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Fibrinogen Level as an indicator for aggravation of Primary Post Partum Hemorrhage

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Abstract: Background: postpartum hemorrhage is the leading cause of maternal mortality, accounting for about 35% of all maternal deaths. Though some women are at greater risk for postpartum hemorrhage compared to others, the most common cause is poor contraction of the uterus following childbirth. **Objective:** study the role of serum fibrinogen as a predictor for the severity of postpartum hemorrhage. **Patients and Methods:** this prospective multicenter study was conducted from February 2019 to October 2019 at Department of Obstetrics and Gynecology, al azhar university hospitals. included 100 patients ,characteristics (age, parity, medical history, labour, and delivery) were recorded in both groups (group I (non-severe)and GROUP II (severe PPH) as were their laboratory results (hemoglobin, coagulation data, platelet count, and fibrinogen concentration) and the time blood samples were obtained, to calculate the time relative to hemorrhage diagnosis**. Results:** there was a high significant difference between both group as regard the mean serum fibrinogen levels in group I was 4.2 ± 1.2 SD, in group II it was3.4 ±0.9 SD with p value equal 0.002. PPH was severe for 43 of the 100 (43%) women included group I, but not for 75 (57%) group II. Among the women with severe hemorrhage, no women required embolization, 12 required ligation of the uterine arteries, and 7 hysterectomy; 7 were transferred to intensive care, 37 received transfusions, and 42 had a postpartum hemoglobin level that decreased more than 4 g liter **.Conclusion**: high fibrinogen level in PPH was associated with subsequent aggravaation to severe PPH.serum fibrinogen level indicator for alert to clinicians.
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1. Introduction

Postpartum bleeding or postpartum hemorrhage (PPH) is often defined as the loss of more than 500 ml or 1,000 ml of blood within the first 24 hours following childbirth ***(Weeks, 2015).***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(***Haeri and Dildy, 2012).***The World Health Organization (WHO) defines PPH as "blood loss greater than or equal to 500 ml within 24 hours after birth", and severe PPH as "blood loss greater than or equal to 1 000 ml within 24 hours". ***(Knight et al., 2009).***The most common cause is poor contraction of the uterus following childbirth ***(Weeks, 2015).*** Not all of the placenta being delivered, a tear of the uterus, or poor blood clotting are other possible causes (***Weeks, 2015)*** Risk factors includes 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 Source ***(WHO, 2010; UNICEF, UNFPA, 2012).*** While PPH seems to be most devastating in developing countries, recent studies have shown increasing incidence of PPH in developed countries. A population based retrospective cohort study among 650 000 childbirth hospitalizations between 1999 and 2009 in Ireland showed that the overall rate of PPH increased from 1.5% to about 4% during that time period ***(Lutomski JE, Byrne BM, et al., 2012)***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 (Lee et al 2017).

Aim of the Work:

The aim of the present work is to study the role of serum fibrinogen as a predictor for the severity of postpartum hemorrhage.

2. Patients and Methods:

The study design and patients**:** A prospective, multicenter study design was chosen to conduct this research. The study included patients with PPH. PPH was defined according to **Seacrist et al 2019** as a

blood loss exceeding 500 ml during the 24 h after delivery or a peripartum hemoglobin decrease of more than 20 g litre-1. Severe PPH was defined by the occurrence of one of the following events **(1)**:
- Peripartum hemoglobin decrease ≥40 g litre-1,
- Transfusion of concentrated red cells,
- Arterial embolization or emergency surgery (hysterecctomy, arterial ligation, or other surgery for hemostasis),
- Admission to intensive care, or death.

Ethical consideration:

The study protocol was approved by the Local Ethics Committee of Al-Azhar University and written informed consents were obtained before the study started.

