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RESEARCH ARTICLE

The Importance of Coagulation Parameters in Patients with Early and Late PPROM: A Case-Control Study Conducted in a Tertiary Center

Tolga Çiftpınar[1], Merve Aldıkaçtıoğlu Talmaç[1], Sultan Mayuncur[2], Semra Yüksel[2], İsmail Özdemir[3]

[1]Department of Gynecologic Oncology, University of Health Sciences, Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Türkiye
[2]Department of Obstetrics and Gynecology, University of Health Sciences, Kanuni Sultan Suleyman Training and Research Hospital, İstanbul, Türkiye
[3]Department of Maternal-Fetal Medicine, University of Health Sciences, Kanuni Sultan Suleyman Training and Research Hospital, İstanbul, Türkiye

ABSTRACT

Objective: Preterm premature rupture of membranes (PPROM) is associated with an increased risk of pregnancy complications. This study evaluated the changes in coagulation parameters in pregnant women with this condition. The aim of the study is to investigate how coagulation parameters, particularly clotting time tests such as PT and aPTT, vary in pregnant patients with PPROM, which is among the causes of premature birth.

Materials and Methods: This case-control study was retrospectively planned and conducted using data from a tertiary center where maternal-fetal treatment and monitoring were provided. The study participants were divided into three groups: the early PPROM group with complaints of water leakage at 12-24 weeks of gestation, the late PPROM group with complaints of water leakage at 24-37 weeks of gestation, and the control group who did not have any complaints at 12-37 weeks of gestation. The coagulation parameters examined were the activated partial thromboplastin time, prothrombin time, INR, and fibrinogen values.

Results: The study comprised 2086 pregnant women, among whom 606 were diagnosed with early PPROM, 609 were diagnosed with late PPROM, and 871 were included in the control group. Notably, significant prolongation was observed in the PT and aPTT values of the early PPROM and late PPROM patients compared to healthy pregnant women.

Conclusion: This study highlighted that the PT and aPTT might be prolonged in pregnant women with PPROM. The potential role of coagulation parameters in the pathophysiology of early and late PPROM may be helpful for effective management of these conditions.

Keywords: Partial thromboplastin time, preterm premature rupture of the membranes, prothrombin time

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INTRODUCTION

Premature birth is a well-known complication of pregnancy that affects both the newborn and mother.[1] The instruments fundamental to the prediction of this challenging condition have not been thoroughly explored. Premature birth mainly occurs for the following reasons: maternal or fetal stress, infection, excessive myometrial distension (such as multiple pregnancies), and fetomaternal hemorrhage.[2] Prior studies have suggested that hypercoagulation may be related to preterm birth.[3] Due to the physiological changes of pregnancy, the coagulation state increases. This occurs even in uncomplicated pregnancies.[4] In most cases, the trigger that initiates preterm labor remains unidentified. Previous studies suggest that thrombin is a uterotonic agent and that high tissue factor (TF) concentrations and the thrombin-antithrombin (TAT) complex play an etiological role in the occurrence of preterm birth.[2,5] However, the issue of coagulation status in patients with preterm birth is controversial. There is still a need for studies in the literature involving many patients for this discussion.

Address for Correspondence: Tolga Çiftpınar, Department of Gynecologic Oncology, University of Health Sciences, Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Türkiye
E-mail: tolgaciftpinar@yahoo.com **ORCID ID:** 0000-0001-7406-0629

