Abnormal Uterine Bleeding (AUB)

Todd R. Jenkins, MD

Division of Women's Reproductive Healthcare

UAB Department of Obstetrics & Gynecology

I have no relevant financial relationships with any ACCME-defined commercial interest* to disclose.

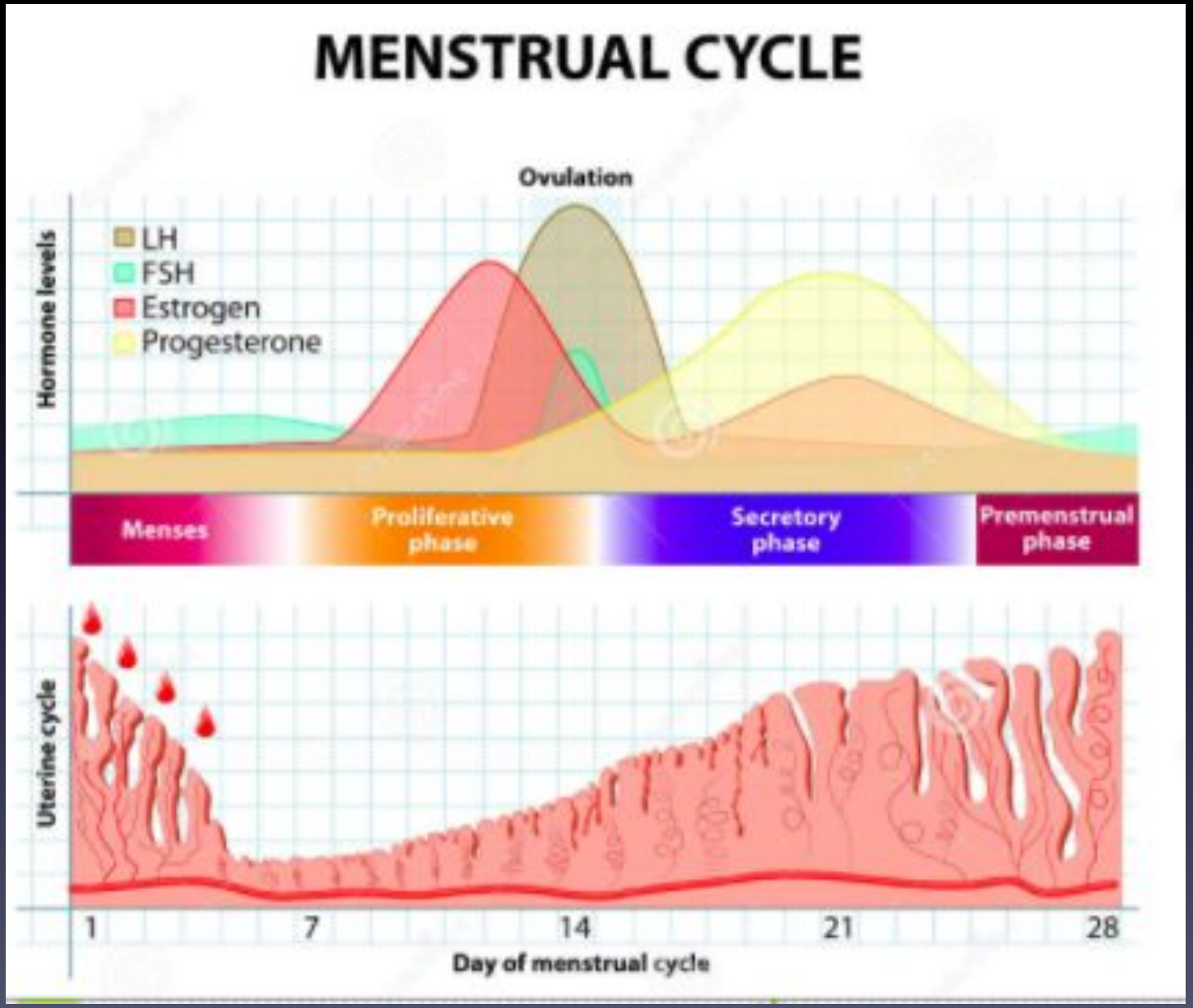
AUB: Learning Objectives

- Review the physiology and characteristics of the normal menstrual cycle
- Discuss the components of the appropriate evaluation of AUB
- Discuss the best treatments for AUB and the rationale behind their usage

