Abnormal Uterine Bleeding: The What, Why and How to Manage

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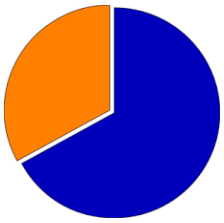
Learning Objectives

- Identify abnormal uterine bleeding (AUB), recognizing variations over the lifespan
- Determine the underlying cause of AUB through an appropriate diagnostic evaluation
- Implement evidenced-based, patient-centered strategies to control AUB

AUB

- ONE-THIRD of all outpatient GYN visits

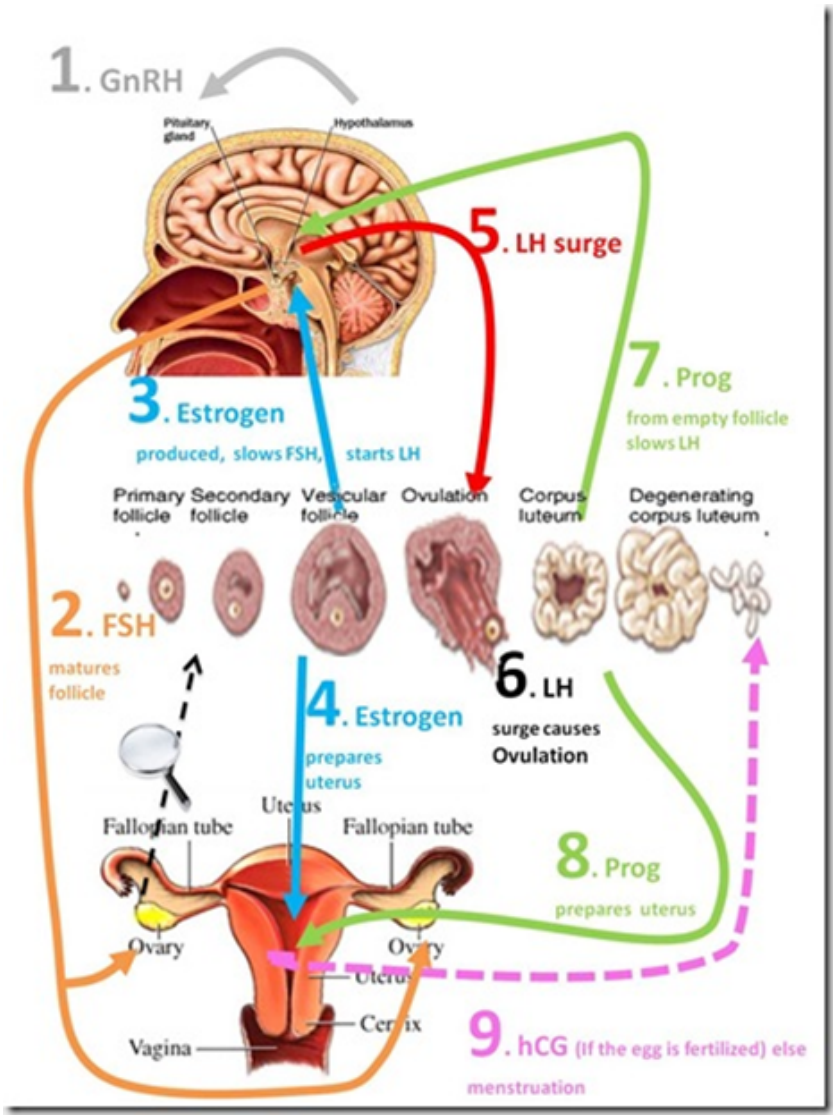


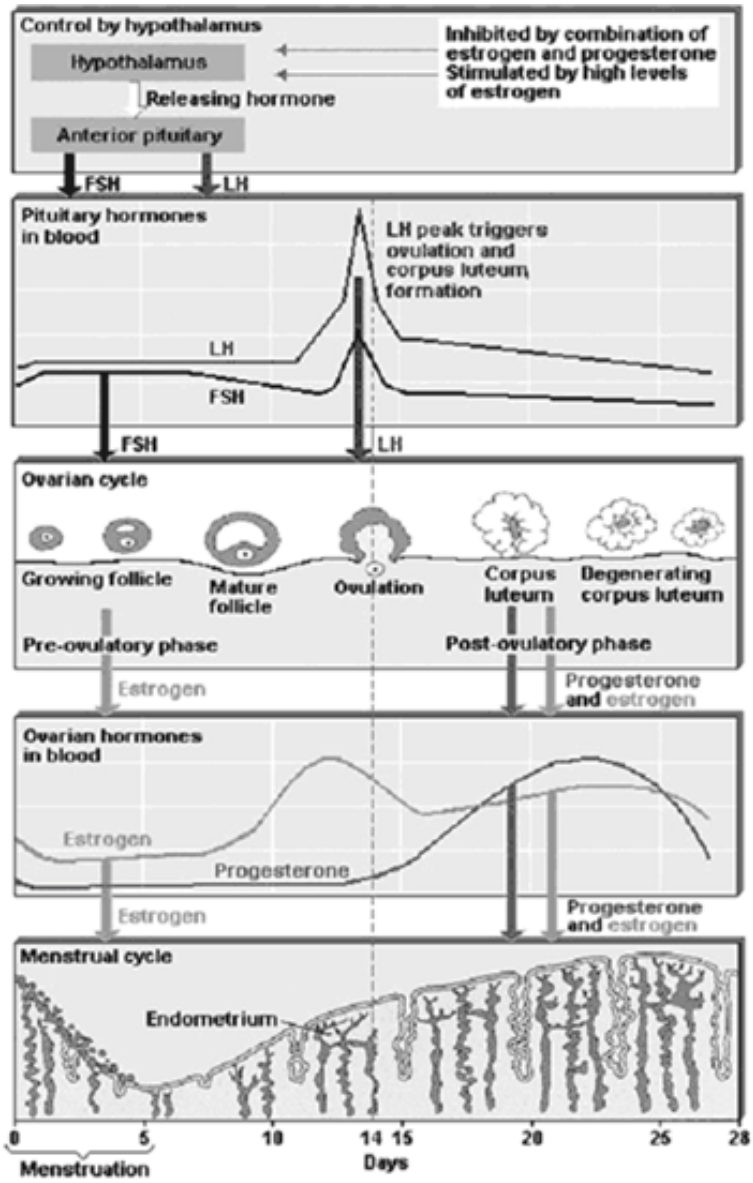
Oberman, E & Rodriguez-Triana, V. *Clin Obstet Gyn* 2018;61:72-75

Meaning Beyond Bleeding

Menstrual Cycle Physiology

- HPO feedback system
  - Hypothalamus
    - GnRH
  - Anterior Pituitary
    - FSH
    - LH
  - Ovary
    - Estrogen
    - Progesterone





Menstrual Cycle Physiology

- Follicular phase:
  Estrogen
