University Of Al-Nahrain
School Of Medicine
Department Of Obstetrics
and Gynecology

Platelet indices in preterm premature rupture of membranes and their relation with adverse neonatal outcomes in Al-imamain Al-kadhumain Medical City in Baghdad: A case-control Study

UNDER SUPERVISION OF :

Dr. Enas Thamer

NAME OF STUDENT :

Hamza Mohsin Jasim
6th Grade

بِسمِ اللهِ الرَّحمنِ الرَّحيم

الَّذِي خَلَقَنِي فَهُوَ يَهْدِينِ (٧٨) وَالَّذِي هُوَ يُطْعِمُنِي
وَيَسْقِينِ (٧٩) وَإِذَا مَرِضْتُ فَهُوَ يَشْفِينِ(٨٠)

صدقَ اللهُ العظيم

سورة الشعراء

Dedication

To our wounded and patient country “Iraq".

To our families for their abundant support.

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Objectives of the study

1- To assess Platelet indices in preterm premature rupture of membranes.

2- To assess the relation of Platelet indices with adverse neonatal outcomes.

Abstract

Aim: Preterm premature rupture of membranes (PPROM) is not only the most common distinguishable cause of preterm delivery, but is also associated with adverse neonatal outcomes. We determined the platelet indices in PPROM cases and evaluated their relationship to adverse neonatal outcomes.

Methods: Thirty patients with PPROM and 30 patients who experienced spontaneous preterm labor at <37 gestational weeks were evaluated. Complete blood counts, birth weights, Apgar scores, presence of sepsis and respiratory distress syndrome (RDS) and neonatal intensive care unit admission were recorded.

Results: Patients with PPROM had increased mean platelet volumes (9.40 vs 10;P= 0.01), plateletcrit (0.19vs 0.21;P= 0.03) and a higher frequency of neonatal sepsis (18% vs 38%;P= 0.02). Platelet indices in the patient group were compared according to the development of RDS. Plateletcrit values were higher in the RDS positive group (0.23±0.05 vs. 0.21±0.04;P= 0.04). The cut-off value for plateletcrit was determined as > 0.22.

Conclusion: Mean platelet volumes and plateletcrit significantly increased and plateletcrit had a predictive value for RDS in PPROM cases. Monitoring plateletcrit may be promising for predicting the development of RDS, one of the most common and serious complications of PPROM rupture.

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List of Abbreviations

PPROM	Preterm premature Rupture Of Membranes
RDS	Respiratory Distress Syndrome
PLT	Platelet
MPV	Mean Platelet Volume
PDW	Platelet Distribution Width
PCT	Plateletcrit
CBC	Complete Blood Count
NICU	Neonatal Intensive Care Unit
RDW	Red Cell Distribution Width
WBC	Wight Blood Cells
Hgb	Hemoglubin
Neu	Neutrophil
Hct	Hematocrit

Chapter One

Introduction

Incidence and Clinical Importance

Preterm premature rupture of membranes (PROM) occurs in 3% of pregnancies and is responsible for approximately one third of all preterm births[1]. Preterm PROM is an important cause of perinatal morbidity and mortality, particularly because it is associated with brief latency from membrane rupture to delivery, perinatal infection, and umbilical cord compression due to oligohydramnios[2]. Even with conservative management, 50–60% of women with preterm PROM remote from term will deliver within 1 week of membrane rupture[3].

Amnionitis (13–60%) and clinical abruptio placentae (4–12%) are commonly associated with preterm PROM[4]. The risk of these complications increases with decreasing gestational age at membrane rupture.

The frequency and severity of neonatal complications after preterm PROM vary with the gestational age at which rupture and delivery occur, and are increased with perinatal infection, abruptio placentae, and umbilical cord compression[5,6,7]. Respiratory distress syndrome (RDS) is the most common serious complication after preterm PROM at any gestation[8].

Other serious acute morbidities including necrotizing enterocolitis, intraventricular hemorrhage, and sepsis are common with early preterm birth but relatively uncommon near term. Remote from term, serious perinatal morbidity that may lead to long-term sequelae or death is common.

