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Serum Fibrinogen Assay in Prediction of Postpartum Hemorrhage and its Role in Treatment

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Abstract

Background: PPH is postpartum haemorrhage. It is uncommon and severe.1 to 5% of neonates are affected with PPH, the incidence of which varies by age 20 to 30 and socioeconomic level. During pregnancy, fibrinogen levels in plasma increase. Blood loss results in coagulopathy and low fibrinogen concentrations. Premature PPH is associated with severe bleeding and transfusions. FC is produced from human plasma without the need for cross-matching or freezing. Postpartum haemorrhage must coagulate. Problems with coagulation induce PPH. Fluids, blood, and ergotamine are agents that induce uterine contractions. Aim: The aim of the present work was to study the role of serum fibrinogen level as a predictor for postpartum hemorrhage and its role in the treatment. Subjects and Methods: This Prospective observational study was conducted in the obstetrics and gynecology unit of Benha University Hospitals and Tokh Hospital. This study included 50 patients in 3rd trimester (34-37 weeks). The duration of the study ranged from 6-12 months. Results: There was significant difference regarding Logistic regression with odds ratios and 95% confidence intervals (CI) predicting Bleeding severity. Conclusion: The fibrinogen level at PPH diagnosis is a marker of the risk of aggravation and should serve as an alert to clinicians.

Key words: Fibrinogen, Postpartum, Hemorrhage.

1. Introduction:

Postpartum hemorrhage (PPH) can be classified as primary (early) or secondary (late). Primary PPH, the most common and severe, occurs within the first 24 hours after delivery. Secondary PPH occurs 24 hours to 12 weeks after delivery. Most cases of morbidity and mortality due to PPH are the result of primary PPH, while secondary PPH results from retained placental fragments, subinvolution of the placental site, infection, and coagulation defects (bleeding diatheses) which cause abnormal excessive bleeding [**1].**

Prolonged labor retained placenta products, chorioamnionitis, Oxytocin used in labor, preeclampsia/eclampsia, multiple gestation, hydroamnios, halogenated anesthesia, previous episode of uterine atony, increasing maternal obesity and raised body mass index, caesarian delivery and induction of labor are risk factors for PPH [**2].**

Coagulation plays an important role in postpartum hemostasis. Primary and especially secondary coagulation disorders are risk factors for PPH that have not been sufficiently evaluated. Pregnancy-induced hypercoagulability tends to reduce the risk of hemorrhage naturally. Pregnancy-related coagulation changes are expressed by a progressive and significant increase in the fibrinogen level, while the standard indicators, such as prothrombin time (PT) and activated coagulation time (ACT), very little [**3**].

Signs and symptoms of PPH may initially include: an increased heart rate, feeling faint upon standing and an increased respiratory rate As more blood is lost the women may feel cold, their blood pressure may drop (hypotension), and they may become unconscious. Treatments may include intravenous fluids, blood transfusions, and the medication ergotamine to cause further uterine contraction. Efforts to compress the uterus using the hands may be effective if other treatments do not work. The aorta may also be compressed by pressing on the abdomen. The World Health Organization has recommended non-pneumatic anti-shock garment to help until other measures such as surgery can be carried out [**4].**

Disseminated intravascular coagulation (DIC) is a syndrome characterized by the systemic activation of blood coagulation, which generates intravascular thrombin and fibrin, resulting in the thrombosis of small- to medium-sized vessels and ultimately organ dysfunction and severe bleeding [**5].**

Fibrinogen is an essential endogenous component of hemostasis, and its plasma concentration increases during pregnancy. Blood loss results in coagulopathy and reduced fibrinogen levels. Massive transfusion is frequently used to treat hemorrhage but can itself result in dilutional coagulopathy. Indeed, fibrinogen is the first coagulation factor to decrease to a critically low level during major blood loss and replacement with RBC [**6].**

The aim of this work was to study the role of serum fibrinogen level as a predictor for postpartum hemorrhage and its role in the treatment.

2. Patients and Methods

This study was conducted in the obstetrics and gynecology unit of Benha University Hospitals and Tokh Hospital.

2.1Type of the study:

Prospective observational study.

2.2Patients:

This study will include 50 patients in 3rd trimester (34-37 weeks).

2.3Inclusion criteria:

- Women aged 22-40 years in 3rd-trimester with singleton pregnancy.

2.4Exclusion criteria:

- Miscarriages (i.e. before 22 weeks of gestation) and bleeding after 24 hrs.

