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The efficacy of antenatal maternal hemogram and coagulation test parameters in predicting atony-related postpartum hemorrhage

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Abstract

This study aims to evaluate the efficacy of maternal hemogram parameters in PPH in term pregnancies. A retrospective analysis was conducted on 84 patients with atony-related PPH and 96 control patients with healthy deliveries, who presented to the Gynecology and Obstetrics Clinic of Samsun Education and Research Hospital between January 1, 2008, and December 31, 2023. Patients' data were retrieved from the hospital's information system. Exclusion criteria included pregnant women under 18 years, those with preeclampsia, chronic hypertension, or bleeding disorders. Evaluated parameters included age, BMI, gravida, parity, gestational age, mode of delivery, prepartum and postpartum hemogram and coagulation parameters, and neonatal outcomes. The mean age was 32.1±6.9 years in the PPH group and 30.1±5.8 years in the control group. Hemoglobin and hematocrit levels were significantly lower in the PPH group (Hb: 9.4±1.0 ng/ml) compared to the control group (Hb: 11.5±1.4 ng/ml, $p<0.001$). Plasma fibrinogen levels were also significantly lower in the PPH group (392.6±69.2 mg/dl) compared to the control group (467.2±69.6 mg/dl, $p<0.001$). A significant positive correlation was observed between plasma fibrinogen levels and 1- and 5-minute Apgar scores ($p=0.002$ and $p<0.0001$, respectively). BMI ≥28.8 was associated with a higher risk of hemorrhage. Maternal hemogram parameters, particularly hemoglobin, hematocrit, and fibrinogen levels, are effective predictors of postpartum hemorrhage. The study emphasizes the importance of monitoring these parameters to identify and manage at-risk pregnancies, thereby reducing maternal morbidity and mortality associated with PPH.

Keywords: postpartum hemorrhage, fibrinogen, hemorrhage risk factors, blood coagulation tests

1. Introduction

Postpartum hemorrhage (PPH) is one of the leading causes of maternal morbidity and mortality related to childbirth (1, 2). PPH is an emergency obstetric condition, occurring in 3-5% of postpartum patients (3). The primary cause of postpartum hemorrhage is uterine atony. Due to the high blood flow in the uterine arteries during the late stages of pregnancy, uterine atony can lead to rapid and severe bleeding. Protocols for the step-by-step active management of postpartum hemorrhage improve outcomes (4,5). The first steps in managing PPH include manual examination of the uterus and injection of oxytocin. In cases of persistent atony, stronger uterotonic prostaglandin analogs are recommended. In severe postpartum hemorrhage cases, advanced interventions such as hemodynamic resuscitation, blood products, uterine artery embolization, and/or surgical arterial ligation or hysterectomy may be required (6).

Risk factors and management protocols for postpartum hemorrhage are continuously updated. In recent years, the importance of fibrinogen and fibrinolysin in major postpartum hemorrhages has been highlighted. Towards the end of pregnancy, the concentration of various clotting factors increases, and the activity of natural anticoagulants and fibrinolytic activity decreases (7, 8). In term pregnant women, fibrinogen levels rise to between 4 and 6 g/L, whereas in non-pregnant women, levels range from 2 to 4 g/L. During pregnancy, an increase in fibrinogen levels is observed, while standard indicators such as prothrombin time (PT) and activated partial thromboplastin time (aPTT) show very little difference. Coagulation plays a crucial role in postpartum hemostasis (9). Coagulation disorders are insufficiently evaluated risk factors for postpartum hemorrhage. In 2007, Charbit et al. demonstrated that fibrinogen levels were lower in women who developed severe postpartum hemorrhage compared to those with mild postpartum hemorrhage (6). Another study conducted in 2012 with 738 patients diagnosed with postpartum hemorrhage also provided informative data indicating that fibrinogen levels can serve as a warning to clinicians regarding postpartum hemorrhage (10). A meta-analysis published in 2023 evaluated hemogram parameters and fibrinogen levels. This study observed that patients with

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postpartum hemorrhage had lower prepartum platelet counts and suggested that parameters such as hemoglobin and fibrinogen could not predict postpartum hemorrhage (11).

