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Role of vaginal fluid creatinine level in prediction of premature rupture of membranes

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Abstract

Aims and Objective: To evaluate the role of vaginal fluid creatinine in prediction of PROM (premature rupture of membranes).

Materials and Methods: It was an analytical cross-sectional study including two groups with 50 women in each group. Group I (cases) included confirmed PROM and Group II were controls without leaking per vaginum. Vaginal fluid sampling was done and creatinine levels were assessed in both groups. Data analysis was done by Student's t-test, Receiving operator characteristic curve and chi square test. Mean value of vaginal fluid creatinine (mg /dL) was higher in the PROM group than the control group (0.75 ± 0.16 and 0.19 ± 0.06 respectively). The best cut-off point for vaginal fluid creatinine for diagnosis of PROM was >0.34mg/dL, with 100% sensitivity, 100% specificity, 100% PPV and 96% NPV (P=0.001).

Conclusion: Vaginal fluid creatinine is a simple, practical, cost-effective test and its incorporation in the low resource setting will be a game changer in the diagnosis of PROM.

Keywords: vaginal fluid creatinine, pregnancy, PROM

Introduction

Premature rupture of membranes (PROM) refers to rupture of the fetal membranes prior to the onset of labour, regardless of gestational age. It is seen in 10% of term pregnancies and 2-4% of preterm pregnancies.

Accurate history, clinical examination and specialized tests are the hallmark for diagnosing PROM. False negative or false positive diagnosis of PROM may lead to inappropriate management and serious maternal and neonatal complications or unnecessary obstetric interventions. A better understanding of the diagnosis and management of PROM allows obstetrician to optimize perinatal outcome and minimize neonatal morbidity. Women with rupture of the membranes typically presents as a fluid or as a steady trickle through vagina. Diagnosis of rupture of membranes depends on clinical ability to document three clinical signs on sterile speculum examination: (1) visual pooling of clear fluid in the posterior fornix of the vagina or leakage of fluid from the cervical os; (2) an alkaline pH of the cervicovaginal discharge, which is typically demonstrated by seeing whether the discharge turns yellow nitrazine paper to blue (nitrazine test); and (3) microscopic ferning pattern of the cervico vaginal discharge on drying (ferning test)

However, these conventional methods are associated with drawbacks. Many bio chemical diagnostic modalities for PROM have been described like measurement of vaginal pH, alpha feto protein, (AFP), insulin growth factor binding protein-1(IGFBP-1), fetal fibronectin level, human chorionic gonadotropin (HCG) and prolactin. These tests are mainly focused on the biophysical and biochemical characteristics of amniotic fluid. An ideal biochemical marker for diagnosis of membrane rupture should have a high concentration in amniotic fluid and a low concentration in maternal blood & cervicovaginal discharge with intact membranes. Amniotic fluid urea and creatinine are one of these biochemical markers that mainly originated from excretion by fetal kidneys and found to be gradually increasing throughout the pregnancy.[1] The foetus starts excreting urine into the amniotic fluid at around 8th to 11th week of gestation.[2] On the other hand, urea and creatinine in cervicovaginal secretions are in accordance with maternal serum levels. Therefore, in the presence of PROM the level of these foetal originated markers should be higher in the amniotic fluid than in normal cervicovaginal secretions. Considering the technical ease and cost effectiveness of vaginal fluid urea and creatinine measurement, introduction of this method into routine use is feasible and practical.

Aims and objectives

1.To determine the role of vaginal fluid creatinine in prediction of PROM (premature rupture of membranes)

2. To find out appropriate cut off value of vaginal fluid creatinine levels to predict PROM.

Materials and methods

The study was conducted in the Department of Obstetrics and Gynaecology, S.M.S. Medical College and Attached Group of Hospitals, Jaipur. Women with singleton pregnancy and gestational age between 20 and 40 weeks were included in the study after taking written informed consent. Pregnant women with vaginal spotting\bleeding, meconium in vaginal fluid leak, recent vaginal infection having history of use of vaginal drugs, pregnant women with regular uterine contractions and with fetal anomalies were excluded.

The study sample was divided into two groups with 50 pregnant women in each group: a) GROUP I (Cases)-Diagnosis of premature rupture of membranes by visualization of amniotic fluid from cervical canal or vaginal pooling of amniotic fluid. b) GROUP II (Control)-Without any complaint or complications.

All the women who participated in study were subjected to full history taking, general and abdominal

examination. Period of gestation in weeks was estimated by last menstrual period or 1st trimester ultra-sonography. Sterile speculum examination was done for inspection of amniotic fluid passing through cervical canal. 5ml sterile normal saline was flushed into the posterior fornix of vagina, then aspirated by the same syringe and sent to the laboratory for creatinine level estimation. Sampling was done before Per Vaginal examination or administration of vaginal drugs. Creatinine in the vaginal fluid sample was estimated by JAFFE'S method. Ultrasonography was done for foetal well-being and AFI (Amniotic Fluid Index).

