

## REVIEW ARTICLE

# Recombinant factor VIIa in massive postpartum haemorrhage

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**SUMMARY.** Massive postpartum haemorrhage is a major cause of maternal and fetal morbidity and mortality. Management mainstays include transfusion therapy, uterotonic agents and surgery. The “off label” use of recombinant activated factor VII appears to have an evolving role in the management of massive postpartum haemorrhage refractory to conventional treatments. The current literature is reviewed.

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**Keywords:** Postpartum haemorrhage; Factor VIIa; Anaesthesia; Obstetrics

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## INTRODUCTION

Recombinant factor VIIa (rFVIIa) (Novoseven, Novo Nordisk A/S, Baagsvaerd, Denmark) is the activated

form of factor VII produced from factor VII cDNA transfected into hamster kidneys. It was initially introduced in 1988 for the treatment of bleeding episodes in factor VIII- and factor IX-deficient patients who failed to respond to standard replacement due to the presence of inhibitory antibodies.<sup>1</sup> Licensing has now been extended to patients with inherited deficiencies of factor VII and to those with Glanzmann's thrombasthenia who exhibit antibodies to the glycoprotein IIb/IIIa complex and are refractory to treatment.

The first case report of rFVIIa use in perioperative bleeding was in 1999.<sup>2</sup> Since then it has been more widely used for coagulopathic states associated with trauma,<sup>3</sup> abdominal surgery,<sup>4</sup> cardiac surgery,<sup>5</sup> urology,<sup>6</sup> and transplant surgery.<sup>7,8</sup> It is not licensed for use in

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perioperative haemorrhage in non-haemophilic patients, or for use in pregnancy.

Postpartum haemorrhage (PPH) is a major cause of maternal and fetal morbidity and mortality in both developed and developing countries. Life-threatening haemorrhage has been estimated to occur in 1 per 1000 deliveries,<sup>9,10</sup> and it is estimated that 125000 women die worldwide from PPH each year.<sup>11</sup> Mainstays of management of major PPH include effective transfusion therapy, uterotonic agents and surgery.<sup>12,13</sup> Several case reports now document out of licence or *off label* use of rFVIIa in severe PPH where conventional treatment methods were ineffective.<sup>14–21</sup>

This review is based on the current available literature on rFVIIa and its use in PPH. Some valuable points on the use of rFVIIa can be deduced from the more extensive data in other areas of surgery.

## MECHANISM OF ACTION

rFVIIa is a 50kD analogue of the naturally occurring serine protease factor VIIa which usually comprises less than 1% of the total circulating factor VII in plasma. Factor VII has a fundamental role in the initiation of coagulation following vascular injury. Following vessel injury, rFVIIa binds to tissue factor expressed on extravascular cells to form a tissue factor:VIIa complex (Fig. 1). This complex subsequently activates factors IX and X to IXa and Xa respectively, ultimately enhancing thrombin generation. Positive feedback also occurs when locally generated factors VIIa, IXa and Xa activate additional factor VII.

rFVIIa is identical in structure and basic function to human VIIa. The precise mechanism of action is controversial but most recent evidence indicates that rFVIIa works as the normal tissue factor, and can bind

weakly to the surface of activated platelets; it may also inhibit fibrinolysis through activation of thrombin-activatable fibrinolytic inhibitor.<sup>22</sup> In addition to tissue-factor-dependent activity, rFVIIa also has tissue-factor-independent activity in that it directly activates factor X on platelet surfaces in a dose-dependent manner. This effect is observed only at higher doses than occur naturally.<sup>2</sup> It is also clear that coagulation is activated by rFVIIa only at the site of tissue factor expression and is localised to the site of vascular injury. In vitro studies have shown that compared with normal clots, the fibrin clots formed in the presence of high thrombin concentration have a different architecture that is stronger and more resistant to degradation by fibrinolytic enzymes.<sup>23–25</sup>

