Abnormal Uterine Bleeding and Amenorrhea

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Edward J. Mayeaux, Jr., MD was a consultant/advisory board member for Merck & Co. (HPV vaccination); Pharmaderm (Condyloma); and Roche Diagnostics (HPV testing)

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Learning Objectives

1. Implement current screening recommendations for endometrial cancer in women who present with postmenopausal bleeding.
2. Identify a plan to communicate ways to increase quality of life and functional activities for women with abnormal uterine bleeding.
3. Formulate a treatment plan for women with abnormal uterine bleeding, including dysfunctional uterine bleeding, menorrhagia, and amenorrhea.
4. Evaluate patients based on their treatment choice, tolerance, and clinical risk profile when selecting a therapeutic intervention for the management of heavy menstrual bleeding.

Epidemiology

Abnormal uterine bleeding (AUB) 1
- Occurs in 9-14% of women between menarche and menopause
- Significantly impacts quality of life
- Imposes notable financial burden

Average age of menarche in U.S. = 12.3 years 2
- Irregular and anovulatory cycles may persist for 1-5 years after onset of menstrual periods


The Normal Menstrual Cycle

Menstrual Phase – Day 1 to 5
- Involves the disintegration and sloughing of the functionalis layer
- Prostaglandin F2-alpha causes contractions and vasoconstriction
- Prostaglandin E2 causes vasodilatation and muscle relaxation


Courtesy of Dr. E.J. Mayeaux, Jr.
The Normal Menstrual Cycle

**Follicular Phase – Day 5 to 14**
- Estrogen produced by developing follicles
  - Stimulated by FSH
- Cellular proliferation and increase in convolutedness of spiral arteries
- Estrogen + feedback causes FSH and LH surge and ovulation

**Luteal Phase – Day 15 to 28**
- Corpus luteum produces progesterone and less potent estrogens
- The functionalis layer increases in thickness
- Glands become tortuous with dilated lumens and stored glycogen

The Normal Menstrual Cycle

Menses
- Estrogen and progesterone cause positive feedback
- FSH and LH production falls
- The spiral arteries become coiled and have decreased blood flow
- They alternately contract and relax, causing sloughing of functionalis layer and menses

Abnormal Uterine Bleeding (AUB)

Menstrual flow outside of normal volume, duration, regularity, or frequency

Abnormal Uterine Bleeding (AUB)

DUB
Anovulatory bleeding “irregular bleeding”
Menorrhagia
Ovulatory bleeding “heavy menstrual bleeding”

Amenorrhea Evaluation

1. DHEA
2. Physical Examination
3. TSH & Prolactin

Evidence of Androgen Excess
Evidence of Estrogen Excess
Adrenal Hyperplasia
Androgen secreting tumor
21-hydroxylase deficiency
HCA/PCOS (DHEA-S > 7000 ng/dL or increased free testosterone > 200 ng/dL)
3. TSH & Prolactin

Hypothyroidism
Hyperthyroidism

4. Progesterone Challenge Test

Both normal
Abnormal
High prolactin
No withdrawal bleeding

5. Estrogen & Progesterone Challenge

Chronic Anovulation: Physiologic PCOS

Tract Abnormality: Asherman's Syndrome Mullerian Agenesia

Ovarian: Gonadal Failure

Karyotype

Abnormal
Normal
High
Low

6. FSH, LH

Intracranial pathology: Pituitary tumor
Pituitary destruction
Hypothalamic Disease

7. MRI

Hypothalamic Amenorrhea: Drug Use Eating Disorder Excessive Exercise Psychosocial Stress Marijuana Use
Consider reevaluation for chronic disease.

**Amenorrhea Evaluation (cont.)**

**True statements about ovulatory AUB characteristics include which of the following?**

A. Periods occur at irregular intervals
B. Periods are often scant and of shorter than normal duration
C. <1% of women develop cancer or hyperplasia if they have no more than one risk factor for endometrial cancer
D. It results from an estrogen-excess state


**DUB is caused by which of the following?**

A. Pregnancy or pregnancy-related disorders
B. Thyroid disease
C. Coagulation disorders
D. None of the above


**Ovulatory AUB Characteristics**

Regular intervals (every 24 to 35 days) with excessive bleeding or duration greater than 7 days
<1% of women develop cancer or hyperplasia if they have no more than one risk factor for endometrial cancer

