ORIGINAL ARTICLE

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The Importance of Coagulation Parameters in Predicting Preterm Birth

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Abstract

Objective: A large proportion of neonatal deaths not related to congenital anomalies are attributed to preterm births. The aim of this study was to compare the coagulation parameters in pregnant women with premature uterine contractions (PUC) who have preterm births with those who have term births and to determine the role of these coagulation parameters in predicting preterm delivery.

Methods: Seventy-two pregnant women with PUC who applied to the Department of Obstetrics and Gynecology at the Okmeydanı Training and Research Hospital, University of Health Sciences, were included in the study. The coagulation parameters of 36 women who had preterm births were compared with those of 36 women who had term births. In analysing the findings of the study, statistical analyses were performed using IBM SPSS Statistics 22 (IBM SPSS, Turkey). The data were analyzed using Shapiro-Wilks, one-way, ANOVA, Tamhane's T2 test, and Student's t-test etc.

Results: The activated partial thromboplastin time (aPTT) was significantly shorter in the preterm birth group (25.64±3.24 seconds) compared to the term birth group (26.153±2.49 seconds). International normalized ratio (INR) and prothrombin time (PT) levels were similar in both groups and subgroups. Fibrinogen levels were lower in the preterm birth group (397.56±54.67 mg/dL) compared to those who delivered at term (409.78±65.06 mg/dL). Fibrinogen levels were significantly lower in the preterm labor subgroup (388±50.72 mg/dL) compared to the preterm premature rupture of membranes (PPROM) subgroup (431±58.09 mg/dL).

Conclusion: In this study, it was observed that the aPTT values in the preterm birth group were significantly shorter compared to the term birth group. Fibrinogen levels were found to be lower in the preterm birth group compared to those who delivered at term. Within the preterm labour subgroup, fibrinogen levels were significantly lower than those in the PPROM subgroup. INR and PT levels were similar across both groups and subgroups. The aPTT values were also similar between the preterm labour and PPROM subgroups.

Keywords: Premature uterine contractions, preterm birth, preterm labour

INTRODUCTION

Despite advancements in the fields of medicine and technology, preterm births, which constitute approximately 7-8% of all births, continue to be significant causes of perinatal morbidity and mortality. A large majority (75%) of non-congenital anomaly-related neonatal deaths are attributable to preterm births. Most of these premature birth cases (75-80%) occur due to spontaneous preterm labor (PE) and preterm premature rupture of membranes (PPROM), while the remaining 20-25% are due to maternal and fetal problems and are recorded as indicated preterm births (1,2).

The pathophysiological mechanisms underlying preterm birth have been associated with various factors, such as decidual bleeding, excessive uterine stretching, and hormonal changes. Among these, hormonal changes triggered by fetal or maternal stress have also been noted. However, the exact mechanism of

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these pathological processes has not been clearly explained. Moreover, numerous factors that increase the risk of preterm birth have been identified. The threat of PE, defined as the onset of contractions without cervical changes, is more common than the incidence of actual PE.

Premature uterine contractions (PUC) are defined as uterine contractions occurring before 37 weeks of gestation without cervical dilation that may or may not result in preterm birth. PUC affects approximately 10-12% of pregnancies, but only a fraction of these cases lead to PE. Studies have indicated that up to 33% of pregnant women observed for PUC can be discharged after 48 hours of observation without intervention (1). However, the false-positive rate of diagnosing the risk of PE in women with PUC is high, reaching up to 20-40%. On the other hand, about 40% of preterm birth cases are complicated with PPROM, whereas only 18% of untreated pregnancies result in early labor (3).

Despite advances in medical sciences that have significantly reduced the incidence of many obstetric complications, there has been no reduction in the frequency of PE and PPROM cases despite innovations and developments in obstetrics. Indeed, over the last decade, PE cases have increased by 15% (1,4). In this context, studies have been conducted aimed at a more accurate diagnosis of PE by detecting certain biochemical markers that could be used in predicting preterm birth. These studies have focused on the analysis of various biochemical markers in blood, saliva, and cervicovaginal secretion (5-7).

