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Original article

Use of Fibrinogen in Prevention and Management of Postpartum Haemorrhage in High Risk Patient

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Abstract:

Background: Postpartum hemorrhage (PPH) remains a leading cause of maternal morbidity and mortality, particularly in high-risk pregnant patients. The early prediction and effective management of PPH are crucial to improving maternal outcomes. Serum fibrinogen levels have emerged as a potential biomarker for predicting and managing PPH. The aim is to study the role of serum fibrinogen level in prediction and anticipation of postpartum hemorrhage and its role in the treatment. **Methods:** This cross-sectional observational study was carried out on pregnant females at high risk of PPH attending Benha University Hospital and Toukh Central Hospital over a six-month period. Detailed clinical assessments, laboratory investigations, and obstetric monitoring were conducted. Serum fibrinogen levels were measured using quantitative analysis. Antenatal and intrapartum care were tailored to patient needs. PPH cases received treatment with fibrinogen concentrate, cryoprecipitate, or fresh frozen plasma as indicated. **Results:** According to serum fibrinogen levels, the mean serum fibrinogen level of the studied cases was 3.6 (±1.15) g/l. There was high statistically significant relation between bleeding severity and serum fibrinogen. According to ROC curve analysis for the use of serum fibrinogen levels to predict severity of bleeding, using serum fibrinogen levels at 3.95, it can predict PPH with 0.859 AUC, sensitivity 100%, specificity 71.9%, PPV 66.7%, NPV 100% and accuracy 82.0%. **Conclusion:** Serum fibrinogen levels show promise as a valuable predictor for PPH in high-risk pregnant patients. Monitoring fibrinogen levels could aid in early identification and timely intervention, potentially reducing the severity and complications of PPH.

Keywords: Postpartum Hemorrhage; Serum Fibrinogen; High-Risk Pregnancy; Predictive Marker; Obstetric Management.

Introduction

Postpartum hemorrhage (PPH) is a major global cause of maternal mortality, particularly in developing countries, claiming around 140,000 lives annually (Zakaria et al., 2019). PPH can be primary (within 24 hours of delivery) or secondary (24 hours to 12 weeks postpartum) [(1)]. Early symptoms may include increased heart rate, dizziness upon standing, and elevated respiratory rate. Risk factors for PPH include prolonged labor, retained placental products, chorioamnionitis, oxytocin use, multiple gestation, and more [(2)].

Coagulation plays a critical role in PPH, with primary and secondary coagulation disorders posing significant risks. PPH can be attributed to dilutional or consumption coagulopathy, often leading to disseminated intravascular coagulation [(3)]. Fibrinogen concentrate (FC) is recommended as a more efficient replacement therapy than traditional blood products like RBC, FFP, and PC [(4)].

Observational studies link low initial fibrinogen levels in PPH to excessive bleeding and transfusion needs. During pregnancy, hemostasis shifts toward a prothrombotic state, marked by elevated levels of procoagulant factors, particularly fibrinogen [(5)].

While FFP is commonly used for acquired fibrinogen deficiencies, fibrinogen concentrate offers faster restoration but may not be widely available. Treatment options for PPH include intravenous fluids, blood transfusions, ergotamine, and manual uterine compression. Uterotonics, with oxytocin as the preferred choice, play a central role in PPH treatment (6).

The purpose of this study was to study the role of serum fibrinogen level in prediction and anticipation of postpartum hemorrhage and its role in the treatment.

Patients and methods

Type of the study

This study was conducted as cross-sectional observational study on pregnant females with high risk of postpartum haemorrhage. A comprehensive sample approach was adopted. All patients with high risk of postpartum haemorrhage fulfilling inclusion criteria attending Benha University Hospital and Toukh Central hospital on Obstetrics and Gynecology department. The patients were collected in 6 months, from July 2022 to January 2023.

An informed written consent was obtained from the patients. Every patient received an explanation of the purpose of the study and had a secret code number. The study was done after being approved by the Research Ethics Committee, Faculty of Medicine, Benha University.

Inclusion criteria were pregnancy between 34 weeks to 37 weeks, Intra uterine fetal death, antepartum haemorrhage, poly hydraminous, placenta previa, macrosomic baby and twins.

