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Relationship between Folate, B12 and Homocysteine levels and Obstetrical Outcomes in Preterm Premature Rupture of Membranes

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Abstract:

Background: When the fetal membranes rupture before the completion of 37 weeks of gestation, it is known as Preterm Pre-labor Rupture of the Membranes (PPROM). This condition occurs in around 2% of all pregnancies. Predicting the occurrence of PPROM involves identifying associated risk factors and using specific biomarkers in order to prevent any adverse maternal or fetal outcomes.

Objectives: To investigate the relationship between folate, B12, and homocysteine in PPROM and assess the maternal and neonatal outcomes of PPROM.

Cases and Methods: A case-control study was conducted on 100 pregnant women at the Department of Obstetrics and Gynecology at Al-Khansaa Maternity Teaching Hospital. The study was conducted between 20th January and 1st July 2022. The participants were women with a single viable fetus and a gestational age 240/7 – 366/7 weeks. The study had two groups of Fifty pregnant each. The first group, known as the "case" group, consisted of pregnant women suffering from PPROM. The second group, known as the "control" group, consisted of pregnant women who were matched for gestational age, had intact membranes, were not in labor, and had no obstetrical complications. The study estimated the levels of serum folate, B12, and homocysteine in both groups. Ethical approval was obtained prior to conducting the study.

Results: No differences were found between the two groups in terms of B12 and demographic data. However, the folate level was found to be lower in the cases than in the controls. On the other hand, the homocysteine level was significantly higher in the cases than in the controls. A homocysteine level of ≥ 28.85 nmol/ml was shown to be associated with a high sensitivity of 90%, specificity of 84%, and accuracy of 87%. Therefore, it could also be used as a reliable tool to predict PPROM. A folate level of ≤3.22 ng/ml, on the other hand, is associated with moderate sensitivity and low specificity.

Conclusion: Homocysteine levels and folate deficiency are reliable indicators of PPROM risk. Elevated homocysteine is a contributing risk factor.

Keywords: B12; Folate; Homocysteine; Preterm Pre-Labor; Rupture of the Membranes.

Introduction:

Premature rupture of the membranes (PROM) is defined as the spontaneous rupture of the fetal membranes with leakage of amniotic fluid before the onset of labor (1). If PROM occurs before 366/7 weeks of gestation, it is referred to as preterm premature rupture of membranes (PPROM), which occurs in approximately 2% of pregnancies and accounts for up to one-third of preterm deliveries(2). A preterm birth (PTB) is a delivery before 37 completed weeks of gestation. The management of pregnancies complicated by PPROM is challenging, controversial, and should be individualized. However, it should focus on confirming the diagnosis, validating gestational age, documenting fetal well-being, and deciding on the mode of delivery which depends on gestational age, fetal presentation, and cervical examination. In pregnancy, an increase of folate breakdown products has been observed, in line with the extra demand due to the rapidly growing placenta and fetus suggesting a possible relationship between folate status in the mother and fetal growth. Folates are also required for the metabolism of homocysteine, whose level is associated with pregnancy complications, such as miscarriage, placental abruption, and hypertension disorders (3).

Among the other outcomes, the rate of preterm birth (PTB), and PPROM, have a major interest in being a leading cause of perinatal morbidity and mortality. These premature births may be medically induced due to maternal or fetal complications (such as

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preeclampsia / eclampsia or intrauterine growth restriction) (4).

The link between B12 deficiency and PTB and PPROM is still the focus of investigators. Some studies have linked the duration of pregnancy to B12 deficiency and found a linear association between maternal levels of B12 and PTB, while other studies suggested that anemia may be the cause of PPROM. One of the causes of anemia is B12 deficiency(5).

Homocysteine (Hcy) is the demethylated product of the essential amino acid methionine. (6). The effects of homocysteine on pregnancy outcomes have also been linked with other adverse antepartum events such as oligohydramnios and meconium staining of amniotic fluid, fetal growth restriction, impairment of placental transport, and delivery of low-birth-weight (LBW) neonates(7).Increased maternal serum levels of Homocysteine might be a biomarker of neonatal diseases, which can be avoided at early-stage pregnancies. Serum levels of homocysteine are significantly higher in pregnant women with preterm births compared with those in healthy pregnant women, and the maternal serum levels of homocysteine before delivery are negatively associated with the birth weight of preterm(7).