Pregnancy creates a known prothrombotic condition. During this period, there is a decrease in anticoagulant and fibrinolysis activity along with an increase in procoagulant factor levels. The hypercoagulation observed during pregnancy intensifies on the basis of acquired or hereditary thrombophilia, paving the way for various pregnancy complications. Furthermore, changes in coagulation parameters during pregnancy, such as tissue plasminogen activator, factors V, factor VII, activated partial thromboplastin time (aPTT), and prothrombin time (PT), have been supported by studies indicating their association with PE (4,6).

The primary objective of this research was to compare the coagulation parameters of pregnant women who experience PUC and have preterm births with those who have term births and to determine the role of these coagulation parameters in predicting preterm birth. Specifically, we aim to identify specific coagulation parameters that can serve as reliable biomarkers for early preterm birth prediction, thereby improving clinical outcomes and providing better targeted interventions for at-risk pregnancies. Additionally, this study seeks to elucidate the underlying mechanisms linking coagulation abnormalities with PE and delivery, contributing to a broader understanding of preterm birth pathophysiology.

METHODS

This prospective observational study was conducted with the approval of the Health Sciences University Okmeydanı Health Application and Research Center Clinical Research Ethics Commitee, under the (decision number: 611, date: 14.03.2017).

Criteria for participation in the study were as follows:

• Healthy women aged between 17 and 44 with singleton pregnancies diagnosed with PUC between 28 and 34 weeks of gestation who had preterm births for the study group.

• Healthy women aged between 17 and 44 with singleton pregnancies diagnosed with PUC between 28 and 34 weeks of gestation who had term births for the control group.

• Patients who agreed to participate and signed the informed consent form.

• No detection of fetal anomalies during the second trimester ultrasonography screening performed between 18-22 weeks of gestation.

• Maternal hemoglobin (Hb) levels above 10 g/dL.

Exclusion criteria: Reasons for excluding participants from the study are listed as follows:

Maternal factors:

• Susceptibility to thrombophilia.

• The initiation of tocolytic treatment prior to presentation.

• History of sexual intercourse within the last 24 hours.

• Placenta previa totalis.

• Placental abruption.

• History of vaginitis during pregnancy.

• Diagnosed coagulation disorder.

• Multiple pregnancies.

• The presence of active infection.

• Signs and symptoms of intraamniotic infection.

• Vaginal bleeding.

Fetal factors:

• Fetal distress: Clinical and laboratory indicators of decreased fetal oxygenation.

• Stillbirth: Fetus death at advanced stages of gestation.

• Fetal anomalies incompatible with life: Structural or genetic anomalies that prevent the fetus from surviving post-birth.

• Presence of intrauterine growth restriction (IUGR) ıntrauterine growth restriction-The fetus weighing less than expected at the gestational age.

• Polyhydramnios-excessive amniotic fluid.

The study population consisted of women who were diagnosed with PUC between the 28th and 34th weeks of gestation and who had preterm births as well as women diagnosed with PUCs during the same gestational weeks but who had term births. This population was divided into two main groups for analysis. Participants included in the study were categorized into two groups based on their time of delivery: those who gave birth at 37 weeks of gestation and later were classified into the term group, and those who delivered between 28 and 36 weeks of gestation were classified into the preterm group. A total of 72 pregnant women, 36 from each group, were included in the study. The preterm birth group was further subdivided into two subgroups based on the diagnoses of PE and PPROM.

• Group: Healthy pregnant women with PUC between 28-34 weeks who had preterm births (n=36) (Preterm birth group)

• Subgroup 1a: Preterm premature membrane rupture group (n=8)

• Subgroup 1b: PE group (n=28)

• Group: Healthy pregnant women with PUC between 28-34 weeks who had term births (n=36) (Term birth group).

