

# The use of recombinant activated factor VII in obstetric and gynaecological haemorrhage

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Recombinant activated factor VII (rFVIIa) was originally developed for the treatment of bleeding in patients with haemophilia A or B and inhibitors. Over the past ten years, it has been successfully used to prevent or control bleeding in several other nonhaemophilic bleeding conditions. Among the newer 'off-label' clinical applications of rFVIIa, there is increasing evidence of its effectiveness in treating obstetric and gynaecological bleeding unresponsive to conventional therapy. The existing literature on the use of rFVIIa in obstetrics and gynaecology is summarised in

this review. Although supported by few and uncontrolled studies, on the whole, the published data suggest a potential role of rFVIIa in the management of obstetric and gynaecological intractable bleeding. However, further evidence is needed to improve the assessment of its optimal dose, effectiveness and safety in such conditions.

**Keywords** Bleeding, gynaecology, obstetrics, postpartum haemorrhage, rFVIIa.

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## Introduction

Recombinant activated factor VII (rFVIIa; NovoSeven<sup>®</sup>, Novo Nordisk, Bagsvaerd, Denmark) was originally developed for the treatment of patients with haemophilia with inhibitors and then used successfully for treating haemorrhage in patients with acquired haemophilia or other inherited bleeding disorders such as factor (F) VII deficiency and Glanzmann's thrombasthenia.<sup>1–7</sup> In the past few years, together with the improved knowledge of its mechanisms of action, rFVIIa has also been used with benefit in many other nonhaemophilic bleeding situations unresponsive to conventional therapy to control excessive bleeding and reduce the exposure to allogenic blood. These include intracerebral haemorrhage, oral anticoagulant-induced haemorrhage, thrombocytopenia, bleeding associated with hepatic failure, major surgery, trauma and life-threatening obstetric and gynaecological hemorrhagic complications.<sup>8–16</sup> These two latter 'off-label' clinical applications of rFVIIa will be discussed in this review. Data were identified by searches of the published literature, including PubMed, references from reviews and abstracts from the most important meetings on this topic.

## Mechanisms of action of rFVIIa

FVIIa plays a key role in the initiation of haemostasis. In fact, according to a cell-based model of coagulation,<sup>17</sup> following injury to the vessel wall, tissue factor (TF) is exposed to circulating blood and TF–FVIIa complexes are formed on the TF-bearing cells, where they activate factor X (FXa), leading to the conversion of prothrombin to thrombin. The limited amount of thrombin formed subsequently activates the co-factors V, VIII and XI, as well as platelets accumulated at the site of injury. The activated platelets expose negatively charged phospholipids, such as phosphatidyl serine, on their membrane and FIXa, FVIIIa and FXIa bind to this surface, leading to the further FX activation and full thrombin generation.<sup>18</sup> The extra thrombin formation results in the activation of thrombin-activable fibrinolysis inhibitor (TAFI), which protects the fibrin clot from premature lysis by down-regulating fibrinolysis.<sup>19</sup> In summary, a full thrombin burst is essential for the formation of a stable fibrin haemostatic plug that is resistant to premature fibrinolysis. In fact, in haemophilia, only limited amount of thrombin dependent on the TF–FVIIa complex is generated, which is insufficient to

consolidate and sustain the fibrin plug.<sup>20</sup> In a cell-based *in vitro* model, it has been shown that the addition of increasing amounts of rFVIIa (between 50 and 150 nm) to activated platelets in the presence of FX produces a linear increase of generation of FXa independently of the presence of TF on the platelet surface.<sup>21</sup> This dose–response mechanism can lead to the generation of significant amounts of thrombin even in the absence of FVIII and FIX, thus explaining the mechanism of action of rFVIIa in those with haemophilia.<sup>12</sup> The direct activation of FIX on activated platelets in the absence of TF, resulting in improved thrombin generation, may also explain the mechanism of action of rFVIIa in acquired coagulopathy following trauma, surgery or other events.<sup>22</sup> Moreover, the binding of rFVIIa to activated platelets may explain why rFVIIa is localised only to the site of bleeding.<sup>17</sup>

