FEDERATION OF OBSTETRIC AND GYNAECOLOGICAL SOCIETIES OF INDIA

TOG Times of Gynaecology®

Issue 67

Science Integra®

COMING SOON IN SEVERE PPH

NovoSeven®

Recombinant Factor VIIa

A fast, non-invasive option to control severe PPH[1,2]

In severe PPH

ACTS FAST. STOPS the LOSS[1-4]

NOW APPROVED FOR

Severe postpartum haemorrhage

when uterotonics are insufficient to achieve haemostasis[1,5]

Rapid bleed control

- achieves peak effect in 10 mins[2,4]

Reduction in invasive procedures

- **44.7% reduction** in invasive procedures*#[3] (p<0.0001)

Convenience

- Formulated to treat fast (<5 min)[2,4]
- Can be stored at room temperature (<25°C)[1]

Scan the QR code to access the HCP portal

*Invasive procedure was defined as arterial embolisation, arterial ligation, peripartum hysterectomy, B-lynch sutures, Bakri Balloon.

#In the RCT, there was a statistically significant difference of 44% relative risk reduction in the chances of invasive procedures with the NovoSeven® group compared to reference group (p<0.0001).

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5. NovoSeven® Prescribing Information India.

For the use only of a registered medical practitioner or a hospital or a laboratory.

Abbreviated prescribing information (and not full package insert)

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 i.v. administration. The product is freeze dried and dissolved in 10mM 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's thrombasthenia with past or present refractoriness to platelet transfusions, or where platelets are not readily available. 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Dosing interval: every second hour until clinical improvement, increased if necessary, to 3 hours for 1 – 2 days and further increased successively to every 4, 6, 8 or 12 hours for as long as treatment is required. A major bleeding episode may be treated for 2 – 3 weeks but can be extended beyond this if clinically warranted. Invasive procedure/surgery: Initial dose - 90 µg per kg body weight given immediately before the intervention. **Dosing interval:** 2-3 hour intervals for the first 24 – 48 hours depending on the intervention performed and the clinical status of the patient. In major surgery, the dose should be continued at 2-4 hour intervals for 6-7 days and subsequently at 6 – 8 hours intervals for another 2 weeks of treatment. Patients undergoing major surgery may be treated for up to 2 – 3 weeks until healing has occurred. **• Acquired Haemophilia:** Initial dose - 90 µg per kg body weight. 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For those patients who are not refractory, platelets are the first line treatment for Glanzmann's thrombasthenia. **• Severe postpartum haemorrhage:** 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. **Children:** Current clinical experience does not warrant a general differentiation in dosing between children and adults, although young children have faster clearance than adults. Therefore, higher doses of rFVIIa may be needed in paediatric patients to achieve similar plasma concentrations as in adult patients. **Pregnancy and lactation:** As a precautionary measure, it is preferable to avoid the use of NovoSeven® during pregnancy. Data on a limited number of exposed pregnancies within approved indications indicate no adverse effects of rFVIIa on pregnancy or on the health of the foetus/newborn child. A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with NovoSeven® should be made considering the benefit of breastfeeding to the child and the benefit of NovoSeven® therapy to the woman. **Elderly:** In patients with factor VII deficiency, where the recommended dose is 15-30 µg/kg rFVIIa, one episode of overdose has been associated with a thrombotic event (occipital stroke) in an elderly (> 80 years) male patient treated with 10-20 times the recommended dose. **Special populations and conditions:** It includes pregnant women and breastfeeding. Kindly refer the above specific sections for details. Data from non-clinical studies as well as post-marketing data show no indication that rFVIIa has a harmful effect on male or female fertility. **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 disseminated intravascular coagulation. In cases of hypersensitivity to residual culture proteins, treatment with antihistamines i.v. 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. 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NovoSeven® is a trademark owned by Novo Nordisk Health Care AG, Switzerland. Imported by: Novo Nordisk India Private Limited, Bangalore.

* The full prescribing information can be obtained at no cost from Novo Nordisk.

For full prescribing information, please contact +91-080-40303200 or write to us at INAgree@novonordisk.com or reach us at **Novo Nordisk India Pvt. Ltd.,** Plot no 32, 47-50, EPIP area, Whitefield, Bangalore - 560066.

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President's Message

From the desk of Dr Hrishikesh D Pai – President, FOGSI

I feel truly blessed and humbled to be installed as 61st President of FOGSI. My presidential theme of this year is "Swasth Nari, Sukhi Nari" or "Healthy Woman, Happy Woman". This theme supported by five pillars of Academics, Fellowship, Research, Advocacy and above all Social Work. The aims to focus on academic, social and community health initiatives for the betterment of women health in our country. In addition, a new CSR program called Badlaav/Change would be launched which is defined by Integration of care (Ekikaran), Equality of treatment (Samanta) and utilizing Technology (Takniki) to implement the change. I request you all to stand with me and contribute to these programs which are meant for the upliftment of women.

