Scientific Research Publishing

Open Journal of Obstetrics and Gynecology, 2021, 11, 369-380
https://www.scirp.org/journal/ojog
ISSN Online: 2160-8806
ISSN Print: 2160-8792

Approach to Massive Bleeding in Obstetrics: Changing Management Paradigms Oriented by Early Goals [Early Goal Therapy in Postpartum Hemorrhage]

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How to cite this paper: Olaya-Garay, S.X., Hernandez, J.D., Murillo-Garcia, D.R. and Garay-Fernández, M.A. (2021) Approach to Massive Bleeding in Obstetrics: Changing Management Paradigms Oriented by Early Goals [Early Goal Therapy in Postpartum Hemorrhage]. *Open Journal of Obstetrics and Gynecology*, **11**, 369-380.
https://doi.org/10.4236/ojog.2021.114037

Received: March 16, 2021
Accepted: April 19, 2021
Published: April 22, 2021

Abstract

Recent findings: Approximately 830 women die every day worldwide as a result of complications related to pregnancy or childbirth with obstetric hemorrhage that remains a major cause of maternal morbidity and mortality. A systematic analysis by the World Health Organization [WHO] on the global causes of maternal deaths from 2003 to 2009 found that bleeding was the leading direct cause of maternal mortality followed by hypertensive disorders and sepsis. Overall, bleeding accounted for 27.1% of all maternal deaths worldwide. The need to implement strategies that mitigate the impact of bleeding in this clinical scenario is increasingly growing. Purpose of review: The purpose of this review is to propose a management strategy based on goals established through dynamic coagulation assessment. Summary: Effective management of obstetric hemorrhage requires rapid recognition, rapid response and mobilization of the multidisciplinary team. Volumetric resuscitation, hemodynamic stability, as well as the simultaneous identification and treatment of the source of bleeding and the resolution of coagulopathy in the shortest possible time remain the cornerstones of the management of Postpartum Hemorrhage (PPH).

Keywords

Bleeding, Coagulopathy, Postpartum, Fibrinogen

1. Introduction

Postpartum hemorrhage is the main cause of maternal mortality worldwide, affecting pregnant patients primarily in low-income countries, mostly associated with healthcare access difficulties, lack of prenatal care, young age, amongst others. The advanced management of this entity is a challenge for healthcare professionals. The ACOG [American College of Obstetricians and Gynecologists [ACOG]] defines postpartum hemorrhage as a cumulative blood loss of 1000 ml or greater, accompanied by signs or symptoms of hypovolemia within the first 24 hours postpartum [including intrapartum hemorrhage], irrespectively of the way of birth [1]. The occurrence of this pathology is associated with factors occurring in pregnant women. Major physiological changes occur during pregnancy. One of these changes is defined by clotting alterations, with increased procoagulant factors [VI, VIII, IX, X, fibrinogen], decreased concentration of nature anticoagulants factors, such as proteins C and S, associated with the increase of fibrinolysis inhibitors such as TAFI [thrombin-activatable fibrinolysis inhibitor], PAI [plasminogen activator inhibitor] 1 and 2 [placental] producing an initial hypercoagulability state, which, depending upon the magnitude of pre and postpartum changes, could increase the risk of maternal hemorrhage and mortality [2]. Additionally, fibrinogen value during gestation is physiologically greater compared with the general population, by 4 - 6 gr/L [3]. It is important to consider that the minimum fibrinogen threshold assuring adequate hemostasis is 50% of the normal value, compared to 25% of the other factors; a mild decrease in fibrinogen will have a major impact on coagulopathy and bleeding development [4]. Therefore, the early replacement of fibrinogen is vital in the treatment of coagulopathy in order to avoid its progression during pregnancy, delivery or postpartum [5].

2. Definition

PPH [postpartum hemorrhage] refers to the excessive bleeding [more than 500 ml] in the genital tract following the delivery. However, women with Cesarean delivery, generally lose more blood; therefore a higher cut-off point of 1000 ml for a significant blood loss, is used [6] [7]. Massive PPH refers to the loss of 30% - 40% of the patient's blood volume; in this sense, the estimation of blood loss may be imprecise, so the American College of Obstetricians and Gynecologists has defined it as a drop in the hematocrit value of >10% compared to its prepartum value [1].

