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*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.


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



## 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.[1] 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.[2] Since then it has been more widely used for coagulopathic states associated with trauma,[3] abdominal surgery,[4] cardiac surgery,[5] urology,[6] and transplant surgery.[7,8] 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,[9,10] and it is estimated that 125000 women die worldwide from PPH each year.[11] Mainstays of management of major PPH include effective transfusion therapy, uterotonic agents and surgery.[12,13] Several case reports now document out of licence or *off label* use of rFVIIa in severe PPH where conventional treatment methods were ineffective.[14–21]

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.[22] 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.[2] 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.[23–25]

## 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.[26] 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.[27] 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.[28]

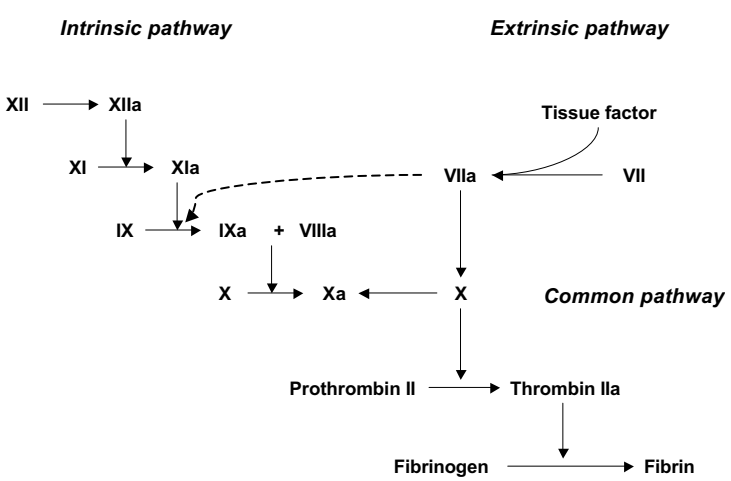


**Fig. 1** Mechanism of action of factor VIIa in the clotting cascade.