## RFVIIA IN NON-OBSTETRIC HAEMORRHAGE

There is an increasing body of evidence to support the use of rFVIIa in the treatment of severe haemorrhage; this has been reviewed elsewhere.<sup>26</sup> It has been shown to reduce blood-product requirement in a variety of clinical circumstances, such as in liver and cardiac surgery, vascular surgery, neurosurgery, trauma and other causes of acquired coagulopathy. A large recent audit in cardiac surgery patients revealed a significant reduction in the use of all types of blood products after rFVIIa administration. Median use of packed red cells, platelets, fresh frozen plasma (FFP) and cryoprecipitate fell from 4, 15, 8 and 10 units respectively before rFVIIa use, to 1, 0, 0 and 0 units after administration of rFVIIa.<sup>27</sup> A significant blood-sparing effect has been demonstrated in a multicentre, randomised, placebo-controlled double-blind trial in trauma, although there was no improvement in mortality.<sup>28</sup>

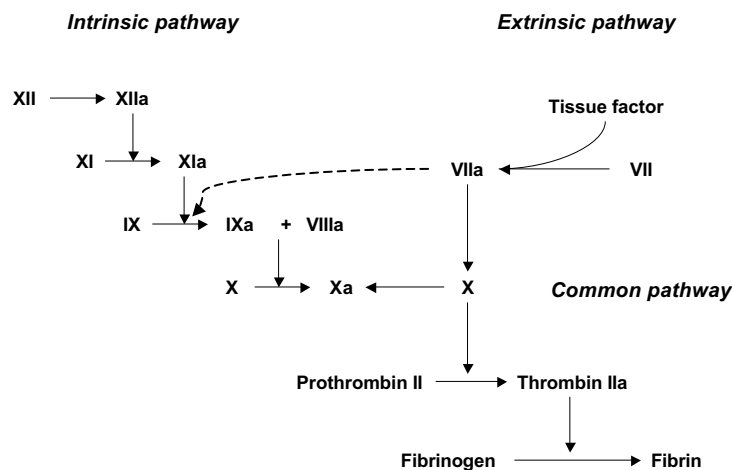


Fig. 1 Mechanism of action of factor VIIa in the clotting cascade.

The later rFVIIa is given, the more blood products will have been given before its use,<sup>27</sup> hence the timely use of rFVIIa for bleeding resistant to conventional therapy may prevent the need for massive transfusion and therefore reduce morbidity and mortality. One study of 50 medical and surgical patients found that rFVIIa was more effective in mild to moderate coagulopathy than in severe coagulopathy, and it was therefore suggested that rFVIIa should be administered promptly, rather than as a last ditch option.<sup>29</sup>

## RFXVIA IN OBSTETRIC HAEMORRHAGE

Massive PPH is a major cause of maternal morbidity and mortality. Life threatening PPH occurs with a frequency of 1 per 1000 deliveries. In the 1994-1996 triennial confidential enquiry into maternal deaths in the United Kingdom was responsible for five deaths,<sup>9</sup> and in the 2000-2002 report ten death.<sup>10</sup> It may occur due to uterine atony, placenta praevia or accreta, uterine rupture, birth canal injury or amniotic fluid embolism. Management involves long established surgical measures such as iliac artery ligation and subtotal or total hysterectomy, and newer, less radical measures that may preserve reproductive function, such as angiographic embolization, uterine compression sutures and methods involving uterine tamponade. These should be used in conjunction with restoration of blood volume, appropriate use of blood products and uterotonic agents. Recent case reports suggest that rFVIIa at a dose of 90-100 µg/kg has a role as a haemostatic agent in obstetric haemorrhage uncontrolled by conventional therapy even in the presence of disseminated intravascular coagulation.<sup>15,16,20</sup> However because of its off-label use the current appropriate dosing in acute bleeding is unknown. Repeat doses can be administered every 2 h. The number of repeated doses for acute haemorrhage in patients without haemophilia has ranged from one to 18 with a single dose being typical.

