Current Concepts in the Treatment of Major Obstetric Hemorrhage

Matthew Schwartz · Anasuya Vasudevan

Published online: 27 September 2013
© Springer Science + Business Media New York 2013

Abstract Major obstetric hemorrhage (MOH) is one of the top three causes of morbidity and mortality in the United States and the main cause of maternal death in the developing world. The growing number of multiple cesarean deliveries, augmented labors, pregnant women of advanced maternal age, maternal obesity, or abnormal placentation have a direct correlation with the observed increase in peripartum blood loss. As awareness of the morbidity and mortality associated with MOH increases, new diagnostic and therapeutic modalities are evolving to address this public health threat. This review presents current opinions and recent clinical advances in the diagnosis and management of, and resuscitation after, massive obstetric hemorrhage.

Keywords Obstetric hemorrhage · Placenta accretae · Uterotonics · Massive transfusion · Fibrinogen

Introduction

Postpartum hemorrhage (PPH) is a leading cause of maternal death worldwide; it is estimated to contribute to at least 30 % of all maternal deaths each year [1, 2]. Even in highly developed countries, for example the US, UK,

Canada, Australia, and France, the incidence of obstetric hemorrhage is increasing [3]. Despite the magnitude of this global problem, there is no uniform consensus on the definition of massive obstetric hemorrhage (MOH). In general, definitions of MOH are based on the volume of blood lost or the number transfusions needed over a given time period. Usually, the term MOH refers to clinical situations in which there is ongoing blood loss and failure to institute immediate resuscitative measures could result in maternal death.

The population at risk of MOH should be identified early. Active resuscitation should be initiated rapidly and the etiology of hemorrhage should be pursued and corrected. Currently, clinical shortcomings and lack of resources in many parts of the world interfere with delivery of peripartum care, and obstetric hemorrhage is still a leading preventable cause of tragic maternal morbidity and mortality.

Definition of Obstetric Hemorrhage

There is no unifying definition of MOH. In a singleton pregnancy, 500 mL blood loss during vaginal delivery and up to 1,000 mL blood loss during cesarean delivery has been accepted as the traditional norm. The generally accepted definition of massive hemorrhage is one or more of the following:

1. Estimated blood loss of 2,500 mL or more.
2. Need to treat coagulopathy.
3. Replacement of entire blood volume or transfusion of more than 10 units of blood in 24 h.
4. Replacement of 50 % of circulating blood volume in 3 h or blood loss of more than 150 mL/min [2, 4, 5].

M. Schwartz · A. Vasudevan (✉)
Department of Anesthesia, Critical Care and Pain Medicine,
Harvard Medical School, Beth Israel Deaconess Medical Center,
330 Brookline Avenue, Boston, MA 02215, USA
e-mail: avasudev@bidmc.harvard.edu

M. Schwartz
e-mail: mschwartz@bidmc.harvard.edu

Estimation of Blood Loss

Early recognition of peripartum blood loss is crucial to initiating resuscitative measures. It is well established that blood loss during childbirth is vastly underestimated, irrespective of the level of training and seniority of the clinicians. Stafford et al. recently investigated this phenomenon in the obstetric population at a high-volume tertiary care center where they compared visual estimates of blood loss by resident physicians with mathematically calculated estimates of blood loss (based on patient weight, height, and pre and post-delivery hematocrit). Of the 90 cesarean deliveries with calculated blood loss of more than 1 L, only 18 % were accurately estimated. Visual estimates for operative vaginal deliveries were often 2–3 times lower than calculated blood loss [6]. Other investigations have shown that focused education and periodic reinforcement improves accuracy of estimation of peripartum blood loss [7, 8]. In addition to training, improving the ability of care givers to recognize early signs of hypovolemia and request additional help has been validated [9•].

Despite losing 1,000–1,500 mL of blood during childbirth, a parturient may not exhibit obvious signs or symptoms of hypovolemia. The reasons for this are twofold.

1. Maternal blood volume increases throughout pregnancy. Because of this increased reserve, signs and symptoms of acute volume loss may not be apparent.
2. After the delivery of placenta, the myometrium clamps down on the spiral arteries, which results in redirection of the uterine blood flow to the maternal circulation, or autotransfusion.

With continued blood loss as a result of such conditions as uterine atony, birth trauma, abnormal placentation, or coagulopathy, the physiological balance is stressed. It is important to recognize major obstetric hemorrhage in a timely fashion, because a parturient's compensatory mechanisms may mask signs of acute hypovolemia. Treatment should be initiated promptly and aggressively to mitigate morbidity and mortality.

Etiology of MOH

Antepartum hemorrhage is usually the result of placenta previa or placental abruption which can be distinguished by clinical and diagnostic modalities. Intrapartum hemorrhage is usually a manifestation of uterine atony, abnormal placentation, retention of products of conception, birth trauma, or depletion of thrombin—either from dilution or consumption of coagulation products [10•, 11, 12].

Tone

Uterine atony is the leading cause of obstetric hemorrhage worldwide. Some of the risk factors for excessive postpartum blood loss are induction of labor, high and prolonged exposure to oxytocin, prolonged labor and/or dystocia, multiple gestation, polyhydramnios, chorioamnitis, and macrosomia. Most patients who have excessive bleeding from uterine atony requiring transfusion have no pre-defined risk factors [13•].

The International Postpartum Hemorrhage (PPH) Collaborative Group which included representatives from Australia, Belgium, Canada, France, the UK and the US reviewed international trends in PPH between the years 1991–2006. Evaluation of the national data bases from these high-resource countries confirm that PPH is increasing worldwide, even in high-resource settings [4]. In an 11-year population based retrospective cohort study from Ireland, 17,000 of the 649,019 (2.6 %) deliveries recorded had an associated diagnosis of PPH. Overall incidence of PPH had increased from 1.5 % in 1999 to 4.1 % in 2009. The risk of atonic PPH increased threefold, from 1 % into 3.4 % [14••]. Between 2000 and 2009, in British Columbia, the incidence of PPH increased by 27 % (95 % CI 21–34 %) between 2000 and 2009 (from 6.3 to 8.0 %) whereas that of atonic PPH increased by 33 % (95 % CI 26–41 %), from 4.8 to 6.4 %. Atonic PPH with blood transfusion increased from 17.8 to 25.5 per 10,000 deliveries and atonic PPH with suturing of the uterus, ligation of pelvic vessels, or embolization increased from 1.8 to 5.6 per 10,000 deliveries [15••]. In the US, analysis of the nationwide inpatient sample (NIS) suggests that biological differences may affect atonic PPH; specifically, Hispanics and Asian and/or Pacific islanders were found to be at significant risk for PPH, irrespective of potential mediators [13•, 15••].

Abnormal Placentation

The second most common cause of MOH is abnormal placentation [13•], including: placenta previa, accretae, increta, and percreta. Each cesarean delivery a woman undergoes increases her risk of developing abnormal placentation [16, 17]. As cesarean delivery has become increasingly more common, the incidence of abnormal placentation has increased. In the 1970s the incidence was believed to be 1 in 4,027 deliveries; this subsequently rose to 1 in 2,052 in the 1980s and to 1 in 533 in the 1990s [18].

