Blood, Sweat & Tears the Hormonal Roller Coaster of Perimenopause

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Disclosures

Vendor:

Cord Blood Registry

Speaker/Spokesperson:

Pharmavite, Bayer, Shield, POCN

Disclosures

This presentation uses use gender-neutral pronouns in most examples.

When the words “woman” and “women” are used, they pertain to cis-women.

Objectives

At the conclusion of this activity, participants will be able to:

- Explain the biology of the perimenopausal transition and how that impacts symptoms

- Describe the etiology and the work up of abnormal bleeding, which impacts 50% of women in the perimenopause transition

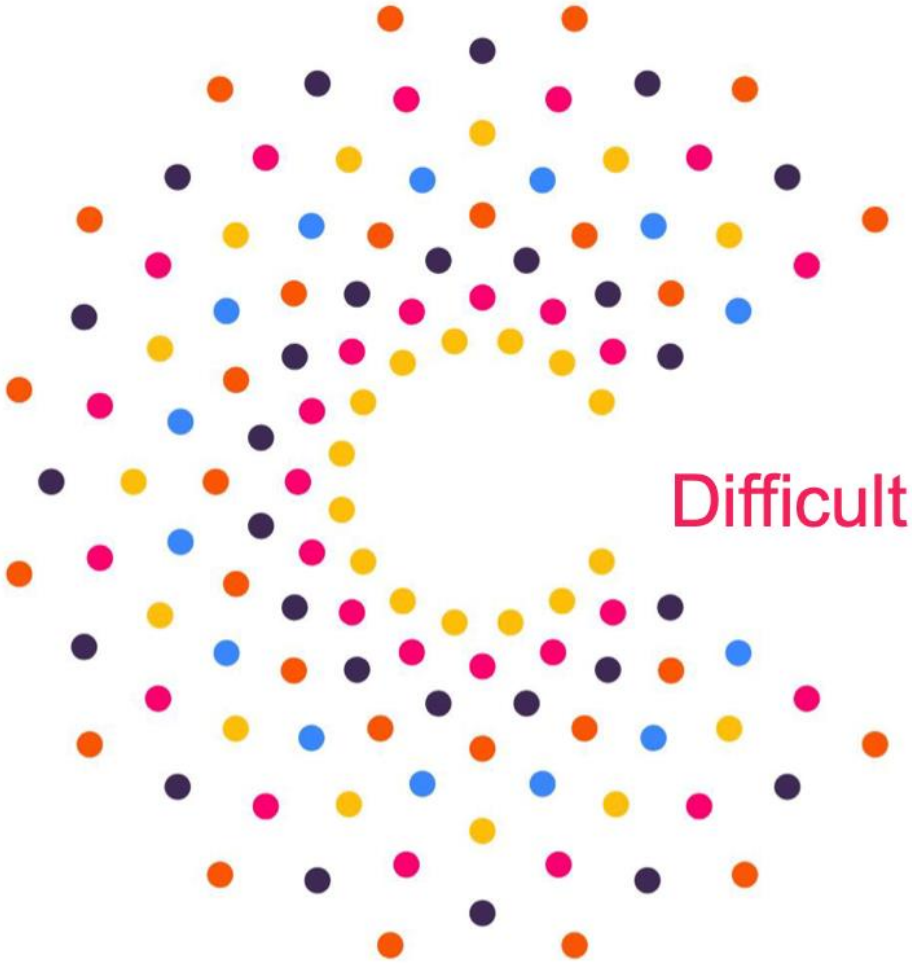
- List pharmacologic treatment options

Influenced by Estrogen

- Collagen – Pelvic floor muscles, joint health
- Neurotransmitters: Serotonin – Mood changes
- Blood vessel health
- Bone mass
- Vagina, vulva, bladder, uterus, breasts
- Weight, distribution of adipose & insulin resistance
- Temperature homeostasis
- Libido, sexuality
- Hair & skin

Women are Surprised by their Symptoms

- “I am too young to be in menopause!”
- “I still am getting my period, but it’s skipping a few months at a time…”
- “The symptoms are not all of the time, so I wonder if it is just me imagining them or if something is seriously wrong?”
- “Could it be my thyroid?”
- “I keep forgetting things - am I developing dementia?”
- “Why can’t I sleep?”
- “Sex is different now - Maybe I’m not attracted to my partner?”



Difficult to connect the dots

Maya : 45, G3P2 banker

- LMP started 2 wks ago, still bleeding
- Periods irregular for 2 yrs
- Warm at night, some night sweats
- Sweating after coffee in am
- Low energy, no interest in sex
- Caring for elderly parents, 2 teens
- Breasts often tender
- Upset about weight gain & Chin hair
- She wonders “Is it my thyroid?”

