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Placental Alpha-Microglobulin 1 as A Marker of Preterm Prelabour Rupture of Membrane

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Abstract

Background Normal pregnancy requires that the physical integrity of the fetal membranes be maintained until term delivery.

Objective To detect preterm prelabour rupture of membrane in pregnant women with history of watery vaginal discharge by measurement of placental alpha microglobulin 1 in cervicovaginal fluid.

Methods A case-control study done at the department of Obstetrics and Gynecology of Al-Imamein Al-Kadhimein Medical City, included 100 pregnant women attending the Outpatient Clinic with a gestational age ranging between 28-36 weeks +6 days, 50 cases with rupture of membrane (study group) and 50 cases without any complaint (control group). All women underwent sterile speculum vaginal examination then nitrazine paper used, finally placental alpha microglobulin1 level was measured by using enzyme linked immunosorbent assay kit in vaginal washing fluid.

Results A highly significant association was found between mean of placental alpha microglobulin 1 in vaginal fluid of women with premature rupture of membrane compared to the control. The validity results of placental alpha microglobulin 1 findings regarding premature rupture of membrane include: sensitivity (100%), specificity (98.0%), +ve predictive value (98.1%), -ve predictive value (100%) and accuracy (99.0%), while for nitrazine; the sensitivity (94.0%), specificity (90.0%), +ve predictive value (90.4%), -ve predictive value (93.7%) and accuracy (92%) and for vaginal fluid sensitivity (80.0%), specificity (72.0%), +ve predictive value (74.1%), -ve predictive value (78.3%) and accuracy (76.0%).

Conclusion The placental alpha microglobulin-1 immunoassay in vaginal fluid wash found to be accurate and noninvasive test, in identifying preterm prelabour rupture of the membrane.

Keywords Placental alpha-microglobulin1, preterm prelabour rupture of membrane, prelabour rupture of membrane

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List of abbreviations: ARM = Artificial rupture of membrane, CDC = Centers for Disease Control and Prevention, FIGO = International Federation of Gynecology and Obstetrics, GA = Gestational age, IVH = Intraventricular hemorrhage, IGFBP-1 = Insulin like growth factor binding protein 1, PAMG-1 = Placenta-specific alpha microglobulin-1, PPROM = Preterm premature rupture of membrane, RDS = Respiratory distress syndrome, SD = Standard Deviation, SPSS= Statistical Package For Social Sciences, WHO = Word Health Organization

Introduction

Preterm premature rupture of membrane (PPROM) is responsible for nearly 40% of all preterm births [(1)]. Preterm birth, in turn, is a major global public health problem being responsible for 35% of the world's 3.1 million annual neonatal deaths. Prematurity is

the second largest direct cause of death in children less than 5 years [2,3].

The etiology of PPROM is multifactorial. Conditions that over distend the uterus, such as multiple gestation and polyhydramnios, may predispose to PPROM. Membranes that rupture prematurely may have different mechanical properties to those that do not rupture prematurely [4].

As well, the role of infection in the etiology of PPROM is clearly of great importance [4]. At term, programmed cell death and activation of catabolic enzymes, such as collagenase and mechanical forces, result in ruptured membranes. PPROM occurs probably due to the same mechanisms and premature activation of these pathways [5].

PPROM occurs from 24-36+6 weeks' gestation. Prematurity is the principal risk to the fetus, while infection morbidity and its complications are the primary maternal risks [5].

The major question regarding management of these patients is whether to allow them to enter labour spontaneously or to induce labor. Evidence supports the idea that induction of labor, as opposed to expectant management, decreases the risk of chorioamnionitis without increasing the cesarean delivery rate [6,7]. It is likely that multiple factors predispose certain patients to PPROM [8].

Diagnosis of PPROM is based on the history of vaginal loss of fluid and confirmation of amniotic fluid in the vagina. Episodic urinary incontinence, leucorrhea, or loss of the mucus plug must be ruled out [9]. A sterile vaginal speculum examination should be performed to confirm the diagnosis, to assess cervical dilation and length and to obtain cervical cultures and amniotic fluid samples for pulmonary maturation tests. On speculum examination, pooling of amniotic fluid in the posterior vaginal fornix can usually be seen [9].

