The Evaluation Of Diagnostic Role Of Vaginal Fluid Urea, Creatinine And -HCG Level For Detection Of Premature Rupture Of Membrane.

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Citation

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Abstract

Purpose: Diagnosis of premature rupture of membrane (PROM) is difficult in equivocal cases. The concentration of -HCG, urea and creatinine are high in amniotic fluid. The purpose of this study is to compare the value of vaginal fluid -HCG, Urea and creatinine level for better diagnosis of PROM.
Methods: This study was performed between November 2007 and November 2008, in the Zeinabieh hospital of Shiraz university medical sciences, Iran. A total of 153 pregnant women were recruited in 3 groups. Group I: patients with diagnosis of PROM confirmed by amniotic fluid pooling and ferning test, Group II: patients in whom diagnosis of PROM was suspected but unconfirmed by amniotic fluid pooling or ferning test and Group III: pregnant women without any complaint. All the patients underwent speculum examination for amniotic fluid pooling, ferning test and vaginal washing fluid for -HCG, urea and creatinin sampling. Results: All the three markers were significantly highest in the experimental group. The sensitivity, specificity, positive predictive value and negative predictive value for -HCG were 84.3%, 94.1%, 92% and 90% respectively. creatinine values were 90.2%, 91.2%, 83.6% and 90% respectively and the values for Urea they were 100%, 76.5%, 70.6% and 96% respectively. Conclusion: The urea has the most sensitivity among the three markers but - HCG and Creatinin are more specific for diagnosis of PROM.

INTRODUCTION

Premature rupture of membranes (PROM) is defined as the rupture of membrane before labor at any time during the gestations [1]. The occurrence of premature rupture of the membranes is 10% of all gestations and about 2-4% of preterm pregnancies [2], with complications such as maternal and fetal infections, cord compression or cord prolapse, abruptio placenta, increased rates of cesarean section, fetal deformity syndrome or premature labor and delivery [3] in which preterm birth is 75% of all the causes of perinatal morbidity and mortality [4]. The management of these patients regardless of gestational age remains controversial; therefore, accurate diagnosis is very important to achieve appropriate interventions [2]. Diagnosis of PROM is easy when the rupture is obvious but difficult when the rupture is slight [5].

Various methods are used to diagnose PROM such as nitrazin and ferning test but have low sensitivity and specificity, or injection of intra-amniotic dye, although are very reliable test but are invasive with serious complications [6 – 8].

The absence of a non-invasive gold standard test for the diagnosis of rupture membrane has led to the search for an alternative biochemical marker, vaginal prolactin (PRL), -Fetoprotein (-FP), fetal fibronectin, Growth hormone (GH), Insulin growth factor binding protein-1 (IGFBP-1), Interlukin-6 (Il-6), human placental lactogen (HPL), diamino-oxidase or their combinations [6-12]. All these tests have advantages as well as drawbacks [6-11].

Kafali H and Oskuzlerc reported that sensitivity, specificity, positive and negative predictive values were 100% in detecting PROM by evaluation of vaginal fluid urea and Creatinine concentration [2]. Other studies have measured beta human chorionic gonadotropin (-HCG) level in the vaginal fluid for diagnosis of PROM [1, 5, 13, and 14]. In recent study sensitivity, specificity, positive and negative predictive values were 95.5, 94.7, 91.3 and 97.3%,

respectively [1].

Therefore, the objective of this investigation was to compare the sensitivity and specificity of β-HCG urea and creatinine level in the vaginal fluid for diagnosis of PROM in pregnant women and devise a simple, rapid, easy and reliable test to order for appropriate management and consequently better outcome of these patients.

METHODS

This study was performed between November 2007 and November 2008, In the Zeinabieh hospital of Shiraz University of Medical Sciences (obstetrics clinic and emergency center), and was approved by the Local Research Ethics Committee of Shiraz University of Medical Sciences. 153 pregnant women with gestational age between 14 - 44 who were eligible for enrollment was precipitated in this study and matching was done by computerized numbering. The patients with uterine contraction, multi-fetal pregnancy, prenatal complication, and vaginal bleeding were excluded this study.

After explaining about the aim of this study and procedure for patients and giving informed consent and taking accurate history and physical exam, all the patients underwent a sterile speculum examination and amniotic fluid pooling with or without valsalva maneuver. The ferning test was applied.

51 patients who were pooling (+) and ferning (+) were considered as confirmed PROM cases (group I), 51 patients who were pooling (+) or ferning (+) were taken as suspected but unconfirmed PROM group (group II), and the other 51 patients who did not have any compliant or complication (normal pregnant women) and presenting for routine prenatal care, with a negative ferning test and absence of amniotic fluid pooling, were taken as the control group (group III). Then vaginal washing fluid urea and creatinine sampling was done as follows: 3cc of sterile saline solution was injected into the posterior vaginal fornix.