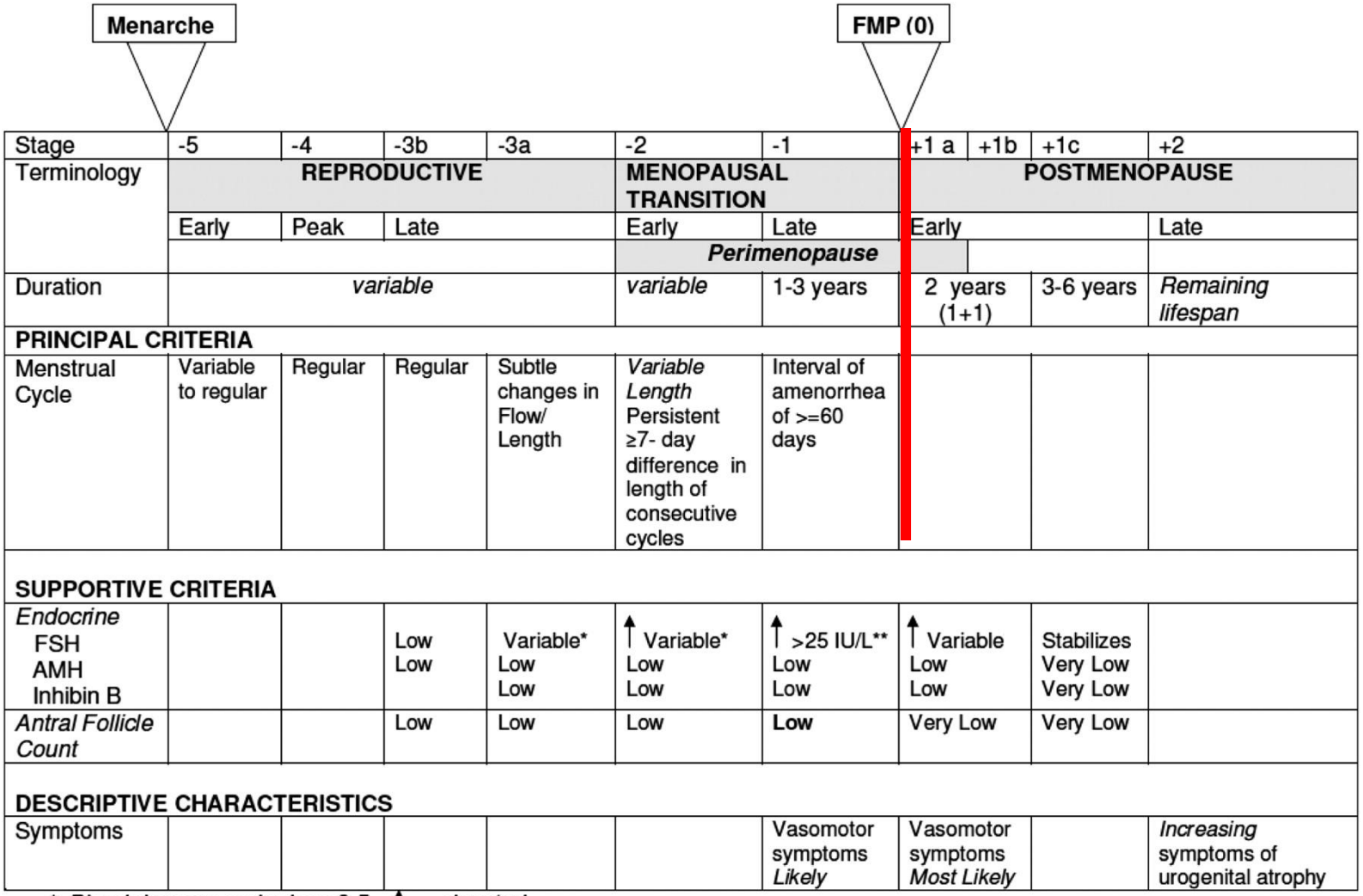
How to start

H & P – Maternal GM Breast Cancer, not using contraception, non-smoker, occasional tension headaches, last mammogram 18 months ago,hx of normal paps, lactose intolerant, low calcium intake

Labs:

- Urine HCG – Neg
- TSH, Free T3, Free T4 - WNL
- Hgb – 10.8 Ferritin – 13.5
- Lipid profile – WNL, Hgb A1C – 5.4
- Vitamin D – 21.2

STRAW – STages of Reproductive Aging Workshop



Stage	-5	-4	-3b	-3a	-2	-1	+1 a	+1b	+1c	+2
Terminology	REPRODUCTIVE				MENOPAUSAL TRANSITION		POSTMENOPAUSE			
	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Duration	*variable*				*variable*	1-3 years	2 years (1+1)		3-6 years	*Remaining lifespan*
PRINCIPAL CRITERIA										
Menstrual Cycle	Variable to regular	Regular	Regular	Subtle changes in Flow/ Length	*Variable Length* Persistent ≥7- day difference in length of consecutive cycles	Interval of amenorrhea of >=60 days				
SUPPORTIVE CRITERIA										
Endocrine FSH AMH Inhibin B			Low Low	Variable* Low Low	↑ Variable* Low Low	↑ >25 IU/L** Low Low	↑ Variable Low Low		Stabilizes Very Low Very Low	
Antral Follicle Count			Low	Low	Low	**Low**	Very Low		Very Low	
DESCRIPTIVE CHARACTERISTICS										
Symptoms						Vasomotor symptoms *Likely*	Vasomotor symptoms *Most Likely*			*Increasing* symptoms of urogenital atrophy

* Blood draw on cycle days 2-5 ↑ = elevated

**Approximate expected level based on assays using current international pituitary standard[67-69]

What stage is Maya in?

Key question

Have you had a period in the last 12 months?