Diagnosis of Abnormal Placentation

Placenta accreta can be diagnosed on the basis of ultrasound, in some cases, as early as the first trimester [19].

Sonographic findings suggestive of placenta accreta include large placental lacunae giving a “Swiss cheese” appearance and loss of retroplacental hypoechoic space. Vascular invasion of the myometrium can also be identified by use of color Doppler. Abnormal placentation has traditionally been diagnosed by ultrasonography. Non-contrast MRI has proven to be a more sensitive and specific imaging modality in the screening and evaluation of abnormal placentation. Non-contrast MRI is 88 % sensitive and 100 % specific in the diagnosis of abnormal placentation versus a respective 77 % sensitivity and 96 % specificity for ultrasonography [20, 21]. MRI is also superior when it comes to the evaluation of placenta invasion of posterior structures such as the bladder (placenta percreta) [16, 22].

Trauma

If hemorrhage continues despite adequate uterine tone, then the parturient should be evaluated for cervical lacerations, vaginal hematoma, and the possibility of uterine rupture [18, 23].

Coagulopathy-Dilutional/Consumptive/Congenital

Although pregnancy is a pro-thrombotic state, obstetric hemorrhage is often complicated by coagulopathy. Coagulation abnormalities, both congenital, for example Von Willebrands disease, and acquired during pregnancy (HELLP syndrome) predispose toward MOH [24–27]. The etiology of the coagulopathy needs to be recognized and treated. For example, if the coagulopathy is related to retained products of conception (e.g. placental tissue), then appropriate operative intervention and resuscitation should be initiated. In their pioneering study, Charbit et al. identified serum fibrinogen level as the single independent predictor of the severity of post-partum hemorrhage. In that study, fibrinogen less than 2 g/L had a positive predictive value of 100 % for developing severe post-partum hemorrhage [28]. De Lloyd et al. [29••] also showed that a decreasing fibrinogen level had the strongest correlation with volume of bleeding compared to other laboratory data in the setting of major obstetric hemorrhage. Fibrinogen concentrations ≥ 2.5 g/L are believed to be needed for ideal clot formation [30].

Management of Obstetric Hemorrhage

The following recommendations are based on literature documenting recent clinical advances in the management of MOH and on the authors' practice at the Beth Israel Deaconess Medical Center, a tertiary care hospital associated with Harvard Medical School.

Initiating Additional Help

When more than ordinary blood loss is suspected, health-care providers should be actively encouraged to call for “help”. Senior obstetricians and obstetric anesthesiologists should be notified immediately. Empowering midwives and caregivers to call for help early can be lifesaving. The Modified Early Obstetric Warning System (MEOWS) developed from the UK recommendations of Confidential enquiry into Maternal and Child health effort has demonstrated that women at risk of hemorrhage may be recognized early and managed with a well-developed bedside monitoring and/or screening tool that assesses worrisome trends in hemodynamic variables and impending shock [9•]. In the US, the mission of the California Maternal Quality Care Collaborative has been developed to eliminate preventable maternal death and injury and to promote equitable maternity care in the state. This important initiative also recognizes the essential role of labor and delivery nurses in its success [31].

Active Management of the Third Stage of Labor

Because uterine atony is one of the leading causes of PPH and maternal death [32–34], active management of the third stage of labor is strongly encouraged [32, 35]. Delivery of the placenta within 10–15 min of delivery of the baby, administration of oxytocin, even in low-resource settings, gentle cord traction, and fundal massage are advocated to promote uterine tone [36•, 37].

Medical Management of Uterine Atony

Ongoing blood loss in the setting of uterine atony generally requires administration of additional uterotonic agents. The most commonly used first-line uterotonic agent is intravenous oxytocin. Additional uterotonic agents include methylergonovine maleate, 15-methylprostaglandin F 2α , and misoprostol-prostaglandin E1. Carbetocin, a longer-acting oxytocin analogue is used in many centers, although its advantages and cost effectiveness are under scrutiny [38–41]. The indications for use, dose, and side effects of these medications are listed in Table 1. The choice of agent is affected by the co-morbidities of the parturient.

Oxytocin Oxytocin is the first-line uterotonic used routinely in the third stage of labor. Although there have been several investigations of the optimum dose of oxytocin, current dosage regimes are highly variable [42–44]. Sheehan et al. evaluated whether there was benefit to infusion (40 IU pitocin) after an initial 5-IU bolus in women who were low risk for obstetric hemorrhage. Although they found no difference in the occurrence of

Table 1 Uterotonics

Drug	Dose and route	Frequency	Special considerations
Oxytocin	10 IU- IM 20–40 IU diluted in 1 L, IV	Continuous IV infusion	Rapid administration can cause hypotension and tachycardia; IV bolus exceeding 3–5 IU may result in arrhythmias and hypotension
Methylergonovine (methergine)	0.2 mg IM	Every 2–4 h	Avoid in hypertensive disease. May precipitate hypertensive crisis
15-Methyl PG F 2 α	0.25 mg IM, myometrium	Every 15–30 min, maximum of 2000 mg	Can precipitate bronchospasm. Avoid among asthmatics
Misoprostol	1000 μ g, suppository	Once	May be dislodged easily especially in the presence of profuse bleeding

major obstetric hemorrhage between the groups, the (perceived) need for an additional uterotonic agent in the bolus and infusion group was lower than for the bolus only group (12.2 vs. 18.4 % $P < 0.0010$). Women were less likely to have a major obstetric hemorrhage in the bolus and infusion group than in the bolus only group if the obstetrician was junior rather than senior (0.57, 0.35–0.92, $P = 0.02$). The investigators concluded that addition of an oxytocin infusion after caesarean delivery reduces the need for additional uterotonic agents but does not affect the overall occurrence of major obstetric hemorrhage [39, 43, 45•]. King et al. evaluated the effect of saline versus oxytocin infusion after a bolus of 5 IU of pitocin for women at risk for uterine atony. Among this at-risk patient population, the investigators found a significant difference in uterine tone immediately after placental delivery which subsequently disappeared after 5 min. Overall, they concluded that addition of an oxytocin infusion did not alter the need for additional uterotonics in the first 24 h [46••].

In our practice, a parturient believed to be at risk of atony during cesarean section usually receives 2–3 IU oxytocin as an intravenous bolus followed by an infusion of 30–40 IU in 1 L. Although these doses are likely to be suprathreshold, we quickly determine the myometrial response to oxytocin and the need for second-line drugs early [43].

Bolus and infusions oxytocin infusion can cause peripheral vasodilatation (particularly in the setting of acute blood loss) resulting in severe maternal hypotension (Table 2).

Methylergonovine Maleate (for Example Methergine) Methylergonovine maleate (e.g. methergine) is an effective second-line uterotonic agent that is typically administered as a 0.2 mg intramuscular injection. Intravenous administration, although approved, is generally avoided, because of vasospastic side effects. Other common side effects are nausea, vomiting, and elevation of systemic arterial pressure from generalized increase in smooth muscle tone. Methylergonovine maleate is contraindicated in women with hypertension, significant cardiac

Table 2 Key points of resuscitation*Antenatal*

- Identify “at-risk” population
- Multidisciplinary planning

Peripartum

- Find and treat the cause of bleeding
- Minimize crystalloid resuscitation
- Maintain RBC:FFP ratio
- Fibrinogen levels of 2–3 g are the normal range in puerperium
- Maintain normothermia
- Replace calcium and treat electrolyte abnormalities
- Do not delay cesarean hysterectomy
- Plan for intensive care admission

disease, diabetes with retinal involvement, specifically, and in general in any patients particularly at risk of vasospasm.

