46° Convegno Nazionale
di Studi di Medicina Trasfusionale
Rimini, 13-15 maggio 2026

La gestione della gravidanza nelle MEC

Elvira Grandone

I.R.C.C.S. Casa Sollievo della Sofferenza

&

Università di Foggia

La sottoscritta, in qualità di Relatrice
dichiara che

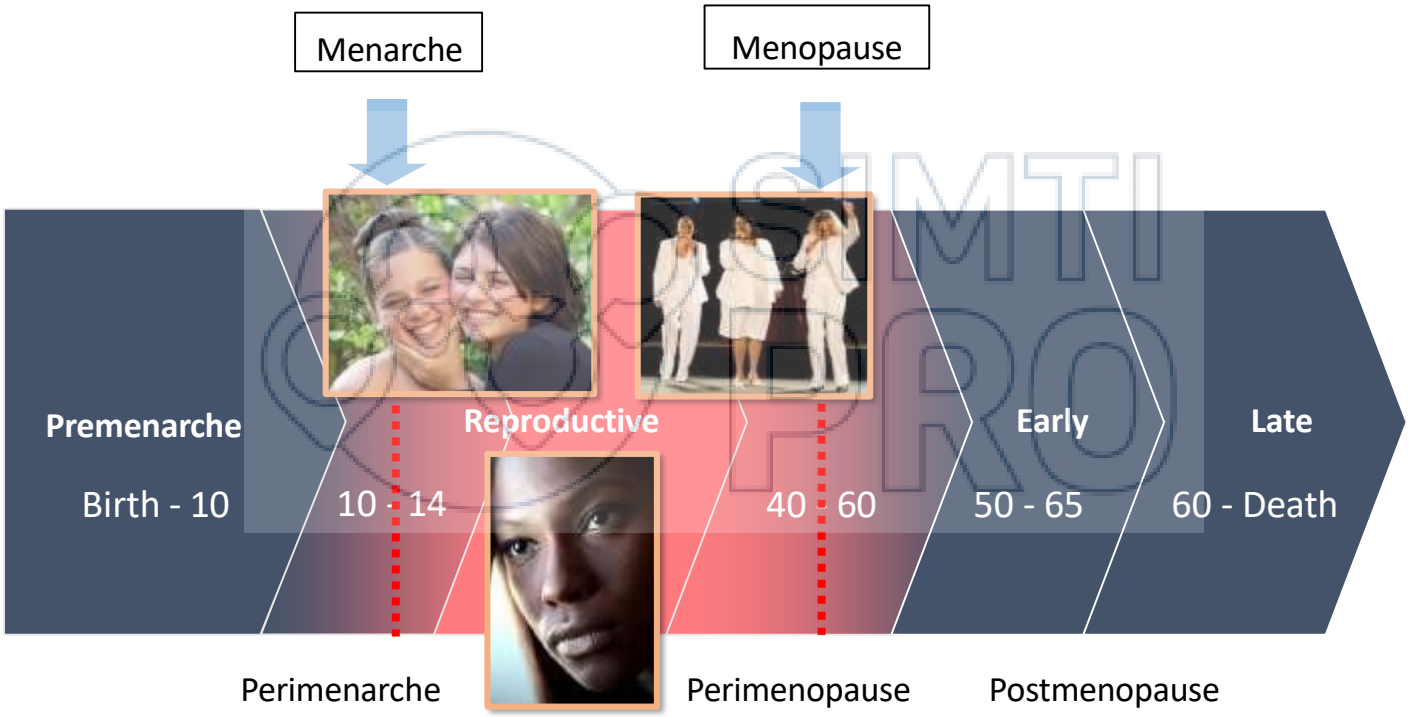
negli ultimi due anni ha avuto i seguenti rapporti anche di finanziamento con i soggetti portatori di interessi commerciali in campo sanitario:

