

*Opinion***Guidelines for the use of recombinant activated factor VII in massive obstetric haemorrhage**Alec WELSH,¹ Claire McLINTOCK,² Stephen GATT,³ David SOMERSET,⁴ Phillip POPHAM⁵ and Robert OGLE⁶¹Department of Maternal-Fetal Medicine, Royal Hospital for Women, Randwick, New South Wales, ²Department of Haematology, University of Auckland, Auckland, New Zealand, ³Department of Anaesthetics, Royal Hospital for Women and Prince of Wales Hospital, Randwick, New South Wales, ⁴Maternal-Fetal Medicine Unit, John Hunter Hospital, Newcastle, New South Wales, ⁵Department of Anaesthesia, Royal Women's Hospital, Melbourne, Victoria, and ⁶Department of Obstetrics, Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia

Recombinant activated factor VII (rFVIIa) is emerging as a novel therapy for the treatment of life or fertility-threatening post-partum haemorrhage (PPH) unresponsive to standard therapy that in some cases may prevent the need for peripartum hysterectomy. The level of evidence to date for use of rFVIIa in PPH is limited to case reports and case series with one nonrandomised study. No high-quality randomised controlled trials have been published at this stage, precluding a quality systematic review. Guidelines have been published for the use of rFVIIa in non-obstetric haemorrhage, though to date none are available for PPH. A multidisciplinary group of Australian and New Zealand clinicians from the fields of obstetrics, anaesthesia and haematology, who have both clinical experience in and/or knowledge of rFVIIa was convened by the manufacturer. This group produced an opinion and guideline based on their experience and the published international literature on the use of rFVIIa. This is intended to be used as a guideline and algorithm for the use of rFVIIa, though any use should be tailored to local practice and resources.

Background

Post-partum haemorrhage (PPH) remains a potentially life-threatening complication of vaginal or caesarean delivery and is a leading cause of maternal mortality in Australia and New Zealand.¹ Although certain risk factors for obstetric haemorrhage can be identified in the antenatal period, for the most part when it occurs it is unpredictable, sudden and often catastrophic and may result in serious morbidity or death. Hypovolaemic shock, multiorgan failure requiring intensive care treatment, disseminated intravascular coagulation, acute renal failure requiring dialysis, hepatic failure and adult respiratory distress syndrome are reported complications.^{2,3}

The World Health Organization defines PPH as blood loss of more than 500 mL or more during or

following delivery, or any amount of blood loss post-partum that causes haemodynamic instability.⁴ It has been argued that the ICD-10-AM definition of PPH (≥ 500 mL, ≤ 750 mL blood loss) used by Australian hospitals is now of diminishing clinical relevance as most healthy pregnant women can withstand this degree of blood loss with little if any physiological disturbance and that efforts should be concentrated on severe or major post-partum haemorrhage. Definitions of severe PPH vary and include blood loss of > 1000 mL, the need for red cell transfusion or the need for hysterectomy. Massive obstetric haemorrhage can be considered that requiring replacement of 50% of circulating blood volume in < 3 h or loss of > 150 mL/min.⁵

The treatment of severe and, in particular, massive PPH is centred on resuscitation, restoration of circulating blood volume, and identification and arrest of bleeding. Effective multidisciplinary team work is essential to coordinate rapid resuscitation with appropriate intravenous fluids, blood component therapy and medical and/or surgical treatment of the underlying cause of the bleeding. If bleeding cannot be successfully controlled by uterine massage or uterotonic

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medications, there are a number of advanced surgical and/or radiological treatment options, as determined by local availability.

Peripartum hysterectomy is a treatment of last resort for PPH because it is associated with loss of reproductive potential and carries additional surgical risk and considerable morbidity. Complications related to surgical interventions include loss of reproductive function, uterine perforation, uterine synechiae (Asherman's syndrome), urinary tract injury and genitourinary fistula, bowel injury and intestinal fistula, vascular injury, pelvic haematoma and sepsis.

The action and role of rFVIIa

Recombinant activated factor VII (rFVIIa) (NovoSeven®; Novo Nordisk Pharmaceuticals Pty Ltd, Bagsvaerd, Denmark) is a recombinant form of the naturally occurring protease. Since 1998, rFVIIa has been approved and used extensively for the control of bleeding or surgery prophylaxis in patients with haemophilia who have inhibitors to coagulation factors.^{6–8} Recently, rFVIIa has been approved for use in Glanzmann thrombasthenia and factor VII deficiency. Outside these indications, any use is considered 'off-label' and the responsibility for, and decision to use rFVIIa rest with the prescribing clinician.