Prostaglandins Prostaglandin F 2 α (Hemabate), 250 μ g as an intramuscular or intramyometrial injection, is also the uterotonic of choice when there are contraindications for ergot alkaloids. The side effects of this agent include severe bronchospasm. As such, its use is relatively contraindicated for patients with asthma or reactive airway disease.

Misoprostol Misoprostol is a synthetic prostaglandin E1 analogue which is a potent inhibitor of gastric secretion. It also is an abortifacient, because it induces myometrial contraction as a side effect. Therefore, in different doses, it has off-label uses for inducing labor and for treatment of postpartum hemorrhage. Up to 1,000 mg can be administered rectally for in the setting of postpartum hemorrhage. It is as efficacious as oxytocin and easy to administer even in resource poor setting—but is more expensive.

Calcium carbonate or gluconate Calcium carbonate or gluconate may be considered in severe uterine atony as an adjunct to the agents listed above.

Surgical Interventions for Management of Obstetric Hemorrhage

Bimanual compression

This obstetric maneuver can be attempted after a vaginal delivery. The uterus is compressed bimanually with one hand in the vagina and the other on the anterior abdominal wall.

Manual removal of placenta and/or dilatation and curettage (D&C) The World Health Organization (WHO) defines retained placenta as lack of expulsion within 30 min of delivery. In the absence of bleeding, the recommendation is that the parturient be observed for a further 30 min (or more) before manual removal of the placenta. If she is bleeding, intervention should be initiated sooner [47].

Uterine balloon tamponade

Balloon (Bakri, Rusch) tamponade can be a reliable therapeutic intervention and can help to guide further decision making. In a prospective-quasi experiment study, Lass et al. evaluated the effect of “tamponade test with the Bakri balloon” on patients with a diagnosis of PPH. They found a significant reduction in both arterial embolization (8.2 vs. 2.3 % odds ratio 0.26, CI 0.09–0.72 and surgical intervention (5.1 vs. 1.4 % odds ratio 0.26, CI, 0.07–0.95), with global success of 86 % [48]. If tamponade fails to control the hemorrhage, an early decision can be made to progress to either the interventional radiology suite or to further surgery. If the patient is unstable, surgical intervention is likely to be the best option.

Uterine compression sutures

Coker and coworkers [49] described these compressive sutures to control bleeding as an alternative to hysterectomy. B-Lynch and other hemostatic compressive sutures are used worldwide and may be a useful first-line surgical intervention for women responsive to bimanual uterine compression [50–52]. B-Lynch compressive sutures do not seem to interfere with future pregnancies; there are reports of women with a B-Lynch compressive suture having spontaneous conception and progressing to term pregnancy [53, 54].

Devascularization Techniques

Interventional Radiology (IR)

Interventional radiology procedures are not ideal in emergent situations when there is active ongoing massive

hemorrhage. In elective situations, an individualized treatment plan should be developed for patients at risk of massive blood loss, e.g. placenta accreta. The role of IR in elective and emergent clinical settings is discussed in depth in the section “[Management of Placenta accreta](#)”.

Surgical Ligation Selective ligation of uterine arteries, internal iliac artery, or hypogastric arteries has been described for control of massive postpartum hemorrhage. These are surgically challenging procedures with varying outcomes. However, despite ligation of these blood vessels, some patients may require cesarean hysterectomy to control hemorrhage. Although fertility is possible after selective artery ligation, patients are at subsequent risk for endometritis, synechiae formation, infertility, secondary hemorrhage, and infection [53, 55].

Cesarean Hysterectomy Peripartum hysterectomy may be indicated in cases of intractable postpartum hemorrhage. In an analysis of the NIS, Bateman et al. found that, in the US, the incidence peripartum hysterectomy in women with a diagnosis of abnormal placentation increased from 32.9 to 40.5 per 100,000 deliveries between the years 1994–1995 and 2006–2007, and hysterectomy for diagnosis of uterine atony increased from 11.2 to 25.9 per 100,000 deliveries [56].

Management of Placenta Accreta

The objectives of antenatal management are:

1. to optimize maternal hemoglobin reserve;
2. to involve multidisciplinary experienced providers;
3. to develop an individualized care plan;
4. to schedule elective preterm cesarean delivery in an optimum location; and
5. to prepare for massive blood loss and cesarean hysterectomy.

Active management of maternal [52, 57–59] anemia is encouraged in all pregnancies and more so after diagnosis of abnormal placentation. Autologous pre-donation may be considered, but maternal anemia is often a limiting factor; this technique may be considered for women with very rare blood types. In the setting of rare blood types, acute normovolemic hemodilution, pre-operative autologous donation, and intraoperative cell salvage are commonly used blood-conservation techniques [60]. Patients should be referred to and delivered in a facility where multi-disciplinary specialists (high-risk obstetric anesthesiologists, interventional radiologists, urologists, neonatologists, maternal fetal medicine specialists, gynecological oncologists and/or general surgeons, blood bank with substantial reserve to handle massive transfusion, intensive care units)

are available. Multidisciplinary team management and delivery in a tertiary care center have been shown to reduce hemorrhage-related morbidity.

The risk of bleeding increases with increasing gestational age. A shortened cervix of less than 30 mm in the third trimester also seems to be associated with increased risk of antenatal bleeding [51, 57, 61]. The American College of Obstetrics and Gynecologists recommend planning for an elective preterm cesarean delivery to avoid emergent cesarean deliveries during active bleeding. There is no benefit in assessing for fetal lung maturity before the planned pre-term delivery. The treatment plan and timing of delivery must be individualized for each patient and neonate.

Role of Interventional Radiology (IR)

The role of IR in obstetric hemorrhage is evolving. The American College of Obstetricians and Gynecologists 2012 Committee opinion states that there is still unclear and inconclusive data regarding the efficacy of occlusive balloons and therefore recommends individualized consideration [58]. Preemptive occlusive balloon catheter placement by an interventional radiologist is a consideration in elective circumstances and in patients who are stable. ACOG recommend balloon catheter occlusion or embolization to reduce blood loss and improve surgical outcome on the basis of individual circumstances rather than as a routine practice, because the data are inconclusive. There is a growing number of case reports and case series where occlusion balloon catheters were utilized in patients with abnormal placentation. Some case series have shown no differences in outcomes and others have reported significant complications [62–64]. In a case–control comparison of women undergoing cesarean hysterectomy with and without internal iliac occlusive balloons, Shrivastava et al. demonstrated no significant difference in estimated blood loss, number of transfused products, or operative time. In fact, three patients with occlusive balloons developed significant complications related to the arterial balloons [65]. In a retrospective case–control study of patients with placenta accreta from 1990 to 2011, 59 patients (50.4 %) had uterine artery balloons placed preoperatively. The mean estimated blood loss (EBL) was significantly lower (2,165 vs. 2,837 mL; $P = 0.02$) for the group that had uterine artery balloons than for the group that did not. There were more cases with an estimated blood loss greater than 2,500 mL and massive transfusions of packed red blood cells (>6 units) in the group that did not have occlusive balloons. Two patients (3.3 %) in this series had complications related to the occlusive balloons. In a series of 11 patients with a diagnosis of abnormal placentation, prophylactic bilateral internal iliac occlusive balloons reduced intra-operative blood loss, number of

transfusions, and duration of surgery [61]. More robust research and experience are required for routine use of preemptive placement of vascular occlusion balloons.

