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## Original Article

# Role of Vaginal Fluid Aspartate Aminotransferase and Alanine Aminotransferase in the Diagnosis of Pre-Labor Rupture of Membranes

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## ABSTRACT

**Background:** Pre-labor rupture of membrane is a common obstetric complication. Rapid and good diagnosis is needed to prevent bad obstetric complication and unneeded hospitalization.

**Aim of work:** The aim of this study was to evaluate the reliability of aspartate aminotransferase [AST] and alanine aminotransferase [ALT] enzymes measurement in vaginal washing fluid for the diagnosis of pre-labour rupture of membranes.

**Patient and method:** This case-control study was carried out in two departments of Obstetrics and Gynecology [Al-Azhar University Hospital, New Damietta and Senbellawein General Hospital], between March 2019 and December 2020. It included 90 pregnant women at gestational age 30-40 weeks. They were divided into two equal groups. Group I [case group, PROM group]: included women with diagnosis of rupture of membranes confirmed by visualization of amniotic fluid passing from the cervical canal, and Group II [control group] included women without any complaint or complication. All were clinically evaluated and the vaginal fluid was aspirated for laboratory analysis.

**Results:** Results revealed significant differences between the studied groups. The mean AST level in the PROM group was  $18.84 \pm 5.74$  and  $3.33 \pm 1.29$  in the control group [ $P < 0.001$ ]. The optimal cutoff concentration for AST levels in vaginal secretions is  $> 8$  IU/L. The mean ALT levels were  $5.09 \pm 2.1$  in the PROM and  $1.13 \pm 0.94$  in the control group, with significant difference between groups [ $P < 0.001$ ]. The cutoff value of  $> 2.5$  IU/L is optimal.

**Conclusion:** Vaginal fluid Aspartate aminotransferase [AST] and Alanine aminotransferase [ALT] have high sensitivity and high negative predictive value. So, they are considered a good screening tests for detection of PROM. Also measuring vaginal fluid AST and ALT levels are cheaper, faster, available and reliable method for detection of pre-labor rupture of membranes.

**Keywords:** Rupture of Membranes; Alanine; Aspartate Aminotransferase; Vaginal Washing Fluid; Amniotic Fluid.

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\* Main subject and any subcategories have been classified according to the research topic.

## INTRODUCTION

Spontaneous rupture of membranes [ROM] is a normal cascade of labor and parturition process but the pre-labor rupture of membranes [PROM] is not. PROM points to rupture of the membranes earlier to the onset of parturition and before the onset of clinically obvious contractions of labor [1].

PROM can occur at any gestational age and is identified as "preterm PROM" if the rupture happens prior to 37 weeks of gestation. If it occurs beyond the 37 weeks, it is called "term PROM" [2].

The diagnosis of PPRM is a challenge and difficult when maternal history of PPRM is not reinforced with vaginal pooling of amniotic fluid or membrane rupture is inappreciable [3]. The diagnosis of PROM is difficult 48 h or in long and preterm rupture of membranes. Since the lack of diagnosis can lead to serious complications, proper diagnosis is required [1].

PPROM reported in 3% of gestations and 30%-40% of preterm labors are related to PPRM. The term PROM was reported as a complication of approximately 8.0% of gestations [1, 3].

PROM is associated with number of adverse maternal and neonatal aftereffects. The most common maternal outcomes associated with PROM are endomyometritis, chorioamnionitis, and wound infection, bacteremia and post-partum hemorrhage [4].

Since many fetal complications are caused by prolonged rupture of membranes, rapid diagnosis of PROM is important [5]. The diagnosis of PROM is currently conducted by the following methods: Maternal history of the sudden departure of fluid from the vagina and direct visualization of clear fluid in the vaginal posterior fornix or fluid leak from the mouth of cervix through examination by sterile speculum [6].

Nitrazine test that examines the alkaline PH of cervico-vaginal secretions. The test has a high rate of false positives in cases of cervicitis, vaginitis, alkaline urine, semen or blood contamination and the use of antiseptics [7].

Fern test is a microscopic crystallization examination of amniotic fluid. The false positives are due to contamination with cervical mucus and semen and false negative in the test because of the wrong technique or contamination with blood [2].

Amnio-dye test, the test includes Amniocentesis and

injecting dye into the amniotic fluid. The definitive diagnosis for PROM is leakage of colored fluid in the vagina after 20 to 30 min and observing the tampon soaked with this color. This is an invasive procedure and associated with the risk of bleeding, placental infection, iatrogenic rupture of amniotic sac and abortion. Amni sure is a simple and rapid and less invasive method which evaluates placental alpha-1 microglobulin in the vaginal fluid, but its cost is high [7].