Exclusion criteria were pregnant women having any medical disorders such as renal diseases, cardiac diseases, blood disease,

Methods:

All patients were subjected to complete history taking during antenatal care visits and thorough clinical examination.

Laboratory investigations including c**o**mplete blood picture to diagnose anemia and blood disorders. Coagulation profile (PT, PTT and INR).

Obstetric ultrasonography and fetal monitoring to diagnose number of babies, viability, gestational age, estimated fetal body weight, placental position and amniotic fluid index.

Measurement of fibrinogen level in high-risk group by quantitative analysis was done. Fibrinogen kits composed of 1-Thrombin reagent prepared from bovine source, 2-Fibrinogen calibrator prepared from human plasma and 3-Owrens buffer PH7.3 By Biomed company for fibrinogen kits made in Egypt.

Procedures

Serum fibrinogen was measured at (30-40) weeks of gestation for one time in this study. Antenatal care was done to correct the Anemia cases before labor. Intrapartum care was done according to the patient case (Normal vaginal delivery, Instrumental vaginal delivery, and Cesarean section). The patients who had postpartum hemorrhage started bleeding after the 3rd stage of labor and within 3 hours labor. The patients who had postpartum hemorrhage were treated with one of the following according to the availability Fibrinogen Concentrate. Cryoprecipitate. Fresh Frozen Plasma.

Statistical analysis

Statistical analysis was performed using IBM SPSS software version 28.0 (Armonk, NY: IBM Corp). Qualitative data were presented as numbers and percentages, while the normality of distribution for quantitative data was assessed using the Kolmogorov-Smirnov test. Descriptive statistics for quantitative data included the range (minimum and maximum), mean, standard deviation, median, and interquartile range (IQR). The significance level was set at 5%. The analysis employed several statistical tests: (1) Student t-test for normally distributed quantitative variables to compare between multiple groups, (2) Receiver Operating Characteristic (ROC) curve analysis to assess the diagnostic performance of the test, with the area under the curve indicating its accuracy, (3) Sensitivity, representing the test's ability to correctly identify individuals with the disease (True Positives), (4) Specificity, indicating the test's capacity to correctly exclude disease-free individuals (True Negatives), (5) Positive Predictive Value (PPV), denoting the probability of the disease being present among those with positive test results, and (6) Negative Predictive Value (NPV), representing the probability that the disease was absent among those with negative test results.

Research ethics committee: Ms.25.5.2022.

Results

The mean age of the studied cases was 31.04 (±4.44 SD) with a range from 24 to 38 years. Among the studied cases there were 20 (40%) primiparous and 30 (60%) multiparous.

According to gestational age the mean age GA of the studied cases was 35.76 (±1.02 SD) with a range from 34 to 37 week. Among the studied cases there were 24 (48%) who had simple vaginal delivery, 10 (20%) who had instrumental vaginal delivery and 16 (32%) who had cesarean section. Among the studied cases there were 18 (36%) with episiotomy, 2 (4%) with severe perineal tears and 27 (54%) with active management of third stage of labor. Among the studied cases there were 34 (68%) with complete placental delivery and 16 (32%) with incomplete placental delivery.

Among the studied cases there were 32 (64%) with non-severe bleeding and 18 (36%) with severe bleeding. Table 1

The mean serum fibrinogen levels of the studied cases was 3.6 (±1.15 SD) with a range from 1.5 to 5.8. Table 2

There was a high statistically significant relation between bleeding severity and serum fibrinogen (P-value < 0.001). Table 3

Table 1: Distribution of the studied cases according to bleeding severity

	Subjects (n = 50)	
Bleeding severity	No.	%
Non-severe	32	64.0
Severe	18	36.0

Table 2: Distribution of the studied cases according to serum fibrinogen levels

	Subjects(n = 50)
Serum fibrinogen levels (g/L)	
Range.	1.5 – 5.8
Mean ± SD.	3.6 ± 1.15

Table 3: Relation between bleeding severity and serum fibrinogen levels.

