Abnormal Uterine Bleeding

MOLLY UHING, MD, FACOG
AVERA WOMEN'S OB/GYN

PRESENTED AND ADAPTED BY: LESLIE SMITH PA-C

History

MENORRHAGIA:

“TO BURST FORWARD MONTHLY”

COINED BY WILLIAM CULLEN, PROFESSOR OF PHYSIC AT THE UNIVERSITY OF EDINBURGH, SCOTLAND.

DYSFUNCTIONAL UTERINE BLEEDING:

WAS COINED, BUT NEVER CLEARLY DEFINED, BY GRAVES IN 1935

Terminology for menstrual abnormalities prior to the FIGO Menstrual Disorders Working Group

Major terms
Menorrhagia (all usages, including "essential menorrhagia," "idiopathic menorrhagia," "primary menorrhagia," "functional menorrhagia," and "ovulatory or anovulatory menorrhagia")
Metrorrhagia
Other terms
Dysfunctional uterine bleeding
Epimenorrhagia
Epimenorrhea
Functional uterine bleeding
Hypermenorrhea
Hypomenorrhea
Menometrorrhagia
Metropathica hemorrhagica
Polymenorrhagia
Polymenorrhea
Uterine hemorrhage

FIGO: International Federation of Gynecology and Obstetrics.

AUB & PALM-COIEN

- Introduced in 2011 by FIGO (International Federation of Gynecology and Obstetric)
- Goal: Universally accepted system of nomenclature
- ACOG supports this standardization and terminology
- Pairs “AUB” with a descriptive term as well as a letter indicating etiology. (Example: heavy menstrual bleeding replacing menorrhagia)
- DUB “Dysfunctional Uterine Bleeding” is recommended to be discontinued

Newly Accepted Terms

- Heavy Menstrual Bleeding
  - Replaces Menorrhagia
- Intermenstrual bleeding
  - Replaces menometrohaggia

PALM-COEIN classification system for abnormal uterine bleeding in nongravid reproductive-age women

Polyp
Adenomyosis
Leiomyoma
Malignancy & hyperplasia

→

Submucosal
Other

Coagulopathy
Ovulatory dysfunction
Endometrial
Iatrogenic
Not yet classified

Basic classification system. The basic system comprises four categories that are defined by visually objective structural criteria (PALM: polyp, adenomyosis, leiomyoma, and malignancy and hyperplasia), four that are unrelated to structural anomalies (COEI: coagulopathy, ovulatory dysfunction, endometrial, iatrogenic), and one reserved for entities that are not yet classified (N). The leiomyoma category (L) is subdivided into patients with at least one submucosal myoma (LSM) and those with myomas that do not impact the endometrial cavity (LO).

Reproduced from: Munro MG, Critchley HO, Broder MS, Fraser IS, FIGO Working Group on Menstrual Disorders. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int J Gynaecol Obstet 2011; 113:3. Illustration used with the permission of Elsevier Inc. All rights reserved.

Structural / PALM

- Polyp
- Adenomyosis
- Leiomyoma
  - Refer to GYN
- Malignancy/hyperplasia
  - Refer to GYN/ONC

- Make an exact diagnosis
- Perform appropriate lab evaluations
- Attempt medical options (in low risk individuals)
- If no improvement, perform endometrial biopsy
  - If continued no improvement, then refer to GYN

Non-structural / COEIN

Non-structural:
Further sub-classified into 3 workable diagnoses

- AUB-C
  - Coagulopathies
- AUB-O
  - Ovulatory
- AUB-E
  - Endometrial origin
- AUB-I
  - Iatrogenic
- AUB-N
  - Not Yet Classified

- AUB-C
  - Systemic disorders of hemostasis (the coagulopathies)
- AUB-O
  - Ovulatory disorders
  - Generally a dysfunctional relationship in the HPO axis that manifests with symptoms of irregular uterine bleeding.
  - Most common at extremes of menses ages
- AUB-E
  - Primary disorders of endometrial origin
  - Caused by the molecular and cellular mechanisms responsible for regulation of the volume of blood lost at menstruation.
  - Other infectious endometrial disorders, such as chlamydial endometritis, should be included here.

