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# Recombinant factor VIIa and other pro-haemostatic therapies in primary postpartum haemorrhage

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Blood products are an essential component of the management of postpartum haemorrhage, although there is lack of evidence to guide optimal use. Prospective intervention studies, including randomized trials, are needed to clarify optimal timing and dosage. The new generation of virally inactivated blood products, such as fibrinogen concentrate, might further enhance our knowledge of the value of individual blood components. It seems likely that antifibrinolytic agents will receive less attention in future. However, rFVIIa promises to be a powerful tool in managing massive obstetric haemorrhage, although many questions concerning its efficacy and safety in differing clinical scenarios remain unanswered.

**Key words:** obstetric haemorrhage; postpartum haemorrhage; recombinant factor VIIa.

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## INTRODUCTION

Although obstetric, surgical and radiological interventions play a life-saving role in the management of postpartum haemorrhage (PPH), this chapter focuses on the utility of haemostatic therapies, an area that has shown huge advances in recent years. Included are the transfusions of fresh frozen plasma (FFP), packed red cells, cryoprecipitate and

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platelets, and the haematological management of massive transfusion and disseminated intravascular coagulation (DIC). Drug therapies such as antifibrinolytics and the relatively newer agent, recombinant activated factor VIIa are also considered.

## **PHYSIOLOGICAL CHANGES TO THE HAEMOSTATIC SYSTEM IN PREGNANCY**

Numerous haematological changes occur during pregnancy. In part, these prepare the mother for birth by protecting against haemorrhage. Their unwanted consequence, however, is to make thrombosis a more common event. These changes include an increase in clotting factors, such as factor VIII, von Willebrand factor (vWF) and fibrinogen and a decrease in the activity of the natural anticoagulant, protein S, due to elevation of C4b binding protein. Fibrinolytic activity is reduced due to an increase in fibrinolytic inhibitors, including alpha-2-antiplasmin, alpha-2-macroglobulin, thrombin activatable fibrinolysis inhibitor (TAFI) and the plasminogen activator inhibitors PAI-1 and placentally derived PAI-2. In addition, plasminogen and tissue plasminogen activator might be decreased.

In the postpartum period, the fibrinolytic system rapidly returns to its pre-pregnancy state, a process that is fully achieved within hours, in part reflecting the loss of the placental plasminogen activator inhibitor PAI-II. The coagulation system takes a greater time to correct, but by 6 weeks postpartum it can be expected that normal levels of most coagulation factors should be observed, although some, such as protein S, might take longer to recover.

The need for these pro-haemostatic changes is apparent when one considers that uterine blood flow increases during pregnancy from <5% to 12% of cardiac output, reaching a rate of 700–900 mL per minute at term.<sup>1</sup> At the point of birth, the potential for catastrophic haemorrhage is obvious. The physiological mechanism essential to achieving haemostasis is contraction of the uterus, influenced by endogenous prostaglandins and oxytocin. As the placenta separates, myometrial contraction causes closure of the terminal ends of the spiral arteries. Preceding fibrin accumulation within the walls of the spiral arteries aids this process, and following the birth of the placenta further fibrin deposition rapidly occurs over the site of attachment.

## **EFFECT OF BLEEDING ON HAEMOSTASIS**

Obstetric haemorrhage is frequently complicated by an acquired coagulopathy, caused by dilutional or consumptive effects on clotting factors, platelets and fibrinogen. One blood volume, rapidly replaced with red cells and crystalloid/colloid might be associated with individual clotting factor levels of <30% of normal. As volume loss occurs, vasoconstriction and a fall in blood pressure cause fluid shift into the vascular space, further exacerbating the dilutional effects of fluid resuscitation. In addition, anaemia contributes to impaired platelet responses. Red cells normally travel through blood vessels in the fast stream in the centre of the lumen, causing platelets to diffuse radially and thereby increasing the chance of adhesion to sites of injury. Decreases in haematocrit allow fast passage of platelets in the central luminal flow, reducing platelet–endothelial-cell interaction. In addition, lower production of adenosine diphosphate (ADP) and thromboxane from red cells, and reduced availability of haemoglobin to scavenge nitrous oxide, inhibit platelet activation and cause vasodilation. Massive haemorrhage with hypovolaemic shock causes tissue hypoxia, acidosis, hypothermia and systemic inflammatory responses, which can trigger disseminated intravascular coagulation (DIC).

