Abnormal Uterine Bleeding: Evaluation of Premenopausal Women

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Objectives

• Define normal and abnormal uterine bleeding
• Review differential diagnosis and evaluation for abnormal bleeding in premenopausal women
• Recommend guidelines for the use of endometrial biopsy
Normal Uterine Bleeding

Classically…

• Cycle length 21 to 35 days
• Menses 2-7 days
• Less than 80 cc per cycle
The Menstrual Cycle
A 24 year old G0 presents with heavy irregular bleeding for 6 months. Her bleeding is every 15-35 days, lasts 4-15 days. She has…

A. Menorrhagia
B. Dysfunctional uterine bleeding (DUB)
C. Menometrorrhagia
Classic Definitions

Excess Bleeding
- Menorrhagia: heavy, regular timing
- Metrorrhagia: light, frequent intervals
- Menometrorrhagia: heavy, frequent, irregular
- Polymenorrhea: regular, <24 days apart
- Intermenstrual spotting: bleeding between menses

Decreased bleeding
- Oligomenorrhea: bleeding >35 days apart
Dysfunctional Uterine Bleeding

• Excessive noncyclic bleeding not caused by anatomic lesion, medications, pregnancy or systemic disease
• Primarily due to anovulation
Challenges with Classic Definitions

- Data is from women in Minnesota, 1930s

- Lack of uniformity across clinical settings

Treloar EA, Boynton, Int J Fertil 1967
Challenges with Classic Definitions

- International meeting of experts 2005 (Menstrual Agreement Process)

- Recommendations:
  - Discontinue use of classic terms
  - Use descriptive terms that patients understand
  - Create uniformity for research

## New Descriptive Terms for AUB

<table>
<thead>
<tr>
<th>Clinical Dimensions</th>
<th>Descriptive Terms</th>
<th>Normal limits (5th to 95th percentiles)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FREQUENCY</strong> (days)</td>
<td>Frequent</td>
<td>&lt;24</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>24-38</td>
</tr>
<tr>
<td></td>
<td>Infrequent</td>
<td>&gt;38</td>
</tr>
<tr>
<td><strong>REGULARITY</strong></td>
<td>Absent</td>
<td>-</td>
</tr>
<tr>
<td>Cycle to cycle variation over 1 year</td>
<td>Regular</td>
<td>Variation ±2-20 days</td>
</tr>
<tr>
<td></td>
<td>Irregular</td>
<td></td>
</tr>
<tr>
<td><strong>DURATION</strong> (days)</td>
<td>Prolonged</td>
<td>&gt;8</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>4.5-8</td>
</tr>
<tr>
<td></td>
<td>Shortened</td>
<td>&lt;4.5</td>
</tr>
<tr>
<td><strong>VOLUME</strong> (monthly mL)</td>
<td>Heavy</td>
<td>&gt;80</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>5-80</td>
</tr>
<tr>
<td></td>
<td>Light</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

Case 2

A 33 yo G1P1 with regular, normal periods but three months of light spotting in between periods. Spotting is 5-9 days a month, randomly distributed between cycles. She uses a copper IUD for contraception.

What is the differential diagnosis?
Four steps:

1. Is it uterine?
2. Is she pregnant?
3. Describe the bleeding.
4. Is it ovulatory?
FIGO Classification: PALM-COEIN

- Polyp
- Adenomyosis
- Leiomyoma
- Malignancy & Hyperplasia

- Coagulopathy
- Ovulatory Dysfunction
- Endometrial
- Iatrogenic
- Not Yet Classified

Munro et al, Fertil Steril 2011;95:2204–8
Evaluation: premenopausal women

Four steps:

1) Is it uterine?
   - Detailed history to r/o GI/GU sources
   - Exam to r/o obvious vulvar, vaginal, cervical lesions
   - Up to date Pap smear
Case 2

During the pelvic exam, the patient is noted to have a 2cm cervical polyp which is removed in the office. She has full resolution of her bleeding at 6 week follow-up.
Evaluation: premenopausal women

Four steps:

1) Is it uterine?

