Chapter

Patient Blood Management in Cesarean Section

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Abstract

Worldwide, every minute a woman dies due to complications during pregnancy, obstetric hemorrhage being the leading cause. However, most of these deaths are preventable with prompt recognition and management. The main objective of its management in the initial phase of resuscitation is to aggressively optimize macro and microhemodynamic parameters by ensuring effective resuscitation. Patient blood management (PBM) consists in the timely application of evidence-based medical and surgical procedures aimed at maintaining hemoglobin concentration, optimizing hemostasis and minimizing blood loss to improve patient outcome, all of these based in three pillars: endogenous erythropoiesis, platelet and coagulation factors function and physiological reserve of anemia. PBM consider various strategies to reach the main goal, including transfusional, non-transfusional and surgical measures. At preoperative period the prevention and treatment of anemia is the corner stone of the PBM guideline. Once at the operating room the fluid management, uterotonic and pro-coagulant drugs, fibrinogen and blood products transfusion play a key role and surgical techniques have to be done if the patient life is threatened. Manage postpartum anemia by appropriate iron administration. Optimize the patient's physiological response to anemia, treat infections and maximize oxygen delivery to minimize transfusions if they are not strictly necessary.

Keywords: obstetric hemorrhages, massive transfusion, pregnancy Anemia, fibrinogen, blood management

1. Introduction

Worldwide, every minute, a woman dies due to complications during pregnancy, obstetric hemorrhage being the leading cause; however, most of these deaths are preventable. Hypovolemic shock is the main consequence of obstetric hemorrhage. Obstetric hemorrhage is one of the five leading causes of maternal mortality in both high-resource countries and resource-limited countries, although the absolute risk of death from obstetric hemorrhage is much lower in the former [1–3].

Prompt recognition, availability of appropriate resources, and adequate responses are critical to preventing mortality and severe maternal morbidity [1–3].

Normally, hemostasis occurs with the separation of the placenta, and control of uterine bleeding is done through a combination of two mechanisms: [4].

- Mechanical hemostasis, whereby contraction of the myometrium compresses the blood vessels supplying the placental bed, resulting in a severe reduction in blood flow [4].
- Local thrombosis, by the presence or release of local decidual hemostatic factors (tissue factor and plasminogen activator inhibitor type 1) and systemic coagulation factors (platelets, circulating coagulation factors), leading to thrombosis of damaged blood vessels supplying the placental bed, resulting in severe reduction of blood flow [4].

Once obstetric bleeding occurs, the goals of treatment are to aggressively optimize macro and microhemodynamic parameters by ensuring effective resuscitation and timely replacement of blood products in addition to subsequent surgical management.

Patient blood management (PBM) consists of the timely application of evidence-based medical and surgical procedures aimed at maintaining hemoglobin concentration, optimizing hemostasis, and minimizing blood loss to improve patient outcome, all of these based on three pillars: endogenous erythropoiesis, platelet & coagulation factor functions, and physiological reserve of anemia, guided by the obstetric hemorrhage scenario. The multidisciplinary approach plays a key role even from preoperative to postoperative period, improving outcomes and reducing morbimortality in this population and hospitalization length and costs.

PBM considers various strategies to reach the main goal, including transfusional, non-transfusional, and surgical measures. In the preoperative period, the prevention and prompt treatment of anemia is one of the cornerstones of the PBM guideline; despite all the physiological changes during pregnancy, every single pregnant woman has an increased risk for a major bleeding due to several risk factors specific to pregnancy and each patient. Once at the operating room, leading causes for postpartum hemorrhage are widely described, so it is important that both the gynecologist and the anesthesiologist be prepared to solve the emergency, the fluid management, uterotonic and pro-coagulant drugs, fibrinogen, and, finally, blood product transfusion with all the concerns about it. Surgical techniques like B-lynch, Hayman technique, or others more advance like postpartum hysterectomy have to be used if the patient's life is threatened [5].

Manage postpartum anemia by appropriate iron administration. Optimize the patient's physiological response to anemia, treat infections, and maximize oxygen delivery to minimize transfusions if they are not strictly necessary.

2. First Pilar: enlargement of red blood cell mass

During pregnancy, physiological changes take place and prepare the woman in several ways, especially for the delivery moment and prevention of blood loss at this time. One of them is the hematological system, where maternal plasma volume expansion reaches a net increase of approximately 50% by 34 weeks' gestation. Red

blood cells rise to 30% above the pre-pregnancy level at term due to an increased concentration of erythropoietin and the erythropoietic effect of progesterone, prolactin, and placental lactoge [5, 6].

The difference in the increase in blood elements results in hemodilution, which is known as physiologic anemia of pregnancy. Despite the hemodilution, the rheological changes ensure enough oxygen delivery, better placental perfusion, less risk for thrombosis, despite the bleeding that occurs with childbirth, the objectives being to improve the main outcome of the first pillar [5, 6].

