Modern Approaches to Obstetric Haemorrhage

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Abstract: Postpartum haemorrhage (PPH) is a major cause of maternal morbidity and mortality worldwide, with an increasing trend in incidence over time also in developed countries. This applies particularly to small hospitals where management protocols may not be appropriate and drugs, equipment or surgical expertise may not be on hand to deal with unexpected severe PPH. The main causes of PPH are uterine atony, retained placenta or placental fragments, and injury of soft tissue. Primary coagulation defects only rarely cause PPH. The focus of this review is on early interventions to restrict the amount of blood loss, i.e. effective use of uterotonic agents, surgical and medical interventions to remove retained placenta or placental fragments, use of balloon tamponade, early use of antifibrinolytics, replacement of low fibrinogen level, avoidance of hydroxyethyl-starch containing solutions, and the administration of red blood cells and platelets to optimise the coagulation.

Keywords: Pospartum haemorrhage, uterine atony, retained placenta, abnormally invasive placenta, interventional radiology, Bakri balloon.

1. INTRODUCTION

Postpartum haemorrhage (PPH) is a major cause of maternal morbidity and mortality worldwide, with an increasing trend in incidence over time also in developed countries. Factors associated with PPH include retained placenta, failure to progress during the second stage of labour, abnormal placentation, birth canal lacerations and uterine rupture, vacuum extraction, large for gestational age newborn, hypertensive disorders, induction of labour, and augmentation of labour with oxytocin [1]. In addition, obesity, high parity, history of previous PPH, intrauterine fetal death, Asian or Hispanic race, precipitous labour, preeclampsia, previous surgery due to endometriosis, and *in vitro* fertilization induced pregnancy have been associated with PPH. A previous caesarean section and in particular repeat caesarean sections predispose to PPH [2-5]. In spite of the numerous risk factors for PPH, many labouring women who start to bleed are previously healthy, and therefore every maternity unit must be prepared to handle these unexpected and occasionally critical emergencies. Primiparity is an independent risk factor for PPH and prior to delivery, these women usually do not have any recognizable risk factors for PPH [6].

Management of PPH includes the treatment of uterine atony, manual and medical interventions to remove the retained products of conception, the use of balloon tamponade, surgery due to birth canal trauma or uterine rupture, prompt replacement of the blood loss, and occasionally, selective arterial embolization (Figure **1**) [7-9]. In case of intractable haemorrhage, external or intra-abdominal aortic compression as well as bi-manual uterine compression may be lifesaving and provide time for more detailed interventions. Postpartum hysterectomy is the last option to control the blood loss. Increasing rates of this surgically demanding procedure have been reported throughout the world. Vaginal birth after caesarean section, primary and repeat caesarean deliveries and multiple births seem to be independently associated with an increased risk for postpartum hysterectomy [5,10,11]. Apart from an irreversible loss of fertility, the procedure may also have deleterious effects on maternal mental and sexual health.

In 2004, we prepared a clinical guideline for the treatment of PPH at Helsinki University Hospital. Thereafter, a literature search has been performed every 1 to 2 years to update this guideline (using keywords such as: uterine atony, retained placenta, balloon tamponade, fibrinolysis, fibrinogen, coagulation and selective arterial embolization; each pairwise with postpartum haemorrhage). This review is based on that literature search last preformed in September, 2013.

2. UTERINE ATONY

Uterine atony is defined as failure of myometrium to contract and retract following delivery. It complicates 5-6% of deliveries and accounts for up to 90% of all PPH cases [12,13]. The common risk factors for uterine atony include induction of labour, prolonged labour, multiple gestation, polyhydramnios, obesity, advanced

