Abnormal Uterine Bleeding (AUB)

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Conflict of Interest Disclosure
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| Consultant/Advisory Board | Agile, AMAG Pharma, Avion, Bayer, ContraMed, Merck, PharmaNest |

Learning Objectives

At the conclusion of this presentation, the participant will be able to:
- List the differential to consider for women of different ages who present with heavy or prolonged bleeding.
- Outline appropriate tests to evaluate them.
- Describe options to treat acute excessive and chronic heavy menstrual bleeding.
New Terminology and Classification System for Abnormal Uterine Bleeding

- New terms to replace older, imprecise terms
- Bleeding described in 4 dimensions:
  - Frequency, duration, volume and variability
- English words (heavy, prolonged, infrequent) replace Greek and Latin terms (menorrhagia)


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Menstrual Bleeding Terminology

<table>
<thead>
<tr>
<th>Clinical Dimensions</th>
<th>Descriptive Terms</th>
<th>Normal Limits (5th to 95th percentiles)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of menses (days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequent</td>
<td>&lt;24</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>24-38</td>
<td></td>
</tr>
<tr>
<td>Infrequent</td>
<td>&gt;38</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Duration of flow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged</td>
<td>&gt;8.0</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>4.5-8.0</td>
<td></td>
</tr>
<tr>
<td>Shortened</td>
<td>&lt;4.5</td>
<td></td>
</tr>
</tbody>
</table>


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Menstrual Bleeding Terminology

<table>
<thead>
<tr>
<th>Clinical Dimensions</th>
<th>Descriptive Terms</th>
<th>Normal Limits (5th to 95th percentiles)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume of monthly blood loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy</td>
<td>&gt;80</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>5-80</td>
<td></td>
</tr>
<tr>
<td>Light</td>
<td>&lt;5</td>
<td></td>
</tr>
<tr>
<td>Regularity of menses, cycle-to-cycle variation over 12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>Variation ± 2-20</td>
<td></td>
</tr>
<tr>
<td>Irregular</td>
<td>Variation &gt; 2-20</td>
<td></td>
</tr>
<tr>
<td>days</td>
<td>days</td>
<td></td>
</tr>
</tbody>
</table>

Other Terms That Are Still Useful

- Amenorrhea
  - Primary
  - Secondary
- Postmenopausal bleeding
- Postcoital bleeding
- Post traumatic bleeding
- Intermenstrual bleeding
- Scheduled vs. unscheduled bleeding

Terms No Longer Used

- Dysfunctional uterine bleeding
- Menorrhagia
- Menorrhagia
- Oligomenorrhea
- Polymenorrhea

PALM-COEIN Classification

Adapted from the Munro. Fertil Steril. 2011;95:2204.
Secondary Amenorrhea

- Amenorrhea in a reproductive woman
  - ≥ 3-6 months in a previously normally menstruating woman
  **OR**
  - > 9 months or 2 times usual interval


Secondary Amenorrhea
Special Issues

- Estrogen status determines concerns
  - Estrogen deficiency $\rightarrow$ osteoporosis, menopausal issues
  - Estrogen unopposed $\rightarrow$ endometrial carcinoma


Differential Diagnosis

- Pregnancy
- PCOS
- Hypothalamic amenorrhea
  - Extreme exercise
  - Starvation
- Chronic medical illness
- Premature ovarian insufficiency (POI)
- Cervical stenosis
Chronic Diseases Causing Amenorrhea

- Uncontrolled juvenile diabetes
- End-stage renal disease
- AIDS
- Malabsorption
- Malignancy
- Androgen excess
- Hepatic failure
- Adrenal insufficiency
- Cushing’s syndrome
- Sarcoidosis
- Acromegaly
- Craniopharyngiomas
- Thyroid dysfunction
- Obesity