PPH is classified as primary if bleeding occurs within the first 24 hours following the delivery, and secondary if bleeding occurs between 24 h and 12 weeks following the delivery.

In addition to the mentioned classification, predisposing factors of hemodynamic decompensation shall be considered in the clinic scenario despite the loss of less blood volume, *i.e.* women with previous anemia or low Body Mass Index [BMI] [8]. Therefore, PPH diagnosis remains a subjective clinical assessment, including any degree of blood loss threatening the woman's hemodynamic stability [9].

3. Disseminated Intravascular Coagulopathy

Disseminated Intravascular Coagulopathy [DIC] may occur in 30% of patients coursing with major obstetric hemorrhage, which could be triggered by several causes: postpartum hemorrhage, placental abruption, preeclampsia-HELLP, retained dead fetus, fatty liver of pregnancy, amniotic fluid embolism and sepsis. On the other hand, non-pregnancy-related causes can be trauma, neoplasms, and sepsis [10] [11].

DIC can lead to a high spectrum of phenomena. On the one hand, the tissue factor, clotting factors and fibrinogen activation triggering the development of vascular thrombosis; and on the other hand, it is associated with the loss, dilution or dysfunction of clotting factors and fibrinogen, which can result in uncontrollable bleeding events and death. DIC mechanisms in pregnant women are related to the loss of clotting factors [obstetric hemorrhage], endothelial activation of coagulation [preeclampsia], trophoblast disruption with an excess of tissue factor [placental abruption or amniotic fluid embolism] or dysfunction of the hepatic synthesis of clotting factors [fatty liver]. By several pathways, those mechanisms lead to the final outcome, which is the fibrinogen decrease. [10].

Regarding the DIC diagnosis in pregnancy, there are some difficulties in the interpretation of the clotting test due to the dynamic changes occurring in pregnancy, which imply a challenge in the clinical approach. Of evaluable clotting factors, the fibrinogen has a more rapid decrease being an early indicator of bleeding severity and progression to DIC. Levels below 2 gr/L in the pregnant woman are associated with greater bleeding, requirements of massive transfusions, requirements of surgical procedures, and procedures such as embolization and admission to ICU [12] [13] [14].

Traditional scores of DIC diagnosis have a high positive predictive value for the diagnosis of non-pregnant women. However, they have not been validated in pregnant women [15] [16]. A specific score for pregnant women has been recently proposed, which has shown to have high sensitiveness and specificity for DIC diagnosis. When patients with placental abruption, preeclampsia and postpartum hemorrhage were included in the model, the area under the curve of ROC analysis was 0.969 [p, 0.001] and the cut-off point of >26 points, had 85.4% of sensitiveness and 96.8% of specificity, establishing a greater discriminative power compared to traditional scores for DIC diagnosis when extrapolated to pregnant women. This score includes the assessment of clotting times and fibrinogen factor value as basic elements for the diagnosis, demonstrating its importance in the detection of the changes identifying the occurrence of DIC in this patient group [17] (**Table 1**).

4. Utility of Viscoelastic Testing in Postpartum Hemorrhage

Principles ruling viscoelastic tests assessing the functional properties in clot formation, fibrin polymerization and fibrinolysis process, have been developed since 1948. ROTEM or thromboelastometry test was developed in 1990, being

Table 1. DIC score in pregnant women was developed by Erez O, *et al.* Being able to demonstrate the increased risk of presenting disseminated intravascular coagulation based on three basic elements, prothrombin time (PT), platelets count and fibrinogen concentration. *Score > 26 points: High probability of DIC (OR 26.1, AUC 0.98; 95%CI: (0.96; 0.99)) [10] [11].