Normal Menstruation

- Frequency
  - Definition:
    - How often she cycles.
  - 21 to 35 days
- Regularity
  - Definition:
    - No more than 7-9 days difference between the shortest to longest cycles.
  - Count cycles from Day #1 of bleeding to the next Day #1
- Duration
  - Definition:
    - Number of days of bleeding in a single menstrual period.
  - Up to 8 days
- Volume
  - Research definition:
    - ≤80 mL vaginal "blood" loss per cycle.
  - Clinical definition:
    - A volume that does not interfere with a woman's physical, social, emotional, and/or material quality of life.


WHAT DO YOU MEAN EVERY MONTH?!

Abnormal Menstruation

- Frequency
  - **Infrequent**: >35 days
  - **Frequent**: <21 days
  - Absent or **Amenorrhea**: >180 days
- Regularity
  - No more than 20 day difference between shortest and longest cycle
  - Most between 7-9 days difference

- Duration
  - **Prolonged**:
    - >8 days
    - Associated with HMB
- Volume
  - **Heavy Menstrual Bleeding (HMB)**
    - >80 mL vaginal “blood” loss
    - Any interference with a woman's physical, social, emotional, and/or material quality of life.

Dr. Uhing's Practical Tips!

Ask your patients: tampons or pads?

- Tampons:
  - Regular: 5 ml
  - Super: 10 ml

Ask your patients: how often do you change?

- Pads
  - Lightdays: 5 ml
  - Maxi: 10 ml
  - Overnight: 15 ml

Changing more than every 2 hours is likely Heavy Menstrual Bleeding!

Evaluation

HISTORY

- Menses Discription
  - Duration
  - Associated pain
  - Severity
    - Clots
    - Flooding
- Age of menarche/menopause
- Medications
  - Herbals
- Surgical history
- Family history of bleeding
- Previous history of bleeding
  - Dental or surgical bleeding
  - Bruising
  - Epistaxis
  - Gum bleeding

PHYSICAL EXAM

- PCOS ???
  - Hirsutism
  - acne
  - Signs of insulin resistance (acanthosis nigricans)
- Weight
- Thyroid disease
  - Nodule?
- Bleeding disorder?
  - Pallor
  - Ecchymosis
  - Petechiae
- Pelvic exam
  - External
  - Speculum (with pap if indicated)
  - Bimanual exam

Evaluation

LABS

- Pregnancy test
- CBC
- TSH
- Chlamydia
  - High risk patients
- Prolactin
- PT, PTT
  - If coagulopathy is on differential

WHAT ELSE?

- Transvaginal US
  - May consider transabdominal in some adolescents.
  - If referring to Gyn, order before visit
- Endometrial biopsy
  - ALL patients 45+ years old
  - Younger patients with hx of unopposed estrogen
  - Those who don't respond to medical management
- GYN referral
  - Hysteroscopy/Directed biopsy/D&C

- You should NOT order as they are rarely needed:
  - Pelvic MRI
  - SIS (saline infused sonohystogram)

When is imaging indicated?

- Any patient with abnormal physical exam
- Symptoms despite treatment

As high as 46.6% of women with AUB will have an intrauterine abnormality

Endometrial thickness?/Who needs an EMB?

- No real value in evaluation of a premenopausal patient
- Normal:
  - Proliferative phase: 4.8 mm
  - Secretory phase: 8-14 mm
- Postmenopausal patients:
  - <5 mm
- Biopsy always needed in situation of PMB and lining >5 mm

Differential diagnosis?

BREAK AUB INTO AGE CATEGORIES WHEN YOU CONSIDER YOUR DIFFERENTIAL AND TREATMENT

Age Based Differential Diagnosis

Age 13 – 18 years

- Persistent anovulation due to immaturity
- Dysregulation of HPO axis
  - Normal physiology
- Hormonal contraception

- Pregnancy
- Pelvic infection
- Tumors
- Coagulopathies
  - 19% of adolescents with hospitalization for AUB will have one

Age Based Differential Diagnosis

Age 19 – 39 years

- Pregnancy
- Structural lesions
  - Leiomyomas
  - Polyps
- Anovulatory cycles
  - PCOS
- Use of hormonal contraception
- Endometrial hyperplasia
  - Malignancy rare at this age