However, an alternative TF-dependent mechanism of action of rFVIIa has been proposed.<sup>23,24</sup> In fact, according to this model, the local function of rFVIIa is mediated by the combined effect of TF expression and platelet accumulation at the site of a vascular lesion. Lisman and De Groot<sup>21</sup> analysed the experimental data available and concluded that both the proposed mechanisms of actions of rFVIIa (i.e. TF dependent and TF independent) are plausible. In fact, if the TF pathway is usually required for the action of rFVIIa, a rFVIIa-mediated thrombin generation can also occur on the activated platelet surface independently of TF. Moreover, the same authors observed that the enhanced thrombin generation from rFVIIa not only accelerates clot formation but also inhibits fibrinolysis by TAFI activation and enhances platelet adhesion and aggregation under flow conditions.<sup>25,26</sup> This latter evidence may explain the therapeutic effect of rFVIIa in patients with thrombocytopenia. In conclusion, according to the current knowledge, rFVIIa induces haemostasis by enhancing thrombin generation on thrombin-activated platelet surfaces, thereby providing the formation of a stable fibrin clot, which is resistant to premature fibrinolysis.

## The use of rFVIIa in postpartum haemorrhage

Severe postpartum haemorrhage (PPH) remains an important cause of maternal mortality.<sup>27,28</sup> Such bleeding is most often because of uterine atony, a complication which occurs in up to 2% of all deliveries and that may lead to massive loss of blood and plasma, with consequent haemorrhagic shock and severe impairment of blood coagulation. However, the aetiology of obstetric haemorrhage involves several other factors that can be divided into the following five groups: placental abnormalities, coagulation disorders, lacerations and trauma, uterine atony, and retained uterine contents.<sup>28</sup> Most important risk factors for PPH are abnormal placental position, previous caesarean section, multiparity, advanced gestation, age > 35 years, obesity, history of PPH, prolonged third stage (>30 minutes), pre-

eclampsia, anaemia at 24 and 29 weeks of gestation and before delivery, coagulation disorders, instrumental vaginal delivery and augmentation of labour.<sup>29–32</sup>

The treatment of life-threatening PPH still remains challenging, and hysterectomy or surgical ligation of the internal iliac arteries bilaterally may be required to control the bleeding. The first-line standard treatment includes both surgical and medical (i.e. replacement transfusion therapy and uterotonic drugs) measurements to control blood loss.<sup>15,33,34</sup> However, additional interventions may be needed in cases with continuing bleeding. In recent years, new therapeutic measures to control the bleeding have gained attention. In particular, there is an increasing number of case reports where empirical ‘off-label’ use of rFVIIa has been effective in the treatment of massive PPH which did not respond to conventional methods.<sup>35–61</sup> The first case report of successful treatment of intractable obstetric haemorrhage in a woman without haemophilia using rFVIIa was published by Moscardo *et al.*,<sup>38</sup> who reported that rFVIIa successfully controlled life-threatening PPH after caesarean section in a woman who developed severe disseminated intravascular coagulopathy (DIC), liver dysfunction and renal failure. Breborowicz *et al.*<sup>41</sup> reported seven cases of peripartum haemorrhage treated with rFVIIa. Six women underwent caesarean section for different indications, and one woman delivered vaginally. In five women, rFVIIa was administered only after emergency hysterectomy, while in the remaining two women, the drug was effective in avoiding hysterectomy. In all but one woman, a single relatively low dose of rFVIIa (range 16.7–48 microgram/kg) was effective in controlling bleeding. Tanchev *et al.*<sup>56</sup> reported four cases of severe bleeding associated with uterine atony which were successfully treated with rFVIIa. Boyer-Neumann *et al.*<sup>48</sup> reported the successful management of caesarean section and the postpartum period using the sequential combination of recombinant FVIII and rFVIIa in an alloimmunised woman with type 3 von Willebrand’s disease. The largest case series is that reported by Ahonen and Jokela<sup>54</sup> who presented 12 cases of severe PPH treated with rFVIIa in addition to standard surgical and medical interventions, and a good response was obtained in 11 of these cases. In 5 of these 12 cases, hysterectomy was performed before the administration of rFVIIa. However, as rFVIIa was effective in avoiding hysterectomy in most of the remaining women, the authors concluded that in cases of intractable PPH with no other obvious indications for hysterectomy, administration of rFVIIa should be considered before surgery.

