A Systematic Approach to the Diagnosis and Management of Abnormal Uterine Bleeding (AUB)

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Disclosures

Advisory Board:
Astellas
Speakers Bureau:
Astellas

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Objectives

- Discuss the Palm-Coein classification system for abnormal uterine bleeding
- Discuss the workup for the diagnosis of abnormal uterine bleeding
- Discuss options for management of abnormal uterine bleeding including pharmacologic and surgical interventions

3

Are You Proactive in Educating Women?

What is a normal menstrual cycle and what is not?

Do you bleed for 3 to 7 days…

How do your periods effect the quality of your life?

- **Life should not be hampered by menstrual cycles**
- **Not normal to wake up at night to change pad, not normal to have to change clothing, have special chair to sit on**

Women may wrongly assume things are normal if they have heard of similar experiences from grandmothers, mothers, cousins, etc.

How do your periods effect the quality of your life: your work, sports, your sexual life, change of plans according to your period

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Educating Women

Is your menstrual cycle normal?

When should you speak to your health care clinician?

Ask about symptoms of anemia.

Any family history of a bleeding disorder?

First years of menses often abnormal with skipped periods.

5

SO….

When addressing AUB…

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When Furniture Gets Old… Out to the Curb!

Photo courtesy of Unsplash.com

7

When Shoes Get Old... Out To the Trash!

Photo courtesy of Unsplash.com

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When Terminology Gets Old... Replace It!

- Menorrhagia
- Metromenorrhagia
- Dysfunctional Uterine Bleeding (DUB)

??????????????????

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Welcome to PALM COEIN

Systematic evaluation of AUB leading to a diagnosis and treatment plan

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PALM COEIN

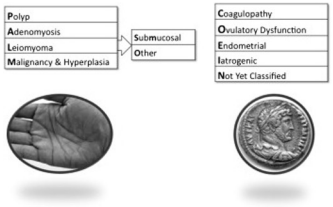

Figure 1. Basic classification system. The basic system comprises four categories that are defined by visually objective structural criteria (PALM: Polyp, Adenomyosis, Leiomyoma, and Malignancy or hyperplasia), four (COEI) that are unrelated to structural anom...

Munro MG, Critchley HOD, Fraser IS, Committee IFMD. The two FIGO systems for normal and abnormal uterine bleeding symptoms and classification of causes of abnormal uterine bleeding in the reproductive years: 2018 revisions. *International Journal of Gynecology & Obstetrics*. 2018;143(3):393-408.

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PALM COEIN

Most common causes of abnormal uterine bleeding:

- Uterine pathologies: STRUCTURAL
  - **P**olyps
  - **A**denomyosis
  - **L**eiomyomas
  - **M**alignancy & hyperplasia

Munro MG, Critchley HOD, Fraser IS, Committee IFMD. The two FIGO systems for normal and abnormal uterine bleeding symptoms and classification of causes of abnormal uterine bleeding in the reproductive years: 2018 revisions. *International Journal of Gynecology & Obstetrics*. 2018;143(3):393-408.

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PALM COEIN

- Systemic conditions: NON-STRUCTURAL
  - **C**oagulopathies
  - **O**vulatory dysfunction
  - **E**ndometrial
  - **I**atrogenic
  - **N**ot yet classified

Munro MG, Critchley HOD, Fraser IS, Committee tFMD. The two FIGO systems for normal and abnormal uterine bleeding symptoms and classification of causes of abnormal uterine bleeding in the reproductive years: 2018 revisions. *International Journal of Gynecology & Obstetrics*. 2018;143(3):393-408.

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A Classification System for Abnormal Uterine Bleeding

IN NONPREGNANT REPRODUCTIVE-AGED WOMEN

PALM COEIN was developed:

- To improve upon poorly defined terms and definitions
- To develop a structured approach to a frequently multifactorial clinical problem

BJOG: An International Journal of Obstetrics & Gynaecology
volume 124, issue 2, pages 185-189, 23 DEC 2016 DOI: 10.1111/1471-0528.14431
http://onlinelibrary.wiley.com/doi/10.1111/1471-0528.14431/full#sic14431-fig-0001

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A Classification System for Abnormal Uterine Bleeding

- Helps the clinician to develop a *diagnosis* for the bleeding rather than a *symptom*
- "Menorrhagia" frequently persists as an ill-defined combination of *symptom and diagnosis*
- "Heavy menstrual bleeding" or "HMB" is frequently used as a *diagnosis* rather than a *symptom*

BJOG: An International Journal of Obstetrics & Gynaecology
volume 124, issue 2, pages 185-189, 23 DEC 2016 DOI: 10.1111/1471-0528.14431
http://onlinelibrary.wiley.com/doi/10.1111/1471-0528.14431/full#sic14431-fig-0001

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FIGO System

FIGO system

•Nomenclature and definitions

- Gone are the terms 'menorrhagia', 'menometrorrhagia', and 'oligomenorrhea', and other poorly defined and inconsistently used terms.

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FIGO System

- There are four basic criteria to define menses:
  - Frequency, duration, regularity, and volume
    - All as reported by the patient.
  - Intermenstrual bleeding is reported only when one can clearly define normal ovulatory menses.
  - Unscheduled bleeding when using hormonal medications is reported separately

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The Menstrual Cycle

What is normal cycling?

