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Haemostatic support in postpartum haemorrhage: A review of the literature and expert opinion

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Postpartum hemorrhage (PPH) is still the main universal cause of death associated to pregnancy, as well as the cause for one quarter of maternal deaths, most of them in countries with low resources, but also in first-world countries.

In case of abnormal puerperal bleeding, typically obstetrics, resuscitation, and coagulopathy treatment measures are simultaneously implemented. An early diagnosis of coagulopathy is essential, since it contributes to the progression toward massive hemorrhage.

The first barrier in the PPH scenario is precisely its definition, since there are no universal criteria. It is based on the bleeding volume, which is hart to monitor and can lead to delays in the treatment.

A multidisciplinary approach should be considered to define PPH, taking into account vital signs, clinical symptoms, and changes in coagulation and in the hemodynamic situation.

Furthermore, standardized treatment algorithms and massive hemorrhage protocols should be developed in order to minimize the morbidity and mortality risk and to improve the progression of PPH cases.

Several pregnancy-specific factors are involved in the pathophysiology of PPH. Uterine blood flow is increased, and it reaches up to 10% of cardiac output, thus furthering the risk of massive hemorrhage after delivery.

In contrast, other changes during pregnancy are aimed at favoring hemostasis.

Specifically, factor VIII and factor von Willebrand and fibrinogen are increased, whereas anticoagulant factors and the fibrinolysis rate are reduced.

Risk factors for PPH include antepartum hemorrhage, induction of labor, instrumental deliveries, and C-sections, chorioamnionitis, fetal macrosomia, polyhydramnios, maternal anemia, thrombocytopenia, hypofibrinogenemia, maternal obesity, multifetal pregnancies, prolonged labor, placental abnormalities, and advanced maternal age.

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Hereditary hemostatic disorders and a previous history of PPH also increase the risk of PPH.

The causes of PPH are typically described as the "4 Ts":

Tone (uterine atony)

Trauma (lacerations, hematomas, uterine inversion, or rupture)

Tissue (retention of placental fragments, invasive placenta)

Thrombin (hereditary bleeding disorders)

Uterine atony occurs in most cases of PPH.

Early coagulopathy is not usual in PPH, but if diagnosis is delayed or if the bleeding volume is underestimated, the onset of coagulopathy seemingly happens earlier, as well as in cases of abruptio placenta and amniotic fluid embolism.

The definition of PPH changes in different countries and different management guides, so reaching a consensus would seem difficult. Furthermore, it is traditionally based on the volume of blood loss, estimated either visually or by weighing gynecological pads, as well as measuring hemoglobin. None of these methods has proven superior to the others, but clearly a visual estimation usually underestimates the losses. Therefore, ideally individual tolerance concepts should be associated to the bleeding, since a pregnant woman can lose over 1000 ml of blood without showing any clinical signs, since her blood volume is increased during pregnancy. Tachycardia is usually the earliest sign of excessive bleeding.

The lack of immediate availability to perform a lab test or a blood gas test in some delivery rooms delays de identification of PPH.

The definition of PPH should be multidisciplinary, comprising vital signs, clinical symptoms, coagulation status, and bleeding rate.

The proposed definition for PPH is an accumulated blood loss over 1000 ml, or any loss associated to shock or tissue hypoperfusion clinical and/or analytical data within 24 hours of birth.

Viscoelastic tests (VETs) are the suggested method for the early identification of coagulopathy, since they are quick and because of the evidence of moderate correlation with fibrinogen levels measured by the Clauss method. However, VETs are more expensive than standard lab tests, and they are not available at all hospitals.

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Low levels of fibrinogen (< 2 grams/liter) during labor or early puerperium are a good predictor of severe PPH progression, although the exact threshold for the replacement of this factor is not clear.

The importance of monitoring fibrinogen levels during labor seems obvious, but this is not the case for antepartum monitoring, on which literature is inconsistent.

