Reproductive Issues in Women with Bleeding Disorders

Andra H. James MD, MPH
Consulting Professor,
Obstetrics & Gynecology
Duke University Medical Center

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Disclosures

Research funding, honoraria or consulting fees from the following companies who manufacture plasma-derived VWF factor, recombinant VWF, recombinant factor VIII, recombinant factor IX or desmopressin:

- CSL Behring – in the past year
- Baxter – in the past year
- Grifols
- Bayer
- Novo Nordisk
- Octopharma

Why Women and Girls?

Why Women and Girls?

- Women and girls are rarely affected by severe hemophilia
- They are equally likely to have other bleeding disorders including VWD
- When they do, they are disproportionately affected due to the bleeding challenges of:
  - Menstruation
  - Miscarriage
  - Childbirth
- We have learned a great deal about bleeding disorders in women in the last 25 years

Types of Bleeding Disorders in Female UDC (n = 319)*

Total VWD	88.7%
Type 1	*61.1 %*
Type 2	*7.8 %*
Type 3	*4.4 %*
Type unknown	*15.4 %*
Factor VIII	12.5%
Platelet disorders	4.7%
Missing diagnoses	6.9%
Other bleeding disorders	15.4%

*19.4% had 2 or more hemostatic defects.
*Byams et al, *Haemophilia,* 17(Suppl 1):6-13

Prevalence of Bleeding Symptoms in VWD

Menorrhagia (heavy menstrual bleeding)	32%-100%
Epistaxis	38%-62%
Bleeding after dental extraction	28%-52%
Ecchymoses	49%-52%
Bleeding from minor cuts or abrasions	36%
Gingival bleeding	26%-35%
Hemarthrosis	20%-28%
GI Bleeding	14%

Reference: *NHLBI*. The Diagnosis, Evaluation, and Management of von Willebrand Disease; 2008.

ACOG Committee Opinion

ACOG

Committee on
Adolescent Health Care

American Academy of Pediatrics

DEDICTED TO THE HEALTH OF ALL CHILDREN™

Committee on Adolescence

Committee Opinion

Number 349, November 2006

Menstruation in Girls and Adolescents: Using the Menstrual Cycle as a Vital Sign

Age of first period	11 to 14 years
Length of cycle	21 to 45 days
Length of period	7 days or less
Product use	3 to 6 pads or tampons per day

Prevalence of Menorrhagia in Women with Bleeding Disorders[1]

von Willebrand Disease	32-100%
Severe platelet dysfunction	
Bernard-Soulier syndrome	51%
Glanzmann's thrombasthenia	98%
Factor XI deficiency	59%
Hemophilia carriage	10-57%
Rare factor deficiencies	35-70%

1. James, *Haemophilia*. 2005; 11:295-307

Causes of Heavy Menstrual Bleeding

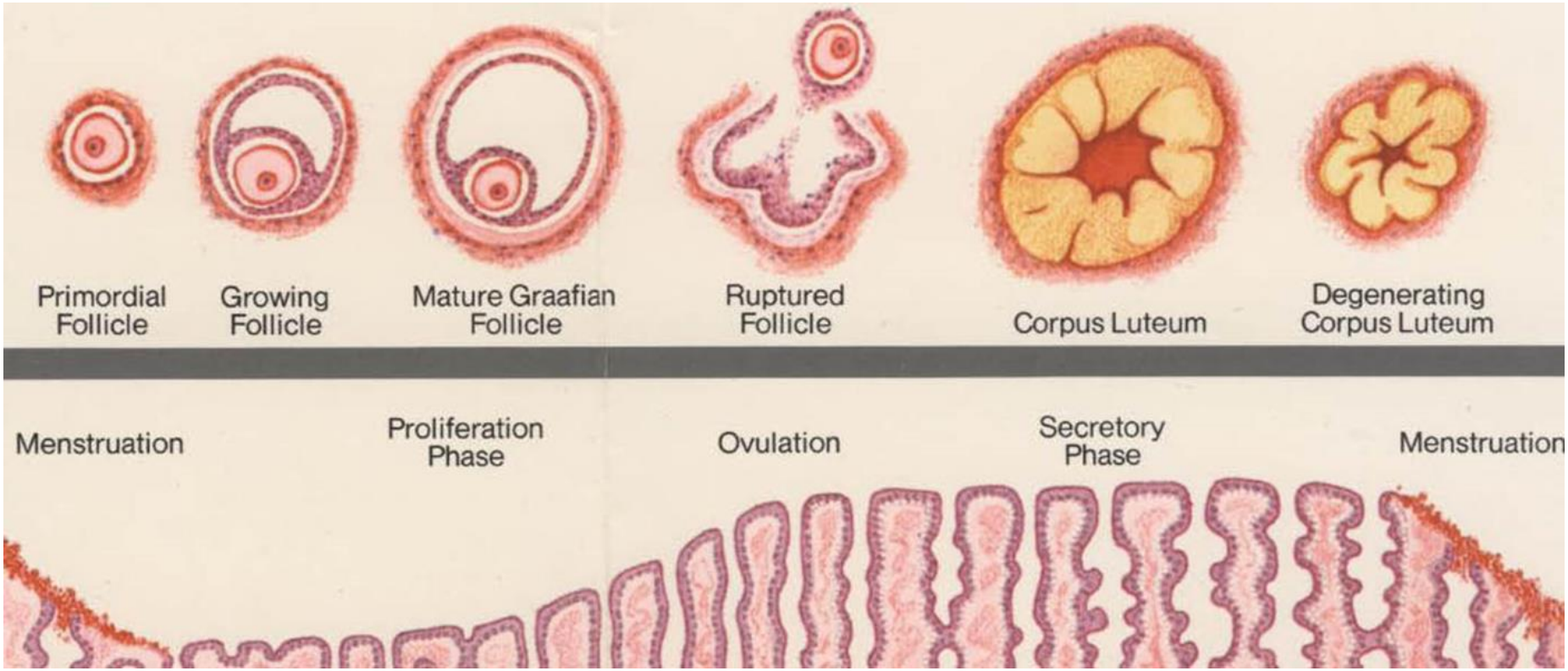
Cause	Age 13-19	Age 20-34	Age 35-49	Age 50+
Adolescent anovulation	→			
Bleeding disorder	→	→	→	→
Local pathology			→	→
New systemic disease		→	→	→
Anticoagulant therapy	→	→	→	→
Post-op complication			→	→
Hypothyroidism		→	→	→
Peri-menopausal anovulation			→	→

