FOGSI TOG
Times of Gynaecology
Practice Points

Factor VII

Practice Points

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Dear FOGSI members,

Postpartum hemorrhage (PPH) is the leading cause of maternal mortality worldwide. It occurs in about 14 million women globally and results in around 70,000 deaths as per WHO. In India, PPH accounts for a significant proportion of maternal mortalities.

Severe PPH is typically defined as blood loss exceeding 1000 mL within 24 hours of delivery. Prediction and assessment of blood loss and prompt identification of its cause are critical for effective management of PPH.

Severe postpartum hemorrhage (SPPH) can lead to life-threatening situations, often necessitating swift and efficient treatment, which may include surgical interventions.

A multi-disciplinary approach to management of PPH is necessary and includes medical, surgical, hematological and radiological aspects and ability to conduct rapid tests. The availability of blood and blood products is very crucial.

The recently launched Recombinant activated factor VII (rFVIIa) is a valuable addition to the treatment options aimed at controlling life-threatening bleeding.

This practice point is a step towards assisting the gynecologists to take informed decisions while using their experience and skill, ultimately contributing to saving lives.

We hope that this information will be helpful in your day-to-day practice.

Best wishes to you all.

Dr Hrishikesh D Pai

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Management of severe PPH: Role of Recombinant Factor VIIa

Severe postpartum hemorrhage: An overview

Pregnancy-related deaths continue to be a significant cause of premature death among women worldwide. Postpartum hemorrhage (PPH) is the main cause of maternal morbidity and mortality, accounting for 25% of maternal deaths globally and a staggering 38% in India.[1-2] PPH is a common occurrence, with reported incidence rates of 2%-4% after vaginal delivery and 6% after cesarean section, mainly caused by uterine atony in 70% of cases. Appropriate management can prevent the majority of maternal deaths associated with PPH.[1]

The global incidence of major obstetric hemorrhage (MOH) ranges from 3.7 to 5 per 1000 births. The incidence of MOH in developed countries varies widely from 0.16%-8.8%. An Indian study conducted in 2015 reported the incidence of MOH to be 5.7 per 1000 births. The World Health Organization (WHO) reported that nearly 5 women in India lose their lives every hour due to complications developed during childbirth, with heavy blood loss caused by hemorrhage being a major factor.[3]

A retrospective study of obstetric intensive care unit (ICU) admissions reported that obstetric hemorrhage accounted for the majority of ICU admissions, comprising 27.7% of cases, with a mortality rate of 33.8% among these admissions.[4]

Definition

According to the Ministry of Health and Family Welfare Government of India, 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 hemodynamically unstable is also termed as PPH.[2] In the most recent WHO definitions (2012), PPH is commonly defined as a blood loss of 500 ml or more within 24 hours after birth.[5]

Definitions of severe hemorrhage

According to the WHO, severe PPH is defined as a blood loss of 1000 ml or more within 24 hours after birth.[5] 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, shock index, etc. Hemorrhage can be classified as severe or massive when there is a blood loss ranging from 1500 mL to 2500 mL, a decrease in hemoglobin levels of 4 g/dL or more, the need for transfusing at least 4 units of red blood cells (RBCs), or the requirement for interventions like hemostatic procedures (such as embolization) or surgery. Some experts also suggest using the speed of blood loss to determine severity, such as when more than 50% of the total blood volume is lost within a period of less than 3 hours or if the rate of blood loss exceeds 150 mL per minute.[6]

Modified shock index

The shock index (SI), a ratio of heart rate (HR) to systolic blood pressure (BP), is an indicator of early hypovolemia and the need for a blood transfusion. A rise in SI has been linked to severe adverse maternal outcomes, including mortality, the need for massive transfusion, low fibrinogen levels, and the transfusion of blood products like fresh frozen plasma.[7] The modified shock index is a bedside assessment defined as the ratio of HR to mean arterial pressure (MAP), with a normal range of 0.5 to 0.7 in healthy adults (Table 1).[8]

Table 1. Shock Index to mortality rates[8]

	Shock index	Mortality rate	Blood products#
No shock	<0.6	10.9% mortality	1.0 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

Method used to estimate the MAP: MAP = DP + 1/3(SP – DP) or MAP = DP + 1/3(PP)
*DP: diastolic blood pressure, MAP: mean blood pressure; PP: pulse pressure; SP: systolic blood pressure.
#The values in the table represent the number of blood product units suggested for patients within each shock index category, not the average.

Risk factors

PPH is a life-threatening situation and a nightmare for obstetricians. Preventive measures, such as anticipating risk factors and active management of the third stage of labor with uterotonics, are crucial. Uterine atony is the most common cause of PPH, followed by trauma to the genital tract, adherent placenta, and other factors. Timely recognition, control of bleeding through various methods, stabilizing the mother's condition, and a multidisciplinary approach are essential for managing PPH. However, second-line treatment remains challenging due to the lack of clear guidelines and sufficient data from randomized controlled trials.[1] The causes of PPH, the "4T" are summarized in Table 2. Some of the contributing risk factors include chorioamnionitis, multiple pregnancies, prepartum hemorrhage, macrosomic infants, maternal obesity, preeclampsia, anemia, primiparity, and prolonged labor.[9]

Table 2. Mnemonics of «4T» of causes of postpartum obstetric hemorrhage.[9]

	Features	Rate (%)
Tone	Atony or uterine inertia	70
Trauma	Uterine trauma (rupture and uterine inversion) and lacerations of the cervix and vagina	19
Tissue	Retention of placenta and clots and abnormal placenta	10
Thrombin	Congenital or acquired coagulopathies	1