At the same time, there is a substantial increase of the coagulation factors I, VII, VIII, IX, X, and XII and von Willebrand factor. Furthermore, there is a decrease of Factor XI and XIII and a physiologic decrease of protein S, while F II and V do not change, resulting in an accelerated but compensated intravascular coagulation state [6].

The main objective of patient blood management strategies in pregnancy is to prevent postpartum hemorrhage (PPH) and decrease morbi-mortality associated with blood products transfusion. Thus, the first step is to recognize risk factors, so women with previous PPH in the last pregnancy, pre-existing anemia, prior cesarean section, multiple gestations, uterine fibroma, preeclampsia, obesity, chorioamnionitis, and fetal macrosomia are at increased risk for PPH [7, 8].

However, almost 61% of women with PPH do not have a risk factor, excluding maternal age and cesarean section. Therefore, we have to consider that all pregnant women have a considerable risk for PPH [7, 8].

From all of the possible risk factors, anemia and iron deficiency are susceptible to modification, and this is where the first pillar of the PBM could be specifically implemented. Pregnant women are the only patients in whom we can detect iron deficiency and anemia long before a potential blood loss at delivery [5].

Anemia affects approximately 40% of pregnant women worldwide with iron deficiency as main cause. Anemia has been associated with several complications like the need for increased health care requirements, intensive care for both the mother and neonate, higher rates of preeclampsia, higher rates of induction of labor, cesarean delivery, blood transfusion and higher rates of infectious disease for both mother and newborn, all of these anemia severity – dependent, increasing maternal y perinatal morbidity and mortality [7, 9, 10].

Anemia treatment has the potential to improve outcomes for affected women and their fetuses and neonates and minimize the illness burden and cost due to this common disease [9].

Once the diagnosis of anemia is done, we have to evaluate the cause of the disease, starting with iron metabolism analysis because it is responsible for 60% of anemia cases. In pregnancy, iron requirement increases considerably, and mother's stores cannot fulfill this need most of the time. Therefore, all guidelines of obstetric care recommend a complete hematological investigation when a low hemoglobin value is detected including transferrin level, iron saturation and supplementation with iron o B12 if needed [5, 10].

Iron metabolism evaluation must be done with ferritin screening (30 – 100 ng/ml as normal cutoff) where values below 30 ng/ml mean clear iron deficiency, even with normal hemoglobin, as it is the best and most practical marker for iron store evaluation. Nevertheless, serum ferritin is also an acute-phase protein, so this value increases during infectious or inflammatory episodes. It is recommended to measure the C – reactive Protein (CRP) levels with normal ferritin in case of low Hb in inflammatory situations [5, 10, 11].

Other markers we can evaluate for iron deficiency are red cell distribution width (RDW) and mean corpuscular hemoglobin (MHC). Transferrin saturation rate is a

marker that shows us the percentage of iron binding sites that are occupied. The normal values are between 20 and 50%, where levels below 20% mean iron deficiency [5, 10].

WHO recommends routine iron supplementation for every pregnant woman, especially in low-income countries, to prevent iron deficiency without anemia and iron deficiency with anemia with 30 – 60 mg/day of oral iron. In cases of mild or moderate anemia, it is advised to have an iron substitution of 160 – 200 mg/day. Iron supplementation usually has gastrointestinal side effects; when it is administrated during the first trimester, it can worsen nausea or gestational emesis, gastric pain, or constipation. Intravenous iron is indicated when there is intolerance to oral iron preparations or when Hb does not increase appropriately (less than 1 g/dl within 14 days) or when there is severe anemia during the third trimester or progressive anemia or if a rapid treatment is needed [5, 10, 11].

The optimal duration of iron deficiency treatment is 6–8 weeks with periodical Hb and serum ferritin screening every 4 weeks [10, 11].

3. Second Pillar: Minimization of bleeding and targeted transfusion therapy

After optimizing the volume of bleeding, the second pillar of management consists of minimizing blood loss, for which it is necessary to identify the forecast of surgical bleeding; adequate management of antiplatelet agents and anticoagulants; optimal anesthetic techniques to minimize bleeding; monitoring of the bleeding and coagulopathy; and devising an anesthetic plan.

According to the Spanish Scientific Society of Anesthesiology, Resuscitation and Pain Treatment, in order to achieve an efficient anesthetic plan, the anesthesiologist is required to use a multimodal approach within their perioperative management, including the following:

- Hypotensive resuscitation
- Use of antifibrinolytics
- Proper use of hemostatic agents

Hemostatic management of intraoperative bleeding requires careful control of coagulation.

4. Hypotensive resuscitation

Its fundamental objective is based on lowering blood pressure until definitive hemostasis and adequate tissue perfusion are achieved [12].

Their approach narrows to using small volumes of crystalloids as they are less likely to create dilutional coagulopathy, and lower blood pressure is less likely to break up or fragment the already formed clot; however, when large volumes of fluid are administered, this can initiate dilution of coagulation factors, resulting in impaired coagulation and coagulopathy [12].

