European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

EHC
european haemophilia consortium
Advocating for people with haemophilia and congenital bleeding disorders

European
von Willebrand Disease
Community

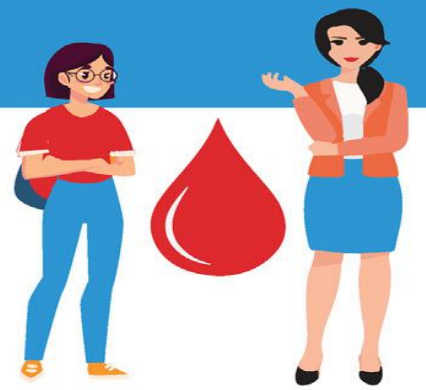
ERN-EuroBloodNet Webinar
von Willebrand Disease (VWD) in women
Family Planning

Debra Pollard

Royal Free Hospital, London UK

EAHAD
European Association for Haemophilia and Allied Disorders

EUROPEAN PRINCIPLES OF CARE FOR WOMEN AND GIRLS WITH INHERITED BLEEDING DISORDERS



Women and Girls with Bleeding Disorders (WGBD) face unique challenges. In order to optimise diagnosis, care and management of WGBD, the EAHAD Women and Bleeding Disorders Working Group have developed the following Principles of Care (PoC):

Equitable access and quality of care for all individuals with bleeding disorders, irrespective of gender

Timely and accurate diagnosis of bleeding disorders in women and girls

Awareness of the additional challenges faced by WGBD throughout life

Comprehensive care of bleeding disorders requires a family centred approach which includes WGBD

Inclusion of a dedicated obstetrician and gynaecologist in the multidisciplinary team

Education of WGBD and their families regarding the menstrual cycle and management

Early recognition and optimal management of heavy menstrual bleeding

Provision of preconception counselling and access to prenatal diagnostics

Provision of a patient centred comprehensive management plan throughout pregnancy and the post partum period

Involvement of WGBD in registries, clinical research and innovation

EHC
european haemophilia consortium

THESE PRINCIPLES OF CARE SERVE AS A FRAMEWORK TO GUIDE HAEMOPHILIA TREATMENT CENTRES WITH THE AIM OF POSITIVELY IMPACTING ON THE HEALTH, WELLBEING AND QUALITY OF LIFE OF WGBD

EAHAD
WOMEN AND BLEEDING DISORDERS WORKING GROUP

What care provision should be expected?

Family Planning

WHAT DOES THIS MEAN?

WHEN DOES IT START?

WHO SHOULD BE INVOLVED?

Family planning in VWD

- Girls and young women need good education from Health Care Professionals to have precise knowledge of their VWD
- Education about options for pregnancy options and care should begin in adolescence
- Personal and family experience may have huge influence
- Personal Knowledge and understanding of VWD and it’s management is key to empowering women to advocate for themselves in all healthcare situations
- Preparation for encountering many, varied health care professionals – not all of whom may understand vWD

Questions for women with VWD when considering planning a family

- Is it the right time? For me? For us?
- Who should I talk to? Family? Treatment Centre?
- Where do I go for information?
- What will happen if I stop my current treatment?
- How will we conceive if I'm bleeding all the time?
- What do I need to do first?
- Are there things I can do to keep healthy?
- I'm pregnant and I didn't plan it……help?

Partners have questions too

Considerations for service development for Centres and NMO's

- 2 patients – mother and baby – don't ignore male partner's needs
- Education programmes – for patients and health care staff
- Consider use of expert/experienced patients with vWD
- Named single point of access for contacting the treatment Centre
- Is it possible to have a health care "navigator" for pregnant women?
- Standardised management and care plans become familiar to others within the institution and are well recognised
- Wherever possible a joint Haematology/Obstetric clinic!

Managing fear and anxiety

- All women have some fear and anxieties around pregnancy, labour and delivery
- All women have some fears around what will happen to their babies
- Some women with vWD may have experienced significant issues during adolescence
- Some women with vWD may have experience of other female family members with poor experiences
- Treatment Centres should have access to psychology/counselling if anxiety becomes unmanageable
- Post natal depression risk should be considered if there are complications with labour, delivery or post partum – primary care (community) physicians should be alerted

Family planning with bleeding disorders

- There are additional considerations for all couples affected by any bleeding disorder
- With good preparation and planning optimal management should be understood – safety of mother and child at all stages is paramount
- Not every health care professional understands VWD
- Education is key to self advocacy to promote better outcomes for all
- Treatment Centres and NMO's should empower women and their partners to actively participate in their care
- Further multi-centre/multi-national research into "What women want" should be carried out to define future service developments

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von Willebrand Disease (VWD) in women
Pregnancy risks and management

Rezan Abdul Kadir, gynaecologist

The Royal Free NHS Trust

London, UK

Karin van Galen, haematologist, University Medical Center Utrecht, Van Creveldkliniek, The Netherlands

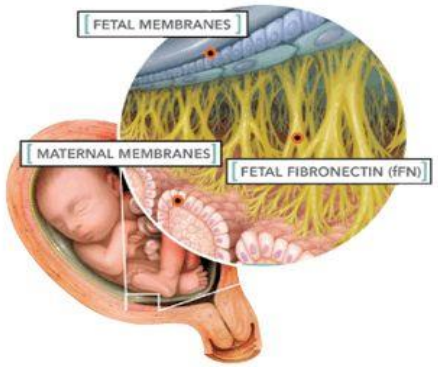
28 November 2024

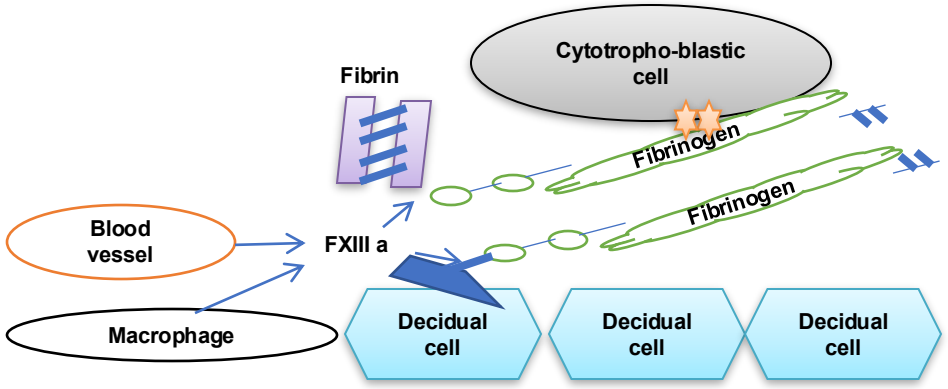
VWD - Fertility and early pregnancy implantation

No evidence for VWD - effect on fertility

Indirect effect ?

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



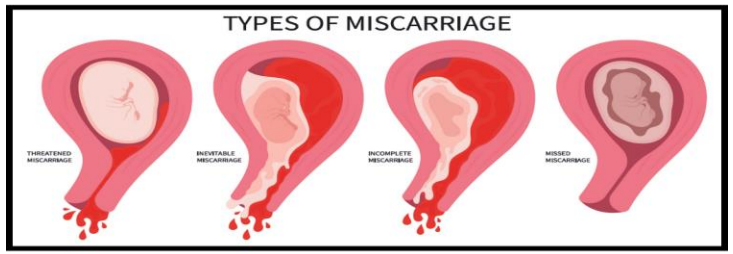


VWD – Miscarriage

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

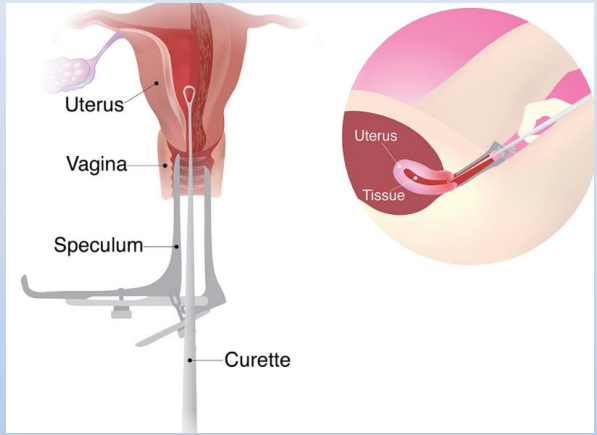
VWD - Is risk of miscarriage increased?