- Macrosomia
- Placenta Previa
- Low Lying Placenta
- Multiple Pregnancy
- Pre-Eclampsia
- Hypertension
- Malignancies
- Diabetes Mellitus
- Chronic Renal Disease
- Chronic Liver Disease

2.5Ethical Consideration:

- Approval of Ethical Scientific Committee of Benha University will be obtained before preceding the study.
- Approval of Obstetrics and Gynecology Department and Ethic Committee in the Faculty of Medicine, Benha University will be obtained before preceding the study
- Informed verbal and written consent will be obtained from the patient before enrollment in the study.

2.6Methods:

Patients will be subjected to the following:

- An informed consent was taken from every patient
- Complete history taking:
- Personal history
- Any complaint
- Obstetric history
- Menstrual history
- Past medical and past surgical history
- Family history
- Complete general examination:
- Vital signs (Blood pressure, Temperature, Heart rate, Respiratory rate).
- Signs of (Pallor, Cyanosis, Jaundice, and Lymph node enlargement).
- Serum fibrinogen was measured at (34-37) weeks of gestation for one time in this study
- The patients who have postpartum hemorrhage were treated with one of the following according to the availability
- Fibrinogen Concentrate.
- Cryoprecipitate.
- Fresh Frozen Plasma.
- All data will be analyzed and compared.

2.7Sample size:

This study base on study carried out by **Zakaria et al., (7)** Epi Info STATCALC was used to calculate the sample size by considering the following assumptions: - 95% two-sided confidence level, with a power of 80%. & an error of 5% odds ratio calculated= 1.115. The final maximum sample size taken from the Epi- Info output was 41. Thus, the sample size was increased to 50 subjects to assume any drop out cases during follow up**Statistical Analysis**

All data were collected, tabulated and statistically analyzed using SPSS 26.0 for windows (SPSS Inc., Chicago, IL, USA). Qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum), mean, standard deviation and median.

The used tests were

- Odds ratio (OR): is a statistic that quantifies the strength of the association between two variables.

3. Results

Table (1) Active management of third stage of labour among the study population

	Study population (n = 50)	
	n	**%**
Active management of third stage of labour		
- Yes		
n (%)	**34**	**68%**
- No		
n (%)	**16**	**32%**

Table (1) showed Active management of third stage of labour among the study population. Number of patients that had Active management of third stage of labour in the study population was 34 (68%).

Table (2) Type of placental delivery among the study population

	Study population (n = 50)	
	n	**%**
Type of placental delivery		
- Complete		
n (%)	**31**	**62%**
- Incomplete		
n (%)	**19**	**38%**

Table (2) showed Type of placental delivery among the study population. Number of patients with Complete Placental delivery in the study population was 31 (62%). Number of patients with Incomplete Placental delivery in the study population was 19 (38%).

Table (3) Bleeding severity among the study population

	Study population (n = 50)	
	n	%
Bleeding severity		
- Sever Bleeding		
n (%)	**20**	**40%**
- Non-sever Bleeding		
n (%)	**30**	**60%**

Table (3) showed Bleeding severity among the study population. Number of patients with Severe Bleeding in the study population was 20 (40%).

Table (4) Measurements of serum fibrinogen levels among the study population

	Study population (n = 50)
Serum fibrinogen levels (g/L)	
Mean ± SD.	**3.87 ± 1.17**
Median (IQR)	**3.9 (3.12 - 4.5)**
Range (Min-Max)	**5.5 (1.5 - 7)**

SD: standard deviation **IQR:** interquartile range

Table (4) showed Measurements of serum fibrinogen levels among the study population. Serum fibrinogen levels in the study population ranged from 1.5 to 7 with mean ± SD = 3.87 ± 1.17.

Table (5) Cause of bleeding among the severe bleeding Group

	Severe bleeding Group (n = 20)	
	n	%
Cause of bleeding		
Decreased serum fibrinogen level		
n (%)	**9**	**45%**
Prolonged labor		
n (%)	**3**	**15%**
Birth canal lacerations		
n (%)	**3**	**15%**
Uterine atony		
n (%)	**3**	**15%**
Uterine rupture		
n (%)	**2**	**10%**

Table (5) showed Cause of bleeding among the severe bleeding Group. Number of patients that had Decreased serum fibrinogen level as the cause of severe bleeding in the study population was 9 (45%). Number of patients that had Prolonged labor as the cause of severe bleeding in the study population was 3 (15%). Number of patients that had Birth canal lacerations as the cause of severe bleeding in the study population was 3 (15%).