Among infants surviving to discharge, RDS (more than 24 hours' oxygen requirement or ventilation in the absence of other evident cause of respiratory compromise) was the most common acute morbidity at any gestational age[11].

Among surviving infants, intraventricular hemorrhage and necrotizing enterocolitis were rare when delivery occurred after 32 weeks. Blood- or cerebrospinal culture–proven sepsis declined rapidly among those delivering between 27 and 30 weeks, with a modest decline in sepsis for each week gained thereafter[8,9,12].

Definitions

Premature rupture of the membranes is defined as spontaneous membrane rupture that occurs before the onset of labor[1,2,3,4,5,6]. When spontaneous membrane rupture occurs before 37 weeks' gestation, it is referred to as preterm PROM. The term "latency" refers to the time from membrane rupture to delivery. "Conservative" management is defined as treatment directed at continuing the pregnancy. Preterm PROM that occurs at or before 26 weeks' gestation complicates 0.6–0.7% of pregnancies, and has been defined as "midtrimester PROM." Although the delineation of midtrimester PROM was clinically relevant in the 1970s and 1980s[17], the limit of fetal viability has progressively declined over the past 3 decades[18].

As such it is currently more clinically relevant to differentiate preterm PROM into "previable PROM," which occurs before the limit of viability (less than 23weeks),

"preterm PROM remote from term" (from viability to about 32 weeks' gestation), and "preterm PROM near term" (approximately 32–36 weeks' gestation). When previable PROM occurs, immediate delivery will lead to neonatal death. Conservative management may lead to previable or periviable birth, but may also lead to extended latency and delivery of a potentially viable infant. Immediate delivery after preterm PROM remote from term is associated with a high risk of significant perinatal morbidity and mortality that decreases with advancing gestational age at delivery[19]. Alternatively, with preterm PROM near term, expeditious delivery of a noninfected and nonasphyxiated infant is associated with a high likelihood of survival and a low risk of severe morbidity.

Preterm Prelabor Rupture of Membranes

Regardless of obstetric management or clinical presentation, birth within 1 week of membrane rupture occurs in at least one half of patients with preterm PROM. Latency after membrane rupture is inversely correlated with the gestational age at membrane rupture [30]. Cessation of amniotic fluid leakage with restoration of normal amniotic fluid volume may occur in the setting of spontaneous preterm PROM and is associated with favorable outcomes . Among women with preterm PROM, clinically evident intraamniotic infection occurs in approxi-mately 15–25% , and postpartum infection occurs in approximately 15–20%; the incidence of infection is higher at earlier gestational ages[34] . Abruptio pla-centae complicates 2–5% of pregnancies with preterm PROM . The most significant risks to the fetus after preterm PROM are complications of prematurity. Respiratory distress has been reported to be the most common com-plication of preterm birth Sepsis, intraventricular hemorrhage, and necrotizing enterocolitis also are asso-ciated with prematurity, but these are less common near to term. Preterm PROM with intrauterine inflammation has been associated with an increased risk of neurode-

velopmental impairment , and early gestational age at membrane rupture also has been associated with an increased risk of neonatal white matter damage[31]. However, there are no data that suggest that immediate delivery after presentation with PROM will avert these risks. Infection and umbilical cord accident contribute to the 1–2% risk of antenatal fetal demise after preterm PROM[33].

Previable Prelabor Rupture of Membranes

Rupture of the membranes before viability occurs in less than 1% of pregnancies. The probability of neonatal death and morbidity associated with PROM decreases with longer latency and advancing gestational age[35]. In a review of preterm PROM between 14 weeks and 24 weeks of gestation, perinatal deaths were more or less equally divided between stillbirths and neonatal deaths[37]. Survival rates were much improved with expectant management following membrane rupture after 22 weeks of gestation compared with membrane rupture before 22 weeks of gestation (57.7% versus 14.4%, respectively)[38]. Most studies of second-trimester and previable PROM are retrospective and include only expectantly managed cases. Thus, they likely overestimate survival rates because of selection bias. Survival data may vary by institution[40]. Significant maternal complications that occur after previable PROM include intraamniotic infection, endo-metritis, abruptio placentae, and retained placenta. Although it occurs infrequently, life-threatening mater-nal infection may complicate expectant management of previable PROM[41]. Maternal sepsis is reported in approxi-mately 1% of cases , and isolated maternal deaths due to infection have been reported in this setting.Latency periods appear to be prolonged with second-trimester preterm PROM compared with later gestational ages[42]. However, 40–50% of patients with previable PROM will give birth within the first week and approximately 70–80% will give birth 2–5 weeks after

