Skin, Bones, Hearts & Private Parts, 2020

Not Enough Pads!
Abnormal Uterine Bleeding

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Disclosures

- Except where noted, all illustrations were purchased from iStockPhoto
- Speakers Bureau/Advisory Board: Hologic, TherapeuticsMD, AMAG, El Camino Hospital
- Vendor: Cord Blood Registry

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Objectives

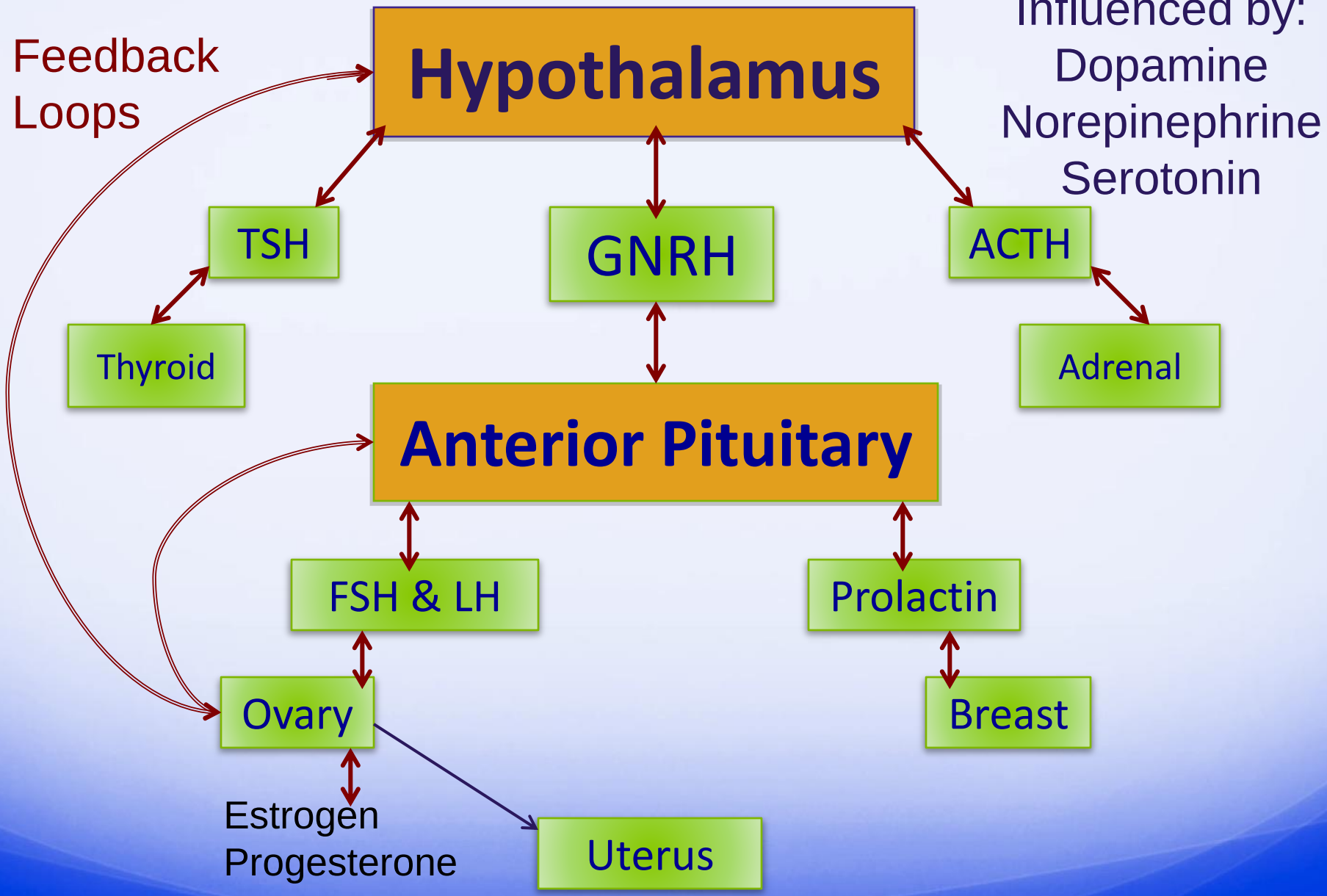
- Describe work up for AUB
- Elucidate the PALM-COEIN classification system
- Describe imaging and labs used in the diagnostic algorithm for AUB
- List pharmacologic treatments with risks/benefits for these conditions

Why Should You Care?

- Many of your patients have questions about:
- Their periods – Pain? Length? Risks?
- Anemic? Tranfusion? Surgery?
- If they're normal
- If they can get pregnant
- Are they too scared to ask?

Start at the Beginning

A Quick Review


Feedback Loops
Hypothalamus
Influenced by:
Dopamine
Norepinephrine
Serotonin
TSH
GNRH
ACTH
Thyroid
Adrenal
Anterior Pituitary
FSH & LH
Prolactin
Ovary
Breast
Estrogen
Progesterone
Uterus

