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A Prospective Case-Control Study on Vaginal Fluid Creatinine for the Detection of Premature Rupture of Membrane (PROM)

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ABSTRACT

PROM occurs in 10% of all pregnancies and is a major cause of preterm birth and perinatal mortality and morbidity. Clinicians are usually uncertain regarding the diagnosis of PROM based on examination and history alone. A misdiagnosis often leads to unnecessary interventions that may be detrimental to mother and fetus. There is currently no ideal non-invasive diagnostic test that can diagnose prolabor rupture of membranes with certainty. This study aims to evaluate the reliability of vaginal fluid creatinine for the diagnosis of PROM in female with singleton pregnancies at 28-42 weeks of gestation. A prospective case control study was performed at Kamla Raja Hospital for a period of 2 year from November 2020 to October 2022. Sample size 200 patients was taken and divided into 2 groups, 100 study group and 100 controls. Out of 100 study group, 50 were in study group 1 (confirmed cases) and 50 in study group II (suspected cases). Patients with history of leaking PV and positive amniotic fluid flow from the cervix were included in group I and patients with history of leaking PV but no amniotic fluid flow from the cervix were included in group II. Vaginal fluid creatinine cut off value set at 0.45 mg/dl has a higher sensitivity (100%) and specificity (82.4%), PPV (66.7%) and NPV (100%) than other tests. P value was <0.001. Vaginal fluid creatinine determination for the diagnosis of PROM is reliable, simple, rapid, and inexpensive.

INTRODUCTION

PROM- Defined as a syndrome characterized by a spontaneous rupture of membranes of chorioamnion which is made up of 4 to 6 layers of chorion and single layer of amnion with collagen rich connective tissue before onset of uterine contraction[1]. Term Premature Rupture Of Membrane (TPROM)-when rupture of membrane soccur after 37 weeks of gestation to 42 weeks[2]. Preterm Premature Rupture Of Membrane (PPROM)- defined as the spontaneous rupture of the amniotic membranes before the onset of uterine contractions beyond 28 weeks or at less than 37 weeks[3].

PROM varies from 2-18% (avg. 10%) in which Term PROM is 70% cases and Preterm PROM 3% cases, in which it is responsible for 30% Preterm delivery (Arias and Tomich 1982). PROM is a major cause of preterm birth and perinatal mortality, and morbidity so correct diagnosis of PROM is crucial for appropriate management and requires a judicious assessment of history, clinical findings, and specialized tests. False positive diagnosis of PROM or failure to identify patients of PROM may lead to inappropriate management, unnecessary obstetric interventions, and serious maternal / neonatal complications.

In clinically asymptomatic and in suspicious patients, the diagnostic tests currently used are measurement of vaginal pH (NITRAZINE TEST), AFP, human chorionic gonadotrophins (HCG), diamine oxidase, prolactin, IGFBP-1, FFN (Fetal fibronectin, and Fern test. However, none of these tests diagnose PROM with 100% certainty. Some studies have been done on vaginal fluid creatinine levels to detect PROM in recent years on the basis that fetal urine is the most important source of amniotic fluid in the third trimester. The ideal test for the diagnosis of PROM in equivocal cases should be simple, rapid, inexpensive, and non-invasive and accuracy of the test should not be hampered by the presence of contaminants like blood, semen, cervical mucus, and urine. An accurate biochemical marker used to detect PROM should have a high concentration in the amniotic fluid, a low concentration in maternal blood and extremely low background concentration in cervicovaginal discharge with intact membranes.The present study evaluates the reliability of creatinine measurement for the diagnosis of PROM and It will help in making the diagnosis of PROM in equivocal cases. This will help in taking prompt decisions for maternal and perinatal outcomes.

MATERIALS AND METHODS

Study design: Prospective case control study.

Study setup and duration: The study was carried out in the dept. of obstetrics and gynecology, Kamla Raja Hospital, G.R.M.C., Gwalior (M.P.) and for a period of 2 year from nov.2020 to oct.2022.