Age 40 years - menopause

- Anovulatory bleeding
  - Normal physiology in response to declining ovarian function
- Endometrial hyperplasia or malignancy
- Endometrial atrophy
- Leiomyomas

Treatments: OCPs

- #1 treatment in US
- Regulates cycles especially with anovulatory bleeding
- Thins endometrial lining
- Can use high dose (5,4,3,2,1-finish pack)for acute bleeding
- Consider continuous dosing
- Not very effective if endometrial distortion by myomas or polyps

Treatment: Progestins

- Oral or IUS
- Commonly used
  - Norethindrone or Medroxyprogesterone
- Cyclic vs continuous
  - Ineffective in ovulatory women during last two weeks of cycle
- Increased menstrual flow by 20%
  - More effective if 21-25 days/month (days 6 – 28)
- Mirena
  - Well tolerated for many
  - Reduces bleeding 79-94%

Treatment: TXA

- Tranexamic Acid (Lysteda)
- # 1 treatment in the world for gynecological bleeding disorders
  - HMB, PPH, and bleeding irregularities caused by contraceptive implants
- Generally well tolerated.
- Reduces bleeding by 50%
  - Better than OCP, progestins or NSAID
    - No increased risk of thromboembolic events

Treatment: TXA

- Tranexemic Acid for heavy menstrual bleeding
- Lukes et al Obstet Gynecol 2010
  - 196 participants from 40 centers
  - Two pretreatment cycles with menstrual flow quantified (mean >80 mL)
- Tranexemic acid or placebo 3.9 g/d for 5 days, for 6 treatment cycles
  - Mean blood loss reduced ◦ by>40%withTXA
    - By 8% with placebo
  - QOL significant improvements
    - Inside the home
    - Outside the home
  - Few adverse events
  - One DVT in placebo group, none in TXA group

Treatment: Surgical options

- Endometrial ablation
  - Several techniques
- Uterine Artery embolization
- Hysteroscopic resection of a discrete lesion
- Hysterectomy
- Oophorectomy
- D&C
  - -diagnosis, not treatment

Abnormal Uterine Bleeding

Any symptomatic variation from normal menstruation (in terms of frequency, regularity, duration, or volume) and also includes intermenstrual bleeding.

- Acute abnormal uterine bleeding:
  - An episode of uterine bleeding in a woman of reproductive age (not pregnant) that is of sufficient quantity to require immediate intervention to prevent further blood loss.
- Chronic abnormal uterine bleeding:
  - Bleeding from the uterine body, that is abnormal in frequency, regularity, duration, and/or volume.
  - Present for the majority of the past six months.

Acute AUB

Acute AUB

- 1) Assess patient, determine clinical acuity
  - Hypovolemia?
  - Hemodynamically stable?
- 2) Determine most likely etiology of bleeding
  - 13% of women with HMB have a variant of VWB
  - 20% may have coagulation disorder of some type
  - CBC, T&S, HCG, Fibrinogen, PT, PTT, VWF antigen, Ristocetin cofactor assay, Factor VIII, TSH, iron, TIBC, ferritin
- 3) Choose appropriate treatment for patient

Evaluation of Acute AUB

- History
- PE
- Labs
  - CBC, T&S, HCG, Fibrinogen, PT, PTT, VWF antigen, Ristocetin cofactor assay, Factor VIII,
  - TSH, serum iron, TIBC, ferritin
  - Consider chlamydia testing
  - ?LFTs
- Pathology
  - Endometrial sampling is a first line test when >45 years old
- Imaging
  - TVUS, only if patient is stable

Treatment of Acute AUB

- 2 objectives in management
  - 1) Control current bleeding
  - 2) Reduce menstrual blood loss in subsequent cycles
- IV conjugated equine estrogen is FDA approved for acute AUB
  - Only treatment that is approved
- 72% of women who received IV estrogen stopped bleeding in 8 hours compared to 38% with placebo
  - 25 mg IV Premarin q 4-6 hours for 24 hours
  - Can use in tobacco users
  - Contraindications: VTE or ATE, breast cancer, liver disease. Caution with CV or TE risk factors.