-Roche, Viatris, Novo-Nordisk, Techdow, LEO-Pharma, Werfen, STAGO

AUB in the Reproductive Years – Clinical Impact

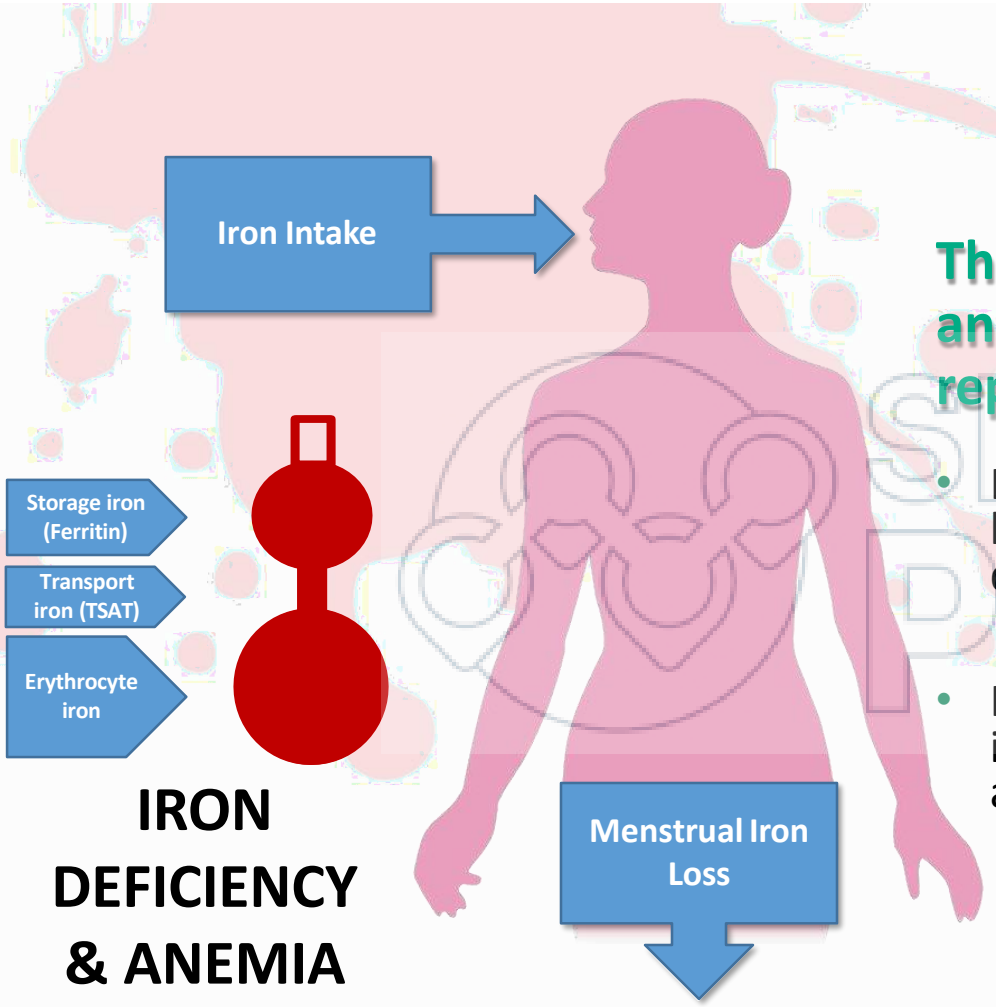
The Affected Populations

FIGO International Federation of Gynecology and Obstetrics
Menstrual Disorders Committee



Malcolm G. Munro M D

FIGO
International Federation of Gynecology and Obstetrics
Menstrual Disorders Committee



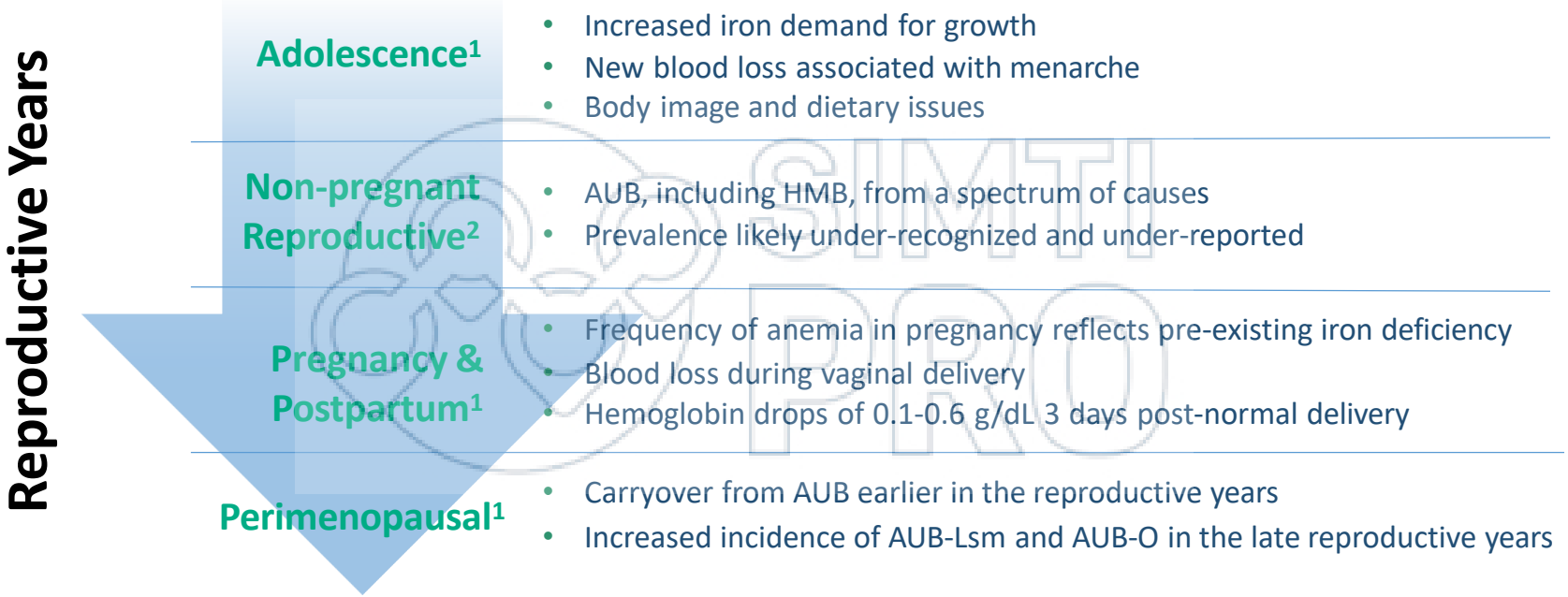
The genesis of iron deficiency (ID) and iron deficiency anemia (IDA) in reproductive aged women

- If nutritional iron intake equals iron loss, then ID and IDA generally don't develop
- If menstrual blood loss exceeds iron intake iron deficiency and then anemia occur:
  - Increased menstrual blood loss (HMB)
  - Decreased nutritional intake