Besides these initiatives, I will continue the strong academic activities of the society, as laid down by my predecessors Presidents. Many national and international conferences have been planned throughout the year.

FOGSI has always been committed to delivering various education programs and journals to help all our fellow members to perform at their best in their areas of expertise and practice.

Several books, FOGSI focus, GCPR s and Journals will also be published. Handholding and guidance will be provided to our members to handle various acts such as MTP, POCSO, PCPNDT, clinical establishments, ART, and Surrogacy.

I congratulate all the editors for their sincere efforts and hard work in writing, collating, editing, and publishing this TOG journal. I hope that this journal will help you stay updated about the latest advancements in the field and provides valuable tips that can be implemented in day-to-day practice.

I wish you all a happy reading and a wonderful year full of academics and extracurricular activities.

"I alone cannot change the world, but I can cast a stone across the waters to create many ripples."
— Mother Teresa

Best wishes!

Dr Hrishikesh D Pai

MD, FRCOG (UK), MSc (USA), FCPS,FICOG
Medical Director -Bloom IVF Group
Director -Corporat Affairs
IFS International Federation of Fertility Societies
Founder Chair Indian SIG, - ASRM American Society of Reproductive Medicine

Editorial Message

Dear FOGSIans,

To take over the steering wheel from an experienced skipper is a challenge for the new one. What course should be taken to go towards old and new destinations? The journal stands on an old foundation of publishing a broad range of articles covering fundamental aspects of obstetrics and gynecology as well as subspecialty topics. We plan to extend this and introduce new items to enhance the readability of the journal. The issues will start with an Editors' Message highlighting contributions and news of specific interest. More wide-ranging medical news will be added in due course, both from the interiors of India and globally.

This will broaden the journals' medical outlook and often take it beyond the traditional scope of obstetrics and gynecology to women's health in a general sense. The editorial team will strengthen its working ties for this purpose. Input from the readers and leading centers and institutions in our country will be necessary, as will the role of our international contributors.

In today's googled-world of databases and alert-e.mails, reading becomes universal and less dependent on specific journals many times. Still, it is good to have at least one journal to grasp on a quiet evening or good afternoon at home or at work, feel the pages glide through your hands as you absorb crisp content across therapy areas that you want to be acquainted with, for your own sake and that of your patients. Many of us prefer a personalized article over reading on a computer screen, which brings us joy.

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Management of severe PPH: Role of Recombinant Factor VIIa

Drug in Focus

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 for 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]

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. According to the WHO, severe PPH is defined as a blood loss of 1000 ml or more within 24 hours after birth.[3] 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.[4]

Management of postpartum hemorrhage

Initial postpartum hemorrhage (PPH) management involves a range of interventions, starting with conservative measures like medications and compression techniques and progressing to more invasive procedures. Adjunctive therapies, such as blood and fluid replacement and the use of anti-shock garments, address blood loss consequences. Uterotonic medications, external uterine massage, and bimanual compression serve as initial, first-line treatments to swiftly mitigate PPH severity.[5]

In PPH management, oxytocin is usually the first medication used. Other uterotonics may follow if oxytocin is not effective. Procedures include placenta and clot removal and uterine balloon tamponade. Laceration repair is done 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. [5]

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.[6]

> “Even with excellent uterotonics and active management of labor, postpartum hemorrhage 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”

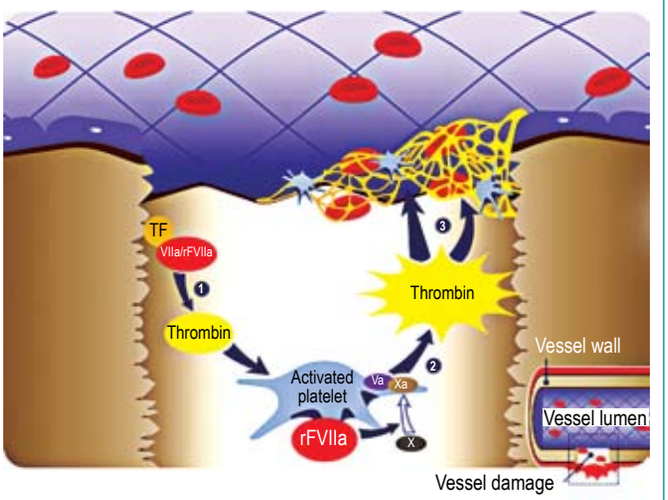
Recombinant factor VIIa: A potential breakthrough for treating severe postpartum hemorrhage.