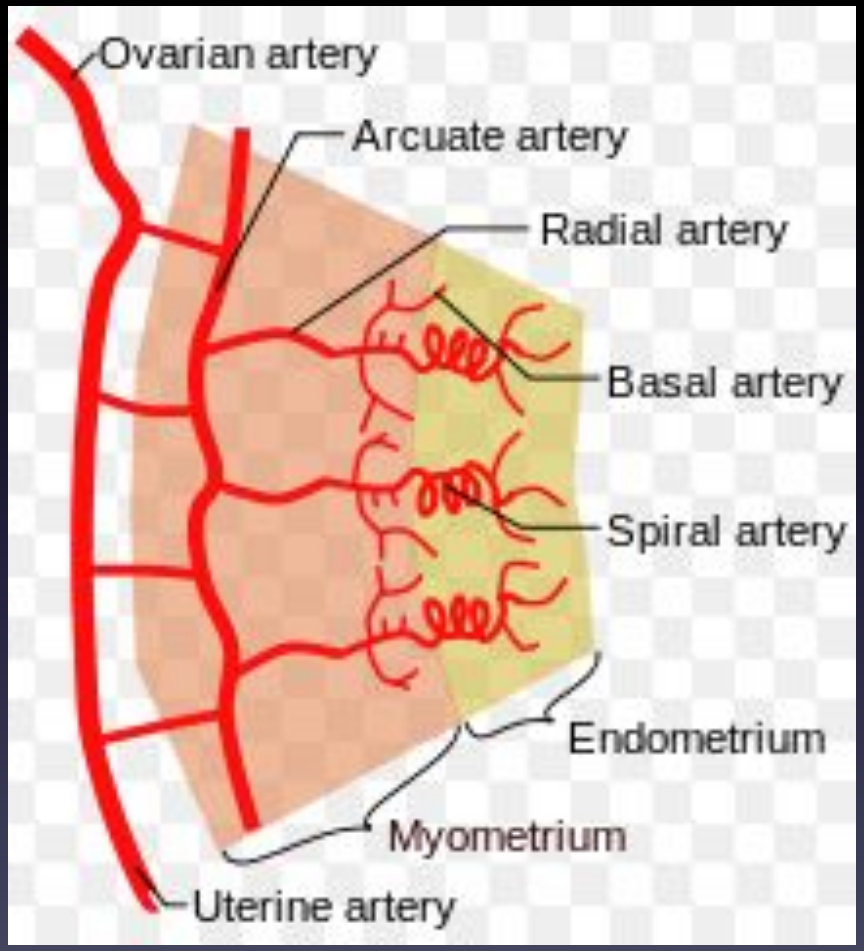
AUB: Faculty Disclosures

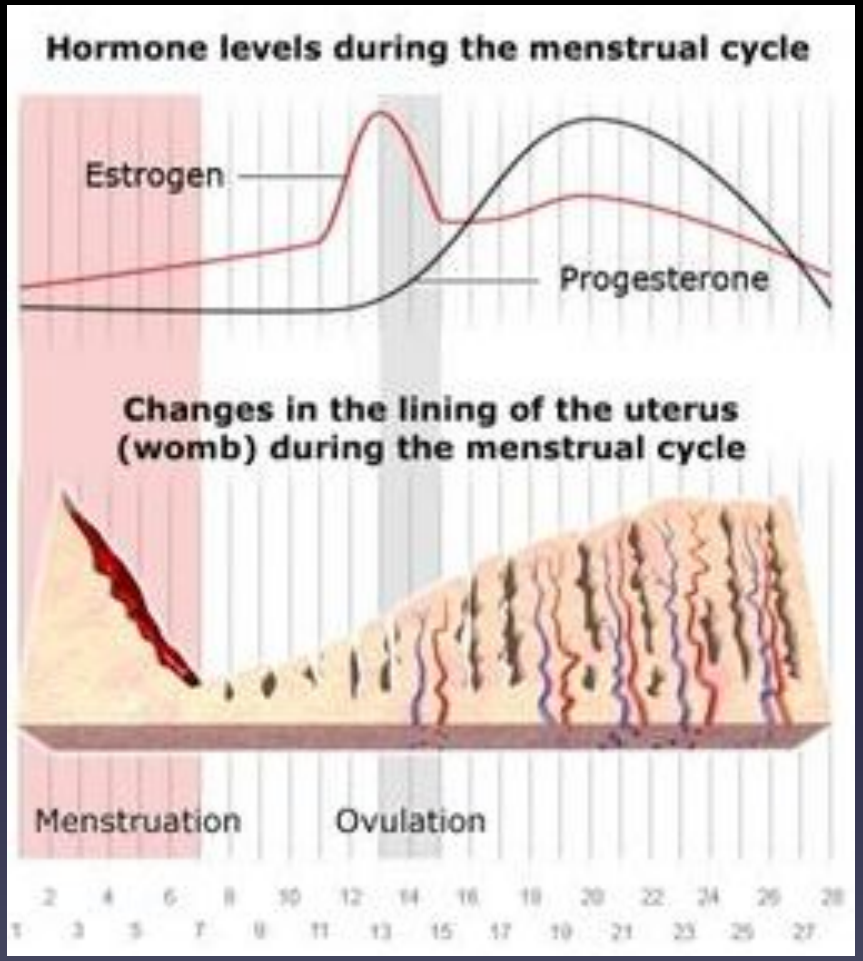
- None

The "Normal" Menstrual Cycle



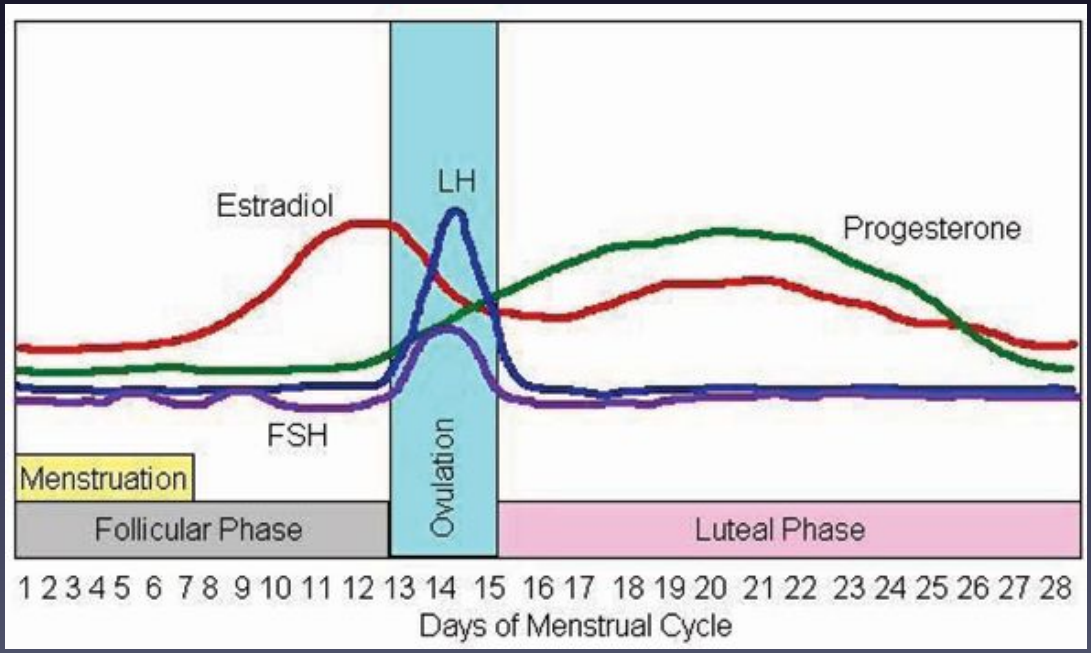
Normal Menstrual Cycle





Normal Menstrual Cycle

- Follicular Phase
  - Duration is highly variable
  - 10.3 – 16.3 days
- Luteal Phase
  - Duration is fairly constant
  - 14 ± 1.4 days