- Ovulation
- Luteal phase:
  Progesterone

Menstrual Cycle Physiology

- Organized sequence of hormonal signals that result in **ovulation** and **predictable, regular bleeding**
- The quantity of hormones produced is not as important as the sequence:
  - Estrogen
  - Followed by estrogen and progesterone
  - Followed by withdrawal of both hormones

Speroff L & Fritz M. *Clinical Gynecologic Endocrinology and Infertility*. 2005.

Normal vs Abnormal Uterine Bleeding

Normal Menstrual Bleeding

- Predictable, regular bleeding
- Bleeding every 24 to 35 days
- Flow for 4-6 days
- Volume of 30 mL

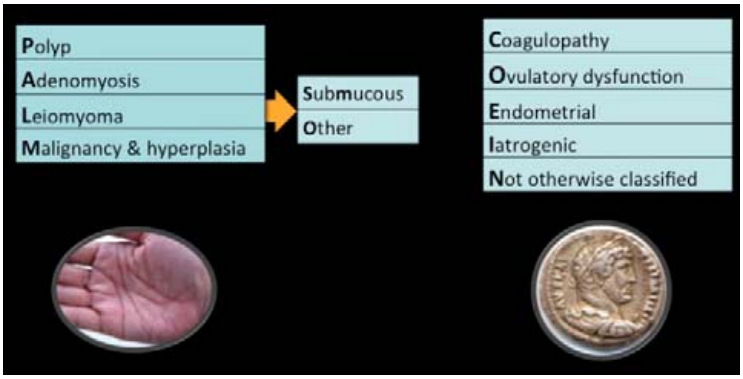
Abnormal Uterine Bleeding

- Unpredictable, irregular bleeding
- Bleeding less than 21 days apart
- Heavy bleeding (> 80mL)
- Bleeding episodes lasting less than 2 days or longer than 7 days
- Bleeding between periods