## DISSEMINATED INTRAVASCULAR COAGULATION

### Pathophysiology

DIC is characterized by widespread intravascular activation of the coagulation system, with loss of localization and control of haemostatic and fibrinolytic processes. Other preceding obstetric events include sepsis, placental abruption, pre-eclampsia and amniotic fluid embolism. The International Society on Thrombosis and Haemostasis (ISTH) describe two stages of DIC.<sup>2</sup> Stage 1 involves the initiation of a massive localized or generalized inflammatory response, with release of host proteases, cytokines and hormones from multiple inflammatory and vascular cell types, causing extensive damage to the microvascular endothelium. Stage 2 has three parts: vasodilatation (causing loss of tight junctions between endothelial cells leading to capillary leak and shock); the escape from regulatory control (activation of coagulation pathways and excessive thrombin generation with microthrombus formation both locally and at distant sites); and the subsequent consumption and exhaustion of platelets and coagulation factors causing the potential for haemorrhage.

### Diagnosis

The diagnosis of DIC requires clinical and laboratory assessment. The most obvious clinical manifestation of acute DIC is uncontrolled generalized bleeding, often starting with oozing from surgical incisions and cannula sites but progressing to more severe haemorrhage, hypotension and shock. Less visible, but just as lethal, is the large- and small-vessel thrombosis that results in ischaemia, infarction and – ultimately – irreversible end-organ damage and death.

Laboratory tests characteristically show a prolongation of the prothrombin time (PT) and the activated partial thromboplastin time (APTT), a drop in fibrinogen and a corresponding rise in fibrinogen degradation products. A scoring system for the diagnosis of DIC has been proposed by the ISTH<sup>2</sup>; it has been found to have sensitivity of 91% and specificity 97%.<sup>3</sup> It consists of a points system in which a specific score is given to each of the following laboratory tests:

- Platelet count:  $>100 \times 10^9/L = 0$ ;  $<100 \times 10^9/L = 1$ ;  $<50 \times 10^9/L = 2$
- Elevated fibrin-related markers, e.g. soluble fibrin monomers/fibrin degradation products: no increase = 0; moderate increase = 2; strong increase = 3
- Prolonged prothrombin time:  $<3$  seconds = 0;  $>3$  seconds but  $<6$  seconds = 1;  $>6$  seconds = 2)
- Fibrinogen level:  $>1$  g/L = 0;  $<1$  g/L = 1.

A total score of 5 or more is considered to be compatible with DIC in the presence of an underlying disorder known to be associated with the condition.<sup>4</sup> Trends in laboratory parameters must be followed, as non-overt DIC can present a window of opportunity for targeting therapy.

### Management

The key to the management of DIC is eliminating the underlying cause, such as sepsis. Blood product replacement is often not required in cases where bleeding is not present. Active haemorrhage, however, accelerates the DIC process by haemodilution,

consumption of platelets and coagulation factors, fibrinolysis, acidosis and hypothermia. Therefore, where DIC complicates PPH, the primary treatment objective must remain the gain of control over the source of blood loss, but the judicious use of blood products is crucial in preventing death from uncontrolled DIC.

## USE OF BLOOD COMPONENT THERAPY IN PPH

### Red cells

The British Committee for Standards in Haematology recommends that red cells are rarely indicated when the haemoglobin (Hb) concentration is  $>10$  g/dL but almost always indicated when it is  $<6$  g/dL.<sup>5</sup> During active bleeding, an Hb  $>8$  g/dL should be aimed for. Alongside the important role red cells play in maintaining tissue oxygenation, they also contribute to haemostasis by a number of mechanisms, as outlined above.

One unit of red cells provided by the National Blood Service in the UK (UK NBS) is  $280 \pm 60$  mL in volume and has a haemoglobin content  $>40$  g/unit.<sup>6</sup> Units are manufactured from whole blood by first passing the blood through a leucodepletion filter, as a precaution against variant Creutzfeldt–Jakob disease, followed by a process of centrifugation, and then separation and extraction of plasma and platelets. The red cells are resuspended in an additive solution and have a shelf life of 35 days when kept at  $4^\circ\text{C} \pm 2^\circ\text{C}$ . All donations are tested routinely for human immunodeficiency virus, hepatitis B virus, hepatitis C virus and human T lymphotropic virus type 1.