### Reducing the need for blood products

rFVIIa is being used more frequently to reduce the need for blood products in obstetric haemorrhage. Analysis of the largest case series to date in obstetric haemorrhage by Ahonen and Jokela revealed a trend to reduced median blood product use of packed red cells, FFP and platelets of 16, 5, 9 units prior to rFVIIa, and 3, 1 and 8 units after rFVIIa respectively.<sup>14</sup> Whilst the cost of factor VIIa has been a major discouragement to its use, this study estimated that a single dose of rFVIIa was similar to the cost of transfusion with 50 units of red cells, an embolization procedure or ICU treatment for 2 days, and thus could be considered cost effective. The cost

in Australia has previously been estimated at A\$6000 (£2400, €3600, US\$4500) per dose for a 70-kg patient.<sup>30</sup>

The use of rFVIIa in massive obstetric haemorrhage does not obviate the need for careful attention to replacement of deficient coagulation factors, red cells, fibrinogen and platelets. British<sup>31</sup> and Israeli<sup>32</sup> guidelines suggest maintenance of a platelet count of greater than  $50 \times 10^9/L$  and fibrinogen concentration greater than 1 g/L. Administration of adequate coagulation factors ensures that, when factor VIIa is given, there will be sufficient circulating levels of platelets and coagulation factors to act as a substrate for optimal rFVIIa effect.<sup>33,34</sup> Avoidance of hypothermia and acidaemia are also crucial for optimal rFVIIa activity. Current evidence indicates that a fall in temperature from 37°C to 33°C reduced rFVIIa activity by 20%, whilst a fall in pH from 7.4 to 7.0 reduced rFVIIa activity by 90%, and reduced factor VII:tissue factor complex by 60%.<sup>35</sup> Failure of rFVIIa to stop bleeding could also be anticipated in the presence of an inhibitor of the final clotting pathway, such as in the presence of an antibody or chemical inhibitor of factor X, V or thrombin.<sup>26</sup> Encountering this situation in clinical anaesthetic practice is unlikely, but such agents are being developed as anticoagulants: melagatran is a direct inhibitor of factor Xa and thrombin, while heparin and idraparinux are antithrombin-dependent inhibitors.

### Resistance to rFVIIa

A small proportion of patients, possibly as many as 7% in some patient groups, fails to respond to rFVIIa.<sup>27</sup> In a recent case series of 12 obstetric patients receiving rFVIIa for PPH, one patient was considered a non-responder and five patients partial responders; however, three of these partial responders received doses considerably lower than the suggested 90-100 µg/kg.<sup>14</sup> Variations in dose requirements for rFVIIa have been demonstrated in patients with haemophilia,<sup>36</sup> and it is also possible that some haemostatic lesions may be resistant to rFVIIa irrespective of the dose used. Poor response to rFVIIa may indicate unrecognised surgical bleeding, inadequate dosage of rFVIIa, or temperature and acid-base abnormalities.

### Timing of its use

Audit data in trauma and cardiac surgery indicate a trend towards earlier use of rFVIIa in bleeding episodes as experience with the drug increases,<sup>27</sup> and suggest a learning curve for both anaesthetists and surgeons. A similar result was seen in a recent case series of rFVIIa use in obstetric haemorrhage; in the first half of the audit, the average use of blood products before the use of rFVIIa was 67.6 units, but only 37.2 units in the second half of the audit, indicating that rFVIIa was being

administered earlier in the bleeding episode.<sup>14</sup> It has been suggested that rFVIIa should be considered when blood loss exceeds 1.5 maternal blood volumes,<sup>14</sup> and although protocols have been developed in other surgical areas in situations where conventional blood replacement therapy has failed,<sup>27</sup> evidence for timing of administration is limited in obstetric haemorrhage.

### Modifying surgical management

The potential role of rFVIIa in the modification of surgical management of major PPH is also worth consideration. Angiographic embolization and hysterectomy are both accepted therapies in major PPH. Angiographic embolization is an effective and safe procedure for obstetric haemorrhage unresponsive to conservative treatment,<sup>37</sup> and since fertility is maintained, it may be the management of choice. However, the major limitation is access to interventional radiology and, in Melbourne, Australia, two of the three tertiary obstetric centres do not have interventional radiology on site. Experience suggests that it is difficult to assess when to administer rFVIIa and when to proceed directly to angiographic embolization; the indications are still to be determined. In cases of diffuse bleeding refractory to transfusion therapy and uterotonic agents, rFVIIa use would seem appropriate, but in the event of a more localised bleeding site it would seem appropriate to proceed to angiography and embolization. In a recent case series of rFVIIa in obstetric haemorrhage, five of the 12 patients underwent embolization after rFVIIa use; in four of these patients bleeding was significantly reduced but not completely stopped before angiographic embolization.<sup>14</sup> Given that many obstetric hospitals do not have on-site interventional radiology, the use of rFVIIa may allow additional time to transfer the patient to a hospital where such facilities exist. Cases of its use for this reason have already been described.<sup>18</sup>

