

# A Critical Review on the Use of Recombinant Factor VIIa in Life-Threatening Obstetric Postpartum Hemorrhage

Massimo Franchini, M.D.,<sup>1</sup> Massimo Franchi, M.D.,<sup>2</sup> Valentino Bergamini, M.D.,<sup>2</sup> Gian Luca Salvagno, M.D.,<sup>3</sup> Martina Montagnana, M.D.,<sup>3</sup> and Giuseppe Lippi, M.D.<sup>3</sup>

## ABSTRACT

The objective of this review was to evaluate and summarize the current literature on the unlicensed use of the novel agent recombinant activated factor VII (rFVIIa) in the management of major postpartum hemorrhage. After a systematic electronic search without temporal limits on MEDLINE, EMBASE, OVID and SCOPUS, the bibliographic references of all retrieved studies and reviews were additionally assessed for further reports of clinical trials. Unpublished works were also identified by searching abstracts from the most eminent conferences on this topic. In total, there were 31 studies that fulfilled our inclusion criteria. These studies incorporated 118 cases of massive postpartum hemorrhage treated with rFVIIa. The median age of the patients was 31.4 years, and cesarean section appeared to increase the risk of postpartum hemorrhage. At a median dose of 71.6 µg/kg, rFVIIa was reported to be effective in stopping or reducing bleeding in nearly 90% of the reported cases. Based on the evidence from the literature, we give some recommendations on the use of rFVIIa in massive postpartum hemorrhage. Nevertheless, although these reports suggest the potential role of rFVIIa in treating massive postpartum hemorrhage refractory to standard therapy, we advise particular caution in interpreting these results, as they are derived from few and uncontrolled studies. Further evidence is needed using well-designed clinical trials to better assess the optimal dose, the effectiveness, and the safety of rFVIIa in such critical bleeding conditions.

**KEYWORDS:** Postpartum hemorrhage, obstetrics, gynecology, bleeding, rFVIIa

Bleeding remains a major cause of morbidity and mortality in obstetrics and gynecology. In particular, postpartum hemorrhage (PPH), which is defined as hemorrhage occurring within 24 hours of delivery, is one of the most difficult challenges for obstetricians and gynecologists everywhere.<sup>1,2</sup> In 2000, the World

Health Organization (WHO) estimated that ~125,000 women died worldwide from postpartum hemorrhage and its sequelae alone. This problem was greatest in developing countries, where the maternal mortality rate from PPH approached 1 in 1000 deliveries. In contrast, in developed countries, the maternal

<sup>1</sup>Servizio di Immunoematologia e Trasfusione – Centro Emofilia, Azienda Ospedaliera di Verona, Verona; Italy; <sup>2</sup>Dipartimento Materno Infantile e di Biologia-Genetica, Sezione di Ginecologia e Ostetricia, Università di Verona, Verona; Italy; <sup>3</sup>Istituto di Chimica e Microscopia Clinica, Dipartimento di Scienze Biomediche e Morfologiche, Università di Verona, Verona; Italy.

Address for correspondence and reprint requests: Massimo Franchini, M.D., Servizio di Immunoematologia e Trasfusione – Centro Emofilia, Ospedale Policlinico, Piazzale L. Scuro, 10 - 37134 Verona,

Italy (e-mail: massimo.franchini@azosp.vr.it).

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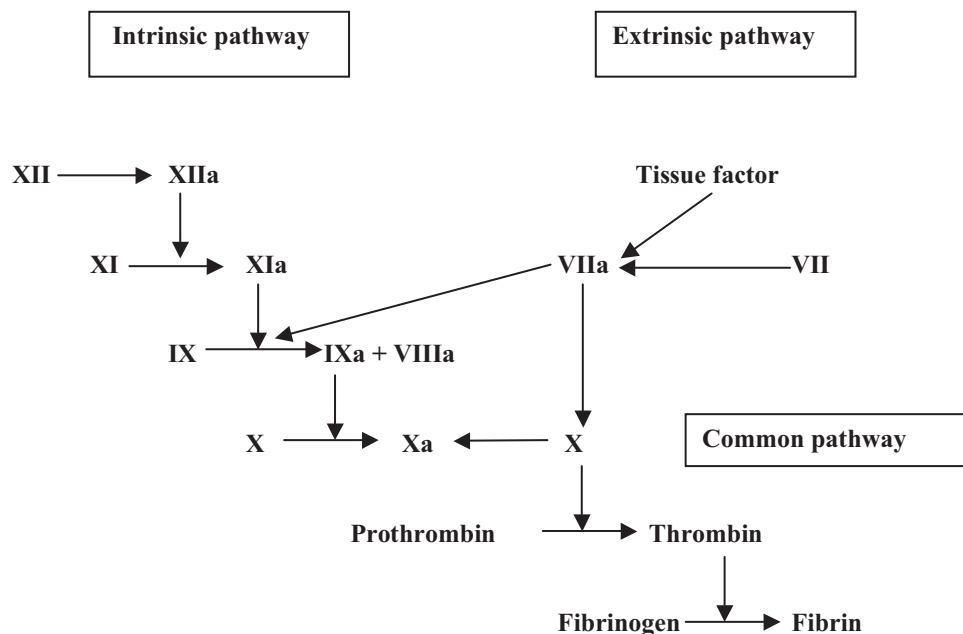
death rate from PPH was 1 in 100,000 deliveries.<sup>3</sup> In the 1997–1999 triennial confidential enquiry into maternal deaths in the United Kingdom, PPH was found to be responsible for 7 deaths, and in the 2000–2002 report it was responsible for 17 deaths.<sup>4</sup> The management of severe PPH is very complex and involves many specialists, including anesthesiologists, interventional radiologists, trauma surgeons, urologists, hematologists, and laboratory technicians.

