New trends in the management of postpartum haemorrhage

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Keywords: postpartum haemorrhage, management, new trends

 South Afr J Anaesth Analg 2014;20(1):44-47

Introduction

If the World Health Organization (WHO) global maternal mortality by cause is examined for the period 1997-2007, haemorrhage constitutes 35% of deaths. Published data from the triennium 2008-2010 in South Africa indicate that if non-pregnancy-related sepsis is excluded, haemorrhage still ranks with hypertension as the most common cause of maternal deaths (24%).

So how can anaesthetists improve this situation and save lives? Sadly, the main reason for the appalling figures in respect of maternal deaths in sub-Saharan Africa is poor access to basic obstetric care, blood products and basic commodities, such as electricity, for the refrigeration of blood and drugs such as oxytocin.[1]

Nevertheless, there are many areas where management, and hence outcomes, could be improved. This article addresses the crucial issues of predicting haemorrhage, assessing blood loss, point-of-care monitoring and transfusion protocols. Surgical techniques and oxytocic therapy are equally important, and are the subject of many other reviews.

Predicting increased transfusion requirements

The first essential factor in predicting haemorrhage is knowledge of the pathology. This is best remembered under the headings of the 4 "Ts":

- Tone (uterine atony or inflammation),
- Tissue (placental complications),
- Trauma (physical injury or previous trauma),
- Thrombin (congenital, or more commonly, acquired coagulation abnormalities).[2]

The Royal College of Obstetricians and Gynaecologists provides odds ratios (ORs) for postpartum haemorrhage (PPH) in particular clinical scenarios. Suspected or proven placental abruption and placenta praevia constitute the highest risk (ORs of 13 and 12, respectively). Multiple pregnancies, retained placenta and mediolateral episiotomy (OR 5), and pre-eclampsia (OR 4) are next in order. However, the anaesthetist should be aware that a large number of cases carry an increased risk of major resuscitation since the OR for any emergency Caesarean section is 4.

The incidence of placenta accreta increases with the number of Caesarean sections. It rises to > 20% after two previous operative deliveries, and to 30% or more after 3-4 Caesarean sections.[3] Likewise, the requirement for hysterectomy increases after two previous Caesarean sections in the presence of a major grade of placentae praevia.[4]

Transfusion requirements are known to be considerable in patients with placenta accreta. One paper quotes the use of > 10 units of packed cells in 26/66 cases.[5] A recent editorial, which emphasises the importance of adequate planning for Caesarean section for placenta accreta, highlights an alarming increase in the condition over the past 40 years.[6] A large retrospective audit in Dublin reports on 358 hysterectomies associated with 852 379 deliveries. As a precipitating cause, placenta accreta increased from 5% between 1966 and 1975, to 47% between 1996 and 2005. There is no doubt that the increased Caesarean section rate is a major contributor to these statistics. Combining the predictors of placenta praevia, the number of previous Caesarean sections and ultrasound findings may increase the sensitivity and specificity of predicting placenta accreta,[7] and by inference, the more dangerous increta and percreta.

Assessment of blood loss

PPH is defined as blood loss of > 500 ml post-vaginal delivery, or 1 000 ml post Caesarean section.[8] Severe PPH

implies >1 500 ml blood loss, at least a 4 U packed cell transfusion, a decrease in haemoglobin (Hb) of 4 g/dl, or any haemorrhage associated with haemodynamic instability. Major haemorrhage involves > 2 500 ml, and massive PPH one blood volume or 10 U of packed cells in 24 hours. Not only should *volume* be assessed, but also the *rate* of blood loss. The "rule of 30" is useful. If the patient's systolic blood pressure drops by 30%, the heart rate rises by 30%, the respiratory rate increases to more than 30/minute, the haemoglobin (Hb) or haematocrit drops by 30%, and the urinary output decreases to <30 mL/hour, the patient is likely to have lost 30% of her blood volume, and is in moderate shock, leading to severe shock. The shock index, defined as the heart rate divided by the systolic blood pressure (normal up to 0.9 in obstetrics), has been shown in a systematic review of the relationship between blood loss and clinical signs, to be an accurate indicator of compensatory changes in the cardiovascular system due to blood loss. A study that examined the accuracy of blood loss estimation after simulated vaginal delivery showed that there was a 16% underestimation at 300 ml loss, which increased to 41% at 2 000 ml blood loss.[10] Active periodic estimation improves the accuracy of the estimation. A pictorial guide to aid visual estimation has been published, based on experience at Queen Charlotte's Hospital, London.[11]