- 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

Haematologist perspective- managing miscarriage/termination of pregnancy

- Operative TOP (curettage)
  - Start tranexamic acid 3 t.i.d. 1000mg from 4 hours before the procedure
  - Mild type VWD – only use desmopressin in case of excessive blood loss
  - More severe types VWD: correct VWF 30-60 min before the procedure
    - desmopressin if known responder
    - iv. clotting factor concentrate;
    - repeat after 12 and 24 hrs only if needed



- TOP with medication
  - Start tranexamic acid 3 t.i.d. 1000mg before blood loss begins
  - Mild type VWD – only use desmopressin in case of excessive blood loss
  - More severe types VWD – correct VWF when blood loss begins
    - Desmopressin if known responder
    - iv. clotting factor concentrate
    - repeat after 12 and 24 hrs only if needed

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

Haematologist perspective- managing antenatal bleeding

- Preconceptive heavy menstrual bleeding
- Increased risk for mucous bleeds during pregnancy
- No tranexamic acid during pregnancy – uncertain if safe
  - Local administration of TXA allowed for minor gum/nose/wound/anal bleeding
- Use of desmopressin during pregnancy – safety discussed
  - Systematic review Arashi et al. JTH 2024 (22) 126-39
    - Seven studies reported DDAVP use during 73 pregnancies for prenatal diagnostic testing, TOP or obstetrical intervention (n=38) or- bleeding (n=2)
    - No adverse bleeding events and rare adverse events were reported- however large amount of missing outcome data
- i.v. clotting factor concentrate – safe in pregnancy
  - Prophylaxis may be needed f.e. in case of excessive repeated nose bleeds in case of insufficient local hemostasis

Desmopressin in pregnancy

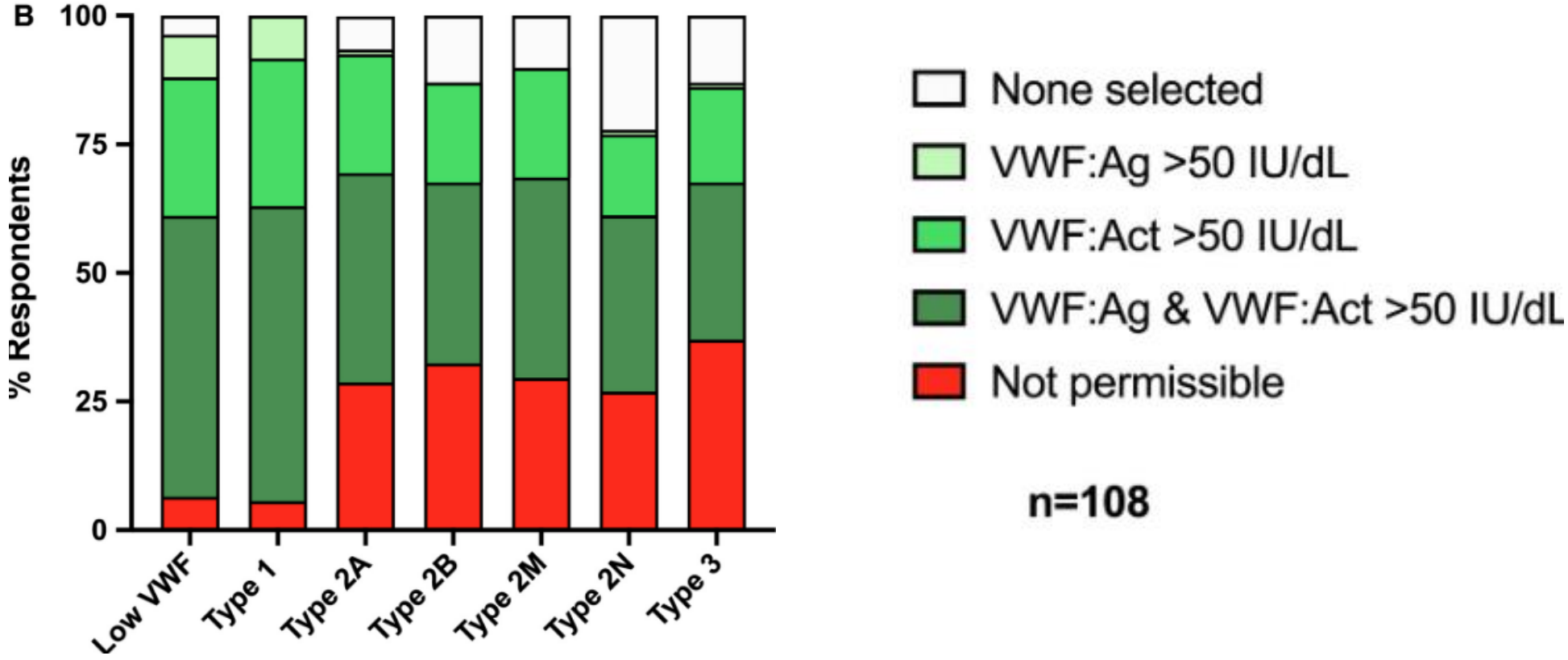
Essentials

- 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

VWD - Labour and delivery risks

- Suitability for Neuraxial analgesia /anaesthesia



Lavin et al. *J Thromb Haemost* 2021

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.

VWD – How to mitigate risks and optimise care during pregnancy and postpartum

- Pre-conceptual care and counselling
- MDT management during pregnancy
- Birth plan
- Postnatal care – regular HTC review

Provision of preconception counselling and access to prenatal diagnostics

Inclusion of a dedicated obstetrician and gynaecologist in the multidisciplinary team

Provision of a patient centred comprehensive management plan throughout pregnancy and the post partum period

