Strategies to reduce blood product utilization in obstetric practice

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Purpose of review
Patient blood management (PBM) aims to improve patient outcome and safety by reducing the number of unnecessary RBC transfusions and vitalizing patient-specific anemia reserves. Although PBM is increasingly recognized as best clinical practice in elective surgery, implementation of PBM is restrained in the setting of obstetrics. This review summarizes recent findings to reduce blood product utilization in obstetric practice.

Recent findings
PBM-related evidence-based benefits should be urgently adopted in the field of obstetric medicine. Intravenous iron can be considered a safe, effective strategy to replenish iron stores and to correct both pregnancy-related and hemorrhage-related iron deficiency anemia. In addition to surgical techniques and the use of uterotonics, recent findings support early administration of tranexamic acid, fibrinogen and a coagulation factor concentrate-based, viscoelastically guided practice in case of peripartum hemorrhage to manage coagulopathy. In patients with cesarean section, autologous red cell blood salvage may reduce blood product utilization, although its use in this setting is controversial.

Summary
Implementation of PBM in obstetric practice offers large potential to reduce blood loss and transfusion requirements of allogeneic blood products, even though large clinical trials are lacking in this specific field. Intravenous iron supplementation may be suggested to increase peripartum hemoglobin levels. Additionally, tranexamic acid and point-of-care-guided supplementation of coagulation factors are potent methods to reduce unnecessary blood loss and blood transfusions in obstetrics.

Keywords
blood transfusion, blood-sparing techniques, iron-deficiency anemia, patient blood management, postpartum hemorrhage

INTRODUCTION
Usage of blood products in obstetric practice has increased over the last two decades [1]. The underlying reasons are multifactorial, but include increase in patients with pregnancy-related iron-deficiency anemia, obstetric surgeries and obstetric-related bleeding. RBC transfusion is often the mainstay to correct anemia, but it is also one of the top five overused procedures [2]. To optimize utilization of blood products, the timely application of multiple strategies designed to maintain hemoglobin concentration, optimize hemostasis and minimize blood loss is warranted and has been defined as patient blood management (PBM) [3]. It further requires rejecting the standard dogma and one-size-fits-all approach, whereby RBC transfusions are used as the primary solution to correct low hemoglobin levels.

There is a large body of evidence that the successful implementation of PBM reduces perioperative blood loss and transfusion needs [4,5–8], perioperative morbidity [6,9], mortality [9,10], length of hospital stay [9,10] and costs [11]. For the obstetric population, reducing morbidity and mortality from hemorrhage is more challenging. Prevention of deaths from obstetric hemorrhage requires effective health systems including family planning, commodities, personnel, infrastructure and ultimately universal access to comprehensive obstetric care for women giving birth [12]. Further, different guidelines propose even contrary strategies...
Implementing PBM in obstetric practice offers the potential to reduce blood loss and transfusion requirements of allogeneic blood products.

- Intravenous iron is suggested to increase hemoglobin levels in both pregnancy-related and hemorrhage-related iron deficiency anemia.
- A coagulation factor concentrate-based concept offers the potential to rapidly diagnose and correct coagulopathy while reducing blood loss and RBC transfusion.
- Early administration of TXA and fibrinogen concentrate might be considered a first-line therapy in cases of PPH in the near future.
- Cell salvage may be feasible in obstetric patients, but potential risks need to be studied.

This article discusses the different ways to reduce allogeneic blood component transfusion in obstetric practice.

DURING PREGNANCY: IDENTIFICATION OF ANEMIA AND INHERITED BLEEDING DISORDERS

Identification of anemia

A rational first step is the optimal preparation of the female patient before delivery. During pregnancy, elevated erythrocyte cell mass and expanded plasma volume are physiological adaptations that are needed for the developing fetus. Consequently, the demand for iron intake is increased. The WHO estimated the prevalence of anemia (hemoglobin level lower than 11 g/dl) in pregnant women to be 38%, the majority caused by iron deficiency [14]. A complete work-up (ferritin and transferrin saturation) is essential, preferably with hematological indices such as hypochromic and microcytic red cells and reticulocytes, classified by degree of maturity, in particular, before parenteral therapy is given. As prepartum iron deficiency anemia is associated with significant maternal, fetal and infant morbidity [15], anemia treatment is recommended. Current options for treatment are, however, limited: these include oral iron supplementation, which can be ineffective and poorly tolerated, and RBC transfusions, which carry inherent risks and should be avoided. If intolerance or unresponsiveness to oral iron occurs, recent studies showed that intravenous iron (e.g. ferric carboxymaltose or iron sucrose) may be considered as a safe, well tolerated and successful alternative [16–18]. A recent meta-analysis confirmed the overall safety of intravenous iron [19]. Avni et al. included a total of 103 trials published between 1965 through 2013 and assessed a total of 10,390 patients with intravenous iron compared with 4,044 patients with oral iron, 1,329 with no iron, 3,335 with placebo and 155 with intramuscular iron. There was no increased risk of infections with intravenous iron, and gastrointestinal adverse events were reduced with intravenous iron.