Parameter	Values	Score
PT difference (seconds)	<0.5 seconds	0
	0.5 - 1.0 seconds	5
	1.0 - 1.5 seconds	12
	>1.5 seconds	25
Platelets	>185,000/mm^3	0
	100,000 - 185,000/mm^3	1
	50,000 - 100,000/mm^3	2
	<50,000	1
Fibrinogen	>4.5 gr/L	0
	4.0 - 4.5 gr/L	1
	3.0 - 4.0 gr/L	6
	3.0 gr/L	25

ruled by the same principles of traditional thromboelastography, with no impact from external stimuli or vibration which also allows the assessment of each component of the clot formation, such as clotting factors by extrinsic or intrinsic [EXTEM o INTEM] pathways, platelet function [EXTEM], fibrin polymerization [FBTEM], fibrinolysis process [APTEM], as well as the heparin effect in the clot formation [HEPTEM]. It also assesses the following parameters: CT-CFT [clotting time and clot formation time], MCF [maximum clot firmness], A5 [amplitude at 5 minutes], ML [maximum lysis percentage [%]] [18].

ROTEM offers several advantages over traditional tests, [PT, PTT, Platelets, Fibrinogen]: it takes less time to outcomes [5 minutes], allows the dynamic assessing and correction of the specific clotting disorder, reduces unnecessary transfusions, minimizes the risk of transfusion-related adverse reactions [19] [20]. Additionally, ROTEM provides information of fibrinogen function by 5-minute amplitude in FIBTEM [FIBTEM A5], which is closely correlated with early fibrin polymerization and serum fibrinogen. It is a priority measurement of assessment for the early recognition of fibrinogen disruption [21] allowing—when abnormally low—the immediate administration of hemo-components [cryoprecipitates], fibrinogen concentrate or hemostatic invasive measurements, to control the hemorrhage.

ROTEM values in pregnancy have been determined to have several changes when compared to the non-pregnant population. If clotting time [CT] is shorter, amplitude [A] and maximum clot firmness [MCF] are greater and fibrinolysis remains unchanged [ML under 15%]. This proves the hypercoagulable condition

of pregnancy [22] [23]. Therefore, ROTEM values of clinic utility in the decision-making process, such as EXTEM [CT and A5] and APTEM [% ML] do not change compared to the non-pregnant population. While FIBTEM [A5] are higher during pregnancy with a cut-off point of A5 of 15 mm compared to A5 of 10 mm in non-pregnant women [24] [25] (**Table 2**). Value for hemostatic intervention considered in several protocols in pregnant women is FIBTEM A5 under 12 mm [or fibrinogen below 2 gr/dl]. Fibrinogen replacement from these cut-off points is correlated to a lower magnitude of bleeding and less need for hemoderivative transfusions [26] [27].

When comparing ROTEM test with traditional clotting tests, the only traditional test highly correlated is the fibrinogen quantification with FIBTEM-A5-A10-A20 value [5, 10 and 20 minutes], while PT and PTT have a low correlation with EXTEM or INTEM values [22].

Therefore the level for hypofibrinogenemia during pregnancy has been defined as a value under 2 gr/L or as a FIBTEM5min value < 12 mm, with an adequate correlation between serum values and functional assessment by thromboelastometry [21] [28].

5. Management of Hypofibrinogenemia

There are 3 plasma derivative products that could be used for the replacement of fibrinogen levels [29]: fresh frozen plasma [FFP], cryoprecipitates and fibrinogen concentrate. Fibrinogen replacement using fresh frozen plasma requires a longer replacement time due to the need of unfreezing and process the sample, establish the group compatibility, associated with the administration of high volumes, risk of pulmonary edema, transfusion-associated circulatory overload—TACO [30] or transfusion-related acute lung injury—TRALI [31]. On the other side, fibrinogen replacement is low or null, given the limited quantity of this factor contained in the plasma. Each 250 ml bag has 250 - 500 mg with a concentration of only 1 - 2 gr per liter; therefore, coagulopathy will not be corrected even with the administration of high volumes of this hemoderivative; by the contrary, it will cause greater dilution, which will result in the worsening of the coagulopathy. A dose of 33.7 ml/kg will be required to achieve an increase of 1 gr/L in serum fibrinogen [32] [33].

