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Update in the management of severe PPH and the role of rFVIIa

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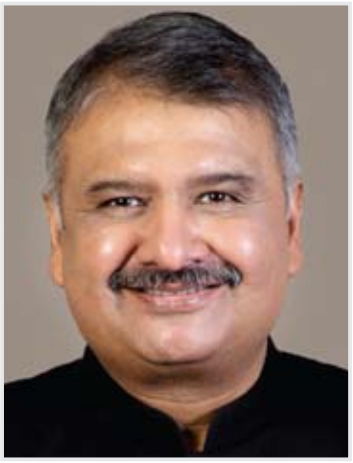

Dr Jaydeep Tank
President, FOGSI

Dear Colleagues,

Postpartum hemorrhage (PPH) is a life-threatening obstetric emergency and the leading cause of maternal mortality worldwide. Any bleeding that results in, or has the potential to result in, hemodynamic instability if left untreated must be classified as PPH. There is a broad consensus within the medical community on the importance of both preventing and promptly treating PPH. The core approach to managing this condition starts with non-invasive and nonsurgical methods, followed by more invasive and surgical interventions if necessary. However, despite these efforts, maternal mortality from PPH remains alarmingly high, underscoring the need for further advancements in treatment protocols.

One promising advancement is the use of recombinant activated factor VII (rFVIIa), which has shown potential in improving outcomes in severe cases of PPH.

As noted by Dr. Jaydeep Tank, President of the Federation of Obstetric and Gynecological Societies of India (FOGSI), "While progress has been made in managing PPH, the need for continuous innovation and adoption of new therapeutic approaches is critical to saving lives. The introduction of therapies like rFVIIa represents a significant step forward in the fight against maternal mortality, and we must continue to explore and implement such advancements to ensure the safety and well-being of women in India and globally."

This ongoing commitment to research and development is essential to reducing the burden of PPH and achieving better maternal health outcomes.

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FOGSI FOCUS: Update in the management of severe PPH & the role of Recombinant Factor VIIa

1. Burden of postpartum haemorrhage & current management

Maternal mortality refers to the death of a woman due to complications arising during pregnancy, childbirth, or within 42 days after pregnancy termination, regardless of the pregnancy's duration and site of pregnancy, but excluding accidental or incidental causes.[1]

Maternal Mortality Ratio is the key indicator of maternal mortality and is defined as the number of maternal deaths per 100,000 live births.[1] As per the latest data from World Health Organization (WHO) and United Nations Children's Fund (UNICEF) (2017), India accounts for 12% of world maternal deaths.[1]

In 2020, the global prevalence of Maternal Mortality Ratio (MMR) was 223 per 100,000 live births.[2] The United Nations' (UN) Sustainable Development Goals (SDG) target is to reduce the global MMR to <70 per 100,000 live births by 2030. The data from the Health Management Information System (HMIS), Census of India, and Sample Registration System (SRS) indicates that 70% of Indian districts (448 out of 640 districts) have recorded MMR above 70 deaths, which is higher than the set SDG target by UN.[1,3]

Postpartum haemorrhage: A leading cause of maternal mortality

Postpartum haemorrhage (PPH) is the most common cause of maternal death.[4] Globally, PPH accounts for about 35% of all maternal deaths. The prevalence of PPH is 2%–4% following vaginal delivery and 6% after a caesarean section.[1] In India, obstetric haemorrhage is the leading cause of maternal death, accounting for 47% of cases.[1,5]

Most deaths from severe PPH typically occur within the first 24 hours after delivery. The progression from the compensated to the decompensated stage of haemorrhage occurs quickly and can be easily missed. Therefore, early prediction, recognition, and intervention are crucial to reduce the risk of severe PPH and improve clinical outcomes.[1,6]

Definition of PPH and severe PPH

Figure 1. Clinical definition of PPH

Ministry of Health and Family Welfare [4]	• PPH is defined as a blood loss of 500 mL or more within 24 hours after birth, or a small blood loss that makes the woman haemodynamically unstable. • Massive/severe PPH is defined as a blood loss of 1,000 mL or more within the same timeframe.
World Health Organization [7]	• PPH is commonly defined as a blood loss of 500 mL or more within 24 hours after birth, while severe PPH is defined as a blood loss of 1,000 mL or more within the same timeframe.

PPH, Postpartum haemorrhage

However, the definition of severe PPH cannot be universal and can vary based on multiple factors such as volume of blood loss, rate of blood loss, and shock index.[8]

Modified shock index: Defined as heart rate (HR) to mean arterial pressure (MAP), with a normal range of 0.5–0.7 in healthy adults (Table 1).[1]

Table 1. Correlation of shock index and mortality rates[1]

Status of shock	Shock index	Mortality rate	Blood products#
No shock	<0.6	10.9% mortality	1 unit
Mild shock	≥0.6 to <1.0		2.8 units
Moderate shock	≥1.0 to <1.4		9.9 units
Severe shock	≥1.4	39.8% mortality	11.4 units

#The values in the table represent the number of blood product units suggested for patients within each shock index category, not the average.

Current management of severe PPH

PPH is managed at four levels: Zero hour, Medical management, Mechanical management, and Surgical management.[1]

- **Zero Hour:** Ensure ABCDE response (airway, breathing, circulation, disability, exposure), collection of blood samples, catheterization, recording of vitals, and shock index.
- **Medical management:** Uterine palpation to rule out atony, genital tract examination for any trauma, manual examination and bedside ultrasound for retained placental tissue, assessment of blood coagulation disorders, pharmacological agents (uterotonics, anti-fibrinolytic agents), blood transfusion.
- **Mechanical management:** Bimanual compression, uterine balloon tamponade, non-pneumatic anti-shock garment, aortic compression.
- **Surgical management:** Uterine compression sutures, stepwise devascularization, uterine artery embolization, hysterectomy.

(For detailed information on the treatment algorithm of PPH, please refer to PPH Prevention and Management: Updated PPH Guidelines by FOGSI).[1]

Various guidelines on PPH often recommend a multidisciplinary approach for the control of the bleeding. Treatment should target the underlying cause of PPH, which may include uterine atony, genital trauma, retained placenta, or coagulopathy. Therapeutic interventions should proceed sequentially from less invasive methods to more complex and aggressive approaches.[9]

Unmet need in the management of severe PPH

Invasive procedures used to treat PPH are associated with various complications and could affect future fertility and pregnancy outcomes.[10] According to a meta-analysis, women who have undergone uterine artery embolization in the past are more likely to experience increased rates of placenta accreta spectrum and postpartum haemorrhage in subsequent pregnancies.[11] The main complications related to emergency peripartum hysterectomy include transfusions, need for re-exploration because of persistent bleeding and febrile morbidity, major surgical complications or maternal death.[12]

Massive transfusion is an essential intervention for haemorrhagic shock but carries significant potential complications. The lethal triad of acidosis, hypothermia, and coagulopathy associated with massive transfusion is linked to a high mortality rate. Furthermore, additional complications include hypothermia, acid/base imbalances, electrolyte irregularities (such as hypocalcemia, hypomagnesemia, hypokalemia, and hyperkalemia), citrate toxicity, and transfusion-associated acute lung injury (TRALI). Blood transfusion in trauma, surgery, and critical care has been identified as an independent predictor of multiple organ failure, systemic inflammatory response syndrome, heightened infection, and increased mortality in various studies.[13]

Despite advancements in healthcare, severe PPH continues to be a significant cause of maternal morbidity and mortality.[1] Therefore, there is a need for rapid-acting non-invasive medical interventions to avoid the need for surgical procedures and to decrease the requirement for massive blood transfusions. A recent and innovative advancement in the treatment of severe PPH involves the utilization of recombinant activated factor VII (rFVIIa).[14, 15]

2. Recombinant factor VIIa

Approved indication of rFVIIa for severe PPH in India

Indian health authority, Central Drugs Standard Control Organisation (CDSCO) approved rFVIIa (Eptacog alfa) "***for treatment of severe PPH when uterotonics are insufficient to achieve haemostasis***" in 2022.[14, 15]

As per label approval, rFVIIa can be considered anytime after the failure of uterotonics to arrest the bleeding in the patient with severe PPH (Figure 2).

Dose range and dose interval[14, 15]

- The recommended dose range for the treatment of bleeding is 60–90 µg per kg body weight administered by intravenous bolus injection.
- Peak coagulant activity can be expected at 10 minutes.
- A second dose can be administered based on clinical response of the individual patient. It is recommended that in case of insufficient haemostatic response, a second dose can be administered after 30 minutes.

rFVIIa: Mechanism of action

The mechanism by which rFVIIa controls bleeding involves its localized action at the site of vascular injury, initiation of the coagulation cascade, generation of thrombin bursts, and formation of a stable haemostatic plug (Figure 3).[16,17]

Localized action

- rFVIIa exerts its action locally at the site of vascular injury, where tissue factor (TF) is expressed and activated platelets are present.

Initiation of the coagulation cascade

- The coagulation cascade is initiated when endogenous factor VIIa or rFVIIa binds to TF, leading to the generation of thrombin in small quantities. ❶

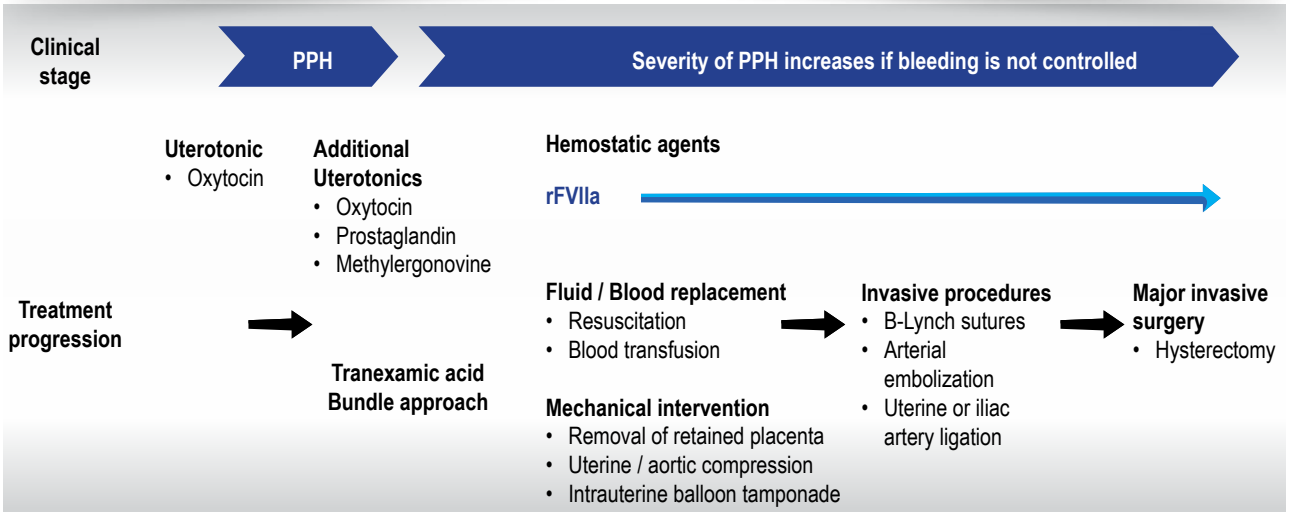
Generation of thrombin bursts

- When given in pharmacological doses, rFVIIa triggers direct activation of FX on activated platelets. ❷
- This leads to increased production of thrombin (Thrombin burst) through the combined action of FXa and FVa.

Formation of a stable haemostatic plug

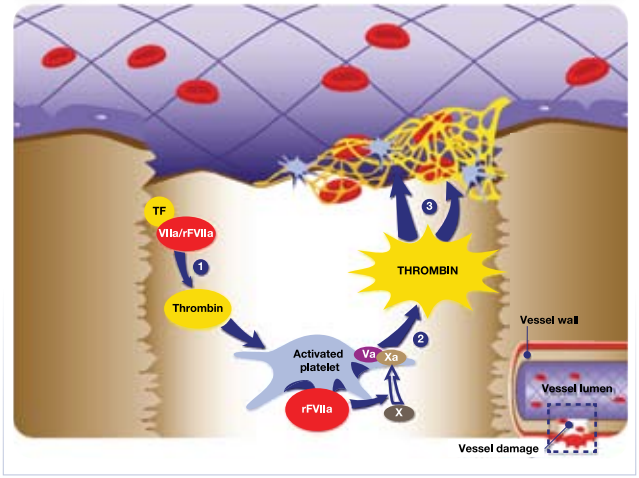
- This thrombin burst leads to the formation of a stable haemostatic plug at the site of vascular injury, which controls bleeding and prevents further blood loss. ❸

Figure 2. Positioning of rFVIIa in the management of severe PPH as per Indian label approval



"International and local guidelines have been developed for the management of PPH, there are variations across the guidelines but they follow a similar escalation protocol"

Figure 3. Mechanism of rFVIIa[17]

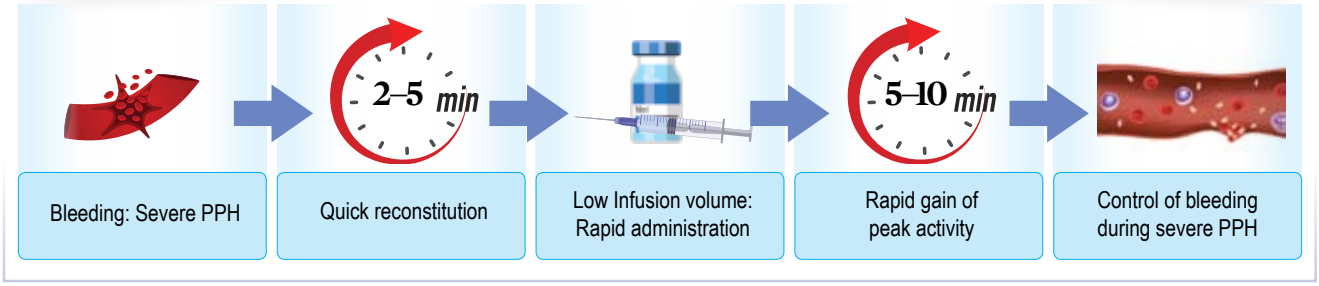


(Please refer to Hoffman M et al. 2001 for detailed explanation of cell-based haemostasis and mechanism of action of rFVIIa)[16]

Rapid and safe initiation of treatment with rFVIIa

- The administration process of rFVIIa begins with reconstituting the drug, typically taking 2–5 minutes, enabling a prompt response in patients with severe PPH.[18]
- Additionally, its low infusion volume of only 5 mL facilitates rapid administration.[18]
- When administered as an IV bolus, rFVIIa reaches its peak activity within 5–10 minutes, making it particularly relevant for the rapid bleed management in a patient with severe PPH (Figure 4).[18]

Figure 4. rFVIIa offers faster control of bleeding with easy and quick reconstitution process, small infusion volume, and rapid gain of peak activity [18]



3. Review of literature: Efficacy and safety of rFVIIa for the management of severe PPH

Global evidences

Recombinant human FVIIa for reducing the need for invasive second-line therapies in severe refractory PPH: A multicenter, randomized, open controlled trial

Lavigne-Lissalde G et al.[19]

- A multi-centre, randomized, open-controlled trial was conducted to evaluate the effect of rFVIIa on reducing the need for invasive second-line therapies such as interventional haemostatic procedures, blood loss, and transfusions in severe refractory PPH.
- A total of 84 females were randomised to either the group receiving one early single rFVIIa infusion of 60 µg/kg with standard of care (n = 42) or the group receiving only standard of care (no rFVIIa; n = 42) after failure of sulprostone therapy for arresting the bleeding.
- The primary efficacy outcome was the reduction in the need for specific second-line therapies (uterine compression sutures, ligation of the uterine or iliac arteries, uterine artery embolization, peripartum hysterectomy, and the bakri balloon method). The primary safety outcome included deaths and thrombotic events within 5 days following rFVIIa infusion.