DUB – Anovulatory Cycles

Most common cause in adolescents and adults
High estrogen with no progesterone
- Continuous development of the functionalis layer
- Blood supply is outgrown and parts of the endometrium slough
- Estrogen promotes healing

Anovulatory DUB Characteristics

Irregular, infrequent periods
Progestrone-deficient/estrogen-dominant state
Flow ranges from absent or minimal to excessive
14% of women with recurrent anovulatory cycles develop cancer or hyperplasia
Extremes of reproductive life and PCOS

DUB – Anovulatory Cycles

Also from excessive estrogen from fatty tissue or exogenous sources
Diminishing number and quality of ovarian follicles
- No FSH trigger
- Estrogen continues to be produced, which usually results in late cycle estrogen breakthrough bleeding

DUB – Luteal Phase Deficiency

Shortened luteal phase – insufficient progesterone
Coexistent with high, low, or normal estrogen
Similar to anovulatory cycles
May be especially prominent in amenorrheic athletes and anorexia

DUB in Adolescence

Proportion of High School Students Who Have Had Sex
At least once, 2003 (Grades 9-12, YRBSS)

AUB Diagnosis

Obtain history and perform physical examination to rule out systemic disease, medication effects, polycystic ovary syndrome, and cervical or vaginal pathology
Laboratory tests for pregnancy, TSH and prolactin levels
Determine by pattern if
- Ovulatory – periods regular but heavy or >7 days
- Anovulatory (DUB) – irregular or infrequent periods
Management Principles

Excluded pregnancy (including ectopic pregnancy) and pelvic infections
All adolescents treated for DUB should maintain a menstrual calendar to monitor response, subsequent episodes of DUB
Monitor for iron deficiency anemia
Additional evaluation and consultation should be obtained if bleeding not controlled with HRT

Dx & Tx of Anovulatory Bleeding

Obtain history and perform physical examination to rule out systemic disease, medication effects, polycystic ovary syndrome, and cervical or vaginal pathology
Laboratory tests for pregnancy, TSH and prolactin levels

Females <35 years with no risks of endometrial cancer
Females ≥35 years or <35 years with recurrent anovulation and/or other risks of endometrial cancer

Endometrial biopsy

Perform TUS or saline infusion sonohysterography to rule out structural abnormality

Treat with combination OCP (ethinyl estradiol, ≤35 mcg) or medroxyprogesterone acetate 10 mg per day for 10 to 14 days per month or norethindrone 2.5-10 mg daily for 5-10 days per month

Dx & Tx of Anovulatory Bleeding

Treat with combination OCP (ethinyl estradiol, ≤35 mcg) or MPA10 mg per day for 10 to 14 days per month

Hyperplasia (no atypia)

Endometrial biopsy normal

Normal Endometrium

Continued irregular or excessive bleeding

Transvaginal ultrasonography

Less sensitive and specific than saline infusion sonohysterography 60-92% sensitive and 62-93% specific for intracavitary abnormality in premenopausal women

Comparison of Imaging/Tissue Sampling for Endometrial Pathology

<table>
<thead>
<tr>
<th>Test</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial biopsy</td>
<td>91% sensitive and 98% specific for detecting cancer</td>
</tr>
<tr>
<td>Office hysteroscopy</td>
<td>94% sensitive and 89% specific for detecting hyperplasia with atypia</td>
</tr>
<tr>
<td>Saline infusion sonohysterography</td>
<td>88% to 99% sensitive and 72 to 95% specific for detecting intracavitary abnormality in premenopausal women</td>
</tr>
<tr>
<td>Transvaginal ultrasonography</td>
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Endometrial Biopsy

- Rarely required in adolescents
- Should be reserved for adolescents with unresponsive uterine bleeding
- DUB histology = disordered proliferative pattern without secretory activity (no progesterone effect)
- EMB with hormonal therapy = hormonal effects and may interfere with biopsy interpretation

Courtesy of Dr. E.J. Mayeaux, Jr.
Obtain history and perform physical examination to rule out systemic disease or enlarged uterus.
Test for pregnancy, measure thyroid-stimulating hormone level, perform complete blood count.
Evaluate for bleeding disorder and treat as indicated if bleeding diathesis present.

Adolescent or adult with possible bleeding disorder?
Yes
No

Perform imaging test for structural abnormality with transvaginal ultrasonography or saline infusion sonohysterography if high risk of endometrial cancer, consider adding endometrial biopsy.