A cohort study showed that lower fluid administration showed fewer signs of shock and less blood product administration, as fibrinogen, hemoglobin, hematocrit,

and platelet concentrations decreased during increased fluid administration, whereas PT and aPTT were more prolonged [13].

Therefore, the most recent studies have reported that resuscitation with >4 L of fluids is associated with subsequent bleeding and more adverse maternal outcomes [14]. Hypoperfusion can be tolerated for short periods of time and may decrease the volume of overall hemorrhage [12].

During hemorrhagic shock, the endothelial glycocalyx is thinned, and administration of crystalloids exacerbates this state, leading to more fluid extravasation and general volume depletion, leading to worsening bleeding [12].

5. Drugs used for intraoperative bleeding administration

Use of synthetic antifibrinolytic agents, such as epsilon-aminocaproic acid (EACA) or tranexamic acid, reduces blood loss and blood transfusion during cardiac procedures and is indicated for blood conservation (Class I, Level A) [15]. The main function of these components is to limit clot formation and ensure adequate blood flow, establishing a dynamic balance with the coagulation system [16].

6. Tranexamic acid

Initially, its use was limited to the treatment of obstetric hemorrhages and hemophiliac patients. Subsequently, it was progressively extended to cardiac surgery and the rest of its current indications [16].

Aminocaproic acid are lysine analogs that reversibly inhibit fibrinolysis by binding to lysine binding sites on plasminogen, limiting plasmin activation, which cleaves fibrin strands [17].

A Cochrane review of the effectiveness and safety of tranexamic acid (TXA), which identified 51 studies of antifibrinolytics, found that TXA produced an RR of RBC transfusion of 0·61 (95 percent ci 0·53 to 0·70) and concluded that "lysine analogues are effective in reducing blood loss during and after surgery, and appear to be free of serious adverse effects" [17].

Dosage and dosing schedules vary depending on the clinical setting, but a 1 g dose is sufficient for most adults, with no evidence to support the use of high doses [16]. CRASH-2 (Clinical Randomization Trial of an Antifibrinolytic in significant bleeding) showed that early administration of 1 g of tranexamic acid (within 3 hours of traumatic injury) followed by a 1 g infusion over 8 hours significantly reduced the risk of death from bleeding and all-cause mortality in traumatic bleeding [17].

In cardiac interventions, the dose range was 2.5 mg/kg to 100 mg/kg, and for the maintenance dose, it was 0.25 mg/kg/h to 4.0 mg/kg/h, over 1 to 12 hours. These variations were also observed in non-cardiac surgery [18].

A meta-analysis showed that TXA significantly reduced blood loss compared with placebo; of the studies that reported the number of transfusions, administration of tranexamic acid was reported to reduce an average of 1.12 units compared with placebo and was not associated with an increase in morbidity or mortality [18].

Based on the CRASH 2 trial, CRASH 3 trial and WOMAN trial results TXA is the first choice for antifibrinolytic therapy in any hemorrhagic scenario due it effectiveness and cost/benefits evaluation [18].

The 2017 WHO recommendation on tranexamic acid for the treatment of obstetric hemorrhage states that tranexamic acid should be recognized as a life-saving intervention and readily available for the management of PPH in settings where emergency obstetric care is provided, regardless of the level of medical care system resources [19].

A meta-analysis of two trials showed that immediate treatment improved survival by >70%, and thereafter, the survival benefit decreased by 10% for each 15 min delay in treatment until 3 h, after which there was no benefit [20].

In an effort to administer TXA as early as possible, in a pre-hospital setting, its use is now supported by UK ambulance services, current research is evaluating alternative dosages and formulations, including intramuscular TXA, which appears more feasible for timely administration in emergencies [20].

7. Other hemostatic agents

7.1 Prothrombin complex concentrate

PCCs or prothrombin complex concentrates are plasma-derived compounds containing highly purified vitamin K-dependent coagulation factors (II, VII, IX, and X) with hemostatic activity [21].

Originally, the main indication for PCC was the reversal of the effect of vitamin K antagonists; however, they are now also used to treat congenital or acquired conditions such as factor II or factor X deficiencies and are useful in the treatment of massive traumatic bleeding [22].

Systematic reviews have identified little scientific evidence on the use of PCC in adult patients with major bleeding; although the use of PCC is safe and recommended for urgent cases of reversal of the effect of vitamin K antagonists, there is currently limited evidence to support its use in the management of major bleeding unrelated to vitamin K antagonists [20].

In addition to a Cochrane review published on PCC for patients with vitamin K antagonists undergoing emergency surgery, PCCs appear to have a very safe profil with a minimal thromboembolic risk in these cases. One report has described the beneficial use of PCC in PPH in one patient with a non-hereditary coagulation deficiency [19].

In a retrospective study of 14 obstetric cases with disseminated intravascular coagulation (DIC), the use of PCCs failed to alter the outcome, which is why the use of PCCs cannot be considered a part of standard clinical practice for obstetric hemorrhage [20].