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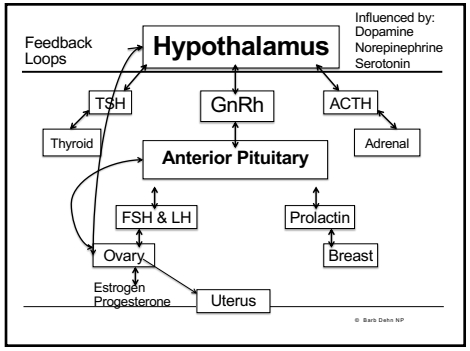

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Menses

- Proliferative phase- follicular phase, estrogen (E2) dominant
  - Endometrial growth from 0.5 to 3.5-5.0mm, relatively smooth surface
- Secretory phase- luteal phase, progesterone dominant
  - Height unchanged, becomes more glandular, sawtooth appearance
  - Menses - decreased E2 and Progesterone

Beshay and Carr 2013

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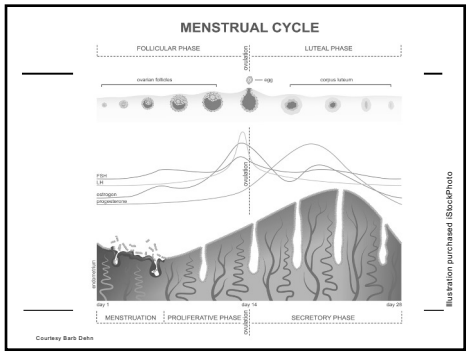

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Normal Cycling

- Normal interval: 21-35 days
- Only 15% of women have 28 day cycles
- Duration of flow 2-8 days, Average: 4-6
- Normal volume is 30 ml of blood

Beshay and Carr 2013

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Endometrial Hemostasis

- Platelets involvement relatively low
- Prostaglandin E2:F2α elevated in women with heavy bleeding
- Nitric Oxide may play a role
  - Vasodilator and inhibits platelet aggregation
- Coagulation cascade after day 1
- Possible role of enhanced fibrinolysis

Beshay and Carr 2013

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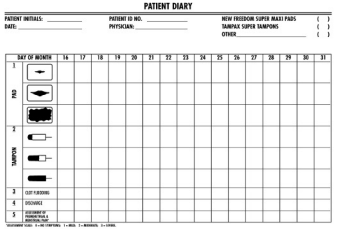
Pictorial Bleeding Assessment Chart (PBAC)



Courtesy Jay Berman MD

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Abnormal Uterine Bleeding

Definition
Causes
Diagnosis
Treatment

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What is Abnormal Uterine Bleeding

- > 1 pad/hour for more than 1 day
- > 7 days at a time
- < 20 days apart
- > 80 cc a month
- Enough to cause anemia
- ENOUGH TO CAUSE DISRUPTION IN LIFESTYLE

ACOG, Committee Opinion. April 2013 (reaffirmed 2015), number 557.

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Prevalence

- 5% of women between 35–49
- Up to 50% of perimenopausal women will experience AUB
- 1.4 million women in the US annually
- 53% of women report: periods interfere with their life
  - Compared with 23% of age-matched community controls

Davidson, BR, et al. J Midwifery Womens Health, 2012.
Britto, LGO, et al. Reproductive Health, 2014

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Diagnostic Evaluation of AUB

- The evaluation of AUB includes:
  - A thorough medical history and physical examination
  - Appropriate laboratory and imaging tests
  - Consideration of age-related factors

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Diagnostic Evaluation of Abnormal Uterine Bleeding

Medical history
- Age of menarche and menopause
- Menstrual bleeding patterns:
  - Duration, onset and quantity
- Severity of bleeding (clots or flooding)
- Family or personal history of bleeding disorders
- Pain (severity and treatment)
- Medical conditions

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Diagnostic Evaluation of Abnormal Uterine Bleeding

Physical exam
- General physical:
  - Signs of systemic illness
    - Bruising
    - Thyromegaly
    - Hirsutism
    - Acne
    - Acanthosis nigricans (associated with insulin resistance)
    - Galactorrhea

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Diagnosis

- Pelvic Examination
  - External
    - Perineal, perianal, vulvar, vaginal, urethral
  - Speculum with pap test and/or HPV test, if needed
  - Bimanual exam
    - Cervical lesions
    - Uterine size and shape
    - Adnexal masses

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Diagnostic Evaluation of Abnormal Uterine Bleeding

Laboratory tests
- Pregnancy test (blood or urine)
- Complete blood count
- Targeted screening for bleeding disorders (when indicated) *
  - Check prothrombin time (PT), partial thromboplastin time (PTT), factor VII, and Von Willebrand's factor antigen

*See Coagulopathy Slides

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Screening for Coagulopathy

Assess for a positive screen
- Heavy menstrual bleeding since menarche
- One of the following:
  - Postpartum hemorrhage
  - Surgery-related bleeding
  - Bleeding associated with dental work

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Screening for Coagulopathy

OR
- Two or more of the following:
  - Bruising one to two times per month
  - Epistaxis one to two times per month
  - Frequent gum bleeding
  - Family history of bleeding symptoms

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COAGULOPATHIES

- Primary hemostasis
  - Thrombocytopenia
    - Congenital, drug induced, liver disease, lymphoma
    - Von Willebrand disease
    - 0.1-0.8% of population
- Secondary hemostasis
  - Factor VIII, XIII, fibrinogen deficiencies
  - Oral anticoagulation therapy
  - Liver disease

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Diagnostic Evaluation of Abnormal Uterine Bleeding

- Thyroid-stimulating hormone level
- Chlamydia trachomatis

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Diagnostic Evaluation of Abnormal Uterine Bleeding

Available Diagnostic or Imaging Tests (when indicated)

- Saline infusion sonohysterography
- Transvaginal ultrasonography
- Magnetic resonance imaging
- Hysteroscopy

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Direct Visualization May be Necessary

- Hysteroscopy

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Diagnostic Evaluation of Abnormal Uterine Bleeding

Available Tissue Sampling Methods (when indicated)

- Office endometrial biopsy
- Hysteroscopic directed endometrial sampling (office or operating room)

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Screening the Endometrium

- All women older than 40 years old with a complaint of AUB
- Women with risk factors for endometrial hyperplasia (obese women, chronic anovulation, history of breast cancer)
- Women of any age with a history of unopposed estrogen exposure

Gentry-Maharaj, A. and C. Karpinskyj (2020). "Current and future approaches to screening for endometrial cancer." Best Pract Res Clin Obstet Gynaecol **65**: 79-97.

40

Screening the Endometrium

- Women taking an estrogen agonist/antagonist (selective estrogen receptor modulator: SERM: tamoxifen)
- Postmenopausal women who resume vaginal bleeding once menstrual cycles have ceased for 1 year

Gentry-Maharaj, A. and C. Karpinskyj (2020). "Current and future approaches to screening for endometrial cancer." Best Pract Res Clin Obstet Gynaecol **65**: 79-97.

