FEBRUARY 24, 2023

Management of Inherited Bleeding Disorders in Obstetrics and Gynecology

Tricia Huguelet, MD
Associate Professor
Section Chief, Pediatric and Adolescent Gynecology
Medical Director, Spots and Dots Clinic, Hemophilia and Thrombosis Center

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Learning Objectives

1. Recognize the **prevalence** of Von Willebrand's Disease and mild platelet function defects in patients presenting for obstetric and gynecologic care
2. Discuss optimal **treatment of acute and chronic heavy menstrual bleeding** in the gynecologic patient with an inherited blood disorder
3. Review best practices in patients undergoing **gynecologic surgery** in the setting of an inherited blood disorder
4. Discuss management strategies for the **laboring patient** with an inherited blood disorder

Prevalence of Inherited Bleeding Disorders in Patients Presenting for ObGyn Care

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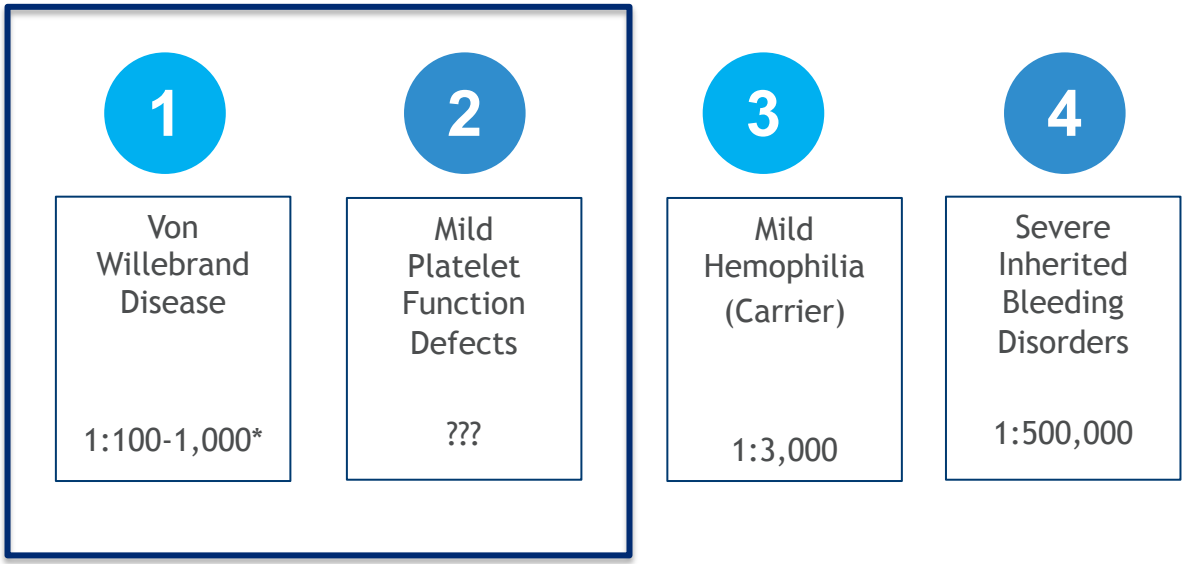
Overview of Bleeding Disorders in Patients with a Uterus

- Inherited Bleeding Disorders affect up to 1% of females in the United States
- 20-30% of women experience heavy menstrual bleeding **and up to 25%** will be diagnosed with an inherited bleeding disorder
- Up to 25% women with severe PPH (> 2liters) will be diagnosed with an IBD

Prevalence of Inherited Bleeding Disorders



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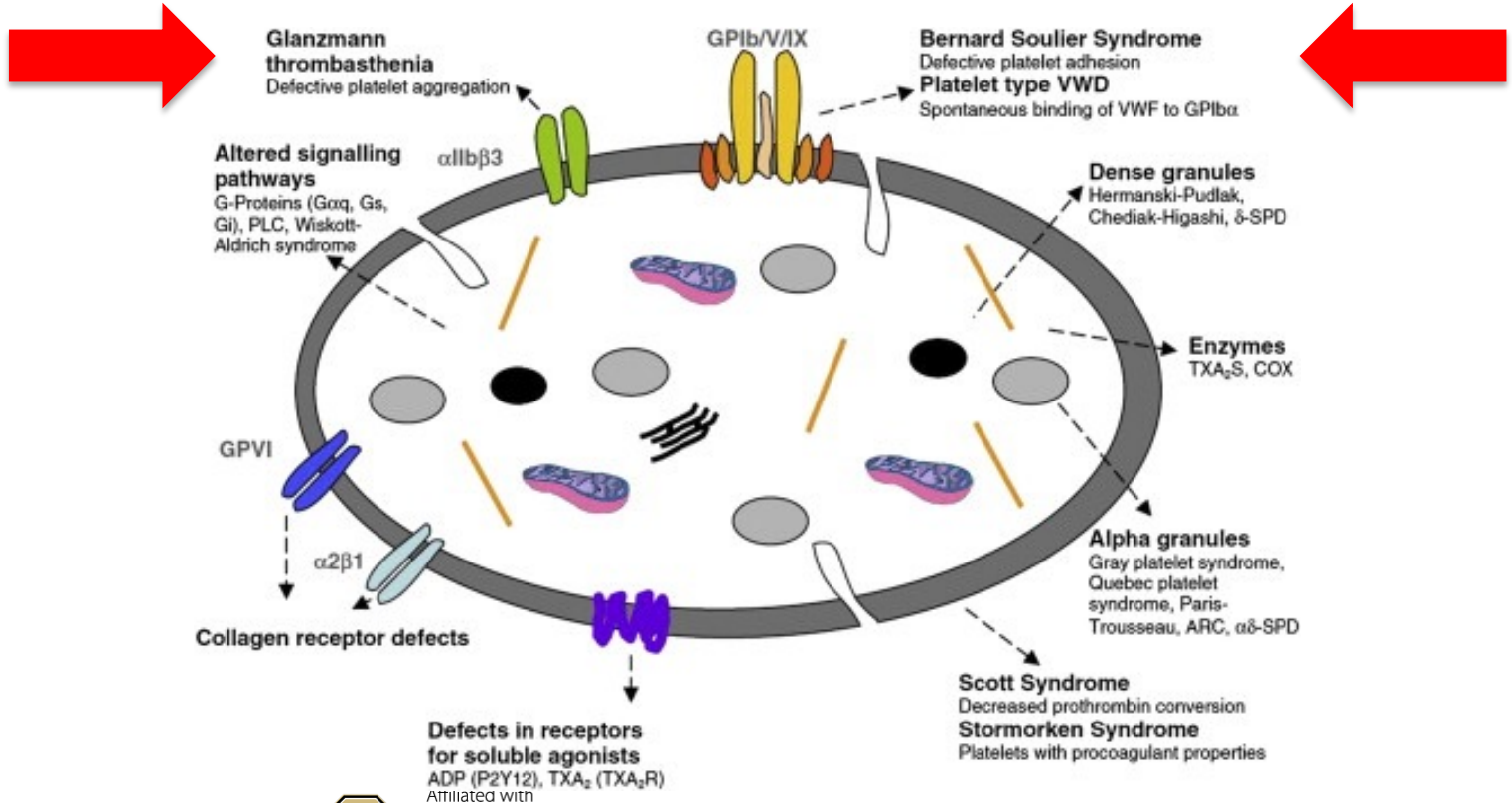
*Type 3 = 1 in 1,000,000

