



BLEEDING DISORDERS IN WOMEN:

Demographics, diagnostic tools and patient management

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Disclosures

Fees for speaking, organizing education, attending to meeting	CSL Behring, Novonordisk, LFB Biomédicaments
	Octapharma, Werfen
Board Membership	CSL Behring



Background

- Inherited bleeding disorders (IBD) are rare and clinical complications vary according to type and severity of the deficiency.
- Girls and women with IBD face multiple bleeding challenges.
- Most significant morbidity and mortality are due to heavy menstrual bleeding (HMB) and postpartum hemorrhage (PPH)
- 1st step for diagnosis and management of these specific bleeding complications is a complete evaluation combining
 - _ Bleeding assessment tools
 - _ Specialized laboratory tests
- Due to heterogeneity of type and severity of deficiencies, therapeutic management not well standardized



Clinical case

- Mrs A, 28 yo, was diagnosed type 1 VWD in childhood.
 - Since diagnosis, no bleeding symptoms reported except epistaxis which decreased at puberty
 - Medical history: tooth extractions under DDAVP treatment without bleeding complications

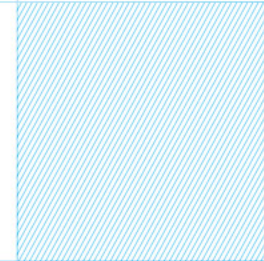
- Clinical and biological phenotype at baseline
 - ISTH BAT (ISTH Bleeding Assessment Tool) = 2
 - Blood group = O Rh+
 - VWD type 1 phenotype
 - FVIII:C = 30 IU/dL
 - VWF:Act: 23 IU/dL, VWF:Ag: 25 IU/dL

Clinical case

- Mrs A, was referred to evaluate bleeding risk during 1st pregnancy and delivery
- Laboratory tests performed at 28 WG showed increased factor levels:
 - FVIII:C: 70 IU/dL
 - VWF:Act: 55 IU/dL, VWF:Ag: 65 IU/dL, Platelet counts = $166 \times 10^9/L$
- Several questions for the multidisciplinary team ?
 - In which type of maternity hospital could she delivered ?
 - Which treatment to prevent PPH?
 - Which type of analgesia ?

Clinical case

- 3 years after, at time of the follow-up consultation, Mrs A reported since 2^d delivery:
 - Heavy Menstrual Bleeding (HMB)
 - Every 6 months iron supplementation
 - No contraception
- Clinical and laboratory tests showed
 - ISTH BAT score = 3 corresponding to HMB
 - Severe anemia despite no clinical signs: Hb = 78 g/L, Platelet counts = 175 G/L, Ferritin = 5 µg/L
- Which therapeutic options?
 - Hormonal therapy
 - Iron supplementation
 - Treatment by tranexamic acid
 - DDAVP



IBD: DEFINITION, DEMOGRAPHICS

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Inherited bleeding disorders

- Von Willebrand Disease (VWD) is VWF deficiency which is large multimeric protein that promotes platelet adhesion to thrombogenic surfaces and carrier FVIII in plasma
- VWD is heterogeneous regarding clinical and biological phenotype
 - Quantitative sub-types : partial VWF deficiency (Type 1) or complete VWF deficiency (Type 3)
 - Qualitative sub-types (Type 2) : subdivided in 4 subgroups according to the underlying mechanism of qualitative VWF deficiency: 2A, 2B , 2M, or 2N. In these forms, VWF and FVIII levels are variable
- Inheritance is autosomal dominant except in type 2N or type 3

- Hemophilia A (HA) and Hemophilia (HB), are a FVIII or FIX deficiency, from mild to severe forms, reaching mainly men. In carriers of hemophilia, clinical symptoms depending of severity of deficiency
- Hemophilia is usually inherited through an X chromosome with an *F8* or *F9* gene mutation.
- However, both the *F8* and *F9* genes are prone to new mutations, and about 30% of all cases result from spontaneous genetic variants

- Others rare bleeding disorders (RBD) includ:
 - FVII, FXI, FV, FII, FX
 - Fibrinogen, FXIII
 - Combined FV+ FVIII deficiency

- More rarely, there is inherited platelet disorders:
 - Among platelet function disorders, receptors abnormalities are described such as Glanzmann's thrombasthenia, Bernard Soulier Syndrome and storage pool abnormalities such as Hermansky-Pudlak syndrome
 - Inherited thrombocytopenia

- Inheritance of these rare disease is mostly autosomal recessive and only homozygote forms reach to bleeding complications



Prevalence of IBD

- VWD is described as the most frequent IBD but symptomatic forms are estimated of 0.01% of general population

- Prevalence of HA or HB
 - Estimated prevalence of hemophilia among males individual is 1 in 5000
 - HA estimated to account for 80%-85% of all cases and HB estimated for 15%
 - Regarding prevalence of carriership of hemophilia, it is estimated 1 per 3000 but real number is unknow
 - Only 3.5% of 206 119 patients with hemophilia included in most recent World Federation of Hemophilia Annual report were girls or women



Prevalence of IBD

- Around world, prevalence of inherited platelet function disorders is estimated to 1 per 3000 patients
- RBD are much less prevalent, with rates ranging from 1 in 500 000 for FVII deficiency to 1 in 2 million for FII and FXIII deficiencies in general population

TABLE 1 Prevalence for severe factor deficiencies, correlation between factor levels measured in the laboratory and clinical manifestations, and inheritance mode of rare inherited bleeding disorders.