The "Normal" Menstrual Cycle

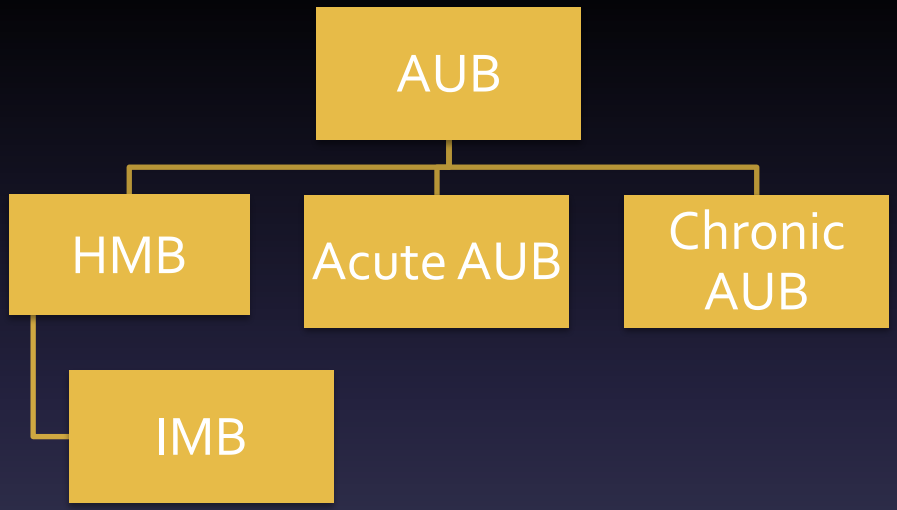
Clinical Dimensions of Menses	Descriptive terms	Normal limits
Frequency of menses (days)	Frequent Normal Infrequent	<24 days 24 – 38 > 38
Regularity of menses (Cycle to Cycle Variation in days)	Absent Regular Irregular	 ±2 to 20 days > 20 days
Duration of flow (days)	Prolonged Normal Shortened	>8 days 4.5 – 8 days <4.5 days
Volume of monthly blood loss (mL)	Heavy Normal Light	>80 mL 5 – 80 mL <5 mL

Munro et al. Int J Gynecol Obstet. 2011;113: 3-13

CLASSIFICATION OF AUB

AUB: Terminology

- **AUB** – Abnormal uterine bleeding
- **HMB** – Heavy menstrual bleeding
- **IMB** – Intermenstrual bleeding



Munro et al. Int J Gynecol Obstet. 2011;113: 3-13

AUB: Terminology

- **<u>Discarded terms</u>**
  - Menorrhagia
  - Metrorrhagia
  - Menometrorrhagia
  - Dysfunctional uterine bleeding

Munro et al. Int J Gynecol Obstet. 2011;113: 3-13

FIGO AUB Classification System

Polyp

Adenomyosis

Leiomyoma

Malignancy & Hyperplasia

Structural Abnormality

Dysfunctional Uterine Bleeding

Iatrogenic

No Structural Abnormality

Munro et al. Int J Gynecol Obstet. 2011;113: 3-13

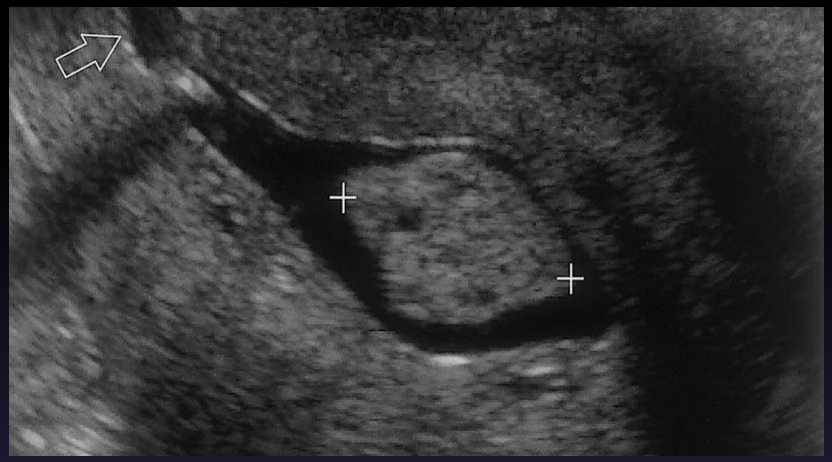
AUB: Structural Abnormalities

- **AUB-P - Polyps**
  - Etiology
    - Unknown
    - Clusters of anomalies in chromosomes 6 and 12, which control proliferative processes
  - Prevalence
    - 7.8 – 35%
    - Increase with age

Salim S. JMIG. 2011;18: 569-81.

AUB: Structural Abnormalities

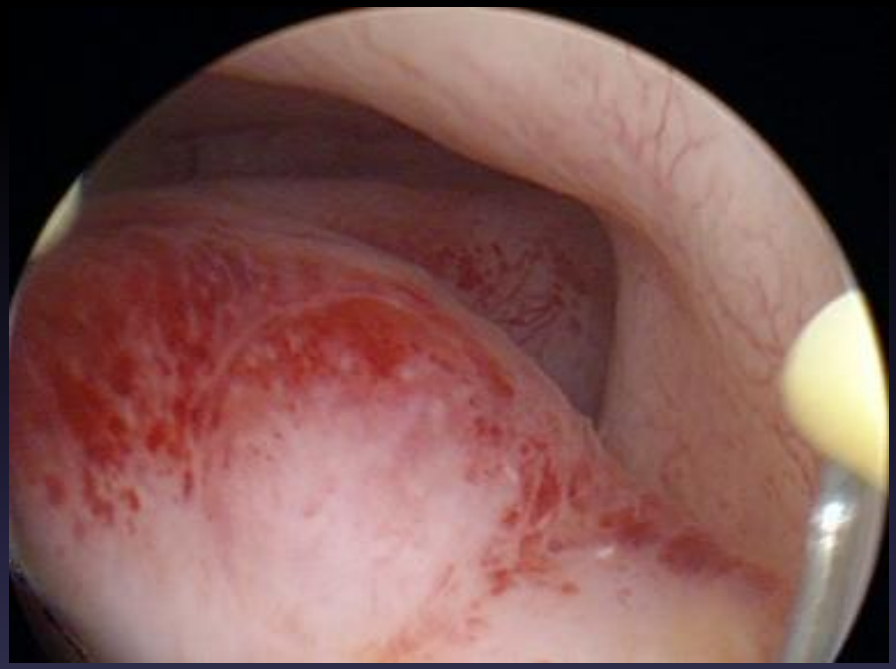
- **Premenopausal Polyps**
  - 64 – 88% have symptoms
  - Present with HMB, AUB, IMB, or postcoital bleeding
  - Symptoms do NOT correlate with number, diameter and site
  - Stromal congestion leads to venous stasis and apical necrosis
  - Polyps caused 39% of all AUB in one study



Polyps < 1 cm are more likely to spontaneously regress

Salim S. JMIG. 2011;18: 569-81.