	Bleeding severity		Test of sig.	p
	Non-severe	Severe		
Serum fibrinogen levels (g/L)				
Range.	2.1 – 5.8	1.5 – 3.6	5.096	<0.001*
Mean ± SD.	4.11 ± 1.01	2.68 ± 0.73		

Figure 1 showed that using serum fibrinogen levels at 3.95, it can predict PPH with AUC of 0.859, level of sensitivity 100%, specificity 71.9%, PPV 66.7%, NPV 100% and accuracy 82.0%.

Among the cases with severe bleeding there were 2 (11.1%) with IUFD, 9 (50%) with macrosomic baby, 4 (22.2%) with placenta previa and 3 (16.7%) with twins. Figure 2

Among the cases with severe bleeding there were 3 (16.7%) with birth canal lacerations, 6 (33.3%) with decreased serum fibrinogen level, 3 (16.7%) with prolonged labor, 4 (22.2%) with uterine atony and 2 (11.1%) with uterine rupture. Figure 3

Among the cases with severe bleeding there were 2 (11.1%) who were treated by cryoprecipitate, 6 (33.3%) who were treated by fibrinogen concentrate and 10 (55.6%) who were treated by fresh frozen plasma. Figure 4

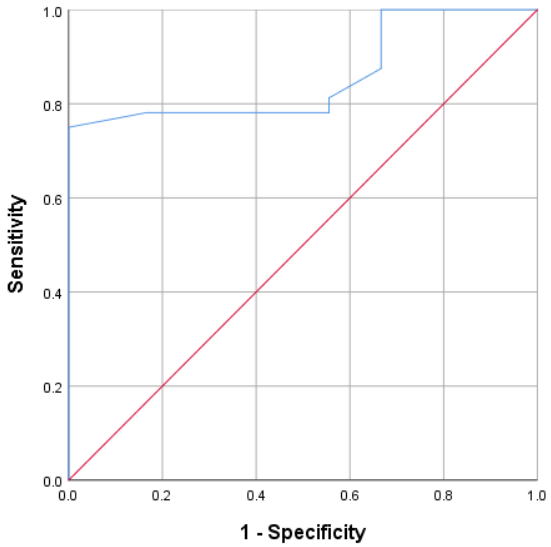

Figure 1: ROC curve analysis for the use of serum fibrinogen levels to predict severity of bleeding.

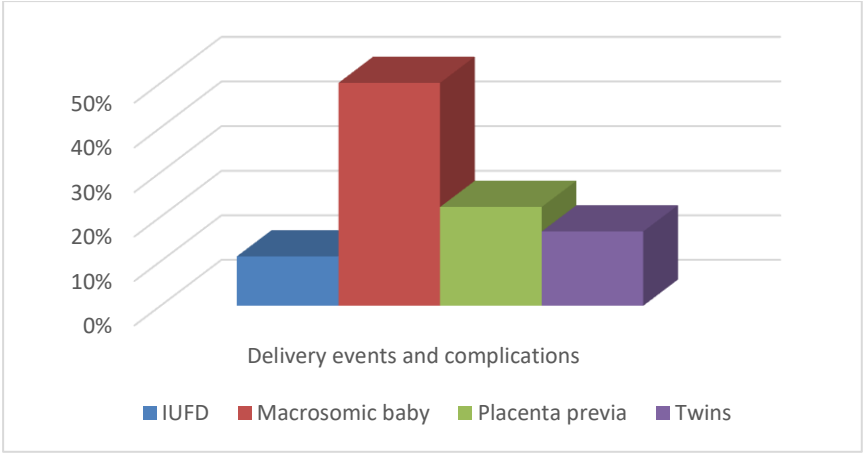

Figure 2: Distribution of the studied cases according to high-risk patients.

