When and how should I transfuse during obstetric hemorrhage?

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Abstract (130 words)

The incidence of maternal hemorrhage and blood transfusion is increasing. Causes of massive hemorrhage, meaning greater than 10 units of erythrocytes, include abnormal placental insertion, preeclampsia, and placental abruption. There has been an adoption of ratio-based transfusion in the management of these bleeds but the use of laboratory data to guide transfusion seems to lead to better outcomes when compared to a ratio-based strategy. Ideally, laboratory data should be obtained from point of care testing. The use of autotransfusion is another strategy for managing massive obstetrical hemorrhage. In this technique, the maternal shed blood is collected, washed, and filtered. It will provide an autologous blood product that avoids many of the complications of allogeneic blood. This review provides advice as to when and how an obstetric patient should be transfused.

Key Words: (1) hemorrhage, (2) obstetrics, (3) transfusion, (4) point of care testing

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Introduction

Blood transfusion affects 0.5 to 3% of women with obstetric hemorrhage, accounting for 1% of the overall use of blood products in high resource countries.[1,2,3,4] Even if it represents an infrequent event, blood transfusion could be lifesaving in the context of acute severe obstetric bleeding. Indeed, obstetric hemorrhage, largely dominated by postpartum hemorrhage (PPH), remains the leading cause of maternal death worldwide.[5]

Blood transfusion in obstetrics presents several difficulties in terms of indications, modalities of administration, and organization of care. One of the main difficulties in obstetric hemorrhage is the unpredictability of the need for blood transfusion. Indeed, more than 50% of blood transfusions for acute obstetric hemorrhage occur in women without any risk factors.[6] Consequently, all pregnant women should be informed during pregnancy about the risk of being transfused at the time of delivery. Specifically, they should be counseled about adverse events that could follow a blood transfusion. For young women, alloimmunization may compromise future pregnancies. Therefore, specific guidelines for blood transfusion are necessary in obstetric hemorrhage.[7,8]

In this review, we first describe the main indications for blood transfusion in the context of obstetric hemorrhage, as well as the potential adverse effects for the mother; then we explore the most recent recommendations on how to transfuse women with severe obstetric hemorrhage.

Epidemiology of Transfusion in Obstetrics

Blood transfusion during PPH is usually indicated when first line treatments, such as uterotonic drugs (oxytocin, methergine, prostaglandins), laceration repair, or manual evacuation of the placenta, have failed to control the bleeding.[9] Therefore, blood transfusion is often associated with second-line obstetrical procedures, such as arterial embolization, intrauterine balloon tamponade or surgical hemostatic interventions (B-Lynch, vascular ligatures, and lastly emergent hysterectomy). Rarely, blood transfusion is required very early in the management of obstetric hemorrhage, when women present with active and uncontrolled

massive bleeding. Early coagulopathy is often observed in this specific context and usually worsens the bleeding.

Recently, an increase in the incidence of severe PPH needing blood transfusion has been reported in several studies from high resource countries. A national cross-sectional study using the 2001-2012 National Inpatient Sample of the Healthcare Cost and Utilization Project from the United States described a significant increase in the rate of severe PPH, defined by the need for blood transfusion and/or other surgical interventions, while the rate of non-severe PPH has remained stable over time.[10] In particular, the rate of postpartum hemorrhage requiring blood transfusion for cesarean delivery more than doubled during the study period, from 2.0 to 4.8 per 1,000 deliveries ($p<0.0001$). A similar increase in obstetric hemorrhage requiring blood transfusion has also been reported in studies using national databases from Canada and Ireland.[11,12] A recent population-based cohort study from Sweden also reported an increasing trend in the rate of massive postpartum transfusion.[13]

Risk factors for blood transfusion in obstetric hemorrhage

Risk factors for PPH have been largely explored but factors associated with severe PPH needing blood transfusion are less studied. The knowledge of risk factors for blood transfusion during obstetric hemorrhage may help to anticipate the need for blood transfusion. (Table 1)