Management of PPH

Initial management of PPH involves identifying the cause and using interventions ranging from conservative measures like medications and compression techniques to more invasive procedures and surgeries. PPH management may include adjunctive therapies like blood and fluid replacement, as well as the use of an anti-shock garment, to address the blood loss and its consequences. Conservative techniques, such as uterotonic medications external uterine massage, and bimanual compression are typically used as "first-line" treatments.[10]

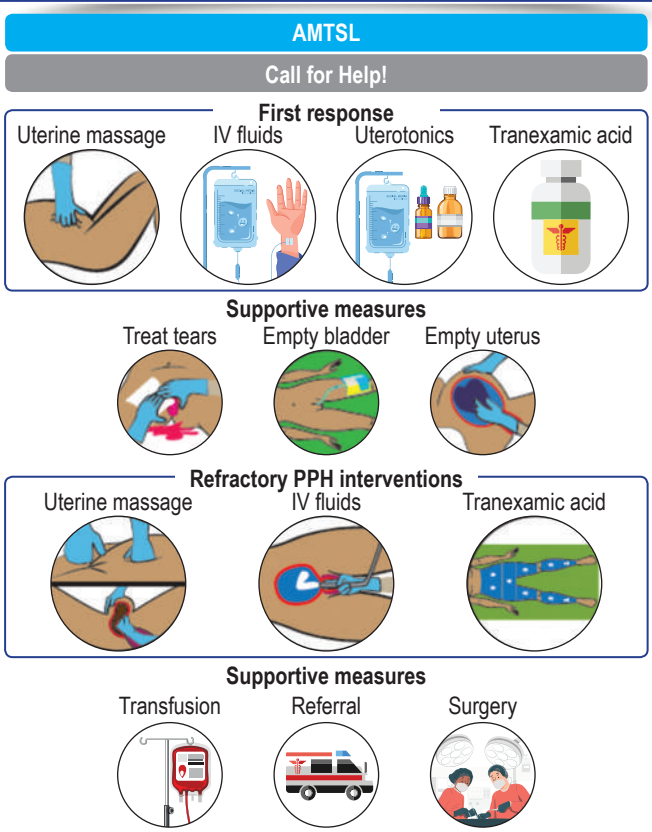
In PPH management, oxytocin is usually the first medication used. Other uterotonics may follow if oxytocin is ineffective. Procedures include placenta and clot removal and uterine balloon tamponade. Laceration repair is performed for genital tract trauma-related PPH. If bleeding persists despite conservative measures, more invasive options like uterine artery embolization are considered. However, these procedures carry risks and may impact future fertility and pregnancy.[10]

As a last resort, hysterectomy is considered. However, despite these various treatments, PPH can still lead to serious complications. Mortality and morbidity from PPH remain high, both in developing and developed countries.[11]

Postpartum Hemorrhage Emergency Care Using a Bundle Approach (PPH EmC) is a different way of conceptualizing PPH emergency response that integrates crucial clinical and systems-based interventions for rapid, effective PPH emergency care. According to WHO guidelines, PPH EmC clinical interventions are evidence-based, cost-effective, and suitable for healthcare providers at all facility levels, making them adaptable to various country settings (Figure 1).[12]

> "Even with excellent uterotonics and active management of labor, PPH remains the leading cause of maternal morbidity and mortality. There is an urgent need for a rapidly active non-invasive medical treatment to be made available for such life-threatening situations to avoid surgical treatments"

Figure 1. Postpartum hemorrhage (PPH) emergency care[12]



AMTSL: Active management of the third stage of labour

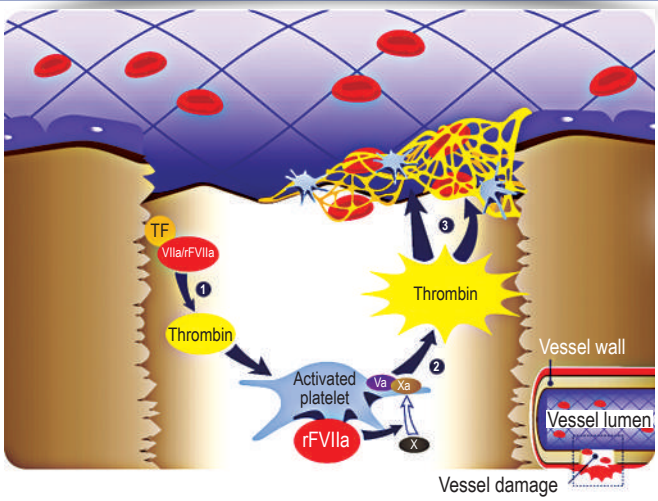
Recombinant factor VIIa: A potential breakthrough for treating severe PPH

One of the recent and novel advancements in the management of severe PPH has been the use of recombinant activated factor VII (rFVIIa). It was initially developed for the treatment of bleeding episodes in patients of hemophilia A & B with inhibitors as well as for bleeding due to acquired hemophilia, factor VII deficiency, and Glanzmann's thrombasthenia, among other conditions. Beyond its currently recognized indications, rFVIIa has been effectively used 'off-label' on an empirical basis in the treatment of severe PPH. From the first reported usage of rFVIIa in obstetric hemorrhage almost two decades back, it has made an impressive journey and saved many lives. In the last decade, there have been several case series documenting the successful management of severe PPH using rFVIIa.[13-14]

rFVIIa: Mechanism of action[15-16]

- rFVIIa functions specifically at the site of vascular damage, where tissue factor (TF) is exposed and activated platelets are present (Figure 2).
- When factor VIIa or rFVIIa binds to TF, it triggers the initiation of coagulation, producing small quantities of thrombin – 1.
- When administered in pharmacological doses, rFVIIa directly triggers factor X on the surface of activated platelets, leading to the generation of thrombin burst – 2.
- This sudden surge in thrombin results in the formation of a stable hemostatic plug that effectively manages and stops the bleeding – 3.

