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Activated factor VII proves to be a lifesaver in postpartum hemorrhage

A patient bleeding to death following delivery is every OB's greatest fear

FAST TRACK

There's strong evidence from dozens of cases: rF-VIIa works well in severe postpartum hemorrhage when other interventions fall short

Obstetricians train relentlessly to respond to severe postpartum hemorrhage in a systematic manner by sequentially intervening with tocolytics, massive transfusion of blood products, surgical procedures (including hysterectomy and pelvic packing[1]), and consultation with interventional radiologists, if available (**TABLE**). Even with optimal therapy, however, postpartum hemorrhage remains a major cause of maternal death throughout the world.[2]

Evidence is growing that recombinant activated clotting factor VII (or rF-VIIa) is a potentially life-saving treatment for women with severe postpartum hemorrhage who are not responding to standard interventions. How does this agent work in such cases?

The coagulation cascade is complex. An abbreviated version reveals the therapeutic role that exogenous rF-VIIa may play:

1. **F-VII binds to tissue factor (TF)** that has been exposed on damaged blood vessels and other cells, resulting in activation of the protease function of F-VII
2. The TF–F-VIIa complex directly **activates F-IX and F-X**
3. This activation accelerates the conversion of **prothrombin to thrombin** and, in turn, of **fibrinogen to fibrin**
4. The enzymatic process is markedly enhanced by the action of **platelet membranes.**

In massive trauma or severe postpartum hemorrhage, exogenous rF-VIIa may enhance complexing of TF and F-VIIa on damaged cells, thereby accelerating clotting locally and reducing the magnitude of blood loss.

Evidence of efficacy

rF-VIIa (NovoSeven [Novo Nordisk]) has been approved by the FDA for treating bleeding in (a) patients with hemophilia who have antibodies to F-VIII and F-IX and (b) patients with F-VII deficiency. rF-VIIa is not approved for treating bleeding associated with major trauma or postpartum hemorrhage. However:

- There are dozens of case reports of patients bleeding to death from severe trauma who apparently have had their life saved by rF-VIIa[3]
- One large clinical trial indicates that rF-VIIa is beneficial for hemorrhage caused by trauma.[4]

In that clinical trial, 301 patients with severe trauma who had received at least 8 units of red blood cells (RBCs) were randomized to standard surgical care plus intravenous injection of placebo or to standard surgical care plus injection of rF-VIIa. Three doses of rF-VIIa were administered: 200 µg/kg after the initial 8 units of RBCs were transfused, 100 µg/kg 1 hour later, and 100 µg/kg 3 hours later. Compared with subjects given placebo injection, those

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TABLE

At your disposal, a range of interventions for obstetric hemorrhage

PHARMACOTHERAPY	
Carboprost	Oxytocin
Methergine	Vasopressin
Misoprostol	Recombinant human factor VIIa*
BLOOD BANKING	
Cryoprecipitate	Platelets
Fresh-frozen plasma	Red blood cells
SURGERY	
Repair of lacerations	Ligation of the hypogastric artery
B-Lynch suture	Other uterine compression sutures
Hysterectomy, supracervical	Pelvic packing
Hysterectomy, total	Pelvic tourniquet
NONSURGICAL PROCEDURES	
Bakri balloon	Uterine packing
Uterine balloon tamponade	
INTERVENTIONAL RADIOLOGY	
Uterine artery balloons	Uterine embolization
CONSULTATION	
Anesthesiologist–intensivist	Trauma surgeon
Gynecologic oncologist	Urologist
Interventional radiologist	

*Not approved by the FDA for this indication.

who received rF-VIIa had fewer transfusions and lower rates of massive transfusion (>12 units), acute respiratory distress syndrome, and multiorgan failure.

In patients with blunt trauma, the percentage of subjects who received more than 12 units of RBCs declined from 33% in the placebo group to 14% in the group treated with rF-VIIa. Overall mortality, however, was not significantly reduced by rF-VIIa. Of note, an equal number of thromboembolic events occurred in the group treated with rF-VIIa and the group treated with placebo. (The trial was supported by the manufacturer of rF-VIIa.[4])

Strong case evidence in ObGyn but no rigorous trials

Dozens of cases have been reported of women with massive postpartum hemorrhage who apparently had their life saved by rF-VIIa.[5–9] rF-VIIa has also been used successfully in severe hemorrhage following gynecologic surgery[10] and after amniotic fluid embolism with coagulopathy.[11]

Regrettably, there are no randomized trials of rF-VIIa in obstetrics to guide your clinical action. In the series cited most often, rF-VIIa was administered after available standard surgical procedures for severe postpartum hemorrhage were used and transfusion had reached the 8- to 30-unit range. This indicates that, in most series, only the most severe cases of postpartum hemorrhage were treated with rF-VIIa. The dose of rF-VIIa in these reports was, typically, in the range of 40 to 120 µg/kg.

An option after others fail

Based on a review of the literature, I propose the following approach to severe postpartum hemorrhage with rF-VIIa when other modalities prove insufficient:

- Start with a dosage of 40 µg of rF-VIIa/kg of body weight to balance the benefit of hemostasis against the risk of harmful thromboembolic events
- Because rF-VIIa has a circulating half-life of approximately 2 hours, consider a second dose of rF-VIIa, as was given in many of the reported cases of postpartum hemorrhage.

Note that, before rF-VIIa was administered in most series, standard surgical intervention had included hysterectomy. In 1 report of 4 cases, however, rF-VIIa was used successfully for postpartum hemorrhage after uterine tamponade had failed but before hysterectomy was performed.[12]

In another series, 11 of 12 patients with massive postpartum hemorrhage responded to rF-VIIa treatment.[13] This report, as well as others, indicates that, first, not all women respond to rF-VIIa treatment and, second, a multimodal approach, including surgery and interventional radiology, is critical to maximizing the success rate.

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What about risks to women of child-bearing age?

- **Thromboembolic events.** There is concern that treatment with rF-VIIa may be associated with intravascular clotting, leading to clinical syndromes of stroke and myocardial infarction. The FDA has issued a warning to clinicians of an increased risk of thromboembolic events with rF-VIIa—specifically, in elderly persons with intracerebral hemorrhage. In persons with atherosclerotic disease, damaged blood vessels may increase the amount of exposed TF; this raises the likelihood that rF-VIIa will bind to cells in the atherosclerotic plaque, triggering the coagulation cascade locally and causing a thrombotic event. It is estimated that the risk of these adverse outcomes is in the range of 25 events for every 100,000 infusions of rF-VIIa.[14]
- **Protection of age?** In young women with massive postpartum hemorrhage, the risk of thrombosis in association with rF-VIIa is likely to be somewhat lower than it is in elderly patients who have preexisting atherosclerotic vascular disease.
- **Cost is a secondary concern.** rF-VIIa is expensive—about $1,400/g—and so should be used judiciously.

Add rF-VIIa to your toolkit

In 2004, the Joint Commission on the Accreditation of Healthcare Organizations recommended that obstetric services practice their response to common obstetric emergencies such as postpartum hemorrhage. Many medical, surgical, and radiologic interventions are available to the ObGyn for postpartum hemorrhage (**TABLE**), and rF-VIIa is an important addition to our armamentarium. Use of this agent in obstetrics is likely to expand significantly; it's to be hoped that, with a multimodal approach to obstetric hemorrhage,[15] we can reduce the maternal death rate from this common problem.

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