UTERINE HEMOSTASIS IS ACHIEVED THROUGH NORMAL PLATELET FUNCTION

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FOUNDATION FOR
Women & Girls
with Blood Disorders

OUTLINE

Case presentation

- Overview of normal hemostasis

Platelets in normal uterine hemostasis

Platelets in abnormal uterine bleeding

GM

- 43 yo F with h/o chronic thrombocytopenia (40-50k) consulted for menorrhagia
- 1 week before, underwent a myomectomy 7/4-7/6/13 for massive vaginal bleeding secondary to prolapsing uterine fibroids; received platelet transfusions
- Patient did well post-procedure and was discharged to home
- Traveled to home ~6 hour car ride ~2 days after surgery to spend time with her family
- Soon after arrival, noted increased vaginal bleeding requiring a pad change every 2 hours
- Patient came to ED, near syncopal; Hb=8
- Given platelet transfusion, treatment with Amicar and seen by gynecology

GM MED HISTORY

- Presentation at 1 yo age with thrombocytopenia
  - ~40-60K; h/o nosebleeds at age 8-9 lasting for hours
  - diagnosed as ITP; unsuccessful treatments with steroids, IVIG
- Hemostatic stressors:
  - childhood injuries (bike trauma, softball injury) without significant bleeding
  - menarche at age 15
    - first cycle lasting for 4 weeks
    - recalls being near syncopal at times and required transfusions.
    - patient developed significant anemia requiring transfusion
    - She was started on OCPs shortly thereafter
    - On OCPs, her menstrual cycles would last 6-7 days and were heavy.
- She recalls being iron deficient during her college years.
- Three children by vaginal delivery (2003, 2005, 2008) without bleeding
- Seen at Cleveland Clinic and diagnosed by genetic testing to be homozygous for Bernard Soulier Syndrome

BERNARD SOULIER SYNDROME

- Autosomal recessive disorder ($1:10^6$)
- Clinical features
  - morphologically enlarged platelets
  - Variable thrombocytopenia
  - Mucocutaneous bleeding
- Deficiency of GP Ib-IX-V complex (vWF receptor) on platelets
- Physiologic role:
  - mediates adhesion to the blood vessel wall at sites of injury by binding vWF
  - facilitates the ability of thrombin at low concentrations to activate platelets

ILLUSTRATIVE CASE

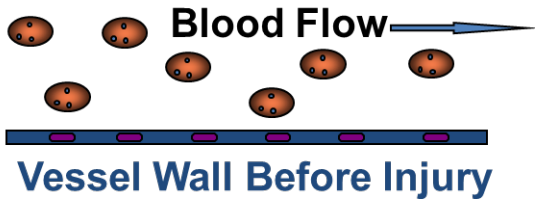
- Variable bleeding history
  - Recurrent epistaxis & heavy menstrual bleeding
  - No bruising or bleeding with childhood trauma or pregnancies
- Iron deficiency
- Bleeding out of proportion to platelet count abnormality
- BSS platelet defect role of platelet adhesion and function in uterine hemostasis

HEMOSTASIS

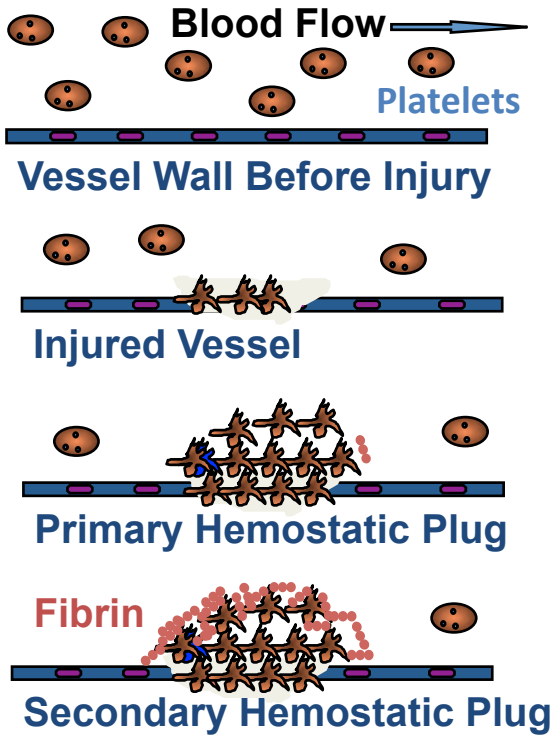
- Finely tuned host defense mechanism
- Involves vessel wall, platelets, and plasma coagulation proteins
- End product of coagulation: generation of a fibrin clot
- Hemostasis: physiologic
- Thrombosis: pathologic

PRIMARY HEMOSTASIS

- Platelets
- Endothelium/vessel wall
- vWF & other adhesive proteins (fibrinogen)



Formation of a Hemostatic Plug



- Platelets do not adhere to normal endothelium.
- Platelets adhere with help from vWF to the subendothelial matrix.
- Platelets aggregate to form the 1º hemostatic plug.
- Platelets accelerate fibrin formation to form the 2º hemostatic plug.