Table 1 summarises the results of the literature. After a careful search, a total of 65 women treated with rFVIIa have been found in the literature. As regards the relationship between age and PPH, the analysis of the data reported in Table 1 confirms that an increased age is a risk factor for the development of PPH: in fact, the median age of the women

Table 1. The use of rFVIIa in obstetric PPH

Authors	Year	Women	Age (years)	Cause of PPH	Type of delivery	Hysterectomy	Initial dose of rFVIIa (microgram/kg)	Number of doses	Response, n (%) <sup>*</sup>
Haya et al. <sup>35</sup>	1998	1	28	1 FVII-Pr	1 CS	0	28	4	1
Muleo et al. <sup>36</sup>	1998	1	22	1 FVII-Pr	1 CS	0	20	9	1
Jimenez-Yuste et al. <sup>37</sup>	2000	1	30	1 FVII-Pr	1 CS	1	13.3	-**	1
Moscardo et al. <sup>38</sup>	2001	1	33	1 At	1 CS	1	90	9	1
Brueckner-Sabine et al. <sup>39</sup>	2001	1	31	1 At	1 CS	1	NR	NR	1***
Monte and Lyons <sup>40</sup>	2001	1	31	1 GT-Pr	1 CS	0	90	1	1
Breborowicz et al. <sup>41</sup>	2002	8	33.9 (26–44)	4 At, 3 DIC, 1 Pr	7 CS, 1 VD	5/8 (62.5)	24.5 (16.7–48)	1	7/8 (87.5)
Zupancic et al. <sup>42</sup>	2002	1	31	1 DIC-HELLP	1 CS	0	90	1	1
Sobieszcyk et al. <sup>43</sup>	2002	1	29	1 IOP	1 CS	1	NR	NR	1
Eskandari et al. <sup>44</sup>	2002	1	NR	1 FVII-Pr	1 VD	0	50	2	1
Sokolic et al. <sup>45</sup>	2002	1	31	1 DIC-HELLP	1 CS	0	90	1	1
Bouwmeester et al. <sup>46</sup>	2003	1	30	1 At-Lac	1 VD	1	60	2	1
Kretzschmar et al. <sup>47</sup>	2003	1	35	1 DIC	1 CS	1	60	1	1***
Boyer-Neumann et al. <sup>48</sup>	2003	1	29	1 VWD	1 CS	0	41	5	1
Dart et al. <sup>49</sup>	2004	1	24	1 HELLP	1 VD	0	90	1	1
Boehlen et al. <sup>50</sup>	2004	1	31	1 At	1 VD	1	120	19	1
Segal et al. <sup>51</sup>	2004	10	NR	3 PA; 2 At; 4 Lac; 1 UM	NR	7/10 (70.0)	88.0 (60–100)	1.1 (1–2)	10/10 (100)
Merchant et al. <sup>52</sup>	2004	3	30	3 HELLP-SLH	3 CS	0/3	90	2	3/3***
Kale et al. <sup>53</sup>	2004	1	31	1 GT-Pr	1 VD	0	36	1	1
Ahonen and Jokela <sup>54</sup>	2005	12	27.7 (24–37)	3 PA, 2 At, 1 PP, 6 Lac	5 CS, 7 VD	5/12 (41.7)	85.1 (42–120)	1	10/12 (83.3)
Shamsi et al. <sup>55</sup>	2005	3	30.7 (27–35)	1 PP, 2 Lac	3 CS	2/3 (66.7)	86.7 (80–90)	1	3/3 (100)
Tanchev et al. <sup>56</sup>	2005	4	NR	4 At	4 VD	0/4	72.0 (61–82)	1	4/4 (100)
Holub et al. <sup>57</sup>	2005	1	28	1 At	1 CS	1	NR	1	1
Hollnberger et al. <sup>58</sup>	2005	3	29.7 (28–31)	1 At, 1 PP, 1 At-Lac	1 CS, 2 VD	0/3	100.0 (60–120)	2	3/3
Nowacka et al. <sup>59</sup>	2005	1	30	1 IOP	1 CS	1	37.5	2	1
Verre et al. <sup>60</sup>	2006	1	24	1 At	1 CS	1	90	1	1
Palomino et al. <sup>61</sup>	2006	3	NR	1 At, 1 PP, 1 placental abruption	2 CS, 1 VD	1/3 (33.3)	40	1	3/3 (100)***
Total		65	30.5 (22–44)		35 CS, 20 VD	30/65 (46.1)	65.9 (13.3–120)	1.8 (1–19)	62/65 (95.4)

At, atony; CS, caesarean section; FVII, factor VII deficiency; GT, Glanzmann's thrombasthenia; IOP, intraoperative bleeding; IVD, instrumental vaginal delivery; Lac, uterine, vaginal or other lacerations; NR, not reported; PA, placenta accreta; PP, placenta percreta; Pr, preventive; SLH, subcapsular liver haematoma; UM, uterus myomatous; VD, vaginal delivery; VWD, von Willebrand's disease.