Where the bleeding point is in the lower uterine segment, subtotal or total hysterectomy is considered the management of last resort,<sup>38</sup> and is a feared outcome due to loss of fertility. In two recent case series a proportion of the patients underwent hysterectomy before administration of rFVIIa,<sup>14,18,39</sup> but now case reports have indicated that the use of rFVIIa may have prevented the need for hysterectomy.<sup>15,39</sup> A role for rFVIIa before proceeding to hysterectomy has been proposed.<sup>40</sup> Due to the rapid onset of action of rFVIIa, it may be suitable to administer it, wait and observe the effect before proceeding to hysterectomy.

### Use in uterine atony

Uterine atony is the most common cause of PPH and one of the main reasons for hysterectomy. rFVIIa has no ef-

fect on uterine tone but its use with uterotonic agents may interrupt the cycle of uterine atony and bleeding that characterises failure of conservative therapy. Such a strategy was used successfully in a case where rFVIIa was used in conjunction with a sulprostone infusion (a metabolism-resistant analogue of PGE<sub>2</sub>) into the uterine cavity which led to rapid resolution of bleeding.<sup>14</sup>

### Use after surgery

Postoperative management of major PPH often requires a period of intensive care management. There are several case reports of successful use of rFVIIa in the intensive care unit following massive PPH after primary or secondary surgery that has not revealed a surgical bleeding point. The use of rFVIIa in these cases led to rapid resolution of surgical drain output, avoided the need for return to the operating room for re-exploration and significantly reduced blood product usage.<sup>19,21,39</sup>

### Jehovah's Witnesses

rFVIIa has been used in the management of haemorrhage in Jehovah's Witnesses, but indications for its use are unclear, and to our knowledge there are no reports of cases involving PPH. However, since it is a synthetic agent, its use does not contravene the beliefs of Jehovah's Witnesses, and it may therefore become incorporated into the management plan for these patients.<sup>41</sup>

### SAFETY

rFVIIa is prepared without the use of blood products or human proteins;<sup>30</sup> since it uses recombinant technology there should be no risk of viral transmission during the manufacturing process. Adverse effects from studies in haemophilia patients include minor complaints such as fever, headache, vomiting and skin hypersensitivity reactions.

Thrombosis, including deep venous thrombosis, pulmonary embolism, myocardial infarction and peripheral arterial thrombosis have all been described.<sup>42-44</sup> The estimated incidence is less than 1% in studies of patients with haemophilia.<sup>44</sup> There is, however, no current information on safety in pregnancy and only limited data from non-haemophiliac patients. Only recently, thrombotic complications of rFVIIa treatment have been described in bleeding patients.<sup>42,45,46</sup> Aledort calculated the risk of thromboses to be 25 per 100 000 infusions.<sup>47</sup> In published placebo-controlled studies the risk was not significantly different between patient and control groups. There are currently no data on the incidence of thrombotic complications with rFVIIa in obstetric patients.

## CURRENT USAGE

To our knowledge there are currently no guidelines for the use of rFVIIa in obstetric haemorrhage, although proposals for guidelines are starting to appear.<sup>46</sup> At our institution the decision to use it is made on the advice of a haematologist; given the paucity of strong evidence for its use in obstetric haemorrhage, this can place the haematologist in a difficult position. To clarify the current indications, we are in the process of establishing a nationwide audit of use in Australia that will initially examine its use over the past year, and later run prospectively. It is hoped that this will provide some evidence for the formulation of usage guidelines.

## CONCLUSION

Recombinant factor VIIa appears to have an evolving role in the management of severe PPH refractory to conventional treatment. Randomised controlled trials are unlikely to be possible in this patient group and, although multiple case reports and case series indicate potential benefit in blood product sparing, published reports represent only level 3 and 4 evidence (NICE guidelines). The drug does not obviate the need for appropriate transfusion of red cells, coagulation factors and platelets and maintenance of normothermia and acid-base balance. There may be limitations to its use, including limited information about safety when used in obstetric patients, cost and non-response in a minority of patients.

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