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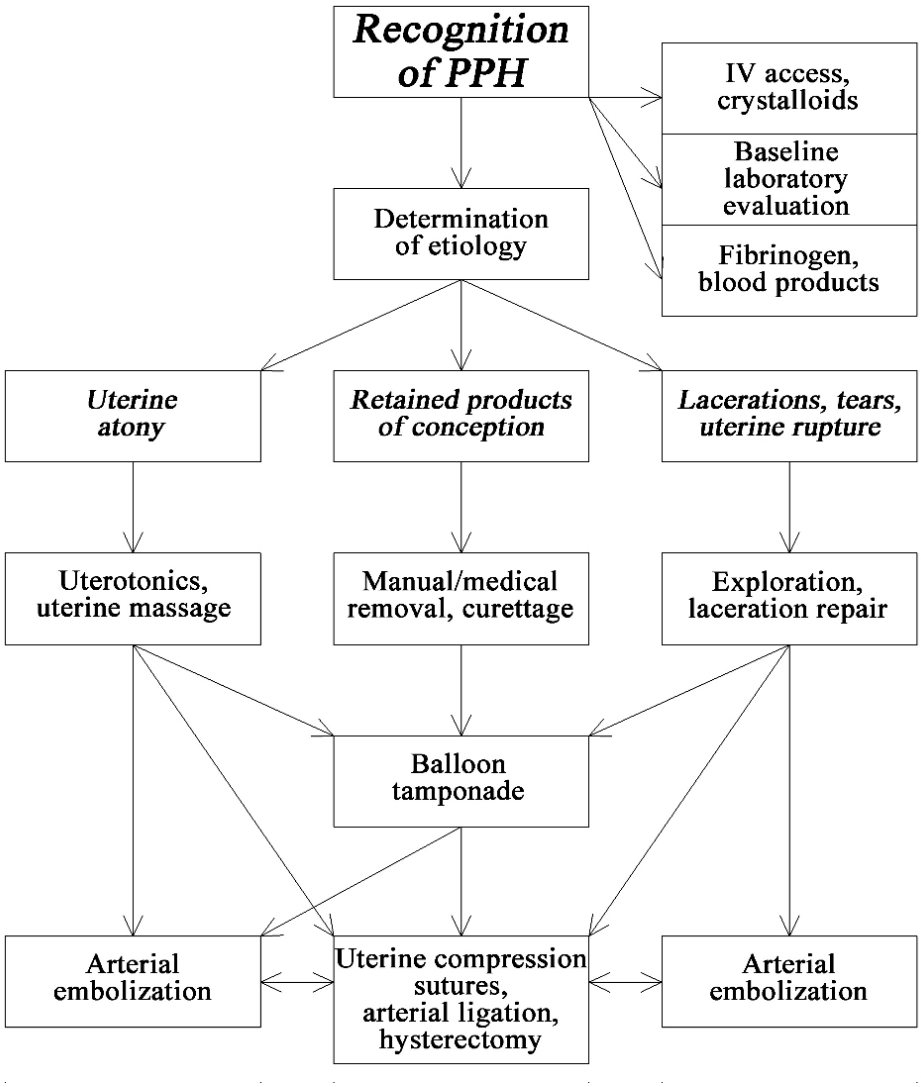

Figure 1: Management plan for the treatment of postpartum haemorrhage (PPH).

maternal age, chorioamnionitis, history of PPH, and the increasing rate of abnormal placentation, i.e. placenta accreta, increta and percreta. However, the various risk factors are not very powerful, and individually fairly common, so reliable prediction of uterine atony may not be practical based on clinical risk factors [12,13]. Thus, vigilance and preparation for this potential emergency are necessary in all women. Active management of the third stage of labour (AMTSL) including intramuscular uterotonics immediately after delivery of the baby, early cord clamping and uterine massage is the most important step in avoiding uterine atony and subsequent PPH. AMTSL reduces the incidence of PPH compared with women who were managed expectantly [14].

Oxytocin remains the first line agent. It induces stimulating rytmical myometrial contractions, particularly in the upper uterine segment. Because of oxytocin receptor desensitization, the second line agents such as ergot alkaloids and prostaglandins are often required (Table **1**) [15,16].

Table 1. Administration of Standard Uterotonic Drugs [9, 15-16]

IV infusion of 30-50 IU of **oxytocin** in sodium chloride 0.9%
Misoprostole 400-600 µg orally or 800-1000 µg rectally
Methylergometrine 0.2 mg IV (maximum of 5 doses)
IV infusion of **sulprostone** (500 µg in 60 min, followed by 500 µg in 3 h, and 500 µg during the next 10-12 h if necessary) or **carboprost** 250 µg IM (maximum of 8 doses)

IV = intravenous, IM = intramuscularly
Superscript numbers refer to the references

Several studies on the use of carbetocin, a novel and promising uterotonic agent, have been published.