Confirmation of the diagnosis can be made by: nitrazine paper test (amniotic fluid is mildly alkaline compared to normal vaginal secretions which are acidic) [10], fern test (after drying, amniotic fluid will form a crystallization pattern called arborization which resembles leaves of a fern plant when viewed under a microscope) [11], tampon test (using amniocentesis to inject dilute indigo carmine dye and looking for leaking of the blue fluid from the cervix onto a tampon) [12], ultrasonography (amniotic fluid index less than 5 cm is considered abnormal) [13], fetal fibronectin (fFN); a glycol protein present in amniotic fluid, placenta and the extracellular substance of decidua, may be normally detected in vaginal secretions up to 20 weeks gestation, and is then undetectable until about 36 weeks [13].

Several other markers have been studied for detection of PPROM including α-fetoprotein (AFP), insulin like growth factor binding protein-1 (IGFBP-1), prolactin, diamine oxidase activity, b-subunit of human chorionic gonadotropin (b-hCG) and placental α-microglobulin-1 (PAMG-1). However, results using such tests have been variable [14,15].

PAMG-1 is a human protein present in blood, amniotic fluid and cervicovaginal discharge of pregnant women. It is secreted from decidual part of the placenta and its concentration in the amniotic fluid is (2,000-25,000 ng/ml, which is several thousand magnitudes higher than that found in their background cervicovaginal discharge when the fetal membranes are intact (0.05-0.2 ng/ml) [16]. Further evidence demonstrated the efficiency of PAMG-1 to demonstrate the existence of injured membranes and leakage of amniotic fluid [17]. Cost benefit analysis was also shown to favor PAMG-1 over the traditional diagnostic methodology sequence [18]. The test is non-invasive, painless, covers the entire spectrum of pregnancy from week 16 to term, is specific for the presence of amniotic fluid and is of low cost. Results are available to the care giver in 5 min. The test is programmed to detect a minimum of 5ng/ml in the tested tissue. It is approved by the Federal Drug Administration (FDA) and is known commercially in the USA as Amnisure TM [19].

This study aimed to detect preterm prelabour rupture of membrane in pregnant women with

history of watery vaginal discharge by measurement of PAMG-1 in cervicovaginal fluid.

Methods

A case control study was conducted in the department of Obstetrics and Gynecology of Al-Imamein Al-Khadimein Medical City for the period from the 1st of February 2017 to the end of October 2017. It included 100 pregnant women attending the Outpatient's Clinic with gestational age ranging from 28-36 wks +6 days. Fifty pregnant women who had diagnosed with PPROM (the study group) and fifty pregnant women referred to obstetrics clinic for periodic check- up with no symptom or sign of rupture membrane (the control group). A verbal consent was obtained from them.

Inclusion criteria

Pregnant women with single viable fetus of gestational age 28-36 weeks +6 days confirmed by the first day of last menstrual period and first trimester ultrasound. Regarding the study group rupture of membranes was confirmed by examination using speculum and observation of cervical fluid leakage or accumulation of fluid in the posterior fornix of the vagina then nitrazine paper test after that ultrasound by specialist sonar doctor for amniotic fluid index.

Exclusion criteria

Congenital fetal malformations confirmed by U/S, fetal growth restriction, fetal distress at the time of presentation, patients with risk of ruptured membrane (diabetes mellitus, polyhydramnios, previous history of ruptured membrane), antepartum hemorrhage.

Samples collection and preparation

Patients were examined in semi recumbent position with good illumination using sterile Cusco speculum (without antiseptics), after waiting a few minutes to see if there is collection of fluid in the speculum.

This is augmented by asking the patient to cough allowing one to observe fluid escaping from the cervix. This means the pooling test is positive, after that we introduce nitrazine papers, which have yellow dye. This paper inserted in the posterior vaginal fornix for 15 seconds then if the color of the paper changes to blue color, the test should be considered as positive.

