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Prepartum Fibrinogen Levels Can Predict Excessive Hemorrhage After Vaginal Delivery

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Abstract

Objective: The aim of this study is to investigate the relationship between maternal prepartum fibrinogen level and other coagulation tests and blood loss in the third stage of labor.

Methods: This prospective clinical study was performed in a tertiary center between September 2021 and March 2022. A total of 1217 singleton pregnancies between 37 and 42 weeks hospitalized for vaginal delivery were included in the study. Maternal predelivery blood samples were taken for complete blood count and biochemical and coagulation tests. Demographic, clinical, and follow-up data of the patients were recorded. Blood loss in the third stage of labor was measured quantitatively with transparent collecting bags. Patients were divided into 2 groups as blood loss < 500 mL and blood loss ≥ 500 mL and then compared among variables. Factors predicting excessive bleeding were defined by regression analysis. Receiver operating characteristic analysis was performed for fibrinogen to predict hemorrhage.

Results: Of the 352 patients, 296 (84.1%) had blood loss < 500 mL and 56 (15.9%) had blood loss ≥ 500 mL. The demographic and clinical features of the groups were similar. The prepartum fibrinogen value was significantly lower in the blood loss ≥ 500 mL group (447.48 ± 79.40 mg/dL vs 486.67 ± 104.77 mg/dL, $P = .008$). There was a significant negative correlation between the blood loss volume and prepartum fibrinogen ($R^2 = -0.123$, $P = .021$). The odds ratio of fibrinogen level to predict hemorrhage was 0.99 with 95% CI (β = −0.004, odds ratio = 0.996 (0.993-0.999), $P = .010$). The cut-off level of fibrinogen to predict blood loss ≥ 500 mL was 452 mg/dL with a sensitivity of 66.1% and a specificity of 57.1%.

Conclusion: Prepartum fibrinogen level could be an indicator to detect postpartum hemorrhage in risk-free population.

Keywords: Postpartum hemorrhage, fibrinogen, labor, third stage

Introduction

Postpartum hemorrhage (PPH) is an obstetric emergency. It is one of the common causes of maternal morbidity and mortality worldwide.[1] The World Health Organization defines PPH as blood loss of ≥500 mL within 24 hours of birth.[2] Postpartum hemorrhage is generally reported to occur in 1% to 3% of births.[3] Many risk factors for PPH have been reported, including abnormal placentation, ablation, family history, precipitous labor, uterine overdistention, obesity, high parity, and history of PPH, and they are often interconnected.[4,5] In addition, coagulopathy has also been reported to cause PPH.[6]

Fibrinogen is the precursor to fibrin, the main component of the clot, and is an important factor in hemostasis. Low fibrinogen levels can lead to impaired clot formation and an increased risk of bleeding.[7] The effects of components of maternal hemostasis on PPH have not been clearly elucidated. There are studies showing that maternal low fibrinogen may be related to increased bleeding; on the other hand, it has also been reported that PPH and prepartum fibrinogen levels are not associated.[8,9] In the current literature, there are studies showing that patients with severe PPH without coagulopathy have relatively lower fibrinogen levels compared to patients without PPH.[9,10] It has also been reported that interventions to increase prenatal fibrinogen levels in patients with serum fibrinogen levels in the normal range do not reduce the risk of PPH.[11] There is no clear data on this subject. Therefore, it is important to define the role of fibrinogen and other coagulation tests in predicting bleeding, especially in patients with a low risk of PPH.

The aim of this study is to investigate whether there is a relationship between maternal prepartum fibrinogen level and other coagulation tests and blood loss in the third stage of labor.

Material and Method

This prospective observational study was carried out at a tertiary referral center between September 2021 and March 2022. Bursa Yuksek Ihtisas Training and Research Hospital ethics committee approval (2011-KAEK-25 2021/03/10) and informed consent were obtained from each participant.

Singleton pregnancies delivered vaginally between 37 and 42 weeks were included in the study. Gestational age was calculated according to first-trimester crown–rump length. Demographic data, comorbidities, family histories, pelvic examination, and ultrasonographic findings of the patients were recorded during hospitalization in the delivery room. Postterm and preterm pregnancies, those with a history of PPH, those with pre- or gestational diabetes or hypertension, those with bleeding diathesis, those with a history of previous cesarean section, those who underwent cesarean section during follow-up, those who received induction other than routine protocol, those who take medications other than vitamins, pregnancies without follow-up, fetal anomalies, those with

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abnormal placentation, macrosomic fetuses (>4000 g), and those with oligo/polyhydramnios were excluded from the study.

