به نام خدا

چهاردهمین کنگره انجمن علمی پیوند سلولهای بنیادی خون ساز وبیست وسومین کنگره سراسری هماتولوژی ایران(اولین کنگره مشترک)

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How to treat patients with bleeding disorder of unknown cause (BDUC)?

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Introduction

- Studies of patients referred with mild bleeding disorder (MBDs) because of a personal or family history of bleeding have demonstrated that only 30% will ultimately be diagnosed such as von Willebrand disease (VWD) or a platelet function defect (PFD).
- Importantly, the most common final diagnosis in this group is the entity broadly called bleeding disorder of unknown cause (BDUC).
- Patients with BDUC already account for more than 10% of registered patients in some hemophilia centers.

Bleeding disorder (Abnormal Bleeding)

Unknown cause?

Management of pregnancy in BDUC

- A 28-year-old woman referred at 24 weeks of gestation in her second pregnancy. She has a significant personal bleeding history (including easy bruising and HMB since menarche). At diagnosis, her ISTH BAT score was calculated at 7.

- Her first pregnancy led to a spontaneous vaginal delivery at 40 weeks of gestation. No hemostatic treatment was given before delivery.

- Unfortunately, the patient experienced a PPH occurring 12 hours after delivery. The PPH was associated with an estimated blood loss of 1000 mL and required treatment with TA, DDAVP, and packed cell transfusion.

Common causes of Post Partum Hemorrhage (PPH)

- Uterine atony
- Lacerations
- Retained placenta or clots
- Systemic bleeding disorders

How to Manage

- Peripartum considerations
- Postpartum preventive measures
- Venous thromboembolism considerations

