

How I treat postpartum hemorrhage

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Worldwide, ~800 women die every day from preventable causes related to pregnancy or childbirth. The single most common cause is severe bleeding, which can kill a healthy woman within hours if care is substandard or delayed. Improved antenatal practices have led to the early

identification of at-risk women and modern technology and new techniques have enabled effective management strategies so that now, in the western world, most of the morbidity and mortality arises from those cases which occur unexpectedly and could not have been predicted.

Prompt and effective management and multidisciplinary involvement is paramount to save the lives of these women. We use a case report to illustrate and discuss the main elements of management of this condition. (*Blood*. 2015;125(18):2759-2770)

Introduction

Primary postpartum hemorrhage (PPH), defined by the Royal College of Obstetricians and Gynaecologists as bleeding of >500 mL in the first 24 hours of childbirth,¹ complicates 13% of deliveries.² Improved awareness, better obstetric care, and involvement of multidisciplinary teams has reduced the incidence of PPH overall, but temporal trends have shown an increase in major obstetric hemorrhage.^{3,4} In the United Kingdom, this remains in the top 3 direct causes of maternal death⁵; across the globe, around 73 000 women die every year from hemorrhage due to childbirth.⁶ Management requires an appreciation of the underlying cause, allowing an individualized approach, with careful consideration to appropriate choice of medical, obstetric, and hematologic intervention. Hematologists need to focus their attention on patient blood management, acute coagulopathy, hemostatic monitoring with targeted use of blood components and hemostatic agents, the impact of massive hemorrhage packs, and efficiency of product delivery. Obstetricians need to be alert to the risk factors for PPH and early predictors of worsening hemorrhage, and consider the effects of different interventions. Attention to the placental site in women with previous caesarean delivery will help with identification and management of the morbidly adherent placenta. Research shows that most maternal hemorrhagic deaths occurred where there were shortfalls in the standard of care.⁵ With modern refinements for investigation and management, this should be a feature of the past.

Case description

The following case occurred recently in our hospital and describes a typical story of massive obstetric hemorrhage (MOH) and the steps involved in the obstetric, hematologic, and medical management. Consent for publication was obtained from the patient.

The 27-year-old woman presented in her second pregnancy. Her first pregnancy resulted in an emergency caesarean section at 9-cm cervical dilation due to prolonged labor, occipitoposterior position, and abnormalities on cardiotocography (CTG). Her booking hemoglobin (Hb) in this pregnancy was 126 g/L with mean cell volume (MCV)

85 fL. Ultrasound scan, at 21 weeks' gestation, showed placenta previa overlying the cervical os. At 21 + 6 weeks, she had an antepartum hemorrhage (APH), estimated at 350 mL, requiring hospitalization for 3 days and discharge on oral iron supplements, with a Hb of 81 g/L and MCV 75 fL.

She was readmitted at 24 + 5 weeks with abdominal pain and further bleeding, estimated at 250 mL. Hb was 93 g/L and platelet $227 \times 10^9/L$. Physical examination showed pulse rate 64 bpm, blood pressure (BP) 91/53 (booking BP 100/60), a tender, tightening uterus, and continued slow vaginal bleeding. Ultrasound confirmed viability of the fetus. The placenta was posterior and lateral, covering the cervix, which was long and closed. The patient was counseled about the possible need for emergency delivery if bleeding was ongoing and warned of uncertain fetal outcome. Four units of compatible packed red cells were requested and dexamethasone was administered for fetal lung maturity.

The time sequence of subsequent events and corresponding actions is shown in Table 1.

Review of management

With such catastrophes, the successful and unsuccessful aspects of the management need to be scrutinized to see where intervention could have been different or timelier. This article will firstly review the different aspects of the management of this case and then the measures that can be taken to prevent such occurrences, or at least be prepared for them as far as possible.

Estimated blood loss

Although her initial blood loss (EBL) had been estimated at 350 mL, her Hb had fallen by 45 g/L, and hematocrit by 20%, suggesting that EBL had been grossly underestimated. Most likely there was concealed retroplacental bleeding related to her subsequently confirmed placental

Submitted October 1, 2014; accepted March 4, 2015. Prepublished online as *Blood* First Edition paper, March 13, 2015; DOI 10.1182/blood-2014-10-512608.

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Table 1. Timing of events, clinical and laboratory assessments, and corresponding actions

Time	Assessment	Laboratory and TEG results	Action
18.40	Pain increasing, contractions every 5 min, cervix distended with blood clot	Hb, 93 g/L, Platelets, $227 \times 10^9/L$	Blood loss measured by weighing sanitary towels and sheets = 900 mL
19.20	Blood loss ongoing, uterus hard, tender and contracting		MOH declared and plans made for emergency caesarean delivery
19.50			General anesthetic given, transfusion started with emergency group O-negative red cells
20.07			Stillborn baby delivered, unresponsive to resuscitation
20.08	The uterus contained 800 mL of clot, the majority being behind the placenta, confirming placental abruption in addition to the placenta previa		Manual delivery of placenta and membranes undertaken with prophylactic antibiotics Uterotonics administered: 2×5 IU bolus doses of syntocinon (oxytocin), 5 min apart followed by an intravenous syntocinon infusion Blood sample sent for PT, APTT, and fibrinogen TXA Ig IV over 10 min
20.15	Ongoing active bleeding from lower uterine segment		
20.20	4 units compatible packed red cells arrive in theater		Transfusion commenced immediately
20.33	TEG (Figure 1) showed prolonged r and k times indicating depletion of clotting factors, and significantly reduced maximum amplitude indicating diminished clot strength	Hb, 80 g/L by HemoCue R time: 10.1 min, K time: 11.8 min, α angle: 24.6° , maximum amplitude: 21.3 mm Platelets: $168 \times 10^9/L$, Hb: 80 g/L, Fibrinogen: 0.2, INR: 3.1, PT: 32 s, APTT: 69.9 s, APTT ratio: 2.3 (although these results were not available until later)	MHP2 requested to contain 4 pools cryoprecipitate, 1 adult dose platelets, 4 units FFP, further 4 units red cells
20.40	Bleeding continuing		Bakri balloon placed in the uterus via the uterine incision and filling port fed down through the cervix and vagina. Uterus closed in 2 layers and the balloon inflated with 450 mL of saline
20.45	Continued constant active bleeding from all surfaces, indicating worsening coagulopathy		Multiple measures taken to arrest the bleeding; local pressure to the uterine surface, diathermy to larger vessels and Surgicel, an absorbable oxidized cellulose polymer, was applied to the bladder base, with closure of the visceral peritoneum in order to create a tamponade effect. Additional uterotonics administered by way of 2 doses of Carboprost 250 mcg 15 min apart Further 1g IV TXA administered over 10 min
21.15	MHP 2 arrives in theater		Two 5-U pools of cryoprecipitate, 1 platelet pool, and 3 units of FFP transfused
21.35	TEG (Figure 2) showed slight improvement in the coagulopathy, determined by the R and K times MA still low	R time: 9.1 min, K time: 6.8 min, α angle: 19.1° , maximum amplitude: 29.8 mm	Further two 5-U pools of cryoprecipitate transfused
22.00	Laboratory results available from 20.30 sample, showing fibrinogen had been severely reduced at 0.2 g/L. Hb was 80 g/L, platelets: $168 \times 10^9/L$, and PT and APTT prolonged to 3.1 and $2.3 \times$ normal, respectively		
22.30	Bleeding continuing but rate slowing		Further two 5-U pools of cryoprecipitate, 3 units of FFP and 1 adult platelet pool transfused
22.56	TEG (Figure 3) demonstrated correction of coagulopathy	R time: 5.6 min, K time: 1.7 min, α angle: 50.8° , maximum amplitude: 40.2 mm	Cell salvaged blood was processed 195 mL transfused
23.45	No further bleeding. Laboratory results showed Hb of 108 g/L, platelets $96 \times 10^9/L$ and a corrected coagulopathy (PT ratio: 15.2 s, APTT ratio: 1.1)		Transferred to ITU, kept sedated and ventilated
Day 2	Hb dropped again to 81 g/L Vaginal pack soaked and Bakri balloon prolapsing into the vagina 3-cm clot present at the uterine fundus		2 units of packed red cells Bakri balloon and vaginal pack were repositioned. Interventional radiology assistance sought Embolization of the uterine arteries performed via a femoral catheter