Results:

Efficacy outcome

- The use of rFVIIa significantly reduced the number of patients who required second-line therapies compared to the standard-of-care group to arrest the bleeding. The primary efficacy outcomes are detailed in Table 2.
- In the standard of care arm, 93% of patients needed second-line therapies, whereas in the rFVIIa arm, only 52% of patients required such treatments for arresting bleeding. This represents an absolute difference of 41% and a relative risk reduction of 44% (RR=0.56).
- After randomization, the percentages of women requiring packed red blood cells, fresh frozen plasma, and platelet concentrate in the standard care arm and rFVIIa group were 67% vs. 60%, 48% vs. 45%, 31% vs. 26%, respectively.
- The fall in haemoglobin (>2g/dL) was higher in the standard care arm than in the rFVIIa group (30% vs. 15%, p=0.18).
- The delivery mode (vaginal or caesarean section) did not affect the primary outcome.

Compassionate treatment

For compassionate reasons, patients assigned to the standard care arm and with very severe PPH received late rFVIIa treatment at similar doses. This was done to avoid an emergency peripartum hysterectomy. Out of 42 patients in the standard arm, 8 received compassionate treatment in the form of late administration of rFVIIa to avoid hysterectomy. As a result, peripartum hysterectomy was avoided in two cases.

Safety outcome

- Two venous thrombotic events were reported in the intervention arm. In both cases, this event was associated with typical risk factors (C-section, placental abruption, IUFD) to develop

Table 2. Efficacy outcome

Outcomes	Standard arm (N=42) n (%)	Intervention arm (N=42) n (%)	Absolute difference [95% CI]	Relative risk [95% CI]	Mean NNT	p
Primary efficacy outcome	39 (93)	22 (52)	41% [18; 63]	0.56 [0.42; 0.76]	2.6	<0.0001
Arterial embolization	24 (57)	12 (29)	28% [-4; 61]	0.5 [0.29; 0.86]	3.5	0.0082
Arterial ligation	12 (29)	9 (21)	8% [-30; 44]	0.75 [0.35; 1.59]	14	0.45
Peripartum hysterectomy	8 (19)	3 (7)	12% [-28; 52]	0.38 [0.11; 1.32]	8.4	0.11
Others	6 (14)	4 (10)	4% [-36; 44]	0.67 [0.20; 2.19]	25	0.5

CI, Confidence interval; NNT, Number needed to treat

thromboembolism (TE) and occurred despite receiving thromboprophylaxis. Recovery was uneventful after the initiation of treatment.

- No maternal death occurred during the trial.
- No additional thrombotic event and no serious adverse event were reported during the first six weeks postpartum.

> *rFVIIa was associated with a 44% relative risk reduction in the requirement of second-line invasive therapies to control bleeding in patients of severe PPH unresponsive to uterotonics as compared to standard care arm.*

Use of recombinant activated factor VII in massive PPH

Bouma L et al., [20]

- A retrospective study was conducted among 27 patients treated with rFVIIa for massive PPH. The study aimed to assess the effect of rFVIIa in terms of reduction of bleeding and prevention of hysterectomy.
- The positive effect was defined as reduction or cessation of bleeding, with uterine preservation (avoidance of hysterectomy) as a key endpoint for maternal morbidity. The mean (± standard deviation) rFVIIa dose per administration was 79±25 µg/kg (3.9 KIU/kg).
- The main cause of PPH was uterine atony which was present in 82% of patients.

Results:

- A total of 27 cases were reported in this descriptive study conducted retrospectively. Among these, 21 patients were administered with rFVIIa to prevent hysterectomy. rFVIIa successfully prevented hysterectomy in 76% of these cases.
- A reduction or cessation of bleeding after rFVIIa administration was observed in 89% of women (24 out of 27).
- Significant reductions in blood product requirements (fresh frozen plasma, red blood cells, and platelets) were observed following rFVIIa administration.
- In 89% of cases, estimated blood loss prior to rFVIIa administration was more than 3 L, and more than 8 red blood cell units were transfused. 63% of cases had blood loss less than 1 L after rFVIIa administration.

> *The study concluded that rFVIIa can be effective in reducing bleeding as well as preventing the need for an emergency hysterectomy.*

Use of recombinant activated factor VII in severe PPH: Data from the Italian Registry: A multicentric observational retrospective study

Barillari G et al.[21]

- A retrospective survey was conducted on patients treated with rFVIIa for severe primary PPH cases.
- The records of anamnestic, clinical, and haemostatic parameters were collected for 35 patients with PPH. These patients were then compared for coagulation parameters and transfusion requirements before and after the intervention with rFVIIa.
- The first dose of rFVIIa was 87.5 µg/kg, and the second was 55 µg/kg*. The second or last dose was given on a need basis.
- The aetiological factors responsible for PPH were uterine atony (60%), uterine or birth canal laceration (17.2%), placenta accreta (14.4%), pre-eclampsia (14.4%), placenta praevia (5.7%), abruptio placentae (2.8%), amniotic fluid embolism (2.8%), and severe retained placenta (2.8%)

Result:

- **Clinical response**: Complete or major response was reported in 80% of patients (Table 3).

Table 3. Clinical response to rFVIIa treatment

Clinical response	Patients (%)
Complete response (reduction >90%)	51.4
Major response (reduction 50–90%)	28.6
Minor response (reduction 30–50%)	8.6
No response (reduction <30%)	11.4

- **Transfusion requirement and estimated blood loss:** Administration of rFVIIa significantly reduced transfusion needs (Table 4).

Table 4. Transfusion requirements before and after rFVIIa administration

	Before rFVIIa	After rFVIIa	Median reduction following rFVIIa (%)	p
Red blood cells (units)	6	2	66.7	<0.002
platelet concentrates (units)	1.5	0	100	<0.001
Fresh frozen plasma (mL)	1250	0	100	<0.029
Colloids and crystalloids (mL)	3000	1250	58.3	<0.0042

- **Estimated blood loss:** The estimated median blood loss was 2,500 mL (1,000–10,250 mL) before rFVIIa treatment and 300 mL (100–1,900 mL) after rFVIIa treatment.
- **Haemostatic parameters:** There was a significant reduction in the international normalised ratio (INR) and a rise in fibrinogen levels administration of rFVIIa (Table 5).

Table 5. Change in haemostatic parameters before and after rFVIIa administration

Haemostatic parameters	Median [range]			% of patients with pathologic values	
	Before rFVIIa	After rFVIIa	Reduction/ increase following rFVIIa (%)	Before rFVIIa	After rFVIIa
International normalized ratio	1.4 [0.96–4.19]	1.07 [0.7–1.9]	↓ 23.5% (p <0.0008)	52.2	4
Fibrinogen	107 [60–386]	170 [75–382]	↑ 58.8%	47.8	3.7

- **Adverse effects of rFVIIa treatment:** No reports of venous (superficial vein thrombosis, deep vein thrombosis, or pulmonary embolism) or arterial complications (ischaemic stroke, myocardial infarction, another arterial occlusion) on the 28th day post-treatment or maternal deaths were observed.

> *Treatment with rFVIIa was associated with improvements in haemostatic parameters, a decreased need for transfusion products, and fewer medical and surgical interventions in patients with PPH.*

Recombinant human factor VIIa prevents hysterectomy in severe postpartum haemorrhage: Single-center study

Huber A et al.[22]

- The aim of this prospective study was to evaluate the effectiveness of rFVIIa in preventing hysterectomy in patients with PPH.
- 22 patients with severe PPH received rFVIIa treatment as a last resort before hysterectomy, following the failure of both medical and surgical (uterine-preserving) management.
- The presence of disseminated intravascular clotting (DIC), which was detected to some extent in 18 patients at the time of treatment, was confirmed by a haematologist in each case.
- rFVIIa was injected intravenously with a single mean dosage of 71 µg/kg body weight.

Results:

- The study results showed that in 91% of cases (20 out of 22 cases), rFVIIa successfully arrested the bleeding and prevented a hysterectomy. Postpartum hysterectomy was required in the remaining two patients with placenta increta (Tables 6 and 7).

Table 6. Blood count values and need for blood products before and after rFVIIa treatment

	Prior to rFVIIa treatment	After rFVIIa injection	p
Mean haemoglobin (Hb)	70.3 g/L (40-18 g/L)	90.8 g/L (66-120 g/L)	<0.001
Mean haematocrit	0.21 (0.12-0.35)	0.26 (0.19-0.35)	<0.002
Erythrocyte concentrates (EC)	9.7 units (2-18 units)	2.6 units	=0.001
Fresh frozen plasma substitutions	6.8 units	1.8 units	<0.001
Thrombocyte transfusion	1.2 units	0.2 unit	<0.001

Table 7. Pre- and post-partial normalisation of coagulative values

	Before rFVIIa treatment	24 hours after rFVIIa treatment	p
Mean values of fibrinogen	1.8 g/L	4.1 g/L	<0.001
PTT	80.50%	100%	<0.001
INR	1.21	1	<0.01

INR, International normalised ratio; PTT, Partial thromboplastin time

- No thromboembolic event was reported in this case series up to 6 weeks postpartum follow-up. Two women had a history of central pulmonary thromboembolism, for which they received anticoagulant medication during pregnancy. Despite their history, both patients did not show any clinical evidence of relapse or thromboembolic complications while receiving rFVIIa therapy.

> *The administration of rFVIIa proved effective in preventing postpartum hysterectomy after conservative medical and surgical interventions had failed.*

Recombinant activated factor VII in the management of severe postpartum haemorrhage: Initial report of a multicentre case series in Japan

Kobayashi T et al. [23]

- A multicentre case study was conducted to evaluate the role of rFVIIa in the management of severe PPH. rFVIIa (median dosage per single dose of 84.0 µg/kg) was received by 25 patients for obstetric haemorrhage.
- The clinicians assessed the effect of rFVIIa on bleeding (Stopped, Decreased, and Unchanged, Table 8).

Results:

- A significant reduction in blood loss was noted before vs. 24 hours after the first/final dose of rFVIIa (7,130 mL vs. 1,260 mL/1,010 mL; p<0.0001).

Table 8. Effects of rFVIIa administration on bleeding

Parameter	After the first administration (%)	After the final administration (%)
Stopped	32	64
Decreased	40	32
Unchanged	28	4

- The study also revealed a decrease in the need for blood products following the rFVIIa administration (Table 9).

Table 9. Requirement of blood products within 24 hours pre- and post-rFVIIa administration

Parameter	Before rFVIIa	After rFVIIa	p
Red blood cell (U)	24	8	<0.0001
Fresh frozen plasma (U)	2,400	1,200	0.0034
Platelet concentrate (U)	20	20	0.0290

- Out of 25 patients, 13 (52%) required a hysterectomy. Of these, 11 patients underwent the procedure before rFVIIa administration. Following the administration of rFVIIa, only two patients needed a hysterectomy.

> *rFVIIa was an effective therapy in massive obstetric haemorrhage; it efficiently controlled bleeding, significantly reduced amount of blood loss, decreased the requirement of blood products.*

Recombinant activated factor VII in obstetric haemorrhage: Experiences from the Australian and New Zealand Haemostasis Registry

Phillips L et al. [24]

- A retrospective study was conducted to evaluate the data obtained from the Australian and New Zealand Haemostasis Registry for all obstetric haemorrhage patients (n=105) treated with rFVIIa.
- Patients received median (interquartile range) individual doses of 92 µg/kg (73–100) of rFVIIa (median total dose 92 µg/kg [58–108])*, and 78% of patients received a single dose.

Results:

- The efficacy was reported in 94 cases, of which, 64% experienced a decrease or cessation of bleeding after the first dose. Following the final dose of rFVIIa, bleeding was decreased or stopped in 76% of patients.
- Only 21% required a hysterectomy after receiving rFVIIa treatment.

> *The positive response rate (for reduction/cessation in bleeding) to rFVIIa was 76% with 64% responding to the first dose. Hysterectomy was avoided in 79% of patients after rFVIIa therapy.*

Use of recombinant activated factor VII: Pakistani experience of managing massive obstetric haemorrhage

Salman N et al. [25]

- A retrospective cross-sectional comparative study evaluated the effect of rFVIIa among 12 patients with PPH.
- rFVIIa was administered intravenously in a dose of 90 µg/Kg body weight to patients when conventional medical and surgical treatment of PPH was found to be ineffective in arresting bleeding.
- Patients were categorized and compared into two groups: the early group (n=6), who received rFVIIa within 6 hours of haemorrhage, and the late group (n=6), who received rFVIIa after 6 hours of haemorrhage.
- The study compared both groups regarding transfusion requirement, ICU/hospital stay, and fertility preservation.

Results:

- The results revealed that all patients in the early group experienced statistically significant lesser ICU/hospital stay and mean transfusion requirement and fertility preservation in all patients.

> *Early administration of rFVIIa was successful in preventing hysterectomy in all patients and reducing hospital/ICU stay and mean transfusion requirement compared to late group.*

Standardized management protocol in severe postpartum hemorrhage: A single-center study

Colucci G et al.[26]

This single-centre study included a study cohort (SC) of 27 women with severe PPH after vaginal or caesarean delivery. The SC was treated as per the standardised intervention and rFVIIa. The protocol for PPH management in both vaginal and caesarean delivery is shown in Figures 5 and 6. The SC was compared to historical cohort 1 (HC 1; n = 20) and historical cohort 2 (HC 2; n = 27) for over a period of 33 months. HC 1 was treated with different strategies with an in-house guideline for rFVIIa administration to manage massive bleeding. HC 2 was treated with no specific guideline.

