Menopause 101:

A Comprehensive Guide for Busy Clinicians

Barb Dehn WHNP-BC, MSCP, FAANP

Iowa NP Conference

@NurseBarbDehn

Disclosures

Vendor:

Cord Blood Registry

Speaker/Spokesperson:

Pharmavite, Bayer, Shield, POCN

OBJECTIVES

1. List the 7 most common menopausal symptoms and describe their biologic basis.
2. Explain the rationale for offering hormonal treatment options for women experiencing premature menopause
3. Elucidate prescription free and prescription treatment options that are evidence-based and recommended to treat the symptoms of menopause
4. List the pharmacologic and non-pharmacologic treatment options for genitourinary syndrome of menopause

Has Anyone Seen Her Hormones?

Definitions

Premenopause	Perimenopause	Menopause	Post Menopause
• Periods are: predictable & regular • Pregnancy possible • Hormones balanced • No change in sex life • No feelings of warmth	• Time of transition • Irregular periods • Fertility uncertain • Hormonal swings • More warmth • Less lubrication • 3-10 years	• No periods for 12 months • Infertility • Declining hormones • Night sweats • Sleep disturbances • Changes in sexuality • Average age 51	• Time after menopause • Lasts 30 – 50+ years • More decline in hormones • Vaginal dryness • Many invisible changes

Other Terminology

- ***Early menopause:*** FMP < age 45 y
- ***Late menopause:*** FMP > age 54 y
- ***Induced menopause:*** Surgical or other cause
- ***Premature menopause:*** FMP < age 40 y
- ***Primary Ovarian Insufficiency:*** POI – ovaries stop functioning normally, may ovulate intermittently, menses may resume

Premenopause

- Her typical pattern of periods
- No change in sexual function
- No sleep disruptions
- No temp changes or sweating when
    - taking a hot shower or bath
    - wearing more than 1 layer of clothes
    - drinking hot coffee or tea
    - having alcohol
    - eating spicy food
    - under stress

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

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?”

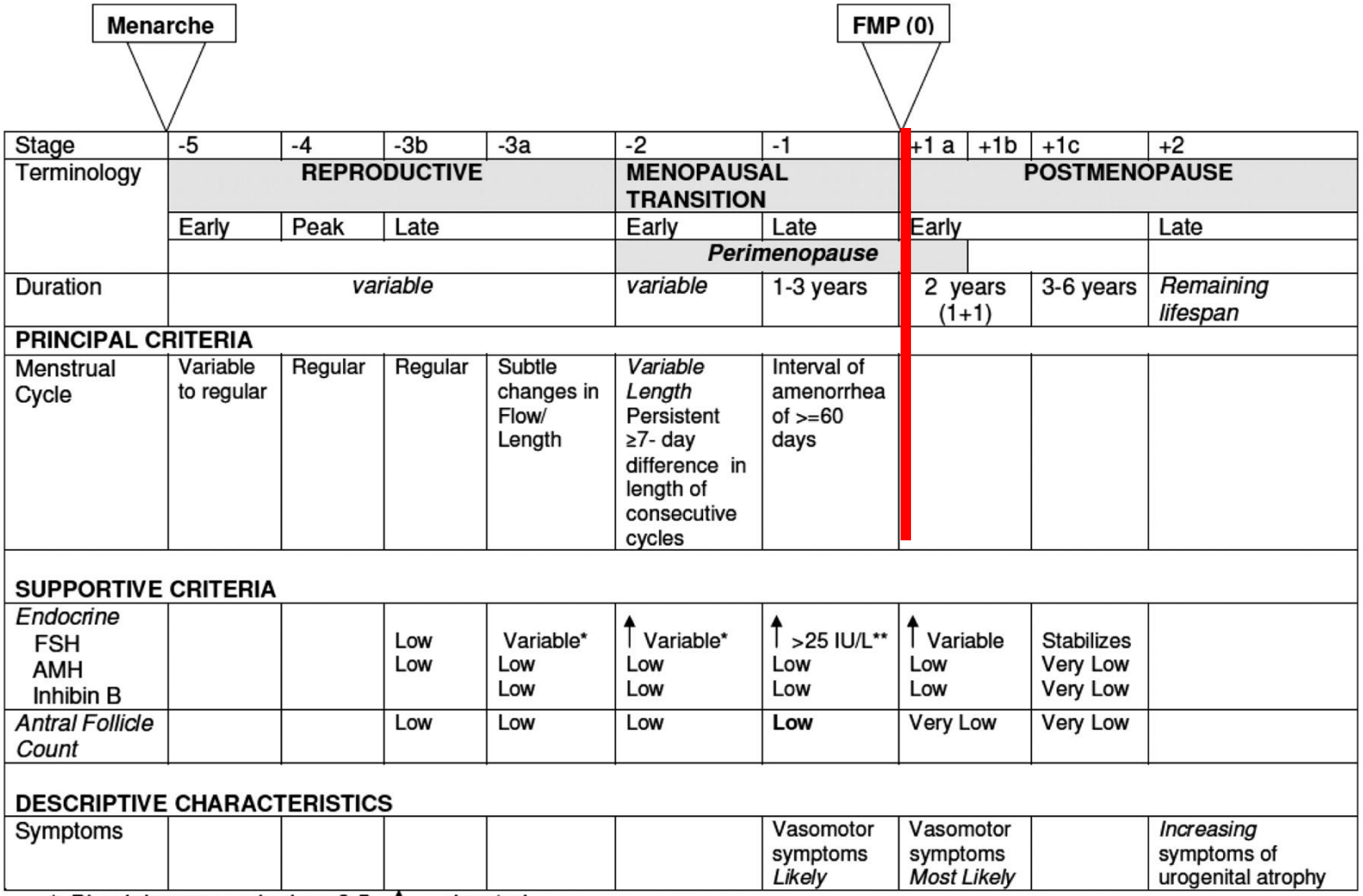
How to start

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?