Monitoring of haemoglobin and coagulation

In assessing the specific pathophysiology involved and the progress of resuscitation, changes in Hb and parameters of coagulation need to be assessed. The HemoCue® device (HemoCue America, Brea, USA) and the Rainbow SET® 158 Radical 7 Pulse CO-Oximeter (Masimo Corporation, Irvine, USA) are currently the available point-of-care monitors of Hb. The former depends upon the azidmethaemoglobin reaction, and the latter applies multiple visible and infrared lights from the light emitter to the finger, and then acquires blood constituent data based on light absorption. A publication from the Stanford University obstetric anaesthesia group has shown that when comparing the Pulse CO-Oximeter to laboratory values, limits of agreement were unacceptably wide.[12] In addition, another study compared the HemoCue® and the Pulse CO-Oximeter in respect of laboratory values, and found that the HemoCue® was associated with narrower and more acceptable limits of agreement with laboratory values.[13] Therefore, current evidence is that the HemoCue® is the best available point-of-care device to be used in combination with assessments of Hb and acid base balance once arterial monitoring has been established early in a resuscitation.

New concepts of coagulation depict the formerly separate intrinsic and extrinsic pathways as being tightly integrated. The tissue factor (extrinsic) pathway initiates thrombin generation which triggers the intrinsic elements to generate the thrombin burst. Thrombin has a central role, also activating factor XIII and stimulating the conversion of fibrinogen to fibrin. Feedback regulation of coagulation also occurs via thrombin, as well as the thrombolytic pathway. Depletion of fibrinogen levels is the central problem in the majority of cases of obstetric haemorrhage.

A survey has shown that standard haemostatic tests (prothrombin time and activated partial thromboplastin time) did not correlate well with the volume of haemorrhage in obstetrics.[14] The fibrinogen level correlated best with blood loss and was the best marker of a developing coagulopathy. In addition, the fibrinogen assay had a long turnaround time.

Therefore, there is increasing support for the use of point-of-care monitoring in cases of obstetric haemorrhage, using the viscoelastic devices, TEG® (thromboelastography) and ROTEM® (thromboelastometry).[15] Laboratory coagulation tests on plasma end with the formation of fibrin strands, but whole blood tests with TEG® and ROTEM® test coagulation and also clot strength, stability and lysis. Reference ranges have been established for pregnancy using TEG®, showing the hypercoagulable state.[16] ROTEM® allows for the addition of activators and inhibitors, to test various aspects of haemostasis. The FIBTEM test is of particular importance in obstetric haemorrhage in which the platelet inhibitor cytochalasin D is added, which allows an assessment of the role of fibrinogen on clot stability. Once again, reference ranges in pregnancy are being established.[17] Bedside assessment of PPH by ROTEM® has shown decreased fibrin-clot quality in PPH, as evidenced by activation at 5 and 10 minutes, as well as maximum clot firmness.[18] These measures correlate with measured fibrinogen levels. A recent investigation found that if fibrinogen was measured by point-of-care TEG® instead of the standard laboratory method, the use of fibrinogen concentrate would be increased and less fresh frozen plasma (FFP) would be given.[19] Expert opinion is that "transfusion monitoring will still require a combination of conventional tests of Hb and coagulation, but perhaps with increased use of point-of-care testing in the future".[20]

Transfusion protocols

Obstetricians and anaesthetists agree that a massive transfusion protocol (MTP) is essential in any institution that deals with obstetric haemorrhage on a regular basis.[21] Some investigators recommend that the MTP is initiated when the coagulopathy is already advanced.[22] A more reasonable approach is that of the Stanford group which recommends the MTP when uncontrollable haemorrhage or the use of > 10 U packed cells is anticipated.[23] As yet, there is no consensus on the components of the transfusion. There is no evidence that the 1:1:1 FFP to red blood cells to platelets ratio (as recommended in trauma resuscitation) should be applied in obstetrics.

There is no doubt that fibrinogen occupies a central role in the transfusion strategy. Plasminogen and its activators are upregulated in early pregnancy, but its inhibitors are also enhanced, resulting in increased levels of fibrinogen. Fibrinolysis is increased in late pregnancy, and this may contribute to decreased levels of fibrinogen after delivery.

