Fluid and blood transfusion management in obstetrics
Brigitte E. Ickx

In this review, we shall consider the oral and intravenous fluid management of pregnant women during labour and operative delivery in the context of neuroaxial blockade. We shall also discuss the use of blood transfusion in the peripartum period, especially during postpartum haemorrhage. Current management of military casualties and major civilian trauma challenges traditional practices of blood product administration in massive haemorrhage and may radically modify transfusion practices during obstetric haemorrhage.

Introduction
Peripartum fluid management remains controversial. The scope of this review is limited to an examination of the best practices of fluid administration in the reduction of complications associated with central neuroaxial blockade both for labour and caesarean section, and an analysis of the risk versus benefit of fluid resuscitation in haemorrhagic shock. Blood transfusion, particularly in the context of major postpartum haemorrhage (PPH), is examined and new therapies based on recent reports of massive transfusion following trauma are proposed. Relevant recent articles were sought from Pubmed, Medline, and the Cochrane Library using appropriate controlled terms: fluid to prevent hypotension for neuroaxial blockade during labour or caesarean section and blood transfusion, peripartum haemorrhage, massive transfusion, and key words (fluids, transfusion, haemorrhage, obstetric). Additional articles were obtained through manual searches.

Fluid management during labour and caesarean section
During uncomplicated labour, oral intake of clear fluids (water, orange juice without pulp, black coffee, clear tea, sports drinks, etc.) improves comfort and satisfaction without increasing maternal risk. The uncomplicated woman undergoing elective caesarean delivery may be allowed to drink small amounts of clear fluids up to 2 h before induction of spinal anaesthesia. Those with additional risks of pulmonary aspiration (obesity, diabetes mellitus, predictable difficult intubation) or labouring women at increased risk of operative delivery (non-reassuring foetal heart pattern) should have restricted oral fluid intake determined on a case-by-case basis. Liberal water intake should not be encouraged as pregnant women have reduced tolerance to water loading, and hyponatraemia can occur in the postpartum period.

Crystalloids are commonly used for vascular loading prior to neuroaxial blockade. Hofmeyr et al. reviewed the need for prophylactic intravenous fluid preloading before regional anaesthesia in labour and concluded that preloading prior to traditional high-dose local anaesthetics might have beneficial maternal and foetal effects in healthy women. However, a low-dose epidural anaesthesia regimen or combined spinal–epidural (CSE) anaesthesia technique may reduce the need for intravenous preloading. Published studies were too small to show whether preloading was beneficial for women having regional anaesthesia during labour using lower dose anaesthetics with or without opioids. Further studies are needed to assess the risks and benefits of intravenous preloading for current anaesthesia techniques.

Caesarean section is usually performed under spinal anaesthesia. The practice of managing the associated maternal hypotension with crystalloid preload has fallen from favour following evidence that, owing to rapid redistribution, it is relatively ineffective. Recent consensus is that spinal anaesthesia should not be delayed in order to administer a fixed volume of fluid. Crystalloid preload generally administered 20–30 min before the induction of spinal anaesthesia offers no advantage over crystalloid co-load administered at the time of identification of cerebrospinal fluid. However, in this setting, crystalloid infusions are more effective than no fluids in preventing hypotension, and colloids are more effective than crystalloids. Volume loading with colloids, either before or during induction, appears to be effective in blunting the haemodynamic disturbance associated with spinal anaesthesia in pregnant women. Of the colloid solutions that have been studied in this role [dextran, albumin, gelatine, hydroxyethyl starch (HES)], the new generation HES solution (HES 130/0.4; Fresenius Kabi, Bad Homburg, Germany) seems the most promising in terms of safety and efficacy. Concerning the optimum
volume of intravenous fluid to be administered, no clear conclusions can be drawn. Overall, no single intervention is sufficient to prevent hypotension and a combination of several measures, including fluid administration, low-dose spinal anaesthesia with or without combined spinal anaesthesia (CSE), the prophylactic or reactive administration of vasopressor, and mechanical methods, is recommended. Some clinicians are reluctant to use colloids because of the risk of anaphylactic type reaction. The effect of colloids on renal function should be minimal in the absence of renal dysfunction. The type of fluid used for loading prior to caesarean section can affect blood coagulation, but any impact on consequent blood loss is theoretical, as it has not been widely investigated. Butwick and Carvalho showed mild coagulation disturbance, as measured in healthy parturients by thromboelastography after 500 ml 6% HES (Hespan) compared with no effects after 1500 ml of lactated Ringer’s solution. Because HES solutions vary in terms of their molecular weight, degree of substitution, C2/C6 ratio, and physicochemical characteristics, they may have differing effects on coagulation. Further studies are warranted to assess the effects on coagulation of the new generation HES solution and other fluid preloading regimens, and quantify any impact on clinical outcome for patients undergoing caesarean section with spinal anaesthesia.