Von Willebrand Disease

Type	Prevalence within VWD	Pathophysiology
Type 1	70–80%	Quantitative defect (reduced absolute amount of VWF) Normal function
Type 2	20%	Qualitative defect (abnormal function)
Type 2A		Loss of high molecular weight multimers
Type 2B		Increased binding of VWF to platelets
Type 2M		Decreased binding of VWF to platelets
Type 2N		Decreased binding of VWF to FVIII
Type 3	Rare (3–5 cases per million)	Quantitative defect (virtual absence of VWF)

Inherited Platelet Disorders



Upwards of 30% of women experience heavy menstrual bleeding in their lifetime

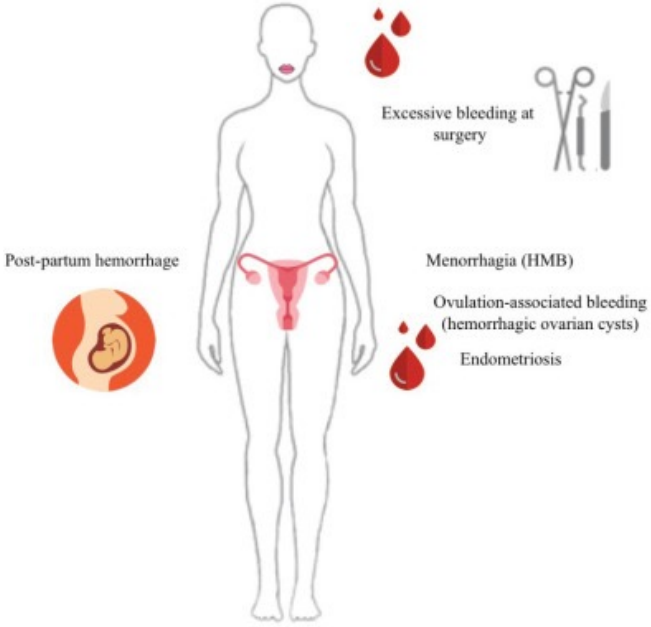
CDC Registry - Symptoms in VWD (n = 319)

Symptoms	Proportion of Patients (%)
Heavy menstrual bleeding	76
Excessive bruising	55
Epistaxis	48
Oropharyngeal bleeding	29
Post-dental procedure bleeding	35
Post-surgical bleeding	37
Excessive bleeding from minor wounds	48
Joint bleeding	16
Muscle bleeding	8

Inherited Platelet Disorders

- Bleeding severity is variable but generally **much more severe** with Glanzmann Thrombasthenia and Bernard-Soulier Syndrome

- Typical clinical symptoms are mucocutaneous bleeding
  - Heavy menstrual bleeding
  - Epistaxis
  - Gum bleeding
  - Ecchymoses (superficial)
  - Surgical bleeding



Lowe, Platelets 2019

Management of Acute and Chronic HMB in Patients with IBDs

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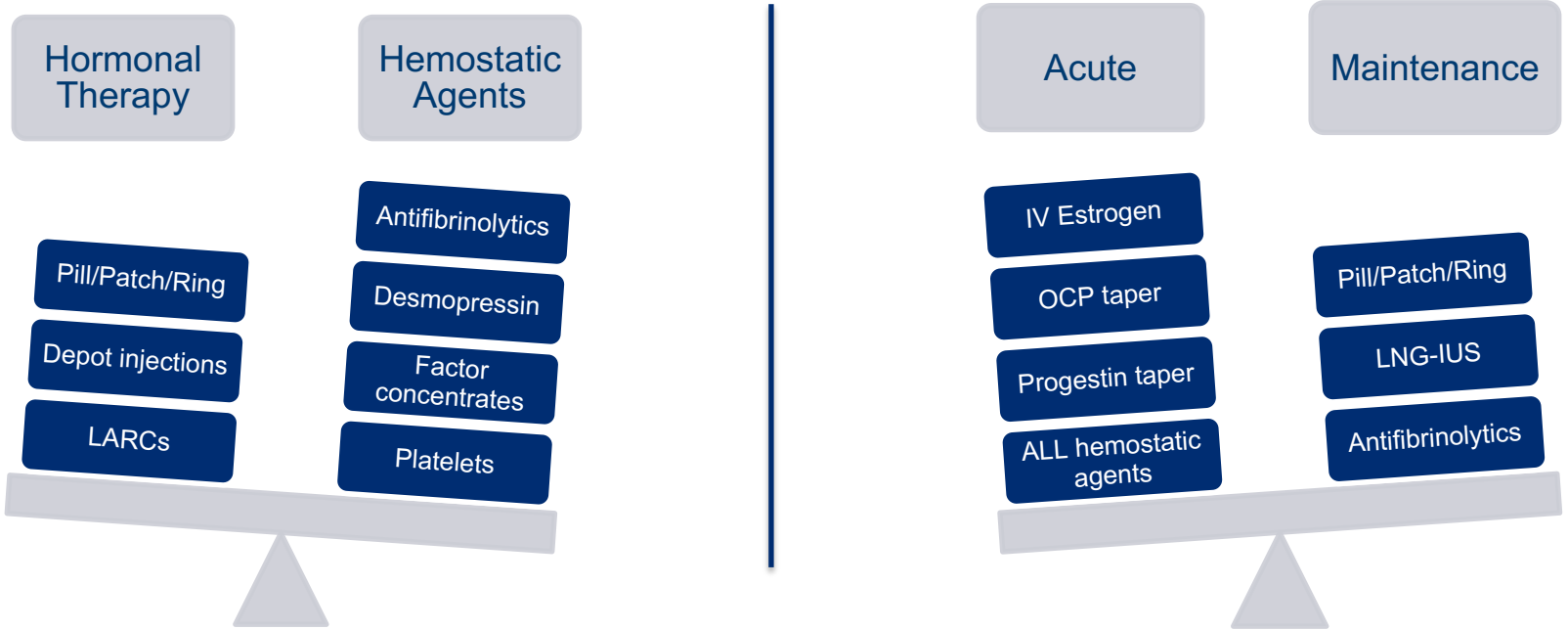
Treatment Approach



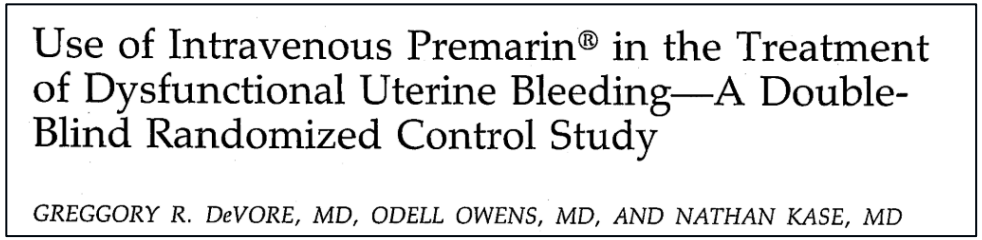
CDC Registry – Treatments for HMB (n= 165)