Anatomy

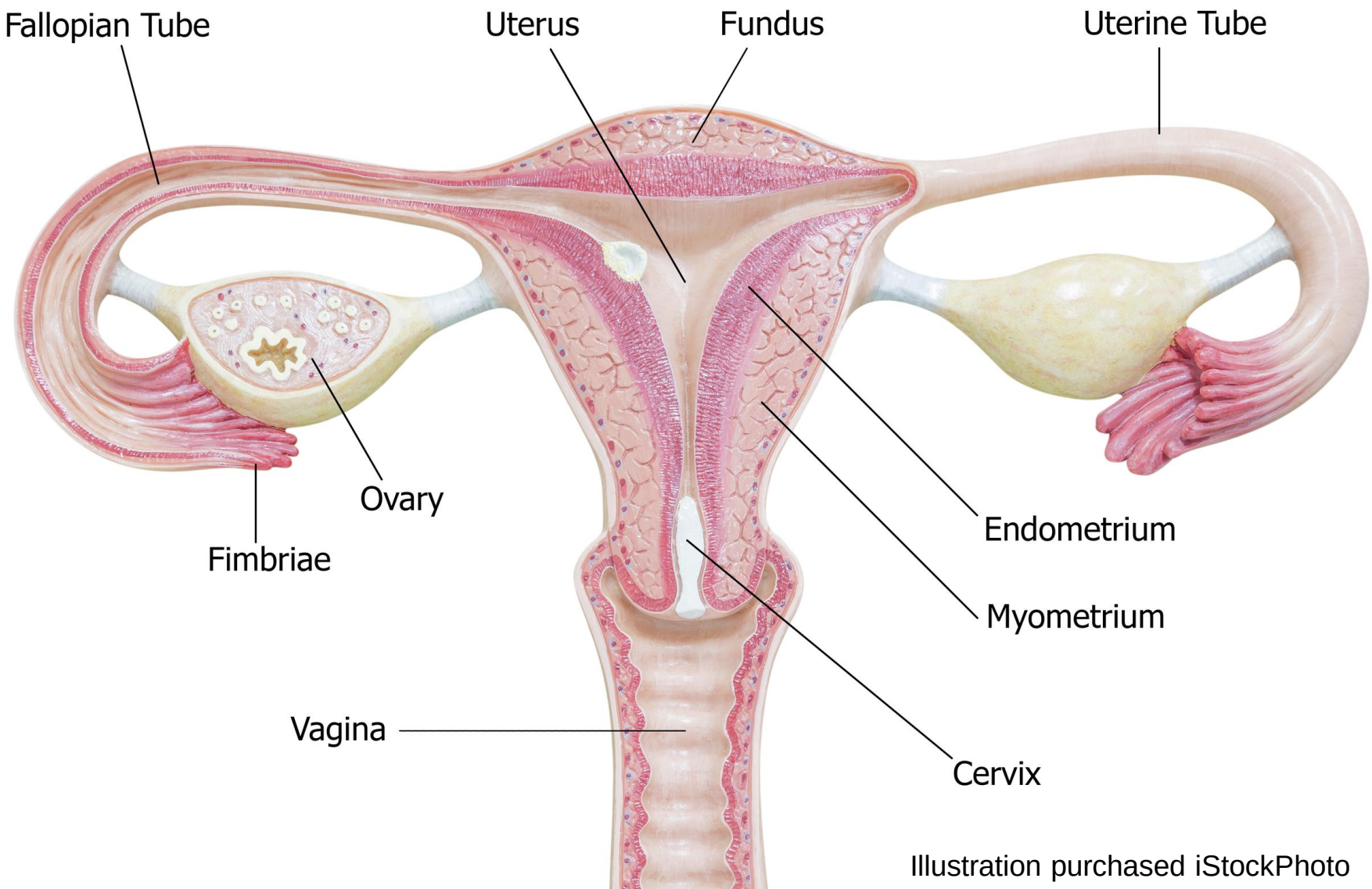


Illustration purchased iStockPhoto

Normal Cycling

- Normal Interval: 21-35 days
- 15% of women have 28 day cycles
- Duration of flow 2 to 8 days, average is 4-6
- Normal volume is 30 ml
- Range: 20 - 80 ml

MENSTRUAL CYCLE

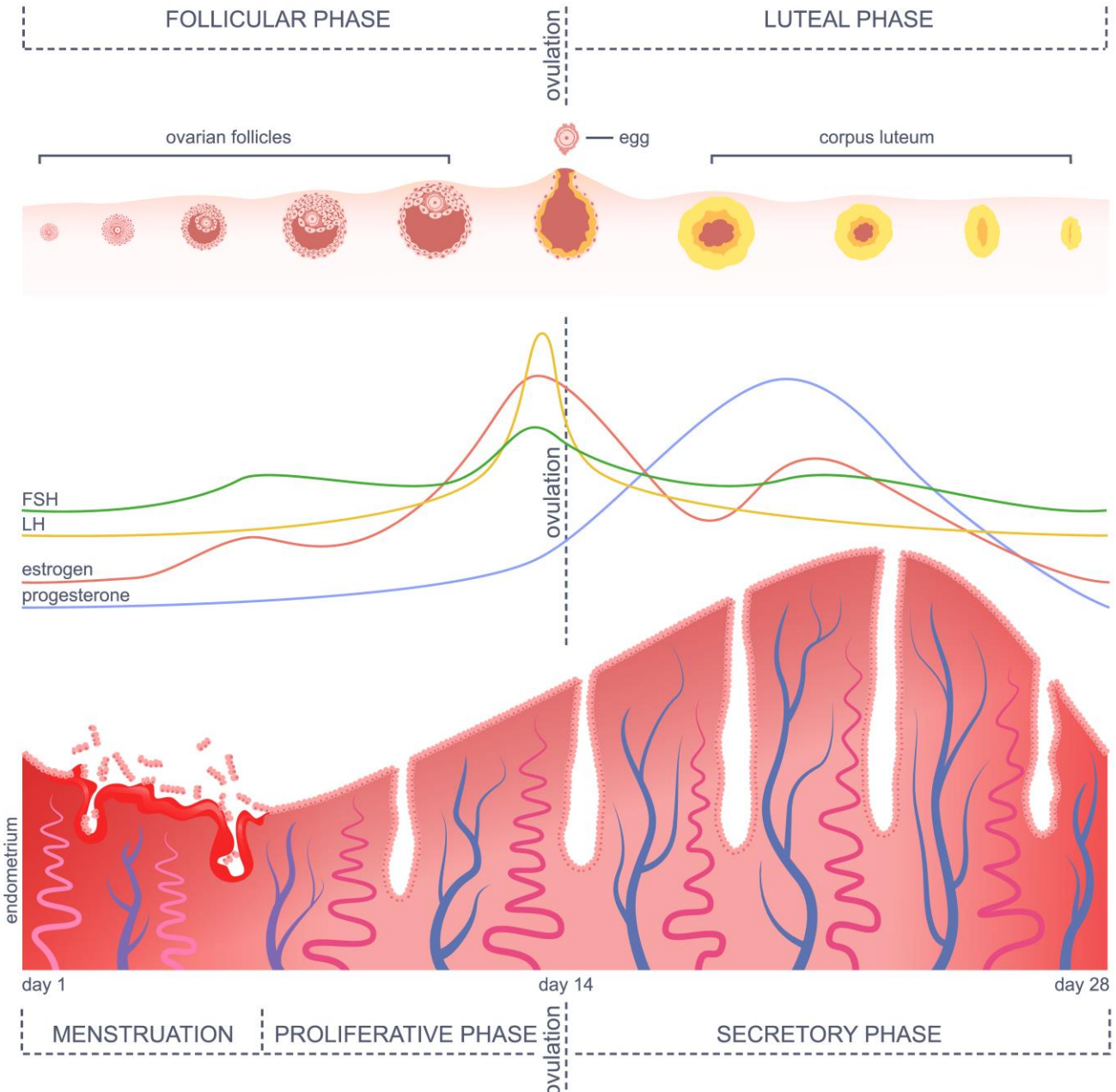


Illustration purchased iStockPhoto

Endometrium

- 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

Fritz MA & Speroff L, Clinical Gynecologic Endocrinology and Infertility, 2011.

Menses

- Shrinkage of endometrial height
- ↓ blood flow → vasoconstriction of spiral arteries (from ET-1 Endothelin-1) → Relaxation → endometrial blanching
- Leads to ischemia, prostaglandin production (high levels PG F2α)

Fritz MA & Speroff L, 2011

What is Abnormal 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 life style

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

Prevalence

- 5% of women between 35 – 49[1]
- Up to 50% of perimenopausal women will experience AUB[1]
- 1.4 million women in the US annually[2]
- 53% of women report that their periods interfered with their life, compared with 23% of age-matched community controls[2]

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

Can the Pill Mask Conditions?