However, it is not known whether fibrinolysis or rapid consumption of fibrinogen is the major contributor to hypofibrinogenaemia post-delivery. What is well established is that a decrease in fibrinogen is an early predictor of severity of PPH. A level of < 2 g/l has a 100% positive predictive value for severe PPH.[24] Fibrinogen levels vary greatly between patients (mean 4.8, range 2.1-9 g/l).[25] Although elevated prepartum fibrinogen levels are not associated with a reduced risk of PPH,[26] early measurement of fibrinogen levels during PPH may be used to predict severity.[27] A recent study showed that the first fibrinogen level and FIBTEM measurement taken after identifying PPH predicted the need for a > 4 U packed cells transfusion.

How should fibrinogen be administered? Practitioners should be aware of the contents of the blood products that are administered at their institution. Cryoprecipitate, the cold insoluble fraction of FFP, contains approximately 10 times the concentration of fibrinogen as FFP. Therefore, while FFP may be useful for volume expansion and for the administration of physiological levels of coagulation factors, it is not the product of choice for the restoration of fibrinogen levels. As a rough guide, in order to raise the fibrinogen level by 1 g/l, 30 ml/kg of FFP needs to be given, compared with 3 ml/kg of cryoprecipitate. FFP may even dilute the fibrinogen during PPH. Fibrinogen concentrate is a virally inactivated lyophilised powder that can be stored at room temperature. No thawing or blood typing is required. When administered in a small volume, this product (not yet available in South Africa) rapidly restores fibrinogen levels. The Fibrinogen Concentrate as Initial Treatment for Postpartum Haemorrhage (FIB-PPH) trial recruited 245 patients in order to assess whether or not 2 g fibrinogen concentrate, used as the first treatment for PPH, reduced the requirement for blood transfusion.[28] Publication of the results is awaited. An excellent recent editorial summarises the approach to hypofibrinogenaemia during PPH.[29]

What of the use of antifibrinolytics for PPH? WHO care pathways for postpartum haemorrhage and retained placenta recommend the use of tranexamic acid for continued bleeding during uterine atony, uterine rupture and lower genital tract trauma. A small unblinded study on 154 women randomised to receive large-dose tranexamic acid versus placebo after > 800 ml blood loss after vaginal delivery, showed a statistically, but not clinically, significant reduction in blood loss in the tranexamic acid group.[30] The prophylactic administration of tranexamic acid in a prospective randomised placebo-controlled trial on 660 women having Caesarean delivery, showed reduced mean blood loss and a reduced risk of massive blood loss in the treatment group.[31] The World Maternal Antifibrinolytic (WOMAN) Trial is in progress.[32] Four thousand women are to be randomised to receive 1 g tranexamic acid intravenously, repeatable once, versus placebo, after 500 ml or 1 000 ml blood loss after vaginal or Caesarean section delivery, respectively. This large trial should resolve the issues of both the potential reduction in blood loss and mortality by tranexamic acid, as well as possible thromboembolic complications.

The role of recombinant activated factor VIIa (rFVIIa) in PPH remains highly controversial. rFVIIa was originally thought to work mainly through a tissue factor-dependent mechanism. It has been discovered that at pharmacological plasma concentrations, rFVIIa binds directly to the activated platelet and compensates for deficiencies of factor VIIIa and IXa.[33] However, several other coagulation factors are also essential for fibrin clot formation. Current recommendations are that this agent should only be used after failure with conventional therapy.[34,35] The dose is 90 µg/kg intravenously over 3-5 minutes, repeatable once. An adequate haematocrit, a platelet count > 50 x 10^9/l, fibrinogen > 1 g/l, pH > 7.2, and temperature > 34^0C are required. These are difficult criteria to achieve during massive obstetric haemorrhage. This agent is also extremely costly, and there has been at least one literature report of pulmonary embolism after its use during PPH.[36] It should be remembered that the Royal College of Obstetricians and Gynaecologists recommends that PPH > 1 l or blood transfusion is an indication for subsequent thromboprophylaxis.