Table 2. ROTEM® parameters defining interventions in the associated coagulopathy. (EXTEM® [tissue factor activation], FIBTEM® [tissue factor activation with platelet inhibition], and APTEM® [tissue factor activation with tranexamic acid/aprotinin]) [18] [27].

ROTEM® parameter	Assessed component	Pregnant woman value	Non-pregnant woman value	Replacement component
FIBTEM-A5	Fibrinogen	Above 15 mm	Above 10 mm	Fibrinogen concentrate Cryoprecipitate
EXTEM-A5	Platelets	Above 47 mm	Above 47 mm	Platelets
EXTEM-CT	Clotting factors	Below 55 seconds	Below 55 seconds	Fresh frozen plasma Prothrombin complex
APTEM-ML%	Fibrinolysis	Below 15%	Below 15%	Tranexamic acid

The use of cryoprecipitates requires a lower volume of administration; each bag contains 10 and 20 ml with approximately 150 mg of fibrinogen and the concentration is 12 - 15 gr per liter. Its main disadvantage is the need to unfreeze, compatibility, procedure, risk of infections and its scant availability.

Fibrinogen concentrate [5], is produced by the plasma fractionation in a great plasma human pool; it includes viral removal and inactivation processes [minimizing the risk of viral infection], its presentation is a lyophilized powder; during the process, all donor's antigens and antibodies are removed reducing the risk of transfusion-related reactions, with a low risk of thrombotic events. In addition to the detailed characteristics, it has advantages in terms of its low administration volume and rapid preparation, with no need to unfreeze. Fibronogen concentrate presentation is 1 gr per each 50 ml, with a concentration of 20 gr/L liter. Serum fibrinogen increase after the administration of 1 gr of fibrinogen is between 0.25 - 0.35 gl/L. Additionally, the impact of fibrinogen concentrate infusion has been studied in FIBTEM correction, evidencing that a vial of fibrinogen concentrate [1 gr], can achieve an increase of 2 mm in FIBTEM; a dose of 25 - 30 ml/kg increases 4 mm. Therefore, regular administration of 3 - 4 gr of fibrinogen as the initial dose in the case of obstetric haemorrhage and hypofibrinogenemia is recommended [34] (**Table 3**).

The role of fibrinogen has been assessed in several sceneries of coagulopathy in pregnant women, but the greater portion of the recently cumulative evidence comes from the postpartum hemorrhage [5].

6. Obstetric Hemorrhage Postpartum

The use of fibrinogen concentrate in postpartum haemorrhage has been the most studied scenario of this component. However, its benefit has not been proven in terms of transfused volume and blood loss when fibrinogen concentrate is administered to a patient with normal fibrinogen values [>2 g/L] [18] [26]. On the contrary, under the evidence of hypofibrinogenemia during bleeding [Fibrinogen < 2 gr/L or FIBTEM < 12 mm], the use of fibrinogen concentrate generates a dose-dependent increase in fibrinogen serum concentration, reduces the need for fresh frozen plasma and reduces the incidence of pulmonary edema [35] [36]. Considering useful the use of fibrinogen concentrates in cases of severe haemorrhage and coagulopathy.

Table 3. Sources of factors (fibrinogen) replacement. Fresh frozen plasma, cryoprecipitates, fibrinogen concentrate. Sour [30] [31] [32] [33].

Fibrinogen replacement	Volume per bag	Fibrinogen contents	Fibrinogen concentration	Increase of serum fibrinogen
Fresh frozen plasma	250 - 300 mL	250 - 500 mg	1 - 2 gr/L	15 - 30 mL/kg to increase 1 gr/L
Cryoprecipitate	10 - 20 mL	150 mg	12 - 15 gr/L	15 - 20 U to increase 1 gr/dL
Fibrinogen concentrate	50 mL	1000 mg	20 gr/L	50 mL increases 0.25 to 0.35 gr/L

Mercier and Bonnet [37] assessed the optimum use of blood derivatives considered the indications of the pro-hemostatic drugs in obstetric haemorrhage, establishing the utility of the previous transfusion of packed red blood cells and platelets, and in defined proportions preventing the dilutional coagulopathy during obstetric haemorrhage. Also, the administration of fibrinogen concentrate, when fibrinogen plasma level remains below 1.0 g/L, and even as soon as evidenced as below 1.5 a 2.0 g/L, the addition of tranexamic acid [1 g], a useful and safe measure. Data on proactive platelets administration are insufficient to recommend this practice routinely.