The first-line standard treatment of massive PPH includes measures directed at improving uterine tone, replacement of lost intravascular volume, blood, and coagulation factors, and surgery (Table 1).<sup>5,6</sup> The latter includes repair of the genital tract, removal of retained products of conception, and strategies to stop bleeding from the placental bed by physical means.<sup>7,8</sup> Arterial embolization may be effective in achieving hemostasis in cases of genital tract trauma (~20%), when surgical control has failed or else is technically difficult. Surgical compression suture techniques exerting a mechanical compression of uterine vascular sinus, such as B-Lynch and Hayman techniques,<sup>9,10</sup> have also been recently introduced with success. Nevertheless, in spite of these conservative procedures, hysterectomy is sometimes necessary to control bleeding.<sup>11</sup>

Recently, recombinant activated factor VII (rFVIIa; Eptacog alfa, NovoSeven; Novo Nordisk, Baagsvaerd, Denmark), a drug originally developed for the treatment of hemophiliacs with inhibitors, has been explored as an adjuvant therapy for hemorrhage control

**Table 1 Current Treatment of Obstetric Hemorrhage**

Pharmacotherapy
Carboprost
Methergine
Misoprostol
Sulprostone
Oxytocin
Vasopressin
rFVIIa (not approved)
Blood banking
Red blood cells
Fresh-frozen plasma
Cryoprecipitate
Fibrinogen
Platelets
Surgery
Repair of lacerations
B-Lynch suture
Hysterectomy (subtotal or total)
Ligation of hypogastric or uterine arteries
Other uterine compression sutures
Pelvic packing
Pelvic tourniquet
Nonsurgical procedures
Uterine balloon tamponade
Uterine packing
Interventional radiology
Uterine artery balloons
Angiographic embolization



**Figure 1** Mechanisms of action of recombinant activated factor VII (rFVIIa). After vessel injury, rFVIIa binds to tissue factor expressed on extravascular cells to form a tissue factor:FVIIa complex. This complex subsequently activates factors IX and X to IXa and Xa, respectively, ultimately enhancing thrombin generation. 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. Coagulation is activated by rFVIIa only at the site of tissue factor expression and is localized to the site of vascular injury.

in various nonhemophilic bleeding situations, including obstetrics and gynecology.<sup>12-16</sup> The direct activation of the common pathway of the coagulation cascade by rFVIIa at sites of vascular injury constitutes the rationale for its use in this clinical setting (Fig. 1).<sup>17</sup> The current knowledge regarding the use of rFVIIa in PPH is critically analyzed in this review.

### LITERATURE SOURCES

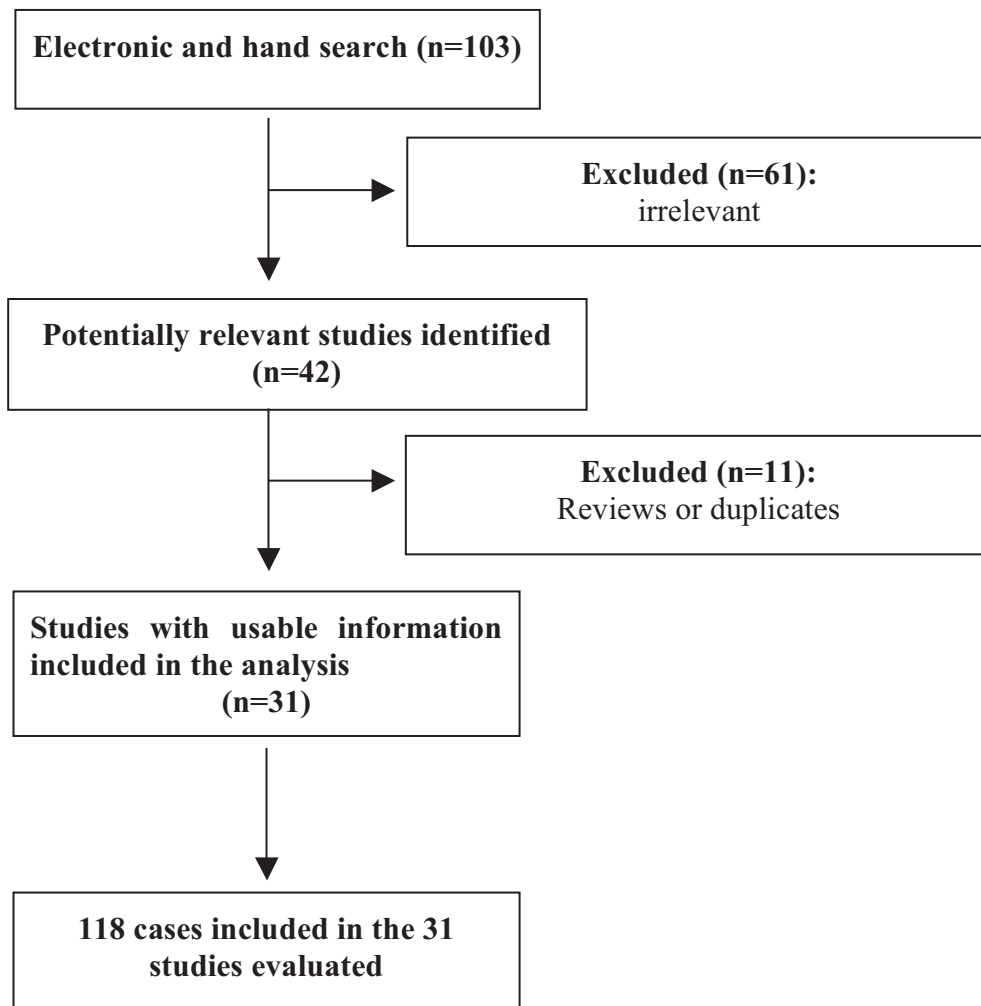
In this systematic review, we first performed an electronic search on PPH and rFVIIa in MEDLINE, EMBASE, SCOPUS, and OVID without temporal limits on the use of rFVIIa in PPH, and using different combinations of the following keywords: "post-partum hemorrhage," "obstetric," "pregnancy," "PPH," "bleeding," "recombinant activated factor VII," "rFVIIa," "NovoSeven," "Eptacog alfa." The bibliographic references of all retrieved studies and reviews were then assessed for additional reports of clinical trials. Unpublished works were subsequently identified by searching the abstract books of the most

important conferences on obstetric and hematologic diseases.