Group O RhD-negative units should be readily accessible, although use should be restricted to cases where delay in transfusion severely jeopardizes patient safety. Hospital blood banks are normally able to provide group specific blood within 15 minutes, reducing the risk of transfusion reactions and antibody formation. All female patients of childbearing age should receive K-negative blood, as antibody formation by K-negative women is an important cause of haemolytic disease of the newborn. If Group O RhD-negative blood is used in the first instance, group-specific blood should be transfused as soon as it is available. Usually 45 minutes is required by hospital blood banks to perform a full cross-match, in which other clinically significant antibodies are screened for and individual units are checked to be compatible with the recipient's blood. In patients found to have no irregular red-cell antibodies, electronic issue (avoiding the need for manual cross-match) can speed up this process, but in patients found to have clinically problematic antibodies, the process of identifying units for transfusion can take much longer. The risk of delaying until cross-matched blood is available should be weighed up against the risk of a haemolytic or other transfusion reaction and future problems the women might encounter with haemolytic disease of the newborn. Occasionally, incompatible units are given to women with irregular red-cell antibodies experiencing life-threatening haemorrhage; this should always be discussed with a transfusion specialist, accessible via the haematologist on call.

The development of artificial red-cell substitutes has been under way for some time, with a form of polymerized human haemoglobin (PolyHeme<sup>®</sup>) currently the subject of Phase III trials in the USA. Potentially, this could provide an off-the-shelf product that would not be group specific or require cross-matching. It is also hoped that viral inactivation steps during processing would reduce the risk of pathogen transmission. Phase III trials of another substitute – Haemolink<sup>®</sup> – were abandoned after concerns arose over an increase in cardiovascular incidents in recipients.

## Platelets

Resuscitation with red blood cells and crystalloid/colloid causes a dilutional thrombocytopenia, giving rise to a platelet count of around  $50 \times 10^9/L$  with transfusion of approximately two blood volumes.<sup>7</sup> In addition, platelet function is affected by a fall in haematocrit and by increased fibrinogen degradation products.

A platelet count of at least  $50,000/\mu L$  should be maintained, although this target is based on a consensus of medical opinion rather than evidence<sup>8,9</sup>, and would depend on the rapidity of blood loss and whether platelet dysfunction is expected.

The UK NBS provides two types of platelet product. First, a pooled platelet bag in which one adult dose contains the platelets from four donations of whole blood, re-suspended in one of the donor's plasma. After separation of the buffy coat from each whole unit by a process of centrifugation, the product is then leucodepleted. Some red-cell contamination will remain. Increasingly, the Blood Service is moving towards the provision of apheresis platelets; this product requires less processing, as apheresis collection from the donor enables only platelets to be collected. The major advantage of this is that one adult dose of platelets can be collected in one session, reducing the risk of pathogen transmission. Disadvantages are in the cost of this method of collection and in the difficulty in recruiting and retaining donors; apheresis sessions can take up to 2 hours and require travel to a main blood donation centre.

One adult dose of platelets as provided by the National Blood Service must contain  $>240 \times 10^9/unit$  platelets. However, it remains important to check the count after platelet transfusion as enhanced consumption of platelets can lead to a failure to increment as expected.

There is some evidence to support the efficacy of proactive administration of platelets during acute haemorrhage. A Danish study published in 2007 prospectively assessed the outcome of patients undergoing ruptured aortic aneurysm repair before (control group) and after implementation of a new proactive transfusion policy.<sup>10</sup> This new policy proposed the administration of two pooled doses of platelets immediately when a rupture of the aorta was suspected and again 30 minutes after unclamping of the aorta. FFP was administered in a 1:1 ratio to the number of units of red cells transfused, and a further two doses of platelets were given if the bleeding was estimated to exceed two blood volumes. The intervention group ( $N = 50$ ) had a higher platelet count on postoperative admission to the intensive care unit than the control group ( $N = 82$ ;  $155 \times 10^9/L$  vs.  $69 \times 10^9/L$ ;  $P < 0.0001$ ), shorter APTT (39 seconds vs. 44 seconds;  $P < 0.001$ ), fewer postoperative transfusions (red cells, two units vs. six units; FFP, two units vs. four units; and platelets, no doses vs. one dose;  $P < 0.01$ ), and a higher 30-day survival rate (66% vs. 44%;  $P = 0.02$ ). However, as the study did not separate a change in platelet transfusion policy from a change in the administration of FFP, it is difficult to conclude whether the early administration of platelets is helpful. There have been no studies looking at the value of proactive platelet transfusion in PPH.