Because of the shortages and obstacles in existing testing approaches, researchers have searched for another indicators in the vaginal amniotic fluid [e.g., prolactin,  $\beta$ -subunit of human chorionic gonadotropin [ $\beta$ -hCG], alpha-fetoprotein, lactate dehydrogenase [LDH], urea and creatinine]. Undivided attention in evaluation of these indicators depends on their presence in amniotic fluid in higher concentrations than normal vaginal secretions. These markers remain unpopular in spite of its value for females with intact membranes or unequivocal membrane rupture due to complexity, cost and low sensitivity of testing in equivocal rupture [8].

For these reasons simple, a noninvasive, inexpensive, and available method is needed for the diagnosis of ruptured membranes.

The evidence being studied proposes that liver enzymes including aspartate aminotransferase and alanine aminotransferase are produced in the amniotic fluid by the fetus from the second half of pregnancy. These levels in amniotic fluid are not related to these levels in serum of mother [9].

## AIM OF THE WORK

The aim of this study is to evaluate the reliability of Aspartate Aminotransferase [AST] and Alanine Aminotransferase [ALT] enzymes measurement in vaginal-washing fluid for the diagnosis of pre-labor rupture of membranes.

## PATIENT AND METHODS

This case-control study was conducted in the Department of obstetrics and gynecology Al-Azhar University [New Damietta] and the Department of obstetrics and gynecology Senbellawein general hospital, ministry of Egyptian health. Ninety pregnant women were included, divided into two equal groups. Group I [case group, PROM group]: include 45 pregnant women with diagnosis of rupture of membranes confirmed by visualization of amniotic fluid passing from cervical canal. Group II [control group]: include 45 pregnant women without any complaint or complication. Pregnant women were included their

gestational age ranging from 30–40 weeks and had singleton pregnancy. Pregnant women were excluded if they had meconium in amniotic fluid, vaginal bleeding, regular uterine contractions, preeclampsia, intrauterine fetal death, presence of fetal distress, the presence of fetal anomalies and maternal medical disorders.

### Ethical considerations

Written consent was obtained from all participants before inclusion in the study, explaining the value of the study, plus the procedures that were conducted. Additionally, the whole study design was approved by the Institution Research Board [IRB] of the faculty of medicine – AL-Azhar University [Damietta]. Confidentiality and personal privacy was respected in all stages of the study. Patients felt free to withdraw from the study at any time without any consequences. Finally, the collected data were not and will not be used for any other purpose. All participants were subjected to complete history taking, general and local examination, speculum examination and obstetric US.

### COLLECTION OF SAMPLES

In pregnant women with ruptured membranes, sterile speculum examination was done while the patient in the lithotomy position, vaginal fluid was aspirated after injection of 3ml of sterile saline into the posterior fornix with the same syringe.

In pregnant women without rupture of membranes, 5ml of sterile saline was poured into the posterior fornix then 3ml was aspirated with the same syringe. The fluid specimens were collected to polypropylene tubes.

Samples were sent to the hospital laboratory then centrifuged for 10 min for the measurement of AST and ALT levels. For measurement of AST and ALT concentration, a

kinetic method was applied by automated machine HITACHI 912 using commercial kites [BM Egypt].

**Statistical analysis of data:** The collected data were organized, tabled and statistically analyzed using statistical package for social sciences [SPSS] version 22 [SPSS Inc, Chicago, USA], running on compatible computer. Demographic data and outcomes of both groups were compared via *T*. test for quantitative parametric measures, Mann–Whitney U test for quantitative non-parametric measures and  $\chi^2$  and Fisher's exact tests for categorical measures. Descriptive statistics of the measured variables were expressed as Mean and standard deviation for metric data, median and interquartile range for discrete data and number and proportions for categorical data. A two-sided *P* value < 0.001 is considered statistically significant. Pearson's correlation coefficient [for metric variables] and Spearman's correlation coefficient [for rank variables] are used to estimate the association between variables.

### RESULTS

Results show no significant differences between the two study groups regarding age, body mass index, gestational age, number of gravidities and parity, past obstetrics history [ectopic pregnancy, still birth and abortion] showed in [Table 1]. There were significant differences between the two study groups concerning past history of Pre-labor rupture of membranes and Amniotic fluid index and showed no significant differences between two study groups regarding mode of delivery [vaginal and cesarean section] and regarding gender of the fetus shown in [Table 2].