In total, we identified 103 references through these searches. After reading the full text of the retrieved articles, we excluded 61 irrelevant references and retained 42 references for further extensive assessment. A further 11 studies were later excluded because they were reviews or duplicated data from other included studies. Thus, we have included in this review 31 studies,<sup>18-48</sup> with information on 118 PPH patients. Figure 2 shows the flowchart of inclusion studies. All the studies included were uncontrolled.

### REVIEW OF THE LITERATURE DATA

The first case report of successful treatment of intractable obstetric hemorrhage in a nonhemophilic patient using rFVIIa was published by Moscardo and colleagues in 2001,<sup>18</sup> who reported that rFVIIa successfully controlled life-threatening PPH after caesarean section in a woman who developed severe disseminated intravascular



**Figure 2** Flowchart of inclusion studies.

coagulopathy (DIC), liver dysfunction, and renal failure. Breborovicz and colleagues<sup>20</sup> reported seven cases of peripartum hemorrhage treated with rFVIIa. Six women underwent caesarean section for different indications, and one woman delivered vaginally. In five cases, rFVIIa was administered only after emergency hysterectomy, whereas in the remaining two cases the drug was effective in avoiding the need for hysterectomy. In all but one case, a single relatively low dose of rFVIIa (range, 16.7 to 48  $\mu\text{g}/\text{kg}$ ) was effective in controlling bleeding. Thanchev and colleagues<sup>37</sup> collected four cases of severe bleeding associated with uterine atony in the postplacental period, successfully treated in all cases with rFVIIa. An additional four cases positively managed with rFVIIa were recently reported by Haynes and colleagues.<sup>46</sup> Segal and colleagues<sup>28,29</sup> reported 10 women successfully treated during 2000–2003 for severe obstetric hemorrhage with one or two doses of 60 to 100  $\mu\text{g}/\text{kg}$  rFVIIa. Sobieszczyk and colleagues<sup>44</sup> published a large case series including 25 PPH cases from an international Internet-based registry. rFVIIa stopped or decreased the obstetric bleeding in all but one patient. Ahonen and colleagues<sup>34</sup> presented 12 cases of severe PPH treated with rFVIIa in addition to standard surgical and medical interventions and found a good response in 11 of them. Interestingly, the authors recorded a learning curve in the use of rFVIIa for surgeons and anesthetists: indeed in the first part of the study, the average use of blood products before the use of rFVIIa was 67.6 units, but this fell to only 37.2 units in the second part of the study, indicating that rFVIIa was being administered earlier in the bleeding episode. The same authors successively published an open, non-randomized study collecting the largest experience (26 cases) on the use of rFVIIa for PPH, with a good or moderate response in two thirds of cases.<sup>48</sup> In this report, the authors also proposed a guideline on the use of rFVIIa in PPH, which suggested that in cases of intractable PPH with no other obvious indications for hysterectomy, administration of rFVIIa should be considered before surgery.

Table 2 summarizes the literature data on the use of rFVIIa in PPH. The median age of the 118 patients enrolled in the 31 studies was 31.4 years. Cesarean section appeared to increase the risk of onset of PPH as, among the 108 deliveries evaluated, 46 (42.6%) were by vaginal route and 62 (57.4%) by cesarean section. Conditions predisposing/worsening obstetric hemorrhage were, in order of frequency, uterine atony (33 of 118 cases, 28.0%), uterine or vaginal lacerations (22 of 118 cases, 18.6%), placenta abnormalities (17 of 118 cases, 14.1%), retained placenta (5 of 118 cases, 4.2%), and uterine bleeding (3 of 118 cases, 2.5%). In 23 cases (19.5%), PPH was complicated by a systemic activation of coagulation resembling DIC. These results are in line with those previously published in the literature.<sup>49,50</sup>

In all cases, transfusion of blood components was performed as the first-line treatment to restore oxygen-carrying capacity (red blood cells) and physiologic hemostasis (fresh-frozen plasma and platelets). As shown in Table 2, in the great majority of the PPH patients, rFVIIa was used in addition to standard medical (i.e., uterotonic drugs) and surgical (hysterectomy was necessary in approximately half of the cases) hemostatic interventions. However, when rFVIIa was used before hysterectomy, it was often able to avoid this invasive surgical procedure, thus sparing reproductive function. At a median dose of 71.6  $\mu\text{g}/\text{kg}$  (range, 10 to 170  $\mu\text{g}/\text{kg}$ ), the drug was reported to be effective in stopping or reducing bleeding in nearly 90% of all the PPH cases. Poor response to rFVIIa was mainly attributed to inadequate dosages, unrecognized surgical bleeding, and severe metabolic abnormalities.<sup>51</sup> However, we advise particular caution in overinterpreting these positive results, due to the potentially serious bias resulting from the likelihood that successful cases are more likely to be reported. The median number of doses administered was 1.6 (range, 1 to 19) with a single dose being typical.