Coagulation factor	Prevalence ^a	Laboratory-clinical data correlation	Transmission mode
Fibrinogen (factor I): Afibrinogenaemia	1/1 000 000	Strong	Autosomal recessive
Factor II	1/2 000 000	Strong	Autosomal recessive
Factor V	1/1 000 000	Weak	Autosomal recessive
Combined factors V + VIII deficiency	1/1 000 000	Strong	Autosomal recessive ^b
Factor VII	1/500 000	Weak	Autosomal recessive
Factor X	1/1 000 000	Strong	Autosomal recessive
Factor XI	1/1 000 000	No	Recessive or dominant
Factor XIII	1/2 000 000	Strong	Autosomal recessive
Combined vitamin K- dependent factor deficiency	Not known	Weak	Autosomal recessive

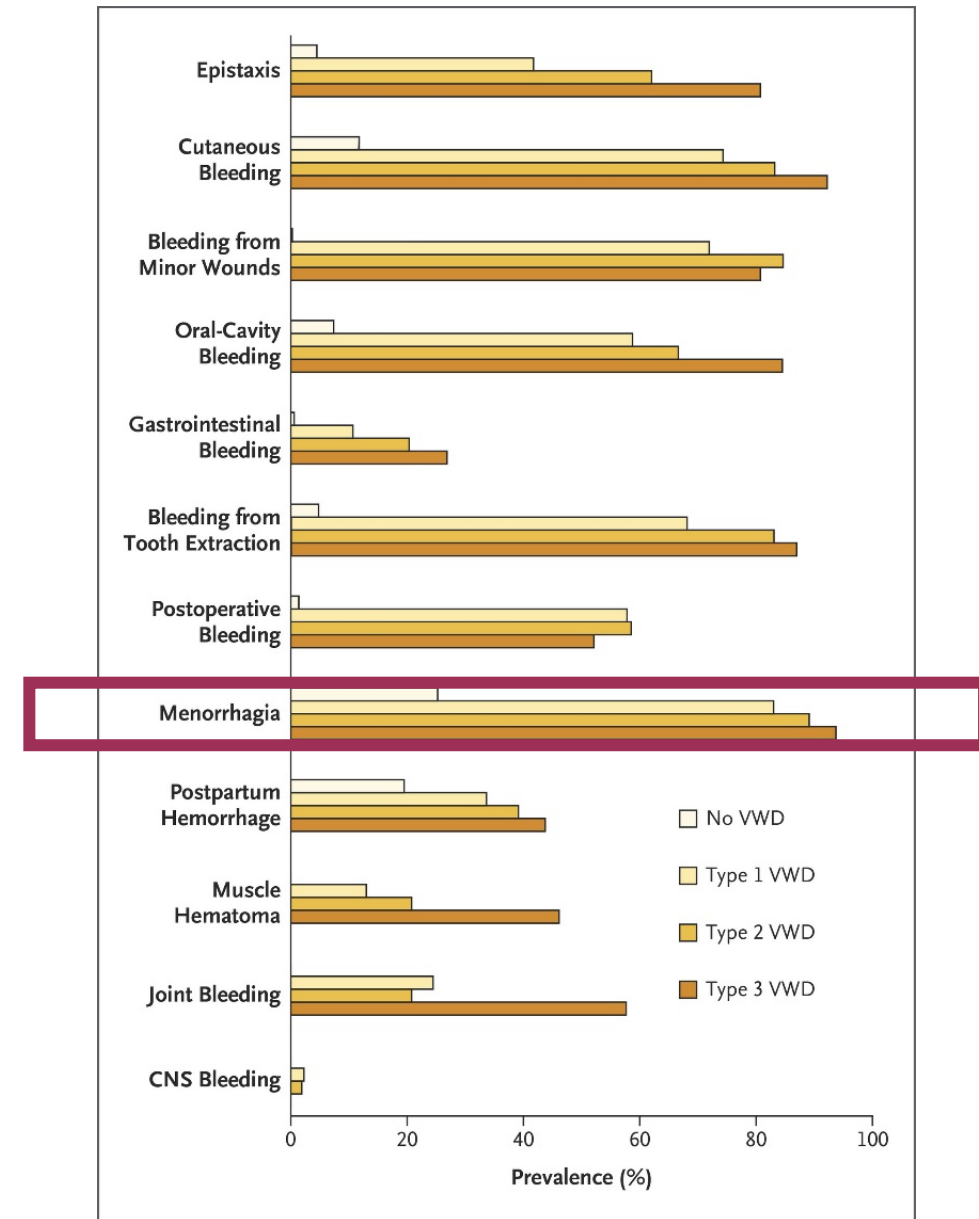


Frequency of HMB

- Approximately one in 5 (12 to 23%) women who presents to a gynaecologist with HMB have an underlying BD.
- Up to 75–80% of adolescent girls and women with an inherited BD, report having HMB.
- This is most commonly cited clinical manifestation
- 1/2 of adolescent girls with IBD present with HMB at menarche