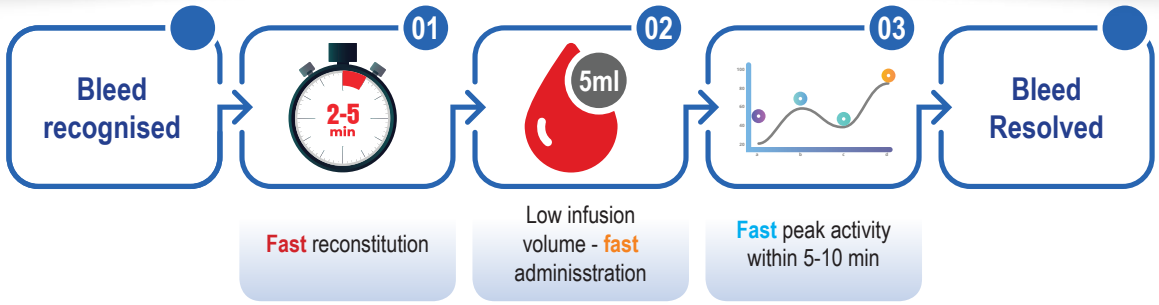
Figure 2. Illustration showing the mechanisms of action of rFVIIa in controlling bleeding at the site of vascular injury[16]



Efficient and rapid management of bleeding with rFVIIa

The prompt and safe initiation of treatment with rFVIIa is critical in managing severe PPH effectively. When dealing with a severe PPH event, the administration process begins with the reconstitution of the medication, which typically takes only about 2 to 5 minutes, ensuring a swift response. Additionally, the low infusion volume of just 5 ml facilitates a quick administration process. Notably, when administered as an IV bolus, rFVIIa achieves its peak activity within 5-10 minutes, which is especially advantageous for addressing severe PPH (Figure 3).[17-18]

Figure 3. Rapid and safe initiation of treatment with rFVIIa[17-18]



> rFVIIa swiftly controls bleeding with rapid reconstitution, low infusion volume, and quick peak activity (5-10 minutes), ensuring rapid resolution.

Long term safety data of rFVIIa

rFVIIa has shown a favorable safety profile with a low reported incidence of thrombotic complications (0.00004%, n=217 TEs) based on the 20-years safety data of 5.4 million standard doses. Its recombinant nature and localized mechanism of action reduce the risk of systemic coagulation activation. However, vigilant monitoring is essential, especially for patients with thrombosis risk factors, to ensure safety.[19-20]

Summary of the safety profile[18]

In cases of severe PPH, complex coagulopathy, and high complications necessitate effective treatments. The favorable safety profile of rFVIIa in the minimal risk of thromboembolic complications, proven in animal models and clinical use can be due to its localized action. Importantly, rFVIIa is free from human plasma components, ensuring no viral contamination, making it a valuable adjunctive therapy for severe PPH.[21]

rFVIIa has a robust safety record, with minimal treatment-related adverse events and excellent tolerance. Analysis of several thousand patients revealed non-serious adverse events at 13% and serious adverse events at less than 1%. Rare non-serious side effects include infusion site pain, fever, headache, vomiting, blood pressure changes, and skin-related hypersensitivity reactions. Importantly, these adverse events are not dose-related, emphasizing the drug's safety in clinical use.[21]

The limited thrombogenic risk of rFVIIa, attributed to its local activation of coagulation, is supported by clinical evidence. All existing studies and case reports on rFVIIa use in PPH consistently describe its favorable safety profile. However, due to the scarcity of published data and the lack of controlled studies, particular caution is recommended while using rFVIIa, especially in patients with PPH and systemic coagulation activation or gynecological cancers, who are at high thrombotic risk. Medical practitioners are urged to follow the currently accepted recommendations with regard to the dose and timing of rFVIIa administration and to monitor closely such women not only for clinical efficacy but also for the onset of adverse events.[22-23]

Efficacy data of rFVIIa in severe PPH

Randomized controlled trial

rFVIIa for reducing the need for invasive second-line therapies in severe refractory PPH.[24]

Lavigne-Lissalde et al. carried out a multicenter, randomized, open-label, controlled trial that assessed the efficacy and safety of a single rFVIIa infusion given to women with severe PPH after sulprostone failure. A total of 84 women with severe PPH unresponsive to uterotonics were randomized to receive one early single rFVIIa infusion (n = 42) with standard of care or standard of care (no rFVIIa; n = 42). The primary efficacy outcome measure was the reduction of the need for specific second-line

therapies, such as interventional hemostatic procedures (uterine compression sutures, ligation of the uterine or iliac arteries, uterine artery embolization and peripartum hysterectomy and the Bakri Balloon, which was used once in this study), of blood loss and transfusion. The primary safety outcome measure was the number of deaths and thrombotic events during the 5 days following rFVIIa infusion.

- The primary efficacy outcomes are detailed in Table 3.
- The use of rFVIIa resulted in a significant reduction in the number of patients who required second-line therapies compared to the standard-of-care group.
- In the standard of care arm, 93% (39 out of 42) of patients needed second-line therapies, whereas in the rFVIIa arm, only 52% (22 out of 42) of patients required such treatments.
- This represents an absolute difference of 41% and a relative risk of 0.56, indicating a substantial benefit of using rFVIIa in managing severe PPH unresponsive to uterotonics.
- There was a 44% relative risk reduction of invasive procedures with rFVIIa in comparison to the standard care arm.
- The delivery mode (vaginal or cesarean section) did not affect the primary outcome (Table 4).