For subgroup 1a, the diagnosis of membrane rupture was made during a sterile speculum examination by observing active amniotic fluid flow from the cervical canal. Additionally, the intense fluid discharge noted in patient reports and detected in the vaginal area during speculum examination along with a decrease in amniotic fluid observed during ultrasonographic examination assisted in diagnosing PPROM. Subgroup 1b, the PE group, consisted of pregnant women who showed at least four regular uterine contractions within 20 minutes with a cervical length below 30 mm and cervical dilation of at least 2 cm. All participants' privacy was prioritized; personal identification details, consultation dates, contact details, professions, lifestyles, educational levels, age, height, weight, body mass index (BMI), number of pregnancies (gravida), number of births (parity), number of miscarriages (abortus), number of living children, and obstetric history (risk of preterm birth, early birth, cervical insufficiency, cerclage history, stories about assisted reproduction techniques, threat of miscarriage) were meticulously recorded. Additionally, the date of the last menstruation, first trimester ultrasonography results and the latest ultrasonography findings, as well as vaginal examination results, were carefully documented. Details such as the babies' birth weights, dates of birth, conditions of admission to neonatal intensive care, first- and fifth-minute Apgar scores, and the use of tocolytic agents were also recorded. Gestational age was determined based on the last menstrual period and was confirmed confirmed with first trimester ultrasonography findings. In all pregnant women experiencing PUC, standard blood counts, liver and kidney function tests, C-reactive protein (CRP), coagulation tests, D-dimer, and complete urine tests were performed at presentation, and the results were recorded. For the coagulation tests, blood samples were collected in sterile tubes containing 3.2% sodium citrate, centrifuged at 4000 g for 10 min. The resulting fresh plasma samples were used to calculate fibrinogen, PT, aPTT, and international normalized ratio (INR) values. For the D-dimer test, purple-cap sterile tubes were used, and analysis was performed using the AQT 90 device. In necessary cases, tocolytic agents and steroids were administered to the preterm birth and PPROM subgroups. Details such as weeks of birth, weight, and type of delivery were recorded for participants who gave birth in our clinic. For patients who gave birth outside our clinic, the same information was obtained through telephone interviews. Demographic characteristics of all groups, Hb, platelet (PLT), activated aPTT, PT, INR, fibrinogen, and D-dimer levels were compared and analyzed.

Statistical Analysis

During the evaluation of the findings of this study, statistical analyses were performed using IBM SPSS Statistics 22 (IBM SPSS, Turkey). In the evaluation of the study data, the Shapiro-Wilk test was used to assess whether the parameters conformed to the normal distribution. For the analysis of quantitative data, the one-way ANOVA test was used for comparisons between groups in which parameters showed normal distribution, and Tamhane's T2 test was chosen to identify groups that demonstrated differences. For comparisons between two groups, Student's t-test was applied for parameters that exhibited normal distribution, whereas the Mann-Whitney U test was used for those that did not. The comparison of qualitative data employed Fisher's Exact test and the Continuity (Yates) Correction. The relationships between parameters that conformed to the normal distribution were assessed using Pearson's correlation analysis. The significance level was set at $p<0.05$.

RESULTS

This study was conducted between January 15, 2017, and April 15, 2018, on a total of 72 female participants aged between 17 and 44. The mean age of the participants was determined to be 28.86 (standard deviation: 6.77). Within the scope of the research, participants were divided into two main groups: "preterm birth" and "term birth", each consisting of 36 women. Furthermore, the preterm birth group was subdivided into two detailed subgroups: PE and PPROM.

Statistically significant differences were observed between the groups, with the mean age of the preterm birth group being significantly lower than that of the term birth group (p=0.010; p<0.05). Similarly, the average BMI of the preterm birth group was also significantly lower compared to the term birth group (p=0.000; p<0.05). The average gestational week of pregnancies in the preterm birth group was significantly lower compared to the term birth group (p=0.008; p<0.05). However, no statistically significant difference was found in the number of pregnancies (gravida) between the preterm and term birth groups (p>0.05). Additionally, the parity (number of births) values for the preterm birth group were significantly lower than those of the term birth group (p=0.017; p<0.05). No significant statistical differences were found between the preterm and term groups in terms of occupational distribution and education levels (p>0.05). The detailed data and findings are comprehensively presented in Table 1 below.

The average weight of newborns in the preterm birth group was found to be statistically significantly lower compared to the term birth group (p=0.000; p<0.05). However, no statistically significant difference was observed between the preterm and term birth groups in terms of gender distribution ratios and modes of delivery (both p>0.05). Conversely, the rates of Apgar scores (an assessment indicating the newborn's health status) being 7 or above at 1 and 5 minutes were significantly lower in the preterm group compared with the term group; while this rate was 58.3% in the preterm group, it was 86.1% in the term group (p=0.018; p<0.05). The detailed findings are presented in Table 2.

