A Stepwise Approach to the Workup and Management of AUB in the Reproductive Aged Patient

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- I have no financial disclosures

Objectives

- Review the definitions & accepted nomenclature
- Discuss the differential for AUB
- Create a thorough workup
- Provide evidence-based management guidelines
Definitions & Nomenclature

- What is normal?
  - Menstrual cycle lasts between 21-35 days
  - Blood loss <80 mL
  - Typical length of menstrual flow is 4-8 days
- What is abnormal?
  - Anything that deviates from the above

In 2011, developed a new classification system

- AUB is now paired with descriptors to denote the bleeding pattern
  - HMB – Heavy Menstrual Bleeding
  - IMB – Intermenstrual Bleeding
- Additional letter qualifiers
  - PALM-COEIN

Abnormal Uterine Bleeding (AUB)
- Heavy menstrual bleeding (AUB/HMB)
- Intermenstrual bleeding (AUB/IMB)

PALM: Structural Causes
- Polyp (AUB-P)
- Adenomyosis (AUB-A)
- Leiomyoma (AUB-L)
  - Submucosal myoma (AUB-Lm)
  - Other myoma (AUB-L)
- Malignancy & hyperplasia (AUB-M)

COEN: Nonstructural Causes
- Coagulopathy (AUB-C)
- Ovulatory dysfunction (AUB-O)
- Endometrial (AUB-E)
- Iatrogenic (AUB-I)
- Not yet classified (AUB-N)

What AUB is NOT...

Common age-based differentials

- Ages 13-18
  - Anovulation
  - Hormonal contraception, pregnancy, PID, coagulopathies, tumors
- Ages 19-39
  - Pregnancy
  - Structural lesions (leiomyomas/polyps)
  - Anovulatory Cycles (PCOS)
  - Hormonal contraception
  - Endometrial hyperplasia
Common age-based differentials

• Age 40 to Menopause
  – Anovulatory bleeding
  – Endometrial hyperplasia/carcinoma
  – Endometrial atrophy
  – Leiomyomas

Workup of AUB

• Thorough history
  – Up to 20% of women presenting with HMB will have an underlying bleeding disorder
  – Ask about medications or herbal remedies
    • Warfarin, Heparin, OCP's
    • Ginkgo, Ginseng, Motherwort


Workup of AUB

• Physical Exam
  – Evaluate for findings consistent with PCOS, bleeding disorders
  – Pelvic Exam ALWAYS!
    • Speculum AND bimanual

www.dmick.net
Workup of AUB

• β-hCG testing
• Complete Blood Count
  – Anemia
  – Thrombocytopenia
• Thyroid stimulating hormone levels
• +/- Prolactin levels
• Chlamydia screening in high risk patients

Workup of AUB

• In patients with a positive screening history of a bleeding disorder...
  – Prothrombin
  – Partial thromboplastin time
  – +/- fibrinogen
  – vonWillebrand Testing
    • von Willebrand Ristocetin cofactor activity
    • von Willebrand factor antigen
    • Factor VIII
  – Bleeding time is NOT sensitive or specific & is NOT indicated

Workup of AUB

• Pap smear
  – In non-adolescents
• Endometrial Sampling
  – A first-line test in pts >45 years old
  – Do in women <45 years old if they have a history of:
    • Unopposed estrogen exposure
    • Failed medical management
    • Persistent AUB
The Accuracy of Endometrial Sampling in the Diagnosis of Patients with Endometrial Carcinoma and Hyperplasia

* A Meta-Analysis

- Meta-analysis
- Compared the use of the pipelle in diagnosing EM cancer & Atypical hyperplasia to the use of other devices when then compared to Hysteroscopy, D&C and/or hysterectomy


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The Accuracy of Endometrial Sampling in the Diagnosis of Patients with Endometrial Carcinoma and Hyperplasia

* A Meta-Analysis

- Sensitivity for diagnosing EM cancer:
  - Premenopausal 91%
  - Postmenopausal 99.6%
- Sensitivity for diagnosing Atypical Hyperplasia
  - 81%
- Specificity >98%
- Great for an initial evaluation, but it should only be an endpoint when it reveals cancer or atypical complex hyperplasia (EIN)

