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Maternal Serum C-Reactive Protein and Mean Platelet Volume as Predictors of Preterm Premature Rupture of Membranes

Khulood Sami Hussein[1*]

[1]*Department of Medical Physiology, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia.*

***Email:** Khussein@kau.edu.sa*

ABSTRACT

Preterm premature rupture of membranes (PPROM), is linked to many complications for both the mother and the baby. Identifying women with an increased risk of PPROM early in pregnancy would lower the incidence of negative perinatal outcomes. This study aims to evaluate the usefulness of maternal C-reactive protein (CRP), platelet count, and mean platelet volume (MPV) in early pregnancy in predicting the development of PPROM later. This prospective study was conducted in the Department of Obstetrics & Gynecology at King Abdulaziz University Hospital, Saudi Arabia for nine months (2019-2020). After common clinical causes of PPROM were excluded, 560 women were included in the study, of which 60 developed PPROM before labor, with the remaining 500 completing their pregnancy with intact membranes. After informed consent, maternal blood samples for platelet count, MPV, and CRP evaluation were collected at the first visit and later at admission for delivery with PPROM (evidenced by vaginal leakage of amniotic fluid) or normal delivery.

The sensitivity and specificity of maternal CRP were 87% and 54% respectively. The sensitivity of platelet count and MPV in predicting PPROM was 67 and 60%, with a specificity of 47% and 62%, respectively. The present study concluded that CRP and MPV are more effective markers than platelet count for early detection of PPROM.

Key words: *C-reactive protein, Preterm premature rupture of membranes, Mean platelet volume, Platelet count, Early pregnancy*

INTRODUCTION

Preterm premature rupture of membranes (PPROM), the term used when the amniotic sac spontaneously ruptures before the 37th week and before the onset of labor, is a complication affecting roughly 3% of all pregnancies [1]. As a frequent trigger of preterm labor [2], PPROM is linked to significant morbidity and mortality of both the mother and baby [3]. Many complications for the mother and newborn are linked to premature delivery [4], so it is crucial to identify women with a higher risk of PPROM early in pregnancy to lower the incidence of negative perinatal outcomes [4, 5].

The mechanisms that may lead to PPROM are numerous. One factor may be changed in the chorioamnionitis membranes, including lower levels of collagen. This, in conjunction with the forces applied from contractions of the uterus, further weakens these membranes [5]. Possible additional factors for PPROM are intraamniotic infection, decidual hemorrhage, and vasculopathy in placentation [4, 6].

Despite the lack of clarity surrounding the pathophysiologic mechanism of PPROM, among its many factors is inflammation [7]. In prior research, the intrauterine infection has been found to spark an increase in the number of cytokines in both amniotic fluid and maternal serum [8, 9]. Based on the close association between inflammatory markers and cytokines, we hypothesize that a first-trimester change in the level of these markers in maternal serum may be linked to PPROM.

Recent studies have focused on several inflammatory markers for their use in detecting membrane rupture early in pregnancy. Maternal serum C-reactive protein (CRP), an acute-phase protein synthesized in the liver by hepatocytes, has been examined for its use in screening for asymptomatic infection among pregnant women with preterm labor or preterm rupture of membranes. Usually detectable in small amounts in serum [10], CRP is often used in obstetrics to detect different inflammatory conditions such as chorioamnionitis and to diagnose infections that may lead to increased risk of premature labor. CRP binds to altered or necrotic membrane structures upon its release. It is thought to have a specific role in repairing and regenerating tissue, suggested by its biological effects including stimulation of leukocyte motility, increased phagocytosis, and opsonization [10]. Elevated levels of both CRP and leukocytes were found in pregnant women who went on to experience PPROM [11, 12].

Another factor in the pathophysiology of inflammation, infection, and malignancy is the activation of platelets [13]. Mean platelet volume (MPV) can be used reliably to gauge platelet size, which indicates their function and activation. An association between both prothrombosis and proinflammation has been found [14], but research on the early predictive value of MPV and platelet count for PPROM is insufficient [9, 15]. With this gap in the literature and given the established link between subclinical intrauterine infection and PPROM mechanisms, there is a need to examine the role of MPV and platelet count in PPROM.