Symptoms	Prevalence
Oral contraceptives	54.5%
Desmopressin	33.9%
Antifibrinolytics	24.2%
Blood or plasma products	7.3%
Clotting factor products	6.1%
Endometrial ablation	4.2%
Levonorgestrel IUD	3%
Uterine artery embolization	3%
Hysterectomy	10.6%

Acute Management of HMB

Hormonal	Non-Hormonal	IV Iron Therapy
Combined Contraceptive Pill Taper *Ethinyl estradiol 35mcg/norgestimate 0.25mg* *PO*	Tranexamic acid *10mg/kg IV TID* *1300mg PO TID*	Iron Sucrose or Ferric Carboxymaltose
Progestin Taper *Norethindrone acetate TID (15mg)* *Medroxyprogesterone acetate TID (60mg)* *PO*	Aminocaproic acid *100mg/kg IV QID* *500mg PO QID*	
Conjugated equine estrogen *Premarin 25mg q 4hrs x 6 doses* *IV*	Desmopressin *IV, IN or SQ*	
Leuprolide acetate *3.75 or 11.25mg* *IM*	VWF Concentrate *IV*	
** Don't' forget foley balloon tamponade!	Platelet transfusion *IV*	
	Recombinant FVII *IV*	

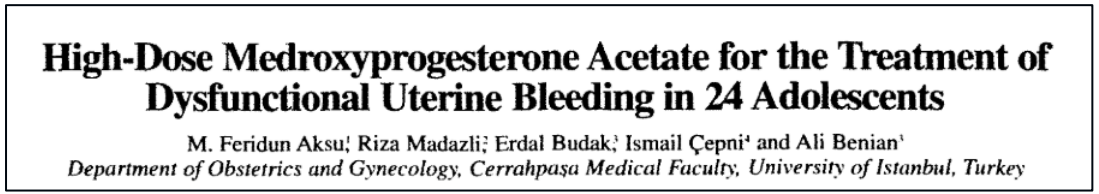
Acute Hormonal Management



Use of Intravenous Premarin® in the Treatment of Dysfunctional Uterine Bleeding—A Double-Blind Randomized Control Study

GREGGORY R. DeVORE, MD, ODELL OWENS, MD, AND NATHAN KASE, MD

- IV CEE 25mg IV q 4 hrs
- Results: 72% vs 38% at 2 doses



High-Dose Medroxyprogesterone Acetate for the Treatment of Dysfunctional Uterine Bleeding in 24 Adolescents

M. Feridun Aksu, Riza Madazli, Erdal Budak, Ismail Çepni and Ali Benian

Department of Obstetrics and Gynecology, Cerrahpaşa Medical Faculty, University of Istanbul, Turkey

- MPA PO 60-120mg Day 1, 20mg QD
- Results: 25% 24 hours, 100% 96 hours

Oral Medroxyprogesterone Acetate and Combination Oral Contraceptives for Acute Uterine Bleeding

A Randomized Controlled Trial

Malcolm G. Munro, MD, Nakia Mainor, MD, Romie Basu, MD, Mikael Brisinger, MD,

- Ortho-Cyclen TID taper vs MPA 20mg TID taper
- Results: Median cessation 3 days, no difference

Maintenance Hormonal Management of HMB

Hormonal	Non-Hormonal	Iron Therapy
Combined contraceptive pill *PO*	Tranexamic acid *PO*	Ferrous sulfate *PO*
Progesterone only pill (norethindrone or MPA) *PO*	Aminocaproic acid *PO*	
Combined contraceptive patch	Desmopressin *IN or SQ*	
Combined ring		
Depot MPA *IM*		
Levonorgestrel intrauterine device		

Treatment of HMB: Levonorgestrel IUS

Cochrane Library

Cochrane Database of Systematic Reviews

Progestogen-releasing intrauterine systems for heavy menstrual bleeding (Review)

- **Cochrane 2020**: 25 RCTs (n=2511) – LNG-IUS *superior* to other medical therapies in reduction in MBL, equal efficacy to ablation, uncertain if better or worse than hysterectomy
- **Cochrane 2022**: 9 systematic reviews in Cochrane Library through July 2021. Reaffirmed LNG-IUS is the best first-line treatment for reducing MBL, followed by antifibrinolytics.

Treatment of HMB + IBD: Levonorgestrel-IUS

Levonorgestrel-releasing intrauterine system for the management of heavy menstrual bleeding in women with inherited bleeding disorders: long-term follow-up☆

Claudia Chi[a,b], Farah Y. Huq[b], Rezan A. Kadir[a,b,*]

→ Significant improvement in PBAC (255 → 35), Hb and QOL

Levonorgestrel-Releasing Intrauterine Device Use in Female Adolescents with Heavy Menstrual Bleeding and Bleeding Disorders: Single Institution Review

Oluyemisi A. Adeyemi-Fowode MD [1,2,*], Xiomara M. Santos MD [1], Jennifer E. Dietrich MD, MSc [1,2], Lakshmi Srivaths MD [1,3]

→ Significant improvement in Hb + Ferritin, 60% amenorrhea

Use of the Levonorgestrel Intrauterine System to Treat Heavy Menstrual Bleeding in Adolescents and Young Adults with Inherited Bleeding Disorders and Ehlers-Danlos Syndrome

Patricia S. Huguelet [1,*], JL Laurin [2], D Thornhill [3], G Moyer [4]

→ 62% amenorrhea Mean continuation 5.08 years

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Chi Contraception 2011, AF JPAG 2017, PH JPAG 2022