- Combined Oral Contraceptives and NuvaRing
- Contain both Estrogen (E2) and Progesterone
- Together they suppress ovarian function
- Influence feedback loops masking thyroid an pituitary conditions
- Increase SHBG – Sex Hormone Binding Globulin - Reduce androgenic symptoms

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

Shivani

- 46 yr old woman with 4 month history of periods lasting 10-17 days, with intermittent spotting in between

- Previously, periods were regular q month
- 2 healthy deliveries, partner had vasectomy
- A few rare night sweats
- Vegetarian, no medications

Shivani

- Pregnancy test neg
- TSH, T-4 wnl, FSH: 15, LH: 7.0
- E_2: 123, Prolactin: wnl
- Hgb A1C: 5.6
- HCT 26.9/ Hgb 8.7
- Ferritin, TIBC, Hgb Electrophoresis: wnl

Shivani

- Limiting her activities
- Passing big clots
- Ruining clothes, sheets
- Worried about hysterectomy
- Where do you begin?

Diagnostic Workup

- H & P, Pregnancy Test
- Blood tests: CBC, TSH, FSH, LH, E 2, Prolactin
  - Depending upon history: Von Willebrands factor
- Vaginal ultrasound – endometrial thickness
- Endometrial biopsy
- Additional tests, such as saline infused sonohysterography & hysteroscopy

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

AUB: Old nomenclature

- Menorrhagia – excessive bleeding but occurs at regular intervals
- Metorrhagia – irregular intervals and/or intermenstrual bleeding
- Menometorrhagia – prolonged and irregularly timed bleeding

Throw these out!

AUB: PALM-COEIN

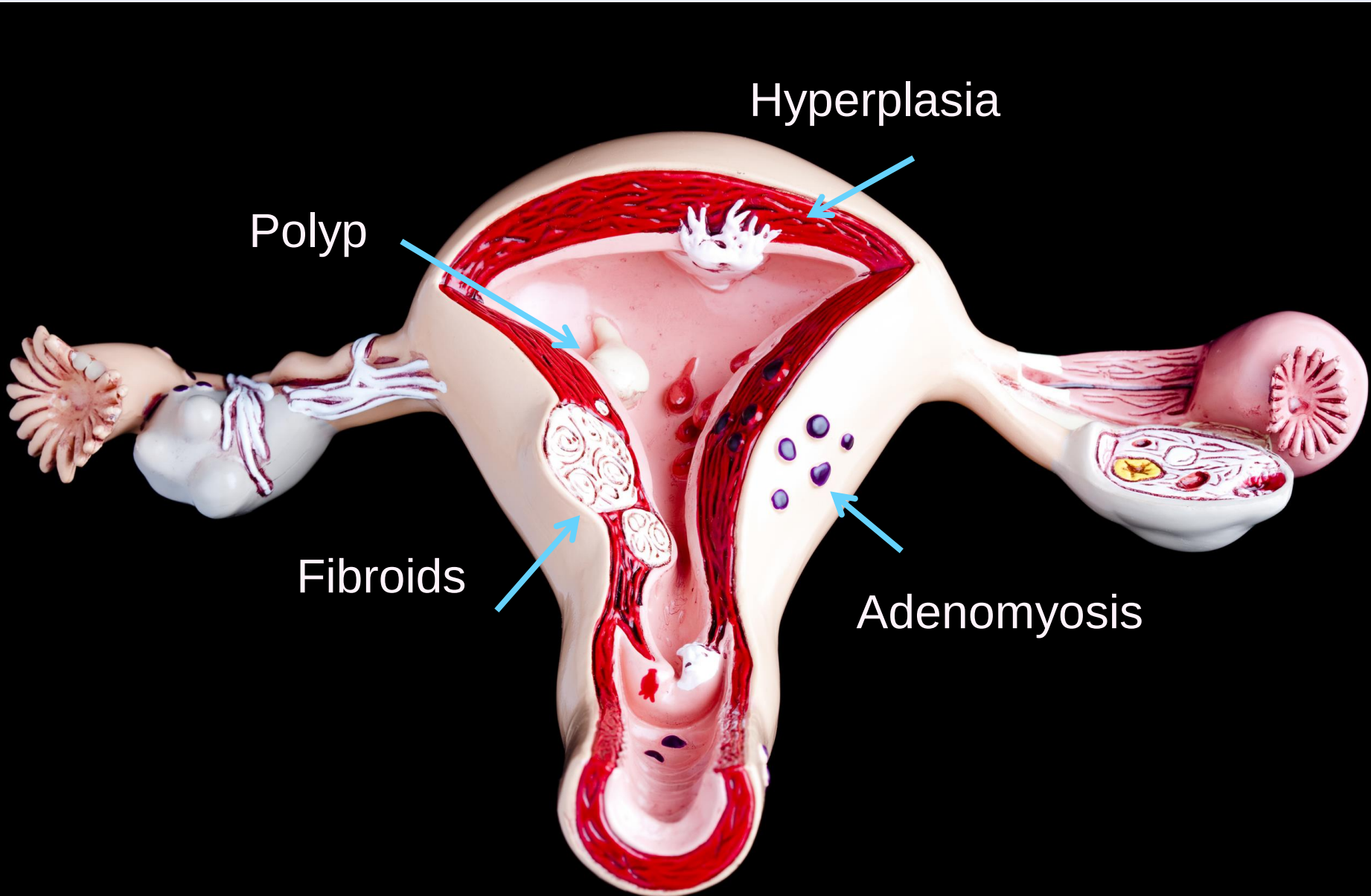
- **PALM - Structural**
- **P** - Polyp
- **A** - Adenomyosis
- **L** - Leiomyoma
- **M** - Malignancy/Hyperplasia

- **COEIN – Non-structural**
- **C** - Coagulopathy
- **O** - Ovulatory
- **E** - Endometrial
- **I** - Iatrogenic
- **N** –Not Classified

