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Research Article

Aquaporin-9 as an Essential Biomarker of the Inflammatory Process in Preterm Prelabour Rupture of Membranes

Aya Dler Ameen[1], Aseel Ghazi Rifat[2]*

[1]*Department of Obstetrics and Gynecology, Azadi Teaching Hospital, Kirkuk, Iraq;* [2]*Department of Obstetrics and Gynecology, College of Medicine, University of Kirkuk, Kirkuk, Iraq*

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Abstract

Background: Preterm pre-labor rupture of membranes (PPROM) is a prevalent obstetric condition causing significant maternal and fetal complications. Aquaporins (AQPs) are membrane proteins that contribute to inflammatory processes and carry out a pivotal role in transmembrane water transport. Since PPROM is an inflammatory process, aquaporin-9 is considered to contribute to its pathogenesis. ***Objective***: To detect the aquaporin-9 concentration in the serum of cases with PPROM and to assess its association with reported adverse outcomes. ***Methods***: A prospective case-control study conducted on a sample of 90 pregnant women, divided into 2 groups: 45 women with PPROM and a control group of 45 healthy pregnant women. The serum aquaporin 9 measured for all participants and compared between the two groups. The pregnant women with PPROM were followed up for neonatal and obstetrical outcomes. ***Results***: The mean aquaporin-9 level was significantly higher in women with PPROM in comparison to controls. The aquaporin-9 level cut-off level > 4.22 ng/ml was with a sensitivity of 86.7% and a specificity of 84.4% for the diagnosis of PPROM. The mean aquaporin-9 level was significantly higher among preterm pregnant women with prelabour rupture of membranes with shorter time to delivery after membrane rupture. ***Conclusions***: Aquaporin-9 is crucial for diagnosing PPROM. Higher levels can predict shorter time to deliver in PPROM cases, influencing management decisions.

Keywords: Aquaporin-9, Inflammatory process, pre-labor membranes rupture.

الأكوابورين-9 كمؤشر حيوي أساسي للعملية الالتهابية في تمزق الأغشية قبل المخاض قبل الأوان

الخلاصة

الخلفية: يُعد تمزق الأغشية المبكر قبل الولادة حالة توليدية شائعة تُسبب مضاعفات خطيرة للأم والجنين. الأكوابورينات (قنوات الماء) هي بروتينات غشائية تُساهم في العمليات الالتهابية وتلعب دورًا في نقل الماء عبر الغشاء. أن تمزق الاغشية المبكر قبل الولادة يعد من العمليات الالتهابية، ويُعتقد أن الأكوابورين 9 يُساهم في تطورها المرضي. **الهدف**: تحديد تركيز الأكوابورين-9 في مصل المصابات بـتمزق الاغشية المبكر قبل الولادة ومقارنته مع مجوعة ضوابط مكونة من نساء حوامل اصحاء مع اغشية سليمة. **الطرائق**: أجريت دراسة حالة وشاهد مستقبلية في مستشفى آزادي التعليمي/ كركوك/العراق، على عينات من 90 امرأة حامل، قُسِّمت إلى مجموعتين: 45 امرأة مصابة بتمزق الأغشية المبكر، ومجموعة ضابطة من 45 امرأة حامل سليمة. تم قياس مستوى الأكوابورين-9 في مصل الدم لدى جميع المشاركات، ومقارنته بين المجموعتين. وتمت متابعة النساء الحوامل المصابات لمتابعة علاقته بنتائج الولادة وحديثي الولادة. **النتائج**: كان متوسط مستوى أكوابورين-9 أعلى بشكل ملحوظ لدى النساء المصابات بتمزق الأغشية المبكر قبل الولادة مقارنةً بالمجموعة الضابطة. كانت قيمة القطع المناسبة من مستوى أكوابورين-9 أكبر من 4.22 نانوغرام/مل، مع حساسية 86.7% وخصوصية 84.4% لتشخيص تمزق الأغشية المبكر. وكان متوسط مستوى أكوابورين-9 أعلى بشكل ملحوظ لدى النساء الحوامل المصابات وارتبطت المستويات الاعلى مع قِصر مدة للولادة بعد تمزق الأغشية. **الاستنتاجات**: يُعدّ الاكوابورين-9 بالغ الأهمية لتشخيص تمزق الاغشية المبكرقبل الولادة ويمكن لمستوياته المرتفعة أن تُنبئ بقصر المدة الى الولادة بعد تمزق الاغشية، مما يؤثر على قرارات العلاج.