Treatment of Acute AUB

- Combined OCs
  - 3 pills PO x 1 week stopped bleeding in 88% women
  - 5,4,3,2,1-finish pack
  - MONOPHASIC 35mcg EE pills
  - Contraindications:
    - Tobacco abuse >35 yrs
    - HTN, VTE or PE, migraine with aura, breast cancer, etc.
- Oral progestins
  - 3 pills PO x 1 week stopped bleeding in 76% women
  - Recommended regimen is 20 mg PO TID x 7 days
  - Contraindications:
    - VTE or PE
    - Breast cancer, liver disease, arterial thromboembolic disease

Treatment of Acute AUB

- Tranexamic Acid (TXA) (Lysteda)
  - Antifibrinolytic drug, prevents fibrin degradation
  - Reduces bleeding by 30-55%
    - Effective intra-operatively and for chronic AUB
    - Has not been studied for acute AUB
  - 1300 mg PO TID x 5 days
  - 10 mg/kg IV (max dose 600 mg) TID
  - Contraindications:
    - Current VTE
    - Acquired impaired color vision
  - Caution use:
    - Hx of thrombosis
    - Concomitant use of COCs

Treatment of Acute AUB

- Placement of 26F Foley with 30 cc for tamponade
- Refer to GYN
  - D&C +/- hysteroscopy
  - Polypectomy
  - Mirena IUD placement
  - Endometrial ablation
  - Hysterectomy
- Consider IR for uterine artery embolization

Chronic AUB

AUB-O

OVULATORY DYSFUNCTION

PALM-COEIN

Further sub-classified into 3 workable diagnoses

- AUB-C
  - Coagulopathies
- AUB-O
  - Ovulatory
- AUB-E
  - Endometrial origin

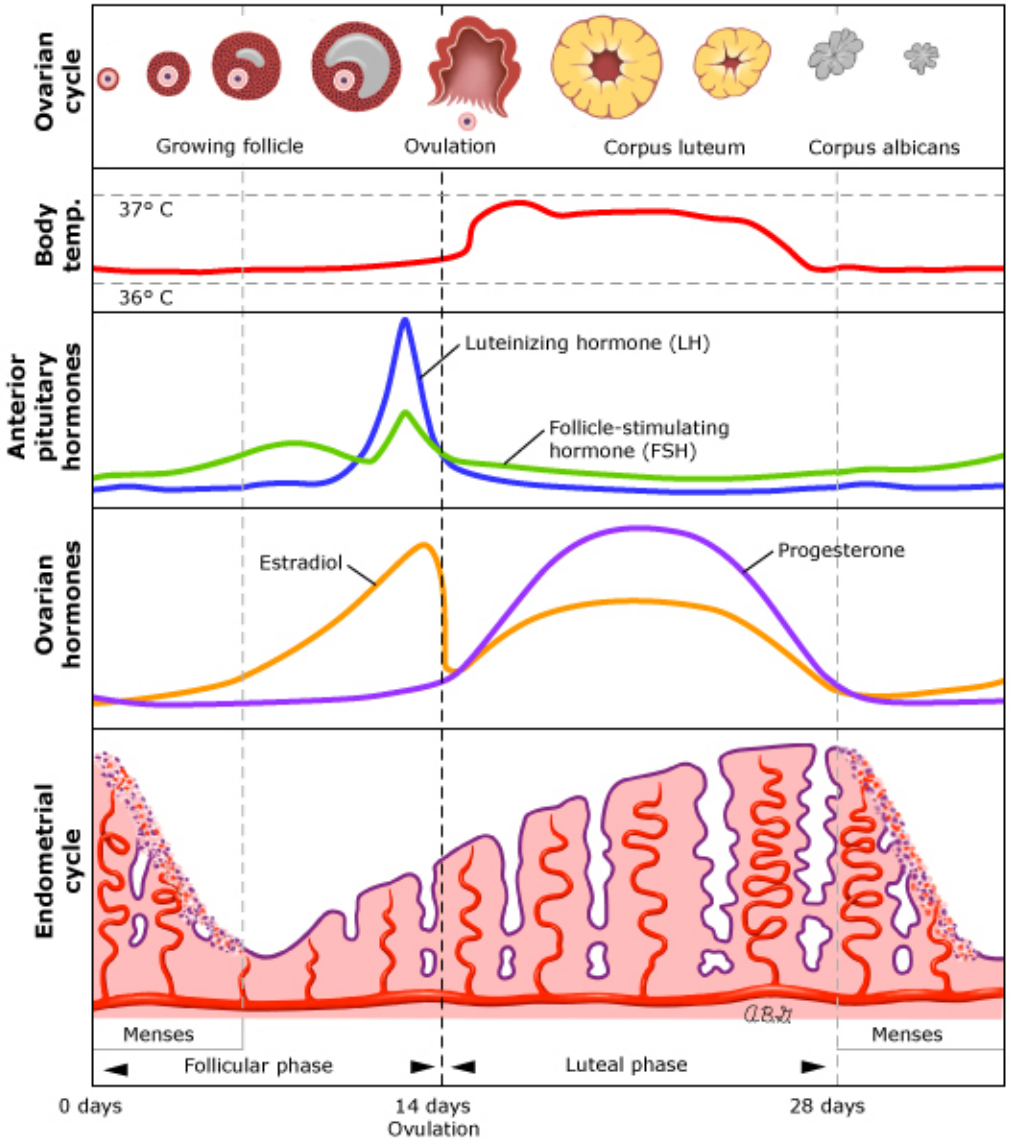
- AUB-C
  - Systemic disorders of hemostasis (the coagulopathies)
- AUB-O
  - Ovulatory disorders
  - Generally a dysfunctional relationship in the HPO axis that manifests with symptoms of irregular uterine bleeding.
- AUB-E
  - Primary disorders of endometrial origin
  - Caused by the molecular and cellular mechanisms responsible for regulation of the volume of blood lost at menstruation.
  - Other infectious endometrial disorders, such as chlamydial endometritis, should be included here.