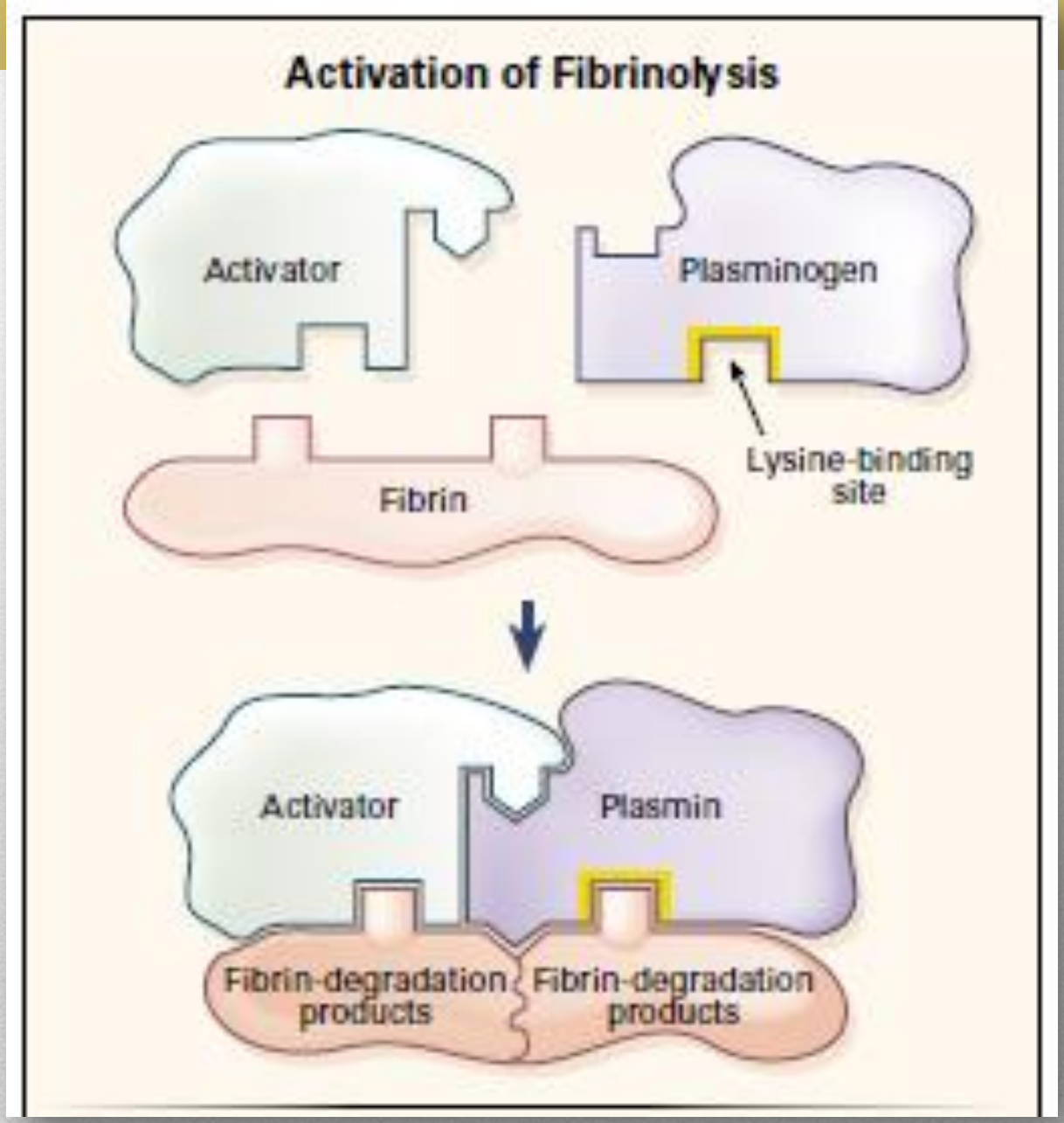
HEMOSTATIC DRUGS

- When bleeding is the consequence of a specific defect of hemostasis, the goal of treatment is to correct the defect. A typical example is the replacement of factor VIII by transfusion in patients with hemophilia.

- Specific treatment may be impossible, however, because bleeding may result from multiple defects or because no cause can be identified or specific treatment is not available .

- In such situations, non-transfusional drugs that help to stop bleeding are indicated.

	Pros	Cons
rFVIIa	Laboratory monitoring not required	Nonspecific and potentially ineffective in some patients. Very frequent dosing (daily, every 2-3 hours) required No laboratory measure of efficacy
Tranexamic acid	Has some efficacy, especially for mucosal bleeding Oral and IV routes.	Likely to be inadequate as a single-agent therapy Should not be administered with aPCC because of DIC risk
Desmopressin	desmopressin should be given when an immediate effect on hemostasis is required at the time of emergency	Duration effect is 6-8 hours Plasma sodium and body weight should be measured daily and excessive administration of fluids avoided.
Aprotinin	Inhhibits trypsin and related proteolytic enzymes	Might transmit the agent responsible for bovine spongiform encephalopathy and new-variant Creutzfeldt–Jakob disease has led to the withdrawal of the drug in Europe and elsewhere.
Platelet	Platelets, via their contributions to the "protein wave" and to the classical first and second waves of hemostasis, play key roles in the arrest of bleeding.	Platelet transfusion carries risks of transfusion reactions