Statistical Analysis

Data collected was entered in MS Excel sheet. Continuous variables were summarized as mean and standard deviation while nominal/categorical variables were expressed as percentages. Unpaired t-test was used for analysis of continuous variables while chi-square test and Fischer Exact test were used for nominal/categorical variable. Diagnostic accuracy was assessed using following terms: Sensitivity, Specificity, PPV and NPV and was calculated using standard formulae. p value < 0.05 was taken as significant. Medcalc 16.4 version software was used for all statistical calculations.

Table 1: sociodemographic factors

Variable	Case	Control	P value
Age			0.551
19-24 years	23(46%)	24(48%)	
25-30years	20(40%)	22(44%)	
>30years	7(14%)	4(8%)	
Residence			0.15
Urban	21(42%)	29(58%)	
Rural	29(58%)	21(42%)	
Socioeconomic status			0.03
Upper	5(10%)	7(14%)	
Middle	14(28%)	25(50%)	
Lower	31(62%)	18(36%)	
Bmi(kg/m2)			0.001
<19	25(50%)	6(12%)	
19.1-24.9	25(50%)	43(86%)	
25-29.9	0(0%)	1(2%)	
>30	0(0%)	0(0%)	
Gravida			
Primigravida	13(26%)	15(30%)	
Multigravida	37(74%)	35(70%)	

Table2: Risk factors of PROM

Previous history of prom			0.02
Yes	18(36%)	8(16%)	
No	32(64%)	42(84%)	
History of anemia			0.001
<10	35(70%)	20(40%)	
>10	15(30%)	30(60%)	
History of smoking			0.027
Yes	15(30%)	6(12%)	
No	35(70%)	44(88%)	

Table 3

Cervical factors (cms)			
Mean cervical dilatation	1.73±0.86	0.98±0.68	0.001
Mean cervical length	1.91±0.81	2.53±0.56	0.001

Table 4

Vaginal fluid creatinine(mg/dl)			0.001
<0.3	0(0%)	47(94%)	
0.3-0.6	11(22%)	3(6%)	
0.6-0.9	29(58%)	0(0%)	
>0.9	10(20%)	0(0%)	
Mean	0.75±0.16 0.	0.19±0.06 0.001	0.001

Gestational age(weeks)	Vaginal fluid creatinine (mg/ dl)
<28	0.43±0.01
28-32	0.55±0.09
32-37	0.77±0.16
>37	0.86±0.16

Results and discussion

PROM is one of the most troublesome issues in today's obstetrics. The initial management of a woman presenting with PROM should focus on confirmation of diagnosis, validating the gestational age, documenting foetal well-being and deciding the mode of delivery.

Demographic data for study groups is represented in table 1. In our study the mean age (years) in PROM and control group were similar, 25.54±4.04 and 25.04±3.61 respectively. In this study 21(42%) cases and 29(58%) controls belonged to urban and rural area respectively. As p value is 0.15 it is statistically significant.

In our study, majority of women with PROM (62%) belonged to lower socio-economic status while in control group majority (50%) belonged to middle socioeconomic status. This is statistically significant as p value is 0.03. The occurrence of PROM was more common in women belonging to lower socioeconomic status due to malnutrition, infection and low hygiene. In a study by Anuradha Chakarvarty et al (2018)[4], low social economic class was a significant risk factor for preterm PROM.

In our study 50% of women with PROM (cases) had a BMI <19kg/m^2. Majority of control group (86%) had BMI of 19.1 -24.9kg/m^2. The mean BMI (kg/m^2) of PROM and control group were 19.27±1.15and 21.01±1.72 respectively. We found that PROM had a statistically significant association with low BMI (p=0.001). In a similar study by Damien Bouvieret al (2019)[5] the risk of premature rupture of membranes was almost 2 times higher in women with low BMI than the control group (AOR-1.91, CI-1.04-3.52). Main etiology is chronic nutritional deficiency due to suboptimal nutritional intake. This causes defective embryonic and placental development predisposing to premature rupture of membranes.

Table 2 demonstrates high risk factors for prediction of PROM. 18(36%) cases and only 8(16%) in control group had a previous history of PROM which is statistically significant (p value is 0.02). Natnael Etsay et al (2018)[3], in their study observed that previous history of premature rupture of membranes was the strongest risk factor for premature rupture of membranes and was 4.45 times higher than the control group (AOR 4.45, CI:1.87,10.6). This might be due to untreated genitourinary infection and short cervical length.