Aim of Study

To explore the relationship between folate, B12, and homocysteine and PPROM, to review the socio-demographical and obstetrical characteristics as possible risk factors for PPROM, and to determine the outcomes (maternal, neonatal) of PPROM.

Patients and Methods

A case-control study included 100 pregnant women with single viable fetuses with gestational age ranging from 240/7 – 366/7 weeks of gestation conducted in the Department of Obstetrics and Gynecology at Al-Khansaa Maternity Teaching Hospital during the period from the 20th of January to the 1st of July 2022. Verbal and written consent was obtained from participants. Ethical approvals were obtained from The Council of Iraqi Board of Health Specialization and administration of Al-Khansaa Maternity Teaching Hospital. Fifty pregnant women with PPROM were case group, and another 50 pregnant women with matched gestational age, intact membranes, not in labor and without any obstetrical complications were the control group. These controls were followed until delivery. Those who developed PTB or PPROM during the follow-up period were excluded. All cases were interviewed using a pre-designed questionnaire that included demographic, obstetrics, and gynecologic information as well as information on the intake of nutritional supplements during pregnancy and dietary pattern. A complete abdominal and pelvic examination was done for all patients. Relevant lab investigations were done (Serum folate, B12, and homocysteine). The women were followed-up to obtain information on the mode of delivery and neonatal outcome. Levels of serum folate, B12, and homocysteine were measured.

The data was analyzed using the Statistical Package for Social Sciences (SPSS) version 26. Normality of the distribution of the continuous variables were tested by Shapiro–Wilk test. The independent t-test (two-tailed), the Chi-square test and Fisher-Freeman-Halton exact tests were used. The receiver operator characteristic curve analysis was done. The choice of the best cutoff point was made using the Youden J index test. A level of P value <0.05 was considered significant.

Results

Table 1 shows that there is no significant association between maternal age and PPROM. There was a significantly higher percentage of employed women among the cases than the controls. Lower educational levels were significantly higher among the cases than controls, as were passive smokers. Not taking folic acid or minerals during pregnancy was significantly higher for the PPROM cases, Table 1.

Table 1: Distribution of the cases and controls by socio-demographic and dietary characteristics

Variables	Categories	Cases		Controls		Total		OR	95%CI	P Value
		NO.	%	NO	%	NO	%			
Maternal Age (Years)	<20	9	18	5	10	14	14	1.8	0.65-4.9	0.373*
	20-30	22	44	28	56	50	50	0.79	0.53-1.17	
	>30	19	38	17	34	36	36	1.19	0.66-1.89	
BMI Groups	Normal (18.5-24.9)	37	74	34	68	71	71	1.09	0.84-1.4	0.509*
	Overweight (25-29.9)	13	26	16	32	29	29	0.81	0.44-1.5	
Employment	Employee	21	42	11	22	32	32	1.91	1.03-3.53	0.032*
	Housewife	29	58	39	78	68	68	0.74	0.56-0.98	
Educational level	Illiterate	10	20	5	10	15	15	2	0.73-5.43	0.001*
	Primary	32	64	18	36	50	50	1.77	1.16-2.72	
	Secondary	6	12	15	30	21	21	0.4	0.17-0.95	
	Higher	2	4	12	24	14	14	0.16	0.04-0.71	
Residence	Rural	23	46	25	50	48	48	0.92	0.61-1.38	0.689*
	Urban	27	54	25	50	52	52	1.08	0.74-1.57	
Passive Smoker	No	22	44	35	70	57	57	0.63	0.44-0.9	0.009*
	Yes	28	56	15	30	43	43	1.86	1.14-3.05	
Folic acid or minerals	None	17	34	3	6	20	20	5.6	1.77-18.13	0.002*
	Before and during pregnancy	9	18	17	34	26	26	0.59	0.26-1.07	
	Only during pregnancy	24	48	30	60	54	54	0.8	0.55-1.15	
Diet pattern	Vegetarian	5	10	0	0	5	5	-	-	N/A
	Mixed	45	90	50	100	95	95	0.98	0.83-1.01	

Chi-square test

As for obstetric characteristics, there were significantly more women with less than three antenatal visits among the PPROM cases than controls. This was also true for short interpregnancy interval <6 months, previous preterm delivery and previous PPROM, table 2.