Table 4. Effect of the delivery mode on the efficacy outcomes. (A) Vaginal delivery (B) Delivery by Cesarean section

	Standard arm (N = 42)	Intervention arm (N = 42)	Absolute difference
A. Principal endpoint Vaginal delivery, N = 41	n (%) N = 22	n (%) N = 19	(%)
Primary efficacy outcome	20 (91)	9 (47)	44
Arterial embolization	16 (73)	7 (37)	36
Arterial ligation	2 (9)	2 (11)	-2
Peripartum hysterectomy	3 (14)	1 (5)	9
Others*	2 (9)	0	9
Arterial embolization alone	15 (68)	7 (37)	31
Arterial ligation alone	0 (0)	1 (5)	-5
B. Cesarean section delivery, N = 43	N = 20	N = 23	
Primary efficacy outcome	19 (95)	13 (57)	38
Arterial embolization	8 (40)	5 (22)	18
Arterial ligation	10 (50)	7 (30)	20
Peripartum hysterectomy	5 (25)	2 (9)	16
Others*	4 (20)	4 (17)	3
Arterial embolization alone	7 (35)	5 (22)	13
Arterial ligation alone	3 (15)	3 (13)	2

*B-lynch sutures, Bakri Balloon and variants with hemostatic inten- tion.

- There was a 44% reduced risk of invasive procedures with rFVIIa in comparison to the standard of care arm.
- Two non-fatal venous thrombotic events were recorded in the rFVIIa arm after 2 days and 5 days, however duration of action of rFVIIa is 90 minutes only.
- In both cases, this event was associated with typical risk factors (placenta abruption, emergency Cesarean section and blood transfusion) and occurred despite thromboprophylaxis.

Table 3. Efficacy outcomes

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* B-lynch sutures, Bakri Balloon and variants with hemostatic intention	6 (14)	4 (10)	4% [–36; 44]	0.67 [0.20; 2.19]	25	0.50

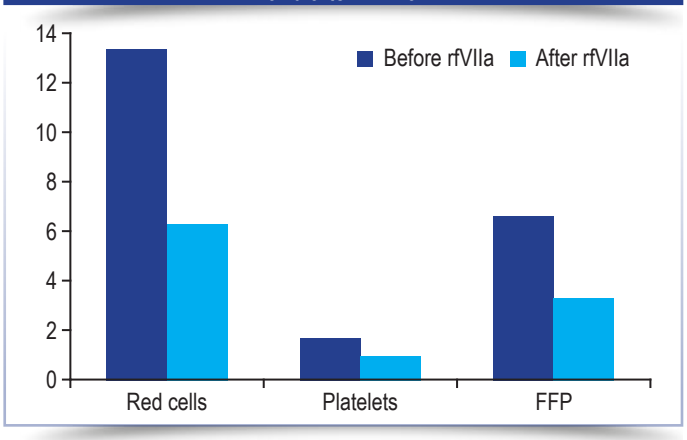
Global Real World Evidences

Use of rFVIIa in massive PPH[25]

Bouma et al. carried out a retrospective, descriptive study to describe the cumulative experience of a cohort that was treated with rFVIIa during the postpartum period especially regarding preventing hysterectomy. A total of 27 cases from all departments of obstetrics and gynecology in the Netherlands who were given rFVIIa for the treatment of massive PPH were included in the study. A standardized case record form was used to evaluate each case. The positive effect of rFVIIa administration was defined as (temporarily) reduction or cessation of bleeding as clearly stated in the patient chart. Preservation of the uterus was used as an endpoint of maternal morbidity.

- The main cause of PPH was uterine atony (82%)
- rFVIIa was administered in 85% of cases before hysterectomy. rFVIIa successfully prevented hysterectomy in 76% of the cases.
- 89% of women (24 out of 27) experienced a reduction or cessation of bleeding after rFVIIa administration. Significant reductions in blood product requirements (FFP, RBC, and platelets) were observed following rFVIIa administration (Figure 4).
- In 89% of cases, estimated blood loss prior to rFVIIa administration was more than 3 L, and more than 8 RBC units were transfused. 63% of cases had blood loss less than 1 L after rFVIIa administration.

Figure 4. Number of administered blood products before and after rFVIIa



> rFVIIa effectively controls PPH in 89% of unresponsive cases, reducing the need for blood products and avoiding emergency hysterectomy.

Summary of other observational studies on the efficacy of rFVIIa Severe PPH Management

- In an Italian retrospective survey of 35 severe primary PPH cases by Barillari et al. rFVIIa administration significantly improved coagulative parameters, reduced transfusion requirements, and facilitated fewer surgical interventions, indicating its safety and efficacy as adjunctive therapy in PPH management, with no observed adverse events or thromboembolic complications.[26]
- In a retrospective study across Southern European countries, Barillari et al. analyzed 45 severe PPH cases treated with rFVIIa. The study revealed that rFVIIa administration significantly improved coagulative parameters, reduced blood product and fluid requirements, suggesting its safety and efficacy as adjunctive therapy for PPH management.[27]
- In a retrospective analysis of 15 women with severe PPH cases with a Sequential Organ Failure Assessment (SOFA) score of 8 or higher, Park et al. found that rFVIIa significantly reduced PPH severity. This underscores the vital importance of prompt rFVIIa administration in severe PPH cases where standard treatments are ineffective.[28]
- Hossain et al. carried out a retrospective study on 34 women with massive PPH to assess the effectiveness of rFVIIa. Patients treated with rFVIIa exhibited lower maternal mortality (28% versus 50%), reduced need for packed red cell transfusions, and improved coagulopathy parameters, indicating rFVIIa as a life-saving intervention for massive PPH.[29]
- Salman et al. conducted a retrospective cross-sectional comparative study to examine the effect of rFVIIa on patients with PPH who received it at