* ***Corresponding author***: Aseel G. Rifat, Affiliation: Department of Obstetrics and Gynecology, College of Medicine, University of Kirkuk, Kirkuk, Iraq; Email: aseel_ghazi1974@uokirkuk.edu.iq

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INTRODUCTION

Preterm pre-labor rupture of membranes (PPROM) is known as rupture of fetal membranes before 37 weeks of gestation and preceding the onset of labor [1]. It is a common obstetric problem, complicating nearly 1–4% of all pregnancies globally. However, the whole impact of maternal morbidities and neonatal mortalities owing to premature deliveries is high in developing nations [2,3]. Like preterm labour, postnatal survival ensuing PPROM is directly correlated with gestational age at delivery and birth weight. Although most women deliver soon thereafter, those who do not go into preterm labor soon after PPROM are in danger of chorioamnionitis, which can be detrimental and potentially lethal to both moms and neonates [4,5]. Fetal membranes consist of two closely adherent structures: amnion and chorion. These structures consist of diverse epithelial, mesenchymal, and trophoblastic cells, which are all embedded in a collagenous matrix. In normal pregnancies, the integrity of these membranes is maintained till term, after which they rupture either spontaneously or artificially to signify the onset of labor. At term, spontaneous rupturing of membranes (SROM) happens when biochemical

processes weaken the fetal membranes. This causes the cellular matrix to change and fetal membrane cells to die [6]. In PPROM, on the other hand, the fetal membranes can become weaker before they even reach birth because of a damaged collagen matrix and inflammatory processes that cause cytokines to be released and the matrix to break down in a chain reaction. Moreover, the chorion-amnion interface is less hydrophobic in PPROM cases. The reduced hydrophobic state implicated in PPROM has been suggested to cause increased friction between the two fetal membranes [7]. The pathogenesis of PPROM is multifactorial; it involves interplay of elements between maternal and neonatal systems. The presence of risk factors such as infection, maternal or fetal stress, excessive uterine stretch, and uterine bleeding will disrupt uterine quiescence, activate the mechanisms, and lead to PPROM [8]. The mainstay diagnosis of PPROM involves an abrupt history of gushing fluid from the vagina and a speculum examination that relies on the obstetrician's experience in recognizing leakage of liquor from the os or pooling in the vaginal fornices [9]. Early detection and management strategies, including hospital admission, administering antibiotics, corticosteroids, short-term tocolysis, and induction of labor, are crucial to prevent further complications and improve outcomes [9]. For this reason, several tests were used to confirm the diagnosis, such as the nitrazine test, fern test, Amnisure test (placental alpha microglobulin-1), and Actim test (insulin-like growth factor binding protein-1). However, taking into account the diagnostic efficacy, cost, and technical feasibility, all these clinical parameters have specific limitations [10]. Aquaporins (AQPs) are a group of minutes, integral membrane proteins that carry out a crucial role in transmembrane transport of water. Aquaporins are extensively distributed in the mammal body, including the female reproductive organ. They play a role in cellular activities, including cell growth and migration, and some aquaporins participate in the formation of human placentas [11]. AQP-9, which belongs to the aquaglyceroporin family, is of exceptional importance since it performs an essential role in water transfer between the maternal and fetal systems in addition to participating in the rapid influx of minute uncharged molecules such as urea, glycerol, purines, and pyrimidines [8]. However, till now the mechanisms regulating AQP-9 role in placental function and fetal membranes are still undetermined. New evidence investigates placental AQP-9 adjustment in normal and pathological pregnancies, suggesting various mechanisms involved in these alterations. In gestational diabetes and pregnancies complicated by polyhydramnios, the expression of AQP-9 is elevated. While in oligohydramnios, its expression was significantly decreased. Maternal serum AQP-9 concentrations were also obviously raised in pre-eclamptic patients with early onset of the disease [12]. Additionally, AQP-9 participates in the inflammatory processes by regulating cellular proliferation, migration, and apoptosis [13]. Since PPROM is thought to be an inflammatory problem caused by several synchronized mechanisms, AQP-9 is likely to play a part in how this problem develops or how the body adapts to it during pregnancy [14]. The purpose of this study was to evaluate serum concentration of aquaporin-9 in cases with PPROM and to assess its association with the adverse outcomes reported in this condition.

