Women’s Health & Anticoagulation

The Anticoagulation Practitioner’s Guide to Uterine Bleeding

Bethany Samuelson Bannow, MD
Assistant Professor, The Hemophilia Center at OHSU
Oregon Health & Science University Portland, OR
Objectives

• Define abnormal uterine bleeding (AUB) and heavy menstrual bleeding (HMB)

• Review rates of AUB in anticoagulated women

• Consider strategies for menstrual management

• Discuss postmenopausal bleeding in the anticoagulated woman
How comfortable do you feel identifying and addressing abnormal uterine bleeding (AUB)?

A. Totally comfortable, address it every visit!
B. Quite comfortable but I don’t always ask about it
C. I know it when I see it (if the patient brings it up)
D. AUB is not an issue for my patients
E. I don’t ask about it because I’m not sure what I can do about it
Normal or Abnormal?

• Average age of menarche: 12.5-12.7 years
• Average age of menopause: 51
• Average cycle length: 28 (21-35) days
• Average duration of menses: 2-7 days
• Median blood loss: 53mL/cycle
You can measure that??

• Yes you can!!

![Diagram of Stomacher Lab-Blender]

Fig. 1. A cross-sectional diagram of the Stomacher Lab-Blender

Newton et al Contraception 1977 16(3)

But you don’t have to!
Menorrhagia I

• 952 women from 3 hospitals
  • 782 completed menstrual evaluation questionnaires (MEQ)
  • 226 undertook menstrual collection
  • 34% had losses > 80mL/cycle

Warner et al AJOG (2004) 190
Menorrhagia I – Clinical Factors

**Blood loss >80ml/cycle**
- Required rate of change of protection (more often than hourly)
- Low ferritin
- Clots > 50-pence (1.1 inch)

**Increased blood loss**
- Patient report of “very heavy” bleeding
- Changing protection overnight
- Number of products used/cycle
# Pictorial Blood Assessment Chart (PBAC)

<table>
<thead>
<tr>
<th>Name: Sabine Mustermann</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date: Week 5/11 5/18</td>
</tr>
<tr>
<td>Sanitary towel</td>
</tr>
<tr>
<td><strong>Intensity of bleeding per sanitary towel</strong></td>
</tr>
<tr>
<td>x 5</td>
</tr>
<tr>
<td>x 20</td>
</tr>
<tr>
<td>and/or Tampons</td>
</tr>
<tr>
<td><strong>Intensity of bleeding per tampon</strong></td>
</tr>
<tr>
<td>x 5</td>
</tr>
<tr>
<td>x 15</td>
</tr>
<tr>
<td>Daily points:</td>
</tr>
</tbody>
</table>

- Sensitivity: 86%
- Specificity: 89%

Hald et al JMIG (2014) 21

www.ismaap.org
HMB vs AUB

• HMB: >80mL blood loss/cycle

• AUB (as defined by ACOG)
  • HMB
  • Bleeding or spotting between periods
  • Bleeding or spotting after sex
  • Menstrual cycle <24 days or >38 days
  • Irregular periods (cycle length varies by more than 7-9 days)
  • Postmenopausal bleeding
If you can ask...

• One question
  • Are your periods moderate, heavy or very heavy?

• Three questions
  • How often do you change protection?
    • Include wearing ‘double’ protection
  • Do you pass clots >1 inch?
  • Do you or have you ever had to take iron supplements?
    • Consider a ferritin level
HMB in Anticoagulated Patients

• Incidence
  • Non-anticoagulated patients: ~33%
  • Anticoagulated patients: 70%

• Complications
  • Iron deficiency
  • Decreased quality of life
  • *AC interruptions*
Which anticoagulant is associated with the highest rates of HMB?

A. LMWH/Warfarin
B. Rivaroxaban
C. Apixaban
D. Edoxaban
HMB and AUB in DOAC Trials

- HMB/AUB not an outcome in major trials
  - Captured only as major or CRNM bleeds

<table>
<thead>
<tr>
<th>DOAC</th>
<th>Incidence – LWMH/VKA</th>
<th>Incidence – DOAC</th>
<th>Relative Risk vs LMWH/VKA</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>4.52%</td>
<td>5.40%</td>
<td>1.18 (0.82-1.71)</td>
<td>0.37</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>4.53%</td>
<td>9.53%</td>
<td>2.10 (1.64-2.69)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>7.13%</td>
<td>8.99%</td>
<td>1.26 (1.01-1.58)</td>
<td>0.044</td>
</tr>
</tbody>
</table>

Godin et al Vascul Pharmacol (2017) Epub
HMB and AUB in DOAC Trials

• Apixaban vs LMWH/VKA (AMPLIFY)
  • CRNM vaginal bleeding: 2.1-2.5%
    • 45% vs 20% of all CRNM bleeds were uterine

• Rivaroxaban vs LMWH/VKA (EINSTEIN)
  • Women without hysterectomy
    • 29.8% on rivaroxaban
    • 15.5% on enoxaparin/warfarin