APTT, activated partial thromboplastin time; FFP, fresh frozen plasma; ITU, intensive care unit; MHP, major hemorrhage blood component packs; PT, prothrombin time; TEG, thromboelastography; TXA, tranexamic acid.

Table 1. (continued)

Time	Assessment	Laboratory and TEG results	Action
Day 3	No bleeding		Extubated and commenced on thromboprophylaxis with LMWH
Day 5	Good recovery		Discharged on oral iron for 4 mo Follow-up arranged for debriefing, counseling, and discussion about future pregnancies

APTT, activated partial thromboplastin time; FFP, fresh frozen plasma; ITU, intensive care unit; MHP, major hemorrhage blood component packs; PT, prothrombin time; TEG, thromboelastography; TXA, tranexamic acid.

abruption, as well as inadequate assessment of visible blood loss. Reliable assessment of blood loss is a well-known problem and one which investigators have tried to address with educational tools. Accuracy has been shown to improve with staff education and use of simulation exercises⁷⁻⁹ but skills diminish after 9 months¹⁰ and training needs to be repeated. Essential objective measures for operative delivery include use of blood collection drapes, weighing swabs, and measurements from drains.

Uterine blood flow

It is not difficult to understand the risk of sudden unexpected massive bleeding when one considers the anatomy and physiology of placental and uterine blood flow. Placental blood vessels progressively dilate as pregnancy advances, to shunt blood from nonplacental to placental tissues. Maternal spiral arteries, stemming from the uterine arteries, undergo remodeling, whereby they lose their vascular resistance due to loss of smooth muscle and elastic lamina from the vessel wall and become straighter and dilated at the mouth of the vessel to ensure adequate blood supply to the fetus. Blood pools in the intervillous spaces, bathing the fetal villi in blood, and returns to the maternal circulation via a series of collecting veins in the basal plate. By term, 80% to 90% of total uterine blood flow is passing through the placenta, with a flow rate of ~600 mL per minute and pressure of 70 mm Hg.

Control of placental blood flow is influenced by myometrial activity and, during the third stage of labor, hemorrhage is prevented by contraction of uterine muscle fibers, causing compression of the spiral arteries and mechanical hemostasis. Uterine atony inhibits this physiological process and predisposes and worsens intractable bleeding. It is the most common reason for PPH, accounting for around 80% of cases. Risk factors for uterine atony are listed in Figure 4, with other risk factors for PPH.

Uterotonics

Our patient was at risk of uterine atony in view of her placenta previa, abruption, and caesarean delivery. Active management of the third stage of labor, involving administration of prophylactic uterotonic drugs at delivery, is routinely recommended¹ and reduces the risk of PPH by 60% and the need for additional uterotonic agents by 50%.¹¹ There is significant variation in practice¹² but systematic review of all the available uterotonics for prevention of PPH found oxytocin to be the first choice¹¹ and a recent Cochrane review supported this recommendation.¹³ Syntometrine (ergometrine-oxytocin) confers a small reduction in the risk of minor PPH¹⁴ compared with oxytocin and is our preferred choice after vaginal delivery in women without hypertension.

For atonic PPH, ergometrine is more commonly used, which provides uterotonic effect for 2 to 4 hours, compared with 15 to 30 minutes

for oxytocin. It can be administered alone or alongside oxytocin although it is contraindicated in women with hypertension and pre-eclampsia and is associated with nausea and vomiting. Prostaglandin F_{2α} (carboprost) was used as a second-line agent in this case. Its efficacy has not been demonstrated by quality clinical trials. However, two case series, comprising 26 and 237 cases, report success in controlling hemorrhage in 85% and 95% of cases^{15,16} and it is often our preferred option for women with active bleeding.

Oral misoprostol (Prostaglandin E1) is widely used in resource-poor settings due to its low cost, thermostability, and ease of administration^{17,18} but has a high incidence of side-effects including shivering, nausea, and pyrexia^{18,19}; efficacy is not superior to oxytocin, used alone or in combination with it.^{17,20} Excess use of uterotonics can cause significant cardiorespiratory complications and risk of uterine rupture and has been identified as a key contributory factor in 28% of maternal deaths in the United Kingdom.⁵

Major obstetric hemorrhage

The MOH alert was called because bleeding was still ongoing after 1000 mL and there was loss of hemodynamic control. This triggers the portering services and laboratory staff to be ready for prompt issue and delivery of appropriate blood components. Thawing of FFP is initiated immediately and MHPs are prepared. PPH is highly variable in cause and severity and ranges from persistent, slow, steady bleeding to catastrophic hemorrhage; therefore, the MOH alert will depend on different criteria according to the clinical setting. Other definitions include ongoing bleeding after 2 units of transfused blood, early signs of coagulopathy, and bleeding rate in excess of 150 mL per minute.

