Abnormal (Dysfunctional) Uterine Bleeding

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BASICS

DESCRIPTION

- Abnormal uterine bleeding (AUB) is uterine bleeding that is irregular in quantity, frequency, or duration.
- May be acute or chronic (occurring >6 months)
- The International Federation of Gynecology and Obstetrics (FIGO) now uses AUB rather than dysfunctional uterine bleeding (DUB).

EPIDEMIOLOGY

Adolescent and perimenopausal women are affected most often.

Incidence

5% of reproductive-aged women will see a doctor in any given year for AUB.

Prevalence

3-30% of reproductive-aged women have AUB.

ETIOLOGY AND PATHOPHYSIOLOGY

- Anovulation accounts for 90% of AUB.
- Adolescent AUB is usually due to an immature hypothalamic-pituitary-ovarian (HPO) axis that leads to anovulatory cycles.
- The mnemonic PALM-COEIN (1) was developed to describe AUB in reproductive aged women.
- PALM (structural causes): polyp, adenomyosis, leiomyoma, and malignancy and/or hyperplasia
- COEIN (nonstructural causes): coagulopathy, ovulatory disorders, endometrial, iatrogenic, and not yet classified
- Coagulopathy
  - 20% of patients with heavy menstrual bleeding have a bleeding disorder.

    - Two most common coagulopathies involved: von Willebrand disease and thrombocytopenia
- Diseases causing ovulatory dysfunction
    - Hyperparathyroidism, hypothyroidism, adrenal disorders, pituitary disease (prolactinoma), PCOS, eating disorders
- Medications (iatrogenic causes)
    - Anticoagulants, steroids, tamoxifen (estrogen receptor antagonists), hormonal contraception, copper IUD, antipsychotic medications (mostly first generation), postmenopausal hormone replacement therapy, antiemetics (metoclopramide and domperidone specifically)
- Other causes of AUB not defined in PALM-COEIN: ectopic pregnancy, threatened or incomplete abortion or hydatidiform mole, upper genital tract infections, advanced or fulminant liver disease, chronic renal disease, nutritional deficiencies, inflammatory bowel disease, excessive weight gain, increased exercise

Genetics

Unclear but can include inherited disorders of hemostasis

RISK FACTORS

- Unopposed estrogen therapy (no. 1 risk factor for endometrial cancer)
- Increasing age, typically >40 years old; obesity; PCOS; diabetes mellitus; nulliparity; early menarche or late menopause (>55 years of age); chronic anovulation or infertility; history of breast cancer or endometrial hyperplasia; tamoxifen use; family history: gynecologic, breast, or colon cancer; thyroid disease

GENERAL PREVENTION

No direct preventive measure for AUB

DIAGNOSIS

The most valuable in diagnosis and determining etiology is history.

HISTORY

- Menstrual history: onset, severity (quantified by pad/tampon use, presence and size of clots), timing of bleeding (unpredictable or episodic) over the last 6 months; also assess menopausal status.
- Association with other factors (e.g., coitus, contraception, weight loss/gain)
- Gynecologic history: gravidity and parity, STI history, previous Pap smear results

- Review of systems (Exclude symptoms of pregnancy, bleeding disorders, stress, exercise, recent weight change, visual changes, headaches, and galactorrhea.)

ALERT

Postmenopausal bleeding is any bleeding that occurs >1 year after the last menstrual period; cancer must always be ruled out (1)[C].

PHYSICAL EXAM

Evaluate for:

- Body mass index, pallor, vital signs, visual field defects (may suggest a pituitary lesion), vaginal discharge, hirsutism or acne, goiter, galactorrhea, purpura, ecchymosis
- Pelvic exam: uterine irregularities and Tanner stage, foreign bodies; rule out rectal or urinary tract bleeding; include Pap smear and tests for STIs (2)[C].

Pediatric Considerations

Premenarchal children with vaginal bleeding should be evaluated for foreign bodies, physical/sexual abuse, possible infections, and signs of precocious puberty.

DIFFERENTIAL DIAGNOSIS

See “Etiology and Pathophysiology.”