Table 5. Summary of cases on the utility of rFVIIa in Fatal Postpartum Hemorrhage

Cases	Cause	Interventions	Pre-rFVIIa outcome	Post-rFVIIa outcome
Case 1	Atonic uterus	• Sequential uterotonics • Volume replacement • Uterine compression • B/L Artery ligation • Subtotal hysterectomy	• Bleeding decreased but continued • Patient lost almost 3.5L blood	• Bleeding decreased substantially after single dose of rFVIIa at 60 mcg/kg • Stopped totally after 2nd dose of 60 mcg/kg • Patient had uneventful postpartum subsequently
Case 2	Cervical tear and vaginal lacerations	• Suturing • Volume replacement • Tranexamic acid • Vaginal packing	• Uncontrollable bleeding • Patient lost almost 2.5L blood	• Bleeding decreased after single dose of rFVIIa at 60 mcg/kg • Stopped completely after 30 minutes of injection • Her rest of hospital stay was uneventful
Case 3	Atonic uterus	• Sequential uterotonics (repeated doses) • Volume replacement • Uterine compression • B/L Artery ligation	• Profuse bleeding • Patient lost almost 2L blood. • Prepared for hysterectomy in case bleeding wasn't arrested	• Bleeding decreased after single dose of rFVIIa at 60 mcg/kg • Arrested completely after 20 minutes of injection. • Patient had an uneventful recovery subsequently
Case 4	Atonic uterus & multiple vaginal lacerations	• All possible uterotonics • Bimanual uterine compression • Patient and her spouse wanted to preserve fertility	• Profuse bleeding • The patient lost almost 2L blood. • 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 min of giving rFVIIa, uterus regained its tone, and bleeding from vaginal tears was significantly reduced. • Vaginal packing done and bleeding was arrested completely. • Vaginal pack removed after 24 hours
Case 5	Atonic uterus & bleeding from the fibroids	• Uterotonic drugs • 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 min.

varying times (early and late administration groups) during treatment. Various patient characteristics were recorded, such as age, parity, cause of bleeding, time since bleeding to rFVIIa administration, transfusion volume response, need for ICU/ventilator support, fertility preservation, and maternal outcome. The study found that there was a significant difference between the early and late administration groups in terms of fertility preservation, transfusion requirement, and duration of ICU/hospital stay.[30]

- Huber et al. conducted a study aimed to evaluate the effectiveness of rFVIIa in avoiding postpartum hysterectomy in the management of severe PPH. The study was conducted on 22 patients with severe PPH where the main cause was uterine atony and pathologic placentation. The rFVIIa was successful in stopping the PPH and preventing hysterectomy in 91% of patients. No thromboembolic event was reported.[31]

Indian Real-World Evidence

rFVIIa in Fatal PPH: An Indian Case Series and Literature Review[32]

Magon et al. reported their personal experience in a series of five cases of severe PPH, all of which were successfully managed using rFVIIa (Table 5).

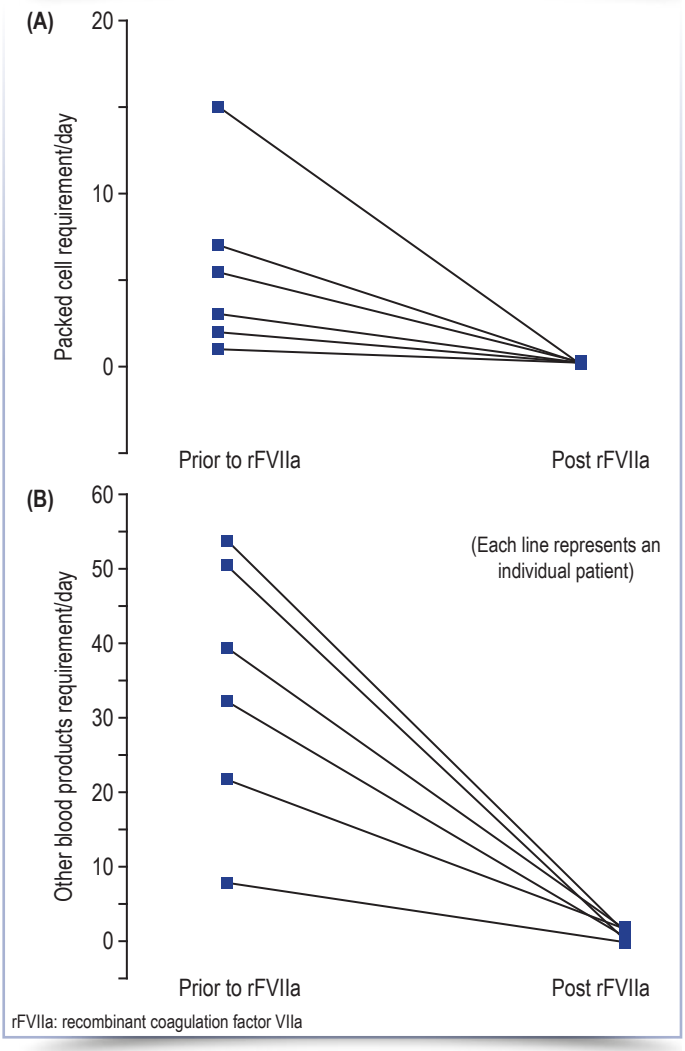
rFVIIa to control PPH in acute fatty liver of pregnancy and other pregnancy-related liver disorders.[33]

Goel et al. carried out a retrospective study aimed to report the use of rFVIIa in patients with acute liver failure due to pregnancy-related liver disorders. Patients with acute liver failure secondary to pregnancy-related liver disorders who received rFVIIa for control of PPH (six patients, all six met diagnostic criteria for acute fatty liver of pregnancy) were analyzed. The administration of rFVIIa was decided on a case-by-case basis after multidisciplinary team consultation.