Anesthesia for Occlusive Balloon Placement

Occlusive balloon placements are performed in the Interventional radiology suite under either regional anesthesia or sedation. General anesthesia is usually not required in elective situations. Use of epidural anesthesia provides an opportunity for transition to a cesarean delivery, using an in-situ epidural if needed [66]. Typically, after establishing a regional anesthetic, the vascular occlusive catheters are placed by the interventional radiologists in the interventional radiology suite. Regional anesthesia has the advantage of limited exposure of the fetus to general anesthesia. Care should be exercised when balloon catheters are inflated in the IR suite, because these maneuvers can reduce uterine artery blood flow resulting in fetal compromise necessitating emergent delivery.

Despite optimum preparation and management, MOH requiring cesarean hysterectomy may be unavoidable.

Operative Delivery—Location of Cesarean Delivery

There are case reports of operative delivery being performed in the interventional radiology suite but this is not yet standard practice [66–69]. There are many advantages to performing the operative delivery in the IR suite, because the radiologist can visualize the bleeding and embolize the vascular areas in real time. In our tertiary care center and many others, cesarean delivery is undertaken in the labor and delivery suite where there is ready access to an operating room with surgical equipment, cell saver, and labor and delivery nurses and physicians who are used to dealing with an awake mother and an anxious spouse. The position of the occlusive balloon should be reconfirmed when patient is positioned on the operating room table and after induction of anesthesia [63].

Resuscitation After Massive Obstetric Hemorrhage

Fundamentals of anesthetic management of resuscitation after MOH include:

1. adequate venous access—large bore peripheral venous access $\pm$ central venous access;
2. monitoring—in addition to standard monitoring—of invasive arterial blood pressure;
3. preparation for massive transfusion—rapid infusers e.g. Level 1/Belmont rapid infuser; and
4. regional anesthesia versus general anesthesia.

Every labor and delivery unit should have a protocol in place to respond to unexpected obstetric hemorrhage.

Varatharajan et al. introduced a MOH protocol in 2005 with the mnemonic “HEMOSTASIS”—*H* help, *E* establish etiology, *M* massage the uterus, *O* oxytocin infusion and prostaglandins, *S* shift to operating room, *T* tamponade, *A* apply compression sutures, *S* systematic pelvic devascularization, *I* interventional radiology, *S* subtotal/total hysterectomy. A retrospective chart review of all obstetric hemorrhage in their unit after implementation of the protocol revealed a trend of reduction of more complex intervention, probably, in part, because of the structure and methodology it imposed on existing training [70].

Blood and blood products should be available in the operating room from the time of skin incision. There should be no hesitation before activation of a massive transfusion protocol which, in our institution, includes: four units of packed red cells, two units of fresh frozen plasma, and one unit of pooled platelets for each blood bank “request” and subsequent issue. After the second request, cryoprecipitate is made available and the on-call hematologist receives notification of activation of massive transfusion protocol.

In our institution, general anesthesia is preferred for patients with hemodynamic instability who need emergent cesarean deliveries. In elective scenarios, general anesthesia is limited to women who may have a difficult airway or to cases where intraoperative conversion to general anesthesia may not be ideal, e.g., maternal obesity. When MOH is expected, massive transfusion can cause airway edema exacerbating difficulty with airway management. Ureteral stents are often placed before the cesarean section to help avert ureteral injury. Invasive monitoring and large-bore venous access is established. In our center, we electively opt for central venous access before the patient develops intraoperative coagulopathy.

Crystalloid/PRBCs/FFP

The objective of resuscitation is to maintain adequate oxygenation and perfusion and to avoid the lethal triad of acidosis, hypothermia, and coagulopathy. Initial volume resuscitation with crystalloid is reasonable to maintain the intravascular volume and cardiac output. However, aggressive crystalloid resuscitation should be avoided in MOH, because excess crystalloid can worsen the underlying consumptive coagulopathy with a dilutational component [71, 72]. In the past decade there has been a movement toward transfusing “high” (e.g. 1:1) ratios of RBC to FFP. This practice initially derived from the treatment of hemorrhagic shock in combat wounds in which high ratios of FFP to RBC were associated with better outcomes [73]. The 2013 European guidelines for management of bleeding and coagulopathy after major trauma recommend FFP to RBC of at least 1:2 [74]. A large observational study

recently showed that for patients with post-partum hemorrhage patients who received FFP to RBC of 1:1.2 versus 1:1.6 had better outcomes in that they required significantly fewer interventional procedures to control bleeding [75•].

Fibrinogen Concentrate/Cryoprecipitate

Monitoring of fibrinogen is essential when treating MOH. The average baseline value of fibrinogen in the pregnant woman during the 3rd trimester is 5 g/L [76]. A recent observational study showed that fibrinogen concentrate was as efficacious as cryoprecipitate in the setting of low fibrinogen secondary to major obstetric hemorrhage [77]. Unlike plasma or cryoprecipitate, fibrinogen concentrate does not have to be ABO-compatible. Pasteurized fibrinogen concentrate can be stored at room temperature in powder form [78]. Although traditional criteria for factor replacement suggest fibrinogen levels <1 g/L as initiator for repletion, practitioners should strongly consider repletion of fibrinogen in major obstetric hemorrhage before plasma levels decrease to 1 g/L.

Platelets Transfusion objectives for platelets in obstetric hemorrhage are not well defined. In the setting of massive blood loss complicating trauma a minimum platelet count of at least 50,000 is preferable. In the setting of ongoing massive hemorrhage in trauma patients, platelets should be maintained at approximately 100,000 [74]. In the setting of obstetric hemorrhage and massive blood loss, the optimum platelet count is yet to be determined and is best guided by the clinical setting.

Cell Salvage Cell Saver should be primed and available with an experienced technician to operate it. The utility and safety of cell salvage in obstetrics is now well established. Historic concerns were based on maternal exposure to fetal squamous cells which were believed to precipitate physiologic processes similar to those in amniotic fluid embolism. However, many case series have supported the safe use of transfusion of salvaged blood to pregnant women without complications [79].

Leukocyte depletion filters used in modern intraoperative cell saver technology effectively remove contaminants which could lead to anaphylactoid and/or amniotic fluid embolism-like syndromes [80]. Additional measures to further reduce contamination of maternal blood include waiting until delivery of the fetus and placenta before beginning the salvaging process. Ralph analyzed the development of antibodies in 70 women who received at least 325 mL salvaged blood and found that only one developed anti-S antibody, supporting the lack of significance of fetal cell contamination [81].