Nyflot et al. in a retrospective multicenter case-control study from Norway (2008-2012) reported that the main risk factor of severe PPH needing blood transfusion is a history of previous severe PPH, (OR= 8.9, 95%CI: 5.3-15.3), followed by using an anticoagulant drug (OR= 4.8, 95%CI:2.7-8.4), gestational anemia (OR=4.3, 95%CI:2.8-6.5), severe preeclampsia - particularly HELLP syndrome (OR=3.0, 95%CI:1.7-5.3), uterine fibroma, multiple gestation, and pregnancy obtained by assisted reproductive technology.[14] Some characteristics of labor have also been described as severe PPH risk factors, such as prolonged duration of labor >12 hours, and operative vaginal delivery.[15]

Risk factors for massive blood transfusion, usually defined as transfusion of 10 or more RBC units, have also been specifically reported in several studies. Table 2 outlines some of the definitions of massive hemorrhage used in the trauma literature. Maternal, pregnancy and delivery characteristics significantly associated with massive transfusion are maternal age >=35 years old, previous cesarean section, multiple gestation, induction of labor, operative vaginal and cesarean delivery. Major risk factors are abnormal placental insertion, preeclampsia, placental abruption, previous cesarean delivery, and cesarean delivery.[15]

Clinical contexts associated with blood transfusion have been recently explored in a secondary cohort analysis of data extracted from the WOMAN trial, an international randomized trial studying the efficiency of tranexamic acid on blood loss from obstetric hemorrhage.[16] In this analysis, delivery outside the hospital (ARR 1.30 95%CI 1.22-1.39), delivery more than 3 hours before hospitalization (ARR 1.09 95%CI 1.01-1.17), cesarean section (ARR 1.16 95%CI 1.08-1.25), and obstetric hemorrhage from other causes than uterine atony significantly increased the risk of blood transfusion.

Blood Ordering A recent single center study has explored indications for emergency-release blood transfusion.[17] Uterine atony was the most frequent cause of PPH requiring emergency-release blood transfusion (40%), followed by placenta abruption/placenta previa (16%), retained placenta (11%), and uterine rupture (5%). A recent French population-based study has also reported that uterine atony remained the most frequent cause of severe PPH needing blood transfusion, followed by placenta retention and perineal wound or episiotomy.[1] This distribution of causes could be explained on one hand by the high frequency of uterine atony and retained placenta as causes of PPH overall, and on the other hand by the severity of the bleeding in hemorrhage secondary to abnormal placenta insertion. Placenta accreta spectrum, previously known as morbidly adherent placenta has now been clearly identified as a major cause of massive transfusion for obstetric hemorrhage.[17,18] Placenta accreta accounts for the most severe obstetric hemorrhage and is the leading cause of emergent hysterectomy.[19] Blood transfusion is needed in 69% of women with placenta percreta and 48% of women with placenta accreta.[17] The prevalence of abnormal placentation has significantly increased with

time in relation to the increase incidence of cesarean delivery.[20] Thankfully diagnosis and management have substantially improved in recent years. Antenatal diagnosis of placenta accreta allows clinicians to plan an adequate strategy of blood transfusion, including the need for massive blood transfusion. This probably partly explains why the antenatal identification of placenta accreta spectrum is associated with a lower maternal morbidity, including a lower quantity of blood loss and lower incidence of blood transfusion, with a lower quantity of RBC transfused.[17] The other causes of massive transfusion are uterine atony (21.2%), placenta abruptio (16,7%) and postpartum hemorrhage associated with coagulopathy (15.0%).[19]

Indeed, pregnant women with inherited or an acquired coagulopathy are also at increased risk for obstetric hemorrhage needing blood transfusion. Of note, these women are particularly at risk of late obstetric hemorrhage, meaning 24 hours to 12 weeks postpartum, as most of the coagulation factors increase during pregnancy. In a case control study using data from the United States Nationwide Inpatient Sample, James et al. reported that women with von Willebrand disease have a five-fold increased risk of being transfused during pregnancy or childbirth as compared with women without von Willebrand disease.[19] Increased incidence of PPH has also been reported in small retrospective studies among hemophilia carriers and women with rare inherited bleeding disorders, such as congenital hypofibrinogenemia and factor deficiencies. [21,22,23]