Iron Deficiency (ID) and Iron Deficiency Anemia (IDA) Clinical Burden

AUB & Anemia may affect girls & women throughout the reproductive years

FIGO International Federation of Gynecology and Obstetrics
Menstrual Disorders Committee



AUB=abnormal uterine bleeding. HMB = heavy menstrual bleeding

1. Friedman AJ, et al. Iron deficient anemia in women across the lifespan *J Womens Health.* 2012;21(12):1282-1289.
2. Percy et al, Iron deficiency and iron deficiency anaemia in women. Best Pract Res Clin Obstet Gynaecol 2017;40:55-67

SOCIAL DETERMINANTS OF HEALTH

Being a carrier of hemophilia can result in feelings of **guilt and self-blame** (especially for those with male offspring as males express more severe disease) and **difficulty in discussing carrier status** with a partner

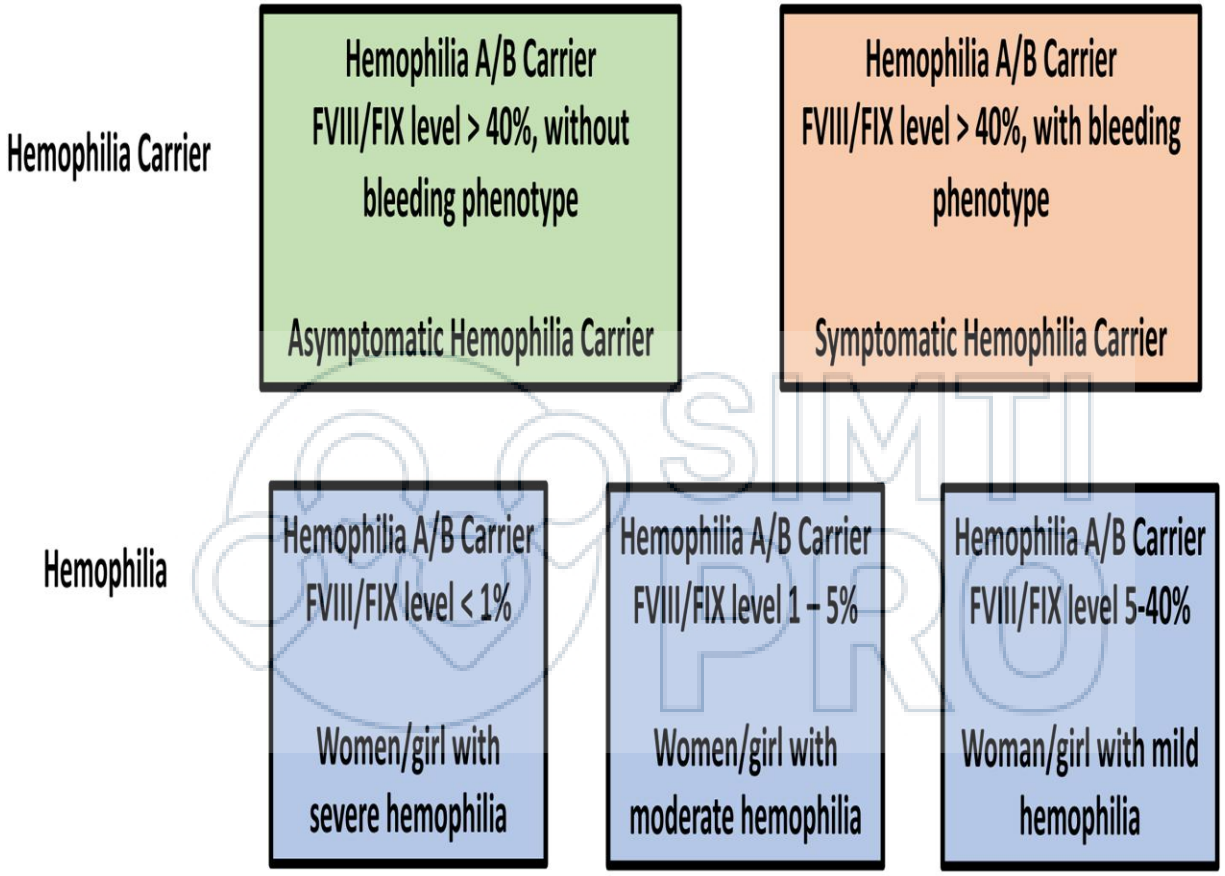
Impact of a genetic bleeding disorder on **psychological wellbeing** and **reproductive choices**

- 1 in 4 women with IBDs reported that their condition either severely **impacted their decision** to have children or **prevented them from having children** due to reasons such as social stigma, barrier to changing IBD treatment, early hysterectomy to control IBD symptoms, and cost of genetic testing/preimplantation diagnosis

Greater impact to reproductive choices seen in those who experienced a delay to diagnosis, often women without a family history, highlighting the **need for clinical awareness**

Proactive engagement from healthcare, including education and counselling by experienced health care workers, support networks for women with bleeding disorders, and improved prenatal support is needed to improve the experience of women with IBDs

Women and bleeding disorders: diagnostic challenges



Paula D. James, Women and bleeding disorders: diagnostic challenges, Hematology Am Soc Hematol Educ Program, 2020, Figure 3.

Women and Girls with Hemophilia

Treatment of Bleeding

Women with hemophilia and symptomatic carriers usually don't experience symptoms daily. They may, however, experience prolonged bleeding after an accident or medical intervention. When this happens, they must be treated in the same way as men with hemophilia.

Desmopressin (DDAVP)

Desmopressin is a synthetic hormone that may help control bleeding in an emergency or during surgery. It can be injected intravenously, administered under the skin (subcutaneously), or given as a nasal spray.

