

FEBRUARY 24, 2023

Management of Inherited Bleeding Disorders in Obstetrics and Gynecology

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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

Learning Objectives

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Prevalence of Inherited Bleeding Disorders in Patients Presenting for ObGyn Care

3

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





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Byams, J Women's Health 2022 4

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Prevalence of Inherited Bleeding Disorders

1	2	3	4
Von Willebrand Disease	Mild Platelet Function Defects	Mild Hemophilia (Carrier)	Severe Inherited Bleeding Disorders
1:100-1,000*	???	1:3,000	1:500,000





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*Type 3 = 1 in 1,000,000 5

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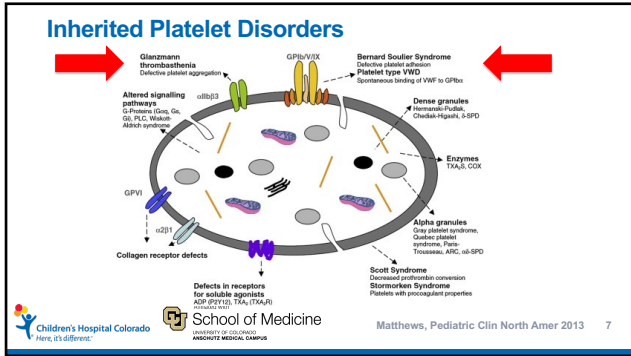
Von Willebrand Disease

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)

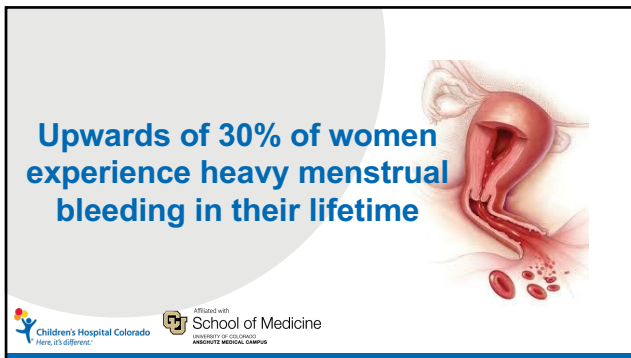


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Reynen, James. Semin Thromb & Hemost 2016 6

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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

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Byams, Hemophilia 2011. 9

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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

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Lowe, Platelets 2019 .0

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Management of Acute and Chronic HMB in Patients with IBDs

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Treatment Approach

Hormonal Therapy		Hemostatic Agents	
Pill/Patch/Ring	Depot injections	LARCs	Antifibrinolytics
Desmopressin	Factor concentrates	Platlets	

Acute	Maintenance
IV Estrogen	Pill/Patch/Ring
OCP taper	LNG-IUS
Progestin taper	Antifibrinolytics
ALL hemostatic agents	

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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%

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Byams. Haemophilia 2011. 13

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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 20mg 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	

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Acute Hormonal Management

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

GREGORY 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. Feridan Akinci, Riza Madatli, Enbal Budak, Ismail Cepel, and Ali Benisan
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

Melahn G. Murray, MD, Nadia Maitoo, MD, Ramir Bawa, MD, Mikael Brattberg, MD

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

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Maintenance Hormonal Management of HMB

Hormonal	Non-Hormonal	Iron Therapy
Combined contraceptive pill <i>PO</i>	Tranexamic acid <i>PO</i>	Ferrous sulfate <i>PO</i>
Progesterone only pill (norethindrone or MPA) <i>PO</i>	Aminocaproic acid <i>PO</i>	
Combined contraceptive patch	Desmopressin <i>IV or SQ</i>	
Combined ring		
Depot MPA <i>IM</i>		
Levonorgestrel intrauterine device <i>Attached with</i>		

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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.

Children's Hospital Colorado School of Medicine Cochrane Database, 2020 and 2022 17
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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 ¹ <small>Claudia Chi^{1,2}, Farah Y. Huz¹, Rezan A. Kadir^{1,2*}</small>	➔	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 <small>Olayemi A. Adeyemi-Fowode MD^{1,2}, Xiomara M. Santos MD¹, Jennifer E. Dietrich MD, MSc^{1,2}, Lakshmi Srivaths MD^{1,2}</small>	➔	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 <small>Patricia S. Huguelet^{1,2}, JL Laurin¹, D Thornhill¹, G. Moyer^{1*}</small>	➔	62% amenorrhea Mean continuation 5.08 years

Children's Hospital Colorado School of Medicine 18
Here, it's different. UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CENTER Chi Contraception 2011, AF JPAG 2017, PH JPAG 2022

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Non-Hormonal Management of HMB in Patients with IBDs

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Platelets and VWF in Primary Hemostasis

With injury, VWF adheres to vessel subendothelial matrix.

With shear, VWF multimers uncoil, platelets adhere and become activated.

Activated platelets release phosphatidylinositol 2-acylglycerol and activate phospholipase C2 to facilitate clotting.

Bleeding caused by platelet dysfunction is followed by thrombolysis and tissue repair.