One of the recent and novel advancement 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 last decade, there have been several case series documenting successful management of severe PPH using rFVIIa.[7-8]

rFVIIa: Mechanism of Action[9-10]

- rFVIIa functions specifically at the site of vascular damage, where tissue factor (TF) is exposed and activated platelets are present (Figure 1).
- 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 1 Illustration showing the mechanisms of action of rFVIIa in controlling bleeding at the site of vascular injury10



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.[11-12]

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.[13-14]

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

Efficacy data of rFVIIa in severe PPH

rFVIIa for reducing the need for invasive second-line therapies in severe refractory postpartum hemorrhage.[15]

Lavigne-Lissalde et al conducted a randomized controlled trial assessing the efficacy and safety of a single recombinant factor VIIa (rFVIIa) infusion in women with severe postpartum hemorrhage (PPH) unresponsive to sulprostone. Eighty-four participants were randomized to receive either an early single rFVIIa infusion with standard care (n=42) or standard care alone (n=42). The primary efficacy outcome was the reduction in the need for specific second-line therapies and the associated blood loss and transfusion requirements. The primary safety outcome included deaths and thrombotic events within 5 days following rFVIIa infusion. The primary efficacy outcomes are detailed in Table 1.

- 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 postpartum hemorrhage 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.

> - 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.

Use of rFVIIa in massive postpartum hemorrhage[16]

Bouma et al conducted a retrospective study on 27 cases treated with recombinant factor VIIa (rFVIIa) for massive postpartum hemorrhage across Dutch obstetrics and gynecology departments. The study aimed to describe the collective experience, focusing on the preventive impact of rFVIIa on hysterectomy. The positive effect was defined as a

Table 1. Efficacy outcomes

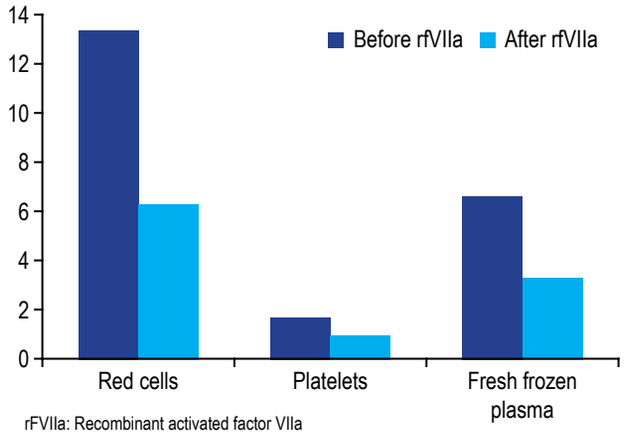
Outcomes	Standard arm (N = 42) n (%)	Intervention arm (N = 42) n (%)	Absolute difference [95% CI]	Relative risk [95% CI]	Mean NNT	p
Primary efficacy outcome	39 (93)	22 (52)	41% [18; 63]	0.56 [0.42; 0.76]	2.6	< 0.0001
Arterial embolization	24 (57)	12 (29)	28% [–4; 61]	0.5 [0.29; 0.86]	3.5	0.0082
Arterial 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

documented (temporary) reduction or cessation of bleeding, with uterine preservation as a key endpoint for 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 2).
- 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 2

Number of administered blood products before and after rFVIIa



rFVIIa: Recombinant activated factor VIIa

Practice points

- PPH is the leading cause of maternal morbidity and mortality worldwide, responsible for approximately 25% of maternal deaths globally, and 38% in India.
- 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 effectively.
- Even with excellent uterotonics and active management of third stage of labor, postpartum hemorrhage 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 blood product requirements.
- 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 Indian studies, rFVIIa has shown to be efficacious in rapidly controlling severe hemorrhage across different causes of PPH.

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

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Recombinant anti–D in preventing maternal alloimmunization: A novel alternative to mono or polyclonal anti-D

Scientific Review

Dr Priyankur Roy
MS, FIRM, FAGE, DRM,
Dip. Gynae-Endoscopy (Germany),
PGDHHM, PGDMLS, FIAOG

Maternal Alloimmunization: An epidemiological aspect

Maternal alloimmunization is the primary cause of hemolytic disease of the fetus and newborn (HDFN), leading to 50,000 fetal deaths annually, predominantly in low– and middle–income countries.[1] Fetal maternal hemorrhage during pregnancy or parturition leads to maternal alloimmunization. Based on the prevalence of blood group antigens within the population, the possibility of alloimmunization varies; the estimated frequency of rhesus antibody-D [Rh(D)] negativity is reported to be around 3%–8% among the African and Indian people, and 0.1%–3% among the Asian population.[2]