NORMAL MENSTRUATION

- Result of autodigestion of non-gestational endometrium
- Menstrual tissue: functionalis layer rich in RBCs, inflammatory cells and proteolytic enzymes

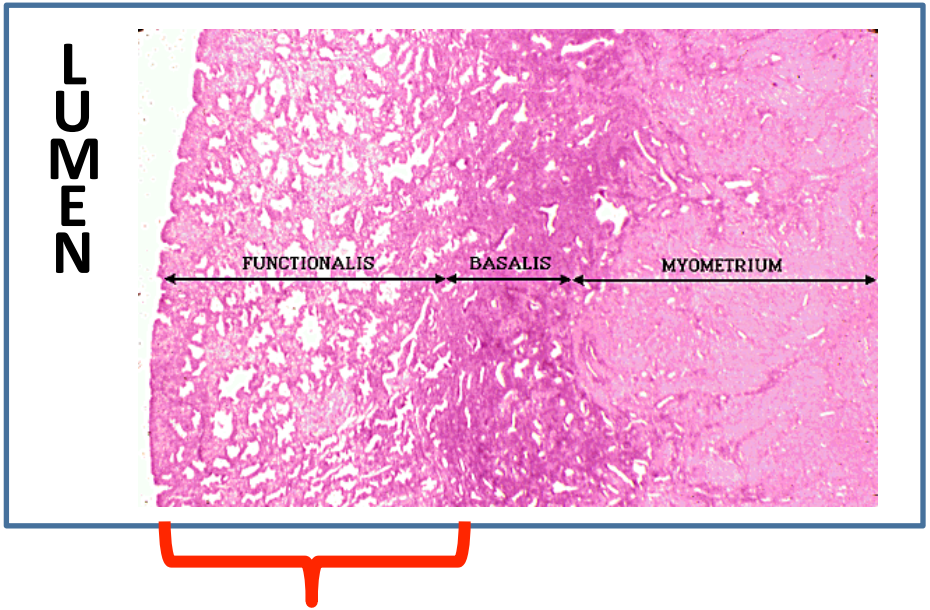


Image: http://education.med.nyu.edu/Histology/courseware/modules/fem-repro-sy/images/female.reproductive.21.gif

UTERINE HEMOSTASIS CHRONOLOGY

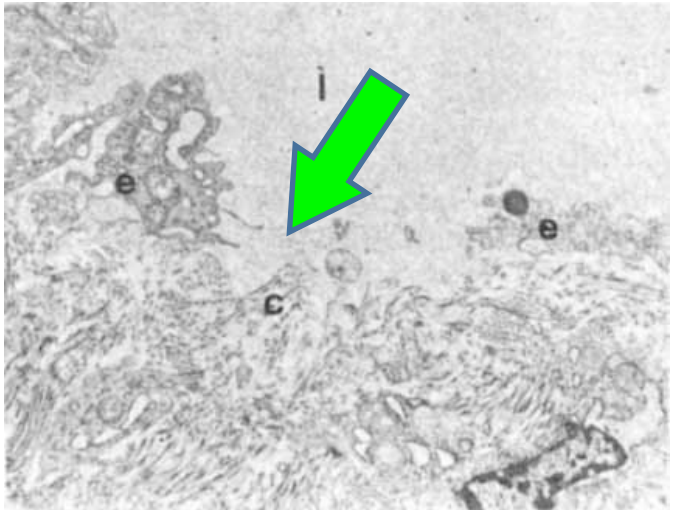
Morphological Study of Normal Menstruation

- Study Aim: mechanisms of hemostasis during first hours of normal menstruation
- Methods:
  - Hysterectomy performed (n=9) during first 72 hours of menstruation
  - Age <46 years; regular cycles/normal menstruation; no hormonal Rx in last 2 cycles
  - Admitted day before menstruation
  - Eight uteri removed between 3 ½ to 72 hours
  - 1 pre-menstrual; 2 control uteri