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

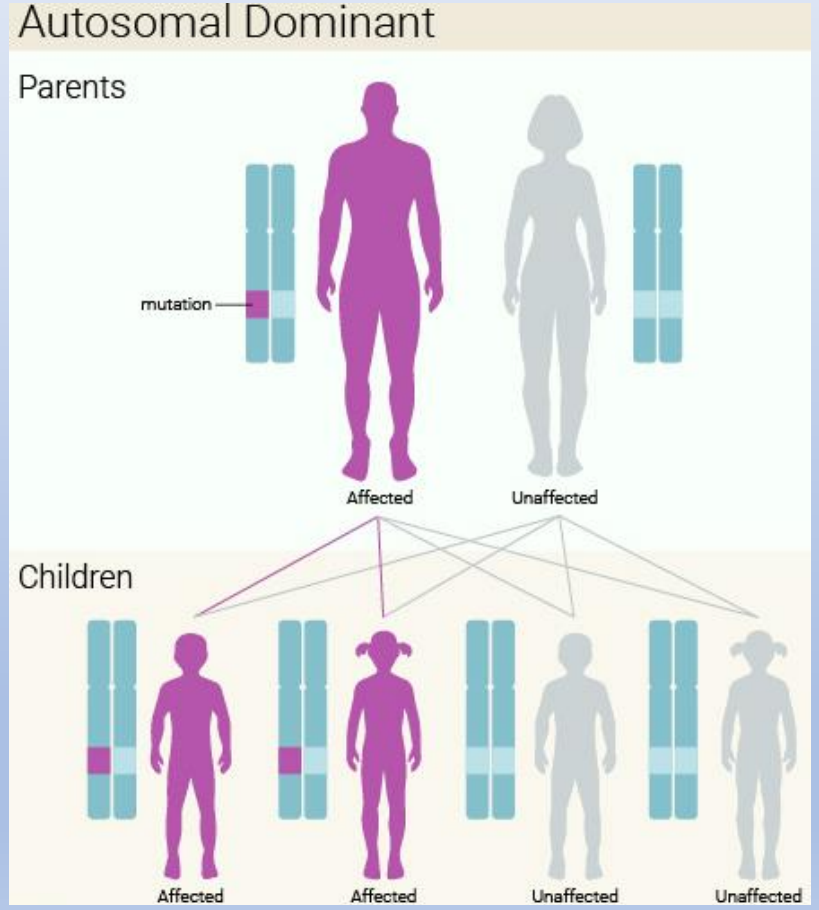
- PND options

Optimise maternal health

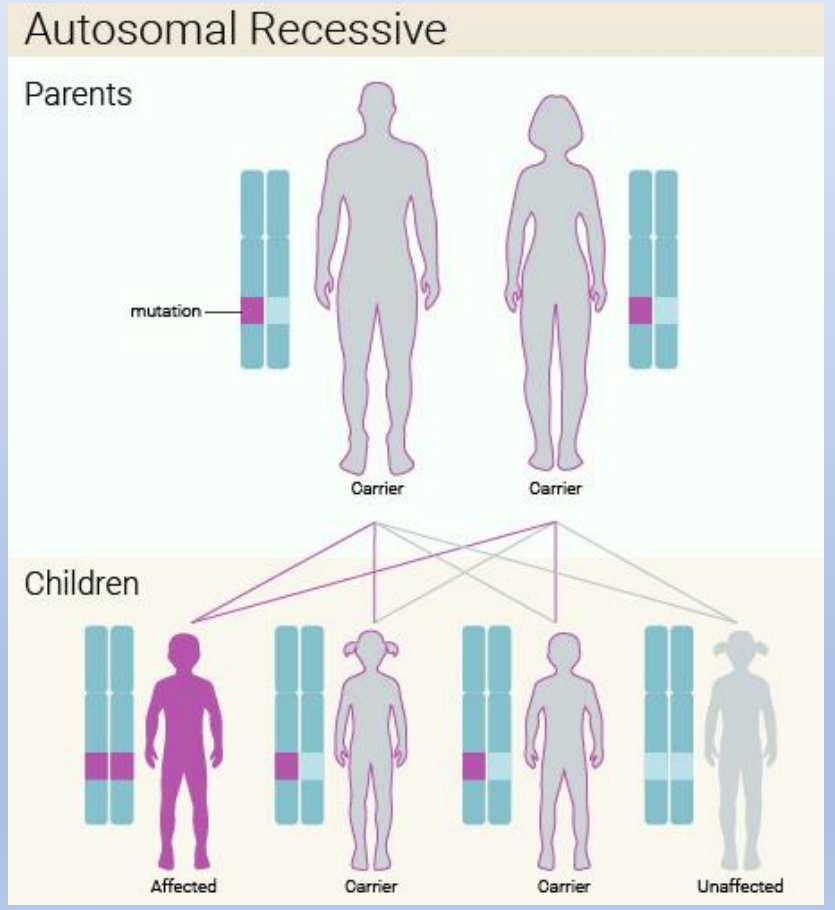
- Mx of HMB + anaemia
- Identification/Mx of obstetric risk
- Where to have antenatal care, what surveillance and where to deliver

Preconceptual care – genetic counselling

VWD type 1/2



VWD type 3/2N



NIH U.S. National Library of Medicine

WBD - Psychological Impact often underestimated

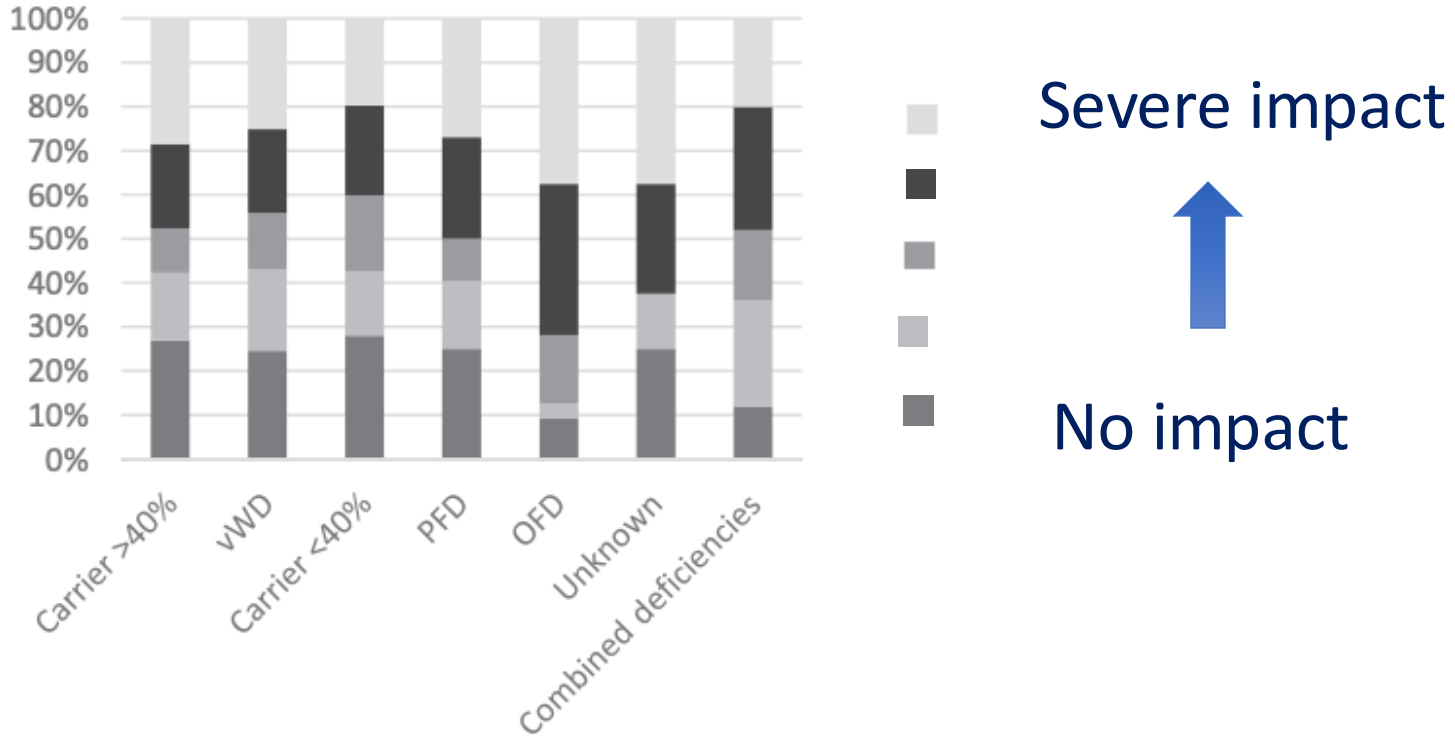
VWD may influence choices about children

- Hormonal therapies to be stopped – heavier periods
- Maternal Guilt - Concerned about the risk of children being affected
- Previous experience PPH – scared for future

- Patient support essential
- Availability of specialist psychological input

Impact of bleeding disorders on choice to have children

- Over-all 25% - Severe impact on their decision or prevented them from having children



Noone et al, Haemophilia 2019

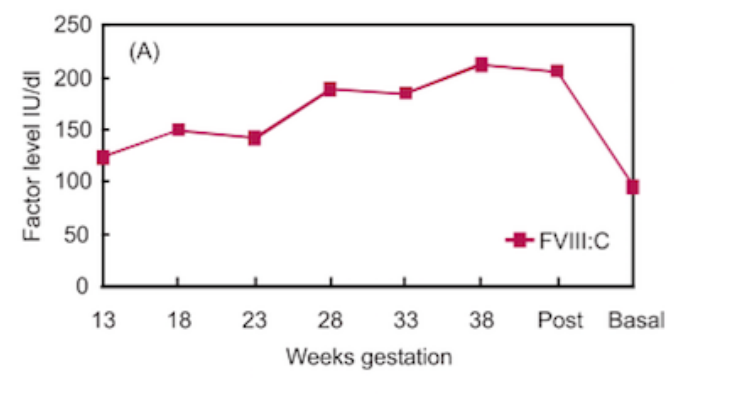
Pregnancy (antenatal) care and Management

- Multi-disciplinary management and collaboration between HTC, Obstetric/midwifery team and neonatal/paediatric team is key for safe delivery of mother and baby
- Most women will not be on prophylaxis prior to pregnancy
  - Normally not required in pregnancy
  - Haemostatic cover if VWF:Act and/or FVIII level <0.50 IU/mL for
    - Invasive procedures – e.g PND tests (CVS, Amniocentesis), cervical cerclage, etc
    - Miscarriage, termination of pregnancy, any or if excess bleeding with miscarriage