Despite modern filtering techniques, Cell Saver cannot completely separate maternal from fetal blood. Therefore, Rh-negative women who receive Cell Saver blood are at risk of alloimmunisation from Rh-positive fetal red blood cells and must receive Rho(D) immune globulin to prevent hemolytic disease of the newborn in future pregnancies.

Recombinant Activated Factor VII Recombinant activated factor VII (rFVIIa) has been used for treatment of MOH, although its precise indications and effectiveness in the treatment of MOH are still unclear. rFVIIa is an attractive adjunct for treatment of massive obstetric hemorrhages. It is believed to act in areas of injured endothelium where tissue factor (TF) is upregulated. At these sites of endothelial injury, rFVIIa and TF bind and activate factor X, subsequently leading to generation of thrombin and to clot formation [82, 83].

Unfortunately, there are no randomized clinical trials supporting use of rFVIIa. Observational and retrospective case studies suggest that in some circumstances use of rFVIIa can be highly efficacious in achieving hemostasis and avoiding peripartum hysterectomy. In these studies, rFVIIa was given for MOH of different etiology, at different doses and at non-uniform intervals [83, 84]. Also, administration of rFVIIa has the potential disadvantage of causing serious thromboembolism in the obstetric population when administered during massive hemorrhage [85, 86]. Given the lack of data supporting the use of rFVIIa, its high cost, and the side effects described above, it is hard to support its routine use for treatment of major obstetric hemorrhage. However, it is a treatment modality to consider when other, more conventional means of controlling major obstetric hemorrhage have failed.

Tranexamic acid (TXA) Tranexamic acid (TXA) prevents hyperfibrinolysis and helps to stabilize fibrin clots by reducing surgical blood loss [87]. TXA has been shown to reduce blood loss in patients undergoing open-heart surgery with cardiopulmonary bypass [88], and also reduce massive blood loss during total knee and hip arthroplasty [89]. Administration of TXA to soldiers suffering from traumatic combat wounds has been shown to reduce the risk of exsanguination [90]. TXA has recently been made available over the counter in the UK for women who suffer from heavy menstrual bleeding [91]. The effect of TXA in MOH is unclear, because high-quality randomized controlled studies on the subject are lacking. Currently, the World Maternal Antifibrinolytic Trial (WOMAN) is the first large scale randomized, international double-blind placebo-controlled study to investigate early intervention with tranexamic acid for women with postpartum hemorrhage. The final results from this trial will not be available until 2015 [92]. A randomized-open trial that assessed

the efficacy of TXA when given to women who had already developed post-partum hemorrhage (as defined by EBL of >800 mL) found statistically significant modest reductions in blood loss. Clinical outcomes between placebo and TXA intervention were similar [93]. Currently, there is no compelling evidence to recommend the routine use TXA in MOH.

Post-operative Disposition

Patients who have received massive transfusion will often require admission to intensive-care units. Post-operative period may be complicated by re-bleed requiring re-laparotomy, transfusion-related lung injury, or oliguria and/or anuria and/or acute renal failure. Intra-abdominal pressure post cesarean delivery is higher than for other surgical patients [94]. In the setting of deteriorating renal function unresponsive to fluid boluses, differential diagnosis of abdominal compartment syndrome should be considered.

Tests for Coagulation

Because coagulation is a dynamic process, clinical evidence of coagulation abnormalities usually precedes abnormal laboratory results. Resuscitation and replacement of clotting factors should be based on the clinical situation. Plasma fibrinogen levels and platelet count are better predictors of the underlying coagulopathy than are prothrombin time (PT) and partial thromboplastin time (PTT) in the setting of ongoing blood loss. De Lloyd et al. found no correlation between the PT and the amount of bleeding in 456 cases of major obstetric bleeding [28, 29••]. The utility of traditional laboratory assays for coagulation (PT, PTT, fibrinogen) is also diminished because these values typically take 30–60 min to perform [95••].

Thromboelastography and thromboelastometry (TEG/ROTEM) have several advantages over traditional laboratory testing. These tests give a picture of the entire coagulation cascade and monitor for disorders such as hyperfibrinolysis at the point of care. Huissoud et al. [72] showed that by using thromboelastometry, low levels of fibrinogen could be detected in women with postpartum hemorrhage at the point of care in approximately 10 min [96]. Furthermore, TEG/ROTEM-based assays enable more rapid and accurate diagnosis of hyperfibrinolysis [97].

The normal range of TEG and ROTEM values for a parturient is yet to be determined, although preliminary studies suggest that these values are reduced in parturients [98••]. More research is needed in the use of TEG/ROTEM among the pregnant population.

Conclusion

Obstetric hemorrhage continues to be a leading cause of maternal mortality and morbidity worldwide. Continued education and improvement in systems to address early recognition of high-risk parturients and transfer to appropriate care centers will improve access to resources. More research is needed on the effect of such treatment as interventional radiology and hemostasis adjuncts such as FVIIa and tranexemic acid in the treatment of obstetric hemorrhage.