#### RECOMMENDATIONS ON THE USE OF rFVIIa IN MASSIVE PPH

Evidence is growing that rFVIIa is a potentially life-saving treatment for women with severe PPH who do not respond to standard interventions. For this reason, NovoSeven is currently recommended by the Italian Ministry of Health for the treatment of PPH in patients unresponsive to standard obstetric management, oxytocic drugs, and standard blood component therapy prior to major invasive therapy.<sup>52</sup>

Although some expert panels have attempted to provide clinical guidelines,<sup>7,53</sup> no definitive recommendations can be prepared regarding the use of rFVIIa in PPH because of the lack of randomized controlled trials. Thus, the decision regarding when to use rFVIIa is still based on personal experiences and/or accounts from other medical specialties. However, from our personal experience, supplemented by this literature review, we provide the following suggested indications regarding dosages, timing, and safety of rFVIIa in PPH.

Although the dose of rFVIIa used varied greatly from study to study, with a range between 10 and 170  $\mu\text{g}/\text{kg}$ , most authors used 90  $\mu\text{g}/\text{kg}$ . However, this dosage was derived from the licensed indication in congenital hemophiliacs with inhibitors rather than from previous controlled trials in PPH patients. Thus, it is reasonable to believe that lower doses could be equally effective, additionally considering the literature data on the use of rFVIIa in life-threatening hemorrhages in patients without preexisting coagulopathies.<sup>15</sup> Furthermore, lower doses could reduce the incidence of drug-related adverse effects. In regard to the number of

Table 2 The Use of rFVIIa in PPH: Results of the Literature

Study (First author)	Patients	Age (y)*	Diagnosis	Delivery	Hemostatic Treatments†		rFVIIa (µg/kg)*		Response ‡,§
					Medical	Surgical	Initial Dose	No. of Doses	
Moscardo <sup>18</sup>	1	33	1 DIC-LF-RF	1 CS	1 At III	1 Hys-Lap	90	9	1
Brueckner <sup>19</sup>	1	31	1 At-HELLP	1 CS	NR	1 Hys-Lap	NR	NR	0 <sup>¶</sup>
Breborowicz, <sup>20</sup> Sobieszcyk <sup>21</sup>	7	33.9 (26–44)	4 At, 1 PA-DIC, 1 Lac-DIC	6 CS, 1 VD	1 EML-PMDFBG, 3 NR	3 Hys-Lap	24.5 (16.7–48)	1	6/7 (85.7)
Zupancic, <sup>22</sup> Sokolic <sup>23</sup>	1	31	1 IOP-DIC 1 DIC-HELLP	1 CS	2 PG-OTC, 1 PG-OTC-TP NR	1 Hys, 3 None None	90	1	1
Bouwmeester <sup>24</sup>	1	30	1 At-DIC	1 VD	1 OTC-TA-PG	1 Hys-IIAL	60	2	1
Kretzschmar <sup>25</sup>	1	35	1 AFE-DIC	1 CS	1 OTC-APT-PG	1 Hys	60	1	0 <sup>5</sup>
Dart <sup>26</sup>	1	24	1 HELLP-HR-IACS	1 VD	None	None	90	1	1
Boehlen <sup>27</sup>	1	31	1 At-DIC	1 VD	1 OTC-TA-PG	1 Hys	120	19	1
Segal <sup>28,29</sup>	10	NR	3 PA, 2 At, 4 Lac, 1 UM	NR	NR	6 Hys-IIAL, 1 Hys 1 Hys-Lap-AE, 1 Lap-PU	88.0 (60–100)	1.1 (1–2)	10/10 (100)
Merchant <sup>30</sup>	3	30	3 HELLP-SLH	3 CS	NR	2 PL, 1 none	90	2	2/3 (66.7)
Lim <sup>31</sup>	1	26	1 DIC-AFE	1 VD	NR	None	90	1	1
Price <sup>32</sup>	1	32	1 HELLP-DIC	1 CS	NR	1 Lap	90	1	1
Gidiri <sup>33</sup>	1	38	1 PA-DIC	1 CS	None	None	170	1	1
Ahonen <sup>34</sup>	12	27.7 (24–37)	4 PA, 2 At, 6 Lac	5 CS, 7 VD	2 UD, 10 NR	5 Hys, 4 AE, 3 NR	85.1 (42–120)	1	10/12 (83.3)
Holub <sup>35</sup>	1	28	1 At-DIC	1 CS	1 UD	1 Hys-Lap-PU	NR	1	1
Shamsi <sup>36</sup>	3	30.7 (27–35)	1 PA, 2 Lac	3 CS	NR	1 Lap-IIAL, 2 Hys-Lap	86.7 (80–90)	1	3/3 (100)
Tanchev <sup>37</sup>	4	NR	4 At	4 VD	1 OTC-PG, 1 UD, 2 none	4 VUT	72.0 (61–82)	1	4/4 (100)
Hollinberger <sup>38</sup>	3	29.7 (28–31)	2 At, 1 PA	1 CS, 2 VD	3 OTC-PG	1 PU-IIAL, 2 none	100.0 (60–120)	2	3/3 (100)
Nowacka <sup>39</sup>	1	30	1 IOP	1 CS	1 OTC	1 PU-Hys	37.5	2	1
Verre <sup>40</sup>	1	24	1 At	1 CS	NR	1 Hys	90	1	1
Palomino <sup>41</sup>	3	NR	1 At, 1 PA, 1 AP	2 CS, 1 VD	NR	1 Hys-HAL, 2 none	40	1	2/3 (66.7) <sup>¶</sup>
Heilmann <sup>42</sup>	1	29	1 At	1 CS	1 DDAVP	1 Lap	90	1	1
Pepas <sup>43</sup>	1	NR	1 HELLP-DIC	1 CS	1 OTC-PG-EGMT	1 Lap-PU-AE	90	2	1
Sobieszcyk <sup>44</sup>	25	30 (23–44)	2 UM, 1 ACS, 8 DIC, 14 NR	16 CS, 9 VD	9 UD, 2 TA, 1 APT, 13 NR	7 Hys, 6 Hys-IIAL, 3 NR	32.2 (10–137)	1.2 (1–2)	24/25 (96.0)