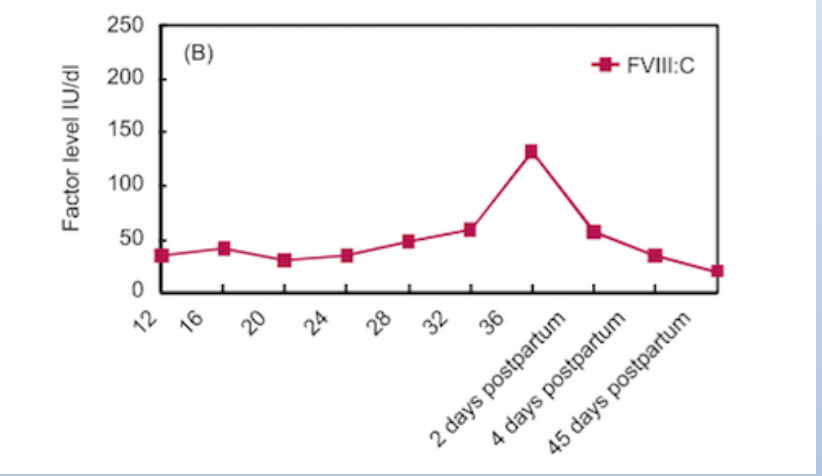
- Birth (delivery) plan – most critical component of antenatal care

MDT plan jointly with the mother - in advance of delivery date

Clotting factor rise in pregnancy



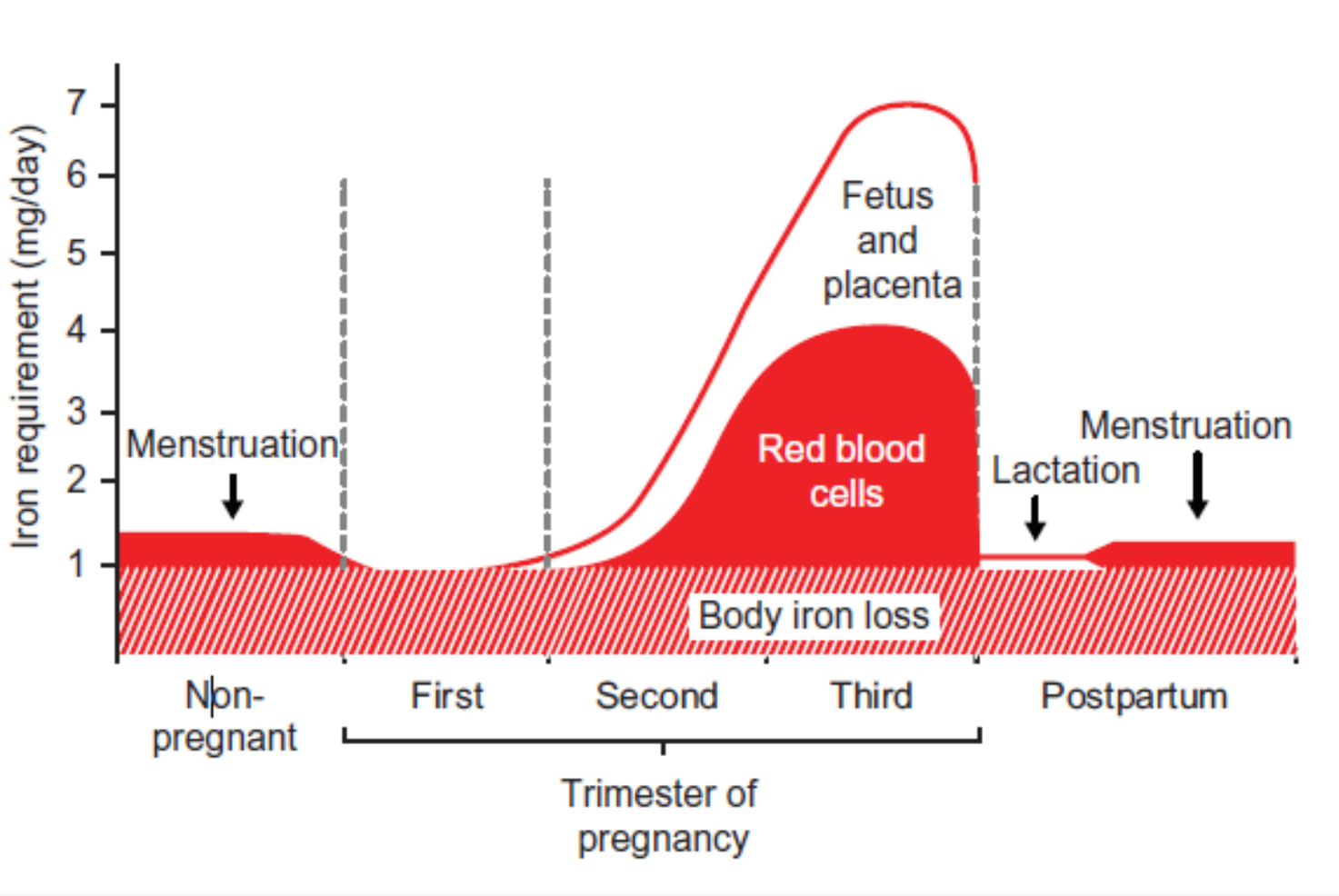
General population



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*

Mandatory iron supplementation



Over 62% of women with haemoglobin <8.5 g/l had PPH, 26% of whom progressed to severe PPH*