2) Is she pregnant?
   Check pregnancy test in at-risk women
A 41 yo G3P2 with 4 months of abnormal bleeding. Regular cycle length every 29-32 days, lasts 7 days, but bleeding is heavy. She changes a tampon every hour for the first 3 days and has to get up at night to change tampons/pads.
Evaluation: premenopausal women

Four steps:
1) Is it uterine?
2) Is she pregnant?
3) Describe the bleeding.
   • Detailed history will guide w/u and treatment
   • Consider menstrual calendar X 2-3 cycles
Tips to assess bleeding history

Factors associated with heavy bleeding:
1. Bleeding history
2. Change pads/tampons $\leq 3$ hour intervals
3. High number of pads/tampons per cycle ($>21$)
4. Require change of tampon/pad during night
5. Have clots $>1$ inch

Warner, Critchley et al, Am Jo Obstet Gynecol, 2004
Case 3

A 41 yo G3P2 with 4 months of abnormal bleeding. Regular cycle length every 29-32 days, lasts 7 days, but bleeding is heavy. She changes a tampon every hour for the first 3 days and has to get up at night to change tampons/pads.

Bleeding is **REGULAR** in timing and duration but **HEAVY** volume (menorrhagia or HMB).
Evaluation: premenopausal women

Four steps:
1) Is it uterine?
2) Is she pregnant?
3) Describe the bleeding.
4) Is it ovulatory?
   - Regular intervals
   • Moliminal symptoms
**Classic Definitions**

**Ovulatory**
- Menorrhagia: heavy, *regular* timing
- Polymenorrhea: *regular*, <24 days apart
- Intermenstrual spotting: bleeding between regular menses

**Anovulatory**
- Metrorrhagia: light, frequent intervals
- Menometrorrhagia: heavy, frequent, irregular
- Oligomenorrhea: bleeding >35 days apart
- Intermenstrual spotting: bleeding between menses
Ovulatory AUB

Hypothalamic-pituitary-ovarian axis intact
Ovulatory AUB: Differential Diagnosis

- Anatomic
  - Fibroids
  - Adenomyosis
  - Polyps

- Bleeding disorder/ Medication
  - VonWillibrands
  - ITP
  - Coumadin

- Idiopathic
Ovulatory AUB: History

- Medical comorbidities
- Medications
- Thyroid symptoms (see Thyroid slides)
- Disorder of hemostasis
  - Heavy menses since menarche OR
  - History of postpartum hemorrhage, bleeding with surgery/dental work OR
  - 2 or more of the following---bruising >5cm or epistaxis 1-2/month, frequent gum bleeding, family history of bleeding

Ovulatory AUB: Physical exam

Fibroids

Adenomyosis
Ovulatory AUB: Blood tests

- CBC, TSH
- Screen for disorders of hemostasis according to history
  - PT, APTT
  - VWF antigen, ristocetin cofactor, factor VIII

Ovulatory AUB: Imaging Options

- Pelvic ultrasound vs. MRI
- In 108 premenopausal women with ovulatory AUB scheduled for hysterectomy: *both performed well for fibroid detection
  *MRI better for exact fibroid location

<table>
<thead>
<tr>
<th>DETECTION OF FIBROIDS</th>
<th>Pelvic Ultrasound</th>
<th>Pelvic MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>91</td>
<td>86</td>
</tr>
<tr>
<td>Positive predictive value (%)</td>
<td>96</td>
<td>92</td>
</tr>
<tr>
<td>Negative predictive value (%)</td>
<td>97</td>
<td>97</td>
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</table>

Ovulatory AUB: Imaging Options

- Overall evaluation of endometrial cavity: MRI, Hysterosalpingogram (HSG), hysteroscopy superior to US
- Endometrial polyps: HSG and hysteroscopy superior to MRI and US
- Submucosal fibroids: MRI superior to all

<table>
<thead>
<tr>
<th>EVALUATION OF UTERINE CAVITY MORPHOLOGY</th>
<th>Pelvic Ultrasound</th>
<th>Pelvic MRI</th>
<th>HSG</th>
<th>Hysteroscopy</th>
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</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>69</td>
<td>76</td>
<td>83</td>
<td>84</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>83</td>
<td>92</td>
<td>90</td>
<td>88</td>
</tr>
<tr>
<td>PPV(%)</td>
<td>71</td>
<td>86</td>
<td>85</td>
<td>80</td>
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<tr>
<td>NPV (%)</td>
<td>82</td>
<td>86</td>
<td>89</td>
<td>91</td>
</tr>
</tbody>
</table>

Dueholm, et al, Fert Sterility, August 2001
Case 3

A 41 yo G3P2 with 4 months of abnormal bleeding. Regular cycle length every 29-32 days, lasts 7 days, but bleeding is heavy. She changes a tampon every hour for the first 3 days and has to get up at night to change tampons/pads.