A recent Cochrane review concluded that for women who undergo caesarean section, 100 µg of intravenous carbetocin results in a statistically significant reduction in the need for therapeutic uterotonics compared to oxytocin, but there is no difference in the incidence of PPH [17]. Comparison between intramuscular carbetocin and syntometrine showed a lower mean blood loss in women who received carbetocin after vaginal delivery. There was no statistically significant difference in terms of the need for therapeutic uterotonic agents, but the risk of adverse effects such as nausea and vomiting were significantly lower in the carbetocin group. Further research is needed to analyse the cost-effectiveness of carbetocin as a uterotonic agent [17].

The use of any uterotonic agent has precautions and contraindications. When combining these agents, especially in haemodynamically unstable patients, the risks of their use must be weighed against that of intractable or uncontrolled haemorrhage [15,16].

3. RETAINED PLACENTA OR PLACENTAL FRAGMENTS

Many cases of PPH are associated with retained placenta, a condition that affects between 0.6 and 3.3% of normal deliveries [18]. Risk factors for placental complications −such as placenta praevia and retained placental products with or without abnormal placentation − include multiple gestations, one or more previous caesarean sections, previous retained placenta, preterm delivery, oxytocin use for several hours, preeclampsia, two or more previous miscarriages, and one or more previous abortions [19].

The retained placenta may simply be trapped behind the closed cervix or it may be easily separated manually from the uterine wall. Occasionally, however, the placenta may invade the myometrium (placenta accreta, increta) and sometimes even the adjacent urinary bladder (placenta percreta). There is a considerable variation between European countries about the timing of manual removal of retained placenta [20]. The UK National Institute for Health and Clinical Excellence guidelines suggest 30 min [21] whereas the World Health Organisation manual for childbirth suggests 60 min [22]. A large study including 12979 consecutive vaginal deliveries showed that the risk of haemorrhage increases after 30 min [18]. On the other hand, delaying the manual removal may lead to spontaneous delivery of the placenta but it is only rarely expelled spontaneously after 60 min. Accordingly, the choice of timing for manual removal depends on the facilities available and the local risks associated with both PPH and manual removal of the placenta [9].

Medical treatment is a novel and promising management option for retained placenta. Two recently published studies from the Netherlands [23] and Finland [24] showed that an intravenous infusion of sulprostone, a synthetic prostaglandin-E2 derivate, has a success rate of 47% and 39.7%, respectively thus reducing significantly the need of manual removal of the retained placenta. In these studies, the decision to use sulprostone was made if the placenta was not expelled within 45 or 40 min after delivery, respectively. Additionally, the blood loss was significantly lower in women with successful placental expulsion than in women who had manual removal of the placenta [24].

4. BALLOON TAMPONADE

During the last decade, uterine balloon tamponade has been added to the treatment modalities of PPH. Different balloons have been used such as a simple condom, Sengstaken-Blakemore, Foley and Rusch catheters [25]. The Bakri balloon is the only balloon exclusively designed and introduced for uterine and birth canal tamponade (Figure **2**) [26]. It can be used to control atonic bleeding after vaginal delivery as well as during caesarean section. The balloon can also be inserted vaginally to reduce haemorrhage caused by vaginal tears and/or paravaginal haematoma [27].

In case of uterine atony, the mechanism of action of the Bakri balloon is not yet well understood. Recent evidence suggests that the uterine stiffness increases immediately after insertion of the balloon, suggesting that the balloon induces uterine contractions [28]. The tamponade effect of a distending balloon within the uterine cavity may actually be caused by several mechanisms including changes in the uterine shape, secondary uterine activity, interactions between the balloon and the endometrium, and the balloon may have an impact on the uterine circulation decreasing the flow through the uterine arteries. Compared with uterine packing e.g. with cotton gauze and some of the other balloons, the Bakri balloon has a channel for blood drainage. Furthermore, it can be easily gradually inflated and deflated for controlling the haemorrhage. The balloon tamponade provides time to optimize the coagulation status and it may also be used for temporary management of PPH during patient transfer to a tertiary hospital for the definitive treatment [27].