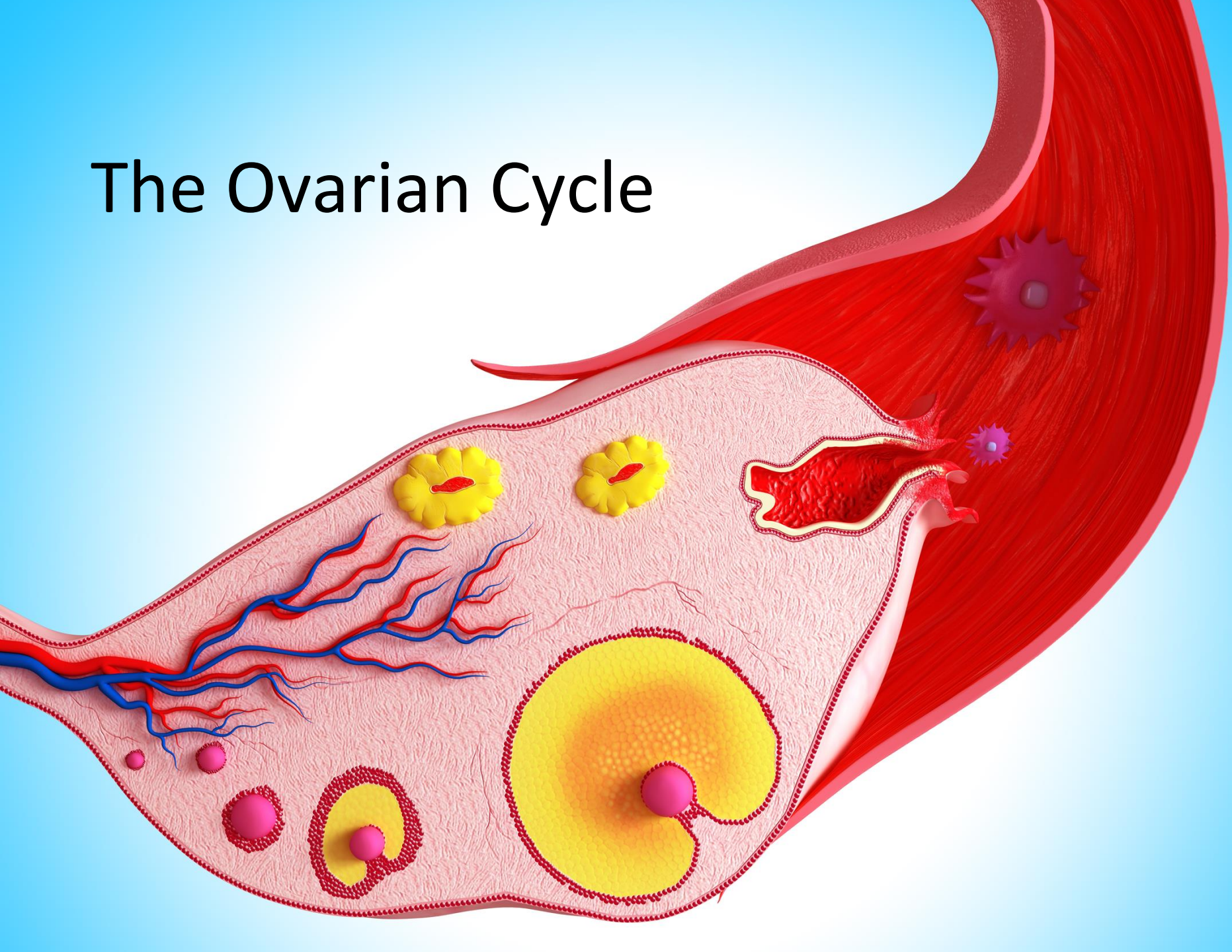
Yes – Perimenopause

No - Menopause

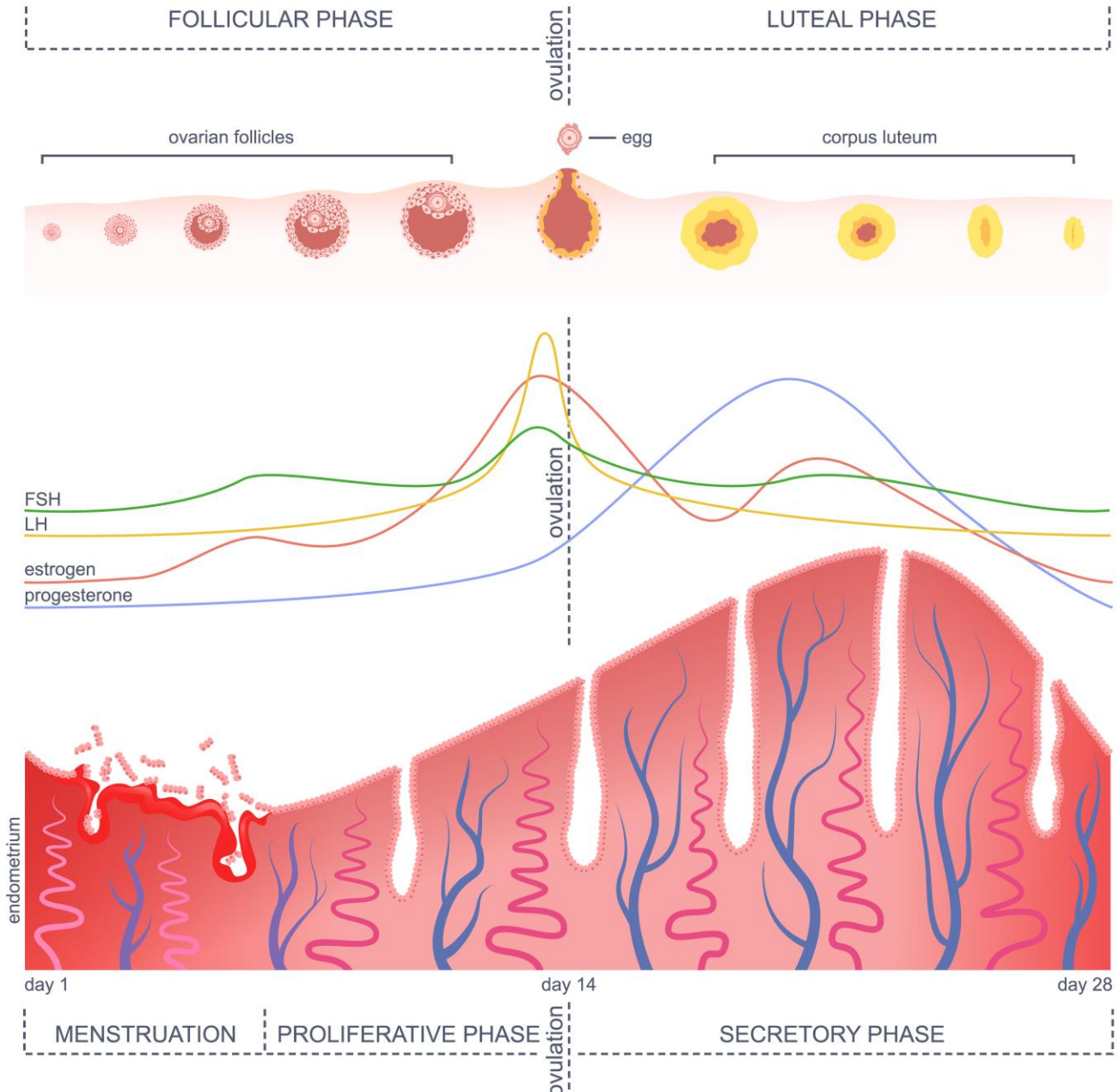
Perimenopause:
A hormonal roller coaster