Speroff L & Fritz M. *Clinical Gynecologic Endocrinology and Infertility*. 2005.

Causes of AUB

FIGO Classification (2011)



Structural entities

Non-structural entities

Munro et al. *Fertil Steril* 2011;95:2204-2208

AUB across the lifespan

Adolescence	Reproductive age	Post-menopausal
von Willebrand	Pregnancy	Atrophy
Anovulatory bleeding	Anovulatory bleeding	Polyps
Pregnancy	Fibroids	Hyperplasia
	Polyps	Endometrial cancer
	Hyperplasia	
	Endometrial cancer	

Evaluating AUB

- Evaluation should
  - Assess the burden of symptoms and goals for treatment
  - Determine underlying cause
  - Provide treatment options with shared decision-making, taking into account a woman's preferences, life style and other health goals

Evaluating AUB: History

- Is she hemodynamically stable?
- Assess bleeding:
  - How often, how much and for how long
  - How is this different than usual?
  - How does this impact your life?

Evaluating AUB: History

- Pay special attention to:
  - Fertility desire
  - Risk factors for uterine cancer (chronic anovulation, PCOS, obesity, unopposed estrogen)
  - History of gynecological pathology
  - Family history of gynecologic or colon cancer (Lynch Syndrome)

Evaluating AUB: History

- History suggestive of excessive blood flow
  - Changing sanitary protection less than every 3 hours
  - Using >20 pads or tampons per cycle
  - Changing protection during the night
  - Passing clots > in size than 1 inch
  - Bleeding lasting longer than 7 days
  - Presence of iron deficiency anemia (but the absence of anemia does not exclude heavy menstrual bleeding)

Duckitt, K. *Maturiatas* 2010;66:251-256

ACOG Committee Opinion No. 557 (2013)

- Screening for underlying bleeding disorder
  - Heavy menstrual bleeding since menarche
  - One of the following conditions:
    - Postpartum hemorrhage
    - Surgery-related bleeding
    - Bleeding associated with dental work
  - Two or more of the following conditions:
    - Bruising, one to two times per month
    - Epistaxis, one to two times per month
    - Frequent gum bleeding
    - Family history of bleeding symptoms

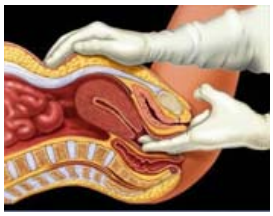
https://www.acog.org/Clinical-Guidance-and-Publications/Committee-Opinions/Committee-on-Gynecologic-Practice/Management-of-Acute-Abnormal-Uterine-Bleeding-in-Nonpregnant-Reproductive-Aged-Women?isMobileSet=false

Testing for Bleeding Disorders

- von Willebrand
  - von Willebrand factor antigen
  - Factor VIII
  - Ristocetin cofactor activity
- Platelet function defects
  - Platelet aggregation or PFA-100
- Coagulation studies
  - PT/INR
  - aPTT
  - Fibrinogen

Moon, L et al. *Curr Opin Obstet Gynecol* 2017;29:328-336

Evaluating AUB: Physical Exam



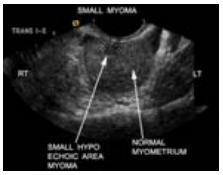
- BMI
- Abdominal exam
  - Abdominal masses
- Pelvic exam
  - Uterine size, shape, masses
  - Cervical lesions
  - Rectal lesions