Study population: A Total of 200 cases out of which 100 were in study group and 100 were in control group. Study group was divided into 2 groups. Study group1 consisting of 50 (confirmed cases) and study group 2 consisting of 50(suspected cases). It was approved by ethical committee of obstetrics and gynecology, at, G.R.M.C., Gwalior for all pregnant women who were included in the study, explanation of the study procedures was done, and informed consent was obtained.

Inclusion criteria: Women with singleton pregnancy with gestational age between 28 to 40 weeks (by LMP or 1st trimester sonography findings).

Exclusion criteria: In this study, pregnant women were excluded if there was pregnancy included - multiple pregnancy, patients with medical complications, vaginal spotting or bleeding or meconium in the vaginal fluid leak, presence of true uterine contractions.

Methods: All participants eligible for the study were given a written informed consent after adequate counseling. A detailed history was obtained regarding age, parity, socioeconomic status, antenatal checkup, duration of rupture of membranes, liquor color and consistency, onset of labor pain as per proforma attached. 200 pregnant women with a singleton pregnancy and gestational age (GA) of 28-40 weeks who were admitted in the Department of Obstetrics and gynecology, Kamla Raja Hospital, Gwalior or from OPD were recruited into this study. This study was approved by the ethical committee of Gajra Raja Medical College, Gwalior. The study group consisted of 100 pregnant women with the complaint of vaginal fluid leakage and control group consisted of 100 normal pregnant women from OPD and labor room who are not in active labor and they were selected randomly. Gestational age was determined either by her LMP or by the sonography of the first half of pregnancy. All women in the study group-1 underwent a sterile speculum examination to confirm amniotic fluid (AF) flowing from the cervix. Positive results were considered as (confirmed PROM group) study group-1, while patients with a complaint of vaginal fluid leakage and no obvious AF flowing were considered as (suspected PROM group) study group-II. There were 50 participants in group 1 and group 2 each and there were 100 participants in the control group. In cases of flowing/pooling AF, for creatinine sampling patient should be lying down at the edge of table and put the speculum for the inspection 3 mL of sterile water is