Results:

- During the study, the number of labile blood product units that were transfused was lower in the study group compared to both historical cohorts. Table 10 shows the defined amount of required blood products.
- Comparing the SC to the HC 1 and HC 2, the estimated total blood loss was notably lower in the SC (HC 1: 4,500 mL; HC 2: 6,000 mL; SC: 3,000 mL, p=0.004).
- In the HC 1, 25% of women underwent hysterectomy, compared to 37% in HC 2, and only 3.7% in the SC (p=0.012), suggesting a decreased need for the procedure after implementing the standardised protocol.

Table 10: Percentages (%) of patients and blood products received.

	Historical Cohort 1 (N=20)	Historical Cohort 2 (N=27)	Study Cohort (N=27)	p
Red blood cell concentrates median (IQR)	12 (8–16)	12 (6–16)	6 (3–9)	0.007
Fresh frozen plasma median (IQR)	10 (7–13)	10 (4–12)	5 (2–8)	0.004
Platelet concentrates median (IQR)	2 (1–3)	1 (0–2)	1 (0–1)	0.020

IQR; Interquartile range

> *The study concluded that standardised management protocol with rFVIIa was effective in reducing the need for labile blood products as well as emergency postpartum hysterectomy compared to other treatment protocols followed for patients in HC 1 and HC 2.*

Figure 5: Protocol for PPH management after vaginal delivery.

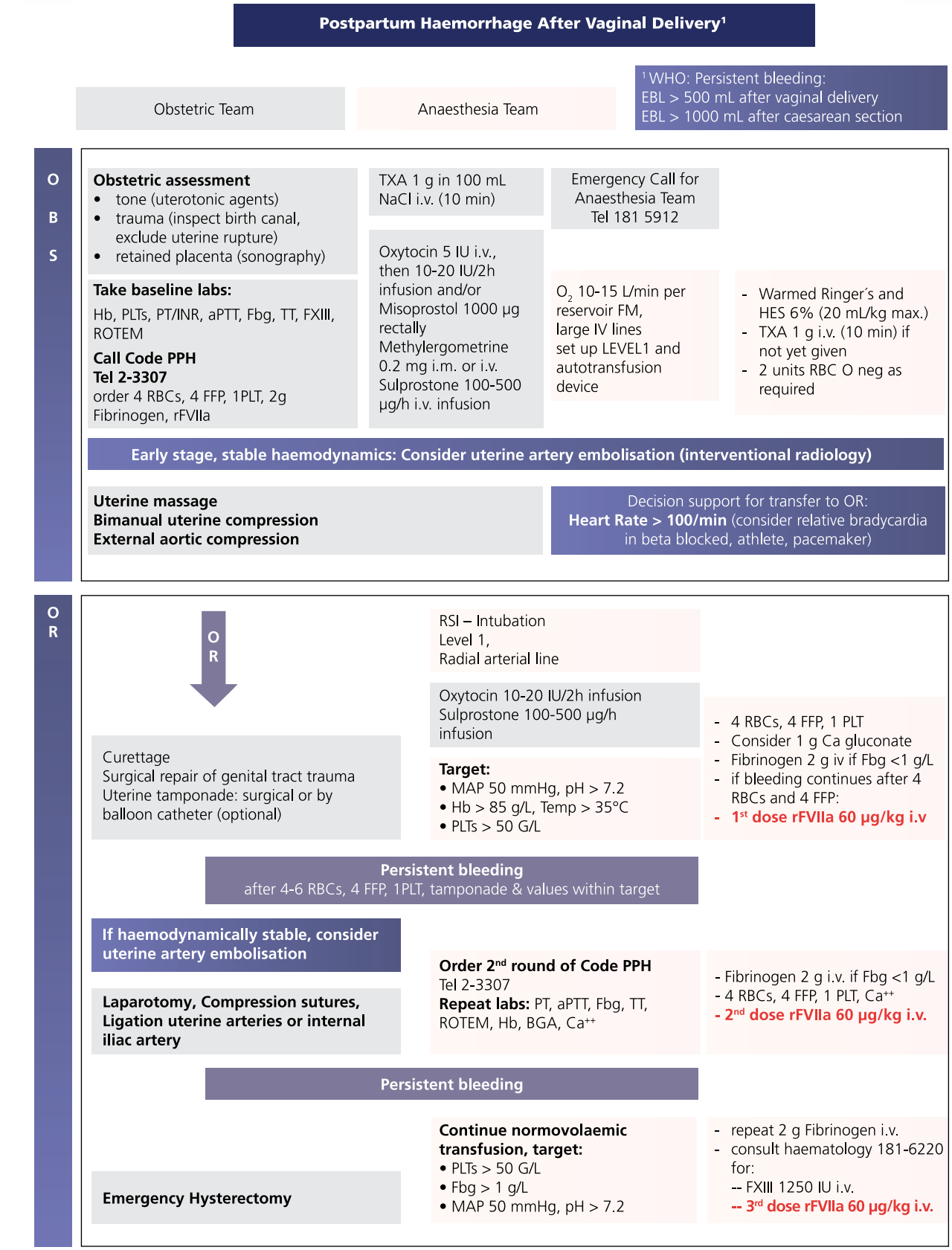
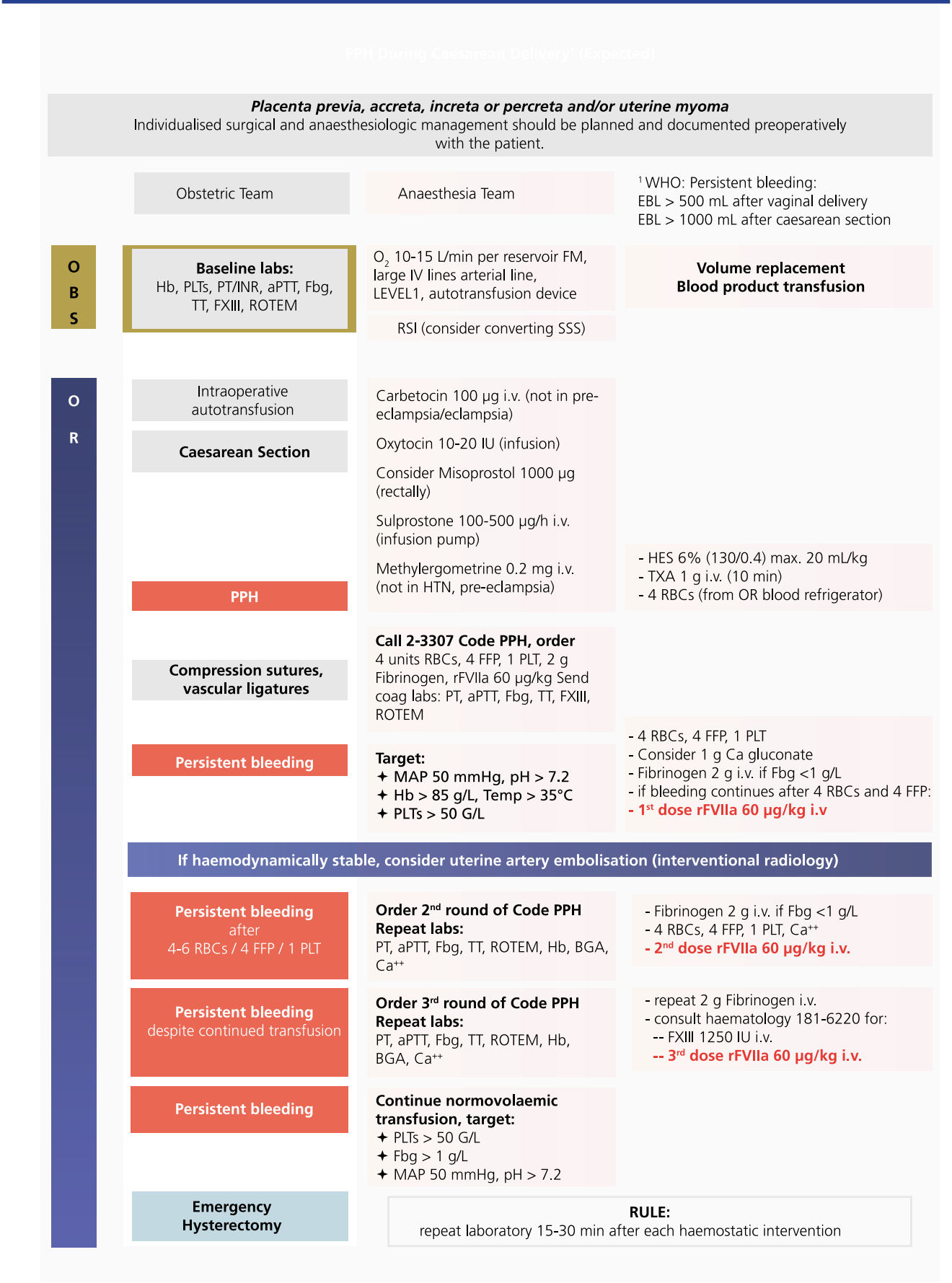


Figure 6: PPH management after caesarean delivery.



Indian evidences

Recombinant factor VIIa: Use in fatal postpartum haemorrhage – Indian experience case series and review of literature

Singi S et al.[27]

- A study was conducted to evaluate the efficacy of rFVIIa in the management of ongoing bleeding in patients (n=10) with massive PPH, unresponsive to aggressive transfusion of blood products.
- The causes of bleeding and surgical interventions are listed in Table 11.

Table 11. Causes of bleeding and surgical interventions.

Particulars	C 1	C 2	C 3	C 4	C 5	C 6	C 7	C 8	C 9	C 10
Cause of Bleeding	AT	PHC	AP	PP	AT	AT	AT	PP	AT	AT
Associated condition	DIC	DIC	DIC	-	DIC		DIC	DIC	ARF TTP	DIC ARF
Interventions	Hys	NIL	Hys	Hys	Hys	Hys	Hys	Hys	Hys	Hys

C: Case, AT: Atonic uterus, AP: Abruptio placenta, ARF: Acute renal failure, DIC: disseminated intravascular coagulation PP: Placenta percreta, ARF: Acute renal failure, Hys: Hysterectomy, PHC: Post hepatitis coagulopathy

Results:

- 9 out of 10 cases ended with a hysterectomy due to excessive bleeding before giving rFVIIa. rFVIIa was administered when bleeding persisted.
- Massive PPH led to DIC in 6 patients.
- All patients were administered rFVIIa at 20–80 µg/kg* doses with adequate blood products. Only 2 patients required a second dose of rFVIIa to arrest the bleeding. A significant reduction in the amount of bleeding after rFVIIa was observed (Table 12).
- Blood product requirements before and after rFVIIa are mentioned in Table 13.
- The amount of bleeding after rFVIIa was decreased (Table 14).

Table 12. Dose of rFVIIa administered

Particulars	C 1	C 2	C 3	C 4	C 5	C 6	C 7	C 8	C 9	C 10
No. of doses	1	1	1	2	1	1	1	2	1	1
Dose in µg/kg	76.8	44.4	48	75 37.5	42.8	45.7	42.1	67.9 45.2	18.7	42.8
Total dose of rFVIIa (mg)	4.8	2.4	2.4	4.8	2.4	2.4	2.4	3.6	1.2	2.4

C: Case

Table 13. Blood products requirement before and after rFVIIa

Particulars	C 1	C 2	C 3	C 4	C 5	C 6	C 7	C 8	C 9	C 10
Blood products requirement before rFVIIa										
Packed cells	25	8	19	12	10	14	11	10	17	3
Fresh frozen plasma	39	28	22	28	22	9	18	12	28	8
Cryo-precipitate	36	5	5	15	10	16	10	15	15	0
Platelets	48	36	24	16	16	16	32	27	23	10
Blood products requirement after rFVIIa										
Packed cells	1	2	1	2	Nil	4	Nil	1	1	Nil
Fresh frozen plasma	4	8	0	12	10	Nil	Nil	4	12	Nil
Cryo-precipitate	0	0	0	4	Nil	0	0	0	0	0
Platelets	4	0	0	0	0	0	0	0	4	Nil

C: Case

Table 14. Amount of bleeding before and after rFVIIa

Particulars	C 1	C 2	C 3	C 4	C 5	C 6	C 7	C 8	C 9	C 10
Bleeding (in Litres) before rFVIIa	25	7	18	15	12	14	10	12	11	10
Bleeding (in Litres) after rFVIIa	1.5	Nil	Nil	0.4	Nil	Nil	Nil	0.2	Nil	Nil

C: Case

"rFVIIa proved to be an effective agent in prompt correction of massive PPH which was refractory to aggressive transfusion of coagulation factors. Administering rFVIIa contributed significantly to curtailing the bleeding and minimizing the requirement of blood products."

Recombinant activated factor VII in postpartum haemorrhage

Magon N et al.[28]

In this study, Magon et al. reported the successful management of five cases of PPH with the use of rFVIIa (Table 15).

Table 15. Case summary and role of rFVIIa in the management

Case	Cause	Interventions	Pre-rFVIIa outcome	Post-rFVIIa outcome
1	Atonic uterus	• Sequential uterotonics, volume replacement, uterine compression, B/L artery ligation, subtotal hysterectomy	• Bleeding decreased but continued and the patient lost almost 3.5 L of blood	• Bleeding decreased substantially after a single dose of rFVIIa at 60 µg/kg and stopped totally after 2nd dose of 60 µg/kg. • Patient had uneventful postpartum subsequently.
2	Cervical tear and vaginal lacerations	• Suturing, volume replacement, tranexamic acid, vaginal packing	• Uncontrollable bleeding and the patient lost almost 2.5 L of blood	• Bleeding decreased after a single dose of rFVIIa at 60 µg/kg. • Stopped completely after 30 minutes of injection. • The rest of the hospital stay was uneventful.
3	Atonic uterus	• Sequential uterotonics (repeated doses), volume replacement, uterine compression, bilateral artery ligation	• Profuse bleeding with 2 L of blood loss • Prepared for hysterectomy in case bleeding was not arrested	• Bleeding decreased after a single dose of rFVIIa at 60 µg/kg. • Arrested completely after 20 minutes of injection. • Patient had an uneventful recovery.
4	Atonic uterus and multiple vaginal lacerations	• All possible uterotonics • Bimanual uterine compression • Patient and her spouse wanted to preserve fertility	• Profuse bleeding with 2 L of blood loss. • Decided to use rFVIIa and prepared to go ahead with laparotomy and proceeded in case bleeding did not get arrested with the same.	• Within 20 minutes of giving rFVIIa, bleeding from vaginal tears was significantly reduced. • Vaginal packing done and bleeding arrested completely. • Vaginal pack removed after 24 hours.
5	Atonic uterus and bleeding from the fibroids	• Uterotonic drugs and all conservative surgical techniques	• Profuse bleeding despite trying uterotonics and all conservative surgical techniques	• rFVIIa was used at 90 µg/ kg and effective volume replacement was done. • Bleeding got arrested within 20 minutes.