Measurement of vaginal fluid PAMG-1

In all patients 5 cc sterile normal saline was poured into the posterior fornix of the vagina by syringe 5 cc and after a few minutes the liquid was aspirated by the same syringe and was sent to the lab of the hospital to centrifuge it for 10 minutes and the enzyme linked immunosorbent assay (ELISA) kit of PAMG-1 were used to measure the concentration of PAMG-1.

Statistical analysis

Statistical Package for Social Sciences (SPSS) version 21 was used. Descriptive statistics presented as (mean ± standard deviation), frequencies & percentages. Chi-square used for categorical variables (Fishers exact test was used when expected variable was less than 20% of total). Independent sample t-test was used to compare between two means. Two by two tables were used to acquire the validity results of multiple tests in comparison to final outcome. ROC curve was used to assess the acceptable cutoff value. In all statistical analysis, level of significance (p value) set at ≤ 0.05.

Results

The mean age of the study group was 29.8±6.9 years and for the control was 29.7±6.6 years. No significant difference was observed between women with PPROM and those with no PPROM regarding women's age (p=0.1). Mean parity of women with PPROM was significantly higher than mean parity of women with no PPROM (p=0.01). A highly significant association was found between lower gestational age of pregnant women and PPROM (p<0.001). All these findings were shown in table 1.

Table 1. Distribution of demographic characteristics between the study and control groups

Variable		Study group		Control group		P value
		No.=50	%	No.=50	%	
Age	<20 years	9	18.0	2	4.0	0.1*NS
	20-29 years	14	28.0	20	40.0	
	≥30 years	27	54.0	28	56.0	
	Mean±SD	29.8±6.9		29.7±6.6		0.1*NS
Parity	Nulliparous	8	16.0	2	4.0	0.1***NS
	1-2 children	15	30.0	18	36.0	
	≥3 children	27	54.0	30	60.0	
	Mean±SD	3.5±2.6		2.5±1.3		0.01*S
Gestational age	28-33 weeks	43	86.0	24	48.0	<0.001*S
	34-36 weeks +6 days	7	14.0	26	52.0	
	Mean± SD	31.4±2.2		32.2±2.9		0.1*NS

*Chi square test, **Independent sample t-test, ***Fishers exact test, NS=Not significant (>0.05), S=Significant (≤0.05)

As shown in table 2, there was a highly significant association between mean of PAMG-1 in the women with PPROM than the women without PPROM (p<0.001).

Table 2. Distribution of PAMG-1 mean between the two groups

Variable	Study group Mean±SD	Control group Mean±SD	P value
PAMG-1 (ng/ml)	1259±378.6	64.2±231.7	<0.001*S

*Independent sample t-test, S=Significant (≤0.05)

There was a highly significant association between positive results of vaginal fluid test and PPROM women (p<0.001). A highly significant association was observed between positive results of nitrazine test and women with PPROM (p<0.001). The positive results of PAMG-1 were significantly associated with PPROM pregnant women (p<0.001). All these findings were shown in table 3.

Table 3. Distribution of diagnostic tests results between the two groups

Variable		Study group		Control group		P value
		No.=50	%	No.=50	%	
Vaginal fluid	Positive	40	80.0	14	28.0	<0.001*S
	Negative	10	20.0	36	72.0	
Nitrazine	Positive	47	94.0	5	10.0	<0.001*S
	Negative	3	6.0	45	90.0	
PAMG-1	Positive	50	100.0	1	2.0	<0.001**S
	Negative	0	0.0	49	98.0	

*Chi square test, **Fishers exact test, S= Significant

The validity results of PAMG-1 findings regarding PPROM were as follows, sensitivity (100%), specificity (98%), +ve predictive value (98.1%), -ve predictive value (100%) and accuracy (99%). All these findings were shown in table 4.

