Acta Anaesthesiol Scand 2010; **54**: 1164–1178
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ACTA ANAESTHESIOLOGICA SCANDINAVICA
doi: 10.1111/j.1399-6576.2010.02309.x

Review Article

Management of post-partum haemorrhage

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Management of post-partum haemorrhage (PPH) involves the treatment of uterine atony, evacuation of retained placenta or placental fragments, surgery due to uterine or birth canal trauma, balloon tamponade, effective volume replacement and transfusion therapy, and occasionally, selective arterial embolization. This article aims at introducing pregnancy- and haemorrhage-induced changes in coagulation and fibrinolysis and their relevant compensatory mechanisms, volume replacement therapy, optimal transfusion of blood products, and coagulation factor concentrates, and briefly cell salvage, management of uterine atony, surgical interventions, and selective arterial embolization. Special attention, respective management, and follow-up are required in women with bleeding disorders, such as von Willebrand disease, carriers of haemophilia A or B, and rare coagulation factor deficiencies. We also provide a proposal for practical instructions in the treatment of PPH.

Accepted for publication 18 August 2010

POST-PARTUM HAEMORRHAGE (PPH) is a major cause of maternal morbidity and mortality worldwide, with an increasing trend in incidence over time also in developed countries, including Australia, Canada, the United Kingdom, and the United States.[1] In spite of growing knowledge and better management facilities, the increase of PPH is astonishing. The risk factors for severe PPH can be categorized into uterine atony, retained placenta, and injury of soft tissue. Uterine atony can occur in cases of over-distended uterus such as polyhydramnion, multiple gestation, prolonged labour, the use of oxytocin, multiparity, and retained placenta. A large study including 154,311 deliveries compared 666 cases of PPH with controls without bleeding events.[2] Factors significantly associated with haemorrhage, in decreasing order of frequency, were retained placenta, failure to progress during the second stage of labour, placenta accreta, birth canal lacerations and uterine rupture, vacuum extraction, large for gestational age newborn, hypertensive disorders, induction of labour, and augmentation of labour with oxytocin. In addition to the risk factors cited above, placenta praevia, history of previous PPH, obesity, high parity, intra-uterine foetal death, Asian or Hispanic race, precipitous labour, 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 one to PPH.[3–5]

Peripartum hysterectomy is a severe complication of PPH and may seriously affect the emotional recovery of the woman. Recently, several studies have reported increasing rates of peripartum hysterectomy.[6,7] Vaginal birth after caesarean section, primary and repeat caesarean deliveries and multiple births seem to be independently associated with an increased risk for peripartum hysterectomy.[7] The role of preexisting or developing coagulation disorder (e.g. pregnancy-related acquired haemophilia) is unknown and may remain unrecognized as an underlying cause of PPH. However, many of the women presenting with PPH seem previously healthy, and therefore, every maternity unit must be prepared to handle these unexpected and occasionally critical emergencies.

Management of PPH includes the treatment of uterine atony, early volume replacement, and blood transfusion therapy, removal of retained products of conception, surgery due to uterine or birth canal trauma, balloon tamponade, and occasionally, selective arterial embolization (Fig. 1).[8,9] External or intra-abdominal aortic compression as well as bi-manual compression of the uterus may be life-saving to control the intractable haemorrhage and provide time for more detailed interventions. Anti-shock trousers may also be of

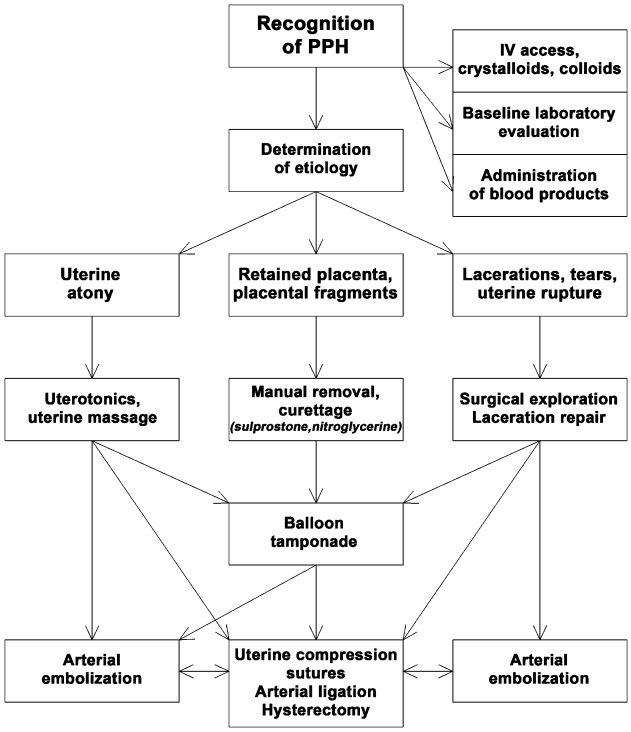

Fig. 1. Management plan for the treatment of post-partum haemorrhage (PPH).

benefit, especially during transportation of the patient.

The present overview highlights haemostatic changes during pregnancy and PPH, volume replacement therapy, and optimal transfusion of blood products and coagulation factor concentrates to treat PPH. We also briefly review the use of cell salvage, uterotonic medications, surgical interventions, and selective arterial embolization. Finally, we provide a proposal for practical instructions in the treatment of PPH.

Pregnancy-induced changes in coagulation and fibrinolysis

During the second and especially the third trimester of pregnancy, increased synthesis and activity of several coagulation factors result in a hypercoagulable state. The amounts of fibrinogen, coagulation factors (F) VII, VIII, IX, X, XII, and von Willebrand factor (vWF) increase, resulting in shortened prothrombin time (PT) and activated partial thromboplastin time (APTT). Prothrombin (FII) and FV levels remain unchanged, while FXI and FXIII are somewhat reduced.[10,11] The natural anticoagulant activity of protein S reduces clearly, whereas protein C and antithrombin remain unchanged during pregnancy. In several studies, protein C resistance without evidence of FV Leiden or phospholipid antibodies has been detected in 40–50% of pregnant women but its clinical significance remains unknown.[12,13] At least partially, these pregnancy-related alterations of coagulation augment the risk of venous thromboembolism together with a slowdown in venous return due to compression of the inferior vena cava following the enormous increase in uterine size.

Some investigators have observed a slight decrease in platelet count during pregnancy, whereas others have observed no change. In gestational thrombocytopaenia, however, platelet counts usually vary between 80 and 150×10^9/l.[10,14] The aetiology remains uncertain but may be dilutional and/or reflect platelet consumption in the uteroplacental unit, particularly during the third trimester. The benign gestational thrombocytopaenia does not pose women to bleed, but during a haemorrhage due to any obstetric reason, they may need platelet transfusions earlier than their counterparts with higher initial platelet counts. Other more severe causes of pregnancy-associated thrombocytopaenia such as pre-eclampsia, thrombotic microangiopathies, idiopathic thrombocytopaenic purpura, and systemic lupus erythematosus have to be ruled out because they contribute significantly to maternal and foetal morbidity.[14]

Plasminogen and its activators (both the tissue- and the urokinase-type) are up-regulated during normal pregnancy because of enhanced production and diminished utilization. However, the production of both plasminogen activator inhibitor-1 by endothelium and plasminogen activator inhibitor-2 by the placenta is markedly enhanced. As a result of many regulatory steps, the overall fibrinolytic capacity is attenuated.[10,11] On the contrary, marked activation of coagulation and fibrinolysis occurs in the uteroplacental circulation[15] and may contribute to the increased levels of fibrin degradation products (D-dimer) detected towards the end of normal pregnancy. In most, if not in all, labouring women with uncomplicated pregnancy, the level of D-dimer is further increased within the first 2 h post-partum whatever the mode of delivery (Fig. 2A).[16,17] This finding probably reflects normal physiology of delivery. However, if a woman suddenly starts bleeding after delivery, the already ongoing breakdown of cross-linked fibrin and augmented fibrinolysis may severely impair the haemostatic outcome. Fibrin degradation products impair fibrin clot formation and platelet aggrega-