Causes of Anovulation

Physiologic	Pathologic

• Adolescence
• Perimenopause
• Lactation
• Pregnancy
	• Hyperandrogenism
	  ○ PCOS
	  ○ CAH
	• Hypothalamic disorders
	  ○ Anorexia
	  ○ Runners/dancers
	• Hyperprolactinemia
	• Thyroid disease
	• Primary pituitary disease
	• Premature ovarian failure
	• Medications
	• Iatrogenic (chemo)

Menstrual cycle



Pathophysiology of Anovulation

- No ovulation = no corpus luteum
- No CL = no progesterone
- No progesterone = continual endometrial proliferation without progesterone induced shedding
- Clinical result = noncyclic unpredictable bleeding that is inconsistent in volume
- Endometrium is fragile, vascular and without stromal support
- Result is areas of bleeding that as they heal, then another area begins to slough, resulting in erratic bleeding

Menarche/Anovulation

- First year, almost all irregular bleeding is immature HPO
- 3rd year after menarche, 60-80% of cycles are 21-34 days
- Worsening problem as teens are becoming more obese

Perimenopause

- Definition:
  - Onset of cycle irregularity until 1 year after last menses (menopause starts)
- Mean age of menopause in developed countries 51.4 years
- Smokers begin menopause 1.74 years sooner
- Average duration of transition is 4 years in North America

Endometrial Evaluation in AUB-O

Age 13-18 years	Age 19-39 years
• Endometrial cancer rate is 0.2 per 100,000	• 20-34 years: 1.6% • 35-44 years: 6.2%

• Clinical history likely includes 2-3 years of AUB and obesity	• Age <40, risks:
	  ○ Nulliparity
	  ○ HTN
	  ○ BMI >30
	  ○ FH
	  ○ Irregular menstruation

Endometrial Evaluation in AUB-O

Age 40 years to menopause	Age 70-74 years

• Endometrial cancer rate is 13.6 – 24 per 100,000
• Women < 45 years old have:
  ○ Less advanced disease
  ○ Higher tumor differentiation
  ○ Better prognosis than >45 years old
• EMB! Any woman >45 years old deserves a biopsy for AUB
	• 87.3 / 100,000 women

Treatment of AUB-O

- It is a medical problem, therefore treatment is medical and not surgical.
- *Mirena IUD, Mirena IUD, Mirena IUD!*
  - Now considered first line therapy for AUB-O
- Progesterone only options
  - Cyclic progestins
  - Micronor
  - Depo Provera
- Combined OCPs
  - Increase SHBG (sex hormone binding globin), reducing androgens
  - Increase Factor VIII and von Willebrand's factor