Common Causes of Secondary Amenorrhea

<table>
<thead>
<tr>
<th>Category</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low or normal FSH: weight loss/anorexia; non-specific hypothalamic; chronic anovulation including PCOS; hypothyroidism; Cushing’s syndrome; pituitary tumor, empty sella, Sheehan syndrome</td>
<td>66%</td>
</tr>
<tr>
<td>Gonadal failure: high FSH 46 XX; abnormal karyotype</td>
<td>12%</td>
</tr>
<tr>
<td>High prolactin</td>
<td>23%</td>
</tr>
<tr>
<td>Anatomic: Asherman syndrome</td>
<td>7%</td>
</tr>
<tr>
<td>Hyperandrogenic states: ovarian tumor; non-classic CAH; undiagnosed</td>
<td>2%</td>
</tr>
</tbody>
</table>


Medications Causing Amenorrhea

- DMPA, LNG IUS, extended-cycle OCs
- Chemotherapeutic agents
- Anesthetics, including cocaine
- Psychoactive drugs: phenothiazines, tricyclic antidepressants, opiates, chlordiazepoxide, amphetamines, diazepam, haloperidol, fluphenazine, chlorpromazine, SSRIs
- Antihypertensives: α-methyl dopa, reserpine, verapamil
- Dopamine receptor agonists: metoclopramide
- Antiemetics: sulpiride, promazine, perphenazine
- Others: cimetidine, cyproheptadine, protease inhibitors
Workup of Secondary Amenorrhea

- History: recent surgical procedures, weight changes, medications, other health problems, radiation therapy, chemotherapy
- Family history: autosomal disorders associated with ovarian failure, endocrinopathy
- Physical exam: galactorrhea, obstruction, hirsutism, virilization, acromegaly
- Lab tests: pregnancy test, FSH, TSH, prolactin
  - Other tests if indicated: androgens

A Treatment Course of Progestin

Appropriate Testing

- TSH as first test
- TSH normal – no more testing needed
  - Unless patient symptomatic
    - Then add free \(T_4\)
  - TSH high – add free \(T_4\); how hypothyroid?
  - TSH low-add free \(T_4\) and free \(T_3\); how hyperthyroid?
- Prolactin
Follow-up Testing:
Women Not Seeking Pregnancy

<table>
<thead>
<tr>
<th>Galactorrhea</th>
<th>PRO</th>
<th>Menses</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>✗</td>
<td>WNL</td>
<td>Normal</td>
<td>None</td>
</tr>
<tr>
<td>✗</td>
<td>WNL</td>
<td>Abnormal</td>
<td>Cone-down sella/MRI/CT</td>
</tr>
<tr>
<td>≥ 25-70</td>
<td>Normal</td>
<td>Repeat in 6-12 months</td>
<td></td>
</tr>
<tr>
<td>≥ 70</td>
<td>Normal / abnormal</td>
<td>CT or MRI</td>
<td></td>
</tr>
</tbody>
</table>

Work-up of Secondary Amenorrhea Ovary Evaluation

- If FSH and LH elevated and E₂ low, consider premature ovarian insensitivity (POI)
  - Repeat tests to confirm if early menopause is suspected
  - Perform karyotype if patient < 30
  - Rule out autoimmune disease if patient < 35
    - Common sites affected include thyroid, adrenal, parathyroid, pancreas

Premature Ovarian Insufficiency

- Age < 40 years
- FSH > 30-40 IU/L on 2 occasions ≥ 1 month apart
  - After 4-6 months of amenorrhea
  - May be transient or progressive
  - Usually results in eventual premature menopause
- 3 mechanism with POI
  - Congenital decrease in primordial follicles
  - Accelerated follicular atresia
  - Inability to recruit primordial follicles

Hypothalamic Amenorrhea

- Hypothalamic amenorrhea is a diagnosis of exclusion with
  - Low-normal gonadotrophins
  - Normal PRO
  - Normal imaging of pituitary
  - No withdrawal bleeding
- Most common cause of amenorrhea, often associated with stress, eating disorders, weight loss?, diabetes??
  - 72% of women had spontaneous return of menses within 6 years