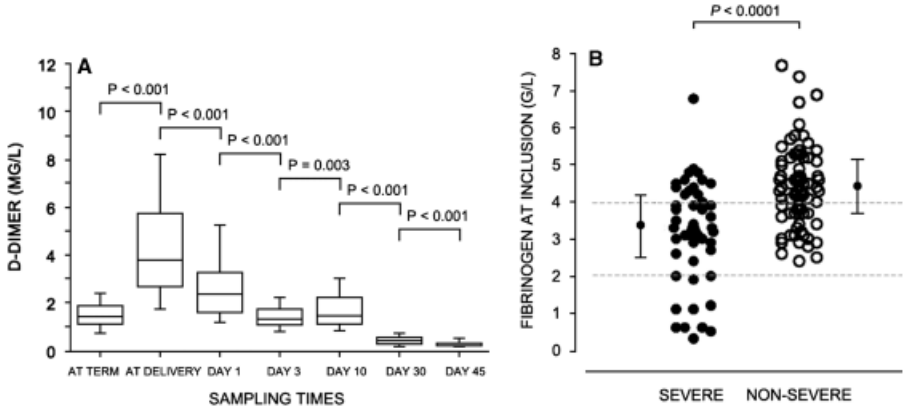

Fig. 2. (A) Evolution of D-dimer levels in 150 women with uncomplicated pregnancy at the antenatal visit (AT TERM), within the 2 h following delivery (AT DELIVERY) and at several days (Day 1–Day 45) after delivery. The boxes represent 50% of the values, the horizontal bars inside the median, and the lower and the upper bars the 10th and 90th percentiles respectively.[16] (B) Individual fibrinogen plasma concentrations in 128 labouring women at the time of study inclusion in those who developed a severe (•) or a non-severe (○) post-partum haemorrhage (PPH). Study inclusion refers to start of the intravenous infusion of sulprostone because of PPH due to uterine atony. Mean ± SD values are reported for both groups.[25] (Both figures are reprinted by permission of John Wiley and Sons.).

tion. Furthermore, large quantities of plasmin degrade fibrinogen, FV, FVIII, FXIII, and vWF.[18] Thromboelastography may help evaluate the role of fibrinolysis.[10] Antifibrinolytics have not been studied in the treatment of PPH but tranexamic acid has been reported to reduce blood loss both after elective caesarean section[19,20] and vaginal delivery.[21] Although the evidence is limited[22] while waiting for a large randomized-controlled trial,* we recommend administering an antifibrinolytic agent such as tranexamic acid as a treatment of PPH due to the biomedical evidence of up-regulated fibrinolytic activity in the local circulation.

Amount of blood loss

Underestimation of blood loss following delivery can be avoided if all shed blood is measured and sponges, wraps, swabs, etc. are carefully weighed. Furthermore, attention must be paid to pick-up signs and symptoms of birth canal/pelvic floor and intra-abdominal or retroperitoneal haemorrhage, particularly after instrumental delivery or caesarean section. A woman can bleed rapidly and profusely into a dead space, leading to the development of a large haematoma that might result in significant haemodynamic instability and challenge renal function due to increasing abdominal pressure.[23]

There are different definitions of PPH. The classical definition is a blood loss of more than 500 ml within 24 h after vaginal delivery or 1000 ml after caesarean section. Severe PPH is usually defined as a blood loss of >1500 ml, a peripartum decline in haemoglobin of 4 g/dl or more, acute transfusion of at least 4 U of red blood cells (RBC), or a haemostatic intervention such as angiographic embolization, surgical arterial ligation, or hysterectomy.[24,25] Major haemorrhage in association with delivery is defined as a blood loss of >2500 ml, a transfusion of 5 or more units of RBCs, or treatment for ensuing coagulopathy.[26] Massive haemorrhage is traditionally defined as the loss of one blood volume or transfusion of at least 10 U of RBCs within a 24-h period.[9]

Because the rate at which blood is being lost is also an important factor, a practical definition for massive blood loss is the loss of 50% of blood volume within a 3-h period or a loss rate of 150 ml/min.[9] Continuing heavy bleed with an estimated blood loss of 1500 ml or more should prompt the staff to initiate the local massive blood loss protocol. This situation could be reached within 10–15 min of delivery, and it must be recognized and appropriate action initiated to ensure maintenance of circulating blood volume and tissue oxygenation while awaiting blood products and laboratory test results to guide the replacement therapy.

Laboratory evaluation

Coagulation is defined by an intimate interplay between RBCs, platelets, plasma factors, vascular wall, and circulatory conditions (Fig. 3). Adequate

*http://clinicaltrials.gov/ct2/show/NCT00872469

RBC mass is essential to improve the blood flow-related interaction between platelets and the vessel wall, mandatory for primary haemostasis. Collection of blood samples for laboratory evaluations should be considered early in the cause of the haemorrhage to rule out impaired blood coagulation already before possible major bleed. These tests should include the haemoglobin level, platelet count, fibrinogen concentration, as well as PT and APTT, the routine laboratory tests of coagulation times. Despite the drawbacks of PT and APTT, i.e. reagent-related variability and inability to recognize important aspects in thrombin generation and clot formation, they remain robust tools for clinicians to manage bleeding problems (Fig. 4).

Volume resuscitation

Main objectives of the initial resuscitation are restoration of blood volume and oxygen-carrying capacity. Exclusively crystalloid resuscitation has several shortcomings because of the huge amounts needed, inducing dilutional acidosis, formation of interstitial oedema, and impairment of microcirculation.[27] On the other hand, the synthetic colloids, for example hydroxyethyl starch solutions (HES), have been reported to impair clot formation and increase blood loss.[28,29] In addition, recent studies show that 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.[30] during major spine surgery was the first clinical trial to confirm the results of earlier experiments of the detrimental effect of colloids on fibrin polymerization and 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.[31] During the early stages of PPH, combining crystalloids and colloids may be favourable without exceeding the recommended daily doses of 50 ml/kg/24 h for HES 130/0.4. Tranexamic acid should be considered, and the loss of fibrinogen substituted with the concentrate (or cryoprecipitate) and/or fresh frozen plasma (FFP) optimally according to laboratory assessments.

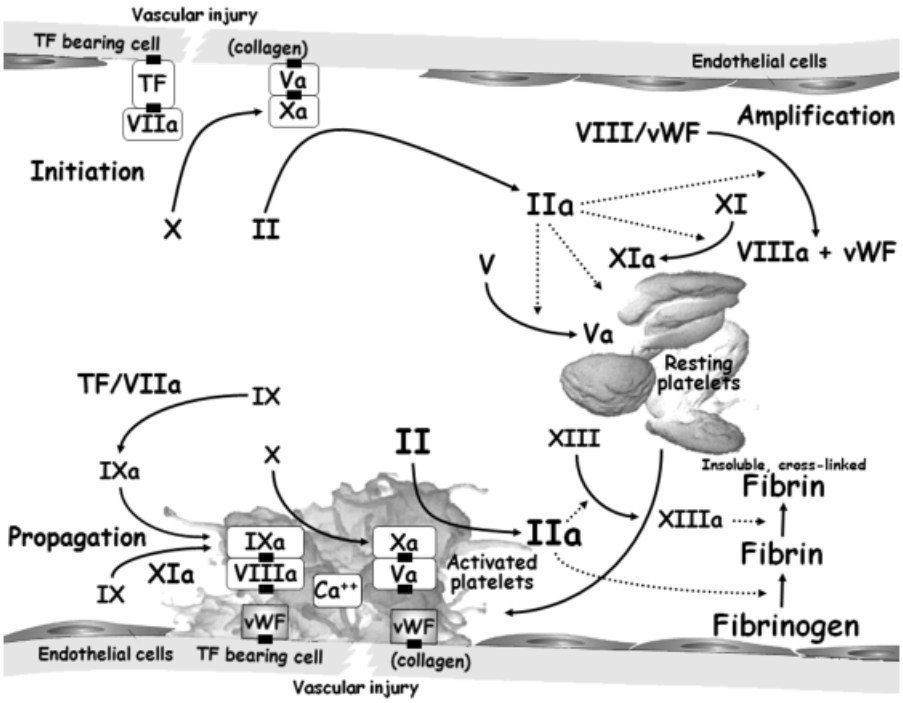

Fig. 3. Cell-based model of haemostasis. On the tissue factor bearing cell, only a small amount of thrombin (IIa) can be generated (initiation), which is not capable of fibrin clot formation. However, thrombin is the most powerful activator of several other coagulation factors and the platelets (amplification). Thereafter, on the activated platelets, huge amounts of thrombin (about 95% on the total amount of thrombin) are generated (propagation), which subsequently results in fibrin clot formation.[40, 89] [II(a) to XIII(a), (activated) coagulation factors II to XIII, respectively; vWF, von Willebrand factor; TF, tissue factor].