As the risk of thromboembolism is increased during pregnancy, thromboprophylaxis with low-molecular-weight heparin is frequently used in women with additional risk factors. These women should also be considered at an increased risk of acute bleeding needing blood transfusion at the time of delivery.[24]

In 2010, the California Maternal Quality of Care Collaborative (CMQCC) proposed a stratification of the risk of obstetric hemorrhage into 3 categories (low, median, high) for pregnant women, based on known clinical and biological risk factors.[25] Validation studies have shown an increasing risk of blood transfusion for peripartum hemorrhage as the risk grade increased.[26,27] Such risk assessment stratification according to the presence of risk factors for blood transfusion is a useful tool for clinicians to plan transfusion strategy in advance, in particular in

determining the need for pretransfusion testing and for predelivery crossmatching. It seems prudent to screen all patients for unusual antibodies. If screening does not show any unusual antibodies, then it is reasonable to order blood as needed. Most hospitals have the capability for electronic crossmatching. Electronic crossmatching allows for crossmatching to occur in under 5 minutes so it is not the historical roadblock to getting blood to the operating room that existed when a serological crossmatch was performed. If unusual antibodies are present, the crossmatching of a patient in the antepartum period would be advised because it will require a serologic crossmatch which can be slow. If the hospital is too small to do electronic crossmatching, it seems reasonable to use the CMQCC stratification tool as a guide.[28] If blood is urgently needed, type 0 Rh negative can always be used with minimal risk.[29]

The risks of allogeneic transfusion are multiple but there are risks relatively unique to the young, obstetrical patient. For women of childbearing age, specific attention should be kept on the risk of alloimmunization secondary to blood transfusion.[30] The antibodies responsible for the most severe forms of hemolytic fetal anemia are the anti RH1 (D), anti RH4 (c) and the anti-KELL1 (Kell). Consequently, women of childbearing age should be transfused with ABO, RhD and K compatible red blood cell units. The respect for blood phenotype should be followed whenever it is possible. However, in cases of life-threatening hemorrhage, blood compatibility should not delay blood transfusion with uncrossmatched blood.

For pregnant women with significant red cell antibodies, transfusion laboratories should be contacted to check the on-site availability of crossmatched blood products before delivery. In women with a rare blood type, the need for blood transfusion should be first prevented by increasing the hemoglobin level during pregnancy with iron supplementation and possibly the use of recombinant erythropoietin if they have renal insufficiency/failure. Secondly, the need for blood transfusion should also be anticipated by managing these women in a tertiary maternity unit with a blood bank on site and all the means to control severe PPH, including arterial embolization.

Acute Management of Active Hemorrhage

Over the last two decades, the concept of damage control resuscitation has arisen. This concept was developed to address the lethal triad of coagulopathy, acidosis and hypothermia that is associated with massive trauma. Through early transfusion, the coagulopathy associated with massive injury is addressed. From the desire to rapidly transfuse these patients, the concept of the massive transfusion protocol (MTP) arose.

The massive transfusion protocol was pioneered to get very rapidly large quantities of blood products to a massively bleeding patient before they exsanguinate. Typically, the products are delivered in 1:1:1 ratios via a cooler. For instance, 6 units of erythrocytes, 6 units of plasma and 6 units of whole blood platelets are delivered to the bedside in an expedited fashion. The use of an MTP may be comforting for a treating clinician in that lots of blood gets delivered to the patient bedside in a rapid fashion, how the blood is administered is the subject of the following discussion. The activation of MTP is used in patients with massive active bleeding and hemodynamic instability.

Ratio based transfusion

A lot of attention has been placed on ratio-based transfusion for the massively bleeding patient. Ratio based means that erythrocytes, plasma and platelets are given in ratios to each other, like what would be found in whole blood. Ratio based transfusion originated from retrospective studies performed in military trauma patients. Borgman et al in 2007 showed that a high ratio of plasma to erythrocytes led to higher survival in massively bleeding combatants.[31] For this study, massively bleeding was defined as needing greater than 10 units of erythrocytes in a 24-hour period. Like all retrospective studies, this result should have been hypothesis generating rather than influential to change transfusion practice. There were numerous problems with this study in that the presentation of patients was very different between the high ratio and low ratio groups. For instance, the high ratio patients had higher hematocrits, less acidosis and lower INRs upon presentation when compared to the low ratio patients. Given that the high ratio patients were not as sick, they would be expected to survive at higher rates.