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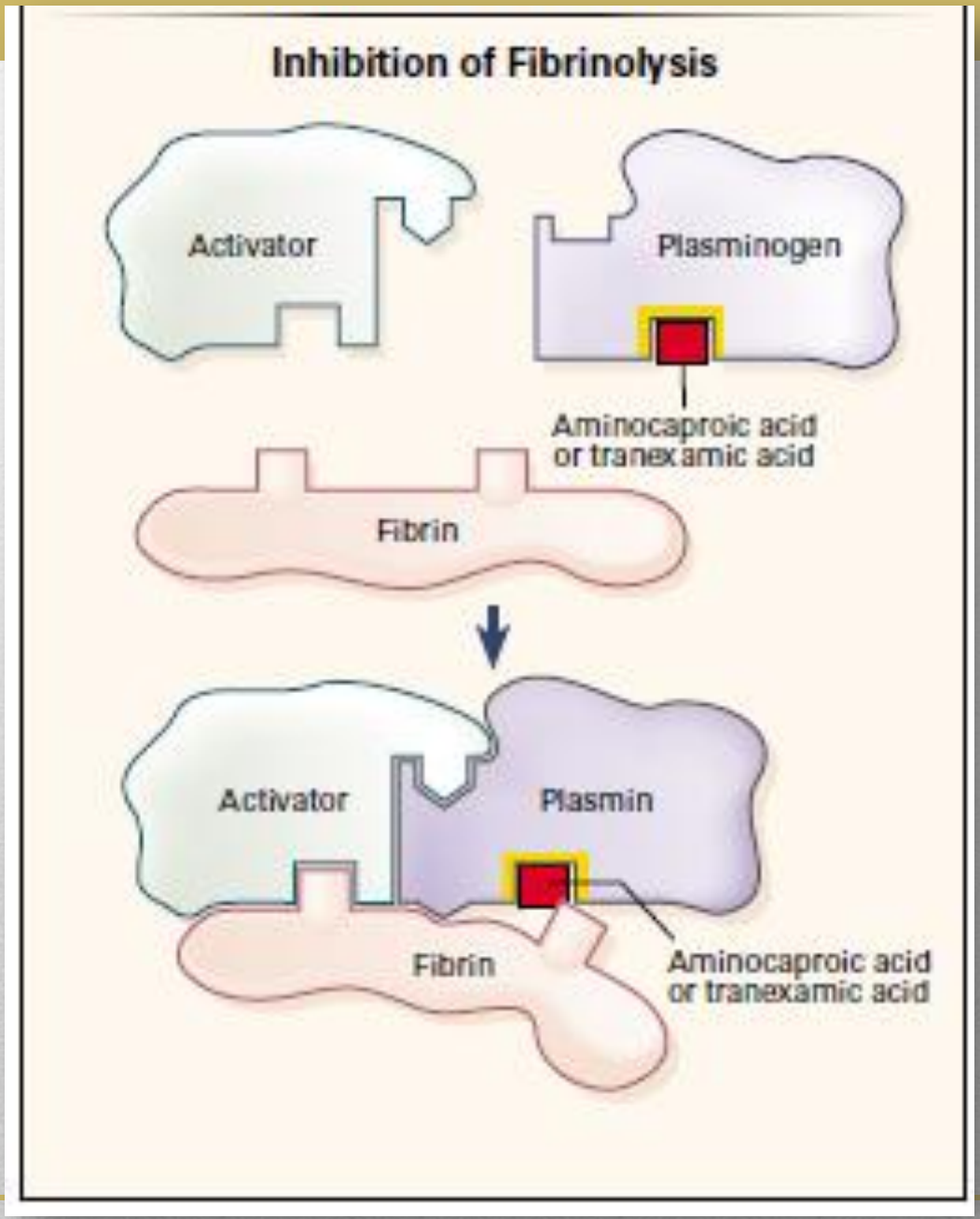

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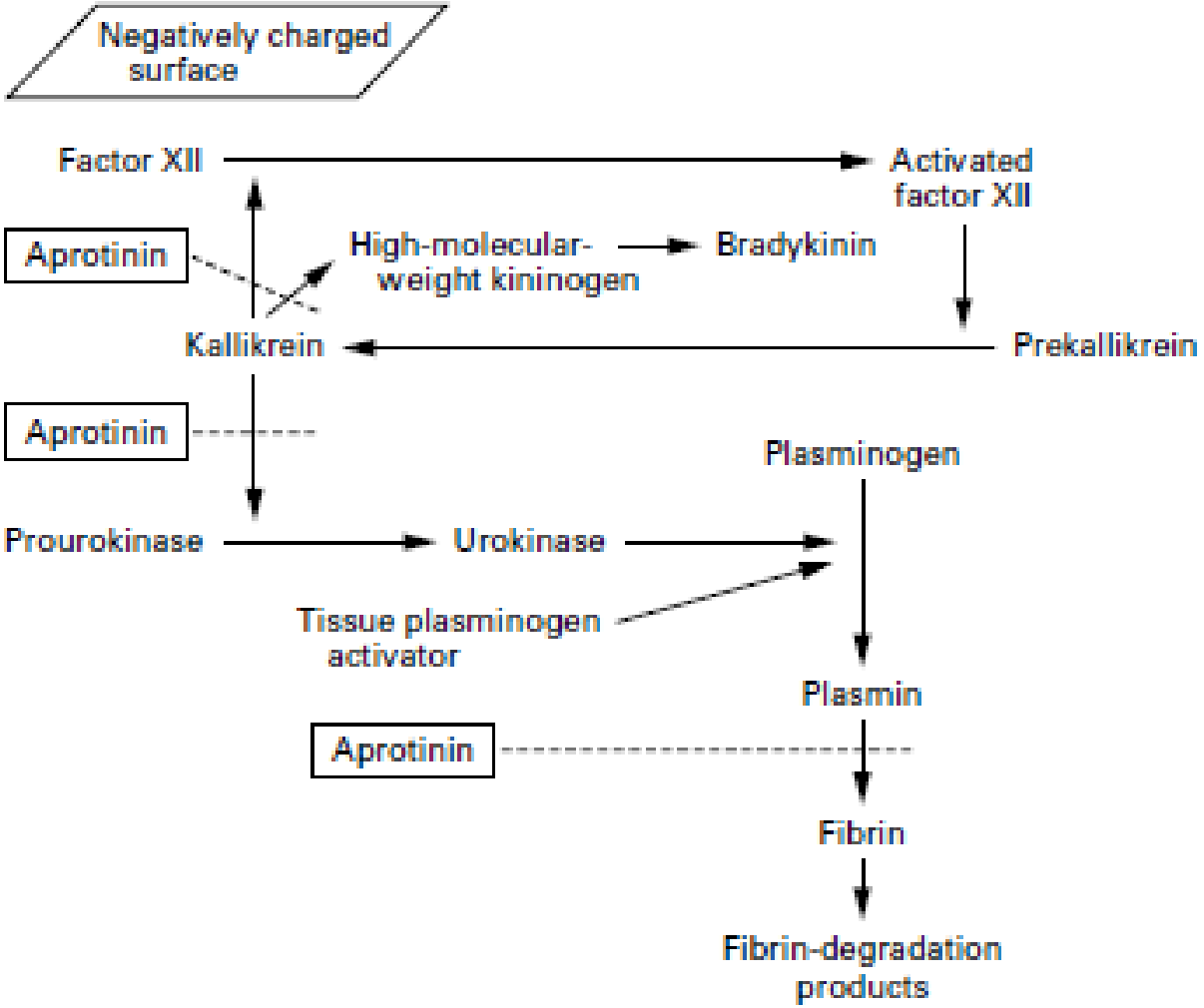
TABLE 1. INDICATIONS FOR THE USE OF THE ANTIFIBRINOLYTIC DRUGS TRANEXAMIC ACID AND AMINOCAPROIC ACID IN THE TREATMENT OF EXCESSIVE BLEEDING.