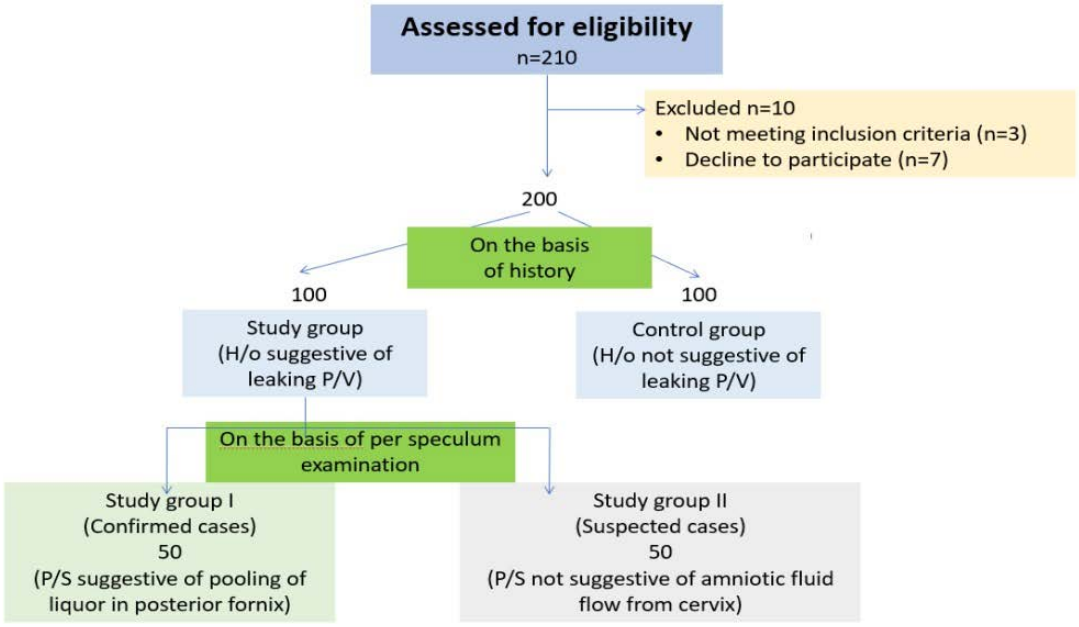

Fig. 1: Representation of criteria for study groups

flushed into the vagina posteriorly via syringe and aspirate the vaginal fluid from the posterior fornix by the same syringe. Samples taken from the OPD were sent immediately and samples taken from the admitted patients during emergency hours were 1st stored in the refrigerator (freezer compartment) in the labor room and then they were sent during the routine hours to the Biochemistry Department, G.R. Medical College, Gwalior. They were centrifuged and kept refrigerated at -30°C. All speculum examinations, sample collections were performed by the same physician. All the patients admitted in KRH (Department of Obst & Gynae) and from OPD were advised USG for AFI (Amniotic fluid Index) detection. Age, parity, GA, and creatinine levels were compared using one-way ANNOVA and c2 test. Receiver operating characteristic (ROC) curve analysis was used to establish an optimal cut-off point. The significance level was set at 0.05 (Fig. 1).

RESULTS

Demographic data, clinical characteristics, and vaginal fluid creatinine level in all three groups are shown in (Table 1). The three groups were similar with respect to maternal age, parity, gestational age, and amniotic fluid index. The mean vaginal fluid creatinine concentration in group I was higher than the other two groups (Fig. 2).

The sensitivity (100%), specificity (82.4%), positive predictive value (PPV) (66.7%), and negative predictive value (NPV) (100%) were highest in detecting PROM by evaluation of vaginal fluid creatinine concentration with a cut-off value of 0.45 mg dL^{-1} (Fig. 3).

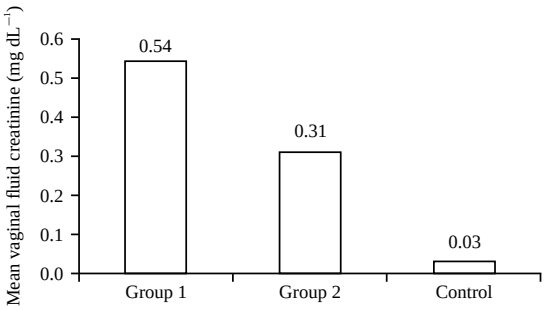

Fig. 2: ROC Curve for vaginal fluid creatinine for diagnosis of PROM

Table 1: Vaginal fluid creatinine for diagnosis of PROM

AUC (95% CI)	0.917 (0.884 – 0.954)
P value	<0.001 (S)
Critical cutoff	0.45
Sensitivity	100%
Specificity	82.4%
PPV	66.7%
NPV	100%

DISCUSSION

In present study most of females were in age group of 20-24 years in both the groups. In Study group 1 (confirmed PROM) = 56%, In study group 2 (suspected PROM) = 52% and In control 57% women were in age group of 20-24 years. This is comparable to similar study by Mansooreh S. Zanjani, Ladan Haghighi *et al.* [4] and Nomosadat Kariman, Maryam Afrakhte *et al.* [5] and J. Begum, Sunil kumar samal *et al.* [6]. This study had showed that PROM occurs more in younger age group. In present study most of women were from rural areas. In Study group 1 (confirmed PROM) = 66%,