> *rFVIIa administration can be considered before resorting to any surgery in cases of severe PPH when hysterectomy is not otherwise clearly indicated.*

Preliminary experience with the use of recombinant activated factor VII to control PPH in acute fatty liver of pregnancy and other pregnancy-related liver disorders

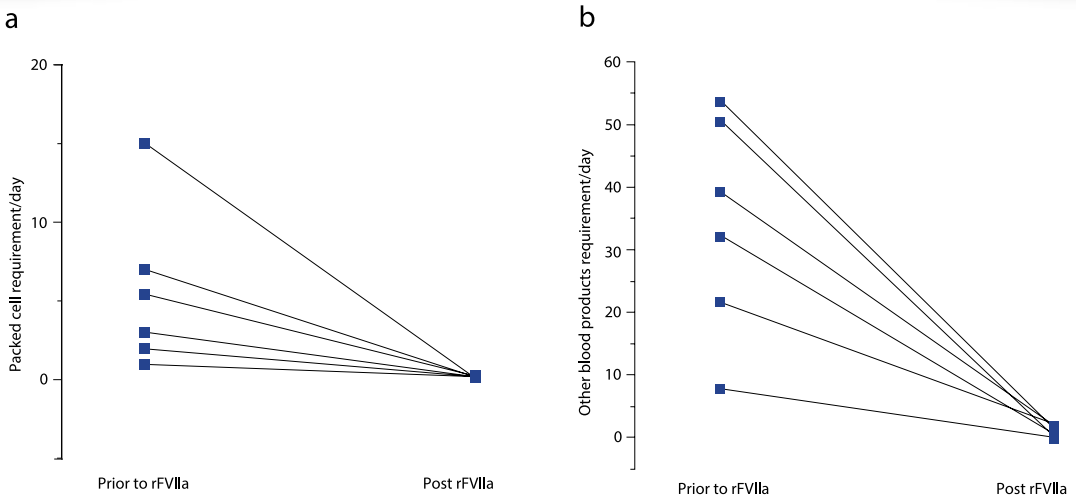
Goel A et al. [29]

- A retrospective study was carried out to report the use of rFVIIa in patients (n=6) with acute liver failure due to pregnancy-related liver disorders.
- There was a persistent severe PPH in six patients despite aggressive treatment (early delivery, coagulopathy corrected appropriately, two patients had prophylactic uterine artery ligation, one had hysterectomy).
- Five patients with caesarean section showed significant intra-abdominal bleeding and one patient with vaginal delivery had bleeding from multiple mucosal sites.

Results:

- rFVIIa administration reduced the requirement of packed red cells (from 6 to 0.1 units/day per patient; p=0.05) and other blood products (from 34 to 1 units/day per patient; p=0.006) (Figure 7).
- Significant improvement in prothrombin time (from 62 to 15 seconds; p=0.05) and activated partial thromboplastin time (from 102 to 34 seconds; p=0.03) was noted after rFVIIa administration.
- Only 1 patient required 2nd dose of rFVIIa.

Figure 7. Significant reduction in daily requirement of packed red cells and other blood products after rFVIIa administration



(PRBCs: packed red blood cells; rFVIIa: recombinant activated factor VII)

> *The administration of rFVIIa was significantly effective in correcting the coagulopathy and reducing the need for PRBCs and other blood products in PPH caused by acute liver failure related to pregnancy-associated liver disorders.*

Long-term safety data

Based on the 30-year safety study published by Neufeld et al, the safety profile of recombinant activated factor VII (rFVIIa) was examined across a cumulative review period from 1 January 1996 through to 31 December 2016. The total exposure over this cumulative review period was approximately 5.4 million standard doses. Thromboembolic events (TEs) reported across all licensed indications were relatively minimal, accounting for 0.00004% (n=217 TEs).[30]

According to the study conducted by Deedler et al., a total of 446 women who were exposed to rFVIIa and 1717 non-exposed controls were examined. Among all the women included in the study, TEs were observed in 1.5% of rFVIIa-exposed women (0.2% arterial and 1.2% venous) and 1.6% of non-exposed women (0.2% arterial and 1.4% venous). The safety analysis indicated that there was no increased incidence of TEs associated with rFVIIa treatment in pregnant patients.[31]

According to a consensus document published by European experts, there is no scientific evidence to suggest that the use of rFVIIa in patients with severe PPH increases the risk of thromboembolic events.[32]

The primary reason for such a favorable safety profile is mainly because of its mechanism of action, as it acts locally only at the site of injury and does not activate systemic coagulation.[33]

Pregnancy is a hypercoagulable state. This is the most important risk factor contributing to thrombosis during pregnancy. Pregnancy increases the risk of Venous thromboembolism (VTE) 4-fold to 5-fold over the nonpregnant state. Overall, the prevalence of VTE in pregnancy is 0.5-2.0 per 1,000 pregnancies and accounts for 1.1 deaths per 100,000 pregnancies. So even if the pregnant patient develops TE event after receiving rFVIIa, it may not be related to rFVIIa. It could be due to the underlying hypercoagulable state of pregnancy.[34]

**Disclaimer: For accurate dosing information & other related details of rFVIIa (Eptacog alfa), please refer to the approved pack insert of NovoSeven®. The recommended dose range of Eptacog alfa for the treatment of bleeding is 60–90 µg per kg body weight as per label approval.*

4. rFVIIa for severe PPH: Indian real-world experience

Interesting cases from Indian authors

Use of rFVIIa in a case of recurrent vaginal haematoma after vaginal delivery

Dr. Asha Verma
Senior Professor, SMS Medical college, Jaipur
Medical Superintendent, Mahila Chikitsalaya, Jaipur

Case presentation:

- A 21-year-old primiparous woman (P1 L1) presented with a vaginal haematoma following a vaginal delivery.
- The initial haematoma measured approximately 8 × 5 cm.
- Drainage was performed by a senior obstetrician, but the following day, a recurrent haematoma of similar dimensions was noted.
- Subsequent drainage procedures were performed, and a laparotomy was conducted to rule out a broad ligament haematoma.
- Drainage of the haematoma was done three times by a senior obstetrician.
- After the 3rd evacuation, haematoma size was 13 × 5 cm.

Treatment:

Considering the recurrent haematoma formation, a decision was made to administer a single dose of 2 mg rFVIIa to aid in its resolution.

Outcome:

- Following the administration of rFVIIa, a notable reduction in haematoma size was observed.
- On the 7th day post-rFVIIa administration, the haematoma measured 4 × 5 cm, and by the 20th day, complete resolution of the haematoma was achieved.

This case highlights the challenges in managing persistent vaginal haematomas post-delivery and the potential role of rFVIIa as a therapeutic option in such cases.

Use of rFVIIa in achieving haemostasis in a patient with persistent bleeding post obstetric hysterectomy

Dr. Atul Ganatra
Consulting Obstetrician Gynecologist & Gynec Endoscopic Surgeon, Fortis Hospital, Mumbai

Case presentation:

- P1L1, 37 years old
- Conceived a twin pregnancy through IVF
- Referred to Fortis Hospital, Mumbai after obstetric hysterectomy for severe PPH following lower segment caesarean section

Upon arrival, the patient was in shock:

- Haemoglobin: 3 g/dL
- Platelets: 75,000 per µL
- International Normalized Ratio: 3
- Fibrinogen: 45 mg/dL
- Pulse: 136/min
- Blood pressure: 70 mm Hg systolic
- Bleeding from vault
- Haematoma upto perinephric space in Figure 8 and post obstetric hystrectomy collpase in Figure 9

Interventions:

- 3 units of packed red blood cells (PRBC), 6 units of fresh frozen plasma, and 6 units of cryoprecipitate were transfused.
- Patient underwent CT angiography, and uterine artery embolization was performed.

Figure 8. CT Scan – Large Haematoma upto perinephric space

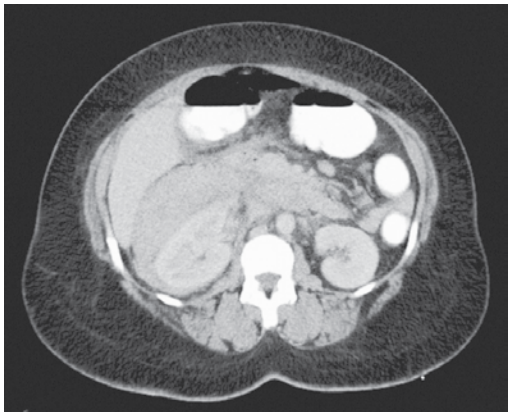
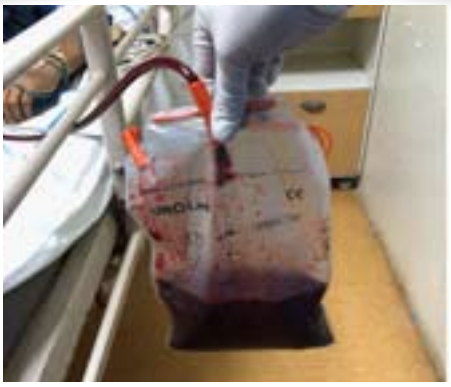


Figure 9. Post obstetric hysterotomy collapse



Despite these interventions, there was persistent bleeding, and the patient's condition continued to deteriorate.

It was decided to administer rFVIIa at this point.

- 2 mg of recombinant activated factor VII (rFVIIa) was administered. Bleeding decreased in 15-20 minutes.
- A second dose of rFVIIa was given after 30 minutes. Bleeding arrested completely after the second dose of rFVIIa.

rFVIIa was successful in achieving haemostasis and stabilizing critically ill patients with persistent bleeding following obstetric hysterectomy and embolization.

Intraoperative use of rFVIIa for atonic severe PPH during a c-section in a patient with HELLP syndrome

Dr. Geeta Sinha
Professor & Head, Department of Obstetrics and Gynecology, Patna Medical college, Patna

Dr. Priyanka Shahi
Senior Resident, Department of Obstetrics and Gynecology, Patna Medical college, Patna

Case presentation:

- A 25-year-old, (G2 P1 L1) at 36 weeks and 5 days of gestation was referred to the emergency department with abnormal liver function test results.
- Upon admission, her haemoglobin was 10.6 g/dL, platelet count was 56,000 per µL, prothrombin test was 18.25 seconds, and serum bilirubin levels were as follows: Total/Direct/Indirect 5.8/2.11/3.69 mg/dL. The patient was diagnosed with jaundice and HELLP syndrome.
- Patient underwent an emergency caesarean section. During the procedure, the uterus became atonic, and the patient started to bleed profusely, with multiple oozing sites from all layers.

Treatment:

- Sequential uterotonics were administered, and 1 gram of tranexamic acid was given.
- Blood transfusions were initiated (1 unit of PRBC, 1 unit of FFP, 1 unit of platelets). Despite these interventions, the bleeding persisted, and the patient had lost 1500 mL of blood by this point.

At this juncture, it was decided to administer recombinant factor VIIa.

Outcome:

- A 2 mg dose of rFVIIa was given, resulting in a decrease in bleeding within 10-15 minutes.
- A second 2 mg dose of rFVIIa was administered after 20 minutes, and the bleeding completely stopped within the following 15 minutes.
- The total amount of blood loss after the administration of rFVIIa was only 300 mL, and invasive procedures were not required to arrest the bleeding.

The timely intraoperative use of rFVIIa successfully stopped the bleeding caused by uterine atony and avoided the need for invasive procedures.

Use of rFVIIa in a case of abruptio placenta with IUD who developed severe atonic PPH

Dr. G. Kuppulakshmi
Professor and Director, FAC
Institute of Obstetric and Gynaecology, Egmore
Madras Medical College, Chennai

Dr. E. Prema Kumari
Professor,
Institute of Obstetrics and Gynaecology Egmore
Madras Medical College, Chennai

Case presentation:

- A 23-year-old primigravida, a known case of gestational diabetes mellitus at 30 weeks of gestation presented with severe pre-eclampsia and abruptio placenta.
- Due to the worsening maternal and fetal conditions, an emergency caesarean section was performed. Patient developed uterine atony postoperatively leading to profuse bleeding.
- Patient's clinical condition rapidly deteriorated due to severe haemorrhage.

Treatment:

- In view of the life-threatening haemorrhage, massive blood transfusion was quickly initiated, including packed red blood cells (PCV 4 units), fresh frozen plasma (8 units), cryoprecipitate (8 units), and platelets (8 units) to correct the coagulopathy.
- Patient's laboratory investigations revealed a Hb: 4.3 mg/dl and platelets: 56,000 per µL
- Despite these efforts, the bleeding persisted, and the patient had lost almost 3 liters of blood.
- Mechanical and surgical measures such as bimanual uterine compression, compression sutures, and uterine artery ligation were attempted but did not effectively control the haemorrhage.

Given the critical nature of the situation, the decision was made to administer a single dose of 2mg of rFVIIa after 1 hour.

Outcome:

- Remarkably, following the administration of rFVIIa, the bleeding ceased after 1 hour.
- The patient did not require any further invasive procedures to arrest the haemorrhage, and her condition stabilized.

The timely administration of rFVIIa proved to be crucial in arresting the life-threatening haemorrhage, ultimately contributing to a positive outcome for the patient.

Use of rFVIIa in a case of severe PPH following placenta previa

Dr. Kusumlata Meena
Senior professor and Unit head, SMS Medical College, Jaipur
Medical Superintendent, Janana Hospital, Jaipur

Case presentation:

- A 30-year-old woman (G5 P4) presented to the emergency department at 32 weeks of gestation with a complaint of bleeding per vagina.
- The patient was diagnosed with antepartum haemorrhage due to placenta previa.
- Following diagnosis, the patient underwent an emergency caesarean section..

Treatment:

- During LSCS, she developed profuse bleeding upon removal of the placenta.
- Bimanual uterine compression was performed initially, but the bleeding persisted.