Maternal venous blood samples were taken for complete blood count, electrolytes (Na, K, Ca, Cl), renal function tests (blood urea nitrogen, creatinine), liver function tests (alanine transaminase, aspartate transaminase), and coagulation tests (activated partial thromboplastin time (aPTT), prothrombin time (PT), fibrinogen). Fibrinogen levels were calculated by the Claus method.[12]

Duration of induction and labor, birth complications, presence of episiotomy or perineal tear, separation time and type of placenta (spontaneous/manual), blood loss of the patients, and newborn birth weight and APGAR scores were recorded.

The induction regimen was applied with an oxytocin infusion pump of 60 units in 1000 mL of crystalloid, and the dose was typically increased until labor was normal or uterine activity had reached at least 200-250 Montevideo units, with a maximum of 40 mU/min. The duration of labor was defined as the time from 6 cm cervical dilatation until the baby is born. The management of the third stage of labor was actively carried out (uterotonic drugs, umbilical cord pulling, and uterine massage). As prophylaxis, oxytocin treatment was given as an intravenously slow bolus of 5 international units (IU), and then 20 IU of oxytocin in 1000 cc 0.9% saline was continued at a rate of 125 mL/h. In case of additional uterotonic need, sublingual or rectal misoprostol and/or intramuscular methylergonovine were administered. The patients were transferred from the delivery room to their rooms at the postpartum second hour.

Blood loss in the third stage of labor was measured with transparent collecting bags. The bag was placed under the patient's bottom immediately after the baby was born and the amount of bleeding in the first 2 hours after birth was measured objectively in milliliters. The gauze pads used during episiotomy repair were weighed and added to the measured blood loss. Then, patients were divided into 2 groups as blood loss < 500 mL and blood loss ≥ 500 mL according to bleeding volume.

Statistical Analysis

Statistical Package for the Social Sciences version 22.0 (IBM SPSS Corp., Armonk, NY, USA) program was used for analysis. The normality of the data was checked by Kolmogorov–Smirnov test. Values were given as mean ± SD or median (min-max). Parametric data were compared with Student's *t*-test, Mann–Whitney *U*-test was used for nonparametric data. Categorical data were analyzed by chi-square test. Correlation analysis was used to find the association of the factors with hemorrhage volume. Logistic regression was performed to identify a model that included factors affecting hemorrhage status. The receiver operating characteristics (ROC) curve was drawn to determine the prepartum fibrinogen threshold value, which predicts excessive bleeding, and the area under the curve was calculated. Alpha level was defined as 0.05.

Results

A total of 1217 patients between 37 and 42 weeks of gestation were evaluated. There were those who had any comorbidity or drug use (n = 285), those with a history of PPH (n = 41), those with fetal anomaly, amniotic fluid anomaly, or placental anomaly (n = 92), and those who had cesarean section during follow-up (n = 458). Initially, 825 patients were excluded from the study with these overlapping data. Of the remaining patients, those whose blood results could not be reached completely, those whose induction protocol was applied different from the one mentioned in the method, those whose blood loss was not measured with a bag, and macrosomic fetuses were also excluded and 352 patients were analyzed for the study. Of these, blood loss <500 mL was in 296 (84.1%) patients and >500 mL was in 56 (15.9%) patients.

The mean age of the patients was 25.59 ± 5.51 years, the mean gestational week was 39.06 ± 1.47, and the mean amount of bleeding was 311.77 ± 167.12 mL. The demographic and clinical features of the groups were similar (Table 1). In the prepartum laboratory tests, the fibrinogen value was 447.48 ± 79.40 mg and significantly lower in the blood loss >500 mL group. Postpartum hemoglobin and hematocrit values were significantly lower in the blood loss >500 mL group (Table 1). Induction of labor was given in 272 (77.3%) patients. In blood loss >500 mL group, patients with induction of labor were significantly high (91.1% vs. 8.9%, P = .005). There are only 3 patients whose placentas were separated manually. Remaining placentas separated spontaneously.