Mirza et al. Expert review of Hematology 2018; *Briley et al. BJOG 2014

Varying international practices in managing pregnant women with VWD

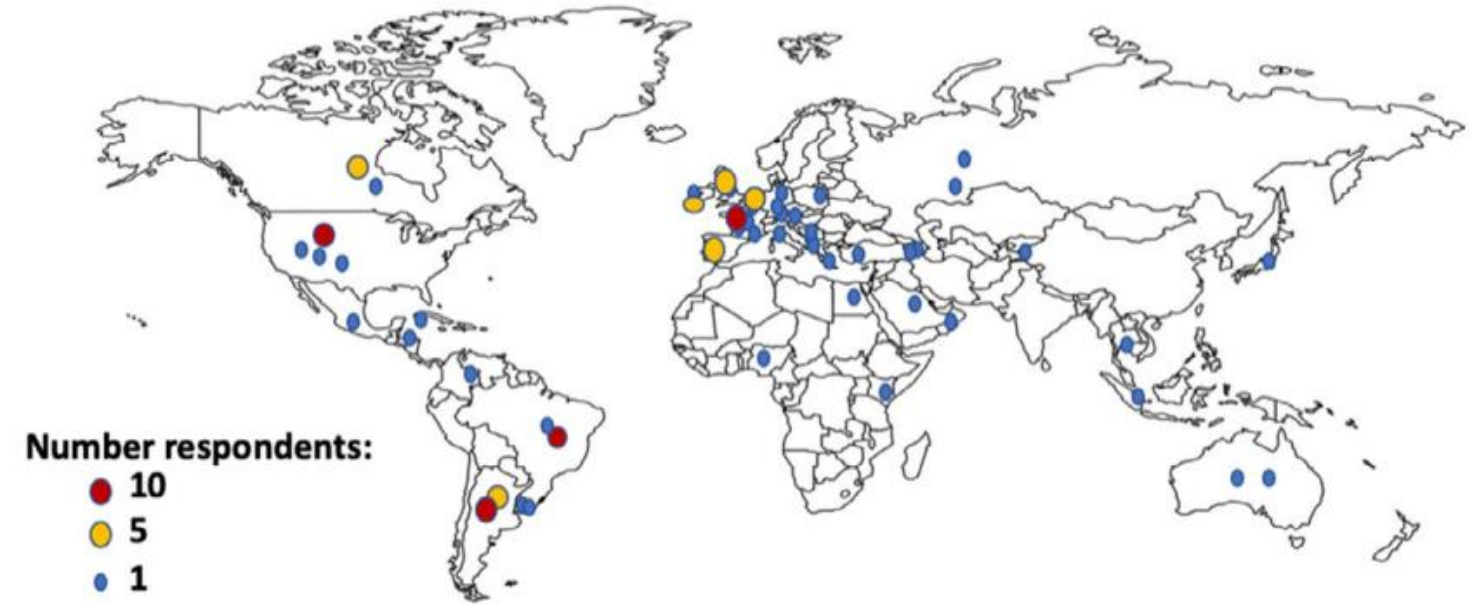
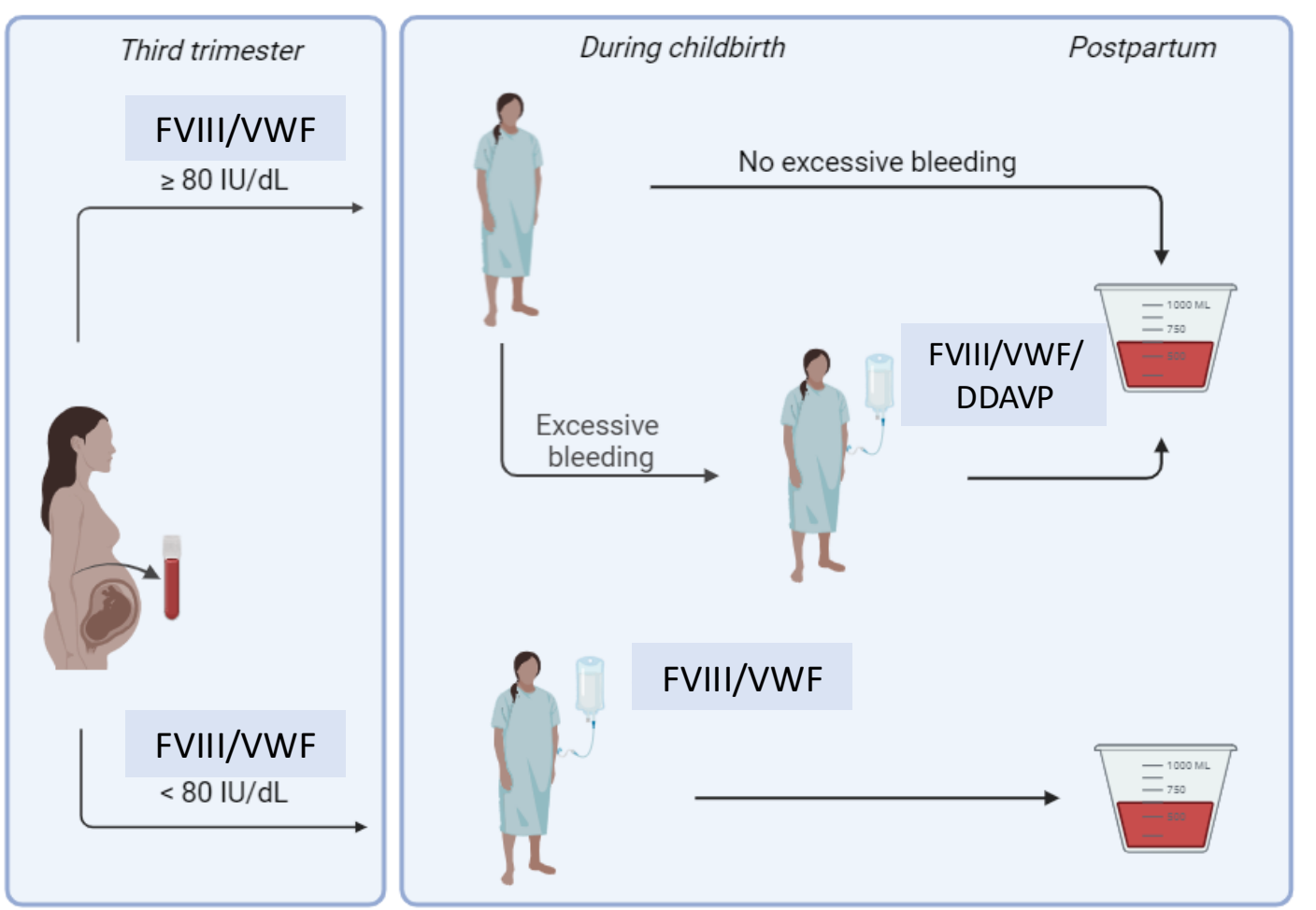


FIGURE 1 Geographical distribution of survey respondents: 10 participants indicated by red dot, 5 by yellow, single participant by blue dot

? Antenatal monitoring of VWF and ferritin levels
? Peripartum optimal VWF target levels
? Postpartum monitoring and PPH definitions
? Suitability for neuraxial anesthesia

Lavin et al. JTH 2021 (20) 82-91

Study design PRIDES study



Postpartum Hemorrhage in Women with von Willebrand Disease After Enhanced Prophylactic Clotting Factor Suppletion *Abstract 2595*

- ASH Poster session 323, Sunday, December 8, 6:00 PM - 8:00 PM

Definitions*

PPH > 1ltr <24hrs

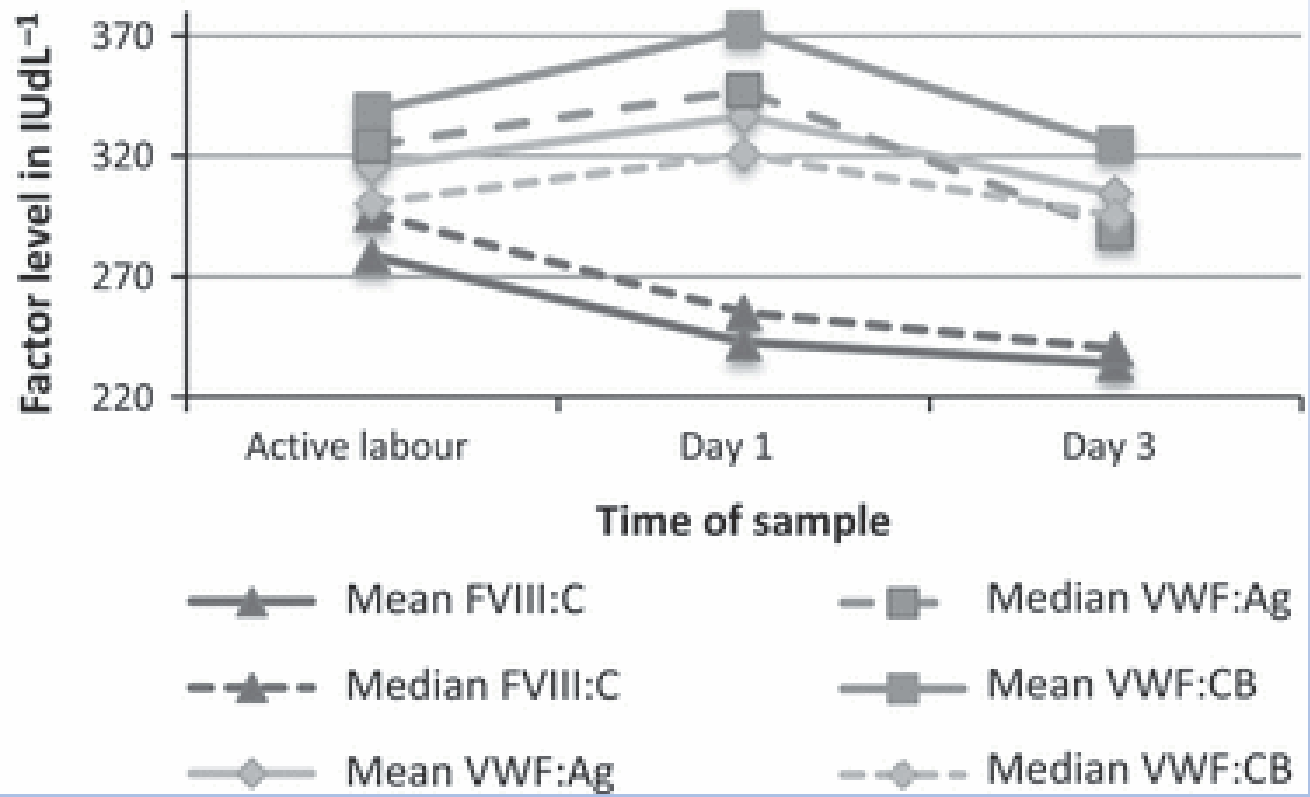
Late PPH bloodloss needing medical attention >24hr and <6w

*2021 VWD guidelines

Multidisciplinary (birth) delivery plan

- Under the direction of the HTC – first draft ready from week 24
- Stakeholders: HBC practitioner, gynaecologist, anaesthetist, obstetrician, paediatrician, clinical geneticist
- Contains at least:
  - The diagnosis with current coagulation results
  - Coagulation correction depending on the mode of parturition
  - Advice on neuraxial anaesthesia for anaesthetists
  - Policy regarding the child: atraumatic parturition?
  - Policy in case of post partum hemorrhage