Evaluating AUB: Diagnostic Testing

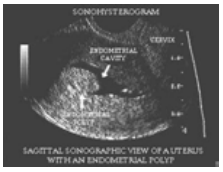
- Pregnancy test
- TSH
- CBC

- Consider:
  - Pap smear, if indicated
  - Pelvic/transvaginal ultrasound
    - Sonohysterogram
  - Endometrial biopsy

Evaluating AUB: Diagnostic Testing



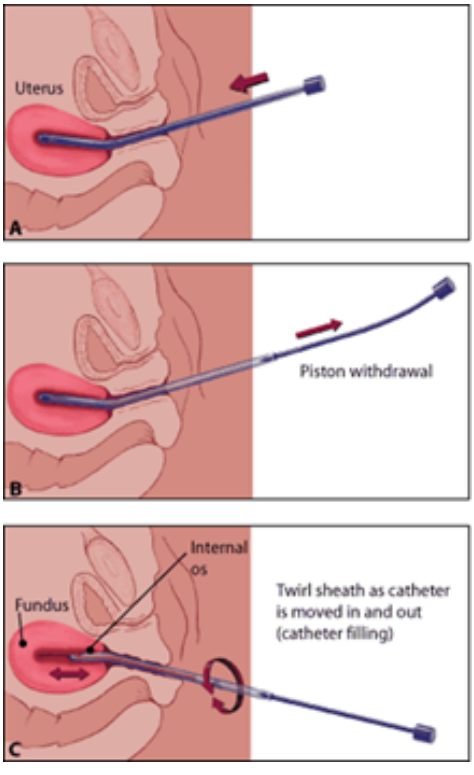
- Transvaginal ultrasound
  - Used to diagnose focal lesions
    - Fibroids
    - Polyps
- Sonohysterogram
  - More sensitive than TVUS at diagnosing intracavity lesions
    - Submucosal fibroids
    - Polyps



Indications for Endometrial Biopsy

- ACOG Practice Bulletin No. 128
  - First-line in women with AUB who are older than 45 years old
  - < 45 years old with risk factors
    - Chronic anovulation
    - PCOS
    - Obesity
  - Ineffective medical management
  - Persistent AUB

ACOG. *Obstetrics & Gynecology* 2012;120:197-206



AUB Classification/Causes

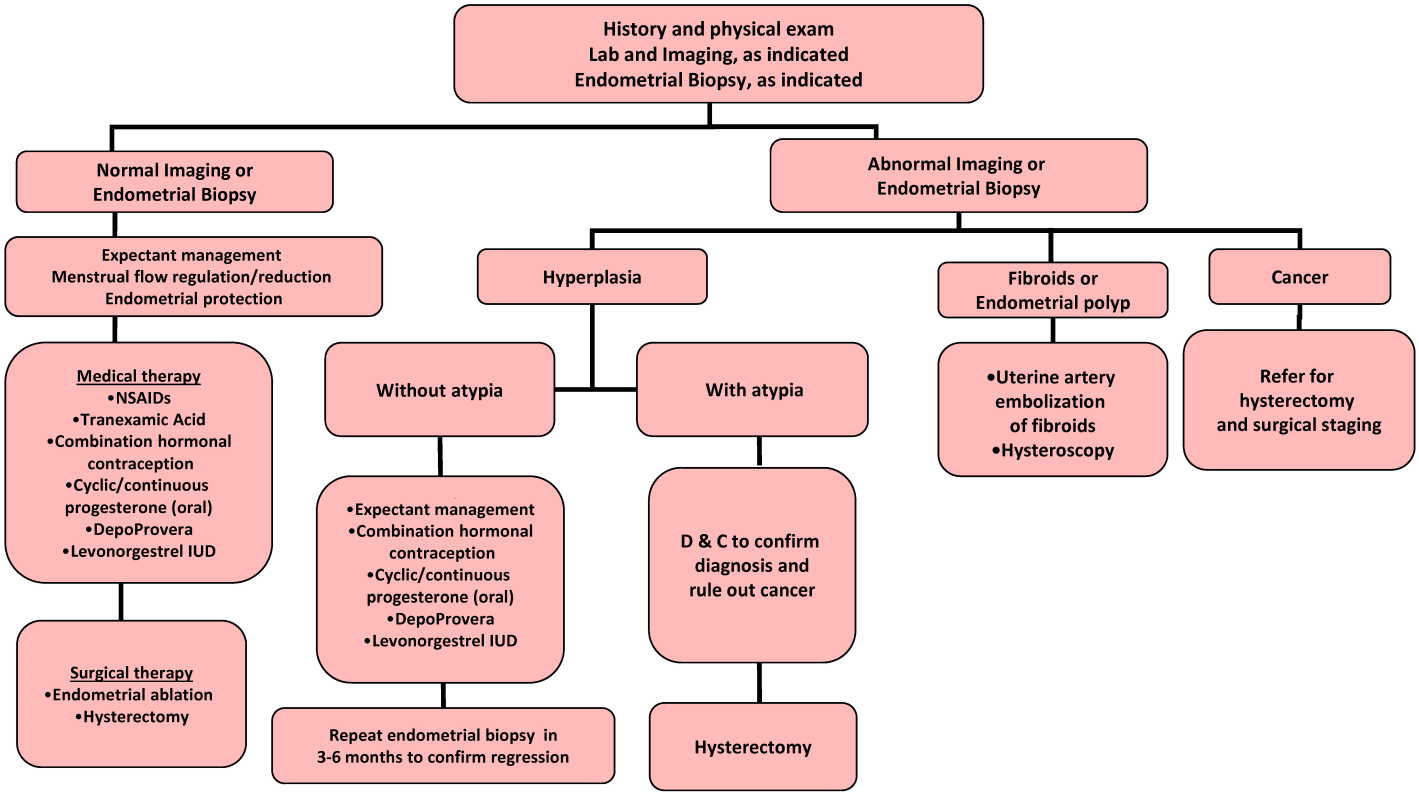
Abnormal uterine bleeding:
- Heavy menstrual bleeding (AUB/HMB)
- Intermenstrual bleeding (AUB/IMB)