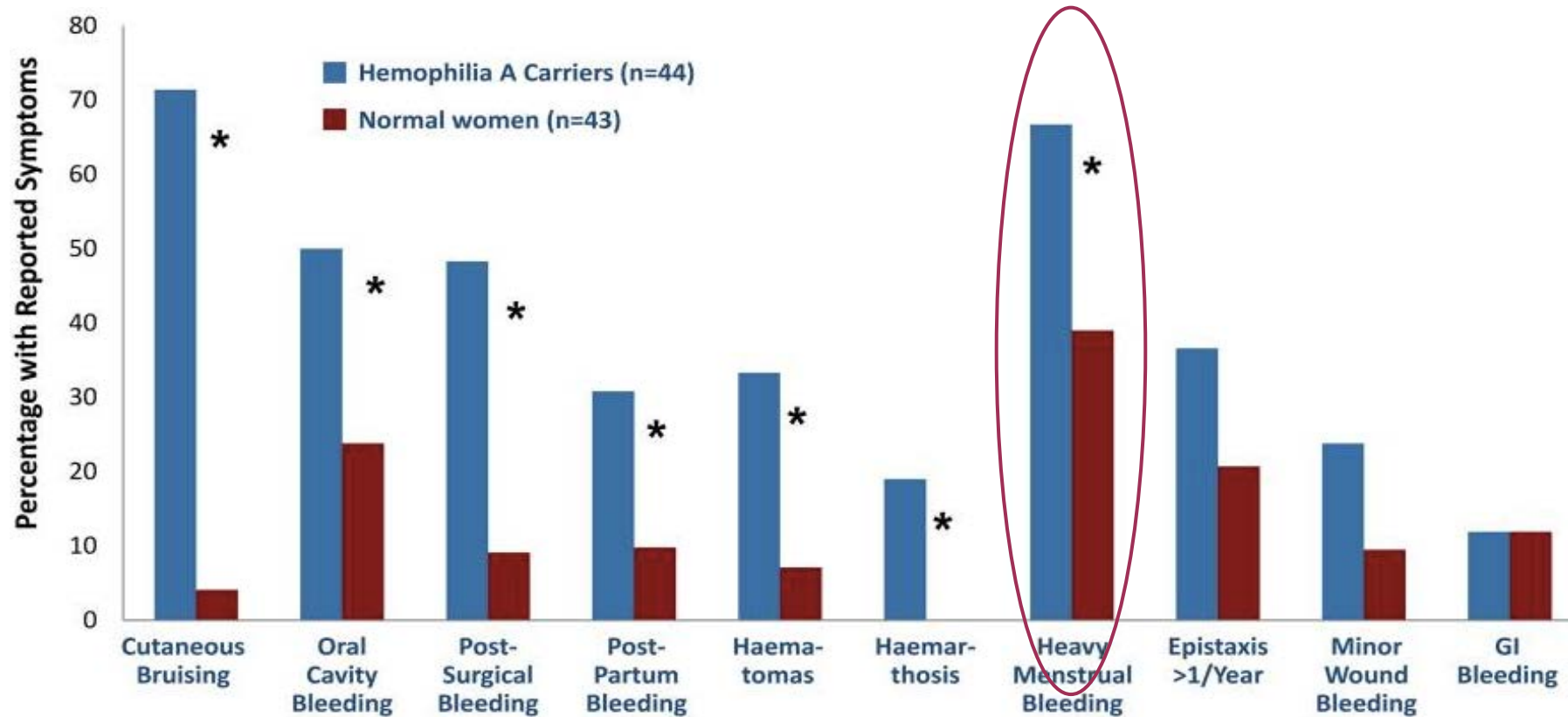
Frequency of HMB in VWD

- Up to 80% reported HMB whatever type
- 20% undergoing hysterectomy: 2 x higher than all women





Frequency of HMB and Hemophilia



*Fisher's Exact Chi Square p value <0.05



Frequency of HMB and RBD

FXIII

- **25-30%**
- Miscarriages

*L.Rugeri. Br J Haematol. 2020.
Kadir RA. Haemophilia 2013.*

FVII

- **≈ 75% severe deficiency**
- Treatment for HBM Prophylaxis (4/21)
- Treatment (16/101)

*STER Registry.
Greifswald Factor FVII Deficiency Study Group.*

FX

- **≈ 25% severe deficiency**
- Treatment for HBM (64%)
- Transfusion (10%)

A Kadir. Haemophilia 2019.