Then, all the fluid was aspirated from the fornix with the same syringe and sent to the Zeinabieh laboratory immediately for detection of BHCG, urea and creatinine level. Then the sample was divided into two parts, 0.5 cc for urea and creatinine detection by auto-analysis spresling 241 with parsazmun kit and urea (urease – GLDH method) and creatinine (JAFFE method) was measured. And for BHCG titer, the other sample (about 2.5cc) was centrifuged at 2500 rpm. The supernatant part of the vaginal washing fluid sample quantification BHCG measurement by ELISA (stat fux 2100) with (IEMA well method) and RADIM kit was measured. The total duration of the assay was 45-60 min.

Some pregnant women who did not know their exact date of their last menstrual period or did not have prior obstetric sonography, underwent ultrasonography for GA detection .All the speculum examinations were done by the same physician and ultrasonography was performed by the same person in order to eliminate inter observer sampling deference.

Then, the patients were followed up until delivery and gestational age at delivery time. Some parameters (age, gravida, parity, abortion, gestational age at sampling and delivery, vaginal fluid BHCG, urea, creatinine level) were compared using one way ANNOVA and scheffe multiple comparison test, and assessment with the kruskal-wallis test, were used to establish an optimal cut off concentration. The results were evaluated with a significant level of $P < 0.05$.

RESULTS

Demographic data for each group are represented in Table 1. There were no significant differences in age, gravida, parity, abortion and live between these groups ($P < 0.05$). However group III showed significant differences in the gestational age at sampling and delivery with groups I and II. Similarly, there was a significant difference in AFI among three groups.

Table 2 shows the mean Urea, creatinine and β-HCG levels among groups considering CI 95%. The mean difference in vaginal fluid urea levels between group I, II and III was statistically significant ($p<0.05$).The sensitivity, specificity, and positive and negative predictive value were 100%, 76.5%, 70.6% and 96%, respectively, in detecting PROM by evaluation of vaginal fluid urea concentration with a cut off value of 3.5mg/dl . The mean vaginal fluid creatinine levels of groups I, II and III were as table 2, where the difference was statistically significant ($p<0.05$). The sensitivity, specificity and positive and negative predictive values were 90.2%, 91.2%, 83.6% and 90% respectively in detecting PROM by evaluation of vaginal fluid creatinine concentration with a cut off value of 0.75mg/dl. We measured the vaginal fluid β-HCG titer in contemporary urea and creatinine in the prediction of PROM, with ($p<0.05$). The sensitivity, specificity and positive and negative predictive value were 84.3%, 94.1%, 92% and 90%

respectively, with a cutoff point of 36mIU/ml.

Figure 3

Fig 1: Receiver operator characteristics curve for vaginal fluid urea, creatinine and -HCG levels

	Group I	Group II	Group III	P value
Maternal age (years) (CI 95%)	25.2±5.7 (23.6,26.8)	25.4±5.6 (23.8,27)	26.7±5.5 (25,28.1)	>0.05
Gravid	1.98±0.19	2.08±0.16	2± 0.18	>0.05
Parity	0.74±0.12	0.94±0.15	0.8±0.15	>0.05
Abortion	0.19±0.12	0.13±0.06	0.17±0.067	>0.05
Live	0.74±0.13	0.94±0.14	0.8±0.15	>0.05
Gestational age at sampling (wks) (CI 95%)	34.5±5.7 (32.9,36.1)	33.35±4.6 (32,34.6)	37.15±2.4 (36.5,37.9)	0.0001
Gestational age at delivery(wks) (CI 95%)	35±5.2 (33.6,36.4)	33.94±4.6 (32.6,35.2)	38.5±0.86 (38.3,38.7)	0.0001
AFI(cm) (CI 95%)	3.71±0.2 (3.66,3.76)	7.47±0.25 (7.41,7.53)	9.95±0.4 (9.84,10.06)	<0.0001

Figure 2

Table-2: Demographic data of vaginal fluid urea, Creatinin and -hcg levels among groups 6. Butwick A, Aleshi P, Yamout I. Obstetric hemorrhage during an EXIT procedure for severe fetal airway obstruction. Can J Anaesth. 2009 Jun;56(6):437-42.

	Group I	Group II	Group III	P Value
Urea(mg/dl) (CI 95%)	9.04±0.57 (8.89,9.19)	4±0.31 (3.92,4.08)	0.313±0.77 (0.1,0.52)	<0.0001
Creatinin(mg/dl) (CI 95%)	0.22±0.08 (0.2,0.24)	0.55±0.04 (0.54,0.56)	0.068±0.02 (0.063,0.073)	<0.0001
B-HCG(mIU/ml) (CI 95%)	334±72 (314.2,353.8)	19.4±2 (17.1,21.7)	4.02±0.9 (3.78,4.26)	<0.0001

{image:3}

DISCUSSION

Correct diagnosis of PROM is of great importance because failure of diagnosis can lead to unwanted obstetric complications such as chorioamnionitis, preterm birth; on the other hand over diagnosis can lead to unnecessary interventions like hospitalization [2, 6].