## Fresh frozen plasma

Prothrombin time and APPT ratios of  $>1.5$  are associated with an increased risk of clinical coagulopathy<sup>9</sup> and, if bleeding is present, correction should be with FFP. The dose of FFP should be large enough to maintain coagulation factors well above the critical level, bearing in mind that the efficacy might be reduced because of rapid consumption. Very approximately, a prothrombin time ratio (PTR) of  $>1.5$  (clotting factors approximately 50% of normal) will be reached after replacement of  $1-1.5 \times$  blood

volume, or transfusion of 8–12 units of packed red cells. A PTR of  $>1.8$  (clotting factors approximately 30% of normal) will be reached after replacement of  $2 \times$  blood volume<sup>11</sup>, although if DIC is present the coagulopathy will be greater. In practice, a dose of 10–15 mL/kg is usually given in the first instance, with clotting studies guiding further replacement. Repeat testing of the coagulation profile is especially important as rapid consumption of clotting factors might necessitate a greater-than-expected requirement for FFP.

The volume of FFP present in one bag supplied by the UK NBS can vary by up to 220 mL, hence the need to prescribe by volume rather than by unit. One bag of FFP is obtained by apheresis from a single donor or recovered from random blood donation. Processing includes viral screening, leucodepletion, centrifugation and extraction of cellular components including platelets. FFP contains all coagulation factors, although the quality control only specifies levels of factor VIII  $>0.70$  IU/mL.

Whereas coagulopathy, as demonstrated by prolonged PT and APTT, is associated with increased mortality in trauma victims<sup>12,13</sup>, little evidence currently exists for an improvement in outcome with FFP. A recent article reviewing the evidence for FFP usage found only one small, randomized controlled trial relevant to this area.<sup>14</sup> This concerned the treatment of DIC in 33 neonates, and was unable to demonstrate a survival benefit with the use of FFP. However, a good rationale exists for the use of FFP in the context of obstetric haemorrhage and while such limited evidence is available to support or refute current practice, accepted massive transfusion protocols including FFP should be followed.

That said, as with platelet transfusions, evidence exists for earlier usage of FFP, which might also support its use in general. A retrospective review of 246 patients at a US Army combat support hospital, each of whom received a massive transfusion ( $>10$  units of red cells in 24 hours) found that a high ratio of 1:1.4 red cells to FFP is independently associated with improved survival, primarily by reducing death by haemorrhage.<sup>15</sup> Again, the early use of FFP for PPH has not been studied.

A virally inactivated plasma product is available (Octaplas<sup>®</sup>). This is made from pooled plasma from voluntary non-UK donors treated with a solvent detergent (tributyl phosphate and octoxinol 9) to reduce the potential for virus transmission. This product has the obvious advantage of viral inactivation and of being a standardized product, but the concentrations of clotting factors are known to be reduced. For example, factor VIII suffers a 20–30% loss and protein S nearly a 50% loss.<sup>16</sup> There is no red-cell contamination and therefore RhD status does not need to be considered, but it is a pooled product, exposing the recipient to multiple donors. There are no published studies of the use of solvent-detergent-treated FFP (SD FFP) in PPH, but evidence exists for its use in other situations. A randomized trial of its use in the liver transplantation showed equivalent correction of coagulation abnormalities (compared with controls who received FFP), with no proven transmission of infection.<sup>17</sup> The group receiving SDFFP did require more other blood components, but this was not found to be statistically significant. Many transplant centres have switched over to the routine use of SD FFP in liver transplant surgery, but recent case reports have highlighted concerns over intraoperative deaths associated with severe coagulopathy in patients managed with SD FFP.<sup>18</sup>

## Cryoprecipitate

Cryoprecipitate is derived from plasma and provides a more concentrated method of administering fibrinogen than FFP; 1 L of FFP contains 2–5 g of fibrinogen whereas

100–200 mL of cryoprecipitate contains 5 g. It also contains significant levels of factor VIII, vWF, fibronectin and FXIII, although quality control does not specify the amount.