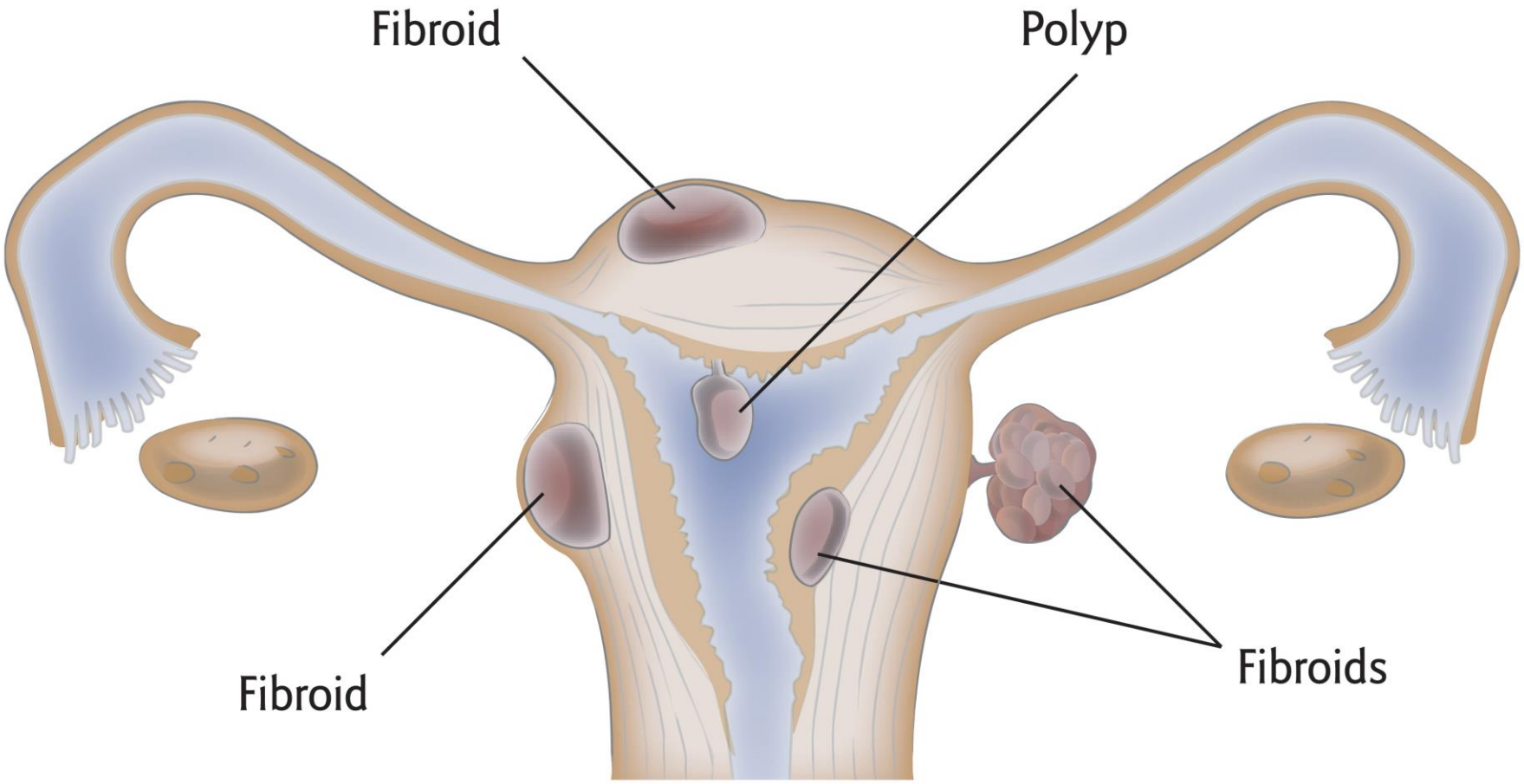
Established by **FIGO -** Fédération Internationale de Gynécologie et d'Obstétrique (the International Federation of Gynecology and Obstetrics).

Munro, MG et al. *Int J Gynecol Obstet.* 2011

Uterine Structural Pathology



Polyps & Leiomyoma



Direct Visualization

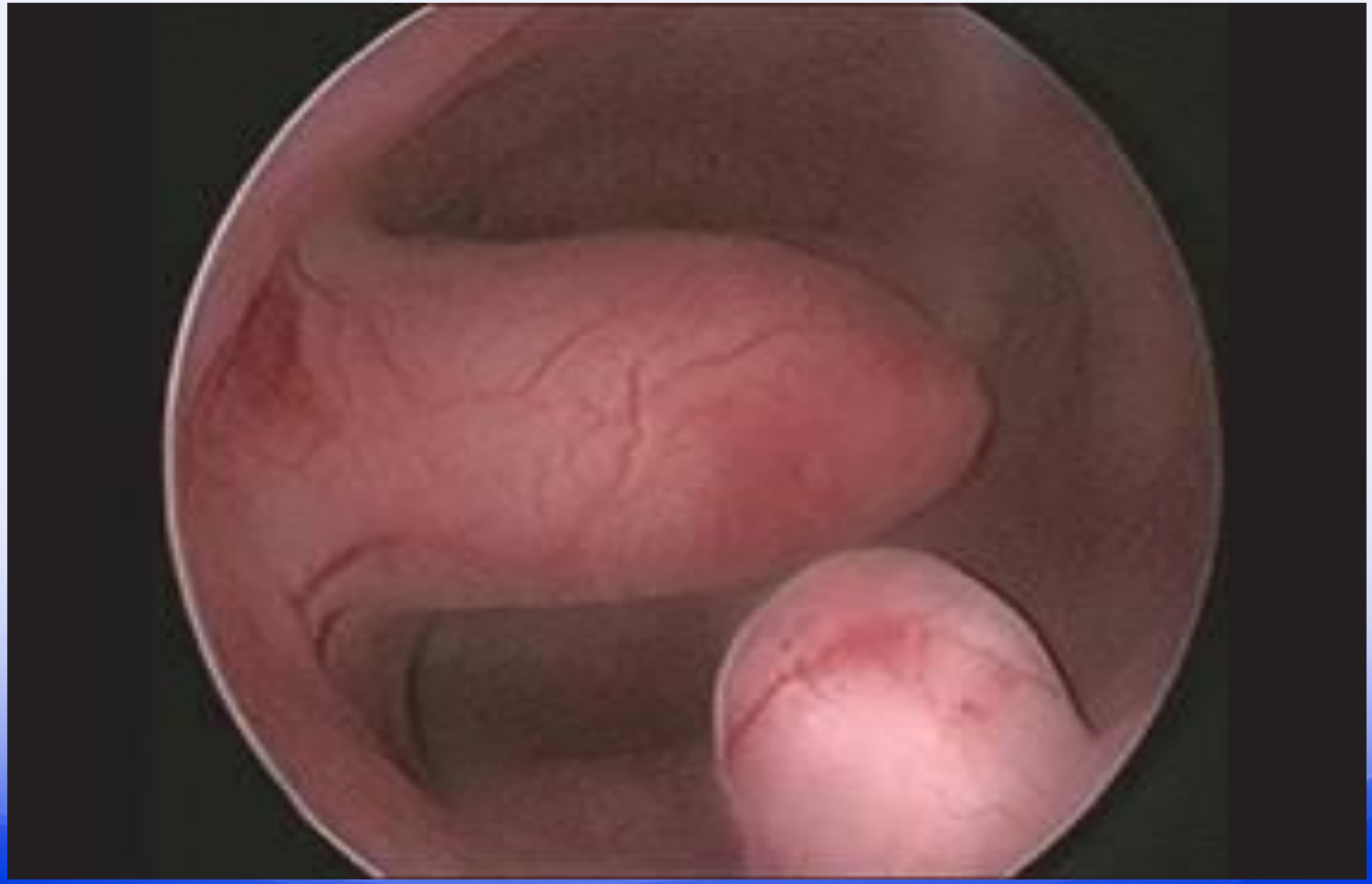
- Hysteroscopy

AUB: Polyps

- Epithelial proliferations
- As many as 25% may resolve spontaneously
- Mostly associated with Intermittent bleeding
- 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.

