The Evidence Based Approach to the Management of Acute AUB

Lauren Castleberry, MD, FACOG
USC Palmetto Health
Assistant Professor

Disclosures

• None

Objectives

• Define Acute Abnormal Uterine Bleeding (AUB)
• Briefly review the etiologies & workup of acute AUB
• Review the evidence for medical management of acute AUB
Acute Abnormal Uterine Bleeding

- Defined as an episode of heavy bleeding, that in the opinion of the clinician, is of sufficient quantity to require immediate intervention to prevent further blood loss.

Assessment of the Patient with Acute AUB

#1: Evaluate for signs of hypovolemia & potential hemodynamic instability

#2: If unstable or hypovolemic, establish appropriate IV access

#3: Evaluate for the most likely etiology

Diagram: Abnormal Uterine Bleeding (AUB)
- Heavy menorrhagia bleeding (AUB-HMB)
- Intermenstrual bleeding (AUB/MB)

Workup of Acute AUB

- Thorough history
  - Focus on:
    - Details of the current bleeding episode
    - Related symptoms
    - Past menstrual, gyn, medical history
  - Ask about medications or herbal remedies
    - Warfarin, Heparin, OCP's
    - Ginkgo, Ginseng, Motherwort

- Up to 20% of women presenting with HMB will have an underlying bleeding disorder
- May include:
  - vonWillebrand Disease
  - Other coagulation factor deficiencies
  - Hemophilia
  - Leukemia
  - Liver Failure

Workup of Acute AUB

• If screen positive for a history of a bleeding disorder...
  – Prothrombin
  – Partial thromboplastin time
  – +/- fibrinogen
  – vonWillebrand Testing
    • von Willebrand Ristocetin cofactor activity
    • von Willebrand factor antigen
    • Factor VIII

Workup of Acute AUB

• Based on clinical findings, other tests may be indicated:
  – hCG
  – Thyroid-stimulating hormone
  – Liver function tests
  – Workup for sepsis or leukemia
  – +/- Endometrial sampling
    • Age >45 years old
    • Age <45 with
      – Unopposed estrogen exposure
      – Failed medical management
      – Persistent AUB
    – +/- pelvic US

• Based on:
  – Clinical stability
  – Overall acuity
  – Suspected etiology
  – Desire for future fertility
  – Underlying medical problems
Objectives of Treatment

#1: to control the current episode of heavy bleeding

#2: to reduce menstrual blood loss in subsequent cycles

The Case

A 35 year old G4P2022 with a history of obesity (BMI 31) and pre-diabetes presents with complaints of heavy menstrual bleeding for the past 12 days. She also has complaints of dizziness. The patient reports her cycles are normally every 35 days that last for 7 days with moderate flow. However, with her current episode of bleeding, she is soaking through one pad every 2 hours. She is not currently sexually active.
On exam:
BP 100/60   Pulse 115
Negative for orthostatic changes.

Pelvic Exam:
~ 50 mL of blood/clot in the vault
Active bleeding noted from the os
No cervical trauma or lesions or vaginal lacerations identified
No cervical motion tenderness or abnormal discharge noted
Uterus 8 weeks sized, no adnexal masses palpable

Labs
Hgb 8.9    Platelets 220    WBC 7
Which of the following medical therapies is/are FDA approved for acute AUB?
A. Levonorgestrel intrauterine device
B. Tranexamic Acid
C. Depo Provera
D. Intravenous conjugated equine estrogen

Intravenous estrogen results in which of the following:
A. Rapid growth of the endometrial epithelium and stroma
B. Vasospasm of uterine arteries
C. Increased platelet aggregation & capillary clotting
D. Increased Fibrinogen, Factor V & Factor XI
E. Increased production of both estrogen & progesterone receptors
F. All of the above

TRUE/FALSE?
When compared in a double-blind, randomized, placebo-controlled trial, 25mg of IV CEE was more effective in stopping vaginal bleeding at 3 hours than placebo.
TRUE/FALSE?

When compared in a double-blind, randomized, placebo-controlled trial, 25mg of IV CEE was more effective in stopping vaginal bleeding at 5 hours than placebo.