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Imaging workup of AUB

- TVUS
- Saline infusion sonohysterography
- Hysteroscopy
- TAUS for adolescents if necessary
- Routine MRI is NOT recommended
Pelvic US

- Helpful to evaluate the myometrium, BUT
  - Sensitivity & Specificity for evaluating intra-cavitary pathology are only 56 and 73% respectively
  - Endometrial stripe thickness is NOT useful in the premenopausal patient
  - Inferior to SIS for detection of intra-cavitary lesions such as polyps and submucosal leiomyomas

Pelvic US vs. SIS

At what point is therapy appropriate?

- IF there is a low risk of endometrial hyperplasia, neoplasia, or structural abnormalities (i.e. adolescents), a trial of therapy is appropriate.

- In patients with increased risk of endometrial hyperplasia or cancer, therapy should only be considered AFTER a complete diagnostic evaluation has been completed.

**Treatment Options**

- **Polyps**
  - Surgical removal

- **Adenomyosis**
  - Medical/surgical options

- **Leiomyomas**
  - Medical/surgical options

- **Malignancy**
  - Medical/surgical options

- **Coagulopathy**
  - Treat the underlying disorder

- **Ovulatory dysfunction**
  - Medical therapy preferred

- **Endometrial**
  - Medical/surgical options

- **Iatrogenic**
  - Stop the offending agent

- **Not yet classified**
  - Medical/surgical options
Treating AUB-O

• Underlying disorder is endocrinologic
  – Fix the underlying etiology if possible, i.e. thyroid
• Surgical treatment is rarely indicated but may be necessary when:
  – Medical therapy fails
  – Medical therapy is contraindicated or not tolerated by the patient
  – The patient has concomitant significant intra-cavitary lesions

The Big Picture
Think of Estrogen as:

FERTILIZER

Think of Progesterone as:

THE WEEDWACKER

The EM lining in an Estrogen Dominant Uterus
The EM lining in a Uterus balanced by Estrogen & Progesterone

Treating AUB-O

- Important for
  - Thinning the endometrium
  - Protecting the endometrium from hyperplastic transition
  - +/- contraceptive effects

Medical options

- Progestin therapy
  - Levonorgestrel IUD
  - Medroxyprogesterone acetate
  - Megestrol acetate
  - Norethindrone acetate
  - Depot medroxyprogesterone acetate
- Combined hormonal contraception
  - Patches, Rings, oral meds
Treating AUB-O

- **Surgical Options**
  - Not preferred as first-line management
  - Include endometrial ablation & hysterectomy

Treating AUB-O

- **Endometrial Ablation**
  - Patient remains at risk for development of hyperplasia/cancer

Treating AUB-O

- **Hysterectomy**
  - Definitive management
AUB Treatment options

- NSAIDs
- Tranexamic Acid
- Hormone therapy
- Uterine Artery Embolization
- Surgery

Medical Treatment Options

- NSAIDs
  - Includes
    - Ibuprofen
    - Naproxen
    - Mefenamic Acid
  - Decreases the rate of PGE-2 & PGF-2 alpha synthesis in the endometrium
    - Leads to vasoconstriction & reduced bleeding

Medical Treatment Options

- NSAIDs (cont’d)
  - Advantages
    - Nonhormonal, noncontraceptive
    - No increased risk of thrombosis
    - Minimal adverse effects
    - Low cost
    - Reduces dysmenorrhea
    - Not a daily medication
Medical Treatment Options

• NSAIDs (cont’d)
  – Benefits
    • 20-50% Menstrual Blood Loss Reduction
    • Efficacy of Naproxen & mefenamic acid is similar

• NSAIDs (cont’d)
  – Timing of use
    • Should start on the first day of the cycle & continue until menstruation ceases
  – Dosing
    • Mefenamic Acid 500 mg TID
    • Naproxen 500 mg x1, then 250-500 mg BID
    • Ibuprofen 600 mg once daily