AUB: Structural Abnormalities



- **Postmenopausal Polyps**
  - Most are symptom free
  - Cause for 21-28% of PMP bleeding
  - Associated with cervical polyps in 24-27%
  - Incidence of carcinoma varies between 0 – 4.8%

ACOG Practice Bulletin #128 – "If the cancer occupies <50% of the surface area of the endometrial cavity, the cancer can be missed by a blind endometrial biopsy…**persistent bleeding with a previous benign pathology requires further testing to rule out a nonfocal endometrial pathology**."

Salim S. JMIG. 2011;18: 569-81.

AUB: Structural Abnormalities

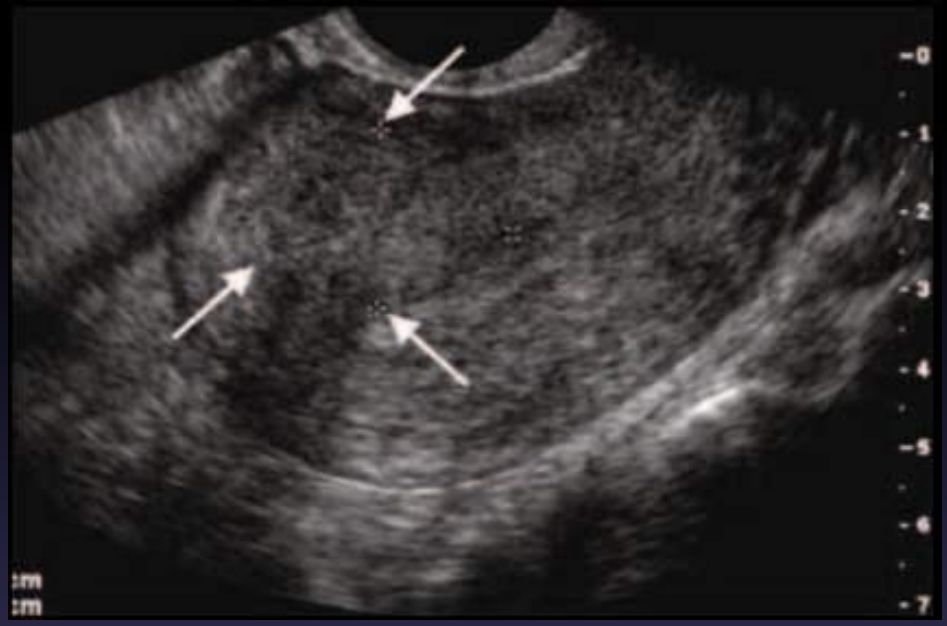
Endometrial Polyp Detection				
	Sensitivity	**Specificity**	**PPV**	**NPV**
TV U/S	91%	90%	86%	90%
SIS	95%	92%	95%	94%
Blind Bx	10%	100%	66%	33%
Dx HSC	90%	93%	96%	93%

ACOG Practice Bulletin #128 – "A positive test result (EMB) is more accurate for ruling in disease than a negative test result is for ruling it out."

Salim S. JMIG. 2011;18: 569-81.

Structural Abnormalities

- **AUB-A - Adenomyosis**
  - Ectopic endometrial glands and stroma within the myometrium
  - Hypertrophy and hyperplasia of surrounding myometrium
  - Prevalence varies from 0.5% - 70%



Usual presentation includes HMB, uterine enlargement, and dysmenorrhea.

Kepkep, K. Ultrasound Obstet Gynecol 2007;30: 341-5

AUB: Structural Abnormalities

Ultrasound Criteria for Adenomyosis

U/S findings	Sens.	Spec.	PPV	NPV	Acc.
Globular configuration	69%	86%	75%	83%	80%
Myometrial A-P asymmetry	62%	64%	50%	74%	63%
Identification of endomyometrial junction	46%	82%	60%	72%	69%
Echogenic linear striations	31%	96%	80%	70%	71%
Myometrial cysts	62%	82%	67%	78%	74%
Heterogeneous myometrium	81%	61%	55%	84%	69%

Kepkep, K. Ultrasound Obstet Gynecol 2007;30: 341-5

Polyp

Adenomyosis

Malignancy & Hyperplasia

Coagulopathy

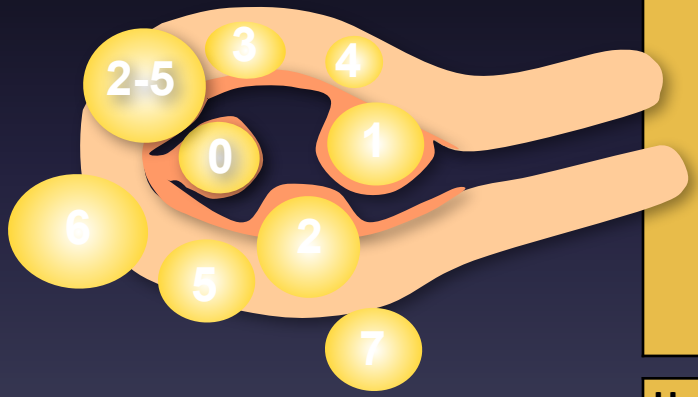
Ovulatory Dysfunction

Endometrial

Iatrogenic

Not Yet Classified

Leiomyoma Subclassification System



S M- Submucosal	0	Pedunculated Intracavitary
	1	<50% Intramural
	2	≥ 50% Intramural
O - Other	3	Contacts endometrium; 100% Intramural
	4	Intramural
	5	Subserosal ≥50% Intramural
	6	Subserosal < 50% Intramural
	7	Subserosal Pedunculated
	8	Other (specify eg. cervical, parasitic)

Hybrid Leiomyomas (impact both endometrium and serosa)	Two numbers are listed separated by a dash. By convention, the first refers to the relationship with the endometrium while the second refers to the relationship to the serosa. One example is below	
	2-5	Submucosal and subserosal, each with less than half the diameter in the endometrial and peritoneal cavities respectively.