Non-Hormonal Management of HMB in Patients with IBDs

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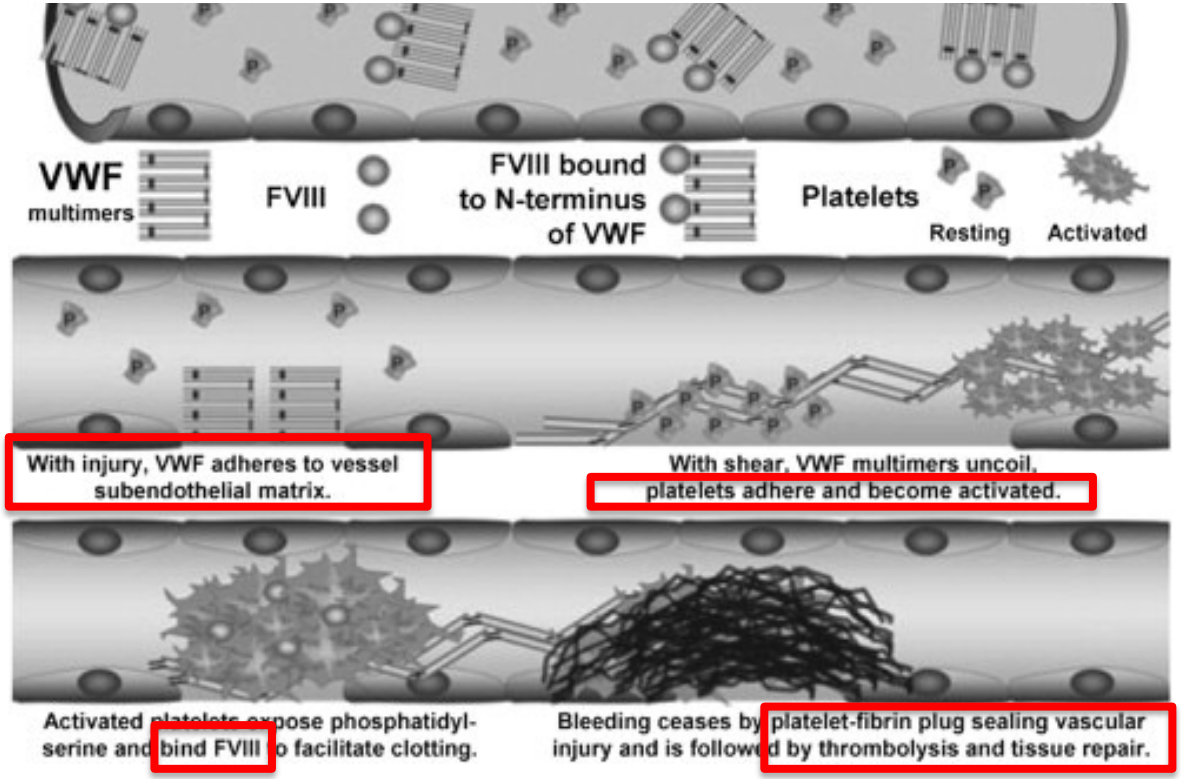
Platelets and VWF in Primary Hemostasis



DDAVP

VWF

Platelets

TXA

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Matthews. Pediatric Clin North Amer, 2013

Maintenance Management of HMB

Hormonal	Non-Hormonal	Iron Therapy
Combined contraceptive pill *PO*	Tranexamic acid *PO*	Ferrous sulfate *PO*
Progesterone only pill (norethindrone or MPA) *PO*	Aminocaproic acid *PO*	
Combined contraceptive patch	Desmopressin *IN or SQ*	
Combined ring		
Depot MPA *IM*		
Levonorgestrel intrauterine device		

Treatment HMB: Antifibrinolytics

Tranexamic Acid Treatment for Heavy Menstrual Bleeding

A Randomized Controlled Trial

Reduction in MBL
40.4% vs. 8.2%

- 196 adult women with HMB (80cc MBL) randomized to TXA vs. Placebo for 6 cycles

Antifibrinolytics for heavy menstrual bleeding (Review)

- **Cochrane 2018**: 13 RCTs (n=1312) TXA versus placebo, progestins, NSAIDs, and LNG-IUS
- **Conclusion**: TXA more effective than progestins and NSAIDS at reducing HMB, but less than LNG-IUS

Maintenance Management of HMB

Hormonal	Non-Hormonal	Iron Therapy
Combined contraceptive pill *PO*	Tranexamic acid *PO*	Ferrous sulfate *PO*
Progesterone only pill (norethindrone or MPA) *PO*	Aminocaproic acid *PO*	
Combined contraceptive patch	Desmopressin *IN or SQ*	
Combined ring		
Depot MPA *IM*		
Levonorgestrel intrauterine device		

Desmopressin (DDAVP)

- **Treatment option for Mild VWD and Mild Platelet Dysfunction**
- Adjunct to antifibrinolytic therapy

Route	Dose
Intranasal	< 50kg: 150mcg (1 spray) > 50kg: 300mcg (2 sprays)
Subcutaneous	0.3 mcg/kg (max 20mcg)
Intravenous	0.3 mcg/kg (max 20mcg)

- Variable routes of administration
- FVIII and VWF levels increase 2-4 fold
- Maximum levels occur 30-60 minutes after IV and 30-120 minutes after intranasal
- Administer with menses onset and repeat at 12-24 hour intervals, for the first 2-3 days of menses

- Side effects include facial flushing, headaches and nausea
- Limit free water intake for 24 hours after administration

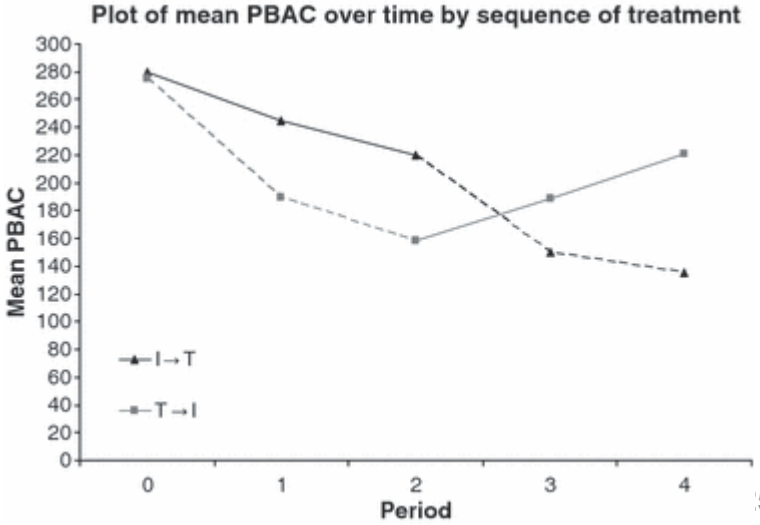
HMB Tx: Oral Tranexamic Acid vs DDAVP

bjh research paper

Multisite management study of menorrhagia with abnormal laboratory haemostasis: a prospective crossover study of intranasal desmopressin and oral tranexamic acid

- RCT Crossover study of 116 women with HMB over 4 menstrual cycles

- Normalization of MBL defined as PBAC < 100
  - 22% DDAVP group
  - 33% TXA group
- Both groups had significant improvement in QOL



Kouides, 2009 BJ Haemotology

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Maintenance Management of HMB

Hormonal	Non-Hormonal	Iron Therapy
Combined oral contraceptive pills	Tranexamic acid oral	Ferrous sulfate
Progesterone only pills	Aminocaproic acid	
Combined patches		
Combined rings		
Progesterone injections		
Levonorgestrel intrauterine device		

Approach to Oral Iron Therapy

IDA Severity	Recommended Dosing
Moderate (Hb 7-10) - Severe (Hb <7)	Ferrous sulfate 2 tablets once daily *(130mg elemental iron)*
Mild (Hb 10-11)	Ferrous sulfate 1 tablet daily *(65mg elemental iron)*
Iron deficiency without anemia (Hb ≥ 12)	Ferrous sulfate 1 tablet every other day

* Continue oral iron therapy for minimum of 3 months and then repeat ferritin

Optimizing Patient Outcome at Time of Gynecologic Surgery

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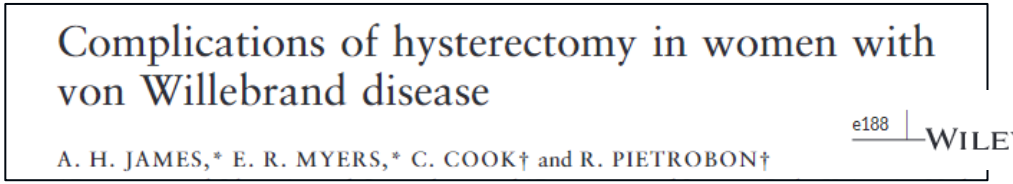
Complications of Hysterectomy in VWD