Christiaens, et al. *Br J Obstet Gynecol.* 1980; 87:425-439

PREMENSTRUAL UTERUS

- Uterus covered by epithelium
- Limited extravasation of blood and infiltration of white cells
- Thin walled vessels in functional layer lose continuity
- Holes in endothelium and loss of basement membrane
- Subendothelium exposed to vessel lumen

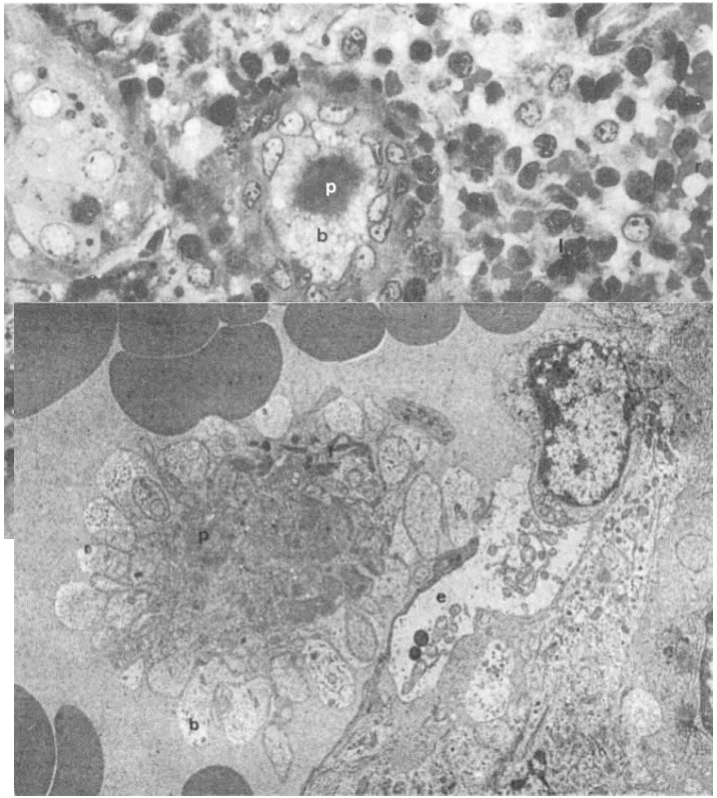


No adherent platelets

Christiaens, et al. *Br J Obstet Gynecol* 1980; 87:425-439

EARLY MENSTRUATION (3.5-13 hrs.)

- Thrombi occlude vessels
- Vessels filled with platelets or degranulated platelets and fibrin
- Increased WBCs
- Thrombi greatest by 7 hours
- Sequential deposition of platelets and fibrin
- Extravasation, disintegration, shedding and plug formation moves gradually toward the basal endometrium



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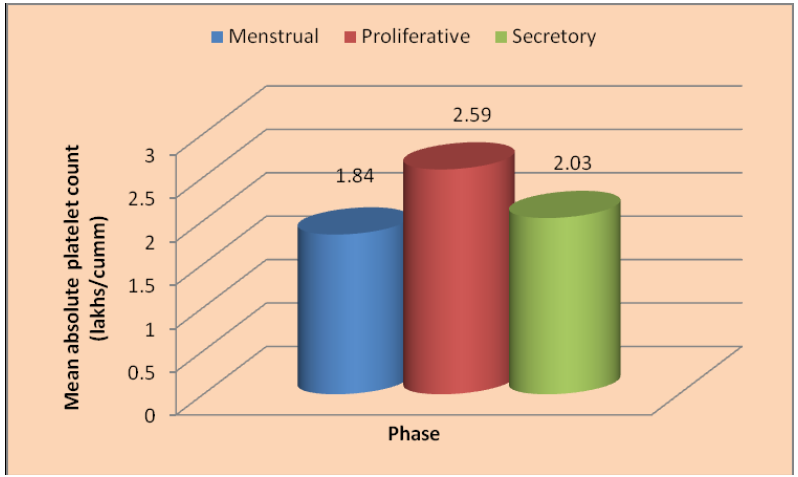
PLTS & SEX HORMONES

Platelet counts change with menstrual cycle



20 females
Samples drawn
Menstrual: 2nd day
Proliferative: 6-9 days
Secretory: 22-24 days

PLTS & SEX HORMONES

- Number of α2- adrenergic receptors peaks at the onset of menses and drops to 74% to 79% of that value during mid-cycle[1]
- Estrogen- and androgen-responsive genes (nitric oxide synthase--an inhibitor of platelet aggregation), superoxide dismutase, gp130, and thromboxane A2, found in megakaryocytes and/or platelets
- Megakaryocytes and platelets express the estrogen receptor (ER) β and androgen receptor (AR)[2]
- Murine β -ER knock-out has normal hemostasis