Predicting postpartum hemorrhage can allow for early intervention and treatment for a potential bleeding situation, potentially improving patient survival by preventing unnecessary treatments. Despite treatment protocols, in cases where bleeding cannot be prevented, if no precautions are taken and the bleeding is not predicted, aggressive measures up to hysterectomy may be necessary. Being able to predict postpartum hemorrhage can save time in patient management, preventing the need for aggressive treatments and reducing mortality and morbidity rates. Numerous studies in the literature have focused on the risk factors for postpartum hemorrhage. In this study, we aimed to identify hemogram and coagulation parameters that could predict postpartum hemorrhage by comparing pregnant women with postpartum hemorrhage to those with healthy deliveries. The results obtained from routine blood samples taken before delivery from these women were retrospectively analyzed.

2. Materials and Methods

Our study included pregnant women between the 37th and 42nd weeks of gestation who applied for delivery to the Gynecology and Obstetrics Clinic of Samsun Training and Research Hospital between January 1, 2008, and December 31, 2023. The data of the patients were obtained from the hospital's information system and analyzed retrospectively. Eighty-four pregnant women with postpartum hemorrhage due to atony were included in the experimental group, and 96 healthy pregnant women were included in the control group. Pregnant women under 18 years old, and those with preeclampsia, chronic hypertension, or bleeding disorders were excluded from the study. The parameters evaluated included age, body mass index, gravida, parity, gestational age, mode of delivery, prepartum hemoglobin, hematocrit, white blood cell count, neutrophil-to-lymphocyte ratio, platelet count, fibrinogen levels, PT, aPTT , international normalized ratio (INR) levels, postpartum hemoglobin, hematocrit, platelet count, fibrinogen levels, whether hysterectomy was performed, baby's birth weight, 1-minute and 5-minute Apgar scores, presence or absence of meconium aspiration, whether the newborn was admitted to the neonatal unit, and whether the newborn was intubated.

The statistical analysis of the data obtained from the study was performed using the SPSS (v21.0, Illinois, US) program. The data were presented as mean ± standard deviation (SD) and median (min-max). The Kolmogorov-Smirnov test was used to analyze the assumption of normal distribution of quantitative results. Multiple group comparisons were performed using the Kruskal-Wallis H test. Bonferroni correction was applied for post-hoc pairwise comparisons following multiple group comparisons. Mann-Whitney U and Student's t-tests were used for pairwise comparisons. The relationship between variables was evaluated using Spearman's Rank correlation analysis. The ROC curve was used to determine the diagnostic value of the study data. The area under the ROC curve (AUC) was considered as a measure of the diagnostic test's discriminative power. Confidence intervals for AUC were calculated, and sensitivity and specificity values were determined. For all tests, a p-value of <0.05 was considered statistically significant.

3. Results

Demographic, clinical, and biochemical characteristics between the control group (n=97) and the PPH group (n=84) were detailed in table 1. Maternal age was significantly (p=0.040) higher in the PPH group (32.1±6.9 years) compared to the control group (30.1±5.8 years). Body mass index (BMI) also differed significantly, with the PPH group showing a median BMI of 28.8 (IQR 25.6-33.0) versus 24 (IQR 23-25) in the control group (p<0.001). No significant differences were observed in gravidity and parity between the two groups. The mode of delivery, categorized into vaginal and Cesarean sections, did not differ significantly between groups. Notably, hysterectomy was only performed in the PPH group (82.1% of cases). Plasma hemoglobin and hematocrit levels were lower in the PPH Group (9.4±1.0 ng/ml and 28.6±4.2%, respectively) compared to the control group (11.5±1.4 ng/ml and 35.4±3.7%, respectively) (p<0.001). PT and aPTT showed no significant difference between the control group and the PPH group. However, INR differed significantly, with the control group recording a median INR of 0.9 (IQR 0.9-1.0), while the PPH group had a median INR of 1.0 (IQR 0.9-1.0) (p<0.001). Serum calcium levels were significantly lower in the PPH group (8.6±0.7 mg/dl) compared to the control group (9.1±0.4 mg/dl) (p<0.001). Additionally, plasma fibrinogen levels were significantly lower in the PPH group (392.6±69.2 mg/dl) than in the control group (467.2±69.6 mg/dl), also showing statistical significance (p<0.001). The PPH group demonstrated significantly lower gestational age at birth, with a median of 38 weeks (IQR 37-39) compared to 39 weeks (IQR 38-40) in the Control Group (p=0.008). Similarly, birth weight was lower in the PPH Group, with an average weight of 3403.1±714.4 grams, compared to 3188.1±501.2 grams in the Control Group (p=0.022). Apgar scores at 1st and 5th minutes post-birth also differed significantly. The PPH group had lower scores at 1st minute with a median score of 7.5 (IQR 7-8) compared to 9 (IQR 9-9) in the control group (p<0.001). At 5th minutes, the scores remained lower in the PPH group with a median score of 8 (IQR 7.3-9) against 10 (IQR 10-10) in the control group (p<0.001). Additionally, the incidence of meconium-stained amniotic fluid was substantially higher in the PPH group, affecting 25 cases (29.8%) compared to only 3 cases (3.1%) in the control group (p<0.001). Admission to the neonatal intensive care unit (NICU) was more frequent in the PPH group, with 15 (17.9%) admissions versus 3 (3.1%) in the control group (p=0.001). Intubation rates were also higher in the PPH group, with 12 (14.3%) instances compared to 3 (3.1%) in the control group (p=0.006).