Consider endometrial biopsy, hysteroscopy, endometrial ablation, or hysterectomy.

Unresponsive to 3-6-month trial of therapy.

Refer for possible fibroidectomy or uterine artery embolization.

Treat with 10 mg of MPA for 21 days/month for 3-6 mo or Norethindrone 2.5-10 mg daily for 5-10 days or Insert levonorgestrel-releasing IUS or Trial of nonsteroidal anti-inflammatory drug or Tranexamic acid 2 650-mg 3x/day days 1-5 of cycle.

Risk factors for bleeding disorders in AUB patients include all of the following EXCEPT which one?

A. Family history of bleeding disorder
B. A patient history of “using lots of pads”
C. History of treatment for anemia
D. History of excessive bleeding with tooth extraction, delivery or miscarriage, or surgery

Ovulatory – Bleeding Disorder?

- Adolescents and women with 1 or more of the following risk factors:
  - family history of bleeding disorder
  - menses lasting 7 days or more with flooding or impairment of activities with most periods
  - history of treatment for anemia
  - history of excessive bleeding with tooth extraction, delivery or miscarriage, or surgery
- von Willebrand disease (vWD), most common
  - 13% of women with menorrhagia

Observe vs Treat with HRT

- Decision for adolescents depends upon:
  - Severity and chronicity of the DUB
  - Patient considerations
  - Guardian considerations
- The primary purpose of hormonal treatment is to stabilize endometrial proliferation and promote cyclic shedding
- >90% of adolescents respond to hormonal treatment.

AUB: Emergency Management

- IV conjugated estrogen 25 mg q 4 hours until bleeding slows or for 12 hours
  - 75% will be controlled in 6 hours
- Oral conjugated estrogen 1.25 mg or estradiol 2 mg for 7-10 days
- Start OCPs or 10 days of monthly progestin after bleeding stops to prevent recurrence
  - Can be given without placebos for 3 months (patients prefer)
Anovulatory Treatment

- Adolescent or <35 years with no Ca risks
  - Mild DUB consists of observation and reassurance
  - Combination OCP – ethinyl estradiol, 30-35 mcg
    - Usually for 3-6 months
    - Treatment of choice in women with known von Willebrand disease who also desire contraception
  - Progestin only treatment – MPA 10 mg/day for 10-14 days/mo or similar
  - Consider Iron therapy


Ovulatory AUB Treatment

- Medroxyprogesterone acetate 10 mg/day for 21 days per month or norethindrone 2.5-10 mg daily for 5-10 days
  - Does not provide contraception
  - Effective short-term therapy
  - Not tolerated long-term as well as levonorgestrel-releasing IUD
  - Caution in patients with severe hepatic dysfunction


Surgical Therapies

- Available evidence suggests that hysteroscopic polypectomy reduces AUB 75 to 100%
- Menorrhagia with submucosal fibroids
  - Surgical resection may allow childbearing and normalize menses
  - Uterine artery embolization
    - ~20 percent of women subsequently undergo a hysterectomy for recurrent AUB

Surgical Therapies

- If unresponsive to medical intervention, endometrial ablation (the surgical destruction of the endometrium) may be considered
  - Permanent - incompatible with continued fertility
- Hysterectomy is definitive treatment
  - Women who no longer wish to conceive
  - Increased number of adverse effects, longer recovery time, and higher initial health care costs
  - May be associated with earlier ovarian failure


Hysterectomy vs Medical Tx

- Women with excessive uterine bleeding for 4 years, unresponsive to medical therapy
- Randomized to hysterectomy or continued medical therapy
- Hysterectomy group: greater improvements in mental health, sexual desire, overall satisfaction
- 53% of medical group eventually received hysterectomy


Quality of Life

- Young patients with irregular bleeding often only need reassurance and observation prior to instituting a drug regimen
- Instruct patients to continue prescribed medications although bleeding may still be occurring at first
- Tell patients that medications will probably not be necessary once cycles become regular
- Discuss ways to maintain a normal BMI

Quality of Life

- Health professionals can help support patients’ self-esteem by providing reassurance and information on physiology, treatments, and hygiene
  - Written educational materials are often helpful
  - Low-literacy and culturally sensitive and inclusive materials often best
- Communication with school or work may be necessary