Use of red blood cells

The urgent need for blood overrides concern about complications in the acute setting. Nevertheless, we need to be mindful of the potential problems associated with transfusion of red cells. Currently, 1 in 7000 units transfused is associated with an acute reaction, which may be hemolytic, allergic, septic, immunologic, or due to circulatory overload. Fortunately, transmitted infections are extremely rare but agents such as prions, with long incubation periods, would have greater significance for obstetric patients, who are expected to survive for many years after the transfusion. Since universal leukodepletion began in 1999, there has been no evidence for the transmission of prions in red cell packs. It is now administrative mistakes that cause the most concern, with 1:180 000 units transfused being incompatible and proving fatal in 5% to 10%. Even in an emergency, attention should be paid to correct sampling, labeling, and administrative procedures.

Transfusion-induced sensitization to red cell antigens such as Kell and c confer a future risk of fetal hemolytic disease. The emergency

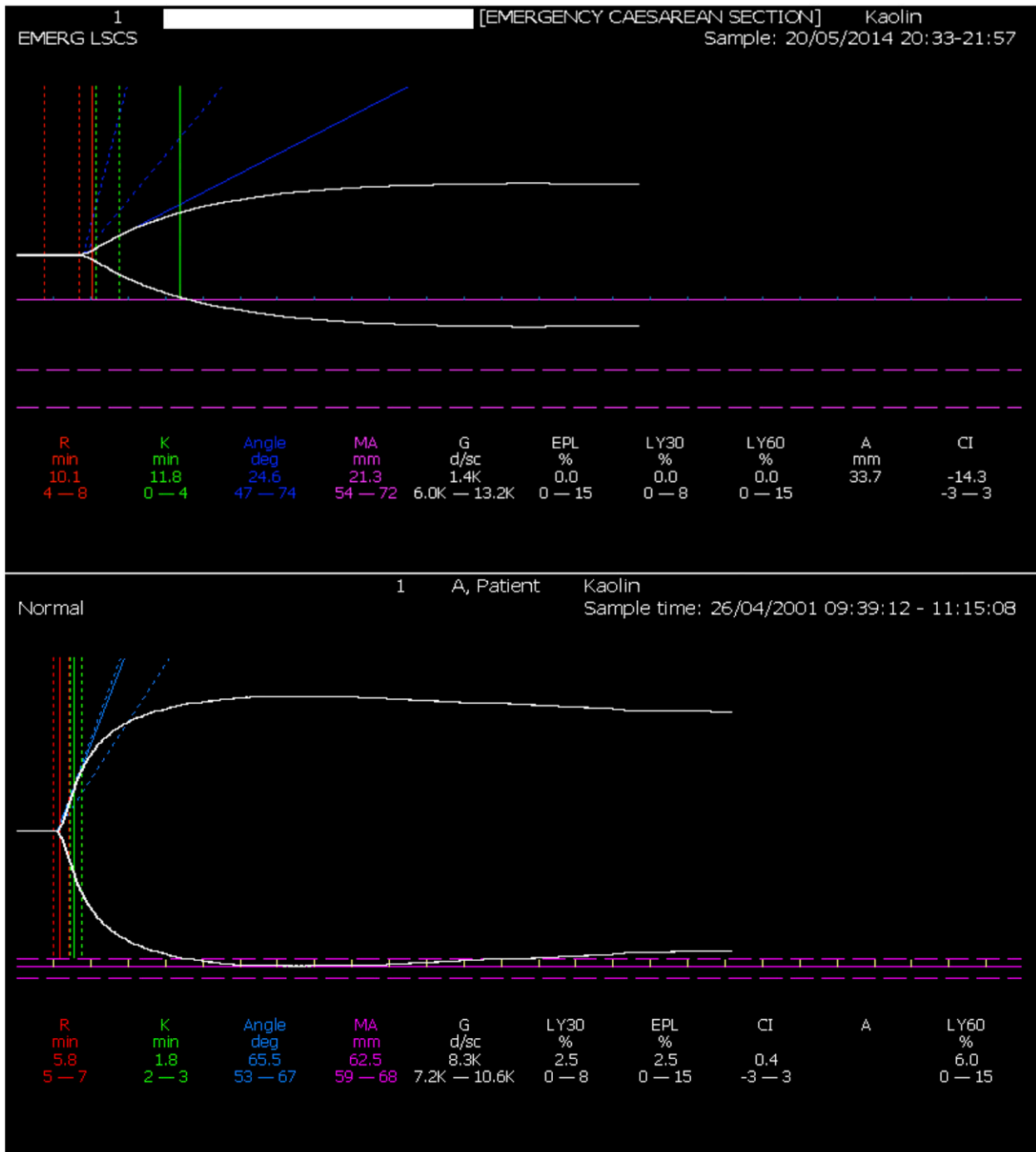


Figure 1. TEG trace 40 minutes into surgery, showing severely prolonged R and K times and reduced α angle and maximum amplitude (MA). A normal TEG trace is given for comparison (lower trace).

situation creates greater opportunity for transfusion of incompatible blood, both through administrative error or the need to use emergency non-cross-matched group-specific or O-negative units. Although RhD-negative blood is always used for ungrouped women, it is the other rh antigens and the Kidd antigen which are most commonly implicated in delayed hemolytic transfusion reactions. This can occur even when the pretransfusion antibody screen was negative, as the antibody may have fallen to undetectable levels but develops a secondary immune response and a boost in titer with re-exposure to the corresponding antigen. The risk of antibody development is ~4%, with delayed hemolysis occurring in very few. This is outweighed by the risk of delaying

transfusion in the emergency setting. We stock our emergency fridge with both O-negative and O-positive units; the latter can be used for women known to be RhD positive, thereby reducing the risk of sensitization to the c antigen, which is more common in RhD-negative units. Group-specific units should be used once the blood group is known and fully compatible units provided as soon as possible.

Optimal red cell transfusion is unknown, with dangers from both inadequate and excessive transfusion. Our practice is to maintain Hb at 80 to 100 g/L and use clinical markers such as volume of blood loss, presence of ongoing bleeding, and the physiological status of the patient to help define red cell requirements.