In a similar retrospective study in massively bleeding civilians, Holcomb concluded that a higher ratio of plasma to erythrocytes led to better outcomes.[32] This study had flaws with the biggest issue being that the outcomes were influenced by survivor bias, meaning that the patients who were in the high ratio group, survived long enough to get more plasma and platelets. The low ratio group patients died sooner and thus they didn't have the opportunity to get high ratios of blood products.

The Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) Trial compared a 1:1:1 transfusion ratio (1 unit of platelets to 1 unit of plasma to 1 unit of erythrocytes) to a 1:1:2 ratio where patients received 2 units of red cells for every unit of plasma and platelets.[33] In this study of the massively injured, no difference in 24-hour and 30-day mortality was demonstrated. By the time this prospective study was published, the management of the bleeding patient with a ratio-based transfusion strategy had been adopted into multiple other disciplines including obstetrics.[34] The problem with adopting this practice into obstetrics is multiple. No evidence has been generated to demonstrate that the same outcomes would be obtained in an obstetrical patient. In fact, the extrapolation is questionable. Mesar et al.[41] looked at the benefit of ratio-based transfusion in several different disciplines ranging from vascular surgery to medicine patients. They found no overall benefit to a ratio-based transfusion.

Another problem with adopting this ratio-based practice into obstetrical hemorrhage is that the incidence of massive bleeding in obstetrical patients is much lower than in trauma patients. In Sweden, a cohort of 517,874 deliveries, massive blood transfusion occurred in 277 women, for an incidence of 5.3 per 10,000 deliveries.[35] So, the vast majority of obstetrical hemorrhage does not meet the criteria to be considered a "massive" hemorrhage based on the definition used in trauma of 10 units of erythrocytes in 24 hours. Some concern has been raised that overzealous transfusion in a non-massively bleeding patient may lead to worsened outcomes.

Several studies have evaluated the effects of aggressive plasma use in the non-massively transfused. Inaba et al. demonstrated that there was a dose-response relationship between plasma administration and overall complications in non-massively transfused trauma patients.[36] They showed that the odds ratio of overall complications rose in a linear fashion as more plasma

was administered. Likewise, Watson et al. demonstrated a similar dose response relationship with plasma where the risk of multi-organ failure increased with more plasma.[37] Johnson et al. showed a similar effect on the rates of multi-organ failure associated with plasma.[38]

This potential for harm, especially in a young woman suffering from a postpartum hemorrhage, would suggest that the more prudent approach would be to give these products based on results from laboratory testing or point of care testing. When a ratio-based strategy is compared to a laboratory testing-based strategy, survival outcomes appear to be better when laboratory data is used to make transfusion decisions. In a randomized, controlled trial of severe trauma victims, Nascimento et al. compared laboratory data collected every two hours to a 1:1:1 ratio-based strategy.[39] This study was stopped early because of the significantly worse 28-day survival rates in the ratio-based transfusion patients. A similar result was found when thromboelastograph guided transfusion was compared to a ratio-based transfusion.[40]

Fibrinogen

Recent attention has been focused upon the importance of fibrinogen replacement during major hemorrhage. This interest was generated by Charbit et al.[41]who showed that lower fibrinogen concentrations were associated with more severe hemorrhage. The positive predictive value for a fibrinogen concentration < 200 mg/dL was 100%. Intuitively, lower fibrinogen concentrations should interfere with adequate clot formation since fibrinogen is a key component of a blood clot. In 2015 a double-blinded, randomized controlled trial was published where patients who had greater than 1500 mL of blood loss were given either 2 g of fibrinogen concentrate or a saline placebo. This study found that the administration of fibrinogen concentrate made no difference in the amount of blood transfused.[42] One of the criticisms of this study was that the fibrinogen concentrate was given to a randomized group who might not have had low fibrinogen concentrations. Most recently, a systematic review was published of trials comparing fibrinogen replacement to placebo.[43] These authors concluded that there is a lack of evidence that early fibrinogen replacement influences bleeding outcomes. This being said, it appears that more research into this area needs to take place.