Efficacy in INR correction is also an advantage of prothrombin complex concentrates over fresh frozen plasma [21]. A retrospective study compared both treatments in patients with intracranial hemorrhage associated with anticoagulation and demonstrated that subjects treated with prothrombin complex concentrates had an average decrease in INR from 2.83 to 1.22 in 4.8 hours vs. a decrease from 2.97 to 1.74 in 7.3 hours in those who received fresh frozen plasma, that is, 4 to 5 times longer and less effective, with a statistically significant difference ($p \leq 0.001$) [21].

A single 40 mL (1000 IU) dose of PCC is functionally equivalent to the adult FFP dose of 10 to 15 mL/kg, or four to five plasma quantity units or 1000 mL volume, all classes of PCC include factors II, IX, and X, whereas the four-factor PCC also contains clinically relevant factor VII.

Some authors suggest a dose of 25–30 IU/kg, supported by the results of an open clinical study, without random distribution, carried out in patients with high INR (between 8.9 and 18 and greater than 20) [21].

In Canada, the approved PCC indications include rapid reversal of vitamin K deficiency in patients with severe bleeding or need for emergency surgery within 6 hours, but it is not recommended for surgery that may get delayed 6 to 12 hours, since in PCC anticoagulant reversal, its effect is temporary due to the short half - life of factor VII factor, which falls after 6 hours [23].

Consequently, intravenous administration with 10 mg of vitamin K with PCC is recommended to activate existing coagulation factors and maintain the reversal effect, as vitamin K1 reaches clinical effect within 6 hours by which PCC effects begin to weaken [23].

The administration of higher doses of prothrombin complex concentrates has been described in relation to the degree of INR prolongation.

It is not recommended to pass a maximum dose of PCC of 3000 IU (120 mL).

7.2 Fibrinogen concentrate

Fibrinogen, also called Factor I, is a blood plasma protein produced by the liver that plays a key role in hemostasis. It is the coagulation factor with the highest plasma concentration, between 150 and 400 mg/dl [24].

In its mechanism of action we have, it acts in both primary and secondary hemostasis; its soluble form serves to bind to activated platelets, forming bridges between them after binding to the glycoprotein IIb -IIIa receptor on its surface, contributing to the platelet aggregation and platelet plug formation during primary hemostasis; subsequently, fibrinogen is converted to fibrin monomers, which are polymerized, with the help of factor XIIIa, to an insoluble form (fibrin) that stabilizes the platelet plug and provides a firm mesh for clot propagation during secondary hemostasis [24].

Hypofibrinogenemia as a result of blood loss, factor consumption, or hemodilu-

Starting INR	Minimum dose (IU/kg)	Maximum dose (IU/kg)
2.0–2.5	22.5	32.5
2.5–3.0	32.5	40
3.0–3.5	40	47.5
> 3.5		47.5

tion is associated with poor patient outcomes and increased mortality in trauma patients [25]. The fibrinogen concentration upon arrival at the hospital may vary depending on the individual, patient factors; for example, low fibrinogen levels have been associated with young age, male gender, long time since injury, low base excess, and high injury severity score [25].

There are several techniques available to determine the fibrinogen concentration; the Clauss technique is recommended for diagnostic purposes or when decisions regarding the clinical management of patients with hemorrhage must be made [18]. The determination of FIBTEM with ROTEM or Functional Fibrinogen in TEG allows rapid detection of changes in fibrinogen levels in trauma patients. In this regard, it has been confirmed that the determination of fibrinogen using the FIBTEM test in ROTEM® is closely related to the values obtained with the Clauss method [18].

Fresh frozen plasma or FFP, cryoprecipitate, and human fibrinogen concentrate are available options for fibrinogen replacement. They contain approximately 2.5, 15, and 20 g/L of fibrinogen, respectively. Both FFP and cryoprecipitate require thawing and crossmatching prior to infusion, with known potential transfusion-related complications and risks. Cryoprecipitate is still not available in many European countries [22].

FIBTEM amplitude at 10 min from onset of clot formation (FIBTEMA10) correlates with fibrinogen concentration and thus allows early identification of fibrinogen deficiency. FIBTEMA10 < 7 mm has been suggested as a trigger for fibrinogen replacement with the aim of raising FIBTEMA10 to at least 10 mm during ongoing bleeding [18].

In maternity patients, fibrinogen levels rise to an average of 5–6 g/L at term (compared to nonpregnant levels of 2.0–4.5 g/L). Low fibrinogen levels are an independent risk factor for the development of severe PPH, with a study that showed levels below 2 g/L with a 100% positive predictive value for the development of severe PPH [14].

In Australia, the most common way to increase plasma fibrinogen levels is to transfuse cryoprecipitate. This plasma-derived blood product contains high levels of fibrinogen, factor VIII, von Willebrand factor, factor XIII, and fibronectin. To provide a 3 to 4 g dose of fibrinogen, about 8 to 10 bags (typically 30 to 40 mL), which require thawing [14].