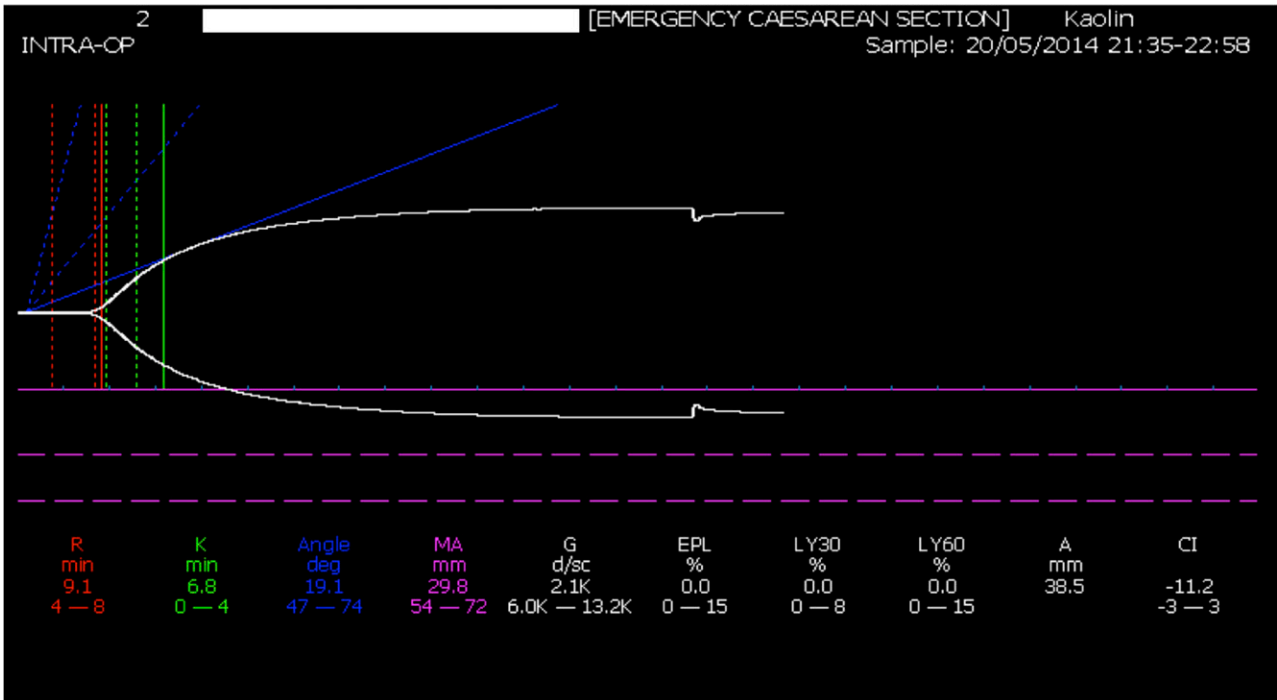


Figure 2. TEG trace toward end of MHP 2 (4 cryoprecipitate, 4 FFP, 1 platelet, and 4 red cells), showing reduction in R and K times and greater MA.

Cell salvage

Intraoperative cell salvage is readily available for obstetric hemorrhage in our center and reduces anemia and use of allogeneic blood. Blood lost during caesarean delivery is suctioned into a reservoir, filtered, washed, resuspended in saline, and reinfused into the patient. A recent local survey showed that the volume of

recovered blood ranged from 380 to 950 mL, depending on the severity of bleeding. The National Institute of Health and Care Excellence guidelines state that it should only be performed by multidisciplinary teams who develop regular experience of its use.²¹ Concern about amniotic fluid embolism, hemolysis, maternal infection, or disseminated intravascular coagulation (DIC) has not been born out.^{22,23} Red cell alloimmunization caused by reinfusing fetal cells is a potential concern and RhD-negative women with

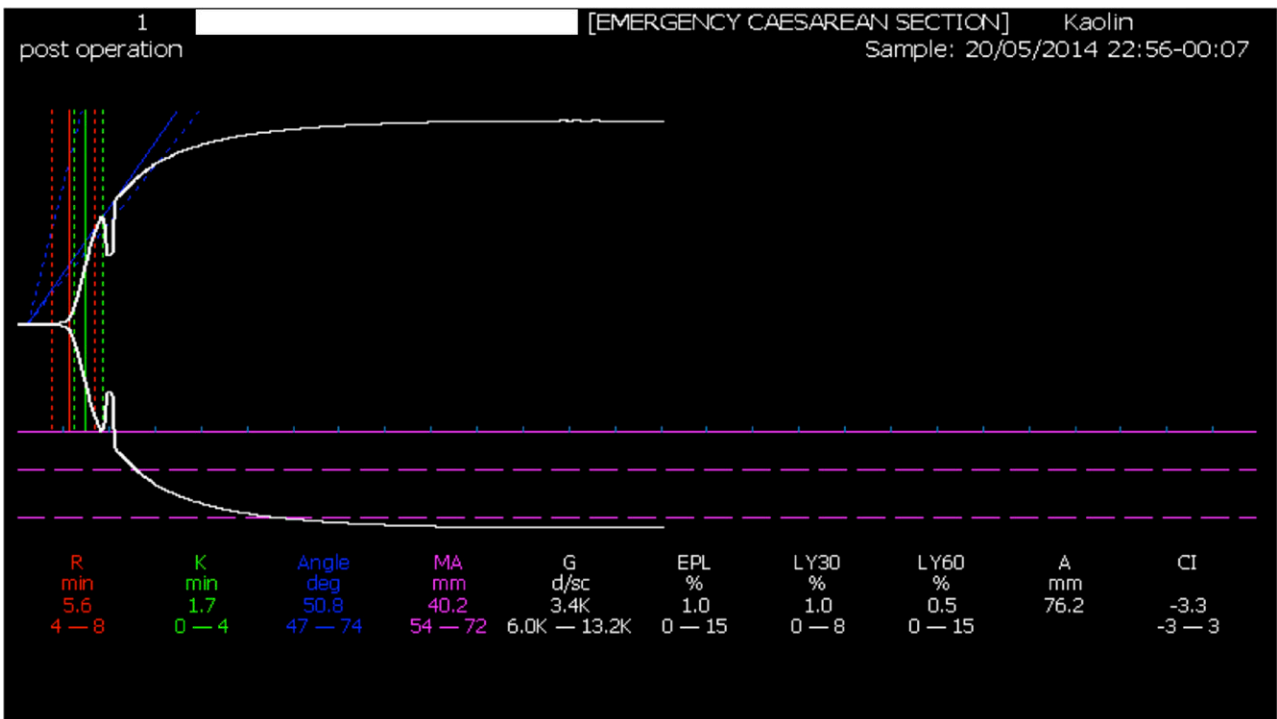


Figure 3. TEG trace following MHP 3 (2 cryoprecipitate, 3 FFP, 1 platelet, red cells), showing near complete correction of coagulopathy.