Complications of hysterectomy in women with von Willebrand disease

A. H. JAMES,* E. R. MYERS,* C. COOK† and R. PIETROBON†

e188 WILEY–Haemophilia

- Estimate incidence of bleeding and other complications in women with VWD undergoing hysterectomy
- Nationwide Inpatient Sample from the Healthcare Cost and Utilization Project of the AHRQ
- Queried all hospital discharge codes for hysterectomy from 1988-2004

- 545 hysterectomies in women with VWD vs 1,357,588 without VWD
- **VWD women younger, higher rates of HMB**

Complications of Hysterectomy in VWD

Complications of hysterectomy in women with von Willebrand disease

A. H. JAMES,* E. R. MYERS,* C. COOK† and R. PIETROBON†

e188 WILEY–Haemophilia

Outcome	Women with VWD	Women Without VWD	P-value
Intraop or Postoperative Bleeding	15 (2.75%)	11, 678 (0.86%)	< 0.001
Blood Transfusion	40 (7.34%)	28, 957 (2.13%)	< 0.001
Infection	4 (0.73%)	5,203 (0.38%)	0.159
DVT/PE	0	1493 (0.11%)	1.000

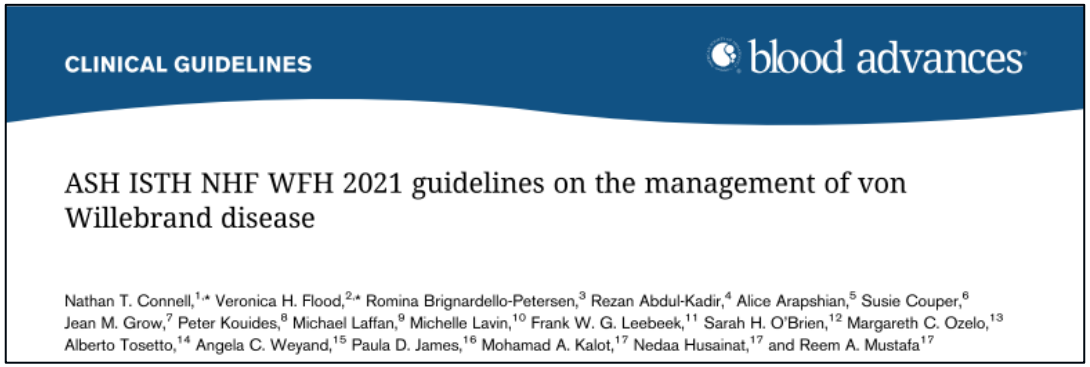
How well do we screen women undergoing surgery for HMB?

- Truven Health MarketScan Research Database (insurance claims database), queried for females age < 40 with HMB undergoing hysterectomy, endometrial ablation, UAE or HSC/D&C
- Excluded patients with fibroids, malignancy of genital tract or previous diagnosis of IBD
- Defined screening as VWF Ag or VWF Activity in prior 12 months
- 8998 women met inclusion criteria
  - 57 women (0.6%) were screened for VWD
  - 1276 women (14%) had coagulation tests (PT, PTT)

Von Willebrand disease screening in women undergoing hysterectomy for heavy menstrual bleeding

e188 WILEY–Haemophilia

Guidelines for Surgery Prophylaxis


CLINICAL GUIDELINES

blood advances

ASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand disease

Nathan T. Connell,[1,*] Veronica H. Flood,[2,*] Romina Brignardello-Petersen,[3] Rezan Abdul-Kadir,[4] Alice Arapshian,[5] Susie Couper,[6] Jean M. Grow,[7] Peter Kouides,[8] Michael Laffan,[9] Michelle Lavin,[10] Frank W. G. Leebeek,[11] Sarah H. O'Brien,[12] Margareth C. Ozelo,[13] Alberto Tosetto,[14] Angela C. Weyand,[15] Paula D. James,[16] Mohamad A. Kalot,[17] Nedaa Husainat,[17] and Reem A. Mustafa[17]

- Limited high-level evidence to guide recommendations
- No clear guidelines to define minor versus major surgery
- Not all bleeding disorders result in same bleeding phenotype
- Risks of VWF Concentrate include inducing inhibitor formation & hypersensitivity reactions
- **Obtaining individualized expert opinion from hematologists and gynecologists with experience managing these patients is critical**

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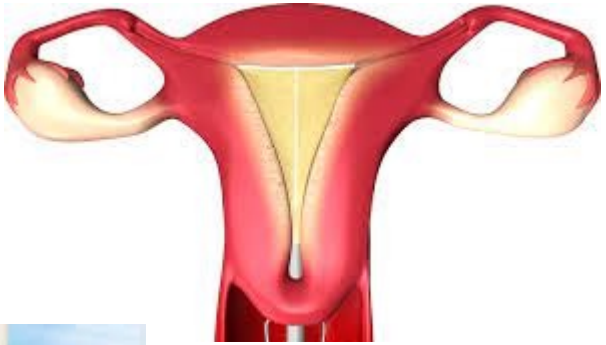
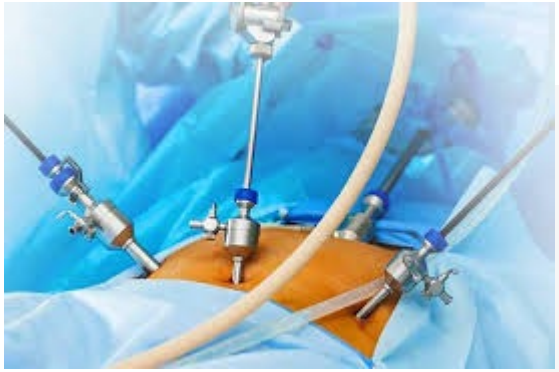
Connell, 2020. Blood Advances.

Surgery Prophylaxis - Minor

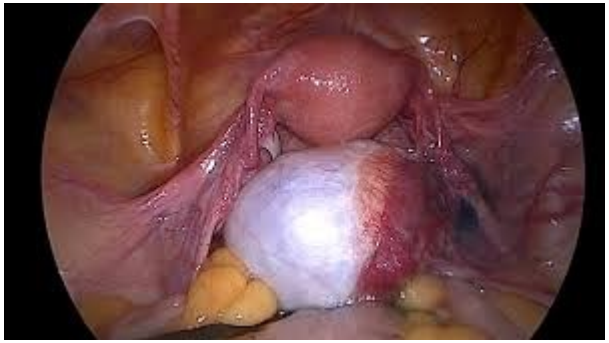


- Avoid NSAIDs and Aspirin preoperatively and postoperatively
- Minor Procedures: Type 1 VWD and Type 2 A-N-M
  - **Tranexamic acid**
  - 1300mg PO TID
  - 1000mg IV (10mg/kg)
- Minor Procedures: Type 2 B and 3
  - **TXA and VWF Concentrate**
  - TXA 1300mg PO TID vs IV
  - VWF 40-60 units IV/kg

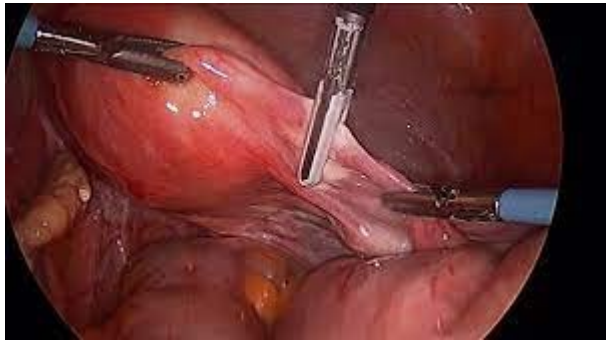


Laffan, 2020. Haemophilia
Connell, 2020. Blood Advances.