Significant decrease of VWF/FVIII on day 3



Huq et al. Haemopilia 2012

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%

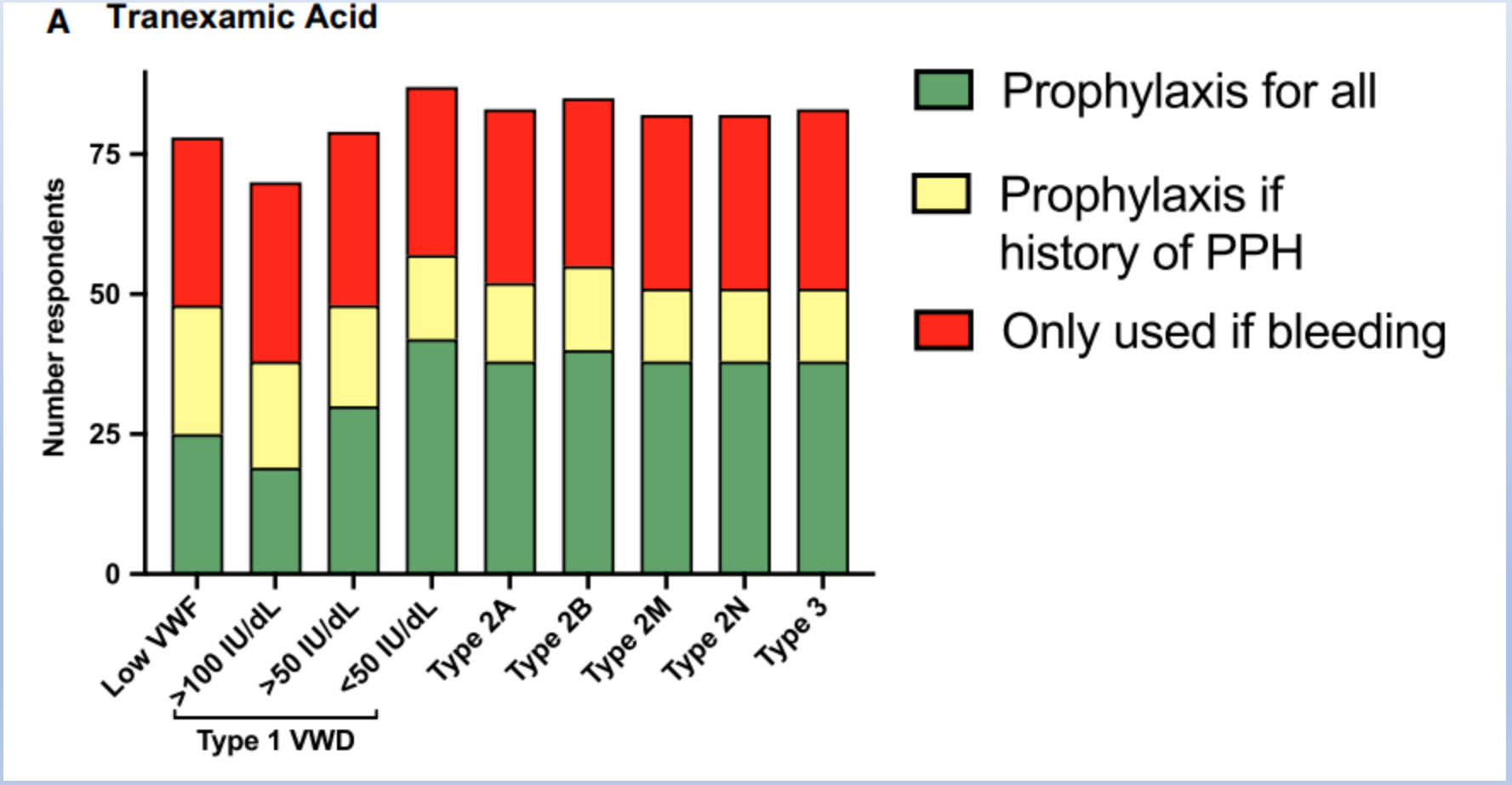
Adapted from Lavin et al, *STH* 2021

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

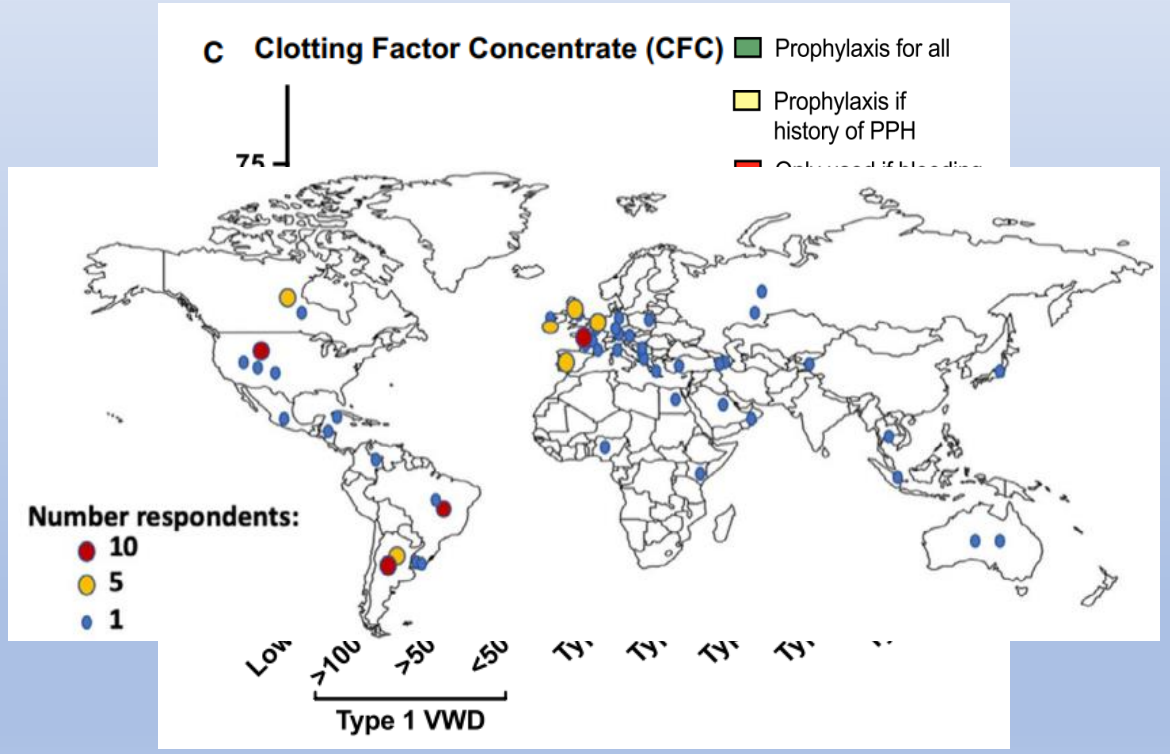
Connell et al. *Blood Adv* 2021

Varying international practices regarding prophylactic tranexamic acid post partum