PALM—structural causes:
Polyp (AUB-P)
Adenomyosis (AUB-A)
Leiomyoma (AUB-L)
  Submucosal leiomyoma (AUB-LSM)
  Other leiomyoma (AUB-LO)
Malignancy and hyperplasia (AUB-M)

COEIN—nonstructural causes:
Coagulopathy (AUB-C)
Ovulatory dysfunction (AUB-O)
Endometrial (AUB-E)
Iatrogenic (AUB-I)
Not yet classified (AUB-N)

https://www.acog.org/Clinical-Guidance-and-Publications/Committee-Opinions/Committee-on-Gynecologic-Practice/Management-of-Acute-Abnormal-Uterine-Bleeding-in-Nonpregnant-Reproductive-Aged-Women?IsMobileSet=false

Management of AUB in Premenopausal Women



Management Option: NSAIDs

- Advantages
  - Readily available
  - Inexpensive
  - Well-tolerated
  - Also treats dysmenorrhea
- Disadvantages
  - Reduces bleeding more than placebo, but less effective than other treatments
  - GI side effects

Lethaby, A. et al. *Cochrane Database Syst Rev* 2012; 9:CD000400

Management Option: NSAIDs

- Commonly used NSAIDs and doses:
  - Ibuprofen 600-800 mg every 6 hours
  - Naproxen sodium 550 mg initially, followed by 275 mg every 6 hours
  - Mefenamic acid 500 mg initially, followed by 250 mg every 6 hours
  - Meclofenamate sodium 100 mg every 8 hours
- Initiate therapy immediately prior to or on first day of menses, maintain recommended dose for 3 to 5 days

Management Option: Tranexamic Acid

- FDA-approved (2009) non-hormonal option for treatment of heavy menstrual bleeding
- Oral anti-fibrinolytic agent
  - An abnormally high rate of clot breakdown (fibrinolysis) in the uterus has been associated with heavy menstrual bleeding
  - An anti-fibrinolytic agent works to help reduce this excessive activity

Management Option: Tranexamic Acid

- Two 650 mg tablets three times daily for up to 5 days during menses
  - Dosage adjustment in renal impairment (creatinine concentration higher than 1.4 mg/dL)
- Contraindicated in women at risk for or with a current or past history of thromboembolic disease
  - Not appropriate with combined hormonal birth control
- Mild to moderate side effects
  - Headache
  - Back pain
  - Abdominal pain