Number of patients that had Uterine atony as the cause of severe bleeding in the study population was 3 (15%). Number of patients that had Uterine rupture as the cause of severe bleeding in the study population was 2 (10%).

Table (6) Type of management among the severe bleeding Group

	Severe bleeding Group (n = 20)	
	n	%
Type of management of Sever Bleeding		
Fibrinogen concentrate		
n (%)	**6**	**30%**
Cryoprecipitate		
n (%)	**2**	**10%**
Fresh frozen plasma		
n (%)	**12**	**60%**

Table (6) showed Type of management among the severe bleeding Group. Number of patients that had Fibrinogen concentrate during management in the study population was 6 (30%). Number of patients that had Cryoprecipitate during management in the study population was 2 (10%). Number of patients that had Fresh frozen plasma during management in the study population was 12 (60%).

Table (7) Mortality rate among the severe bleeding Group

	Severe bleeding Group (n = 20)	
	n	**%**
Mortality rate		
Died		
n (%)	**2**	**10%**
Alive		
n (%)	**18**	**90%**

Table (7) showed Mortality rate among the severe bleeding Group. Number of patients who died in the study population was 2 (10%). Number of patients who was still alive in the study population was 18 (90%).

Table (8) Logistic regression with odds ratios and 95% confidence intervals (CI) predicting Bleeding severity

	Bleeding severity			
	OR	**95% CI Lower**	**Upper**	**P**
Serum fibrinogen levels				
	3.392	**1.571**	**7.320**	**0.002**

OR: Odds ratio **CI**: Confidence Interval **p**: p value

Table (8) showed Logistic regression with odds ratios and 95% confidence intervals (CI) predicting Bleeding severity. Odds ratio of Serum fibrinogen levels was 3.392, and the Confidance Interval was Ranged from 1.571 to 7.320.

4. Discussion

In the study in our hands, as regard as regard Active management of third stage of labour among the study population. Number of patients that had Active management of third stage of labour in the study population was 34 (68%). As regard Type of placental delivery among the study population. Number of patients with Complete Placental delivery in the study population was 31 (62%). Number of patients with Incomplete Placental delivery in the study population was 19 (38%).

In the study of Zakaria et al.,[7], regarding No. of patients have Active management of third stage of labour in group A was 40, in group B it was 29 Comparison between both groups showed no significant difference. No. of patients have placenta separated manual 12, with complete separation in 38 pt and incomplete separation in 7 patients in group A, in group B The No. of patients have placenta separated manual 13, with complete separation in 23 pt and incomplete separation in 7 patients. Comparison between both groups showed no significant difference.

Also, Charbit et al., [8] revealed that there was no statistically significant difference between both groups (severe, non-severe PPH) as regard third stage of labour, and management of third stage of labour.

Furthermore, Cortet et al., [9] demonstrated that there was no statistically significant difference between both groups (severe, non-severe PPH) as regard management of third stage of labour.

Postpartum hemorrhage (PPH) is related to several factors and is frequently associated with coagulopathy of dramatic initiation. PPH is a major cause of maternal mortality and morbidity. It causes increased risk of mechanical ventilation, and hysterectomy, and prologns intensive care unit and hospital stays. Coagulation, especially thrombocytopenia, is affected by pregnancy. The procoagulant factors increase and fibrinolysis is reduced. With circulating volume expansion, effective replacement fresh frozen plasma (FFP), red blood cells (RBC), and platelet concentrate (PC) (including coagulation factors) is very important for managing PPH. Fibrinogen is a very important agent for bleeding, and when its concentration decreases, severe surgical blood loss may happen[**10].**

Our results showed that as regard Bleeding severity among the study population. Number of patients with Severe Bleeding in the study population was 20 (40%).

Our results were in agreement with study of Zakaria et al., [7] as they reported that 43% of their studied group had severe PPH (group 2) and 57% had non- severe PPH (group 1).

Similarly, in the study of Charbit et al., [8], 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.

Also, Cortet et al., [9] demonstrated that PPH was severe for 323 of the 738 (43.8%) women included, but not for 415 (56.2%).