- Significant improvement in prothrombin time (from 62±45 to 15±3 s; p-value=0.05) and activated partial thromboplastin time (from 102±61 to 34±6 s; p-value=0.03) was noted after rFVIIa administration.

- rFVIIa administration reduced requirement of packed red cell (from 6±5 to 0.1±0.2 units/day per patient; p-value 0.05) and other blood products (from 34±18 to 1±1 units/day per patient; p-value 0.006) (Figure 5).

Figure 5. After rFVIIa administration, there was significant reduction in daily requirement of packed red cells (p-value=0.05) and other blood products (p-value=0.006) in the six study patients.



rFVIIa: recombinant coagulation factor VIIa

> "rFVIIa is a useful adjunct to standard management in PPH secondary to acute liver failure of pregnancy-related liver disorders."

Review of Literature of Indian cases[13]

- rFVIIa has shown effectiveness in managing severe PPH in several cases: post-hysterectomy, arresting hemorrhage from multiple vaginal lacerations, as an adjunctive to surgical hemostasis, and as a rescue therapy when PPH is refractory to other methods.
- Over the last decade, rFVIIa has proven to be safe and effective in controlling life-threatening PPH, serving as both initial and life-saving therapy.
- rFVIIa is associated with very few adverse events and is well tolerated.
- It does not carry risk of viral transmission because it is free of any human protein. It causes localized hemostasis and has low thrombogenicity.
- It has a low risk of anaphylaxis and has no anamnestic responses.

> "As per the Indian experiences, rFVIIa has shown to be efficacious in rapidly controlling severe hemorrhage across different causes of PPH."

rFVIIa – Indian approval

The Central Drug Standard Control Organization (CDSCO) has approved the use of rFVIIa, Eptacog alfa, for an additional indication. The new indication is "for the treatment of severe PPH when uterotonics are insufficient to achieve hemostasis."[34]

Product characteristics of rFVIIa in severe PPH

- Recombinant coagulation factor VIIa (rFVIIa) is produced in baby hamster kidney cells (BHK Cells) by recombinant DNA technology.[35]
- rFVIIa is indicated for the treatment of severe PPH when uterotonics are insufficient to achieve hemostasis.[18]
- Appropriate multidisciplinary expertise should be consulted in the management of severe PPH. In addition to obstetricians, this includes anesthesiologists, critical care specialists and hematologists.[18]
- Standard management practices should remain implemented, based on the individual patient's requirements. Maintenance of adequate fibrinogen concentration and platelet count is recommended to optimize the benefit of rFVIIa treatment.[18]

Table 6. Pharmaceutical Specifications for rFVIIa Injection

Pharmaceutical form	Powder and solvent for injection
Components	• White lyophilized powder of rFVIIa • Clear colorless solution as solvent
Strength	• 1mg/Vial and 2mg/Vial
Reconstituted solution	• Contains 1 mg/ml rFVIIa (Activated)
Shelf life and storage	• Shelf life is 36 months • Before reconstitution: Up to 25°C • After reconstitution: 6 hours at 25°C and 24 hours at 5°C

Dose range and dose interval[18]

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.

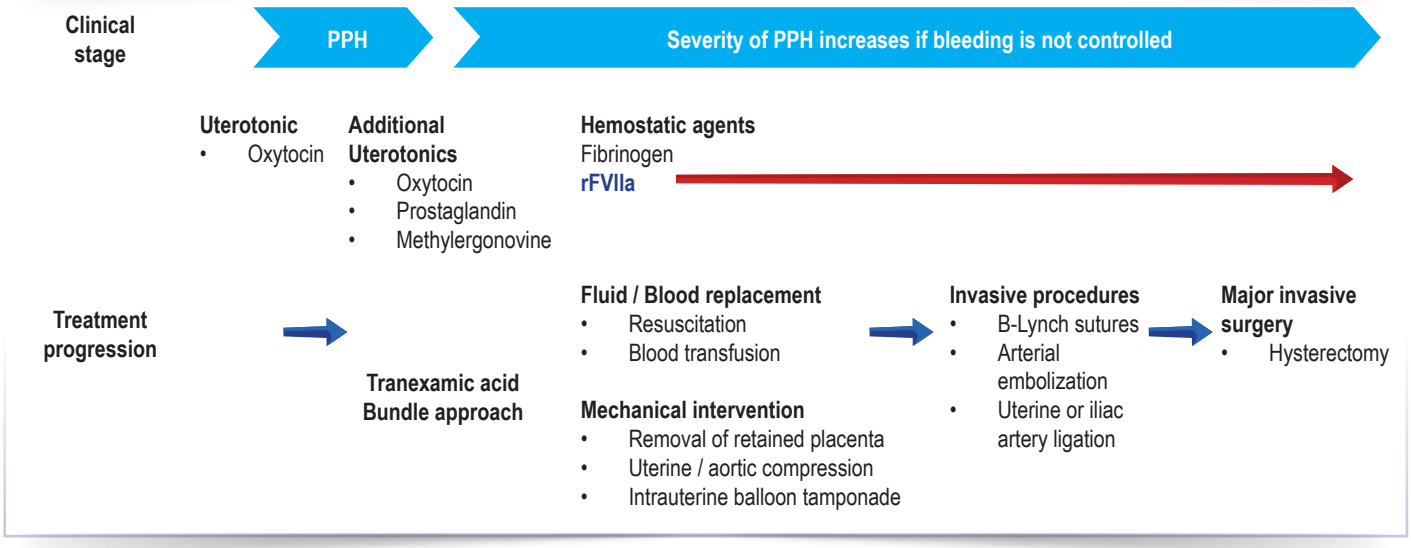
Recommended timing of administration[18]

rFVIIa permits effective control of obstetric bleeding, the administration of rFVIIa is therefore recommended in patients with severe PPH when not responding to uterotonics (Figure 6).