Table 4. Validity test results of PAMG-1 in the study groups

Validity test			Study group No. (%)	Control group No. (%)	Total No. (%)
PAMG-1	Positive	No. (%)	50 (98.1)	1 (1.9)	51 (100.0)
	Negative	No. (%)	0 (0.0)	49 (100.0)	49 (100.0)
	Total	No. (%)	50 (50.0)	50 (50.0)	100 (100.0)
Sensitivity			100%		
Specificity			98%		
+ve predictive value			98.1%		
-ve predictive value			100%		
Accuracy			99%		

The validity results of vaginal fluid pooling test findings regarding PPROM were as follows: sensitivity (80%), specificity (72%), +ve predictive value (74.1%), -ve predictive value (78.3%) and accuracy (76%). All these findings were shown in table 5.

Table 5. Validity test results of vaginal fluid pooling test in the study groups

Validity test			Study group No. (%)	Control group No. (%)	Total No. (%)
Vaginal fluid pooling test	Positive	No. (%)	40 (74.1)	14 (25.9)	54 (100)
	Negative	No. (%)	10 (21.7)	36 (78.3)	46 (100)
	Total	No. (%)	50 (50.0)	50 (50.0)	100 (100)
Sensitivity			80.0%		
Specificity			72.0%		
+ve predictive value			74.1%		
-ve predictive value			78.3%		
Accuracy			76.0%		

The validity results of nitrazine test findings regarding PPROM were as follows: sensitivity (94%), specificity (90%), +ve predictive value (90.4%), -ve predictive value (93.7%) and accuracy (92%). All these findings were shown in table 6.

The acceptable cut off points and the corresponding validity tests values PAMG-1 in prediction of PPROM from healthy pregnant women were shown in table 7 and figure1, cutoff PAMG level of >363.5 had acceptable validity results (100% sensitivity, 82.4% specificity, 100%PPV, 80.5% NPV and accuracy 94%).

Table 6. Validity test results of Nitrazine test findings in the study groups

Validity test			Study group No. (%)	Control group No. (%)	Total No. (%)
Nitrazine	Positive	No. (%)	47 (90.4)	5 (9.6)	52 (100.0)
	Negative	No. (%)	3 (6.3)	45 (93.7)	48 (100.0)
	Total	No. (%)	50 (50.0)	50 (50.0)	100 (100.0)
Sensitivity				94%	
Specificity				90%	
+ve predictive value				90.4%	
-ve predictive value				93.7%	
Accuracy				92%	