Fibrinogen replacement can take place by either giving cryoprecipitate or fibrinogen concentrate. In the United States, fibrinogen concentrate is prohibitively expensive; however, in Europe, cryoprecipitate is hard to find because fibrinogen concentrate is less expensive and easily administered. In a comparison of the efficacy of the two in cardiac surgery, they were found to be equivalent.[44]

Point of care laboratory testing vs traditional laboratory tests

When managing a hemorrhaging patient, getting coagulation and hemoglobin laboratory information is critical to make decisions about how to transfuse a patient. Traditional laboratory-based information requires a blood sample to be drawn and sent to a location away from the operating room or labor room where the patient is bleeding. Stat turn-around times, meaning the time to draw the blood to the time that meaningful results are received, are generally expected to take around 60 minutes.[45] Having point of care testing at the patient bedside decreases this timing for obtaining biological data and thus allows for real time decision making regarding resuscitation management.

There are a wide variety of point of care devices available. The Hemocue is a colorimetric hemoglobin monitor which requires 10 µL of blood to measure a hemoglobin. If a capillary blood sample is used, it's important to not milk the finger after the needle prick in that this can dilute the sample with lymphatic fluid. The most accurate hemoglobin will be from a venous or arterial blood draw.

There are also two devices manufactured by Massimo that can continuously measure hemoglobin or do spot checks of hemoglobin by shining 7 infrared lights through a finger to derive a hemoglobin concentration. There has been some concern raised that these devices are inaccurate which has limited the adoption of the technology.[46,47]

Viscoelastic testing has been advocated for coagulation function monitoring. These devices include the rotational thromboelastometry (Rotem, Instrumentation Laboratory, Bedford, MA), thromboelastograph (TEG, Haemonetics, Inc., Boston, MA), and the Sonoclot (Sienco, Inc., Boulder, CO). All three devices place a pin into a cup of blood and then either move the pin or the cup. As the blood clots, its viscoelastic properties change with increasing degrees of drag

being placed onto the pin which in turn is translated into an electrical signal. Characteristics of the coagulation system can be derived from the shape of the signal that is generated. The TEG 6s works differently in that it uses ultrasound to measure the vibration of a clot as it forms. This signal is then translated into the characteristic TEG signature. A fourth device has recently been approved by the Food & Drug Administration which works similarly to the TEG 6s using ultrasound to measure clot formation (Quantra, Hemosonics, Charlottesville, VA).

In the management of hemorrhage in cardiac surgery, liver surgery and in trauma surgery, multiple systematic reviews have shown a significant reduction in blood product use, and a decrease in the number of bleeding events when viscoelastic testing was utilized.[48,49] Most of the studies included in these systematic reviews have compared before and after implementation of viscoelastic based testing. The same result has been observed when viscoelastic based testing has been compared against standard coagulation testing.[50] In addition, to better hemorrhage control, viscoelastic testing has been shown to be predictive of venous thromboembolic events in the critically ill.[51,52]

The incidence of maternal death in the United States is on the rise. Twenty percent of these deaths result from coagulation dysfunction e.g. hemorrhage or thrombotic complications. Viscoelastic testing may be able to provide some of the same benefits to the obstetrical patient as has been seen in the critically ill. In two studies of obstetrical hemorrhage with viscoelastic testing, blood product use decreased, the rate of hysterectomy decreased, the length of hospitalization and the length of ICU admission also decreased.[53,54]

