and urea.

Tigga MP *et al.* [20] concluded that AFP is the most reliable marker for the diagnosis of PROM followed by creatinine. Creatinine estimation is a rapid cheap and easily available test with 100 % sensitivity, 92% specificity. In our study sensitivity of creatinine was 74.4% with specificity 84.8%, PPV 81.6%, NPV 80.2%. Taheripannah *et al.* [21] 96% sensitivity and 79.4% specificity for prolactin, could help in detecting membranes rupture, and found prolactin as the marker with the most sensitivity and specificity values. Mohamed and Mostaf [22] found 100% sensitivity and specificity for urea and creatinine.

Kafali and Oksuzler [23] studied urea and creatinine of vaginal liquid with a 12 mg/dL cut-off point for urea and 0.6 mg/dL for creatinine and found that the specificity and sensitivity of both markers was 100%. In our study cut off point for urea was 3.2 mg/ml with 79% sensitivity and 82.3% specificity which is comparatively less.

Kariman *et al.* [24] investigated 179 pregnant women. For urea, they found 90% sensitivity, 79% specificity, and 83% and 87.5% positive and negative predictive values with a 6.0 mg/dL cutoff point. For creatinine, with a 0.45 mg/dL cut-off point, the authors found 100% sensitivity, specificity, PPV and NPV. Kariman *et al.* also found that mean level of vaginal fluid urea and creatinine in the PROM group was significantly higher than the intact *et al.* membranes groups. Creatinine had a higher diagnostic value than urea. In our study, creatinine had less diagnostic value which might be because of the difference in laboratory analysis methods and cut-off points.

Shahin and Raslan [5] demonstrated lower predictive values for prolactin than in our study. This may be because of the different cut-off points or smaller sample size. In our study we found prolactin as the marker with the most sensitivity and specificity values. In our study sensitivity of prolactin, creatinine and urea was 87.7%, 79.5% and 74.4% respectively. This concludes that Prolactin has more diagnostic value followed by urea and creatinine estimation in vaginal fluid in diagnosing PROM.

Conclusion

To conclude vaginal fluid urea, creatinine and prolactin is a simple and reliable test for diagnosis of PROM. We found that the levels of the mentioned markers were significantly higher in the patients with PROM in comparison to those without PROM. Prolactin and β -hCG have more diagnostic value than urea and creatinine in detecting PPROM, and can be used in suspected cases.

These tests are not expensive, and can be used in any medical center. Creatinine assay is gold standard diagnostic test for PROM with higher sensitivity and specificity. Cut-off value for rupture of membranes in different gestational ages in future studies in pregnancy should be calculated.

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