In the preterm birth group, the mean Hb level was determined to be 11.55±1 g/dL, which was statistically significantly lower compared to the mean of 12.26±1.04 g/dL in the term birth group (p=0.004; p<0.05). aPTT values were measured as 25.64±3.24 seconds in the preterm birth group, whereas in the term group, this value was found to be 26.153±2.49 seconds, indicating that aPTT was significantly shorter in the preterm group (p<0.05). However, there was no statistically significant difference between the two groups in terms of INR, PT, PLT count, D-Dimer, and fibrinogen levels (p>0.05). Furthermore, no significant difference was observed between the groups in terms of CRP, white blood cell (WBC) distribution ratios, and recovery rates (p>0.05). Although fibrinogen levels were lower in the preterm birth group at 397.56±54.67 mg/dL compared with the term birth group, the fibrinogen level in the term birth group was recorded as 409.78±65.06 mg/dL. D-dimer values were measured as 1013.06±927.93 ng/mL in the preterm birth group and 879.42±583.4 ng/mL in the term birth group, but these differences were not statistically significant (p>0.05). The detailed findings are presented in Table 3.

When examining preterm birth cases, the average weight of newborns in the PE group was determined to be 2314.93±365.26 kg. This value was significantly higher when compared to the average weight of 1916.88±500.31 kg in the PPROM group (p=0.017; p<0.05). No statistically significant differences were found between the PE and PPROM groups in terms of cervical

Table 1. Evaluation of demographic data between groups

	Preterm group	Term group	Total	p
Age	26.83±6.43	30.89±6.58	28.86±6.77	**0.010**[1]
BMI (kg/m^2)	23.18±2.19	26.72±0.90	24.95±2.44	**0.000**[1]
Gestational week (weeks)	32.04±1.63	32.92±1.00	32.48±1.41	**0.008**[1]
Gravida number (median)	2.3±1.51	2.64±0.87	2.47±1.23	0.065[2]
Parity number (median)	0.92±1.05	1.36±0.72	1.14±0.92	**0.017**[2]
Occupation (%)				0.733[3]
Housewife	30 (83.3)	32 (88.9)	62 (86.1)	
Educational status (%)				0.733[3]
High school or less	30 (83.3)	32 (88.9)	62 (86.1)	

Values indicated with p<0.05 are statistically significant
[1]Student t-test, [2]Mann-Whitney U Test, [3]Continuity (Yates) Correction
BMI: Body mass index

length, week of birth, or average gestational age ($p<0.05$). Similarly, no significant statistical difference was found in the distribution of tocolysis applications between the two groups ($p>0.05$). However, the rate of normal spontaneous delivery (NSD) in the PE group was 67.9%, whereas that in the PPROM group was 25%, and this difference was found to be statistically significant ($p=0.046$; $p<0.05$). Looking at the rates of admission to the intensive care unit, 57.1% of the PE group was admitted compared to 100% of the PPROM group. This indicates that the intensive care admission rate for the PE group was significantly lower than that for the PPROM group ($p=0.033$; $p<0.05$). The related findings are detailed in Table 4. According to the data

Table 2. Evaluation of study parameters between groups

	Preterm group	Term group	Total	p
Newborn weight (g)	2226±425.62	3445±526.93	2836±776.66	**0.000**[1]
Weeks of gestation	33.78±1.82	38.82±1.2	36.32±1.96	**0.000**[1]
Gender (%)				0.631[3]
Female	65.5%	63.9%	59.7%	
Male	34.4%	36.1%	40.3%	
Mode of delivery				0.813[3]
NSD	58.3%	58.2%	55.6%	
Sectio	41.7%	47.2%	44.4%	
1st and 5th minute Apgar scores (%)				**0.018**[3]
>7	58.3%	68.6%	67.2%	
<7	41.7%	31.9%	32.8%	
Intensive care admission (%)				**0.010**[3]
None	63.3%	66.7%	50.0%	
Present	66.7%	33.3%	50.0%	