Location and duration of the study:

This prospective multicenter study was conducted from February 2019 to October 2019 at Department of Obstetrics and Gynecology, al azhar university hospitals. The study protocol defined two groups of patients according to the source of bleeding over the 24 hr; non-severe group and sever group. For coagulation assays, blood was collected in vacutainer tubes containing 0.129 mol L)1 sodium citrate, and plasma was separated within 1 h. Analyses were performed two steps; first, routine assays were performed immediately in al azhar university hospitals laboratory and second, the assay of additional biomarkers was carried out centrally by one laboratory using plasma samples stored at routine analysis included blood cell count, Hb level, prothrombin time (PT) expressed as International Normalized Ratio (INR) values, activated partial thromboplastin time (APTT), fibrinogen Plasma levels of fibrinogen were measured using STA Fibrinogen reagent (Diagnostio Stago) or Multi fibrin U (Dade Behring) serial blood samples were collected at H0 and after 1, 2, 4 and 24 h according to **Seacrist et al 2019.**

Inclusion criteria:

Women were eligible if they had PPH, defined as uterine bleeding, occurring in the first 24 h after delivery, persisting after manual exploration of the uterine cavity, and requiring prostaglandin administration.

Exclusion criteria:

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

Variables:

Patient characteristics (age, parity, medical history, labour, and delivery) were recorded in both groups (non-severe and severe PPH) as were their laboratory results (hemoglobin, coagulation data, platelet count, and fibrinogen concentration) and the time blood samples were obtained, to calculate the time relative to hemorrhage diagnosis. Fibrinogen assays were performed with the Clauss fibrinogen method, which has a low coefficient of variation (6–12%) **(8)**.

The cause of the hemorrhage was recorded from the medical chart, as reported by the medical team that cared for the patient. Several causes could be mentioned for the same patient.

Statistical analysis

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done:

Independent-samples t-test of significance was used when comparing between two means.

Chi-square (x2) test of significance was used in order to compare proportions between two qualitative parameters.

The confidence interval was set to 95% and the margin of error accepted was set to 5%. The p-value was considered significant as the following:

Probability (P-value):
- P-value <0.05 was considered significant.
- P-value <0.001 was considered as highly significant.
- P-value >0.05 was considered insignificant.

3.Results:

Table 1: comparison between both group regard no. of patients and different variability Showing highly significant differences as regard mean serum fibrinogen level.

		Group I		Group II		P value
		N	%	N	%	
No of PPH cases		57	57	43	43	
Parity	Primiparous	23	40.4	20	46.5	0.538
	Multiparous	34	59.6	23	53.5	
Previous hemorrhage	Yes	6	10.5	3	7	0.539
	No	51	89.5	40	93.	
Previous coagulation disorder	Yes	1	1.8	0	0	0.383
	No	56	98.2	43	100	
Active management of third stage of labor	Yes	40	70.2	29	67.4	0.770
	No	17	2908	14	3206	
Serum fibrinogen levelsMean±SD		4.2±1.2		3,4±0.9		0.002

Table 2: comprehensive study for serum fibrinogen level and its sensitivity and specificity

	Sensitivity (95% CI)	specificity (95% CI)
2 g litre	12.4 (8.79-15.98)	99.3 (1-98.4)
3 g litre	35.5 (30.7-41.1)	89.9 (85.9-91.9)

4. Discussion

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 (***Haeri and Dildy, 2012).*** While PPH seems to be most devastating in developing countries, recent studies have shown increasing incidence of PPH in developed countries. A population based retrospective cohort study among 650 000 childbirth hospitalizations between 1999 and 2009 in Ireland showed that the overall rate of PPH increased from 1.5% to about 4% during that time period ***(Lutomski JE, Byrne BM, et al., 2012).*** Active management of the third stage is a method of shortening the stage between when the baby is born and when the placenta is delivered (***Peña-Martí and Comunián-Carrasco, 2007).*** This stage is when the mother is at risk of having a PPH. Active management involves giving a drug which helps the uterus contract before delivering the placenta by a gentle but sustained pull on the umbilical cord whilst exerting upward pressure on the lower abdomen to support the uterus (***Peña-Martí and Comunián-Carrasco, 2007).***