7. Amniotic Fluid Embolism

The utility of fibrinogen concentrate in amniotic fluid embolism has been evidenced from case reports. A characteristic of amniotic fluid embolism is its catastrophic manifestation during labor with cardiovascular collapse, hypoxemia, cardiac arrest and severe coagulopathy, being the latter one a pathognomonic indication of the entity. Pathophysiology of coagulopathy is related to the exaggerated consumption of clotting factors and hyperfibrinolysis [38] [39]. Marked hypofibrinogenemia [serum values or even non-quantifiable FIBTEM 5] has been observed, with successful improvement by the administration of high doses of fibrinogen concentrate of up to 14 gr, obtaining a rapid replacement of fibrinogen serum levels and thromboelastometry and the successful correction of coagulopathy [39].

8. Placental Abruption

Placental abruption is an entity characterized by the consumption and loss of clotting factors. It is manifested as severe or hidden obstetric bleeding, associated with intrauterine death and early coagulopathy. Lyophilized fibrinogen concentrate has shown to be efficient, safe, and free of adverse reactions [thrombosis or anaphylaxis] with an easy dosage. Furthermore, placental abruption was the only group not reporting deaths following the fibrinogen replacement, which suggests a probable benefit in terms of survival [40]. A series of cases using the ROTEM test and traditional tests driving the coagulopathy therapy by placental abruption, evidenced a marked fibrinogen decrease in all cases [Fibrinogen < 1 gr/L or FIBTEM < 5 mm]. FFP was used in two cases, being ineffective to correct the coagulopathy and replacing the fibrinogen, requiring high plasma volumes [8 - 12 units] with the additional issue of overload, pulmonary edema, mechanical ventilation and admission to ICU. On the other side, fibrinogen concentrate was used in 2 patients for the management of coagulopathy, with a rapid correction of fibrinogen levels and coagulopathy improvement with no overload, no pulmonary edema or need of mechanical ventilation [41].

9. Fatty Liver of Pregnancy

Fatty liver is a rare condition in pregnancy, characterized by acute liver failure

more frequently occurring in the 3rd trimester with high mortality when not treated early. Coagulopathy is one of the most frequent of its manifestations, characterized by hypercoagulability and hypofibrinogenemia. In a case report of a patient with fatty liver, a severe status of hypofibrinogenemia was evidenced using the ROTEM test and fibrinogen serum levels, achieving a complete and rapid fibrinogen replacement improving the coagulopathy, with no need of fresh plasma, cryoprecipitate or other components, *i.e.*, with none of the complications associated to the hemoderivative transfusions [42]

Clotting assessment in several sceneries of obstetric bleeding, defines the priorities for its management, including the early recognition of hypofibrinogenemia, the early use of antifibrinolytic agents [especially in postpartum bleeding] and the efficient replacement of fibrinogen. Interventions aimed to mitigate the impact of coagulopathy in the morbidity and mortality related to this patient group.

10. Conclusions

Postpartum hemorrhage continues to be the most common cause of maternal mortality worldwide. Interventions aimed at improving outcomes should be based on early evaluation, surgical and medical control, and re-evaluation of the coagulation compromise (**Figure 1**).