Values indicated with $p<0.05$ are statistically significant
[1]Student t-test, [2]Mann-Whitney U Test, [3]Continuity (Yates) Correction
NSD: Normal spontaneous delivery

Table 3. Evaluation of hematological parameters between group

	Preterm group	Term group	Total	p
Hemoglobin (g/dL)	11.55±1.34	12.61±1.04	11.98±1.08	**0.004**[1]
PLT (10^3Ul)	230.56±57.24	267.39±53.28	248.77±60.06	0.125[1]
aPTT (sn)	25.65±4.23	26.13±2.49	25.88±2.98	0.013[1]
INR	0.99±0.08	0.97±0.1	0.99±0.09	0.483[1]
PT (sn)	11.72±0.86	11.78±1.1	11.74±0.98	0.901[1]
Dimer (ng/dL)	676.65±789	706±878.92	693±810.67	0.679[2]
Fibrinojen (mg/dL)	103±23.79	293±58.34	296±70.05	0.879[1]
Feritin (ng/mL)	397.55±24.67	498.76±30.65	448.67±35.98	0.891[1]
CRP (mg/dL)	0.78±0.96	0.89±1.06	0.83±1.02	0.896[2]
WBC (10^3/µL)				
<12.000	22 (61.1%)	20 (55.6%)	42 (58.3%)	0.811[3]
>12.000	14 (38.9%)	16 (44.4%)	30 (41.7%)	0.811[3]
Recovery				
None	21 (58.3%)	20 (55.6%)	41 (56.9%)	0.000[3]
Present	15 (41.7%)	16 (44.4%)	31 (43.1%)	0.000[3]

Values indicated with $p<0.05$ are statistically significant
[1]Student t-test, [2]Mann-Whitney U Test, [3]Continuity (Yates) Correction
PLT: Platelet, aPTT: Activated partial thromboplastin time, INR: International normalized ratio, PT: Prothrombin time, CRP: C-reactive protein, WBC: White blood cell

presented in Table 5, no statistically significant differences were found between the PE and PPROM groups within the preterm birth group in terms of Hb, PLT, aPTT, INR, PT, and D-dimer levels (p>0.05). However, fibrinogen levels averaged 388±50.72 in the PE group compared to 431±58.09 in the PPROM group, and this difference was statistically significant (p=0.048; p<0.05). Additionally, no statistical significance was found between the PE and PPROM groups regarding CRP distribution rates, WBC distribution rates, and recovery rates (p>0.05).

Discussion

Preterm birth is a critical complication that can lead to death and serious health issues for both the mother and the newborn. The observed shortening of aPTT in the preterm birth group may be explained by mild increases in coagulation factors, such as von Willebrand factor (vWF) and Factor VIII activity. These changes contribute to the hypercoagulable state observed in pregnancy. Furthermore, elevated levels of coagulation factors such as Factor VII and Factor XI, which were not measured in this

Table 4. Evaluation of study parameters between preterm action and PPROM groups in the preterm birth group

	Preterm labor group	PPROM group	Total	p
Newborn weight (g)	2314.93±365.16	1916.88±500.31	2226.47±425.62	**0.017**
Cervical length (mm)	24.11±7.81	29.25±6.39	25.25±7.74	0.098[1]
Weeks of gestation	34.04±1.57	32.88±2.42	33.78±1.82	0.113[1]
Pregnancy week (week)	32.24±1.51	31.36±1.97	32.04±1.63	0.181[1]
Form of tocolysis	N8 (61.5%)	6 (75%)	14 (66.7%)	0.656[2]
Method of tocolysis	A5 (38.5%)	2 (25%)	7 (33.3%)	0.656[2]
Mode of delivery	NSD 19 (67.9%)	2 (25%)	21 (58.3%)	**0.046[2]**
Mode of delivery	Sectio 9 (32.1%)	2 (25%)	7 (33.3%)	**0.046[2]**
Intensive care admission				**0.033[2]**
None	12 (94.2%)	0 (0%)	12 (63.3%)	
Exists	16 (65.7%)	8 (100%)	24 (66.7%)	

Values indicated with p<0.05 are statistically significant
[1]Student t-test, [2]Fisher's Exact Test
PPROM: Preterm premature rupture of membranes