In most PPH cases, the first therapeutic maneuvers are obstetric, through the administration of uterotonics, uterine manual compression measures, removal of placental remnants, tear suture, or insertion of intrauterine balloon tamponade.

Treating the coagulopathy should be considered at an early stage and concurrently with the strategies mentioned. Prohemostatic strategies in PPH include tranexamic acid, replacing coagulation factors using factor concentrates or frozen fresh plasma and platelets.

Tranexamic acid (TXA) proved effective to reduce mortality due to puerperal bleeding in the WOMAN trial, although the benefit of its prophylactic use during vaginal delivery could not be ascertained in the TRAAP trial. The TRAAP2 trail provided evidence of a bleeding reduction with the prophylactic use of oxytocin and TXA in C-section births.

Fibrinogen must be supplemented and restored to plasma levels over 2 grams/liter through the administration of concentrates of this factor or with cryoprecipitate in PPH cases. However, there is not enough evidence to support a systematic early administration of fibrinogen to improve the evolution of PPH (studies FIB-PPH, OBS, and FIDEL).

The use of cryoprecipitate at early stages of PPH was studied in the ACROBAT trial, with promising preliminary results.

The use of prothrombin complex concentrate and recombinant activated factor VII is not backed by any clinical trial, and so it is not recommended on a general basis.

Procedure algorithms can reduce transfusion requirements and morbidity associated to PPH. Hemostatic therapy is proposed, guided by the bleeding volume, administering TXA (1 gram, within 3 hours of birth), if this is > 500 ml, and establishing a strict monitoring plus a lab test or VET.

A fibrinogen concentrate will be administered if there is evidence of a deficiency (FIBTEM < 12 mm or Clauss < 2 gr/l), with a recommended starting dose of 4 grams.

The platelet count should stay above 50,000, and the consensus recommends the transfusion of platelets at levels of 75,000. In the rare cases of persistent bleeding, the use of factor XIII concentrate is proposed to stabilize the fibrin mesh.

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As a last resort, recombinant activated factor VII may be administered, although its safety and efficacy have not been ascertained.

As with the procedure algorithm, the proposal is for every institution to promote training through PPH case simulation, as well as to record and review PPH cases in order to determine aspects to improve.

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Acute obstetric coagulopathy during postpartum hemorrhage is caused by hyperfibrinolysis and dysfibrinogenemia: an observational cohort study

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Coagulopathy occurring around postpartum hemorrhage (PPH) has not been correctly described. An attempt has been made to relate it to other better known conditions, such as disseminated intravascular coagulation (DIC) or trauma-induced coagulopathy (TIC), in order to suggest a more appropriate management, but it is still seen as a different condition. The differences include the baseline or "pre-bleeding" situation, which in a term-pregnant woman is physiologically procoagulant, since during the third trimester of pregnancy an increase of procoagulant factors—such as fibrinogen—is observed, together with a decrease of anticoagulants, which distorts the interpretation of analytical values. The possibility that the coagulopathy precedes bleeding may also be considered, as would happen with an amniotic fluid embolism or placental alterations.

Based on a study carried out with over 500 patients suffering from PPH, the authors observed that the coagulopathy usually occurred in patients losing over 3 liters, and it was defined as dilutional coagulopathy. These patients showed a progressive decrease of factors (on account of consumption and dilution by fluid therapy), which stayed within a normal range for non-pregnant women while bleeding was under 3 liters, with no increase of D-Dimer (DD). Hence, the DIC component was ruled out. Moreover, only 2% of these patients had baseline fibrinogen under 2 g/dl, which has been described by other authors as a risk and prognosis factor to develop massive PPH. Besides fibrinogen, low levels have been observed for factor XIII, and no minimum hemostatic levels could be determined in a pregnant patient. In such situations, the administration of frozen fresh plasma has not proven efficient.