Very recently, a small pilot study showed that intravenous iron could also be an attractive alternative to RBC transfusion in severe postpartum anemia. Holm et al. [20] randomized women with a postpartum hemorrhage exceeding 1000 ml and a hemoglobin between 5.6 and 8.1 g/dl to 1500 mg of intravenous iron isomaltoside or RBC transfusion. Although RBC transfusion was associated with a higher hemoglobin on day 1, only intravenous iron was associated with increased reticulocytosis during the first week, repleted iron stores and a higher hemoglobin after 3-12 weeks.

Inherited bleeding disorders

Obtaining a thorough patient history regarding any previous bleeding is also recommended. A patient history should include standardized questions, such as frequency of nose bleeding, hematoma (without trauma or high frequency), gum bleeding, specific drugs or prolonged menorrhhea. Koscielny et al. [21] identified the three most important questions: prolonged bleeding after scrapes or cuts, frequency of prolonged bleeding and usage of nonsteroidal anti-inflammatory drugs or platelet inhibitors. Monitoring of hemostasis is usually performed by conventional laboratory testing, for example prothrombin time, activated partial prothrombin time and platelet count. Abnormal results might give a hint to, but never prove or exclude an inherited coagulopathy as a predicted risk factor for PPH. Also, pregnancy-related procoagulatory conditions may blur most of hemostasis assays, which additionally underline the low sensitivity and specificity of these conventional tests in the obstetric field [22,23].

The most common inherited bleeding disorder is von Willebrand disease (vWD), followed by hemophilia A and B and factor VII deficiency. In patients with vWD, the severity of bleeding depends on the underlying pathophysiology. Although type 1 vWD is usually mild, types 2 or 3 vWD can be associated with moderate or significant bleeding. Because of increased risk of PPH, managing pregnant women with vWD requires a multidisciplinary approach and special considerations, for example monitoring...
of factor VIII and vW factor levels prior to delivery (treatment if levels <0.50IU/ml), therapy with desmopressin in type 1 and most type 2 vWD, therapy with plasma-derived factor VIII and vW factor replacements in types 2B and 3 vWD and if patients do not respond to desmopressin [24].

**PERIPARTUM HEMORRHAGE**

**Surgical conditions and uterotonics**

Life-threatening peripartum bleeding has an incidence of about 2–10%. The obstetric team needs to check for conditions that need to be treated first, for example atony, surgical problems (e.g. rupture or dissections of the uterus) or a possible retention of the placenta. Although the different surgical strategies are beyond the scope of this article, it should be emphasized that surgical interventions are the most effective in reducing allogenic blood product utilization. These interventions include early bimanual compression of the uterus, aortic compression, suturing of possible lower genital tract bleeding, uterine artery clamps, (manual) removal of the placenta, arterial embolization, uterine compression sutures as the B-Lynch suture, internal iliac artery ligation or a total or subtotal hysterectomy [12**,13**].

The amount of blood loss should be measured using specific collection bags, but much more important is the time frame and dynamic of bleeding. During surgical control of hemorrhage, permissive hypotension may be used to limit ongoing blood loss, although this procedure is a double-edged sword prior to delivery [25]. Uterotonic medications are used to promote uterine contractions in cases of uterine atony prior to surgical intervention. Women usually receive oxytocin prophylactically to prevent atony, if no contraindication exists, as atony is suggested to be the main reason for the increasing incidence of PPH in resource-rich countries. Oxytocin is also the first-line uterotonic drug for the treatment of PPH, including when women have already received this drug for the prophylaxis of PPH. If intravenous oxytocin is unavailable, or if the bleeding does not respond to oxytocin, the use of intravenous ergometrine (e.g. metherine), oxytocin-ergometrine fixed dose or a prostaglandin drug (e.g. sulprostone and misoprostol) is recommended. Decisions in such situations must be guided by the experience of the provider, the availability of the drugs and by known contraindications [12**].