membrane rupture[43]. The rate of pulmonary hypoplasia after PROM before 24 weeks of gestation varies widely among reports, but is likely in the range of 10–20%. Pulmonary hypoplasia is associated with a high risk of mortality, but is rarely lethal with membrane rupture sub-sequent to 23–24 weeks of gestation, presumably because alveolar growth adequate to support postnatal development already has occurred. Early gestational age at membrane rupture, and low residual amniotic fluid volume are the primary determinants of the incidence of pulmonary hypoplasia[44]. Prolonged oligohydramnios also can result in fetal deformations, including Potter-like facies (eg, low-set ears and epicanthal folds) and limb contractures or other positioning abnormalities. The reported frequency of skeletal deformations varies widely (1.5–38%) but many of these resolve with postnatal growth and physical therapy[45] .

Causes and Risk Factors

There is no single known cause of premature rupture of membranes. Though it is possible for the condition to occur for unknown reasons, certain risk factors have been identified[17]. These include:

- Poor nutrition or dehydration
- Smoking during pregnancy
- An infection in the cervix, uterus or vagina
- Prior cervical surgery or biopsy
- Even though none of these risk factors are necessarily related to chronic conditions, women with a prior incidence of PROM or PPROM are statistically at greater risk of the condition reoccurring in a future pregnancy.

Chapter Two
Methods & Materials

2.1 Study setting

In this case-control study, Fifty women from those who were referred to Al-imamain Al-kadhumain Medical City, Baghdad city, Capital of Iraq, selected as a result of PPROM (study group) and 50 women who experienced spontaneous preterm labor before 37 weeks of gestation (control group) were enrolled. PPROM is defined as rupture of the membranes at < 37 weeks of gestation. The study performed In Al-imamain Al-kadhumain Medical City in Baghdad, during the years of 2018-2019.

2-2. Inclusion and exclusion criteria

Inclusion criteria were women selected as a result of PPROM confirmed by observation of pooling of fluid from cervix by speculum examination

Exclusion criteria were as follows: multiple gestations; previous history of hematopoietic system disorders, malignancies, gestational diabetes, pre-eclampsia and any other systemic diseases; infections of urinary, respiratory or gastrointestinal tracts; and any acute or chronic infectious conditions. In addition, patients who had fetuses with intrauterine growth restriction; structural or chromosomal abnormalities; who underwent invasive diagnostic or therapeutic procedures, such as amniocentesis and cervical cerclage; or any other surgical procedures, were also excluded.

2-3. Methods of study

In our hospital, patients with PPROM are assessed by clinical signs and symptoms together with one of the following tests: white blood cell count in CBC, C-reactive protein and fetal heart rate monitoring to diagnose the presence of intrauterine infection. PPROM has been managed in our hospital since we started data collection as follows:

•Labor is induced in pregnancies complicated with PPROM at and after 34 weeks of gestation.

•An oral dosage of 6 g/24 h of penicillin is prescribed as antibiotic prophylaxis for a maximum of10 days or until labor starts spontaneously.

•If infection is suspected, labor is induced.