Benefits of administering anti–D immunoglobulin prophylaxis

Researchers found that passive immunization of Rh(D)–negative mothers with anti–D (anti–Rh(D) immunoglobulin [IgG]) soon after parturition could protect women from sensitization against Rh(D)–positive red blood cells.[3] Thus, anti–D IgG prophylaxis is part of routine obstetrical care for Rh(D)–negative women at risk, which led to a dramatic fall in the number of Rh affected babies. Also, it is an immunological success story in the conquest of HDFN across the world.[1] Evidences showed that the incidence of Rh sensitization reduced from 14% to 1% in Rh(D)–negative women delivering Rh(D)–positive newborns due to the administration of anti–D IgG prophylaxis after delivery of Rh(D)–positive newborns. Also, administration of anti–D IgG prophylaxis in the antenatal period reduced the incidence of Rh sensitization from 1.8% to 0.07%.[1] Therefore, guideline for prophylactic use of Rh(D) immunoglobulin in pregnancy care recommended administration of anti–D IgG prophylaxis in every non-sensitized Rh(D) –negative woman at 28 weeks of gestation during each pregnancy, immediately after delivery of every Rh(D)–positive child, or in any event such as abortion, miscarriage where the Rh(D)–negative mother is exposed to the Rh(D) antigen.[3]

Recommendations from the guideline[4]

Strong recommendation according to the guideline for prophylactic use of Rh(D) immunoglobulin in pregnancy care[4]
All pregnant women should undergo screening to identify ABO/Rh blood type and antibodies in their early pregnancy period.
Non-invasive prenatal testing (NIPT) must be conducted from 11^{+0} weeks of pregnancy for better accuracy in all Rh(D)–negative mothers.
Targeted antenatal Rh(D) immunoprophylaxis Rh(D)–negative mothers with no preformed anti–D antibodies.
Antenatal Rh(D) IgG must be administered in Rh(D)–negative mothers with no preformed anti-D antibodies to prevent Rh(D) alloimmunization.
Postnatal Rh(D) immunoprophylaxis should be continued in all Rh(D)–negative mothers with no preformed anti–D antibodies and Rh(D)–positive newborn (predicted by NIPT for fetal RhD)
Rh(D) immunoprophylaxis dose is not increased in Rh(D)–negative mothers with high body mass index.

Shortcomings of conventional mono and polyclonal anti-D immunoglobulin

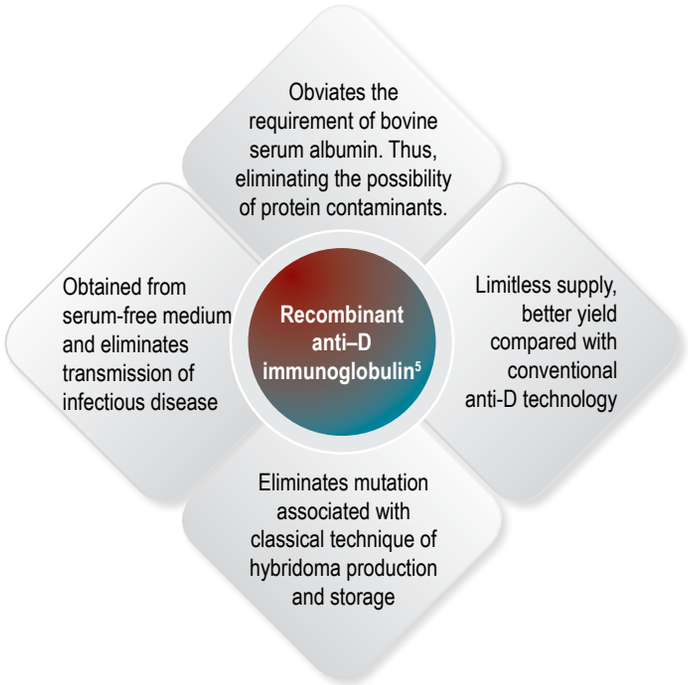
Conventional anti-D IgG prophylaxis[5]

- Polyclonal anti–D IgG prophylaxis: Fractionation of immunoglobulin from pooled plasma of donor (Rh[D]) –negative men who were deliberately immunized with Rh[D]–positive red blood cells).
- Monoclonal anti–D immunoglobulin: Produced by hybridoma technology.

Limitations[5]

- Shortage of volunteer Rh(D) –negative human donor
- Limited capacity of production (low yield)
- Risk of transmission of viral/prion diseases
- Hybridoma technology is time-consuming and laborious.
- Low availability of growth supplements such as fetal bovine serum (FBS)
- FBS might contain protein contaminants

Recombinant anti–D immunoglobulin: A novel successor of hybridoma-derived antibodies



Efficacy and safety of recombinant anti–D IgG when used in post-partum immune-prophylaxis