Fibrinogen is an essential endogenous component of hemostasis, and its plasma concentration increases during pregnancy. Blood loss results in coagulopathy and reduced fibrinogen levels. Massive transfusion is frequently used to treat hemorrhage but can itself result in dilutional coagulopathy. Indeed, fibrinogen is the first coagulation factor to decrease to a critically low level during major blood loss and replacement with RBC. Observational studies of patients with PPH indicate that a low fibrinogen concentration in the

initial stage of PPH is associated with excessive subsequent bleeding and blood transfusion [**11].**

The present study showed that as regard Measurements of serum fibrinogen levels among the study population. Serum fibrinogen levels in the study population ranged from 1.5 to 7 with mean ± SD = 3.87 ± 1.17.

Whereas in the study of Eldesouky et al., [12], the mean fibrinogen level in both the severe and non-severe groups can be considered to have been normal at diagnosis since the values were within the consensus range of 2–4 g litre21 for nonpregnant women (i.e. 3.4 and 4.2 g litre21). Nonetheless, when they consider normal fibrinogen ejhm.journals.ekb.eg 4193 values among pregnant women, the values for women in the non-severe PPH group corresponded to the 15th percentile, and for the severe group, the 7th. These values are close to those observed by Kaufner et al [13], respectively, 4.4 and 3.3 g litre 21. In Eldesouky et al., [12] study, a fibrinogen level between 2 and 3 g litre 21, usually considered normal, was nonetheless associated with a higher risk of severe PPH. The risk was multiplied by almost 12 when the fibrinogen level was, 2 g litre 21. This result points in the same direction as that of Kaufner et al [13], who showed that fibrinogen had a positive predictive value of 100% for severe PPH at a threshold of 2 g litre21. These observations should encourage obstetrics teams not to accept fibrinogen values established outside of pregnancy as normal during pregnancy, but instead to use as their reference values measured in pregnant women, especially during the third trimester.

Also, Karlsson et al. [14]and Finlayson et al. [15] found that a low fibrinogen level at PPH diagnosis is associated with a higher risk of severe PPH, independs ently of the other laboratory indicators. Fibrinogen is one of the most important components of coagulation. It is the principal factor for the final stage of clot formation, initiated by the intrinsic and extrinsic coagulation pathways. The fibbrinogen level increases during pregnancy from the first through the third trimester. This increase is part of a set of adaptations of the coagulation system that limit the risk of PPH. The mean fibrinogen level during the 9th month is 5 g litre21, well above the 3 g litre21 normally observed outside pregnancy. During PPH, the fibrinogen level decreases rapidly, influenced by two principal mechanisms: the blood loss itself, which induces depletion of coagulation factors, and the consumption of factors associated with coagulation activation.

In practice, bleeding persists not because of the reduced fibrinogen but because the obstetric cause has continued. The reductions in the fibrinogen level can nonetheless contribtutes to the continuation of the bleeding, to the extent that it is the factor that decreases fastest during major bleeding. Kaufner et al [13]reported the speed of this decrease during PPH [13].

Furthermore, Zakaria et al., [7] revealed that the mean Serum fibrinogen levels in group A was 4.2 ± 1.2 SD, in group B it was 3.4 ± 0.9 SD with p value equal 0.002. Comparison between both groups showed high significant difference.

In addition, Charbit et al., [8] stated that at H0, and through H4, women with severe PPH had significantly lower fibrinogen, than women with non-severe PPH.

Moreover, Charbit et al., [8] revealed that the mean fibrinogen concentration at diagnosis was 4.2 g litre21 [standard deviation (SD) 1.2 g litre21] among the patients without worsening and 3.4 g litre21 (SD0.9 g litre21) (P,0.001) in the group whose PPH became severe.

The current study showed that as regard Cause of bleeding among the severe bleeding Group. Number of patients that had Decreased serum fibrinogen level as the cause of severe bleeding in the study population was 9 (45%). Number of patients that had Prolonged labor as the cause of severe bleeding in the study population was 3 (15%). Number of patients that had Birth canal lacerations as the cause of severe bleeding in the study population was 3 (15%). Number of patients that had Uterine atony as the cause of severe bleeding in the study population was 3 (15%). Number of patients that had Uterine rupture as the cause of severe bleeding in the study population was 2 (10%).

However, in the study of Okada et al., [16], the main causes of PPH in their studied group was atonic bleeding followed by uterine inversion.

Whereas in the study of Cortet et al., [9], the main causes of PPH in their studied group was uterine atony followed by incomplete delivery of placenta.