Desmopressin does not work for every woman. All women with hemophilia A with clotting factor levels of less than 50% should have their response to the medication tested before they need to use it. Desmopressin is not effective for hemophilia B, as it does not raise levels of factor IX.

Desmopressin should not be used in some instances, for example, in cases of head trauma and in women who are at risk of heart problems. Doctors should be familiar with the medication and how it should be used before prescribing it.

Clotting factor concentrates

In women for whom desmopressin doesn't work or is not recommended, infusions of clotting factor concentrates may be necessary when the risk of severe bleeding is high, such as before or during surgery.

Antifibrinolytic agents

The antifibrinolytic drugs tranexamic acid and aminocaproic acid, given orally or intravenously, are used to prevent the breakdown of blood clots in certain parts of the body such as the mouth and uterus. They can be used to control heavy menstrual bleeding and during minor surgeries and dental procedures.

Hormone therapy

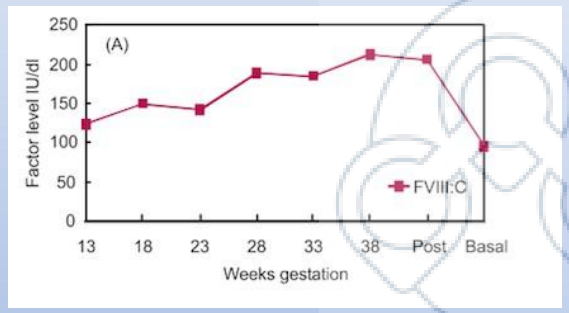
Hormone therapy can be used to help control excessive menstrual bleeding. This includes combined hormonal contraceptives (which can be given orally, as skin patches, or vaginally) and the levonorgestrel releasing intrauterine device/system (IUD or IUS).

COAGULATION FACTORS IN PREGNANCY

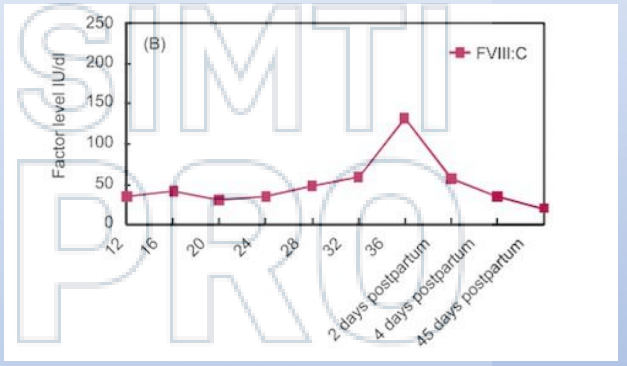
Coagulation factor	Change from non-pregnant state
Antithrombin III	No change
Plasma fibrinogen (factor I)	↑
Factor II	No change
Factor V	No change
Factor VII	↑
Factor VIII	↑
Factor IX	No change
Factor X	↑
Free protein S	↓
Plasminogen activator inhibitor 1	↑
Plasminogen activator inhibitor 2	↑
Protein C	No change
von Willebrand factor	↑

https://www.cambridge.org/core/books/maternal-critical-care/physiological-changes-of-pregnancy/06AAE1CF94F4A096194A0C60495AD81D.

Clotting factor rise in pregnancy



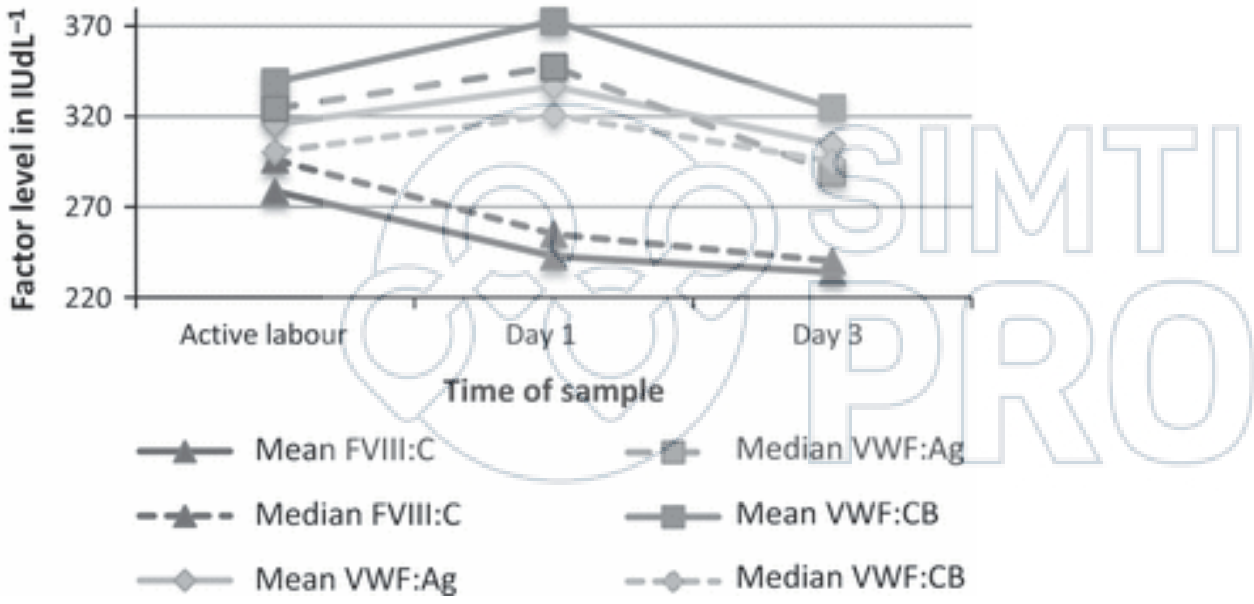
General population



Women with von Willebrand disease

Kouides, P. A. (2001). *Obstetric and gynaecological aspects of von Willebrand disease. Best Practice & Research Clinical Haematology, 14(2), 381–399*