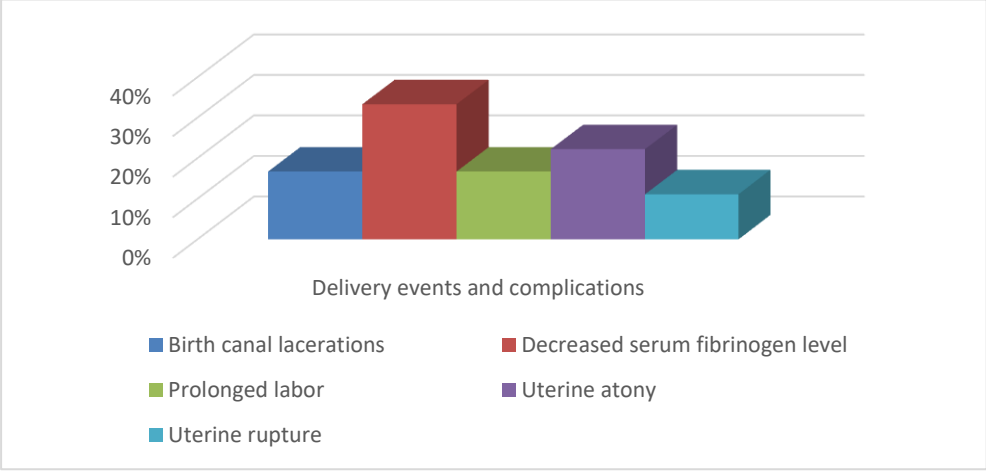

Figure 3: Distribution of the studied cases according to associated cause of bleeding.

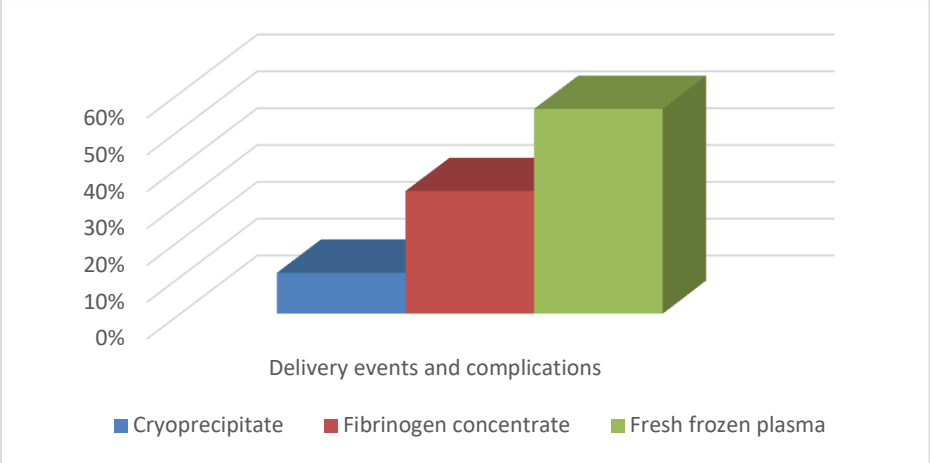

Figure 4: Distribution of the studied cases according to associated Type of management of Sever Bleeding

Discussion

Postpartum hemorrhage (PPH) is classified into primary (within 24 hours after delivery) and secondary (24 hours to 12 weeks post-delivery) forms, with primary PPH being the most common and severe, associated with risk factors like prolonged labor, retained placenta, and coagulation disorders [(1)]. Coagulation plays a key role in postpartum hemostasis, with primary and secondary coagulation disorders being significant risk factors for PPH. Pregnancy-induced hypercoagulability naturally reduces hemorrhage risk, characterized by increased fibrinogen levels. PPH symptoms include an initial increase in heart rate, dizziness, and elevated respiratory rate, progressing to coldness, hypotension, and potential unconsciousness [(7)]. Treatment options involve intravenous fluids, blood transfusions, ergotamine, uterine compression, and non-pneumatic anti-shock garments as recommended by the World Health Organization. Disseminated intravascular coagulation (DIC) is a syndrome involving systemic blood coagulation activation leading to thrombosis and bleeding. Fibrinogen, a crucial hemostasis component, increases during pregnancy but can decrease significantly due to blood loss, necessitating interventions like massive transfusion and fibrinogen replacement [(8)].

The main aim of this study was to investigate serum fibrinogen levels as predictors for PPH and their role in treatment.

In the current study according to gestational age, the mean age of the studied cases was 35.76 (±1.02 SD) with range from 34 to 37 week. In a study [(9)], 129 deliveries were included. One case was excluded from the analysis because blood samples were lacking after H0. This hemorrhage did not require transfusion or hemostatic intervention. Among the 128 cases of PPH, 50 (39%) presented at least one criterion of severity over the first 24 h postpartum, forming the severe group. Age was > 38 years.