Table 1. Demographic, Clinical Characteristics, and Laboratory Results of the Groups

	Blood Loss < 500 mL (n = 296)	Blood Loss ≥ 500 mL (n = 56)	*P*
Maternal age (years)	25.90 ± 5.54	25.85 ± 5.40	NS
Gravida[a]	3 (1-9)	2 (1-9)	NS
Parity[a]	1 (0-8)	1 (0-6)	NS
BMI (kg/m^2)	27.10 ± 4.69	27.71 ± 4.55	NS
Gestational week	39.06 ± 1.49	39.07 ± 1.37	NS
Duration of induction (minutes)	199.64 ± 226.60	189.10 ± 139.58	NS
Duration of labor (minutes)	387.70 ± 309.82	338.48 ± 223.60	NS
Birth weight	3221.56 ± 382.25	3332.14 ± 432.72	NS
Blood loss (mL)	253.44 ± 96.57	620.08 ± 114.60	<.001
Prepartum values			
Hemoglobin (g/dL)	11.40 ± 1.44	11.06 ± 1.42	NS
Hematocrit (%)	34.80 ± 3.72	33.86 ± 4.25	NS
Platelets (×10^3 cells/mL)	237.05 ± 72.38	235.28 ± 57.77	NS
PT (%)	11.72 ± 1.28	11.61 ± 0.73	NS
aPTT (seconds)	24.40 ± 4.26	24.55 ± 2.70	NS
Calcium	8.64 ± 0.47	8.56 ± 0.55	NS
Fibrinogen (mg/dL)	486.67 ± 104.77	447.48 ± 79.40	.008
Postpartum values			
Hemoglobin (g/dL)	10.92 ± 1.54	9.97 ± 1.21	<.001
Hematocrit (%)	33.58 ± 4.05	31.39 ± 4.49	<.001
Platelets (×10^3 cells/mL)	230.32 ± 69.49	226.98 ± 58.77	NS

Values are given as mean ± SD unless otherwise specified.
Mann–Whitney test was performed. P < .05 was considered significant.
aPTT, activated partial thromboplastin time; BMI, body mass index; PT, prothrombin time; NS, nonsignificant.
[a]Values are given as median (min-max).

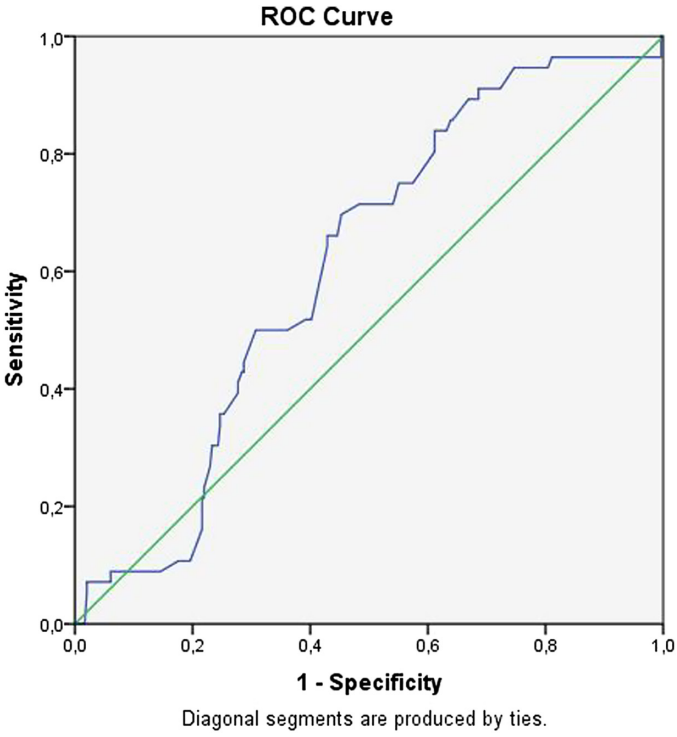

Figure 1. Receiver operating characteristic curve for prepartum fibrinogen to predict postpartum hemorrhage (area under curve (95% CI) = 0.661 (0.540-0.682), *P* = .008).

There was no difference between the groups in terms of manual separation (*P* = .406).

According to Spearman's correlation analysis, there was a significant negative correlation between the blood loss volume after vaginal delivery and prepartum fibrinogen level (R^2 = −0.123, *P* = .021). The accuracy detection rate of the logistic regression model that included prepartum PT, aPTT, fibrinogen, and calcium levels to predict the amount of blood loss was 84.1% (R^2 = 0.044). The odds ratio (OR) of fibrinogen level to predict PPH was 0.99 with 95% CI (β = −0.004, OR = 0.996 (0.993-0.999), *P* = .010).