Uterine Atony (Tone) Multiparity Multiple pregnancy Previous PPH Patient factors-age>40yrs, BMI>35, Asian ethnicity Prolonged labour Placenta praevia	Coagulopathy (Thrombin) Congenital bleeding disorders Acquired coagulopathies Anticoagulants Placental abruption Pre-eclampsia Sepsis Amniotic fluid embolism
Trauma/surgery (Trauma) Perineal or vaginal trauma Caesarean delivery Instrumental vaginal delivery Uterine rupture	Placenta (Tissue) Retained placenta Morbidly adherent placenta – accreta, percreta Placental abruption Placenta praevia

Figure 4. Preexisting and intrapartum risk factors for PPH.

an RhD-positive fetus often require an increased dose of anti-D prophylaxis, after Kleihauer testing.

Coagulopathy

Around 25% of cases of major obstetric hemorrhage are associated with coagulopathy, which results from varying degrees of consumption of clotting factors, dilution of remaining factors by fluid volume replacement, and endothelial activation from hypothermia and acidosis. The nature of the coagulopathy initially depends on the cause of the hemorrhage. That associated with hemorrhage from surgical trauma or laceration, or from uterine atony, is more likely to be dilutional in the early stages, whereas placental abruption causes early hypofibrinogenemia and amniotic fluid embolism can rapidly lead to DIC. Consideration of the etiology of the hemorrhage may therefore help to determine the predominant nature of the coagulopathy in early PPH. Ongoing bleeding exacerbates all types of coagulopathy and with progression of hemorrhage the distinction becomes impossible. Use of predictive markers in the early stages is therefore paramount in guiding appropriate product replacement before coagulopathy escalates. Our patient had profound hypofibrinogenemia, now recognized as an important early coagulation abnormality associated with MOH.²⁴⁻²⁶ Fibrinogen is consumed in widespread clot development and enhanced fibrinolytic factors accelerate breakdown of fibrin and fibrinogen. The resulting degradation products interfere with platelet activation and fibrin creation and hyperfibrinolysis occurs, whereby fibrinolytic activity is greater than fibrin formation, leading to severely diminished clot strength.

Point-of-care tests

The value of conventional tests such as PT, APTT, international normalized ratio (INR), and fibrinogen is lessened by time delays between taking the sample and providing the results. Even in the most efficient centers, it often takes 30 to 60 minutes or even longer, by which time another 5 to 6 L of blood could have been replaced and the coagulation status changed. Furthermore, PT and APTT are not sensitive markers in the obstetric population due to the underlying hypercoagulable state of pregnancy; elevation of factors VII and VIII (FVII and FVIII), during normal pregnancy, causes shortening of the

PT and APTT, respectively. A review of 18 501 pregnancies identified 456 cases with blood loss exceeding 1500 mL; PT did not correlate with the APTT or volume of blood loss.²⁶

Due to the distance between our delivery suite and the pathology laboratories, the introduction of near patient tests, several years ago, was essential. Thromboelastography (TEG) and thromboelastometry (ROTEM) are capable of providing a useful assessment of the coagulation status within minutes (Figure 1). They are performed on whole blood and provide information on the time taken for first fibrin strand formation, the velocity of clot formation, the strength of the formed clot, and fibrinolysis (Table 2). They have been used to demonstrate the hypercoagulable state of pregnancy²⁷⁻²⁹ and the resolution to non-pregnant values in the puerperium.^{30,31} There are numerous case reports of the use of TEG and ROTEM to guide replacement of blood components in the management of PPH^{32,33} and studies have confirmed a reduction in blood loss and associated transfusion of blood products with the use of these tests in other settings.³⁴⁻³⁶ A Cochrane systematic review of 9 randomized controlled trials (RCTs) (involving 776 bleeding patients) concluded that TEG or ROTEM significantly reduced blood loss, but there was no impact on mortality, amount of blood transfused, or length of stay in hospital and intensive care units.³⁷ However, recent modifications to the techniques, using activators and inhibitors, have allowed more targeted analysis, dependent on the clinical scenario. In particular, the technique to quantify fibrinogen has been refined, enabling early detection of hypofibrinogenemia and suitable replacement.²⁴ As with all tests, it is important that validated reference ranges for pregnancy are used when interpreting results.³⁷⁻³⁹ Our pregnancy ranges are derived from a local study of 100 low-risk pregnancies.

The TEG software allows immediate online access to the tracing in the laboratory, which we find crucial to the involvement of the multidisciplinary team. We also use the HemoCue bedside test or the blood gas analyzer throughout MOH to provide regular Hb measurements. Repeated point of care tests are helpful, as the clinical situation evolves, to optimize targeted blood component therapy (Figure 5).

Predictors of worsening hemorrhage and coagulopathy

Fibrinogen level and platelet count both give early warnings of ensuing problems. A retrospective study of 797 pregnancies demonstrated that a platelet count $<100 \times 10^9/L$ or a fibrinogen concentration $<2.9 \text{ g/L}$ during labor was associated with an almost 20-fold increase in the

Table 2. Main TEG variables

TEG variable	ROTEM equivalent	Interpretation	Derivation	Main determinants	Main corrective component
R time	Clotting time	Initiation of clot	Time from start of sample placement in cup to the first detectable fibrin strands (amplitude 2 mm)	Activity of coagulation factors	FFP
K time	Clot formation time	Amplification of clot	Time taken to achieve a certain level of clot strength (amplitude 20 mm)	Activity of coagulation factors	FFP
α angle	Clot formation time	Thrombin burst: the speed at which the fibrin builds up and crosslinking takes place	Formed by the slope of the TEG tracing from the horizontal line	Presence and interactions of fibrinogen	Fibrinogen
Maximum amplitude	Maximum clot firmness	Ultimate strength of the clot	Height of the TEG tracing from the horizontal line	Platelets (predominantly) and fibrin	Platelets
Clot lysis at 30 and 60 min (LY30 and LY60)	LY30, LY45, LY60	Degree of fibrinolysis	Amount of clot lysis at specific time points, by percent decrease in amplitude	Activity of fibrinolytic factors	TXA