Fibrinogen concentrate is available as a lyophilized powder in 1- or 2-gram vials, and the protein is reconstituted with 50 or 100 mL, respectively, of sterile water. The final concentration, therefore, is 2 g/100 ml. It can be kept at room temperature, with a durability of 5 years [24].

Pharmacokinetic studies in patients with congenital afibrinogenemia show that substitution of 1 mg/kg of fibrinogen increases the plasma concentration by around 1.38–1.5 mg/dl, with a volume of distribution of 90–100 ml/kg [24]. The infusion rate should not exceed 5 ml/min (1 g/10 min), although cases have been described with a much higher transfusion rate without thrombus formation being observed in the vessel [24].

Fibrinogen concentrate prevents adverse effects associated with allogeneic blood products, including transfusion-related acute lung injury and incompatibility [20].

The administration of CCP together with factor XIII and fibrinogen (guided by the results of TEM) more effectively reversed the associated coagulopathy and the need for massive transfusion than conventional plasma therapy, without observable differences in the development of multi-organ failure, in hospital stay or mortality [14].

7.3 Clot stability and FXIII (Fibrin Stabilizer)

FXIII is known to be an essential contributor to clot strength through its ability to cross-link and stabilize fibrin; however, most bleeding management guidelines currently do not include measurement and subsequent supplementation of FXIII [25].

Clot instability due to FXIII deficiency has been identified in some cases by ROTEM; in the neurosurgical setting, a postoperative FXIII level < 60% was found to be an independent risk factor for postoperative ICH [14].

In cases of bleeding and low FXIII activity (e.g., <30%), the administration of FXIII concentrate (30 IU/kg) is suggested, [25] although other studies recommend its use at a dose of 20 IU/kg of ideal weight, either by cryoprecipitates or plasma [26].

7.4 Activated recombinant human factor VII (rhFVIIa)

Recombinant human factor VIIa (rhFVIIa) is a tissue factor, activated prohemostatic agent, the efficacy of rhVIIa has been demonstrated in nonrandomized studies

in severe postpartum hemorrhage. The risk of thromboembolic complications has not been systematically investigated; it requires correction of hypothermia, acidosis, fibrinogen levels, and anemia; therefore, if bleeding could not be controlled by other measures, rhFVIIa could reduce the need for second-line therapies [13].

In a prospective cohort study with 22 patients with severe PPH, rhVIIa contributed to PPH control, and hysterectomy was avoided, and in life-threatening PPH, rFVIIa administration could be used; however, this should not replace or postpone vital interventions, but it should be noted that patients should be monitored for thromboembolism, especially if rhVIIa is administered in combination with tranexamic acid [13].

8. Administration of blood products

8.1 Packed red blood cells

There is a lack of evidence to support the benefit of blood transfusions, specifically in the case of hemodynamically stable patients undergoing elective surgery. Furthermore, it is an independent risk factor for adverse effects [18].

It is recommended to base its administration on clinical (blood pressure, heart rate) and biological (lactate, base excess) parameters, with a hemoglobin target of 8 g/dl, considering figures >9 g/dl for risk patients (heart disease). ischemic, cardiac surgery, etc.) considering the transfusion of red blood cells in most patients only when the Hb concentration is less than 7 g/ dL [26].

The Transfusion Requirements in Septic Shock (TRISS) trial showed that severely ill patients with septic shock could safely benefit from an Hb threshold of 7 g/dL132. Furthermore, an RCT of upper gastrointestinal bleeding in 921 patients, of whom a third were admitted with signs of hypovolemic shock (systolic BP <100 mmHg), demonstrated that an Hb threshold of 7 g/dl was safe and increased survival at 45 days when applied from the earliest phase [19].

The indication for blood transfusion should be more restrictive without fixed criteria for red blood cell transfusions; Hb below 6 g/dl generally requires a transfusion of 1 RGC, while this is rarely the case in a hemodynamically stable situation with an Hb of 8 g/dL or higher. Between 6 and 8 g/ dL, the indication for transfusion should be more restrictive, depending on the clinical situation and the patient's symptoms, since the best recommendation is to avoid the transfusion of packed red blood cells [13].

8.2 Fresh frozen plasma

Fresh frozen plasma (FFP) has limited clotting capacity and is inferior to fibrinogen concentrate for the treatment of hypofibrinogenemia. As a colloidal infusion, FFP is given for volume resuscitation in situations with severe hypovolemia and concomitant coagulopathy [13].

We suggest transfusing a standard dose of plasma (15–20 mL/kg) in ongoing severe PPH guided by abnormal coagulation tests (e.g., prolonged TEG time) [19].

From an empirical point of view, the administration of fresh plasma should be started after the loss of 1–1.5 blood volumes. During massive hemorrhage, early administration of fresh plasma is recommended to prevent or treat coagulopathy, taking into account that thawing of FFP requires a long time, and therefore, timely organization of FFP is recommended [26].