In ROC analysis, the cut-off level of fibrinogen determined to predict the blood loss ≥ 500 mL was 452 mg/dL. The sensitivity for this value was 66.1% and the specificity was 57.1% (area under curve (95% CI) = 0.661 (0.540-0.682), *P* = .008) (Figure 1).

Discussion

In the current prospective clinical study, we evaluated patients who had no risk factors for PPH and delivered vaginally. We showed a negative association between maternal prenatal fibrinogen level and postpartum blood loss in these subjects. Furthermore, we found that fibrinogen level was a predictor of blood loss ≥ 500 mL (OR = 0.996, 95%CI = 0.993-0.999, *P* = .01). To detect the PPH ≥ 500 mL after vaginal delivery, we calculated the threshold of prepartum fibrinogen level as 452 mg/dL with a sensitivity of 66.1% and a specificity of 57.1%. However, we could not report any relation between other coagulation parameters and blood loss in vaginal deliveries.

In a recent study, predelivery fibrinogen levels were found to be similar in women with blood loss < 500 mL and in women with blood loss ≥ 500 mL.[10] However, that study also reported that each 1 g/L increase in fibrinogen levels reduces the risk of ≥1000 mL blood loss by 0.405 times (*P* = .004).[10] Unlike our study, they included women with risk factors for PPH such as macrosomia, gestational diabetes, and history of atony. So that it could be concluded that the number of women diagnosed with PPH might have been higher in their patients. In our study, we had only 2 patients with blood loss ≥ 1000 mL.

Fibrinogen is the final element of the coagulation cascade, a precursor to plug formation.[7] Low serum fibrinogen concentrations were associated with increased bleeding in major surgeries.[13] Our results were in line with this data. On the other hand, Karlsson et al[9] could not find an association between the prepartum fibrinogen levels and PPH. They defined PPH as blood loss > 1000 mL and they included both cesarean and vaginal deliveries in their study, unlike us.[9] Another study indicated that higher fibrinogen levels did not reduce the risk of PPH.[11] In that study, the researchers evaluated the serum fibrinogen 6-24 days before delivery, whereas we measured it just before labor.[11] Peyvandi et al[11] concluded in their retrospective study that predelivery fibrinogen level was a poor predictor of PPH. However, they measured the fibrinogen level as 4.8 ± 0.9 in the PPH group, comparable to ours.

We aimed to define a cut-off value of predelivery fibrinogen to predict PPH. We detected that fibrinogen level less than 452 mg/dL in risk-free population could alert the clinician about PPH. Yamada et al[14] found a cut-off value of 3.3 g/L to indicate blood loss > 700 mL in vaginal deliveries in their retrospective study. Nevertheless, they were unable to report a significant correlation between antenatal fibrinogen concentrations and estimated blood loss. They included women without PPH risks, but they checked the fibrinogen level 21 days before delivery unlike us.[14]

In the current study, the frequency of PPH in vaginal deliveries was calculated as 15.9%. This rate was higher than represented in a previous report.[2] Our findings are based on an objective estimation of blood loss. We measured blood loss quantitatively and prospectively. It could be concluded that many reports based on subjective estimation might underestimate the frequency of PPH. Moreover, variations in PPH criteria (e.g., >500 mL, >700 mL, >1000 mL, presence/absence of symptoms) might also contribute to differences in reported incidence.

The prospective design, including risk-free population for PPH, measuring fibrinogen levels just before labor, analysis of other coagulation factors, using a quantitative method to detect blood loss, similar labor induction methods between the groups, and standard management of the third stage of labor in all women are the strengths of the study. Relatively small numbers of the patients, not analyzing postpartum fibrinogen levels, and measuring the hemorrhage only in the first 2 hours postpartum could be considered as limitations.

Conclusion

Our results showed that prenatal fibrinogen level is an indicator that could alert clinicians about PPH. Postpartum hemorrhage is an important obstetric emergency. It is possible to be prepared for PPH management by predicting PPH in the risk-free population. For further interpretation, large prospective studies on this subject are needed.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Bursa Yüksek İhtisas Training and Research Hospital (Date: March 18, 2021, Approval No: 2011-KAEK-25 2021/03/10)

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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