The importance of fibrinogen in the context of PPH is well established. In multivariate analysis fibrinogen was the only marker associated with the occurrence of severe PPH<sup>19</sup>, and, in this setting, cryoprecipitate should be given to maintain fibrinogen levels above 1.0 g/L.<sup>9</sup> The fibrinogen concentration halves after every 0.75 blood volume replaced and, as a rough guide, it is likely to fall to <1 g/L after replacement of 12 units of red cells or 1.5 × blood volume<sup>11</sup>; however, co-existing DIC will complicate this picture.

Cryoprecipitate is prepared by controlled thawing of frozen plasma to precipitate high-molecular-weight proteins, including factor VIIIc, vWF and fibrinogen.<sup>11</sup> Usually, five single donations are pooled into one bag and an adult dose constitutes two pools. The obvious disadvantage of this product is the high number of donors to which the recipient is exposed, with the increase in risk of pathogen transmission. Whereas expert opinion advocates the use of cryoprecipitate when fibrinogen levels fall below 1.0 g/L, its efficacy has not been proven.<sup>14</sup>

A pasteurized human fibrinogen concentrate is available and has the advantage of viral inactivation and known fibrinogen content. Good evidence exists for its efficacy and safety in the treatment of bleeding episodes in patients with congenital deficiencies of fibrinogen<sup>20</sup> and some is starting to emerge in patients with acquired deficiencies.<sup>21</sup>

### Massive obstetric haemorrhage protocols

All obstetric units should have a massive transfusion protocol that should be implemented in situations of severe PPH. It should be developed in collaboration with the haematologists, blood bank and obstetricians. It is recommended that these protocols are accessible in all relevant clinical and laboratory areas and that regular ‘drills’ are performed to improve awareness and confidence and to ensure that the blood transfusion chain works efficiently.<sup>9</sup> Protocols do exist for the empirical transfusion of a batch of blood products in situations of massive haemorrhage (e.g. six units of group O RhD-negative red cells, four units of fresh frozen plasma, and one adult dose of platelets).<sup>22</sup> In general, this is not considered best practice in the UK, where blood product transfusion is tailored to the patient’s haematology and coagulation results as detailed in the sections above. However, where there is a potentially dangerous delay in obtaining laboratory results, it might be necessary to provide some blood components initially.

### ANTIFIBRINOLYTIC AGENTS

Tranexamic acid (TA) is often listed as an option to be considered in guidelines for the management of PPH. This antifibrinolytic agent competitively inhibits the activation of plasminogen to plasmin. It has many established uses, including the control of menorrhagia and the prevention or treatment of haemorrhage in patients with congenital bleeding disorders, including haemophilia and von Willebrand disease. In these settings, administration is typically by the oral route and side effects are predominantly gastrointestinal, including vomiting and diarrhoea.

Intravenous administration, as in the use of TA during PPH, can be associated with hypotension. There are also reports of thromboembolic disease and TA should not be used when there is fulminant DIC because of its potential to exacerbate microvascular thrombosis and expedite end-organ damage.

The evidence for the use of TA in the treatment of PPH is very limited and based predominately on anecdotal reports. The commonly cited case published in 1996 by As et al concerns a 30-year-old woman pregnant following in-vitro fertilization.<sup>23</sup> At 35 weeks gestation, she presented with massive vaginal bleeding, estimated at 1.5 L. Following emergency caesarean section, ergometrine, a syntocinon infusion, fluid resuscitation and eight units of packed red cells, the woman remained haemodynamically unstable with poor urine output. At this stage, the decision was taken to administer 1 g TA intravenously; this was repeated 4-hourly until a total of 3 g had been administered. Bleeding reportedly slowly stopped with this treatment, although a further 19 units of red cells and two units of FFP were transfused. Further surgical intervention was avoided and the patient survived and made a return to full health. Blood coagulation results are not detailed in the article, although the authors state that there was no objective evidence of coagulation disturbance.