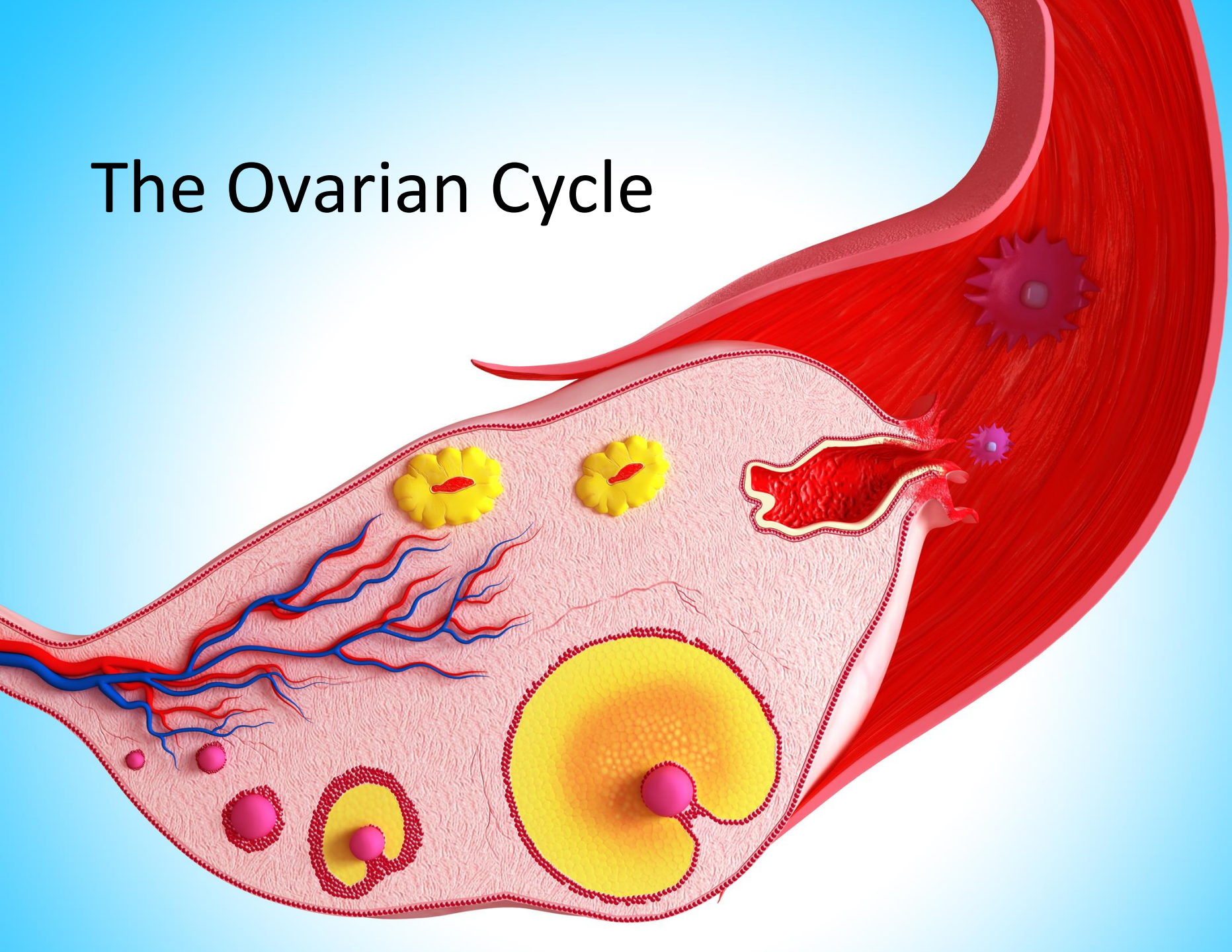
Yes – Perimenopause

No - Menopause

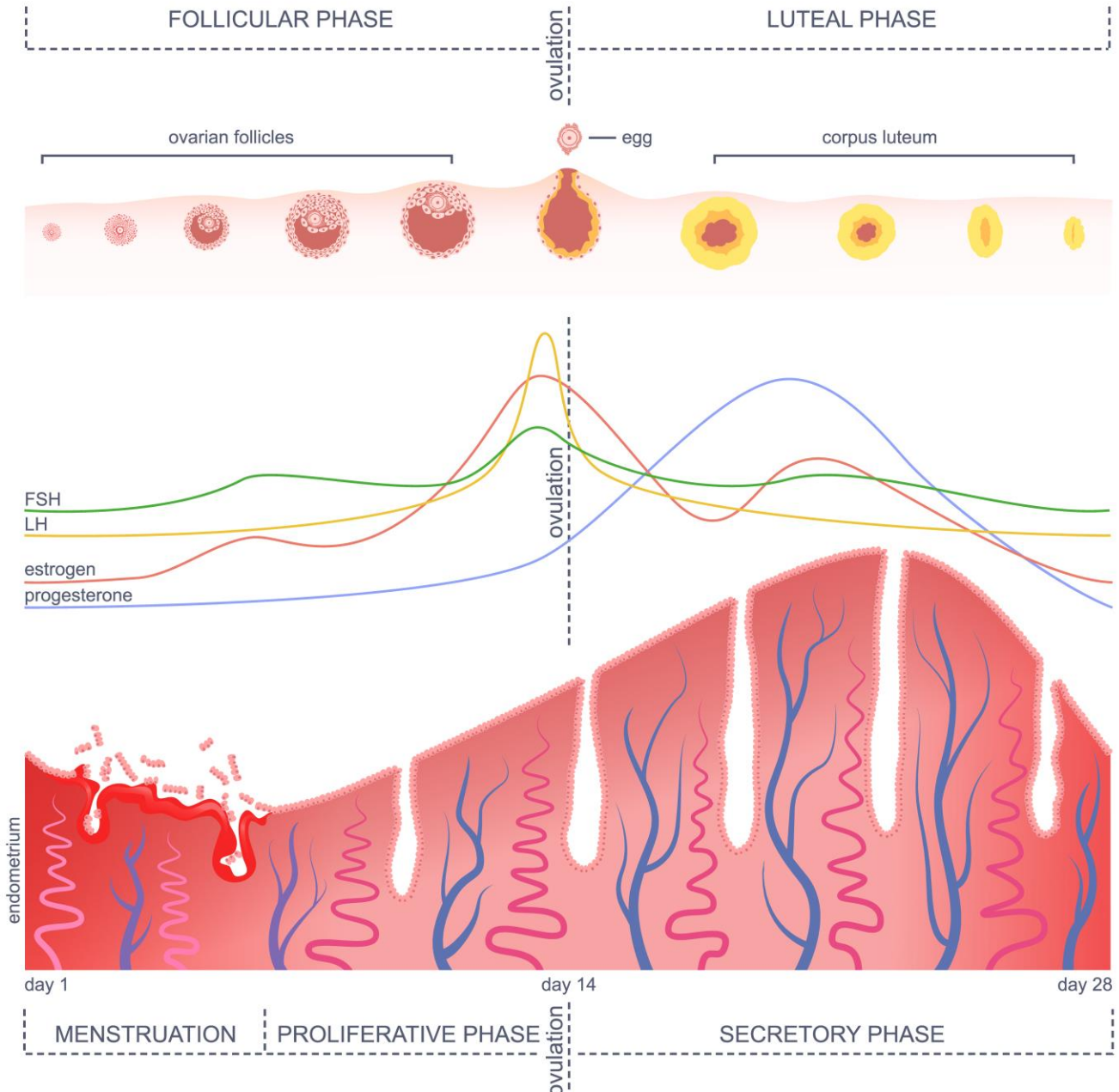
Perimenopause:
A hormonal roller coaster

- 3 to 7+ years
- Irregular periods
- VMS
- Sleep disruption
- Exhaustion
- Brain fog
- Changes in sexuality
- Weight redistribution, changes in hair & skin