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Screening the Endometrium

- All women with abnormal endometrial cells
- Atypical glandular cells on the Pap test
  - If ≥ 35 years or at risk for endometrial neoplasia
    - Unexplained vaginal bleeding
    - Conditions suggesting chronic anovulation

Perkins RB, Guido RS, Castle PE, et al. 2019 ASCCP risk-based management consensus guidelines for abnormal cervical cancer screening tests and cancer precursors. J Low Genit Tract Dis 2020;24:102–31.

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Using PALM COEIN

Making a diagnosis
- Structural?
- Non-structural?

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AUB: PALM-COEIN

- **PALM - Structural**
  - **P** - Polyp
  - **A** - Adenomyosis
  - **L** - Leiomyoma
  - **M** - Malignancy/Hyperplasia
- **COEIN – Non-structural**
  - **C** - Coagulopathy
  - **O** - Ovulatory
  - **E** - Endometrial
  - **I** - Iatrogenic
  - **N** –Not Classified

Established by **FIGO -** Fédération Internationale de Gynécologie et d'Obstétrique (the International Federation of Gynecology and Obstetrics).

Munro MG, Critchley HOD, Fraser IS, Committee IFMD. The two FIGO systems for normal and abnormal uterine bleeding symptoms and classification of causes of abnormal uterine bleeding in the reproductive years: 2018 revisions. *International Journal of Gynecology & Obstetrics*. 2018;143(3):393-408.

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AUB-P

Polyps

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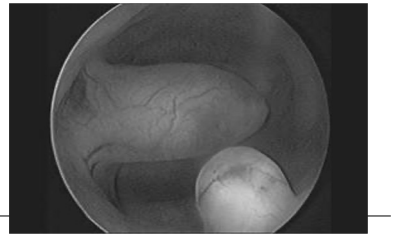
AUB: P
Polyps

- Endometrial proliferations
- As many as 25% may resolve spontaneously
- Mostly associated with "intermittent bleeding" as presenting sign
- Risk of malignancy – 1.7% for pre-menopause
- Risk of malignancy – 5.4% for post menopause
- Size *not* correlated with risk

Hamani Y, et al. *Eur J Obstet Gynecol Reprod Biol*. 2013
Raz, N., et al. (2021). "Endometrial polyps: diagnosis and treatment options - a review of literature." Minim Invasive Ther Allied Technol **30**(5): 278-287.

46

Polyps



Courtesy Barb Dehn

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PELVIC PATHOLOGY

- Polyps
  - Bleeding because of vasculature and friable
  - Bleeding is usually random
    - not necessarily related to menstruation
  - Malignancy is rare
- Inflammation
- Central blood vessel on ultrasound: must use doppler
  - Not seen in fibroids

Hamani Y, et al. *Eur J Obstet Gynecol Reprod Biol*. 2013
Raz, N., et al. (2021). "Endometrial polyps: diagnosis and treatment options - a review of literature." Minim Invasive Ther Allied Technol **30**(5): 278-287.

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Polyp Treatment

- Intra-Uterine polypectomy via hysteroscope
- Up to 25% regress, particularly if less than 10 mm
- Symptomatic postmenopausal polyps should be excised for histologic assessment
- Removal in infertile women improves fertility
- Surgical risks associated with hysteroscopic polypectomy are low.

AAGL. *Min Invas Gynecol.* 2012
Rac, N., et al. (2021). "Endometrial polyps: diagnosis and treatment options - a review of literature." Minim Invasive Ther Allied Technol **30**(5): 278-287.

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AUB-A

Adenomyosis

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AUB: Adenomysis

- Uterine lining grows into the adjacent muscular tissue (myometrium)
- May have no signs or symptoms – difficult to diagnose
- Excessive menstrual bleeding
- Painful menstruation and intercourse
- Uterus may be enlarged
- Hysterectomy is gold standard for diagnosis, but diagnosis may be made with:
  - High resolution ultrasound
  - Hysteroscopy

Peric H, Fraser IS. *Best Pract Res Clin Obstet Gynaecol.* 2006.
Abbott, J. A. (2017). "Adenomyosis and Abnormal Uterine Bleeding (AUB-A)-Pathogenesis, diagnosis, and management." Best Pract Res Clin Obstet Gynaecol **40**: 68-81.

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Adenomyosis

- Mostly older 40's and 50's
- Pain and bleeding
- Increasingly found with infertility evaluation
- MRI and Ultrasound
- Traditional diagnosis by hysterectomy
- Attempts to treat with minimally invasive surgeries

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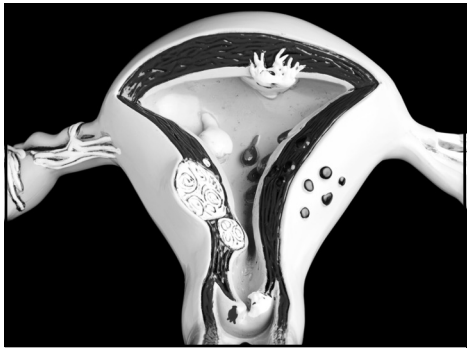

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Adenomyosis

- Treatment
  - NSAIDS
  - Hormone therapy: oral contraceptives
  - Levonorgestrel progestin containing IUDs
  - Hysterectomy
- Resolves with menopause
- Doesn't affect fertility

Peric H, Fraser IS. *Best Pract Res Clin Obstet Gynaecol.* 2006.
Abbott, J. A. (2017). "Adenomyosis and Abnormal Uterine Bleeding (AUB-A)-Pathogenesis, diagnosis, and management." Best Pract Res Clin Obstet Gynaecol **40**: 68-81.

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AUB- A Pharmacologic Therapy

- NSAIDs, which are effective at reducing the amount of bleeding, discomfort and cramping
- GnRH agonist
- Combined hormonal contraceptives
- Levonorgestrel progestin containing IUDs
- Depo Medroxyprogesterone Acetate (Depo Provera)
- Prescription ant-fibrinolytic medications: Tranexamic acid (Lysteda) TID help reduce excessive blood loss

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Tranexamic acid

- Higher plasminogen activators in the endometrium of women with AUB
- Tranexamic acid is a synthetic lysine derivative that blocks lysine binding sites on plasminogen = preventing fibrin degradation
- More effective than mefenamic acid
- Over a few cycles reduces blood loss by 60%

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Tranexamic acid

- 1 to 1.5 g tid – qid for 3 to 4 days on day 1
- Reduce the dose in pt with renal failure
- Side effects are dose dependent
- Increased risk of DVT, contraindicated with thromboembolic disease
- Nausea, vomiting, diarrhea, and dyspepsia, as well as disturbances in color vision.