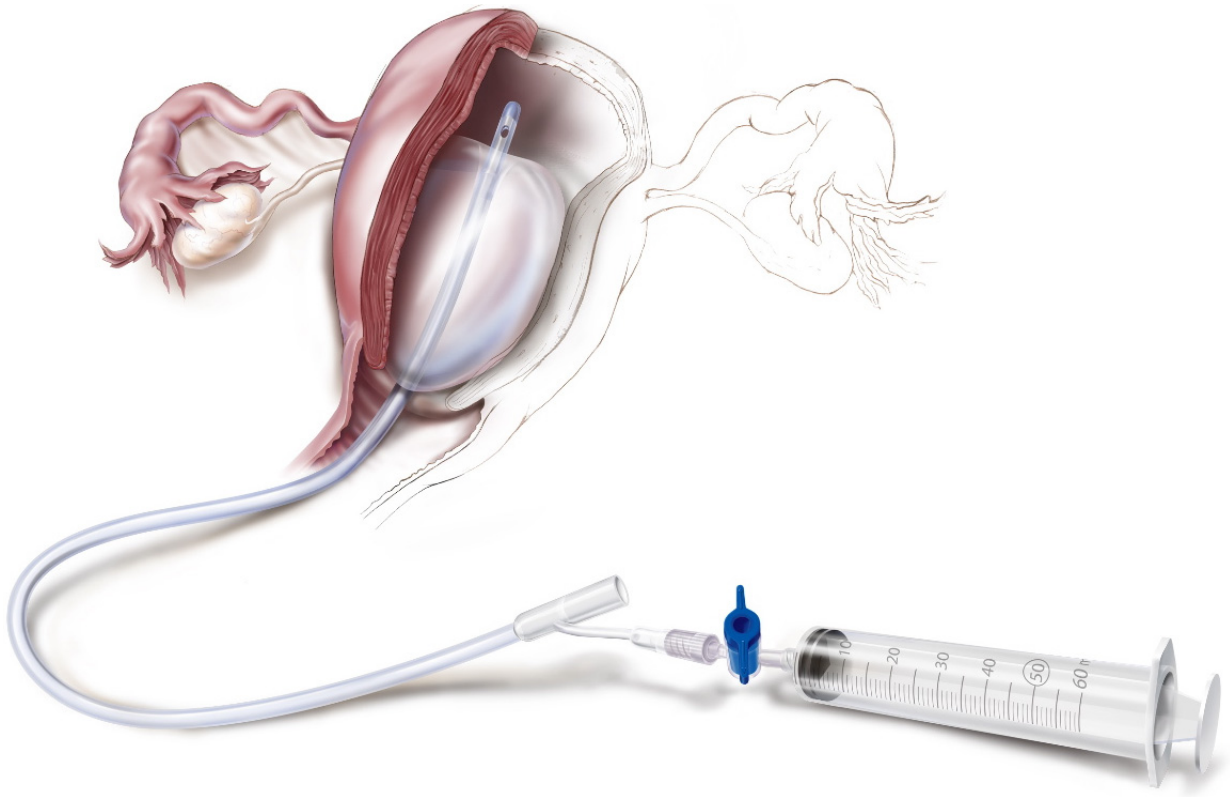

Figure 2: The Bakri balloon (with a channel for blood drainage) for uterine and/or vaginal tamponade treatment. (©2007 Lisa Clark courtesy of Cook Medical Inc.)

The balloon is filled to the desired level of 250 to 500 ml saline as appropriate to the uterine size. If the bleeding site is located in the lower uterine segment, e.g. in case of PPH due to placenta praevia, the balloon is inflated with 250 ml and traction applied to insure compression – e.g. by connecting the distal end of the balloon catheter to an intravenous fluid bag of 500 to 1000 ml. The balloon is usually left in situ for 12 to 24 hours. Thereafter, the balloon is deflated gradually and removed completely when adequate haemostasis is achieved. In so far the largest published case series of 50 women with PPH management by the Bakri balloon tamponade, the overall success rate was 86% [27], similar to that in earlier but smaller case series.