Brekelmans et al Thromb Haemost (2017) 117

Martinelli et al Blood (2016) 127 (11)
AUB & Rivaroxaban

• 319 women of reproductive age

• Rivaroxaban vs warfarin
  • HMB 73% vs 67%
  • Prolonged menstrual bleeding 27% vs 8.3%
  • Unscheduled contact with a provider: 41% vs 35%
  • Medical or surgical interventions: 25% vs 7.7%
  • *Adaptation of anticoagulant treatment:* 15% vs 1.9%

De Crem et al Thrombosis Research (2015)136(4)
HMB & Rivaroxaban

• 121 women of reproductive age
  • HMB in 41% (rivaroxaban) vs 18% (VKA)

• Interventions for HMB (rivaroxaban vs VKA)
  • Anticoagulation interruption (2-3 days): 24% vs 9%
  • Tranexamic acid: 12% vs 0
  • Temporary switch to LMWH: 13% vs 0
  • Permanent switch to LMWH or apixaban: 21% vs 2%

Bryk et al Vascul Pharmacol (2016) Epub
HMB & Recurrent VTE

• Compared to VKA, rivaroxaban use predisposed to:
  • HMB: OR 3.2 (1.4-8.2)
  • Interventions during menstruation: OR 4.0 (1.6-11.6)
  • Interruption of anticoagulant treatment: OR 3.2 (1.1-11.6)

• Risk of recurrent VTE for patients with HMB
  • On rivaroxaban: 5.3 (1.1-33.3)
  • On VKA: OR 2.5 (0.1-33.3)
My preferred management strategy for HMB:

A. Refer back to the PCP
B. Refer (or recommend referral) to gynecology
C. Modify the anticoagulant (agent, dose or duration)
D. Nothing in particular, it is unavoidable in some patients
Management of HMB

Non-anticoagulated Patients
• Hormonal therapy
• Hemostatic agents
• Surgical intervention

Anticoagulated Patients
• Hormonal therapy
• Hemostatic agents
• Surgical intervention
• Change anticoagulants
Hormonal Therapies - Progesterone

• Levonorgestrel intrauterine system (Mirena®, Liletta®, Skyla®)
  • Amenorrhea ~ 40%
  • >99% effective
  • No evidence of increased VTE risk

• Subcutaneous implant (Nexplanon®, Implanon®)
  • Amenorrhea ~ 20%
  • >99% effective
  • No evidence of increased VTE risk

Le Moigne et al Haematologica (2016)
Hormonal Therapies - Progesterone

• Progesterone pill (mini-pill)
  • Increased AUB
  • Low efficacy for pregnancy prevention
  • No evidence of increased risk of VTE

• Medroxyprogesterone IM (Depo Provera®)
  • Amenorrhea- 55%
  • >99% effective (when used correctly)
  • Increased risk of recurrent VTE
Hormonal Therapies - Combined

• OCPs/patches/vaginal ring
  • Estrogen doses
    • Low (<50µg), intermediate (50µg), high (>50µg)
  • Progestin types
    • 2nd generation (levonorgestrel, norgestrel)
    • 3rd generation (desogestrel, gestodene, norgestimate)
    • Drospirenone

• Can be used to skip menses
• 91% effective
Isn’t estrogen contraindicated???

• Annual risk of recurrent VTE while on anticoagulation
  • Estrogen therapy: 3.7%
  • Progestin only therapy: 3.8%
  • No hormonal therapy: 4.7%

• Risk of recurrent VTE in pregnancy
  • Antepartum: 4.1-7.5%
  • Postpartum: up to 15.5%

Martinelli et al Blood (2016) 127 (11)
Nonhormonal Options

• Antifibrinolytics
  • Tranexamic acid (TXA) or aminocaproic acid (amicar)
  • Theoretical concern for VTE

• Surgical interventions
  • Extreme cases, in patients who have completed child-bearing
    • Endometrial ablation
    • Uterine artery embolization
    • Hysterectomy
Additional Strategies

• Trial of alternative anticoagulant
  • Avoid holding drug!

• Consider iron deficiency with and without anemia

• Consult your friendly local gynecologist!
  • Expand clinical services
  • Opportunities for collaboration
Postmenopausal Bleeding

• Bleeding that occurs after 1 year of no periods
  • Always abnormal

• Perimenopause = “around menopause”
  • Can last up to 10 years
  • Irregular bleeding
  • Heavy bleeding

• Evaluated and managed by gynecology
Postmenopausal Bleeding on AC

• Posthoc analysis of AMPLIFY
  • 21% of CRNM vaginal bleeds were postmenopausal
  • 55% had a prior known gynecological diagnosis
    • Fibroids
    • Cancer
    • Endometrial hyperplasia
Uterine Bleeding Pearls

• Premenopausal women: always, always ask!
  • Are your periods very heavy?
  • How often do you change protection?
  • Do you pass clots > 1 inch?
  • Are you or have you ever been iron deficient?

• Postmenopausal women: always, always ask!
  • Are you having ANY vaginal bleeding?
Uterine Bleeding Pearls

• IUDs are your friend!

• OCPs are safer than pregnancy!
  • Especially while anticoagulated!

• Make friends with your local gynecologist!
  • They will be SO glad you care!