Medical Treatment Options

• Tranexamic Acid
  – For women who do not desire or should not use hormonal treatment
  – Anti-fibrinolytic agent
    • Blocks the conversion of plasminogen to plasmin → reduced fibrinolysis
  – Advantages
    • May be used while trying to conceive
    • Only taken during menses
Medical Treatment Options

- Tranexamic Acid
  - Risks
    - Increased cost (in the U.S.)
    - FDA labeling lists a history of or elevated risk of VTE as a contraindication
      - Not yet supported by any studies
  - Benefits
    - Reduces menstrual blood loss (MBL) by 26-54% in women with HMB
    - More effective than NSAIDs
    - LESS effective than LNG-IUS

Tranexamic Acid Treatment for Heavy Menstrual Bleeding
A Randomized Controlled Trial

- Randomized, placebo-controlled trial
  - TA group 115
  - Placebo 72
- Treatment was with TA 3.9g/day x 5 days
- 3 primary endpoints; mean reduction in MBR had to be:
  - Significantly greater than placebo
  - Greater than 50 mL
  - Greater than a predetermined meaningful threshold of 36 mL

Lukes, et al.

- Reduction in MBL
  - TA group
    - 69.6mL (40.4%)
  - Placebo group
    - 12.6mL (8.2%)
Medical Treatment Options

- Hormone therapy
  - Combined contraceptives
  - Progestins

Medical Treatment Options

- Combined Contraceptives
  - Pill/patch/ring
    - Only one OCP brand has been FDA approved for HMB
    - Is a short-interval hormone free pill (26/2)
  - Advantages
    - Make cycles more regular, lighter & reduce dysmenorrhea
    - Provide contraception
    - Provides endometrial protection
  - Risks
    - Increased risk of VTE

Take a look at the numbers

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Risk Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-pregnant, non-OCP user</td>
<td>1-5/10,000 woman years</td>
</tr>
<tr>
<td>Female patient on OCP/Ring/Patch</td>
<td>3-9/10,000 woman years</td>
</tr>
<tr>
<td>Pregnant patient</td>
<td>5-20/10,000 woman years</td>
</tr>
<tr>
<td>Postpartum patient</td>
<td>40-65/10,000 woman years</td>
</tr>
</tbody>
</table>

Food and Drug Administration. Combined hormonal contraceptives (CHCs) and the risk of cardiovascular disease endpoints. Silver Spring (MD): FDA; 2011.
Medical Treatment Options

• Combined Contraceptives
  – Benefits
    • Can reduce MBL by 35-69%
  – Dosing
    • Cyclic (monthly withdrawal bleed)
    • Extended (q3-4 months)
    • Continuous (no withdrawal bleed)

Medical Treatment Options

• Progestins
  – Levonorgestrel intrauterine device (LNG-IUS)
  – Depot medroxyprogesterone acetate
  – High dose oral progestins

Medical Treatment Options

• LNG-IUS
  – Advantages
    • Decreases the risk of hemorrhage
    • Provides endometrial protection against hyperplasia & cancer
    • FDA approved for HMB
  – Risks
    • Cost
    • Possibly has a higher expulsion rate in women with uterine fibroids (relative contraindication)
Medical Treatment Options

• LNG-IUS
  – Benefits
    • Decreases MBL by 71-95%
  – Dose
    • 20 mcg/24 hours (Mirena)

Medical Treatment Options

• Depot Medroxyprogesterone Acetate
  – Advantages
    • May be used in patients with contraindications to estrogen
    • Contraceptive
  – Benefits
    • 49% reduction in MBL after two months
  – Risks
    • Weight gain
    • Breakthrough bleeding
  – Dose
    • 150 mg IM every 3 months

Medical Treatment Options

• High dose oral progestins
  – Advantages
    • May be used in patients with contraindications to estrogen
    • Cyclic vs. daily dosing
    • Cyclic dosing can create predictable, moderate withdrawal bleeding
    • FDA approved
  – Benefits
    • Oral MPA given continuously for 2 months decreased MBL by 33%
Medical Treatment Options

- High dose oral progestins
  - Risks
    - May increase risk of VTE
  - Dose
    - Norethindrone acetate 5mg (1-3 tablets daily)
    - Medroxyprogesterone acetate 5-30 mg daily

The Bottom Line...