A review by Engelsen et al of the cases of emergency hysterectomy performed over a 15-year period in a Norwegian obstetrics department listed three cases in which TA had been used in an attempt to avoid peripartum hysterectomy.<sup>24</sup> Few other details are listed about these cases specifically, and clearly this treatment was ineffective at preventing definitive surgical intervention. Among the complications suffered by the women it was recorded that one patient suffered a deep vein thrombosis, but there is no mention as to whether this occurred in one of the patients who received TA.

Aprotinin is extracted from bovine lung and inhibits the action of tissue and plasma kallikrein (through the formation of reversible enzyme-inhibitor complexes).<sup>25</sup> Aprotinin has been used in cardiac surgery and liver transplantation and is known to cause arterial and venous thrombosis as well as hypersensitivity reactions on repeated exposure. There is some limited evidence for its use in PPH<sup>26</sup>, but worldwide marketing of the drug was suspended recently, pending final results from the Canadian Blood Conservation Using Antifibrinolytics Trial (BART). This high-risk cardiac surgery trial has been halted after more patients receiving aprotinin died within the first 30 days of the trial than patients taking epsilon-aminocaproic acid or TA.

All papers discussing the clinical use of antifibrinolytics in haemorrhage either reference the three reports described above or concern the management of patients with congenital bleeding disorders. It is clear that although antifibrinolytic agents will continue to play an important role in the prevention of obstetric haemorrhage in patients with conditions such as vWD and platelet function disorders, more convincing evidence for their role in the management of PPH is required if they are to be used on a more regular basis.

## RECOMBINANT FACTOR VIIA

Recombinant factor VIIa (rFVIIa) is the activated form of factor VII produced from the factor VII cDNA transfected into hamster kidney cells. It has been used for the last 20 years in the management of patients with haemophilia complicated by inhibiting antibodies to factor VIII.<sup>27</sup>

Endogenous factor VII acts locally at the site of tissue injury and vascular wall disruption by binding to exposed tissue factor. The factor VIIa-TF complex mediates the activation of factor X, which subsequently converts prothrombin into thrombin. The small amount of thrombin generated through this pathway activates factors V, VIII and XI and the platelets, enhancing its own production in a powerful positive feedback loop.<sup>28</sup> Recombinant factor VIIa is also capable of binding directly to the surface of activated platelets, accelerating coagulation at the local site of injury. Stabilization of

the clot occurs by factor VIIa-mediated activation of thrombin-activatable fibrinolysis inhibitor. Because of its potent thrombin-generating capacity, rFVIIa has been used as a haemostatic agent in a number of different clinical settings.

### Use of rFVIIa for general surgery and trauma

Although rFVIIa is not currently licensed for use in massive haemorrhage in non-haemophilic patients, randomized controlled trials have demonstrated it to reduce postoperative bleeding in patients undergoing major surgery.<sup>29,30</sup> Also, a post-hoc analysis on the effect of rFVIIa on patients from two randomized, placebo-controlled, double-blind trials of rFVIIa as an adjunctive therapy for bleeding in patients with severe trauma (60 rFVIIa-treated and 76 placebo subjects) found that transfusion requirements and organ failure rates were significantly reduced, with patients suffering from coagulopathy deriving the most benefit.<sup>31</sup>

### Evidence for use of rVIIa in postpartum haemorrhage

There have been several hundred cases of rFVIIa administration to women with severe primary PPH worldwide, most of which remain unreported.<sup>28</sup> Numerous case reports and case series have been published over the last 8 years. Review articles have followed, but there are no published randomized controlled trials specifically considering the use of rFVIIa in PPH. However, registry data do now exist and give an indication of the safety and efficacy of rFVIIa in this setting.

Several non-randomized studies have been conducted in this area. The most recent is a retrospective case-matched analysis of the use of rFVIIa in the treatment of massive PPH in patients since 2003 ( $N = 6$ ).<sup>32</sup> The investigators found no statistical difference in the transfusion requirements or the severity of the coagulopathy between the six patients who had received rFVIIa and six matched cases. In both groups, the prothrombin time improved with management.

Another retrospective study compared 26 women who received rFVIIa with 22 women who were treated during the same time period without using rFVIIa.<sup>33</sup> The study found that rFVIIa had only been administered to those women with more severe bleeding and worse coagulopathy, compared to the control subjects. The response to rFVIIa was considered good in approximately two-thirds of the patients, defined as bleeding  $\leq 1000$  mL after administration and no requirement for additional interventions, except suturing of vaginal lacerations. In those who showed poor or no response, the ongoing bleeding was arterial. One patient treated with rFVIIa suffered a pulmonary embolism and was subsequently found to have antithrombin deficiency. The value of these two studies is limited by their retrospective nature and small patient numbers.