Diagnostic Work-Up of Secondary Amenorrhea Without Obvious Etiology

Secondary Amenorrhea Treatments: Target the Cause

- Correct thyroid or prolactin dysfunctions
  - Provide progestin protection for endometrium until normalizes
- Estrogen deficient conditions
  - Provide estrogen and progestin
- Unopposed estrogen conditions
  - Provide progestin cyclically or suppression
Infrequent Menses

- Less severe manifestations of problems causing amenorrhea
  - Medical problems
  - Thyroid dysfunction
  - Prolactin excess
  - Obesity
  - Medications
  - PCOS

ACOG Clinical Manifestations of PCOS

- Menstrual disorders
- Infertility
  - Ovarian hyperstimulation syndrome
  - Multifetal pregnancy
  - Gestational diabetes and hypertension
- Skin disorders
  - Hirsutism, acne, androgenic alopecia
- Insulin resistance
  - Metabolic syndrome; nonalcoholic fatty liver disease, sleep apnea
- Endometrial cancer risk factors (but not cancer?)
- Mood disturbances and depression

Revised 2003 PCOS Criteria (2 out of 3 Criteria)
1. Oligo-ovulation or anovulation
2. Clinical and/or biochemical signs of hyperandrogenism
3. Polycystic ovaries with
   - Exclusion of other etiologies: congenital adrenal hyperplasia, androgen-secreting tumors, Cushing syndrome
**Workup for PCOS: Overview**

- Personal history
- Family history of endocrine, reproductive, metabolic disorders
- Physical examination
  - BP, BMI, waist circumference
  - Check for presence of acne, hirsutism, androgenic alopecia, acanthosis nigricans
- Laboratory tests

**ACOG Physical Examination Elements for PCOS**

- Blood pressure
- BMI
- Waist circumference
  - > 35 inches is abnormal
- Presence of acne, hirsutism, androgenic alopecia, acanthosis nigricans

**ACOG Suggested Evaluation for PCOS Laboratory Tests**

- Evidence of biochemical hyperandrogenemia
  - Total testosterone and SHBG
  - Bioavailable and free testosterone
- Exclusion of other causes of hyperandrogenism
  - TSH
  - Prolactin
  - 17-hydroxy progesterone
  - Consider screening for Cushing or acromegaly
ACOG Screening Labs

- FBS + 2 hour glucose after 75 g load
- 2-5 fold increased risk of DM
- 40% PCOS have glucose intolerance
- No recommended screening test for insulin resistance
  - Little utility to routine testing of insulin levels in women with PCOS
  - Does not predict who will respond to therapy
- Fasting lipid panel


PCOS: Overall Goals of Treatment

- Reduce production and circulating levels of androgens
- Estrogen containing contraceptive
- Protect endometrium from unopposed estrogen
- Achieve normal body weight
- Lower lifetime risk for cardiovascular disease, diabetes
- Plan and prepare for pregnancies

ACOG CVD Prevention in PCOS

- Lifestyle modifications are the best approach to modify risks for cardiovascular disease and diabetes
- Calorie restriction rather than composition of diet itself
- Recent studies have suggested little benefit to the addition of Metformin above lifestyle therapy alone
  - Data are insufficient to recommend insulin-sensitizing agents prophylactically to prevent diabetes in women with PCOS

Acute Excessive Menstrual Bleeding

- Can present as very serious medical emergency
- Acute blood loss not generally well tolerated
- Etiologies vary, but after special conditions are ruled out, hormonal therapies can arrest/slow acute flow
- Special conditions to rule out
  - Pregnancy-related bleeding
  - Aborting fibroid; actively bleeding polyp
  - Trauma
  - Complications of known condition
  - Terminal bleeding from endometrial cancer
  - Anticoagulant

Severe Acute Excessive Bleeding: Medical Therapies Appropriate If Patient Stable

- Initial therapy
- Transitional therapy (days 2-7)
- Follow-up (days 7-21)