Table 1. Demographic, clinical and biochemical data of patients[a]

		Control Group (n=97)	PPH Group (n=84)	*p*
Maternal characteristics				
Age (years)		30.1±5.8	32.1±6.9	**0.040**[b,*]
BMI (kg/m²)		24 (23-25)	28.8 (25.6-33.0)	**<0.001**[c,*]
Gravidity		3 (2-4)	3 (2-4)	0.247[c]
Parity		2 (1-2)	2 (1-2)	0.435[c]
Mode of delivery	**Vaginal**	60 (61.9%)	57 (67.9%)	0.400[d]
	Cesarian section	37 (38.1%)	27 (32.1%)	
Hysterectomy	**Yes**	0 (0%)	15 (82.1%)	N.A
	No	97 (100%)	69 (17.9%)	
Plasma Hemoglobin (ng/ml)		11.5±1.4	9.4±1.0	**<0.001**[b,*]
Plasma Hematocrit (%)		35.4±3.7	28.6±4.2	**<0.001**[b,*]
Plasma WBC (10^3/µl)		10.6 (8.3-12.8)	12.4 (10.0-16.5)	**<0.001**[c,*]
Plasma PLT (10^3/µl)		228.0±61.6	186.8±46.8	**<0.001**[b,*]
Plasma PT (sec.)		10.9 (10.6-11.5)	11 (10.6-11.5)	0.449[c]
Plasma APTT (sec.)		23.9±3.0	24.5±3.1	0.166[c]
Plasma INR		0.9 (0.9-1.0)	1.0 (0.9-1.0)	**<0.001**[c,*]
Serum Calcium (mg/dl)		9.1±0.4	8.6±0.7	**<0.001**[b,*]
Plasma Fibrinogen (mg/dl)		467.2±69.6	392.6±69.2	**<0.001**[b,*]
Fetal characteristics				
Gestational age at birth (weeks)		39 (38-40)	38 (37-39)	**0.008**[c,*]
Birth weight (g)		3188.1±501.2	3403.1±714.4	**0.022**[b,*]
Apgar score (1st min.)		9 (9-9)	7.5 (7-8)	**<0.001**[c,*]
Apgar score (5th min.)		10 (10-10)	8 (7.3-9)	**<0.001**[c,*]
MSAF		3 (3.1%)	25 (29.8%)	**<0.001**[d,*]
NICU		3 (3.1%)	15 (17.9%)	**0.001**[d,*]
Intubation		3 (3.1%)	12 (14.3%)	**0.006**[d,*]

Abbreviations: PPH, post-partum hemorrhage; BMI, body-mass index; WBC, white blood cells; PLT, platelets; PT, prothrombin time; APTT, activated partial thromboplastin time; INR, international normalized ratio; MSAF, meconium stained amniotic fluid; NICU, neonatal intensive care unit
[a]Data are given as mean±SD, median (IQR) and as number (percentage)
[b]Student's T Test
[c]Mann-Whitney U Test
[d]Pearson $\chi 2$ test
[*]$p < 0.05$ indicates statistical significance

Table 2. The correlation of plasma fibrinogen, serum calcium levels and other coagulation parameters levels with other investigated maternal and fetal study parameters