Other useful parameters are derived from these variables. The shape of the waveform is also important.

incidence of postpartum hemorrhage.⁴⁰ In bleeding patients, fibrinogen ≤ 2 g/L had a positive predictive value for worsening hemorrhage of 100%, whereas 4 g/L had a 79% negative predictive value.²⁵ A falling platelet count in early PPH²⁵ or a falling Clauss fibrinogen predict progression to transfusion and invasive procedures.^{41,42} Our patient's first fibrinogen level was severely reduced at 0.2 g/L, an ominous sign of the course of events. However, the result was not available within a clinically useful time frame and it was the TEG results that prompted the need for cryoprecipitate. A ROTEM-based fibrinogen (Fibtem), which measures fibrin-based clot strength after platelet inhibition, provides a result within 10 minutes and is a useful biomarker of worsening hemorrhage; in an observational study of 356 women, the Fibtem at 1000 or 1500 mL of blood loss was independently associated with progression to >2500 mL.⁴³

Clinical predictors include the cause of the hemorrhage, preexisting patient factors and obstetric events (Figure 4). In our case, there was manual delivery of the placenta, in order to remove the bleeding surfaces and facilitate uterine contraction without delay. A prospective randomized clinical study of 100 women undergoing caesarean delivery did not show a difference in perioperative blood loss between spontaneous removal and elective manual removal of the placenta⁴⁴; however, this study did not relate to women already bleeding. The progressive coagulopathy precluded the use of neuraxial anesthesia for our patient but, in comparison, general anesthesia has been associated with a 6-fold greater incidence of PPH and a 5-fold increase in transfusion requirements.⁴⁵

Major hemorrhage packs

Delays in obtaining laboratory coagulation results, as highlighted in this case, have led to the empirical use of MHPs in formula-driven strategies. They comprise FFP, platelets, cryoprecipitate, and red cells, in varying proportions, depending on the stage in the process. High plasma-to-blood ratios are increasingly used, following the success of this practice in severely injured combat casualties. When coagulation results are available, empirical treatment can be replaced by directed therapy, according to the results. Our first pack contains 4 units of red cells and 4 units of FFP. We then tailor each MHP and prioritize the component to be used first, based on our knowledge of the cause of hemorrhage and real-time results from TEG and HemoCue. With recent knowledge and understanding of the

importance of maintaining higher fibrinogen levels, we are using cryoprecipitate earlier in the course of PPH than previously. To date, guidelines have offered different recommendations⁴⁶⁻⁴⁸ and those from the Royal College of Obstetricians and Gynaecologists suggest maintaining the Hb >80 g/L, PT and APTT <1.5 times the mean control, platelets $>75 \times 10^9/L$, and fibrinogen >1 g/L. However, these are not evidence based and given that fibrinogen increases in normal pregnancy, with a level at term of 4 to 6 g/L, compared with 1.5 to 4 g/L in the general population,^{49,50} this fibrinogen level is likely to be inadequate. Studies suggest a level of >2 g/L to be more appropriate.^{25,51,52}

Fibrinogen replacement

Cryoprecipitate provides a richer source of fibrinogen than FFP. Each unit contains >140 mg of fibrinogen, along with FVIII, FXIII, von Willebrand factor (VWF), and fibronectin. A typical adult therapeutic dose is 1 unit per 5 to 10 kg of body weight (2 pools of 5 units), which would be expected to increase plasma fibrinogen levels by around 1 g/L. As it contains less immunoglobulin than FFP, there is less need for AB compatibility. Virally inactivated purified fibrinogen concentrate was introduced for the management of patients with congenital hypofibrinogenemia or afibrinogenemia. It has been successfully used in acquired hypofibrinogenemic states.^{53,54} Studies have supported its efficacy in massive obstetric haemorrhage.⁵⁵⁻⁵⁷ There is no evidence for preemptive use in early MOH, when fibrinogen is normal⁵⁸ but guided by results from ROTEM, it has led to reduced requirements for blood components and lower risk of circulatory overload,⁵⁷ which can be particularly serious for women with preeclampsia. A multicenter placebo RCT is ongoing to further clarify the value of fibrinogen concentrate in this setting.⁵⁹

Tranexamic acid

The evidence base for early use of TXA in massive hemorrhage is rapidly expanding and our practice has seen increased use of TXA for PPH associated with both vaginal and caesarean delivery. Its efficacy, in reducing blood loss and transfusion requirements, in both these settings has been confirmed.⁶⁰⁻⁶² For speed and simplicity we use a