PALM-COEIN Classification of Abnormal Uterine Bleeding

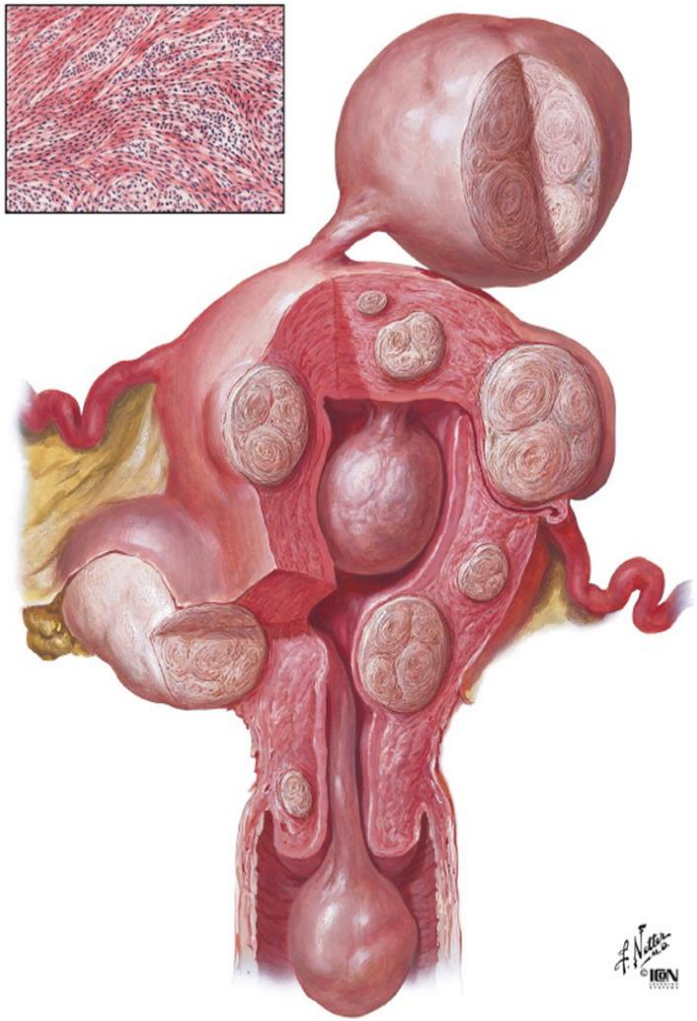
- polyp;
- adenomyosis;
- leiomyoma (fibroids);
- malignancy and hyperplasia;
- coagulopathy (bleeding disorder);
- ovulatory dysfunction (anovulation);
- endometrial;
- iatrogenic; and
- not yet classified

Munro, et al. for the FIGO Working Group on Menstrual Disorder, *Int J Gynaecol Obstet.* 113:1-13, 2011

The Menstrual Cycle



Fibroids as an Example of Local Pathology



Prevalence of Bleeding Disorders in Women with Menorrhagia

von Willebrand Disease	5-20%[1, 3-7]
Platelet dysfunction	<1-47%[1,3,7,8]
Factor XI deficiency	<1-4%[1,2,3]
Hemophilia carriage	<1-4%[1,2,3]
Rare factor deficiencies	<1%[1,2,3]

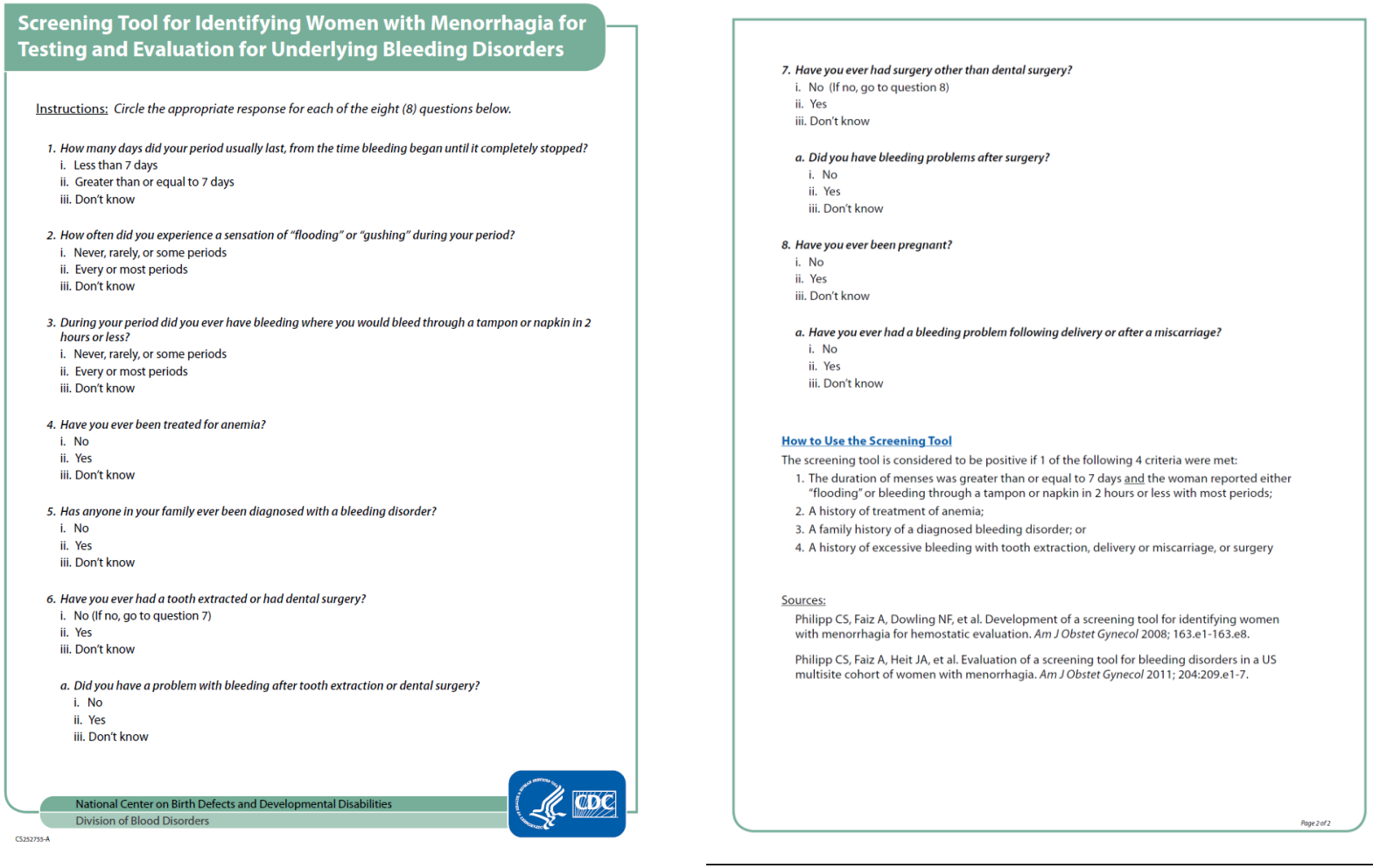
1. Kadir, et al. *Lancet* 1998; 351(9101):485-489
2. Krause, et al. *Thromb and Haemost* 2001S P1137
3. Dilley, et al. *Obstet and Gynecol* 2001; 97:630-6
4. Woo, et al. *Blood Coagul Fibrinolysis*; 13:89-93
5. Goodman-Gruen, et al. *J Women's Health Gend Based Med* 2001;10(7):677-680.
6. Edlund M, et al. *Am J Hematol*. 1996; 53(4):234-238.
7. James, et al. *Am J Obstet Gynecol.* 2004;191:449-455.
8. Philipp, et al. *J Thromb Haemost* 2003;1:477-484.