Bleeding is **REGULAR** in timing and duration but **HEAVY** volume (menorrhagia).

- No PMH
- No medications
- Exam: nl size uterus
- Hct 29
Submucosal Fibroid: Ultrasound vs. MRI
# Ovulatory AUB: Treatment

**Proven benefit in randomized trials:**

<table>
<thead>
<tr>
<th>SURGICAL</th>
<th>MEDICAL</th>
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<tbody>
<tr>
<td>Endometrial Ablation</td>
<td>NSAID</td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>Tranexamic Acid</td>
</tr>
<tr>
<td>Fibroids</td>
<td>Hormonal contraception</td>
</tr>
<tr>
<td>Myomectomy</td>
<td>Cyclic progestin</td>
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<tr>
<td>Uterine Artery Embolization</td>
<td>LNG-IUD (more effective than other hormonal treatment or NSAIDs)</td>
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<tr>
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<td>GnRH agonists</td>
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<td>Mifepristone (fibroids)</td>
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</table>

**No randomized trials to date:**

<table>
<thead>
<tr>
<th>SURGICAL (for Fibroids)</th>
<th>MEDICAL</th>
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</thead>
<tbody>
<tr>
<td>MR Guided Focused Ultrasound</td>
<td></td>
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<tr>
<td>Radiofrequency ablation</td>
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</tbody>
</table>
In meta-analysis of 12 randomized trials (n=1,049 women):

-- 58% of “medical management” group had undergone surgery within 2 years.

- Surgery (hysterectomy or endometrial ablation) decreased bleeding more than oral medication.
- LNG-IUD comparable to surgery for improvement in quality of life.

49 yo G2P2 with 5 months of heavy bleeding. Regular cycle length and duration, but heavy bleeding resulting in significant anemia with hct of 25%. Endometrial biopsy?

A. Yes
B. No
38 yo G2P2 with 5 months of irregular bleeding. Bleeding is every 2-3 weeks, lasts 5-12 days, and heavy. Has to change tampon every 1-2 hours for the first few days.

A. Yes
B. No
Endometrial Biopsy

Endometrial Cancer Facts

• 4th most common cancer in women (2.5% lifetime risk)
• Average age 61 but 25% occur pre-menopausally
• Rare to have cancer without abnormal bleeding
• Risk factors: unopposed estrogen (anovulation), obesity, nulliparity, diabetes, hypertension
“...based on age alone, endometrial assessment to exclude cancer is indicated in any woman older than 35 years who is suspected of having anovulatory uterine bleeding.”
“Endometrial sampling should be performed in patients with **AUB** who are >45 years as a first-line test.....

and <45 years with a history of unopposed estrogen exposure, failed medical management, and persistent AUB”
13-18 years: if medical treatment has failed after thorough investigation of all potential other causes and co-morbid disorders.

19-39 years: do not respond to medical therapy or have prolonged periods of unopposed estrogen stimulation.

40-menopause: all women >45 years who present with suspected anovulatory uterine bleeding should be evaluated with endometrial biopsy.

ACOG Practice Bulletin, Number 136, July 2013
Normal Perimenopause

• 12% suddenly stop menstruating
• 18% have longer, heavier menses
• 70% have short, irregular menses

Should we perform EMB on 88% of perimenopausal women?

Treloar EA, Boynton, Int J Fertil 1967
Suggested guidelines for performing endometrial biopsy

Premenopausal, age > 45 years:

- Heavy, irregular bleeding: YES
- Risk factors for cancer: YES
- Perimenopausal infrequent/scant bleeding: NO
- Regular bleeding pattern: NO

ACOG guideline: Level C evidence (not studies, consensus and expert opinion)
AUB: Thyroid disorders

|                               | HYPERthyroid | HYPOTHYroid |
|                               |             |             |
| Frequency of abnormal cycles  | 21%         | 23%         |
| Oligo/amenorrhea              | 63%         | 55%         |
| Heavy bleeding                | 37%         | 30%         |

- Consider checking TSH in women with any type of AUB
- Check TSH/Free T4 if suspect hypothalmic/pituitary lesion to detect central hypothyroidism

Case 6: Anovulatory bleeding

A 24 yo G0 with 8 months abnormal bleeding. Bleeding is every 10-45 days, lasts 5-20 days, heavy for most days of bleeding. BMI 33.
Evaluation: premenopausal women