5. ANTIFIBRINOLYTICS

The overall fibrinolytic capacity is attenuated during pregnancy. However, marked activation of coagulation and fibrinolysis occurs in the utero-placental circulation [29] resulting in increased levels of fibrin degradation products (D-dimer) detected towards the end of normal pregnancy and delivery [30]. The fibrinolytic activity [31] and the level of D-dimer is further increased immediately postpartum whatever the mode of delivery [32]. The utero-placental activation of coagulation and fibrinolysis likely reflects physiology of normal pregnancy and delivery. However, in case of PPH, the already on-going fibrin breakdown and augmented fibrinolysis may severely impair the haemostasis and increase the blood loss. Once the fibrinolytic process is initiated, it produces positive feedback, leading to more efficient plasminogen activation [33]. The vicious circle of hyperfibrinolysis results in impaired platelet aggregation and fibrin polymerisation by fibrin degradation products (Figure **3**). While α2-antiplasmin normally rapidly complexes and inactivates free plasmin, the capacity of α2-antiplasmin may be overwhelmed and free plasmin starts to degrade fibrinogen, FV, FVIII, FXIII, and von Willebrand factor [34].

Tranexamic acid reduces blood loss after elective caesarean delivery [35] as well as blood loss and maternal morbidity in the treatment of PPH after vaginal delivery [36]. The on-going large randomized double-blind, placebo controlled WOMAN trial will quantify the effects of early administration of tranexamic acid on death, hysterectomy and other

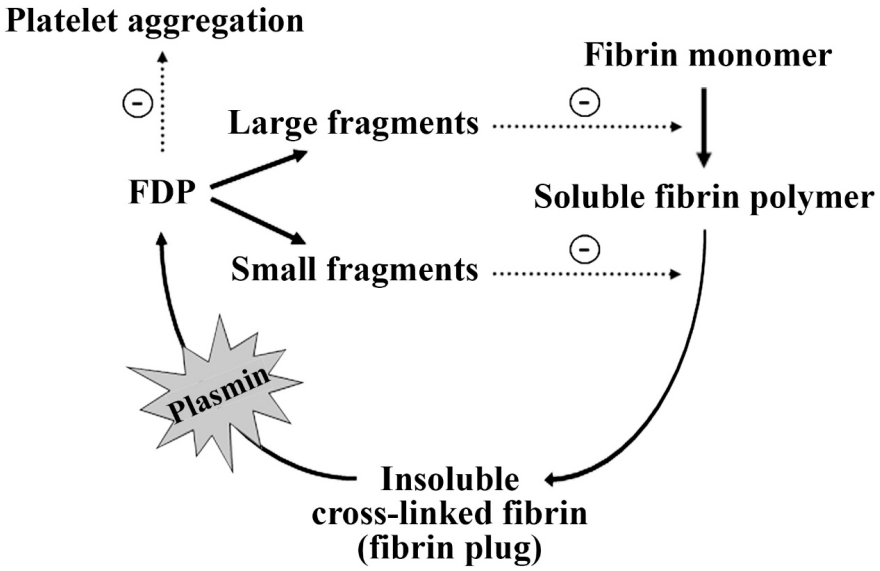

Figure 3: The deleterious effects of enhanced fibrinolysis on haemostasis, i.e. enhanced breakdown of the fibrin plug, impaired platelet aggregation and fibrin clot formation. Dotted line and ⊖, inhibition of the corresponding step in the haemostatic process.

relevant outcomes (http://clinicaltrials.gov/ct2/show/NCT00872469) [37]. Although the evidence so far is limited [35], the most benefit is likely achieved when tranexamic acid is administered early after the blood loss exceeds 500 ml [9].

6. FIBRINOGEN

Simon *et al*. showed that the mean fibrinogen concentration in 797 women at the time of delivery was 4.8 g/l but the range was particularly wide from 2.1 to 9.0 g/l. There were 26 women whose fibrinogen was less than 2.9 g/l [38]. Szecsi *et al*. determined the gestational age-specific reference intervals for coagulation tests during normal pregnancy [30]. The authors recruited 801 women during the first trimester of pregnancy. About half of these women had no complications during pregnancy, vaginal delivery, or postpartum period. Their fibrinogen concentrations increased most dramatically from week 28 to approximately twice the non-pregnant levels late in pregnancy. The mean fibrinogen level at the time of delivery was 4.9 g/l and the range was 3.3 to 6.9 g/l [30].