		Age	BMI	Gravidity	Parity	Gestational age at birth	Birth weight	Apgar score (1st min.)	Apgar score (5th min.)
Plasma Fibrinogen	***r***	-0.123	**-0.164**[†]	-0.022	0.010	0.031	**-0.161**[†]	**0.233**[‡]	**0.305**[‡]
	p	0.099	**0.027**[*]	0.771	0.891	0.683	**0.030**[*]	**0.002**	**<0.000**[*]
Serum Calcium	***r***	**-0.223**[‡]	**-0.223**[‡]	-0.006	0.024	0.125	-0.054	**0.252**[‡]	**0.252**[‡]
	p	**0.003**[*]	**0.003**[*]	0.931	0.745	0.094	0.473	**0.001**[*]	**0.001**[*]
Plasma Hemoglobin	***r***	-0.043	**-0.364**[‡]	0.007	0.017	**0.197**[†]	-0.033	**0.298**[‡]	**0.420**[§]
	p	0.566	**<0.000**[*]	0.931	0.820	**0.008**[*]	0.659	**<0.000**[*]	**<0.000**[*]
Plasma Hematocrit	***r***	-0.076	**-0.342**[‡]	-0.012	-0.014	**0.210**[‡]	-0.022	**0.329**[‡]	**0.489**[§]
	p	0.308	**<0.000**[*]	0.867	0.852	**0.005**[*]	0.773	**<0.000**[*]	**<0.000**[*]
Plasma PLT	***r***	**-0.188**[†]	**-0.234**[‡]	**-0.178**[†]	-0.113	0.030	-0.067	0.070	**0.199**[†]
	p	**0.011**[*]	**0.002**[*]	**0.016**[*]	0.131	0.688	0.370	0.346	**0.007**[*]
Plasma PT	***r***	0.020	0.031	-0.125	**-0.148**[†]	-0.135	0.008	-0.124	-0.057
	p	0.794	0.675	0.093	**0.047**[*]	0.070	0.918	0.096	0.446
Plasma APTT	***r***	-0.031	-0.025	0.036	-0.023	0.124	0.022	-0.068	-0.059
	p	0.682	0.737	0.626	0.756	0.096	0.771	0.360	0.430
Plasma INR	***r***	0.129	**0.192**[†]	-0.109	-0.109	**-0.183**[†]	0.097	**-0.302**[‡]	**-0.277**[‡]
	p	0.084	**0.010**[*]	0.145	0.145	**0.014**[*]	0.193	**<0.000**[*]	**<0.000**[*]

Abbreviations: BMI, body-mass index; CNP, c-type natriuretic peptide
[*]$p < 0.05$ indicates statistical significance
[†]Very weak correlation
[‡]Weak correlation
[§]Medium correlation

The correlation analysis of plasma fibrinogen and serum calcium levels with various maternal and fetal parameters, detailed in Table 2, revealed several statistically significant relationships. Plasma fibrinogen exhibited significant but very weak negative correlations with body mass index (BMI) (r=-0.164, p=0.027) and birth weight (r=-0.161, p=0.030).

Additionally, it showed significant positive weak correlations with Apgar scores at the 1st minute (r=0.233, p=0.002) and 5th minutes (r=0.305, p<0.0001). Serum calcium also showed significant negative correlations with BMI (r=-0.223, p=0.003) and significant positive correlations with Apgar scores at both the 1st minute (r=0.252, p=0.001) and 5th minutes (r=0.252, p=0.001) assessments. For other coagulation parameters, several correlations were observed. Intriguingly, plasma hemoglobin levels and hematocrit showed medium positive correlations with the 5th minute Apgar score (r=0.420 and r=0.489 respectively; both p<0.0001). Detailed data have been.

Table 3. Details of the ROC curves for discrimination of thresholds of maternal plasma fibrinogen levels

Diagnostic scan					ROC curve		
Cutoff (mg/dl)	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**AUC**	**CI (95%)**	***p***
391.5	91.8	59.5	69.39	87.89	0.786	0.719-0.853	<0.001

Abbreviations: PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve; CI, confidence interval

On ROC curve analysis, the optimal cutoff point for identifying increased risk of PPH were found to be 391.5 mg/dL (91.8% sensitivity and 59.5% specificity) for plasma fibrinogen. The positive predictive value (PPV) was 69.39%, the negative predictive value (NPV) was 87.89%. According to the ROC analysis, AUC was 0.786 (95% CI: 0.719-0.853) (Table 3 and Fig.1).