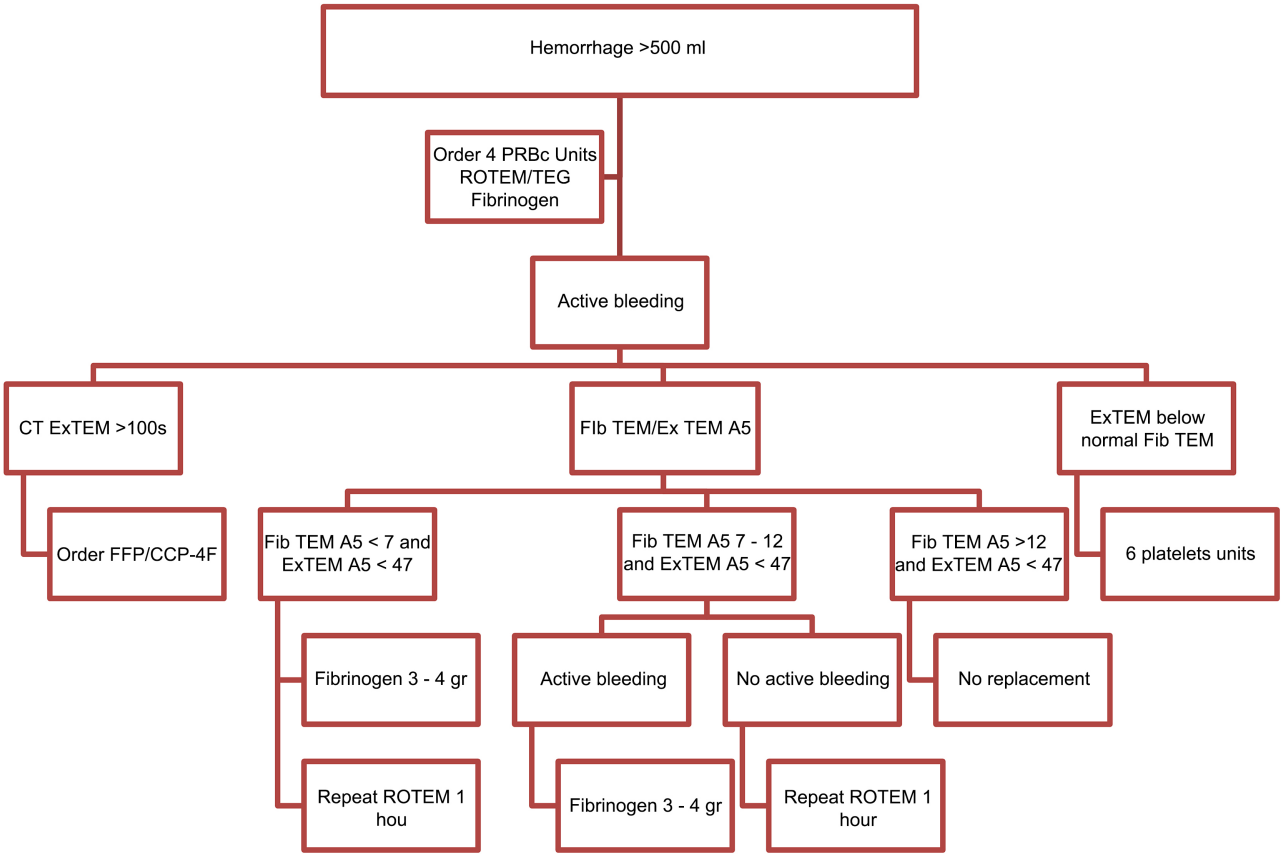

Figure 1. Algorithm proposed for the management of postpartum bleeding.

Uterine atony is the most common cause of postpartum hemorrhage with more and more frequent cases. However other causes include trauma to the genital tract [*i.e.*, vaginal or cervical lacerations], uterine rupture, retained placental tissue, and maternal coagulation disorders.

11. Key Points

- The proper use of tranexamic acid has been shown to improve outcomes in the treatment of established postpartum hemorrhage.
- Viscoelastic testing helps guide the administration of factor concentrates or transfusion, which can result in decreased use of blood products and better outcomes. Detecting low fibrinogen levels should be a priority.
- The use of adjuvant pharmacological agents and clotting factor concentrates, along with appropriate blood product transfusion and surgical treatment, is becoming part of the standard of care and will likely improve maternal outcomes. 4.1. Authors and Affiliations template is designed so that author affiliations are not repeated each time for multiple authors of the same affiliation. Please keep your affiliations as succinct as possible (for example, do NOT post your job titles, positions, academic degrees, zip codes, names of building/street/district/province/state, etc.). This template was designed for two affiliations.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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