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Preterm premature rupture of membranes (PPROM) is a condition in pregnancy where the amniotic sac breaks before the onset of labor.[6] This condition is associated with an increased risk of pregnancy complications, including infection, preterm birth, and fetal distress.[7] During pregnancy, specific changes occur in the body, which can affect the blood clotting process. The coagulation process involves the binding of several proteins and is called the coagulation cascade. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) tests are blood tests used to measure certain stages of the coagulation cascade.[8] PT is used to evaluate the extrinsic and common pathways of coagulation. The international normalised ratio (INR) value is obtained by standardizing the PT to eliminate interlaboratory differences. The aPTT is used to assess the intrinsic and common mechanisms of coagulation. Increased blood volume and changes in hormone levels can affect the clotting process during pregnancy.[9] Therefore, PT and aPTT tests can be performed during pregnancy. These tests are used to detect pregnancy-related clotting problems. While there is some evidence to suggest that pregnancy itself is a procoagulant state, there is no direct evidence to suggest that early and late PPROM specifically causes hypercoagulation in pregnancy. This study aimed to estimate the hemostatic parameters of pregnant women with premature uterine contractions and water leakage in a large patient population and to establish possible coagulation markers that can be used as an investigative tool to identify women at risk of preterm delivery.

MATERIALS and METHODS

This study was an observational case-control study and was planned retrospectively. The coagulation test results (activated partial thromboplastin time (aPTT), prothrombin time (PT), INR, and fibrinogen tests) of healthy pregnant women without complaints of water leakage and pregnant patients diagnosed with PPROM, who were hospitalized during a period of 5 years (between 01.01.2015 and 01.01.2020), were examined. The clinic where the study was conducted is a tertiary center with approximately 1500 deliveries per month and special services for the treatment of PPROM patients. Healthy pregnant women who presented to the hospital for routine ultrasonography examination were evaluated as the control group. The groups were matched similarly regarding demographic criteria such as gestational age, the number of births, and maternal age. This study was conducted in accordance with the ethical standards of the Helsinki Declaration and Ethics Committee approval, which was received from University of Health Sciences, Kanuni Sultan Süleyman Training and Research Hospital Clinical Research Ethics Committee with decision number KAEK/2020.07.99/03.07.2020. Among the pregnant women with water leakage complaints before the 37th gestational week, those with a positive Amnisure test were classified as having PPROM and included in the study. Pregnant women with evidence of vascular disease (hypertension, preeclampsia, pregnancy-induced hypertension, IUGR), a diagnosis of placental abruption or diabetes mellitus, a history of past thromboembolic events, thrombophilia, and multiple pregnancies were not included. Routine blood tests were requested at regular intervals from patients with no other disease, and patients presented to the pregnancy outpatient clinic for routine examination. A control group was formed by selecting the appropriate number of patients from this patient population, with similar demographic data as the study groups. The study participants were divided into three groups: the early PPROM group with complaints of water leakage at 12–24 weeks of gestation, the late PPROM group with complaints of water leakage at 24–37 weeks of gestation, and the control group who did not have any complaints at 12–37 weeks of gestation. In the power analysis, a 5% margin of error, 80% power, and a standard effect size of 0.29 were determined. It was sufficient to include n = 190 patients in each group. However, with the advantage of being a tertiary center, many patients could be screened. Accordingly, 606 patients were included in the early PPROM group, 609 patients were included in the late PPROM group, and 871 patients were included in the control group.

Data analysis was performed using SPSS (version 21.0; SPSS Inc., Chicago, IL, USA). All data were prepared as the mean ± standard deviation or the median ± min-max. One-way ANOVA was used to compare parametric variables. Tukey's HSD was used as a post hoc test to compare subgroups. Pearson correlation analysis was used to estimate the relationships between variables. A p value less than 0.05 was considered statistically significant for all calculations.

RESULTS

A total of 2086 pregnant women were included in the study. Among these, 606 patients were classified as having early PPROM, 609 were classified as having late PPROM, and 871 were included in the control group. Demographic data, including maternal age, gestational age, gravidity, parity, and educational status, were compared between the three groups (Table 1).