CLINICAL SITUATION	STUDY	GRADE OF EVIDENCE*
Primary menorrhagia	Bonnar and Sheppard[8]	A
Upper gastrointestinal bleeding	Henry and O'Connell[10]	A
Dental extraction in patients with coagulation disorders	Walsh et al.[15] Forbes et al.[16] Sindet-Pedersen et al.[18]	A
Bleeding associated with thrombocytopenia	Gardner and Helmer[19] Bartholomew et al.[20]	B


Negatively charged surface
Factor XII
Activated factor XII
Aprotinin
High-molecular-weight kininogen
Bradykinin
Kallikrein
Prekallikrein
Aprotinin
Plasminogen
Prourokinase
Urokinase
Tissue plasminogen activator
Plasmin
Aprotinin
Fibrin
Fibrin-degradation products

Desmopressin is **used to treat central cranial diabetes insipidus**.

This is a condition that causes the body to lose too much fluid and become dehydrated. It is also used to control bedwetting (nocturnal enuresis), and the frequent urination and increased thirst caused by certain types of brain injury or brain surgery.

Plasma concentrations of factor VIII, and von Willebrand factor can be increased for a short time by the administration of 1-deamino-8-D-arginine vasopressin (desmopressin), an analogue of arginine vasopressin.

In such patients, the effect of desmopressin may be mediated by the attainment of supranormal plasma concentrations of von Willebrand factor and the appearance of ultralarge multimers of this factor, which support platelet adhesion to the vascular subendothelium more actively than multimers of normal size.

Increased hemostasis may also be mediated by high plasma concentrations of factor VIII, a rate-accelerating factor in the process of fibrin formation.