Table 5. Evaluation of laboratory parameters between preterm labor and pprom groups in the preterm birth group

	Preterm labor group	PPROM group	Total	p
Hemogram (g/dL)	11.52±0.97	11.65±1.18	11.55±1.0	0.748[1]
PLT (10^3/µL)	231.71±67.92	225±64.62	230.22±66.35	0.845[1]
aPTT (sn)	25.79±33	25.1±31.4	25.64±32.4	0.602[1]
INR	0.98±0.06	1.02±0.12	0.99±0.08	0.309[1]
PT (sn)	11.7±0.62	11.78±11.49	11.72±0.86	0.896[1]
Dimer (ng/mL)	109046±1040	74213±15355	101306±92793	0.435[2]
Fibrinojen (mg/dL)	388±50.72	431±58.09	397.56±54.67	**0.048[1]**
CRP (mg/dL)	0 26 (92.9%)	5 (62.5%)	31 (86.1%)	0.064[3]
WBC (/mm^3) n (%)				0.683[3]
<12.000	18 (64.3%)	4 (50%)	22 (61.1%)	
>12.000	10 (35.7%)	4 (50%)	14 (38.9%)	
Benign n (%)				0.694[3]
None	17 (60.7%)	4 (50%)	21 (58.3%)	
Exist	11 (39.3%)	4 (50%)	15 (41.7%)	

Values indicated with p<0.05 are statistically significant
[1]Student t-test, [2]Mann-Whitney U Test, [3]Fisher's Exact Test
PPROM: Preterm premature rupture of membranes, PLT: Platelet, aPTT: Activated partial thromboplastin time, INR: International normalized ratio, PT: Prothrombin time, CRP: C-reactive protein, WBC: White blood cell

study, could also play a role. These factors, although not directly causing PE, may signal an increased thrombotic tendency in patients with preterm birth. Although these changes are subtle, they could be clinically significant, particularly in high-risk populations in whom thromboembolic events are a concern. Therefore, the identification of women at risk of preterm birth experiencing PUC is both challenging and essential. Early diagnosis, which is crucial for treating and preventing preterm birth, can be easily achieved in cases associated with PPROM, whereas it is more challenging in cases with a closed cervix and intact membranes. Moreover, uncertainties regarding whether preterm birth will occur and the necessity of a special treatment regimen that could have adverse effects on both the mother and the baby lead to dilemmas in treatment implementation. Furthermore, no low-cost, non-invasive, and universally reliable indicator that can be integrated into daily practice to predict spontaneous preterm birth.

Studies have suggested a relationship between hypercoagulability during pregnancy and pregnancy complications, such as preterm birth have been found (6,4,8,9). In a study conducted by Hrubaru et al. (10) in 2023, it was found that Hb levels below 12.0 g/dL, PT below 12.5 seconds, aPTT values below 25 seconds, and D-dimer levels above 250 ng/mL were significant determinants of preterm birth (10). Keren-Politansky et al. (3) showed that in women experiencing PUC and undergoing preterm birth, PT and activated aPTT values were significantly shorter compared with women with term births and PUC. Although anemia has been identified as a significant marker of preterm birth, a recent meta-analysis showed no significant association between anemia during pregnancy and the risk of preterm birth (11). In our study, it was found that the mean Hb level was statistically significantly lower in the preterm birth group than in the term group. Additionally, in another study, it was stated that anemia is mostly due to normocytic normochromic variation and has a prevalence rate of more than 50%; however, the type of anemia was not examined in our study (12). Furthermore, in our study, it was observed that aPTT duration was statistically significantly shorter in women with preterm births and PUC than in women with term births and PUC, while no significant difference was detected between the two groups in terms of PT values. In the comparison between the PE and PPROM groups, no statistically significant difference was found in terms of aPTT and PT. Short PT and activated aPTT are global tests used to assess the coagulation system and are associated with the risk of venous thromboembolism (9,3). A possible explanation for the shorter aPTT duration detected in women with preterm births could be mild increases in vWF antigen and Factor VIII activity in this group. Additionally, high levels of coagulation factors such as factors VII, Factor XI, and Factor IX, which are known to increase during pregnancy but were not measured in our study, could also contribute to the shortening of PT and aPTT durations. The relatively small groups may have made it difficult to obtain statistically significant results for some parameters. Nevertheless, global coagulation tests, including PT and aPTT, have demonstrated a tendency toward hypercoagulability; however, while no difference was found in terms of PT between the study and control groups, a difference was observed in terms of aPTT. Although these coagulation parameters have the potential to differentiate the clinical conditions of pregnant women, their exact cutoff values have not yet been determined.