Bradley, L. & Gueye, N. *Am J of Obstet Gynecol* 2016;214:31-44

Management Option: Combined Oral Contraceptives (COCs)

- Advantages
  - Menstrual cycle more predictable
  - Extended regimen can reduce withdrawal bleeding episodes
  - Contraceptive and non-contraceptive benefits
  - BID to TID dosing for acute bleeding

- Disadvantages
  - Daily use essential with oral contraceptives
  - Possible systemic side effects
  - Need to consider contraindications to estrogen

Edelman, A. et al. *Cochrane Database Syst Rev* 2014; 7:CD004695

Management Option: Oral Progestins

- Options
  - Medroxyprogesterone acetate (Provera) 10 mg
  - Norethindrone 5 mg
  - Prometrium 200 - 400 mg

- Advantages
  - Daily regimens more effectively reduce HMB
  - Cyclic regimen can provide endometrial protection in women with AUB-O
  - Can use for acute bleeding episode to stabilize the endometrium (higher doses)
- Disadvantages
  - No contraceptive effect
  - Possible systemic side effects

Bradley, L. & Gueye, N. *Am J of Obstet Gynecol* 2016;214:31-44

Management Option: IM Progestin

- Depot medroxyprogesterone acetate (DMPA) 150 mg IM

- Advantages
  - one injection every 12-15 weeks
  - ~ 60% of women amenorrheic at 1 year
  - effective contraception
- Disadvantages
  - Irregular bleeding possible
  - Possible systemic side effects
  - IM Injection
  - Concerns about BMD loss with long-term use

Arias R et al. *Contraception* 2006;74:234-238

Management Option: 52 mg LNG-IUD

- Advantages

  - FDA-approved for treatment of heavy menstrual bleeding (Mirena IUD)
  - Highly effective, easy to use contraception
  - Rare systemic hormonal side effects
  - More effective than other medical options
  - Can be used as the progestin component of an HRT regimen
- Disadvantages
  - Irregular bleeding or spotting first 3-6 months
  - Requires insertion and removal by a health care provider
  - Small risk of infection and perforation with insertion

Lethaby, A. et al. *Cochrane Database Syst Rev* 2015; 4:CD002126

Comparison of Medical Management Options

	NSAIDs	Tranexamic Acid	COCs	DMPA	LNG-IUS
Efficacy	20% to 50%	~40%	~50%	~60%	~90%
Dosing	3-4x daily during menses	3x daily during menses	Daily	3 months	5 years
Change in bleeding pattern	Modest ↓ blood loss	Modest ↓ blood loss	Modest ↓ blood loss	Reduction in blood loss to amenorrhea	Reduction in blood loss to amenorrhea
Side effects	G.I.	Well tolerated	Hormonally related	Hormonally related	Rare Hormonal
Contraceptive effect	None	None	Moderately effective	Highly effective	Highly effective
Typical use pregnancy rate	Unchanged	Unchanged	9%	6%	0.2%

Clinical Practice Guidelines

All guidelines included promote the use of medical therapy as the first-line treatment strategy

	Canada	Finland	France	UK/NICE	USA/ACOG**
Type of AUB covered	AUB	HMB	HMB	HMB	AUB-O
Order of efficacy (if recommended)					
COC	*'reduce effectively'*	*'recommended'*	3.	2.	2.
Luteal-phase progestin	*'not effective'*	*'not effective'*	NA	*'not to be used'*	3.
Extended-cycle progestin	*'reduce effectively'*	*'recommended'*	4.	3.	
DMPA	*'reduce effectively'*	*'not recommended'*	NA	3.	
LNG-IUS	*'reduce effectively'*	*'recommended'**	1.	1.	1.
Tranexamic acid	*'can be used'*	*'recommended'*	2.	2.	2.
NSAID	*'can be used'*	*'recommended'*	5.	2.	3.
Reference	Singh et al., 2013 [36]	www.kaypahoito.fi [37]	Marret et al., 2010 [38]	www.nice.org.uk [39]	ACOG Practice bulletin, 2013 [40]