Cell salvage

Although it is not a substitute for allogeneic blood transfusion, cell salvage has been embraced in the UK as an adjunct to acute resuscitation in PPH, and the National Institute for Health and Care Excellence guidelines recommend it. The risks of amniotic fluid embolism are thought to be very low if leucocyte depletion filters are used. Infection is also uncommon.[37]

A suggested detailed strategy is as follows:

- No strategy of management of PPH is effective without early referral, availability and rapid couriering of blood products, and a well-defined call-out system of senior anaesthetists and obstetricians.
- Excessive crystalloids and colloids should be avoided.
- A massive transfusion protocol should be initiated when >10 U packed cells transfusion is anticipated, or if 1 500 ml of blood has been lost, and the continuing rate of loss remains high and uncontrollable.
- Although not proven, a reasonable ratio of blood products is red blood cells to FFP to platelets of 6:4:6.
- O-negative or group-specific red blood cells should be administered.
- Ideally, an early estimate should be made of fibrinogen consumption or fibrinolysis with ROTEM® or TEG®, and/or a laboratory assessment of fibrinogen level (Clauss test).
- No more than 4 U FFP should be infused initially.
- Cryoprecipitate (or fibrinogen concentrate, when available) should then be administered to maintain fibrinogen levels > 1.5 g/l (3 ml/kg raises fibrinogen level by 1 g/l).

- The platelet count should be maintained > 50 x 10^9/l, using random donor-pooled platelets.
- Tranexamic acid 1 g should be given intravenously, repeatable once, until proved otherwise.
- A controversial option is recombinant activated factor VIIa as a last resort, 90 µg/kg intravenously, repeatable once.

Urgent access to definitive care remains a major stumbling block in limited-resource areas in the developing world. However, recent advances in the prediction and assessment of blood loss, a better understanding of coagulation mechanisms, point-of-care monitoring and the availability of a massive transfusion protocol, should improve the efficacy of management of PPH in the labour ward and during Caesarean sections. Central to success are the flair and leadership skills of the anaesthetist in the co-ordination of the resuscitation.