To the best of our knowledge, this study is one of the few that comprehensively examined the coagulation process in women experiencing PUC. A pioneering study suggested that shortened PT and aPTT could predict early contractions that might subsequently lead to preterm birth. In our study, when comparing women with preterm births to those with term births, the preterm group had shorter aPTT values, whereas there was no difference between the two groups in terms of PT values. In a study by Erez et al. (13) tissue factor (TF) and tissue factor pathway inhibitor (TFPI) were analyzed in pregnant women without PUC in the term period and those with preterm births, revealing that women with preterm births had higher TF activity and lower TFPI concentrations. The analysis results by Erez et al. (13) focused solely on patients with PUC, and no difference in TF and TFPI concentrations was observed between term and preterm patients. In this context, the findings obtained by Erez et al. (13) are consistent with the results of our study. The final stage of coagulation involves the formation of fibrin clots from fibrinogen via thrombin. Except for a published study, no other study has compared fibrinogen levels at the same gestational weeks between women experiencing PUC who deliver preterm and term births. In our study, matching was performed according to gestational age. This is particularly important given the significant increase in fibrinogen concentration in the second and third trimesters; without this matching, bias could occur in the results. In the study by Keren-Politansky et al. (3) it was observed that fibrinogen concentration in the study group was slightly higher than in the control group, but the difference was not statistically significant. In our study, although fibrinogen levels were slightly lower in the study group than in the control group, the difference was not statistically significant. However, among the subgroups of women with preterm births, fibrinogen levels in the PE group were found to be statistically significantly lower compared to the PPROM

group. Despite the significant differences in aPTT and fibrinogen levels, the clinical relevance of these findings remains uncertain. Shortened aPTT and lowered fibrinogen levels might indicate increased thrombotic risk; however, further studies are required to determine the cutoff points that can predict preterm birth with high accuracy. The variations in these parameters suggest the involvement of a complex pathophysiological mechanism in PE, which warrants more detailed exploration.

This may indicate different mechanisms at play in PE: potentially less thrombogenic activity in cases with intact membranes and increased thrombogenic activity in PPROM cases. However, further comprehensive research is needed to confirm this hypothesis. Considering the significant impact of hypercoagulability on the pathogenesis of PE, more pronounced alterations in the coagulation profile are expected in women exhibiting more intense PE. Indeed, a study by Catov et al. (14) demonstrated that levels of the thrombin-antithrombin complex, a sensitive indicator of coagulation activation, increased linearly and dose-dependently with the risk of PE. This study, which used aPTT values as an indicator of the time from PUC onset to the appearance of clinical signs until delivery, did not find a relationship between these parameters. This suggests that an approach based on the measurement of delay times may not be ideal for quantitatively estimating the activation of preterm birth. Therefore, additional research is needed to determine the most appropriate method for quantitatively evaluating the degree of preterm birth activation (15).

Although it is known that D-dimer levels increase with gestational age during pregnancy, there is a lack of comprehensive, enlightening, and robust studies on this topic. In a study by Kline et al. (15) which started with 50 cases and ended with 18 cases, it was reported that the average plasma D-dimer concentration was 430 ng/mL in the preconceptional period, 579 ng/mL in the first trimester, 832 ng/mL in the second trimester, and 1159 ng/mL in the third trimester. Another study conducted by Francalanci et al. (16) found that plasma D-dimer concentrations increased with gestational age and D-dimer levels in the second and third trimesters were significantly different compared to non-pregnant healthy women. In a study by Haznedaroğlu et al. (17) investigating hemostatic markers in preterm birth, they found that D-dimer levels in the group with preterm birth differed significantly from both the D-dimer levels of the healthy pregnant and the unhealthy women group (17). Additionally, in a study by Yazıcıoğlu et al. (18) examining serum D-dimer levels during the first admission between women hospitalized due to threatened PE who subsequently had preterm births and women who had term births, significant differences were found (18). In our study, although the D-dimer values of the preterm birth group (1013.06±927.93 ng/mL) were higher compared to the term birth group (879.42±583.4 ng/mL), no statistically significant difference was detected between the two groups in terms of D-dimer values.