Table 1. Demographic data of the study and control groups

	Early PPROM group (n=606)		Late PPROM group (n=609)		Control group (n=871)		p
	n	%	n	%	n	%	
Maternal age (years)	28 (18–43)		28 (18–44)		28 (18–42)		0.067
Education							<0.001
None	1	0.2	15	2.5	0	0	
Elementary School	30	5	14	2.3	37	4.2	
Middle School	194	32.0	181	29.6	253	29.0	
High School	328	54.1	352	57.6	514	59.0	
University	49	8.1	43	7.0	61	7.0	
Master's Degree	4	0.7	6	1.0	6	0.7	
Gravidity	2 (1–12)		2 (1–10)		2 (1–11)		0.57
Parity	1 (1–11)		1 (0–6)		1 (0–9)		0.53
Gestational age	18.51±2.95		28.94±3.51		29.26±3.70		<0.001

PPROM: Preterm premature rupture of membranes

Table 2. Comparison of coagulation test results

	Early PPROM group (n=606)	Late PPROM group (n=609)	Control Group (n=871)	p
PT (sec)	12.06±1.04	11.88±0.99	11.86±0.93	<0.001
aPTT	25.48±3.53	25.96±5.26	24.92±3.27	<0.001
INR	0.98±0.09	0.96±0.08	0.97±0.08	<0.001
Fibrinogen value	432±126	403±114	423±120	<0.001
Platelet value	260±66	252±120	250±69	0.076

PPROM: Preterm premature rupture of membranes; PT: Prothrombin time; aPTT: Activated partial thromboplastin time; INR: International normalised ratio

Table 3. The correlations among the groups

	PT p value	APTT p value	INR p value	Fibrinogen value p value	Platelet value p value
Early PPROM-late PPROM	0.004	0.100	<0.001	<0.001	0.193
Early PPROM-control	<0.001	0.023	0.100	0.357	0.076
Late PPROM-control	0.908	<0.001	0.121	0.006	0.953

PT: Prothrombin time; aPTT: Activated partial thromboplastin time; INR: International normalised ratio; PPROM: Preterm premature rupture of membranes

There was a significant difference among the groups in the PT, APTT, INR, and fibrinogen values (p<0.001). The comparison of coagulation test results among the groups is shown in Table 2.

When the PPROM groups were compared with the control group, the PT and APTT values differed significantly (p<0.001). The correlation between the groups is shown in Table 3.

DISCUSSION

Early and late PPROM are well-known complications of pregnancy that can affect both the newborn and mother.[10] The mechanisms essential to these challenging conditions have yet to be fully explored. Earlier studies have suggested that hypercoagulability may be related to amniotic fluid in the early weeks of pregnancy.[11] The incidence of preterm premature rupture of membranes (PPROM) is estimated to

be approximately 0.5% before 27 weeks gestation and approximately 1% between 27 and 34 weeks gestation, based on various studies.[12] Similarly, the incidence of early PPROM in the study population was 0.2%. This study aimed to investigate the changes in coagulation parameters in a large patient series of pregnant women with amniotic fluid leakage in the early weeks of pregnancy. This study revealed a significantly longer PT and aPTT in PPROM patients than in healthy pregnant women. Based on the literature, it is understood that there are few studies investigating coagulation parameters such as PT, aPTT, and fibrinogen values in patients with PPROM.[13,14] Our study showed that these values varied significantly compared to those of the control group. This study was a retrospective study, and the results of the patients' situations were considered. Our opinion is that this change in the coagulation tests is due to the state of coagulopathy that PPROM can cause in the body, rather than PPROM occurring because of the coagulopathy.

The PT test is a blood test that measures the time it takes for blood to clot.[15] In pregnant women, the PT can indicate the body's ability to form blood clots, as blood coagulability is increased during pregnancy. However, the PT can be affected by various factors, including changes in hormone levels, blood volume, and liver function.[16] In PPROM patients, some evidence suggests that the PT may be prolonged compared to that in women with normal pregnancies. However, there is also evidence that the PT is shortened, although the number of patients in these studies was limited.[11] This may be due to the release of factors from the amniotic fluid, which can activate the coagulation system and lead to increased consumption of clotting factors. Additionally, PPROM is often associated with inflammation and infection, which can further affect the coagulation system and lead to a more prolonged PT.[17] In our study, it was shown that PT was prolonged in a high number of pregnant women with PPROM.