Therefore, this prospective study aimed to explore whether PPROM is preceded by any variations in the volume and number of platelets as measured by a basic complete blood count (CBC). Additionally, our study aimed to measure the diagnostic value of these markers as predictors of PPROM and further to assess the association between PPROM and serum CRP concentrations as an inflammation factor and determine its diagnostic value as a predictor of PPROM.

MATERIALS AND METHODS

Saudi Arabia has universal free health care for all citizens and legal residents. Extensive prenatal care is part of the maternal healthcare services in the country, with health education targeting expectant mothers. Prenatal care also includes screening for infectious diseases, with the goal of prevention and management, and prophylactic medication is offered [16]. As part of this care for pregnant women, their histories are taken, and they undergo screening for conditions like anemia and hypertensive disorders. This widely available prenatal care begins in the first trimester and offers a minimum of eight visits for women with normal pregnancies [17]. This prospective study involved expectant mothers in their first trimester who visited the Department of Obstetrics and Gynecology, King Abdulaziz University Hospital (KAUH), Saudi Arabia from September 2019–May 2020 for a routine prenatal checkup. During the visit, demographic data, maternal characteristics, and medical history were collected for each woman. Also, each participant underwent a physical examination including abdominal obstetric ultrasound to confirm gestational age and normality of pregnancy.

All participants in this study met the following inclusion and exclusion criteria:

Inclusion criteria

Age ≥ 18 years, singleton pregnancy, recalling the exact date of the last menstruation, viable fetus, gestational age 6–14 weeks at the first prenatal visit, and body mass index (BMI) of 18–25 kg/m².

Exclusion criteria

Multiple pregnancies, poor obstetric history, gestational diabetes, systemic diseases, prior history of hematopoietic disorders, malignancies, acute or chronic inflammatory conditions, or being on any medications. Additional exclusion criteria were any history of complications in prior pregnancy including fetal growth restriction, structural or chromosomal abnormalities of the fetus, or women who had undergone invasive diagnostic or therapeutic procedures, including amniocentesis and cervical cerclage, or any other surgery, and previous preterm birth.

Participants who met the eligibility criteria were tracked until delivery, with a focus on the presence of PPROM as the main outcome. Diagnosis of PPROM was done through sterile speculum examination (to confirm pooling of amniotic fluid from the vagina) and a positive Nitrazine test.

Initial blood samples were collected at each woman's first visit to establish a baseline, and upon admission with signs of PPROM or at the onset of labor (for those with normal pregnancies). Any specimens with evidence of clotting were thrown out. The platelet parameters were assessed using the Sysmex XN-9000 fully automated hematology analyzer on blood samples collected in ethylenediamine tetra-acetic acid (EDTA) anticoagulant. The samples were analyzed within 2 hours from the time of collection to avoid bias caused by excessive platelet

swelling and to keep variation due to sample aging to a minimum [18]. Serum CRP levels were measured by high sensitivity enzyme-linked immunosorbent assay (ELISA) (Roche Diagnostics Systems, using the Hitachi automated analyzer).

After giving a comprehensive explanation of the procedure involved, researchers obtained written consent from all participants. The Biomedical Committee at the Faculty of Medicine, KAUH approved the collection and use of these samples and data for research.

Statistical analysis

The presence of PPROM was evaluated in study participants based on first trimester measures of CRP, platelet count, and MPV. Statistical analysis was done using SPSS version 21.0 for Windows (SPSS Inc., IL, USA). The number of participants in each group (PPROM and term delivery) and their respective percentages/proportions were used as summary statistics for categorical variables, while means and standard deviations were used for continuous variables. The Shapiro-Wilk normality test was used on the continuous variables. The p-values of independent samples t-test were used to compare differences between means and proportions in the two groups (PPROM and term delivery). To evaluate how well CRP, platelet count, and MPV values served as predictors for PPROM, the following measures were recorded: sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV), likelihood ratios (LR) with 95% Confidence Intervals (CI), and odds ratios (OR) with 95% CI. Odds ratios were reported and interpreted using the guidelines set out by Szumilas (2010) [19]. P-values of <0.05 were deemed statistically significant.