Prosper <sup>45</sup>	1	43	1 AFE-DIC	1 CS	None	None	60	1	1
Haynes <sup>46</sup>	4	30.2 (27–36)	2 PA, 1 At-DIC, 1 IOP	2 CS, 2 VD	2 OTC-PG-EGMT	1 Hys, 1 Hys-IIAL 1 Hys-AE, 1 AE	76.2 (70–85)	1	4/4 (100)
Jirapinyo <sup>47</sup>	2	40.0 (36–44)	2 At	2 CS	1 OTC-PG	1 Lap, 1 Hys	100	1	2/2 (100)
Ahonen <sup>48</sup>	26	33.0	9 At, 9 Lac, 5 Ret, 3 PA	10 CS, 16 VD	NR	NR	100 (73–122)	NR	20/26 (76.9)
Total	118	31.4 (23–44)		62 CS, 46 VD			71.6 (10–170)	1.6 (1–19)	104/118 (88.1)

\* Absolute number or median (range).

† Almost all patients were transfused with several units of blood components.

‡ Number (percentage).

§ Defined as cessation or significant reduction of bleeding.

\* One patient died of multiorgan failure (MOF).

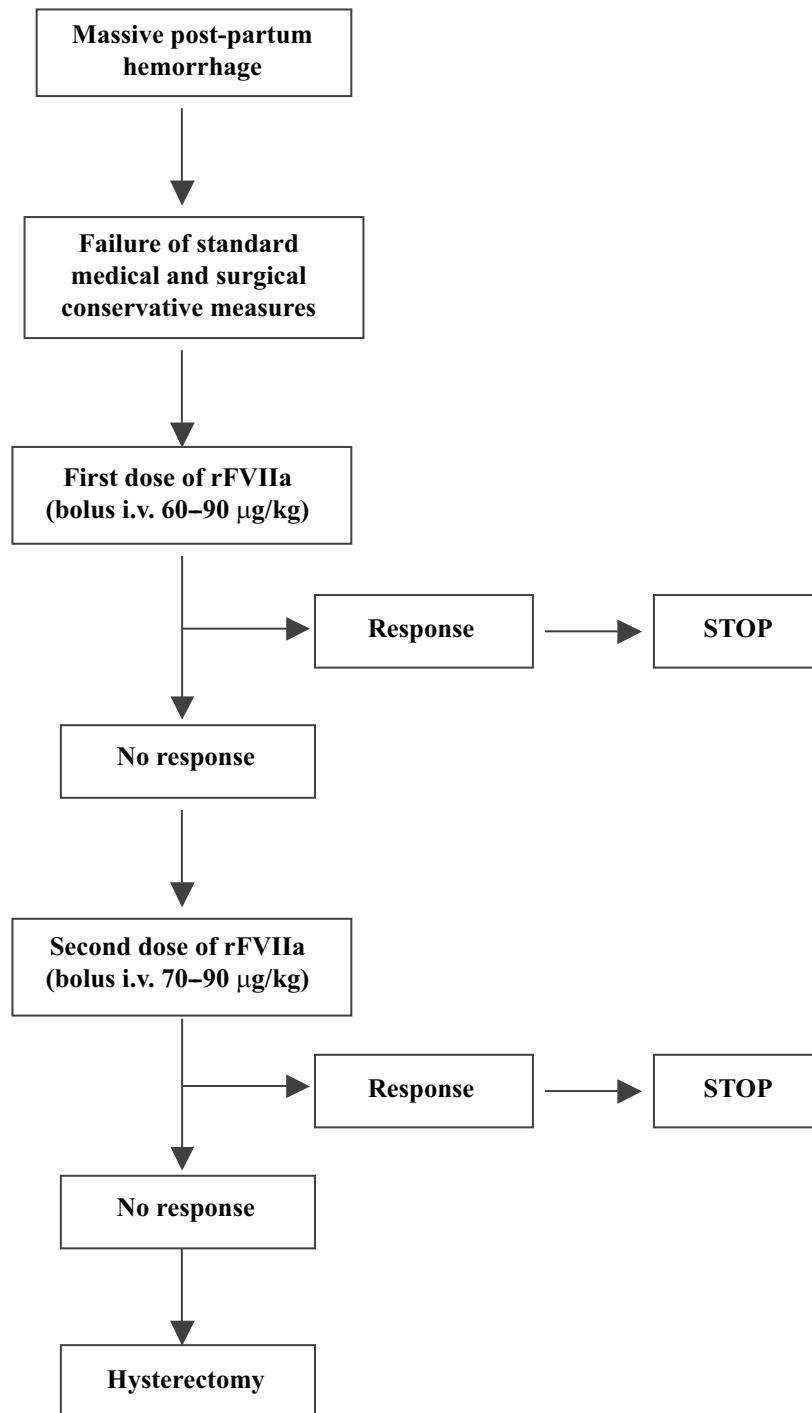
NR, not reported; rFVIIa, recombinant factor VII activated; AP, abruptio placentae; PA, placenta abnormality; At, atony; Lac, uterine, vaginal, or other lacerations; VD, vaginal delivery; CS, cesarean section; DIC, disseminated intravascular coagulation; HELLP, hemolysis, elevated liver enzymes and low platelets; IOP, intraoperative bleeding; UM, uterus myomatosis; SLH, subcapsular liver hematoma; Ret, retained placenta; AFE, amniotic fluid embolism; RF, renal failure; AT III, antithrombin III; hys, hysterectomy; lap, laparotomy; EML, etamsylate; PMD, phytonadione; FBG, fibrinogen; PG, prostaglandin; OTC, oxytocin; TP, teripressin; TA, tranexamic acid; IIAL, internal iliac artery ligation; APT, aprotinin; HR, hepatic rupture; ACS, abdominal compartment syndrome; AE, arterial embolization; PU, packing of uterus; PL, packing of liver; UD, uterotonic drugs; DDAVP, desmopressin; EGMT, ergometrine.