Significant decrease of VWF/FVIII on day 3



Huq et al. Haemopilia 2012

Preconceptual care

Assessment of VWD type/severity/ phenotype/ bleeding risk

- Coagulation factor levels
- Bleeding risk (BAT) - response to treatment
- Response to treatment – DDAVP test
- Genetics – when appropriate

Genetic counselling - VWD transmission

- PND options

Optimise maternal health

- Mx of HMB + anaemia
- Identification/Mx of obstetric risk
- Where to have antenatal care, what surveillance and where to deliver

von Willebrand Disease (vWD)

- **Most common** hereditary coagulation disorder
- Caused by missing or defective von Willebrand factor (vWF), a plasma protein that binds to factor VIII to help stabilize platelets during clotting process

- **3 types:**
  - **Type 1:** AD. 60-80% of patients. Reduced levels of vWF (quantitative defect)
    - Mostly normal lives, with some bleeding following surgery (dental extractions), noticeable heavy bruising, or HMB
  - **Type 2:** AD. 20-30%. Dysfunctional vWF (qualitative defect)
    - Tendency to bleed varies between individuals
  - **Type 3:** AR. Very rare, most severe. Absent or undetectable levels of vWF
    - Severe mucosal bleeding, no detectable vWF antigen, low factor VIII, + family history

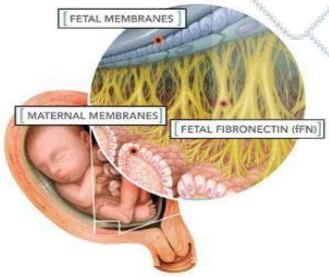
- **Pregnancy implications:**
  - Antepartum hemorrhage is uncommon
  - **PPH risk of 20-40%**

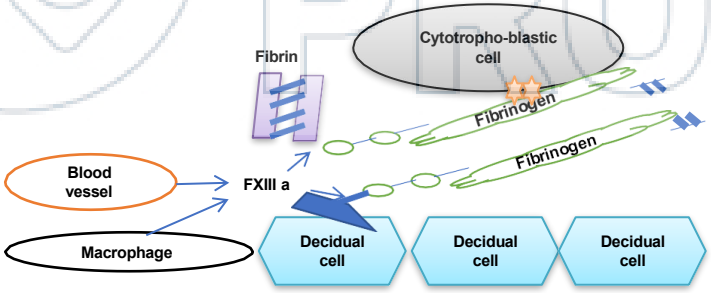
VWD - Fertility and early pregnancy implantation

No evidence for VWD - effect on fertility

Indirect effect ?

- Prolonged and heavy periods - impact on endometrium
- Impact on QoL and sexual relationship



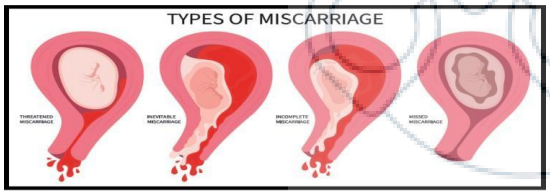


VWD – Miscarriage

Miscarriage - spontaneous loss of pregnancy before the fetus reaches viability (24 weeks of gestation)

Miscarriage rate in the general population

- First trimester (before 13 weeks)= 15% of pregnancies
- Second trimester (13-24 weeks) – 1-2% of pregnancies



Threatened miscarriage – vaginal bleeding in pregnancy till 24 weeks - majority do not actually miscarry - >80% when FH +ve

Causes of miscarriage

- Chromosomal abnormalities ≅ 60% of miscarriages
- Other reported causes immunological, endocrine, haemostatic, uterine/cervical abnormalities, etc

VWD - Is risk of miscarriage increased?

- Data from retrospective studies - no difference in pregnancy loss compared to general population including women with type 3 severe VWD
- A higher incidence of threatened miscarriage in the first trimester in one study but no increase in the miscarriage rate
- There is an increased risk of bleeding complications – following miscarriage, termination of pregnancy, invasive procedures (PND, obstetric interventions)
  - 10% - haemorrhage requiring blood transfusion after a miscarriage or termination of pregnancy
  - 10% - readmitted to hospital with a secondary bleeding after miscarriage

Kadir 1998, Lak M 2000, James 2007, Skeith 2017

VWD - Antenatal bleeding and antenatal complications

- Antenatal bleeding – vaginal bleeding after 24 weeks – conflicting data in VWD
- No increased risk of antenatal complications

Table 4 The odds of obstetric complications among women with (VWD) compared with women without VWD

Pregnancy or delivery complication	ICD-9 codes	Number of cases	Odds ratios with 95% CI	*P*-value
Pre-eclampsia and gestational hypertension	642.0, 642.1, .642.2, 642.3, 642.4, 642.5, 642.7, 642.9	327	0.9 (0.7, 1.20)	0.51
Eclampsia	642.6	13	2.7 (0.7, 10.9)	0.16
Placental abruption	641.2	53	1.0 (0.5, 1.8)	0.80
Antepartum bleeding	640.0, 640.8, 640.9, 641.10, 641.3, 641.8, 641.9,	280	10.2 (7.1, 14.6)	< 0.01
Gestational diabetes	648.8	112	0.6 (0.4, 0.9)	0.02
Fetal growth restriction	656.5	49	0.7 (0.3, 1.5)	0.34
Preterm labor	644	417	0.6 (0.3, 1.2)	0.13
Intrauterine fetal death	656.4	24	1.6 (0.7, 3.9)	0.20