**Haemorrhage, fluid and blood transfusion**

Many of the physiological cardiovascular and haemostatic changes in pregnancy may be viewed as preemptive developments in anticipation of blood loss at delivery. Total blood volume increases gradually from the first trimester and reaches a plateau in the last weeks of pregnancy. Plasma volume increases proportionally more than red cell mass, leading to haemodilution and a relative anaemia. In a healthy pregnant woman at term, physiological hypervolaemia modifies the response to blood loss. An increase in resting heart rate, peripheral vasodilatation, and the widened pulse pressure in pregnancy can delay the classical signs of shock. Dilutional anaemia is common and haemoglobin concentrations are lowest between 28 and 34 weeks gestation. Pregnancy is associated with increases in several coagulation factors, including fibrinogen, factors VII, VIII, IX, X, XII, and von Willebrand factor, decreases in anticoagulant protein S, and an increase in activated protein C resistance. Fibrinolytic activity and tissue plasminogen activator activity decrease as thrombin-activated fibrinolysis inhibitor (TAFI) and plasminogen activator inhibitor (PAI) levels increase.

Although PPH is a leading cause of maternal mortality worldwide, in Europe and North America it is relatively well managed and blood components are readily available. In these regions, PPH is rarely lethal and only one or two maternal deaths per 100,000 live births are attributable to haemorrhage. However, the incidence of PPH in high-resource countries is likely to increase. Although PPH requiring transfusion occurs in less than 1% of deliveries, women who deny blood components or who refuse transfusion (Jehovah’s Witnesses) are at an increased risk of death. Owing to the unforeseeable nature of PPH and, in most cases, the paucity of risk factors, the situation may not be recognized in time to provide adequate treatment. Physicians typically underestimate, rather than overestimate, blood loss, often resulting in delays in the initiation of blood transfusion and other resuscitative efforts. Maintenance of perfusion pressure and blood volume is provided initially with crystalloids or colloids while waiting for blood products. The optimal fluid type for use in hypovolaemic patients has been the subject of much debate; most studies have concentrated on traumatic haemorrhage. Peripartum haemorrhage is different because it usually occurs in an environment in which blood products are readily available and the response is well rehearsed. Nevertheless, PPH is an exsanguinous process in which failure to treat promptly will contribute to morbidity and mortality. Anaemia is better tolerated than hypovolaemia, regardless of the cause of fluid loss. However, two difficulties arise in the pregnant woman compared with other patient groups. First, hypovolaemia is much more difficult to recognize owing to the physiological changes that occur during pregnancy. Second, oxygen delivery is compromised when blood volume shrinks in the presence of a reduced haemoglobin concentration. Crystalloids and colloids are effective in restoring preload and cardiac output, but contribute further to haemodilution. Some colloids have direct effects on haemostasis and should be avoided. Although colloids expand the plasma volume more rapidly and last longer than crystalloids, in critically ill patients, albumin does not offer any advantage in terms of morbidity or mortality compared with saline.

Studies with other colloids, namely HES 130/0.4 are planned or completed but not yet published (http:/clinicaltrials.gov). Resuscitation with a large volume of 0.9% saline is not recommended because of the potential development of hyperchloremic acidosis, though the clinical significance of this is still unclear. There is an argument for the use of balanced fluid resuscitation using fluid (crystalloids and colloids) containing a physiological balance of electrolytes. Hypertonic saline has also been proposed in haemorrhagic shock, but its exact role is currently unclear. In obstetrics, only one study, conducted in the distant past, described the use of hypertonic saline in the setting of preeclampsia; its use has not been studied in obstetric haemorrhagic shock. Owing to the anaemia frequently present in the peripartum period, dilution with clear fluids must have a limit, and, provided that intravascular volume remains adequate for perfusion, a haemoglobin concentration of 7 g/l (equivalent to a haematocrit of 0.21) provides sufficient oxygen-carrying capacity to maintain cardiopulmonary function in healthy patients. Excessive amounts of colloid expander may...
contribute to worsening coagulation in a bleeding patient, though the new generation of HES solutions (13/0.4) have a smaller impact on coagulation. Currently, there is no consensus regarding the best fluid administration strategy in bleeding patients.