References

1. Dyer RA, Reed AR, James MF. Obstetric anaesthesia in low-resource settings. Best Pract Res Clin Obstet Gynaecol. 2010;24(3):401-412.
2. Solomon C, Collis RE, Collins PW. Haemostatic monitoring during postpartum haemorrhage and implications for management. Br J Anaesth. 2012;109(6):851-863.
3. Usta IM, Hobeika EM, Musa AA, et al. Placenta previa-accreta: risk factors and complications. Am J Obstet Gynecol. 2005;193(3 Pt 2):1045-1049.
4. Grobman WA, Gersnoviez R, Landon MB, et al. Pregnancy outcomes for women with placenta previa in relation to the number of prior cesarean deliveries. Obstet Gynecol. 2007;110(6):1249-1255.
5. Stotler B, Padmanabhan A, Devine P, et al. Transfusion requirements in obstetric patients with placenta accreta. Transfusion. 2011;51(12):2627-2633.
6. Beilin Y, Halpern SH. Placenta accrete: successful outcome is all in the planning. Int J Obstet Anesth. 2013;22(4):269-271.
7. Weiniger CF, Einav S, Deutsch L, et al. Outcomes of prospectively-collected consecutive cases of antenatal-suspected placenta accreta. Int J Obstet Anesth. 2013;22(4):273-279.
8. Ahonen J, Stefanovic V, Lassila R. Management of post-partum haemorrhage. Acta Anaesthesiol Scand. 2010;54(10):1164-1178.
9. Pacagnella RC, Souza JP, Durocher J et al. A systematic review of the relationship between blood loss and clinical signs. PLoS One. 2013;8(3):e57594.
10. Toledo P, McCarthy RJ, Hewlett BJ, et al. The accuracy of blood loss estimation after simulated vaginal delivery. Anesth Analg. 2007;105(6):1736-1740.
11. Bose P, Regan F, Paterson-Brown S. Improving the accuracy of estimated blood loss at obstetric haemorrhage using clinical reconstructions. BJOG. 2006;113(8):919-924.
12. Butwick A, Hilton G, Carvalho B. Non-invasive haemoglobin measurement in patients undergoing elective Caesarean section. Br J Anaesth. 2012;108(2):271-277.
13. Skelton VA, Wijayasinghe N, Sharafudeen S, et al. Evaluation of point-of-care haemoglobin measuring devices: a comparison of Radical-7 pulse co-oximetry, HemoCue® and laboratory haemoglobin measurements in obstetric patients. Anaesthesia. 2013;68(1):40-45.
14. De Lloyd L, Bovington R, Kaye A, et al. Standard haemostatic tests following major obstetric haemorrhage. Int J Obstet Anesth. 2011;20(2):135-141.
15. Kozek-Langenecker SA. Perioperative coagulation monitoring. Best Pract Res Clin Anaesthesiol. 2010;24(1):27-40.
16. Polak F, Kolnikova I, Lips M, et al. New recommendations for thromboelastography reference ranges for pregnant women. Thromb Res. 2011;128(4):e14-e17.
17. Armstrong S, Fernando R, Ashpole K, et al. Assessment of coagulation in the obstetric population using ROTEM® thromboelastometry. Int J Obstet Anesth. 2011;20(4):293-298.
18. Huissoud C, Carrabin N, Audibert F, et al. Bedside assessment of fibrinogen level in postpartum haemorrhage by thrombelastometry. BJOG. 2009;116(8):1097-1102.
19. Urwyler N, Theiler L, Hirschberg M, et al. Standard vs. point-of-care measurement of fibrinogen: potential impact on clinical decisions. Minerva Anestesiol. 2012;78(5):550-555.
20. Stocks G. Monitoring transfusion requirements in major obstetric haemorrhage: out with the old and in with the new? Int J Obstet Anesth. 2011;20(4):275-278.
21. Clark SL, Hankins GD. Preventing maternal death: 10 clinical diamonds. Obstet Gynecol. 2012;119(2 Pt 1):360-364.
22. Pacheco LD, Saade GR, Gei AF, Hankins GD. Cutting-edge advances in the medical management of obstetrical hemorrhage. Am J Obstet Gynecol. 2011;205(6):526-532.
23. Gutierrez MC, Goodnough LT, Druzin M, Butwick AJ. Postpartum hemorrhage treated with a massive transfusion protocol at a tertiary obstetric center: a retrospective study. Int J Obstet Anesth. 2012;21(3):230-235.
24. Charbit B, Mandelbrot L, Samain E. et al. The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage. J Thromb Haemost. 2007;5(2):266-273.
25. Simon L, Santi TM, Sacquin P, Hamza J. Pre-anaesthetic assessment of coagulation abnormalities in obstetric patients: usefulness, timing and clinical implications. Br J Anaesth. 1997;78(6):678-683.
26. Peyvandi F, Biguzzi E, Franchi F, et al. Elevated prepartum fibrinogen levels are not associated with a reduced risk of postpartum hemorrhage. J Thromb Haemost. 2012;10(7):1451-1453.
27. Cortet M, Deneux-Tharaux C, Dupont C, et al. Association between fibrinogen level and severity of postpartum haemorrhage: secondary analysis of a prospective trial. Br J Anaesth. 2012;108(6):984-989.
28. Wikkelsoe AJ, Afshari A, Stensballe J, et al. The FIB-PPH trial: fibrinogen concentrate as initial treatment for postpartum haemorrhage: study protocol for a randomised controlled trial. Trials. 2012;13:110.
29. Butwick AJ. Postpartum hemorrhage and low fibrinogen levels: the past, present and future. Int J Obstet Anesth. 2013;22(2):87-91.
30. Ducloy-Bouthors AS, Jude B, Duhamel A, et al. High-dose tranexamic acid reduces blood loss in postpartum haemorrhage. Crit Care. 2011;15(2):R117.
31. Gungorduk K, Yildirim G, Asicioglu O, et al. Efficacy of intravenous tranexamic acid in reducing blood loss after elective cesarean section: a prospective, randomized, double-blind, placebo-controlled study. Am J Perinatol. 2011;28(3):233-240.
32. Shakur H, Elbourne D, Gulmezoglu M, et al. The WOMAN Trial (World Maternal Antifibrinolytic Trial): tranexamic acid for the treatment of postpartum haemorrhage: an international randomised, double blind placebo controlled trial. Trials. 2010;11:40.
33. Ahonen J. The role of recombinant activated factor VII in obstetric hemorrhage. Curr Opin Anaesthesiol. 2012;25(3):309-314.
34. Mercier FJ, Bonnet MP. Use of clotting factors and other prohemostatic drugs for obstetric hemorrhage. Curr Opin Anaesthesiol. 2010;23(3):310-316.
35. Welsh A, McLintock C, Gatt S, et al. Guidelines for the use of recombinant activated factor VII in massive obstetric haemorrhage. Aust NZ J Obstet Gynaecol. 2008;48(1):12-16.
36. McCarthy GC, Allen TK, Habib AS. Pulmonary embolism after administration of recombinant activated Factor VII for major obstetric hemorrhage. J Clin Anesth. 2012;24(6):508-509.
37. Allam J, Cox M, Yentis SM. Cell salvage in obstetrics. Int J Obstet Anesth. 2008;17(1):37-45.