DIAGNOSTIC TESTS & INTERPRETATION

Initial Tests (lab, imaging)

- All patients: urine hCG and CBC: For acute heavy/hemorrhagic bleeding, a type and crossmatch should be obtained.
- If coagulopathy is suspected, prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen level; if abnormal, get von Willebrand factor, ristocetin cofactor assay, and factor VIII.
- Consider other tests based on differential diagnosis:
  - Suspected hormonal abnormalities: TSH, prolactin level, follicle-stimulating hormone (FSH)
  - Concern for infection: STI screening, KOH prep, vaginitis panel
  - Possible congenital adrenal hyperplasia: 17-Hydroxyprogesterone
  - Possible PCOS: testosterone and/or dehydroepiandrosterone sulfate (DHEA-S) if PCOS is suspected

- TVUS in postmenopausal AUB
  - American College of Obstetricians and Gynecologists (ACOG) continues to recommend endometrial sampling for postmenopausal women with AUB but states that a thin, homogeneous endometrial thickness (ET) < 4 mm does not require endometrial sampling unless bleeding is persistent or recurrent, whereas ET > 4 mm should prompt further evaluation (based on ACOG 2018 guidelines) (3) [C]. Sampling of thin endometrium is often unsatisfactory for histologic evaluation.
  - Incidentally found endometrial measurement > 4 mm without associated bleeding in postmenopausal women should not trigger evaluation; however, assessment based on individual risk factors is appropriate.
- TVUS, sonohysterography, and hysteroscopy may be similarly effective in detection of intrauterine pathology in premenopausal women with AUB.

Follow-Up Tests & Special Considerations

It is appropriate to initiate medical therapy in females < 35 years of age if low risk of uterine anatomic/histologic abnormality or adenomyosis prior to performing an endometrial biopsy (EMB)

Diagnostic Procedures/Other

- Pap smear to screen for cervical cancer if age > 21 years (2)[C]
- EMB
  - Women aged > 45 years with AUB to rule out cancer or premalignancy
  - Postmenopausal women with ET ≥ 4 mm
  - Women aged 18 to 45 years with AUB, a history of unopposed estrogen, and failed medical management
  - Women of any age without risk factors if they have abnormal findings following imaging (2)
  - Perform on or after day 18 of cycle, if known; secretory endometrium confirms that ovulation occurred.
- Hysteroscopy with targeted biopsy if suspected intrauterine lesion with negative EMB; NPV for endometrial cancer with negative hysteroscopy at any age is 99.5%.

Test Interpretation

Pap smear could reveal carcinoma or inflammation indicative of cervicitis. Most EMBs show proliferative or dyssynchronous endometrium (suggesting anovulation) but can show simple or complex hyperplasia without atypia, hyperplasia with atypia, or endometrial adenocarcinoma.

TREATMENT

GENERAL MEASURES

NSAIDs (naproxen sodium 500 mg BID, mefenamic acid 500 mg TID, ibuprofen 600 to 1,200 mg/day)

- Decreases amount of blood loss and pain compared with placebo
- "Surgical" approaches (including LNG-IUD) generally superior to medical approaches for long-term control (4)[A]

MEDICATION

First Line

- Acute, emergent, nonovulatory bleeding
  - Conjugated equine estrogen (Premarin): 25 mg IV q4h (max of 6 doses) stops bleeding within 8 hours in 72% of individuals, or 2.5 mg Premarin PO q6h should control bleeding in 12 to 24 hours (2)[A].
  - Tranexamic acid (TXA) 1.3 g PO or 10 mg/kg IV (max of 600 mg/dose) TID
  - Intrauterine tamponade by filling 26F foley bulb with 30 mL saline
  - D&C if no response after 2 to 4 doses of Premarin or sooner if bleeding >1 pad per hour
  - Change to oral contraceptive pill (OCP) or progestin for cycle regulation
- Acute, nonemergent, nonovulatory bleeding:
  - Monophasic combined OCPs with 35 μg of estrogen TID for 7 days shown to stop bleeding in 88% of women
  - Medroxyprogesterone acetate 20 mg PO TID for 7 days shown to stop bleeding in 76% of women in 3 days
- Nonacute, nonovulatory bleeding
  - Levonorgestrel IUD (Mirena) is the most effective (71-95% decrease in blood loss) form of progesterone delivery and not inferior to surgical management (4)[A].
  - Progestins: medroxyprogesterone acetate (Provera) 10 mg/day for 5 to 10 days each month; daily progesterone for 21 days per cycle results in significantly less blood loss (5)[A]; medroxyprogesterone acetate (Depo-Provera) 150 mg q12wk
  - OCPs: 20 to 35 μg daily estrogen plus progesterone (Consider especially for anovulatory females <18 years old who are not yet sexually active.)
  - TXA 1.0 to 1.5 g by mouth three times a day; avoid in patients with hypercoagulable states.