METHODS

Study design and patient selection

This prospective case-control study was accomplished in Azadi Teaching Hospital/Kirkuk/Iraq, over a period of eight months from February 1st to September 30st, 2024. The participants were ninety pregnant women between 20 and 39 years of age with singleton viable pregnancies. The participants were split into two groups: 45 women with preterm pre-labour rupture of membranes (PPROM) and 45 healthy pregnant women with comparable gestational age and intact membranes as a control group. The gestational age of the participants was estimated through last menstrual cycle calculation and confirmed by first trimester ultrasound image.

Inclusion criteria

Cases of PPROM were selected from those who were admitted to the labor room, based on the definition of the American College of Obstetricians and Gynecologists (ACOG) criteria as ruptured membranes between 24 and 36 weeks^{+6} days of gestation and prior to the onset of labor [1]. They were diagnosed clinically by history (sudden gush of fluid) and physical examination (a sterile speculum visually showed pooling of amniotic fluid leaking through the cervix) and confirmed by an ultrasound report of reduced liquor. The control group was selected from healthy pregnant women attending the outpatient clinic for routine antenatal care visits between 24 and 36 weeks^{+6}. They were followed up for 2 weeks by phone contact to confirm a normal pregnancy course.

Exclusion criteria

Women with the following were excluded from entering the study: membrane rupture before 24 or after 37 gestational weeks, multi-fetal pregnancy, fetal death in utero, signs and symptoms of systemic infection or chorioamnionitis, antepartum hemorrhage, gestational hypertension and diabetes mellitus, chronic diseases, anti-inflammatory drug and steroid usage, history of cervical surgery or cerclage, and history of oligohydramnios in current pregnancy.

Outcome measurements

The data was gathered by researchers through direct contact with pregnant women who attended labour

room with PPROM and/or their saved records and filled in a constructed questionnaire. The questionnaire involved detailed history (age, occupation, duration of membrane rupture, last menstrual period, gravidity, parity, miscarriage, previous modes of delivery, previous history of PPROM, and past medical and surgical history). An examination was performed, including a general examination for vital signs. Body mass of study participants was calculated using BMI=Weight (kg)/Height (m^2) [15]. The body mass index was categorized into underweight (<18.5 kg/m^2), normal (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), and obese (≥30 kg/m^2). Abdominal examination for any tenderness, symphysio-fundal height, uterine contractions, and fetal heart rate assessment by cardiotocography. Speculum examination and prevaginal examination were done if mandatory. Five ml of venous blood was drawn from each selected woman. Serum aquaporin-9 was measured for all participants by a special kit using ELISA, besides the general investigations such as complete blood count and blood glucose. Ultrasound scanning was done for measuring the amniotic fluid index and gestational age by Radiologist in the hospital. Pregnant women with PPROM were followed up by researchers until delivery, recording time of delivery after membrane rupture, mode of delivery, fetal outcome including birth weight, Apgar score after one and five minutes, and neonatal intensive care unit (NICU) admission. The Apgar score of the neonates after 1 minute and 5 minutes was classified into: Reassuring (7.0 - 10), Moderately abnormal (4.0 - 6.0), and Low (0 - 3.0). [16]. The birth weight was classified into extremely low birth (<1 kg), very low birth weight (1.0 - 1.5 kg), low birth weight (>1.5 - <2.5 kg), and normal (≥ 2.5 kg) [16].

Ethical consideration

Verbal permission was obtained from all of the participants prior to their inclusion in the study and data collection. Administrative authorities were granted from the Iraqi Council of Medical Specializations and approval from the hospital authorities and the ethical committee at the College of Medicine, University of Kirkuk, No. 64 on 1/3/2024.

Statistical analysis

All pregnant women's data entered through utilizing computerized statistical software (SPSS) "version 22." Descriptive statistics were expressed as (mean ± standard deviation) and the frequencies as percentages. Multiple contingency tables were organized, and suitable statistical tests were applied. The chi-square test was employed for categorical variables (Fisher's exact test was used when the expected variable was less than 20% of the total variable), and the independent sample t-test was achieved to determine the correlation between means. ROC curve analysis was applied to assess the predictability of aquaporin-9 level for PPROM. For interferential analysis, the level of significance (p-value) was established at < 0.05 and the results were illustrated as tables and/or graphs.

RESULTS

The age of the participants was between 20 and 39 years old. No significant differences were noticed among women with PPROM and controls in respect of age (p= 0.6) and occupation (p= 0.536). The body mass index was significantly higher among women with PPROM compared with the control (p= 0.009), as 75.6% of PPROM women were overweight, compared to 48.9% of controls (Table 1).