Prevalence of Bleeding Disorders in Adolescents with Menorrhagia

von Willebrand Disease	5-36%[1-7]
Platelet dysfunction (depending on how defined)	2-44%[1,3,5-7]
Factor XI deficiency	<1-4%[8-11]
Low factor VIII	8%[5]
Thrombocytopenia	13-20%[3,4]

1. Claessens EA & Cowell CA 1981
2. Smith YR, et al. 1998
3. Bevan JA, et al. 2001
4. Oral E, et al. 2002
5. Philipp CS, et al. 2005
6. Jayasinghe Y, et al. 2005
7. Mikhail S, et al. 2007
8. Kadir RA, et al. 1998
9. Krause M, Al E 2000
10. Dilley A, et al. 2001
11. Philipp CS, et al. 2003

Screening for Bleeding Disorders in Women with Menorrhagia



Screening Tool for Identifying Women with Menorrhagia for Testing and Evaluation for Underlying Bleeding Disorders

Instructions: *Circle the appropriate response for each of the eight (8) questions below.*

1. *How many days did your period usually last, from the time bleeding began until it completely stopped?*
   i. Less than 7 days
   ii. Greater than or equal to 7 days
   iii. Don't know

2. *How often did you experience a sensation of "flooding" or "gushing" during your period?*
   i. Never, rarely, or some periods
   ii. Every or most periods
   iii. Don't know

3. *During your period did you ever have bleeding where you would bleed through a tampon or napkin in 2 hours or less?*
   i. Never, rarely, or some periods
   ii. Every or most periods
   iii. Don't know

4. *Have you ever been treated for anemia?*
   i. No
   ii. Yes
   iii. Don't know

5. *Has anyone in your family ever been diagnosed with a bleeding disorder?*
   i. No
   ii. Yes
   iii. Don't know

6. *Have you ever had a tooth extracted or had dental surgery?*
   i. No (If no, go to question 7)
   ii. Yes
   iii. Don't know

   a. *Did you have a problem with bleeding after tooth extraction or dental surgery?*
      i. No
      ii. Yes
      iii. Don't know

7. *Have you ever had surgery other than dental surgery?*
   i. No (If no, go to question 8)
   ii. Yes
   iii. Don't know

   a. *Did you have bleeding problems after surgery?*
      i. No
      ii. Yes
      iii. Don't know

8. *Have you ever been pregnant?*
   i. No
   ii. Yes
   iii. Don't know

   a. *Have you ever had a bleeding problem following delivery or after a miscarriage?*
      i. No
      ii. Yes
      iii. Don't know

How to Use the Screening Tool

The screening tool is considered to be positive if 1 of the following 4 criteria were met:

1. The duration of menses was greater than or equal to 7 days and the woman reported either "flooding" or bleeding through a tampon or napkin in 2 hours or less with most periods;
2. A history of treatment of anemia;
3. A family history of a diagnosed bleeding disorder; or
4. A history of excessive bleeding with tooth extraction, delivery or miscarriage, or surgery

Sources:

Philipp CS, Faiz A, Dowling NF, et al. Development of a screening tool for identifying women with menorrhagia for hemostatic evaluation. *Am J Obstet Gynecol* 2008; 163.e1-163.e8.

Philipp CS, Faiz A, Heit JA, et al. Evaluation of a screening tool for bleeding disorders in a US multisite cohort of women with menorrhagia. *Am J Obstet Gynecol* 2011; 204:209.e1-7.

National Center on Birth Defects and Developmental Disabilities
Division of Blood Disorders

CS252755-A

How to use the screening tool

The screening tool is considered positive if:

1. The duration of menses was greater than or equal to 7 days and the woman reported either “flooding” or bleeding through a pad or tampon in 2 hours or less with most periods.
2. A history of treatment of anemia
3. A family history of a diagnosed bleeding disorder, or
4. A history of excessive bleeding with tooth extraction, delivery or miscarriage, or surgery.

The Work-Up for A Bleeding Disorder

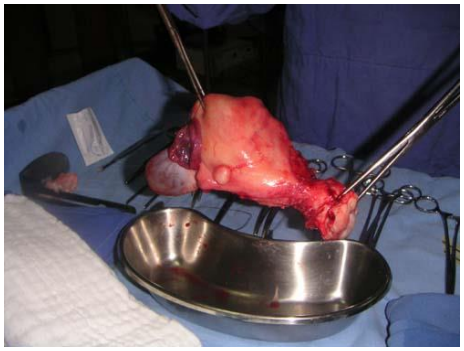
The laboratory assessment should include, as necessary:

- CBC
- prothrombin time (PT)
- activated partial thromboplastin time (aPTT)
- VWF:RCo, VWF:Ag and FVIII
- platelet function (platelet aggregation studies)
- other clotting factors
- other non-hematologic tests including, perhaps, tests of thyroid function

James et al. Von Willebrand disease and other bleeding disorders in women: consensus on diagnosis and management from an international expert panel. *Am J Obstet Gynecol,* 2009

Treatment for Heavy Menstrual Bleeding (n = 165) in the UDC

Oral contraceptives	90 (54.5%)
Desmopressin	56 (33.9%)
Antifibrinolytics	40 (24.2%)
Blood or plasma products	12 (7.3%)
Clotting factor products	10 (6.1%)
Endometrial ablation	7 (4.2%)
Levonorgestrel IUD	5 (3.0%)
Uterine artery embolization	3 (1.8%)
Platelet transfusion	1 (0.6%)



21/198 (10.6%) menstruating/menopausal women with HMB underwent hysterectomy specifically to control HMB

Byams, et al. *Haemophilia*, 17(Suppl 1):6-13

Other Gynecological Bleeding in Women with von Willebrand Disease vs. Controls[1]

Condition	Cases n = 102	Controls n = 88	P value
Menorrhagia	95%	61%	<0.01
Ovarian cyst	52%	22%	<0.0001
Endometriosis	30%	13%	0.005
Fibroid	32%	17%	0.02
Endometrial hyperplasia	10%	1%	0.01
Polyps	8%	1%	0.04
Hysterectomy	26%	9%	<0.01