Nevertheless, a small subgroup of patients experienced severe coagulopathy at an earlier stage, characterized by dysfibrinogenemia and hyperfibrinolysis, described by the authors as acute obstetric coagulopathy (AOC). Fibrinolysis was assessed based on the levels of plasminogen, DD, and plasmin/antiplasmin (PAP) complex. PAP levels in patients with AOC were 30 times higher than in other patients with PPH; these levels were also higher than the ones observed in TIC. This

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The Role of Thromboelastography during the Management of Postpartum Hemorrhage: Background, Evidence, and Practical Application

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Introduction

80% of maternal mortality is caused by postpartum hemorrhage (PPH), which is related to coagulopathy, particularly **hypofibrinogenemia**. In order to guide the treatment, conventional coagulation tests (CCT) are used, which can take as long as one hour, as well as point-of-care viscoelastic tests (POC-VET), providing a quick diagnose (10 minutes) and continuous monitoring. Nevertheless, there is no conclusive scientific evidence on the use of POC-VET in PPH.

The article we discuss is an **outstanding update** on the issue: definitions, etiology, types of coagulopathy, and their treatment [CCT and POC-VET (ROTEM & TEG)].

Definition of postpartum hemorrhage

It is the occurrence of blood loss within 24 hours of delivery. Most guides, as well as the WHO, define PPH as bleeding ≥ **500 mL**, considered severe when estimated as **≥ 1000 mL**, regardless of the delivery method.

Changes in coagulation during pregnancy

Pregnancy prepares women to prevent massive hemorrhage during delivery, hence becoming a **prothrombotic state**. This is due to an increase in coagulation factors, particularly **fibrinogen** (which can go up to 4-6 g/L) and **factor VIII** (which causes shortening of TP and TTPa). The only factor that decreases during pregnancy is the clot stabilizing factor (**factor XIII**).

Coagulopathy of postpartum hemorrhage

The coagulopathy of PPH is fundamentally due to the **loss of fibrinogen**. Hence, that is the main pillar for its treatment. During PPH, factor deficiency is infrequent, except for massive hemorrhage

situations with a blood loss > 2000 mL. Likewise, thrombocytopenia has only been reported in 10% of PPHs, and it is seldom significant. Empiric transfusion of frozen fresh plasma (FFP) ratios versus red blood cell concentrates has not been studied in PPH, and the existing evidence in massive hemorrhage of traumatized patients has been assumed.

Coagulopathy of postpartum hemorrhage depending on the hemorrhage etiology.

Early. Due to a loss of fibrinogen through consumption. It is mostly associated to PPH caused by placental abruption.

Late. Due to the persistence of bleeding, where the loss and dilution of coagulation factors plays a more significant role.

1. **Uterine atony or uterine trauma**. Lead to over 80% of PPHs, but the ratio of patients that eventually develop coagulopathy is very low, and due to the loss of **fibrinogen**. It has been proven that even with losses over 2000 mL only 20% of patients had fibrinogen values < 2 g/L. In such situations, POC-VET-guided transfusion is recommended. **Retention of conception products**. It is not considered a cause of PPH as such, but it is closely linked to the presence of uterine atony.

2. **Placenta praevia / Placenta accreta**. Placenta praevia occurs in 0.5% of pregnancies, and placenta accreta, in 0.05%. In these cases, blood loss happens very quickly, leading to serious coagulopathy and challenging surgery. The main cause is hypofibrinogenemia, which in the case of placenta accreta may be observed in up to 39.5% of patients. In such situations, POC-VET-guided transfusion is recommended.

3. **Placental abruption**. It occurs in 0.65% of pregnancies. With this condition, PPH might be serious and early. Placental abruption is the etiology most commonly associated to **hypofibrinogenemia** (40% PPH). Up to 10 g of fibrinogen might be required to correct coagulopathy and control hemorrhage. A late restoration of fibrinogen can quickly lead to massive hemorrhage. Unlike all other etiologies, **thrombocytopenia** with values < 75x10^9/L is also involved. In such situations, POC-VET-guided transfusion is recommended.