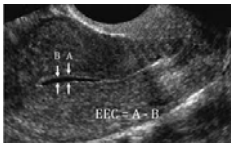
Postmenopausal Bleeding (PMB)

- Spontaneous bleeding or spotting more than one year after the final menstrual period
- History
  - How much, how often and for how long
  - Final menstrual period
  - Medications
    - Menopausal hormone therapy (MHT)
    - Tamoxifen
  - Symptoms of genitourinary syndrome of menopause (GSM)

Evaluating PMB

- Physical exam
  - Rule out other sources of bleeding
  - Signs of GSM
  - Pessary use

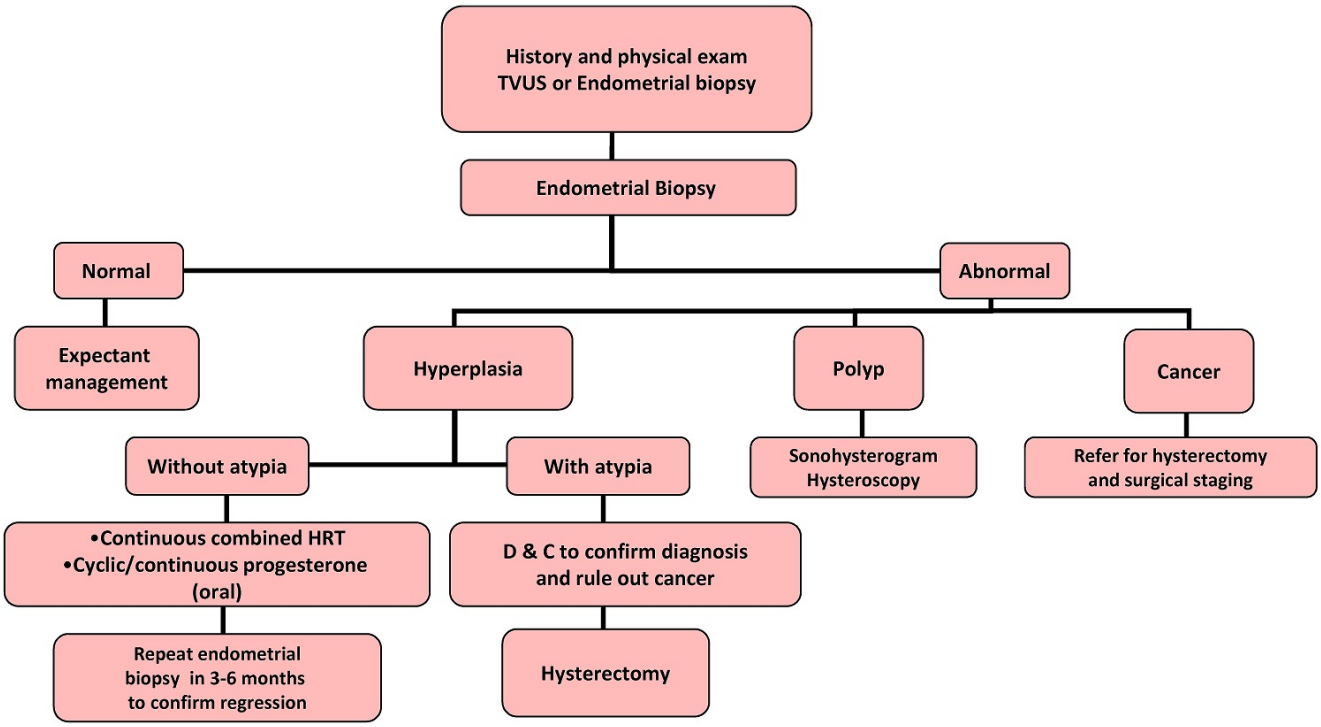
Evaluating PMB



- Diagnostic tests
  - Pap smear, if indicated
  - Endometrial biopsy or
  - Transvaginal ultrasound, with measurement of endometrial stripe thickness
    - if ≤ 4 mm, likelihood of endometrial cancer is <1%
    - Refer for endometrial assessment if endometrial stripe is greater than 4 mm or with any abnormal appearance