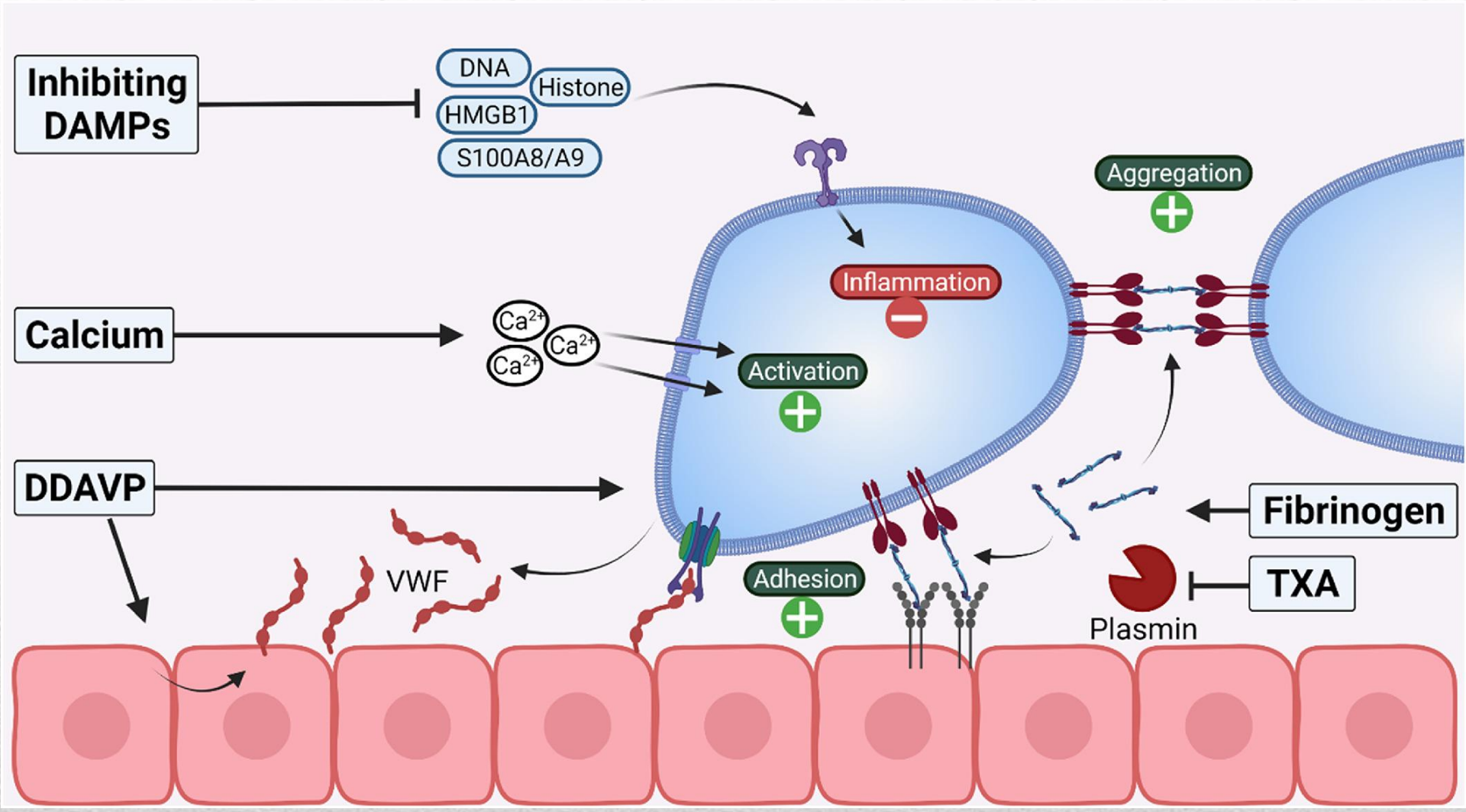

Inhibiting DAMPs
DNA
Histone
HMGB1
S100A8/A9
Calcium
Ca2+
Ca2+
Ca2+
DDAVP
VWF
Inflammation
Activation
Aggregation
Adhesion
Fibrinogen
TXA
Plasmin

TABLE 2. INDICATIONS FOR THE USE OF DESMOPRESSIN IN THE TREATMENT OF EXCESSIVE BLEEDING.

CLINICAL SITUATION	STUDY	GRADE OF EVIDENCE*
Mild hemophilia A or type I von Willebrand's disease	Mannucci et al.[65] Kobrinsky et al.[66] de la Fuente et al.[67]	B
Congenital defects of platelet function	Rao et al.[77] DiMichele and Hathaway[78]	C
Uremia	Mannucci et al.[68]	C
Cirrhosis	Mannucci et al.[69] Burroughs et al.[80]	C
Drug-induced bleeding (aspirin, ticlopidine)	Kobrinsky et al.[66] Mannucci et al.[69]	C

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Management

- We would start on TA 1 g 3 times per day at time of delivery and continue for a further 7 to 10 days postpartum.
- If the patient develops bleeding complications while on antifibrinolytic therapy, we would treat with DDAVP (0.3 mg/kg in 100 mL normal saline).
- Platelet transfusion would be considered third-line treatment or if there is a contraindication to DDAVP.
- For women with BDUC who have previously developed bleeding complications (including PPH) despite being on TA treatment, we would use a combination of TA and DDAVP at time of delivery.
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- Finally, we would discuss the risk of secondary PPH and advise the patient to go to the emergency room if she develops significant bleeding despite TA after her discharge from hospital.

Thanks for attention