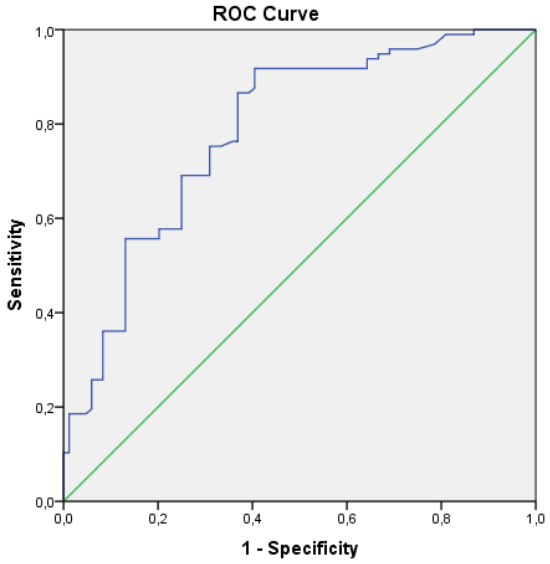

Fig. 1. Receiver operating characteristic curves for fibrinogen as screening tests for postpartum hemorrhage

4. Discussion

PPH is classified into early hemorrhage (within the first 24 hours after birth) and late hemorrhage (24 hours to 12 weeks after birth). Early hemorrhage is often severe and is associated with prolonged labor, retained placenta, and coagulation disorders (12). PPH is reported to occur in 3% to 5% of births (13). An analysis of population-based data from the United States National Inpatient Sample showed that the rate of PPH increased from 2.7% in 2009 to 4.3% in 2019 (13). The primary cause of postpartum hemorrhage is uterine atony.

In recent years, the incidence of PPH has been increasing worldwide (14). Due to its complex etiology and pathogenesis, preventing PPH is challenging. Early diagnosis and treatment are urgently required to prevent PPH. Some studies have reported that coagulation disorders are considered one of the four main causes of postpartum hemorrhage (15-17).

Our study included 84 individuals in the postpartum hemorrhage group and 96 individuals in the control group. The average age of women in our study was calculated as 32.1±6.9 years in the postpartum hemorrhage group and 30.1±5.8 years in the control group. Advanced maternal age is considered an independent risk factor for postpartum hemorrhage. In Japan, Ohkuchi et al., in their study of 10,053 women with singleton births, found through multivariate analysis that maternal age ≥35 years was an independent risk factor for postpartum hemorrhage (18). Ijaiya et al. from Nigeria found that the risk of postpartum hemorrhage in women aged ≥35 years was twice as high as in those aged ≤25 years (19). Okogbenin et al. from Nigeria also reported that obstetric hemorrhage increases with age (20). According to the authors, the risk is 0.1% at age 20 and increases to 0.7% at age ≥40. The results of our study also found that the average age in the postpartum hemorrhage group was significantly higher, consistent with the predictions of other studies.

Although grand multiparity has traditionally been considered a risk factor for postpartum hemorrhage, our study did not find a significant difference among cases analyzed based on parity. Ockuchi found that primiparity posed a risk for vaginal postpartum hemorrhage in his study (18). Additionally, no significant difference in postpartum hemorrhage was observed between patients who had vaginal deliveries and those who had cesarean deliveries. Similar results were found in a study by Zakaria et al. in 2019 (21).

In our study, there was no significant relationship between BMI and the amount of postpartum hemorrhage, similar to the findings of Kınay et al. (22). However, Budwick et al. found a moderate increase in the risk of postpartum hemorrhage in obese women (23). In our study, a BMI ≥28.8 was associated with a higher risk of hemorrhage.

In our study, hemoglobin and hematocrit levels were significantly lower in the postpartum hemorrhage group compared to the control group (PPH group; Hb: 9.4±1.0 ng/ml, control group; 11.5±1.4 ng/ml, p<0.001). Similar to our results, the literature indicates that anemic women have a higher risk of developing PPH due to uterine atony during childbirth. Studies have shown that severe anemia can impair myometrial contractility due to reduced oxygen transport to the uterus (24, 25). There are few studies addressing the causal relationship between severe anemia and PPH, and there is no consensus on the threshold hemoglobin value that may increase the risk of

uterine atony.Such research provides obstetricians with a new and improved tool to identify pregnant women at risk and thus provide them with standard care. The design of our study suggests that further research is needed in this area.