•A single course of dexamethasone treatment is routinely used between 24 and 34 weeks of gestation. A single repeat dose is administered if the first course of dexamethasone was completed 14 days. The criteria for NICU admission in our hospital are as follows: transient problems requiring cardio-respiratory monitoring, need for peripheral intravenous fluid therapy, jaundiced infants requiring peripheral intra-venous fluid therapy and closer monitoring, preterm less than 32 weeks of gestation, RDS, neonatal sepsis, exchange transfusion and sustained assisted ventilation. A diagnosis of sepsis is made with the presence of at least three of the following: temperature instability, tachypnea (> 70/min), feeding intolerance, abdominal distension, hepatosplenomegaly, dyspnea, lethargy, tachycardia (heart rate > 190 bpm) and bradycardia (heart rate < 90 bpm). Infants with respiratory distress, tachypnea, nasal flaring, grunting and a grainy shadow, air bronchogram and a white lung in chest X-ray are diagnosed with RDS. The medical records of participants were examined for maternal CBC values at the time of hospitalization, birth weights of neonates, 1 and 5 min Apgar scores, development of neonatal sepsis, development of neonatal RDS and NICU admission. We analyzed whether there was any alterations in PLT indices between the PPROM group and control. Moreover, we looked for a relationship between PLT indices measured by CBC and neonatal outcomes in PPROM cases. Complete blood count parameters were measured by an automated blood counter. Nurses took blood samples by venipuncture, which were collected in tubes containing

tripotassium-ethylenediaminetetraacetic acid(EDTA) to prevent coagulation. We recorded data of the following parameters from CBC records: white blood cell count (WBC), hemoglobin (Hgb), hematocrit (Hct), red cell distribution width (RDW), PLT count, MPV,PCT, PDW and neutrophil count (Neu).

2-4. Statistical analysis

After collecting the necessary information, data entered in SPSS version 23.0. To describe the data of central tendency and dispersion, mean and standard deviation (SD) were used. The correlation estimated with the Fisher's exact test. The level of significance less than 0.05 considered statistically significant.

Chapter Three
Results

This case-control study conducted to evaluate platelet indices in PPROM women compared with controls. The clinical and laboratory characteristics of patients and the control group are summarized in **Table 1**.

Table 1: The clinical and laboratory characteristics of patients and the control group.

	PPROM (n = 30)	Control (n = 30)	P
Age (years)	26 (17:42)	25 (17:41)	0.30†
Gestational age at delivery (weeks)	32 (27:36)	35 (25:35)	0.80†
Gravida (n)	3 (1:5)	2 (1:6)	0.92†
Parity (n)	2 (0:4)	1 (0:5)	0.80†
WBC ($\times 10^3/mm^3$)	11 (6.4:27.2)	10.3 (6.4:16.7)	0.27†
Neu ($\times 10^3/mm^3$)	8.2 (4:25.2)	7 (3:14.4)	0.22†
PLT ($\times 10^3/mm^3$)	220 (135:355)	224 (111:495)	0.80†
Hgb (g/dl)	11.19±1.32(8.11:13.21)	11.14±1.35(7.42:12.70)	0.72‡
Hct (%)	36.29± 3.82 (25:41.32)	36.30±3.95(22.51:42.34)	0.96‡
PCT (%)	0.22 (0.13:0.34)	0.20 (0.11:0.29)	**0.04**†
MPV (fl)	9.98 (7.40:12.60)	9.20 (0.43:12.60)	**0.02**†
PDW (%)	16.30 (4.95:18.30)	16.10 (14.43:16.92)	0.34†
RDW (%)	14.21 (11.40:22.30)	14.06(12.60:18.10)	0.29†

A P value of <0.05 was considered as statistically significant. †Mann Whitney U test; ‡Independent samples t test.

Compared to controls, patients with PPROM had higher MPV (9.20 vs 9.98; P = 0.02) and PCT (0.20 vs 0.22; P = 0.04) values.

The neonatal outcome s of patients and the control group are listed in Table 2. The frequency of neonatal sepsis was higher in the PPROM group (70% vs 33.3%; P = 0.01). Complete blood count parameters did not differ significantly between sepsis positive and negative PPROM groups (P > 0.05). Moreover, they were similar in NICU admission positive and negative PPROM groups. Contrary to these results, in the RDS positive PPROM group, maternal PCT values were significantly higher (0 .22 ± 0.05 vs 0.20± 0.04;P = 0.04).