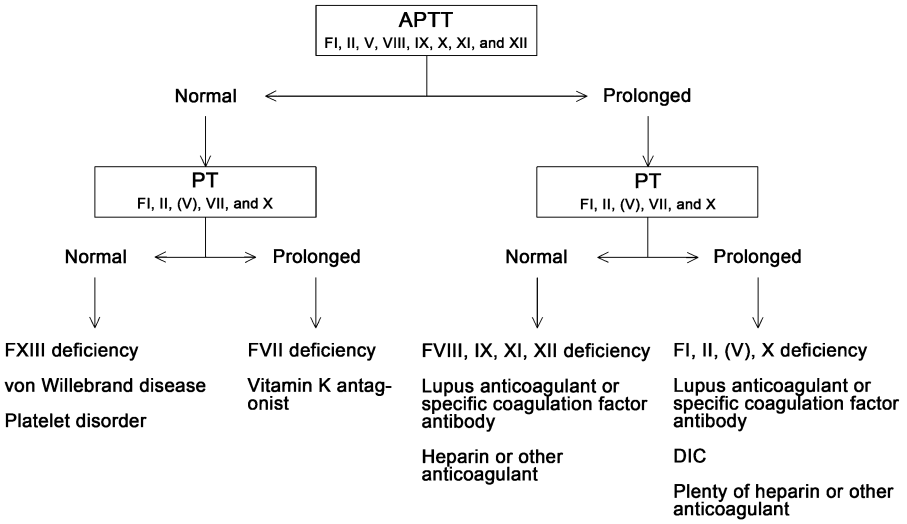

Fig. 4. Interpretation of the activated partial thromboplastin time (APTT) and prothrombin time (PT) in bleeding tendency. Coagulation factors that are included in the APTT and PT measurements are given in the boxes. PT using the Owren method (in Scandinavian countries and in the Netherlands) is not sensitive to FV deficiency, while PT using the Quick method (in most European countries, Australia, USA) is also sensitive to FV deficiency. Clinicians need to appreciate that prolongation of APTT is laboratory reagent-specific and some reagents are more sensitive to coagulation factor deficiencies, lupus anticoagulant, and heparin than others. Consult your laboratory on these issues. The currently most abundantly used anticoagulants warfarin and heparin are depicted in the algorithm. Heparin may also be present in the arterial line flushing solution. Other anticoagulants, such as inhibitors of thrombin and FXa, prolong APTT and PT reagent-dependently and unspecifically. (FI, fibrinogen; FII, prothrombin; FV to FXIII, coagulation factors V to XIII, respectively.) (Modified from Duodecim Medical Journal *1997; 113: 1263–70 by permission of The Finnish Medical Society Duodecim).*

RBCs

RBC transfusion is indicated for the rapid correction of inadequate oxygen-carrying capacity of the blood. 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 patient's clinical condition, response to initial fluid resuscitation, and her initial haemoglobin level 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.[9]

Institutionally, every effort should be made for packed RBCs to be available as soon as possible. At a haemoglobin level of 7–8 g/dl or less and ongoing haemorrhage, type-specific uncross-matched RBCs should be requested. Following the use of type-specific uncross-matched blood, the risk of an unexpected antibody is low (1–4%), depending on previous transfusions, and the risk of a transfusion reaction in a patient receiving type-specific uncross-matched RBCs is even lower. The risk and consequences of delayed replacement with blood in massive haemorrhage are much more severe.[9] A blood sample for an antibody screen in any labouring woman at a high risk of PPH will facilitate the availability of fully cross-matched blood.

In the very rare situation where blood replacement is required immediately, group O RhD-negative blood should be requested. It may be necessary to install a satellite blood fridge near the delivery suite for an emergency supply of type O RhD-negative blood (2–4 U) where difficulties may arise in the delivery of RBCs within an acceptable timescale. Even when a woman carries anti-c or -e, transfusion of type O RhD-negative blood, which is c- and e-positive, before the antibody status is known will be life saving.[9] Delay in obtaining antigen-negative blood could well be too late. It is imperative that a cross-matching sample is collected before the infusion of emergency blood and that the transfusion laboratory is informed to make more blood available.

Obstetric patients are usually otherwise fit and healthy women and there is no concern about myocardial ischaemia. However, a case series of 55 labouring women aged 28–35 years with no

previous history for cardiovascular diseases (except for one pulmonary embolism 2 months earlier) identified low systolic and diastolic arterial blood pressure (<88 mmHg and <50 mmHg, respectively) and increased heart rate (>115 beats/min) as independent predictors of myocardial injury.[32] Therefore, every effort should be made to avoid or restore the combination of low haemoglobin level, hypovolaemia, hypotension, and tachycardia. Furthermore, currently, increasing number of women with preexisting disorders become pregnant, which enhances the risk of complications during and after PPH.

Fibrinogen, FFP, and platelets

Massive PPH is always associated with a reduction in coagulation factor levels and frequently with thrombocytopaenia.[5] It is generally believed that an increased bleeding tendency or microvascular bleeding does not occur until 1.5 blood volumes are lost.[33] However, obstetric haemorrhage is strongly associated with a pelvic consumption coagulopathy and occasionally with a disseminated intravascular coagulation (DIC), which necessitates rapid correction.[9,34] In massive PPH, the low level of platelets, fibrinogen, FV, and FVIII leading to prolongation of PT and APTT as well as consumption of antithrombin and increased levels of fibrin degradation products (D-dimer)[5] may indicate the presence of DIC. However, many cases of PPH associated with a huge localized consumption of coagulation factors are incompatible with systemic DIC. Accordingly, with successful management of PPH, the D-dimer level decreases promptly within 12–24 h simultaneously with a slow increase in antithrombin levels.[5] Also, a rare possibility of acquired haemophilia, i.e. an antibody formation against FVIII, can only be revealed by laboratory tests with severely prolonged APTT and low FVIII level. The carriers of haemophilia may present with the same laboratory finding, albeit to a lesser extent.

The mainstay of the haemostatic support is using FFP, fibrinogen concentrate (or cryoprecipitate), and platelets. Simple routine laboratory tests to guide the replacement therapy should be urgently available. At the time of delivery, the mean fibrinogen concentration in 797 labouring women was 4.8 g/l but the range was particularly wide, 2.1–9.0 g/l.[35] Charbit et al.[25] recently showed that fibrinogen at the time of diagnosis of PPH can be used to guide the management of PPH. The negative predictive value of fibrinogen >4 g/l was 79% and the positive predictive value of a concentration ≤2 g/l was 100%. Thus, at a fibrinogen level of 2 g/l or less, clinicians should be aware of the high risk of severe haemorrhage (Fig. 2B). 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. Thus, fibrinogen is critical not only for clot strength but also to accelerate clot initiation and propagation.[36] However, both in the study by Charbit et al.[25] with 128 women and the other study by Simon et al.[35] with 797 women, the large variation in fibrinogen levels hampers the interpretation regarding when to start fibrinogen treatment during the early stages of PPH. An early determination of fibrinogen is helpful to guide the replacement therapy. Fibrinogen can be readily determined by a simple assay in most institutions on an emergency basis. Recently, a new rotation thromboelastometry system accorded with fibrinogen levels in PPH. This point-of-care device may be of help in guiding fibrinogen transfusion.[37] However, if the ongoing haemorrhage exceeds 2–3 l and FFP is not yet available, 3–4 g of fibrinogen concentrate (or cryoprecipitate) should be administered while waiting for the fibrinogen determination.[5] Fibrinogen concentrate can be stored at the operating theatre to be readily available for infusion.

Transfusion of FFP and platelets should be optimally guided by the results of the coagulation tests and blood counts, i.e. to maintain PT and APTT shorter than 1.5 times the control value and the platelet count $>50–70 \times 10^9$/l. One unit contains $70–80 \times 10^9$/l platelets, and 8 U in a normal weight adult would be anticipated to increase the platelet count by $40–50 \times 10^9$/l if there is no ongoing haemorrhage. However, transfusion of FFP (and platelets) should not be withheld before the available laboratory test results if a coagulopathy is clinically suspected and the patient is continuing to bleed.[9] FFP should be requested and transfused empirically in a 1:1 ratio to RBC units.[38] It is imperative to check the coagulation tests (at least PT, APTT, and fibrinogen) and blood counts at regular intervals, e.g. after every 4 h or 3–4 U of RBCs and FFP transfused. If the fibrinogen level remains <2 g/l despite the transfusion of FFP, fibrinogen concentrate (or cryoprecipitate) may also be required.[5,25]

Coagulation factor concentrates

A single factor deficiency, unless very low, seldom causes spontaneous bleeding problems.[39] In clinical conditions, however, a combination of modest deficiencies of several coagulation factors can cause a vicious circle resulting in impaired coagulation. In experimental haemostasis where the rest of the coagulation factors are intact, thrombin generation is maintained down to FX levels as low as 1–5% before declining sharply. In contrast, delayed platelet activation can be compensated only when FX is supplemented by over 10%.[40,41] Clinical data indicate that only patients with very low FV levels of <2% have severe spontaneous bleeding tendency.[39] Again, in a cell-based model system with FV-deficient platelets, however, a rapid increase in thrombin formation was observed from 1% to 30% FV levels. Decreasing plasma FV concentrations below 50% resulted in a significant and progressive reduction of platelet activation.[41] Platelets from healthy individuals carry about 20% of the circulating pool of FV, and the addition of FV had little effect on the rate of thrombin generation.[41] However, little is known about the amount of FV in stored platelets, but FV may reside in the microvesicles that are shed from the stored platelets. Decreasing level of FVIII, FIX, or FXI below 50% results in a modest decline in thrombin generation, with a dramatic decline after the level falls below 10–20% of normal.[40]

During the early phases of an instantaneous massive PPH, the levels of several coagulation factors remain very low[5] and often significantly lower than needed for greater thrombin generation or effective platelet activation.[40,41] It is usually not feasible to obtain the plasma concentrations of single coagulation factors during the course of PPH. However, determination of PT, APTT, and the fibrinogen level provides reasonable global information about the coagulation factor availability, although these tests do not indicate thrombin generation capacities and changes in FXIII activity (Fig. 4).[5,9]

In massive PPH, effective replacement therapy with fibrinogen and FFP usually yields acceptable levels of FVIII without the use of FVIII concentrate.[5] However, if APTT remains higher than 1.5 times the control value in spite of FFP (and fibrinogen), administration of FVIII/vWF concentrate should be considered.