A further study retrospectively identified 34 patients with PPH of greater than 1500 mL over a 19-month period, 18 of whom had received rFVIIa.<sup>34</sup> Patient treatment and data collection were performed at a single centre in Pakistan, and statistical analysis undertaken at Yale University, USA. The subjects who had been given rFVIIa had lower maternal mortality [5/18, 28% vs. 8/16, 50%; odds ratio (OR) 0.04 (0.002, 0.83)] and received a lower number of packed-red-cell transfusions (4.094.46 vs. 9.6196.7,  $P = 0.007$ ), than the comparison group, despite lower haemoglobin levels ( $P = 0.02$ ) and more severe coagulopathies determined by PT and APTT ( $P = 0.03$  and  $P = 0.05$ ). There was no difference in the rate of hysterectomy between the two groups, and no adverse effects attributable to rFVIIa were identified.

Two recent large reviews of published case reports have been performed. Although the studies above are not included, there is a large overlap between the two reviews in the reports examined. The first, by Scarpelini et al in 2007, examined 24 publications describing use of rFVIIa in 56 patients.<sup>35</sup> In 50 cases (89%), the drug was used in patients without pre-existing disorders of coagulation, with the most common pathology being PPH. Other uses included bleeding related to gynae-oncological surgery (for pelvic sarcoma, vaginal sarcoma, and endometrial cancer) and congenital haematological disease. The majority of patients received 90–120 µg/kg of rFVIIa repeated shortly afterwards if necessary. The efficacy of the drug, defined as cessation or significant decrease in bleeding, was 98%. No adverse events were reported.

A further review article published by Franchini in early 2007 presents data on 65 patients who received FVIIa for obstetric PPH<sup>36</sup>, although 7 of these had a congenital disorder of coagulation. The efficacy of the drug was defined as reduction or cessation of haemorrhage but, when used as secondary prophylaxis in patients with congenital coagulation disorders, the desired endpoint had been achieved if bleeding was prevented. The efficacy was deemed to be 95% ( $N=62$ ) in PPH with a median dose (in those without congenital factor VII deficiency) of 73 µg/kg. More than one dose of rFVIIa was administered in 27% of cases. There were no adverse events reported in any of the cases reviewed, but the authors were unable to determine whether use of factor VIIa reduced the rate of hysterectomy, as in many cases this had been performed before administration of the product.

### Registry data

There have been two large studies of registry data: the North European FVIIa in Obstetric Haemorrhage Registry (NEFOH) and a registry from Australia and New Zealand. The Australian study considers 694 cases from 37 hospitals reported to the Haemostasis Registry (which collects retrospective and contemporaneous data on all use of rFVIIa at participating institutions for non-haemophilic patients with critical bleeding).<sup>37</sup> Unfortunately for this article, obstetric bleeding only totalled 4% ( $N=27$ ) of these cases; 68% of the obstetric patients were deemed to have shown a decrease ( $N=12$ ) or cessation ( $N=5$ ) in bleeding (although no single definition appears to have been used) and 85% of patients survived to 28 days. Forty-four adverse events (6% of patients) were considered to be possibly linked to the administration of rFVIIa and two adverse events were thought to be directly related to the administration of rFVIIa (clots in drains with tamponade and right atrial thrombus formation). The events considered possibly to relate to rFVIIa include three pulmonary emboli and eight cerebrovascular accidents. No adverse events associated with rFVIIa were identified in the obstetric group. The median dose given to all patients was 90 µg/kg, but it was not possible to determine from the published data the mean dose in the subset of obstetric patients.