In postpartum hemorrhage, TEG parameters have been compared to traditional laboratory assays. Rigouzzo et al. found that the TEG provided rapid detection of hypofibrinogenemia and thrombocytopenia.[55] Algorithms for obstetrical care with viscoelastic testing have also been described. Collis and Collins in a review of hemostatic management of obstetric hemorrhage have proposed a Rotem based algorithm for management of bleeding.[56] Similarly, Butwick has proposed a TEG based algorithm for obstetric hemorrhage management.[57] Hill et al. developed a TEG based algorithm which not only facilitated blood product administration but also drove other parts of their resuscitation management such as placing another intravenous line and

activation of a massive transfusion protocol.[58] Another Rotem based algorithm was used to guide plasma transfusion in 605 women who were suffering from moderate to severe bleeding. With this algorithm, the authors found a 98% reduction in plasma transfusion.[59] Lastly, a Rotem guided algorithm was used to reduce the total number of blood products in major obstetric hemorrhage where the algorithm drove administration of fibrinogen concentrate. It also reduced the incidence of postpartum circulatory overload.[60,61]

In the event that a hospital doesn't have access to viscoelastic testing, Nascimento and colleagues demonstrated in trauma patients that laboratory-based transfusion decisions were superior to a 1:1:1 transfusion practice.[62]

Autotransfusion

The concept of autotransfusion was originally proposed by William Highmore in 1874 as he observed a maternal death from hemorrhage. [63] This death inspired him to start collecting shed maternal blood following delivery and reinfusing it. This practice was performed for several decades until the use of allogeneic transfusion was perfected. Unwashed shed blood is still used in many parts of the undeveloped world to resuscitate patients suffering from maternal hemorrhage. So, the idea that amniotic fluid contaminated blood posed a risk was tested from the inception of this concept.

Early in the history of autotransfusion blood washing machines, the manufacturer of the original devices labeled them contraindicated in obstetrical hemorrhage. This arose from the difficulty of doing a clinical trial proving the safety of this technology when amniotic fluid might get entrained into the salvaged blood. It was simply easier to label the devices as being contraindicated.

In 2000, Waters et al. published a study reporting on the washing and filtration of shed maternal blood from cesarean sections.[64] In this study, he compared a washed, filtered blood sample with that of a sample of maternal blood drawn at the time of placental separation. It was found that the autotransfusion sample was equivalent to the maternal sample across several different parameters intended to assess amniotic fluid contamination. In 2011, Liumbruno et al[65] published a review of 1665 cases where salvaged blood was reinfused during a variety of

obstetrical procedures. They reported no adverse events following any of the reinfusions. So, autotransfusion in the parturient appears safe.

As a result, the latest generation of autotransfusion devices have received labeling that does not exclude obstetrical hemorrhage. In response, several organizations have endorsed the use of autotransfusion during obstetrical hemorrhage. These organizations would include Confidential Enquiry into Maternal and Child Health (UK), National Institute for Health and Clinical Excellence (UK)[66], Obstetric Anesthetists Association (UK)[67], Association of Anaesthetists of Great Britain and Ireland (UK), California Maternal Quality Care Collaborative, American College of Obstetrics & Gynecology.[68]

Where blood is not an option

Caring for patients where blood is not an option (BNAO), can be challenging in obstetrics. The broadest category of BNAO patients are Jehovah's Witnesses. The primary focus in the antepartum period should be to make sure that any iron deficiency is managed. While oral iron is commonly prescribed, compliance with its use is limited. If the patient is anemic going into the third trimester, thought should be given to intravenous iron. The cost is remarkably low and the common fear of allergic reactions is overstated. Erythropoietin is generally not needed in this population because endogenous erythropoietin is elevated and should facilitate the production of erythrocytes. During delivery, thought should be given to using autotransfusion systems to collect shed blood and readminister it. Other issues worth paying attention to are identifying these patients upon admission and understanding what they will accept and not accept. Most BNAO patients will not accept the major components of erythrocytes, plasma and platelets. Some will accept cryoprecipitate, albumin, and autotransfusion. So, a conversation with the patient as to their wishes needs to take place before delivery. A refusal of transfusion consent also needs to be developed to document their refusal.

Conclusion

Blood transfusion in obstetrics is common and is occurring more often than in previous years. Ideally, women should deliver in a hospital that has a blood bank in case that they do bleed. If possible, blood transfusions should be guided by laboratory testing and precaution should be

taken to prevent alloimmunization in this specific population. Autotransfusion should be used whenever possible to minimize the exposure to allogeneic blood.

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