<table>
<thead>
<tr>
<th>Drug</th>
<th>Menstrual Blood Loss Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td>20-50%</td>
</tr>
<tr>
<td>Tranexamic Acid</td>
<td>26-54%</td>
</tr>
<tr>
<td>Combined Oral Contraceptives</td>
<td>35-69%</td>
</tr>
<tr>
<td>High Dose Oral Progestones</td>
<td>33%</td>
</tr>
<tr>
<td>Depo Medroxyprogesterone Acetate</td>
<td>49%</td>
</tr>
<tr>
<td>LNG-IUS</td>
<td>71-95%</td>
</tr>
</tbody>
</table>

Treatment Options

- IR Uterine Artery Embolization
  - Indicated for women with uterine fibroids
  - Contraindicated for women who have not completed childbearing
Surgical Treatment Options

- Surgical interventions
  - D&C with Hysteroscopic myomectomy/polypectomy
    - For intra-cavitary lesions
  - Abdominal myomectomy
    - May require future cesarean sections
    - Fibroids may return
  - Endometrial ablation
    - Minimally invasive
    - Requires another form of contraception
    - Efficacy equivalent to the LNG-IUS in reducing MBL
  - Hysterectomy
    - Definitive but with major risks of surgery

Postmenopausal Bleeding

- Most common presenting sign of endometrial cancer in PMP patients
  - 90% of patients
- Most common cause though is vaginal/endometrial atrophy
- However, 1-14% of women with PMP bleeding will have Endometrial Cancer
- So... PMP is CANCER UNTIL PROVEN OTHERWISE!!

TVUS for postmenopausal bleeding

<table>
<thead>
<tr>
<th>Reference</th>
<th>Endometrial Thickness</th>
<th>Number of Women</th>
<th>Number of Cases of Cancer</th>
<th>Negative Prediction Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kattas 1995</td>
<td>≤4 mm</td>
<td>1,168</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Ferraz 1996</td>
<td>≤4 mm</td>
<td>900</td>
<td>2</td>
<td>99.6%</td>
</tr>
<tr>
<td>Guell 2000</td>
<td>≤4 mm</td>
<td>163</td>
<td>1</td>
<td>99.4%</td>
</tr>
<tr>
<td>Epstein 2003</td>
<td>≤4 mm</td>
<td>87</td>
<td>0</td>
<td>100%</td>
</tr>
</tbody>
</table>

*Based on transvaginal ultrasonography*
EMB for postmenopausal bleeding

- An alternative first approach
- Failure/insufficient tissue for diagnosis occurs in up to 54%
- If TVUS is performed & the EM thickness is ≤4mm, no additional evaluation is needed...
- HOWEVER, if bleeding recurs or persists, additional evaluation is indicated

Limitations to US

- Factors that can make assessment difficult:
  - An axial uterus
  - Marked obesity
  - Coexisting myomas
  - Previous uterine surgery
- Failure to identify a thin, distinct endometrial thickness should lead to additional evaluation
- If fluid is present, it should NOT be included in measuring endometrial thickness

Incidentally found thickened EM lining

- Only a small amount of data available
- The significance of a measurement >4mm incidentally discovered is unclear
- Assessment should be individualized based on patient characteristics and risk factors
- Bottom Line: TVUS is NOT an established tool to screen for uterine cancer in the asymptomatic patient
Conclusions

- PALM COEIN is the new classification system for abnormal uterine bleeding
- DUB is no longer an acceptable term
- A thorough workup will evaluate for both structural and nonstructural causes
- The medical treatment with the greatest reduction in menstrual blood loss is the LNG-IUS

References

- Food and Drug Administration. Combined hormonal contraceptives (CHCs) and the risk of cardiovascular disease endpoints. Silver Spring (MD): FDA; 2011.
- Kaunitz, Andrew. Management of Abnormal Uterine Bleeding. In: UpToDate, Barton RL (Ed), UpToDate (Accessed on February 18, 2016).