Table 1: Distribution of PPROM cases and controls according to general characteristics

Variables		Groups		*p*-value*
		PPROM	Control	
Age (year)	20-29	17(37.8)	15(33.3)	0.6
	30-39	28(62.2)	30(66.7)	
BMI (kg/m^2)	Normal	11(24.4)	23(51.1)	0.009
	Overweight	34(75.6)	22(48.9)	
Occupation	Housewife	31(68.9)	27(60)	
	Governmental employee	13(28.9)	15(33.3)	0.536
	Private sector employee	1(2.2)	3(6.7)	

Values were expressed as frequency and percentage. *Chi square test.

Table 2 demonstrates obstetric characteristics of PPROM cases and controls. There were significant differences among the groups regarding gravidity, as the pregnant women with primi-gravidity represented 28.9% of PPROM women, while they represented 11.1% of controls. There were significant differences in the history of previous miscarriages and PPROM between the two groups. The history of previous miscarriage was predominant in the control group (33.3%), while a previous history of PPROM was present in 22.2% of cases compared to 4.4% of controls. There was no significant difference in gestational age (p= 0.3) and antenatal care (p= 0.6) between women in the PPROM and control groups. Regarding the previous mode of delivery, women with PPROM had a significantly higher rate of previous cesarean section delivery (54.8%) compared to the control group (17.5%). The mean aquaporin-9 level among women with PPROM was 4.8436 ng/ml, which is significantly higher in comparison to controls (3.651 ng/ml) (p<0.001). As demonstrated in Figure 1. Receiver operating characteristic (ROC) curve analysis revealed that the appropriate aquaporin-9 level cutoff value in diagnosing PPROM

was 4.022 ng/ml with a large AUC of 82 and acceptable validity findings (sensitivity 86.7%, specificity 84.4%, and accuracy 85%), as demonstrated in Table 3 and Figure 2.

Table 2: Distribution of PPROM cases and controls according to obstetrical characteristics

Variables		Studied groups		*p*-value
		PPROM	Control	
Gravidity history	Primigravida	13(28.9)	5(11.1)	0.03*
	Multigravida	32(71.1)	40(88.9)	
Miscarriage history	Yes	7(15.6)	15(33.3)	0.05**
	No	38(84.4)	30(66.7)	
Previous PPROM	Yes	10(22.2)	2(4.4)	0.013**
	No	35(77.8)	43(95.6)	
Previous mode of delivery	Vaginal delivery	14(45.2)	33(82.5)	0.001*
	Cesarean section	17(54.8)	7(17.5)	
Gestational age (week)	<28	6(13.3)	2(4.4)	
	28-31	17(37.8)	17(37.8)	0.3*
	32-36+6	22(48.9)	26(57.8)	
Antenatal care	Regular	22(48.9)	31(68.9)	0.610*
	Poor	23(51.1)	14(31.1)	

Values were expressed as frequency and percentage. * Chi-square test, ** Fishers exact test.

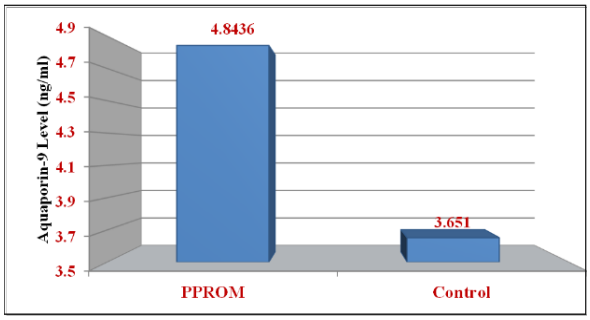

Figure 1: Aquaporin-9 level in regard to PPROM cases and controls.

Table 3: Aquaporin-9 cut off levels for diagnosis of PPROM

Aquaporin-9 (ng/ml)	Sensitivity (%)	Specificity (%)	Accuracy (%)
3.6263	73.3	55.6	59
4.022	86.7	84.4	85
4.249	60	68.9	64

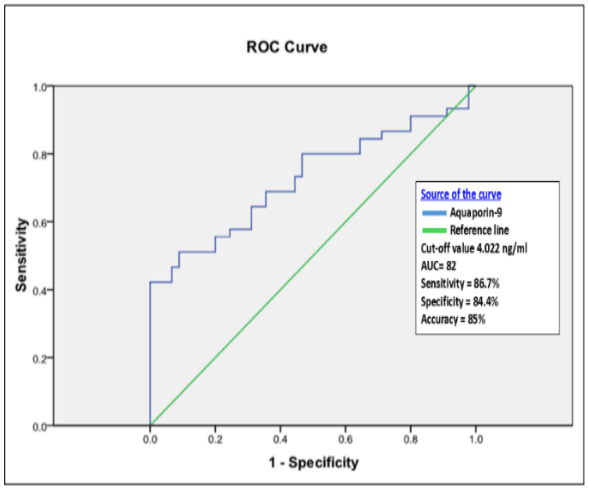

Figure 2: ROC curve of aquaporin-9 for the diagnosis of PPROM (AUC= 82).