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

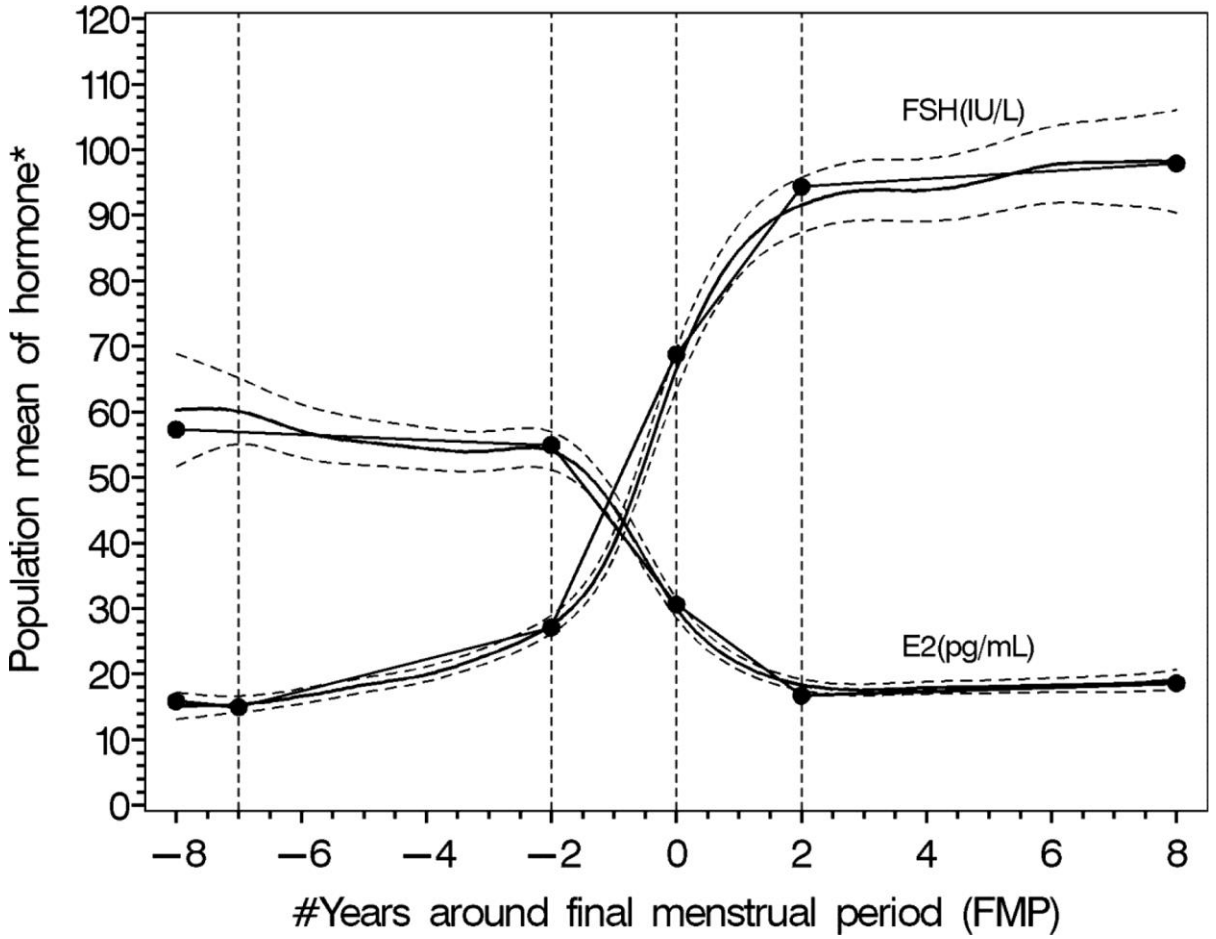
The Ovarian Cycle



MENSTRUAL CYCLE



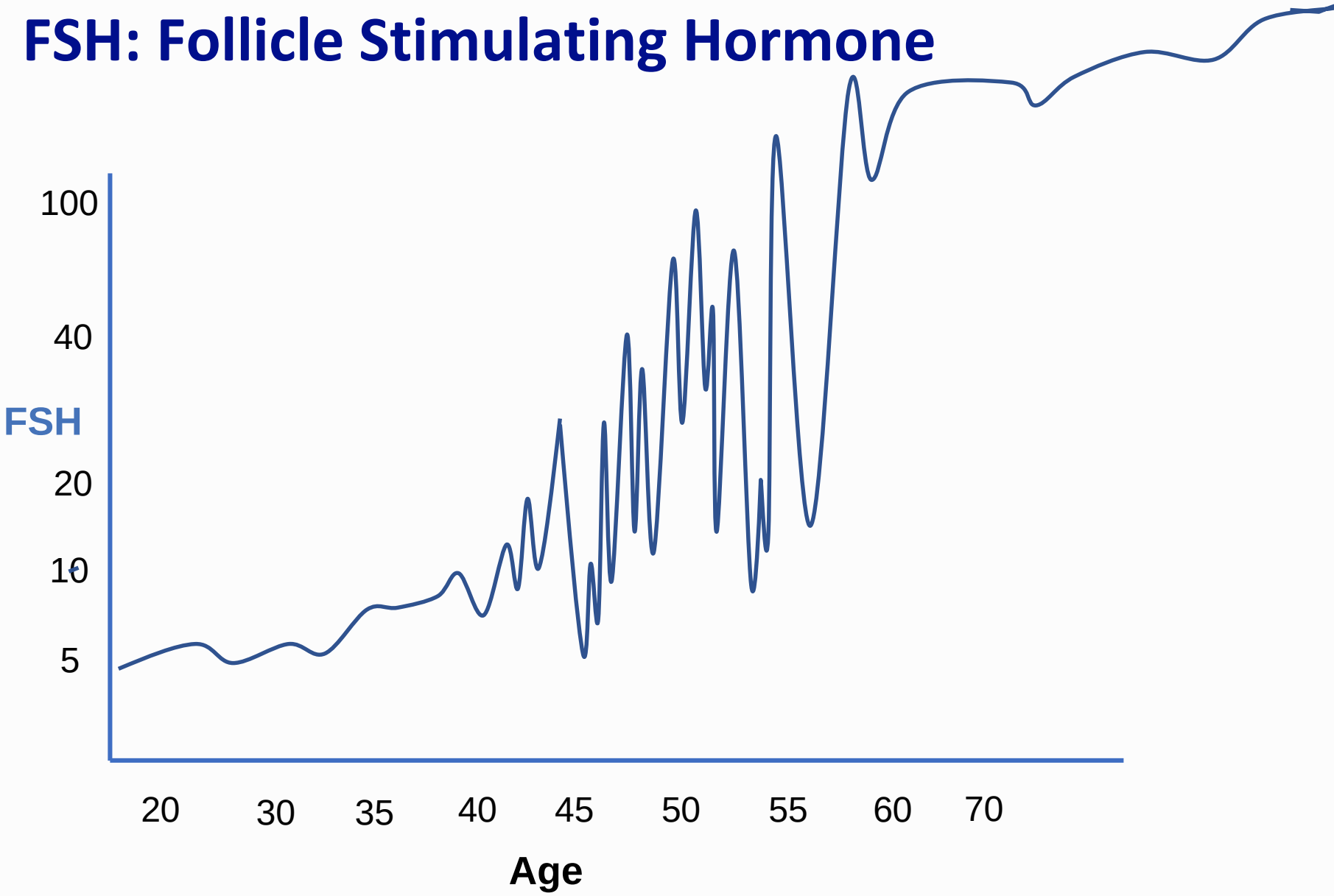
Changes in Estradiol & FSH



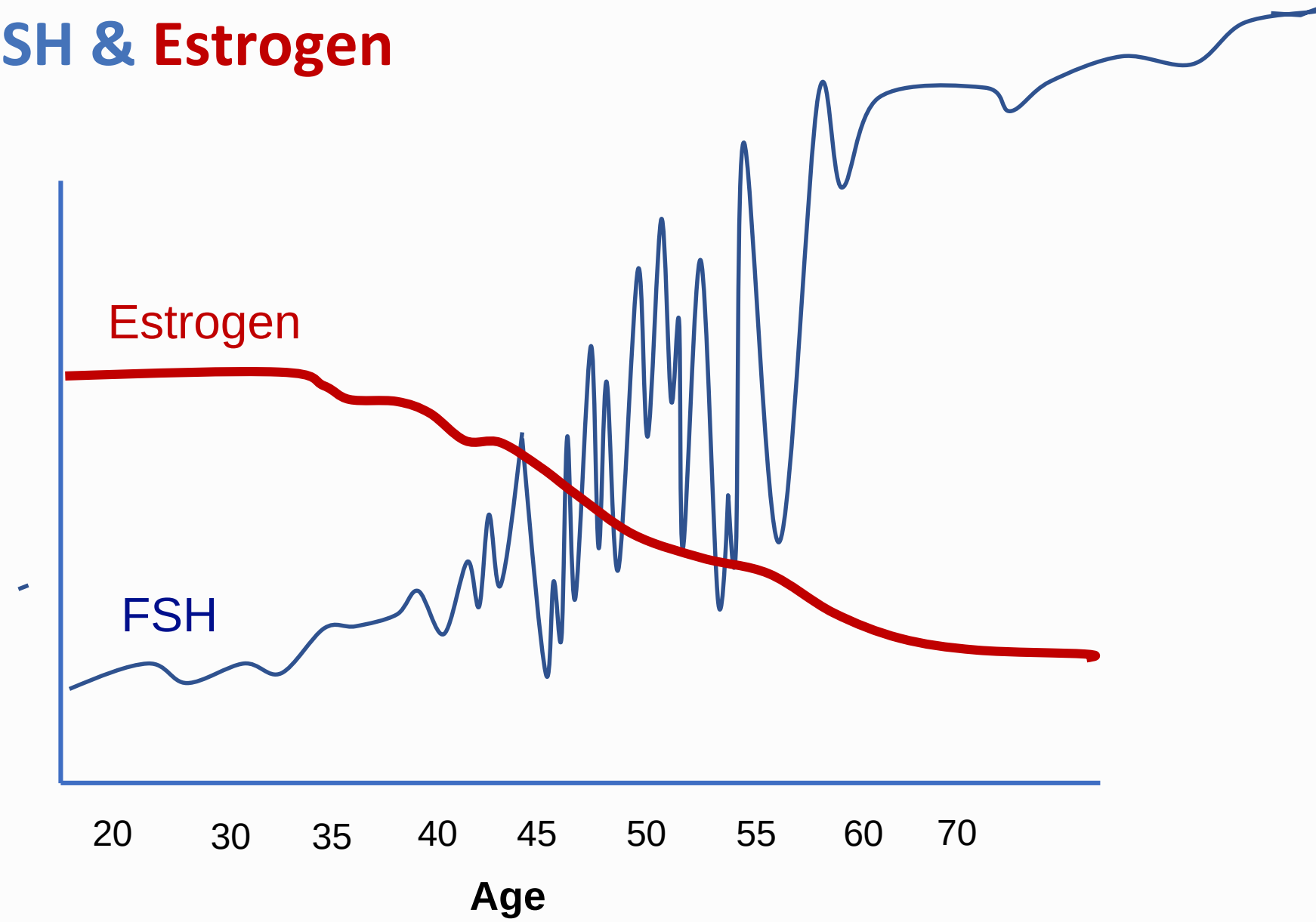
Hormone Testing?