Polyps



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.

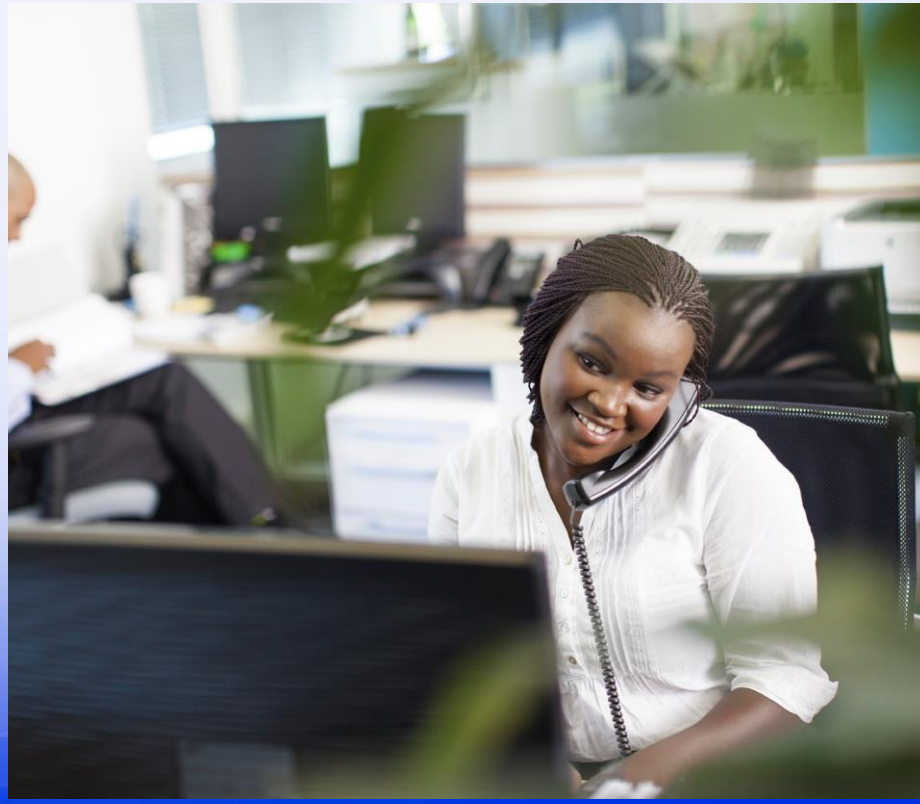
AAGL, *Min Invas Gynecol.* 2012

Shivani

- Has polyps and submucosal fibroids
- Elects to have both fibroids removed via the hysteroscope and to have endometrial ablation at same time
- Back to work after a weekend to recover
- Complete amenorrhea in 6 months

Amelia

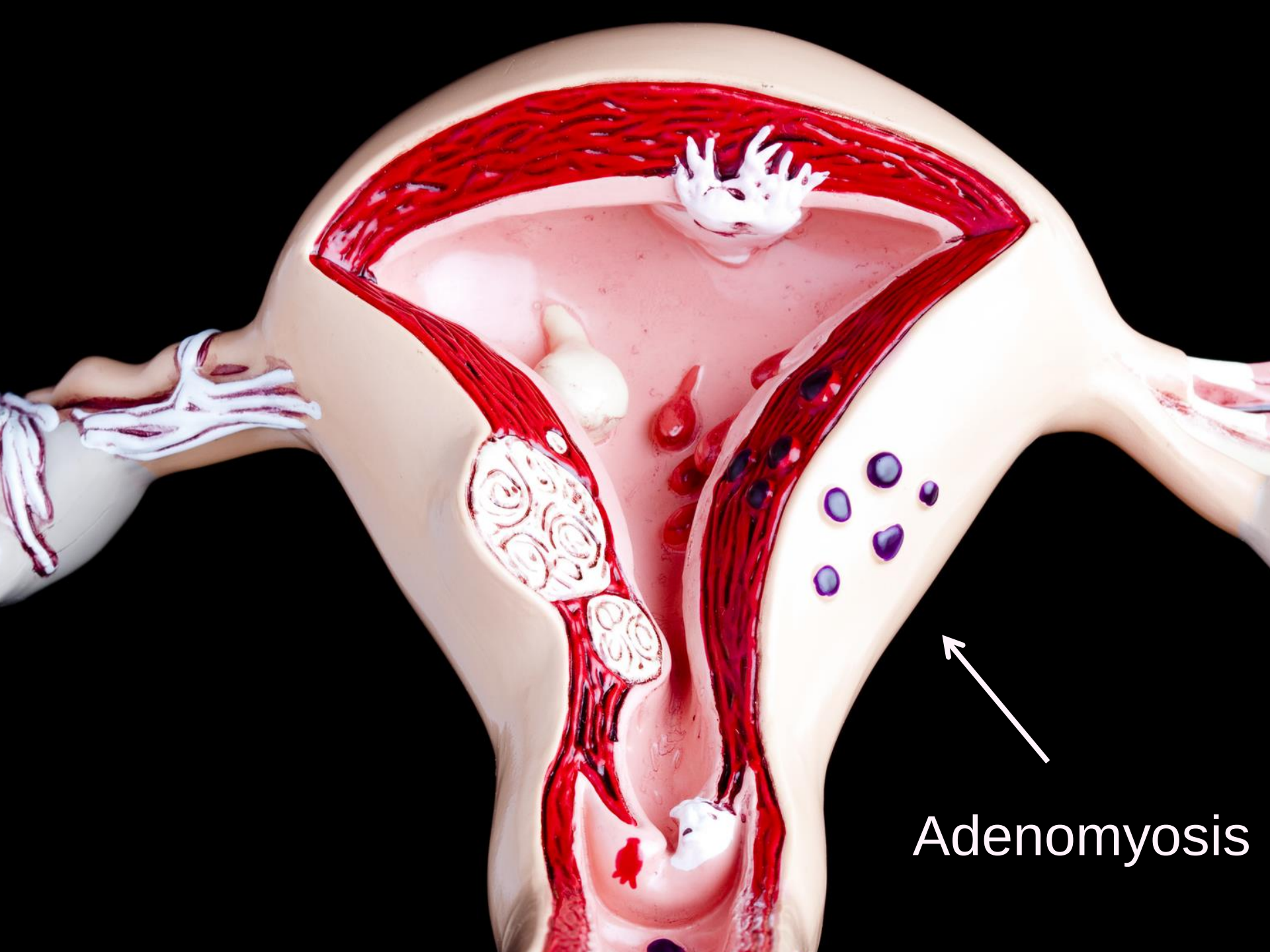
- 28 year old woman desires pregnancy
- Very heavy, painful periods
- Pain worsens mid cycle
- Pain with intercourse
- Hypothyroid



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

Peric H, Fraser IS. *Best Pract Res Clin Obstet Gynaecol.* 2006.