Compliance with Ethics Guidelines

Conflict of Interest Matthew Schwartz and Anasuya Vasudevan declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Walfish M, Neuman A, Wlody D. Maternal haemorrhage. *Br J Anaesth*. 2009;103(Supplement 1):i47–56.
2. WHO. Trends in Maternal Mortality. Geneva, Switzerland; 2010.
3. Dolea C, AbouZahr C, Stein C. Global burden of maternal hemorrhage in the year 2000. GBD 2000 Working Paper, World Health Organization, Geneva. <http://www.who.int/evidence/bod> (2003). Accessed 1 June 2013
4. Knight M, Callaghan WM, Berg C, Alexander S, Bouvier-Colle M-H, Ford JB, et al. Trends in postpartum hemorrhage in high resource countries: a review and recommendations from the International Postpartum Hemorrhage Collaborative Group. *BMC Pregnancy Childbirth*. 2009;9(1):55.
5. British Committee for Standards in Haematology, Stainsby D, MacLennan S, Thomas D, Thomas D, Isaac J, Hamilton PJ. Guidelines on the management of massive blood loss. *Br J Haematol*. 2006;135(5):634–41.
6. Stafford I, Dildy GA, Clark SL, Belfort MA. Visually estimated and calculated blood loss in vaginal and cesarean delivery. *Am J Obstet Gynecol*. 2008;199(5):519.e1–7.
7. Bose P, Regan F, Paterson-Brown S. Improving the accuracy of estimated blood loss at obstetric haemorrhage using clinical reconstructions. *BJOG*. 2006;113(8):919–24.
8. Dildy GA III, Paine AR, George NC, Velasco C. Estimating blood loss: can teaching significantly improve visual estimation? *Obstet Gynecol*. 2004;104(3):601–6.
9. • Singh SS, McGlennan AA, England AA, Simons RR. A validation study of the CEMACH recommended modified early obstetric warning system (MEOWS). *Anaesthesia*. 2012;67(1):12–8. *A prospective study that evaluates and validates the usefulness of the modified early obstetric warning system as a bedside tool for predicting morbidity.*
10. •• Balki M, Erik-Soussi M, Kingdom J, Carvalho JCA. Oxytocin pretreatment attenuates oxytocin-induced contractions in human myometrium in vitro. *Anesthesiology*. 2013. *An eloquent in vitro study to evaluate the effect of varying doses of oxytocin on myometrial contractility and evaluate the contractility index.*
11. Wetta LA, Szychowski JM, Seals S, Mancuso MS, Biggio JR, Tita AT. Risk factors for uterine atony/postpartum hemorrhage requiring treatment after vaginal delivery. *Am J Obstet Gynecol*. 2013;28:1–6.
12. Grotegut CA, Paglia MJ, Johnson LNC, Thames B, James AH. Oxytocin exposure during labor among women with postpartum hemorrhage secondary to uterine atony. *Am J Obstet Gynecol*. 2011;204(1):56.e1–6.
13. • Bateman BT, Berman MF, Riley LE, Leffert LR. The epidemiology of postpartum hemorrhage in a large, nationwide sample of deliveries. *Anesth Analg*. 2010;110(5):1368–73. *An epidemiological study of the US population to evaluate epidemiology of PPH and predisposing factors for excessive blood loss during child birth.*
14. •• Lutomski JE, Byrne BM, Devane D, Greene RA. Increasing trends in atonic postpartum haemorrhage in Ireland: an 11-year population-based cohort study. *BJOG*. 2011;119(3):306–14. *A population based study from Ireland which is identifying the rising trends in postpartum hemorrhage and its association with the mode of delivery, blood transfusions, and morbidly adherent placenta.*
15. •• Mehrabadi A, Hutcheon JA, Lee L, Liston RM, Joseph KS. Trends in postpartum hemorrhage from 2000 to 2009: a population-based study. *BMC Pregnancy Childbirth*. 2012;12:108. *A population-based study from British Columbia identifying the rising trend in bleeding from uterine atony.*
16. Hull AD, Moore TR. Multiple repeat cesareans and the threat of placenta accreta: incidence, diagnosis, management. *Clin Perinatol*. 2011;38(2):285–96.
17. Hull ADA, Resnik RR. Placenta accreta and postpartum hemorrhage. *Clin Obstet Gynecol*. 2010;53(1):228–36.
18. Wu S, Kocherginsky M, Hibbard JU. Abnormal placentation: twenty-year analysis. *Am J Obstet Gynecol*. 2005;192(5):1458–61.
19. Ballas JJ, Pretorius DD, Hull ADA, Resnik RR, Ramos GAG. Identifying sonographic markers for placenta accreta in the first trimester. *J Ultrasound Med*. 2012;31(11):1835–41.
20. Lim PS, Greenberg M, Edelson MI, Bell KA, Edmonds PR, Mackey AM. Utility of ultrasound and MRI in prenatal diagnosis of placenta accreta: a pilot study. *AJR Am J Roentgenol*. 2011;197(6):1506–13.
21. Warshak CRC, Eskander RR, Hull ADA, Scioscia ALA, Mattrey RFR, Benirschke KK, et al. Accuracy of ultrasonography and magnetic resonance imaging in the diagnosis of placenta accreta. *Obstet Gynecol*. 2006;108(3 Pt 1):573–81.
22. Baughman WC, Corteville JE, Shah RR. Placenta accreta: spectrum of US and MR imaging findings. *Radiographics*. 2008;28(7):1905–16.
23. Lewis G. Reviewing maternal deaths to make pregnancy safer. *Best Pract Res Clin Obstet Gynaecol*. 2008;22(3):447–63.
24. Su LL, Chong YS. Massive obstetric haemorrhage with disseminated intravascular coagulopathy. *Best Pract Res Clin Obstet Gynaecol*. 2012;26(1):77–90.
25. Thachil J, Toh C-H. Disseminated intravascular coagulation in obstetric disorders and its acute haematological management. *Blood Rev*. 2009;23(4):167–76.
26. Chi C, Kadir RA. Inherited bleeding disorders in pregnancy. *Best Pract Res Clin Obstet Gynaecol*. 2012;26(1):103–17.
27. Shahbazi S, Moghaddam-Banaem L, Ekhtesari F, Ala FA. Impact of inherited bleeding disorders on pregnancy and postpartum hemorrhage. *Blood Coagul Fibrinolysis*. 2012;23(7):603–7.