There were significant differences between the two groups in AST and ALT levels in vaginal washing fluid showed in [Table 3]. [Table 4] shows sensitivity, specificity, positive predictive value and negative predictive value of both AST and ALT and cut off point

**Table [1]:** Comparison between cases and control groups regarding patient characteristics

Items		Case group n= 45	Control group N=45	Test	p
Age [year]		25.69 ±5.41	24.80±6.13	0.729	0.468
BMI [kg/m <sup>2</sup> ]		30.65 ±3.74	30.42 ±4.44	0.271	0.787
Gravidity	Primigravida	8 [17.8%]	9 [20%]	1.067	0.634
	Multigravida	37 [82.2%]	36 [80%]		
Parity	Nulliparity	9 [20%]	10 [22.2%]	2.349	0.105
	Multiparty	36 [80%]	35 [77.8%]		
Gestational age		35.27 ±3.01	34.27±3.15	1.539	0.127
Past obstetric history	Ectopic pregnancy	2 [4.4%]	1[2.2%]	0.967	0.423
	Stillbirth	1[2.2%]	2[4.4%]	0.967	0.423
	Abortion	14 [31.1%]	10 [22.2%]	1.509	0.371

**Table [2]:** Comparison between cases and control groups regarding the past PROM, mode of delivery, amniotic fluid index and fetal gender.

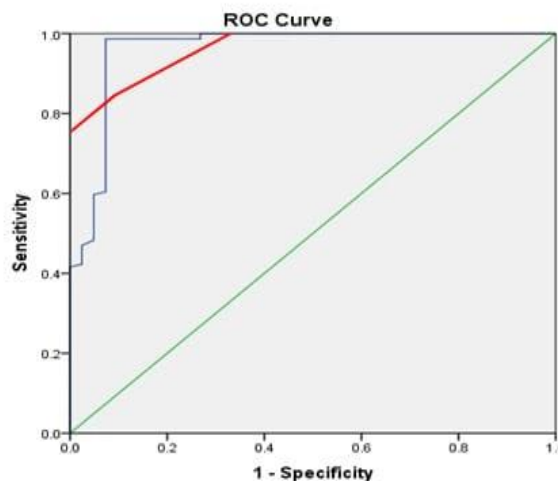
Items		Case group N =45	Control group N =45	Test	p
Past history of RROM		10[40%]	6 [13.3%]	6.124	<0.001*
Mode of delivery	Vaginal	22 [48.9%]	18 [40%]	2.124	0.112
	CS	23[51.105]	27[60%]		
Amniotic fluid index [AFI]	Median	8 [4-10]	10 [5-15]	5.884	<0.001*
	Mean	7.22±1.56	9.72 ±2.39		
Gender of fetus	Male	24 [53.3%]	26 [57.8%]	0.18	0.67
	Female	21 [46.7%]	19 [42.2]		

**Table [3]:** Comparison between groups regarding AST and ALT levels

	Items	Case group N = 45	Control group N = 45	test	p
AST	Median	19 [10-30]	3 [1-6]	8.624	<0.001*
	Mean	18.84±5.74	3.33±1.29		
ALT	Median	5 [2-9]	1 [0-3]	5.017	<0.001*
	Mean	5.09±2.1	1.13±0.94		

**Table [4]:** predictive ability of AST and ALT in differentiating cases from the control group

	AST	ALT
Cut off point	>8	>2.5
Sensitivity	97.8%	84%
Specificity	95.7%	94%
Positive predictive value	96.4%	96%
Negative predictive value	94.3%	88%
Accuracy	95.2%	92%



**Figure [1]:** Receiver operating characteristic [ROC] curves for Aspartate aminotransferase [blue line] and Alanine aminotransferase [red line] as diagnostic of pre-term labor of membranes

**DISCUSSION**

In the current study, both groups were matched regarding age, body mass index, height and weight. There were no significant statistical differences between the two study groups [PROM group and control group] regard the demographic characteristics, gestational age and number of gravidities and parity, which allowed us to compare the two groups confidently as it alleviate the effect of many confounding factors and added much to the homogeneity of

the study groups. Our study shows that there are significant differences in AST and ALT enzymes levels within the two groups. The mean AST level in the PROM group was 18.84±5.74 and 3.33±1.29 in control group [P<0.001]. The optimal cutoff concentration for AST levels in vaginal secretions to determine PROM was established by ROC curve, the cutoff value of AST >8 IU/L is optimal with a sensitivity level of 97.8% at a specificity of 95.7%, with positive and negative predictive values of 96.4% and 94.3%, respectively.

On the other hand, our study shows that the mean ALT level was  $5.09 \pm 2.1$  for the PROM group and  $1.13 \pm 0.94$  in the control group, which shows a significant difference between the two groups [ $P < 0.001$ ]. The cutoff value of  $> 2.5$  IU/L is optimal as a margin for diagnosis. This yields an 84.0% sensitivity, 94.0% a specificity, and 96.0% and 88.0% for positive and negative predictive values, respectively.