Surgery Prophylaxis - Major



- Major Procedures: Type 1
  - **DDAVP**
  - 0.3mcg/kg IV or SQ (max 20mcg)
  - Optimal to confirm DDAVP response before using, but patients likely to respond if VWF > 0.30 IU/mL
  - Limit fluid intake to < 1 Liter given anti-diuretic activity



- Major Procedures: Type 2 and Type 3
  - **VWF Concentrate (Humate-P)**
  - 40-60 units IV/kg

- **Goal: FVIII and VWF Activity ≥ 0.50 for at least 3 days postop**

Laffan, 2020. Haemophilia
Connell, 2020. Blood Advances.

Labor Management

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Overview of Bleeding Disorders in Patients with a Uterus

Journal of Thrombosis and Haemostasis, **5**: 1165–1169

ORIGINAL ARTICLE

Bleeding events and other complications during pregnancy and childbirth in women with von Willebrand disease

A. H. JAMES and M. G. JAMISON
Department of Obstetrics and Gynecology, Duke University Medical Center, Durham, North Carolina, USA

- National Inpatient Sample (NIS) Database queried for hospital discharges for pregnancy and VWD
- 4067 deliveries with VWD
- **Increased risk for PPH (OR 1.5, CI 1.1-2.0) and 5-fold increased risk of blood transfusion**
- **Maternal mortality rate was 10x higher than controls (5 of 4067)**

Physiologic Coagulation Changes of Pregnancy

1	2	3
INCREASED	DECREASED	UNCHANGED
FACTOR VII	Factor XI	Factor II
FACTOR VIII	Factor XIII	Factor V
Factor IX	Protein S	Factor IX
Factor X		Platelets
Factor XII		
VWF		
Fibrinogen		
PAI-1		

VWD Management - Antepartum

- Preconception counseling
- Multidisciplinary care with Hematology, Obstetrics and Anesthesiology
- FVIII and VWF levels should be obtained at the following time-points during pregnancy
  - Active bleeding any trimester
  - Planned invasive procedures
  - 34-36 weeks gestation
- Goal: Factor levels > 50% with active bleeding, invasive procedures, and labor

Reynen, James. Semin Thromb & Hemost, 2016
Weyan. Hematol Onc Clin North Amer, 2021

VWD Management – Intrapartum

- VWF Levels < 50% have increased risk of bleeding at delivery and postpartum
- Admit labs: CBC, PT/PTT, VWF Ag, VWF Activity, FVIII level
- Women with factor levels > 50% should be offered the option of regional anesthesia
- Vaginal delivery is generally considered safe for VWD and Mild Platelet Disorders, but a prolonged second stage should be avoided
- Operative delivery and intrapartum invasive procedures should be avoided until the status of the fetus is confirmed

Reynen, James. Semin Thromb & Hemost 2016
Pacheco. Obstet Gynecol 2024

Treatment Options by VWD Type

Type	Recommended initial treatment when FVIII or VWF:RCo is <0.50 IU/mL
Type 1	DDAVP
Type 2	DDAVP factor concentrate
Type 2A	DDAVP factor concentrate
Type 2B	*Avoid DDAVP* First line factor concentrate
Type 2M	DDAVP factor concentrate
Type 2N	DDAVP factor concentrate
Type 3	Factor concentrate

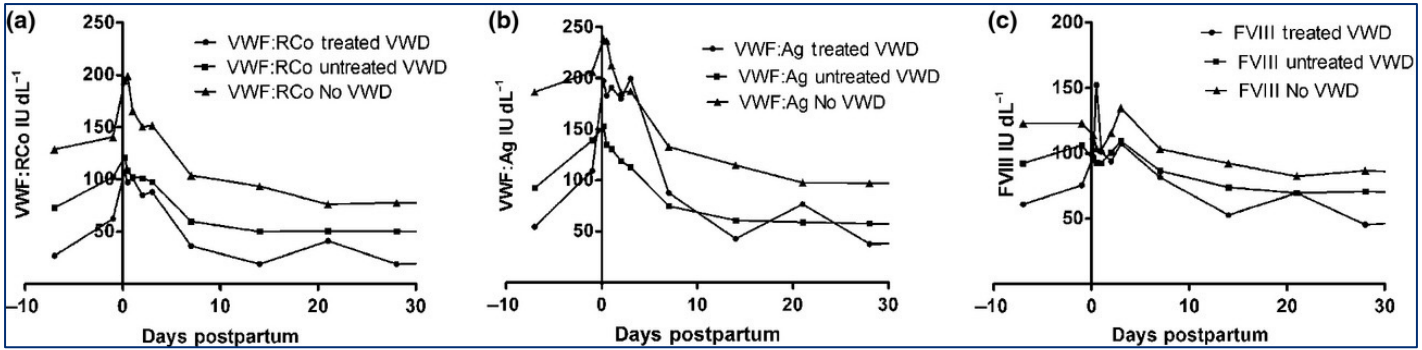
DDAVP

- 0.30 mcg/kg IV over 30 minutes

VWF Concentrate

- 40-80 units/kg IV load
- 20-40 units/kg IV q 12 hours

VWD Management - Postpartum



- VWF and FVIII levels persist until 48hours pp and then began to decline to pre-pregnancy levels
- Levels approach baseline by one week postpartum and reach baseline by 3 weeks pp
- Risk of PPH is elevated in VWD compared to controls, particularly DELAYED PPH

- **Maintain VWF levels > 0.50 IU/mL for 3 days post-SVD and 5 days post-C/S**
- **Prescribe Tranexamic acid 1300mg PO TID for 10-14 days postpartum**

Pacheco. Obstet Gynecol 2024
Reynen, James. Semin Thromb & Hemost 2016
James. Haemophilia 2014

How well do we follow the guidelines?

- Truven Health MarketScan Research Database, queried database for patients with confirmed VWD Diagnosis and Live Delivery
- 2238 pregnant women with VWD, 2009 - 2013
- Aim = Assess frequency of 3rd trimester VWF labs

Laboratory monitoring during pregnancy and post-partum hemorrhage in women with von Willebrand disease

Sarah H. O'Brien[1,2] | Joseph R. Stanek[1] | Dominder Kaur[3] | Katherine McCracken[4] | Sara K. Vesely[5]

How well do we follow the guidelines?