AUB: Structural Abnormalities

- **AUB-M - Malignancy and Hyperplasia**
  - Most often detected based upon results of office biopsy or surgical curettage
  - Hyperplasia
    - Benign endometrial hyperplasia
    - Endometrial intraepithelial neoplasia (EIN)
  - Up to 40% of patients with a biopsy diagnosis of EIN (complex with atypia) will have a concomitant endometrial adenocarcinoma present

Nonstructural Abnormalities

- C – Coagulopathy
- O – Ovulatory Dysfunction
- E – Endometrial
- I – Iatrogenic
- N – Not classified

AUB: Nonstructural Abnormalities

- **AUB-C - Coagulopathy**
  - Prevalence
    - 0.8 – 1.3% of the general population
    - 13% of women presenting with HMB
  - Etiologies
    - Von Willebrand's disease (10%)
    - Platelet Dysfunction
    - Factor XI deficiency
    - Factor X deficiency
  - Category includes patient's taking anti-coagulants

Munro et al. Int J Gynecol Obstet. 2011;113: 3-13.

AUB: Nonstructural Abnormalities

- **AUB-O - Ovulatory**
  - Presentation
    - Combination of unpredictable timing of bleeding and variable amount of flow
    - Wide range of presentations
      - Amenorrhea
      - Extremely light and infrequent bleeding
      - Episodes of unpredictable and extreme AUB
  - Cause
    - Absence of predictable cyclic progesterone production from a corpus luteum

Munro et al. Int J Gynecol Obstet. 2011;113: 3-13.

AUB: Nonstructural Abnormalities

- **AUB-O – Ovulatory Dysfunction**
  - Etiology
    - Polycystic Ovarian Syndrome (PCOS)
    - Hypothyroidism
    - Hyperprolactinemia
    - Mental stress
    - Obesity
    - Anorexia
    - Weight loss
    - Extreme exercise
    - Adolescence
    - Menopausal transition

Munro et al. Int J Gynecol Obstet. 2011;113: 3-13.

AUB: Nonstructural Abnormalities

- **AUB-E – Endometrial**

"When AUB occurs in the context of predictable and cyclic menstrual bleeding typical of ovulatory cycles and particularly when no other definable causes are identified, the mechanism is probably a primary disorder of the endometrium."

Munro et al. Int J Gynecol Obstet. 2011;113: 3-13.

AUB: Nonstructural Abnormalities

- **AUB-E - Endometrial**
  - Deficiencies of local production of vasoconstrictors
    - Endothelin-1
    - Prostaglandin $E_{2\alpha}$
  - Excessive production of plasminogen activator
  - Increased local production of substances that promote vasodilation
    - Prostaglandin E_2
    - Prostacyclin I_2
  - Disorders of endometrial repair (inflammation)
    - Chlamydia

Munro et al. Int J Gynecol Obstet. 2011;113: 3-13.

AUB: Nonstructural Abnormalities

- **AUB-E - Endometrial**
  - Tests measuring these abnormalities are **not** currently available to clinicians
  - "The diagnosis of AUB-E should probably be determined by **exclusion** of other identifiable abnormalities in women of reproductive age who seem to have normal ovulatory function."

Munro et al. Int J Gynecol Obstet. 2011;113: 3-13.

AUB: Nonstructural Abnormalities

- **AUB-I - Iatrogenic**
  - Breakthrough bleeding (BTB) using gonadal steroids is the major component of AUB-I."
    - Oral contraceptives
    - Continuous or cyclic progesterone
    - IUD or implant related bleeding
  - Cigarette smoking
    - Reduces the level of contraceptive steroids because of enhanced hepatic metabolism
  - Systemic agents that interfere with dopamine metabolism
    - Amitriptyline
    - Serotonin uptake inhibitors

Munro et al. Int J Gynecol Obstet. 2011;113: 3-13.

AUB: Nonstructural Abnormalities

- **AUB-N - Not Yet Classified**
  - Disorders that would be identified or defined only by biochemical or molecular biology assays
  - Arteriovenous malformations
  - Myometrial hypertrophy
  - Category for new etiologies

Munro et al. Int J Gynecol Obstet. 2011;113: 3-13.

EVALUATION OF AUB

AUB: Evaluation Guidelines

FIGO Recommendations

1. General Assessment
2. Determination of Ovulatory Status
3. Screening for Systemic Disorders of Hemostasis
4. Evaluation of the Endometrium
5. Evaluation of the Structure of the Endometrial Cavity
6. Myometrial Assessment

AUB Evaluation: History

- General Assessment: History
  - Bleeding pattern
  - Symptoms of anemia
  - Sexual and reproductive history
  - Associated symptoms
  - Systemic cause of AUB
  - Chronic medical illness
  - Medications
  - Family history

AUB Evaluation: History

- General Assessment: Ovulatory Status
  - Regular cycles
  - Mittleschmerz
  - Pre-ovulatory mucus
  - Moliminal symptoms
  - Predictable bleeding

AUB Evaluation: History

Screening for Systemic Disorders of Hemostasis

Has the patient suffered from excessive or heavy bleeding in any of the following situations?

- Heavy menstrual bleeding since menarche
- **One** of the following
  - Postpartum hemorrhage
  - Surgical-related bleeding
  - Bleeding associated with dental work
- **Two** of the following
  - Bruising 1-2x per month
  - Epistaxis 1-2x per month
  - Frequent gum bleeding
  - Family history of bleeding symptoms