A. H. JAMES and M. G. JAMISON
Journal of Thrombosis and Haemostasis, 5: 1165–1169

VWD – Risk of PPH

Post-partum bleeding (PPH) – Increased risk of primary (first 24 hours after birth) and secondary (after 24 hour – 6-12 weeks postnatal) PPH

Maternal and neonatal bleeding complications in relation to peripartum management in women with Von Willebrand disease: A systematic review

- 5561 articles → 16 cohorts + 71 cases (total 811 deliveries)
- 619 deliveries in cohort studies: Primary PPH 32%
- 365 cases: Primary PPH 34%
- Secondary PPH 13%

Punt M *et al. Blood Rev* 2020;10.1016/j.blre.2019.100633.

Postnatal care
VWD – Increased risk for Secondary PPH

Plasma VWF FVIII levels fall progressively post partum

Study	Number of women	Type 1	Type 2	Type 3	Rate of secondary PPH
Xu *et al*	n=55	29	25	1	2.3%
Lavin *et al*	n=32	32			8%
Sood *et al*	n=11	11			9%
Govorov *et al*	n=34	21	9	3	12%
Castaman *et al*	n=23	12	11		13%
Kadir *et al*	n=31	27	4	2	20%
Greer *et al*	n=8	3	5		25%
Ramsahoye *et al*	n=13	7	6		38.4%
Makhamreh *et al*	n=17			17	56%

Secondary PPH rates in general population = 2%

Adapted from Lavin et al, *STH* 2021

LG AICE 2024

- Poiché i livelli di FVIII/VWF tendono a normalizzarsi al termine della gravidanza nella maggior parte dei casi di tipo 1 e 2 N, raramente si osservano emorragie dopo il parto.

- Al contrario, le altre pazienti di tipo 2 e 3 necessitano solitamente di una terapia sostitutiva dopo il parto per prevenire emorragie immediate o tardive. L' incidenza dell'emorragia post-operatoria e' variabile in assenza di profilassi nei pazienti di tipo 1 con fenotipo emorragico piu' severo, mentre nei tipi 2 e 3 il trattamento profilattico è sempre necessario.

LG AICE 2024

Postnatal care

- Improved education for our patients and healthcare colleagues of the risk of secondary PPH in VWD is essential
- Women should understand the signs of secondary PPH and how to access care
  - Explain lochia; Know red flags for bleeding & when to return
  - Telephone/virtual consultation follow up
  - Pathway (joint Obstetreic/haem) for management if occurs
- 2021 VWD Guidelines suggest postpartum use of Tranexamic acid
  - TXA reduced the risk of Secondary PPH (RR, 0.42; 95% CI, 0.20-0.91)
  - Tranexamic acid 25mg/kg (typically 1000-1300 mg) PO tds
  - For 10 to 14 days or longer if blood loss remains heavy
  - Safe to use while breast-feeding - Concentration in breastmilk of 1% of peak serum concentration
  - No increased risk of VTE

Connell et al. *Blood Adv* 2021

Hemophilia A (Factor VIII deficiency)

- Caused by mutation of VIII gene leading to Factor
- X-linked recessive males are affected, females are carriers or rarely display mild phenotype

Hemophilia B (Factor IX deficiency)

- Caused by mutation of IX gene leading to Factor IX deficiency
- Rare
- X-linked recessive

Pregnancy implication:

Besides risk of genetic inheritance of fetus, carriers of hemophilia are at risk of PPH if they have reduced coagulation factor levels at term.

Hemophilia C (Factor XI deficiency)

- Extremely rare (<1/100,000) but more common in Ashkenazi Jews (8% incidence)
- Can be AR or AD inheritance
- Extremely variable bleeding patterns **20% risk of PPH**

- Risk stratified in obstetrics by %XI level
  - **>40% XI level**
    - manage as routine, generally fine for neuraxial anesthesia
  - **<40% XI level**
    - consider prophylactic administration of antifibrinolytic agents to decrease PPH
    - Administration of factor XI prior to neuraxial anesthesia
  - **<20% with prior bleeding history**
    - consider factor XI replacement in labor continued for 24-48 hrs PP

INTRAPARTUM MANAGEMENT

- **vWF:**
  - Desmopressin acetate (DDAVP) for mild forms
  - vWF and VIII factor replacement for severe forms
  - TXA for prevention of PPH at delivery
- **Hemophilia A/B:**
  - Concentrates of factor VIII (for Hemophilia A) or clotting factor XI (for B)
  - Consider DDAVP adjunctive therapy
- **Hemophilia C:**
  - FPP
  - TXA post-partum
- **Hemophilia carrier status is NOT a contraindication to vaginal delivery**
  - Elective section may be considered to reduce risk of ICH on individual basis
  - FSE, vacuum and forceps deliveries are contraindicated

Desmopressin in pregnancy

Essentials

- Desmopressin (DDAVP) use in pregnancy is still debated due to safety concerns.
- This systematic review assessed maternal and neonatal outcomes after DDAVP use in pregnancy.
- DDAVP use seems effective and safe in pregnant women, with attention to hyponatremia occurrence.
- DDAVP exposure during pregnancy seems safe for the child, especially during delivery.