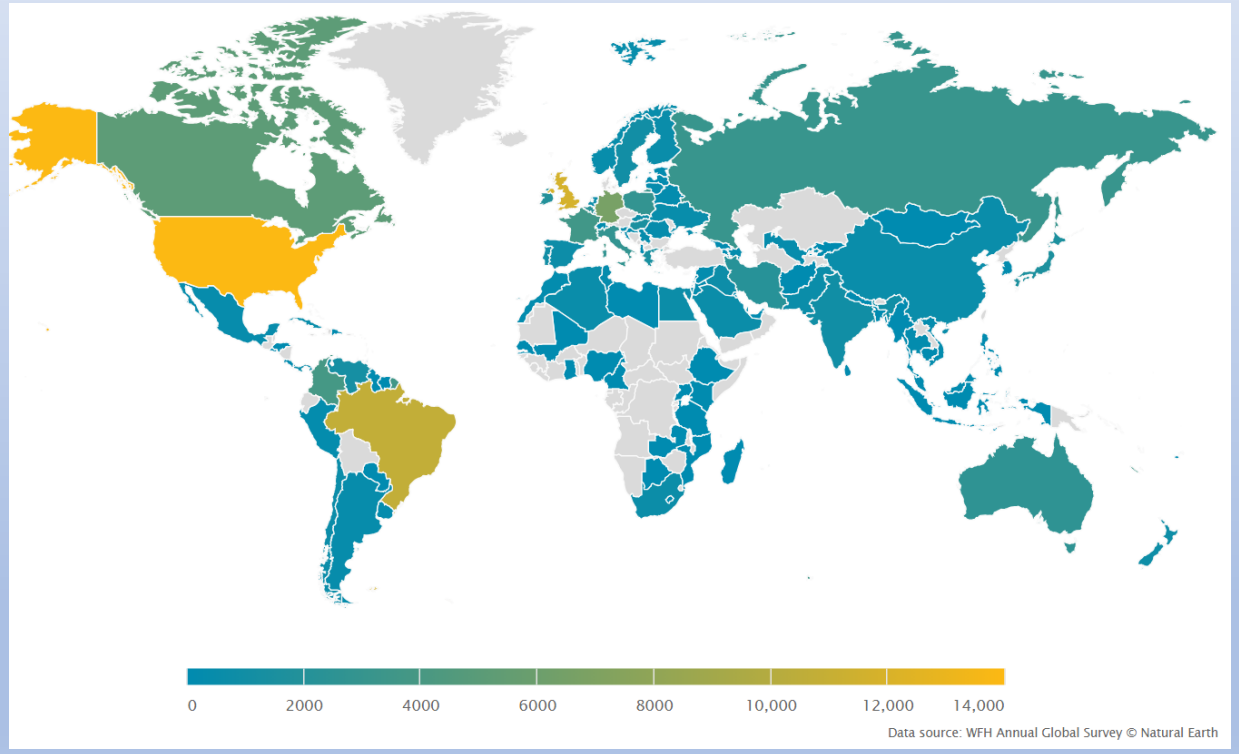


Lavin et al. JTH 2021 (20) 82-91

Global disparity in availability of CFC and VWD diagnostic testing

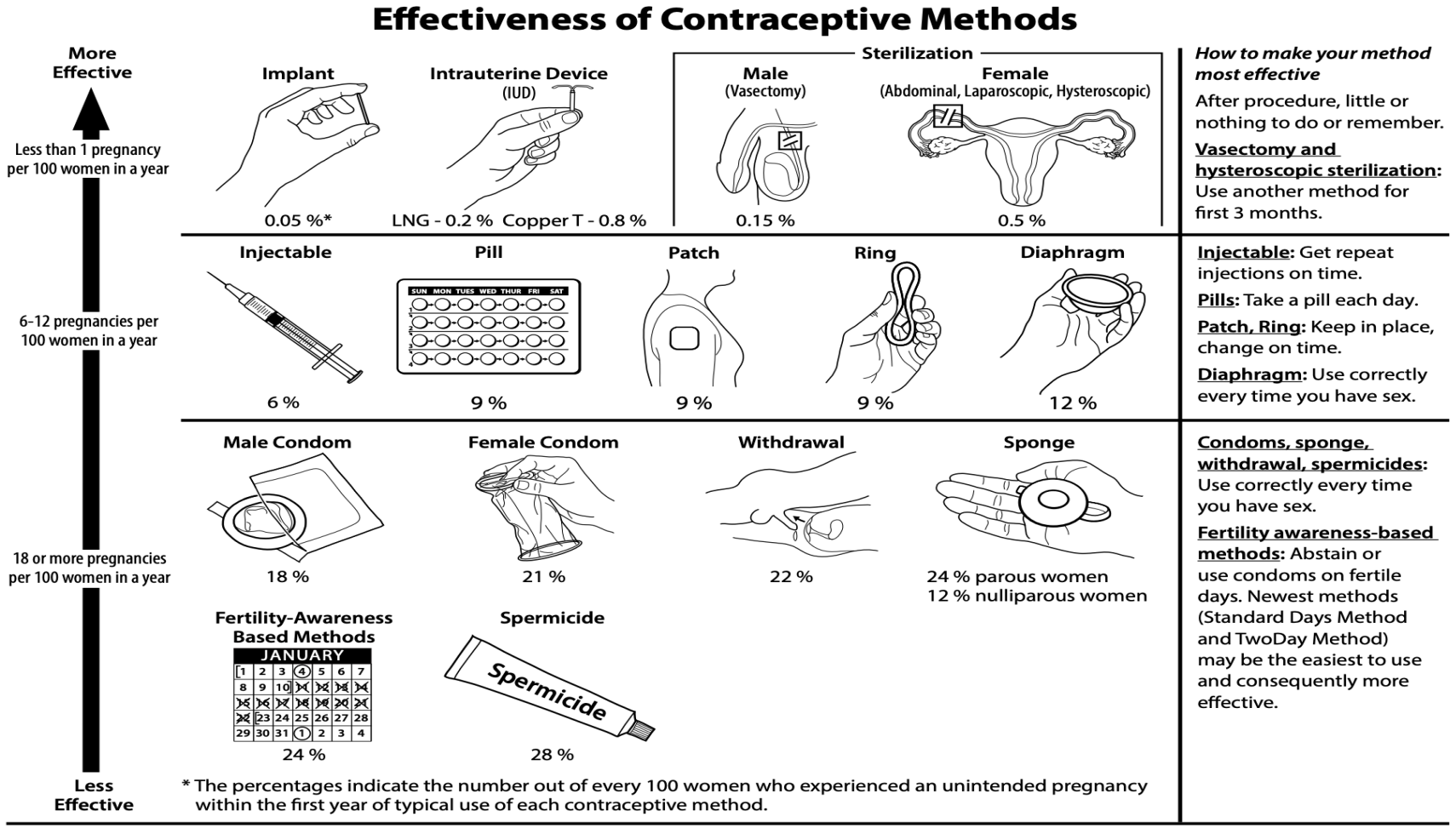


Lavin et al. JTH 2021 (20) 82-91



WFH'22: VWD Patients per 100,000, 0 means < 1 patient per 100,000 people
wfh.org

Postnatal care - contraceptive advice



U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

CONDOMS SHOULD ALWAYS BE USED TO REDUCE THE RISK OF SEXUALLY TRANSMITTED INFECTIONS.

Other Methods of Contraception

Lactational Amenorrhea Method: LAM is a highly effective, *temporary* method of contraception.

Emergency Contraception: Emergency contraceptive pills or a copper IUD after unprotected intercourse substantially reduces risk of pregnancy.

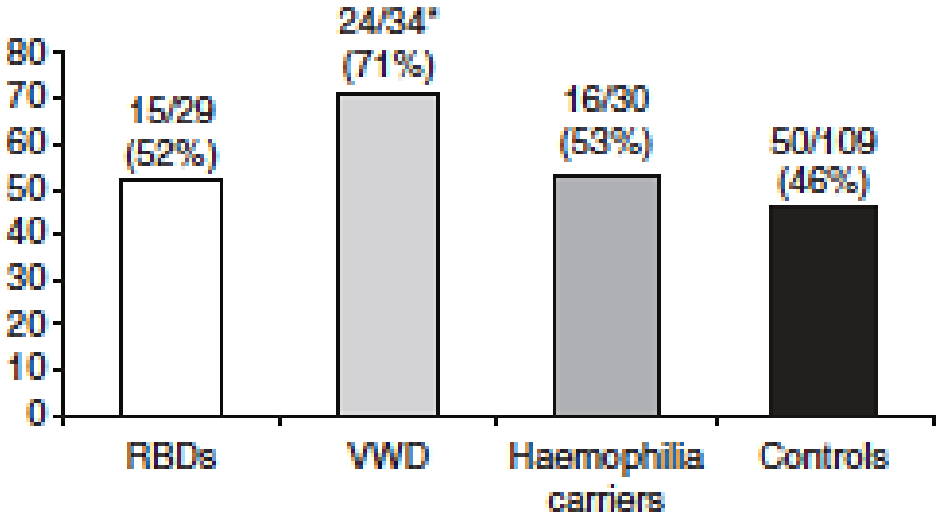
Adapted from WHO's Family Planning: A Global Handbook for Providers (2001) and Trussell et al (2011).