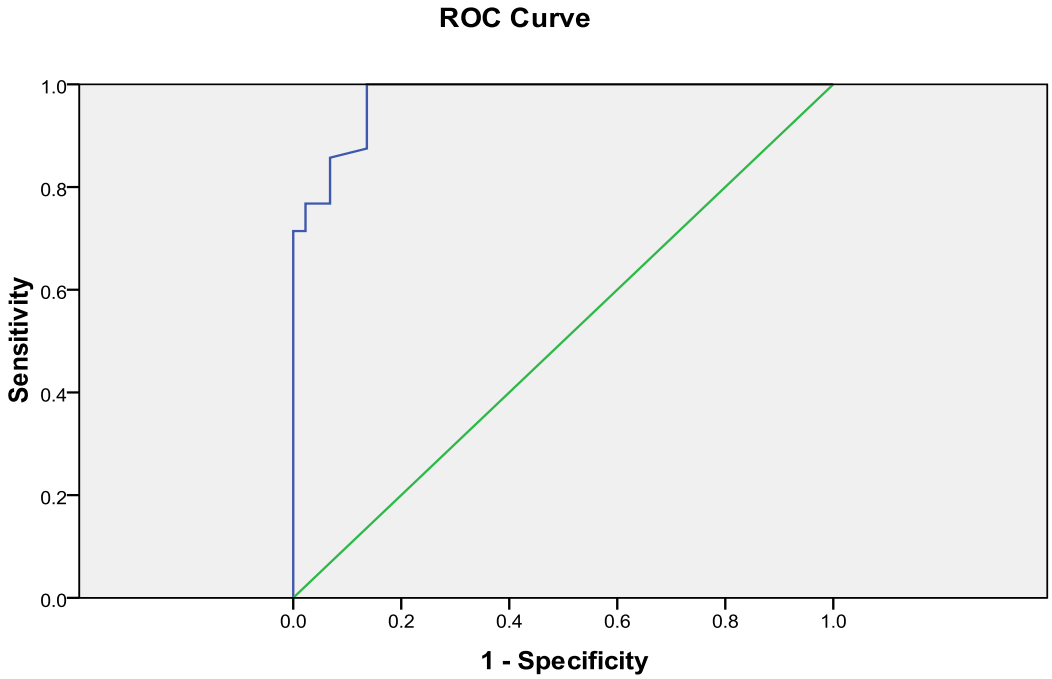

Figure 1. ROC curve for PAMG-1 prediction of PPROM (AUC=0.9)

Table 7. Coordinates of the ROC Curve of serum PAMG-1 in PPROM

Cutoff point	Sensitivity	Specificity	PPV	NPV	Accuracy
> 363.5	100%	82.4%	100%	80.5%	94%

Discussion

Unfortunately, there is absence of an accurate and simple diagnostic tool to establish the diagnosis as the traditional way to diagnose PPROM is subjective. However, each of these standard diagnostic methods was associated with high false positive or negative results [20]. Failure to genuinely exclude preterm PPROM in women presenting with symptoms of rupture of membranes could lead to unnecessary iatrogenic intervention resulting in delivery of

preterm babies with resultant problems of prematurity [21].

The present study revealed that there is no significant difference between the age and the PPROM but the significant association found with the gestational age which is in agreement to Lee et al., study in 2009 regarding women age but with no association was found with gestational age, and this may be due to differences in sample size collection [22].

Current study conclude that the (PAMG-1) test has high sensitivity, specificity, positive predictive value, negative predictive value and accuracy in the diagnosis of PPROM when its compared with other standard or usual clinical technique of assessment (Nitrazine test and vaginal fluid pooling test), and this is in agreement with that mentioned by Ng et al., 2013 [20], although in the current study the (PAMG-1) test was more accurate and had a better negative predictive value. In his study, the PMAG-1 had an overall sensitivity 97.5%, specificity of 100%, PPV of 100%, and NPV of 75.0% and the accuracy was 95.7%.

In a study done by Cousins et al. in 2005 [23], comparing between the AmniSure rapid immunoassay test (PAMG-1) with standard methods for diagnosing rupture of fetal membranes, found that the PAMG-1 is highly accurate with a sensitivity and specificity of 98% and 100%, respectively. Moreover, Lee et al., in 2007 [24], concluded that the PAMG-1 immunoassay test had significantly higher sensitivity compared to the combined conventional clinical tests, including speculum examination of fluid leakage, vaginal pooling, nitrazine and ferning tests, having sensitivity of 98.7% and 87%, respectively, but comparable specificity of 87.5% and 100%, respectively.

In a study of Yildiz et al., 2009 [25], PAMG-1 test confirmed PPROM with sensitivity of 85% and specificity of 100%, positive predictive value of 100% and negative predictive value of 87.5%, respectively. In comparison, those values for nitrazine test were 90.5%, 92.5%, 95.0%, 90.9%. Therefore, PAMG-1 immunoassay had an excellent specificity of 100% ($p > 0.05$) which is going with the results of our study.

Albayrak M et al. (26) 2011 found that the PAMG-1 test had sensitivity (97.4%), specificity (96.7%), positive predictive value (98.9%), negative predictive value (92.2%) and a diagnostic accuracy of (97.2%) which is less than our results finding that may be attributed to the different sample size.

This study concluded that he placental PAMG-1 immunoassay found to be quick, accurate and noninvasive, in identifying rupture of the membrane.

The current study recommends that PAMG-1 is cost effective and better predictor for detecting rupture of membrane when the diagnosis is in doubt.

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Author contribution

Dr. Seger: cases collection, obtaining the results of the tests used in the study. Dr. Al-Moayed, Dr. Abdulrasul and Dr. Mushatat: supervised the study and wrote the article and revised it.

Conflict of interest

The authors declare no conflict of interest for the present research outcome.

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