Table 2: Distribution of the cases and controls by obstetric characteristics

Variables	**Categories**	**Cases**		**Control**		**total**		**OR**	**95%CI**	**P value**
		NO.	**%**	**NO**	**%**	**NO**	**%**			
Parity	Null	19	38	17	34	36	36	1.18	0.66-1.89	0.897*
	1-4	18	36	20	40	38	38	0.9	0.55-1.49	
	5 or more	13	26	13	26	26	26	1	0.52-1.94	
History of Miscarriage	No	36	72	29	58	65	65	1.24	0.93-1.66	0.142*
	Yes	14	28	21	42	35	35	0.67	0.38-1.16	
Gestational age groups	24-27+6	0	0	1	2	1	1	-	-	0.351*
	28-31+6	2	4	6	12	8	8	0.33	0.07-1.57	
	32-33+6	18	36	16	32	34	34	1.13	0.65-1.95	
	34-36	30	60	27	54	57	57	1.11	0.79-1.56	
Antenatal Care Visits	≥4	7	14	19	38	26	26	0.37	0.17-0.8	0.022*
	<3	27	54	21	42	48	48	1.28	0.85-1.95	
	None	16	32	10	20	26	26	1.6	0.81-3.18	
Inter-pregnancy Interval	Primi	15	30	4	8	19	29	1.07	0.58-1.98	0.029*
	<6 months	9	18	5	10	14	14	1.8	0.65-4.99	
	6-12 months	7	14	4	8	11	11	1.75	0.55-5.61	
	>1 year	7	14	25	50	22	22	0.47	0.21-1.05	
	>2 years	6	12	6	12	12	12	1	0.35-2.89	
	>3 years	6	12	6	12	12	12	1	0.35-2.89	
Previous preterm labor	No	43	86	49	98	92	92	0.87	0.78-0.99	0.027*
	Yes	7	14	1	2	8	8	7	0.89-54.83	
Previous PROM	No	43	86	49	98	92	92	0.87	0.78-0.99	0.027*
	Yes	7	14	1	2	8	8	7	0.89-54.83	
Previous caesarean section	No	42	84	43	86	85	85	0.97	0.83-1.15	0.779*
	Yes	8	16	7	14	15	15	1.14	0.45-2.91	

Chi-square test

PPROM cases needed significantly more antibiotics and steroids than controls. Neonatal outcome was significantly worse among the cases than controls (shorter GA at birth, lower birth weight, and Apgar scores) with significantly more admissions to NICU among the cases than controls. The mean serum folate was significantly lower in cases of PPROM than controls, while the mean serum homocysteine level was significantly higher among the cases than controls. The mean level of serum B12 was not significantly different between the two groups, table 3.

Table 3: Distribution of medical treatment, delivery variables, biomarkers and neonatal outcomes among the cases and controls

Variables		Case	Control	Total	P value
		No. (%)	No. (%)	No. (%)	
Antibiotics	Yes	45 (90)	1 (2)	47 (47)	<0.0001*
	No	5 (10)	49 (98)	53 (53)	
Tocolytic	Yes	19 (34)	0 (0)	19 (20)	N/A
	No	31 (66)	50 (100)	81 (80)	
Steroid	Yes	38 (76)	2 (4)	40 (40)	<0.0001*
	No	12 (24)	48 (96)	60 (60)	
Mode of delivery	C/S	11 (22)	12 (24)	23 (23)	0.812*
	Vaginal delivery	39 (78)	38 (76)	77 (77)	
Starting of labor	Induction of labor	22 (44)	13 (26)	35 (70)	0.059*
	Spontaneous	28 (56)	37 (74)	65 (74.7)	
Neonatal outcome Mean ±SD	Birth weight	2.2 ±0.50	3.3 ±0.38	2.8 ±0.74	<0.0001**
	GA at delivery	33.9 ±1.75	38.9 ±1.02	36.4 ±2.9	<0.0001**
	APGAR score at 1 min	5.8 ±1.66	7.1 ±1.33	6.4 ±1.62	<0.0001**
	APGAR score at 5min	6.9 ±1.8	8.0 ±1.25	7.5 ±1.63	<0.001**
NICU admission	No	26 (52)	46 (92)	72 (72)	<0.0001*
	Yes	24 (48)	4 (8)	28 (28)	
S. folate Mean ±SD		2.6 ±1.45	5.6 ±4.4	4.1 ±3.57	<0.0001**
S. B12 Mean ±SD		1236.2 ±427.28	1076.5 ±607.82	1156.3 ±528.83	0.132**
S. homocysteine Mean ±SD		61.8 ±21.5	21.8 ±22.79	41.8 ±29.84	<0.0001**