CS 231556

Women with VWD – heavy menstrual bleeding

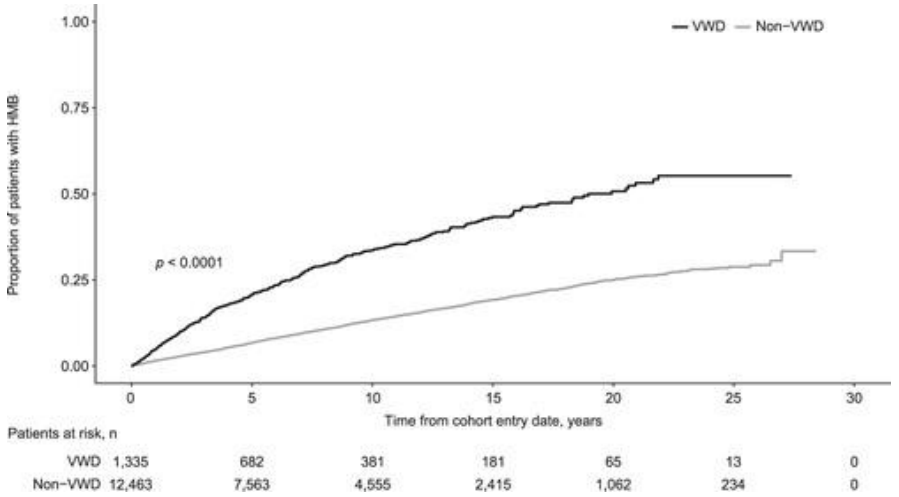
HMB - The commonest bleeding symptom in VWD

- HMB – overall 50–70% of WGBD[1]
- Iron deficiency anaemia in 20–40%



UK general practice population-based matched cohort[2]

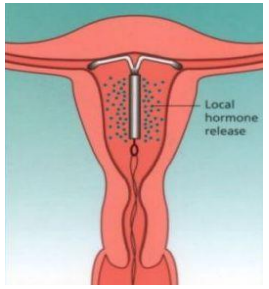
- Women with VWD vs. without VWD – IRR ≅ 3
- Median age first presentation – 5 years earlier



Cumulative incidence of HMB in women with or without VWD[2]

1. Kadir RA, et al. Haemophilia 1999;5:40–48; 2. Hagberg KW, et al. J Womens Health (Larchmt). 2022;31(9):1262–1270

Hormonal therapies – effective contraception and control of HMB



Levonorgestrel, 20 µg/24 hr suppresses endometrial growth

Levonorgestrel Intrauterine System

- Most effective LARC
- Most effective medical treatment for HMB

Discontinuation = 20%

- Irregular bleeding/ spotting
- Progestogenic side effects

(breast tenderness, bloatedness, headache)

Counselling and education improve acceptance and tolerability

Expulsion rate 0.5–8% - first 6 week - check up at 6 week

Perforation rate 1/1000

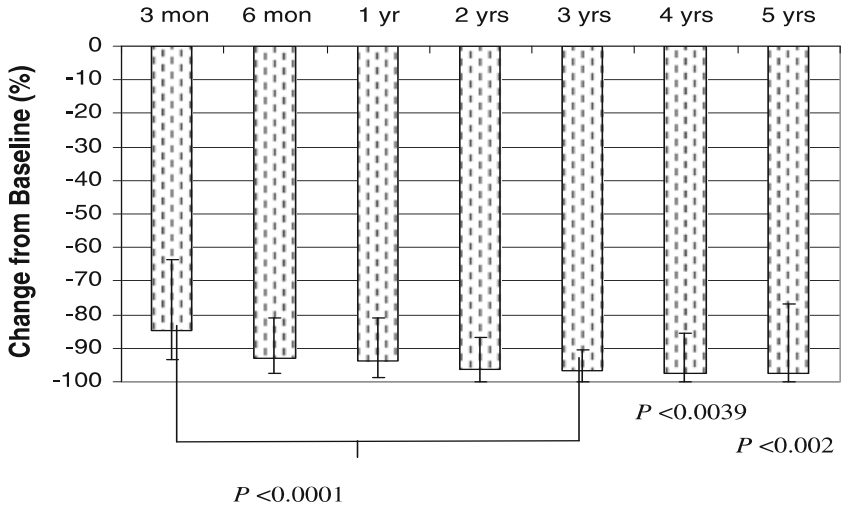
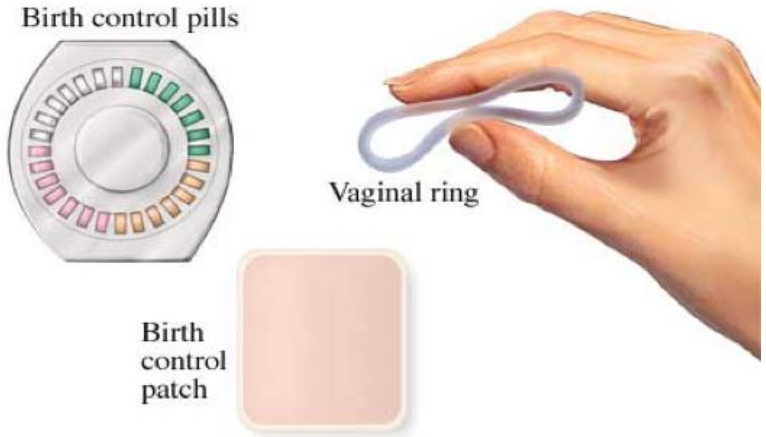


Fig. 1 Median % decrease of MBL (interquartile range) from baseline to up to 5 years of treatment (FAS)

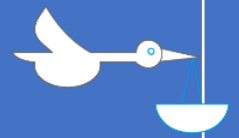
1. NICE guideline 88. 2011 (Updated December 2023). Available at: https://nice.org.uk/guidance/ng88. Accessed January 2024.

Other effective hormonal therapy

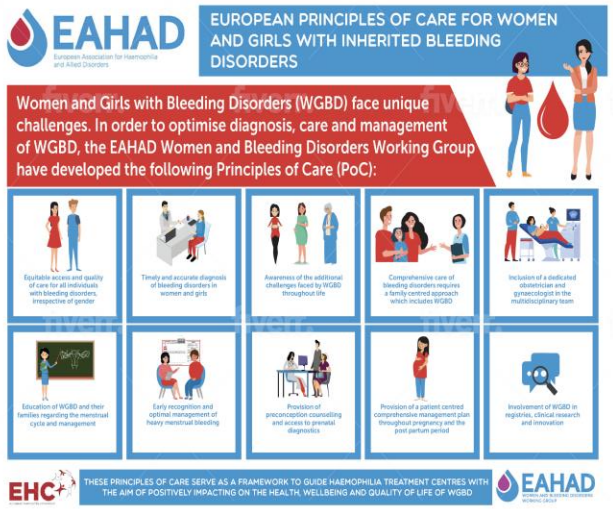
Combined hormonal contraceptives - containing estrogen and progestagen



- Effective contraception, good cycle control
- Controls menstrual pain and PMS
- Inhibit ovulation - prevent ovulation bleeding
- Extended use e.g. ‘tricycle’ - reduce menstrual episodes with limited complications

									
Life stage	**Childhood**	**Menarche Adolescence**	**HMB Young adulthood**	**(Pre) Conception**	**Pregnancy**	**Delivery**	**Breast feeding**	**HMB**	**Menopause**
Education needs	-Testing for clotting factor levels -Bleeding symptoms -Introduce MDT	-Normal menstrual cycle -Sexual education -ID(A) symptoms -Genetic testing	-PBAC -Ovulation bleeding -Hormonal suppression -Inheritance	-Genetic counselling -Choices including PGD -Current treatment perspectives	-PND -MD delivery plan	-Secondary PPH -ID(A) symptoms	-Safe use of TXA -Contracep-tion / hormonal suppression	-PBAC -Treatment options depending on fertility choices	-Hormonal suppression -Gynae input

Conclusions



https://youtube/nrgCMJBn4Uw

- Women with VWD – are at risk bleeding symptoms and face different challenges during different stages of their reproductive life
- Should any women with VWD be advised against pregnancy to avoid complications – NO
- Women with VWD can have a safe pregnancy and delivery
  - Early diagnosis and treatment through increased awareness and education of WGBD and HCP
  - Access to HTC and management by joint multi-disciplinary team for preconceptual care and pregnancy care
  - MDT birth plan
  - Regular FU and review to optimize health and QOL and provide family planning advice

Essentials

- There is limited published evidence regarding the optimal management of pregnant women with VWD
- Significant variations in clinical practice exists, especially regarding neuraxial anesthesia
- The optimal plasma von Willebrand factor therapeutic targets and treatment approaches in preventing post partum hemorrhage remain to be elucidated
- Iron supplementation, postpartum surveillance and pre-emptive (prescription) of tranexamic acid are mandatory
- More effort is needed to reduce global inequity in care for (pregnant) women with von Willebrand disease