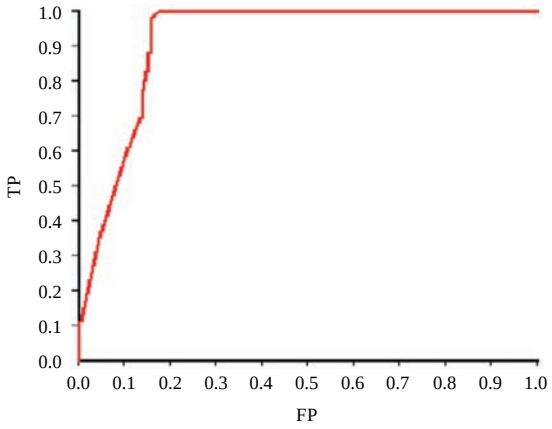

Fig. 3: Comparison of mean vaginal fluid creatinine among study groups

In study group 2 (suspected PROM) = 56% and In control 62% women belong to rural areas. In group 1 34%, group 2 44% and In control 38% women belong to urban areas. So this study had showed that women with PROM belong more commonly to rural areas. Unhygienic conditions in rural areas lead to more chances of vaginal and intrauterine infections. Thus it leads to more cases of PROM. In present study most of women were unbooked. In Study group 1 (confirmed PROM) 76% women were unbooked and in study group 2 (suspected PROM) 80% women were unbooked. In study group 1 24%, study group 2 20% and in control 27% were booked. Similar results were shown in study done by Anjana devi *et al*[7]. In present study most of women were referred. In Study group 1 (confirmed PROM) 62% women were referred and In Study group2 (suspected PROM) 44% were referred. In study group1 38%, study group 2 56% and in control 68% were directly taken. In present study most of women belong to lower socioeconomic class. In Study group1 (confirmed PROM) 50% and in Study group2 (suspected PROM) 26% women belong to lower socioeconomic class. Similar results were shown in the study done by Anjana devi et al(7) 88.4% in this scale. The major factor that leaded to increase PROM cases was malnutrition which leaded to increase in infections and fetomaternal morbidity. In present study most of cases had received only primary education. In Study group 1 (confirmed PROM) 30% and In Study group 2 (suspected PROM) 38% women had received primary education. In a study done by Feliza Vida D. Cortez *et al*. [8] results showed that majority of women with PROM had received education till high school. In present study most of cases were primigravida. In Study group 1 (confirmed PROM) 60% women, In Study group 2(suspected PROM) 58% women and in control 56% women were primigravida. In study group1 40%, in study group2 42% and in control 44% women were multigravida. This is comparable to similar study Umed Thakor *et al*.[9] 53.2%. In present study 68% women of group1, 42% women of group2 and 54% women of control were of ≥37 weeks gestation. 32% women of group 1, 58% women of group 2 and 46% women of control were of <37 week gestation. This is comparable to a study conducted by Shwetha Patil *et al*. This implies that the risk increases with increasing gestational age due to mechanical stretching of membranes. In present, in group 1 (confirmed PROM) mean creatinine value of 0.54mg dL^{-1} was found, in study group 2 (suspected PROM) mean creatinine value of 0.31mg dL^{-1} was found and In control group mean creatinine value of 0.03 mg dL^{-1} was found. This is comparable to similar studies of Mansooreh S. Zanjaniand Ladan Haghighi[4] in which mean creatinine value was 1.74 mg dL^{-1} and study done by Kariman *et al.*[5] showed mean creatinine value of 1.58 mg dL^{-1}. Li HY *et al*. found that measurement of creatinine in vaginal fluid is cheaper, easier and faster than HCG. In another study Gurbuz *et al*.[10] reported that measurement of vaginal fluid creatinine with a cut-off value of 0.12 mg dL^{-1} and sensitivity, specificity, PPV, NPV of 100% in detecting PROM, is cheaper and faster than other methods. Kafali *et al.*[11] reported that determination of urea or creatinine in vaginal fluid for the diagnosis of PROM is a reliable, simple an rapid test with sensitivity, specificity, PPV, NPV of 100% with a cut-off value of 12 and 0.6mg dL^{-1}, respectively.

CONCLUSION

PROM is defined as rupture of chorioamniotic membranes before the onset of labor. Incidence of PROM is 2-18% in all pregnancies. PROM is a significant obstetric condition because it is associated with high risk of maternal and fetal morbidity and mortality. That's why an appropriate and accurate diagnosis of PROM is crucial to optimize pregnancy outcome. It will allow the obstetric care providers to make correct diagnosis of PROM and thus to minimize maternal and neonatal morbidity and mortality.

The study results are showing that PROM is more prevalent in younger age group , women belong to rural areas, unbooked cases, referred cases, lower socioeconomic class according to kuppuswami scale, who have only received primary education. According to this study determination of vaginal fluid creatinine is a reliable, simple, cheap, and rapid test with sensitivity 100%, specificity 82.4%, PPV 66.7%, NPV 100%with a cut-off value of 0.45mg dL^{-1}. It costs much lesser than hospitalization and other tests with similar sensitivity and specificity in suspicious cases.

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