Afibrinogenemia

- **HMB frequent**
- Varies according to severity of deficit

*M. VIJAPURKAR, Hemophilia 2009
Y Zhang, Clin Appl Throm Hemost 2020*

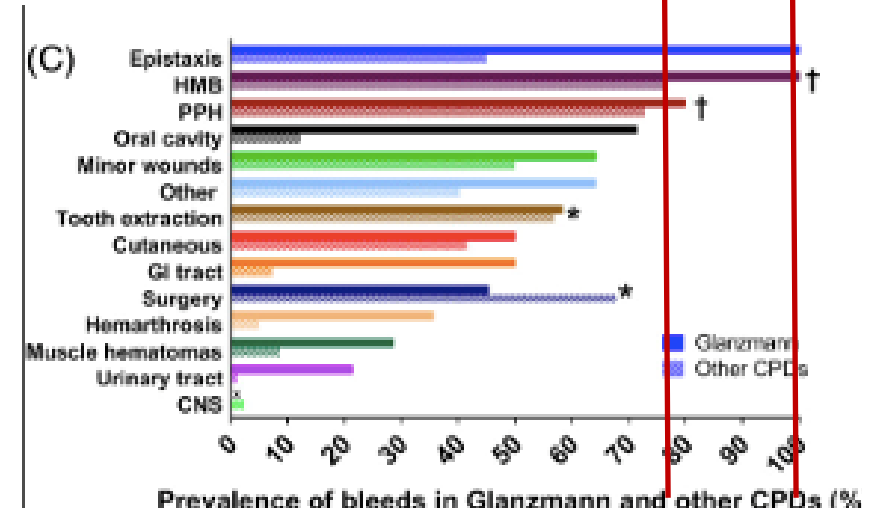
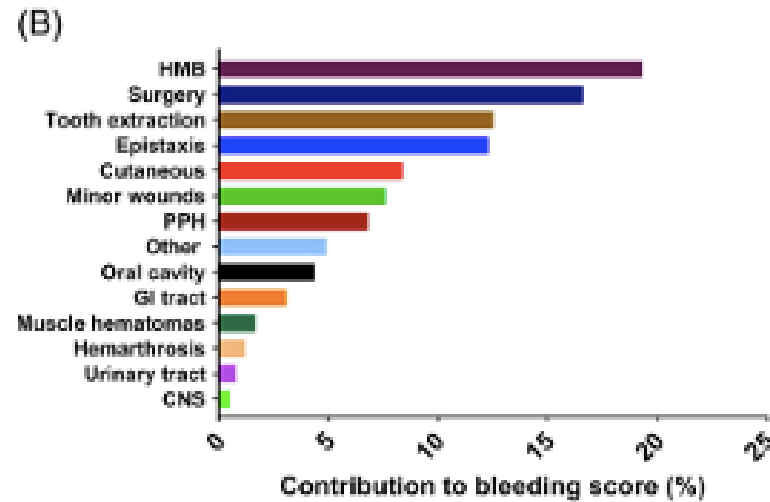
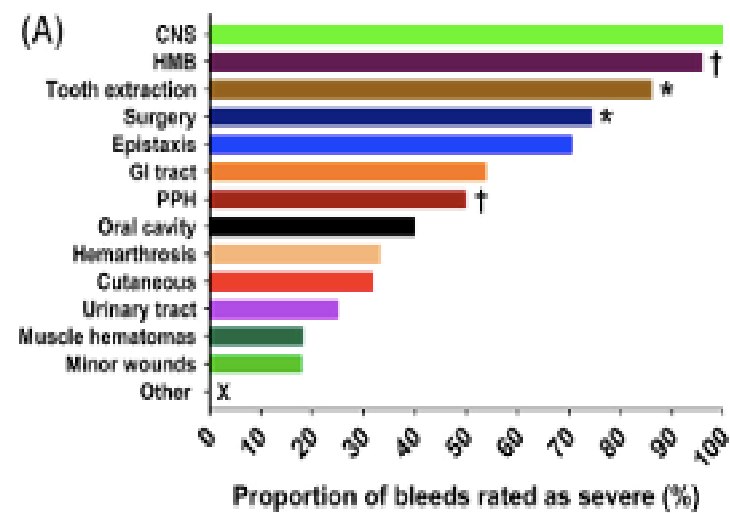


Frequency of HMB and Inherited Function Platelets disorders

Severe

Frequent

Variability according to
type





BLEEDING ASSESSMENT AND LABORATORY TESTS

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- 1st step to diagnose bleeding disorders is to identify clinical phenotype which already provide information about type of the deficiency and orient to laboratory testing
 - Spontaneous hemarthrosis or hematoma are frequent in patients with moderate to severe HA or HB
 - Spontaneous epistaxis, bruising or heavy menstrual bleeding (HMB) are frequently described in patients with VWD or platelet disorders
 - Neonatal intracranial hemorrhage mostly evoked in severe fibrinogen or FXIII deficiencies
 - Moreover, bleeding complications occurring after minor surgical procedures could suggest minor deficiencies

- In women with IBD, 2 circumstances increase bleeding risk
 - Menorrhagia is one of most common bleeding manifestation impacting women with IBD. Often undiagnosed and poorly treated, menorrhagia leads
 - to symptomatic iron deficiency anemia with risk of blood transfusion
 - to a negative effect on their quality of life
 - Pregnancy and especially childbirth could also expose these women to life-threatening bleeding. Even if 1st cause of PPH is uterine atony, women with IBD are at significant risk of hemorrhage at time of delivery
- Heterogeneity of biologic forms of these disease contribute to the under-diagnosis and under-treatment of these bleeding disorders