4. **Amniotic fluid embolism**. A coagulopathy caused by massive consumption of **fibrinogen** and **factor V**. Subsequently, **thrombocytopenia** and **factor consumption** takes place. In this condition, **early hyperfibrinolysis** occurs, and early treatment with tranexamic acid is fundamental. In such situations, POC-VET-guided transfusion is recommended.

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5. **Preeclampsia**. It occurs in 5% of pregnancies, and when complicated with the HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count), a coagulopathy can appear in up to 15% of patients. Moreover, placental abruption is associated to preeclampsia, thus coagulopathy is usually combined.

6. **Sepsis**. PPH occurs together with an infection, and management can be very complicated, since both fibrinogen and coagulation factors, such as platelets, can be altered.

PPH treatment algorithms based on POC-VET

Let's recall the parameters provided by POC-VET:

CT (ROTEM) / R(TEG): Time it takes for a clot to form. It depends on coagulation factors or the presence of heparin.

CFT (ROTEM) / K (TEG): Time it takes for the clot to widen from 2 to 12 mm. It depends on fibrinogen and platelets.

A5, A10, A20 (MA) (ROTEM) / A5, A10, A20 (MCF) (TEG): Clot width after 5, 10, 20 minutes (maximum width). It depends on fibrinogen, platelets, and factor XIII.

LY 30 (ROTEM) / ML 30 (TEG): Clot lysis percentage after 30 minutes.

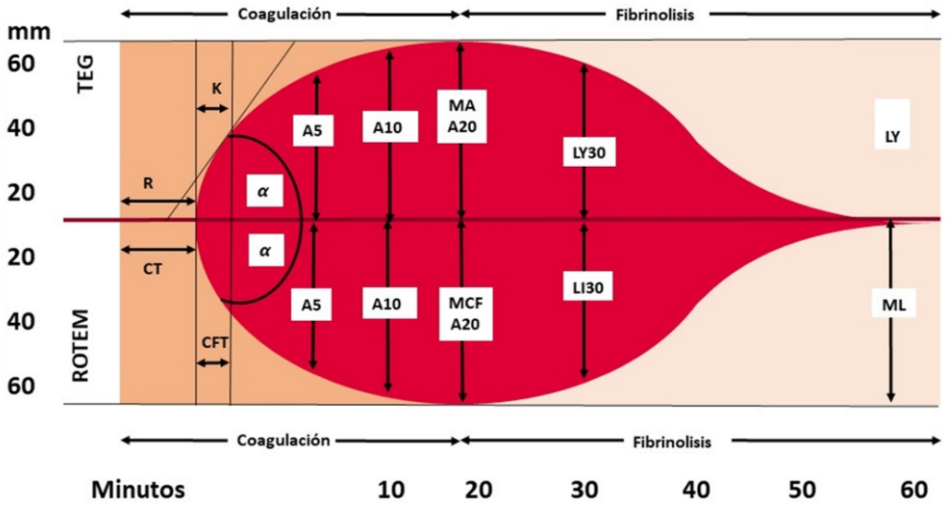

Figure 1. Description of POC-VETs (ROTEM & TEG).

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POC-VET-guided fibrinogen administration: It is very useful. Indeed, it has been proven that cut-off points of 17mm for MA 10 (TEG) and 11 mm for FIBTEM A5 (ROTEM) predict a Clauss fibrinogen < 2 g/L, with a 0.74-0.76 sensitivity; a specificity of 0.96-0.97; a positive predictive value of 0.54-0.57, and a negative predictive value of 0.98-0.99.

POC-VET-guided FFP administration: No robust triggers have been found yet that allow POC-VET-guided transfusion of prothrombin complex concentrate or FFP. This is due to the low incidence of factor deficiency in PPH. The early use of FFP is not recommended either in the treatment of PPH, since it contains a very low level of fibrinogen (≈2 g fibrinogen / 1 L PFC).

POC-VET-guided platelet administration: No robust triggers have been found yet that allow POC-VET-guided transfusion of platelets. This is due to the low incidence of **thrombocytopenia** in PPH.