Published Prospective Studies

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Number of Subjects Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous conjugated equine estrogen(^1)</td>
<td>17</td>
</tr>
<tr>
<td>Combined birth control pill (Norgestrel 0.5 mg + EE 50mcg) PO QID x 2-4d very slow taper(^2,3)</td>
<td>9 + 9</td>
</tr>
<tr>
<td>MPA 60-120 mg PO x 1d + 20 mg PO x 4d (^4)</td>
<td>24</td>
</tr>
</tbody>
</table>

High Dose Progestin Treatments for Acute Uterine Bleeding (n=40)

MPA 20mg given orally 3 times a day for 7 days, then once daily for 21 days

vs.

35 mcg EE/1 mg NETA given orally 3 times a day for 7 days, then 20 mcg EE/1 mg NETA once daily for 21 days

<table>
<thead>
<tr>
<th></th>
<th>MPA</th>
<th>COC</th>
</tr>
</thead>
<tbody>
<tr>
<td>No surgery</td>
<td>100%</td>
<td>95%</td>
</tr>
<tr>
<td>Cessation of bleeding</td>
<td>76%</td>
<td>88%</td>
</tr>
<tr>
<td>Days to Cessation</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Patient satisfaction (0-4)*</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>


Complimentary Therapies with Hormonal Therapies in Acute Setting

- Antiemetics to reduce nausea and vomiting associated with high-dose hormonal therapy
- Especially helpful in therapies using estrogen
- NSAIDs to reduce acute bleeding; can be used in conjunction with hormonal therapy
- Iron supplements, if anemic
- Menstrual calendars
- Re-evaluate in appropriate intervals

Indications for Procedures: D&C, Embolization, Radiation, Hysterectomy

- Acute hemorrhage due to anatomical issue or delayed surgical complication
- Aborting fibroid
- Uterine artery perforation
- Septic or incomplete abortion
- Malignancy
- Failure to respond to medical therapy
Chronic Heavy Uterine Bleeding: Definition

- Deviations from textbook definitions of normal cycles
- Deviations from an individual's own established patterns of normal cycles
- Adverse impact on quality of life

Menstrual bleeding is heavy when it is heavy to the woman:

Objective definitions are irrelevant for an individual who is inconvenienced, discontent, or made anxious by the perception of an excessively heavy menstrual flow.

Heavy Bleeding: Reality vs Perception

Actual Menstrual Blood Loss Per Cycle


PALM-COEIN Classification

Adapted from the Munro. Fertil Steril. 2011;95:2204.
Uterine Polyp
Seen During Hysteroscopy

Adenomyosis

Illustration of Fibroid on Uterus
Prevalence of Bleeding Disorders in Women with Heavy Bleeding

- 115 women with physician-diagnosed menorrhagia
  - 47% had hemostatic abnormality
    - Platelet aggregation: 44%
    - von Willebrand factor: 7%
    - Coagulation factors: 5%


Systemic Diseases

- Thyroid disorders
- Liver cirrhosis or active hepatitis
- Adrenal hyperplasia
- Renal failure
- Hypersplenism
Medications That Increase Blood Loss
- Steroid hormones
- Digitalis
- Dilantin
- Anticoagulants
- Tranquilizers
- IUD (usually copper or plastic)

Heavy Bleeding Work-Up: Goals
- Establish whether heavy bleeding is due to a treatable organic disorder
- Determine whether bleeding is ovulatory or anovulatory
- Assess burden of symptoms as well as patient expectations from therapy

Heavy Bleeding Work-Up: History
- Menstrual history
  - Determine if regular or irregular pattern
- Medication and medical history
  - Identify any current medications that may affect menstrual cycle or risk of excess menstrual bleeding
- Sexual history
  - Determine birth control method, desire and potential for pregnancy, risk for sexually transmitted diseases
Laboratory Evaluation of Heavy Uterine Bleeding