Munro et al. Int J Gynecol Obstet. 2011;113: 3-13

AUB Evaluation: Exam

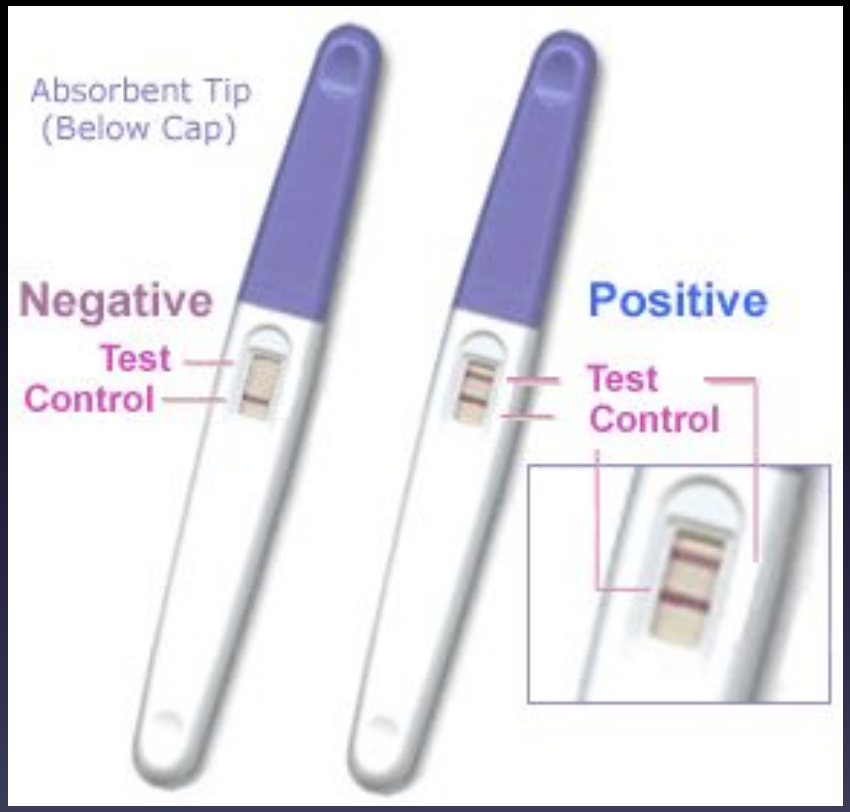
- General Assessment – Exam
  - Vital signs – BP, pulse, BMI, orthostatics
  - Neck exam - thyroid
  - Abdominal exam – tenderness, distension, mass
  - Bimanual exam
  - Rectal exam – as indicated
  - Testing – Pap and STI screening, as indicated
  - Labs – CBC, urine pregnancy
    - TSH, PRL, Coags, VW panel, Free testosterone – as indicated

Bradley et al. AJOG 2015

AUB Evaluation: Exam

General Assessment

- Rule out other location for bleeding
  - Rectal bleeding
  - Hematuria
  - Trauma



Munro et al. Int J Gynecol Obstet. 2011;113: 3-13

AUB: Evaluation Guidelines

Evaluation of the Endometrium (ACOG)

- Endometrial biopsy
  - "Endometrial tissue sampling should be performed in patients with AUB who are older than 45 years as a first line test"
  - "Endometrial sampling also should be performed in patients younger than 45 years with a history of unopposed estrogen exposure (such as obesity or PCOS), failed medical management, and persistent AUB."

ACOG Practice Bulletin #128. July 2012

AUB: Evaluation Guidelines

Evaluation of the Structure of the Endometrial Cavity (ACOG)

- Transvaginal ultrasound
  - "Any patient with an abnormal physical examination…should undergo transvaginal ultrasound."
  - "When symptoms persist despite treatment in the setting of a normal pelvic exam."
- Indications for SIS or office hysteroscopy
  - When there is clinical suspicion for endometrial polyps or submucosal leiomyomas

ACOG Practice Bulletin #128. July 2012

AUB: Evaluation Guidelines

Evaluation of the Structure of the Endometrial Cavity (ACOG)

- Transvaginal ultrasound
  - "Measurement of endometrial thickness in premenopausal women is **NOT** helpful in the evaluation of AUB."

ACOG Practice Bulletin #128. July 2012

AUB: Evaluation Guidelines

Myometrial Assessment

- Transvaginal ultrasound
  - Assess presence and location of myomas (AUB-L)
  - Assess for adenomyosis (AUB-A)
    - At least 3 criteria must be present for diagnosis
- MRI
  - Helpful in delineating fibroid location prior to myomectomy
  - Not required in most situations.

Munro et al. Int J Gynecol Obstet. 2011;113: 3-13

TREATMENT OPTIONS

AUB Treatment

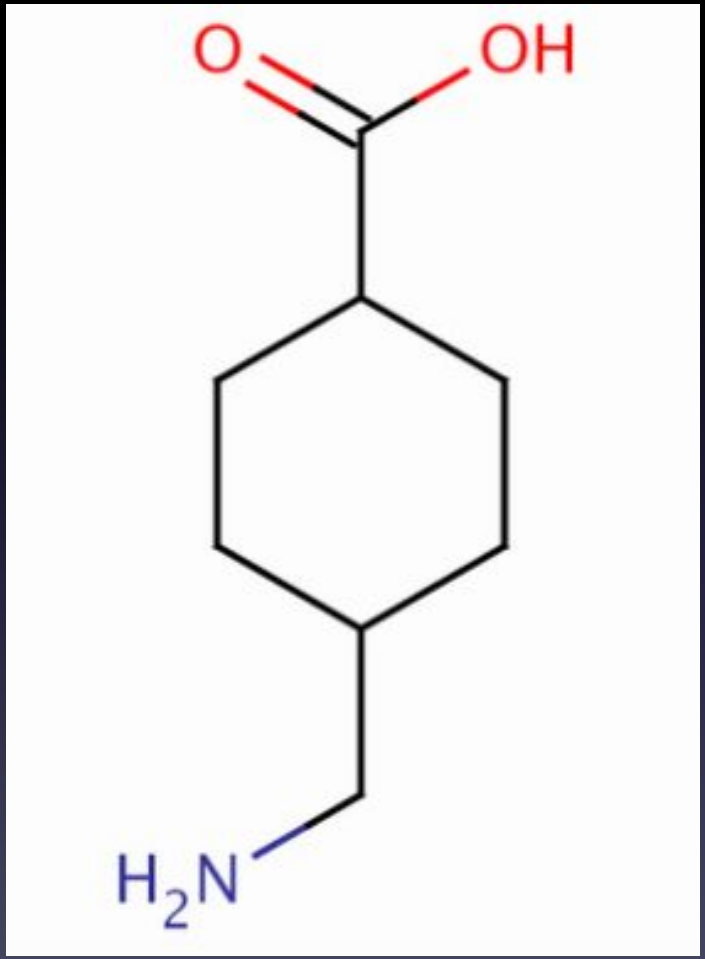
- HMB
  - NSAID's
  - Transexamic acid
  - Levonorgestrel intrauterine system (LNG-IUS)
  - Combined OCP
  - Cyclic or continuous progestin
  - Injectable progestin (DMPA)