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

- Placebo-controlled
- 17 patients in each group
- Mean baseline Hgb 12
- 25mg IV CEE given initially and then again at 3 hours
- Bleeding Cessation rates evaluated at 3 & 5 hours

Bleeding Cessation Rates

- At 3 hours, placebo was more effective
- At 5 hours, rates of bleeding cessation with IV CEE was more effective
- Women with endometritis did not respond to therapy with IV CEE
Progesterone treats AUB by:
A. Stabilizing endometrial friability
B. Inhibiting endometrial growth by triggering apoptosis
C. Inhibiting angiogenesis
D. Stimulating conversion of estradiol to the less active estrone
E. All of the above

In a study comparing medroxyprogesterone acetate and oral contraceptives for the treatment of acute AUB, the median number of days to cessation of bleeding in both groups was:
A. 1 day
B. 2 days
C. 3 days
D. 4 days

Oral Medroxyprogesterone Acetate and Combination Oral Contraceptives (COC's) for Acute Uterine Bleeding: A Randomized Controlled Trial


Eligibility Criteria:
- Non-pregnant
- Hemodynamically stable
- Premenopausal women at least 18 years of age
- Required emergent medical or surgical intervention
- Hgb at least 8 g/dL

Interventions:
- Medroxyprogesterone acetate (MPA) 20 mg TID x 7 days
- Norethindrone 1mg/Ethinyl Estradiol (E2) 35 μg TID x 7 days

- Both were followed by either dose above once daily, respectively, for 3 weeks
- 20 patients in each group
Oral Medroxyprogesterone Acetate and Combination Oral Contraceptives for Acute Uterine Bleeding: A Randomized Controlled Trial

- **Primary Outcome**
  - The avoidance of unscheduled surgery in the 28 day follow-up period
- **Additional outcomes:**
  - Days to cessation of bleeding
  - Pad and tampon counts
  - Patient satisfaction scores
  - Degree of ancillary symptoms such as cramping & side effects associated with the meds (i.e. nausea/bloating)

**Results**

- All pts receiving MPA & 95% of OC patients avoided an unscheduled surgical procedure
  - One OC pt underwent a non-elective D&C for acute bleeding
- **Median Number of days to cessation of bleeding in BOTH groups was 3 (P= .400)**

**Table 3. Ancillary Symptoms and Treatment Side Effects**

<table>
<thead>
<tr>
<th>Symptom (Median of Average)</th>
<th>MPA</th>
<th>OCP</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloating</td>
<td>0</td>
<td>0</td>
<td>.444</td>
</tr>
<tr>
<td>Week 1</td>
<td>0.00</td>
<td>0.00</td>
<td>.831</td>
</tr>
<tr>
<td>Week 2</td>
<td>0.00</td>
<td>0.00</td>
<td>.567</td>
</tr>
<tr>
<td>Cramping</td>
<td>1</td>
<td>1</td>
<td>.745</td>
</tr>
<tr>
<td>Baseline</td>
<td>1</td>
<td>1</td>
<td>.745</td>
</tr>
<tr>
<td>Week 1</td>
<td>0.00</td>
<td>0.63</td>
<td>.496</td>
</tr>
<tr>
<td>Week 2</td>
<td>0.00</td>
<td>0.00</td>
<td>.754</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>0</td>
<td>.269</td>
</tr>
<tr>
<td>Baseline</td>
<td>0</td>
<td>0</td>
<td>.269</td>
</tr>
<tr>
<td>Week 1</td>
<td>0.00</td>
<td>0.57*</td>
<td>.710</td>
</tr>
<tr>
<td>Week 2</td>
<td>0.00</td>
<td>0.00</td>
<td>1.000</td>
</tr>
</tbody>
</table>

MPA, medroxyprogesterone acetate; OCP, oral contraceptive pill.
Scored from 0 = none to 4 = unbearable.
* Statistically significant compared with week 2 by signed rank test.
Patient Favorability

<table>
<thead>
<tr>
<th>Percentage of patients that would use the treatment again</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medroxyprogesterone Acetate</td>
</tr>
<tr>
<td>OCP’s</td>
</tr>
</tbody>
</table>