In patients with FXIII deficiency, a low level of 5–30% has been shown to be sufficient in preventing spontaneous bleeding.[42] However, two recent studies suggest that a level of 60% or less may be associated with an increased intra-operative bleeding in various surgery or increased risk of postoperative haematoma after neurosurgery.[43,44] Therefore, in association with continuing haemorrhage, administration of FXIII concentrate is recommended at least if the blood loss exceeds one blood volume.[5]

There are numerous case reports and case series on the empirical off-label use of recombinant activated factor VII (rFVIIa) in PPH.[5,45–48] Although some preliminary guidelines have been published,[5,49] the case reports and series illustrate that the practise in using rFVIIa in PPH is far from uniform.[50] Recombinant FVIIa is extremely expensive and should not be used to compensate for an inadequate replacement therapy. It is unlikely that rFVIIa could work optimally if there is a lack of the basic components of the coagulation cascade (Fig. 5). Therefore, early and effective administration of RBCs, FFP, fibrinogen concentrate (or cryoprecipitate), and platelets as well as the control of uterine atony are essential in the treatment of PPH. Furthermore, in case of no response to the first dose of rFVIIa, every effort should be made to reveal localized bleeding to be managed by surgery or selective arterial embolization.[5]

Recent observations do not provide any evidence to extend the use of rFVIIa into less severe cases of PPH or into its prophylactic use.[5] Randomized placebo-controlled trials in less severe or in massive PPH are urgently required to optimize the use of rFVIIa in obstetric haemorrhage.[†]

The only exception for a reserved use of rFVIIa might be an unstable patient who has to be transferred to a hospital where more demanding surgery or a selective arterial embolization can be performed. By eventually reducing the blood loss for a short period, rFVIIa may give some additional time for more blood products to be available and accordingly, time for more effective replacement therapy. The short half-life of FVIIa of about 2 h has to be kept in mind. However, new longer acting substitutes are being developed.

There is one case report on the successful use of prothrombin complex concentrate (including coagulation factors II, VII, IX, and X) in the treatment of massive and intractable haemorrhage after a caesarean section.[51] Prothrombin complex concen-

[†]*http://clinicaltrials.gov/ct2/show/NCT00370877*

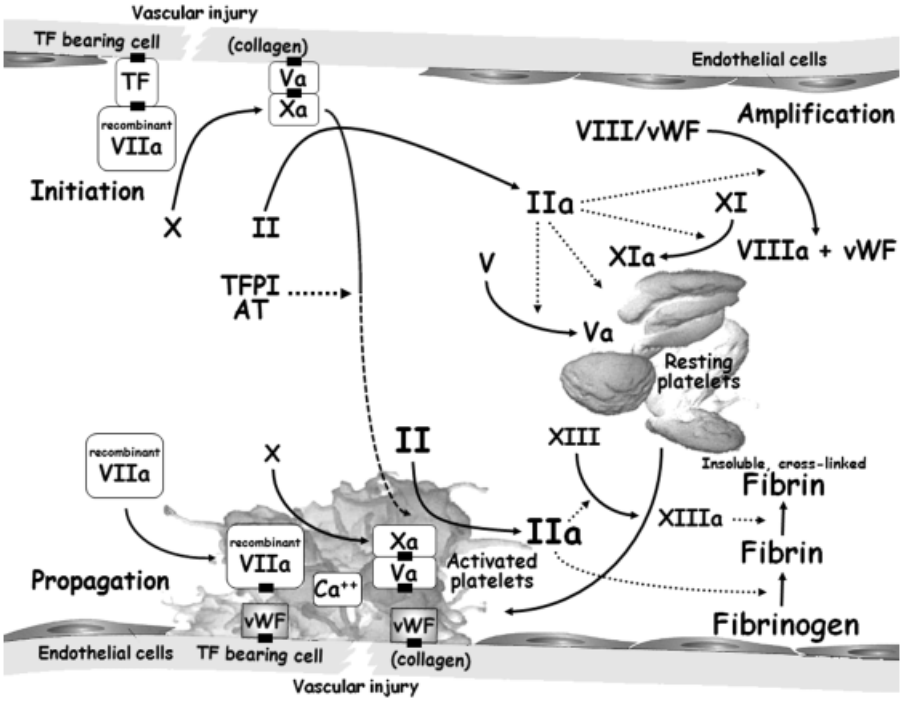

Fig. 5. Mechanism of action of recombinant activated factor VII (rFVIIa). Originally, rFVIIa was proposed to work mainly through a TF-dependent mechanism. However, FXa produced at the TF-bearing cell is unable to move to the activated platelet surface because at normal plasma levels, both AT and TFPI rapidly and effectively inhibit FXa in the fluid phase. It was later discovered that at very high, i.e. pharmacologic plasma concentrations, rFVIIa binds to the activated platelet and compensates for the deficiency of FVIIIa and FIXa. However, it is very important to note that in addition to rFVIIa, several other coagulation factors are needed to result in fibrin clot formation ([89]). [II(a) to XIII(a), (activated) coagulation factors II to XIII, respectively; vWF, von Willebrand factor; TF, tissue factor; TFPI, tissue factor pathway inhibitor; AT, antithrombin].

trate is recommended for use in the treatment or prophylaxis of haemorrhage in patients with vitamin K deficiency, liver disease, or congenital deficiency of the relevant clotting factors. Although it has not been studied in the management of PPH, it may be a helpful adjunctive tool, especially upon shortage of FFP. Venous thromboembolism is a feared complication after PPH in general and particularly after the use of prothrombin complex or rFVIIa concentrate. Indeed, in every woman after the successful management of PPH, mechanical and/or medical thromboprophylaxis must be applied within 12–24 h after cessation of the haemorrhage.[5]

Desmopressin stimulates endogenous release of FVIII and vWF, and it increases platelet adhesiveness. It can be administered as intravenous or subcutaneous injection or intranasal spray. Desmopressin can be used to prevent haemorrhage in type 1 von Willebrand disease and it may be beneficial in patients on aspirin therapy.[52] In case of an active bleeding event, however, a coagulation factor concentrate including FVIII and vWF and/or platelets should be administered.

Substitution of the loss of ionized calcium and magnesium is beneficial for recuperating haemostatic capacity as platelets and activation of coagulation factors rely on these cations. Transfusions are given in citrated anticoagulant, which further increases the consumption of these vital cations due to chelation. Furthermore, avoidance and correction of acidosis and hypothermia are important because of their deleterious effects on the haemostasis; acidosis interferes with coagulation factor complex assembly while hypothermia can reduce the production and activity of coagulation factors, impair platelet function, and enhance fibrinolysis.[53,54]

Women with congenital bleeding disorders

The most common bleeding disorders include von Willebrand disease and platelet function disorders, typically impairing the critical primary haemostasis without proper substitution therapy. Carriers of haemophilia A and B may have low respective

coagulation factor levels needing attention, as well as those with even more rare bleeding disorders such as FV, FXI, and FXIII deficiencies and dysfibrinogenemias.[55]

These bleeding disorders associate with impaired natural development of placenta and should be recognized as a risk factor for miscarriages with associated bleeding problems. When pregnancy is detected, the haematologist should make a careful plan for securing haemostasis during pregnancy. Prophylactic vWF substitution should be guided in those women who use it normally, and specific plans should be made for possible interventions and finally for delivery. This is important also for several days after vaginal delivery or caesarean section. Planning needs to be performed in close collaboration with the obstetrician so that a clear individual protocol for specific substitution therapy with tailored laboratory follow-up is provided. These demanding cases should be centralized in experienced comprehensive care centres with 7-day/24-h haematological surveillance and laboratory services.[56] Paediatric expertise to handle the newborn with a possible or antenatally diagnosed bleeding disorder is a natural link in this chain.