Table 4: Obstetrical and neonatal outcomes of women with PPROM

Variables	Subcategories	Frequency(%)
Time of delivery after membranes rupture	≤1 day	23(51.1)
	>1 day	22(48.9)
Mode of delivery	Vaginal delivery	33(73.3)
	Cesarean section	12(26.7)
Birth weight	Extremely low	2(4.4)
	Very low	16(35.6)
	Low	15(33.3)
	Normal	12(26.7)
Apgar score after 1 min	Reassuring	15(33.3)
	Moderately abnormal	27(60)
	Low	3(6.7)
Apgar score after 5 min	Reassuring	13(28.9)
	Moderately abnormal	26(57.8)
	Low	6(13.3)
NICU admission	Yes	29(64.4)
	No	16(36.6)
Total		45(100)

Table 4 demonstrates pregnancy and neonatal outcomes in PPROM cases. Time to delivery after membranes rupture for women with PPROM was one day or less in 51.1% of them. The mode of delivery was vaginal in 73.3% of the women with PPROM, while the rest of them (26.7%) were delivered by cesarean section. Neonatal birth weight was normal in 26.7%, low in 33.3%, very low in 35.6%, and extremely low in 4.4% of cases. The Apgar score of neonates after one minute was moderately abnormal in 60%, while low in 6.7% of them, and after 5 minutes it became reassuring in 28.9%, moderately abnormal in 57.8%, and low in 13.3% of them. 64.4% of neonates were admitted to NICU. The Pearson correlation analysis showed that there was a significant negative correlation between aquaporin-9 level and time to delivery (r= -0.29, *p*= 0.04); the mean aquaporin-9 level was significantly higher in PPROM pregnant women having shorter time to delivery after membranes rupture. No significant

correlation was observed for aquaporin-9 level with mode of delivery, birth weight, Apgar score, or NICU admission in PPROM (Table 5).

Table 5: Pearson correlation between aquaporin-9 level in PPROM with obstetrical and neonatal outcomes

Variable	Aquaporin-9 level	
	r-value	*p*-value
Time to delivery	- 0.29	0.04
Delivery by caesarean section	0.22	0.13
Birth weight	0.16	0.27
Apgar score after 1 min	0.02	0.89
Apgar score after 5 min	0.174	0.252
NICU admission	0.06	0.6