Pitfalls of the Study

- No placebo group
- Heterogeneous group of patients
  - May be a strength of the study though since this reflects real-world scenarios
- Sample size was insufficient to demonstrate actual equivalence between the regimens
  - Though no statistically significant difference was shown
- Dosing decisions were based on textbook recommendations (expert opinion)

But what about the patients with contraindications to estrogen use?
Using results from the Munro trial...
- Median time to bleeding cessation with high-dose oral medroxyprogesterone acetate (MPA) is 3 days

... and pharmacologic data
- Depot Medroxyprogesterone Acetate (DMPA) serum levels are therapeutic 3 days after injection

The following regimen was developed:
- DMPA 150 mg IM + MPA 20mg PO TID x 3 days

Primary Outcomes
1. Efficacy of the therapy in stopping uterine bleeding measured by:
   • Percentage of women who stopped bleeding
   • Mean time to bleeding cessation
   • Drop in Hgb
2. Treatment Feasibility
3. Tolerability

Prospective, single-arm, pilot study

Results
- 48 women
- All reported taking medication as directed
- No patient lost to follow-up until after her bleeding had stopped
- No surgical or additional medical treatments required during the 5 day study period
- Mean time to bleeding cessation was 2.6 days
**TABLE 3**

Response to treatment by study day

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of women (null) bleeding</th>
<th>Number of women who stopped bleeding in prior 24 h</th>
<th>Cumulative number of women who stopped bleeding</th>
<th>Percent of women who stopped bleeding</th>
<th>Mean number of sanitary protection products used in prior 24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (day 0)</td>
<td>48</td>
<td>38</td>
<td>12</td>
<td>12</td>
<td>8.5</td>
</tr>
<tr>
<td>Day 1</td>
<td>28</td>
<td>8</td>
<td>20</td>
<td>20</td>
<td>42.7</td>
</tr>
<tr>
<td>Day 2</td>
<td>28</td>
<td>140</td>
<td>34</td>
<td>70.8</td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td>29</td>
<td>0</td>
<td>39</td>
<td>81.3</td>
<td></td>
</tr>
<tr>
<td>Day 4</td>
<td>9</td>
<td>5</td>
<td>38</td>
<td>81.0</td>
<td></td>
</tr>
<tr>
<td>Day 5</td>
<td>0</td>
<td>9</td>
<td>43</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>

* Number of products used by women who were still bleeding. ** One woman was still spotting on day 3 but was lost to follow-up. *** Four women had spotting but no longer required sanitary protection products.

---

**TABLE 4**

Baseline subject characteristics and baseline and day 3 hemoglobin values

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>40.7 (8.59)</td>
<td>42.0</td>
<td>19-53</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>34.9 (8.09)</td>
<td>33.0</td>
<td>21.5-51.2</td>
</tr>
<tr>
<td>Hemoglobin, baseline, g/dL</td>
<td>10.9 (1.58)</td>
<td>11.1</td>
<td>6.9-14.5</td>
</tr>
<tr>
<td>Hemoglobin, day 3, g/dL</td>
<td>10.9 (1.69)</td>
<td>11.2</td>
<td>6.9-14.2</td>
</tr>
</tbody>
</table>

* Hemoglobin on day 3 was lower than the value from the point of care test (hemocue); this value was determined using the patient’s digitized for study participation.

---

**Satisfaction**

<table>
<thead>
<tr>
<th>Rating of 1-3</th>
<th>1, Poor</th>
<th>2, Good</th>
<th>3, Excellent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Score</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Score</td>
<td>2.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td># of women ranking it a 1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% of patients that would recommend their treatment to a friend</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
A New Progestogen Only Medical Therapy For Outpatient Management of Acute, Abnormal Uterine Bleeding: A Pilot Study

- Limitations
  - Single-arm, non-comparative pilot clinical trial
  - Only patients deemed eligible for outpatient management
  - Only studied short term response to therapy (5 days)
  - High satisfaction rate may be a reflection of receiving:
    - Treatment on site
    - Personal attention from one of the investigators

And then there’s TXA...