28. Charbit B, Mandelbrot L, Samain E, Baron G, Haddaoui B, Keita H, et al. The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage. *J Thromb Haemost.* 2007;5(2):266–73.
29. de Lloyd L, Bovington R, Kaye A, Collis RE, Rayment R, Sanders J, et al. Standard haemostatic tests following major obstetric haemorrhage. *Int J Obstet Anesth.* 2011;20(2):135–41. *A retrospective study that demonstrates the association between fibrinogen levels and increasing volume of hemorrhage.*
30. Bolliger D, Szlam F, Molinaro RJ, Rahe-Meyer N, Levy JH, Tanaka KA. Finding the optimal concentration range for fibrinogen replacement after severe haemodilution: an in vitro model. *Br J Anaesth.* 2009;102(6):793–9.
31. Bingham D, Lyndon A, Lagrew D, Main EK. A state-wide obstetric hemorrhage quality Improvement initiative. *MCN Am J Matern Child Nurs.* 2011;36(5):297–304.
32. WHO. World Health report 2005: make every mother and child count. 2005.
33. Khan KSK, Wojdyla DD, Say LL, Gülmezoglu AMA, Van Look PFAP. WHO analysis of causes of maternal death: a systematic review. *Lancet.* 2006;367(9516):1066–74.
34. Hogan MC, Foreman KJ, Naghavi M, Ahn SY, Wang M, Makela SM, et al. Maternal mortality for 181 countries, 1980–2008: a systematic analysis of progress towards Millennium Development Goal 5. *Lancet.* 2010;375(9726):1609–23.
35. Leduc D, Senikas V, Lalonde AB, Ballerman C, Biringer A, Delaney M, et al. Active management of the third stage of labour: prevention and treatment of postpartum hemorrhage. *J Obstet Gynaecol Can.* 2009;31:980–93.
36. Magann EF, Niederhauser A, Doherty D, Chauhan S, Sandlin A, Morrison J. Reducing hemodynamic compromise with placental removal at 10 versus 15 minutes: a randomized clinical trial. *Am J Perinatol.* 2012;29(08):609–14. *A prospective randomized study that evaluates hemodynamic compromise following 10 versus 15 minutes of placenta removal.*
37. Magann EF, Lutgendorf MA, Keiser SD, Porter S, Siegel ER, McKelvey SA, et al. Risk factors for a prolonged third stage of labor and postpartum hemorrhage. *South Med J.* 2013;106(2):131–5.
38. Higgins L, Mechery J, Tomlinson AJ. Does carbetocin for prevention of postpartum haemorrhage at caesarean section provide clinical or financial benefit compared with oxytocin? *J Obstet Gynaecol.* 2011;31(8):732–9.
39. Cordovani D, Balki M, Farine D, Seaward G, Carvalho JCA. Carbétocine et césarienne programmée: étude randomisée contrôlée pour la détermination de la dose efficace. *Can J Anesth/J Can Anesth.* 2012;59(8):751–7.
40. Rosseland LA, Hauge TH, Grindheim G, Stubhaug A, Langesaeter E. Changes in blood pressure and cardiac output during caesarean delivery: the effects of oxytocin and carbetocin compared with placebo. *Anesthesiology.* 2013;119(3):541–51.
41. Holleboom CAG, Eyck J, Koenen SV, Kreuwel IAM, Bergwerff F, Creutzberg EC, et al. Carbetocin in comparison with oxytocin in several dosing regimens for the prevention of uterine atony after elective caesarean section in the Netherlands. *Arch Gynecol Obstet.* 2013;287(6):1111–7.
42. Stephens LC, Brussels T. Systematic review of oxytocin dosing at caesarean section. *Anaesth Intensive Care.* 2012;40(2):247–52.
43. Butwick AJ, Coleman L, Cohen SE, Riley ET, Carvalho B. Minimum effective bolus dose of oxytocin during elective caesarean delivery. *Br J Anaesth.* 2010;104(3):338–43.
44. Carvalho JCA, Balki M, Kingdom J, Windrim R. Oxytocin requirements at elective caesarean delivery: a dose-finding study. *Obstet Gynecol.* 2004;104(5, Part 1):1005–10.
45. Sheehan SR, Montgomery AA, Carey M, McAuliffe FM, Eogan M, Gleeson R, et al. Oxytocin bolus versus oxytocin bolus and infusion for control of blood loss at elective caesarean section: double blind, placebo controlled, randomised trial. *BMJ.* 2011;343(1):d4661–1. *A double blind, placebo controlled, prospective randomized trial that evaluates the effect of oxytocin bolus followed by oxytocin infusion on blood loss at elective caesarean sections which concluded that the oxytocin infusion reduces the need for additional uterotonic agents.*
46. King KJ, Douglas MJ, Unger W, Wong A, King RAR. Five Unit Bolus Oxytocin at Cesarean Delivery in Women at Risk of Atony. *Anesth Analg.* 2010;111(6):1460–6. *A prospective randomized double blind trial that evaluated the effect of supra therapeutic dose of oxytocin and the need for additional uterotonics on women with at least one risk factor for uterine atony undergoing a cesarean delivery.*
47. Russell RT. WHO guidelines for the management of postpartum haemorrhage and retained placenta World Health Organization WHO Press, Geneva, Switzerland, 2009, ISBN 978-92-4-159851-4, 55 pp., CHF/US \$ 15.00 (in developing countries: CHF/US \$ 10.50). *Hum Fertil (Camb).* 9 Dec 2010.
48. Laas E, Bui C, Popowski T, Mbaku OM, Rozenberg P. Trends in the rate of invasive procedures after the addition of the intra-uterine tamponade test to a protocol for management of severe postpartum hemorrhage. *Am J Obstet Gynecol.* 2012;207(4):281.e1–7.
49. B-Lynch C, Coker A, Lawal AH, Abu J, Cowen MJ. The B-Lynch surgical technique for the control of massive postpartum haemorrhage: an alternative to hysterectomy? Five cases reported. *Br J Obstet Gynaecol.* 1997;104(3):372–5.
50. El-Hamamy E, Wright A, B-Lynch C. The B-Lynch suture technique for postpartum haemorrhage: a decade of experience and outcome. *J Obstet Gynaecol.* 2009;29(4):278–83.
51. Habek D, Kulaš T, Bobić-Vuković M, Selthofer R, Vujić B, Ugljarević M. Successful of the B-Lynch compression suture in the management of massive postpartum hemorrhage: case reports and review. *Arch Gynecol Obstet.* 2005;273(5):307–9.
52. Price N, B-Lynch C. Technical description of the B-Lynch brace suture for treatment of massive postpartum hemorrhage and review of published cases. *Int J Fertil Womens Med.* 2005;50(4):148–63.
53. Sentilhes L, Gromez A, Marpeau L. Fertility after pelvic arterial embolization, stepwise uterine devascularization, hypogastric artery ligation, and B-Lynch suture to control postpartum hemorrhage. *Int J Gynaecol Obstet.* 2010;108(3):1.
54. Sentilhes L, Trichot C, Resch B, Sergeant F, Roman H, Marpeau L, et al. Fertility and pregnancy outcomes following uterine devascularization for severe postpartum haemorrhage. *Hum Reprod.* 2008;23(5):1087–92.
55. Palacios-Jaraquemada MJ. Efficacy of surgical techniques to control obstetric hemorrhage: analysis of 539 cases. *Acta Obstet Gynecol Scand.* 2011;90(9):1036–42.
56. Bateman BTB, Mhyre JMJ, Callaghan WMW, Kuklina EVE. Peripartum hysterectomy in the United States: nationwide 14 year experience. *Am J Obstet Gynecol.* 2012;206(1):63–8.
57. Wohlmuth CTC, Gumbs JJ, Quebral-Ivie JJ. B-Lynch suture: a case series. *Int J Fertil Womens Med.* 2005;50(4):164–73.
58. Committee on Obstetric Practice. Committee opinion no. 529: placenta accreta. *Obstet Gynecol.* 2012;120(1):207–11.
59. Robinson BKB, Grobman WAW. Effectiveness of timing strategies for delivery of individuals with placenta previa and accreta. *Obstet Gynecol.* 2010;116(4):835–42.
60. Catling S. Blood conservation techniques in obstetrics: a UK perspective. *Int J Obstet Anesth.* 2007;16(3):241–9.
61. Stafford IA, Dashe JS, Shivers SA, Alexander JM, McIntire DD, Leveno KJ. Ultrasonographic cervical length and risk of hemorrhage in pregnancies with placenta previa. *Obstet Gynecol.* 2010;116(3):595–600.