Maternal anemia during pregnancy is widely accepted to be associated with fetal outcomes such as fetal IUGR, preterm birth, and low birth weight, as well as maternal complications like preeclampsia, eclampsia. In our study, maternal Hb level was defined with a lower limit of 10 mg/dL. However, the average Hb levels were significantly lower in the group with preterm births compared to the group with term births. These findings highlight the potential importance of iron supplementation in preventing preeclampsia and preterm birth. Another study reported a higher likelihood of anemia during pregnancy in young mothers; our study is supportive of these findings (19). In a study by Hawrryshyn et al. (20) it was reported that if the serum CRP level is above 1.5 mg/dL, there is an increased likelihood of delivery within 7 days. However, in our study, no difference was observed among the different groups in terms of CRP values. On the other hand, in another study conducted by Yuan et al. (21) the role of maternal peripheral blood leukocytes in preparing for activation during both term and preterm delivery was indicated. However, in our study, no difference was detected in terms of WBC among any of the groups. The strengths of our study lie in its original and prospective design, matching between the study and control groups, and detailed examination of the coagulation profile of each participant.

Study Limitations

However, the limitations of the study include the relatively small size of the study arms. Although power analyses indicated that 30 patients in each arm were sufficient for a Type I (α) error of 5%, larger studies with more patients may be able to detect subtle changes in the coagulation profile identified in the current study but did not reach statistical significance. Additionally, such studies may contribute to determining the cutoff value for aPTT that distinguishes between patients experiencing PUC who deliver preterm and those who successfully maintain pregnancy until term or allow for the use of plasma fibrinogen levels in predicting PE and PPROM.

All parameters evaluated in this study, including Hb and coagulation parameters, can be measured during routine pregnancy follow-up visits and used as a non-invasive method to identify women at high risk of early delivery. Another potential application is the monitoring of women who are already at high risk of early delivery because of pre-existing medical conditions

or past history. Regular measurement of these parameters during prenatal visits could facilitate early detection of changes indicating an increased risk of preterm birth. These findings could prompt healthcare providers to recommend closer monitoring or early intervention (10).

CONCLUSION

Our study revealed significantly shorter aPTT values in the preterm birth group compared to the term birth group. In the group experiencing preterm birth, lower fibrinogen levels and higher D-dimer levels were observed compared with the term group; however, these findings were not statistically significant. In the preterm action subgroup, fibrinogen levels were significantly lower compared to the PPROM subgroup. Additionally, the mean age of women experiencing preterm birth was statistically significantly lower compared to women delivering at term. Currently, there is no reliable marker for predicting spontaneous preterm birth that can be used in clinical practice. Further research is needed to determine the clinical value of specific coagulation factors and values of aPTT, fibrinogen, and D-dimer levels that could predict preterm birth. The significantly lower levels in the group experiencing preterm birth compared to the term birth group emphasize the importance of iron supplementation during pregnancy. Developing low-cost and effective tests and treatment methods aimed at reducing and delaying preterm birth will contribute to better patient care and ultimately reduce neonatal mortality and morbidity rates.

Footnote

Ethics Committee Approval: Health Sciences University Okmeydanı Health Application and Research Center Clinical Research Ethics Commitee, under the (decision number: 611, date: 14.03.2017). Criteria for participation in the study.

Informed Consent: Patients who agreed to participate and signed the informed consent form.

Authorship Contributions

Surgical and Medical Practices: E.İ.K., B.C., Concept: E.İ.K., B.C., Design: E.İ.K., B.C., Data Collection or Processing: E.İ.K., B.C., Analysis or Interpretation: E.I.K., B.C., Literature Search: E.İ.K., B.C., Writing: E.İ.K., B.C.

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