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

FSH: Follicle Stimulating Hormone



FSH & Estrogen



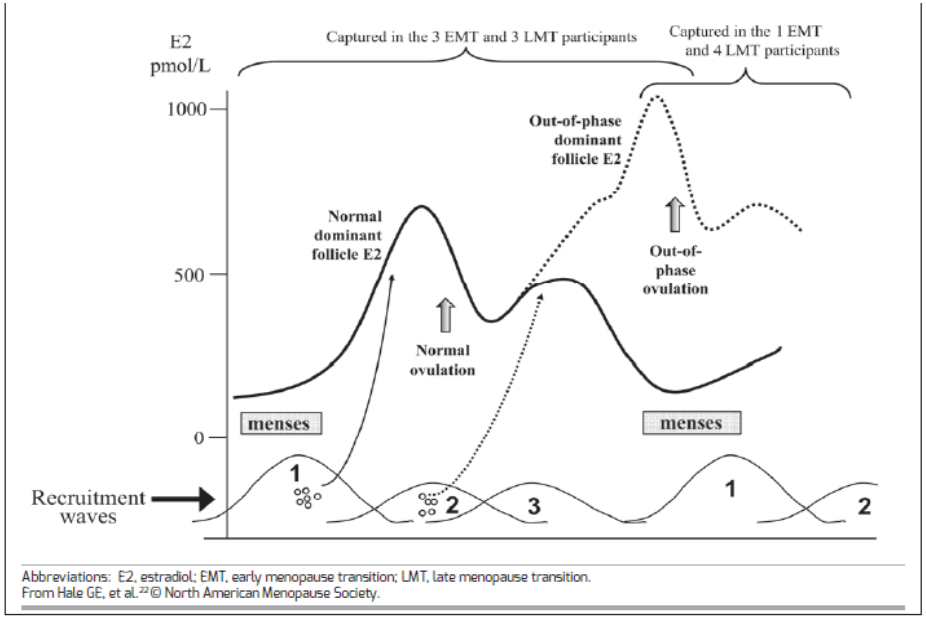
When do we test Hormones

- **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

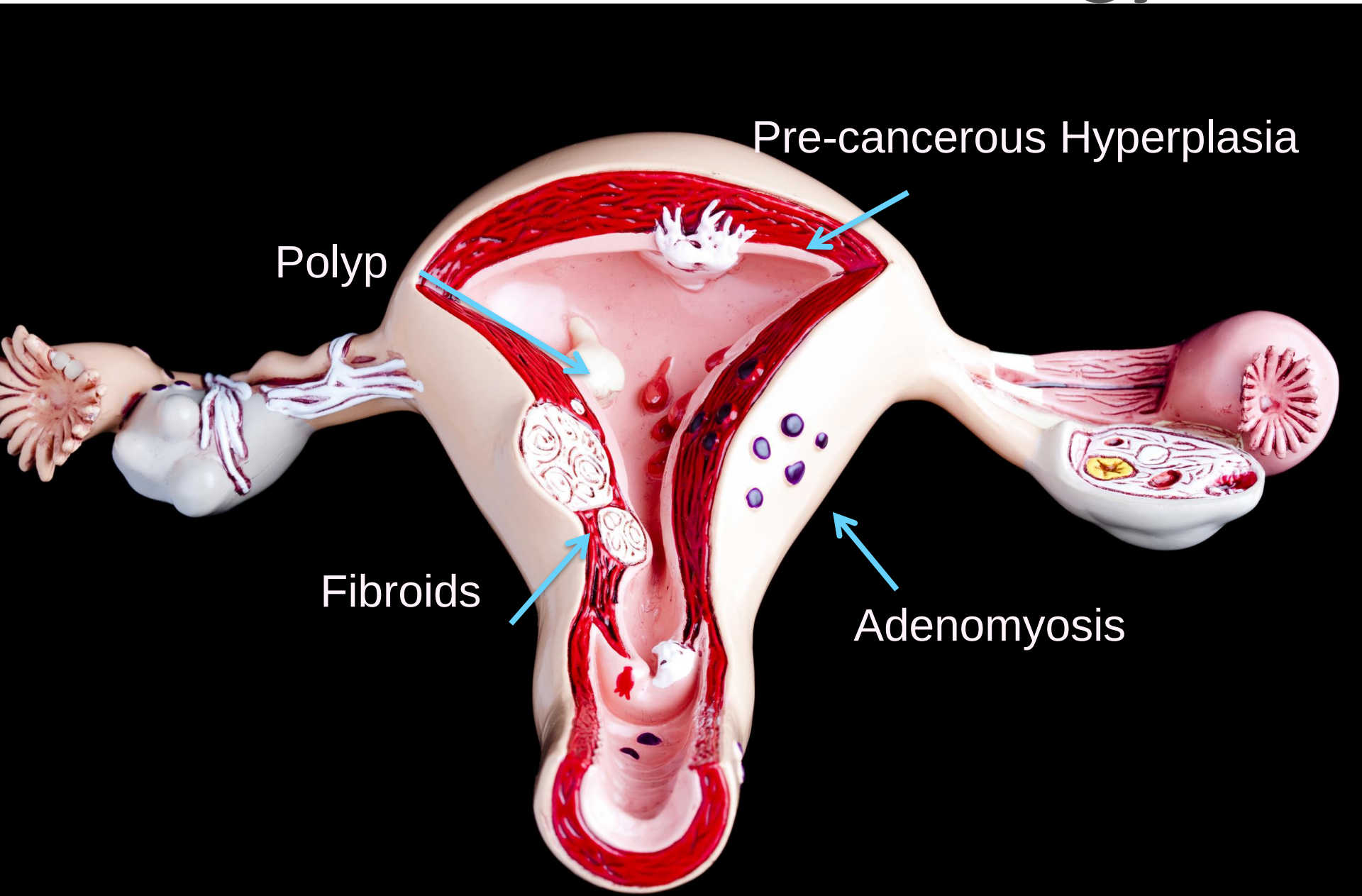
AUB: PALM-COEIN

- **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

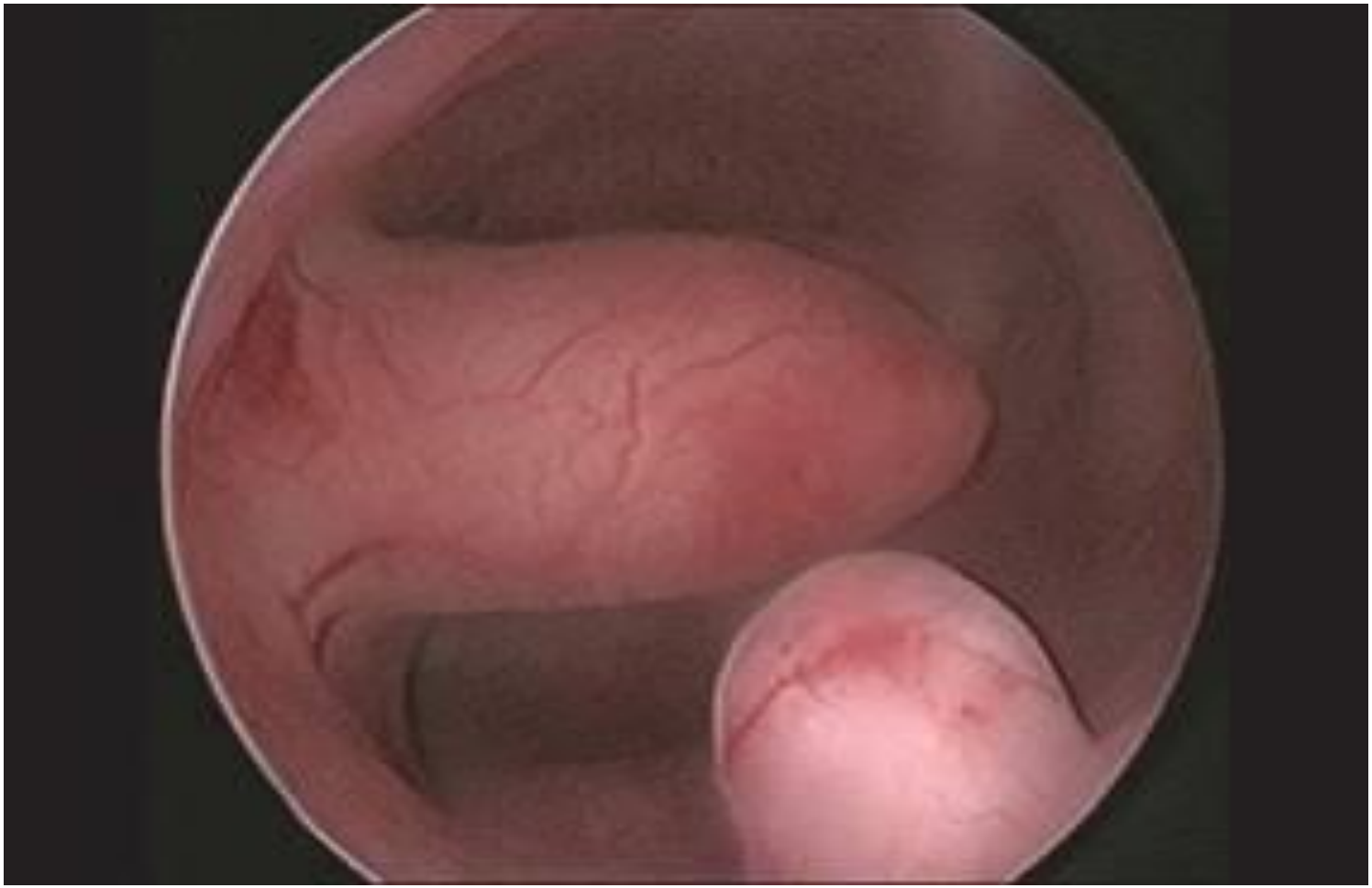
Hysteroscopy

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.