Chi square test** ****Student t-test

After the application of Receiver operator curve (ROC) analysis for the serum homocysteine and folate levels, it was found that the serum homocysteine cut-off value according to the Youden G index test is ≥ 28.85 nmol/ml associated with high sensitivity, specificity, and accuracy (90, 84, and 87% respectively). The serum folate level of ≤3.22 ng/ml is associated with moderate sensitivity and low specificity, thus it is a poor predictor for PPROM, figures1, 2, and table 4.

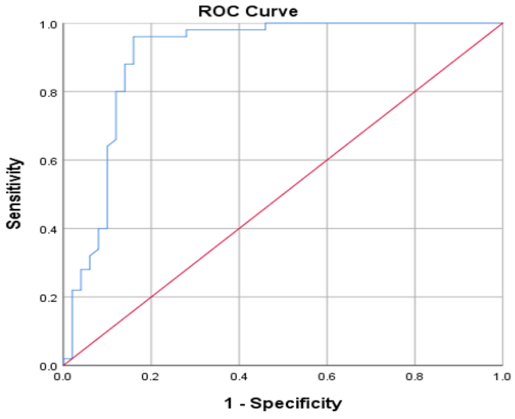

Figure 1: ROC curve of Homocysteine

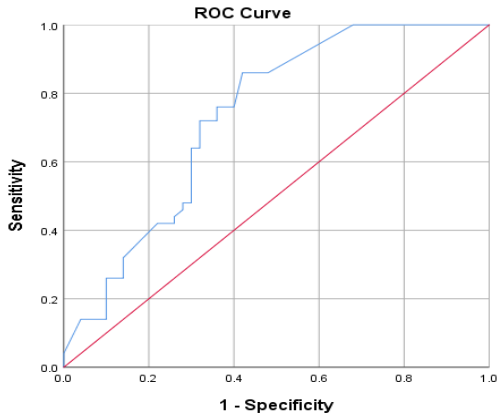

Figure 2: ROC curve of folate

Table 4: Predictive ability of serum homocysteine and folate levels

Indicator	Homocysteine	Folate
AUC	0.903	0.733
95% CI	0.836-0.970	0.634-0.833
Cutoff point	≥28.85	≤3.22
Odd ratio	5.625	2.25
95% CI	2.961-10.687	1.45-3.49
Sensitivity	90.0%	72%
Specificity	84.0%	68%
PPV	84.9%	69.2%
NPV	89.4%	70%
Accuracy	87.0%	70%

Discussion

The prediction of PPROM relies on the identification of associated risk factors such as (maternal age, BMI, occupation, educational level, passive smoking, taking folic acid / minerals during pregnancy, dietary pattern, parity, miscarriage, gestational age, antenatal care visit, interpregnancy interval, previous PPROM, preterm birth or caesarean section) and the use of specific biomarkers (Folate, B12, homocysteine) to prevent adverse maternal and fetal outcomes. Assefa et al (8) found no difference in maternal age between PPROM cases and controls. We could not reach the same finding as the cases and controls in the current study were age matched. Zhang et al (9) found underweight (BMI <18.5 Kg/m2) to be a risk factor for PPROM. In the current study underweight women were excluded from the study groups, and we did not find an association for the other BMI groups and the two study groups.