Charbit *et al*. showed in 128 women that fibrinogen at the time of diagnosis of PPH can be used to guide the management of PPH [39]. The negative predictive value of a fibrinogen level higher than 4 g/l was 79% while all 11 women whose fibrinogen was 2 g/l or less developed a severe PPH. This is in accordance with experimental thromboelastography findings showing that at fibrinogen 0.5 g/l, clot is not formed. Clot formation begins at 0.75 g/l while all parameters of clot formation augment markedly from 0.75 to 3 g/l [40]. Thus, fibrinogen is critical not only for clot strength but also to speed clot initiation and propagation. However, the large variation in the initial fibrinogen level and the varying consumption of fibrinogen during different types of PPH hamper the interpretation when to start fibrinogen supplementation during the early stages of PPH. An early determination of the fibrinogen concentration is helpful to guide the replacement therapy. Fibrinogen can be determined in 30 to 50 min by a simple assay in most institutions. The FIBTEM® test of the thromboelastometry system (ROTEM®) has been shown to correlate well with the fibrinogen level in PPH. The FIBTEM® maximum clot firmness at 5 min run time is available within 10-15 min after drawing the blood sample (Table **2**) [41]. Fibrinogen concentrate can be stored at the operating theatre to be readily available for infusion.

Table 2. Aims of the Transfusion Therapy [7-9, 41, 51]

Haemoglobin level 100 g/dl
Platelet count 100 E9/l
APTT normal
TT > 40% (INR < 1.5)
Fibrinogen level > 2 g/l or FIBTEM (ROTEM®) MCF ≥ 7 mm at 5 min (≥ 9 mm at 15 min)*

TT = thromboplastin time, INR = international normalized ratio, APTT = activated partial thromboplastin time, MCF = maximum clot firmness
*Values for FIBTEM are tentative and based on one study including 37 women with PPH [41] Superscript numbers refer to the references

7. HYDROXYETHYL-STARCH SOLUTIONS AND HYPERTONIC SALINE

Exclusively crystalloid resuscitation in a bleeding patient has several shortcomings, including large infusion volumes, thus provoking dilutional acidosis, formation of interstitial edema and impaired microcirculation [9]. On the other hand, the synthetic colloids such as hydroxyethyl-starch (HES) solutions impair clot formation and increase blood loss [42]. Even the new generation medium-molecular weight, low-substituted HES 130/0.4 profoundly disturbs fibrin polymerization compared with crystalloids. The extensive study by Mittermayr *et al*. during major spine surgery [43] and that by Fenger-Eriksen *et al*. during cystectomy [44] were the first clinical trials to confirm the results of earlier experimental studies demonstrating the detrimental effect of colloids on fibrin polymerization, and suggest the administration of fibrinogen concentrate as a possible therapeutic approach. Furthermore, in case of fibrinolysis, the presence of HES 130/0.4 or gelatin solution facilitates clot disintegration to a greater extent than a crystalloid, because the weaker clots in the presence of colloids dissolve faster [45].

In addition to the adverse haemostatic effects, several studies have questioned the safety of HES solutions in critically ill patients, with particular concern that their use increases the risk of acute kidney injury [46]. Subsequently, in June 2013 the European Medicines Agency (EMA) concluded following a review of the available evidence that the benefits of HES solutions no longer outweigh their risks and therefore recommended that the marketing authorizations for these medicines be suspended (www.ema.europa.eu). Accordingly, many European hospitals already decided to abandon the use of HES solutions. Later the last year, EMA allowed the use of the HES solutions in restricted patient populations provided that the patient's kidney function should be monitored for 90 days after administration. At the maternity hospitals in Helsinki we decided not to use HES or gelatin [47] solutions. Our revised PPH treatment protocol now includes the use of hyperoncotic albumin (20%) [48] instead of other colloids.

Despite a large body of literature showing that hypertonic saline with or without dextran improves haemodynamic and metabolic responses, modulates immune function and reduces brain edema in a number of experimental injury models and several small and large animal species, clinical trials of hypertonic resuscitation early after the injury have failed to demonstrate significant benefit for resuscitation of haemorrhagic shock [49,50]. Hypertonic saline has not been studied in the setting of PPH and therefore, it can not be recommended for the volume resuscitation in PPH.