The approach to the diagnosis of rupture membrane 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 a nitrazine/ ferning positive vaginal pool of fluid. The nitrazine test can be falsely positive if the vaginal PH is increased by the blood of serum contamination or alkaline antiseptics, or if bacterial vaginosis is present. The ferning test should be performed on a sample collected from the posterior fornix or lateral vaginal sidewall to avoid cervical mucus, which may also yield a false positive result [1, 2 and 6].

Prolonged leakage with minimal residual fluid can lead to a false negative nitrazine or ferning test. Should initial testing be negative but a clinical suspicion of rupture membrane remain, the patient can be retested after prolonged recumbence or alternate measures can be considered [2].

Ultrasound evaluation may prove useful if the diagnosis remains after speculum examination. The diagnosis of membrane rupture can be confirmed unequivocally with ultrasound-guided amnioinfusion of indigocarmin (1ml in 9ml of sterile normal saline), followed by observation for passage of blue fluid per vagina [2]. Although oligohydroamnious without evident fetal urinary tract malformations or fetal growth restriction may be suggestive of rupture membrane, ultrasound alone cannot diagnose or exclude rupture membrane with certainly [2, 6].

Alternative biochemical markers for diagnosing PROM have been investigated. Markers such as diamnio- oxydase, prolactin, alpha-feto-protein, fetal fibronectin, and IGFBP-1 have advantages and disadvantages. However, despite the improved diagnostic value of these markers, they have not become popular because of their complexity and cost [1].

In a study done by Esim and Turan, diagnosis of PROM was identified by -HCG level in vaginal fluid of 114 pregnant women. They concluded that -HCG is a reliable, simple and rapid test for diagnosis of PROM [5].

Gurbuz and co-workers studied about the level of creatinine in vaginal fluid of 54 pregnant women and concluded that creatinine assay in vaginal fluid is a cheap and fast method for detection of PROM [6].

In the present study, we compared 3 biochemical markers (-HCG, urea and creatinin) for diagnosis of PROM. -HCG is a glycoprotein produced exclusively by syncitiotrophoblasts in the placenta. It is present in the amniotic fluid as well as maternal blood and urine, at concentrations ranging from approximately 2000-70000mIU/ml and it seems be helpful in diagnosis of PROM[1, 5]. Also, vaginal fluid creatinin and urea may be helpful in diagnosis of PROM because fetal urine is one of the important sources of amniotic fluid

volume [2].

Vaginal fluid (-HCG, urea and creatinin) determinations have been used in the clinical studies to diagnose PROM [1-2]. But the aim of this study was to compare diagnostic values of -HCG, urea and creatinin in the vaginal fluid. All the three markers were significantly higher in the group I (documented rupture of membrane) than in suspicious groups (group II), ($p<0.05$) and also significantly higher in group II (suspicious case) than in the control group (group III). The sensitivity, specificity and positive and negative predictive values in -HCG were 84.3%,

94.1%, 92% and 90%, with the cut off value of 36 mIU/ml. These results are compatible with those other studies study [15]. All our patients were in the 2nd and 3rd trimester and it seem the fluid -HCG level appears to serve as a reliable marker of PROM at least during the second and third trimesters [15].

Moreover in the present study, the creatinine sensitivity, specificity and positive and negative predictive values were 90.2%, 91.2%, 83.6% and 90%, respectively in detecting PROM with cut off point of 0.75mg/dl. This is compatible with other studies [2, 6]. As to urea, there is only one other study in which 100% sensitivity and specificity was detected [2]. Also we detected similar sensitivity for the urea but less specificity than that of the former study (76.5%). We did not evaluate analysis of creatinine and Urea in the amniotic fluid according its gestational age. It has been reported that creatinine and Urea concentration in the amniotic fluid increased gradually between 20 and 32 wks of gestation, which might be a cause of difference between the statistics in different studies.

Receiver Operating Characteristic (ROC) curve analysis was used to establish the optimal cut off concentration for vaginal washing fluid of -HCG Urea and creatinine level. The cut off values of 3.5 mg/dl for Urea, 0.75mg/dl for creatinine and 36mIU/ml for -HCG were found (Fig 1).

CONCLUSION

In summary, we have found that determination of vaginal fluid urea, creatinine and -HCG concentration in the 2nd and 3rd trimesters is a valuable method for diagnosis of PROM and can be used as an adjunctive test in equivocal case. Between them, Urea has the best sensitivity although -HCG and creatinine are more specific for diagnosis of PROM. In the present series, the simplicity of the test makes them an alternative choice in the clinical practice.

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