DISCUSSION

The preterm pre-labor rupture of membranes is a common source of preterm birth and multiple neonatal and maternal complications. In order to prevent surgical interventions and minimize hospitalization, early and prompt diagnosis enables gestational age-individualized interventions to be designed, thereby optimizing perinatal outcome and minimizing critical complications [14]. The current study found no differences between women with PPROM and controls in respect of age and occupation. These observations are in agreement with the outcomes of Bouvier *et al.* [17]. A large prospective cohort study in Canada revealed that age and occupation were not significant risk factors of PPROM, while Boskabadi *et al.* [16], in a study carried out in Iran, revealed that women's characteristics like older age and employee occupation are significant risk factors of PPROM. Additionally, our study showed significant variations in BMI between the two studied groups, as 75.6% of PROM women were overweight compared to 48.9% of controls. This was inconsistent with results data from Sun *et al.* study [18] from China that documented the impact of rising body mass index of pregnant women on the development of PPROM. In our study a history of previous PPROM was documented in 22.2% of cases, in comparison to 4.4% of controls; this observation matches the result of Bouvier *et al.* [17] large prospective cohort study in Canada. Moreover, pregnant women with primigravidity represented 28.9% of PPROM compared to 11.1% of control women. Similarly, Rode *et al.* [5], in a retrospective cohort study in Denmark, reported that primigravidity and nulliparity of pregnant women were increasing the risk of PPROM. However, this result is in disagreement with Abouseif *et al.* [19] study in Egypt, which mentioned that increased gravidity of pregnant women was accompanied by high risk of PPROM; this inconsistency may be related to discrepancies in methodology and patient sampling between studies. In the current research, the history of miscarriage was predominant in the control group (33.3%). This contradicts the results of Lin *et al.* [20] study in China, which reported that a positive miscarriage history increased future risk of PPROM. This inconsistency might be attributed to differences in sociocultural factors between study populations, in addition to differences in methodology and selection criteria between different studies. In the present study, previous cesarean section delivery was present in 54.8% of women with PPROM, in comparison with 17.5% in controls. Similarly, a retrospective cohort study conducted in the United States of America by Williams *et al.* [21] found that previous cesarean section was associated with higher chances of PPROM in subsequent pregnancies. Although extreme prematurity was more predominant in the PPROM group than in the controls, no significant variation was found regarding gestational age between the two groups. Furthermore, no significant differences were observed among patients with PPROM and controls regarding antenatal care. These findings are in alignment with the results of Agarwal *et al.* [22] retrospective cohort study in India. Aquaporins were found to play a pivotal role in the diagnosis of adverse pregnancy outcomes in addition to their future roles in the management of different gestational disorders, as their values are adjusted in the implantation process, in the uterus and the fetal cells together, and in the regulation of the amniotic fluid stream. Aquaporins also appear to be very pivotal for the normal placental functions, and in the course of parturition they participate in the regulation of myometrial activity and ripening of the cervix [13,23]. The present study found that the mean aquaporin-9 level was significantly higher among women with PPROM (4.8436 ng/ml) in comparison to controls (3.651 ng/ml). This result is parallel to the findings of Ölmez *et al.* [14] prospective case-control study in Turkey, which found a higher mean serum aquaporin-9 level among pregnant women with PPROM (804.46 pg/mL) in comparison to healthy pregnant women (505.97 pg/mL). The observed difference in aquaporin-9 level between the two studies may be related to differences in the timing of sample collection as well as differences in procedures and units used for assessment. Recently, Luo *et al.* [24] stated that aquaporin 1 was essential in the expression of aquaporin-9 in the placenta, which in turn played a significant role in prelabor preterm rupture of membranes among pregnant women. In our study, the aquaporin-9 level appropriate cutoff value in the diagnosis of PPROM was 4.022 ng/ml with a sensitivity of 86.7% and specificity of 84.4%. This shows that aquaporin-9 is very important for correctly diagnosing PPROM cases when the history and exam are not clear, which means fewer treatments and stays in the hospital when the membranes are intact. These findings are approximate to the results of Mittal *et al.* [25] cross-sectional study in the United States of America, which reported that the aquaporin-9 level of pregnant women with PPROM was significantly higher due to the regulatory effect of aquaporins in the inflammatory process and energy equilibrium in PPROM and found that the cutoff value of 5 ng/ml was with a sensitivity of 80%, specificity of 90%, and accuracy of 87%. This study found that time to delivery for women with PPROM was one day or less from membrane rupture in 51.1% of them.

Additionally, the mean aquaporin-9 level was found to be negatively correlated with time to delivery after membranes rupture (p= 0.04). This was in alignment with results of Ölmez *et al.* [14] in Turkey. Indicating that the detection of high aquaporin-9 levels can affect the decision about the management strategies and patient's triage. Our study found that the delivery mode was vaginal in 73.3% of women with PPROM. The neonatal birth weight of cases with PPROM was low in 33.3%, very low in 35.6%, and extremely low in 4.4% of the cases. These findings are close to the results of Nossair *et al.* [26] prospective case-control study in Egypt; furthermore, the Apgar score at one minute of neonates was moderately abnormal in 60% and low in 6.7% of them, and 64.4% of them needed NICU admission. These findings are similar to the results of the Herzlich *et al.* [27] study in Palestine. No significant correlation was detected between aquaporin level and birth weight, Apgar score, or neonatal care unit admission; these findings are in agreement with the Ölmez *et al.* Study [14].

Study limitations

It is worth mentioning that our study has certain limitations. Firstly, the data originated from a single center and relatively small in size. The other point is that the study was limited to patients with PPROM and did not include those who were term with premature rupture of membrane, so it is not clear whether the elevation noted in aquaporin-9 level was merely related to premature rupture of membrane or whether being preterm additionally influenced the results.

Conclusions

Aquaporin-9 level at a cutoff value of 4.022 ng/ml is a valuable marker for diagnosing PPROM. Higher levels of this marker can predict shorter time to delivery in PPROM cases, influencing management decisions and triage of cases. Larger-sized multicenter studies are needed prior to adopting it as a marker for the diagnosis of PPROM and predicting time to delivery in obstetrical units.

Conflict of interests

The authors declared no conflict of interest.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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