- Do not use estrogen if contraindications exist (suspicion for endometrial hyperplasia or carcinoma, history of DVT, migraine with aura, or smoking in women >35 years of age [relative contraindication]).
- Precautions
  - Failed medical treatment requires further workup and consideration of surgical management.
  - Consider DVT prophylaxis when treating with high-dose estrogens (2)[C].

Second Line

- Gonadotropin-releasing hormone (GnRH) agonists: leuprolide (varying doses and duration of action)
- GnRH antagonists (elagolix 300 mg BID): FDA approved for heavy menstrual bleeding due to uterine fibroids in premenopausal women combined with add-back therapy (1 mg estradiol/0.5 mg norethindrone acetate once a day)
- Danazol (200 to 400 mg/day for a maximum of 9 months) is more effective than NSAIDs but is limited by androgenic side effects and cost; now replaced by GnRH agonists
- Metformin or clomifene (Clomid) alone or in combination in women with PCOS who desire ovulation and pregnancy

ISSUES FOR REFERRAL

If an obvious cause for vaginal bleeding is not found in a pediatric patient, refer to a pediatric endocrinologist or pediatric/adolescent gynecology.

ADDITIONAL THERAPIES

- Antiemetics if treating with high-dose estrogen or progesterone (2)[C]
- Iron supplementation if anemia (usually iron deficiency) is identified

SURGERY/OTHER PROCEDURES

- Hysterectomy in cases of endometrial cancer, if medical therapy fails, or if other uterine pathology is found
- Endometrial ablation, less expensive than hysterectomy and associated with high patient satisfaction; this is a permanent procedure and should be avoided in patients who desire continued fertility.
- Uterine artery embolization if bleeding is refractory to medications or confirmed fibroids

ADMISSION, INPATIENT, AND NURSING CONSIDERATIONS

- Significant hemorrhage causing acute anemia with signs of hemodynamic instability; with acute bleeding, replace volume with crystalloid and blood, as necessary.
- Pad counts and clot size can be helpful to determine and monitor amount of bleeding.
- Discharge criteria: hemodynamic stability and control of vaginal bleeding

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Once stable from acute management, recommend follow-up evaluation in 4 to 6 months for further evaluation.

Patient Monitoring

Women treated with estrogen or OCPs should keep a menstrual diary to document bleeding patterns and their relation to therapy.

DIET

No restrictions, although a 5% reduction in weight can induce ovulation in anovulation caused by PCOS

PATIENT EDUCATION

https://www.acog.org/Patients

PROGNOSIS

- Varies with pathophysiologic process
- Most anovulatory cycles can be treated with medical therapy and do not require surgical intervention.

COMPLICATIONS

Iron deficiency anemia, mood disorders

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See Also

- Dysmenorrhea; Menorrhagia (Heavy Menstrual Bleeding)
- Algorithm: Abnormal Uterine Bleeding

Codes

ICD10

- N93.9 Abnormal uterine and vaginal bleeding, unspecified
- N93.8 Other specified abnormal uterine and vaginal bleeding

Clinical Pearls

- AUB is irregular uterine bleeding that occurs in the absence of pregnancy or pathology, making it a diagnosis of exclusion.
- Anovulation accounts for 90% of AUB.
- EMB should be performed in
  - Women aged >45 years with AUB
  - Women aged 18 to 45 years with AUB and a history of unopposed estrogen and failed medical management