Adenomyosis

Adenomysis

- Ultrasound or MRI
- Rx: NSAIDs
- Hormone therapy, such as oral contraceptives
- Hysterectomy
- Doesn't affect fertility
- Resolves with menopause

Peric H, Fraser IS. *Best Pract Res Clin Obstet Gynaecol.* 2006.

Pharmacologic Tx

- NSAIDs, which are effective at reducing the amount of bleeding, discomfort and cramping.
- Prescription anti-fibrinolytic medications such as Tranexamic acid (*Lysteda*) taken three times each day are also employed to help reduce excessive blood loss.
-

Adenomyosis Tx Options

- NSAIDs
- Anti-fibrinolytics – Tranexamic
- GnRH agonist
- OCs
- Progestin containing IUDs
- Depo Medroxyprogesterone Acetate (Depo Provera®)

Dysmenorrhea

- Dysmenorrhea – Painful periods
- Endometrial lining contains prostaglandins (PG F2α)
- These are released throughout the pelvis
- Cramping, nausea, diarrhea, constipation, urinary difficulty
- Treatment: NSAIDs

NSAIDs

- Prostaglandins higher in endometrium of women w AUB higher than in women w/o
- ↑'d levels of Nitric oxide ↑❼s prostaglandins via the cyclooxygenase (COX) pathway
- Inhibiting COX and reducing blood loss
- Few side effects

Lethaby A, et al. *Cochrane Database Syst Rev*. 2007;(4): CD000400.

NSAIDs - Naproxen

- Also reduces the amount of bleeding
- OTC Naproxen 220mg
- Not to exceed 660 mg in 24 hours
- Prescription: Naproxen Sodium 550 mg
- 1 every 12 hours
- Not to exceed 1100 mg/day

NSAIDs - Mefenamic acid

- Mefenacmic 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 w Peptic Ulcer

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%

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 w people with thromboembolic disease
- Nausea, vomiting, diarrhea, and dyspepsia, as well as disturbances in color vision.

Levonorgestrel (LNG) IUD

- Can reduce menstrual blood loss within 5-26 days by up to 96%
- Delivers 20 mcg of levonorgestrel q 24 hrs
- 50% of women using the 5 year system, Mirena will have amenorrhea
- There can be some variable spotting

Oral Contraceptives

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

Contraceptive Ring: NuvaRing

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

Amelia

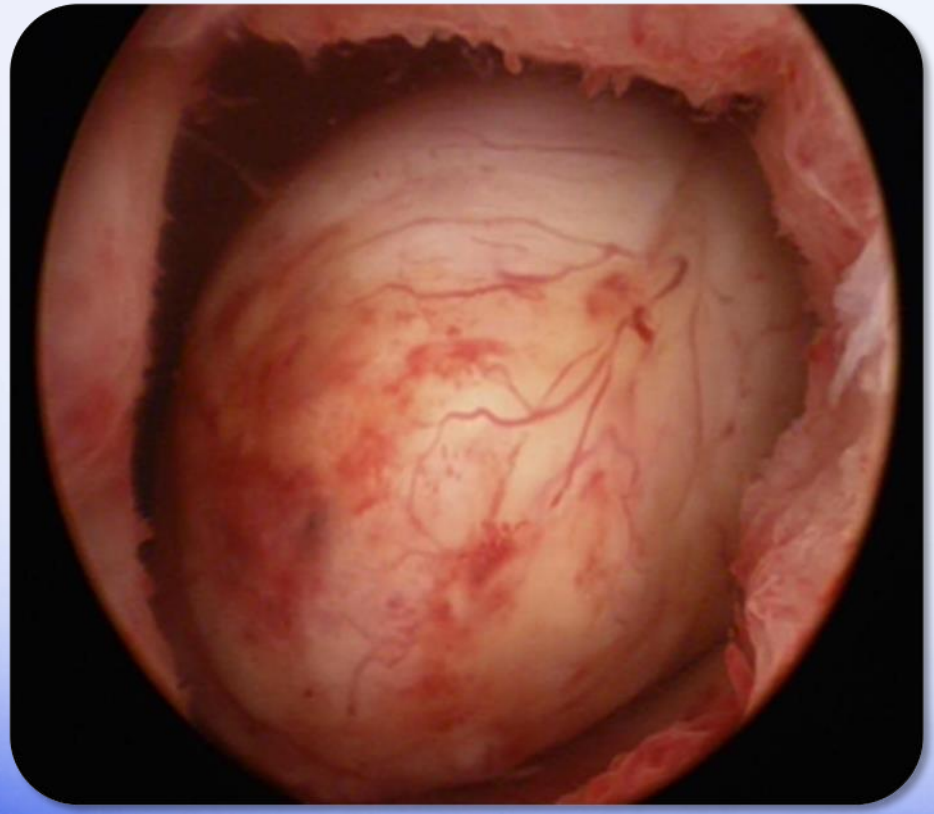
- Diagnostic work up reveals 1 small fibroid and adenomyosis
- Pt reassured that surgery is not necessary
- Uses Tranexamic Acid for pain during menses
- Conceives within 6 months
- Delivers a normal healthy infant