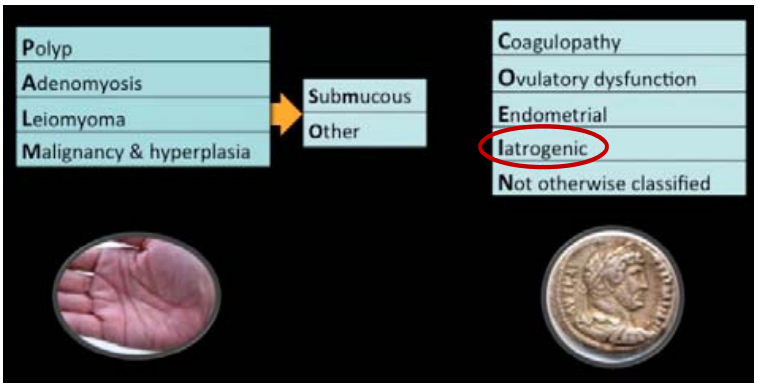
ACOG Committee Opinion No. 734 *Obstet & Gynecol* 2018;131:e124-e129

Management of Postmenopausal Bleeding



Causes of AUB

FIGO Classification (2011)



Structural entities | Non-structural entities

Munro et al. *Fertil Steril* 2011;95:2204-2208

Unscheduled Bleeding on Hormonal Contraceptives

- Can be a common side effect
  - Concern when abrupt change in bleeding pattern
  - Concern with persistent, irregular bleeding despite intervention
- Not necessarily indicative of decreased efficacy of the method

Unscheduled Bleeding on Hormonal Contraceptives

- Potential causes
  - Correct method use?
  - Correct IUD position?
  - Medication interactions?
  - Pregnancy?
  - Infection? (vaginitis, STI, PID)
  - Structural pathology? (of uterus, cervix, vagina, perineum—or neoplasia)
  - Trauma, endocrinopathies, bleeding disorders?

Combined Hormonal Methods

- Change to different brand of pills
  - Really no science behind this
  - Can increase estrogen dose (20 to 30 mcg)
  - Try different progestin formulation
- Switch to a different method altogether
  - Ring may have more steady hormone absorption than pills

Depo-Provera (DMPA)

- Get next injection early
  - 8-10 weeks from previous injection
- Mefenamic acid or Naproxen 500 mg BID x 5 days
- Conjugated estrogen 1.25 mg or estradiol 2 mg po daily x 14 days
- COCs for 1-3 cycles
- Doxycycline 100 mg BID x 10-14 days
- Tranexamic acid 1300 mg TID x 5 days

Zigler, R & McNicholas, C. *Am J Obstet Gynecol* 2017;216:443-450

ENG Implant (Nexplanon)

- 10% dissatisfied with bleeding pattern
- Mefenamic acid or Naproxen 500 mg BID x 5 days
- Conjugated estrogen 1.25 mg or estradiol 2 mg po daily x 14 days
- COCs for 1-3 cycles
- Doxycycline 100 mg BID x 10-14 days
- Tranexamic acid 1300 mg TID x 5 days
- Tamoxifen 10 mg BID x 7 days

Zigler, R & McNicholas, C. *Am J Obstet Gynecol* 2017;216:443-450

LNG IUD

- May improve after the first 3-6 months
- Naproxen 500 mg BID x 5 days
- Conjugated estrogen 1.25 mg or estradiol 2 mg po daily x 14 days
- COCs for 1-3 cycles
- Tranexamic acid 1300 mg TID x 5 days

Zigler, R & McNicholas, C. *Am J Obstet Gynecol* 2017;216:443-450

Patient Counseling

- Provide anticipatory guidance regarding possible bleeding pattern when starting a method
  - What to expect
  - What is abnormal and what should be reported
  - When to follow up
- "**Contact me** if you do not like your bleeding pattern to discuss options before stopping _____."

Summary

- AUB should be evaluated for an underlying cause, especially in women with risk factors for neoplasia
- The PALM-COEIN classification system provides a framework for determining an underlying cause
- AUB can be controlled with a variety of evidence-based strategies, depending on the cause and a woman's preferences and goals