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Levonorgestrel (LNG) IUD

- Can reduce menstrual blood loss within 5-26 days by up to 96%
- Delivers 20 mcg of levonorgestrel q 24 hrs
- There can be some variable spotting
- Approximately 20% of levonorgestrel intrauterine system users experience amenorrhea during at least 1 90-day interval by the first year after insertion

Sergison JE, Maldonado LY, Gao X, Hubacher D. Levonorgestrel intrauterine system associated amenorrhea: a systematic review and meta-analysis. Am J Obstet Gynecol. 2019 May;220(5):440-448.e8. doi:

58

Oral Contraceptives

- Suppress ovarian function
- Low dosages can reduce endometrial proliferation, prostaglandin production and pain
- Consider pills containing 20 mcg or less

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Contraceptive Ring: NuvaRing

- Non Biodegradable, flexible vaginal ring
- Delivers 15 mcg of ethinyl estradiol per day
- 120 mcg etonogestrel/day
- Works in the same way as combined oral contraceptives to reduce endometrial stimulation and proliferation

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AUB-L

Leiomyoma (Fibroids)

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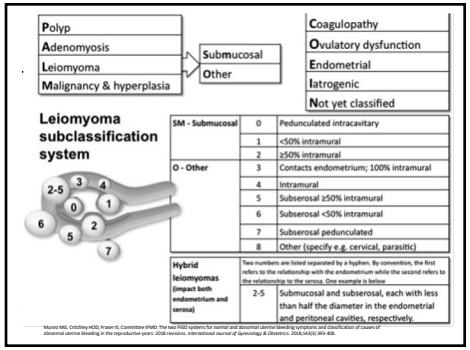

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AUB- L
Leiomyoma (Fibroids)

- Benign calcifications of the uterus
- In women with AUB: present in about 50%
- Estimated 50% in women > 50 years old
- Patient may present with
  - Bladder or intestinal discomfort
  - Pelvic pain or pressure
  - Heavy menstrual bleeding with clots
  - Dyspareunia
- Treatment depends on size, location & desire for fertility

ACOG Practice Bulletin No. 228: Management of Symptomatic Uterine Leiomyomas: Correction, Obstetrics & Gynecology: October 2021 - Volume 138 - Issue 4 - p 683 doi: 10.1097/AOG.0000000000004557

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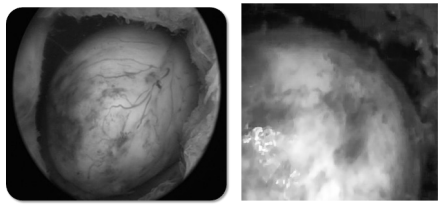
Leiomyoma: Fibroid



Courtesy Barb Dahn

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AUB- L Submucosal Fibroids

- AUB most likely from submucosal leiomyoma's
- Impinge on uterine cavity and endometrium
- Detected via:
  - Transvaginal Ultrasound
  - Sonohysterography – Saline infused U/S
  - Hysteroscopy
  - MRI
  - Computed tomography (CT)

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Treatment options

- GnRH agonists: Leuprolide acetate – abruptly withdraws E_2, fibroids regress
- GnRh antagonists with add back
- Uterine Artery Embolization – interferes with blood supply leading to regression
- See & treat with Hysteroscopy used for fibroids within the endometrium
- *Intrauterine* morcellation
- Laproscopic, robotic or abdominal myomectomy
- Hysterectomy-abdominal, vaginal, laparoscopic or robotic

ACOG Practice Bulletin No. 228: Management of Symptomatic Uterine Leiomyomas: Correction, Obstetrics & Gynecology: October 2021 - Volume 138 - Issue 4 - p 683 doi: 10.1097/AOG.0000000000004557

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What not to do

- Blind D & C
  - No benefit
  - Will miss pathology or have incomplete removal
- Extra-uterine morcellation in the pelvic cavity via a laparoscope
  - Associated with an increased risk of seeding leiomyosarcoma into the pelvic cavity

Seidhoff, MT, Am J Obstet Gynecology, 2015

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When is Treatment Appropriate?

- Interfering with life or lifestyle
- Pain, bleeding, pressing on other organs
- Rapid growth
- Rarely is hysterectomy necessary
- Refer to a minimally invasive Gyn specialist

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Pharmacologic Therapy

Symptom
- NSAIDS
- Iron
- OC's
- Progestin
- Antifibrinolytic
- LNG-IUD

Direct Effect
- GnRH agonists
- GnRh antagonists

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NSAIDS

- NSAIDS for bleeding
- Cochrane review found NSAIDS
  - More effective than placebo
  - Less effective than tranexamic acid
  - Less effective than danazol
  - Less effective than LNG-IUS
- Fewer adverse events than danazol
- No clear evidence of difference between luteal progestogen ,OCP, or antifibrinolytic
- Small number of studies, underpowered. Quality is fair.

Bofill Rodriguez M, Lethaby A, Farquhar C. Non-steroidal anti-inflammatory drugs for heavy menstrual bleeding. *Cochrane database of systematic reviews (Online)*. 2019;9(9):Cd000400.

70

Fe Therapy

- Oral most common
- IV
- Helpful for anemia associated with bleeding from fibroids

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Tranexamic Acid

- Bleeding symptoms only
- Antifibrinolytic
- Inhibits clot dissolving enzymes in endometrium
- Potential risk for VTE
- Cyclic use for 5 days

Bryant-Smith AC, Lethaby A, Farquhar C, Hickey M. Antifibrinolytics for heavy menstrual bleeding. *Cochrane Database of Systematic Reviews*. 2018(4).

72

Tranexamic Acid

- 1300mg tid x5 days
- Superior to placebo
- Similar to cyclic progestogens
- Superior to NSAIDS
- Superior to herbal medicines(Safoof Habis and Punica granatum)
- May be less effective than LNG-IUS

Bryant-Smith AC, Lethaby A, Farquhar C, Hickey M. Antifibrinolytics for heavy menstrual bleeding. *Cochrane Database of Systematic Reviews*. 2018(4).