Cell salvage

In spite of numerous case reports on the use of cell salvage, all without incident, and the fact that the disposable kit for a single case costs <1–2 U of RBCs, there is still a marked reluctance to use cell salvage in obstetrics.[57] Concerns about amniotic fluid embolism in cell salvage have not been realized. Amniotic fluid embolism is an anaphylactoid reaction rather than a real embolic event. It would nevertheless appear prudent to avoid contaminating cell-salvaged blood with amniotic fluid, and so the current practice is to salvage the shed blood only after the initial suction contents, including the amniotic fluid, have been discarded. However, recent work has demonstrated that the cell salvage process, combined with a leucocyte-depleting filter, can be effective in significantly reducing amniotic fluid contaminants, allowing the use of same suction device throughout the entire procedure.[58] Another concern about the use of cell salvage is rhesus immunization. This may occur if foetal red cells are aspirated and re-transfused into the maternal circulation. The risk has been estimated to be similar to that present in a normal vaginal delivery. Rhesus immunization can be prevented with prompt testing and anti-D treatment. It is imperative to note, however, that while salvaged blood can help restore the oxygen-carrying capacity of the blood, the coagulopathy must be simultaneously corrected as salvaged blood does not contain coagulation factors.[57]

Uterotonic agents

Manual massage and the use of uterotonic medications such as oxytocin, prostaglandins, and ergot alkaloids are essential to prevent and treat PPH due to uterine atony (Table 1). The use of any uterotonic agent has precautions and contraindications[59] and especially when combining these agents, the risks of their use must be weighed against the risks of intractable or uncontrolled haemorrhage.

Surgical measures for PPH

Approximately 85% of women who have a vaginal birth will sustain some degree of perineal trauma, and of these, 60–70% will undergo suturing.[23,60] Surgical measures to control PPH include repair of genital lacerations, evacuation of retained placenta or placental fragments, balloon tamponade, exploratory laparotomy with a view for uterine compression sutures, systematic pelvic devascularization (uterine/ovarian/quadruple/internal iliac), subtotal or total abdominal hysterectomy, and rarely, repair of a ruptured uterus (Fig. 1).[23,61]

In cases of genital tract trauma and retained products of conception, the need for surgical measures is straightforward. However, for PPH due to uterine atony or coagulopathy, the appropriate timing for surgical interventions is not clearly defined. In case of severe haemorrhage, the patient should be moved to the operating theatre, with a view for surgical measures. The general condition of the patient, her haemodynamic stability, the amount and rate of blood loss, the effectiveness of conservative measures, the likely cause of PPH, and the skill and experience of the team, as well as the availability of resources, should be considered in the decision-making process. A woman presenting with post-partum collapse due to massive PPH may require an emergency laparotomy and radical surgical procedures such as hysterectomy to save her life once lower genital lacerations are excluded as the bleeding site. As far as possible, however, conservative medical or surgical measures should

Table 1.

Proposal for a guideline in the treatment of PPH.

Recommendation grade A, B, C, D, or good practice point (GPP), see Appendix (Concerning uterotonic agents, the grade of evidence refers not necessarily to the combined use of two or more uterotonics).

General

As early as possible, insert two large bore cannulae and one line for the medications to secure good venous access (GPP).
Secure arterial line before its insertion becomes difficult (usually in active haemorrhage of about 2000 ml) (GPP).
Warm the patient and use one to two efficient fluid warmers (A).
Administer Ringer's/saline and HES 130/0.4 in about 1 : 1 ratio (HES 130/0.4 not more than 50 ml/kg/24 h). The use of HES solutions should be restricted to the early stages of replacement therapy before FFP is available (D).
Determine frequently the blood-gas analysis and correct low ionized calcium (D).
Consider administration of 10 mmol of magnesium concentrate in 30 min (GPP).
Efficient replacement therapy is the best way to avoid/correct acidosis (D).
If the blood loss is 500–1500 ml, administer 1 g of tranexamic acid IV (D).
If the blood loss exceeds 2000 ml, consider a second dose of tranexamic acid (GPP).
If the patient fails to receive tranexamic acid during the early stages of the haemorrhage, use it as soon as possible at any time during the bleeding event (GPP).
Consider to continue administration of tranexamic acid 1 g i.v. every 6 h for the first 12–24 h after cessation of the bleeding (not in case of confirmed DIC) (GPP).
In case of uterine atony, use i.v. infusion of 30–50 IU of oxytocin in 0.9% saline (A).
Consider 400–600 μg of misoprostole orally or 800–1000 μg rectally (A).
Consider prostaglandin such as i.v. infusion of sulprostone (500 μg in 60 min, followed by 500 μg in 3 h, and 500 μg during the next 12 h if needed) or carboprost 250 μg i.m. (A).
Consider methylergometrine 0.2 mg i.v. (A).
Remember the importance of uterine massage (A).
Always consider mechanical and pharmacological venous thromboembolism prophylaxis within 12–24 h after cessation of the haemorrhage (D).

Blood products and coagulation factor concentrates

Transfusion of packed RBCs is usually needed if the blood loss exceeds 1500–2000 ml (pay attention to the patient's size) (D).
In case of active haemorrhage and a haemoglobin level of <7–8 g/dl (and no known RBC antibodies; maternity card), transfuse type-specific uncross-matched RBCs (D).
If the haemoglobin declines below 5–6 g/dl or there are signs of myocardial ischaemia (an increasing ST depression) and you have to wait for type-specific uncross-matched RBCs, transfuse 2–4 U of type O RhD-negative RBCs (D).
Even if the woman carries anti-c or -e, transfusion of type O RhD-negative blood, which is c- and e-positive, before the antibody status is known will be life saving (D).
Before you start transfusion of FFP or at the latest after a blood loss of about 2000 ml, determine haemoglobin, platelet count, PT, APTT, and fibrinogen (GPP).
In case of active haemorrhage, repeat determination of the coagulation screen regularly (GPP).
Transfuse 1 U of FFP for every RBC unit or according to PT and APTT (C).
If the blood loss exceeds 2000–3000 ml and you have to wait for FFP, administer 3–4 g of fibrinogen. Thereafter, FFP is sufficient and fibrinogen concentrate is usually not needed (except sometimes in case of DIC or a recurrent profuse haemorrhage) (GPP).
Transfuse platelets according to the platelet count – usually 8–12 U at a time (GPP).
If the platelet count is less than 150×10^9/l before delivery (in about 7% of labouring women), order platelets earlier than usually (GPP).
Aim at a haemoglobin level of 8–10 g/dl, a platelet count higher than $50–70 \times 10^9$/l, PT and APTT shorter than 1.5 times upper normal range, and a fibrinogen level >2 g/l (C).
Targeting a haemoglobin level of 8–10 g/dl is useful, but avoid excess RBC transfusion (frequent haemoglobin determinations) (GPP).
If the blood loss exceeds 4000–5000 ml and/or APTT is prolonged more than 1.5 times the upper normal range in spite of transfusion of FFP, consider 900–1000 IU of FVIII/vWF concentrate (GPP).
If the blood loss exceeds 6000–7000 ml, also consider 1250 IU of FXIII concentrate (GPP).
If the blood loss exceeds 6000–7000 ml, consider 90–120 μg/kg of rFVIIa concentrate (GPP).

be attempted to preserve future fertility if the woman is haemodynamically stable.[23]

Traditionally, the surgical management of major PPH unresponsive to conventional medical therapy relied on hysterectomy and bilateral ligation of the internal iliac arteries.[23] Over the past 10–15 years, a number of new, simpler, and effective surgical procedures have emerged that could be used before restoring into hysterectomy.[62–64] These haemostatic sutures usually involve apposition and compression between the anterior and the posterior uterine wall. After achieving haemostasis, it is imperative to check the bladder, bowel, and ureter to exclude any direct trauma.[23] According to a recent systematic review, the success rates in the treatment of PPH are 84% for balloon tamponade, about 92% for uterine compression sutures, and about 85% for iliac artery ligation or uterine devascularization.[65] There is no evidence to suggest that any of the various methods is superior for the management of PPH, and the treatment approach is always chosen according to the bleeding site and delivery mode (Fig. 1).

Retained placenta covers a number of pathologies: some placentas are simply trapped behind the closed cervix, some are adherent to the uterine wall but easily separated manually whereas others are pathologically invading the myometrium and sometimes even the adjacent urinary bladder (placenta accreta, percreta, and increta). Although routine uterotonics for the prophylaxis of PPH

decrease the median length of the third stage, they have no effect on the rate of retained placenta at 60 min. The choice of timing of manual removal is a balance between the PPH risk of leaving the placenta *in situ*, the likelihood of spontaneous delivery, and the knowledge from caesarean section studies that the manual removal itself may cause haemorrhage.[66] There is a considerable variation between European countries about the timing of manual removal of retained placenta.[67] The UK National Institute for Health and Clinical Excellence guidelines suggest 30 min,[68] whereas the World Health Organisation manual for childbirth suggests 60 min.[69] A large study including 12,979 consecutive vaginal deliveries showed that the risk of haemorrhage increases after 30 min.[70] On the other hand, delaying the manual removal will lead to spontaneous delivery of many placentas. In the only randomized trial to recruit women after 60 min of the third stage had elapsed, however, none of the placentas in the control group was spontaneously delivered over the subsequent 30 min.[71] 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.[72]

Medical management is also an option for retained placenta. In women who are haemodynamically stable and there are no signs of PPH, the placenta may be delivered by sublingual or intravenous nitroglycerine.[73] A preliminary report showed that an intravenous infusion of sulprostone, a synthetic prostaglandin-E2 derivate, delivered the placenta in 52% of retained placentas as compared with 18% for placebo.[74] We have also confirmed in 100 women that 36 (36%) of retained placentas could be removed by using sulprostone infusion (unpublished data). However, the need for manual removal cannot be reduced by the use of umbilical vein oxytocin.[75]