doses, in the majority of the cases reported in the literature, a single dose was administered; however, in a minority of cases, additional doses were also required to achieve the hemostatic efficacy.

Thus, based on these considerations, we would recommend a bolus dose of rFVIIa of 60 to 90  $\mu\text{g}/\text{kg}$ , which, due to the short half-life of the drug, may be repeated within 30 minutes if there is evident lack of clinical improvement.

Although many experts recommend the use of rFVIIa in PPH patients after the standard treatment has been shown to be ineffective, we believe it is equally important to avoid using rFVIIa as a drug of “last resort” to be used only after everything else fails. In fact, patients with PPH would by this late stage be so metabolically compromised that no therapy would reverse their decline, and rFVIIa might thus be of no value.<sup>54</sup> Therefore, an early intervention to control PPH at onset appears to be crucial for the success of rFVIIa. In particular, we advise that rFVIIa should always be administered before the decision of obstetric hysterectomy (Fig. 3). If the indication still persists after its use, the drug will improve the course of the operation with a reduction of surgery-related blood loss. On the other hand, it must be stressed that rFVIIa should not be considered as a substitute for, nor should it delay, the performance of life-saving procedures such as embolization or surgery.

Finally, another important issue concerns the safety of rFVIIa in massive PPH, especially considering the thrombogenic potential of this agent.<sup>55</sup> Data regarding the use of rFVIIa in a wide variety of coagulopathic cases, including trauma, suggest that thrombosis is not usually a problem.<sup>56,57</sup> Similarly, data from the rFVIIa extended-use registry supports the lack of thrombotic complications in acute bleeding episodes of many etiologies, including postpartum bleeding.<sup>58</sup> However, the data sheet for NovoSeven quotes a serious adverse reaction rate of 0.6%, which includes both arterial thrombotic events such as myocardial infarction or ischemia, cerebrovascular disorders and bowel infarction, and venous thrombotic events such as pulmonary embolism and thrombophlebitis.<sup>59</sup> Therefore, it is recommended that rFVIIa be used with caution in the presence of sepsis, disseminated malignancy, or after the use of other coagulation bypassing agents. Nevertheless, although it might seem a paradox to use rFVIIa in the presence of a systemic activation of coagulation, a recent literature review did not record thrombotic complications in DIC patients treated with rFVIIa.<sup>60</sup> The scarce thrombogenic potential of rFVIIa, due to the local activation of coagulation, is confirmed by the clinical practice, as all studies and case reports to date on the use of rFVIIa in PPH describe a remarkable safety profile for this drug, even in the presence of a concomitant DIC.



**Figure 3** Protocol algorithm on the use of rFVIIa in PPH. This protocol is valid for those PPH cases where there are no obvious indications for hysterectomy.

Nevertheless, due to the paucity of published data, and the lack of controlled studies, we advise that physicians closely monitor such patients not only for their clinical bleeding conditions but also for the onset of thrombotic complications.

Our suggested protocol algorithm on the use of rFVIIa in PPH is shown in Fig. 3.

## CONCLUSION

There is an increasing number of case reports where empirical “off-label” use of rFVIIa has been shown to be effective in the treatment of massive PPH that did not respond to conventional treatments. However, to date, no randomized controlled trials or prospective clinical studies have been performed in PPH, and all data

available in the literature are derived from uncontrolled studies, including single cases or small series of patients. Furthermore, the variations in policies for the immediate management of PPH in Europe make the comparison of the therapeutic approaches to PPH among different studies even more difficult.<sup>61</sup>

Thus, considering the absence of controlled studies and the complexity of this syndrome, we greatly encourage the pursuit and publication of studies that describe in detail the diagnostic criteria adopted to define the entity of blood loss, its causes, and, above all, the sequence of medical/surgical procedures applied. Only with these data will it be possible to improve our experience, with the aim of better assessing the optimal dose, timing of administration, and the safety profile of rFVIIa in massive obstetric hemorrhage.