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Danazol

- Oral anabolic steroid
- Hypothalamic pituitary axis, and ovaries high androgen/ low estrogen
- Masculinizing effects limits use: acne, weight gain, hot flushes, irritability, hirsutism with male pattern baldness, liver injury, breast atrophy
- Dose 50-800 mg /day
- No evidence that it affects fibroids.
- Effective in reducing bleeding, usefulness is limited by side effects.

Ke LQ, Yang K, Li CM, Li J. Danazol for uterine fibroids. *Cochrane Database of Systematic Reviews*. 2009(3).
Beaumont HH, Augood C, Duckitt K, Lethaby A. Danazol for heavy menstrual bleeding. *Cochrane Database of Systematic Reviews*. 2007(3).

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Aromatase Inhibitors

- Letrozole and anastrozole
- Inhibits aromatization step in steroid synthesis
- Single trial
  - Adverse events: hot flushes, vaginal atrophy
  - Similar volume reduction to GnRH agonist
  - Not statistically significant
  - Poor quality study
  - Insufficient evidence to support in women with fibroids

Song H, Lu D, Navaratnam K, Shi G. Aromatase inhibitors for uterine fibroids. *Cochrane Database of Systematic Reviews*. 2013(1).

75

Cyclic Progestins

- Used for bleeding not volume reduction
- Low or very low quality suggests cyclic progestins are inferior to:
  - Tranexamic acid
  - Danazol
  - LNG-IUS

Bofill Rodriguez M, Lethaby A, Low C, Cameron IT. Cyclical progestogens for heavy menstrual bleeding. Cochrane Database Syst Rev. 2019 Aug 14;8(8)

76

Oral Contraceptives

- COC cyclic, extended or continuous.
- Treatment of bleeding not fibroid.
- COC effective for short term.
- No long-term studies on effectiveness with fibroids.

Bradley LD, Gualtieri MA. The medical management of abnormal uterine bleeding in reproductive-aged women. *Am J Obstet Gynecol*2019;214(1):31-44.
ACOG Practice Bulletin No. 228: Management of Symptomatic Uterine Leiomyomas: Correction, Obstetrics & Gynecology: October 2021 - Volume 138 - Issue 4 - p 683 doi: 10.1097/AOG.0000000000004557

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LNG-IUS

- Bleeding only
- Not useful for distorted or large uterine cavities

Bofill Rodriguez M, Lethaby A, Jordan V. Progestogen-releasing intrauterine systems for heavy menstrual bleeding. *Cochrane Database of Systematic Reviews*. 2020(6).

78

Leuprolide Acetate

- IM injection
- Increase LH/FSH first increases estrogen, continued therapy causes drop in estrogen level
- Amenorrhea in most women
- 35-65% volume reduction within 3 months
- Add-back for fibroids only low dose replacements studied
- Progestin may decrease vasomotor symptoms and may preserve bone density but may increase fibroid volume
- Mostly studied in short term preoperative use.
- Long term use with add back

Moroni RM, Martins WP, Ferriani RA, et al. Add-back therapy with GnRH analogues for uterine fibroids. *Cochrane Database of Systematic Reviews*. 2015(1).
Lewis TD, Malik M, Britten J, San Pablo AM, Catherino WH. A Comprehensive Review of the Pharmacologic Management of Uterine Leiomyoma. *Biomed Res Int*. 2018;2018:2414609-2414609.

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GnRh Antagonists

Elagolix
Relugolix

Reduction in heavy menstrual bleeding in women with fibroids

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Medical therapy for HMB from fibroids

- GnRH agonists and antagonists have varying limitations on duration of use
- GnRh antagonists are the newest FDA approved treatment
- The two approved medications are both limited to 24 months of use due to risk of bone loss that may not be reversible
- Should not be used in women over 35 who smoke or have uncontrolled hypertension
- Should not be used in women with a history of thromboembolic events

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Elagolix with add-back

- Oral GnRH antagonist 300mg twice daily with estradiol 1mg and norethindrone acetate 0.5 mg add-back.
- Recently approved for use for up to 2 years.
- 791 women

Schlaff WD, Ackerman RT, Al-Hendy A, et al. Elagolix for Heavy Menstrual Bleeding in Women with Uterine Fibroids. *New England Journal of Medicine*. 2020;382(4):328-340.

82

Elagolix

Reduction in Heavy Menstrual Bleeding in Women with Uterine Fibroids

- Primary end point (a menstrual blood loss [MBL] volume of <80 ml in the final month and a ≥50% reduction in MBL volume from baseline to the final month)
- A significantly greater percentage of women who received elagolix with add-back therapy met the criteria for the primary end point than women who received placebo.

Schlaff WD et al. N Engl J Med 2020;382:328-340

83

Elagolix

Mean Percent Change from Baseline to 6 Months in Bone Mineral Density.

- At 6 months: Differences in the percent change in bone mineral density between women who received elagolix with add-back therapy and women who received placebo were not significant
- The differences in the percent change in bone mineral density between the elagolix-alone group and the placebo group were significant
- Except for the between-group difference at the femoral neck in Elaris UF-2.

Schlaff WD et al. N Engl J Med 2020;382:328-340

84

Elagolix Treatment Considerations

- Exclude pregnancy OR start within 7 days from the onset of menses
- Advise women to use non-hormonal contraception during treatment and for 28 days after discontinuing Elagolix
- Assessment of BMD by DXA is recommended at baseline and periodically thereafter
- Should not be used in women over 35 who smoke, have uncontrolled hypertension or have a history of thromboembolic events
- One capsule twice a day
- Limit use to 24 months

85

Relugolix

- The trial included 768 premenopausal women with HMB associated with uterine fibroids.
- Response was defined as a volume of menstrual blood loss of less than 80 ml and a reduction of at least 50% from the baseline volume of menstrual blood loss over the last 35 days of the treatment period.
- The primary end-point analysis in each trial was the comparison of relugolix combination therapy with placebo.