- Pregnancy test
- CBC, and if patient anemic, TIBC, Fe, ferritin and other appropriate tests to evaluate
- Test for bleeding disorders (if positive screen)
- Thyroid function tests (if clinically suspected)
- Cervical cytology (if not done recently)
- Screen for cervical infections, (if indicated)
- Liver function tests (if alcohol or substance abuse or other risk factors)
- Endometrial evaluation (if bleeding suspicious)

Saline Infusion Sonography – Polyps

Indications for Endometrial Sampling for AUB
Abnormal Uterine Bleeding

- Woman age ≥ 45
- Woman age < 45
  - Unopposed estrogen stimulation from:
    - PCOS or infrequent menses
    - Feminizing ovarian tumors
    - Obesity
    - Diabetes
  - Medication: SERM, estrogen
  - Failed medical management, persistent AUB
- Lynch syndrome (ANPCC)

Heavy Menstrual Bleeding: Factors Influencing Therapies

- Age of patient
- Severity of symptoms
- Presence of associated pelvic pathology
- Fertility plans

**NOTE:** Most therapies recommended are **off-label**

- The only drugs that are FDA-approved for the treatments of heavy bleeding are cyclic MPA, LNG-IUS20mg, tranexamic acid, E2/V/DNG oral contraceptive

Chronic Heavy Menstrual Bleeding: Medical Therapies

- Prostaglandin normalization: NSAIDs
  - Inhibit cyclooxygenase
  - Converts arachidonic acid to prostaglandin
  - Bind to prostaglandin receptors
  - Metaanalysis shows no one NSAID superior to another
- Decrease fibrinolysis
  - Antifibrinolytics


Chronic Heavy Menstrual Bleeding: Medical Therapies

- Coordinate endometrial sloughing
  - Combined hormonal contraceptives
  - Progestin 7-12 days each cycle
- Suppress endometrium
  - DMPA, continuous progestin, extended-cycle COCs, vaginal rings
  - GnRH, Danazol
  - Levonorgestrel-releasing IUS

## NSAID Regimens

- **Mefenamic acid**
  - 500 mg TID first 4-5 days of menses
  - 500 mg TID from 4-5 days prior to menses to cessation
  - 500 mg initially; 200 mg QID for 3-5 days

- **Naproxen**
  - 500 mg at onset and 3-5 hours later; 500 mg BID for 5 days
  - 500 mg in AM and 250 in PM for two days; 250 mg BID for 7 days
  - 500 mg: 250 mg QID for 4 days
  - 550 mg: 275 mg QID for 5 days

- **Ibuprofen**
  - 800 mg TID for 5 days (Norplant trial)


## Tranexamic Acid Approved in US

- **Dose:** 650 mg 2 tabs orally 3 times daily for up to 5 days during menses
- **Placebo controlled trials:** 38% greater reduction in blood loss
- **Adverse events:** headache, sinus pain, muscle and joint pain, anemia, fatigue
- **Might raise risk of thrombosis**
  - **"Women who use hormonal contraception should use tranexamic acid only for strong medical indications for which benefits outweigh risks"**


## Progestin Methods to Prevent Endometrial Thickening and Uncoordinated Sloughing

- **MPA 10 mg orally daily for 12 days on cycle days 15-26 (FDA-approved)**
- **MPA 5 mg orally daily**
- **Norethindrone 5 mg orally cycle days 19-26**
- **Progestin-only pills**
- **DMPA 150 mg IM every 11-13 weeks**
- **Levonorgestrel-releasing IUS**
Summary

- Menstrual bleeding disorders are common
  - Up to 20% of women experience debilitating symptoms of heavy bleeding at some point in menstrual history¹
  - Heavy menstrual bleeding may signal systemic disorders, coagulopathies, disease of reproductive system²
  - The cause of most heavy menstrual bleeding is benign and symptoms are often effectively managed with hormonal therapies³