## REFERENCES

- Bonnar J. Massive obstetric haemorrhage. *Baillieres Best Pract Res Clin Obstet Gynaecol* 2000;14:1–18
- Jansen AJ, van Rhenen DJ, Steegers EA, Duvekot JJ. Postpartum hemorrhage and transfusion of blood and blood components. *Obstet Gynecol Surv* 2005;60:663–671
- Khan KS, Wojdyla D, Say L, Gulmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. *Lancet* 2006;367:1066–1074
- CEMACH. The Confidential Enquiries into Maternal Deaths in the United Kingdom. Available at: <http://www.cemach.org.uk>. Accessed December 27, 2007
- ACOG. Practice Bulletin. Clinical management guidelines for obstetrician-gynecologists number 76, October 2006: postpartum hemorrhage. *Obstet Gynecol* 2006;108:1039–1047
- Burtelow M, Riley E, Druzin M, Fontaine M, Viele M, Goodnough LT. How we treat: management of life-threatening primary postpartum hemorrhage with a standardized massive transfusion protocol. *Transfusion* 2007;47:1564–1572
- Sobieszczyk S, Breborowicz G. Management recommendations for postpartum hemorrhage. *Arch Perinat Med* 2004;10:1–4
- Mousa HA, Alfirevic Z. Treatment of primary postpartum haemorrhage. *Cochrane Syst Database Rev* 2003;CD003249
- Allam MS, B-Lynch C. The B-Lynch and other uterine compression suture techniques. *Int J Gynaecol Obstet* 2005;89:236–241
- Ghezzi F, Cromi A, Uccella S, Raio L, Bolis P, Surbek D. The Hayman technique: a simple method to treat postpartum hemorrhage. *BJOG* 2007;114:362–365
- Bouwmeester FW, Bolte AC, van Geijn HP. Pharmacological and surgical therapy for primary postpartum hemorrhage. *Curr Pharm Des* 2005;11:759–773
- Nègrier C, Lienhart A. Overall experience with Novoseven®. *Blood Coagul Fibrinolysis* 2000;11(suppl 1):19–24
- Hedner U, Erhardtsen E. Potential role for rFVIIa in transfusion medicine. *Transfusion* 2002;42:114–124
- Franchini M, Zaffanello M, Veneri D. Recombinant factor VIIa. An update on its clinical use. *Thromb Haemost* 2005;93:1027–1035
- Ghorashian S, Hunt BJ. “Off-license” use of recombinant activated factor VII. *Blood Rev* 2004;18:245–259
- Franchini M, Lippi G, Franchi M. The use of recombinant activated factor VII in obstetric and gynaecological haemorrhage. *BJOG* 2007;114:8–15
- Lisman T, De Groot PG. Mechanism of action of recombinant factor VIIa. *J Thromb Haemost* 2003;1:1138–1139
- Moscardo F, Perez F, de la Rubia J, et al. Successful treatment of severe intra-abdominal bleeding associated with disseminated intravascular coagulation using recombinant activated factor VII. *Br J Haematol* 2001;114:174–176
- Brueckner S, Sedemund-Adib B, Malik E, et al. Treatment of a post partum bleeding complication with recombinant factor VIIa [abstract]. *Blood* 2001;98:80b
- Breborowicz GH, Sobieszczyk S, Szymankiewicz M. Efficacy of recombinant activated factor VII (rFVIIa, NovoSeven®) in prenatal medicine. *Arch Perinat Med* 2002;8:21–27
- Sobieszczyk S, Breborowicz GH, Markwitz W, Mallinger S, Adamski D, Kruszynski Z. Effect of recombinant activated factor VII (rFVIIa; NovoSeven) in a patient in haemorrhagic shock after obstetrical hysterectomy. *Ginekol Pol* 2002;73:230–233
- Zupancic Salek S, Sokolic V, Viskovic T, Sanjug J, Simic M, Kastelan M. Successful use of recombinant factor VIIa for massive bleeding after caesarean section due to HELLP syndrome. *Acta Haematol* 2002;108:162–163
- Sokolic V, Bukovic D, Fures R, et al. Recombinant factor VIIa (rFVIIa) is effective at massive bleeding after cesarean section – a case report. *Coll Antropol* 2002;26(Suppl):155–157
- Bouwmeester FW, Jonkhoff AR, Verheijen RHM, van Geijn HP. Successful treatment of life-threatening postpartum hemorrhage with recombinant activated factor VII. *Obstet Gynecol* 2003;101:1174–1176
- Kretzschmar M, Zahm DM, Remmler K, Pfeiffer L, Victor L, Schirmeister W. Pathophysiological and therapeutic aspects of amniotic fluid embolism (anaphylactoid syndrome of pregnancy): case report with lethal outcome and overview. *Anaesthesist* 2003;52:419–426
- Dart BW, Cockerham WT, Torres C, Kipikasa JH, Maxwell RA. A novel use of recombinant factor VIIa in HELLP syndrome associated with spontaneous hepatic rupture and abdominal compartment syndrome. *J Trauma* 2004;57:171–174
- Boehlen F, Morales MA, Fontana P, Ricou B, Irion O, de Moerloose P. Prolonged treatment of massive postpartum haemorrhage with recombinant factor VIIa: case report and review of the literature. *BJOG* 2004;111:284–287
- Segal S, Shemesh IY, Blumental R, et al. Treatment of obstetric hemorrhage with recombinant factor VIIa (rFVIIa). *Arch Gynecol Obstet* 2003;268:266–267
- Segal S, Shemesh IY, Blumental R, et al. The use of recombinant factor VIIa in severe postpartum hemorrhage. *Acta Obstet Gynecol Scand* 2004;83:771–772
- Merchant SM, Mathew P, Vanderjagt TJ, Howdieshell TR, Crookston KP. Recombinant factor VIIa in management of spontaneous subcapsular liver hematoma associated with pregnancy. *Obstet Gynecol* 2004;103:1055–1058
- Lim Y, Loo CC, Chia V, Fun W. Recombinant factor VIIa after amniotic fluid embolism and disseminated intravascular coagulopathy. *Int J Gynaecol Obstet* 2004;87:178–179