Al-Hendy A et al. N Engl J Med 2021;384:630-642

86

Relugolix

Efficacy
- In the 2 trials, 72.1% and 71.2% of women responded to treatment, compared to approximately 16% with placebo
- Women achieved sustained reduction in MBL volume to 24 weeks of treatment
- At week 24, the mean reduction in MBL volume was 83.7% compared to 17.2% in the placebo group

Change in Bone Mineral Density
- At week 24, the mean percent change in lumbar spine BMD from baseline was -0.23% compared to +0.18% in the placebo group
- Assessment of bone density by DXA is recommended when starting and periodically thereafter

Al-Hendy A et al. N Engl J Med 2021;384:630-642

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Relugolix Treatment Considerations

- Exclude pregnancy and discontinue any hormonal contraceptives
- Use effective non-hormonal contraception during treatment and for 1 week after the final dose
- Should be started no later than 7 days after menses has started
- Dosing is one pill once a day
- The recommended total duration of treatment is 24 months

Myfembree (prescribing information). Brisbane, CA: Myovant Sciences; 2021

88

AUB-M

- Endometrial Hyperplasia/Malignancy

89

AUB – Malignancy Endometrial Hyperplasia

- More common in younger women (< 50) with PCOS and chronic anovulation
- More common in post menopausal women with unopposed E_2 stimulation
- High index of suspicion with any bleeding
- Ultrasound to measure endometrial echo
- Family history important
- Premenopausal malignancy
  - Consider genetic testing: Lynch (hereditary non-polyposis colorectal cancer-HNPCC syndrome)

Armstrong, A.J. J Min Invas Surgery. 2012.
Papakonstantinou, E. and G. Adonakis (2022). "Management of pre-, peri-, and post-menopausal abnormal uterine bleeding: When to perform endometrial sampling?" Eur J Obstet Gynecol Reprod Biol **518**(2): 252-259.

90

AUB- M
Diagnosis

Deciphering EMB: Endometrial biopsy
Reported as:
•Benign proliferative – estrogenic
•Benign secretory – Indicates progesterone and ovulation
•Hyperplasia
•Atypical hyperplasia
•Cancer

Papakonstantinou, E. and G. Adonakis (2022). "Management of pre-, peri-, and post-menopausal abnormal uterine bleeding: When to perform endometrial sampling?" Gynecological Endocrinology **38**(3): 253-259.

91

AUB- M
Treatment

- Correct any hormonal imbalance
- Remember often seen with PCOS
- Add a progestin to her regimen if on estrogen treatment
- Progestin containing IUD
- Oral progesterone
  - Medroxyprogesterone Acetate (Provera) 10mg q hs
  - Micronized Progesterone (Prometrium) 100-200 mg q hs

Papakonstantinou, E. and G. Adonakis (2022). "Management of pre-, peri-, and post-menopausal abnormal uterine bleeding: When to perform endometrial sampling?" Gynecological Endocrinology **38**(3): 253-259.

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AUB- M
Malignancy

- Hysterectomy with BSO, lymph node sampling
- Treatment dependent upon the level of invasion
- May need radiation and/or chemotherapy

93

AUB-C

- Coagulopathy

94

AUB – Von Willebrands

- Von Willebrands – A group of (generally) inherited disorders of coagulation related to a defect in von Willebrand factor, critical for the normal function of factor VIII
- Incidence: 13%
- History will suggest: prolonged bleeding, postpartum hemorrhage

Shankar M, BJOG, 2004

95

AUB – C
Coagulopathy

- Hemophilia, thrombocytopenia – rare
- Inherited deficiencies in prothrombin, fibrinogen, factor V, factor VII, factor X, and factor XII
- Platelet function disorders: 98% of women with Bernard-Soulier syndrome or Glanzmann's thrombasthenia
- Women on anticoagulant therapies

96

Screening

- Heavy menstrual bleeding since menarche
- One of the following conditions:
  - Postpartum hemorrhage
  - Surgery-related bleeding
  - Bleeding associated with dental work

OR

- Two or more of the following conditions:
  - Epistaxis, one to two times per month
  - Frequent gum bleeding
  - Family history of bleeding symptoms

ACOG Committee Opinion Von Willebrand Disease in Women, 2013

97

Treatment Von Willebrands

- Consultation with hematologist
- Progestin containing IUD, Implant
- Progestin Only Pill, Combined OCPs
- Tranexamic acid – antifibrinolytic
- Inhibit conversion of plasminogen to plasmin, which inhibits fibrinolysis helps to stabilize clots.
- Reduces menstrual bleeding by 30–55%

Lukes, AS, et al. Obstet Gynecol, 2010.

98

AUB-O

- Ovulatory (anovulatory)

99

AUB – O
Ovulatory

Perimenopause:
Changes in both menstrual flow and frequency are common with the following potential presentation:

- Lighter bleeding
- Heavier bleeding
- Duration of bleeding may change with each period
- Cycle length often changes
- Skipped menstrual periods

Papakonstantinou, E. and G. Adonakis (2022). "Management of pre-, peri-, and post-menopausal abnormal uterine bleeding: When to perform endometrial sampling?" Eur J Obstet Gynecol Reprod Biol **118**(2): 252-259.

100

ANOVULATORY AUB

- Unpredictable in timing and volume
- Causes of anovulation
  - PCOS
  - Insulin resistance emerging role
  - Hyperprolactinemia, hypothyroidism
  - Obesity
  - Eating disorders, stress, exercise
  - Contraceptive

Papakonstantinou, E. and G. Adonakis (2022). "Management of pre-, peri-, and post-menopausal abnormal uterine bleeding: When to perform endometrial sampling?" Eur J Obstet Gynecol Reprod Biol **118**(2): 252-259.

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ANOUVULATORY AUB

- Endometrial biopsy in any chronic anovulatory AUB regardless of age.

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Treatment

- Determination of ovulatory vs. anovulatory is critical
- Anovulatory
  - Determine etiology
  - Biopsy if > 1 year duration
    - Regardless of age

ACOG Practice Bulletin No. 136, July 2013. Reaffirmed 2018. Management of Abnormal Uterine Bleeding Associated With Ovulatory Dysfunction. Obstet Gynecol. 2013 Jul;122(1):176-185. doi: 10.1097/01.AOG.0000431815.52679.bb.