The significantly higher number of employed women in the PPROM group than the controls may be attributed to the physical and mental stress associated with work probably initiating uterine contractions was also suggested by Abouseif et al (10). The significantly higher number of women with lower education levels in the PPROM group than the controls was also reported by Nossair et al (11), and Bouvier et al (12). This may be related to the lower utilization of antenatal care and low socioeconomic status among those women. Rural versus urban residence did not appear to be associated with either of the study groups. This result is different from that reported by Lisonkova et al (13) which indicated an increase in PROM and preterm delivery in rural areas.

Passive smokers appeared to be more at risk of PPROM than non-smokers, which highlights the effect of smoking on the risk of PPROM. A similar result was found by Rau et al (14), suggesting that women exposed to tobacco smoke suffer the consequences of its chemical content.

In the current study, women who did not receive folic acid or minerals before or during pregnancy had five times the risk of developing PPROM than the controls, which is similar to the results of Islam et al (15) who reported that taking iron, folic acid, vitamin B complex, and vitamin C supplements after 14 weeks of gestation can prevent the occurrence of PPROM in women with a PROM history.

Parity did not appear to be significantly different between the cases and controls. Sae-Lin et al (16) reported that nulliparous women were more at risk of having PPROM than multiparous women. The same authors reported that previous miscarriage was not associated with the occurrence of PPROM, similar to the findings of the current study. The absence of or the poor utilization of antenatal care was more common among PPROM cases, similar to the results of Jamal et al(17).

The interpregnancy interval (IPI) of <6 months and 6-12 months was significantly more frequent among cases than controls, similar to the results of Shree et al (18) and Jena et al (19). Cases with a previous history of preterm labor were more likely to develop PPROM, similar to the results of Sea Lin et al (16). Women who had previous PPROM were seven times more likely to develop PPROM similar to the results of Assefa et al (8), which may be due to short cervical length. Assefa, et al (8) reported that women with a history of Cesarean section (C/S) were three times more likely to develop PROM than those who didn't have this history. The current did not find similar results. A previous Caesarean section may lead to a higher incidence of placental abnormalities such as previa and adherent placenta which are associated with structural abnormalities of fetal membrane and predispose to rupture.

Cases of PPROM required significantly more antibiotics, and steroids than controls as part of expectant management in cases. The current study found that the mode of delivery was not associated with any of the study groups. Of the PPROM cases, a fifth were delivered by C/S while Kayiga et al (20) reported a C/S rate of 30%, Magsi et al (21), had a C/S rate of 29.5%. Vaginal delivery was reported by Cayuga et al (20) to be 69.5% and Eleje et al (22) to be 81.1% compared to the 78% found by the current study.

Labor induction was used in less than half of the PPROM cases in the current study. The decision depends on the condition of the mother and baby and policy of the study locality where all patients enter expectant management. Van Der Ham et al(23) study reported that 84% of their cases had inducted labour.

Neonatal outcomes were significantly worse in the PPROM group than controls in the current study in terms of birth weight, Apgar score, and NICU admission rate. A similar result was found by Esteves et al (24), and Sim et al (25) studies.

In the current study, the mean folate level was significantly lower in cases of PPROM than controls. Mishra et al (26), and Li et al (27) studies found that folate deficiency is associated with an increased risk of

PPROM. The mean B12 level was not different between the two groups. Similar results were found by Mishra et al (11), and Ozturk et al (28) studies. A higher level of homocysteine was significantly associated with PPROM. Hyper-homocysteinemia increased the risk of PPROM by more than five times than controls which is comparable to the results found by Mishra et al (26), and Sembiring et al (29).
ROC curve analysis found that folate levels equal to or lower than 3.22 ng/ml were associated with 72% sensitivity and 68% specificity, while in Mishra et al (30) cut off for folate of <_3ng/ml was with a risk of 1.46 in PPROM group. Homocysteine level in this study equal or more than 28.85 nmol/ml was associated with 90% sensitivity, 84% specificity, and 89.4% negative predictive value. Camera et al(31), found that homocysteine level of > 15nmol/ml was associated with a risk of 2.15 more in the cases with 83.3% sensitivity, and 68.8% specificity, thus it is a good predictor for PPROM and also a good marker for the ruling out the risk in the absence of other risk factors. (32, 33)

Conclusions: Homocysteine and folate levels are good markers for predicting PPROM. An elevated level of homocysteine is one of the risk factors for PPROM.