- A randomized controlled trial was conducted on Rh(D)–negative pregnant women who were not given antenatal anti–D and had delivered Rh(D)–positive babies and showed negative indirect Coombs tests (ICTs) at baseline. Researchers compared properties such as safety, efficacy, and immunogenicity of recombinant anti–D IgG with conventional polyclonal anti-D IgG prophylaxis in the trial. The subjects were randomized in a 2:1 ratio to recombinant anti–D group (n=144 women) and polyclonal anti-D group (n=71 women). The recombinant anti–D group was administered with 300 mcg of recombinant anti–D IgG, and the polyclonal anti-D group was administered with 300 mcg of conventional polyclonal anti-D IgG; the drugs were administered in both groups intramuscularly within 72 hours of delivery. Researchers conducted ICT at 72 hours, 90 and 180 days after injection of anti–D IgG; and bridging enzyme-linked immunosorbent assay (ELISA) was performed to quantify antibodies against recombinant anti–D IgG at 90 and 180 days.[5]

Finding showed that[5]:

» The baseline characteristics such as type of delivery, gestational age, and demographic of the recombinant anti–D group were comparable with the polyclonal anti-D group.

» At 180 days, researchers reported that 86.71% of subjects in the recombinant anti–D group and 91.04% in the polyclonal anti-D group had a negative ICT result. Moreover, Fisher's exact test calculation depicted that the p-value for ICT results at 90 days was p=0.30 and 180 days was p=0.49;

the results were not statistically significant owing to a comparable efficacy among recombinant anti–D and polyclonal anti-D group.

» Subjects in both groups (n=4) subjects in each group; < 1% in each group) experienced mild adverse events such as pyrexia, abdominal pain, itching, hypertension owing to a similar safety profile of recombinant anti–D IgG to polyclonal anti-D IgG.

» The ELISA test confirmed that no subjects developed antibodies against recombinant anti–D proving that recombinant anti–D IgG is non-immunogenic.

- Researchers conducted a randomized study on 46 healthy Rh(D)–negative pregnant women to investigate the safety and pharmacokinetics of recombinant anti–D. The subjects were administered with placebo or recombinant anti–D (dose: 30–3000 µg) intravenously (i.v.), and 12 among these subjects were administered with recombinant anti–D intramuscularly (i.m.); the subjects were observed for 6 months after administration.[6] Researchers found that[6]:

  » During the trial, 14 treatment-emergent adverse events (AEs) were reported in nine subjects. However, the AEs related to the treatment were mild or moderate and were observed evenly among subjects in the recombinant anti–D and placebo groups.

  » No human antibodies against recombinant anti–D IgG were reported in 6 months after its administration.

  » The mean serum exposure to recombinant anti–D IgG increased from 4.4 at 30 µg i.v. to 22,557 ng/ml.day at 3000 µg i.v. Also, the terminal elimination half-life ranged from 18–22 days, and absolute bioavailability was 73%-80% after IM administration.

Recombinant anti–D IgG was well-tolerated and safe intravenously and intramuscularly in Rh(D)–negative pregnant women. Also, the pharmacokinetic profile of recombinant anti–D IgG is similar to conventional polyclonal anti-D IgG. Thus, recombinant anti–D IgG is an effective and safe alternative to conventional polyclonal anti-D.[6]

Summary

- The conventional polyclonal anti-D IgG is accompanied by the risk of transmission of infectious disease and low production yield, whereas monoclonal anti–D IgG exhibited certain inherent limitations of hybridoma technology. These shortcomings led to research for an alternative method.
- Recombinant anti–D IgG eliminates infectious disease transmission and prevents classical hybridoma production technology problems.
- The efficacy and safety of recombinant anti–D was similar to the conventional polyclonal anti-D. Also, recombinant anti–D were non-immunogenic. Thus, recombinant anti–D IgG is well-tolerated, safe, effective, and suitable alternative to current anti–D IgG to prevent maternal alloimmunization.

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Association of Folate and Vitamin B12 with gestational diabetes mellitus: Mechanisms and fetal implications