- 32% (n = 714) had 3rd trimester VWF levels monitored
- PPH occurred in 6.4% of the study cohort
- Frequency of PPH lower in monitored (4.9%) versus unmonitored group (7.3%), p = 0.23 (CI -4.4% to -0.3%)

Laboratory monitoring during pregnancy and post-partum hemorrhage in women with von Willebrand disease

Sarah H. O'Brien[1,2] | Joseph R. Stanek[1] | Dominder Kaur[3] | Katherine McCracken[4] | Sara K. Vesely[5]

Platelet Dysfunction - Intrapartum

- Mild Platelet Dysfunction
  - Utilize tranexamic acid with or without DDAVP
  - Avoid operative vaginal delivery
  - Active management of third stage of labor

- Severe Platelet Dysfunction (GT, BS)
  - Consult Hematology
  - Platelet transfusion often needed during labor and up to 2 weeks postpartum
  - Recombinant FVII also use for GT

Take Home Points

- 20-30% of patients with HMB have an underlying inherited bleeding disorder
- Tranexamic acid has wide utility in both obstetric and gynecologic management
- DDAVP is contraindicated in patients with Type 2B and Type 3 VWD
- Multidisciplinary care is critical to optimize patient outcome

Thank you

A Few Comments about Laboratory Monitoring

Factors that increase plasma VWF levels

Hormonal

High-dose estrogen

Pregnancy

Stress

Sepsis

Severe illness

Strenuous exercise

Phlebotomy

Chronic endothelial activation

Cardiovascular disease

Hypertension

Diabetes

Aging

Age-related increases may also be related to comorbidities

Why Check a Ferritin?

Table 2
Conventional test results in the progression of iron deficiency

	Iron Depletion	Iron-Restricted Erythropoiesis	Iron Deficiency Anemia
Hemoglobin concentration	Normal	Normal	Reduced
Mean corpuscular volume	Normal	Normal-Reduced	Reduced
Reticulocyte hemoglobin content[a]	Normal	Reduced	Reduced
Serum iron concentration	Normal	Reduced	Reduced
Serum ferritin concentration	Reduced	Reduced	Reduced
Total iron binding capacity	Normal	Increased	Increased
Soluble transferrin receptor	Normal	Increased	Increased

Why Ferritin?

Original Study

Iron Deficiency without Anemia: A Common Yet Under-Recognized Diagnosis in Young Women with Heavy Menstrual Bleeding

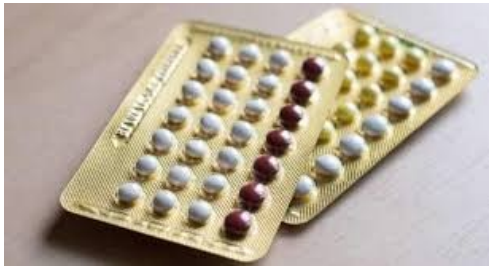
Stephen Johnson MD [1], Abigail Lang BS [2], Mollie Sturm MPH [3], Sarah H. O'Brien MD, MSc [3,4,*]

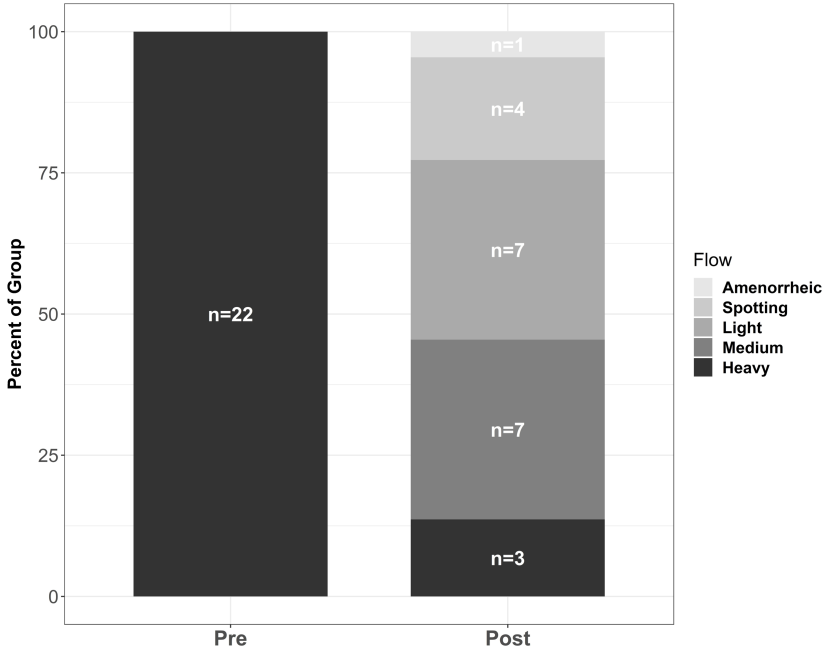
- 114 adolescents, ages 9-19 presenting with heavy menstrual bleeding for outpatient care
- 51% with ferritin < 20 ng/mL: of these, only 41% were anemic and 46% were microcytic

< 50% of Iron Deficiency cases in adolescents detected with screening with Hb or CBC alone

Treatment in IBDs: Antifibrinolytics + OCPS

- Pilot study of 22 adolescents using TXA and OCPs dual therapy as first line therapy
- 90% patient compliance at 6+ months
- No thromboembolic events





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Antifibrinolytics and Thrombotic Risk

- Controversy stems from mechanism of action: tissue plasminogen activator inhibitor and therefore prevents degradation of fibrin

- Observational Data: TXA with 3-fold increased risk for VTE but not statistically significant (CI 0.65 – 15.78)

- Product labeling
  1. Current or past history of thrombosis
  2. Increased risk of thrombosis
  3. Retinal vein or arterial occlusion
  4. ***Concurrent use of combination oral contraceptive pills (U.S. Only)***

Sundstrom, BJOG 2008
Thorne, Contraception 2018

Antifibrinolytics + COCP and Thrombotic Risk

- Sweden: 19 years of prescribing TXA for HMB (238,000 women years of use), **no VTE risk**
- Cochrane Review: 13 RCTs of TXA for HMB, **no VTE risk**
- RCT and PPH: International, randomized placebo-controlled trial of 20,600 women treated with TXA for postpartum hemorrhage, **no VTE risk**
- General Surgery: Large, placebo-controlled trials with use of TXA in major surgery, **no VTE risk**