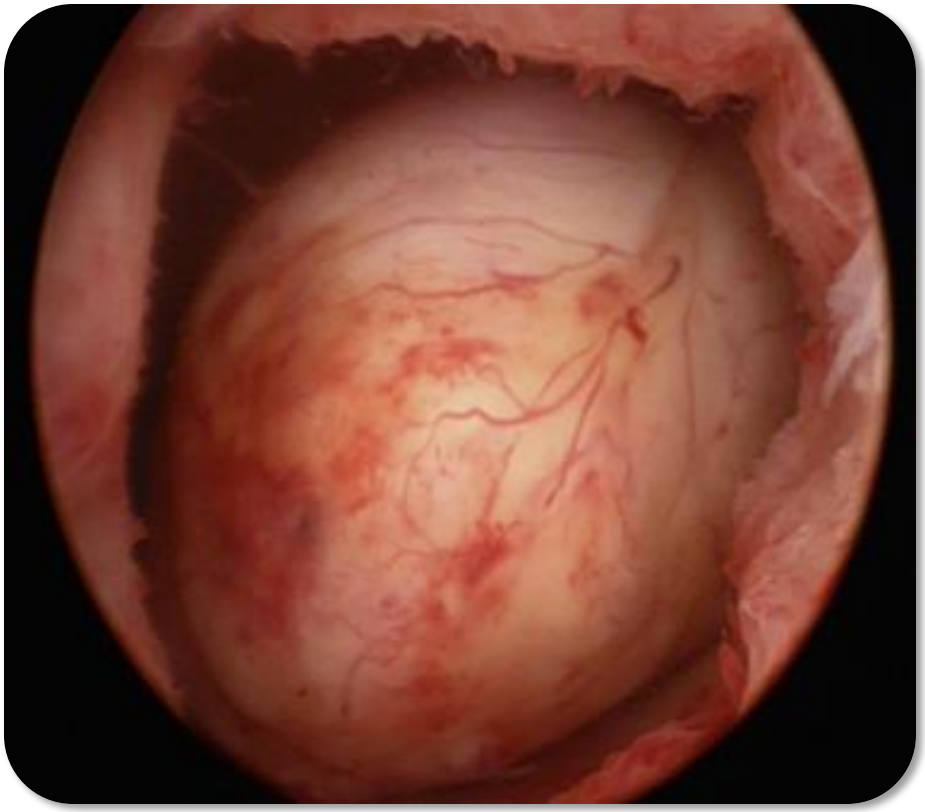
Treating Adenomyosis

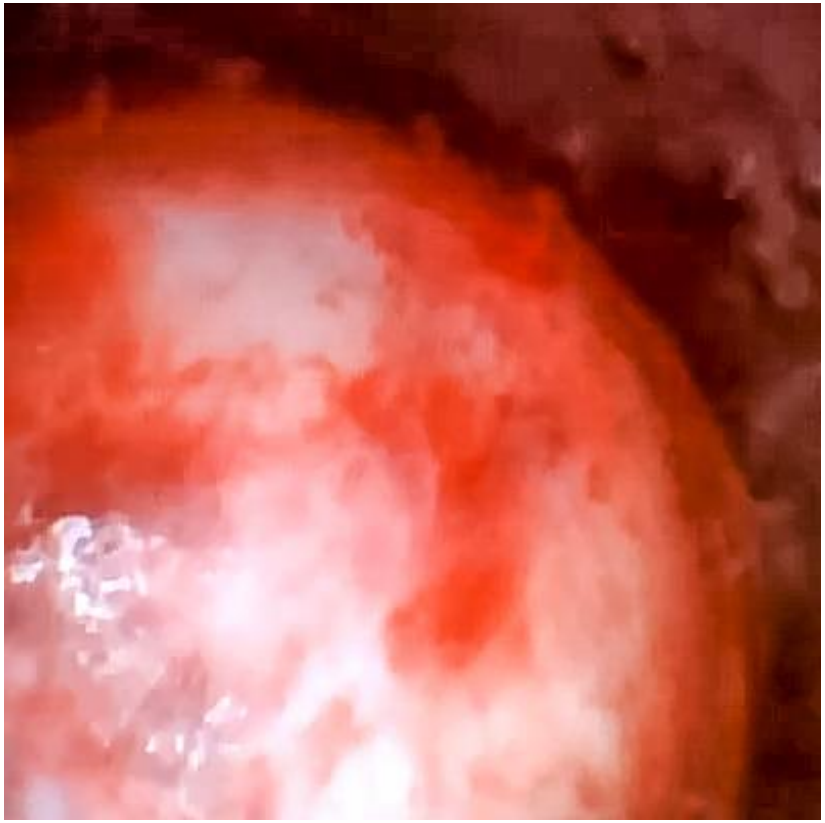
- **Polyps** – Remove via hysteroscopy
- **Adenomyosis**
  - NSAIDs
  - Tranexamic acid
  - Myfembree – to decrease bleeding. A GnRH Antagonist with a combination of Estrogen/Progesterone (off label)
  - Combination Oral Contaceptives
  - Progesterone containing IUDs

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





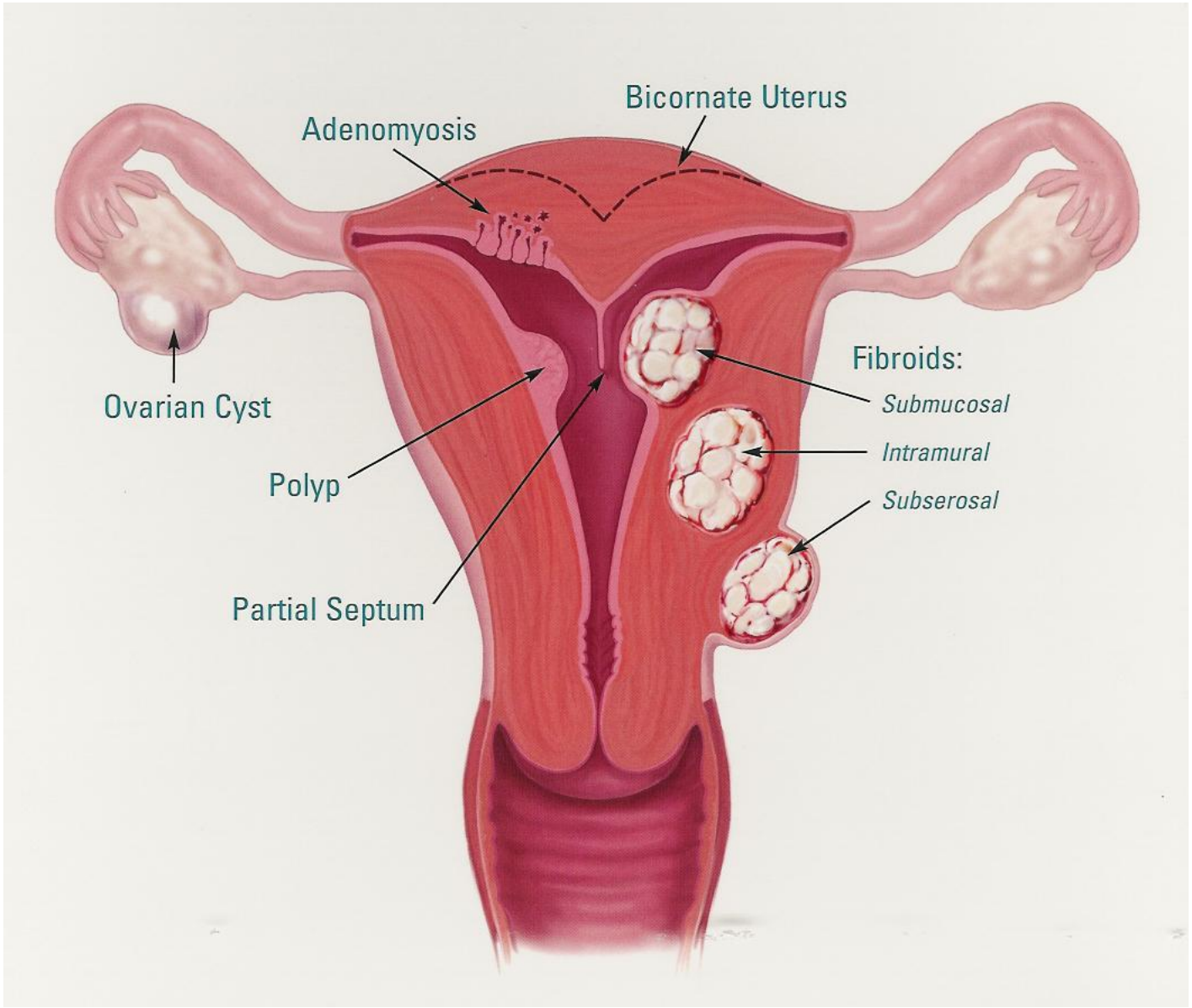


Illustration Purchased from iStockphoto

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

AUB: PALM-COEIN

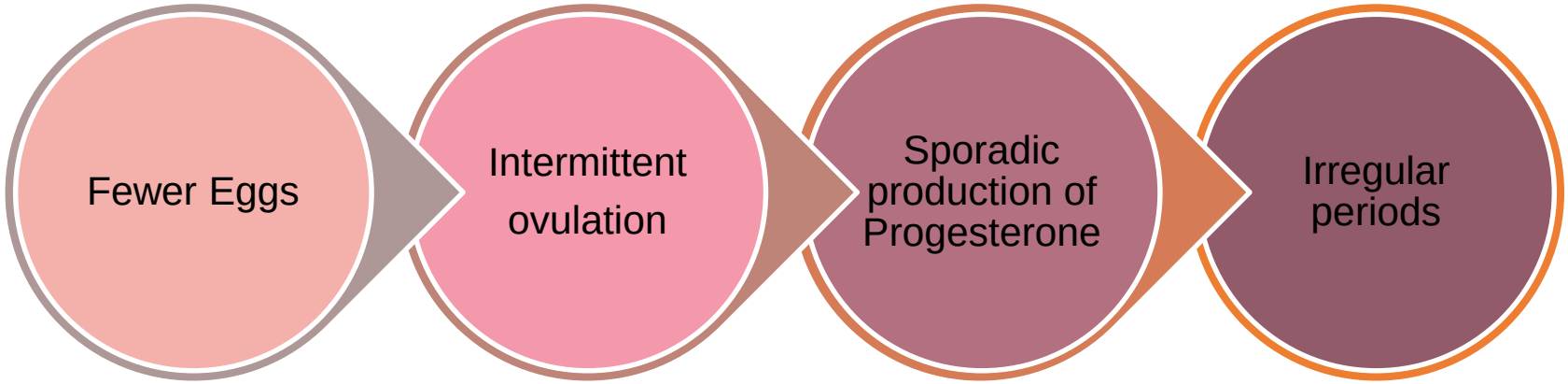
- **PALM - Structural**
- **P** - Polyp
- **A** - Adenomyosis
- **L** - Leiomyoma
- **M** - Malignancy/Hyperplasia

- **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).

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


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.