In Focus

Dr. Elizabeth Jacob
MD (PGI), DNB, FICOG

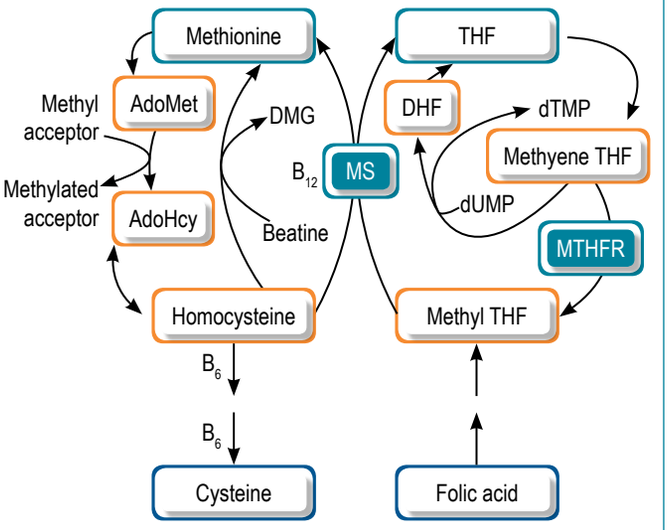
Impact of gestational diabetes mellitus

Gestational diabetes mellitus (GDM) is a common disorder during pregnancy that affects 12.9% of pregnant women worldwide. During pregnancy, the disease is characterized by new-onset of impaired glucose tolerance and insulin resistance, which can result in various adverse maternal and neonatal outcomes. Women with GDM are at an increased risk of preeclampsia, cesarean section, and post-partum diabetes mellitus, while neonates are at higher risk of obesity and diabetes mellitus later in life. Thus, identification and modification of potential risks factors for GDM can significantly impact both maternal and neonatal health.[1] Various studies have identified a relationship between maternal B vitamin imbalance, with high folate (Vitamin B9) and low vitamin B12 levels, and an increased risk of developing GDM.[2]

Role of folate and vitamin B12 during pregnancy

Folate and vitamin B12 are two essential nutrients for early pregnancy that are metabolically interlinked in one-carbon metabolism. Both are required for DNA methylation and production of nucleotides which are needed for increased cellular replication and fetal growth. Folate is one-carbon unit donor for the re-methylation of homocysteine to methionine and then to S-adenosylmethionine. Folate along with vitamin B12 as cofactor is necessary to maintain normal homocysteine levels, as high homocysteine levels are known to cause various pregnancy complications due to its pro-inflammatory effect (Figure 1). As a result, both these nutrients (folate and vitamin B12) are closely intertwined in this

FIGURE 1 Interrelation between folate, vitamin B12 and homocysteine metabolism[3]



AdoHcy: Adenosylhomocysteine; AdoMet: Adenosylmethionine; DHF: Dihydrofolate; DMG: Dimethylglycine; MS: Methionine synthase; MTHFR: Methylenetetrahydrofolate reductase; THF: Tetrahydrofolate

important metabolic function and deficiency of either of them can potentially result in pregnancy-related complications.[1,3]

Folate and/or B12 deficiency cause macrocytic anemia, neurological manifestations like cognitive decline and psychological disorders, and severe developmental delay in infants. Folate deficiency has long been linked to the development of neural tube defects (NTD) and congenital heart defects in the fetus.[2]

Folate, Vitamin B12, and Gestational Diabetes Mellitus: A link

The relationship between folate and vitamin B12 status and GDM is gaining interest in obstetrics. In the last twelve years, several studies have linked high folate in combination with low vitamin B12 status in mothers to an increased risk of GDM, as well as insulin resistance (IR) in offspring. A study including pregnant women found that mothers with vitamin B12 deficiency and high folate concentrations have the highest risk of GDM, with an odds ratio (OR) of 3.08 compared to high folate alone (OR=1.98) mothers, and that high vitamin B12 concentrations reduce the risk of GDM (OR=0.30).[2]

When a high folate/low vitamin B12 status was combined with a higher maternal age and pre-pregnancy BMI, Li et al., showed an even greater increase in GDM risk, indicating that nutrient imbalances and maternal factors can act synergistically to increase GDM risk.[2] Lai JS et al., also assessed the cross-sectional associations of plasma folate, vitamins B6, B12, and homocysteine concentrations with GDM and glycemia at 26 weeks' gestation in 913 pregnant women. The study demonstrated that higher maternal folate with low vitamin B12 levels were associated with higher GDM risk.[4]

The methyl-trap resulting in elevated homocysteine levels and impaired methylation reactions, as well as alterations in mitochondrial metabolism may be the contributory factors.[2]

Methyl-trap and gestational diabetes mellitus

In the presence of normal/high folate, vitamin B12 deficiency inhibits the intracellular conversion of 5-methyltetrahydrofolate to tetrahydrofolate and homocysteine to methionine, resulting in a functional folate deficiency, and a reduction in de novo purine and thymidine generation. The resultant impaired DNA synthesis could play a role in the development of IR.[2]

High folate levels in low vitamin B12 conditions can also oxidize the cobalt of vitamin B12, resulting in the formation of cob(II)alamin from the active methylcobalamin and cob(I)alamin forms of the enzyme. This prevents vitamin B12 from accepting the methyl group from 5-methyltetrahydrofolate as this reaction requires a highly reduced enzymatic. This could enhance the methyl-trap mechanism and the development of a functional folate deficiency and the exacerbating IR.[2]

Excessive folic acid consumption and gestational diabetes mellitus

High dose of folic acid supplementation in pregnant women can result in the appearance of un-metabolized folic acid in plasma. The presence of un-metabolized folic acid is linked to altered natural killer (NK) cell cytoactivity and this immune dysregulation has been associated in GDM pathology, through altering cell infiltration and signaling pathways.[2]

Association of elevated homocysteine and low methionine with gestational diabetes mellitus