Age, initial dose of rFVIIa and number of doses are represented as absolute number or median (range).

\*Response is defined as cessation or significant reduction of bleeding. When rFVIIa was used as a prophylaxis, the haemostatic efficacy was defined as the absence of bleeding.

\*\*rFVIIa was administered in bolus at a dose of 13.3 microgram/kg followed by a continuous infusion at 3.33 microgram/kg/hour for 48 hours, which was then reduced to

1.66 microgram/kg/hour and maintained for another 48 hours.

\*\*\*rFVIIa had reduced the bleeding, but one woman died because of multi-organ failure.

\*\*\*\*A woman died of a cardiac arrest.

described was 30.5 years. Similarly, caesarean section appears to increase the risk of onset of PPH, as 20 women (36.4%) were delivered by vaginal route and 35 (63.6%) by caesarean section out of the 55 women for whom information on the mode of delivery was available. As expected, uterine atony was the leading cause of PPH (21 women, 32.3%), followed by vaginal or uterine lacerations (14 women, 21.5%), placental abnormalities (11 women, 16.9%) and HELLP (haemolysis, elevated liver enzymes and low platelet count) syndrome (six women, 9.2%). In seven women (10.8%), PPH was associated with a congenital coagulation disorder, while in six women (9.2%), DIC also complicated the clinical picture. Thirty out of the 65 women (46.1%) underwent hysterectomy; however, the impact of rFVIIa on avoiding the need for emergency hysterectomy and preservation of reproductive function is difficult to determine, as in many cases, this surgical procedure was performed before the drug was administered. The median dose of rFVIIa administered was 65.9 microgram/kg. However, when the cases of congenital FVII deficiency, which are known to require significantly lower doses of rFVIIa, were excluded from the analysis, the median dose of rFVIIa administered was 72.9 microgram/kg. In most cases (73%), only a single dose of rFVIIa was required. In two cases,<sup>36,37</sup> rFVIIa was administered as a continuous infusion. Although the results reported in Table 1 seem to indicate that rFVIIa was able to control bleeding in the majority of the cases, we advise particular caution in interpreting these data, as all the cases reviewed were uncontrolled.

Based on the reported literature, some experts suggest the use of rFVIIa in PPH when the standard treatment is ineffective.<sup>62,63</sup> Sobieszczyk and Breborowicz<sup>62</sup> recommend a dose of rFVIIa of 40–60 microgram/kg which may be repeated if there is a lack of clinical improvement within 15–30 minutes from the initial administration of the drug.

Most of the cases reported in Table 1 refer to the use of rFVIIa in life-threatening PPH as an adjuvant to standard surgical and medical interventions. However, rFVIIa has also been successfully used for prophylaxis of peripartum haemorrhage in pregnant women with inherited coagulation disorders.<sup>64</sup> Only a few cases have been described in the literature, mostly in women with Glanzmann's thrombasthenia and FVII deficiency.<sup>35–37,53</sup> As expected, the doses used were lower than those required for women with acute postpartum bleeding.

### The use of rFVIIa in postpartum acquired haemophilia A

Among the coagulation disorders associated with PPH, postpartum acquired haemophilia A deserves a particular mention.<sup>65</sup> In fact, postpartum development of an inhibitor against FVIII is a rare but severe complication of pregnancy.<sup>66–68</sup> After the description of the first patient by Rosenthal *et al.* in 1937,<sup>69</sup> several other studies have reported

cases of postpartum acquired haemophilia A.<sup>70</sup> Overall, postpartum FVIII inhibitors constitute 7–21% of acquired haemophilia A cases.<sup>71</sup> Pregnancy-associated FVIII inhibitors must be recognised early to decrease maternal morbidity and mortality. Since women with acquired inhibitors do not usually have a personal or family history of bleeding episodes, it is the presence of unexplained excessive and/or prolonged vaginal bleeding or large soft-tissue haematomas from multiple sites during the postpartum period that may lead the obstetrician to suspect a coagulation inhibitor. The laboratory diagnosis of acquired haemophilia A is based on the demonstration of an isolated prolongation of the activated partial thromboplastin time, not corrected by incubating the patient's plasma with equal volumes of normal plasma (mixing study), associated with a normal prothrombin time, reduced FVIII levels and formal evidence of a FVIII inhibitor in a patient with no previous personal or family history of bleeding.<sup>72</sup> The diagnosis of an inhibitor is confirmed by specific assays of the factor and the inhibitor using the Bethesda assay.