Subsequently, a decision was made to administer a single dose of 2 mg rFVIIa to control the bleeding.

Outcome:

- Post administration of rFVIIa, the bleeding was significantly reduced within 30 minutes and eventually ceased completely.
- The amount of blood loss before the administration of rFVIIa was 1100 ml, which reduced to 200 ml after rFVIIa administration.
- Notably, the patient did not require any additional surgical interventions to control the bleeding.
- Furthermore, the patient did not develop any side effects following the administration of rFVIIa.

The prompt administration of rFVIIa effectively controlled the bleeding, leading to a significant reduction in blood loss and avoiding the need for further surgical interventions.

Use of rFVIIa during referral in patient of severe PPH with traumatic vaginal delivery

Dr. Minakshi Misra
Professor and Head, Department of Obstetrics and Gynecology, Government Medical College, Dausa, Rajasthan.

Referral history

An 18 years old patient (P1 L1) was referred to our hospital with history of vaginal delivery of a female child weighing 2.5 kg at 3:39 AM at a private hospital. She was referred to the hospital (District hospital, Sikar) due to persistent bleeding from multiple vaginal and cervical tears.

In the labour room:

- Upon arrival, the vaginal packing was removed and found to be fully soaked with blood.
- Multiple tears were identified at the cervix (3 o'clock position), right and left vaginal walls, and episiotomy site.
- Attempts were made to repair the tears and episiotomy in the labour room with resuscitative measures, including crystalloid, haemocele, and a 20-unit oxytocin drip.
- Despite uterine contraction, continuous bleeding persisted.
- Inj. Tranexamic acid 1 gm IV stat was administered, but the bleeding continued.
- The patient was then shifted to the operating theatre (OT). Two units of PRBC were arranged and transfused. The CBC report showed a platelet count of 78,000/µL.

In the operating theatre - findings and management:

- The patient was oozing from all sides of vagina and deteriorating vital signs (BP 60/40 mm Hg, Pulse 140 beats/minute). A noradrenaline drip was started. The attendants were initially refusing to arrange fresh frozen plasma and random donar platelet, so the hospital arranged it.
- **The patient's condition was continuously communicated to the attendants. Attendants requested the transfer of the patient to Jaipur.**

Considering the situation, it was decided to give rFVIIa before the transfer with an intention of arresting the bleed during the transfer.

- 2 mg Inj. rFVIIa IV was slowly administered in the OT and then the patient was shifted to the ground floor from the first-floor OT on a noradrenaline drip.
- But the patient's condition deteriorated, and she started gasping. She was shifted to the pediatrics OPD for oxygenation. The ambulance arrived after half an hour.

Treatment given before administering rFVIIa:

Suturing of all tears and episiotomy followed by packing with roller gauze, Oxygenation, 20 units of oxytocin drip (Labour Room), Inj. Tranexamic acid 1 gm IV stat (Labour Room), Crystalloid drip, Haemacale drip, Inj. Ethamsylate 1 amp IV stat (OT), 2 units of PRBC, Noradrenaline drip, 4 fresh frozen plasma, 2 random donar platelet (RDP) (1 RDP during transfer).

Outcome with rFVIIa:

The patient stopped gasping just before the transfer, 15-20 minutes post-administration of rFVIIa. She was referred with the second RDP drip ongoing in the ambulance.

Follow-up: The patient's condition improved during the transfer from our hospital to Jaipur. **She did not require any surgical intervention or transfusion of blood products in Jaipur.**

rFVIIa can play a crucial role in areas where adequately equipped ICU facilities and blood banks are not available. With the help of rFVIIa, a patient may reach a tertiary care hospital in a better condition for further surgical management if required.

Successful management of severe PPH complicated by DIC with rFVIIa

Dr. Padmaja Samant
Professor and Head,
Department of Obstetrics and Gynecology,
Seth GS medical college and KEM Hospital, Mumbai

Case presentation:

- A 35-year-old woman, (G3 P1 A1), at 39 weeks and 6 days of gestation delivered vaginally.
- Following the delivery, uterus became atonic, and patient started bleeding profusely.
- Her vitals were as follows: Systolic blood pressure (SBP) of 90 mmHg, pulse rate of 120 per minute, and a shock index of 1.33.
- Due to her deteriorating condition, the patient was intubated.
- Laboratory investigations revealed a drop in haemoglobin levels from 8 g/dL to 6.5 g/dL and a decrease in platelet count from 240,000 per µL to 60,000 per µL.

Interventions:

- Sequential uterotonics (Oxytocin, misoprostol, carboprost, methergine) were administered along with 1 g of tranexamic acid.
- Additionally, 6 units of fresh frozen plasma, 6 units of cryoprecipitate, 4 units of platelets, and 1 fibrinogen concentrate were given.
- The patient underwent obstetric hysterectomy. At this point, the approximate blood loss was 1000 mL, while white blood cells and D-dimer levels were observed to be rising, indicating DIC.

At this crucial point, given the onset of DIC, the decision was made to administer rFVIIa.

Outcome:

- Following the administration of 1 mg of rFVIIa, there was initial improvement with bleeding decreasing within 15-20 minutes, although it continued.
- Subsequently, two additional doses of 1 mg of rFVIIa were given at 30-minute intervals, resulting in complete cessation of bleeding within 2 hours.
- The total blood loss before rFVIIa administration was 1000 mL, reducing to 400 mL after its administration.
- A total of 10 packed cells (including before and after rFVIIa administration) were given to stabilise the patient, and FFP was given along with plasma exchange (PLEX).
- The patient was discharged after being treated for infection, possibly attributed to surgery and ICU stay.

rFVIIa effectively achieved haemostasis in the presence of persistent bleeding post hysterectomy in a patient with sepsis and DIC.

Intraoperative use of rFVIIa during LSCS in patient with deranged LFT, KFT, and severe pre-eclampsia

Dr. Premlata Mittal
Senior Professor and Head,
Department of Obstetrics and Gynecology,
SMS Medical College, Jaipur

Case presentation:

- A 29-year-old primigravida at 33 weeks and 5 days of gestation was referred to the emergency department from a peripheral hospital with a history of abnormal liver and kidney function tests, elevated blood pressure, and haematuria.
- Upon admission, it was revealed that the patient was suffering from pre-eclampsia. Her obstetric history indicated that she had conceived through IVF.
- On examination, her blood pressure was 160/102 mmHg, and her heart rate was 88 beats per minute. Blood parameters, including haemoglobin,

platelets, and haematocrit, were all within normal limits.

- The patient underwent an emergency lower segment caesarean section (LSCS), during which the uterus became atonic, resulting in severe bleeding.
- To manage the bleeding, uterotonics and antifibrinolytics were administered. However, these medications were ineffective in controlling the haemorrhage.
- Mechanical interventions, such as bimanual uterine compression and insertion of balloon tamponade, were performed.
- Despite these measures, the bleeding continued, resulting in an 800 mL blood loss.

Treatment:

To prevent further haemorrhage, a single 2 mg dose of rFVIIa was administered intraoperatively.

Outcome:

- Bleeding was arrested in 20 minutes, and further invasive procedures were not required.
- Patient had an uneventful recovery.

rFVIIa was successful in arresting the bleeding due to uterine atony during LSCS in a patient with deranged LFT, KFT, and severe pre-eclampsia.

Use of rFVIIa in a case of atonic Severe PPH with couvelaire uterus and placental abruption

Dr. Sudha Gandhi
Professor & head,
Department of Obstetrics and Gynecology,
RNT Medical College, Udaipur

Case presentation:

- A 24-year-old primigravida at 34 weeks of gestation was transferred from the medical department due to a history of abdominal pain and no per-vaginal bleeding.
- The patient also had a concurrent diagnosis of acute lymphatic leukemia.
- Subsequently, she was diagnosed with abruptio placenta.
- Following this, an emergency caesarean section was performed, during which uterus became atonic resulting in severe bleeding and uterus was found to be Couvelaire uterus.
- Patient's blood parameters at that time were as follows: Haemoglobin – 5.1 g/dL, platelets – 34,000 per µL, WBC - 96,000 per µL.

Treatment:

- Initially, the condition was managed by administering uterotonics, antifibrinolytics, and blood products in an attempt to control the haemorrhage.
- Unfortunately, these interventions proved ineffective, and the patient experienced significant blood loss, amounting to 2000 mL.
- **Recognizing the severity of the situation and the failure of initial treatments, a decision was made to administer a single dose of 2 mg rFVIIa.**

Outcome:

- Following the administration of rFVIIa, the bleeding decreased and eventually ceased completely. The patient did not require any additional invasive procedures to control the bleeding.

A single dose of rFVIIa effectively achieved haemostasis in the presence of severe PPH resulting from uterine atony and placental abruption associated with a Couvelaire uterus.

Clinical experience from eight different centers

Below are the case details of 81 cases from 8 different centers across India where rFVIIa was used to arrest the bleeding in patients with severe PPH. Information regarding baseline characteristics, haematological parameters, the dose of rFVIIa, blood loss and blood product requirements before and after rFVIIa administration, as well as surgical interventions required before and after rFVIIa administration, is outlined in the tables below (Tables 16, 17 and 18).

Table 16. Baseline characteristics and treatment outcome after rFVIIa

Case	Age (yrs)	Obstetric history	Weeks of gestation	Type of delivery	Cause of PPH	Associated condition	Dose of rFVIIa*	Number of rFVIIa doses	Surgical & mechanical interventions used		Outcome
									Before rFVIIa	After rFVIIa	
1	26	P2	–	Emergency Caesarean	Atony Coagulation Disorder	Eclampsia Thrombocytopenia	2 mg	1	—	—	Good response Bleeding arrested
2	35	G2P1	35	Emergency Laparotomy	Adherent placenta	Twin pregnancy with placenta adherent to cornu of uterus	3 mg	1	Hysterectomy	—	Good response Bleeding was less than anticipated
3	24	G3P2	39	Vaginal	Trauma	Rupture uterus HIV & HbsAG reactive	2 mg	1	Laparotomy f/b repair of rupture uterus	—	Good response Bleeding decreased
4	34	G2P1	41	Caesarean	Trauma	—	3 mg	1	Bimanual compression	Uterine artery ligation	Good response Bleeding decreased
5	34	G3P2	26	Emergency Laparotomy	Trauma	Rupture uterus	3 mg	1	Internal iliac ligation	Hysterectomy	Good response Bleeding decreased
6	32	P4	—	Vaginal	Atony Trauma	Antepartum eclampsia	2 mg	1	Hysterectomy	—	Good response Bleeding decreased
7	26	G2P1	34	Emergency Caesarean	Atony	Abruptio placenta, Retroplacental clot, DIC	3 mg	1	Bimanual compression of uterus	B/L internal iliac ligation	Good response Bleeding decreased
8	24	G2P1	35	Emergency Caesarean	Antepartum haemorrhage f/b Atony	—	1 mg	1	Bimanual compression of uterus	—	Good response Bleeding arrested
9	32	P3	—	Vaginal	Atony Trauma	—	2 mg	1	Repair of vaginal vault tear	—	Good response Bleeding arrested
10	37	G4P3	37	Emergency Caesarean	Atony Trauma	—	3 mg	1	Hysterectomy	B/L Internal iliac ligation	Good response Bleeding decreased
11	30	G2P1	41	Emergency Caesarean	Atony	—	3 mg	1	Bimanual compression of uterus Uterine artery ligation	B/L Internal iliac ligation	Good response Bleeding decreased
12	28	G3P2	35	Emergency Caesarean	Atony	—	2 mg	1	Bimanual compression of uterus Uterine artery embolization	—	Good response Bleeding arrested
13	20	P1	—	Emergency Caesarean	Bleeding from stitch line	Deranged coagulation profile	3 mg	1	Laparotomy f/b rectal sheath haematoma drainage	—	Good response Bleeding arrested
14	27	P1	—	Vaginal	Trauma	—	3 mg	1	—	Vulval Haematoma Drainage	Good response Bleeding arrested
15	43	G4P3	39	Emergency caesarean	Atony Trauma	Cord prolapse and placental abruption f/b uterus rupture	3 mg	1	—	Hysterectomy	Partial response Bleeding decreased however hysterectomy was required due to rupture uterus
16	22	P1	—	Vaginal	Atony	Still birth	2 mg	1	—	—	Good response Bleeding arrested
18	28	G2P1	32	Emergency Caesarean	Atony	Still birth Placental abruption Couvelaire uterus	3 mg	1	Bimanual compression of uterus	—	Good response Bleeding arrested
19	26	P2	—	Vaginal	Atony	IUD, Sepsis, DIC, Deranged coagulation profile	3 mg	1	Balloon tamponade	—	Good response Bleeding arrested
20	24	G3P1	40	Vaginal	Trauma	—	3 mg	1	Bimanual compression of uterus Uterine artery ligation	Hysterectomy	Partial Response Bleeding decreased but continued
21	26	G2P1	38	Vaginal	Atony Trauma	—	3 mg	1	Bimanual compression of uterus Hysterectomy	—	Good response Bleeding arrested
22	—	G2P1	40	Emergency Caesarean	Trauma	—	2 mg	1	Bimanual compression of uterus Uterine artery ligation Intrauterine packing	—	Good response Bleeding arrested
23	35	P3	—	Vaginal	Atony Trauma	—	3 mg	1	Bimanual compression of uterus	—	Good response Bleeding arrested
24	17	G1	37	Emergency Caesarean	Atony Trauma Coagulation disorder	Eclampsia	2 mg	1	Bimanual compression of uterus Haemostatic sutures	—	Good response Bleeding arrested
25	29	G2P1	37	Emergency Caesarean	Atony	Hypothyroidism Pre eclampsia	2 mg	1	Uterine artery ligation	—	Good response Bleeding arrested