In the study in our hands, as regard type of management among the severe bleeding Group. Number of patients that had Fibrinogen concentrate during management in the study population was 6 (30%). Number of patients that had Cryoprecipitate during management in the study population was 2 (10%). Number of patients that had Fresh frozen plasma during management in the study population was 12 (60%). Regarding Mortality rate among the severe bleeding Group. Number of patients who died in the study population was 2 (10%). Number of patients who was still alive in the study population was 18 (90%).

While in the study of Sahin & Ozkan, [17], group I: Fibrinogen levels were ≤150 mg/dl (n: 31), Group II: Fibrinogen levels were >151 mg/dl (n: 18). In the peroperative period, there was no difference between the 2 groups in terms of RBC transfussion. In intraoperative and ICU admission period, patients in Group I had higher INR, APTT, and PT values than in the other group. Fibrinogen concentration (FC) replacement according to fibrinogen level was given, ranging from to 1 to 6 gr in Group I and 1–2 gr in Group II intraoperatively and at ICU 2–8 gr FC was given in both groups. In the intraoperative and ICU admission period, blood transfusion requirements of patients after fibrinogen replacement were evaluated and there was no statistically significant difference between groups. There were no differrences between

groups in duration of intensive care unit stay, hospital stay, and mechanical ventilation.

Low fibrinogen is associated with excessive bleeding in postpartum hemorrhage. A study showed that prescription of 1 to 4 g of fibrinogen can significantly reduce the need for blood transfusion [18]. Decrease in need for blood transfusion in those receiving fibrinogen compounds was also confirmed [19]. Akbari et al., [20] suggested that patients receiving fibrinogen needed an average of 600–800 cm3 less blood for resuscitation compared to FFP (fresh frozen plasma) and control groups.

Fibrinogen plays a role in platelet aggregation during secondary hemostasis. If blood coagulation factors and fibrinogen levels are depleted due to massive bleeding, secondary hemostatic mechanisms do not work, resulting in coagulopathy. Therefore, maintaining adequate fibrinogen levels is important for hemostasis in patients with massive bleeding. Even though a previous study has reported that fibrinogen was associated with the need for MT in PPH, they do not consider fibrinogen to be an appropriate marker for initiating MT in emergent settings as it takes time to get the results of fibrinogen levels[21].

Our results showed that regarding Logistic regression with odds ratios and 95% confidence intervals (CI) predicting Bleeding severity. Odds ratio of Serum fibrinogen levels was 3.392, and the Confidance Interval was Ranged from 1.571 to 7.320.

Our results were supported by study of Charbit et al., [8] as they reported that the multivariate logistic regression model showed that, at each time point from H1 to H4, Fibrinogen was the only parameter independently and constantly associated with the occurrence of severe bleeding.

In the study of **Niepraschk-von Dollen et al., [22]** , Predelivery fibrinogen levels in women with blood loss C1000 mL (Group III 4.22 ± 0.82 g/L) were significantly lower than in women with blood loss \1000 mL (Group I and Group II 4.67 ± 0.75 g/L; p = 0.004). Predelivery fibrinogen levels did not significantly differ between women with blood loss \500 mL and those with blood loss C500 and \1000 mL (4.67 ± 0.75 vs. 4.67 ± 0.84 g/L; p = 0.985). They further calculated univariate logistic regression to test the predictive value of predelivery fibrinogen for PPH (OR 1.003; 95 % CI 0.7.40–1.360; p = 0.985) and S-PPH (OR 0.405; 95 % CI 0.219–0.750; p = 0.004). The ROC curves supported these results, showing fibrinogen to be a predictor of S-PPH; the area under the curve was 0.665 (95 % CI 0.548–0.782; p = 0.006). For this prediction of blood loss C1000 mL, we identified two cut-off values: fibrinogen level of 4.080 g/L with a specificity of 78.2 % and sensitivity of 54.2 % (positive predictive value, 8.2; negative predictive value, 97.9), and a fibrinogen level of 4.46 g/L with a sensitivity of 70.8 % and specificity of 58.6 % (positive predictive value, 5.8; negative predictive value, 98.2). The area under the curve for blood loss of C500 mL was 0.502 (95 %CI 0.433–0.570; p = 0.959).

5. Conclusion

Fibrinogen is an important endogenous component of hemostasis, and its content in plasma rises throughout pregnancy. Human plasma is used to create fibrinogen concentration (FC), which is virally inactivated and does not need cross-matching or freezing before use. Using RBC, FFP, and PC is connected with a number of problems related to transfusions. Recent research suggests that with FC replacement, PPH may be effectively treated to achieve hemostasis.

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