Acquired postpartum haemophilia A may occur following any pregnancy but is more common in primigravidas. It arises most commonly from 1 to 4 months after delivery, but it may occur as late as 1 year afterwards.<sup>70,73</sup> By contrast, FVIII inhibitors have rarely been detected during pregnancy or labour, but when they do occur during this period, they are frequently associated with severe uterine bleeding. The course of the natural history of postpartum acquired haemophilia A is benign as the majority of autoantibody inhibitors (more than 60%) tend to disappear spontaneously after a median period of 30 months and usually do not recur with subsequent pregnancies.<sup>65</sup> While the clinical severity and frequency of bleeding can be variable and often related to inhibitor titre, the site of bleeding is also heterogeneous and related to the time elapsed between delivery and appearance of the inhibitors.<sup>74</sup> Thus, vaginal bleeding is the predominant symptom if the inhibitor develops within few days after delivery, while ecchymoses and soft-tissue bleeding are more frequent if the postpartum FVIII inhibitor appears later.

With regards to treatment, the initial aim of management is to control acute bleeding, while the long-term aim is to accelerate eradication of the inhibitors. While the latter objective may be obtained with immunosuppressive therapy (i.e. corticosteroids and/or cytotoxic drugs),<sup>75</sup> the therapeutic options used to control bleeding include agents which can increase plasma FVIII levels (i.e. desmopressin and FVIII concentrates) in clinically mild cases with low inhibitor titres and by-passing agents (i.e. activated prothrombin complex concentrates and rFVIIa) in patients with high-titre FVIII antibodies and severe bleeding.<sup>71,76</sup> There are few cases reported in literature on the use of rFVIIa in postpartum acquired haemophilia A.<sup>73,77–80</sup> Mazzucconi *et al.*<sup>80</sup> described four postpartum inhibitor cases treated with high-dose immunoglobulin and dexamethasone; in two women, bleeding

symptoms were stopped by the concomitant use of rFVIIa at a dose of 90 microgram/kg every 12 hours for 4 days. Other cases successfully treated with rFVIIa have been collected by Baudo and de Cataldo in the Register of acquired FVIII inhibitors from the Italian Association of Haemophilia Centres.<sup>73,77</sup> Moreover, rFVIIa has been successfully used for the home treatment of women with postpartum FVIII inhibitors.<sup>79</sup>

## The use of rFVIIa in gynaecology

With regards to the use of rFVIIa in gynaecology, there is an increasing number of reports documenting its effectiveness in controlling intractable postoperative bleeding.<sup>81–90</sup> Panek *et al.*<sup>83</sup> described a case of successful treatment of massive intra-abdominal haemorrhage complicating debulking surgery for advanced ovarian cancer with rFVIIa. In fact, after the administration of two doses of rFVIIa 20 microgram/kg, the woman fully recovered with no further blood loss and complete restoration of haemostasis. Sajdak *et al.*<sup>84</sup> reported two cases of successful use of rFVIIa in gynaecological oncological patients (endometrial cancer and vaginal sarcoma) without pre-existing coagulopathy and concluded that rFVIIa may be an important and effective drug in severe bleeding in gynaecological oncology. Similarly, Erikci *et al.*<sup>90</sup> reported the successful treatment of an episode of severe uterine bleeding after chemotherapy in a woman with acute myeloid leukaemia. Ciacma *et al.*<sup>89</sup> reported four postmenopausal women who each received rFVIIa (dose range, 17–70 microgram/kg)

to control severe postoperative haemorrhage associated with elective hysterectomy for benign uterine fibroids, carcinoma of the endometrium, cervical and uterine cancer, or metastatic carcinoma of the genital tract. Bleeding resolved within 12 hours in three women after a single dose of rFVIIa. In the woman with metastatic disease, bleeding was markedly reduced after each of two doses of rFVIIa and resolved completely within 12 hours of the second dose. Table 2 reports the available literature on the use of rFVIIa in gynaecological bleeding. So far, 14 cases have been described mainly involving women operated for gynaecological cancers. However, in one case, the drug was used for an episode of intractable menorrhagia secondary to congenital FVII deficiency<sup>82</sup> and in another case as a prophylaxis in a woman with Glanzmann's thrombasthenia undergoing surgical removal of a pelvic mass.<sup>87</sup> The median dose of rFVIIa administered in the 14 cases reported was 51.6 microgram/kg, while the median number of doses injected was 1.8 (in one case,<sup>81</sup> rFVIIa was administered in continuous infusion). Overall, the data reported in Table 2 suggest that rFVIIa may offer an effective means of controlling bleeding associated with gynaecological surgery when conventional surgical and pharmacologic measures are unsuccessful.