Case	Age (yrs)	Obstetric history	Weeks of gestation	Type of delivery	Cause of PPH	Associated condition	Dose of rFVIIa*	Number of rFVIIa doses	Surgical & mechanical interventions used		Outcome
									Before rFVIIa	After rFVIIa	
27	37	G3P2	38	Caesarean	Coagulation Disorder	Thrombocytopenia	3 mg	1	Uterine artery ligation	—	Good response Bleeding arrested
28	30	G1	38	Vaginal	Atony Trauma	—	2 mg	1	B/L Internal iliac Ligation Intravaginal packing	—	Good response Bleeding arrested
29	21	P1	—	Caesarean	Atony Coagulation disorder	DIC Jaundice	2 mg	1	Uterine artery ligation Compression sutures	—	Good response Bleeding arrested
30	38	G2P1	37	Caesarean	Atony	—	1 mg	1	Uterine artery ligation	—	Good response Bleeding arrested
31	25	P2	—	Vaginal	Atony	—	1 mg	1	—	—	Good response Bleeding arrested
32	26	G2P1	35	Vaginal	Atony	—	3 mg	1	B/L internal iliac ligation Compression sutures	Uterine artery embolization	Good response Bleeding decreased
33	23	G1	33	Emergency Caesarean	Atony	Couvelaire uterus Placental abruption	2 mg	1	—	—	Good response Bleeding arrested
34	33	P2	—	Emergency Caesarean	Atony	—	2 mg	1	B/L internal iliac ligation	—	Good response Bleeding arrested
35	26	P1	—	Vaginal	Atony Trauma	Vault tear Still birth	3 mg	1	Uterine artery ligation	Hysterectomy Internal iliac ligation	Partial response Bleeding continued
36	22	P1	—	Vaginal	Retained placenta f/b atony	—	3 mg	1	Bimanual compression of uterus	B/L uterine artery ligation Laparotomy f/b Hysterectomy	Partial response Bleeding continued
37	26	G3P2	40	Emergency Caesarean	Atony	—	2 mg	1	Hysterectomy	—	Good response Bleeding arrested
38	29	G3P2	35	Emergency Caesarean	Atony	—	3 mg	1	—	Hysterectomy	Partial response Bleeding decreased, but continued
39	24	P2	—	Vaginal	Trauma	—	1 mg	1	—	—	Good response Bleeding arrested
40	25	G2 P1	36	Emergency Caesarean	Atony	DIC	2 mg	2	—	—	Good response Bleeding arrested
41	25	P5	—	Emergeny Caesarean	Atony	—	1 mg	1	—	—	Good response Bleeding arrested
42	24	G1	32	Vaginal	Atony	—	2 mg	2	Balloon tamponade	—	Good response Bleeding arrested
43	26	P1	—	Caesarean	Atony Retained Placenta	Thrombocytopenia	1 mg	1	Curettage	—	Good response Bleeding arrested
44	24	P1	—	Emergency Caesarean	Bleeding from Stitch site	—	1 mg	1	—	—	Good response Bleeding arrested
45	28	P2	—	Vaginal	—	DIC	1 mg	1	—	—	Good response Bleeding arrested
46	37	P3	—	Caesarean	—	Jaundice	2 mg	1	—	—	Good response Bleeding arrested
47	30	P3	—	Caesarean	Trauma Atony	—	1 mg	1	Balloon tamponade	—	Good response Bleeding arrested
49	24	G1	37	Emergency Caesarean	Atony Trauma	—	1 mg	1	Bimanual compression of uterus	—	Good response Bleeding arrested
50	24	G4 P3	34	Emergeny Caesarean	Atony	—	1 mg	1	—	Compression sutures	Good response Bleeding decreased
51	—	P1	—	Vaginal	Trauma	—	1 mg	1	—	—	Good response Bleeding arrested
52	—	G1	38	Emergeny Caesarean	Coagulation abnormalities	Jaundice	2 mg	2	—	—	Good response Bleeding arrested
53	22	G1	34	Vaginal	Atony	—	1 mg	1	Bimanual compression of uterus	—	Good response Bleeding arrested
54	29	G3 P2	38	Vaginal	Atony	PLHA	1 mg	1	—	—	Good response Bleeding arrested
55	28	G1	32	Vaginal	Atony	—	1 mg	1	—	—	Good response Bleeding arrested
56	22	G2	39	Vaginal	Atony	—	1 mg	1	—	—	Good response Bleeding arrested
57	25	P3	—	Vaginal	Atony	Jaundice	1 mg	1	Bimanual compression of uterus	—	Good response Bleeding arrested
58	35	G5 P4	27	Vaginal	Trauma	DIC	1 mg	1	Haematoma drainage	—	Good response Bleeding arrested
59	26	P3	—	Vaginal	Atony	—	1 mg	1	—	—	Good response Bleeding arrested

Case	Age (yrs)	Obstetric history	Weeks of gestation	Type of delivery	Cause of PPH	Associated condition	Dose of rFVIIa*	Number of rFVIIa doses	Surgical & mechanical interventions used		Outcome
									Before rFVIIa	After rFVIIa	
61	28	P 3	—	Vaginal	Atony	—	2 mg	2	—	—	Good response Bleeding arrested
62	26	P3	—	Vaginal	Atony Trauma	—	3 mg	2	Vaginal tear repair	—	Good response Bleeding arrested
63	30	G3P2	32	Vaginal	—	Eclampsia	3 mg	2	Bimanual compression of uterus	—	Good response Bleeding arrested
64	19	G1	37	Caesarean	Placental site bleeding (Placenta Previa)	Breech presentation	2 mg	1	Uterine packing	—	Good response. Bleeding arrested. Patient discharged after stitch removal next day in good condition
65	29	G3 P1	40	Caesarean	Atony Placental site bleeding	—	2 mg	1	Uterine packing	—	Good response. Bleeding arrested. Patient discharged after stitch removal next day in good condition
66	26	G5 P1	36	Vaginal	Atony	DIC Thrombocytopenia	2 mg	1	Uterine packing Vaginal packing	—	Patient referred to higher centre due to non availability of RDP. FFP and 2RDP were transfused at higher center. Patient survived, no invasive procedure required
67	17	P1	—	Vaginal	Traumatic	Thrombocytopenia	2 mg	1	Cervical tear repair Vaginal packing	—	Patient was in DIC along with thrombocytopenia, also started gasping. PCV, FFP, RDP transfused before referral to higher centre along with rFVIIa Patient survived and no further invasive management required at higher centre.
68	28	P2	—	Vaginal	Atony	Rupture	2 mg	1	Baloon tamponade	Hysterectomy (done at higher centre)	rFVIIa decreased the bleeding. Patient could reach higher center where hysterectomy was done and survived.
69	21	P1	—	Vaginal delivery	Traumatic	Recurrent vaginal haematoma which was drained three times	2 mg	1	Cervico—vaginal exploration with haematoma drainage Laparotomy to rule out a broad ligament haematoma	—	Haematoma dissolved No further formation of new haematoma
70	34	G2 P1	26	Emergency Caesarean	Atony	Hypothyroidism, on thyroxin therapy IUFD with abruption	1 mg	1	Uterine artery ligation	—	Good Response. Bleeding arrested
71	29	G1	33	Emergency Caesarean	Atony	Referred from periphery with deranged LFT, RFT and Pre eclampsia	2 mg	1	Balloon tamponade Bimanual compresion of Uterus	Balloon Tamponade	Good Response. Bleeding arrested
72	28	G3 P2	35	Emergency Caesarean	Atony	—	2 mg	1	Bimaual compression of uterus	—	Good Response. Bleeding arrested
73	30	G5 P4	32	Emergency Caesarean	Placenta previa	—	2 mg	1	Bimanual compression of uterus	Bimanual compression of uterus	Good Response Bleeding arrested
74	26	G3 P2	36	Elective Caesarean	Placenta percreta and placenta previa	—	2 mg	2	—	—	Good Response Bleeding was less than anticipated during OT
75	43	G3 P1	36	Emergency Caesarean	Atony	—	2 mg	1	Bimanual compression of uterus	Bimanual compression of uterus	Good esponse Bleeding arrested
77	32	P4	—	Vaginal	Atony	Gestational thrombocyto-penia	2mg	1	Bimanual compression of uterus SR cannula	—	Good Response Bleeding decreased and later got completely arrested
78	20	—	36	Vaginal	Atony	AFLP	2mg	3	Bimanual uterine compression Ballon tamponade	—	Good Response Bleeding decreased later got completely arrested However, patient died due to AFLP, hepatic encephalopathy, AKI & MODS.
79	23	G1 P1	30	Emergency LSCS	Atony	Abruption placenta IUD Severe pre eclampsia GDM	2 mg	1	Bimanual uterine compression sutures Uterine artery ligation	—	Good Response Bleeding decreased and later got completely arrested
80	37	P1 L1	—	LSCS	Trauma	—	2 mg	2	Uterine artery embolization Hysterectomy	—	Good Response Bleeding decreased and later got completely arrested
81	—	G3 P1 A1	39	Vaginal	Atony	DIC Sepsis	1 mg	3	Hysterectomy	—	Good Response Bleeding decreased and later got completely arrested in 2 hours

G, Gravidity; P, Parity; AKI, Acute kidney injury; MODS, Multiple organ dysfunction syndrome; AFLP, Acute fatty liver of pregnancy; RDP, Random Donor platelets; DIC, Disseminated intravascular coagulation; PLHA, People living with HIV/AIDS

Table 17. Blood product requirements before and after rFVIIa

Case	Before rFVIIa				After rFVIIa				Amount of bleeding	
	Packed cell volume	Fresh frozen plasma	Cryoprecipitate	Platelet	Packed cell volume	Fresh frozen plasma	Cryoprecipitate	Platelet	Before rFVIIa (ml)	After rFVIIa (ml)
1	1	2	—	—	1	—	—	—	1000	300
2	1	2	—	—	1	1	—	—	2000	500
3	2	2	—	2	2	2	—	2	1800	500
4	1	2	—	2	1	2	—	2	1500	500
5	3	4	—	—	3	2	—	—	2500	500
6	3	2	—	2	4	4	—	2	2000	500
7	2	2	—	2	1	2	—	—	1000	300
8	1	2	—	—	—	—	—	—	800	200
9	2	2	—	—	2	2	—	—	1000	800
10	2	2	—	2	3	2	—	—	1200	500
11	2	2	—	1	2	2	—	1	1000	1200
12	—	—	—	—	—	—	—	—	—	—
13	1	2	—	2	—	—	—	—	800	500
14	1	2	—	2	1	—	—	2	2000	500
15	—	2	—	2	—	2	—	—	—	—
16	—	—	—	—	—	—	—	—	—	—
17	—	—	—	—	—	—	—	—	—	—
18	1	4	—	2	1	3	—	—	1000	800
19	1	2	—	1	2	2	—	1	1000	200
20	1	2	—	2	2	2	—	2	1500	500
21	2	4	—	1	1	—	—	—	1500	500
22	2	4	—	—	2	0	—	—	1500	500
23	3	4	—	—	1	2	—	—	2000	500
24	2	4	—	—	—	—	—	—	2000	300
25	1	2	—	2	—	—	—	—	2000	300
26	2	3	—	1	2	2	—	2	—	500
27	1	4	—	4	1		—	3	1000	300
28	2	2	2	2	1	3	—	4	2000	300
29	—	2	—	—	—	—	—	—	1000	500
30	1	1	—	—	1	1	—	—	1500	200
31	2	2	—	—	2	—	—	—	2000	200
32	1	2	—	—	2	2	—	2	1800	500
33	2	2	—	4	3	2	—	3	2000	800
34	2	2	—	2	2	2	—	4	2000	500
35	2	2	—	2	6	3	—	—	2500	1500
36	2	4	—	2	4	4	—	4	1500	1500
37	3	2	—	3	1	2	—	—	1500	500
38	1	2	—	2	—	2	—	2	2000	500
39	2	2	—	—	1	1	—	—	1500	200
40	1	1	—	1	—	1	—	1	1500	350
41	—	—	—	—	1	—	—	—	1500	200
42	7	—	—	5	—	—	—	—	1000	100
43	—	—	—	5	—	—	—	3	750	200
44	2	3	—	2	2	1	—	1	—	—
45	—	—	—	—	—	—	—	—	—	—
46	1	2	—	2	—	4	—	3	1500	300
47	1	2	—	—	2	1	—	—	1000	300
48	1	—	—	—	1	1	—	1	—	—
49	—	—	—	—	—	—	—	—	700	150
50	1	4	—	2	—	—	—	—	1500	300

Case	Before rFVIIa				After rFVIIa				Amount of bleeding	
	Packed cell volume	Fresh frozen plasma	Cryoprecipitate	Platelet	Packed cell volume	Fresh frozen plasma	Cryoprecipitate	Platelet	Before rFVIIa (ml)	After rFVIIa (ml)
52	—	—	—	—	—	—	—	—	—	—
53	1	3	1	—	—	—	—	—	800	100
54	1		—	—	—	—	—	—	3000	200
55	—	2	—	—	—	—	—	—	1000	50
56	—	1	—	—	1	1	—	—	1000	100
57	3	4	—	—	—	2	—	—	900	150
58	1	2	—	—	—		—	—	700	—
59	—	1	—	—	—		—	—	—	—
60	—	7	—	1	—	1	—	—	1500	300
61	1	2	—	2	—	—	—	—	—	—
62	2	—	—	—	1	—	—	—	—	—
63	—	—	—	—	—	3	—	—	—	—
64	2	2	—	—	—	—	—	—	—	—
65	1	4	—	—	—	—	—	—	—	—
66	1	4	—	—	1		—	2	—	—
67	2	4	—	2	—	—	—	—	1500	500
68	2	—	—		—	—	—	—	—	100
69	8	11	—	4	—	—	—	—	—	—
70	1	3	—	2	2	2	—	2	700	200
71	—	2	—	—	1	2	—	—	800	400
72	2	4	—	4	1	—	—	—	700	—
73	1	—	—	—	1		—	—	1100	200
74	1	4	—	—	4	4	—	—	2000 Total (before and after rFVIIa)	—
75	2	4	—	4	2	—	—	—	1500	300
76	1	4	—	—	2	4	—	—	1500	400
77	5	5	24	8	3	2	4	4	3000	500
78	4	16	18	16	—	—	8	—	3000	500
79	4	8	8	8	1	4	4	4	3000	500
80	3	6	6	—	—	—	—	—	—	—
81	6	6	6	4	6	With plasma exchange	—	—	1000	400