AUB Treatment

- Nonsteroidal anti-inflammatory drugs (NSAIDS)
  - Suppress prostaglandin synthetase by inhibiting cyclooxygenase
  - Alter the equilibrium between:
    - Thromboxane A2 – vasoconstriction/platelet aggregation
    - Prostacyclin – vasodilation and prevents platelet aggregation
  - Reduces blood loss by as much as 40%
  - Can be used in patients attempting conception

AUB Treatments

- Transexamic Acid
  - Competitively blocking plasminogen binding sites
  - Preventing plasma formation, fibrin degradation, and clot degradation
- 1 gram PO q6-8 hrs. during menstruation
- 40% reduction in blood loss



Bradley et al. AJOG January 2016

AUB Treatments

- Transexamic Acid
  - Proven to be superior to the following:
    - Placebo
    - Mefenamic acid
    - Luteal phase progestins
  - Can be used in patients attempting conception

Bradley et al. AJOG January 2016

AUB Treatment

Levonorgestrel IUS

- Releases 20 mcg of progestin every 24 hrs.
- Reduces the endometrial thickness
- Reduces the mean uterine vascular density

Bradley et al. AJOG January 2016

AUB Treatment

Levonorgestrel IUS

- Reduction in menstrual blood loss
  - 86% after 3 months
  - 97% after 12 months

Lethaby et al. Cochrane 2005
Mansour et al Best Practice 2007
Anderson et al Obst Gynecol 1990
Kaunitz et al Obstet Gynecol 2009

Bradley et al. AJOG January 2016

AUB Treatment

Levonorgestrel IUS

- Randomized controlled trials have demonstrated the LNG-IUS to be superior to:
  - Luteal phase oral progesterone (MPA)
  - Norethindrone for 21 days
  - Continuous oral norethisterone
  - DMPA
  - Combination OCP's
  - Mefenamic acid
  - Endometrial ablation

Bradley et al. AJOG January 2016

AUB Treatments

<u>Combination hormonal contraceptive</u>

- Pills, vaginal rings, and the transdermal patch have all been shown to afford:
  - Cycle control
  - Reduce menstrual blood loss
  - Reduce the incidence of irregular bleeding

AUB Treatment

Estrogen

- Prevents FSH secretion
- Prevents development of a dominant follicle
- Provides endometrial stability
- Enhances the progestational impact

Progesterone

- Prevents the LH surge and ovulation
- Creates an atrophic endometrial lining
- Reduces overall blood loss at the time of withdrawal bleeding

AUB Treatment

- Progestogen-only Formulations
  - Medroxyprogesterone acetate (Provera) 2.5-10mg daily
  - Norethindrone (Aygestin) 2.5-5mg daily
  - Megestrol acetate (Megace) 40-320mg daily
  - Micronized progesterone (Prometrium) 200-400mg daily
- Dosing options
  - Cyclically – begin on day 5 for 21 days
  - Continuous dosing

Bradley et al. AJOG January 2016

AUB Treatment

- Progestogen-only Formulations
  - Endometrial effects
    - Stabilizes endometrial fragility
    - Inhibits the growth of the endometrium by triggering apoptosis
    - Inhibits angiogenesis
    - Stimulates conversion of estradiol to estrone

AUB Treatment

- Progestogen-only Formulations
  - Ovarian effects
    - Prevents ovulation
    - Prevents ovarian steroidogenesis
    - Interrupts the production of estrogen receptors
    - Interrupts the estrogen-dependent stimulation of the endometrium

AUB Treatment

- Progestogen-only Formulations
  - "The use of a luteal phase (cyclic) progestin alone has not proved to be successful in the treatment of ovulatory HMB".
  - "In women with anovulatory bleeding, a cyclic progestin given for 12-14 days each month leads to regulation of the menstrual cycle in 50% of women".

Bradley et al. AJOG January 2016

AUB Treatment

- Injectable progesterone (DMPA)
  - Produces amenorrhea in >50% of users after 1 year
  - DMPA Trial (3900 women)
    - 12 months – 57% experienced AUB
    - 24 months – 32% experienced AUB
    - 37% experienced weight gain of > 10lbs at 24 months

Bradley et al. AJOG January 2016

AUB Treatment

- "There is a lack of clinical data on the utility of DMPA for the treatment of acute or chronic AUB".

Bradley et al. AJOG January 2016


ComputerHope.com

SPECIAL POPULATIONS

AUB: Obesity

- Obese women suffer from ovulatory dysfunction because:
  - Elevated estrogen levels due to increased peripheral androgen aromatization
  - Elevated free estradiol and testosterone as a result of a reduction in SHBG
  - Insulin levels are elevated secondary to insulin resistance
  - Elevated insulin levels stimulates androgen production in the ovarian stroma and disrupts normal follicular development

Bradley et al. AJOG January 2016

AUB: Leiomyoma

- Submucosal fibroids cause unpredictable and heavy uterine bleeding
  - Unsteady vasculature of the endometrium
  - Inadequate rebuilding and healing
  - Increased endometrial surface area
  - Inadequate uterine contractions to compress the vessels on the surface of the endometrium

Bradley et al. AJOG January 2016

AUB: Leiomyoma

- Medications shown to reduce bleeding in women with fibroids
  - LNG-IUS
  - Combined OCP
  - NSAIDS
  - Danazol
  - Transexamic acid
- "Medical therapies are most successful in the absence of a submucosal myoma".

Bradley et al. AJOG January 2016

AUB: Leiomyoma

- GnRH Agonists
  - Down-regulate GnRH receptors, thereby inhibiting gonadotropin secretion
  - Menopausal symptoms limit their usefulness
  - Uterine volume can be reduced by 30-60% after 3 months use
  - Can improve anemia
  - Know plan for what you will do after therapy before you start!