**Coagulopathy and point-of-care techniques**

To be one step ahead of coagulopathy, it is mandatory to keep pH higher than 7.2, body temperature higher than 35.0°C, ionized calcium higher than 1 mmol/l and appropriate levels of coagulation factors. Coagulopathy may be caused by hereditary conditions, dilution, amniotic fluid embolism or others.

Conventional laboratory coagulation tests (thromboplastin time, activated partial thromboplastin time, platelet count and fibrinogen concentration) may be of limited use to predict or detect coagulopathy and to monitor treatment, in particular in women with ongoing peripartum bleeding [22]. Further, platelet count is purely quantitative and cannot detect preexisting, drug-induced or acquired platelet dysfunctions. Additionally conventional coagulation tests neither convey any information about clot stability over time, nor do they provide any information regarding fibrinolysis (hyperfibrinolysis). Thus, it is crucial to recognize that conventional coagulation tests cannot detect clinically significant coagulation defects that contribute to bleeding, hypofibrinolysis or hyperfibrinolysis, hypercoagulability and platelet aggregation within PPH.

In contrast to standard laboratory tests, point-of-care (POC) techniques including whole blood platelet function tests (impedance aggregometry) and viscoelastic tests (thromboelastometry/thrombography) reflect the hemostatic status in more detail. Furthermore POC test results are available much faster (analysis time of 20–25 min [26]) compared to conventional laboratory tests (turnaround time of 40–90 min after blood drawing [27]). However, none of the currently available POC techniques can provide adequate information about all aspects of the complex process of blood clotting.

Aggregometric testing of whole-blood samples is used mainly to study platelet function [28]. In bleeding patients whose hematocrit is above 30% and platelet count exceeds 70/nl, aggregometric tests (e.g. Multiplate and PFA-100) can be used to screen for disorders of primary hemostasis, for example vWD, and to quantify the effect of antiplatelet medications. Viscoelastic POC techniques (e.g. rotation thrombelastometry (ROTEM) and Thromboelastography (TEG)) are based on thromboelastometry/thrombography, which was described decades ago by Hartert [29]. They are used to measure the time until clot formation begins, the dynamics of clot formation and the solidity and stability of clots over time, including the presence of hyperfibrinolysis. Aggregometric tests combined with viscoelastic methods yield a far broader diagnostic spectrum formation than a conventional laboratory testing of coagulation. Mallaiah et al. [30*] recently reported an algorithm for ROTEM-guided fibrinogen administration in major obstetric
bleeding and showed a significant reduction in allogenic blood consumption by taking the clot firmness at 5 min.

Tranexamic acid
It is currently debated whether prophylactic tranexamic acid (TXA) may prevent postpartum blood loss, especially after cesarean delivery. TXA reduces bleeding by preventing plasmin from degrading fibrin and stabilizing blood clots. Consequently, it is called an antifibrinolytic drug. Guidelines are inconsistent in their statements concerning the use of TXA in obstetric patients [13**], although hyperfibrinolysis has been confirmed as a potential source of bleeding especially in this population. In trauma patients, TXA has already shown its excellent capability to reduce RBC transfusions as well as hemorrhage-related mortality [31]. Potential side-effects of TXA have been reported (e.g. deep vein thrombosis and seizures), which may be the reason for cautious use and its weak recommendation in the field of obstetrics. Simonazzi et al. [32] recently reported in a meta-analysis with 2365 women undergoing cesarean delivery that prophylactic TXA given before cesarean skin incision significantly decreased blood loss. Yet, high-quality data are still lacking. The world maternal antifibrinolytic (WOMAN) trial recently randomized 15,000 women with a clinical diagnosis of PPH either to a bolus of 1 g TXA or placebo to evaluate the effect of TXA on death and hysterectomy. As recruitment is complete, the results will hopefully be published soon [33].