1. Jones, SB, et al. *Clin Pharmacol Ther*. 1983;34:90
2. Khetawat, et al. *Blood*. 2000;95:2289-2296
3. Jayachandran, et al. *J Gerontol A Biol Sci Med Sci.* 2005; 60 (7):815-819

ABNORMAL UTERINE BLEEDING

- Definition: menstrual loss >60-80 mL/cycle
  or >7 days
- Prevalence ~9-14% of reproductive age women
- Causes multifactorial
  ~50% remain unidentified
- Menorrhagia may be most reliable prognostic indicator of hemostatic disorder

AUB AS INDICATOR OF AN UNDERLYING BLEEDING D/O

- Case / control study of HMO
- 121 women with AUB and 123 controls
- Testing:
  - Bleeding time, vWF panel, Factors II, V, VII, IX, X, XI, and XII, platelet aggregation
  - Abnormal studies repeated
- Only 1 patient in each group with a FH of diagnosed bleeding disorder

Dilley, et al. *Obstet Gynecol.* 2001; 97:630-6

PREVALENCE OF BLEEDING DISORDERS

Diagnosis	Menorrhagia (n=121)	Controls (n=123)	p	Odds Ratio (95% CI)
von Willebrand Disease	8 (6.6%)	1(0.8%)	0.02	8.6 (1.3, 194.6)
Factor deficiencies (FVII & FXI)	2 (1.6%)	0	0.2	NA
Platelet defects	3 (2.5%)	3 (2.4%)	1.0	1.0 (0.2, 6.0)
Total	**13 (10.7%)**	**4 (3.2%)**	**0.01**	**3.6 (1.2, 13.0)**

Dilley, et al. *Obstet Gynecol.* 2001; 97:630-6

OTHER NON-MENSTRUAL SXS

	Bleeding Disorder			
Bleeding Sxs	Yes (n=17)	No (n=227)	p	OR (95%CI)
Bruising	6 (35.3%	52 (22.9%)	0.3	1.8 (0.6, 5.2)
Epistaxis	1 (5.9%)	4 (1.8%)	0.3	3.4 (0.13, 29)
Gum Bleeding	0	25 (11%)	0.2	0(0, 1.7)
Post-operative bleeding	0	9 (5.5%)	0.5	0 (0, 6.0)
Bleeding after dental surgery	1 (6.7%)	15 (7.9%)	0.9	0.9 (0.04, 5.3)
Postpartum bleeding	1 (6.7%)	26 (18.6%)	0.7	0.5 (0.06, 3.8)

Sixty-five (54%) of 121 menorrhagia (HMB) reported no other symptoms

Dilley, et al. *Obstet Gynecol.* 2001; 7:630-6)

EVALUATION FOR PLT DISORDERS

- Family history of bleeding
- Duration of bleeding from menarche
- Bleeding history (particularly hemostatic stressors: child birth, dental procedures)
- Laboratory testing:
  - PT/aPTT, Fibrinogen
  - vWD (D1-4 of menstrual cycle)
  - Platelet aggregation studies

TREATMENT

Local

- uterine curettage
- uterine artery embolization
- hysterectomy

Systemic treatments

- IV/oral estrogens
- High dose oral contraceptives (combined oestrogen and progestin)
- High dose oral progestins
- Anti-fibrinolytic therapies
- Targeted therapies: desmopressin, factor concentrate, or blood products

HEMOSTATIC THERAPIES

Agent	Mechanism of Action	Dose
Vasopression/DDAVP	• Increases FVIII and vWF levels • Increases adhesion of plts to vessel walls	IV: 0.3 mcg/kg Spray: 150 mcg spray/nostril
Anti-fibrinolytic agents (Tranexamic acid/Amicar)	• TA: Displaces plasminogen from fibrin • Amicar: blocks binding of plasminogen to fibrin	*Acute bleeding*: TA: 10 mg/kg q 8h IV Amicar: 1 g/h IV or 1-4 g q 4- 8h *Chronic bleeding:* TA: 1 g q 6-8hrs Amicar: 500 mg -1g q8h
Humate P/vWF	Replacement of vWF	40-60 units vWF: RCo activity loading; followed by 40-60 U q 12 h
Platelets	Replacement	1 unit as needed

CONCLUSIONS

Platelet function essential for normal menstruation

- As revealed by histologic data
- And high incidence of abnormal uterine bleeding in patients with platelet disorders

Platelets respond to hormonal cues

Multi-disciplinary approach employing local and systemic measures can ameliorate bleeding caused by defective platelets.

THANK YOU