Bradley et al. AJOG January 2016

AUB: Inherited bleeding disorders

- Prevalence
  - 84% of women with von Willebrand disease present with HMB
  - 10-20% of all women with AUB have an inherited bleeding disorder
  - 50% of adolescents with HMB will be diagnosed with a coagulopathy

Bradley et al. AJOG January 2016

AUB: Inherited bleeding disorders

- Treatment
  - Similar to women without a bleeding disorder
  - NSAIDS are contraindicated
  - Estrogen enhances von Willebrand factor and factor VIII
  - If standard treatment fails:
    - Consult Hematology
    - Desmopressin during 2-3 heavy days of cycle

Bradley et al. AJOG January 2016

AUB: Anticoagulation

- Prevalence
  - 70% experience changes in cycle
    - 50% experience a greater number of days
    - 66% experience HMB
- "LNG-IUS remains the superior method to control and significantly reduce menstrual blood loss in this group of patients".
- Transexamic acid and estrogen-containing contraceptives are contraindicated

Bradley et al. AJOG January 2016

AUB: Anticoagulation

- "LNG-IUS remains the superior method to control and significantly reduce menstrual blood loss in this group of patients".
- "Women on progestin-only methods should be monitored very closely because they face a higher risk of thrombosis than nonusers of hormonal medications".

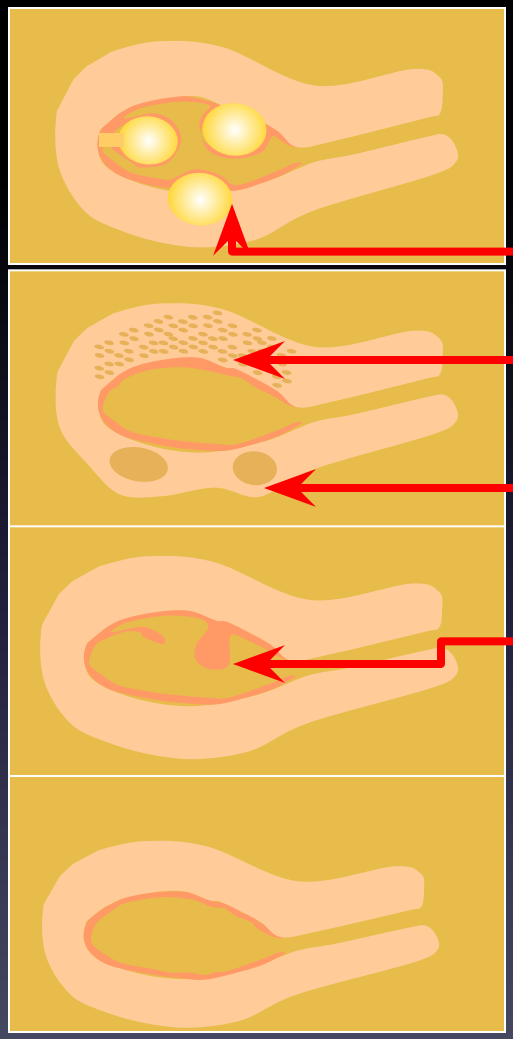
Bradley et al. AJOG January 2016

Additional Information

AUB PALM-COEIN

Classification Categorization

Single Entity Examples



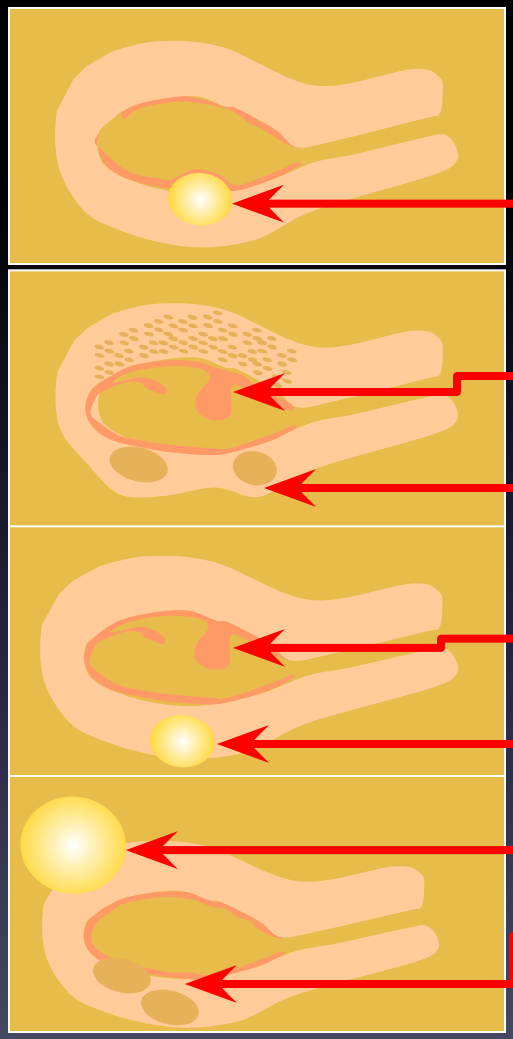
$P_0\ A_1\ L_0\ M_0$ - $C_0\ O_0\ E_0\ I_0\ N_0$

$P_1\ A_0\ L_0\ M_0$ - $C_0\ O_0\ E_0\ I_0\ N_0$

$P_0\ A_0\ L_0\ M_0$ - $C_0\ O_0\ E_0\ I_0\ N_0$

Classification Categorization

Multiple Entity Examples



$P_1\ A_1\ L_0\ M_0\ -\ C_0\ O_0\ E_0\ I_0\ N_0$

$P_1\ A_0\ L_{1(O)}\ M_0\ -\ C_0\ O_0\ E_0\ I_0\ N_0$

$P_0\ A_1\ L_{1(O)}\ M_0\ -\ C_1\ O_0\ E_0\ I_0\ N_0$

AUB Treatment

- Options for Treatment of Acute AUB
  - IV conjugated equine estrogen (CEE)
  - Oral transexamic acid
  - Multi-dose combined monophasic OCP
  - Multidose oral progestin
  - GnRH agonist with aromatase inhibitor

AUB Treatment – Acute AUB

- Conjugated equine estrogen (CEE)
  - Rapid growth of the endometrial epithelium and stroma
  - Stimulating vasospasm of uterine arteries
  - Promotes platelet aggregation and capillary clotting
  - Increasing fibrinogen, factor V, and factor XI
  - Increases the production of estrogen and progesterone receptors

AUB Treatment – Acute AUB

- Conjugated equine estrogen (CEE)
  - 25 mg dose of IV CEE q4-6 hrs.
  - Transition to progesterone alone or combination OCP's for 10-14 days
  - If still bleeding at 24 hours, consider hysteroscopy, dilation and curettage