The use of large volumes of fresh plasma can lead to transfusion-associated circulatory overload (TACO), probably the most common complication today, while others, such as acute respiratory distress syndrome (ARDS), lung injury related to transfusion (TRALI), and hemolytic reactions, are exceptional. PFC should not be used prior to a procedure to correct mild to moderate elevated INR (less than 2.0) [26].

8.3 Platelet concentrate

Platelets play a key role in hemostasis and clot formation. Although very few trauma patients have low platelet counts on admission, it is very likely that platelet deficiency will develop over time depending on treatment [13]. The insufficient number of platelets is characterized by EXTEMCA10 < 40 mm (but normal FIBTEM amplitude) and low platelets (<50,000/L), which will indicate the need for administration of platelet concentrate [25].

Platelet transfusions have been considered a safe and potentially effective intervention in major bleeding; the results of the PATCH trial demonstrated that platelet transfusion increased the risk of death in patients receiving antiplatelet therapy (mainly aspirin) and presenting with acute spontaneous intracerebral hemorrhage (stroke), although methodological limitations have been described [20].

There are no solid data on the number of platelets necessary to guarantee primary hemostasis in different clinical situations, so its administration is also based on the severity of the bleeding and the particular circumstances that caused the massive bleeding. It is recommended to maintain a platelet count >50 × 109/l in patients with active bleeding, and it is suggested to increase it to 75–100 × 109/l in situations of uncontrolled massive bleeding or head trauma [26].

Long-term prophylactic platelet transfusions should be avoided due to the risk of complications (including alloimmunization and platelet refractoriness) [18].

8.4 Improvement of platelet function: desmopressin

Desmopressin, 1-desamino-8-D-arginine vasopressin (DDAVP) is a synthetic analog of the antidiuretic pituitary hormone arginine vasopressin. In vivo, it causes an increase in factor VIII levels and stimulates the release of von Willebrand factor from endothelial cells, which promotes platelet adhesion to wound sites. DDAVP can be used to correct the anti-hemostatic effect of aspirin and clopidogrel and can also be applied as part of the treatment for platelet dysfunction or von Willebrand's disease and also as an alternative use for enhancement of platelet increase [22].

8.5 Cryoprecipitates

Cryoprecipitate is a high molecular weight protein concentrate containing coagulation factors VIII and XIII and von Willebrand, together with fibronectin and platelet microparticles. It is obtained in blood banks from a PFC unit by thawing it at low temperature (1–6°C). The precipitated proteins are separated by centrifugation, and the supernatant is removed, leaving the insoluble precipitate, which is later resuspended in 5–20 ml of plasma that is then frozen again and stored at −18°C. Each unit of cryoprecipitate is generally collected in bags *(pool)* of five units [24].

Mortality and the number of RGC units transfused in 24 h are higher in patients who receive cryoprecipitate transfusions compared to those who do not. Mortality at

30 days was higher in patients who received cryoprecipitate transfusions compared with those who did not [12].

The number of cryoprecipitates transfused was higher in those who received cryoprecipitate transfusions compared to those who did not receive cryoprecipitate. No evidence was found for the critical impact parameters [18].

Consider transfusing cryoprecipitates in patients without major bleeding who have the following:

clinically significant bleeding
Fibrinogen levels below 2 g/l

9. Third Pillar:optimizing postoperative/postpartum treatment of anemia

Apart from the identification and appropriate action in each phase of obstetric hemorrhage, another fundamental pillar in the management of severe primary obstetric hemorrhage is the assessment with laboratory tests that include: blood biometrics, fibrinogen, coagulation studies, and lactate and base deficit (arterial blood gases) as they are tools to evaluate systemic tissue perfusion and are called **"optimal laboratory,"** since hemoglobin and hematocrit do not accurately reflect the amount of blood lost acutely [27].

Within coagulation studies should be requested fibrinogen concentration, prothrombin time, and activated partial thromboplastin time; this coagulation panel should be repeated every 30 to 60 minutes to observe trends until bleeding is controlled; coagulation studies are usually normal in the early stages of bleeding, but they can be abnormal when comorbidities exist, such as placental abruption, liver disease, stillbirth, sepsis, or amniotic fluid embolism. Eventually, significant bleeding without replacement of clotting factors will result in clotting abnormalities [27].

Fibrinogen is a cable point in the assessment of hemostasis since it falls to critically low levels before other clotting factors during a hemorrhage, so the level of fibrinogen is the most sensitive indicator of a significant loss of blood in progress, since its fall is related to the loss of fibrinogen through bleeding, increased fibrinolytic activity, and hemodilution secondary to fluids administered to maintain blood pressure during initial resuscitation, so it can be used to guide the aggressiveness of treatment [28, 29]. The normal level of fibrinogen in a full-term pregnancy is 350 to 650 mg/dl, which is almost twice that of a non-pregnant woman (200 to 400 mg/dl); a low level of fibrinogen (less than 200 mg/dL) is a predictor of major bleeding that is associated with the need for transfusion of multiple units of blood and blood products, the need for surgical treatment of bleeding, and increased maternal morbidity and mortality [30, 31].