In terms of history of anaemia, haemoglobin was <10 gm/dl in 35(70%) women in case group and 20(40%) women in control group. Our study observed that PROM had a statistically significant association with anaemia (p<0.001). Similar findings were observed in a study by Nusrat Mahjabeen et al (2021)[6], where maternal anaemia on admission was significantly associated with an increased risk of preterm PROM. Anemia increases the risk of maternal infections, and induces a state of chronic hypoxia leading to oxidative stress which damages the erythrocytes and fetoplacental unit.

There was history of smoking in 15(30%) women in case group and 6(12%) women in control group (p value 0.027). So there was statistically significant difference between both groups regarding previous history of PROM, anaemia and smoking. In a study by Damien Bouvier et al[5], history of smoking was significant risk factor for premature rupture of membranes. (p<0.05).

Another study by Helena Choltus et al (2021) concluded that maternal smoking is a risk factor for premature prelab our rupture of membranes. Cigarette Smoke Condensate exposure induces receptor for advanced glycation end- products (RAGE) which causes inflammation leading to increased gelatinase activity and thus pathological weakening of membranes.[7]

In Table 3, we observed that women with PROM have more cervical dilatation and less cervical length which were statistically significant (p-0.001). In our study, mean cervical dilatation (CMS) in PROM and control group were 1.73±0.86 and 0.98±0.68 respectively. The mean cervical length (CMS) in PROM and control group were 1.91±0.81 and 2.53±0.56cms. Both the parameters were statistically significant (p=0.001). In a study by Kuruoğlu et al (2019)[8], the mean cervical dilatation and mean cervical effacement were significantly higher in the PROM group (P=0.01). The authors suggested that this difference was attributed to the onset of labor in the PROM patient. In a similar study by Gezer et al (2016)[9], the mean cervical dilatation in cases and control were 1.14±0.97 and 0.33±0.55 respectively(p<0.001). The mean cervical effacement (%) was also statistically significant, 24±27.4 in PROM group and 8.3±17.9 in control. It is either due to short cervical length or inherent collagen deficiency.

In Table 4, mean vaginal fluid creatinine (mg/dL) in women with PROM and control were 0.75±0.16 and 0.19±0.06 respectively, which was statistically highly significant (p=0.001).

Similar findings were observed in a study done by Begum et al (2017)[1], where the mean value of vaginal fluid creatinine was higher in the PROM group than in the control group (0.67 ± 0.31 vs. 0.16 ± 0.09), which was statistically significant. In a similar study by Kadar et al (2018)[10], it was observed that the mean concentration of creatinine was 1.22 ± 0.28 mg/dL in the case group and 0.36 ± 0.26 mg/dL in the control group, which was statistically significant. We found a positive correlation between increasing gestational weeks and vaginal fluid creatinine which was statistically significant (p= 0.001). Women with >37weeks of gestation (term PROM) had a mean vaginal fluid creatinine (mg/dL) of 0.86±0.16, which was high compared to women with preterm PROM ((<28weeks =0.43± 0.01, 28- 32weeks= 0.55± 0.09, 32-37 weeks= 0.77± 0.16).

Abha Sharma et al (2020)[11] studied the biochemical profile of amniotic fluid for the assessment of foetal and renal development. It seems evident in their study that the origin of these two markers (urea and creatinine) is a function of filtration in the foetal kidneys. The increasing growth profile of creatinine and urea throughout normal pregnancy is due to glomerular filtration and maturation of tubular function. Since creatinine represents the most accurate renal marker upto 100% specificity, the authors considered it as good indicator of maturation and renal function.

Conclusion

In a common clinical situation where the obstetrician encounters a woman with possible ruptured membranes, diagnostic accuracy is the key to successful management and improved perinatal outcome. Early and accurate diagnosis of premature rupture of membranes allows for gestational age–specific obstetric interventions, designed to optimize the perinatal outcome and minimize the serious complications. Conversely, a false diagnosis of PROM may lead to unnecessary obstetric intervention including hospitalization, inadvertent administration of antibiotics and corticosteroids, and even induction of

labor. The present study was done to find out the role of vaginal fluid creatinine in predicting PROM and timely obstetric intervention to minimise the feto-maternal risk, especially in a low resource setting. In the present study vaginal fluid creatinine was found to be a reliable marker for prediction of PROM. Moreover, we observed a positive correlation between vaginal fluid creatinine and gestational age. Vaginal fluid creatinine is a simple, practical, cost-effective and easily accessible test and its incorporation in the low resource setting will be a game changer in the diagnosis of PROM. Further studies can be taken up with different gestational age groups for determination of cut-off values of vaginal fluid creatinine for diagnosing
PROM.

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