32. Price G, Kaplan J, Skowronski G. Use of recombinant factor VIIa to treat life-threatening non-surgical bleeding in a postpartum patient. *Br J Anaesth* 2004;93:298-300
33. Gidiri M, Noble W, Rafique Z, Patil K, Lindow SW. Caesarean section for placenta praevia complicated by postpartum haemorrhage managed successfully with recombinant activated human coagulation Factor VIIa. *J Obstet Gynaecol* 2004;24:925-926
34. Ahonen J, Jokela R. Recombinant factor VIIa for life-threatening post-partum haemorrhage. *Br J Anaesth* 2005;94:592-595
35. Holub Z, Feyereisl J, Kabelik L, Rittstein T. Successful treatment of severe post-partum bleeding after caesarean section using recombinant activated factor VII. *Ceska Gynekol* 2005;70:144-148
36. Shamsi TS, Hossain N, Soomro N, et al. Use of recombinant factor VIIa for massive postpartum haemorrhage: case series and review of literature. *J Pak Med Assoc* 2005;55:512-515
37. Tanchev S, Platikanov V, Karadimov D. Administration of recombinant factor VIIa for the management of massive bleeding due to uterine atonia in the post-placental period. *Acta Obstet Gynecol Scand* 2005;84:402-403
38. Hollnberger H, Gruber E, Seelbach GB. Major post-partum hemorrhage and treatment with recombinant factor VIIa. *Anesth Analg* 2005;101:1886-1887
39. Nowacka E, Krawczynska WR, Teliga CJ, et al. Recombinant factor VIIa for severe bleeding during cesarean section for quadruplet pregnancy. Case report. *Anesth Inten Teap* 2005;37:259-262
40. Verre M, Bossio F, Mammone A, Piccirillo M, Tancioni F, Varano M. Use of recombinant activated factor VII in a case of severe postpartum haemorrhage. *Minerva Ginecol* 2006;58:81-84
41. Palomino MA, Chaparro MJ, de Elvira MJ, Curiel EB. Recombinant activated factor VII in the management of massive obstetric bleeding. *Blood Coagul Fibrinolysis* 2006;17:226-227
42. Heilmann L, Wild C, Hojnacki B, Pollow K. Successful treatment of life-threatening bleeding after cesarean section with recombinant activated factor VII. *Clin Appl Thromb Hemost* 2006;12:227-279
43. Pepas LP, Arif-Adib M, Kadir RA. Factor VIIa in puerperal hemorrhage with disseminated intravascular coagulation. *Obstet Gynecol* 2006;108:757-761
44. Sobieszczyk S, Breborowicz G, Platikanov V, Tanchev S, Kessler CM. Recombinant factor VIIa in the management of postpartum bleeds: an audit of clinical use. *Acta Obstet Gynecol Scand* 2006;85:1239-1247
45. Prosper SC, Goudge CS, Lupo VR. Recombinant factor VIIa to successfully manage disseminated intravascular coagulation from amniotic fluid embolism. *Obstet Gynecol* 2007;109:524-525
46. Haynes J, Laffan M, Plaat F. Use of recombinant activated factor VII in massive obstetric hemorrhage. *Int J Obstet Anesth* 2007;16:40-49
47. Jirapinyo M, Manonai J, Herabutya Y, Chuncharunee S. Effectiveness of recombinant activated factor VII (rFVII a) for controlling intractable postpartum bleeding: report of two cases and literature review. *J Med Assoc Thai* 2007;90:977-981
48. Ahonen J, Jokela R, Korttila K. An open non-randomized study of recombinant activated factor VII in major postpartum hemorrhage. *Acta Anaesthesiol Scand* 2007;51:929-936
49. Selo-Ojeme DO, Okonofua FE. Risk factors for primary postpartum haemorrhage. A case control study. *Arch Gynecol Obstet* 1997;259:179-187
50. Chichakli LO, Atrash HK, Mackay AP, Musani AS, Berg BJ. Pregnancy-related mortality in the United States due to hemorrhage: 1979-1992. *Obstet Gynecol* 1999;94:721-725
51. Karalapillai D, Popham P. Recombinant factor VIIa in massive postpartum hemorrhage. *Int J Obstet Anesth* 2007;16:29-34
52. Ministero della Salute. Raccomandazione n°6 - Raccomandazione per la prevenzione della morte materna correlata al travaglio e/o parto. Available at: <http://www.ministerosalute.it>. Accessed December 27, 2007
53. Vincent JL, Rossaint R, Riou B, Ozier Y, Zideman D, Spahn DR. Recommendations on the use of recombinant activated factor VII as an adjunctive treatment for massive bleeding - a European perspective. *Crit Care* 2006;10:1-12
54. Clark AD, Gordon WC, Walker ID, Tait RC. 'Last-ditch' use of recombinant factor VIIa in patients with massive haemorrhage is ineffective. *Vox Sang* 2004;86:120-124
55. O'Connell KA, Wood JJ, Wise RP, Lozier JN, Braun MM. Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. *JAMA* 2006;295:293-298
56. Lynn M, Jeroukhimov I, Klein Y, Martinowitz U. Updates in the management of severe coagulopathy in trauma patients. *Intensive Care Med* 2002;28:S241-S247
57. Laffan M, O'Connell NM, Perry DJ, Hodgson AJ, O'Shaughnessy D, Smith O. Analysis and results of the recombinant factor VIIa extended-use registry. *Blood Coagul Fibrinolysis* 2003;14(Suppl 1):S35-S38
58. Erhardtsen E. Ongoing NovoSeven trials. *Intensive Care Med* 2002;28:S248-S255
59. Novo Nordisk Limited. NovoSeven summary of product characteristics. Version no. 3; N7/IBEC/015/3. Baagsvaerd, Denmark: Novo Nordisk
60. Franchini M, Manzato F, Salvagno GL, Lippi G. The potential role of recombinant factor VII activated for the treatment of severe bleeding associated with disseminated intravascular coagulation: a systematic review. *Blood Coagul Fibrinolysis* 2007;18:589-593
61. Winter C, Macfarlane A, Deneux-Tharaux C, et al. Variations in policies for management of the third stage of labour and the immediate management of postpartum haemorrhage in Europe. *BJOG* 2007;114:845-854