Contraindications[18]

Hypersensitivity to the active substance or to any of the excipients listed below or to mouse, hamster, or bovine protein.

Figure 6. 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[18, 36-39]



PRACTICE POINTS

- Postpartum hemorrhage (PPH) still remains the leading cause of maternal morbidity and mortality worldwide, responsible for approximately 25% of maternal deaths globally, and 38% in India.
- Severe PPH is one of the indication for ICU admission in about 27.7% of obstetric patients.
- The common causes of PPH are uterine atony, trauma to the genital tract during child birth, adherent placenta, coagulopathy and other factors.
- Timely recognition, control of bleeding through various methods, stabilizing the mother's condition with a multidisciplinary approach is essential for managing PPH effectively.
- Even with excellent uterotonics and active management of third stage of labor, PPH still remains the leading cause of maternal morbidity and mortality.
- rFVIIa proved to be an effective agent in achieving hemostasis in patients with severe PPH and has been shown to reduce bleeding as well as the need for blood transfusion and blood products.
- rFVIIa maintains a favorable safety profile, with no new or unexpected safety concerns.
- The favorable safety profile of rFVIIa can be attributed to its recombinant nature and localized mechanism of action at the site of vascular injury.
- As per the data published globally and few Indian studies, rFVIIa has shown to be efficacious in rapidly controlling massive hemorrhage across different causes of severe PPH.