Permissive hypotension to avoid ‘popping the clot’ before interventional techniques (surgery or vascular embolization) is advocated in the management of trauma, but validation by factual clinical data is poor to date. This is not an option prior to delivery in pregnant patients because maintenance of a normal blood pressure is of paramount importance for the viability of the foetus.

Guidelines for the management of major haemorrhage recommend fresh frozen plasma (FFP) when specific laboratory thresholds are reached, notably a prolongation in prothrombin time or activated partial thromboplastin time of 1.5 times the normal value and ongoing bleeding. Peripartum bleeding can be torrential, so, rather than wait for guideline thresholds to trigger the request, the instruction for FFP is administered after a given number of packed red blood cells (PRBCs) have been transfused. Recently, this approach has been challenged, and experience gleaned from the management of military casualties and major trauma victims suggests that early use of plasma transfusion may be more effective in massive bleeding and that RBCs in conjunction with clotting factors should be given in roughly similar proportions, particularly early in resuscitation. Several studies demonstrate a high ratio of FFP to RBCs to be independently associated with improved survival, primarily by reducing death from haemorrhage. This subject has been reviewed recently in the setting of severely injured patients. All previous trials were retrospective, observational, or before and after studies and do not represent high levels of evidence. Yet the massively transfused patient clearly does poorly when a large number of RBC units are administered with minimal plasma. Good sense suggests that a plasma to RBC ratio approaching 1:1 is optimal in the setting of haemorrhage. The best evidence also suggests that early plasma repletion is important. However, the optimal plasma to RBC ratio may be difficult to determine for ethical and epidemiological reasons. The concept of a ratio will always be empirical and the best evidence for any given ratio will remain limited. In the absence of a convincing transfusion ratio, the use of a massive transfusion protocol itself, with concurrent rapid access to products and improved training of all participants, may be the primary factors behind recent reports of improved survival.

There is a real need to measure the coagulation status of massively transfused patients in something close to real time in order to individualize transfusion needs. Rapid serial estimations of the platelet count, prothrombin time, activated partial thromboplastin time, and fibrinogen can only be achieved when good support is available from the coagulation laboratory, and, although the information is retrospective, the underlying trend can be helpful. These tests will never predict the risk of bleeding because they were not designed for this purpose, but they may be helpful as indicators of the severity of the coagulopathy. The correction of abnormal coagulation variables through the administration of clotting factors, but in the absence of bleeding, is not advised. Point of care devices such as Thromboelastography (Haemoscope, Niles, Illinois, USA) and Thromboelastometry (Pentapharm, Munich, Germany) may offer the means of monitoring coagulopathy and guiding treatment, especially in the presence of hyperfibrinolysis, but they are not in widespread use and, consequently, the necessary experience and familiarity are lacking. Most cases of obstetric haemorrhage will be managed without them.

Resuscitation with RBCs and crystalloid/colloid causes dilutional thrombocytopenia, giving rise to a platelet count of around 50 × 10^9l^-1 following transfusion of two blood volumes. In addition, platelet function is affected by a fall in haematocrit and by increased fibrinogen degradation products. In a bleeding patient, a platelet count of at least 50000 ml^-1 should be maintained, though this target is based on a consensus of medical opinion rather than evidence and depends on the rapidity of blood loss and on whether platelet dysfunction is expected. Possible benefits of proactive platelet transfusion in PPH have not been investigated.

Concentrates of coagulation factors
The traditional target level of fibrinogen advocated by several transfusion guidelines (1 g l^-1) may be underestimated in the setting of PPH. Charbit et al. showed that fibrinogen was the only marker associated with severe PPH and that a fibrinogen level of 2 g l^-1 or less was associated with a positive predictive value of 100% for severe haemorrhage. Hence, fibrinogen or cryoprecipitate should perhaps be given more rapidly in order to prevent coagulopathy. FFP contains variable amounts of fibrinogen and is too dilute to increase levels sufficiently without causing fluid overload. Substitution therapy with a fibrinogen concentrate, pasteurized, expensive but not available in all European countries, improved global laboratory coagulation results and, as a supplementary intervention, appeared to diminish requirements for RBCs, FFP, and platelet substitution during massive haemorrhage. Serious bleeding in women with uterine atonia, abruptio placenta, and placenta praevia is often associated with excessive fibrinolysis and fibrinogenolysis, resulting in very low levels of plasma fibrinogen and high levels of fibrin D-dimer. Strengthening the logic of fibrinogen substitution as a therapy in this subgroup. However, the efficacy of the administration of fibrinogen concentrates has not been studied in the obstetric setting and deserves further investigation.
In some European countries, prothrombin complex concentrates (PCCs), containing factors II, VII, IX, X, and some anticoagulants are proposed for massively transfused patients. This strategy is founded on the interesting experimental observation that PCCs were shown to be effective in normalizing coagulation and controlling bleeding after dilutional coagulopathy. However, randomized clinical controlled trials are necessary before this practice can be universally recommended, as PCCs are only licensed for the rapid reversal of vitamin K antagonist and selective congenital factor deficiency.

