UTERINE HEMOSTASIS IS ACHIEVED THROUGH NORMAL PLATELET FUNCTION

Gow Arepally, MD
Duke University Medical Center
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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.
- 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:
  o mediates adhesion to the blood vessel wall at sites of injury by binding vWF
  o 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

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

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

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

Platelet counts change with menstrual cycle

20 females
Samples drawn
Menstrual: 2\textsuperscript{nd} 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

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

## PREVALENCE OF BLEEDING DISORDERS

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

### OTHER NON-MENSTRUAL SXS

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

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

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

Platelet function essential for normal menstruation
  o As revealed by histologic data
  o 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