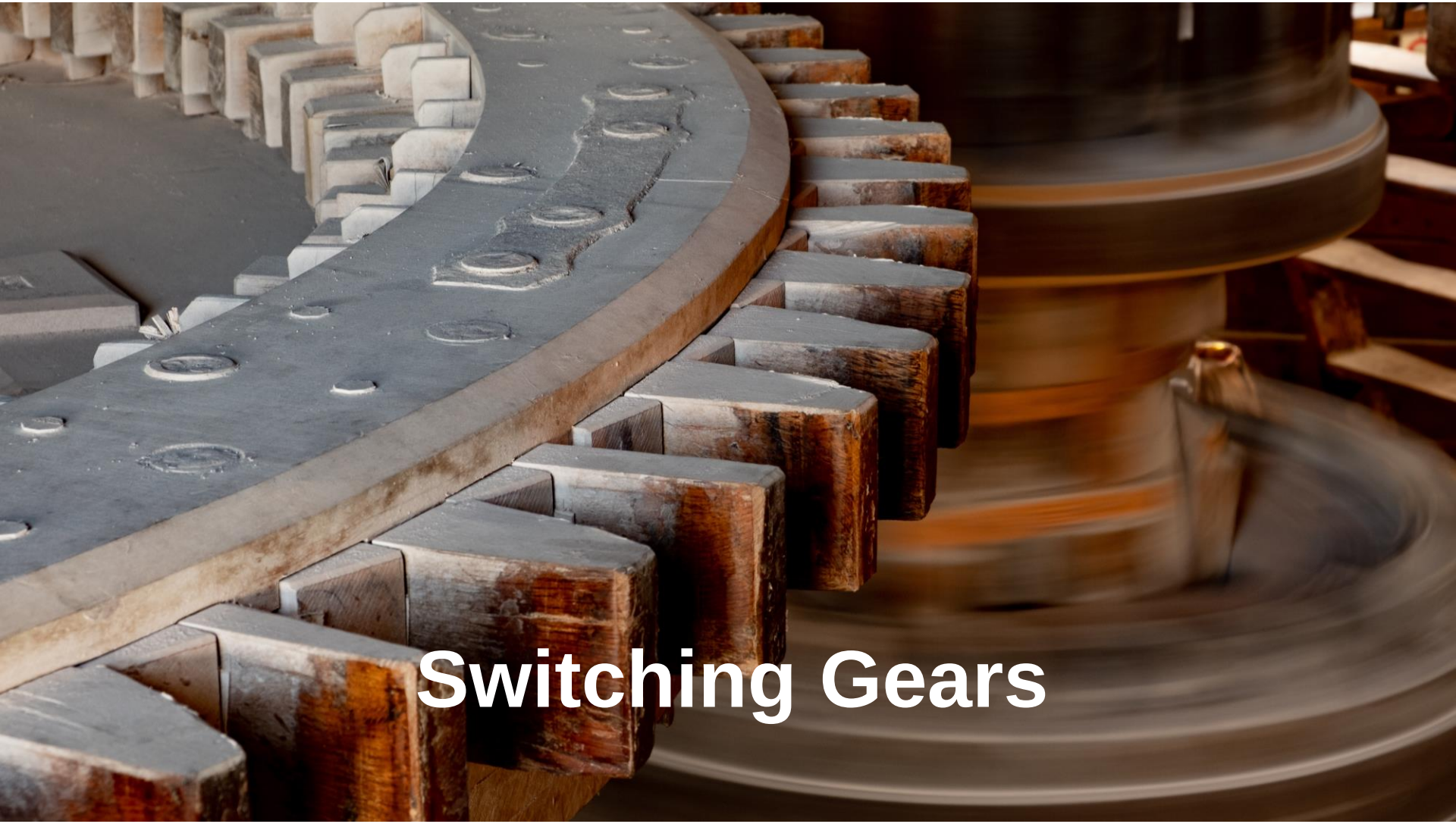
Headache in Midlife Women

- 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


Switching Gears

Menopause Society 2024 Summary

- Use shared decision-making
- Conduct periodic re-evaluation of benefit-risk profile
- Avoid hormones if > 10 years since FMP due to CV risk
- Transdermal routes may decrease risk of VTE and stroke
- Short-term estrogen-progestogen (E + P) use does *not* significantly increase breast cancer risk.
- Risk of breast cancer may be *decreased* with estrogen alone.
- Age 65 or > is *not* a reason to stop

Menopause Society 2024 Summary continued

- New non-hormonal therapy (NK3 Antagonist have been approved by the FDA for VMS
- Consider Oxybutynin, Gabapentin, SSRIs, SNRIs, CBT
- For women with GSM, vaginal estrogen or DHEA *may be used at any age for extended duration*
- Bone loss can be measured with DEXA if risk factors present before 65
- Screen for CV and DM risk
- Progesterone is ***NOT*** needed for vaginal estrogen
- Pelvic Floor Physical Therapy is a mainstay of treatment for incontinence: To locate:
  - APTAPelvicHealth.org (American Physical Therapy Association)

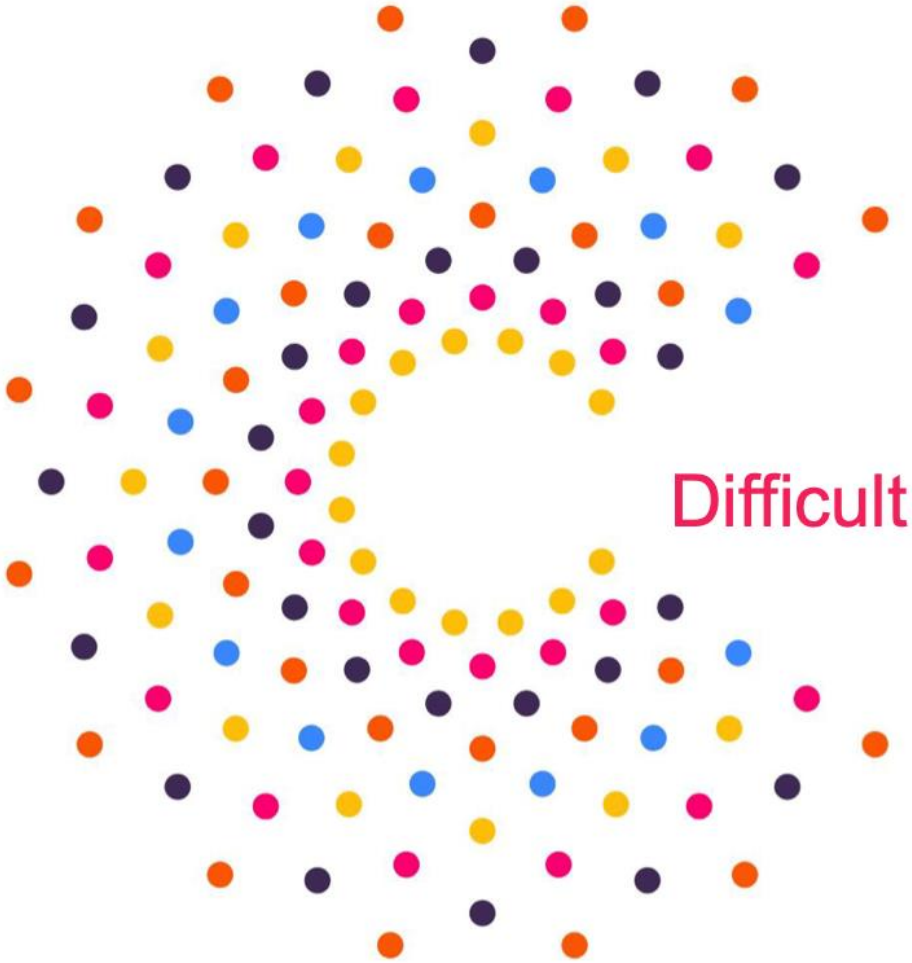
Early, Induced, Surgical Menopause & POI

- Because of estrogen deficiency, there's much higher risks of:
- Early death
- Bone loss
- Heart disease
- Cognitive disorders
- Affective disorders.

Do use Hormone therapy until at least the mean age of menopause unless contraindications present.

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

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

Vague symptoms – Few clinicians link to menopause

- Muscle & Joint aches
- Profound Exhaustion
- Brain fog
- Toilet paper is sticking
- Libido left without waving goodbye
- And so much more….

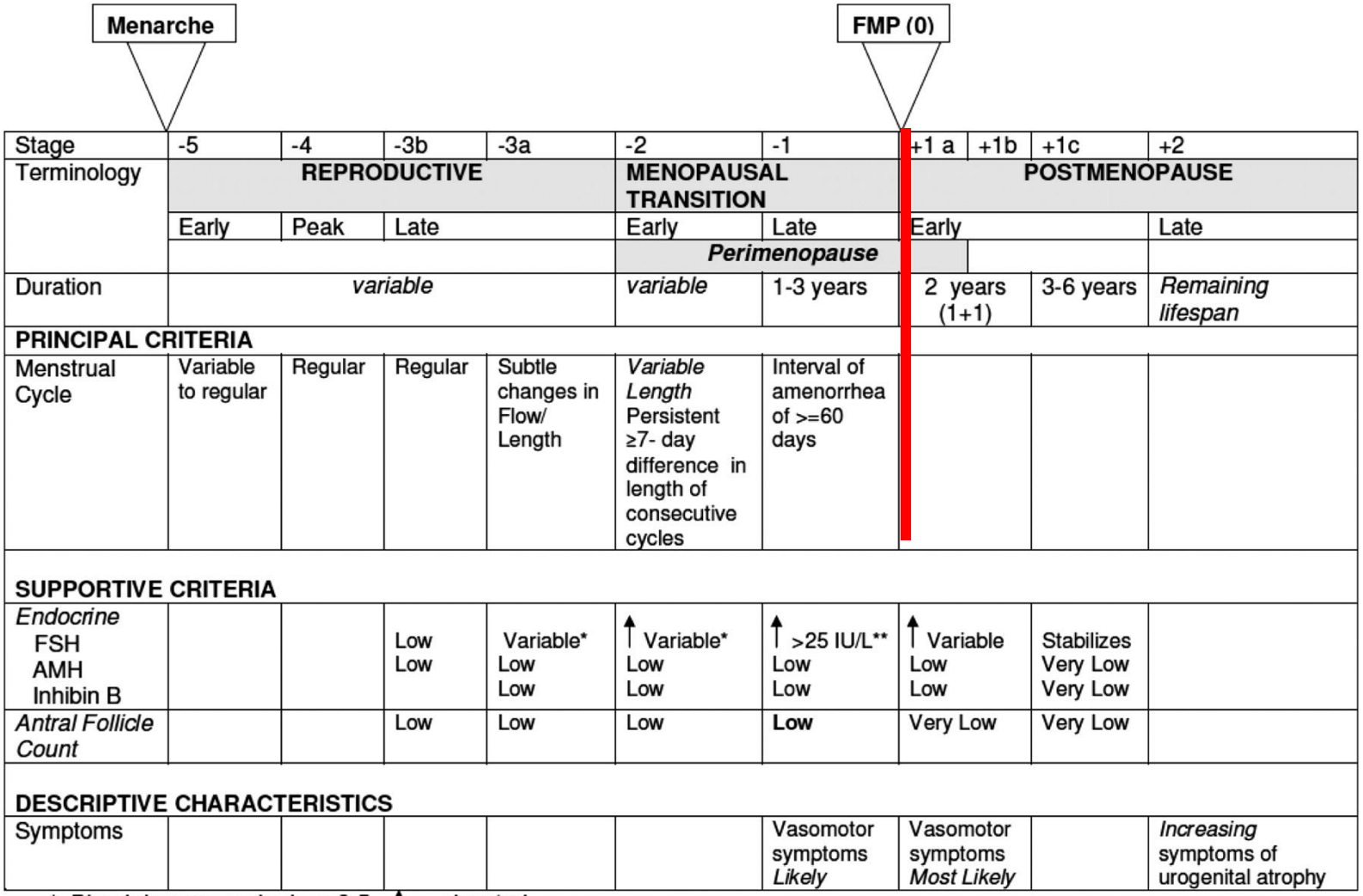
It’s all related to declining Estrogen

Angela: 53, G2P2, Lawyer, cyclist, FMP >14 months ago

- 7+ drenching Night sweats/night
- Hot flashes interrupt work
- Exhausted & Irritable
- Brain fog
- Occasional stress incontinence
- Less sexual satisfaction
- Ruining clothes from sweating

