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Serum Fibrinogen as Adetection of Severity of Postpartum Hemorrhage

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ABSTRACT

Background: 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. The most common cause is poor contraction of the uterus following childbirth. However, the placenta being delivered, a tear of the uterus or poor blood clotting are other possible causes.

Objective: the aim of the present work was to 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 2017 to October 2017 at Department of Obstetrics and Gynecology, Sayd Galal Hospital, Al-Azhar University.

Results: PPH was severe for 43 of the 100 (43%) women included, but not for 57 (57%). Among the women with severe haeb hemorrhage, no women required embolization, 12 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 litre. None of the women died.

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

Keywords: Fibrinogen, post partum Hemorrhage

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 [(1,2)].

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[(3)].

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), vary little [(4)].

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[(5)].

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 [(1, 6)].

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 [(7)].

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.

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 **Cortet *et al.*** [(1)] 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)]:

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- 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 2017 to October 2017 at Department of Obstetrics and Gynecology, Sayd Galal Hospital, Al-Azhar University.

The study protocol defined two groupe of patiants acoording to the sourse 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 the Sayd Galal Hospital 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 Multifibren U (Dade Behring) serial blood samples were collected at H0 and after 1, 2, 4 and 24 h according to **Cortet *et al.*** [(1)].

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. Fit brinogen 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 (x^2) 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.

RESULTS

Table (1): Comparison of study groups as regards No. of pt used in both groups

PPH	N	%
Non severe (GI)	57	57
Severe (GII)	43	43
Total	100	100

Table (2): Comparison of study groups as regards parity of the pt

Parity		Group I		Group II		Total	
		N	%	N	%	N	%
Primiparous		23	40.4	20	46.5	43	43
Multiparous		34	59.6	23	53.5	57	57
Total		57	100	43	100	100	100
Chi-square	X^2	0.380					
	P-value	0.538					

Table (3): showed the mean No. of primiparous in group A was 23 in group B it was 20, The mean No. of multiparous in group A was 34 in group B it was 23 Comparison between both groups showed no significant difference.

Table (3): Comparison of study groups as regards presence of twin's pregnancy

Twinning		Group I		Group II		Total	
		N	%	N	%	N	%
Singleton		55	96.5	41	95.3	96	96
Twins		2	3.5	2	4.7	4	4
Total		57	100	43	100	100	100
Chi-square	X^2	0.083					
	P-value	0.773					

Table (3): showed the No. of patients have twin pregnancy in group A was 2, in group B it was 2 Comparison between both groups showed no significant difference.

Table (4): Comparison of study groups as regards mode of delivery

Delivery		Group I		Group II		Total	
		N	%	N	%	N	%
Simple vaginal delivery		49	86.0	34	79.1	83	83
Instrumental vaginal delivery		8	14.0	9	20.9	17	17
Total		57	100	43	100	100	100
Chi-square	X^2	0.826					
	P-value	0.363					

Table (4): showed the No. of patients have 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.

Table (5): Comparison of study groups as regards presence of episiotomy

Episiotomy		Group I		Group II		Total	
		N	%	N	%	N	%
Yes		21	36.8	21	48.8	42	42
No		36	63.2	22	51.2	58	58
Total		57	100	43	100	100	100
Chi-square	X^2	1.448					
	P-value	0.229					

Table (5): showed the No. of patients have episiotomy in group A was 21, in group B it was 21 Comparison between both groups showed no significant difference.

Table (6): Comparison of study groups as regards presence of severe perineal tears

Severe perineal tears		Group I		Group II		Total	
		N	%	N	%	N	%
Yes		2	3.5	3	7.0	5	5
No		55	96.5	40	93.0	95	95
Total		57	100	43	100	100	100
Chi-square	X^2	0.621					
	P-value	0.431					

Table (6): showed the No. of patients have severe perineal tears in group A was 2, in group B it was 3 Comparison between both groups showed no significant difference.

Table (7): Comparison of study groups as regards presence of active management of third stage of labour

Active management of third stage of labour		Group I		Group II		Total	
		N	%	N	%	N	%
Yes		40	70.2	29	67.4	69	69
No		17	29.8	14	32.6	31	31
Total		57	100	43	100	100	100
Chi-square	X^2	0.086					
	P-value	0.770					

Table (7): showed the 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.

Table (8): Comparison of study groups as regards mode of delivery of placenta

Delivery of placenta		Group I		Group II		Total	
		N	%	N	%	N	%
Manual		12	21.1	13	30.2	25	25
Complete		38	66.7	23	53.5	61	61
Incomplete		7	12.3	7	16.3	14	14
Total		57	100	43	100	100	100
Chi-square	X^2	1.804					
	P-value	0.406					

Table (8): showed the No. of patients have placenta separated manual 12, with complet 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 complet separation in 23 pt and incomplete separation in 7 patients. Comparison between both groups showed no significant difference.

Table (9): Comparison of study groups as regards serum fibrinogen levels

Groups	Serum fibrinogen levels	T-test	
	Mean ± SD	t	P-value
Group I	4.2 ± 1.2	3.771	0.002*
Group II	3.4 ± 0.9		

Table (9): showed 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.

Table (10): Comparison of study groups as regards median time used for collection of the 1st sample

Groups	Median time	T-test	
	Mean ± SD	t	P-value
Group I	45.5 ± 4.2	6.617	<0.001**
Group II	40.2 ± 3.8		

Table (10): showed the mean median time used for collection of the 1st sample in group A was 45.5 minuts ±4.2 SD, in group B it was 40.2 minuts ± 3.8 sd. Comparison between both groups showedhigh significant difference.

DISCUSSION

PPH remains a major cause of maternal morbidity and mortality related to childbirth. In most cases, PPH is due to bleeding from the placental site, which is due to uterine atony. Because the flow of blood is high in the uterine arteries at the end of pregnancy, uterine atony can rapidly result in severe hemorrhage. Protocols for stepwise activemanagement of PPH improve outcome [1,9].

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

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 comparison between both groups showed no significant difference.

The No. of patients have twin pregnancy in group A was 2, in group B it was 2 Comparison between both groups showed no significant difference.

Cortet *et al.* [1] and **Weeks** [5] 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 coaguilation factors, and the consumption of factors associated with coagulation activation [1].

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 litre21 for non-pregnant women (i.e. 3.4 and 4.2 g litre21). Nonetheless, when we consider normal fi) brinogen

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 **Charbit *et al.* [9],** 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 litre21. This result points in the same direction as that of **Charbit *et al.* [9]**, who showed that fibrinow gen 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.

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. **Charbit *et al.* [9]** 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 have 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.

Bouvier-Colle *et al.* [10] who foune 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 **Charbit *et al.* [9]**, 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 sugb gests 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´ animateurs en Obstetrics , on the other hand, recommends fibrinogen infusion when the level decreases below 2 g litre . A recent work in vitro shows that a concentration of at least 2 g litre of fibrinoo gen is necessary for optimal clot formation. The study sugT gests that even a threshold of 3 g litre could be useful[1, 11].

In our study, a fibrinogen level below 2 g litre 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 minuts ±4.2 SD, in group B it was 40.2 minuts ± 3.8 sd. Comparison between both groups showedhigh significant difference.

Deneux-Tharaux *et al.* [12] who foune 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 multidisM ciplinary obstetric and medical management. Nonetheless, coagulation disorders are often underestimated and an optimal and rapid correction might improve obstetric mano agement. 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. Nonethec less, the early correction of fibrinogen has never been assessed in obstetrics, and there is no consensus about it [1].

CONCLUSION

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

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