Another pillar of the assessment is viscoelastic tests such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM), which are very useful when available, as they are useful to guide the administration therapy of plasma and other coagulation products. These tests provide a global assessment of complete hemostasis (time to clot development, clot stabilization/resistance, and clot dissolution) and can be performed at the bedside, so results are available within minutes. The results are useful for choosing only the transfusion-specific blood components that a patient requires and evaluating the efficacy of the interventions performed [32, 33]. The use of viscoelastic testing has led to fibrinogen replacement much earlier than with standard coagulation tests, and this early and aggressive fibrinogen replacement is thought to prevent severe coagulopathy and reduce maternal morbidity and mortality [33].

Once the initial treatment was established, bleeding control was achieved, and optimal laboratory tests were run; the objectives in the patient after obstetric hemorrhage are: [26].

- Hemoglobin>7.5 g/dL
- Platelets >50,000/mm^3
- Fibrinogen >200 mg/dL
- Prothrombin time less than 1.5 times the control value
- Activated partial thromboplastin time less than 1.5 times the control value

The first objective is to obtain a hemoglobin of 7.5 g/dl; to make the corrections, we must remember that most guides recommend continuing to transfuse patients with hemoglobin values lower than 7.5 to 8 g/dl; however, our recommendation is to maintain a hemoglobin level of at least 8 g/dl after transfusion, since values below this level may be associated with hemostasis altered by lower platelet adhesion and high blood velocity, as well as an increased likelihood of myocardial ischemia; however, a common practice is to maintain blood transfusion in any patient with hemoglobin less than 7 g/dl, regardless of whether it is symptomatic or not, and to transfuse symptomatic patients with a hemoglobin value <8 g/dL [33].

Iron supplements are also recommended because the amount of iron lost is not completely replaced with transfused blood. Oral supplements are an option, and single-dose parenteral iron therapy is another option. The advantages of parenteral iron are that hemoglobin levels increase faster, anemia symptoms improve earlier, and less gastric discomfort occurs compared to oral therapy. However, most women with mild to moderate anemia resolve anemia quickly enough with oral iron, and this measure is inexpensive and convenient [33].

Erythropoietin may increase the rate of recovery to normal hemoglobin levels; however, it does not have an immediate effect and has not been shown to reduce transfusion requirements after bleeding, is also no more effective than iron therapy in this setting, and is expensive, so its use is not advised. However, for the few women with severe anemia who do not respond to iron therapy due to dull erythropoiesis due to infection and/or inflammation, some hematologists consider recombinant human erythropoietin to be an alternative to transfusion.

Regarding the second objective, there are no universally accepted guidelines for the replacement of blood components in patients with obstetric bleeding; recommendations are usually based on expert opinion, as there is no strong evidence from randomized trials, and these opinions are often extrapolated from data from studies in trauma patients, that is, a 1:1:1 replacement; in this case, our suggestion is to administer a packet of platelet apheresis only if the platelet count is less than 50,000/mm^3 [34, 35].

To achieve the objectives of hemostasis and prevention of coagulopathy, it is recommended that you try to raise the level of fibrinogen to a value >300 mg/dl in those situations in which there is active bleeding and in which resuscitation is still being performed, given the highest level of normal basal fibrinogen in pregnancy; however, if we face a controlled bleeding, a fibrinogen value greater than 200 mg/dl will be the objective; the correction of fibrinogen deficiency can be done by using

fresh frozen plasma, cryoprecipitate, and fibrinogen concentrates. It is important to emphasize that critically low levels of fibrinogen cannot return to normal using only fresh frozen plasma, without the use of cryoprecipitate or fibrinogen concentrates, since their irrational use only increases the risk of fluid overload and transfusion complications because they only contain a small concentration of fibrinogen in a large volume [35].

Cryoprecipitate is an option for correcting fibrinogen deficiency, but it also contains other clotting factors (VIII, XIII, von Willebrand). The dose depends on the measured and target fibrinogen levels. A reasonable approach is 30 units for fibrinogen <50, 20 units for fibrinogen <100, and 10 units for fibrinogen from 100 to 200. The advantages of cryoprecipitate are that large amounts of fibrinogen can be administered in a low-volume and that it is a low-cost product, and its disadvantages are that it takes time to thaw and prepare for transfusion and that it carries a risk of transmissible infections, since it is a pooled blood product that has not undergone any pathogen inactivation procedure [29, 30].

Another option for correction is fibrinogen concentrate containing approximately 1000 mg of fibrinogen. Usually given alone, it can be used in combination with cryoprecipitate; it is especially useful when fibrinogen levels are critically low (i.e., <100 mg/dl) [36].

Three-factor (II, IX, X) and four-factor (II, VII, IX, X) prothrombin complex concentrates (II, IX, X) are available and have been suggested as an alternative to fresh frozen plasma. The perceived advantages are a reduced risk of volume overload, without the need for thawing or blood typing, and a reduced risk of transfusion-related acute lung injury and allergic reactions. The disadvantages include a very high cost and an increased risk of thrombosis [37].