RESULTS AND DISCUSSION

Five hundred and sixty pregnant women were included in this study. **Table 1** outlines the clinical characteristics of the participants. Of the 560 subjects, 60 women experienced PPROM, at a rate of 10.7%. One of the pregnant women in the control group was a smoker. No significant differences were found between the PPROM and term delivery groups concerning maternal age, parity, BMI, and gestational age at the time of sampling (P>0.05). However, there was a significant difference in mean CRP levels at initial screening between the PPROM and term delivery groups. Compared to women with normal pregnancies, those who went on to develop PPROM had significantly higher mean CRP concentrations (5.95 ± 2.80 mg/L vs 2.21 ± 1.94 mg/L; P=0.004). Likewise, women with PPROM had higher platelet counts (250.7 vs 228.5; P <0.01) and higher MPV (9.6 vs 8.2; P <0.01) than those in the control group. As to be expected with the nature of this study, women with PPROM delivered earlier than their counterparts with normal pregnancies (31.6 vs 39.2 weeks; P<0.01), and the rate of cesarean delivery was higher than that of vaginal delivery (62% vs 38%). Differences in the cesarean section rate and the vaginal delivery rate between the PPROM group and the term delivery group also reached statistically significant levels (P=0.001). The neonatal mortality rate was 40% (n=24) among PPROM cases, significantly higher than that of the control group 11% (n=55); P=0.001.

Table 1. Demographic and clinical characteristics of the participants in the first trimester

	PPROM (n=60) (mean±SD)	Term Delivery (n=500) (mean±SD)	P-value
Maternal age (years)	24.2± 3.6	23.9 ± 3.9	0.780
Parity	1.3 ± 1.1	1.2 ± 1.1	0.448
BMI	22.62 ± 1.11	22.33 ± 1.21	0.220
GA sampling (weeks)	9.44 ± 2.24	9.54 ± 1.88	0.801
GA delivery (weeks)	31.5 ± 3.0	39.2 ± 1.3	0.001
CRP (mg/L)	5.95 ± 3.87	2.56 ± 1.94	0.004
WBC ($\times 10^3/mm^3$)	9.14 ± 1.6	7.02 ± 1.01	0.001
Plt ($\times 10^3/\mu L$)	250.5 ± 55.0	228.7 ± 42.2	0.001
MPV (fl)	9.6 ± 1.30	8.2 ± 1.10	0.001
Cesarean delivery	37 (62%)	92 (18%)	0.001
Normal delivery	23 (38%)	408 (82%)	0.001
Neonatal mortality	24 (40%)	55 (11%)	0.001

GA, gestational age; CRP, C-reactive protein; WBC, white blood cell; Plt, platelet count; MPV, mean platelet volume; SD, standard deviation.

Table 2 shows the biochemical results of the participants during PPROM (cases) or at admission for delivery (controls). Increases in CRP levels from initial sampling to admission were seen in women in both the PPROM and term delivery groups, but the rise was much higher in those with PPROM, reaching statistical significance (10.71 ± 6.40 mg/L vs 4.51 ± 2.32 mg/L; P=0.001). Compared to those with normal pregnancies, women with PPROM had significantly higher platelet counts (305.7 ± 62.5 vs 230.5 ± 43.1; P<0.01) but significantly lower mean platelet volume (8.1 ± 1.1 vs 9.0 ± 1.1; P <0.01).

Table 2. Laboratory characteristics of the studied women during PPROM and at admission for delivery

	PPROM (n=60) (mean±SD)	**Term Delivery (n=500) (mean±SD)**	**P- value**
CRP (mg/L)	10.71 ± 6.40	4.51 ± 2.32	0.001
Plt (×10^3/µL)	305.7 ± 62.5	230.5 ± 43.1	0.001
MPV (fl)	8.1 ± 1.1	9.0 ± 1.1	0.001

CRP, C-reactive protein; Plt, platelet count; MPV, mean platelet

Table 3 summarizes how well CRP, Plt, and MPV performed as predictors for PPROM. With the cutoff value of ≥ 7.5 mg/L, CRP predicted PPROM with a sensitivity of 87%, a specificity of 54%, a positive predictive value of 87%, a negative predictive value of 53%, a positive likelihood ratio of 1.89, and a negative likelihood ratio of 0.24.