Recombinant FVIIa works locally at the site of vascular injury, where tissue factor (TF) is exposed and activated platelets are found. The role of FVIIa in the induction of haemostasis includes the direct activation of factor IX to factor IXa and factor X to factor Xa following the binding of FVIIa to exposed TF. Binding of factor VIIa or rFVIIa to TF initiates the coagulation cascade with the key final steps being activation of prothrombin to form thrombin that results in cleavage of fibrinogen to form a stable fibrin plug. At pharmacological doses, rFVIIa directly activates factor X on the surface of activated platelets at the site of injury independently of TF, factors VIII and IX. This results in a 'thrombin burst' with the conversion of prothrombin into large amounts of thrombin and the local formation of a stable fibrin clot that may control bleeding.^{9,10}

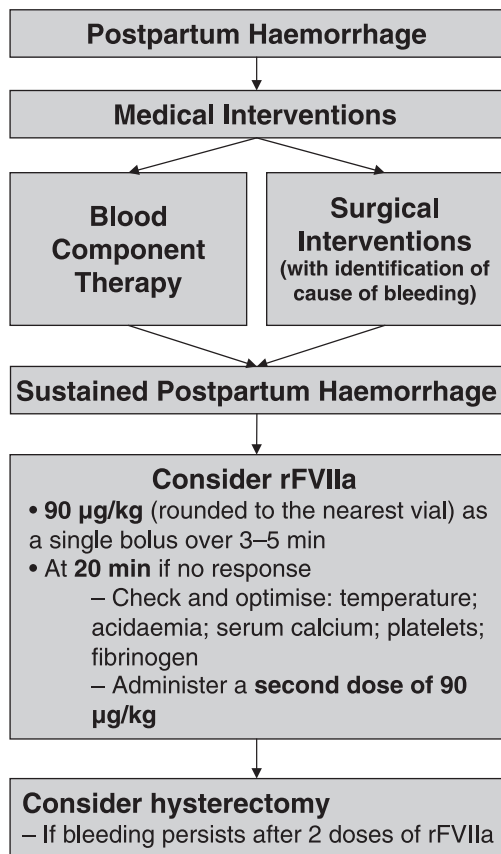
Two recent large reviews have summarised the existing literature on the use of rFVIIa in non-obstetric settings. First, European consensus guidelines that confirm the role rFVIIa as an adjunct to surgery for massive bleeding in certain indications only have been published.¹¹ The numbers of patients in the trial and case series data were much greater than the worldwide obstetric experience, though the nature of these data limited the strength of the authors'

recommendations. Second, an American review group evaluated the literature on rFVIIa in a number of medical indications, including a small number in obstetrics and gynaecology,¹² and suggested that its use for PPH is appropriate only after attempted significant clotting factor replacement.

The use of rFVIIa in obstetric haemorrhage

In obstetrics, rFVIIa is emerging as a novel therapy for the treatment of life or fertility-threatening PPH unresponsive to standard therapy that may in some cases prevent the need for peripartum hysterectomy. Our multidisciplinary review panel identified only a number of case reports and case series^{13–16} documenting its role and use in management of severe PPH, precluding formal systematic analysis of its use. A review article published in 2006 summarised the internationally published literature to date, identifying 65 cases of rFVIIa used for obstetric haemorrhage and making the observation that rFVIIa may be of value, though providing no suggestions for dosage or timing.¹⁷ Consideration for use of rFVIIa in PPH must take into account efficacy, side-effects and costs of rFVIIa versus other medication, blood products and hospitalisation. The level of evidence on which to make this decision is at present limited. To date, no randomised controlled studies have been published in PPH. A single non-randomised study¹⁸ of rFVIIa for PPH that retrospectively compared 38 parturients who had received rFVIIa with 26 women, over the same time period, who had not recently been published¹⁸. The nature of this study limited their conclusions, though the authors felt that costs of rFVIIa restricted its use to cases of severe ongoing haemorrhage where other conventional methods to arrest bleeding had failed. Some individual centres in Australia have developed guidelines on using rFVIIa in severe PPH. No dose finding studies have been completed but in the recent review of 65 cases,¹⁷ a mean dose of 65.9 µg/kg (13.3–120 µg/kg) was administered. Experience in Australia and New Zealand has been collected in the Monash Haemostasis Registry,¹⁹ where the median dose used has been 90 µg/kg, and will be submitted for publication independent of this guideline. The dosage of 90 µg/kg is based on consensus experience of clinicians (including haematologists) within the Monash Haemostasis Registry, being that most commonly used in haemophilia.