Antifibrinolytics + COCP and Thrombotic Risk

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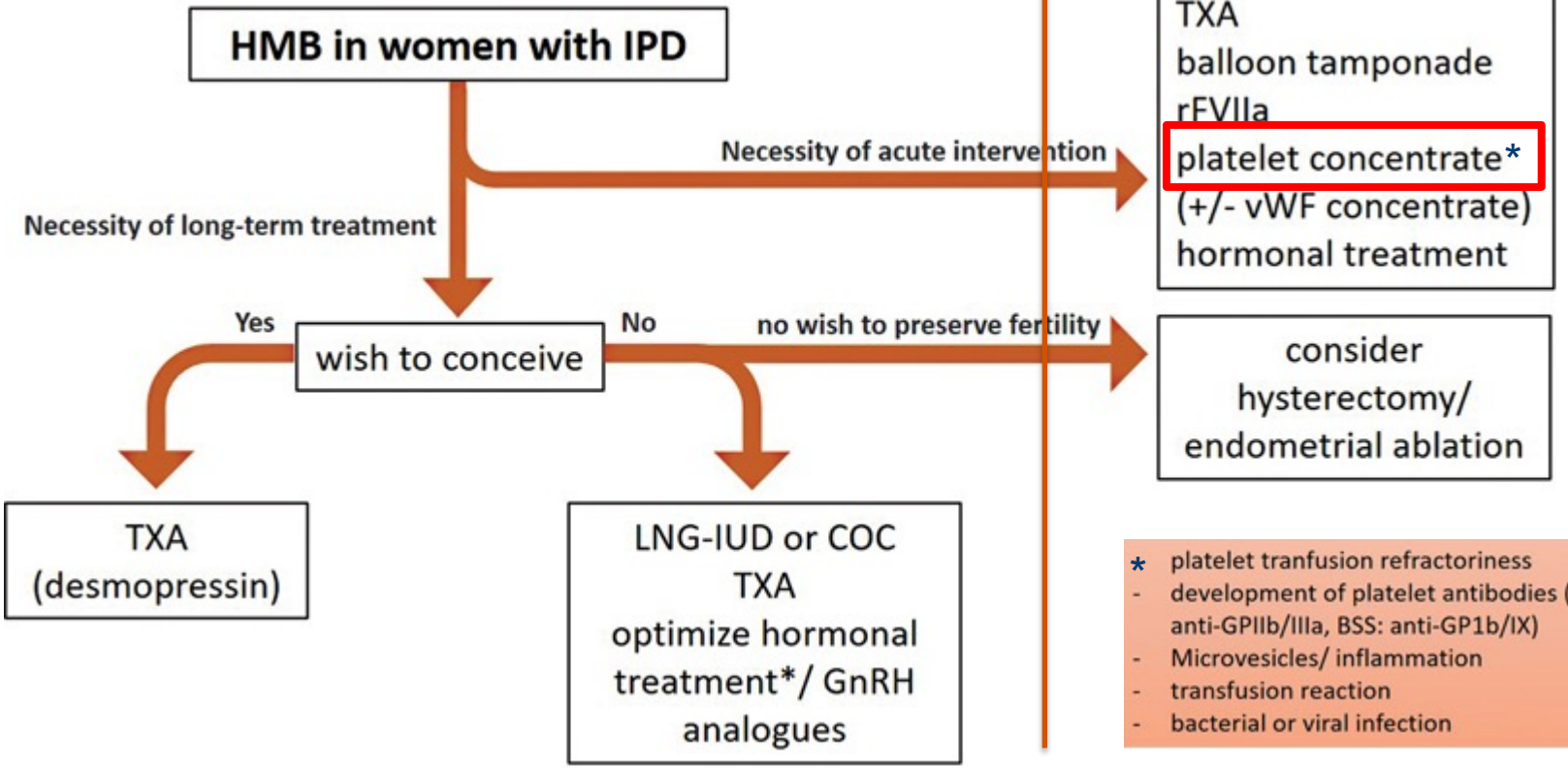
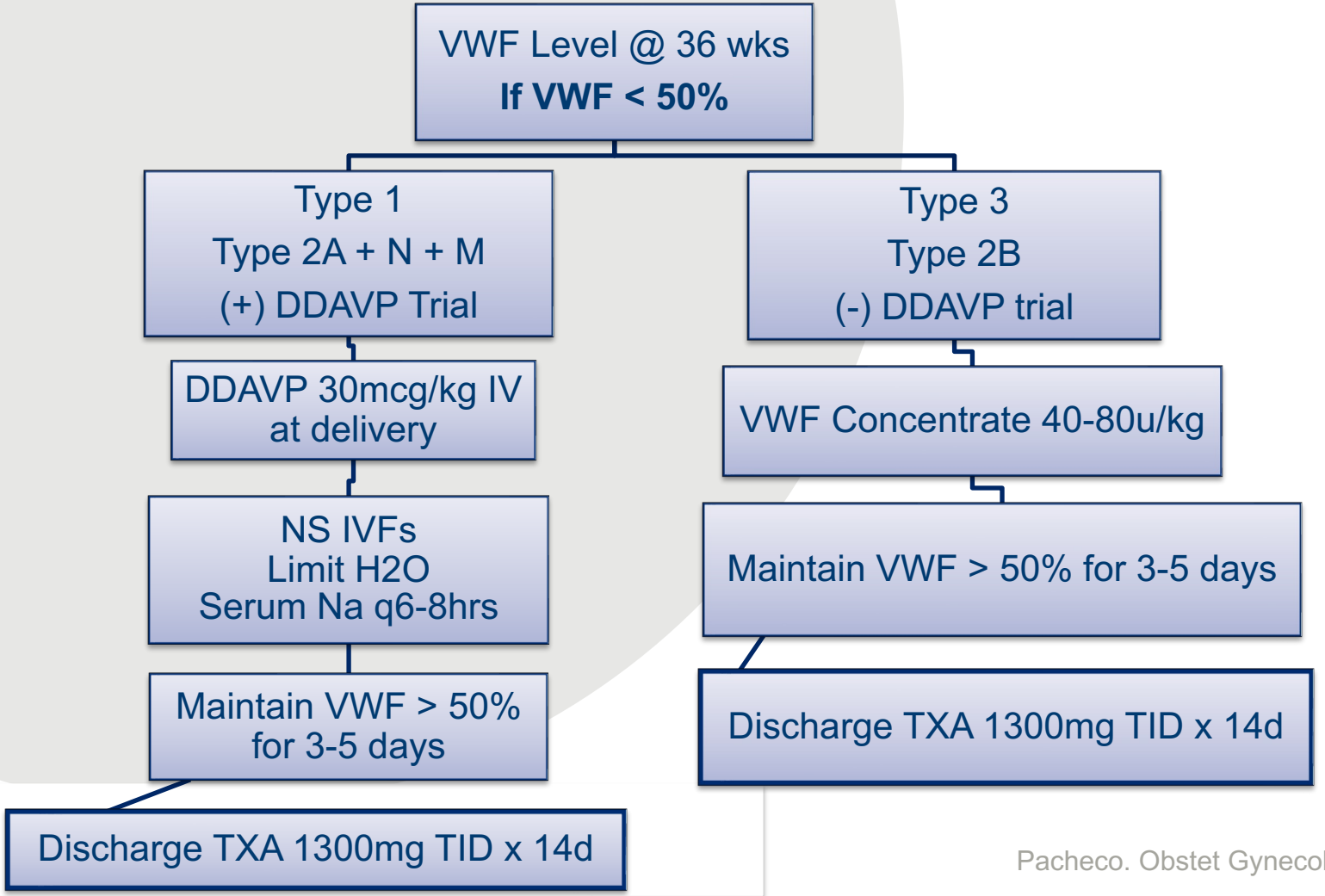
Conclusion:

The extensive clinical experience demonstrating the safety of short-term TXA exposure and its very beneficial effects for acute HMB suggest that the benefits of therapy, even when combined with COCPs, **for most women will outweigh potential risks.**

Women with increased risk beyond COCPs should probably avoid this combination therapy.

Platelet Dysfunction





Pacheco. Obstet Gynecol 2024