103

Medical Management

- Iron
  - May relieve principal symptom of fatigue 2^0 to anemia
- Antifibrinolytics
  - Tranexmic acid
    - RCT 41% reduction in bleeding
    - GI side effects

ACOG Practice Bulletin No. 136, July 2013. Reaffirmed 2018. Management of Abnormal Uterine Bleeding Associated With Ovulatory Dysfunction. Obstet Gynecol. 2013 Jul;122(1):176-185. doi: 10.1097/01.AOG.0000431815.52679.bb.

104

Medical Management

- Cyclooxygenase Inhibitors (NSAIDS)
  - RCT show some benefit
  - Mefanemic acid
  - Naprosyn
  - Ibuprofen

ACOG Practice Bulletin No. 136, July 2013. Reaffirmed 2018. Management of Abnormal Uterine Bleeding Associated With Ovulatory Dysfunction. Obstet Gynecol. 2013 Jul;122(1):176-185. doi: 10.1097/01.AOG.0000431815.52679.bb.

105

Progestins

- Similar results for Levonorgestrel IUD
  - 79% reduction in bleeding
- Continuous administration
  - May work for ovulatory menorrhagia
    - Depot MPA
      - 80% amenorrhea at 1 year
      - No trials for AUB

ACOG Practice Bulletin No. 136, July 2013. Reaffirmed 2018. Management of Abnormal Uterine Bleeding Associated With Ovulatory Dysfunction. Obstet Gynecol. 2013 Jul;122(1):176-185. doi: 10.1097/01.AOG.0000431815.52679.bb.

106

Contraceptive Implant

- Progestin containing contraceptive implant (Nexplanon®) – Subdermal, single rod
- Progestin only – Etonorgestrel
- Highly effective contraception, 0.05% failure rate
- 3 years of benefit

ACOG Practice Bulletin No. 136, July 2013. Reaffirmed 2018. Management of Abnormal Uterine Bleeding Associated With Ovulatory Dysfunction. Obstet Gynecol. 2013 Jul;122(1):176-185. doi: 10.1097/01.AOG.0000431815.52679.bb.

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Progestin Containing Implant

- Bioavailability remains constant throughout the life of the device
- There is no evidence to suggest accumulation over time
- Half-life elimination time is approximately 25 hours
- Immediate return to fertility when removed

ACOG Practice Bulletin No. 136, July 2013. Reaffirmed 2018. Management of Abnormal Uterine Bleeding Associated With Ovulatory Dysfunction. Obstet Gynecol. 2013 Jul;122(1):176-185. doi: 10.1097/01.AOG.0000431815.52679.bb.

108

AUB-E

- Endometrial

109

AUB - Endometrial

- The cause of AUB-E: Local disorders of the normal hemostatic mechanisms
- Combination of excesses of vasodilating prostaglandins such PG I_2 or PG E_2, or deficiencies in vasoconstricting agents such as PG F2α.
- Or Infections, such as *Chlamydia trachomatis*.
- No commercially available tests to detect such disorders.

Lee, J et al. Biology of Reproduction, 2013.

110

AUB – E Endometrial

NSAID Management
- Mefenamic acid
  - 250 to 500 mg taken 2 – 4 times/day
- Ibuprofen
  - 600 mg every 4 – 6 hours
- All NSAIDs must be taken with food
- Contraindicated in women with peptic ulcer

111

AUB-I Iatrogenic

- Usually from estrogen & progestin containing contraceptives, especially progestin – only agents
- Missed contraceptive pills
- Certain medications that impact cytochrome p-450 pathway: anticonvulsants and some antibiotics
- Cigarette smoking
- Street drugs
- Anticoagulants

112

Combined Contraception

- Many non-contraceptive benefits
- Reduce endometrial height
  - Decreases bleeding, cramping, pain
  - Reduced risk of PID
  - Suppresses endometriosis
- Reduces risk of ovarian cysts
- Suppress the hormonal roller coaster in PCOS

113

AUB-N

- Not otherwise classified

114

AUB-N
Not Otherwise Classified

- Catch-all category includes the rare and poorly defined and/or poorly examined uterine conditions such as:
  - Caesarean section scar bleeding
  - Arteriovenous malformations
  - Myometrial hypertrophy

115

Medical Management of AUB

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Medical Options for Treating AUB

Medical options:
- Treat identified coagulation disorders
- Combined oral contraceptive – Pills, Ring, Patch
- Progesterone – Oral, IUD, IM injection
- Hormonal implant
- GnRH agonists
- GnRH antagonists
- Antfibrinolytic medications
- NSAIDs

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Levonorgestrel Containing – Intrauterine System

Levonorgestrel
- Office procedure
- 8 years
- Provides contraception
- May have 3-6 months of prolonged unscheduled bleeding
- 20% of women have amenorrhea by the end of the first year

- If this is used for a Polyp or Fibroid – about 30% of women go on to other procedures

Sergison JE, Maldonado LY, Gao X, Hubacher D. Levonorgestrel intrauterine system associated amenorrhea: a systematic review and metaanalysis. Am J Obstet Gynecol. 2019 May;220(5):440-448.e8. doi:

118

Surgical Options for Treating AUB

119

Surgical Options for Treating AUB

- Hysteroscopic polypectomy
- Hysteroscopic myomectomy
- Abdominal myomectomy
- Endometrial ablation
- Radiofrequency ablation of fibroids
- Hysterectomy

120

Hysterectomy

- Surgical removal of the uterus
- Most definitive treatment for AUB
- Major procedure
- Abdominal, vaginal, LAVH, Robotic
- Significant risks
- Recovery period of 6 – 8 weeks
- Psychological issues

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Alternatives to Hysterectomy

- Myomectomy
- UAE (uterine artery embolization)
- Hysteroscopic Myoma Mechanical Tissue Removal
- Polyp resection
- Endometrial Ablation
  - Traditional
  - Global

122

Myomectomy

- Preservation of fertility main advantage
- Pre-op suppression useful
- Autologous blood helpful
- Anterior incision better
- Techniques vary
- Laser, harmonic scalpel

123

Uterine Artery Embolization

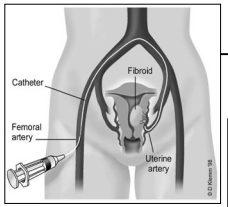
124

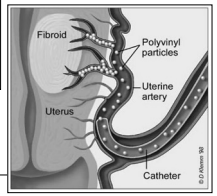
Uterine Artery Embolization: UAE

- Option for women with AUB who are unresponsive to medical therapy and desire future fertility.[3,18]
- Minimally invasive, catheter threaded to the specific Uterine Artery nourishing the fibroid.
- Magnetic Resonance–guided Focused Ultrasound (MRgFUS): Emerging radiologic technique : which uses MRI to identify the location of fibroids and high-intensity focused ultrasound energy to destroy leiomyomas without injury to surrounding tissues.