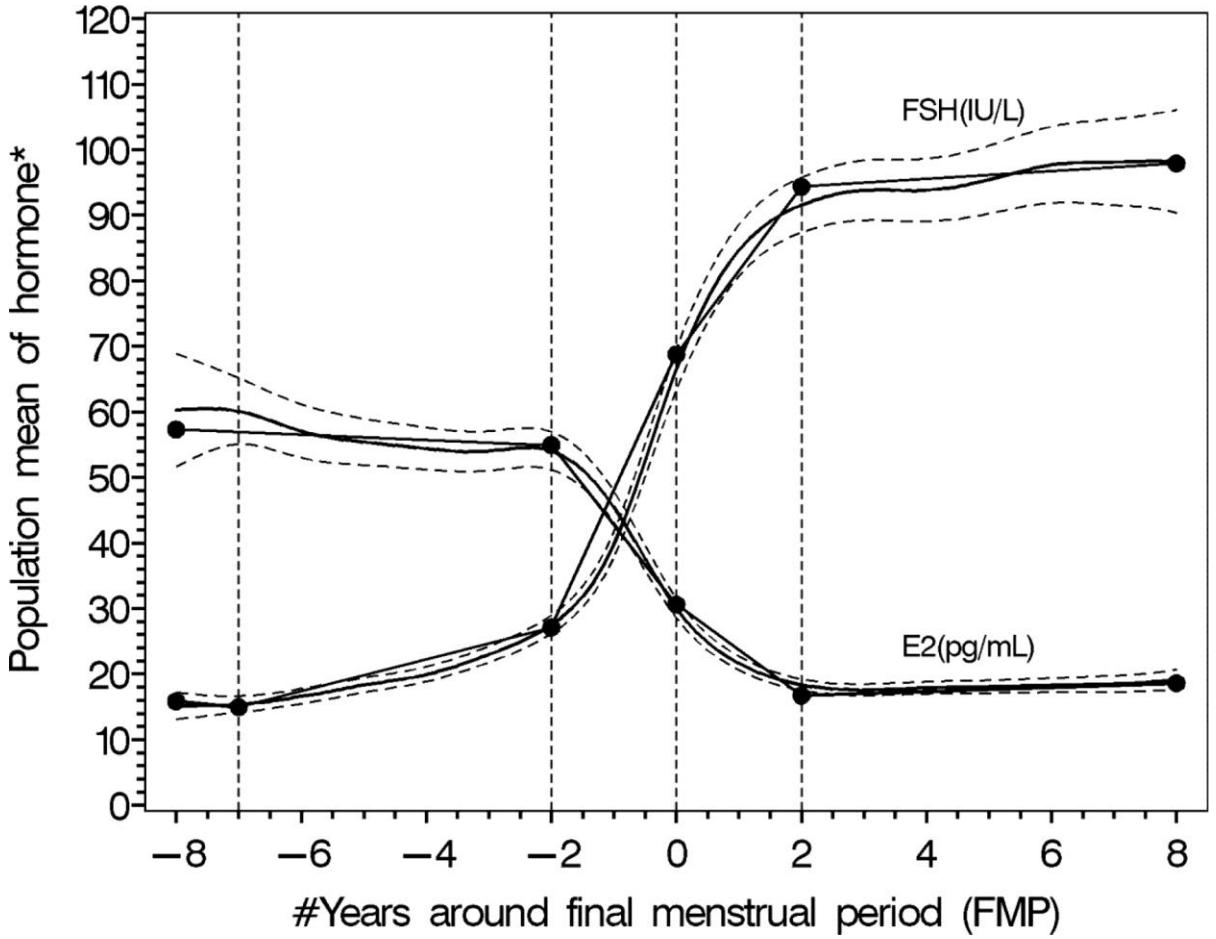
The Ovarian Cycle



MENSTRUAL CYCLE



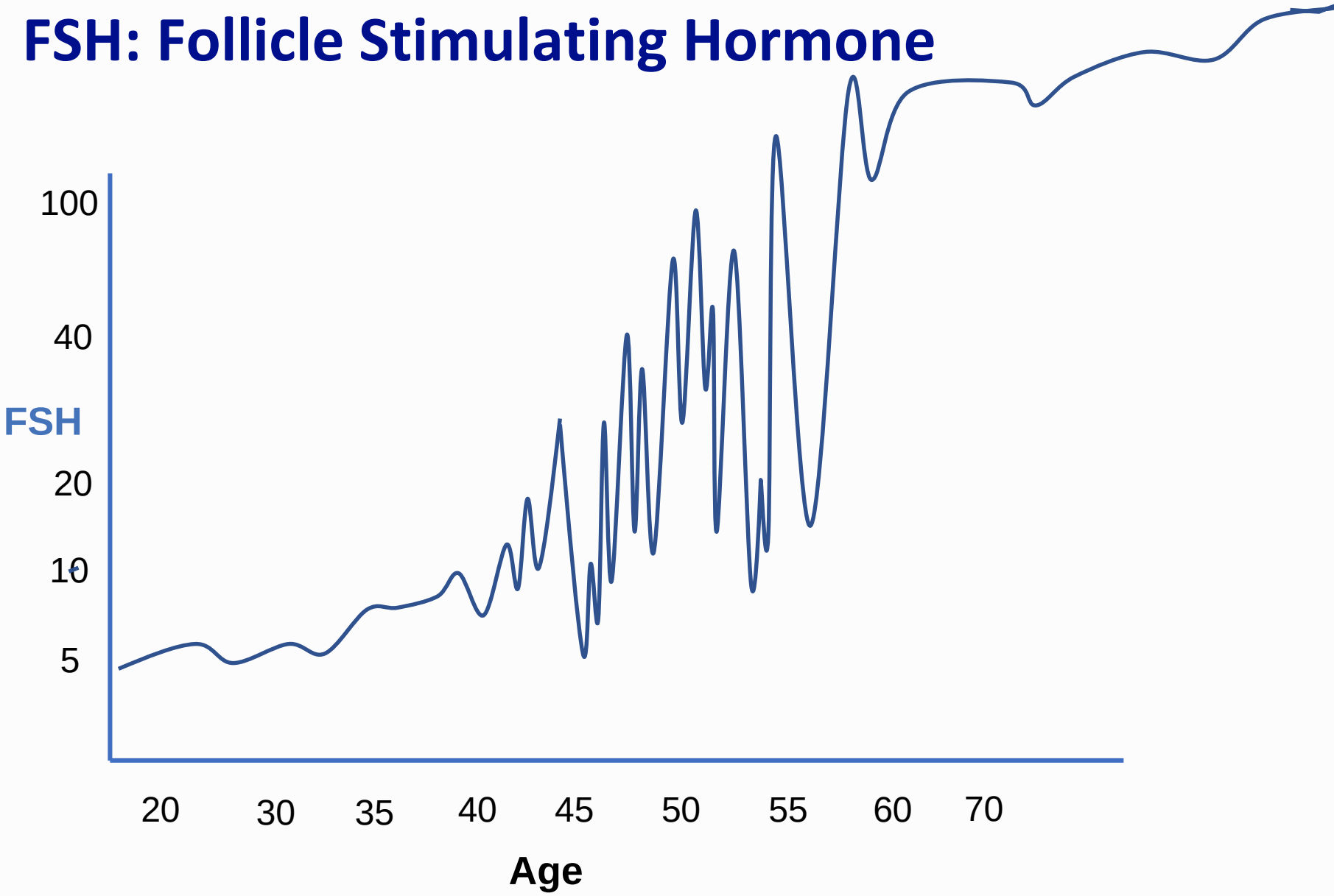
Changes in Estradiol & FSH



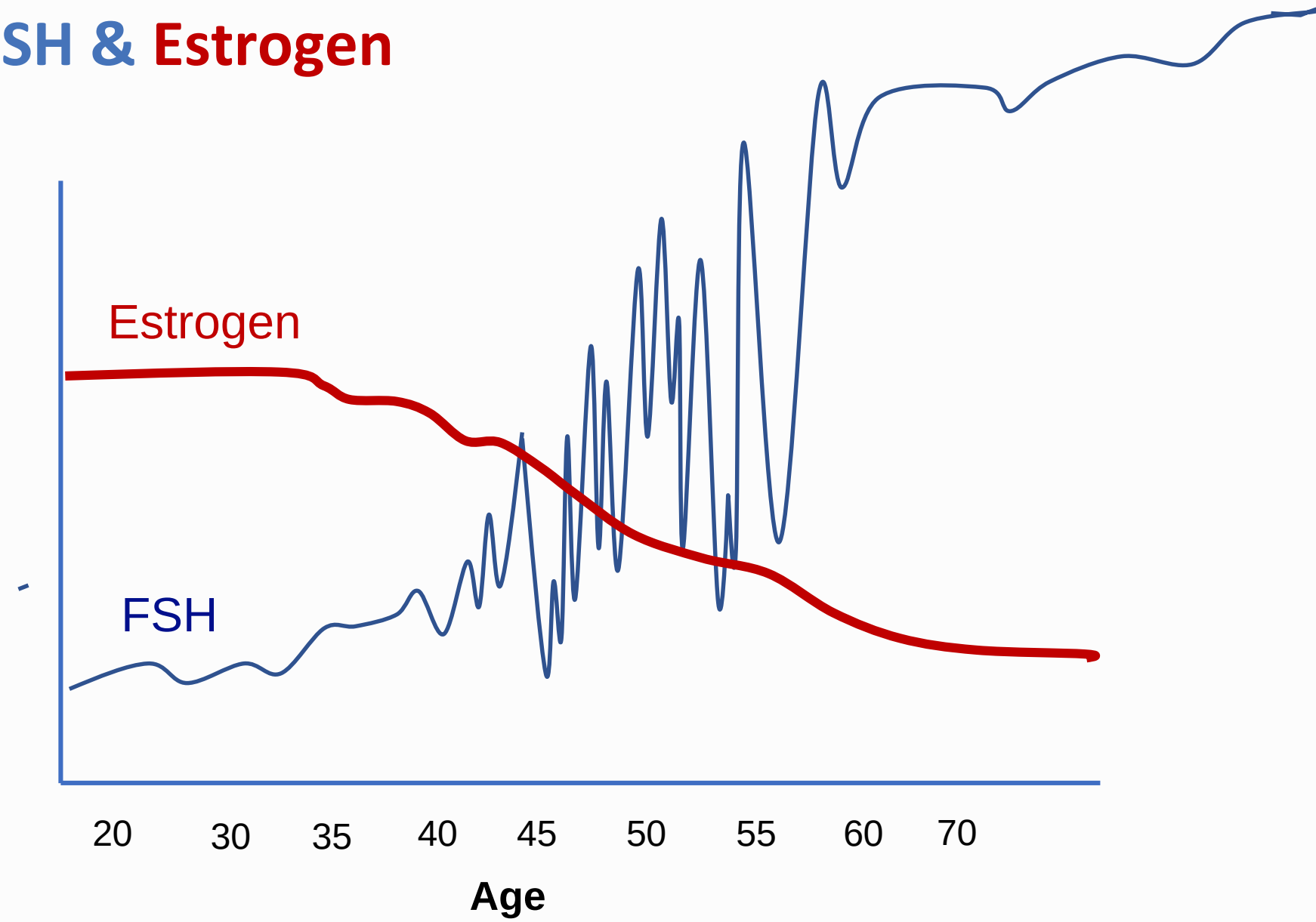
Hormone Testing?