PPROM in pregnancy can lead to increased levels of certain clotting factors in the blood, which can prolong the aPTT.[18] The aPTT test is a laboratory test that measures the time it takes for blood to clot. It is used to monitor the effectiveness of blood-thinning medications and diagnose bleeding disorders. A longer aPTT can indicate a potential clotting disease in a pregnant woman, increasing the risk of complications such as deep vein thrombosis or placental abruption.[19] During pregnancy, the body undergoes several changes that can affect blood clotting.[20] Hormonal changes can increase the levels of clotting factors in the blood while simultaneously reducing the levels of anticoagulants, which can lead to a hypercoagulable state. In cases of PPROM, there is an increased risk of infection, which can further increase clotting factors in the blood.[21] Similarly, our study found that the aPTT values were longer in pregnant women in the PPROM groups than in the control group.

Thrombin can bind to many cell surface receptors that regulate the cellular response through protease activity. In addition to the coagulation system, these include proteinase-activated receptor-1 (PAR-1). After thrombin binding, PAR-1 receptors activate several signaling pathways in cells, resulting in the production of matrix metalloproteinases and cytokines.[22] In cases such as premature rupture of the membranes of the placenta during pregnancy, tissue destruction and inflammation may develop due to the effects of thrombin on PAR-1 receptors.[23] Thrombin, via PAR-1 receptors, increases the inflammatory response by increasing the production of cytokines released as a result of infection or inflammation. As a result, destruction of the membranes of the placenta, edema, bleeding, and other signs of inflammation may occur. In addition, due to the effects of thrombin on PAR-1 receptors, the risk of delivery may be increased during PPROM. During pregnancy, thrombin production increases, and blood clot tendency increases. Excessive thrombin formation is associated with complications such as preeclampsia and HELLP syndrome.[24] These conditions harm the coagulation system by increasing thrombin production and platelet activation. In such cases, the prolongation of the PT and aPTT can be observed. The prolongation of the PT and aPTT in our study may be a precursor to this path. Studies including obstetric results should be planned to elucidate this issue.

In a previous study, it was observed that women who experienced preterm labor had shortened PT and aPTT values, indicating the activation of both intrinsic and extrinsic pathways in preterm birth. The observed shortening of the aPTT in women with preterm labor could potentially be explained by the slightly elevated VWF antigen levels and factor VIII activity found in the preterm birth group. However, it is important to note that this study had limitations in terms of its relatively small sample size.[11] In contrast, our study benefited from a significantly large sample size, which strengthens and supports the findings of the previous study. The study's limitations include its retrospective nature and the limited number of included coagulation parameters. However, when we look at the literature, we see that this study has the most extensive series evaluating the values of coagulation parameters in these two disease groups.

CONCLUSION

In conclusion, PPROM is a complex and significant complication of pregnancy that can have serious consequences for both the mother and newborn. The mechanisms underlying this condition are not fully understood, but our study suggests that coagulation parameters, such as prothrombin time PT and activated partial thromboplastin time (aPTT), may be altered in pregnant women with PPROM. Our findings indicate that both PT and aPTT are prolonged in women with PPROM, which could reflect a hypercoagulable state that contributes to the pathophysiology of this condition. The results also highlight the potential role of coagulation markers in the management and monitoring of PPROM patients. Further studies are needed to investigate the exact mechanisms behind these changes and their clinical implications for the treatment and outcomes of PPROM. Monitoring coagulation parameters may provide valuable insights into the risk factors associated with PPROM and help in the development of more targeted therapeutic strategies to manage this condition effectively.

Disclosures

Ethics Committee Approval: The study was approved by the University of Health Sciences, Kanuni Sultan Süleyman Training and Research Hospital Clinical Research Ethics Committee (No: 2020.07.99, Date: 03/07/2020).

Informed Consent: Informed consent was obtained from all participants or their caregivers, where applicable.

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