A vitamin B12 deficiency, in addition to a functional folate deficiency, reduces the conversion of homocysteine to methionine. This can lead to two issues:

1. **Low methionine levels:** Because methionine is an essential amino acid, its deficiency can

decrease protein synthesis and lean tissue deposition. As increased adipose tissue volume impairs insulin sensitivity, a decrease in lean tissue mass can promote IR.[2]

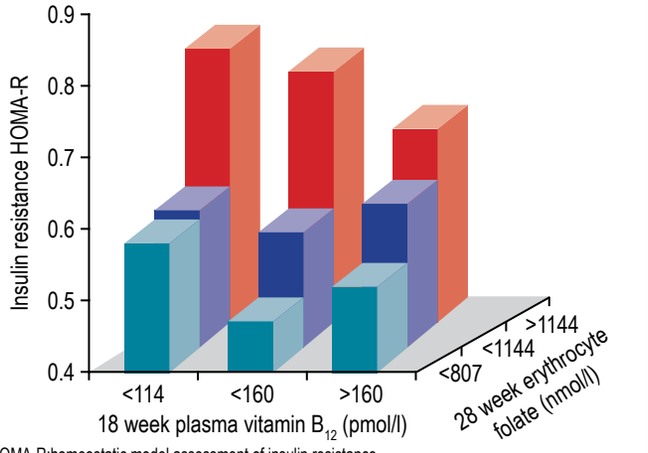
Methionine deficiency causes DNA hypomethylation and altered methylation has been linked to the pathogenesis of type 2 diabetes mellitus (T2DM). A similar mechanism may be involved in GDM.[2]

2. **High homocysteine levels:** Hyperhomocysteinemia (elevated homocysteine concentrations in plasma) have been associated with various diseases, including cardiovascular disease, dementia, osteoporosis, preeclampsia, and spontaneous pregnancy loss. Some of the pathogenetic consequences of high homocysteine include oxidative stress mediated apoptosis, endothelial and DNA damage. While several studies have also linked elevated homocysteine levels to the development of T2DM via IR and endothelial dysfunction, it is unclear whether this relationship is applicable to GDM risk. Some studies have demonstrated that women with GDM have significantly increased homocysteine concentrations as compared to non-GDM pregnant women.[2]

Maternal folate/vitamin B12 status and fetal implications

Yajnik et al., conducted a study to examine the association between maternal vitamin B12, folate, and total homocysteine (tHcy) status during pregnancy, children adiposity and insulin resistance at 6 years (n=674). The study showed that higher maternal folate concentrations at 28 weeks gestation, and lower maternal vitamin B12 concentrations at 18 weeks of gestation were associated with higher homeostatic model assessment of insulin resistance in children. The children of mothers with lowest vitamin B12 and highest folate concentrations were the most insulin resistant (Figure 2).[5]

FIGURE 2 Insulin resistance in children at 6 years in association with maternal vitamin B12 (18 weeks) and erythrocyte folate (28 weeks)



*HOMA-R:homeostatic model assessment of insulin resistance

Conclusion

Both folate and vitamin B12 are essential factors for nuclei acid synthesis, methyl group generation and conversion of homocysteine to methionine. Hence, balance of these factors needs to be looked into with further studies to understand the potential implications for maternal, fetal and neonatal health.

A systematic review and meta-analysis conducted also showed that no association was observed between serum folate and risk of GDM in majority of studies. Further, conflicting results were also observed between the risk of GDM with vitamin B12 deficiency.[1]

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Gynec-o-Pedia

1. Premenstrual syndrome (PMS) has a constellation of possible symptoms. Which of the following would NOT be expected?

A. Abdominal bloating ❑
B. Weight loss ❑
C. Constipation ❑
D. Anxiety ❑
E. Breast tenderness ❑

2. A 46-year-old, non-pregnant, morbidly obese woman presents with irregular periods over the past 6 months. Which of the following represents the most appropriate initial management in this setting?

A. Oral contraceptives ❑
B. Endometrial ablation ❑
C. Office hysteroscopy ❑
D. Dilation and curettage (D&C) ❑
E. Endometrial biopsy ❑

3. A 48-year-old woman presents to the office with a several year histories of low pelvic pain. Which of the following is the LEAST likely cause?

A. Interstitial cystitis ❑
B. Adenomyosis ❑
C. Ectopic pregnancy ❑
D. Herniated disc ❑
E. Inflammatory bowel disease ❑

4. A number of screening tests are performed in all pregnancies at designated gestational ages. Which of the following screening tests is correctly matched with the gestational age?

A. Glucose load test at the first prenatal visit ❑
B. Fetal anatomic survey at 34–36 weeks ❑
C. Chlamydia test at 22–24 weeks ❑
D. Group B β-hemolytic streptococcus (GBS) carrier status at 35–37 weeks ❑
E. Rubella serology at the 6-week postpartum visit ❑

5. A patient who is a chronic hepatitis B carrier delivers vaginally at 39 weeks' gestation. The baby should receive which of the following therapies on the first day of life?