125

UAE





Courtesy Jay Berman MD

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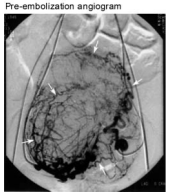
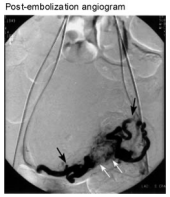
Angiograms

Pre-embolization angiogram



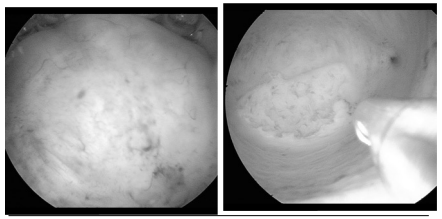
Post-embolization angiogram



Courtesy Jay Berman MD

127

Hysteroscopic Mechanical Tissue Removal



Courtesy Jay Berman MD

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Endometrial Ablation

Minimally invasive alternative to hysterectomy

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Endometrial Ablation

- Appropriate for women who have finished childbearing
- Post ablation pregnancies can be very problematic, **use contraception!**
- May normalize menstruation or produce amenorrhea.[8]
- Has not been studied in postmenopausal women
- Should not be used with suspected uterine cancer or hyperplasia

Gimpelson RJ, *Int J Women's Health*, 2014

130

Endometrial Ablation

- Baumann (1948): 387 ablations
  - Procedure performed blindly, steelball electrode
- Goldrath (1981) ND:YAG Laser
  - Destruction performed with laser
- Rollerball
  - Electric current through the rollerball
- Trans cervical resection of the endometrium
  - Hysteroscopic loop removal of endometrium

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Endometrial Ablation Techniques

Global Endometrial Ablation

- Hydrothermablation (HTA)
  - Hysteroscopic: free flowing hot water
- Novasure
  - Bipolar mesh
- Balloon Rx (Thermachoice)
  - 2016 Removed from market
- Minerva
  - Bipolar with plasma formation array (heat device)
- Mara
  - Controlled low pressure water vapor

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Preparation for Endometrial Ablation

- Bipolar mesh
  - May be done at any time in the cycle
- Hydrothermablation
  - May preference thin endometrium
    - Early in cycle
    - Days to week after withdrawal bleed after 10 days of combined oral contraceptive or progestin

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Radio Frequency Ablation of Leiomyomas

Acessa

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MRI Subject 4

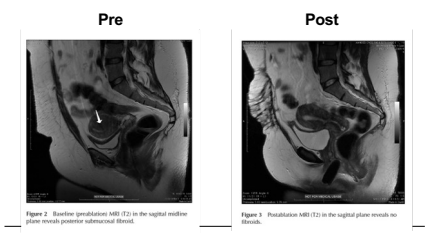

Figure 2 Baseline (pre-ablation) MRI (T2) in the sagittal midline plane reveals posterior submucosal fibroid.

Figure 3 Postablation MRI (T2) in the sagittal plane reveals no fibroids.

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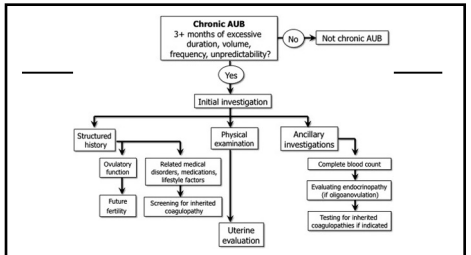

Fig. 4. Initial evaluation. For a diagnosis of chronic abnormal uterine bleeding (AUB), the initial assessment requires the patient to have experienced 1 or a combination of unpredictability, excessive duration, abnormal volume, or abnormal frequency of menses...

Malcolm G. Munro, Hilary O.D. Critchley, Michael S. Broder, Ian S. Fraser. **FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age.** International Journal of Gynecology & Obstetrics, Volume 113, Issue 1, 2011, 3–13. http://dx.doi.org/10.1016/j.ijgo.2010.11.011

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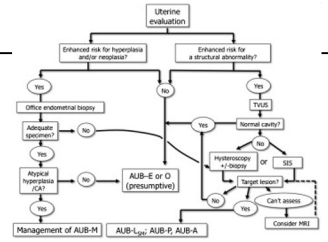

Uterine evaluation. The uterine evaluation is in part guided by the history and other elements of the clinical situation such as patient age, presence of an apparent chronic ovulatory disorder, or the presence of other risk factors for endometrial hyperplasia ...

Malcolm G. Munro, Hilary O.D. Critchley, Ian S. Fraser **The FIGO classification of causes of abnormal uterine bleeding in the reproductive years** Fertility and Sterility, Volume 95, Issue 7, 2011, 2204–2208.e3. http://dx.doi.org/10.1016/j.fertnstert.2011.03.079

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Summary

- AUB is common reason for women to seek care
- AUB requires careful history and physical assessment
- Classification of disorder helps to select appropriate Treatment
- Using PALM COEIN leads to a diagnosis that is structural or non-structural and an appropriate treatment plan!

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Walk our patients systematically through the steps: AUB is not a diagnosis, but a symptom that requires a diagnosis!

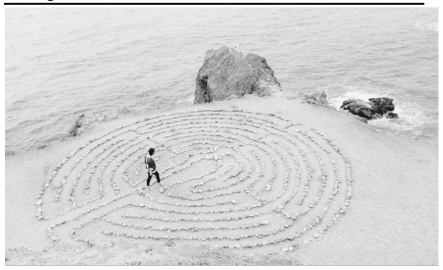

Photo courtesy of Unsplash.com

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Questions?

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