In the current study according to parity, among the studied cases there were 20 (40%) primi-parous and 30 (60%) multiparous. In a study 129 deliveries were

included. One case was excluded from the analysis because blood samples were lacking after H0 [9]. This hemorrhage did not require transfusion or hemostatic intervention. Among the 128 cases of PPH, 50 (39%) presented at least one criterion of severity over the first 24 h postpartum, forming the severe group. Parity was > 4.

In the current study according to delivery type, among the studied cases there were 24 (48%) who had simple vaginal delivery, 10 (20%) who had instrumental vaginal delivery and 16 (32%) who had cesarean section. A study identified 181 women who had undergone MT, making the estimated incidence of MT associated with postpartum haemorrhage (PPH) 23 per 100 000 maternities (95% confidence interval 19–26) per year. The median estimated blood loss was 6 l (interquartile range 4.5–8.0 l) [10]. The majority of women presented outside working hours (63%), 40% had had previous caesarean sections and 3% had normal vaginal births without risk factors. The main cause for MT was uterine atony (40%) and the main mode of birth was caesarean section (69%).

In the current study according to delivery events and complications, among the studied cases there were 18 (36%) with episiotomy, 2 (4%) with severe perineal tears and 27 (54%) with active management of third stage of labor and according to type of placental delivery, among the studied cases there were 34 (68%) with complete placental delivery and 16 (32%) with incomplete placental delivery. In a study 899 women delivered vaginally during the study period of 2 years. Among these 6.45% (58 women) had various complications during third stage of labor. 55% were primigravida. Complications which were observed to occur during third stage of labor were perineal tear 4% (37/899 deliveries). Atonic PPH occurred in 0.5% (9/899 deliveries) Traumatic PPH was in 1.44% (13/899 deliveries and 0.3% cases had retained placenta. Associated condition in perineal tear cases were 92% had big size babies 5% cases were preterm labor and in 3% cases ventouse application was done [11].

In the current study according to bleeding severity, there were 32 (64%) with non-severe bleeding and 18 (36%) with severe bleeding. Our results were in agreement with study reported that 43% of their studied group had severe PPH (group 2) and 57% had non- severe PPH (group 1) [12].

Similarly, in the study, among the 128 cases of PPH, 50 (39%) presented at least one criterion of severity over the first 24 h postpartum, forming the severe group [9]. Also, demonstrated that PPH was severe for 323 of the 738 (43.8%) women included, but not for 415 (56.2%) [13].

In the current study according to serum fibrinogen levels, the mean serum fibrinogen levels of the studied cases was 3.6 (±1.15 SD) with a range from 1.5 to 5.8 years. In a study according to serum fibrinogen levels, the mean serum fibrinogen levels of the studied cases was 3.3 [2.5;4.2] for severe bleeding group and 4.4 [3.7;5.1] for non-severe bleeding group [9].

In the current study, there was a high statistically significant relation between bleeding severity and serum fibrinogen.

In a study, the predictive power of each laboratory parameter in relation to the severity of bleeding was evaluated using AUCs. The highest value was found for fibrinogen (AUC = 0.75; P < 0.0001) [9].

In the current study according to Roc curve analysis for the use of serum fibrinogen levels to predict severity of bleeding, using serum fibrinogen levels at 3.95, it can predict PPH with AUC of 0.859, level of sensitivity 100%, specificity 71.9%, PPV 66.7%, NPV 100% and accuracy 82.0%.

In a study, ROC curve analysis for fibrinogen showed that the cutoff point of 4.0 g L−1 had the highest discriminatory power, with a sensitivity of 74% and a specificity of 65%. By contrast, PT and APTT were of little help to predict the severity of bleeding [(9)].

In the current study, high-risk patients experiencing severe bleeding had various associated factors: IUFD (11.1%), macrosomic baby (50%), placenta previa (22.2%), and twins (16.7%).