Coagulation factors
Several studies have shown that low levels of fibrinogen are associated with progression of bleeding, the need for invasive interventions and transfusions of RBC and fresh frozen plasma, respectively. Thus, the important role of coagulation factors for hemo-stasis is evident. Niepraschk-von Dollen et al. [34] recently evaluated 1019 pregnant women with planned vaginal delivery and found that maternal pre-delivery fibrinogen levels were significantly lower in women with severe PPH. Aawar et al. [35] are currently investigating whether early infusion of fibrinogen concentrate during severe PPH, with the aim of correcting a low fibrinogen, reduces the total number of allogeneic blood products compared to a placebo. Until more detailed information are available, it is suggested to keep fibrinogen level higher than 2 g/l in patients with PPH.

If coagulopathy persists despite fibrinogen supplementation, and if the international normalized ratio is higher than 1.4, or if viscoelastic measures reveal a deficiency of prothrombin-complex coagulation factors II, VII, IX and X, then repletion of these factors is indicated. A dosage of 15–30 ml/kg FFP would be necessary to increase the concentration of these factors. However, the use of a prothrombin-complex concentrate, which contains factors II, VII, IX and X, proteins C and S, heparin and antithrombin, represents an attractive alternative because of the smaller volumes required to supplement the deficiency (recommended dose 20–30 IU/kg) [36]. Administration of the recombinant factor VIIa should only be considered as a rescue therapy to prevent hysterectomy.

Erythrocytes and platelets
During ongoing life-threatening bleeding, a hemoglobin level between 8 and 9 g/dl should be targeted. Transfusion of platelets is indicated if platelets are less than 50·10⁹/l and PPH is still present [13**].

As soon as bleeding has been stopped, a restrictive transfusion regime is recommended in hemodynamically stable patients (RBC only if hemoglobin is <6–7 g/dl), as many women are healthy patients.

Massive hemorrhage/transfusion protocol
If massive bleeding is ongoing, a massive hemorrhage/transfusion protocol might be the most effective way to reduce the total number of RBCs and other blood products. Currently, there is no specific massive hemorrhage/transfusion protocol with proven superiority [13**]. In our department, we use an RBC: FFP: pooled platelets ratio of 1.5:1:1 in life-threatening PPH. Importantly, any fixed protocol should be stopped if there is adequate time to involve POC-diagnostics to adapt to a more specific strategy, including a coagulation factor concentrate-based concept.

Autologous cell salvage
The use of washed cell salvage has been reported to be efficacious in reducing the need for allogeneic RBC transfusion and risk of infection in nonobstetric surgery. In our recent meta-analysis including 47 trials, the use of washed cell salvage reduced the rate of exposure to allogeneic RBC transfusion by relative 39%, risk of infection by 28% and length of hospital stay by 2.31 days [37]. The use of cell salvage in obstetric patients, however, is controversial. Although manufacturers of these systems do not recommend cell salvage for PPH, a few studies confirm its feasibility. Milne et al. recently reported 884 obstetric hemorrhage cases in which intraoperative blood salvage was utilized. Sufficient blood was...
collected by intraoperative blood salvage to permit reinfusion in 189 of 884 (21%) women. Patients who experienced bleeding or who underwent a cesarean hysterectomy were the most likely to receive reinfusion of intraoperative blood salvage-processed blood [38*], thus highlighting the potential of reducing the need for allogeneic RBC transfusion. Several questions are not yet fully answered in blood salvage during cesarean delivery, for example fetal red cell (consequently causing anti-D antibody formation) or amniotic fluid contamination in salvaged blood.

CONCLUSION

Implementation of PBM in obstetric practice offers the potential to reduce blood loss and transfusion requirements of allogeneic blood products, even though large clinical trials are missing in this specific field. Intravenous iron supplementation may be suggested to increase peripartum hemoglobin levels. Furthermore, tranexamic acid and POC-guided supplementation of coagulation factors reduce unnecessary blood loss and blood transfusions in obstetrics.

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Conflicts of interest

H.N. has no conflicts of interest.


REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

5. This large prospective cohort study including data from 129,719 patients from four different hospitals demonstrates that there is no adverse effect of a more conscious RBC transfusion strategy on patient safety.
15. Excellent review on current international guidelines and controversially discussed topics in obstetrics, highlighting the lack of evidence in this specific field.
Obstetric and gynecological anesthesia


This article shows the benefits of an ROTEM-guided management to reduce diagnostic time between blood sampling and having the final results.


A recent meta-analysis suggesting that TXA should be used routinely during cesarean section.


This article supports the current understanding of the importance of fibrinogen in PPH.


This study shows that cell salvage is feasible in the obstetric field with no relevant side-effects reported.