Concerns regarding the cost of rFVIIa that were raised in the non-randomised controlled trial for PPH must be balanced against perceived savings in intensive

Flow chart for management of PPH**INTERVENTIONS**

(Notify local transfusion specialist of possible need for activation of Massive Blood Transfusion Protocol)

Medical:

- Treat: haemodynamic instability; hypothermia; acidosis
- Uterine massage / compression
- Uterotonic agents
- Coagulation studies and treat coagulopathy

Blood Component Therapy

- 4 U packed red blood cells (PRBCs)
 - Coagulopathy correction
 - 4 U PRBCs
 - 4 U FFP
 - Single adult dose of platelets
 - Repeat PRBCs, FFP and platelets
 - Administer calcium as appropriate
- Repeat (b) and (c) as necessary

Surgical (as available and appropriate)

- EUA and repair
- Uterine tamponade
- B-Lynch suture
- Arterial ligation
- Radiological arterial embolisation

Checklist for 'off-label' use of rFVIIa in obstetrics

- Remember the high risk of thromboembolism
- Consider physical measures for thromboprophylaxis
- Monitor all women for signs of improvement and adverse events.
- Report all patients receiving rFVIIa to the Haemostasis Registry (Monash University)

<http://www.med.monash.edu.au/epidemiology/traumaepi/haemostasis.html>

Figure 1 Flow chart for management of post-partum haemorrhage.

care and blood product costs. In the absence of case-controlled studies direct comparison is impossible. An attempt to address these issues was made in a pharmaco-economic evaluation of non-obstetric use of rFVIIa from New Zealand.²⁰ The authors concluded that the use of two doses of rFVIIa to control bleeding would maintain cost neutrality provided they were given relatively early in the transfusion episode (after 14 U of packed red blood cells). If cost neutrality were also associated with a reduction in hysterectomies performed, potentially this may be perceived as a benefit to treatment, though no case-controlled studies have been performed to confirm or refute this.

Given the relative rarity of severe PPH and the lack of individual experience of use of rFVIIa in this situation, a multidisciplinary group was convened (by the manufacturer) in order to consider guidelines for its use. The rFVIIa guidelines presented here are intended to be used within the context of guidelines for the management of massive blood transfusion (MBT), the details of which are beyond the scope

of this article. For further information to aid in devising protocols for MBT, the reader is referred to the Australian and New Zealand Society of Blood Transfusion/National Health and Medical Research Council Guidelines, as endorsed by Royal Australian and New Zealand College of Obstetricians and Gynaecologists and available on the internet (<http://www.anzsbt.org.au/publications/index.cfm>). We recommend that introduction of rFVIIa be overseen locally by a multidisciplinary group of clinicians with a local transfusion specialist. We suggest a local register be kept to monitor use of rFVIIa and that, in addition, clinicians should consider reporting all cases of usage to the Monash Haemostasis Registry. A management algorithm for the use of rFVIIa in obstetrics is summarised in Figure 1 for quick reference.

NovoSeven is available as a single glass vial of 1.2, 2.4 or 4.8 mg white lyophilized powder and is reconstituted with sterile water for injections. NovoSeven should be stored at 2–8 °C and should

be administered within three hours after reconstitution. NovoSeven is administered as an IVI bolus for more than three to five minutes (NovoSeven Product Information). For a guide to the dosing schedule see Appendix A.