Tranexamic Acid (TXA) Treatment for Heavy Menstrual Bleeding:
A Randomized Controlled Trial

- Double Blinded
- Randomized
- Adult women aged 18-49
  - History of Heavy Menstrual Bleeding
  - At least 50 mL in the initial pretreatment cycle & average of 80 mL over two pretreatment cycles
  - No obvious cervical or uterine pathology
    - Myomas allowed as long as not so significant to require surgery
- TXA 1.3 g TID (or at least 6 hours apart) for 5 days
Tranexamic Acid (TXA) Treatment for Heavy Menstrual Bleeding: A Randomized Controlled Trial

- **Primary Endpoints:**
  - Mean reduction in menstrual blood loss with TXA that was:
    1. Significantly greater than in the placebo group
    2. Greater than 50 mL from the baseline
    3. Greater than a reduction in MBL that was perceived meaningful to women (36 mL)

- **Results**
  - 196 patients randomized
    - TXA 123
    - Placebo 73
  - Modified intent to treat
    - TXA 115
    - Placebo 72
  - Completed the study
    - TXA 94
    - Placebo 54

Fig. 2. Menstrual blood loss change over study course. Effects of tranexamic acid (n=115) and placebo (n=72) use on menstrual blood loss as measured by the alkaline hematin method are illustrated over the time course of the study. **P** values are for the comparison between tranexamic acid and placebo.

(Olson, C. O. Tranexamic Acid for Heavy Menstrual Bleeding. *Obstet Gynecol* 2019)
Tranexamic Acid (TXA) Treatment for Heavy Menstrual Bleeding: A Randomized Controlled Trial

• Limitations:
  – Use of COX-2 inhibitors, NSAIDS and hormones prohibited during the menstrual/study cycle
  – Only studied patients with chronic HMB, not acute AUB

• Conclusions:
  – TXA was well tolerated
  – TXA significantly improved
    • Menstrual Blood Loss
    • Health-related quality of life

To Sum it Up

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Schedule</th>
<th>Impact</th>
<th>Patient Favorability</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Conjugated Equine Estrogen</td>
<td>25 mg IV</td>
<td>Q 4-6 hours a24 hours x24 hours</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Medroxyprogesterone Acetate</td>
<td>20 mg PO</td>
<td>3x/day for 7 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined Oral Contraceptives (Monophasic)</td>
<td>35 mcg of Ethinyl Estradiol</td>
<td>TID x 7 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medroxyprogesterone Acetate + IM Depot</td>
<td>DMPA 150 mg MPA 20 mg</td>
<td>Once x3 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tranexamic Acid</td>
<td>1.3g PO</td>
<td>3x/day for 5 days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Back to the Case

A 35 year old G4P2022 with a history of obesity (BMI 31) and pre-diabetes presents with complaints of heavy menstrual bleeding for the past 12 days. She also has complaints of dizziness. The patient reports her cycles are normally every 35 days that last for 7 days with moderate flow. However, with her current episode of bleeding, she is soaking through one pad every 2 hours. She is not currently sexually active.
On exam:
BP 100/60  Pulse 115
Negative for orthostatic changes.

Pelvic Exam:
~ 50 mL of blood/clot in the vault
Active bleeding noted from the os
No cervical trauma or lesions or vaginal lacerations identified
No cervical motion tenderness or abnormal discharge noted
Uterus 8 weeks sized, no adnexal masses palpable

Labs
Hgb 8.9  Platelets 220  WBC 7

The Case (continued)

• How would you treat her...
  – Assuming she is not currently contemplating a pregnancy?
  – Keeping in mind her BMI?

Things to keep in Mind...

• Be careful that the patient does not have contraindications to hormonal therapy
• Bleeding that does not respond to initial treatment requires additional investigation
In Conclusion

• Treatment of AUB first requires an evaluation for likely etiologies
  – Always perform a pelvic exam!
• Available treatment methods should be considered while being cognizant of possible contraindications
• Consider the patient’s comorbidities and reproductive plans when deciding on a treatment method

References