Placentation disorders include placenta praevia and adherent placenta (accreta, percreta, and increta). The incidence of abnormal placentation has increased with the rising caesarean delivery rate.[76] It is of essential importance to identify parturients with placental disorders already during the pregnancy in order to anticipate massive PPH. Doppler ultrasonography and magnetic resonance imaging are used to diagnose abnormal placentation. The primary treatment of adherent placenta includes a scheduled caesarean delivery by uterine vertical incision and avoidance of removal of the placenta before hysterectomy.[77] The role of prophylactic internal iliac artery balloon occlusion followed by an eventual selective arterial embolization has not yet been established (Fig. 6).[77–79] Conservative management by leaving the placenta *in situ* may be considered, e.g. in case of bladder invasion to avoid hysterectomy-associated massive PPH and bladder injury. It must be emphasized that preservation of fertility is not the goal, because the risk of adherent placenta in the subsequent pregnancy is considerably high. Some authors also have advocated the use of medical treatment with methotrexate to hasten the involution of the placenta.[80] The gradual involution during the following months should be closely monitored and the woman informed about the risks of the conservative treatment. Complications such as infection of the placental residue and/or a secondary haemorrhage may occur.[77,81]

Selective arterial embolization

The use of interventional radiology in the treatment of PPH is increasing, although its use may be limited by difficulties with the transfer of unstable patients and availability of a 24-h service. The technique includes femoral artery puncture and selective stepwise catheterization of the pelvic arteries. Emergency embolization is performed with pledgets of gelatin sponge or gelatin sponge slurry. Gelatin sponge is the agent of choice because it causes a temporary arterial occlusion with recanalization of blood flow within weeks.[82]

There are no randomized controlled trials, but case series and systematic reviews have reported high success rates of about 70–90% in the haemostatic control of the pelvis.[65,83] In case of PPH after vaginal delivery, arterial embolization can be performed before laparotomy if the haemodynamics are stable; embolization can also be performed during a caesarean section procedure, after compressive sutures, and if stepwise uterine devascularization fails (Fig. 1). Embolization may be especially helpful in cases where the bleeding site is difficult to expose and access such as upper vaginal lacerations, large midline paravaginal haematomas, or cervical tears after vaginal delivery. If the exact bleeding site cannot be identified, a subselective embolization of the uterine or vaginal arteries is performed because each of these has been separately reported as the most common source of haemorrhage. For similar reasons, bilateral embolization is often performed because the

blood loss can continue through transpelvic vascular supply after unilateral embolization.[82]

The procedure has many advantages, including minimal morbidity and low complication rates, shorter hospital stay, preservation of fertility, it can be carried out under local anaesthesia, and success can be verified.[84,85] However, the procedure can cause rare complications such as feet ischaemia, bladder and rectal wall necrosis, and sciatic nerve injury.[86] Late recurrent haemorrhage is a rare, but a serious problem. Correction and follow-up of the coagulation status is therefore important. Repeated embolization or hysterectomy may be required.[82,83]

Foetal-related complications as a result of exposure to radiation during pregnancy include spontaneous abortion, teratogenesis, growth retardation, development delay, and induction of childhood cancer. The dose of radiation believed to produce these complications is very large compared with the doses used during catheter insertion and interventional radiology.[87] Furthermore, the dose associated with uterine artery embolization is unlikely to result in a measurable increase in the genetic risk to the patient's future children.[88]

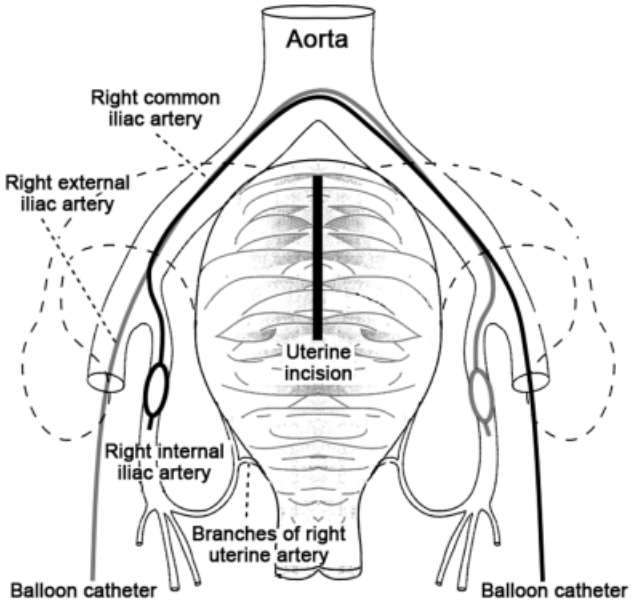

Fig. 6. *In a planned caesarean section (and hysterectomy) for placenta accreta, balloon catheters are inserted before surgery into both internal iliac arteries. Uterine incision is made to avoid profuse haemorrhage. Immediately after abdominal delivery, the uterine blood flow can be reduced by inflation of the balloons. Furthermore, a selective arterial embolization can be performed. In an emergency case of post-partum haemorrhage, one (or both) femoral artery is cannulated and an angiography is performed. Thereafter, a unilateral or bilateral selective or subselective embolization with pledgets of gelatin sponge or gelatin sponge slurry can be performed to stop the haemorrhage. (Reprinted from* Duodecim Medical Journal *2008; 124: 41–9 by permission of The Finnish Medical Society Duodecim).*

Summary

Women continue to suffer sequels from obstetric haemorrhage. Every maternity unit must be prepared and equipped to handle these often unexpected and occasionally critical emergencies at the frontline. Close collaboration with haematologists with special competence in cases of congenital and acquired bleeding disorders, and immunological thrombocytopaenia is mandatory to offer the pregnant woman with the best available management options and preparation for delivery and its follow-up.

Successful management involves prompt recognition of the PPH, good communication within the delivery suite, operating theatre and laboratory, early volume resuscitation with crystalloids and colloids, transfusion of blood products and coagulation factor concentrates, removal of retained products of conception, treatment of uterine atony, and surgery and interventional radiology (when appropriate and available) to control the haemorrhage. Randomized-controlled trials on several topics are needed. Meanwhile, however, we present a proposal for practical instructions in the treatment of PPH based on the existing knowledge and our own experience (Table 1).

In cases where the amount of blood loss was inappropriate to the obstetric cause of the haemorrhage, the native coagulation status of the woman should be examined after recovery of the menstruation and, at the earliest, 3 months after the cessation of breast feeding. Furthermore, it must be noticed, that 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 h 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.

References

1. Knight M, Callaghan WM, Berg C, Alexander S, Bouvier-Colle M-H, Ford JB, Joseph KS, Lewis G, Liston RM, Roberts CL, Oats J, Walker J. Trends in postpartum hemor-