Guidelines for the use of rFVIIa

- 1 Use of rFVIIa for PPH is off-label usage and any decision to use rFVIIa rests exclusively with the prescribing clinician.
- 2 Patients at increased risk of PPH should be identified and appropriate action should be taken to minimise this risk.
- 3 All patients should have active management of the third stage of labour.
- 4 Appropriate medical interventions should be carried out to reduce the magnitude of critical bleeding before initiating administration of rFVIIa:
 - Maintain haemodynamic stability
 - Prevent and reverse hypothermia
 - Prevent acidaemia and if bleeding is prolonged measure ionised calcium and blood gases
 - Detect unanticipated underlying maternal coagulopathy – early blood tests for FBC, PT, APTT and fibrinogen
- 5 Initial obstetric interventions should be performed including:
 - Uterotonic agents
 - Uterine massage and/or tamponade
 - Examination under anaesthesia and repair
- 6 Further management should be in consultation with the local transfusion specialist, who should be notified early of the possible need for activation of a local MBT protocol.
- 7 Appropriate surgical and/or radiological interventions should be carried out as dictated by local practice and resources including:
 - B-Lynch suture
 - Internal iliac or uterine artery ligation
 - Internal uterine tamponade (Bakri or Rusch balloon catheters)
 - Uterine artery radiological embolisation
- 8 If bleeding is persistent and not responsive to directed therapy.
 - (a) 4 U of packed red blood cells (PRBCs)
 - (b) Coagulopathy correction with 4 U of PRBCs, 4 U of fresh frozen plasma (FFP) and a single adult dose of platelets
 - (c) Repeat: PRBCs, FFP and platelets (as above) with addition of ~8 U of cryoprecipitate
 - Administer calcium as appropriate
 - Repeat cycles (b) and (c) as necessary
- 9 Once all surgical and non-surgical definitive haemostasis procedures to arrest active bleeding have been attempted and bleeding continues with between 8 and 12 U of PRBC transfusion, and prior to hysterectomy, rFVIIa (NovoSeven) could be considered:
 - 90 µg/kg (rounded to the nearest vial) of rFVIIa should be administered as a single bolus injection over three to five minutes.
 - If, after 20 min, there is no response to rFVIIa and significant bleeding is ongoing, ensure that temperature, acidaemia, serum calcium, platelets and fibrinogen have been optimized before administering a second dose of rFVIIa (90 µg/kg).
 - In centres where no resources exist to conduct arterial ligation or radiological embolisation, rFVIIa may be considered prior to these surgical interventions.
- 10 If bleeding persists after two doses of rFVIIa then consider hysterectomy.

Recombinant factor VIIa should only be used where the clinician/s considers that the benefits outweigh the risk of critical bleeding. Following administration of rFVIIa women should be monitored for signs of improvement and for adverse events. It is strongly recommended that all patients receiving off-label rFVIIa be reported to the Haemostasis Registry (Monash University):

<http://www.med.monash.edu.au/epidemiology/traumaepi/haemostasis.html>

Use in pregnancy, where women are already at a higher risk of thromboembolism, requires special consideration of the risks and benefits associated with rFVIIa. In certain pathological conditions where there is an increased thrombogenic risk, for example, amniotic fluid embolism, air embolism, septicaemia and disseminated intravascular coagulopathy (DIC), there should be heightened awareness of the risk of thromboembolism. Physical measures for venous thromboembolism (VTE) prophylaxis (pneumatic calf compression devices, thromboembolic deterrent stockings) should be instituted immediately, and pharmacological measures (prophylactic dose unfractionated or low molecular weight heparin) should be considered within 24 h of cessation of haemorrhage.

In massive haemorrhage, transfusion targets for correction of coagulopathy generally include a platelet count of $> 50 \times 10^9/L$, an aPTT of $> 1.5 \times$ upper limit of normal range, haemoglobin of $> 70 \text{ g/L}$ and fibrinogen of $> 1 \text{ g/L}$. Coagulopathy may either be caused by the underlying obstetric complication such as amniotic fluid embolism, placental abruption or caused by massive transfusion

itself. Given the physiological elevation of fibrinogen levels in pregnancy, a level of 1 g/L represents a significant degree of fibrinogen consumption. In this clinical setting one may wish to consider factor replacement (with cryoprecipitate or fibrinogen concentrate) at higher levels of fibrinogen, perhaps aiming for 1.5–2 g/L.

Disclosure/Conflict of Interest

Members of the Australian Obstetrics Clinical Advisory Board have acted as consultants to Novo Nordisk and as such have received financial remuneration for attendance at meetings to devise these guidelines. The guidelines were produced by the clinicians involved and do not directly represent the views or wishes of Novo Nordisk.

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Appendix A Recommended dosage schedule for rFVIIa

Bodyweight (kg)	Recommended dosage (mg) (~90 µ/kg)
≤ 27	2.4
28–40	3.6
41–53	4.8
54–67	6.0
68–80	7.2
81–93	8.4
94–107	9.6
108–120	10.8
121–133	12.0
134–147	13.2
148–160	14.4
161–173	15.6
174–187	16.8
188–200	18.0