1. Kirtava, et al. *Hemophilia* 2003; 9: 292-297

Ovulation

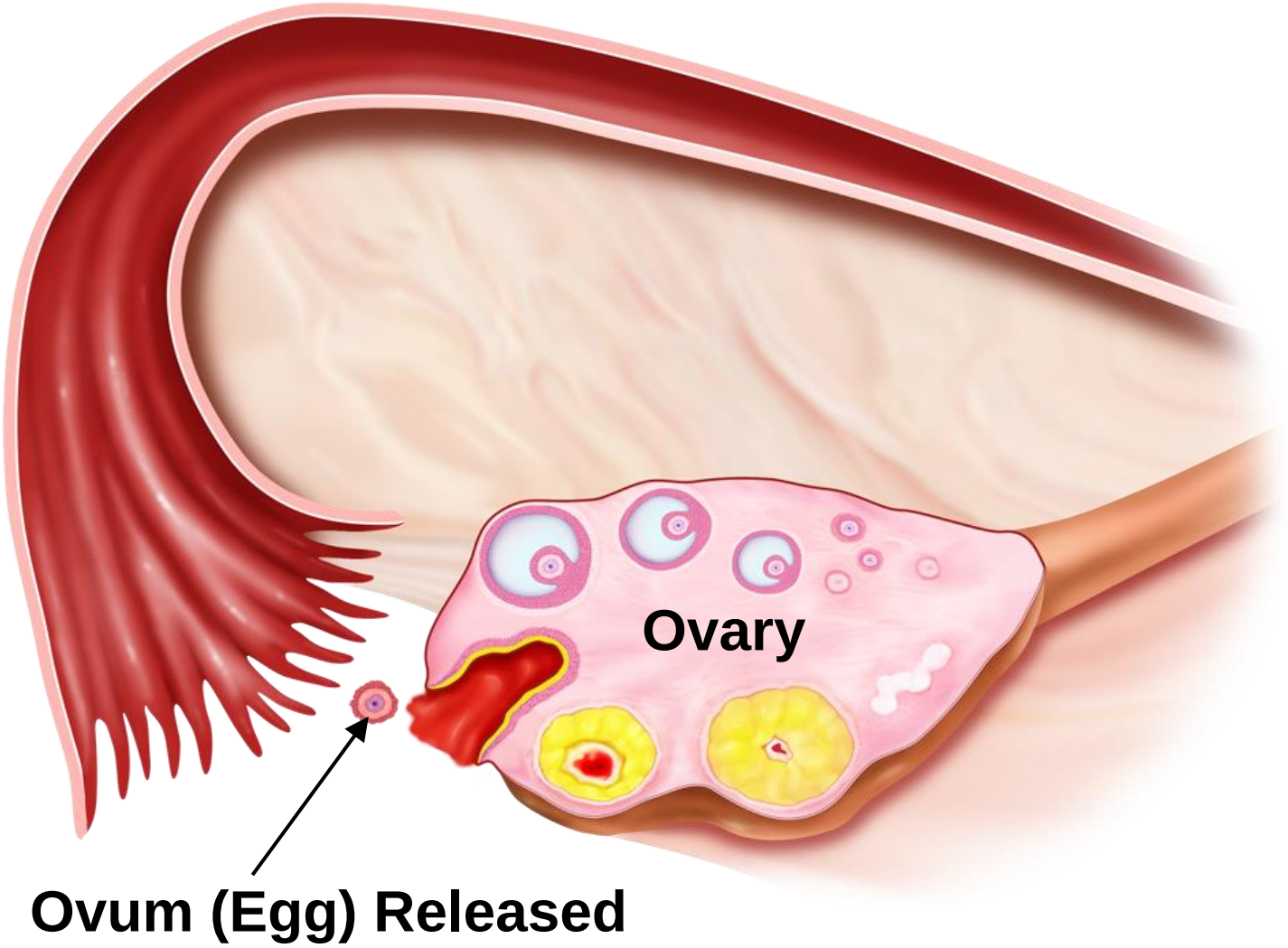


Image: MedMedia Solutions for FWGBD

Bleeding Disorders with Reports of Hemorrhagic Ovarian Cysts[1]

- von Willebrand Disease (6.8%)
- Hemophilia carriage
- Afibrinogenemia
- Factor X deficiency
- Factor XIII deficiency (20%)
- Platelet defects

1. James, et al. *Haemophilia*, 2005

Other Gynecological Bleeding in Women with VWD vs. Controls[1]

Condition	Cases n = 102	Controls n = 88	P value
Menorrhagia	95%	61%	<0.01
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Endometriosis

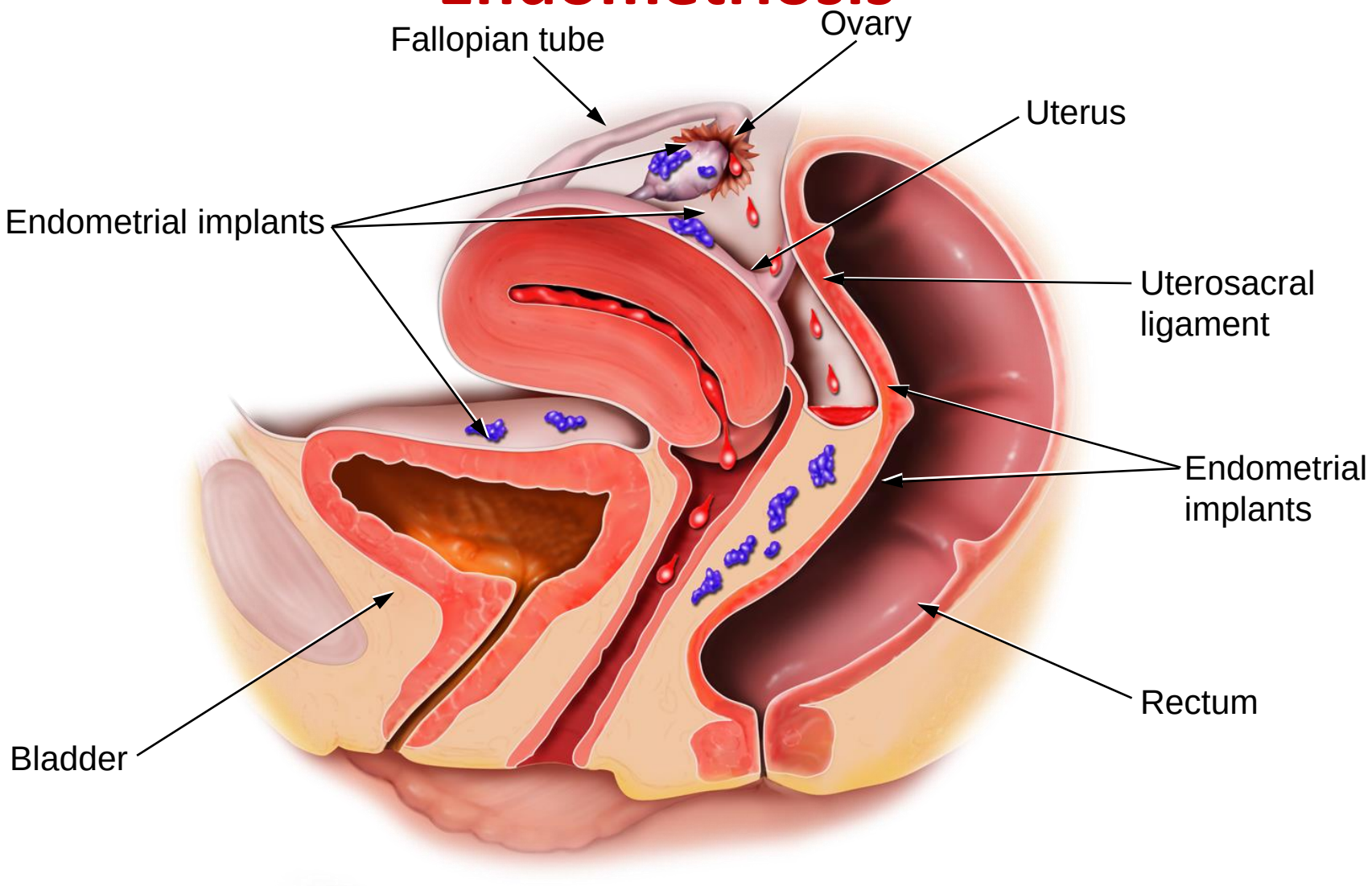

Image: MedMedia Solutions for FWGBD

Endometriosis

- Prevailing theory – results from retrograde menstruation
- Retrograde menstruation more likely with menorrhagia
- Menorrhagia more likely in women with bleeding disorders