Fibrinogen (clotting factor 1) is normally found in the blood at levels of 200-450 mg/dl before pregnancy (26). During the activation of the coagulation cascade, thrombin converts fibrinogen into fibrin polymers that form the occlusive clots (27). During pregnancy, the average fibrinogen level rises to 500 mg/dl (28). Low fibrinogen levels or reduced function severely impair hemostasis. Observational studies suggest a relationship between low fibrinogen levels at the onset of postpartum hemorrhage and the subsequent severity of bleeding. During PPH, fibrinogen levels rapidly decrease due to two primary mechanisms: blood loss leading to the depletion of clotting factors and the consumption of factors associated with coagulation activation (29). In our study, plasma fibrinogen levels in the postpartum hemorrhage group (mean 392.6±69.2 mg/dl) were significantly lower than those in the control group (mean 467.2±69.6 mg/dl) ($p<0.001$). There was a significant correlation between plasma fibrinogen and serum calcium levels, similar to fibrinogen. A weak but significant negative correlation was found between plasma fibrinogen levels and BMI ($p=0.027$) and birth weight ($p=0.030$). Additionally, there was a significant positive correlation with the 1-minute and 5-minute Apgar scores ($p=0.002$ and $p<0.0001$). These values are close to those observed by Kaufner et al., with fibrinogen levels of 440 mg/dl and 330 mg/dl, respectively (30). In a study by Zakaria et al. in 2019, fibrinogen levels typically considered normal, ranging from 200 to 300 mg/dl, were still associated with a higher risk of severe postpartum hemorrhage. When fibrinogen levels were 200 mg/dl, the risk increased almost 12-fold (21). This result is consistent with Kaufner et al., showing that fibrinogen levels at the 200 mg/dl threshold have a 100% positive predictive value for severe postpartum hemorrhage (30). Karlson et al. in 2016 and Finlayson et al. in 2019 found that low fibrinogen levels were superior in indicating the risk of PPH, independent of other laboratory indicators (31, 32).

These studies and the literature indicate that fibrinogen levels are of vital importance during pregnancy. When evaluating fibrinogen levels during pregnancy, it should be kept in mind that they are higher compared to non-pregnant adult values. Furthermore, it should not be forgotten that fibrinogen is the best and earliest marker indicating the severity of postpartum hemorrhage. Although the primary cause of postpartum hemorrhage is not fibrinogen deficiency, decreases in fibrinogen levels contribute to the continuation of bleeding and the worsening of the clinical situation, as it is the fastest-decreasing factor in major hemorrhages. In our study, similar to the study by Kaufner et al., the only coagulation variable that remained independently associated with severe hemorrhage was fibrinogen level (30).

Clinical studies and experimental data from intensive care units show that the early use of fibrinogen can reduce the need for other blood derivatives. There is no consensus on the transfusion threshold value for fibrinogen during hemorrhage. The RCOG (Royal College of Obstetricians and Gynaecologis) recommends cryoprecipitate infusion when fibrinogen levels are ≤100 mg/dl. The Club d'Anesthésie et de Réanimateurs en Obstétrique recommends fibrinogen infusion when levels fall below 200 mg/dl. A recent in vitro study showed that a minimum fibrinogen concentration of 200 mg/dl is necessary for optimal clot formation. The study also suggests that even a threshold of 300 mg/dl could be beneficial (29). Larger studies are needed to determine the optimal fibrinogen threshold value.

Maternal hemogram parameters, particularly hemoglobin, hematocrit, and fibrinogen levels, are effective predictors of postpartum hemorrhage. Fibrinogen is a critical component of physiological coagulation and an important biomarker for assessing coagulation function in the body. For these reasons, this study aimed to determine the impact of antepartum blood fibrinogen and hemogram parameters on postpartum hemorrhages. The study emphasizes the importance of monitoring these parameters to identify and manage at-risk pregnancies, thereby reducing maternal morbidity and mortality associated with PPH.

Conflict of interest

The authors declared no conflict of interest.

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None to declare.

Authors' contributions

Concept: S.S.Ü., Y.C.Ü., Design: S.S.Ü., Y.C.Ü., Data Collection or Processing: Ö.D.Ü., Y.C.Ü., S.E., S.M.A., C.S.Ç., Z.Y., C.M.S., S.Ç., Analysis or Interpretation: S.S.Ü., S.Ç., Literature Search: Ö.D.Ü., C.S.Ç., Z.Y., C.M.S., S.Ç., Writing: Y.C.Ü., S.E., S.M.A.

Ethical Statement

Approval was obtained from Samsun University Non-invasive Clinical Research Ethics Committee, the study started. The ethics committee decision date is 22/05/2024 and the number of ethical committee decisions is 2024/10/2.

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