8. RED BLOOD CELLS AND PLATELETS

Coagulation is defined by an intimate interplay with red blood cells (RBC), platelets, plasma factors, vascular wall and circulatory conditions. Adequate RBC mass is essential to improve the blood flow-related interaction between platelets and the vessel wall, mandatory for primary haemostasis [9,51]. RBC transfusion is also indicated for the rapid correction of inadequate oxygen-carrying capacity of the blood (Table **2**). Transfusion will always be necessary when the blood loss exceeds 40% of the patient's blood volume. Blood losses of 30-40% of the blood volume will probably require RBC replacement. The initial haemoglobin level of the patient, her clinical condition, the response to the initial fluid resuscitation as well as signs of inadequate oxygenation (base deficit, lactate production) impact the decision-making. Spleen will contract and deliberate stored blood cells and normal haemoglobin in an acutely bleeding patient does not imply normal RBC mass, but may indicate haemoconcentration from blood loss and inadequate volume replacement [8,9].

Platelets are the first line of defence against bleeding. They attach to the damaged vessel wall and form the initial platelet plug. Furthermore, the platelet surface is specialized to coordinate assembly of the coagulation factor complexes and the platelet is probably the only cell on which propagation of coagulation occurs effectively [52]. Some studies have shown a slight decrease in the platelet count during pregnancy whereas others have noted no change. In gestational thrombocytopenia, however, platelet counts usually vary between 80 and 150 x 10^9/l [53]. The aetiology remains uncertain but may be dilutional and/or reflect platelet consumption in the utero-placental circulation, particularly during the third trimester. The benign gestational thrombocytopenia does not pose women to bleed but in case of PPH due to any obstetric reason, these women may need platelet transfusions earlier than their counterparts with higher initial platelet counts (Table **2**). Other more severe causes of thrombocytopenia such as preeclampsia, thrombotic microangiopathies, idiopathic

thrombocytopenic purpura and systemic lupus erythematosus have to be ruled out because they contribute significantly to maternal morbidity.

9. SELECTIVE ARTERIAL EMBOLIZATION

Over the past two decades, the role of pelvic arterial embolization (PAE) has evolved from a novel treatment option to playing a significant role in the management of obstetric haemorrhage. To date, interventional radiology offers a minimally invasive, fertility-preserving alternative to conventional surgical treatment [54]. Case series and systematic reviews have reported high success rates of about 70 to 90% in the haemostatic control of the pelvis [55,56]. A recent retrospective analysis of 73 patients during a 10-year period at our institution yielded a similar success rate (submitted) [57]

Embolization may be especially helpful in cases where the bleeding site is difficult to expose and access such as upper vaginal lacerations, deep paravaginal haematomas or cervical tears after vaginal delivery. If the exact bleeding site cannot be identified, embolization of the uterine or vaginal arteries is performed since each of these has been separately reported as the most common source of haemorrhage. For similar reasons, bilateral embolization is often performed because otherwise the blood loss can continue through crossing vascular supply.

Prophylactic use of the balloon catheters in the internal iliac arteries with or without uterine artery embolization has been described in cases of abnormal placentation where excessive bleeding is expected [58] In cases of abnormally invasive placenta, accurate examination in late pregnancy and carefully planned cesarean delivery with embolization facilities are important to control the intraoperative blood loss [59].

10. CONCLUSIONS

Labouring women continue to suffer substantial morbidity and mortality from PPH. Every maternity unit must be prepared and equipped to handle these often unexpected and occasionally critical emergencies. Successful management consists of prompt recognition of the PPH, good communication within the delivery suite, operating theatre and laboratory, treatment of uterine atony, removal of retained products of conception, balloon tamponade, early volume resuscitation, early administration of tranexamic acid, administration of fibrinogen concentrate and other blood products, as well as surgery and interventional radiology when appropriate and available to control the haemorrhage. Early recognition of the PPH risk factors and simulation training are also of great importance.

Finally, in every woman with successful management of PPH, graduated compression stockings should be applied early and administration of low-molecular-weight heparin should be considered within 12-24 hours after cessation of the haemorrhage to prevent venous thromboembolism. Pneumatic compression stockings and foot pumps are proper alternatives if the risk of re-bleed is considered high and the initiation of low-molecular-weight heparin must be postponed.

CONFLICTS OF INTEREST

Ahonen Jouni: Travel support (Sanofi Aventis, Octapharma, Leo Pharma, Fresenius Kabi, CSL Behring) and lecture fees (Leo Pharma, CSL Behring)

Stefanovic Vedran: Travel support (Medix Biochemica) and lecture fees (Medix Biochemica, Cook Medical)

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