Unmodifiable risk factors for excessive postpartum hemorrhage (EPH) include a history of EPH (OR = 2.3–10.5), delivering a large-for-gestational-age fetus (> 4000 g) (OR = 1.7–1.9), and uterine abnormalities like uterine fibroids (OR = 2.0–2.7) (Girault et al., 2018). Pregnancy complications such as maternal anemia (hemoglobin < 9 [g/dL]) (OR = 4.1), hypertensive disorders (OR = 1.6–3.6), gestational diabetes mellitus (OR = 1.6), multiple gestation (OR = 1.5–3.7), polyhydramnios (OR = 2.6), and preterm delivery (OR = 2.6) are significantly correlated with EPH [(14)]. Maternal fever (OR = 1.7–2.5), labor induction (OR = 1.5–1.7), and instrumental (OR = 1.2–2.9) or operative delivery (OR = 1.4–5.7) also increase the risk of EPH. Retained placenta raises the risk of immediate postpartum hemorrhage (OR = 3.5–4.1) as well as in subsequent pregnancies (Nyfløt et al., 2017).

In a study, specific etiologies of hemorrhage included severe hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome, abruptio placentae, and uterine rupture, all observed in the severe group. Various risk factors associated with postpartum hemorrhage were analyzed, but their incidence did not significantly differ between the two groups (P = 0.8) [(9)].

In the current study, severe bleeding cases were categorized by their causes: birth canal lacerations (16.7%), decreased serum fibrinogen levels (33.3%), prolonged labor (16.7%), uterine atony (22.2%), and uterine rupture (11.1%).

The primary cause of PPH is uterine atony, accounting for 60-80% of cases and 20-30% of maternal deaths [(14)]. PPH can also result from cesarean section (CS), with a reported ratio of 0.3-6%. The prevalence of PPH has been increasing, potentially due to rising incidences of uterine atony and CS. Emergency hysterectomies (5.8-6.3/10,000 births), blood transfusions, B-Lynch sutures (10.7/10,000 births), and uterine artery embolizations are strongly associated with uterine atony. Other common causes of excessive postpartum bleeding include genital tract injuries or episiotomy (16.7%), placental abnormalities (such as retained placenta, abnormal placental implantation, or placental abruption, accounting for 4-36%), and coagulopathies (e.g., anticoagulant treatment or DIC, contributing to 7.4% of cases) [(14)].

Regarding the type of management of severe bleeding, in a study of 21 614 deliveries, 77 cases of MOH were identified. Of the 77 cases, 34 (44%) received cryoprecipitate (n = 14) or fibrinogen concentrate (n = 20). The mean (±SEM) dose utilized was 2·21 ± 0·35 pools of cryoprecipitate and 4 ± 0·8 g of fibrinogen. There was a stronger

correlation between the increase in fibrinogen level and dose of fibrinogen (Pearson co-efficient 0·5; P = 0·03) than dose of cryoprecipitate (Pearson co-efficient 0·32; P = 0·3) [15]. A work suggests that the threshold for fibrinogen replacement in the bleeding parturient should be 2 g L^{-1} as fibrinogen concentrations below this level are highly correlated with a risk of severe postpartum haemorrhage [9]. Traditionally, FFP and cryoprecipitate have been used to replenish fibrinogen, but both are administered in significant volumes with a litre of FFP or 260 mL of cryoprecipitate required to increase plasma fibrinogen concentration by 1 g L^{-1}. Fibrinogen concentrate provides rapid replacement in low volumes with limited evidence suggesting that 3 g of fibrinogen concentrate increases the plasma fibrinogen by 1 g L^{-1}. It has been used successfully in pregnancy in women with acquired hypofibrinogenaemia in case reports and retrospective series and data in approximately 28 cases of obstetric haemorrhage are encouraging [16-18].

Conclusion

Fibrinogen is an important endogenous component of hemostasis, and its content in plasma rises throughout pregnancy. So, fibrinogen assays is required in the investigation of Postpartum haemorrhage. Decreased fibrinogen is a measure of the severity for blood loss and a risk factor for development of severe Postpartum haemorrhage. Fibrinogen concentrate (FC) is produced from human plasma but has viral inactivation and does not require cross-match or thawing before use. Fibrinogen concentrate is a good choice of hemostatic therapy for ongoing bleeding in PPH.

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