DDAVP

VWF

Platelets

TXA

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Matthews. Pediatric Clin North Amer, 2013 20

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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		

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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






Obstet Gynecol 2011, Cochrane Review 2018 22

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Maintenance Management of HMB

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



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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

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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

Plot of mean PBAC over time by sequence of treatment

Period	T->T (Mean PBAC)	T->I (Mean PBAC)
0	280	280
1	200	200
2	160	180
3	140	180
4	120	140

Kouides, 2009 BJ Haematology

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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		

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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



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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. PIETROBONI

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

James 2009, Haemophilia 29

29



Complications of Hysterectomy in VWD

Complications of hysterectomy in women with von Willebrand disease

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

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

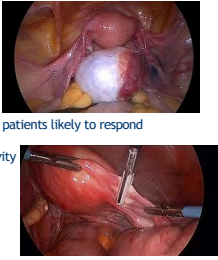



James 2009, Haemophilia 30

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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 \geq 0.50 for at least 3 days postop



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Laffan, 2020. Haemophilia
Connell, 2020. Blood Advances. 34

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Labor Management

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Overview of Bleeding Disorders in Patients with a Uterus

Journal of Thrombosis and Haemostasis, 9: 1165-1169

ORIGINAL ARTICLE

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

A. H. JAMES and M. C. JAMIESON
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)

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James. J Thromb Haem 2007 36

36

Physiologic Coagulation Changes of Pregnancy

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

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Reynen, James. Semin Thromb & Hemost, 2016 38
Weyan. Hematol Onc Clin North Amer, 2021

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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

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Reynen, James. Semin Thromb & Hemost 2016 39
Pacheco. Obstet Gynecol 2024

39

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

Reynen, James. Semin Thromb & Hemost 40 2016

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VWD Management - Postpartum

- WVF and FVIII levels persist until 48 hours 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 WVF 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 41
James. Haemophilia 2014

41

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 WVF labs

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

Sarah H. O'Brien^{1,2} | Joseph R. Stanek¹ | Dominder Kaur³ | Katherine McCracken⁴ | Sara K. Vesely⁵

O'Brien, 2020. J Thromb Haemost 42



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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. Stanek¹ | Dominder Kaur³ | Katherine McCracken⁴ | Sara K. Vesely⁵



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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



Gresela, Thrombosis Research 2019 44

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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



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Thank you

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A Few Comments about Laboratory Monitoring

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Factors that increase plasma VWF levels

<p>Hormonal</p> <p>High-dose estrogen Pregnancy</p>	<p>Stress</p> <p>Sepsis Strenuous exercise</p> <p>Severe illness Phlebotomy</p>
<p>Chronic endothelial activation</p> <p>Cardiovascular disease Hypertension Diabetes</p>	<p>Aging</p> <p>Age-related increases may also be related to comorbidities</p>

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Why Check a Ferritin?

	Iron Depletion	Iron-Restricted Erythropoiesis	Iron Deficiency Anemia
Hemoglobin concentration	Normal	Normal	Reduced
Mean corpuscular volume	Normal	Normal-Reduced	Reduced
Reticulocyte hemoglobin content*	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

Children's Hospital Colorado | School of Medicine | Powers, Hematol Oncol Clin North Am 2016. 49

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Why Ferritin?

Original Study

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

Stephen Johnson MD¹, Abigail Lang BS², Mollie Sturm MPH³, Sarah H. O'Brien MD, MSc^{1,4*}

- 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

Children's Hospital Colorado | School of Medicine | Johnson, JPAG 2016. 50

50

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

Children's Hospital Colorado | School of Medicine | Khalighi, Huguelet, Oral Abstract NASPAG ACRM 2022. 51

51



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
 - Current or past history of thrombosis
 - Increased risk of thrombosis
 - Retinal vein or arterial occlusion
 - Concurrent use of combination oral contraceptive pills (U.S. Only)



 Sundstrom, BJOG 2008
 Thorne, Contraception 2018 52



52

Antifibrinolytics + COCP and Thrombotic Risk



 Contents lists available at ScienceDirect
Contraception
 journal homepage: www.elsevier.com/locate/con



Commentary
 Heavy menstrual bleeding: is tranexamic acid a safe adjunct to combined hormonal contraception?

- 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



 Thorne, Contraception 2018. 53



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Antifibrinolytics + COCP and Thrombotic Risk

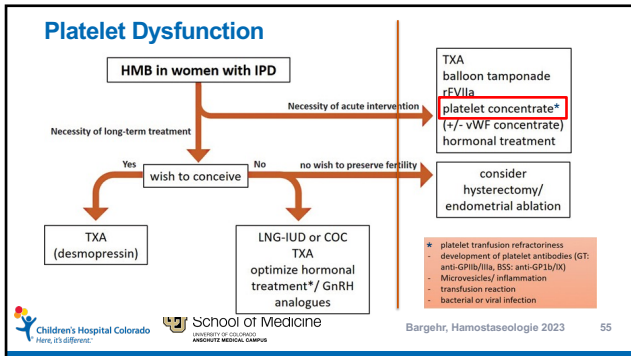


 Contents lists available at ScienceDirect
Contraception
 journal homepage: www.elsevier.com/locate/con

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.

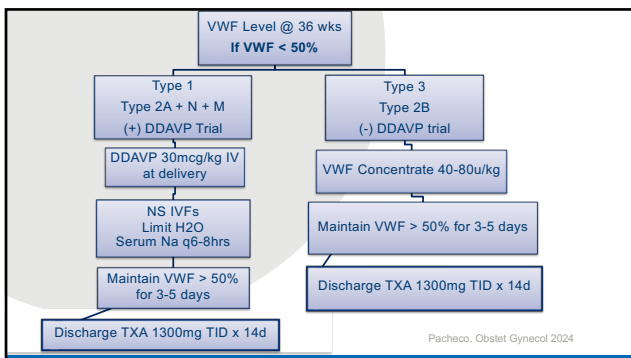
Women with increased risk beyond COCPs should probably avoid this combination therapy.



 Thorne, Contraception 2018. 54

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