- First step of diagnosis and of management is knowledge of abnormal quantity of menses and acknowledgement of symptoms and recognition of decrease of their quality of life
- Low ferritin level in adolescents with HMB, without anemia, is associated with fatigue and decreased cognition specifically affecting verbal learning and memory
- Adolescents with heavy bleeding may have impaired school attendance and performance, decreased participation in sports, and may present with symptoms of depressed mood or anxiety

- To diagnose bleeding disorders, an extensive knowledge of hemostasis laboratory tests is necessary
 - Specific laboratory tests for measurements for coagulation factors could confirmed type and severity of factor deficiency.
 - However, these tests are not always available except in special coagulation laboratories.
- Screening laboratory tests includes at least:
 - FBC and ferritin measurements are essential for assessment of anemia
 - PT and aPTT are not enough to diagnose moderate clotting factor deficiency or to eliminate type 2 VWD which could be associated with normal FVIII:C level
- In women with menorrhagia, laboratory testing should be carried out if there a positive bleeding history but is always required in adolescent girls

- Several clotting factors measurement are required
 - VWF:Act, VWF:Ag, FVIII:C for the diagnosis of VWD
 - FVII level if isolated prolonged PT
 - FVIII, IX, XI levels if isolated prolonged aPTT
 - FII, V, X, fibrinogen measurement if combined prolonged PT or aPTT
- In second line, because defects not screened by standard tests, platelet function analysis and FXIII levels could be performed
- In VWD, specialized laboratory tests are necessary for diagnosis of subtype in order to give tailored treatment
 - VWF:CB, RIPA, multimers and genetic tests
 - Interpretation of VWF levels required blood group and fibrinogen



Evaluation and diagnosis of HMB

- Screening of factor levels and bleeding scores in each women are essential to implement an adequate follow up and treatment
- Main issue for women with IBD is to be able themselves to identify HMB
van Galen¹
- Knowledge of screening tools helping to quantify these bleeding have to be diffused to women and also to physicians

Evaluation and diagnosis of HMB

- Screening HMB includes
 - Quantification of heavy menses:
 - Duration of menses greater than or equal to 7 days and if woman reported either “flooding” or bleeding through a tampon or napkin in 2 hours or less with most periods
 - Menses > 80 ml
 - Use of a Pictorial Blood Loss Assessment Chart such as **Higham score** is also a good method to quantify heavy menses and also to evaluate the treatments
 - History of treatment of anemia
 - Family history of diagnosed bleeding disorder or history of excessive bleeding after tooth extraction, delivery or miscarriage, or after surgery

- Developed and validated in VWD, Bleeding Assessment Tools (**ISTH BAT**) accurately distinguish normal to abnormal bleeding. Each symptom (epistaxis,menorrhgia, PPH....) is scored, or with higher level of medical intervention receiving a higher score
- BAT have been shown to be an effective measure of bleeding severity in patients known to have IBD
- Should be performed in all woman with HMB in order to help the interpretation of screening laboratory tests



PATIENT MANAGEMENT IN IBD

WHICH TREATMENT FOR WHICH BLEEDING RISK ?

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Clinical case

- Mrs A, 28 yo, is referred to evaluate bleeding risk during 1st pregnancy and delivery
 - She was diagnosed type 1 VWD in childhood.
 - Since the diagnosis, no bleeding symptoms reported except epistaxis which decreased at puberty
 - She benefited of tooth extractions under DDAVP treatment without bleeding complications

- Clinical and biological phenotype before pregnancy
 - ISTH BAT (ISTH Bleeding Assessment Tool) = 2
 - FVIII:C = 30 IU/dL
 - VWF:Act = 23 IU/dL, VWF:Ag = 25 IU/dL
 - Platelet counts = $256 \times 10^9/L$

Clinical case

- The laboratory tests performed at 28 WG showed
 - FVIII:C = 70 IU/dL
 - VWF:Act = 55 IU/dL, VWF:Ag= 65 IU/dL
 - Platelet counts = $166 \times 10^9/L$

- Several questions for the multidisciplinary team ?
 - In which type of maternity hospital could she delivered ?
 - Which treatment to prevent PPH?
 - Which type of analgesia ?