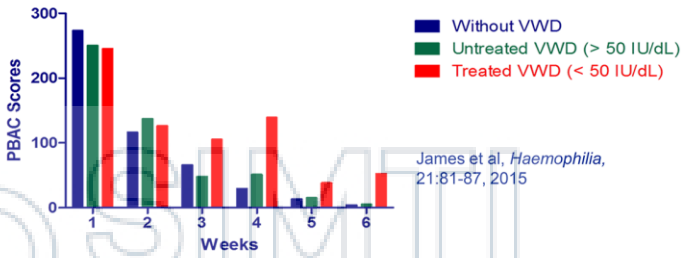
Arashi et al. JTH 2024 (22) 126-39

Management of Pregnant Women Who Have Bleeding Disorders

Hemostatic Changes in Pregnancy

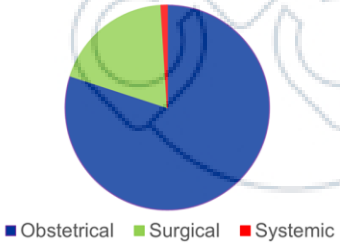
↑ fibrinogen	↔ factor II
↑ factor VII	↔ factor V
↑ factor VIII	↔ factor IX
↑ factor X	↓ free protein S
↑ VWF	↔ protein C
↑ PAI-1	↔ antithrombin (III)
+ PAI-2	

Postpartum Bleeding in Women +/- VWD

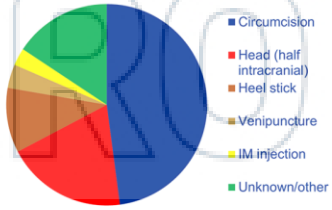


James et al, *Haemophilia*, 21:81-87, 2015

Causes of Postpartum Hemorrhage



Sites of Bleeding in Newborns with Hemophilia



Kulkarni et al, *Haemophilia*, 13:1291-1290, 2009

Andra H. James,Luis D. Pacheco,Barbara A. Konkle, Management of pregnant women who have bleeding disorders, Hematology Am Soc Hematol Educ Program, 2023,

Table 2. Specific therapy at the time of delivery for VWD subtypes

Subtype	Specific therapy for VWD
1	• Most will not require treatment. • If VWF levels <50% or 0.5 IU/mL at 36 weeks' gestation, treatment is required at the time of delivery. A higher threshold for treatment such as 0.8 IU/dL or 1.0 IU/mL has been adopted by some experts and may be considered. • VWF and FVIII levels should be followed to guide dosing. • Consider cautious use of desmopressin if a desmopressin trial was performed outside of pregnancy and efficacy was documented.
2	Expect that treatment will be required with VWF concentrates.
2A	• Most will require VWF concentrates. • Some may respond to desmopressin (requires previous desmopressin trial with documented efficacy).
2B	• Treat with VWF concentrates. • Desmopressin is contraindicated as it may worsen thrombocytopenia.
2M	• Most will require VWF concentrates. • Some may respond to desmopressin (requires previous desmopressin trial with documented efficacy).
2N	• Most will require VWF concentrates. • Some may respond to desmopressin (requires previous desmopressin trial with documented efficacy).
3	• Requires VWF concentrates.

James AH. et al., Am Soc Hematol Educ Program, 2023

Table 3. Treatment of other coagulation factor deficiencies

Deficiency	Treatment*
Factor VII deficiency	
20%-50%—mild	
10%-20%—moderate; at risk for mild or provoked bleeding	
<10%—severe	Low-dose rFVIIa or plasma
Factor XI deficiency	
20%-60%—variable risk for bleeding	
<20%—still variable risk for bleeding	Plasma or FXI concentrate where available
Fibrinogen deficiency	
<60mg/dL—at risk for miscarriage	Fibrinogen concentrates where available are the treatment of choice for patients with quantitative or qualitative deficiencies; otherwise, cryoprecipitate for antepartum as well as peripartum prophylaxis.
<100mg/dL—at risk for placental abruption	
<150mg/dL—at risk for placental abruption in labor and PPH	
Factor XIII deficiency	
<10%—severe; high risk for miscarriage and PPH	FXIII concentrate where available for antepartum as well as peripartum prophylaxis

*Includes the general guidance described under "Management of pregnant women with any bleeding disorder."

James AH. et al., Am Soc Hematol Educ Program, 2023

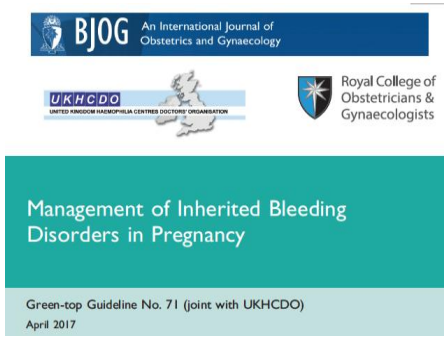
What is the prepregnancy and antenatal management?
vWD

What is the prepregnancy and antenatal management? Prior to conception, the bleeding phenotype should be assessed, historical diagnosis reviewed and response to DDAVP established.

Safe management requires a multidisciplinary approach.

All women with VWD should have VWF antigen levels and activity, and factor VIII levels checked at booking, in the third trimester and prior to any invasive procedures. Target peak VWF activity levels should be 1.0 iu/ml and levels maintained above 0.5 iu/ml until haemostasis is secured.