“I don’t feel like myself"

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

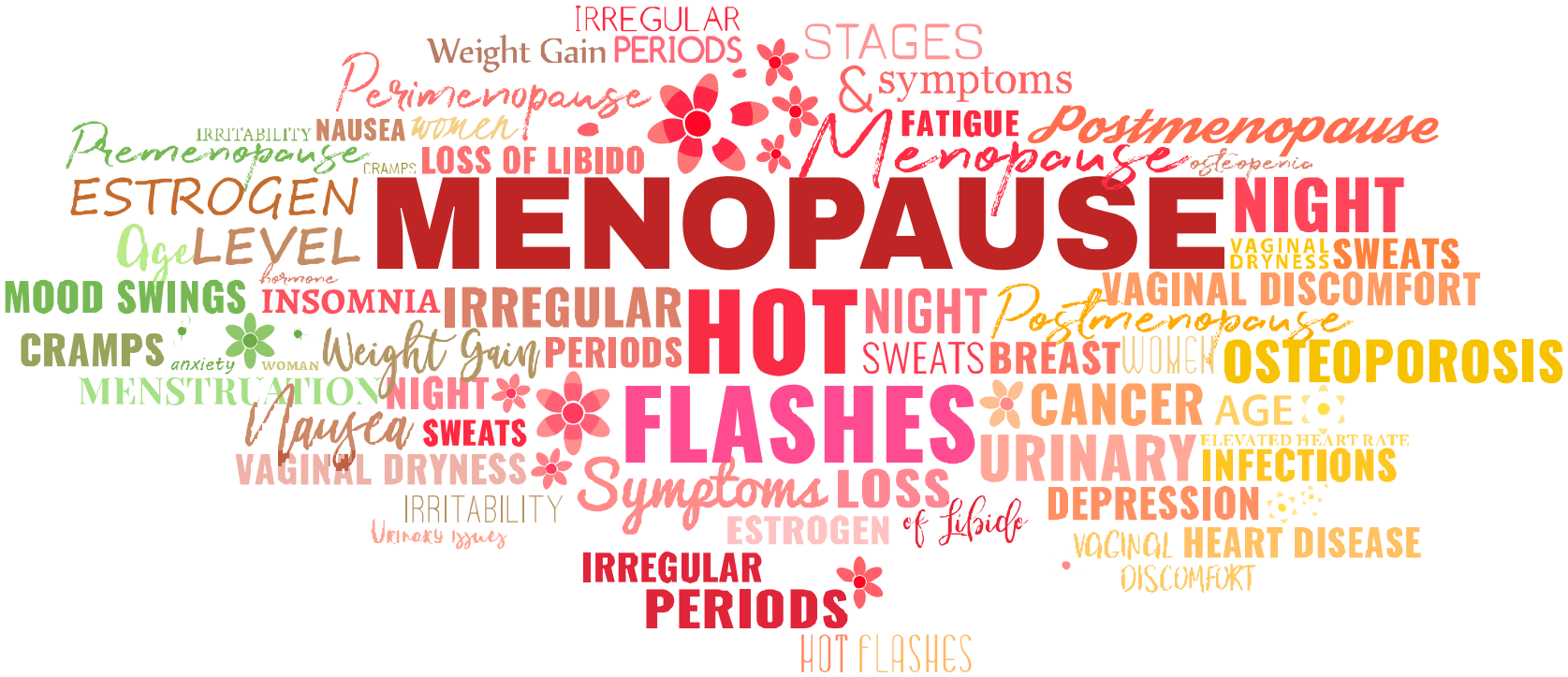
**Approximate expected level based on assays using current international pituitary standard[67-69]

Menopause overview

- Normal & Natural Biologic Event
- Average age: 52
- Final menstrual period (FMP) =

  absence of menses for 12 consecutive months
- Permanent end of fertility
- Estrogen levels decline
- Multiple symptoms

North American Menopause Society, 2024


IRREGULAR
Weight Gain PERIODS
STAGES
& symptoms
Perimenopause
IRRITABILITY NAUSEA women
FATIGUE
Postmenopause
Premenopause
CRAMPS LOSS OF LIBIDO
Menopause
osteopenia
ESTROGEN
MENOPAUSE
NIGHT
Age LEVEL
VAGINAL DRYNESS SWEATS
hormone
MOOD SWINGS
INSOMNIA
IRREGULAR
HOT
NIGHT
Postmenopause
VAGINAL DISCOMFORT
CRAMPS
anxiety
WOMAN
Weight Gain
PERIODS
SWEATS
BREAST
WOMEN
OSTEOPOROSIS
MENSTRUATION
NIGHT
FLASHES
CANCER
AGE
Nausea
SWEATS
URINARY
ELEVATED HEART RATE
INFECTIONS
VAGINAL DRYNESS
Symptoms
LOSS
DEPRESSION
IRRITABILITY
Urinary Issues
ESTROGEN
of Libido
VAGINAL
HEART DISEASE
DISCOMFORT
IRREGULAR
PERIODS
HOT FLASHES

Your Plan

Angela’s chief concern?

Validate and normalize

Questionnaire

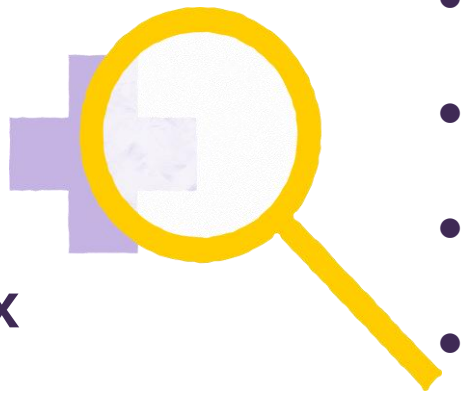
What symptoms might be interrelated?

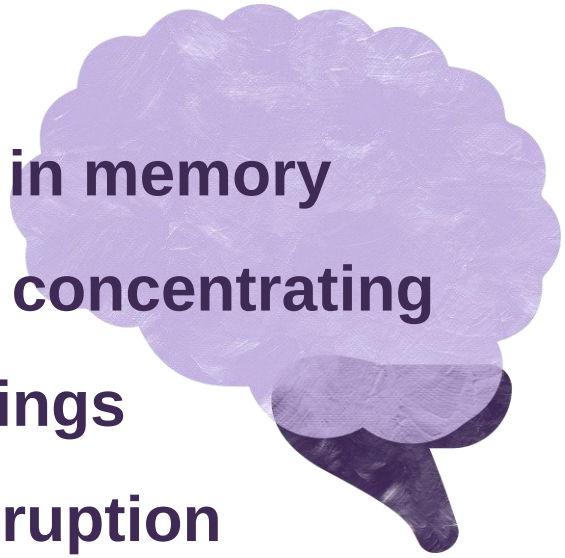
H & P

Labs

Symptoms

- Hot flashes & night sweats
- Fatigue
- Exhaustion
- Muscle & joint aches
- Palpitations
- Itching skin
- Pain with sex
- Low libido
- Bladder symptoms
- Dry mouth/eyes





- Brain fog
- Changes in memory
- Difficulty concentrating
- Mood swings
- Sleep disruption
- Irritability
- Anxiety & depression
- Having little interest in activities

There is no 1 universal menopausal syndrome

- 80% of women: Vasomotor symptoms = HF & NS
- 60% Vulvovaginal symptoms, dyspareunia, low libido
- 80% Sleep disturbances
- 65% Cognitive concerns (memory, concentration)
- 31% Psychological symptoms (depression, anxiety, moodiness)
- Bone Loss – 20% loss in first 7 years

North American Menopause Society, 2024

SWAN: Study of Women's health Across the Nation

SWAN is a multi-site longitudinal, epidemiologic study in the US designed to examine the health of women at midlife[1].