Clinical case

- Mrs A, referred at 40 WG to the local maternity .
- Laboratory tests performed 1 week before showed:
 - FVIII:C: 100 IU/dL
 - VWF:Act: 73 IU/dL, VWF:Ag: 100 IU/dL
- She had vaginal delivery under epidural analgesia
- She received no treatment and had no hemorrhagic complications



PPH in women with IBD

- Because PPH is one of most life-threatening complication in all women around the world, pregnancy and especially childbirth expose these women to life-threatening bleeding
- Even if 1st cause of PPH is uterine atony, women with IBD are at significant risk of hemorrhage at time of delivery
- Diagnosis and management of women with IBD need knowledge of physiologic variations of coagulation factor levels during pregnancy.
 - During pregnancy several clotting factors increased in order to prevent bleeding risk of delivery
 - Main increased factor levels are on FVIII, VWF and fibrinogen

- In women with VWD, PPH still occurs despite increased of FVIII and VWF during pregnancy.
- Bleeding risk is depending of the type of VWD and factor levels at time of delivery
- Actual risk of PPH in haemophilia carriers is hard to estimate. Rate of PPH was been reported to range of 13% to 22% and rate of secondary PPH in the range of 9% to 20%
- Due to rarity of RBD and Platelet disorders few study are available regarding bleeding risk at time of delivery

- In practice, due to the heterogeneity of type and severity of the deficiencies, and consequently therapeutic management of these women remains not well standardized
- Required clotting factor or platelets count thresholds for invasive prenatal diagnostic test, for delivery , for neuroaxial anesthesia are still discussed
- Any recommendation regarding products, dosing, duration of therapy, or threshold for treatment are based on observationnel studies or expert opinions
- At each step of pregnancy, treatment options and their limitations need to be share between multidisciplinary team and woman



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- Multidisciplinary management of women is strongly recommended
- No evidence permitted to experts to make proposition for delivery bleeding risk regarding:
 - Minimal FVIII: C and VWF levels requiring treatment
 - Duration of treatment
- Guidelines panel suggests use of tranexamic acid during at least 10 days

Recommendation 8

The guideline panel *suggests* the use of tranexamic acid over not using it in women with type 1 VWD or low VWF levels (and this may also apply to types 2 and 3 VWD) during the post-partum period) (conditional recommendation based on low certainty in the evidence of effects ⊕⊕○○).

Good practice statements: Tranexamic acid may be given systemically via the oral or IV route. The oral dose is 25 mg/kg (typically 1000-1300 mg) 3 times per day for 10 to 14 days or longer if blood loss remains heavy.

- In women with VWD, guidelines recommend an assessment of clotting factor levels from 3rd trimester, levels which
 - Determine bleeding risk at delivery
 - Which allow multidisciplinary team to counsel women about the modalities and location of the childbirth

- Normalization of factor levels observed in majority of moderate form of type 1, permit physiologic delivery with only a tailored monitoring

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- Despite no strong evidence to make propositions, majority of authors propose:
 - Vaginal delivery or Cesarean section can be performed when FVIII:C and VWF:Act is > 50 IU/dL and platelet counts $> 50 \times 10^9/L$
 - Factor levels should be maintained > 50 IU/dL at least
 - 3 days after vaginal delivery
 - 5 days after Cesarean section

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- Regarding neuroaxial analgesia, recommendations are more precise
 - Targeting VWF:Act > 50 IU/dL to allow neuroaxial anesthesia
 - VWF:Act > 50 IU/dL for at least 6H after epidural removal

Recommendation 7

In women with VWD for whom neuraxial anesthesia during labor is deemed suitable, the panel *suggests* targeting a VWF activity level of 0.50 to 1.50 IU/mL over targeting an activity level of >1.50 IU/mL to allow neuraxial anesthesia (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Remarks:

- Neuraxial anesthesia refers to spinal, epidural, or combined spinal-epidural procedures performed for surgical anesthesia for operative deliveries or pain relief during labor.
- This recommendation focused on the outcomes of the anesthesia procedure itself and not on the effects of the VWF levels on PPH, in which VWF activity levels of >1.50 IU/mL may be advised in some situations.
- Individual risk assessment should be performed, taking into account patient diagnosis and history, and for this reason, the panel advocates a third-trimester visit where VWF and FVIII activity levels can be checked and a prospective plan formed for anesthesia and delivery.
- This recommendation is intended for women who desire or require neuraxial anesthesia and does not address suitability of neuraxial anesthesia itself.
- VWF activity levels should be maintained at >0.50 IU/mL while the epidural is in place and for at least 6 hours after removal.

- Despite available guidelines, some issues are not resolved
- Consensual modalities are
 - Mode of delivery should be guided by obstetric indications
 - VWF:Act > 50 IU/dL and platelet counts $50 \times 10^9/L$ for VG or CS in Type 1
 - VWF:Act target of 50-100 IU/dL for neuraxial anesthesia
- Discussed modalities are
 - Factor levels according to the type of VWD
 - In type 2 and 3 VWD, factor replacement required to achieved FVIII and VWF levels > 100 IU/dL
- Dutch study reported than 50% of women with VWD with VWF levels >50 IU/dL in 3rd trimester, despite treatment with VWF concentrate aiming at level 100 IU/dL had PPH.