- Limited value for most patients
- Hair and Saliva testing is not independently validated

FSH: Follicle Stimulating Hormone



FSH & Estrogen



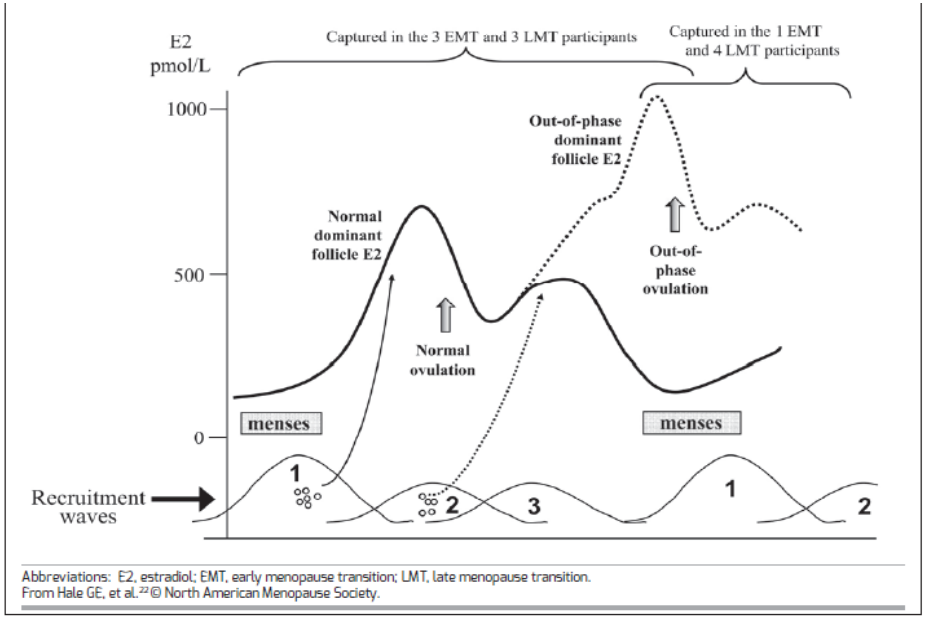
When do we test Hormones

- **Birth Control Pill or IUD**
- **Under 48 with no periods**
- **Heavy Bleeding**
- **Hysterectomy or Ablation**
- **Unusal or unexplained symptoms**

Perimenopause: The LOOP Phenomenon

Luteal-Out-Of-Phase event

- Estradiol surges twice
- May explain common perimenopausal symptoms
- Mastalgia
- Migraine
- Growing fibroids
- Endometrial hyperplasia
- Polyps



Hale GE, et al. *Menopause*. Hale GE, et al. *J Steroid Biochem Mol Biol*. 2014.

What does she need next?

- Education about symptoms
  - Breast pain, chin hair
  - Tender breasts, weight gain
- Bleeding – U/S? Hysteroscopy? EMB?
- Iron, Vitamin D supplementation
- Are her headaches a concern?
- ? Higher risk for breast cancer?
- Energy & Sleep
- Sexual health

Skin changes

- 30% decline in skin collagen in the first 5 years after menopause
- ~2% per year decline over next 20 years
- Greater correlation between skin thickness and collagen content to yrs since menopause *versus* chronologic age
- Estrogen receptors are present in significant numbers in skin

Kamp E, et al. Clin Exp Dermatol. 2022

Hair changes

- Increase in the ratio of androgen to estrogen may influence hair changes in some women
- Female pattern hair loss (thinning on crown) most common diagnosis
- Hair width can thin
- Large “rogue hairs” can appear on the chin, neck, upper lip around menopause
- Loss of pubic hair, eyebrows, eyelashes

Rinaldi F, et al. Biomedicines. 2023

Pharmacology - unwanted hair

- Vaniqa – Eflornithine
- It does not remove the hair but rather slows its growth
- The cells responsible for hair growth depend upon polyamines, proteins which require an enzyme ornithine decarboxylase (ODC)
- Eflornithine blocks ODC

Laser hair removal ***only*** works on dark pigmented hair

Pharmacology – Eyelashes/Eyebrows Hair Growth

- Latisse: Bimatoprost ophthalmic solution 0.03%
- Increases eyelash growth, including length, thickness, and darkness.
- Prolongs the active growth phase—or anagen phase
- Rare side effect – permanent darkening of the iris and eyelid

Pharmacology – Head Hair Growth

- **Minoxidil 2%** Prolongation of growth or anagen phase and increase in follicle hair size
- 20% of women will see moderate hair growth
- More will see hair loss slow or stop
- May see more hair fall out in first 4 weeks as new hair pushes out old hair

Weight Gain

- Declining estrogen leads to
  - Insulin resistance
  - Slower BMR
- Loss of Subcutaneous fat with a redistribution and deposition of abdominal fat
- Number of calories needed is drastically reduced
- Sarcopenia - Loss of skeletal muscle
- Need for more exercise - especially weight bearing

Marsh ML, et al. Nutrients. 2023

Vitamin D & Calcium recommendations

- Serum levels should be > 30 ng/ml
- Supplementation with 600 – 4,000 IU/day recommended to reduce risk of bone loss and to prevent muscle pain

- Calcium intake – 2-3 servings/day of calcium rich food is optimal
- Avoid supplementing if adequate dietary calcium otherwise increased risk of coronary artery calcifications

Mei Z, et al.. Front Physiol. 2023

Your Plan

- Education about symptoms
  - ✓ Breast pain, chin hair & weight gain
- Mammogram
- Ultrasound ? Hysteroscopy? EMB?
- Iron, Vit D, Ca^{+} supplementation
- Why are her breasts tender?
- ? Higher risk for breast cancer?
- Are her headaches a concern?
- What are her risks?

Perimenopausal Bleeding:

- 90% of women experience changes 4 - 8 years prior menopause
- Mostly due to oligo ovulation and fluctuating levels of hormones
- Erratic progestational influence on endometrium
- Menstrual changes in midlife women:
  - Lighter – 32%
  - Heavier – 29%
  - Longer – 20%
  - Shorter – 24%
  - Skipped menses is common