NEFOH collected data from nine European countries between 2000 and 2004.<sup>28</sup> In all, 65 out of 531 hospitals known to use rFVIIa reported its use in primary PPH in a total of 128 patients; 113 forms were returned (88%), with 97 (86%) classified as treatment (where other interventions had failed) and 16 (14%) as secondary prophylaxis (usage to support other successful interventions). Five cases were excluded due to secondary haemorrhage (four) and DIC (one). Improvement (defined as reduced bleeding) was found in 80% of treatment patients and in 75% of the secondary prophylaxis group. Failure to respond (defined as bleeding unchanged or worse) was seen in 15 cases. Most women (88 of 108, 81%) received a single dose only, the most common

dose being 7.2 mg or less (68 of 75, 91%), which equates to approximately 90 µg/kg. Five of the treated women died and four suffered from deep vein thrombosis following treatment (one of these was felt to be unrelated to rFVIIa). One woman in the treatment group sustained a myocardial infarction, although she had suffered a cardiac arrest before the administration of rFVIIa.

### Studies in progress

A group headed by the Centre Hospital University of Nimes is currently recruiting patients to a randomized controlled trial of rFVIIa use in PPH in France and Switzerland.<sup>38</sup> The stated aim of this trial is to evaluate the use of the rFVIIa given as a salvage therapy in women with severe PPH that is ongoing after all the currently available medical and surgical treatments. The group plans to compare its early use, before elective surgery or arterial embolization, to its late use, after embolization or surgery, before salvage hysterectomy. Primary outcome measures are to include the estimation of the rate of haemorrhage, before and 1 hour after the end of the rFVIIa infusion. The group also plans to look at haematological parameters (such as haemoglobin) and therapeutic interventions aimed at controlling PPH (i.e. selective arterial embolization, ligation of hypogastric arteries and hysterectomy). This study aims to evaluate: first, the reduction in absolute risk of arterial embolization, surgery or hysterectomy in patients receiving a unique early infusion of rFVIIa (60 µg/kg body weight); and second, the number of women necessary to treat to avoid one of these interventions. Recruitment began in December 2006 and is planned to continue until December 2009.

### Should rFVIIa be used in postpartum haemorrhage?

Overall, whereas the safety and efficacy of rVIIa appears promising, high-level evidence for its use in PPH is still lacking. However, it does appear that where rFVIIa is being used for this indication, few adverse events are being reported. It is hoped that the randomized, controlled trial described above will start to provide a higher quality of evidence than is currently available amongst the published data, allowing better recommendation and guidelines for which circumstances rFVIIa is safe, clinically effective and cost effective in the control of PPH.

### CONCLUSION

Unfortunately, the evidence for all haemostatic therapies in the management of PPH is somewhat limited. The use of blood products is not disputed but there is lack of evidence to guide optimal use. Recent and future studies looking at the new generation of virally inactivated blood products, such as fibrinogen concentrate, will hopefully enhance knowledge of the value of individual blood components in this setting. In particular, further randomized controlled trials are needed to assess the way in which we use traditional transfusion products, clarifying optimal timing and dosage.

Given the advent of rFVIIa, it seems likely that antifibrinolytic agents will receive less attention in future. rFVIIa promises to be a powerful tool in managing massive obstetric haemorrhage, but many questions concerning its efficacy and appropriateness in differing clinical scenarios remain unanswered to date. Randomized controlled trials are being established, hopefully leading the way in providing a long-awaited evidence base for this therapy in the management of postpartum haemorrhage.

### Practice points

- Obstetric haemorrhage is frequently complicated by an acquired coagulopathy, caused by dilutional or consumptive effects on clotting factors, platelets and fibrinogen.
- Massive haemorrhage with hypovolaemic shock causes tissue hypoxia, acidosis, hypothermia and systemic inflammatory responses triggering disseminated intravascular coagulation (DIC).
- Where DIC complicates PPH, the primary treatment objective must remain the gain of control over the source of blood loss, but the judicious use of blood products is crucial in preventing death from uncontrolled DIC.
- The British Committee for Standards in Haematology recommends that red cells are rarely indicated when the haemoglobin (Hb) concentration is  $>10$  g/dL but almost always indicated when it is  $<6$  g/dL.
- All obstetric units should have a massive transfusion protocol, ratified by local haematologists, anaesthetists, obstetricians and the blood-bank team. This should be implemented without delay in situations of severe PPH.
- Although the safety and efficacy of rVIIa appears promising, high-level evidence for its use in PPH is still lacking.

### Research agenda

- There is a need to establish the optimal way in which we use traditional transfusion products, clarifying the most appropriate timing and dosage.
- Randomized trials of rFVIIa to establish its effectiveness and safety when given 'early', i.e. before caesarean hysterectomy, are required.

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