A single-centre study of management of pregnant women with von Willebrand disease

[Z. Xu](#), [Y.Dargaud](#), [V.Chamouard](#), [S.Le Quellec](#), [A.Lienhart](#), [S.Meunier](#), [L.Rugeri](#)

Novembre 2018

- 86 deliveries in 55 women (53% type 1, 45% type 2 et 1 type 3)
- Before delivery, normalization of factor levels (FVIII:C and VWF:Act > 50%) were observed in 71% type 1 et 61% type 2
- Depending to the correction of factor levels in each type, no treatment was administrated in 66% deliveries including 72% VD
- Epidural/spinal analgesia performed in 37%
- Overall incidence of primary PPH = 6,9 %, and secondary PPH was 2,3%
- Using a individualized strategy, women with severe VWD can be expected to have a normal risk of post partum period

- As in VWD, haemophilia carriers women have increased risk of PPH
- Experts suggests to maintain factor levels > 50 IU/dL :
 - To permit neuroaxial analgesia
 - To prevent bleeding risk, at least 3 days after VD and 5 days after CS

- In other RBD, hemorrhagic threshold is still discussed and any recommendation regarding products, dosing, duration of treatment are based on observational studies or expert opinions

TABLE 3 Coagulation factor thresholds for bleeding risk proposed by Mannucci et al,⁴ Peyvandi et al,⁵ UK Guidelines Mumford et al¹ and FRCH (this review).

Coagulation factor concerned	Half life	Coagulation factor threshold				
		Mannucci et al. 2004	Peyvandi et al. 2012		UK Guidelines Mumford A et al. 2014	FRCH proposals 2021
			Threshold to “remain asymptomatic”	Threshold to “avoid severe bleeding”		
Fibrinogen	80 h	0.5 g/L	1 g/L	“Detectable”	1–1.5 ^a g/L	0.5 g/L
Factor II	100 h	20–30 IU/dL	—	—	20 IU/dL	30 IU/dL ^b
Factor V	25 h	15–20 IU/dL	12 IU/dL	15 IU/dL	15–20 IU/dL	20 IU/dL
Factor VII	4–6 h	15–20 IU/dL	25 IU/dL	8 IU/dL	10–20 ^a IU/dL	20 IU/dL
Factor X	40–60 h	15–20 IU/dL	56 IU/dL	10 IU/dL	20 IU/dL	20 IU/dL
Factor XI	50 h	15–20 IU/dL	26 IU/dL	25 IU/dL	20 IU/dL	15–30 IU/dL ^c
Factor XIII	150 h	2–5 IU/dL	3 IU/dL	15 IU/dL	10–20 IU/dL	20 IU/dL
Factor V + Factor VIII	FV 25 h and FVIII 12 h	15–20 IU/dL	43 IU/dL	8 IU/dL	FV: 15 IU/dL and FVIII: 50 IU/dL	FV: 20 IU/dL and FVIII: 50 IU/dL

^aFor delivery in pregnant women.

Disease	Pregnancy and Delivery	Disease	Pregnancy and Delivery	Disease	Pregnancy and Delivery
Fibrinogen disorders	<i>Pregnancy:</i> • Prophylaxis to obtain fibrinogen level >1 g/L in the first trimester and 2 g/L afterwards. • To obtain a fibrinogen level >1.5–2 g/L, treatment for at least 3 days. <i>Delivery:</i> Fibrinogen for at least 3 days to obtain a fibrinogen level >1.5–2 g/L.	FV deficiency	<i>Pregnancy:</i> Not needed. <i>Delivery:</i> • Dose: 15–25 mL FFP/kg from first contractions or before caesarean section • Target FV level: >25%. Then, 10 mL/kg FFP every 12 h for at least 3 days.	FXI deficiency	<i>Pregnancy:</i> not needed. <i>Delivery:</i> If FXI <15% at pregnancy end and no surgery/trauma-induced bleeding history, tranexamic acid; HEMOLEVEN® (human FXI; 10–15 IU/kg) only if abnormal bleeding. If FXI >15% at pregnancy end, tranexamic acid and HEMOLEVEN® only in case of abnormal bleeding.
FII deficiency	<i>Pregnancy:</i> not needed. <i>Delivery:</i> • Dose: 20–40 IU/kg PCC from first contractions or before caesarean section • Target FII level: 20%–40% Additional PCC injections to maintain FII >20% for at least 3 days.	FVII deficiency	<i>Pregnancy:</i> not needed. <i>Delivery:</i> 15–30 µg/kg eptocog alfa (NovoSeven®) every 4–6 h for at least 3 days if FVII level <20% and symptomatic disease, especially in case of caesarean section; only in case of complications in the other cases.	FXIII deficiency	<i>Pregnancy:</i> prophylaxis with FXIII (FIBROGAMMIN®, NovoThirteen®) to maintain FXIII level >10%–20% in the first two trimesters and FXIII >30% afterwards. <i>Delivery:</i> Additional injection of 10–40 IU/kg FIBROGAMMIN® from first contractions or before caesarean section.
		FX deficiency	<i>Pregnancy:</i> not needed. <i>Delivery:</i> • Dose: (i) 20–40 IU/kg PCC from first contractions or before caesarean section to obtain a FX level > 20% for at least 3 days • (ii) max 60 IU/kg/day COAGADEX® (plasma-derived FX concentrate) • (iii) 15–25 mL/kg FFP if PCC or COAGADEX® not available	FV + FVIII deficiency	<i>Pregnancy:</i> not needed. <i>Delivery:</i> if FV <20% at pregnancy end, 15–25 mL/kg FFP from first contractions or before caesarean section to reach FV >25%. Then, 10 mL/kg FFP to maintain FV >20% for at least 3 days. FVIII may be used to maintain FVIII >50% for at least 5 days.