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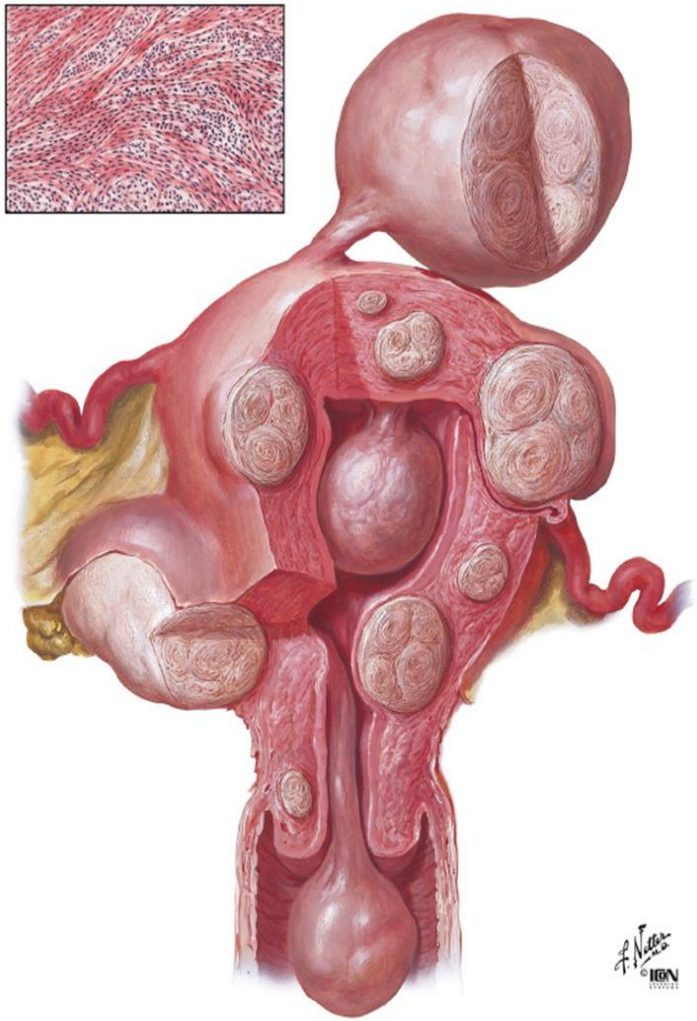

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1. Kirtava, et al. *Hemophilia* 2003; 9: 292-297

Pregnancy and Childbirth

Photo used with permission from Duke University

Bleeding with Childbirth

- Most bleeding at the time of childbirth is obstetrical bleeding (due to failure of the uterus to contract or retained placenta)
- Less often surgical bleeding (incisions or lacerations)
- Sometimes due to a bleeding disorder
  - Most bleeding disorders at the time of delivery are acute, like DIC, resulting from one of the above
  - Occasionally due to a preexisting bleeding disorder:
    - Thrombocytopenia
    - Platelet dysfunction
    - Von Willebrand disease
    - Hemophilia carriage
    - Rare bleeding disorders

Hemostatic Changes During Pregnancy

↑ fibrinogen

↑ factor VII

↑ factor VIII

↑ factor X

↑ von Willebrand factor

↑ PAI-1

+ PAI-2

↔ factor II

↔ factor V

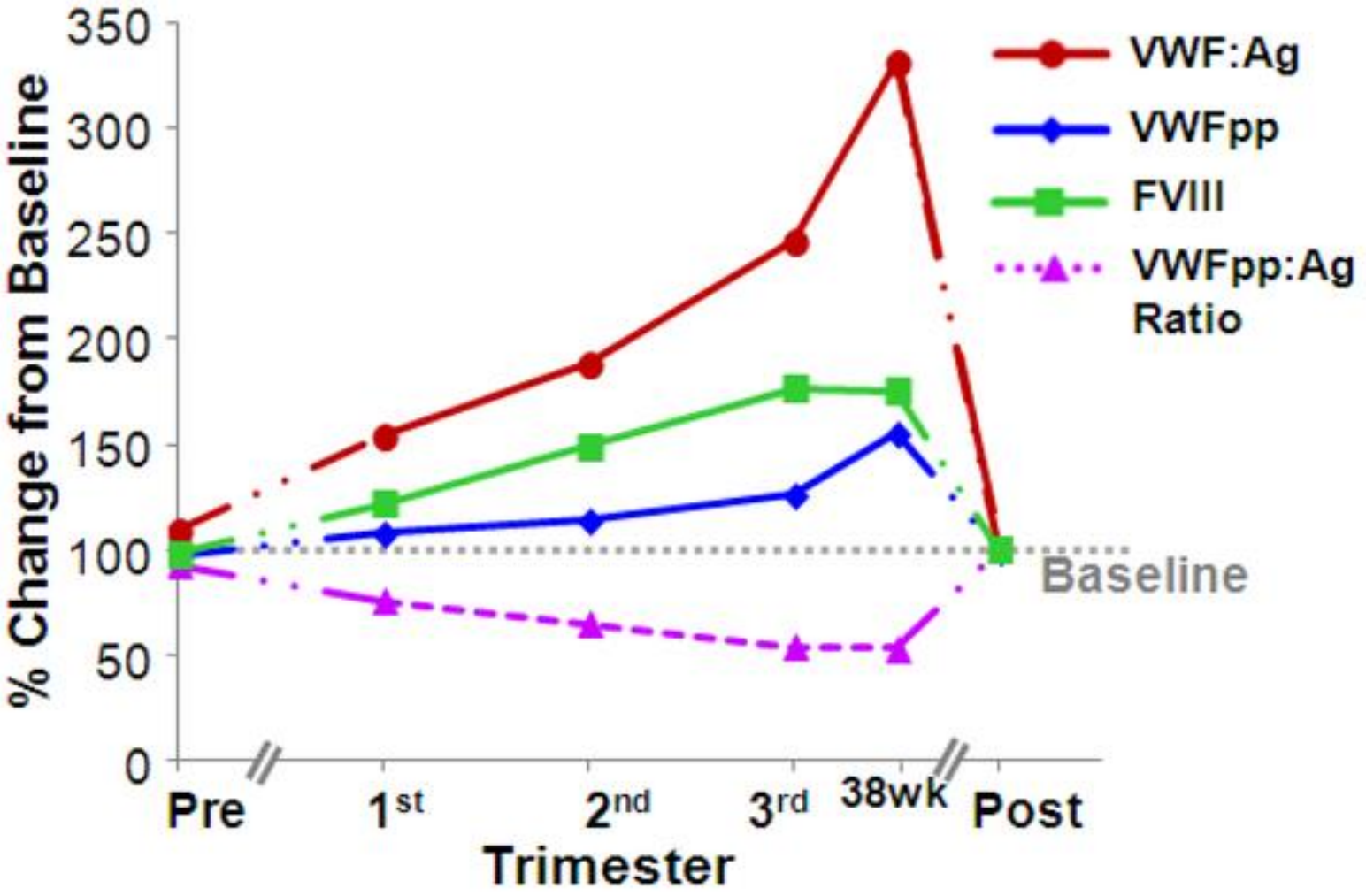
↔ factor IX

↓ free protein S

↔ protein C

↔ antithrombin (III)

Bremme, 2003; Medcalf, 2005



Drury-Stewart DN, Lannert KW, Chung DW, Teramura GT, et al.
PLoS ONE 9(11): e112935, 2014.