Four steps:
1) Is it uterine? YES.
2) Is she pregnant? Upreg neg.
3) Describe the bleeding. Heavy, frequent, irregular, prolonged (menometrorragia).
3) Is it ovulatory? NO.
Anovulatory AUB: Differential Diagnosis

ANOVULATORY AUB

- Estrogenic (excess bleeding)
- Hypoestrogenic (decreased bleeding)
Anovulatory AUB: Differential Diagnosis

- **Estrogenic**
  - Physiologic
    - Adolescence
    - Perimenopause
  - Hyperandrogenic
    - PCOS
    - CAH
    - Cushings
  - Systemic disease/ Medications
    - Renal or liver disease
    - Chronic steroids

- **ANOVULATORY AUB**
Anovulatory AUB: Differential Diagnosis

- ANOVULATORY AUB
  - Hypoestrogenic
    - Hypothalamic (stress, anorexia, mass lesion)
    - Hyperprolactinemia
    - Ovarian Failure (Premature: POF)
Miscellaneous

Ovulatory, but irregular
  • Infection
    Usually light/frequent bleeding
Endometrial hyperplasia/cancer
    Usually heavy/frequent

Anovulatory, iatrogenic
  – Use of hormonal contraception
Anovulatory AUB: History

**History (Estrogenic)**
- Hirsutism, other androgen excess
- Medications
- Chronic disease

**History (Hypoestrogenic)**
- Galactorrhea
- Hot flashes, other menopausal symptoms

**Physical**
- BMI
- Hirsutism
- Acanthosis nigracans
Anovulatory AUB: Tests and Imaging

**Labs**
- CBC
- TSH
- Prolactin
  - for hypoestrogenic (oligomenorrhea) only
- FSH
  - For hypoestrogenic if <40 years to diagnose premature ovarian failure
Androgens for PCOS if no clinical manifestations
  (Be aware of accuracy of free testosterone assay in your clinic)

**Consider EMB**

**Imaging**
- Not necessary unless abnormal exam or does not respond to treatment
Case 6: Anovulatory bleeding

A 24 yo G0 with 8 months abnormal bleeding. Bleeding is every 10-4 days, lasts 5-20 days, heavy for most days of bleeding. BMI 33.

- No PMH. No meds.
- Removes hair from upper lip and chin every 2 weeks.
- Exam: obese, coarse dark hair upper lip, uterus/adnexa not palpable.
- Labs: Hct 30. TSH wnl.
Case 6: Anovulatory bleeding

A 24 yo G0 with 8 months abnormal bleeding. Bleeding is every 10-14 days, lasts 5-20 days, heavy for most days of bleeding. BMI 33.

- No PMH. No meds.
- Removes hair from upper lip and chin every 2 weeks.
- Exam: obese, coarse dark hair upper lip, uterus/adnexa not palpable.
- Labs: Hct 30. TSH wnl.

**Diagnosis:** Polycystic ovarian syndrome

**Treatment:** Oral contraceptives to

  * decrease bleeding
  * prevent hyperplasia
  * decrease hirsuitism
Anovulatory AUB: Treatment

For estrogogenic anovulatory bleeding:

<table>
<thead>
<tr>
<th>SURGICAL</th>
<th>MEDICAL</th>
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<tbody>
<tr>
<td>Endometrial Ablation Hysterectomy</td>
<td>Hormonal contraception</td>
</tr>
<tr>
<td></td>
<td>Cyclic progestin</td>
</tr>
<tr>
<td></td>
<td>LNG-IUD (more effective than other hormonal treatment or NSAIDs)</td>
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</table>

For hypoestrogenic anovulatory bleeding:

<table>
<thead>
<tr>
<th>SURGICAL</th>
<th>MEDICAL</th>
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<tbody>
<tr>
<td></td>
<td>Dopamine agonists for high prolactin</td>
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<tr>
<td></td>
<td>Estrogen/progestin replacement or hormonal contraception for POI</td>
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</tbody>
</table>
Summary

• Distinguish ovulatory (regular) vs. anovulatory (irregular) bleeding

• If ovulatory, likely anatomic cause
  – Order pelvic imaging (ultrasound vs. MRI)
  – Consider surgery for long term treatment

• If anovulatory, most likely estrogenic:
  – Consider endometrial biopsy
  – Prevent endometrial hyperplasia with progestin