Fibrinolysis and POC-VET-guided tranexamic acid administration: The WOMAN clinical trial (Lancet, 2017) proved that an early administration of tranexamic acid (1 + 1 g) reduced mortality caused by PPH, with no higher risk of thrombosis. The trial was not based on any viscoelastic test, therefore the administration of tranexamic acid should not be discontinued if there is no hyperfibrinolysis in POC=VET. A likely explanation is that tranexamic acid reduces fibrinogen degradation products and the plasmin-antiplasmin complex.

Summary of the treatment algorithm suggested by Anesthesiology in Cardiff, Wales

1) **Estimated blood loss > 1000 mL?:**
   1. If the patient suffers from von Willebrand disease, on antiaggregation or anticoagulation, check with the hematologist.
   2. Ca^{2+} > 1 mmol/L + pH > 7,2 + temp. > 36° C.
   3. **Tranexamic acid** if not yet administered (1 g and, if bleeding persists, 1 g more).

2) **Is there hypofibrinogenemia?** (Fibrinogen ≤ 2 g/L):
   1. FIBTEM A5 = 7-11 mm **or** CFF A10 = 10-17 mm **4 g fibrinogen**.
   2. FIBTEM A5 < 7 mm **or** CFF A10 < 10 mm **6 g fibrinogen**.

   Where FIBTEM (ROTEM) and CFF (TEG) are the channels analyzing fibrinogen.

3) **If the bleeding persists, repeat viscoelastic test before any further action**, to ensure that the fibrinogen is already corrected. If it is not, administer fibrinogen again. If it is:

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4) **Is there any alteration in coagulation factors?**: Elevated PT / aPTT
   1. EXTEM CT > 75 s or CK-R > 7.6 min → Weight gain > 50 Kg **4 units FFP**.
   2. EXTEM CT > 75 s or CK-R > 7.6 min → Weight gain ≤ 50 Kg **3 units FFP**.

5) **If bleeding persists, check blood platelet count:**
   1. Platelets ≤ 75x10^9/L → **1 platelet pool**.

Conclusions

In cases of PPH, fibrinogen deficiency is very common. Coagulation factor and platelet deficiencies are less frequent.

The current scientific evidence suggests:

- The administration of **tranexamic acid** as first-line treatment for PPH, with POC-VET guidance not required.
- The administration of TCC- or POC-VET-guided **fibrinogen** is recommended. The latter is preferred on account of its early result.
- The administration of **FFP** can be guided by TCC or POC-VET, although evidence for the latter is scarce.
- The administration of **platelets** can be guided by TCC, but there is not enough evidence to guide it by POC-VET, partly because of the low incidence of **thrombocytopenia** in PPH.

massive hyperfibrinolysis has been suggested as one of the mechanisms of dysfibrinogenemia, due to the interference allegedly caused by fibrinogen degradation products upon its polymerization. These patients also showed particularly low levels of FV, FVIII, and FXIII, which hints at a specific non-generalized consumption of a group of factors.

Thus, the authors describe AOC as a pattern clinically indistinguishable from amniotic fluid embolism. However, it was diagnosed in one single case of patients with AOC. Conversely, other patients with placental alterations presented PPH without AOC. Because of this, it is hard to characterize patients at risk of suffering from AOC, which should be suspected in all patients with PPH, low level of fibrinogen and significant increase of DD.

Regarding the prognosis, the occurrence of AOC has been connected to an increase of maternal and neonatal morbidity and mortality. At this point, the authors stress the importance of an early diagnosis of fibrinogen deficiency and its replacement (in larger quantities than the ones used in other scenarios), as well as antifibrinolytic agents. This allowed the authors to determine that need for transfusion of patients with AOC was not significantly higher than the rest of PPH patients.

To sum up, the authors present an infrequent condition (1/1000 deliveries) we are just starting to learn about, but an early diagnosis of which will be vital for the appropriate management of PPH.