Table 2: The neonatal outcome s of patients and the control group

		PPROM (n = 30)	Control (n = 30)	P
Birth weight (g)		2225 (700:3000)	2010 (700:3150)	0.08 †
Birth weight	<1500 g	7 (%23.3)	7 (%23.3)	0.48 †
	1500–2500 g	9 (%30.0)	13 (%43.3)	
	>2500 g	14 (%46.6)	10 (%33.3)	
Sepsis (+) (n ,%)		21 (%70.0)	10 (%33.3)	**0.01** †
RDS (+) (n ,%)		26 (%86)	18 (%60)	0.08 †
NICU(+) (n ,%)		26 (%86)	24 (%80)	0.88 †
Apgar < 7 (n)		8 (2:9)	8 (0:9)	0.50 †
Apgar > 7 (n)		9 (3:10)	9 (0:10)	0.65 †

A P value of <0.05 was considered as statistically significant. †Mann Whitney U test; ‡Independent samples t test.

Chapter Four

Discussion

The primary findings of the present study are that MPV and PCT values are higher and sepsis is more common in women with PPROM. Moreover, PCT values are higher in RDS positive PPROM patients and a PCT value > 0.22 is significantly related to a5.86 times increased risk of RDS in patients with PPROM. In PPROM patients, the time interval between membrane rupture and delivery is a major risk factor for the development of maternal and neonatal complications [9]. The most common and serious complications of PPROM are RDS, intra-ventricular hemorrhage, necrotizing enterocolitis and sepsis [3]. There is an inverse relationship between severity and incidence of these complications and gestational age. Although it is quite clear that labor should be induced as soon as possible in women at≥37 weeks of gestation, how clinical management should be performed at < 37 gestational weeks is controversial [10]. According to the American College of Obstetricians and Gynecologists and the Royal College of Obstetrics and Gynaecology, in women at≥34 weeks of gestation, delivery should be considered. Because current guidelines were established on limited evidence, whether immediate delivery is essential for patients with PPROM at≥34 weeks of gestation is questionable because of iatrogenic prematurity [3,18,19]. Expectant management is particularly crucial for pregnancies between 23 and30 weeks of gestation complicated with PPROM. Because these fetuses are extremely preterm and much more prone to neonatal mortality and morbidity, there is broader consensus on expectant management for this group of patients [20, 21]. If expectant management is preferred, caution is recommended in regard to infectious complications. Recent studies have shown that neonatal sepsis is more common in pregnancies complicated with early onset PPROM and in PPROM cases complicated with histologic chorioamnionitis [22, 23]. Similar to these findings, sepsis was more common in the PPROM patients in our study. On the other hand, Morriset al. stated in the PPROMT trial that immediate delivery did not reduce

neonatal sepsis, but did increase the likelihood of RDS and mechanical ventilator support for the baby and cesarean section for the mother [24]. While an appropriate waiting time is important to provide a favorable cervix and neonatal lung maturation, early intervention will result in failure to induce labor and an increase in operative delivery and cesarean section rates [25]. Recent improvements have allowed us to better understand the role of PLTs in immunity, inflammation and angiogenesis [26]. PLTs are disc shaped particles 1–2μm in size, with a life cycle of 8–10 days and are released into circulation during megakaryocyto-poiesis [27]. They are cytoplasmic fragments of megakar-yocytes and their functional and morphologic capabilities may be affected by several factors, such as thrombopoietin, granulocyte-macrophage colony stimulating factor, interleukin 1,interleukin 6 and tumor necrosis factor alpha [28]. In inflammatory processes with an increased risk of thrombosis, PLTs in the circulation increase in number and size, migrating to the site of infection where they should be heavily consumed [28]. As they migrate, they regulate their own functions by changing their shapes and releasing biologically active substances [29]. This may explain the possible mechanisms to understand how PLT indices such as MPV, PDW and PCT are altered in some cases. In several studies, a number of diseases, such as hypertension; diabetes; myocardial infarction; cerebrovascular disease; and inflammatory diseases, such as systemic lupus erythematosus, inflammatory bowel disease and rheumatoid arthritis, PLTs indices were altered. Gasparyanet al. reviewed data on MPV, which may function as a prothrombotic or a pro-inflammatory agent in different clinical settings. The data suggested MPV is increasingly used as a marker to determine disease activity or the effectiveness of anti-inflammatory treatment in chronic inflammatory diseases. In systemic infections, the sizes of PLTs in the circulation increase as the severity of disease increases, whereas MPV decreases in cases of high and low grade infections and