Table 18. Haematological parameters during rFVIIa administration				
Case	**Haemoglobin (g/dL)**	**Platelet (Per µL)**	**Coagulation profile**	**Liver function test**
1	11	80,000	—	—
2	9	1,64,000	—	—
3	8	86,000	—	—
4	9.5	1,60,000	—	—
5	7.4	50,000	—	—
6	7	80,000	—	—
7	7.2	84,000	—	—
8	—	—	—	—
9	7.5	18,000	—	—
10	7.9	4,30,000	—	—
11	12.1	—	—	—
12	—	—	—	—
13	10	—	—	—
14	7.3	—	—	—
15	10.2	—	—	—
16	4.7	—	—	—
17	9.3	—	—	—
18	7.9	85,000	INR - 1.02, PT - 13.8 sec	—
19	6.5	62,000	—	—
20	8.6	1,13,000	INR - 1.67, PT - 21.8 sec	SGOT -125 IU/L, SGPT -106 IU/L
21	4.9	41,000	—	—
22	8.4		—	—
23	7.4	50,000	—	—
24	8	50,000	—	—
25	9.4	2,16,000	—	—
26	5	1,40,000	—	—
27	11.6	40,000	—	—
28	11.5	—	—	—
29	8.5	1,50,000	INR - 1.8, PT - 24.1 sec, aPTT - 34.2 sec	Serum bilirubin (mg/dL), T/D: 6.8 /5.7
30	10.5		—	—
31	3.5	70,000	—	—
32	7.5	51,000	—	—
33	5.1	34,000	—	—
34	7.4	—	—	—
35	8.2	2,00,000	—	—
36	7.4	—	—	—
37	7.8	—	—	—
38	10.5	1,70,000	—	—
39	6.7	40,000	—	—
40	10.6	56,000	—	Serum bilirubin (mg/dL), T/D/I :5.8/2.11/3.69
41	3.2	48,000	—	Serum bilirubin (mg/dL), T/D/I: 5.4/1.8/1.9
42	8.1	43,000	—	Serum bilirubin (mg/dL), T/D/I: 10.1/5.1/5.0
43	4.2	19,000	—	—
44	3	96,000	—	—
45	6.5	1,33,000	—	—
46	8.7	44,000	—	Serum bilirubin (mg/dL), T/D/I:8.2/4.9/3.3, SGPT – 1276 IU/L
47	2.4	32,000	—	Serum bilirubin (mg/dL), T/D/I: 2.1/0.8/0.4
48	11.9	1,60,000	—	—
49	12.1	1,41,000	—	Serum bilirubin (mg/dL), T/D/I : 0.6/0.3/0.3 SGPT – 20 IU/L, SGOT - 62 IU/L

Case	Haemoglobin (g/dL)	Platelet (Per µL)	Coagulation profile	LFT
50	10	2,17,000	—	Serum bilirubin (mg/dL), T/D/I : 0.9/0.2/0.8 SGPT – 20 IU/L, SGOT – 26 IU/L
51	—	—	—	—
52	7.2	42,000	PT - 9.2 sec, aPTT - 22.6 sec	—
53	15.2	34,000	—	Serum bilirubin (mg/dL), T/D/I : 4.42/2.5/1.9
54	5.4	72,000	—	Serum bilirubin (mg/dL), T/D/I: 1.3/0.7/0.6
55	7	50,000	—	Serum bilirubin (mg/dL), T/D/I : 4.3/2.3/2.0
56	8	92,000	PT - 10.6 sec, aPTT - 28.6 sec	Total bilirubin = 3.98 mg/DL
57	3.2	1,07,000	—	Serum bilirubin (mg/dL), T/D/I: 11.6/6.2/5.4
58	6.22	—	—	—
59	—	—	—	—
60	8.3	45,000	INR - 1.14, PT - 14.52 sec	Serum bilirubin (mg/dL), T/D/I : 17.9/6.7/11.2
61	4.3	43,000	—	—
62	10.3	57,000	—	SGPT – 296 IU/L, SGOT – 149 IU/L
63	9.5	80,000	—	—
64	11.3	2,98,000	—	—
65	10.1	—	D-dimer : 2619 mg/L	—
66	5.5	34,000	INR- 2.35, D-dimer- 9125 mg/L	—
67	9.5	78,000	—	—
68	6.7	38,000	—	—
69	8.0	2,16,000	—	Serum bilirubin (mg/dL), T/D : 0.7/0.1
70	7.4	1,26,000	PT - 13.05 sec	—
71	13.1	2,27,000	PT - 14 sec	—
72	7.6	83,000	PT - 15 sec	—
73	8.2	1,98,000	—	—
74	13	2,87,000	—	—
75	—	—	—	—
76	—	—	—	—
77	6.1	73,000	—	—
78	7.3	66,000	—	—
79	4.3	56,000	—	—
80	3	75,000	INR - 3, Fibrinogen: 45 mg/dL	—
81	5.5	60,000	D-dimer >1000 mg/L	—

PT, Prothrombin time; INR, International normalized ratio; aPTT, Activated partial thromboplastin time; LFT, Liver function test; SGPT, Serum glutamic pyruvic transaminase; SGOT, Serum glutamic oxaloacetic transaminase

#Disclaimer: The case details presented here are based on the available data provided voluntarily by the obstetricians. It is important to note that not all details pertaining to the cases are captured in the tables due to the limited scope of the document. The use of rFVIIa was considered by obstetricians based on the patient's condition and as per the local treatment protocol. Evaluation of the response to rFVIIa is based on subjective evaluations by obstetrician. These real-life cases are intended for reference purposes for other obstetricians practicing in India. For further details on the cases, we recommend reaching out to the respective authors directly or contacting fogsifocusonrfviia@gmail.com. For accurate dosing information & other related details of rFVIIa (Eptacog alfa), please refer to the approved pack insert of NovoSeven®. The recommended dose range of Eptacog alfa for the treatment of bleeding is 60-90 µg per kg body weight as per label approval.

5. Recommendations on the positioning of rFVIIa in the treatment algorithm of severe PPH

Five distinct clinical scenarios for PPH were identified, and various cases covering all four T's (Tone, Tissue, Trauma, Thrombin) were presented for different scenarios by obstetricians from eight different centres. The recommendations provided here were formulated based on extensive discussions of these cases, drawing from the collective experience of different centres across India.

Scenario 1: Severe PPH following vaginal delivery

Atonic PPH

- rFVIIa can be considered after the failure of standard medical and mechanical methods (including uterine massage, balloon tamponade, PPH suction cannula, and removal of retained placenta, if any) in controlling the bleeding.
- It can be a valuable adjunct while preparing for further invasive procedures (if still deemed necessary) such as compression sutures, uterine artery ligation, uterine artery embolization, and hysterectomy.

First step	Second step	Third step
• Medical interventions (Uterotonics, tranexamic acid, IV fluids, blood/blood products) • Mechanical methods (Uterine massage, balloon tamponade, PPH suction cannula, removal of remaining placenta (if any)	rFVIIa	• Compression sutures • Uterine artery ligation • Uterine artery embolization • Hysterectomy

Traumatic PPH

- rFVIIa can be considered after the failure of medical interventions and mechanical methods in controlling the bleeding, and before advancing to further invasive procedures such as internal iliac artery ligation, uterine artery embolization, and hysterectomy.
- rFVIIa can help in arresting the bleed. However, surgical repair of tears should remain the mainstay of the treatment.
- rFVIIa can be useful in cases where there is excessive bleeding (despite vaginal packing) due to small vaginal or cervical tears and episiotomy wounds that are difficult to suture due to edematous mucosa.

First step	Second step	Third step
• Medical interventions (Uterotonics, tranexamic acid, IV fluids, blood/blood products) • Mechanical methods (identification and site-specific suturing of lacerations, vaginal packing)	rFVIIa	• Internal iliac artery ligation • Uterine artery embolization • Hysterectomy

Severe PPH secondary to placental abnormalities

- rFVIIa may be considered as part of the conservative management approach for placenta accreta (focal accreta).
- rFVIIa can be considered in cases of undiagnosed placenta accreta during vaginal delivery, particularly when a patient experiences substantial bleeding upon manual placental removal.
- Administration of rFVIIa can also help stabilize the patient before transferring them to the operating room for laparotomy if required.

For the conservative management of placenta accreta

First step	Second step	Third step
• Medical interventions (Uterotonics, tranexamic acid, IV fluids, blood/blood products) • Mechanical methods (Balloon tamponade, uterine packing)	rFVIIa	• Stepwise devascularization • Segmental resection • Uterine artery embolization • Hysterectomy

Scenario 2: Severe PPH during caesarean section

Atonic PPH

- Use of rFVIIa can be considered after the failure of medical interventions, mechanical methods, and surgical measures (including uterine compression sutures and uterine artery ligation) but before uterine artery embolization or hysterectomy.

First step	Second step	Third step
• Medical Interventions (Uterotonics, Tranexamic acid, IV fluid, blood/ blood products) • Mechanical methods (Uterine packing & balloon tamponade) • Surgical measures (Compression sutures & uterine artery ligation)	rFVIIa	• Uterine artery embolization • Hysterectomy

Traumatic PPH

- rFVIIa can be considered in cases of significant bleeding resulting from surgical trauma after the failure of medical interventions, mechanical methods, and surgical measures (stepwise devascularization), but before uterine artery embolization or hysterectomy.
- **While rFVIIa can help control bleeding, surgical repair of the tear should remain the mainstay of treatment.**

First step	Second step	Third step
• Medical Interventions (Tranexamic acid, IV fluid, blood/blood products) • Mechanical methods (Uterine packing, laceration suturing, vaginal packing) • Surgical measures (stepwise devascularization)	rFVIIa	• Uterine artery embolization • Hysterectomy

Severe PPH secondary to placental abnormalities

- rFVIIa can be considered after the failure of medical interventions, mechanical methods, and uterine artery ligation, but prior to performing uterine artery embolization or hysterectomy when attempting to preserve the uterus.
- Consideration of rFVIIa is recommended in cases of persistent bleeding following obstetric hysterectomy.
- It is recommended to have rFVIIa readily available in the labor room when managing cases of placental abnormalities in individuals who have a high risk of developing severe postpartum haemorrhage.

For the conservative management of placenta accreta

First step	Second step	Third step
• Medical Interventions (Uterotonics, tranexamic acid, IV fluid, blood/ blood products) • Mechanical methods (Uterine packing and balloon tamponade) • Stepwise devascularization • Conservative methods	rFVIIa	• Uterine artery embolization • Hysterectomy

While performing obstetric hysterectomy

First step	Second step	Third step
• Hysterectomy	• rFVIIa along with other standard measures	NA

Scenario 3: Severe PPH following a caesarean section

- After a caesarean section, if there is severe bleeding following laparotomy incision closure, it is recommended to consider administering rFVIIa in combination with uterine artery embolisation without delaying relaparotomy.
- rFVIIa can be considered if the patient is developing a haematoma due to bleeding from the suture site or from an unidentified origin.

First step	Second step	Third step
• Medical interventions (Uterotonics, tranexamic acid, IV fluids, blood/blood products) • Mechanical methods (Uterine massage and balloon tamponade)	• rFVIIa • Uterine artery embolization	If not performed before closing the laparotomy • Compression sutures • Uterine artery ligation • Hysterectomy

Scenario 4: Severe PPH in a peripheral district hospitals

- In the event of severe PPH at peripheral district hospitals, when considering transfer to a tertiary care hospital, it is advisable to consider the administration of rFVIIa during the transfer to reduce the risk of worsening bleeding during transit.

- The patient should be thoroughly evaluated for prerequisite of giving rFVIIa by an obstetrician. Transfusion of fresh frozen plasma, cryoprecipitate, or platelets should be considered based on the requirement along with rFVIIa. The decision to administer rFVIIa before transfer should be made based on the current clinical status and the expected duration of the transfer to the receiving center.
- Use of rFVIIa should not cause a delay in the patient's transfer to a tertiary care hospital, nor should it impede the initiation of second-line uterotonic treatment (such as prostaglandins) and, where available, intra-uterine balloon tamponade.
- It is crucial to initiate transfer as early as feasible after administering rFVIIa, without waiting to assess the response of rFVIIa in controlling the bleeding.
- Administering rFVIIa while transferring patients from peripheral setups may help control bleeding during transit, allowing enough time to prepare the patient for any required procedures in tertiary care center.

Scenario 5: Severe PPH post-hysterectomy

- Administration of rFVIIa can be considered in conjunction with standard measures if there is persistent severe bleeding and difficulty achieving haemostasis post obstetric hysterectomy.
- However, rFVIIa should be used early in the management of severe PPH rather than as a last resort to prevent potential complications associated with massive blood transfusion or invasive procedures.
- rFVIIa may prove beneficial when the source of bleeding remains unidentified post-hysterectomy. rFVIIa can bind with tissue factor (TF) at the site of injury and form a local haemostatic plug based on its mechanism of action.
- While uterine artery ligation or embolisation can effectively control arterial bleeding, it may not be as effective in managing diffuse venous oozing. In cases of diffuse venous oozing before or after obstetric hysterectomy, rFVIIa can be beneficial.

First step	Second step	Third step
• rFVIIa along with other standard measures	NA	NA

Additional practical considerations for using rFVIIa in severe PPH

Are there any clinical considerations or prerequisites that should be taken into account before initiating rFVIIa for severe PPH?

- Maintenance of adequate fibrinogen concentration and platelet count is recommended to optimize the benefit of Eptacog alfa (activated) treatment.
- rFVIIa works by activating factor X on activated platelets, ultimately generating a thrombin burst. This thrombin burst requires a sufficient quantity of fibrinogen to convert into fibrin. Therefore, maintaining adequate fibrinogen concentration and platelet count is recommended to optimize the benefits of Eptacog alfa (activated) treatment.[16,35]
- The optimal haematological parameters recommended for the administration of rFVIIa are as follows: no hypothermia, i.e., a core body temperature >35°C and no acidosis (pH >7.2); no hypo-fibrinogenemia or severe thrombocytopenia (fibrinogen >1–2 g/L and platelets >50,000/mm^3). However, it is not mandatory to maintain these parameters, and the use of rFVIIa can be considered irrespective of these parameters based on the patient's condition and the clinician's decision.[32]
- Transfusion of cryoprecipitate/FFP and platelet concentrate can be considered to support patient stabilization.
- Thus, it is advisable to administer rFVIIa early in the treatment of severe PPH rather than at a later stage following extensive blood loss or in cases of DIC, where there are chances of having insufficient fibrinogen and platelet levels.

Do we require any monitoring during rFVIIa therapy?

- There is no need for any specific monitoring for rFVIIa / Eptacog alfa therapy.[35]
- The patient should continue to be monitored as usual according to standard department protocols, and no further specific tests or extra monitoring are required for the management of severe PPH following rFVIIa administration.
- Additionally, medical or surgical/invasive treatments should be considered as indicated according to the clinical situation and the standard treatment algorithm, if required.

How to decide on the requirement of the 2nd dose of rFVIIa?

- The decision should be based on the clinical judgment of the severity of bleeding and the clinical status of the patient.

Can rFVIIa be used in patients who have developed severe PPH secondary to coagulation disorder?