rhage in high resource countries: a review and recommendations from the International Postpartum Hemorrhage Collaborative Group. BMC Pregnancy Childbirth 2009; 9: 55.
2. Sheiner E, Sarid L, Levy A, Seidman DS, Hallak M. Obstetric risk factors and outcome of pregnancies complicated with early postpartum hemorrhage: a population-based study. J Matern Fetal Neonatal Med 2005; 18: 149–54.
3. Combs CA, Murphy EL, Laros RK Jr. Factors associated with postpartum hemorrhage with vaginal birth. Obstet Gynecol 1991; 77: 69–76.
4. Rouse DJ, Leindecker S, Landon M, Bloom SL, Varner MW, Moawad AH, Spong CY, Caritis SN, Harper M, Wapner RJ, Sorokin Y, Miodovnik M, O'Sullivan MJ, Sibai BM, Langer O. The MFMU cesarean registry: uterine atony after primary cesarean delivery. Am J Obstet Gynecol 2005; 193: 1056–60.
5. Ahonen J, Jokela R, Korttila K. An open non-randomized study of recombinant activated factor VII in major postpartum haemorrhage. Acta Anaesthesiol Scand 2007; 51: 929–36.
6. Haynes K, Stone C, King J. Major morbidities associated with childbirth in Victoria: obstetric haemorrhage and associated hysterectomy. Public Heath Group, Department of Human Services, Melbourne, 2004. Available at http://www.health.vic.gov.au/maternitycare/ (accessed 12 July 2010).
7. Whiteman MK, Kuklina E, Hillis SD, Jamieson DJ, Meikle SF, Posner SF, Marchbanks PA. Incidence and determinants of peripartum hysterectomy. Obstet Gynecol 2006; 108: 1486–92.
8. Mousa HA, Walkinshaw S. Major postpartum haemorrhage. Curr Opin Obstet Gynecol 2001; 13: 595–603.
9. Macphail S, Talks K. Massive post-partum haemorrhage and management of disseminated intravascular coagulation. Curr Obstet Gynaecol 2004; 14: 123–31.
10. Hellgren M. Hemostasis during normal pregnancy and puerperium. Semin Thromb Hemost 2003; 29: 125–30.
11. O'Riordan MN, Higgins JR. Haemostasis in normal and abnormal pregnancy. Best Pract Res Clin Obstet Gynaecol 2003; 17: 385–96.
12. Clark P, Brennand J, Conkie JA, McCall F, Greer IA, Isobel D, Walker D. Activated protein C sensitivity, protein C, protein S, and coagulation in normal pregnancy. Thromb Haemost 1998; 79: 1166–70.
13. Mahieu B, Jacobs N, Mahieu S, Naelaerts K, Vertessen F, Weyler J, Jacquemyn Y, Van der Planken M. Haemostatic changes and acquired activated protein C resistance in normal pregnancy. Blood Coagul Fibrinolysis 2007; 18: 685–8.
14. Sainio S, Kekomäki R, Riikonen S, Teramo K. Maternal thrombocytopenia at term: a population-based study. Acta Obstet Gynecol Scand 2000; 79: 744–9.
15. Higgins JR, Walshe JJ, Darling MRN, Norris L, Bonnar J. Hemostasis in the uteroplacental and peripheral circulations in normotensive and pre-eclamptic pregnancies. Am J Obstet Gynecol 1998; 179: 520–6.
16. Epiney M, Boehlen F, Boulvain M, Reber G, Antonelli E, Morales M, Irion O, De Moerloose P. D-dimer levels during delivery and the postpartum. J Thromb Haemost 2005; 3: 268–71.
17. Ghirardini G, Battioni M, Bertellini C, Colombini R, Colla R, Rossi G. D-dimer after delivery in uncomplicated pregnancies. Clin Exp Obstet Gynecol 1999; 26: 211–2.
18. Wojciechowski PJ, Samol N, Walker J. Coagulopathy in massive transfusion. Int Anesthesiol Clin 2005; 43: 1–20.
19. Gai MY, Wu LF, Su QF, Tatsumoto K. Clinical observation of blood loss reduced by tranexamic acid during and after caesarean section: a multicenter, randomized trial. Eur J Obstet Gynecol Reprod Biol 2004; 112: 154–7.
20. Mayur G, Purvi P, Ashoo G, Pankaj D. Efficacy of tranexamic acid in decreasing blood loss during and after cesarean section: a randomized case controlled prospective study. J Obstet Gynecol India 2007; 57: 227–30.
21. Yang H, Zheng S, Shi C. Clinical study on the efficacy of tranexamic acid in reducing postpartum blood loss: a randomized, comparative, multicenter trial. Zhonghua Fu Chan Ke Za Zhi 2001; 36: 590–2.
22. Ferrer P, Roberts I, Sydenham E, Blackhall K, Shakur H. Anti-fibrinolytic agents in postpartum haemorrhage: a systematic review. BMC Pregnancy and Childbirth 2009; 9: 29–34.
23. Chandraharan E, Arulkumaran S. Surgical aspects of postpartum haemorrhage. Best Pract Res Clin Obstet Gynaecol 2008; 22: 1089–102.
24. Waterstone M, Bewley S, Wolfe C. Incidence and predictors of severe obstetric morbidity: case–control study. Br Med J 2001; 322: 1089–94.
25. Charbit B, Mandelbrot L, Samain E, Baron G, Haddaoui B, Keita H, Sibony O, Mahieu-Caputo D, Hurtaud-Roux MF, Huisse MG, Denninger MH, De Prost D. The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage. J Thrombost Haemost 2007; 5: 266–73.
26. Scottish Confidential Audit of Severe Maternal Morbidity. 5th Annual Report 2007. Reproductive Health Programme, NHS QIS.
27. Fries D, Innerhofer P, Schobersberger W. Time for changing coagulation management in trauma-related massive bleeding. Curr Opin Anaesthesiol 2009; 22: 267–74.
28. Kozek-Langenecker S. Effects of hydroxyethyl starch solutions on hemostasis. Anesthesiology 2005; 103: 654–60.
29. Westphal M, James MFM, Kozek-Langenecker S, Stocker R, Guidet P, Van Aken H. Hydroxyethyl starches. Anesthesiology 2009; 111: 187–202.
30. Mittermayr M, Streif W, Haas T, Fries D, Velik-Salchner C, Klingler A, Oswald E, Bach C, Schnapka-Koepf M, Innerhofer P. Hemostatic changes after crystalloid or colloid fluid administration during major orthopedic surgery: the role of fibrinogen administration. Anesth Analg 2007; 105: 905–17.
31. Mittermayr M, Streif W, Haas T, Fries D, Velik-Salchner C, Klingler A, Innerhofer P. Effect of colloid and crystalloid solutions on endogenous activation of fibrinolysis and resistance of polymerized fibrin to recombinant tissue plasminogen activator added ex vivo. Br J Anaesth 2008; 100: 307–14.
32. Karpati PCJ, Rossignol M, Pirot M, Cholley B, Vicaut E, Henry P, Kévorkian J-P, Schurando P, Peynet J, Jacob D, Payen D, Mebazaa A. High incidence of myocardial ischemia during postpartum hemorrhage. Anesthesiology 2004; 100: 30–6.
33. Erber WN. Massive blood transfusion in the elective surgical setting. Transfus Apheresis Sci 2002; 27: 83–92.
34. Thachil J, Toh C-H. Disseminated intravascular coagulation in obstetric disorders and its acute haematological management. Blood Rev 2009; 23: 167–76.
35. Simon L, Santi TL, Sacquin P, Hamza J. Pre-anaesthetic assessment of coagulation abnormalities in obstetric patients: usefulness, timing and clinical implications. Br J Anaesth 1997; 78: 678–83.