Recombinant factor VIIa (rFVIIa) is the activated form of factor VII produced by genetic engineering. It is licensed in Europe for the management of patients with haemophilia complicated by inhibiting antibodies to factor VIII or IX and in patients with Glanzmann’s thrombasthenia. Off-label use of rFVIIa has been reported to halt the process of coagulopathy, secure haemostasis, and improve laboratory values in massive haemorrhage. Its successful use has been reported in postsurgical bleeding and in consumptive coagulopathy. Recombinant activated factor VII has, therefore, been suggested as a potential haemostatic agent in massive obstetric haemorrhage. Its use has resulted in the publication of several case reports and case series reporting obstetric haemorrhage. Although considered contraindicated in hypercoagulable states, such as disseminated intravascular coagulation (DIC), it has been used in this setting without apparent adverse events. With regard to case reports and series, a publication bias in favour of rFVIIa must be suspected, and the difficulties of attributing a thrombotic event to rFVIIa deserve to be acknowledged. The haemostatic effect of rFVIIa (not licensed for obstetric haemorrhage) requires adequate levels of platelets and fibrinogen and correction of acidosis and temperature abnormalities. Overall, although the safety and efficacy of rFVIIa appear promising, high-level evidence for its use in PPH is still lacking. A randomized trial is currently underway in France (http://clinicaltrials.org).

Antifibrinolytics
As fibrinolysis is frequent when coagulopathy develops in obstetric patients, the administration of antifibrinolytic agents has been advocated when massive transfusion takes place. Use of the lysine analogue tranexamic acid has been reported occasionally in the literature and some case reports have reported reduced blood loss in puerperal haemorrhage. The recently updated PPH treatment guidelines prepared by the WHO state that tranexamic acid might be used in the treatment of PPH if other measures fail. However, the guidelines point out that the quality of evidence on which this recommendation is based is low. A large, international, randomized, placebo-controlled clinical trial is planned to determine the role of tranexamic acid in this situation (World Maternal Antifibrinolytic trial, WOMAN; clinicaltrial.org).

Whole blood
A few physicians believe that replacing blood in patients who are bleeding with large amounts of fresh whole blood is the most appropriate approach to address the shock and coagulopathy that rapidly develop. In obstetric practice, some have advocated reconsideration of whole blood transfusion. This creates other logistical problems and the unavoidable obligation of blood screening and viral detection will render the procedure so lengthy that a number of coagulation factors will be destroyed. In the actual and legal blood safety and quality regulations, it is not possible and not ethical to provide fresh whole blood in settings other than military casualties.

Other considerations
Finally, but importantly, a patient will hardly be resuscitated if hypothermic, coagulopathic, and acidic. Every effort should be attempted to avoid what the trauma experts identify as the ‘lethal triad’. Lastly, a well-organized PPH protocol with a clear definition of individual roles using newer surgical, pharmacological, and transfusion approaches should aid in decreasing the morbidity and mortality associated with massive haemorrhage.

Conclusion
Many strategies in obstetric practice have changed in recent years, including approaches to fluid loading for neuroaxial analgesia and anaesthesia. With regard to blood transfusion for a parturient who is heavily bleeding and for those with continuing loss, replacement with a fluid that most closely approaches the composition of the blood lost is probably the best approach. Although blood transfusions are extremely important and often lifesaving in many cases of severe PPH, awareness of the risks of blood transfusion, including those related to transfusion-transmitted infectious diseases, haemolytic transfusion reactions, anaphylaxis, transfusion-related acute lung injury, and transfusion-associated cardiac overload, should also be kept in mind. More studies are warranted, especially in obstetric haemorrhage.

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References