Clinical case

- 3 years after, at time of the follow-up consultation, Mrs A reported since 2^d delivery:
 - Heavy Menstrual Bleeding (HMB)
 - Every 6 months iron supplementation
 - No contraception
- Clinical and laboratory tests showed
 - ISTH BAT score = 3 corresponding to HMB
 - Higham score = 360
 - Severe anemia despite on clinical sings: Hb = 78 g/L, Platelet counts = 175 G/L, Ferritin = 5 µg/L
- Which therapeutic options?
 - Hormonal therapy
 - Iron supplementation
 - Treament by tranexamic acid
 - DDAVP

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GOOD PRACTICE STATEMENTS. When feasible, the panel encourages the development of multidisciplinary clinics in which gynecologists and hematologists see patients jointly to facilitate the management of heavy menstrual bleeding for patients with bleeding disorders.

Gynecology: heavy menstrual bleeding. RECOMMENDATION 6A. The panel *suggests* using either hormonal therapy (combined hormonal contraception [CHC] or levonorgestrel-releasing intrauterine system) or tranexamic acid over desmopressin to treat women with VWD with heavy menstrual bleeding who do not wish to conceive (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Recommendation 6b

The panel *suggests* using tranexamic acid over desmopressin to treat women with VWD and heavy menstrual bleeding who wish to conceive (conditional recommendation based on very low certainty in the evidence ⊕○○○).

HMB management

- Concerning treatment of HMB, experts are agreed with treatment based on 3 complementary approaches
 - Either hormonal therapy (combined hormonal contraception [CHC] or levonorgestrel-releasing intrauterine system). Physician have a huge role to explain and to convince women about benefit of these molecules
 - Treatment by tranexamic acid: 1g at least twice daily
 - Iron supplementation if necessary

Clinical case

- Treatment prescribed at the end of the consultation
 - Oral Iron supplementation for at least 3 months
 - Treatment by tranexamic acid: 1g twice daily during all duration of heavy menses
 - Levonorgestrel-releasing intrauterine system

- 3 months later clinical and laboratory tests showed
 - ISTH BAT score = 0
 - Highman score = 0 due to amenorrhea
 - Hb = 119 g/L, Ferritin = 25 µg/L

HMB management

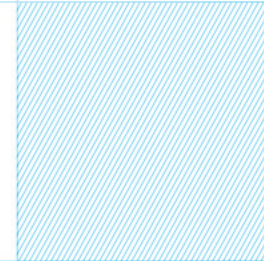
- Because multidisciplinary management is essential and recommended by guidelines
- Since January 2021, we develop in Lyon a 1st multidisciplinary organization dedicated to HMB
 - _ > 300 women from France referred
 - _ Preliminary data showed:
 - Demographics, median (range):
Age = 30 y (10-57), BMI = 22.3 (15.8-49.0), Higham score = 348.5 (60-2750) ISTH BAT score = 3 (0-9)
 - 27% presented anemia but 66% presented an iron deficiency
 - Ultrasound was normal in 62%
 - Adenomyosis was the main gynecological etiology (14%).
 - VWF activity (<40%) was found in 9 (4%) women.

HMB management in girls

- Because ½ of adolescent girls with IBD present with HMB at menarche, it is necessary to prepare girls and their parents to this event
- Recommendations suggest that during clinical follow-up, several consultations have to be planned
 - Endocrinologist pediatrician could determine at what step of puberty is the girl
 - Hematologist in association with gynecologist could give information about : What are the menses, what are heavy periods, how to evaluate themselves using Pictorial Blood Loss Assessment Chart such as Higham score.

HMB management

- In order to prevent the clinical complications of HMB, it is essential to develop information about available guidelines to physicians and therapeutic education program to women and girls and their parents
- These education programs are essential to reassure girls and parents by providing procedures to diagnose, to care and support these complications



IN CONCLUSION

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- Because IBD are underdiagnosed in women, and because HBM is one of most common bleeding manifestation impacting women with IBD, 1st steps for the diagnosis and the management of this specific bleeding complications is:
 - Evaluation of using bleeding evaluation tools
 - Evaluation of the impact of their quality of life; impact on their social, educational, professional and sexual life
- Also assessment of factor deficiency using screening and specialized laboraroty tests.

- Pregnancy and especially childbirth in women with IBD required to be followed by a multidisciplinary team in which gynecologists and hematologists, paediatrician which could offer most appropriate treatment for each woman
- Bleeding risk has to be evaluated at each step of pregnancy from potential invasive prenatal diagnostic test, to delivery, or neuroaxial anesthesia
- Treatment options and their limitations need to be shared between the multidisciplinary team and the woman
- In all IBD, it remains a lot of issues regarding clotting factors thresholds. Prospective international studies are necessary to have more evidence in order to make new recommendations and then improve the level of care of these women

Thank you for your attention