36. Nielsen VG, Cohen BM, Cohen E. Effects of coagulation factor deficiency on plasma coagulation kinetics determined via thrombelastography®: critical roles of fibrinogen and factors II, VII, X and XII. Acta Anaesthesiol Scand 2005; 49: 222–31.
37. Huissoud C, Carrabin N, Audibert F, Levrat A, Massignon D, Berland M, Rudigoz R-C. Bedside assessment of fibrinogen level in postpartum haemorrhage by thrombelastometry. BJOG 2009; 116: 1097–102.
38. Borgman MA, Spinella PC, Perkins JG, Grathwohl KW, Repine T, Beekley AC, Sebesta J, Jenkins D, Wade CE, Holcomb JB. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. J Trauma 2007; 63: 805–13.
39. Al Dieri R, Peyvandi F, Santagostino E, Giansily M, Mannucci PM, Schved JF, Béguin S, Hemker HC. The thrombogram in rare inherited coagulation disorders: its relation to clinical bleeding. Thromb Haemost 2002; 88: 576–82.
40. Monroe DM, Hoffman M. What does it take to make the perfect clot? Arterioscler Thromb Vasc Biol 2006; 26: 41–8.
41. Allen GA, Wolberg AS, Oliver JA, Hoffman M, Roberts HR. Impact of procoagulant concentration on rate, peak and total thrombin generation in a model system. J Thromb Haemost 2004; 2: 402–13.
42. Hsieh L, Nugent D. Factor XIII deficiency. Haemophilia 2008; 14: 1190–200.
43. Wettstein P, Haeberli A, Stutz M, Rohner M, Corbetta C, Gabi K, Schnider T, Korte W. Decreased factor XIII availability for thrombin and early loss of clot firmness in patients with unexplained intraoperative bleeding. Anesth Analg 2004; 99: 1564–9.
44. Gerlach R, Tölle F, Raabe A, Zimmermann M, Siegemund A, Seifert V. Increased risk for postoperative hemorrhage after intracranial surgery in patients with decreased factor XIII activity. Implications of a prospective study. Stroke 2002; 33: 1618–23.
45. Moscardo F, Pérez F, de la Rubia J, Balerdi B, Lorenzo JI, Senent ML, Aznar I, Carceller S, Sanz MA. Successful treatment of severe intra-abdominal bleeding associated with disseminated intravascular coagulation using recombinant activated factor VII. Br J Haematol 2001; 113: 174–6.
46. Ahonen J, Jokela R. Recombinant factor VIIa for life-threatening post-partum haemorrhage. Br J Anaesth 2005; 94: 592–5.
47. Alfirevic Z, Elbourne D, Pavord S, Bolte A, van Geijn H, Mercier F, Ahonen J, Bremme K, Bødker B, Magnúsdóttir EB, Salvesen K, Prendiville W, Truesdale A, Clemens F, Piercy D, Gyte G. Use of recombinant activated factor VII in primary postpartum hemorrhage. Obstet Gynecol 2007; 110: 1270–8.
48. Phillips LE, McLintock C, Pollock W, Gatt S, Popham P, Jankelowitz G, Ogle R, Cameron PA. Recombinant activated factor VII in obstetric hemorrhage: experiences from the Australian and New Zealand haemostasis registry. Anesth Analg 2009; 109: 1908–15.
49. Welsh A, McLintock C, Gatt S, Somerset D, Popham P, Ogle R. Guidelines for the use of recombinant activated factor VII in massive obstetric haemorrhage. Aust N Z J Obstet Gynaecol 2008; 48: 12–6.
50. Haynes J, Laffan M, Plaat F. Use of recombinant activated factor VII in massive obstetric haemorrhage. Int J Obstet Anesth 2007; 16: 40–9.
51. Glynn JC, Plaat F. Prothrombin complex for massive obstetric haemorrhage. Anaesthesia 2007; 62: 202–3.
52. Franchini M. The use of desmopressin as a hemostatic agent: a concise review. Am J Hematol 2007; 82: 731–5.
53. Kirkpatrick AW, Chun R, Brown R, Simons RK. Hypothermia and the trauma patient. Can J Surg 1999; 42: 333–43.
54. Meng ZH, Wolberg AS, Monroe DM, Hoffman M. The effect of temperature and pH on the activity of factor VIIa: implications for the efficacy of high-dose factor VIIa in hypothermic and acidotic patients. J Trauma 2003; 55: 886–91.
55. Rare bleeding disorder database. Available at http://www.rbdd.org/ (accessed 12 July 2010).
56. Chi C, Lee CA, Shiltagh N, Khan A, Pollard D, Kadir RA. Pregnancy in carriers of haemophilia. Haemophilia 2008; 14: 56–64.
57. Allam J, Cox M, Yentis SM. Cell salvage in obstetrics. Int J Obstet Anaesth 2008; 17: 37–45.
58. 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: 225–9.
59. Vercauteren M, Palit Ş, Soetens F, Jacquemyn Y, Alahuhta S. Anaesthesiological considerations on tocolytic and uterotonic therapy in obstetrics. Acta Anaesthesiol Scand 2009; 53: 701–9.
60. McCandlish R, Bowler U, Van Asten H, Berridge G, Winter C, Sames L, Garcia J, Renfrew M, Elbourne D. A randomised controlled trial of care of the perineum during second stage of normal labour. Br J Obstet Gynaecol 1998; 105: 1262–72.
61. Doumouchtsis SK, Papageorghiou AT, Vernier C, Arulkumaran S. Management of postpartum hemorrhage by uterine balloon tamponade: prospective evaluation of effectiveness. Acta Obstet Gynecol 2008; 87: 849–55.
62. 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? Br J Obstet Gynaecol 1997; 104: 372–5.
63. Cho JH, Jun HS, Lee CN. Hemostatic suturing technique for uterine bleeding during cesarean delivery. Obstet Gynecol 2000; 96: 129–31.
64. Tamizian O, Arulkumaran S. The surgical management of postpartum haemorrhage. Curr Opin Obstet Cynecol 2001; 13: 127–31.
65. Doumouchtsis SK, Papageorghiou AT, Arulkumaran S. Systemic review of conservative management of postpartum hemorrhage: what to do when medical treatment fails. Obstet Gynecol Surv 2007; 62: 540–7.
66. Hidar S, Jennane TM, Bouguizane S, Lassoued L, Bibi M, Khairi H. The effect of placental removal method at cesarean delivery on perioperative hemorrhage: a randomized clinical trial ISRCTN 49779257. Eur J Obstet Gynecol Reprod Biol 2004; 117: 179–82.
67. Deneux-Tharaux C, Macfarlane A, Winter C, Zhang W-H, Alexander S, Bouvier-Colle M-Hthe EUPHRATES Group. Policies for manual removal of placenta at vaginal delivery: variations in timing within Europe. BJOG 2009; 116: 119–24.
68. National Collaborating Centre for Women's and Children's Health (NCCWCH). Intrapartum care. Care of healthy women and their babies during childbirth. London: RCOG Press, 2007.
69. WHO. Pregnancy, childbirth, postpartum and newborn care: a guide for essential practice, 2nd edn. Geneva: WHO, 2006: B11pp.
70. Combs CA, Laros RK. Prolonged third stage of labour: morbidity and risk factors. Obstet Gynecol 1991; 77: 863–7.
71. Bider D, Dulitzky M, Goldenberg M, Lipitz S, Mashiach S. Intraumbilical vein injection of prostaglandin F2 alpha in retained placenta. Eur J Obstet Gynecol Reprod Biol 1996; 64: 59–61.

72. Weeks AD. Retained placenta. Best Pract Res Clin Obstet Gynaecol 2008; 22: 1103–17.
73. Bullarbo M, Tjugum J, Ekerhovd E. Sublingual nitroglycerin for management of retained placenta. Int J Gynaecol Obstet 2005; 91: 228–32.
74. van Beekhuizen HJ, de Groot ANJA, De Boo T, Burger D, Jansen N, Lotgering FK. Sulprostone reduces the need for the manual removal of the placenta in patients with retained placenta: a randomized controlled trial. Am J Obstet Gynecol 2006; 194: 446–50.
75. Weeks A, Alia G, Vernon G, Namayanja A, Gosakan R, Majeed T, Hart A, Jafri H, Nardin J, Carroli G, Fairlie F, Raashid Y, Mirembe F, Alfirevic Z. Umbilical vein oxytocin for the treatment of retained placenta (Release Study): a double-blind, randomized controlled trial. Lancet 2010; 375: 141–7.
76. Flood KM, Said S, Geary M, Robson M, Fitzpatrick C, Malone FD. Changing trends in peripartum hysterectomy over the last 4 decades. Am J Obstet Gynecol 2009; 200: 632. e1-6.
77. Eller AG, Porter TF, Soisson P, Silver RM. Optimal management strategies for placenta accreta. BJOG 2009; 116: 648–54.
78. 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: e1–5.
79. Ojala K, Perala J, Kariniemi J, Ranta P, Raudaskoski T, Tekay A. Arterial embolization and prophylactic catheterization for the treatment for severe obstetric hemorrhage. Acta Obstet Gynecol Scand 2005; 84: 1075–80.
80. O'Brien JM, Barton JR, Donaldson ES. The management of placenta percreta: conservative and operative strategies. Am J Obstet Gynecol 1996; 175: 1632–8.
81. Luo G, Perni SC, Jean-Pierre C, Baergen RN, Predanic M. Failure of conservative management of placenta previapercreta. J Perinat Med 2005; 33: 564–8.
82. Winograd RH. Uterine artery embolization for postpartum haemorrhage. Best Pract Res Clin Obstet Gynaecol 2008; 22: 1119–32.
83. Touboul C, Badiou W, Saada J, Pelage J-P, Payen D, Vicaut E, Jacob D, Rafii A. Efficacy of selective arterial embolisation for the treatment of life-threatening postpartum haemorrhage in a large population. Plos One 2008; 3: e3819.
84. Ledee N, Ville Y, Musset D, Mercier F, Frydman R, Fernandez H. Management in intractable obstetric haemorrhage: an audit study of 61 cases. Eur J Obstet Gynecol Reprod Biol 2001; 94: 189–96.
85. Eriksson L-G, Mulic-Lutvica A, Jangland L, Nyman R. Massive postpartum hemorrhage treated with transcatheter arterial embolization: technical aspects and long-term effects on fertility and menstrual cycle. Acta Radiol 2007; 48: 635–42.
86. Maassen MS, Lambers MDA, Tutein Nolthenius RP, van der Valk PHM, Elgersma OE. Complications and failure of uterine artery embolisation for intractable postpartum haemorrhage. BJOG 2009; 116: 55–61.
87. Gershon AS, Faughnan ME, Chon KS, Pugash RA, Clark JA, Bohan MJ, Henderson KJ, Hyland RH, White RI Jr. Transcatheter embolotherapy of maternal pulmonary arteriovenous malformations during pregnancy. Chest 2001; 119: 470–7.
88. Nikolic B, Spies JB, Lundsten MJ, Abbara S. Patient radiation dose associated with uterine artery embolization. Radiology 2000; 214: 121–5.
89. Hoffman M. A cell-based model of coagulation and the role of factor VIIa. Blood Rev 2003; 17: S1–5.

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Appendix

Table A1

Grading scheme	
Recommendation grade	Evidence
A	Directly based on category I evidence
B	Directly based on Category II evidence, or Extrapolated recommendation from category I evidence
C	Directly based on Category III evidence, or Extrapolated recommendation from category I or II evidence
D	Directly based on Category IV evidence, or Extrapolated recommendation from category I, II, or III evidence
Good practice point (GPP)	The view of the Guideline Development Group
Evidence category	**Source**
I	Evidence from Meta-analysis of randomized-controlled trials (Ia), or At least one randomized-controlled trial (Ib)
II	Evidence from At least one controlled study without randomization (IIa), or At least one other type of quasi-experimental study (IIb)
III	Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case–control studies
IV	Evidence from expert committee reports or opinions and/or clinical experience of respected authorities

National Institute for Clinical Excellence (NICE): Caesarean section, Clinical guideline 13, 2004. http://www.nice.org.uk/nicemedia/pdf/CG013NICEguideline.pdf