For most antenatal procedures, a single preoperative treatment is sufficient, but in some cases, a second dose may be required at 12–24 hours, depending on the nature of the procedure and the measured levels.



What is the antepartum management?

Antenatal care should be delivered in the context of a multidisciplinary team setting with haematologists and obstetricians with expertise in this field.

Maternal factor VIII/IX should be checked at booking, before any antenatal procedure and in the third trimester; factor VIII levels rise in pregnancy, but factor IX tends to remain stable.

Aim for factor VIII/IX levels of at least 0.5 iu/ml to cover surgical or invasive procedures, or spontaneous miscarriage. If treatment is required, factor levels of 1.0 iu/ml should be aimed for and not allowed to fall below 0.5 iu/ml until haemostasis is secure.

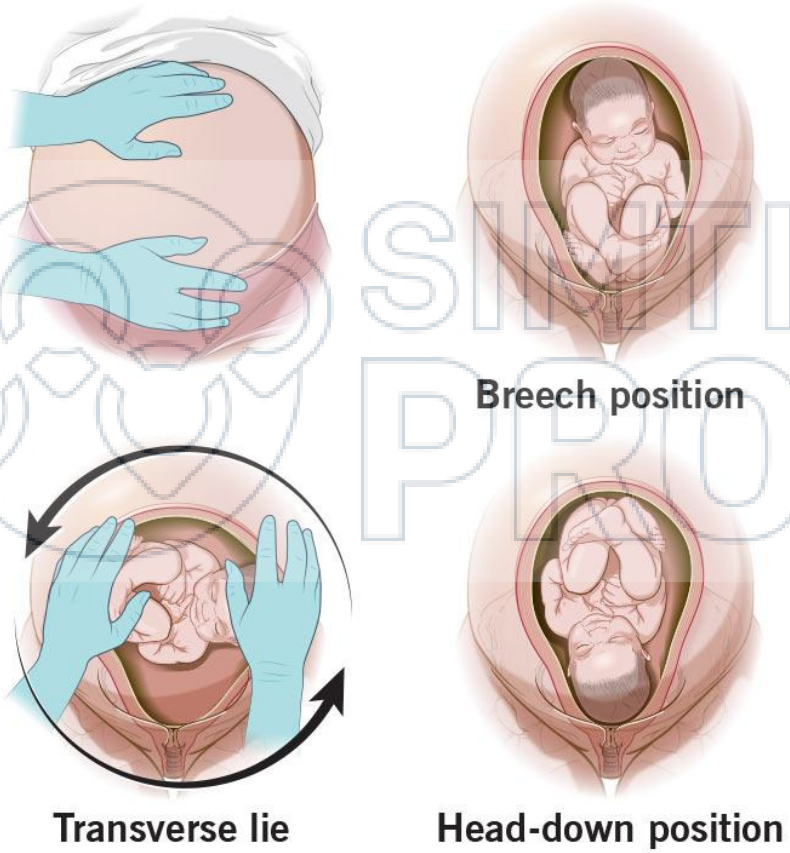
Tranexamic acid should be considered in combination with treatment for all those with levels of less than 0.5 iu/ml or as sole therapy for those with levels above 0.5 iu/ml if clinically indicated. Following miscarriage, it should be continued until the bleeding settles.

Desmopressin (DDAVP) can be used antenatally to raise factor VIII levels. Due to the antidiuretic effect, fluids should be restricted to 1 litre for 24 hours after use or, if not possible, electrolytes should be monitored.

If antenatal diagnosis has not been performed in a male fetus, then he should be managed as if he is affected.

External cephalic version should be avoided in affected or potentially affected male fetuses and female fetuses who are obligate or possible carriers of severe haemophilia B.

External Cephalic Version (ECV)



What is the antepartum management?
HA and HB

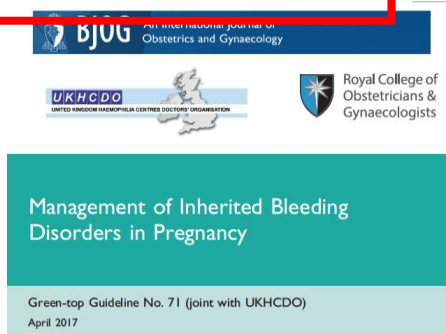
Recombinant factor VIII should be used if levels obtained with DDAVP are insufficient or in a known nonresponder.

Recombinant factor IX is required to cover invasive or surgical procedures in women with factor levels less than 0.5 iu/ml.

When giving treatment to raise clotting factor levels, it is important to monitor the response to treatment by measuring the plasma clotting factor concentration before and after infusion, and 4–6 hours following treatment to facilitate dosing.

Following any invasive or surgical procedure, a plan for ongoing treatment is required to maintain the coagulation factor in the normal range for a suitable duration, determined by the nature of the procedure.

A clear plan for the intrapartum care of a carrier and the baby should be available in advance of 37 weeks of gestation. The woman should be seen in the anaesthetic clinic and the neonatologists should be informed of the intended delivery of a baby with haemophilia.



Maschi alle prese con l' invidia

«Socrate volle usurpare l'opera femminile. In greco "maieutica" è l'arte della levatrice.
Se l'attribuì dicendo che lui aiutava gli uomini a partorire qualche idea, un pensiero. Chiamò maieutica la sua filosofia. Che misera riduzione del termine: in campo maschile generava un po' d'aria riscaldata, una flatulenza cerebrale.

Nascere è lavoro di donne…..»

Erri de Luca