With cutoff values of ≥ 220 x 10^3/µL and ≤ 8.5 fL, the platelet count and MPV predicted PPROM with a sensitivity of 67% and 60%, a specificity of 47% and 62%, a positive predictive value of 70% and 81%, a negative predictive value of 43% and 35%, a positive likelihood ratio of 1.26 and 1.57 and a negative likelihood ratio of 0.70 and 0.66, respectively.

Table 3. Diagnostic performance of CRP, Plt, and MPV for prediction of PPROM

	CRP (mg/L)	**Plt (×10^3/µL)**	**MPV (fl)**
Cut-off	≥ 7.5 mg/L	≥ 220 ×10^3/µL	≤ 8.5 fL
Sensitivity	0.87	0.67	0.60
Specificity	0.54	0.47	0.62
PPV (%)	0.87	0.70	0.81
NPV (%)	0.53	0.43	0.35
LR$^+$ (95% CI)	1.89 (1.4–2.4)	1.26 (1.04–1.48)	1.57 (1.32–1.81)
LR$^-$ (95% CI)	0.24 (0.12–0.36)	0.70 (0.60–0.80)	0.66 (0.57–0.76)
Diagnostic OR	10.61	1.8	2.35
Odds Ratios	7.9 (1.99–31.90)	1.81 (0.61–5.38)	2.41 (0.74–7.81)

We collected data on 560 women in their first trimester of pregnancy and found that 10.7% went on to develop PPROM. Rupture of the amniotic sac before labor occurs in 3% of all births, a figure that rises to 11% with preterm births [20]. Estimating the likelihood of PPROM has been based primarily on characteristics of the pregnant woman and her obstetric history. Of these, the greatest risk factor is a history of previous preterm labor or PPROM [21]. However, following our exclusion criteria, no risk factors were identified in the study participants.

It is widely accepted that the majority of premature births and PPROM cases stem from underlying infection. Currently, an accepted approach for PPROM is expectant management, but this approach increases the risk of chorioamnionitis. Therefore, expectant management must include monitoring for signs and symptoms of possible infection.

It is crucial to detect women at risk of PPROM early to provide preventive interventions. Detecting infection is most commonly done using total leukocyte count, differential leukocyte count, urine culture, and vaginal culture as laboratory markers. However, these tests are generally unreliable. CRP stands out among acute phase proteins as a highly sensitive marker of infection at an early stage, rising dramatically in less than 24 hours. CRP in maternal blood has been widely used to detect the risk of preterm labor in women with PPROM [22]. In our study, patients in the PPROM group had CRP concentrations that were significantly higher than those with normal

pregnancies ($P< 0.05$). We found the sensitivity of maternal CRP in predicting PPROM to be 87%, with a specificity of 54%, a positive predictive value of 87%, and a negative predictive value of 53%.

CRP levels in the body rise at times of acute injury, infection, or other inflammatory stimuli, making it a key blood indicator of systemic inflammation. As increasing levels of serum CRP suggest an inflammatory response, CRP is valuable as a general indicator, but this marker will not identify the location of the inflammation or its underlying cause. Proinflammatory cytokine interleukin-6 is likely to have a key role in the synthesis of CRP by hepatocytes [23].

CRP concentrations vary according to gestational age [24], and higher levels are also linked to high BMI and other indicators of adiposity [25]. In the current study, significant differences in CRP levels were observed between the cases and controls at early gestation, despite there being no differences in gestational age and BMI at sampling between the two groups of women.