A. Hepatitis B immune globulin (HBIG) ❑
B. Hepatitis B vaccination ❑
C. HBIG and hepatitis B vaccination ❑
D. None of the above ❑

Answers: 1. B; **2.** E; **3.** C; **4.** D; **5.** C

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*Invasive procedure was defined as arterial embolisation, arterial ligation, peripartum hysterectomy, B-lynch sutures, Bakri Balloon.

#In the RCT, there was a statistically significant difference of 44% relative risk reduction in the chances of invasive procedures with the NovoSeven® group compared to reference group (p<0.0001).

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5. NovoSeven® Prescribing Information India.

For the use only of a registered medical practitioner or a hospital or a laboratory.
Abbreviated prescribing information (and not full package insert)

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 i.v. administration. The product is freeze dried and dissolved in 10mM 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's 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: • Haemophilia A or B with inhibitors or expected to have a high anamnestic response** *Mild to moderate bleeding episodes (including home therapy):* Two dosing regimens: 1) Two to three injections of 90 µg per kg body weight administered at three-hour intervals. One additional dose of 90 µg per kg body weight can be administered if required. 2) One single injection of 270 µg per kg body weight. The duration of the home therapy should not exceed 24 hours. There is no clinical experience with administration of a single dose of 270 µg per kg body weight in elderly patients. Serious bleeding episodes: Initial dose - 90 µg per kg body weight. Dosing interval: every second hour until clinical improvement, increased if necessary, to 3 hours for 1 – 2 days and further increased successively to every 4, 6, 8 or 12 hours for as long as treatment is required. A major bleeding episode may be treated for 2 – 3 weeks but can be extended beyond this if clinically warranted. Invasive procedure/surgery: Initial dose - 90 µg per kg body weight given immediately before the intervention. **Dosing interval:** 2-3 hour intervals for the first 24 – 48 hours depending on the intervention performed and the clinical status of the patient. In major surgery, the dose should be continued at 2-4 hour intervals for 6-7 days and subsequently at 6 – 8 hours intervals for another 2 weeks of treatment. Patients undergoing major surgery may be treated for up to 2 – 3 weeks until healing has occurred. **• Acquired Haemophilia:** Initial dose - 90 µg per kg body weight. Dosing interval: The initial dose interval should be 2-3 hours, which subsequently can be increased successively to every 4, 6, 8 or 12 hours for as long as treatment is judged to be indicated. **• Congenital Factor VII deficiency:** The recommended dose range is 15 – 30 µg per kg body weight every 4 – 6 hours until haemostasis is achieved. Dose and frequency of injections should be adapted to each individual. **• Glanzmann's thrombasthenia:** The recommended dose is 90 µg (range 80 – 120 µg) per kg body weight at intervals of two hours (1.5 – 2.5 hours). At least three doses should be administered to secure effective haemostasis. The recommended route of administration is bolus injection as lack of efficacy may appear in connection with continuous infusion. For those patients who are not refractory, platelets are the first line treatment for Glanzmann's thrombasthenia. **• Severe postpartum haemorrhage:** 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. **Children:** Current clinical experience does not warrant a general differentiation in dosing between children and adults, although young children have faster clearance than adults. Therefore, higher doses of rFVIIa may be needed in paediatric patients to achieve similar plasma concentrations as in adult patients. **Pregnancy and lactation:** As a precautionary measure, it is preferable to avoid the use of NovoSeven® during pregnancy. Data on a limited number of exposed pregnancies within approved indications indicate no adverse effects of rFVIIa on pregnancy or on the health of the foetus/newborn child. A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with NovoSeven® should be made considering the benefit of breastfeeding to the child and the benefit of NovoSeven® therapy to the woman. **Elderly:** In patients with factor VII deficiency, where the recommended dose is 15-30 µg/kg rFVIIa, one episode of overdose has been associated with a thrombotic event (occipital stroke) in an elderly (> 80 years) male patient treated with 10-20 times the recommended dose. **Special populations and conditions:** It includes pregnant women and breastfeeding. Kindly refer the above specific sections for details. Data from non-clinical studies as well as post-marketing data show no indication that rFVIIa has a harmful effect on male or female fertility. **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 disseminated intravascular coagulation. In cases of hypersensitivity to residual culture proteins, treatment with antihistamines i.v. 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 but 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). 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* The full prescribing information can be obtained at no cost from Novo Nordisk.

For full prescribing information, please contact +91-080-40303200 or write to us at INAgree@novonordisk.com or reach us at **Novo Nordisk India Pvt. Ltd.,** Plot no 32, 47-50, EPIP area, Whitefield, Bangalore - 560066.

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