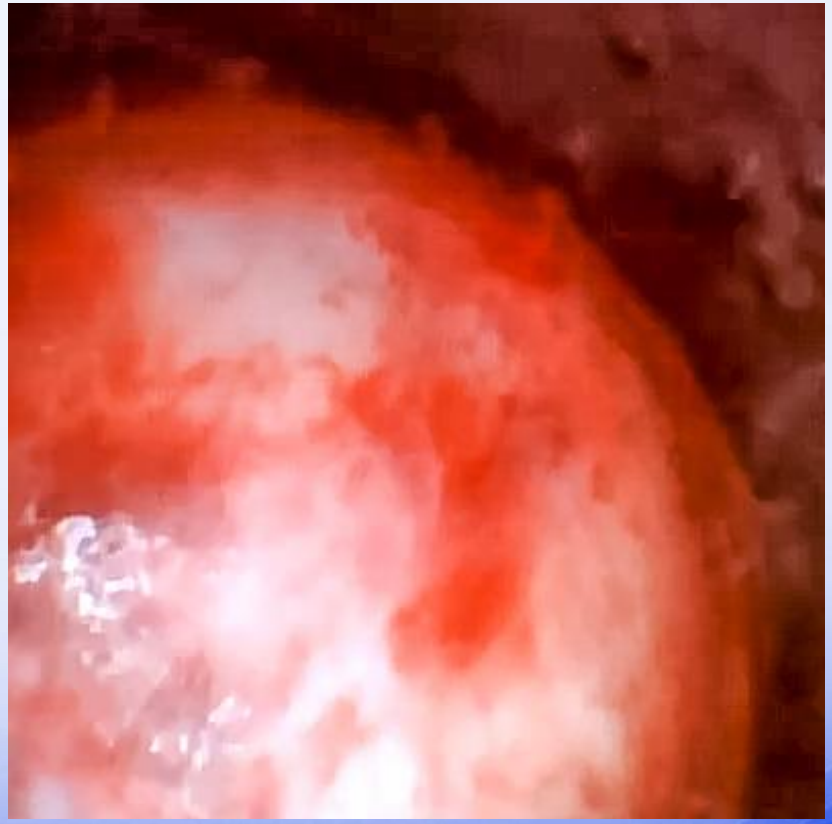
Leiomyoma = Fibroids

- Benign Calcifications of the Uterus.
- In women w AUB: present in approx 50%
- Present in 1/3 of women > 30
- Estimated 50% in women > 50
- Asymptomatic or cause bladder, intestinal discomfort, bleeding & dyspareunia
- Tx depends on size, location & desire for fertility

ACOG, Practice Bulletin, 2012

Leiomyoma: Fibroid





Submucosal Leiomyoma

- AUB most likely from submucosal leiomyomas
- Impinge on Uterine cavity and endometrium
- Detected via transvaginal US, sonohysterography, MRI, EndoSee, computed tomography (CT), or hysteroscopy

Treatment options

- GnRH agonists (Lupron Depot) – abruptly withdraws E_2, fibroids regress
- Uterine Artery Embolization – interferes with blood supply leading to regression
- See & treat with Hysteroscopy used for fibroids within the endometrium
- Intrauterine morcellation – Myosure
- Laproscopic removal, hysterectomy

AAGL, *J Min Invas Gynecol.* 2012

GnRH agonist: Leuprorelin

- Competitive agonists at GnRH receptors in the pituitary
- This desensitizes the GnRH-releasing cells = a hypogonadotropic state leads to:
  - Hypoestrogenism
  - Endometrial atrophy
  - Amenorrhea

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.[19]

Intra-Uterine Fibroid Removal

- New minimally invasive intra-uterine procedures are now being utilized
- Small telescoping instruments can be inserted through a hysteroscope to remove fibroids
- New technologies use reciprocating cutters to shave off fibroid tissue while sparing the myometrium

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

Why treat?

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

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 stripe

Armstrong, AJ, J Min Invas Surgery, 2012.

Eileen

- Post menopausal x 7 years
- No menopausal hormone therapy, on thyroid replacement medication for years
- 6 month hx of intermittent spotting
- Busy caring for her elderly mom

How We Diagnose?

- H & P
- Labs: Urine HCG, CBC, TSH, Free T-4, Thyroid Antibodies, FSH, $E_{2,}$ Coagulation Panel if indicated
- Ultrasound/ Sonohysterography
- Endometrial Biopsy for stripe > 8 mm for new onset.
  - > 3 mm for persistent
- Hysteroscopy: See and Treat with Surgical Sampling