Researchers have explored the extent to which serum CRP levels can predict different obstetric conditions. Some have found no link between CRP levels and the risk of premature delivery. Bakalis *et al*. reported that maternal serum CRP at 11–13 weeks gestation is not an effective indicator of early preterm delivery [26]. Similarly, Ghezzi *et al*. found no link between serum CRP levels in the mother and preterm delivery risk [27].

In contrast, Lohsoonthorn *et al*. reported a positive association between increases in serum CRP levels in women in early pregnancy and the risk of preterm delivery [28]. Pitiphat *et al*. studied 117 women with preterm deliveries (cases) and 117 with term deliveries (controls) to investigate the link between CRP levels and preterm delivery risk. Median CRP levels were higher in cases than in controls (3.2 vs 2.4 mg/L) [29]. Similarly, Moghaddam Banaem *et al*. examined concentrations of CRP and PPROM risk in 778 women in the first half of pregnancy and found much higher median CRP concentrations in women with PPROM than in women who had term deliveries (7 vs 2.4 mg/L), leading to their conclusion that CRP may be employed in early pregnancy to screen patients for risk of PPROM [11]. Aggarwal *et al*. also concluded that CRP was the earliest and most reliable diagnostic indicator of PPROM [30]. Our findings are in line with these studies showing that maternal serum CRP concentrations in early pregnancy were elevated in women who subsequently developed PPROM and may be an effective predictor of PPROM.

Moreover, we found that as a predictor for PPROM, the optimal cutoff value of maternal CRP concentrations in the first trimester was ≥ 7.5 mg/L. This cutoff value varies greatly in the literature: Grgic *et al*. [31] used 4 mg/L as their cutoff value, Pitiphat *et al*. used a cutoff value of ≥ 8 mg/L [29], and Ertas *et al*. [32] reported a CRP cutoff value of 9.66 mg/L. These differences may be explained by variations in the inclusion and exclusion criteria each study employed as well as differences in the time of sampling. Regardless of the cutoff value, the elevation in levels of CRP reported in PPROM cases indicates stimulation of inflammation due to increased cytokine secretion [33].

White blood cell counts are widely viewed as a way to identify infection before its clinical signs are obvious. In this study, we found higher white blood cell levels in women with PPROM than in controls, which could be a result of infection, inflammation, or other gestational conditions. Our findings are following those of Greig (1998), who suggested that elevated WBC counts are an optimal diagnostic marker for significant systemic infection, but this marker lacks specificity [34]. Tzur *et al*. examined maternal WBC levels in the first trimester and the risk of developing complications later on in the pregnancy and found a significant link between first-trimester leukocytosis and PPROM [12]. These studies indicate a clear association between levels of inflammation markers and incidence of PPROM due to increased cytokine secretion.

The part played by platelets in inflammation, immunity, and angiogenesis has become clearer with recent research [35]. Disc-shaped particles with a diameter of 1–2 μm, platelets are generated during megakaryocytopoiesis and remain in circulation for 8–10 days [36]. The functional and morphologic capabilities of these cytoplasmic fragments of megakaryocytes may be impacted by several factors, including thrombopoietin, granulocyte-macrophage colony-stimulating factor, interleukin 1, interleukin 6, and tumor necrosis factor-alpha [37]. In cases of inflammation with a higher thrombotic risk, circulating platelets grow in size and number, moving to the infection site, where they are often heavily consumed [38]. As they move, platelets change shape and release biologically active substances [39], which may explain the possible mechanisms by which platelet indices change.

Alterations in platelet indices have been found in many studies on various diseases such as hypertension, diabetes, inflammatory bowel disease, rheumatoid arthritis, and obstetric abnormalities. For instance, Ahmed *et al*. observed that women with elevated MPV in the second and third trimesters of pregnancy are more likely to develop preeclampsia [40]. Myatt *et al*. also reported that first trimester MPV was significantly higher in women who subsequently developed preeclampsia [41]. They also suggested that platelet volume could be used to detect

women at risk with subclinical vascular dysfunction [41]. The pathophysiologic role of platelets in these studies was inflammation leading to thrombosis. Increased MPV and thrombocytopenia arise from heightened consumption of platelets at the site of damaged vascular endothelium in impaired placentation [40, 41].