Treatment of AUB-O

- Encourage weight loss and increased exercise
  - 10% body weight reduction will decrease serum testosterone and ovulation may resume
- Surgical options:
  - Endometrial ablation (Novasure, Minerva)
    - ***CAUTION*** ablation in AUB-O because of underlying risks for endometrial hyperplasia and malignancy
    - Ablation makes evaluation of cavity difficult
    - Initial symptom of bleeding may be masked
  - Hysterectomy
- Quality of life is similar between:
  - Hysterectomy
  - Mirena IUD

AUB-C

COAGULOPATHIES

AUB-C

- Structured history to screen for coagulopathies (AUB-C) also known as disorders of systemic hemostasis.
  - 1. Heavy menstrual bleeding since menarche
  - 2. One of the following:
    - Postpartum hemorrhage
    - Surgical related bleeding
    - Bleeding associated with dental work
  - 3. Two or more of the following symptoms:
    - Bruising 1–2 times/month
    - Epistaxis 1–2 times/month
    - Frequent gum bleeding
    - Family history of bleeding symptoms

- Note: Initial screening for an underlying disorder of hemostasis in patients with excessive menstrual bleeding should be by a structured history:
- A positive screen comprises any of the following: heavy bleeding since menarche, one item from list 2, or two or more items from list 3.
- Patients with a positive screen should be considered for further evaluation, including a consultation with a hematologist and/or testing for von Willebrand factor and Ristocetin cofactor.

- Modified from Kouides et al. (26).
- Munro. FIGO classification system for causes of AUB. Fertil Steril 2011.

AUB-E

ENDOMETRIAL IN ORIGIN

Intermenstrual bleeding (IMB)

- Intermenstrual bleeding (IMB)
  - When AUB occurs between well-defined cyclical menses.
  - Often light and short
  - Cyclic or acyclic
    - premenstrual, postmenstrual, mid-cycle

Cyclic IMB

- Cyclic premenstrual IMB
  - Predictably occurs early in the cycle (follicular phase)
- Cyclic postmenstrual IMB
  - Cyclical IMB that occurs late (luteal phase) in the cycle
  - May be indicative of a luteal phase defect (late cycle bleeding)
- Cyclic mid-cycle IMB
  - Consistently occurring between regular menstrual periods.
  - This is a physiologic event in 1-2% cycles.
  - Associated with the physiologic nadir in circulating estradiol levels at mid-cycle.

- *Differential of cyclic lesions:*
  - *Endometriosis*
  - *Endometrial polyps*
  - *Structural lesions of the genital tract*

Acyclic IMB

- Acyclic IMB
  - Irregular and acyclic
  - Usually benign
  - Post-coital bleeding falls into this category

- *Differential of acyclic lesions:*
  - *Cervical polyps*
  - *Chronic cervicitis*
  - *Rarely cancer of the cervix/endometrium*

Summary

- Characterize bleeding according to PALM-COIEN system
  - Structural vs. non-structural
  - AUB-O, AUB-C, AUB-E
- If structural, define lesion and remove
- If anovulatory, use progestin
  - Mirena IUD is your best friend!
- If ovulatory use, use OCPs or longer duration of progestin (21 + days)
- Tranexemic acid works!
  - Acute AUB or HMB

Dr. Uhing's Practical tips!

- If radiology says on sonogram:
  - Heterogeneous endometrium
  - Recommend direct visualization
  - Cannot rule out neoplasia
- Refer straight to GYN for hysteroscopy

- *"One size fits all"* for AUB work up:
  - EMB, sonogram
  - TSH, Prl, CBC

- ALWAYS biopsy:
  - Any type of abnormal bleeding over age 45
  - AUB <45 years old, if:
    - Hx of unopposed estrogen
    - Failed medical mgmt
    - Persistent AUB
  - PCOS patients with significant amenorrhea at any age
  - ANY Postmenopausal bleeding

- Menstrual cells on pap smear are NEVER normal after age 45!!
  - ALWAYS endometrial biopsy