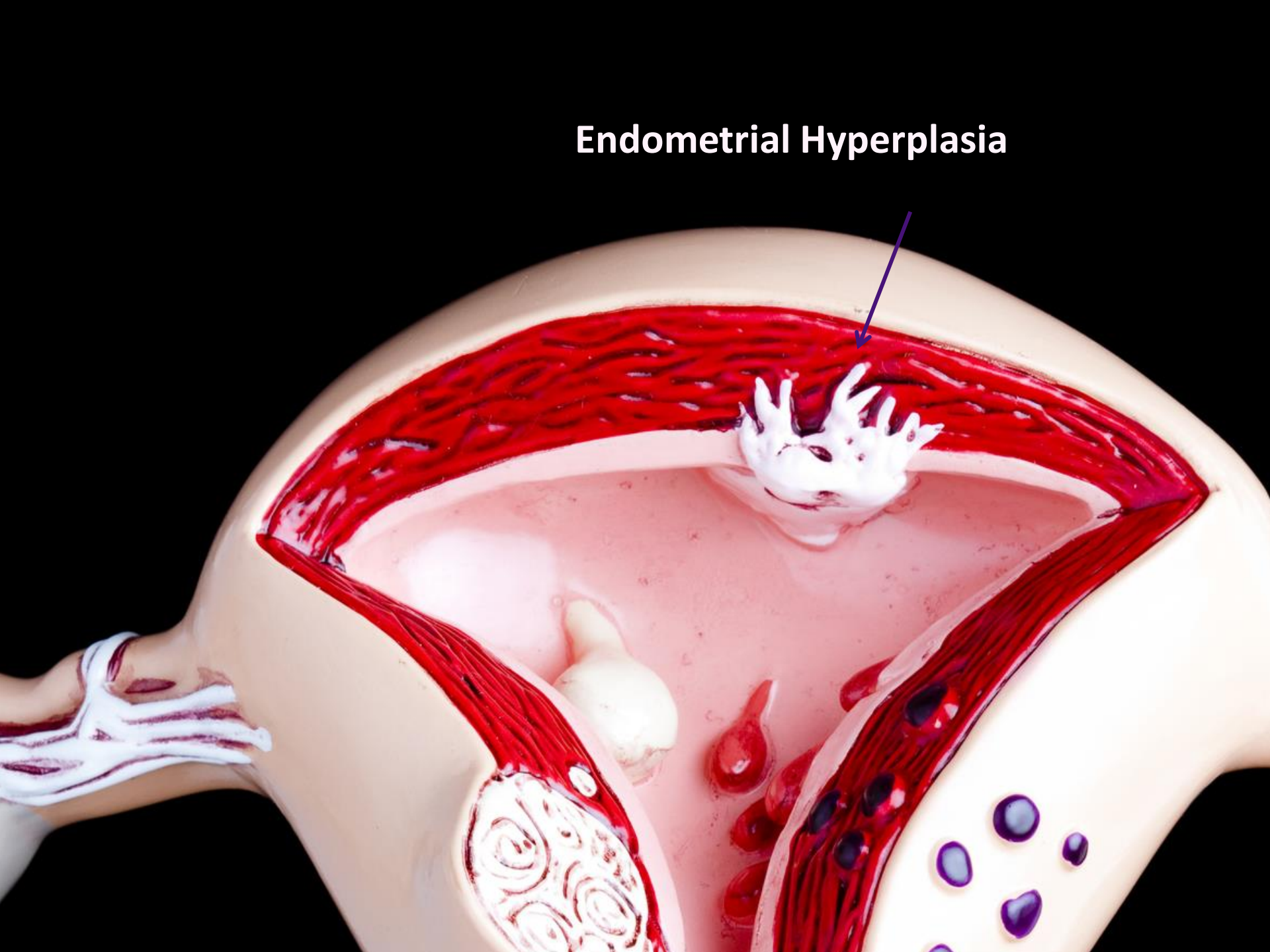
Deciphering EMBs

- Reported as:
- Benign Proliferative – Estrogenic
- Benign Secretory – Indicates Progesterone and ovulation
- Atypical Hyperplasia
- Cancerous

Hyperplasia types

- Simple w/o atypia: 1% risk progress to CA
- Complex w/o atypia: 3% risk progress to CA
- Simple with atypia: 8% risk progress to CA
- Complex with atypia: 29% progress to uterine cancer
  - 17 to 59% of cases have coexistent uterine cancer.

Endometrial Hyperplasia



Treating Hyperplasia

- Correct any hormonal imbalance
- Remember often seen with PCOS
- Being sure to add a progestin to her regimen if on Estrogen treatment
- Progestin containing IUD, Oral Progesterone, Medroxyprogesterone Acetate (Provera)

Eileen

- All labs wnl
- Endometrial stripe 13 mm
- EMB revealed endometrial cancer
- Pt elected to have a hysterectomy – Stage 1

Treating Malignancy

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

AUB - Coagulopathy

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

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

Katrina

- Age 17, plays soccer, few bruises on her arms
- Long Hx heavy periods since menarche
- On Fe for anemia from pediatrician
- History: frequent nosebleeds

Screening vWF

- 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

vWF

- vWF is essential for platelet adhesiveness and maintenance of nml levels of factor VIII.
- 3 recognized variants of vWD:
  - Type 1 - 60%–80% (mild), may be clinically insignificant, even in women with chronic AUB.
    - commonly overlooked, only be dx w certainty using specific testing for vWF levels.
    - Type 2 - qualitative deficiency that may manifest solely with bruising or AUB without impaired clotting – labs: vWF = 10 - 45% of nml.

ACOG Committee Opinion Von Willebrand Disease in Women, 2013

vWF

- Type 3 – most severe, least common, usually presents at menarche.
- Labs: no measurable vWF
- Diagnosis should be considered in any woman with chronic HMB, especially if she does not pass simple screening tests

ACOG Committee Opinion Von Willebrand Disease in Women, 2013

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.

Katrina

- Hgb 10.3, HCT 26.1
- vWF; 25% of normal
- Type 2 Von Willebrands
- Elects to use Progestin containing IUD
- Cautioned to avoid NSAIDs

Treatment von Willebrand

- DDAVP – *Desmopressin* – IV injection or via a nasal spray – Stimate
- Synthetic hormone similar to vasopressin
- Controls bleeding by stimulating more von Willebrand factor stored in the endothelium enhancing factor VIII levels
- Effective in type 1 and some subtypes of type 2 vWF

AUB: Ovulatory

Perimenopause

Changes in both menstrual flow and frequency are common and usually normal:

- Lighter bleeding
- Heavier bleeding
- Duration of bleeding
- Cycle length often changes
- Skipped menstrual periods

AUB: Ovulatory

- PCOS
- LOOP events
- Hypothyroidism
- Hyperprolactinemia
- Hyperandrogenism
- Lifestyle factors
- Medications: Tricyclic antidepressants, Phenothiazines
- Street drugs
- Stress

LOOP Events in Perimenopause

- LOOP (**L**uteal **O**ut-**O**f-**P**hase) events – the development of follicles with release of high levels of estradiol in the luteal phase
- This represents a 2nd spike of E_2
  - At a time when levels should be declining
- LOOP events are associated with sporadic episodes of AUB and breast tenderness

Hale,GE et al. Menopause, 2009

AUB - Endometrial

- The cause of AUB-E: Local disorders of the normal hemostatic mechanisms
- Combination of excesses of PA or vasodilating prostaglandins such PG I_2 or PG E_2, or deficiencies in vasoconstricting agents such as ET-1 and PG F2α.
- Or Infections, such as *Chlamydia trachomatis*.
- No commercially available tests to detect such disorders.

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

AUB - Iatrogenic

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

AUB – N (*Not otherwise classified*)

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

Medical Options

- Treat vWF
- Combined Oral Contraceptives
- Progesterone – Oral, IUD or IM injection
- Hormonal implant
- GnRH agonists – Leuprorelin
- Antifibrinolytic medications - Tranexamic acid
- NSAIDs

Levonorgesterol Containing – Intrauterine System (Mirena®)

Levonorgesterol

- office procedure
- 5 years
- Provides contraception
- May have 3-6 months of prolonged unscheduled bleeding
- 40% of women have amenorrhea
- If this is used for a Polyp or Fibroid – about 30% of women go on to other procedures

Gupta, JO et al. NEJM, 2013

Surgical Treatment

- Hysteroscopic polypectomy
- Hysteroscopic myomectomy
- Abdominal myomectomy
- Uterine Artery Embolization
- Endometrial Ablation
- Hysterectomy

Endometrial Ablation

- Minimally invasive alternative to Hysterectomy, used for:
  - AUB –Polyps
  - AUB-Adenomyosis
  - AUB-Leiomyoma
  - AUB-Coagulopathy
  - AUB-Ovulatory
  - AUB-Endometrial

Ablation

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

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

Ablation

- Impedance- guided bipolar radiofrequency: *NovaSure*
- Fluid-filled thermal balloon:*ThermaChoice*
- Microwave: *Microwave Endometrial Ablation*
- Cryoablation: *Her Option*
- Free-fluid thermal: *ThermAblator*

Hysterectomy

- Surgical removal of the uterus
- Most definitive Rx for abn bleeding
- Major procedure
- Abdominal, vaginal, LAVH, Robotic
- Significant Risks
- Recovery period of 6-8 weeks
- Psychological issues

Hysterectomy

- Most common non-obstetric major surgery
- Fibroids are most common reason
- Asymptomatic fibroids don't require treatment
- Submucosal fibroids:
  - After hysteroscopic myomectomy: 16% had 2nd surgery
  - After hysteroscopic myomectomy + Endometrial Ablation: 5 % required a second surgery

Thank You

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