References

1. Tasneem F, Sirsam S, Shanbhag V. Clinical study of post-partum hemorrhage from a teaching hospital in Maharashtra, India. Int J Reprod Contracept Obstet Gynecol 2017;6:2366–9. **2.** Guidance Note on Prevention and Management of Postpartum Hemorrhage. [Internet] 2015. [Accessed: July 21, 2023]. Available from: https://nhm.gov.in/images/pdf/programmes/maternal-health/guidelines/Guidance_Note_on_Prevention_&_Management_of_Postpartum_Haemorrhage.pdf. **3.** Agrawal S, Singh A, Biswas R, Singh A. Retrospective review of maternal deaths and maternal near misses due to major obstetric haemorrhage at a tertiary care centre in India. Int J Reprod Contracept Obstet Gynecol 2019;8:3431-4. **4.** Bhat PB, Navada MH, Rao SV, et al. Evaluation of obstetric admissions to intensive care unit of a tertiary referral center in coastal India. Indian journal of critical care medicine: peer-reviewed, official publication of Indian Society of Critical Care Medicine. 2013 Jan;17(1):34. **5.** World Health Organization. WHO recommendations for the prevention and treatment of postpartum haemorrhage. World Health Organization; 2012 **6.** Schorn MN, Phillippi JC. Volume replacement following severe postpartum hemorrhage. J Midwifery Womens Health. 2014 May-Jun;59(3):336-43. **7.** Chaudhary M, Maitra N, Sheth T, et al. Shock Index in the Prediction of Adverse Maternal Outcome. J Obstet Gynaecol India. 2020;70(5):355–359. **8.** FOGSI. PPH Prevention and Management: Updated PPH Guidelines. [Internet] 2022. [Accessed: September 14, 2023]. Available from: https://www.fogsi.org/wp-content/uploads/tog/pph-prevention-and-management-updated-sept-2022.pdf. **9.** José E De L H, Muñoz DM, Enríquez Mogollón JA, et al. Effectiveness of Hayman's Compressive Suture in the Management of Postpartum Hemorrhage. Int Gyn & Women's Health 3(4)- 2019. IGWHC.MS.ID.000166. **10.** Likis FE, Sathe NA, Morgans AK, et al. Management of Postpartum Hemorrhage [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2015 Apr. (Comparative Effectiveness Reviews, No. 151.) Introduction. Available from: https://www.ncbi.nlm.nih.gov/books/NBK294453/ **11.** Park SC, Yeom SR, Han SK, et al. Recombinant activated factor VII as a second line treatment for postpartum hemorrhage. Korean Journal of Critical Care Medicine. 2017 30;32(4):333–9. **12.** FIGO. PPH Emergency Care Using a Bundle Approach (PPH EmC). [Internet] 2020. [Accessed: September 14, 2023]. Available from: https://www.jhpiego.org/wp-content/uploads/2020/07/MGH-PPH-EmC-Executive-Summary_July-2020.pdf **13.** Magon N, Babu K. Recombinant Factor VIIa in Post-partum Hemorrhage: A New Weapon in Obstetrician's Armamentarium. N Am J Med Sci. 2012 Apr;4(4):157–62. **14.** Jan JY, Lin SY, Lin CH, Lee CN, Fan SZ, Han YY. Recombinant activated factor VII as a promising adjuvant therapy for postpartum hemorrhage in the practice of obstetric anesthesia: experience from a university hospital in Taiwan. J Obstet Gynaecol Res. 2011 Jul;37(7):901-7. **15.** Hoffman M, Monroe DM 3rd. The action of high-dose factor VIIa (FVIIa) in a cell-based model of hemostasis. Semin Hematol. 2001 Oct;38(4 Suppl 12):6–9. **16.** Hawryluk GW, Cusimano MD. The role of recombinant activated factor VII in neurosurgery: hope or hype? J Neurosurg. 2006;105(6):859–68. **17.** Morfini M. Rapid rFVIIa enhanced on-demand dosing in haemophilia inhibitor patients. Eur J Haematol. 2016;96(2):111–8. **18.** Summary of product characteristics - INN-eptacog alfa (activated). [Internet] 2023. [Accessed: July 21, 2023]. Available from: https://www.ema.europa.eu/en/documents/product-information/novoseven-epar-product-information_en.pdf. **19.** Neufeld EJ, Négrier C, Benchikh El Fegoun S, et al. Recombinant activated factor VII in approved indications: Update on safety. Haemophilia. 2018;24(4):e275–e277. **20.** Neufeld EJ, Négrier C, Arkhammar P, et al. Safety update on the use of recombinant activated factor VII in approved indications. Blood Rev. 2015;29 Suppl 1:S34–41. **21.** Sobieszczyk S, Breborowicz G. The use of recombinant factor VIIa. In: A Comprehensive Textbook of Postpartum Hemorrhage (2nd Edition). Arulkumaran SS, Karoshi M, Keith LG, Lalonde AB, B-Lynch C (Eds) (2012). **22.** Franchini M, Franchi M, Bergamini V, et al. A critical review on the use of recombinant factor VIIa in life-threatening obstetric postpartum hemorrhage. Semin Thromb Hemost. 2008;34(1):104–12. **23.** Franchini M, Lippi G, Franchi M. The use of recombinant activated factor VII in obstetric and gynaecological haemorrhage. BJOG. 2007;114(1):8–15. **24.** Lavigne-Lissalde G, Aya AG, Mercier FJ, et al. Recombinant human FVIIa for reducing the need for invasive second-line therapies in severe refractory postpartum hemorrhage: a multicenter, randomized, open controlled trial. J Thromb Haemost. 2015;13(4):520–9. **25.** Bouma LS, Bolte AC, van Geijn HP. Use of recombinant activated factor VII in massive postpartum haemorrhage. Eur J Obstet Gynecol Reprod Biol. 2008 Apr;137(2):172-7. **26.** Barillari G, Frigo MG, Casarotto M, et al. Use of recombinant activated factor VII in severe post-partum haemorrhage: data from the Italian Registry: a multicentric observational retrospective study. Thromb Res. 2009 Dec;124(6):e41–7. **27.** Barillari G, rFVIIa-PPH South European Registry Study Group. Use of Recombinant Activated Factor VII in Severe Postpartum Haemorrhage: Data from the South European Registry. A Multicentric Observational Retrospective Study. Blood. 2008;112(11):4065. **28.** Park SC, Yeom SR, Han SK, et al. Recombinant Activated Factor VII as a Second Line Treatment for Postpartum Hemorrhage. Korean J Crit Care Med. 2017;32(4):333–339. **29.** Hossain N, Shansi T, Haider S, et al. Use of recombinant activated factor VII for massive postpartum hemorrhage. Acta Obstet Gynecol Scand. 2007;86(10):1200–6. **30.** Salman N, Rafay A, Junaid R, et al. Use of Recombinant Activated Factor VII: Pakistani Experience of Managing Massive Obstetric Haemorrhage. Niger J Med. 2022;63(5):267-72. **31.** Huber AW, Raio L, Alberio L, et al. Recombinant human factor VIIa prevents hysterectomy in severe postpartum hemorrhage: single center study. J. Perinat. Med. 2012;40(1):43-9. **32.** Magon N, Babu KM, Kapur K, Chopra S, Joneja GS. Recombinant activated factor VII in post partumhaemorrhage. Niger Med J 2013;54:289–94. **33.** Goel A, Nair SC, Viswabandya A, et al. Preliminary experience with use of recombinant activated factor VII to control postpartum hemorrhage in acute fatty liver of pregnancy and other pregnancy-related liver disorders. Indian J Gastroenterol. 2013 Jul;32(4):268-71. **34.** Novo Nordisk Eptacog Alfa gets CDSCO panel nod for additional indication. [Internet] 2022. [Accessed: July 21, 2023]. Available from: https://medicaldialogues.in/news/industry/pharma/novo-nordisk-eptacog-alfa-gets-cdsco-panel-nod-for-additional-indication-100818. **35.** Montacir O, Montacir H, Eravci M, et al. Bioengineering of rFVIIa Biopharmaceutical and Structure Characterization for Biosimilarity Assessment. Bioengineering (Basel). 2018;5(1):7. **36.** World Health Organization. WHO recommendations Uterotonics for the prevention of postpartum haemorrhage: Web annex 7: Choice of uterotonic agents. World Health Organization; 2018. **37.** WHO recommendation on routes of oxytocin administration for the prevention of postpartum haemorrhage after vaginal birth [Internet]. Geneva: World Health Organization; 2020. Executive summary. Available from: https://www.ncbi.nlm.nih.gov/books/NBK564758/ **38.** Weeks AD, Akinola OI, Amorim M, Carvalho B, Deneux-Tharaux C, Liabsuetrakul T, Meremikwu M, Miller S, Nabhan A, Nagai M, Wahabi H. World Health organization recommendation for using uterine balloon tamponade to treat postpartum hemorrhage. Obstetrics and gynecology. 2022 Mar;139(3):458. **39.** NovoSeven Prescribing Information. Available at: https://www.fda.gov/media/70442/download. Accessed on: October 26, 2023.