In their review of research on the role of MPV as a clotting or a proinflammatory agent, Gasparyan *et al*. found that MPV is used more and more as an indicator of disease activity or a measure of efficacy of anti-inflammatory therapy in conditions involving chronic inflammation. In systemic infections, the increase in circulating platelet size is directly proportional to the severity of the disease. In contrast, lower MPV is seen in the presence of high- and low-grade infections and in treatment to reduce inflammation [14]. Aynioglu *et al*. reported altered platelet indices such as elevated platelet count in women with recurrent loss of pregnancy [42]. Another study found an association between higher MPV and the severity of gestational hypertension [43]. In their study of the association between the relationship of gestational diabetes and various platelet indices, Shahbaz *et al*. found platelet count and MPV values to be statistically significantly higher in cases compared to healthy pregnancies [44].

The effectiveness of using platelet indices to predict preterm labor has also been studied. Gioia *et al*. examined the relationship between MPV and altered umbilical artery maternal-fetal Doppler velocimetry and found a significant increase in MPV in women with this condition, with an MPV value of ≥ 10 being linked to adverse neonatal outcomes [8].

While platelet indices have been studied for their importance as general predictors of various obstetric conditions, the role of these indices in predicting PPROM has not been investigated to the same degree. Research carried out by Beyan *et al*. casts doubt on the effectiveness of MPV as a predictor of PPROM [45]. However, Ekin *et al*. found significantly lower first trimester MPV in patients who subsequently developed PPROM, suggesting that MPV may play a part in the early detection of PPROM [9]. In contrast, Dundar *et al*. reported significantly higher MPV in women who developed PPROM than in those with term deliveries [15]. The results of our study are in line with Dundar *et al*. We found that platelet count and MPV before the second trimester were significantly higher in women who went on to experience PPROM than in those who did not. We also found that MPV has greater effectiveness than platelet count as a predictor of PPROM, in line with previous research [9].

The differences in study results may be due to variations in study design, the underlying characteristics of participants, the timing of sample collection, and inadequate control for confounding. Take blood collection as an example. Researchers have observed that when serum CRP is collected in the third trimester (28 weeks), there is a stronger link between CRP levels and preterm delivery than when serum CRP levels are measured during a woman's first visit for prenatal care (first and early second trimesters). Differences in research results in this area may also be explained by disparities in the prevalence of subclinical infections seen in diverse study populations.

Our current study has several strengths. First, blood samples were analyzed within two hours from the time of collection, with analysis being carried out in the same lab, by the same technician, using the same automated counter throughout the research period. Second, strict exclusion criteria were used to ensure the enrollment of a homogeneous group of women in the early stages of pregnancy, strengthening our conclusion. Third, measuring MPV and CRP levels using samples collected in the first trimester helped to elucidate the temporal relationship between higher levels of MPV and CRP and subsequent risk of PPROM in pregnant women. Among the limitations of this study was the small number of participants who experienced PPROM (60 out of 560). Additionally, this study did not collect data on nutritional status and lifestyle factors such as physical activity, which may affect MPV.

CONCLUSION

Our study is the only one that investigates the effectiveness of maternal platelet count, MPV, and CRP levels during the first trimester as predictors of PPROM in the Western region of Saudi Arabia. While the accurate prediction of PPROM is still difficult, the findings of this study suggest that CRP and MPV are more effective markers than platelet count for early detection of PPROM. Our data can thus provide a reference for the detection of asymptomatic women with subclinical intraamniotic infection at higher risk of developing PPROM and with later preterm delivery. Given the multifactorial etiology of PPROM, early screening of all women with a single test is problematic. To develop an accurate and effective way to estimate PPROM risk, screening techniques that combine CRP and MPV with other biological indicators should be considered. Further research on women in their first trimester of pregnancy is needed to confirm our findings.

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ETHICS STATEMENT: The studies involving human participants were reviewed and approved by Biomedical Ethics Research Committee at the Faculty of Medicine, King Abdulaziz University. The patients/participants provided their written informed consent to participate in this study.

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