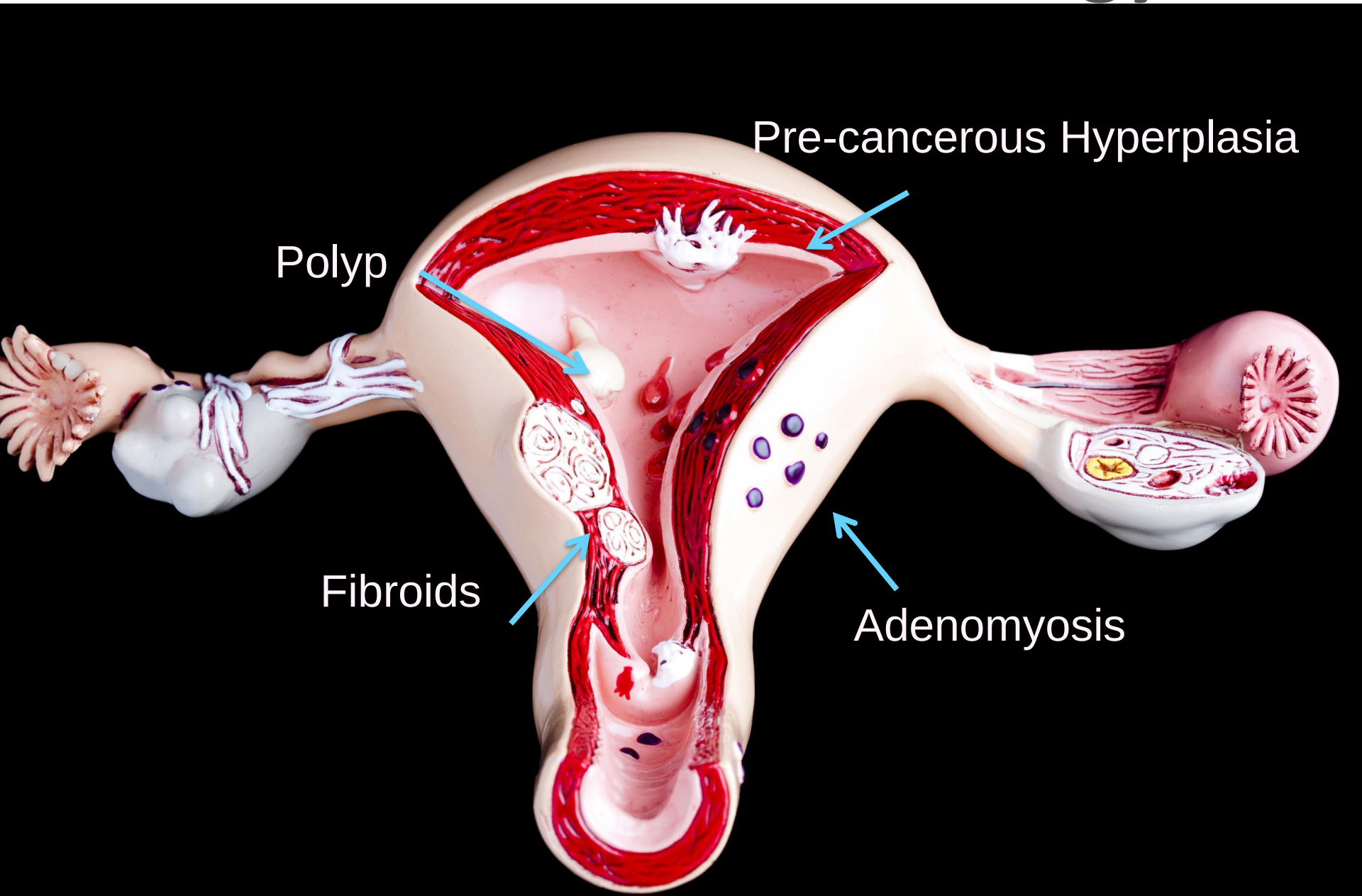
AUB: PALM-COEIN

- **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).

Uterine Structural Pathology



Direct Visualization for Structural Causes

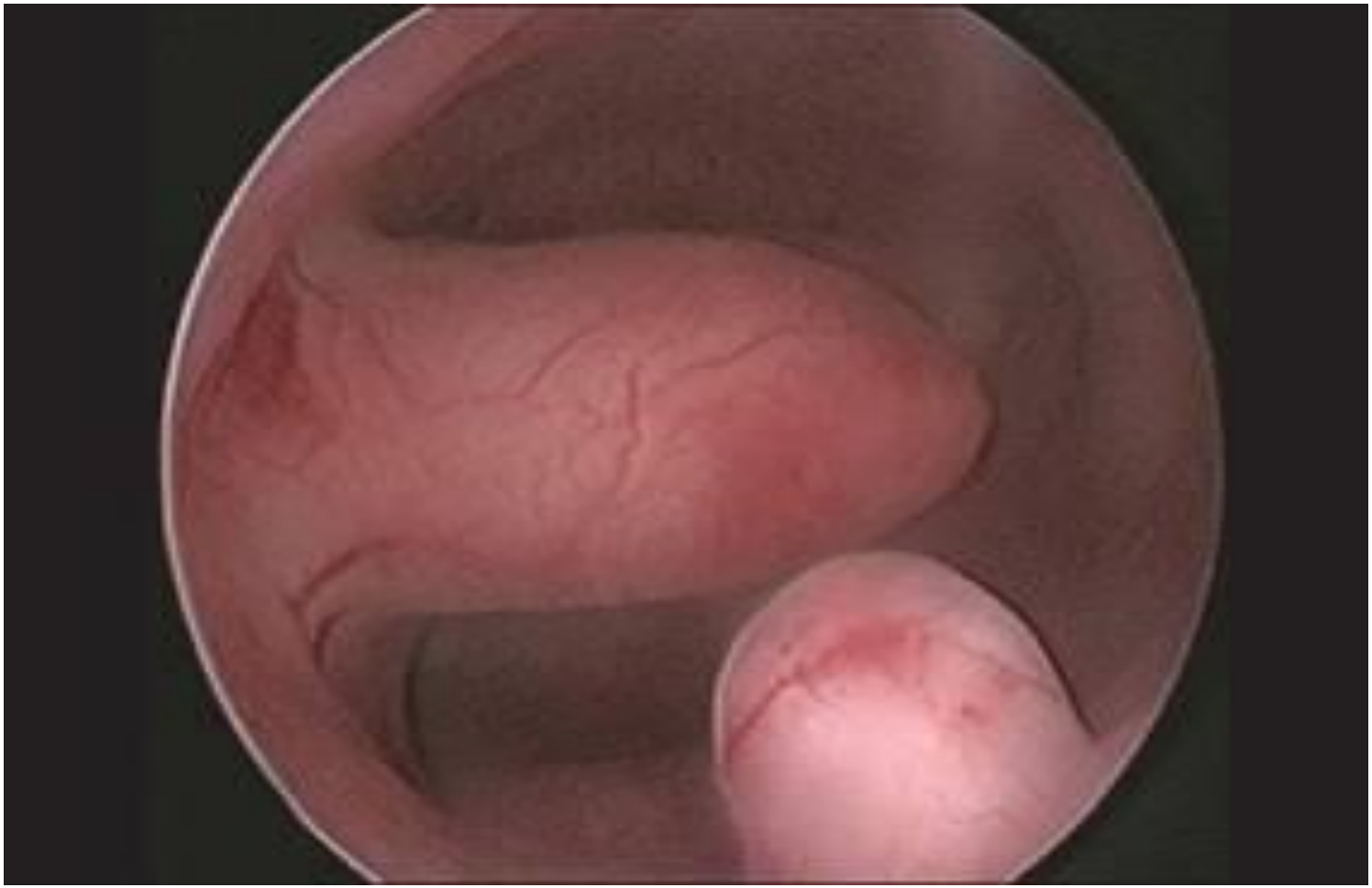
Hysteroscopy

Photos courtesy Dr. Paul Indman

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

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.