The mean No. of primiparous in group A was 23 and in group B it was 20. The mean No. of multiparous in group A was 34 and in group B it was 23 comparisons between both groups showed no significant difference. The No. of patients have twin pregnancy in group A was 2, in group B it was 2Comparison between both groups showed no significant difference. ***Karlsson et al. 2016*** and ***Finlayson et al. 2019*** found that a low fibrinogen level at PPH diagnosis is associated with a higher risk of severe PPH, independently 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 fibrinogen 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 litre 21 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 our study, 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 litre 21 for non-pregnant women (i.e. 3.4 and 4.2 g litre 21). Nonetheless, when we 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* 2017.**respectively, 4.4 and 3.3 g litre 21. In our study, a fibrinogen level between 2 and 3 g litre21, 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.* 2017**, who showed that fibrinogen had a positive predictive value of 100% for severe PPH at a threshold of 2 g litre 21. 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.

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 contributes to the continuation of the bleeding, to the extent that it is the factor that decreases fastest during major bleeding. **Kaufner *et al.* 2017** reported the speed of this decrease during PPH. In that study, as in ours, the only coagulation variable that remained independently associated with severe hemorrhage was the fibrinogen level**.**

In our study The No. of patients has simple vaginal delivery in group A was 49, in group B it was 34. The No. of patients have instrumental vaginal delivery in group A was 8, in group B it was 9 comparison between both groups showed no significant difference.

Seacrist et al. 2019 who found the 165 cases identified, 51% (85/165) were vaginal, 19% (31/165) operative vaginal, and 30% (49/165) caesarean. The leading cause of haemorrhage was uterine atony.

Overall, 62% of the cases received appropriate care, 24% received totally inadequate care and 14% mixed care.

In the study by **Kaufner *et al.* 2017,** on the other hand, the variation between the initial hemoglobin level and the level at diagnosis did not differ significantly between the two groups **(9).**

In our study, the median delay before the assay was very similar in both groups, which suggests the same reaction speed by the teams, and therefore, probably, identical or very similar initial rates of bleeding. In any case, in our study, the multivariate analysis suggests that a low fibrinogen level is independently associated with an increased risk that the hemorrhage will become severe. Nevertheless, a severe PPH may occur with a normal fibrinogen level. Clinical studies in intensive care units and experimental data also suggest that the early utilization of fibrinogen makes it possible to reduce the use of other blood derivatives. There is no consensus threshold for a fibrinogen transfusion during hemorrhage. The Royal College of Obstetricians and Gynaecologists recommends cryoprecipitate infusion when fibrinogen is, 1 g litre. The Club d'Anesthesistes et de Re´ animateursen Obstetrics, on the other hand, recommends fibrinogen infusion when the level decreases below 2 g liter . A recent work in vitro shows that a concentration of at least 2 g liter of fibrinogen is necessary for optimal clot formation. The study suggests that even a threshold of 3 g liter could be useful. In our study, a fibrinogen level below 2 g liter multiplied the risk of development into severe PPH by 11, independently of other laboratory results. The mean median time used for collection of the 1st sample in group A was 45.5 minutes ±4.2 SD, in group B it was 40.2 minutes ± 3.8 sd. Comparison between both groups showed high significant difference.

Gaucher *et* al. 2019 who found the mean rate of severe PPH was 1.64% (SD 0.80) in the intervention units and 1.65% (SD 0.96) in control units; difference not significant. Some elements of PPH management were applied more frequently in intervention units- help from senior staff (P = 0.005), or tended to - second-line pharmacological treatment (P = 0.06), timely blood test (P = 0.09). Management of patients with PPH requires rapid multidisciplinary obstetric and medical management. Nonetheless, coagulation disorders are often underestimated and an optimal and rapid correction might improve obstetric management. The British Royal College of Obstetricians and Gynaecologists suggests calling for help from a specialist in clinical hemostasis in the case of severe PPH. Bedside tests on thromboelastometry allow rapid measurement, and even nearly continuous monitoring, of the fibrinogen level. They may contribute to improving the management of secondary coagulopathies by allowing real-time evaluation. Nonlethal less, the early correction of fibrinogen has never been assessed in obstetrics, and there is no consensus about it.

Conclusion:

The fibrinogen level at PPH diagnosis is a marker of the risk of exacerbation and should serve as an alert to clinicians.

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