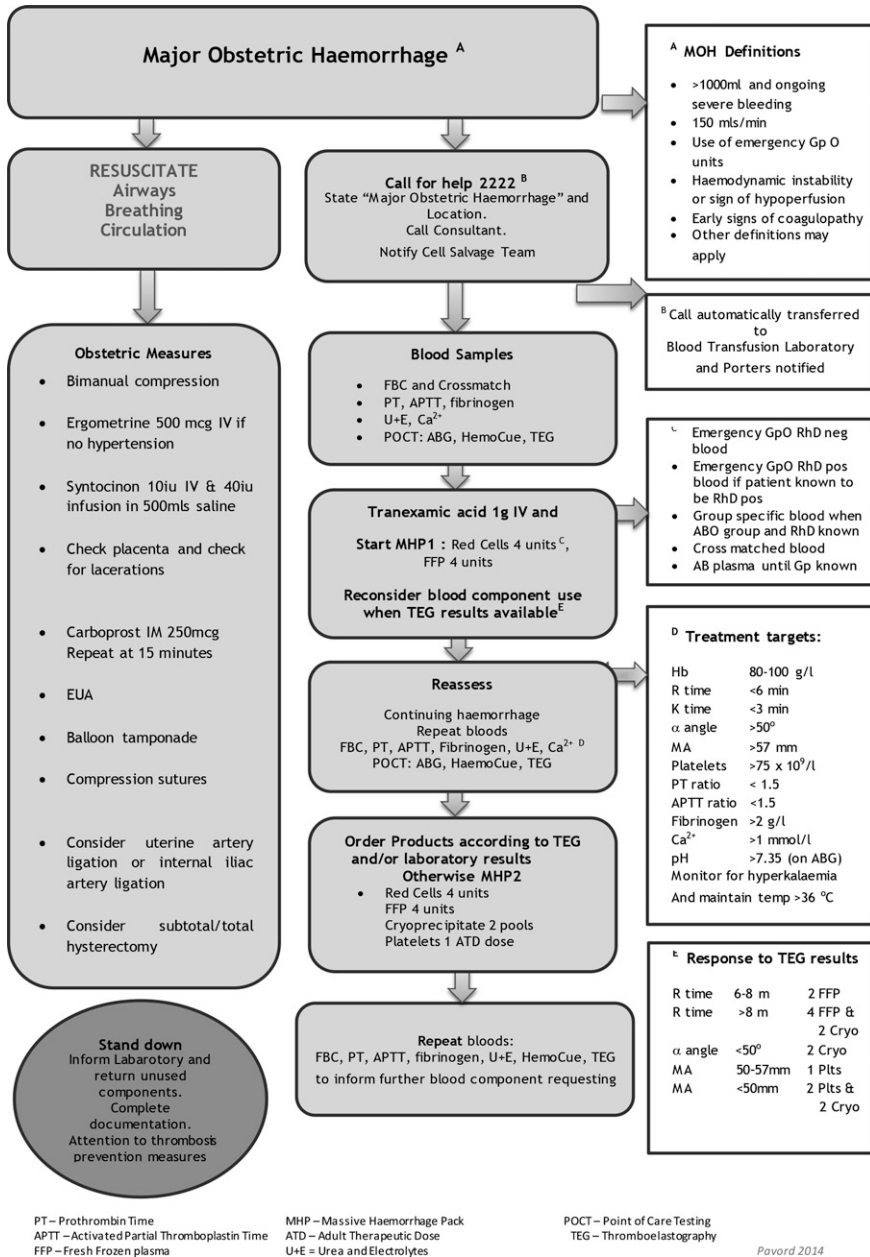


Figure 5. Algorithm for management of MOH. TEG thresholds based on local normal ranges.

standard dose of 1 g IV, repeated after 30 minutes as necessary. A large international study is investigating the effect of IV tranexamic acid on the incidence of hysterectomy and mortality in women with PPH.⁶³

Recombinant FVIIa

Recombinant activated FVII (rFVIIa; Novo Nordisk A/S) has been used empirically during obstetric hemorrhage as a last-ditch attempt to prevent hysterectomy, with anecdotal evidence of success.⁶⁴ Hemostasis is achieved by direct activation of platelets, the tenase complex, and tissue factor-mediated coagulation. It is effective in up to 80% of cases⁶⁵ but thrombotic events have been observed in 2.5% of treated cases,⁶⁶ including deep venous thrombosis, pulmonary embolism, cerebral thrombosis, and myocardial infarction. Data from trials with rVIIa, outside the setting of pregnancy, also warned of heightened

thrombotic risk, leading the manufacturers to advise against this off-license use of rFVIIa (Novonordisk SPC). However, given its high efficacy, further trials are required before it can be dismissed. A recent RCT of rFVIIa (60 mcg/kg) use in women with PPH refractory to uterotonics demonstrated reduced need for interventional second-line therapies in a third of patients, with nonfatal venous thrombosis in 1 in 20.⁶⁷ Platelet and fibrinogen thresholds of >50 × 10⁹/L and >1 g/L, respectively, were ensured. rFVIIa is used occasionally in our center when hemorrhage has not been controlled by other means and has avoided the need for hysterectomy. Vigilance with thromboprophylactic measures, when the emergency situation is over, is paramount.

Surgical and radiologic interventions in PPH

Intrauterine balloon tamponade is increasingly used as the first-line procedure when medical treatment of uterine atony has failed. In the

Table 3. Advantages and disadvantages of different interventions

Technique	Advantages	Disadvantages	Success rate % (95% CI)
Balloon tamponade eg, Bakri, Rusch balloon, Sengstaken-Blackmore tube, or condom catheter	Simple technique Low cost Can avoid laparotomy		84.0 (77.5-88.8)
Brace suture eg, B lynch, modified compression sutures	Simple technique Low cost	Requires laparotomy in event of vaginal delivery Case reports of infection, uterine necrosis, and Asherman syndrome	91.7 (84.9-95.5)
Uterine artery ligation Internal iliac artery ligation	Reduces blood supply to uterus Further reduction in blood supply by occluding vaginal and uterine arteries	Vaginal artery still supplying uterus Requires higher level of surgical training	84.6 (81.2-87.5)
Interventional radiology	Useful as second-line treatment	Specialist equipment and skills limit availability Case reports of uterine necrosis, infection, and vascular perforation	90.7 (85.7-94.0)

Wikkelsø et al.⁵⁸
CI, confidence interval.

event of continuing bleeding, subsequent intervention will depend on the skills and experience of the operator, hemodynamic status of the woman, and the availability of resources. The techniques are safe and effective and preserve fertility⁶⁸ (Table 3).

Prevention of obstetric hemorrhage

Identification of high-risk women

Risk factors for obstetric hemorrhage are listed in Figure 4. They can be categorized into the 4 “T”s, based on the predominant mechanism. Uterine atony (“Tone”) is the most common cause; failure of the myometrium to contract allows continued bleeding from the spiral arteries. Risk factors for uterine atony are well established,^{69,70} however, they only have moderate positive predictive value for PPH and hence limited clinical utility. Most cases of uterine hemorrhage are not predictable but for those with known preexisting factors, such as placenta previa or previous PPH, we discuss and agree upon a delivery plan in advance. This may include blood tests on arrival in labor, IV access, availability of appropriate blood or blood products, cell salvage on stand-by, and active management of the third stage of labor. The unpredictability of labor emphasizes the need to frequently reevaluate the risk, to preempt ensuing problems, using the available techniques for monitoring and intervention. This is highlighted by a recent observational study of over 10 000 women in primary care who were considered to be “low obstetrics risk” but whose risk of PPH increased by 2.35- and 46.95-fold in association with prolonged second or third stage of labor, respectively.⁷¹ It is also important during caesarean delivery where PPH occurs in 5% to 10%, with uterine atony, abnormal placentation, uterine trauma, and sepsis being the main causes. Caesarean hysterectomy occurs in around 0.1%, usually for morbidly adherent placenta, but is associated with a high incidence of hemorrhage and hospitalization in intensive care.⁷²