62. Sadashivaiah JJ, Wilson RR, Thein AA, McLure HH, Hammond CJC, Lyons GG. Role of prophylactic uterine artery balloon catheters in the management of women with suspected placenta accreta. *Int J Obstet Anesth*. 2011;20(4):282–7.
63. Thon SS, McLintic AA, Wagner YY. Prophylactic endovascular placement of internal iliac occlusion balloon catheters in parturients with placenta accreta: a retrospective case series. *Int J Obstet Anesth*. 2011;20(1):7.
64. Bishop S, Butler K, Monaghan S, Chan K, Murphy G, Edozien L. Multiple complications following the use of prophylactic internal iliac artery balloon catheterisation in a patient with placenta percreta. *Int J Obstet Anesth*. 2011;20(1):4.
65. Shrivastava V, Nageotte M, Major C, Haydon M, Wing D. Case-control comparison of cesarean hysterectomy with and without prophylactic placement of intravascular balloon catheters for placenta accreta. *Am J Obstet Gynecol*. 2007;197(4):402.e1–5.
66. Fuller AJ, Carvalho B, Brummel C, Riley ET. Epidural anesthesia for elective cesarean delivery with intraoperative arterial occlusion balloon catheter placement. *Anesth Analg*. 2006;102(2):585–7.
67. O'Rourke NN, McElrath TT, Baum RR, Camann WW, Tuomala RR, Stuebe AA, et al. Cesarean delivery in the interventional radiology suite: a novel approach to obstetric hemostasis. *Anesth Analg*. 2007;104(5):1193–4 table of contents.
68. Jeffrey AA, Clark VV. The anaesthetic management of caesarean section in the interventional radiology suite. *Curr Opin Anaesthesiol*. 2011;24(4):439–44.
69. Kodali BSB. Bloodless trilogy? Anesthesia, obstetrics and interventional radiology for cesarean delivery. *Int J Obstet Anesth*. 2010;19(2):2.
70. Varatharajan L, Chandrarahan E, Sutton J, Lowe V, Arulkumaran S. Outcome of the management of massive postpartum hemorrhage using the algorithm "HEMOSTASIS". *Int J Gynaecol Obstet*. 2011;113(2):152–4.
71. Goodnough LT, Daniels K, Wong AE, Viele M, Fontaine MF, Butwick AJ. How we treat: transfusion medicine support of obstetric services. *Transfusion*. 2011;51(12):2540–8.
72. Spinella PC, Holcomb JB. Resuscitation and transfusion principles for traumatic hemorrhagic shock. *Blood Rev*. 2009;23(6):231–40.
73. Borgman MA, Spinella PC, Perkins JG, Grathwohl KW, Repine T, Beekley AC, et al. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a Combat Support Hospital. *J Trauma*. 2007;63(4):805–13.
74. Spahn DR, Bouillon B, Cerny V, Coats TJ, Duranteau J, Fernandez-Mondejar E, et al. Management of bleeding and coagulopathy following major trauma: an updated European guideline. *Crit Care*. 2013;17(2):R76.
75. •• Pasquier P, Gayat E, Rackelboom T, La Rosa J, Tashkandi A, Tesniere A, et al. An observational study of the fresh frozen plasma. *Anesth Analg*. 2013;116(1):155–161. *A retrospective study of PPH that analyses the RBC:FFP ratio over a four year period and conclude that the higher FFP:RBC ratio was associated with a lower requirement of advanced interventions.*
76. Huissoud C, Carrabin N, Bouchaib M, Fontaine O, Levrat A, Massignon D, et al. Coagulation assessment by rotation thrombelastometry in normal pregnancy. *Thromb Haemost*. 2009;101(4):755–61.
77. Ahmed S, Harrity C, Johnson S, Varadkar S, McMorro S, Fanning R, et al. The efficacy of fibrinogen concentrate compared with cryoprecipitate in major obstetric haemorrhage—an observational study. *Transfusion Med*. 2012;22(5):344–9.
78. Fenger-Eriksen C, Ingerslev J, Sørensen B. Fibrinogen concentrate—a potential universal hemostatic agent. *Expert Opin Biol Ther*. 2009;9(10):1325–33.
79. Sullivan JV, Crouch ME, Stocken G, Lindow SW. Blood cell salvage during cesarean delivery. *Int J Gynaecol Obstet*. 2011;115(2):161–3.
80. Sullivan I, Faulds J, Ralph C. Contamination of salvaged maternal blood by amniotic fluid and fetal red cells during elective caesarean section. *Br J Anaesth*. 2008;101(2):225–9.
81. Ralph CJ, Sullivan I, Faulds J. Intraoperative cell salvaged blood as part of a blood conservation strategy in caesarean section: is fetal red cell contamination important? *Br J Anaesth*. 2011;107(3):404–8.
82. Shibeko AM, Woodle SA, Lee TK, Ovanesov MV. Unifying the mechanism of recombinant FVIIa action: dose dependence is regulated differently by tissue factor and phospholipids. *Blood*. 2012;120(4):891–9.
83. Kobayashi T, Nakabayashi M, Yoshioka A, Maeda M, Ikenoue T. Recombinant activated factor VII (rFVIIa/NovoSeven®) in the management of severe postpartum haemorrhage: initial report of a multicentre case series in Japan. *Int J Hematol*. 2011;95(1):57–63.
84. Phillips LE, McLintock C, Pollock W, Gatt S, Popham P, Jankelowitz G, et al. Recombinant activated factor VII in obstetric hemorrhage: experiences from the Australian and New Zealand haemostasis registry. *Anesth Analg*. 2009;109(6):1908–15.
85. Danilenko-Dixon D. Risk factors for deep vein thrombosis and pulmonary embolism during pregnancy or post partum: a population-based, case-control study. *Am J Obstet Gynecol*. 2001;184(2):104–10.
86. Iau P, Ong V, Tan WT, Koh PL, Hartman M. Use of activated recombinant factor VII in severe bleeding—evidence for efficacy and safety in trauma, postpartum hemorrhage, cardiac surgery, and gastrointestinal bleeding. *Transfus Med Hemother*. 2012;39(2):139–50.
87. McCormack PL. Tranexamic acid: a review of its use in the treatment of hyperfibrinolysis. *Drugs*. 2012;72(5):585–617.
88. Casati V, Valle Della P, Benussi S, Franco A, Gerli C, Baili P, et al. Effects of tranexamic acid on postoperative bleeding and related hematochemical variables in coronary surgery: Comparison between on-pump and off-pump techniques. *Journal Thorac Cardiovasc Surg*. 2004;128(1):83–91.
89. Eubanks JD. Antifibrinolytics in major orthopaedic surgery. *J Am Acad Orthop Surg*. 2010;18(3):132–8.
90. Collaborators C-2T. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet*. 2010;376(9734):23–32.
91. Edlund MM. Nonhormonal treatments for heavy menstrual bleeding. *J Womens Health (Larchmt)*. 2011;20(11):1645–53.
92. Shakur HH, Elbourne DD, Gülmezoglu MM, Alfirevic ZZ, Ronsmans CC, Allen EE, 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. *Trans IRE Prof Group Audio*. 2010;11:40.
93. Ducloy-Bouthors A-S, Jude B, Duhamel A, Broisin F, Huissoud C, Keita-Meyer H, et al. High-dose tranexamic acid reduces blood loss in postpartum haemorrhage. *Crit Care*. 2011;15(2):R117.
94. Abdel-Razeq SS, Campbell K, Funai EF, Kaplan LJ, Bahtiyar MO. Normative postpartum intraabdominal pressure: potential implications in the diagnosis of abdominal compartment syndrome. *Am J Obstet Gynecol*. 2010;203(2):149.e1–4.
95. •• de Lange NMN, Lancé MDM, de Groot RR, Beckers EAME, Henskens YMY, Scheepers HCJH. Obstetric hemorrhage and coagulation: an update. Thromboelastography, thromboelastometry, and conventional coagulation tests in the diagnosis and prediction of postpartum hemorrhage. *Obstet Gynecol Surv*. 2012;67(7):426–35. *A review and update of TEG/ROTM in obstetrics.*

96. Huissoud C, Carrabin N, Audibert F, Levrat A, Massignon D, Berland M, et al. Bedside assessment of fibrinogen level in postpartum haemorrhage by thrombelastometry. *BJOG*. 2009;116(8):1097–102.
97. Solomon C, Collis RE, Collins PW. Haemostatic monitoring during postpartum haemorrhage and implications for management. *Br J Anaesth*. 2012;109(6):851–63.
98. •• Karlsson OO, Sporrang TT, Hillarp AA, Jeppsson AA, Hellgren MM. Prospective longitudinal study of thromboelastography and standard hemostatic laboratory tests in healthy women during normal pregnancy. *Anesth Analg*. 2012;115(4):890–8. *A prospective evaluation of the TEG? ROTEM results in pregnant women through various trimesters and post partum period.*