Authors' declaration:
The manuscript is an original work, not previously published or sent to other journals. We hereby confirm that all the figures and tables in the manuscript are ours. The project was approved by the local ethical committee of the Iraqi board for medical specialization, code no. = 524.
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Author contributions:
Study conception & design: (Ahmed Jasim Mohammed). Literature search: (Aya Sabah Dawood). Data acquisition: (Aya Sabah Dawood). Data analysis & interpretation: (Aya Sabah Dawood). Manuscript preparation: (Aya Sabah Dawood). Manuscript editing & review: (Ahmed Jasim Mohammed)

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العلاقة بين الفوليت، فيتامين ب 12 والهيموسيستين في تمزق الغشاء الأمنيوسي المبكر قبل حدوث الولادة

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الخلاصة

الخلفية: عندما تتمزق أغشية الجنين قبل إتمام الأسبوع 37 من الحمل، يعرف ذلك باسم تمزق الأغشية قبل الأوان (PPROM). تحدث هذه الحالة في حوالي 2% من جميع حالات الحمل. يتضمن التنبؤ بحدوث PPROM تحديد عوامل الخطر المرتبطة به واستخدام مؤشرات حيوية محددة من أجل منع أي نتائج سلبية على الأم أو الجنين.

الأهداف: دراسة العلاقة بين حمض الفوليك وB12 والهوموسيستين في PPROM وتقييم النتائج الأمومية والوليدية لـ PPROM..

المنهجية: أجريت دراسة الحالات والشواهد على 100 امرأة حامل في قسم أمراض النساء والولادة في مستشفى الخنساء التعليمي للولادة. أجريت الدراسة في الفترة ما بين 20 يناير و1 يوليو 2022. وكان المشاركون من النساء اللواتي لديهن جنين واحد قابل للحياة وعمر الحمل 7/240 - 7/366 أسبوع. شملت الدراسة مجموعتين كل منهما خمسين حاملا. المجموعة الأولى، المعروفة باسم مجموعة "الحالة"، تتألف من النساء الحوامل المصابات بـ PPROM. أما المجموعة الثانية، والمعروفة باسم المجموعة "الضابطة"، فتتكون من نساء حوامل متطابقات في عمر الحمل، ولديهن أغشية سليمة، ولم يكن في حالة مخاض، ولم يكن لديهن أي مضاعفات توليدية. وقدرت الدراسة مستويات حمض الفوليك في الدم، B12 والهموسيستين في كلا المجموعتين. تم الحصول على الموافقة الأخلاقية قبل إجراء الدراسة.

النتائج :ولم يتم العثور على فروق بين المجموعتين من حيث B12 والبيانات الديموغرافية. ومع ذلك، فقد وجد أن مستوى حمض الفوليك أقل في الحالات منه في مجموعة التحكم. من ناحية أخرى، كان مستوى الهوموسيستين أعلى بكثير في الحالات منه في مجموعة التحكم. تبين أن مستوى الهوموسيستين الذي يبلغ ≤ 28.85 نانومول/مل يرتبط بحساسية عالية بنسبة 90%، ونوعية بنسبة 84%، ودقة بنسبة 87%. لذلك، يمكن استخدامه أيضا كأداة موثوقة للتنبؤ بـ PPROM. من ناحية أخرى، يرتبط مستوى حمض الفوليك الذي يبلغ 223.22. نانوجرام/مل بحساسية معتدلة ونوعية منخفضة.

الإستنتاجات: تعد مستويات الهوموسيستين ونقص حمض الفوليك مؤشرات موثوقة لخطر PPROM. ارتفاع الهوموسيستين هو عامل خطر مساهم.

الكلمات المفتاحية: بي 12، تمزق الغشاء الامنيوسي قبل حدوث الولادة، فوليت، هيموسيستين.