- As per the approved indication, rFVIIa can be used in any case of severe PPH, irrespective of the cause of PPH, after the failure of uterotonics to achieve haemostasis, based on the clinician's decision.[35]
- rFVIIa can help in arresting the bleeding that occurs due to coagulation abnormalities. However, correction of underlying coagulopathy should remain the mainstay of treatment.
- rFVIIa is already approved in patients with acquired haemophilia, congenital factor VII deficiency, and Glanzmann's thrombasthenia for the prevention of bleeding during surgery or invasive procedures. In such patients, rFVIIa can be used even peri-operatively to prevent anticipated bleeding.[35]
- Evidence suggests that rFVIIa has proven effective in arresting the bleeding in cases of severe PPH complicated with HELLP syndrome, with improvement in coagulation parameters.[29]

What are the contraindications for using rFVIIa?

- Contraindications include hypersensitivity to the active substance or to any of the excipients listed below or to mouse, hamster, or bovine protein.[35]
  - » Powder: Sodium chloride, Calcium chloride dihydrate, Glycylglycine, Polysorbate 80, Mannitol,
  - » Sucrose, Methionine, Hydrochloric acid (for pH adjustment), Sodium hydroxide (for pH adjustment)
  - » Solvent: Histidine, Hydrochloric acid (for pH adjustment), Sodium hydroxide (for pH adjustment), Water for injections.

Summary of recommendations

Scenarios		First step	Second step	Third step
Severe PPH following vaginal delivery	**Atonic PPH**	• Medical interventions (Uterotonics, tranexamic acid, IV fluids, blood/ blood products) • Mechanical methods (Uterine massage, balloon tamponade, PPH suction cannula, removal of remaining placenta (if any)	rFVIIa	• Compression sutures • Uterine artery ligation • Uterine artery embolization • Hysterectomy
	Traumatic PPH	• Medical interventions (Uterotonics, tranexamic acid, IV fluids, blood/ blood products) • Mechanical methods (Identification and site-specific suturing of lacerations, vaginal packing)	rFVIIa	• Internal iliac artery ligation • Uterine artery embolization • Hysterectomy
	Severe PPH secondary to placental abnormalities	• Medical interventions (Uterotonics, tranexamic acid, IV fluids, blood/ blood products) • Mechanical methods (Balloon tamponade, uterine packing)	rFVIIa	• Stepwise devascularization • Segmental resection • Uterine artery embolization • Hysterectomy
Severe PPH during caesarean section	**Atonic PPH**	• Medical Interventions (Uterotonics, tranexamic acid, IV fluid, blood/blood products) • Mechanical methods (Uterine packing & balloon tamponade) • Surgical measures (Compression sutures & uterine artery ligation)	rFVIIa	• Uterine artery embolization • Hysterectomy
	Traumatic PPH	• Medical interventions (Tranexamic acid, IV fluid, blood/blood products) • Mechanical methods (Uterine packing, laceration suturing, vaginal packing) • Surgical measures (stepwise devascularization)	rFVIIa	• Uterine artery embolisation • Hysterectomy
	Severe PPH secondary to placental abnormalities (For the conservative management of placenta accreta)	• Medical Interventions (Uterotonics, tranexamic acid, IV fluid, blood/blood products) • Mechanical methods (Uterine packing and balloon tamponade) • Stepwise devascularization • Conservative methods	rFVIIa	• Uterine artery embolization • Hysterectomy
	Severe PPH secondary to placental abnormalities (While performing obstetric hysterectomy)	• Hysterectomy	rFVIIa along with other standard measures	NA
Severe PPH following a caesarean section		• Medical interventions (Uterotonics, tranexamic acid, IV fluids, blood/blood products) • Mechanical methods (Uterine massage and balloon tamponade)	rFVIIa Uterine artery embolization	If not performed before closing the laparotomy. • Compression sutures • Uterine artery ligation • Hysterectomy
Severe PPH post-hysterectomy		• rFVIIa along with other standard measures	NA	NA

6. Abbreviated prescribing information[36]

Generic Name

Eptacog alfa (activated)

Human Recombinant Coagulation Factor VII activated, r-DNA origin

Brand Name

NovoSeven® 1 mg, NovoSeven® 2 mg

Presentation

Powder and solvent for solution for injection: White lyophilised powder. Solvent: clear colourless solution. NovoSeven® is a single-use product for IV administration. The product is freeze dried and dissolved in 10 mM histidine solvent for use.

Indication

NovoSeven® is indicated for the treatment of bleeding episodes and for the prevention of bleeding in those undergoing surgery or invasive procedures in the following patient groups:

- In patients with congenital haemophilia with inhibitors to coagulation factors VIII or IX > 5 Bethesda Units (BU)
- In patients with congenital haemophilia who are expected to have a high anamnestic response to factor VIII or factor IX administration
- In patients with acquired haemophilia
- In patients with congenital FVII deficiency
- In patients with Glanzmann thrombasthenia with past or present refractoriness to platelet transfusions, or where platelets are not readily available

Severe postpartum haemorrhage: NovoSeven® is indicated for the treatment of severe postpartum haemorrhage when uterotonics are insufficient to achieve haemostasis.

Dosing and administration

Severe postpartum haemorrhage: The recommended dose range for the treatment of bleeding is 60–90 µg/kg body weight administered by IV bolus injection. Peak coagulant activity can be expected at 10 minutes. A second dose can be administered based on the clinical response of the individual patient. It is recommended that in case of insufficient haemostatic response, a second dose can be administered after 30 minutes.

Contraindications: Hypersensitivity to the active substance or to any of the excipients or to mouse, hamster, or bovine protein

Special warnings and precautions: Caution should be exercised when administering NovoSeven® to patients with a history of coronary heart disease, to patients with liver disease, to patients post-operatively, to neonates, or to patients at risk of thromboembolic phenomena or DIC. In cases of hypersensitivity to residual culture proteins, treatment with antihistamines IV should be considered. If allergic or anaphylactic-type reactions occur, the administration should be discontinued immediately. In case of shock, standard medical treatment for shock should be implemented. Thrombosis has been reported in FVII-deficient patients receiving NovoSeven® during surgery; however, the risk in factor VII-deficient patients is unknown.

Undesirable effect: The most frequently reported adverse drug reactions are decreased therapeutic response, pyrexia, rash, venous thromboembolic events, pruritus, and urticaria. These reactions are reported as uncommon (≥ 1/1,000, < 1/100).

Shelf-Life: The shelf-life of the drug product is 36 months when the product is stored below 25°C. The expiry date is indicated on the carton and label.

Storage: Store powder and solvent below 25°C and protected from light. Do not freeze. For storage conditions of the reconstituted medicinal product, see section 8.2 shelf-Life in the full package insert.

Disclaimer

The abbreviated package insert is updated from the CDSCO-approved package insert (F. No. 4-51/NovoNordisk/PAC-R Eptacog alfa/2021-BD dated 25 Nov 2022). NovoSeven® is a trademark owned by Novo Nordisk Health Care AG, Switzerland. Imported by: Novo Nordisk India Private Limited, Bangalore Note: For detailed information on this product, please refer to full package insert

7. References

1. Federation of Obstetrics and Gynecological Society of India. PPH Prevention and Management: Updated PPH Guidelines 2022. Available at: https://www.fogsi.org/wp-content/uploads/tog/pph-prevention-and-management-updated-sept-2022.pdf. Accessed on Nov 11, 2024.
2. World Health Organization. Maternal Mortality [Internet]. Available at: https://www.who.int/news-room/fact-sheets/detail/maternal-mortality. Accessed on Nov 11, 2024.
3. Transforming our world: The 2030 Agenda for Sustainable Development. Available from https://sdgs.un.org/2030agenda. Accessed on Nov 11, 2024.
4. Maternal Health Division Ministry of Health and Family Welfare Government of India. Guidance Note on Prevention and Management of Postpartum Haemorrhage 2015. Available at: https://nhm.gov.in/images/pdf/programmes/maternal-health/guidelines/Guidance_Note_on_Prevention_&_Management_of_Postpartum_Haemorrhage.pdf. Accessed on Nov 11, 2024.
5. Meh C, Sharma A, Ram U, et al. Trends in maternal mortality in India over two decades in nationally representative surveys. BJOG. 2022;129(4):550–61.
6. Liu C, Yu F, Xu Y, et al. Prevalence and risk factors of severe postpartum haemorrhage: A retrospective cohort study. BMC Pregnancy Childbirth. 2021;21(1):332.
7. World Health Organization recommendations for the prevention and treatment of postpartum haemorrhage. Available at: https://iris.who.int/bitstream/handle/10665/75411/9789241548502_eng.pdf?sequence=1. Accessed on Nov 11, 2024.
8. Factor VII. Practice Points. Available from https://www.fogsi.org/wp-content/uploads/tog/Nova-TOG-Factor-VII-practice-points-V11.pdf. Accessed on Nov 11, 2024.
9. Escobar M, Nassar A, Theron G, et al; FIGO Safe Motherhood and Newborn Health Committee. FIGO recommendations on the management of postpartum haemorrhage 2022. Int J Gynaecol Obstet. 2022;157 Suppl 1(1):3–50.
10. Likis F, Sathe N, Morgans A, et al. Management of postpartum haemorrhage. Rockville (MD): Agency for Healthcare Research and Quality (US); 2015. Report No.: 15-EHC013-EF.
11. Matsuzaki S, Lee M, Nagase Y et al. A systematic review and meta-analysis of obstetric and maternal outcomes after prior uterine artery embolization. Sci Rep. 2021;11(1):16914.
12. Bodelon C, Bernabe-Ortiz A, Schiff M, et al., (2009). Factors associated with peripartum hysterectomy. Obstet and Gynecol. 2009;114(1):115–23.
13. Sihler K, Napolitano L. Complications of massive transfusion. Chest. 2010;137(1):209–20.
14. NovoSeven® Summary of Product Characteristics.
15. The Central Drugs Standard Control Organisation (CDSCO). Recommendations of the SEC (Oncology & Haematology) [Internet]. Available at: https://cdsco.gov.in/opencms/resources/UploadCDSCOWeb/2018/UploadCommitteeFiles/Recommendations%20Oncology%20%20Haematology%20dated%2024.08.2023.pdf. Accessed on Nov 11, 2024.
16. Hoffman M, Monroe D 3rd. The action of high-dose factor VIIa (FVIIa) in a cell-based model of hemostasis. Semin Hematol. 2001;38(4 Suppl 12):6–9.
17. Hawryluk G, Cusimano M. The role of recombinant activated factor VII in neurosurgery: Hope or hype? J Neurosurg. 2006;105(6):859–68.
18. Morfini M. Rapid rFVIIa enhanced on-demand dosing in haemophilia inhibitor patients. Eur J Haematol. 2016;96(2):111–18.
19. Lavigne-Lissalde G, Aya A, Mercier F,et al. Recombinant human FVIIa for reducing the need for invasive second-line therapies in severe refractory postpartum haemorrhage: A multicenter, randomized, open controlled trial. J Thromb Haemost. 2015;13(4):520–29.
20. Bouma L, Bolte A, van Geijn H. Use of recombinant activated factor VII in massive postpartum haemorrhage. Eur J Obstet Gynecol Reprod Biol. 2008;137(2):172–77.
21. Barillari G, Frigo M, Casarotto M, et al; Italian rFVIIa-PPH Study Group. Use of recombinant activated factor VII in severe post-partum haemorrhage: Data from the Italian Registry: A multicentric observational retrospective study. Thromb Res. 2009;124(6):e41–7.
22. Huber A, Raio L, Alberio L, et al. Recombinant human factor VIIa prevents hysterectomy in severe postpartum haemorrhage: Single center study. J Perinat Med. 2011;40(1):43–9.
23. Kobayashi T, Nakabayashi M, Yoshioka A, et al. Recombinant activated factor VII (rFVIIa/NovoSeven®) in the management of severe postpartum haemorrhage: Initial report of a multicentre case series in Japan. Int J Hematol. 2012;95(1):57–63.
24. Phillips L, McLintock C, Pollock W, et al; Australian and New Zealand Haemostasis Registry. Recombinant activated factor VII in obstetric haemorrhage: Experiences from the Australian and New Zealand Haemostasis Registry. Anesth Analg. 2009;109(6):1908–15.
25. Salman N, Rafay A, Junaid R, et al. Use of recombinant activated factor VII: Pakistani experience of managing massive obstetric haemorrhage. Niger Med J. 2022;62(5):267–72.
26. Colucci G, Helsing K, Biasiutti F, et al. Standardized management protocol in severe postpartum hemorrhage: a single center study. Clin Appl Thromb Hemost. 2018;24(6):884–93.
27. Singi S, Fernandez E, Pandya S et al. Recombinant factor VIIa: Use in fatal post partum haemorrhage - Indian experience case series and review of literature. Indian J Hematol Blood Transfus. 2009; 25(1):1–5.
28. Magon N, Babu K, Kapur K, et al. Recombinant activated factor VII in post partum haemorrhage. Niger Med J. 2013;54(5):289–94.
29. Goel A, Nair S, Viswabandya A et al. Preliminary experience with use of recombinant activated factor VII to control postpartum haemorrhage in acute fatty liver of pregnancy and other pregnancy-related liver disorders. Indian J Gastroenterol. 2013 Jul;32(4): 268–71.
30. Neufeld E, Négrier C, Benchikh E Fegoun S, et al. Recombinant activated factor VII in approved indications: Update on safety. Haemophilia. 2018;24(4):e275–e277.
31. Caram-Deelder C, McKinnon Edwards H, Zdanowicz J, et al. Efficacy and safety analyses of recombinant factor VIIa in severe postpartum haemorrhage. J Clin Med. 2024;13(9):2656.
32. Surbek D, Blatný J, Wielgos M, et al. Role of recombinant factor VIIa in the clinical management of severe postpartum haemorrhage: consensus among European experts. J Matern Fetal Neonatal Med. 2024;37(1):2332794.
33. Hedner U. Mechanism of action of factor VIIa in the treatment of coagulopathies. Semin Thromb Hemost. 2006;32 Suppl 1:77–85.
34. Devis P, Knuttinen M. Deep venous thrombosis in pregnancy: Incidence, pathogenesis and endovascular management. Cardiovasc Diagn Ther. 2017;7(3):S309–19.
35. NovoSeven Pack Insert. Data on File.
36. NovoSeven® Abbreviated Prescribing information

8. Annexure

Acknowledgements

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Accessibility

Recombinant Factor VIIa (rFVIIa) is included in the Essential Drug List (EDL) of the following 16 states in India.

Andhra Pradesh , Assam, Bihar, Delhi, Jammu & Kashmir, Karnataka, Kerala, Madhya Pradesh, Maharashtra, Odisha, Punjab & Chandigarh, Rajasthan, Tamil Nadu , Telangana, Uttarakhand, and West Bengal.

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