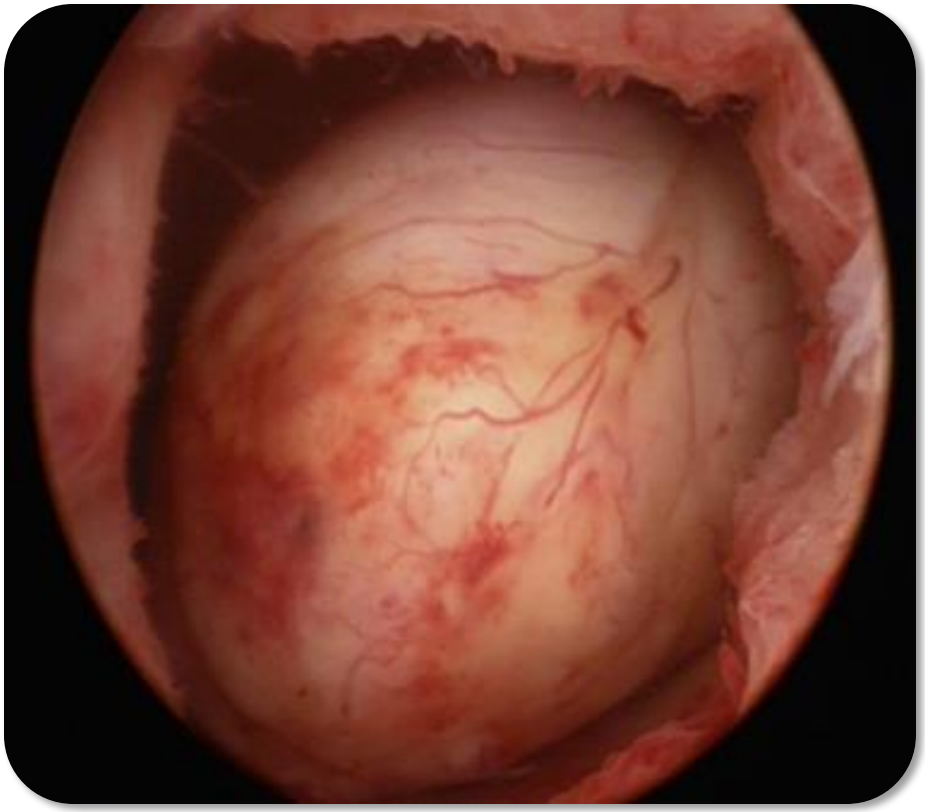
Treating Adenomyosis

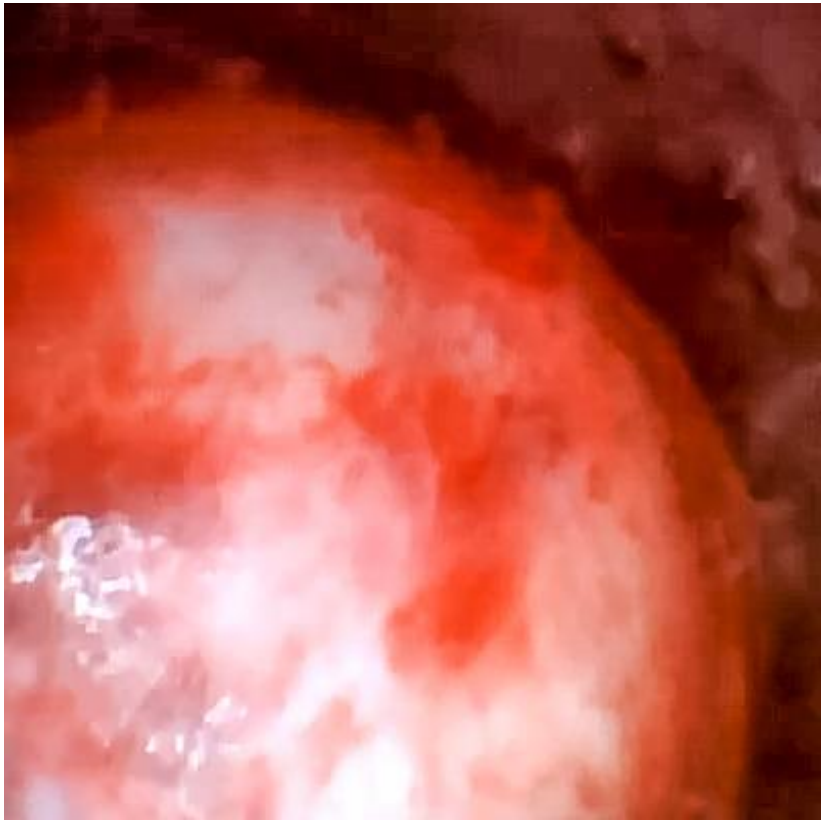
- **Polyps** – Remove via hysteroscopy
- **Adenomyosis**
  - NSAIDs
  - Tranexamic acid
  - Myfembree – to decrease bleeding. A GnRH Antagonist with a combination of Estrogen/Progesterone (off label)
  - Combination Oral Contaceptives
  - Progesterone containing IUDs

Leiomyoma = Fibroids

- Benign Calcifications of the Uterus.
- Present in 1/3 of women > 30
- Estimated 50% in women > 50
- Higher incidence in African American women
- Asymptomatic or cause bladder, intestinal discomfort, bleeding & dyspareunia
- Tx depends on size, location & desire for fertility

Leiomyoma: Fibroid





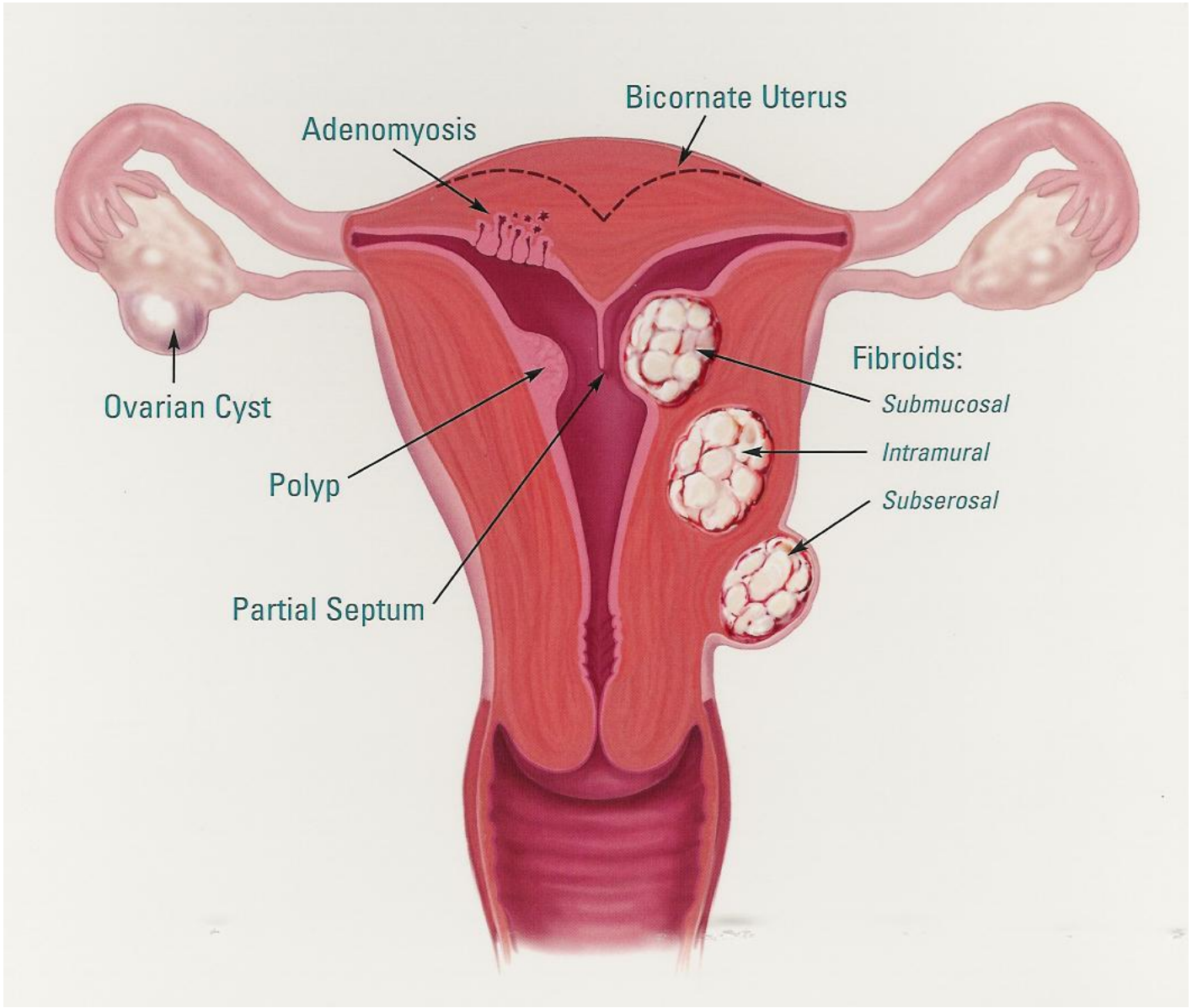


Illustration Purchased from iStockphoto

Treating Leiomyoma Fibroids
Minimally invasive

- Monitor q 6 months for growth and effects for the woman
- **Uterine Artery Embolization (UAE)**
- **Endometrial Ablation** – minimally invasive for submucosal fibroids if < 3 cm, while preserving the uterus
- **Radio Frequency Ablation (RFA)** – minimally invasive procedure using laproscopy and ultrasound to locate and then to shrink and destroy fibroids while preserving the uterus
- **Myfembree** – GnRH antagonist (*relugolix*) combined with estradiol, and norethindrone acetate). Once-daily oral, FDA-approved. Treats heavy menstrual bleeding from uterine fibroids in premenopausal women
  - Can cause bone loss