Women with preexisting bleeding disorders

A personal or family history of bleeding tendency or abnormal laboratory parameters such as thrombocytopenia should alert the obstetrician to seek hematologic advice. The key factor for the management of women with known bleeding disorders is appropriate risk assessment and advance planning for hemostatic cover to reduce the bleeding risk.⁷³ Women with von Willebrand disease (VWD) or carrier state for

hemophilia require FVIII and FIX levels and von Willebrand activity (ristocetin cofactor activity) to be above 50 IU dL⁻¹ for delivery and regional anesthesia.⁷⁴ As FVIII and VWF increase in pregnancy, hemophilia A carriers and patients with type 1 VWD usually have normal levels at term and rarely require treatment. However, if third-trimester levels are inadequate, as more frequently occurs in hemophilia B carriers or types 2 and 3 VWD, we would cover delivery with the relevant factor concentrate, administered at the onset of labor and maintained for at least 3 days postpartum or 5 days following caesarean delivery.⁷⁴

For most rare congenital factor deficiencies, baseline factor level does not correlate with propensity to bleed and for heterozygous women; it is usually sufficient to have factor concentrate available in the case of hemorrhage or surgical intervention, but not as routine prophylaxis.⁷⁵ However, women with homozygosity and/or a bleeding phenotype require treatment with specific factor concentrate (for fibrinogen, FVII, FXI, and FXIII deficiencies) or if this is unavailable, prothrombin complex concentrate (FII and FX deficiencies) or solvent detergent-fresh frozen plasma (FV and FXI deficiencies). Women with afibrinogenemia or FXIII deficiency require replacement therapy throughout pregnancy to prevent fetal loss.⁷⁶

TXA, given orally or IV, may be a useful adjunct to factor replacement or be used alone in less severe cases. Administration 2 hours before delivery ensures peak plasma levels at the time of hemostatic challenge.⁷⁷ Oral TXA, 1 g 3 or 4 times daily, for 2 to 3 weeks is also beneficial in reducing postpartum blood loss.

Women on anticoagulation

Women on anticoagulation require careful planning. It is usually sufficient to stop prophylactic anticoagulation at the onset of labor and resume 6 to 12 hours postpartum but we decide this on a case-by-case basis. Those on full anticoagulation need a careful assessment of the balance of risks of thrombosis and hemorrhage.⁷⁸ Our practice is to continue with therapeutic low-molecular-weight heparin (LMWH) until 24 hours before a planned induction of labor. If we wish to minimize interrupted anticoagulation, we would switch to an IV infusion of unfractionated heparin until the onset of established labor, or 4 hours prior to regional anesthesia, checking the APTT has returned to normal. Prophylactic LMWH is given at 6 to 12 hours after delivery, providing hemostasis is secure and therapeutic anticoagulation recommenced on the first day postpartum following uncomplicated vaginal delivery, or escalated more slowly after a complicated or surgical delivery. For

Table 4. Risk factors for anemia in pregnancy

Risk factors for maternal anemia
Previous anemia
Short interval between pregnancies <1 y
Teenage pregnancy
Multiparity ≥ 3
Vegetarianism
History of recent bleeding

patients with acute deep venous thrombosis within a week of delivery, we would consider inserting a temporary inferior vena caval filter but generally our use of filters is minimal.

Patient blood management

No woman should enter the intrapartum period already anemic and local processes should be in place to avoid such occurrences. The most common cause of anemia is iron deficiency. It is highly prevalent in the obstetric population, with estimates of 18% to 20% and 40% entering pregnancy with no iron stores at all. Anemia not only reduces tolerance to acute hemorrhage but iron deficiency may contribute to uterine atony because of depleted uterine myoglobin levels necessary for muscle action. There is good correlation between the hemoglobin at booking and that prior to delivery and therefore opportunities to discuss preventative measures such as dietary and cooking modifications and pregnancy spacing should be taken, ideally prior to conception. Routine iron supplementation is not currently recommended but UK national guidelines recommend that local strategies are in place for identification of at-risk women (Table 4) and the early detection and management of iron deficiency.⁷⁹

Postpartum management

Postpartum anemia is best managed with iron supplements. Audits suggest that iron is underutilized and blood transfusions are administered inappropriately in the postpartum period.^{80,81} Blood transfusion should be reserved for those with risk of further bleeding, imminent cardiac compromise, or symptoms requiring immediate attention. We give 100 mg of elemental iron for 3 months to women with Hb <100 g/L in the postpartum period.⁷⁹ If more rapid correction of Hb is required, IV iron carboxymaltose or iron isomaltoside can be used. The need for thromboprophylaxis should also be considered, once bleeding is controlled and hemostasis secure.⁸² Following PPH, women are at risk of venous thrombosis, as a result of the surgery, trauma, prolonged recovery, immobility and hospitalization, hemostatic products (particularly rFVIIa and fibrinogen concentrate), and any underlying DIC.

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After discharge from hospital, we always make time for debriefing and effective counseling, as there is a high degree of posttraumatic stress for both the woman and her partner. Women can be reassured that uterine-sparing radiologic and surgical techniques for the management of severe PPH do not appear to adversely affect menstrual and fertility outcomes.^{83,84} The risk of recurrent postpartum hemorrhage is high, with 10% risk of recurrent abruption and 5% risk of recurrent placenta previa. Additional imaging will be required for the early detection of morbidly adherent placentas in women who underwent caesarean delivery. Supplementary uterotonics are likely to be used routinely.

Staff education

Given the unpredictable nature of postpartum hemorrhage, we all must understand the initial steps in the assessment and management of this emergency. We ensure our hospital protocols are kept up to date and maintain education of multidisciplinary staff, using simulation exercises and practice drills, focusing on early recognition of PPH, identification of etiology, accurate and timely estimation of blood loss, and the speedy management of this condition. The drills include obstetricians, hematologists, anesthetists, biomedical scientists in blood bank and hemostasis laboratories, theater porters, nurses and midwives, and anyone else crucial to this emergency. A key concern in this case was the significant delay in obtaining the initial blood components and our policy was subsequently changed to include a designated porter with sole responsibility for speed of transport of blood samples and blood components.

Conclusion

In conclusion, PPH is the largest contributor to maternal mortality worldwide. Skilled multidisciplinary care is required before, during, and after childbirth to prevent PPH as far as possible but when it occurs, timely recognition, management, and treatment can make the difference between life and death for mother and baby.

Authorship

Contribution: S.P. and H.M. wrote the paper.

Conflict-of-interest disclosure: The University Hospitals of Leicester NHS Trust is participating in the OBS 2 trial of use of fibrinogen concentrate, which is sponsored by CSL Behring.

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