## Conclusions

The current literature on the use of rFVIIa in obstetric and gynaecology is limited. On the whole, the published data

**Table 2.** The use of rFVIIa in gynaecological bleeding

Authors	Year	Women	Age (years)	Disease	Surgery	Initial dose of rFVIIa (microgram/kg)	Number of doses	Response, n (%)*
Laffan and Cummins <sup>81</sup>	2000	1	62	1 CC	1 DS	80	–**	1
White <i>et al.</i> <sup>82</sup>	2000	1	34	1 Men-FVII	1 EA	40	5	1
Panek <i>et al.</i> <sup>83</sup>	2002	1	40	1 OC	1 DS	20	2	1
Sajdak <i>et al.</i> <sup>84</sup>	2002	2	54.5 (42–67)	1 EC-UB, 1 VS-VB	–	15.5 (10–21)	2	2/2 (100)
Danilos <i>et al.</i> <sup>85</sup>	2003	1	45	1 EPS	1 DS	80	1	1
Weilbach <i>et al.</i> <sup>86</sup>	2004	1	38	1 UL	1 Hys	92	1	1
Coppola <i>et al.</i> <sup>87</sup>	2004	1	19	1 PM-GT	1 DS	90	78	1
Mairos <i>et al.</i> <sup>88</sup>	2004	1	41	1 UB-GT	1 Hys	NR	2	1
Ciacma <i>et al.</i> <sup>89</sup>	2005	4	66.3 (58–72)	1 EC, 1 MC, 1 UL, 1 UCC	4 Hys	48.0 (17–70)	1.3 (1–2)	4/4 (100)
Erikci <i>et al.</i> <sup>90</sup>	2006	1	41	1 AML-UB	–	40	1	1
Total		14	50.1 (19–72)			51.6 (17–92)	1.8 (1–78)	14/14 (100)

AML, acute myeloid leukaemia; CC, cervical carcinoma; DS, debulking surgery; EA, endometrial ablation; EC, endometrial carcinoma; EPS, extraperitoneal pelvic sarcoma; FVII, factor VII deficiency; GT, Glanzmann's thrombasthenia; Hys, hysterectomy; MC, metastatic carcinoma; Men, menorrhagia; NR, not reported; OC, ovarian cancer; PM, pelvic mass; UB, bleeding from uterus; UCC, uterine and cervical carcinoma; UL, uterine leiomyomas; VB, vaginal bleeding; VS, vaginal sarcoma. Age, initial dose of rFVIIa and number of doses are represented as absolute number or median (range).

\*Response is defined as cessation or significant reduction of bleeding.

\*\*rFVIIa was administered preoperatively in bolus at a dose of 80 microgram/kg followed by a continuous infusion at 10 microgram/kg/hour for 8 hours.

show that rFVIIa may be an alternative haemostatic agent in women with life-threatening PPH or in gynaecological post-operative bleeding unresponsive to conventional therapy. rFVIIa appeared to be particularly effective in the management of obstetric and gynaecological patients with inherited bleeding disorders, in particular those with Glanzmann's thrombasthenia, where the frequent presence of platelet alloantibodies greatly complicates the treatment of bleeding episodes.

It should be outlined that all the currently available data in literature are derived from uncontrolled studies including single cases or small series of patients. Thus, the real effectiveness of rFVIIa in these bleeding situations can be overestimated, those cases with a positive outcome preferentially being reported. Not only does the effectiveness of rFVIIa in obstetric and gynaecological bleeding need further evaluations but so too do the appropriate dosage and cost/benefit ratio, since this is an expensive drug (approximately 1 euro per microgram).

The safety of rFVIIa in massive PPH and gynaecological bleeding is an issue of concern, especially with the recent report of a high rate of thromboembolic adverse events after the use of rFVIIa in women without a pre-existing coagulopathy.<sup>91</sup> Although the analysis of the 79 cases treated with rFVIIa for severe obstetric and gynaecological bleeding in the reported literature revealed no thrombotic episodes, we recommend particular caution in using this drug in women at higher thrombotic risk such as those with PPH and systemic activation of coagulation or with gynaecological cancers.

In conclusion, due to the paucity of published data, we advise the physicians to follow the currently accepted recommendations<sup>62</sup> with regards to the dose and timing of rFVIIa administration and to monitor closely such women not only for the clinical efficacy but also for the onset of adverse events. ■

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