Reports of Miscarriage in Women with VWD

Chediak et al, 1986	10 pregnancies in 6 women	30%
Foster et al, 1995	69 pregnancies in 31 women	22%
Ramsahoye et al, 1995	24 pregnancies in 13 women	?
Caliezi et al, 1998	2 pregnancies in 1 woman with type 3	0%
Kadir et al, 1999	84 pregnancies in 31 women	25%
Lak et al, 2000	100 women with type 3	“normal”
Burlingame et al, 2001	5 pregnancies in 2 women	0%

Reports of Miscarriage in Women with Other Bleeding Disorders

Kadir et al, 1998	82 pregnancies in 32 hemophilia carriers	31%
Lak et al, 1999	18 women with afibrinogenemia	17% >2
Yang et al, 2004	19 pregnancies in 5 women with factor IX deficiency	16%
Kadir et al, 1997	28 pregnancies in 11 women with factor XI deficiency	4%
Burrows et al, 2000	16 women with factor XIII deficiency	63% >1

Increased Peripartum Bleeding Among Women with VWD

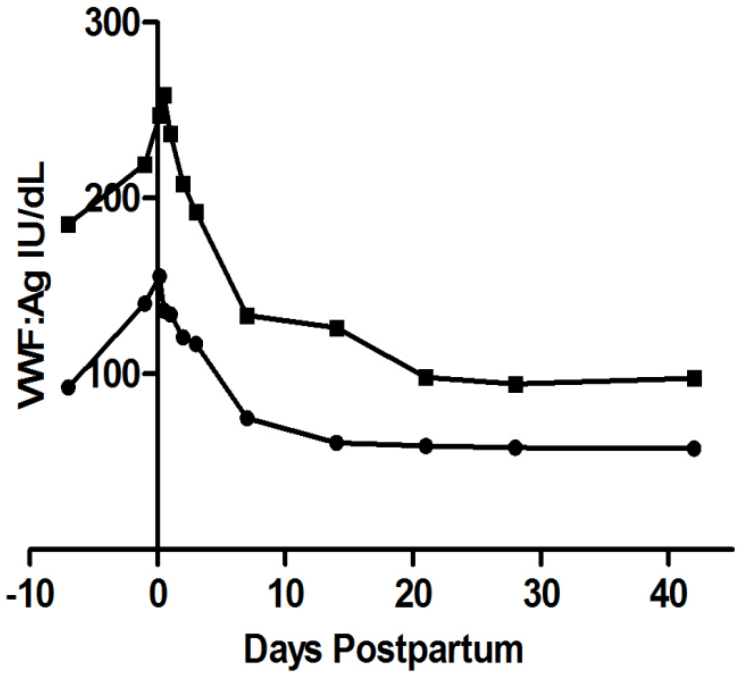
Condition	Odds Ratios	P value
Antepartum bleeding	10.2 (7.1, 14.6)[1]	< 0.01
Postpartum hemorrhage	1.5 (1.1, 2.0)[1]	< 0.01
Severe PPH	3.31 (1.01–10.85)[2]	
Perineal hematoma	3.3 (0.8, 13.4)[1]	0.09

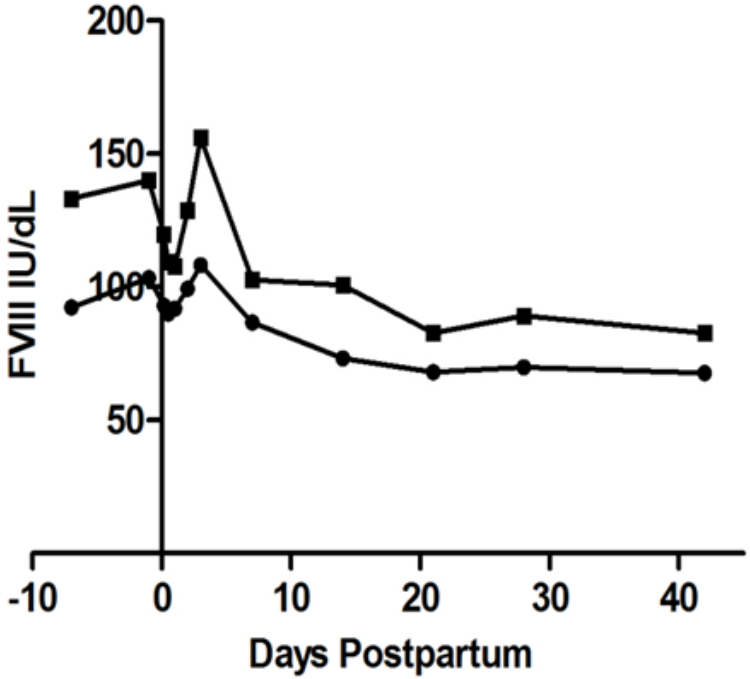
1. James and Jamison, *J Thromb Haemost,* 5:1165-9, *2007*
2. Al-Zirqi et al, *BJOG,* 115:1265-1272, 2008

Reports of delayed PPH

Report	Bleeding Disorder	# Women	# Deliveries	Rate
Ramsahoye et al, 1995	VWD	24	24	25%
Kadir et al, 1998	VWD		54	20%
Kadir et al, 1998	FXI def		25	24%
James et al, 2014	VWD	32	35	0%
Kadir et al, 1997	Hemophilia carriage		46	11%
Greer et al, 1991	Hemophilia carriage	23	43	2%

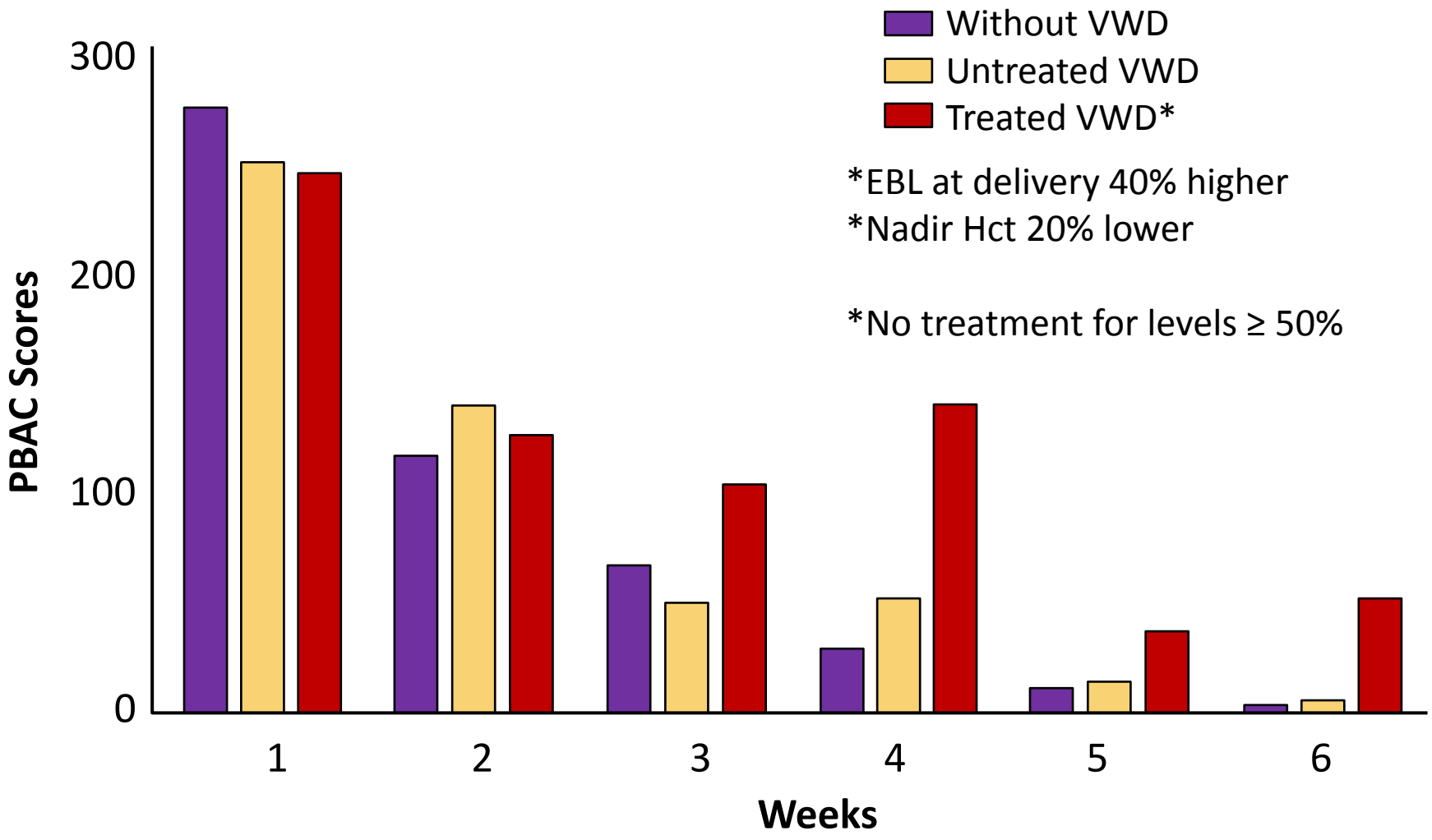
VWF and FVIII Levels Postpartum in Women with and without VWD