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Iron supplementation

- Look for treatments with fewer Adverse Effects
- Pts with bariatric surgery have malabsorption issues
- Consider using:
  - Ferric Maltol
  - IV Iron
  - Dietary sources
  - With any supplement remember:
    - Avoid calcium
    - Take with Vitamin C
    - Decrease black tea

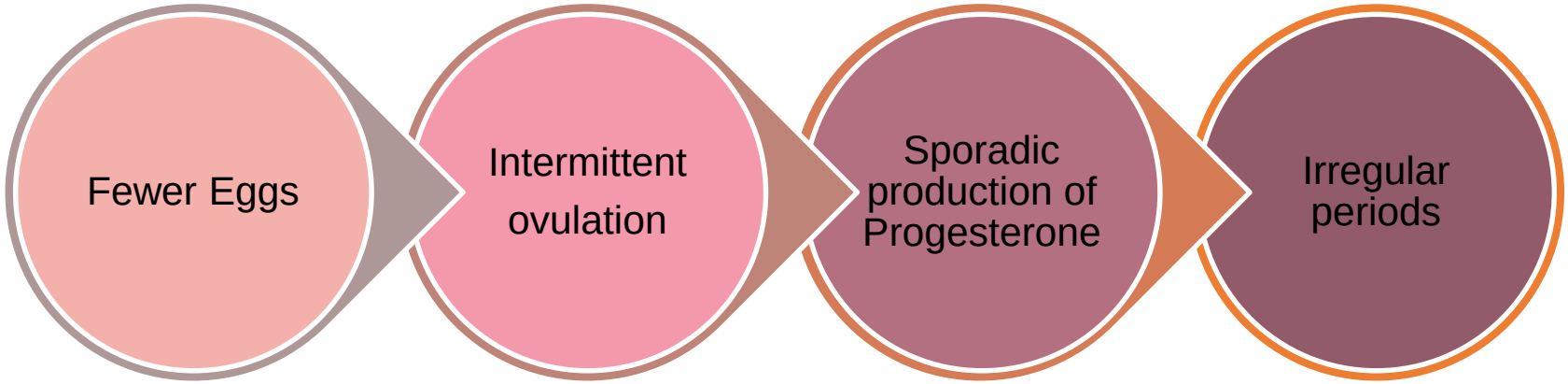
Swedish Flower Pollen extract

- Available on line/no prescription
- Non-allergenic
- Mechanism of action: serotonergic
- No hormonal effects - No endometrial activity
- Sub pharmacologic levels of phytoestrogens
- RCT of 54 women: 65% had decreased HF compared to 38% in control group
- Hot flash reduction of about 1/3 the # of HF, NS
- Dose: 2 per day

Winther, K & Hedman, C. Climacteric, 2005

S-Equol

- Available on-line without prescription
- Soy Metabolite – acts preferentially on Estrogen receptor Beta
- Structurally similar to estrogen
- No impact on breast or endometrium
- 50% reduction in HF
- Improved sleep by 50 minutes/night
- Reduced vaginal irritation
- 2 tablets/day


Fewer Eggs
Intermittent ovulation
Sporadic production of Progesterone
Irregular periods

Ovulatory causes: Progesterone containing IUD (Levonorgestrel 52 mg)

- No impact on Hot Flashes or night sweats
- Provides direct endometrial suppression for anovulation and adenomyosis
- Provides contraception
- Effective for 8 years
- May be used with menopausal hormone therapy (off –label)
- Ok for smokers, women with migraine
- Use pre-procedure analagesia – NSAIDs and/or Paracervical block
- Amenorrhea in 40% of patients
- 80% of patients will have a significant reduction in overall bleeding

Combined Hormonal Contraceptives
Pill, ring or patch

- Alleviation of hot flashes and night sweats, helps with sleep
- Contraception
- Endometrial suppression: anovulation and adenomyosis
- Endorsed by The Menopause Society until age 54
- Use 20 – 30 mcg doses of EE
- Consider least androgenic progestins (Drospirenone)
- Consider extended cycling with no hormone free interval
- Ok, as long as patient does not have any contraindications
  - Migraine with aura
  - Smoking
  - Unexplained vaginal bleeding and the others

Hormonal Contraception & Cancer Risk ?

- According to the CDC, some Combined Oral Contraceptive (COCs) methods are associated with an increased risk of breast cancer[1]
- COCs used after age 40 decrease the risk of Ovarian cancer[1]
- Large Swedish study found increased risk in women taking oral progestin-only pills (POPs)[2]
  - May be attributable to smoking and higher BMI which prevents these women from using combined methods[2]

1. Smrekar K, Lodise NM. Nurs Womens Health. 2022
2. Nur U, et al. BMC Cancer. 2019

Breast Cancer Risk Models

- **Gail Model –** does *not* include breast density

- **Tyrer-Cuzick Model –** incorporates breast density
- **Breast Cancer Surveillance Consortium (BCSC)**
  - Modification of Gail with breast density

These models predict 10 year and lifetime risk and should be used with shared decision making for screening/imaging recommendations

Kim G & Bahl M. J Breast Imaging. 2021

Breast Cancer Genetic Testing

- **Women with NO hx of breast cancer and have:**
- A family member with a *BRCA1/2* inherited gene mutation (or other inherited gene mutation related to breast cancer)
- A family history of cancer *and* have Ashkenazi Jewish heritage
- A first degree relative diagnosed with breast cancer at age 50 or younger
- A close family member diagnosed with ovarian cancer, male breast cancer, pancreatic cancer, or high-risk or metastatic prostate cancer

National Comprehensive Cancer Network (NCCN). 2024.

Headache in Midlife Women

- Associated with abrupt decreases in estradiol, eg. menstrual periods and perimenopause
- The link between increased rates of migraines and perimenopause well accepted among neurologists
- Perimenopause, the prevalence +/or intensity of headaches often increases, especially in women with a history of menstrual migraines.
- At natural menopause there is a decrease in migraines in women who experience migraine *without* aura
- In women with pure menstrual migraines (migraines only seen with menses), there is often complete resolution of symptoms with menopause

What does she need next?

- Education about symptoms
  - Breast pain, chin hair
  - Tender breasts, weight gain
- Bleeding – U/S? Hysteroscopy? EMB?
- Iron supplementation
- Are her headaches a concern - **No**
- ? Higher risk for breast cancer? **No**
- Energy & Sleep
- Sexual health

Stay Tuned

Resources for Clinicians

- International Menopause Society Practitioner's Toolkit
- The Menopause Society
- Lets Talk Menopause
- Modifiable and Validated forms from:
  - Menopause.org – 8 pages
  - Australasian Menopause Society
    - Also has a scorecard for symptom tracking

Thank You

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Iowa NP Conference

@NurseBarbDehn

Questions

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