Recombinant human activated factor VII has been successfully used to control intractable bleeding associated with uterine atony, placenta acreta, or uterine rupture; although this therapy appears to show promise for patients with bleeding refractory to standard therapy, medication is very expensive, and some studies have reported failure in 50% of patients and a possible increase in thrombotic events. Doses range from 16.7 to 120 mcg/kg in a single bolus injection for a few minutes, and repeat the dose every two hours until hemostasis is achieved, usually controlling bleeding within 10 to 40 minutes of the first dose [38].

We additionally recommend:

Maintain oxygenation: Oxygen saturation should be maintained at >95% by administering oxygen (10 to 15 l/minute) through a face mask; if the objective is not achieved, the need for tracheal intubation and mechanical ventilation should be assessed [26, 39].

Avoid hypothermia and **acidosis:** Blood fluids and components must be normothermic to avoid hypothermia, which has been linked to coagulopathy in traumatized patients.

Warming devices (blankets, devices to heat all intravenous fluids, insulating water mattresses, and/or upper and lower body forced-air heating devices) should be used to maintain normothermia (temperature ≥ 35.5°C), since hypothermia results in sympathetic stimulation with increased myocardial oxygen consumption, particularly if chills occur, which can lead to myocardial ischemia. Other adverse consequences of hypothermia include sepsis, coagulopathy, decreased platelet function, and increased mortality [40].

The combination of hypothermia and acidosis increases the risk of clinically significant bleeding despite adequate replacement of blood, plasma, and platelets [26, 40].

In addition, in any mass transfusion situation in which multiple units of blood are rapidly transfused, calcium and potassium should be monitored, with timely treatment of abnormalities. The most common electrolyte abnormalities are low levels of ionized calcium and hyperkalemia. Both disorders, if severe, can lead to cardiac arrest or significantly depressed heart function that prevents optimal resuscitation.

Ionized calcium: Ionized calcium should be measured at baseline and then every 15 to 30 minutes during a massive transfusion and then every hour for the next few hours after transfusions have stopped due to possible hypercalcemia and rebound hypokalemia.

An ionized calcium level < 1 mmol/L (normal 1.1 to 1.3 mmol/L) disrupts clotting and puts the patient at risk of cardiac arrest. Emergency replacement can be achieved by infusion of 1 gram of calcium chloride over two to five minutes through a central line; alternatively, 1 to 2 grams of calcium gluconate can be empirically infused intravenously for two to three minutes for every four units of red blood cells transfused. Hypocalcemia has a linear relationship, a low concentration correlates with a lower concentration of fibrinogen, and a higher likelihood of developing severe acidosis and a lower platelet count.

Potassium: Hyperkalemia can result from rapid transfusion of multiple red blood cell units, especially if they are older units and if they were transfused at a high infusion rate. When an urgent reduction in K+ is needed, a commonly used regimen for delivering insulin and glucose is 10 to 20 units of regular insulin in 500 mL of 10% dextrose, administered intravenously over 60 minutes.

10. Conclusions

Worldwide, every minute, a woman dies due to complications during pregnancy, obstetric hemorrhage being the leading cause; however, most of these deaths are preventable. Hypovolemic shock is the main consequence of obstetric hemorrhage [2, 3].

Patient blood management (PBM) consists of the timely application of evidence-based medical and surgical procedures aimed at maintaining hemoglobin concentration, optimizing hemostasis, and minimizing blood loss to improve patient outcome, considering various strategies to reach the main goal, including transfusional, non-transfusional, and surgical measures.

Despite of the hemodilution, the rheological changes ensure enough oxygen delivery, better placental perfusion, and less risk for thrombosis, despite the bleeding that occurs with childbirth, to improve these objectives being the main outcome of the first pillar [5, 6]. Anemia treatment has the potential to improve outcomes for affected women and their fetuses and neonates and minimize the illness burden and cost due to this common disease [9].

After optimizing the volume of bleeding, the second pillar of management consists of minimizing blood loss, for which its necessary to identify the forecast of surgical bleeding; adequate management of antiplatelet agents and anticoagulants; optimal anesthetic techniques to minimize bleeding; monitoring of the bleeding and coagulopathy; and devising an anesthetic plan.

Apart from the identification and appropriate action in each phase of obstetric hemorrhage, another fundamental pillar in the management of severe primary obstetric hemorrhage is the assessment with laboratory tests that include: blood

biometrics, fibrinogen, coagulation studies, and lactate and base deficit (arterial blood gases) as they are tools to evaluate systemic tissue perfusion and are called **"optimal laboratory."**

The objectives in the patient after obstetric hemorrhage are: [26].

- Hemoglobin>7.5 g/dL
- Platelets >50,000/mm^3
- Fibrinogen >200 mg/dL
- Prothrombin time less than 1.5 times the control value.

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