James et al, *Haemophilia,* 21:81-7, 2015

Modified PBAC Scores in Postpartum Women



James, et al. *Haemophilia*, 2014

There is no consensus on duration of treatment with VWF after delivery

	Type of VWD	Treatment for Delivery	PP Treatment	Total days PP Prophylaxis
1a	1	VWF - continuous	VWF – continuous x 3d; bolus x another 11 d	14
1b*	1	VWF - continuous	VWF – continuous x 3d; bolus x another 11 d	14
2	2A	VWF - continuous	VWF - bolus x 2 wk	14
3a	2M	VWF - bolus	VWF - bolus x 3d	3
3b*	2M	VWF - bolus	VWF - bolus x 3d	3
4	2B	VWF - bolus	VWF - bolus x 1 wk	7
5	1	desmopressin	VWF - bolus x 24h	1
6	2B	VWF - bolus	VWF - bolus x 48h	2
7	1	VWF - bolus	VWF - bolus x 21	21
8	1	VWF - continuous	VWF – continuous x 24h; bolus x 1 dose 1 wk PP	7
9	1	desmopressin	VWF - bolus x 48h	2
10	2(? subtype)	VWF - continuous	VWF – continuous x 6d	6
11	2M	VWF - bolus	None	0
12	2B	VWF - bolus	VWF - bolus x 21d	21
13	?	VWF - bolus	VWF - bolus x 8d	8
14	1	VWF - bolus	VWF - bolus x 4d	4
15	1	VWF - bolus	VWF - bolus x 48h	2

James et al, *Haemophilia,* 21:81-7, 2015

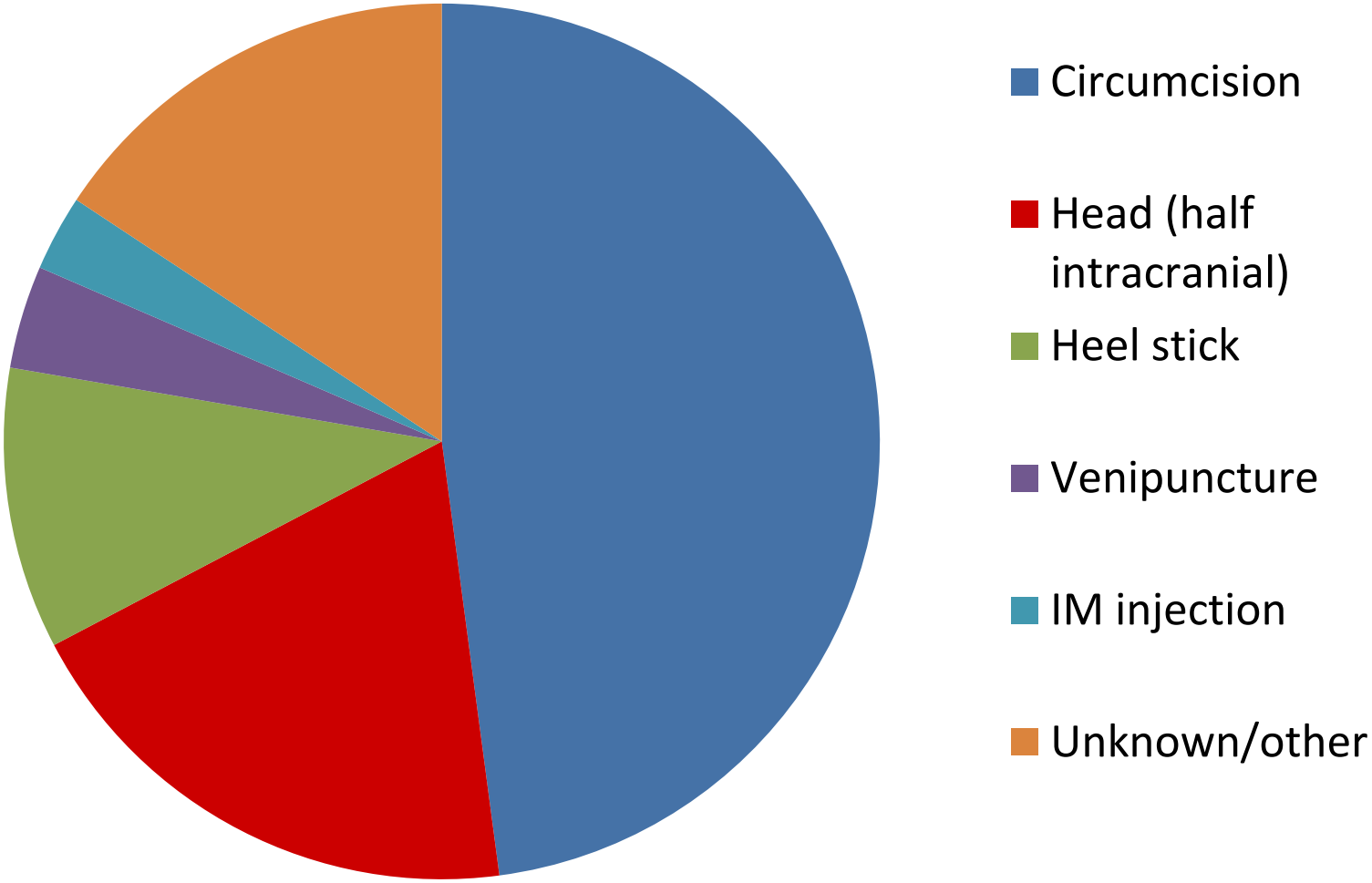
Desmopressin

- Can be used during pregnancy to raise VWF and/or FVIII prior to procedures .
- Desmopressin causes fluid retention and can cause hyponatremia.
- UK guidelines recommend that fluids be restricted to 1000 mL for 24 hrs after administration.
- Since women
  - routinely receive 2-3 times that amount of fluid at delivery,
  - routinely receive oxytocin, which also causes fluid retention and
  - invariably undergo redistribution of fluid from the extravascular space after delivery

At the time of delivery, desmopressin must be used with extreme caution, if at all.