Ghasemi et al. [10] conducted a case-control study that agreed with our study. 160 pregnant females, gestational age 28 to 40 weeks. Group 1 [case group] involved 80 pregnant women who had diagnosis of PPRM. Group 2 [control group] involved 80 pregnant women referred to Obstetrics clinic for periodic check-up. The mean AST level in group 1 is  $16.5 \pm 12.3$  and in group 2 was  $9.1 \pm 7.9$  the sensitivity and specificity and positive and negative predictive values for aspartate aminotransferase were obtained 79.7%, 56.2%, 64.2%, and 73.7%. While ALT level in group 1 was  $5.0 \pm 4.8$  and in group 2 was  $3.3 \pm 2.6$ , the sensitivity and specificity and positive and negative predictive values for alanine aminotransferase was obtained 78.4%, 48.7%, 60.1%, 69.6%. There was a significant difference between two groups in terms of aspartate aminotransferase and alanine aminotransferase levels. In this study, the best cut-off point for AST was 7.5 IU/L and for ALT 2.5 IU/L.

Asgharnia et al. [11] conducted a similar study on 74 pregnant females with PPRM and 74 pregnant women without PPRM between 26<sup>th</sup>-36<sup>th</sup> weeks of gestation. In case group AST level in vaginal-washing fluid was  $12.77 \pm 10.06$  and  $6.91 \pm 10.92$  in control group with high significant difference between groups. The AST cutoff point for the PROM diagnosis was 4.5 IU/L. The sensitivity, specificity, positive and negative predictive values were 82.4%, 63.5%, 69.32% and 78.33% successively. There was no significant difference between groups regarding ALT level. Our study conflicts with Asgharnia *et al.*, which may be due to different gestational ages. Kale et al. [9] suggested that AST more than 3 IU/L was diagnostic of PPRM with the sensitivity, specificity, PPV and NPV of 91%, 83%, 80%, and 93%, respectively. ALT levels showed non-significant difference between groups.

In a study by Farag et al. [12] on 100 pregnant females divided into two equal groups, at a gestational age 26 and 37 weeks, the diagnostic accuracy of AST vaginal fluid [cut-off, 4.5 IU/L] in PPRM. AST levels in vaginal fluid had lower diagnostic accuracy than free T<sub>3</sub> and free T<sub>4</sub>.

According Martinez et al. [13] who compared the accuracy of the conventional ferning test, the AST vaginal fluid had a better sensitivity and specificity [Ferning test produced 51.4% and 70.8% sensitivity and specificity, respectively]. In

addition, ferning test requires microscopic examination and good human experience.

Movahed et al. [14] compared accuracy of other markers namely creatinine and lactate dehydrogenase in vaginal fluid in pregnant females with PPRM between 28<sup>th</sup> and 32<sup>th</sup> weeks of gestations. The sensitivity and specificity of both markers were 72% and 35%, and 85 and 80%, consecutively. In Shahin and Raslan [15] study, the accuracy of alpha fetoprotein [AFP] was 94%, while prolactin and  $\beta$ -HCG had low diagnostic accuracy. In Esim et al. [16] study, the sensitivity and specificity were 68% and 95%, when vaginal fluid  $\beta$ -HCG was measured to be used in the diagnosis of PROM.

Our study shows a significant difference between the two groups of study regarding past history of pre-labor rupture of membranes, which supported by Assefa et al. [17] they found that past history of PROM had to be the strongest risk factor for premature rupture of membranes.

We found no significant difference between the groups regarding delivery mode, which was supported by Namli et al. [18] who concluded that there was no factor leading to increase the rate of C/S in PROM at the term more than the non-term PROM. Also, this may prevent physicians from taking an invasive or hostile method towards PROM cases at term.

Peelen et al. [19] found that male fetuses were at a higher risk of PPRM between 27 and 37 weeks. In contrast with the current trial that showed no significant difference between groups.

**Conclusion:** Vaginal fluid levels of AST and ALT have high sensitivity and high negative predictive value. So, they are considered a good screening test for the detection of PROM. Also measuring vaginal fluid AST and ALT levels are cheaper, faster, available and reliable technique for the detection of PROM.

**The limitation** of this study was that it concentrated only on detection of the cut off value, sensitivity and specificity of both vaginal-washing fluid levels of AST and ALT to diagnose pre-labor rupture of membranes. The study did not associate between these markers and perinatal outcomes in women how had pre-labor rupture of membranes. More studies are needed to compare between vaginal AST, ALT and other markers for detection of PROM.

#### Financial and Non-financial Relationships and Activities of Interest

None

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# International Journal

The background of the cover is a light blue gradient. It features a faint, semi-transparent graphic of a stethoscope on the left side, a globe in the center, and a white ECG (heart rate) line running across the bottom. The overall theme is medical and global.

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