during anti-inflammatory treatment [11]. In addition, PLT indices were reported to be disturbed in some obstetric conditions, such as recurrent pregnancy loss, pre-eclampsia, gestational diabetes and preterm labor [12–15]. Ayniogluet al. showed that there was a relationship between recurrent pregnancy loss and altered PLT indices, such as a higher PLT count and PCT [12]. Another study demonstrated that MPV became higher as the severity of hypertension in pregnancy increased [13]. Sahbazet al. evaluated the relationship of gestational diabetes with different PLT indices and determined a statistically significant increase in PCT, MPV and PDW values compared to healthy pregnancies [14]. Whether PLT indices are of value for predicting preterm labor was also examined and PCT values were found to be significantly higher in preterm deliveries [26, 27]. Gioiaet al. investigated the association of MPV and oxygen metabolic changes in pregnancies affected by altered umbilical artery maternal-fetal Doppler velocimetry. They found that MPV was significantly higher in patients with abnormal umbilical artery Doppler velo-cimetry and an MPV value≥10flwas significantly related to adverse neonatal outcomes, such as RDS and brain damage [17]. Predictive values of PLT indices are have generally been investigated in the literature to determine different obstetric conditions. However, their roles in PPROM and relationships to adverse neonatal out-comes have not been comprehensively studied. Beyanet al. reported that MPV may not be useful as a marker in predicting PPROM [25]. Contrary to this study, Ekinet al. cited that MPV and PLT count at first trimester of pregnancy can be used for an early diagnosis of PPROM and revealed that the PLT count was significantly higher and MPV significantly lower during the first trimester in women who developed PPROM in the following weeks [16]. In the present study, we found that MPV and PCT were significantly higher in the PPROM group compared to controls. We also evaluated whether there was an association in patients with PPROM between adverse neonatal outcomes and MPV, PCT and

PDW. Pregnancies complicated with PPROM were grouped according to the development of RDS and it was observed that PCT was higher in patients who developed RDS.

Chapter five

Conclusion
Recommendations
References

CONCLUSION

According to this study, as the time interval between membrane rupture and delivery increases, the risk of maternal and neonatal infections also rises. Controversy over the appropriate management remains. The appropriate time interval for expectant management is important to provide a favorable cervix and consequently decrease operative deliveries, allow neonatal lung maturation and avoid iatrogenic prematurity. Therefore, it is critical to decide how long to wait until labor starts spontaneously or to determine the appropriate time to induce labor. Determining the markers to predict neonatal complications in antenatal surveillance during expectant management are crucial. We suggest that in cases of PPROM, monitoring PCT maybe promising to predict the development of RDS, which is one of the most common and serious complications of PPROM.

Recommendations

1-Patients with PROM before 34 0/7 weeks of gesta-tion should be managed expectantly if no maternal or fetal contraindications exist.

2-To reduce maternal and neonatal infections and gestational-age-dependent morbidity, a 7-day course of therapy with a combination of intravenous ampi-cillin and erythromycin followed by oral amoxicil -lin and erythromycin is recommended during expectant management of women with preterm PROM who are less than 34 0/7 weeks of gestation.

3-Women with preterm PROM and a viable fetus who are candidates for intrapartum GBS prophy-laxis should receive intrapartum GBS prophylaxis to prevent vertical transmission regardless of earlier treatments.

4-A single course of corticosteroids is recommended for pregnant women between 24 0/7 weeks and 34 0/7 weeks of gestation, and may be considered for pregnant women as early as 23 0/7 weeks of gestation who are at risk of preterm delivery within 7 days.

5-Women with preterm PROM before 32 0/7 weeks of gestation who are thought to be at risk of imminent delivery should be considered candidates for fetalneuroprotective treatment with magnesium sulfate.

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