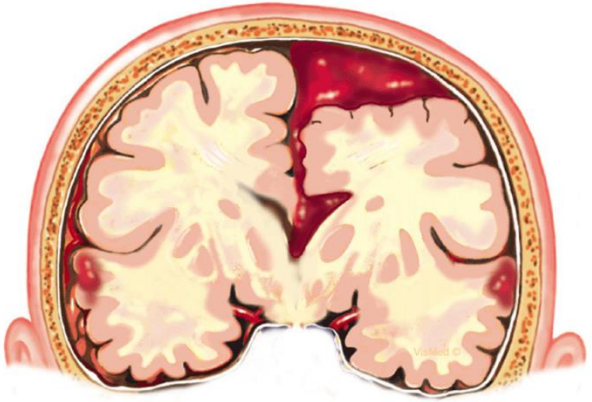
The Fetus or Newborn

19% of Bleeding in Infants with Hemophilia is Head Bleeding



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

Risk of Intracranial Hemorrhage and the Mode of Delivery



Mode of Delivery	Intracranial Hemorrhage
Vaginal (n = 381)	16 (2.8%)
Cesarean (n = 184)	1 (0.5%)

Odds of intracranial hemorrhage with vaginal delivery are increased 8-fold

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

Risk is greater with operative vaginal delivery in any fetus/neonate

	Gardella et al, 2001	Towner et al, 1999
SVD	1.0	1.0
Vacuum	2.4 (0.9, 6.2)	2.1 (1.7, 2.9)
Forceps	1.3 (0.4, 4.1)	2.9 (1.8, 4.4)
Cesarean after labor	-	2.1 (1.6, 2.7)
Cesarean before labor	-	0.7 (0.4, 1.3)

Gardella et al, *Am J Obstet Gynecol,* 185:896-902, 2001
Towner et al, *N Engl J Med,* 341:1709-14,1999.

Mode of delivery for the fetus who is or may be severely affected

- Obstetricians caring for women who are carriers of hemophilia should discuss the maternal and fetal risks of a vaginal delivery versus a planned cesarean delivery.
- The option of a planned cesarean delivery should be recommended when an affected or potentially affected infant is anticipated.
- In those women who elect vaginal delivery, forceps and vacuum extraction, interventions that triple the risk of intracranial hemorrhage in affected infants, should be avoided, as should fetal scalp electrodes during labor.

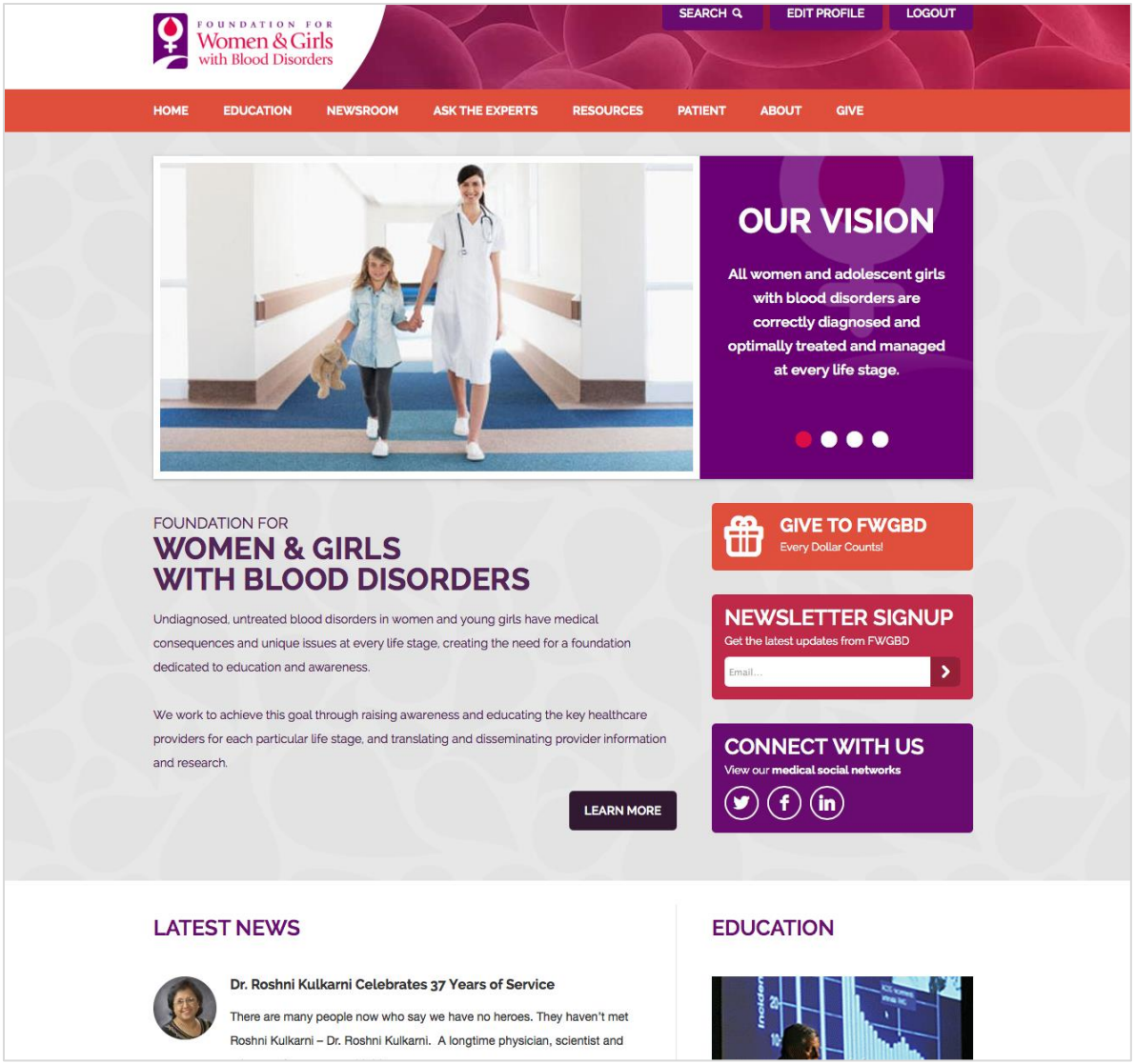
National Hemophilia Foundation MASAC Guideline #192

Preconception Counseling for the Hemophilia Carrier

- Women who are at risk for being carriers of hemophilia should have their carrier status determined before they become pregnant.
- If factor levels are inconclusive, genetic mutation analysis should be done
- Women/families should be acquainted with the methods of diagnosing a potentially affected infant prior to delivery –
  - preimplantation genetic diagnosis,
  - invasive prenatal diagnosis (CVS, amnio and cordocentesis),
  - ultrasound determination of fetal gender.

National Hemophilia Foundation MASAC Guideline #192

fwgbd.org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All women and adolescent girls with blood disorders are correctly diagnosed and optimally treated and managed at every life stage.
FOUNDATION FOR
WOMEN & GIRLS
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Undiagnosed, untreated blood disorders in women and young girls have medical consequences and unique issues at every life stage, creating the need for a foundation dedicated to education and awareness.
We work to achieve this goal through raising awareness and educating the key healthcare providers for each particular life stage, and translating and disseminating provider information and research.
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Dr. Roshni Kulkarni Celebrates 37 Years of Service
There are many people now who say we have no heroes. They haven't met Roshni Kulkarni – Dr. Roshni Kulkarni. A longtime physician, scientist and
EDUCATION

Conclusion

- Women are rarely affected by severe hemophilia.
- They are equally likely to have other bleeding disorders including VWD
- When they do, they are disproportionately affected due to the bleeding challenges of:
  - Menstruation
  - Miscarriage
  - Childbirth
- Optimal care is provided by reproductive health care providers who understand bleeding disorders and hematologists who understand the reproductive implications of bleeding disorders