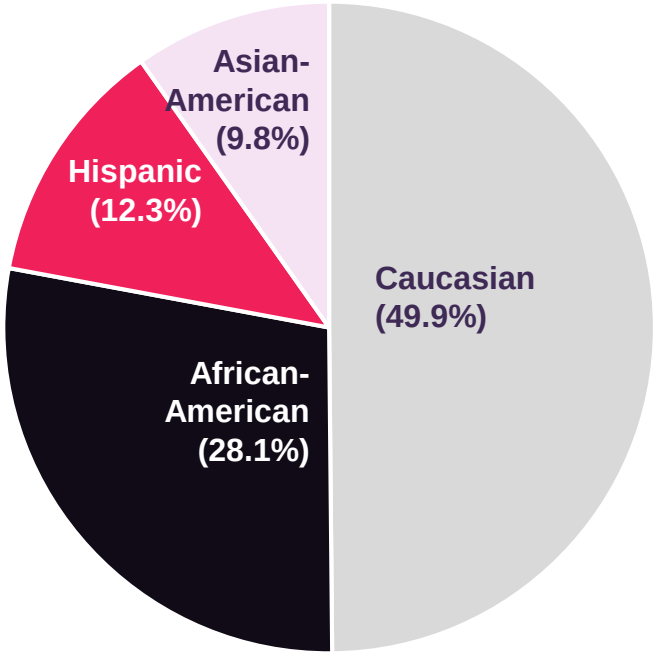
Cross-sectional survey >15,000 women of various ethnicities about their menopausal symptoms[1,2].

SWAN was designed in 1994 and included long term follow-up on participants.

Analysis of data from SWAN has shown that ethnic background influences a woman's perception of her symptoms.

N=15,160 women aged 42-52

SWAN survey demographics



Green, R, & Santoro, N., Women's Health, 2009.

Relationship of ethnicity and common menopausal symptoms

shown as % women experiencing that symptom or Odds Ratio (vs Caucasian)

	Most (%)	Least (%)
Early / premature menopause (cessation of menstruation before age of 40 / 45)	Hispanic (3.7)	Japanese (0.8)
Vasomotor Symptoms (hot flashes and/or night sweats)	African-American* (46.5)[3]	Chinese (28.9)[3]
Vaginal Symptoms	Hispanic (17.9-58.6)	Caucasian (21.2)ǂ
Depressive Symptoms	Japanese (OR: 1.39, 95% CI: 0.93-2.17, vs Caucasian)	Chinese (OR: 0.5, 95% CI: 0.33-0.79, vs Caucasian)
Trouble Falling Asleep	Hispanic (14.4)	Japanese (6.5)

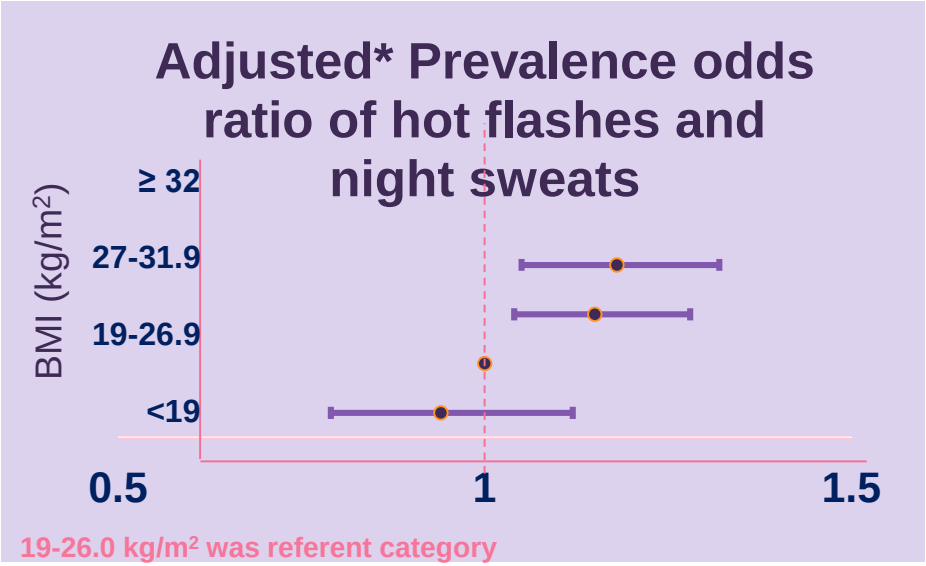
*Hispanic women reported more embarrassment or discomfort associated with hot flashes

ǂOther ethnic groups not compared

Green R. & Santoro, N., Women's Health 2009.

Relationship of BMI and VMS

Subset of SWAN 4,324
Is there a relationship between BMI and hot flashes and night sweats.



Higher BMI is associated with higher prevalence of night sweats and hot flashes in women with BMI ≥27 compared to 19-26.9 kg/m^2 (or less)

Gold, et al., Am J Epidemiol, 2000

*adjusted for smoking, physical activity, age, education, race ethnicity, marital status, menstrual status, parity, employed, difficulty paying for basics;, and participating site

What does she need next?

Shared Decision Making

Education

Discuss her goals and concerns

Review treatment options

Help her get more sleep

Causes of sleeplessness

- Night sweats typically occur in first half of night
- Advancing age early awakening more common
- Sleep disorders
  - 53% have sleep apnea, restless legs, or both
- Stress/depression
- Pain: muscle aches, joint pain, arthritis
- Other conditions: GERD, SOB, CVD, allergies
- Medications

Tandon VR, et al. J Midlife Health. 2022

A Cascade Effect

Night sweats

Interrupted sleep

Fatigue

Irritability, mood changes

Kronenberg, F. *Ann NY Acad Sci*. 1990.

Sleep Disturbances associated with reduced Estrogen

- Many Women have sleep complaints at menopause[1]
- Estrogen *ALONE* improves women's subjective reports of sleep quality, even when there are NO menopausal symptoms[2]
- Compared with nonusers of estrogen, women who *DO* use estrogen, they report increased REM sleep, and reduced time awake

1. Baker, F. C. et al. Sleep Medicine Clinics, 2018.
2. Polo-Kantola, P. et al. Am J Obstet Gynecol, 1998.

Sleep Fragmentation

VMS Induced

Sleep Cycle

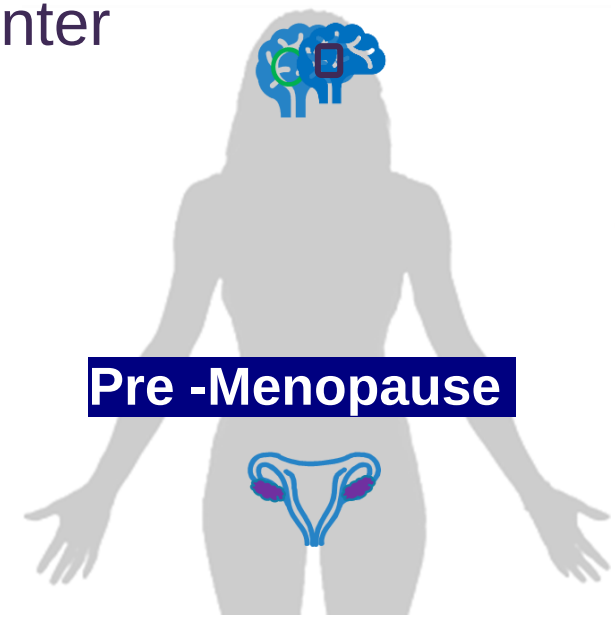
Disruptions

- While asleep – Multiple mini-awakenings
  - Fragmented sleep cycles
- 2-10 times as often as becoming fully alert
- Moving out of Delta Wave sleep multiple times into lighter sleep
- Leads to reductions in total restorative sleep

Joffe H, et al. *Menopause,* 2013.

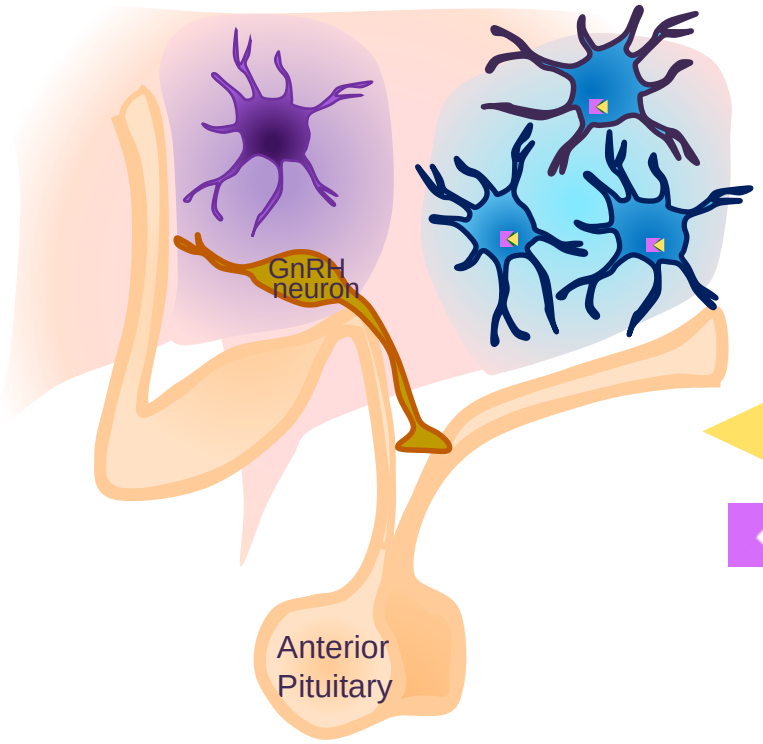
Thermoregulation Pre-Menopause

Estrogen sensitive KNDy neurons are located adjacent to the thermoregulatory center



Thermoregulatory neuron (Median Preoptic Nucleus)

Infundibular Nucleus



KNDy Neurons
Kisspeptin
Neurokinin
Dynorphin

Estrogen

Estrogen Receptor (ER)

Adapted from, Christ et al., JAMA. 2023

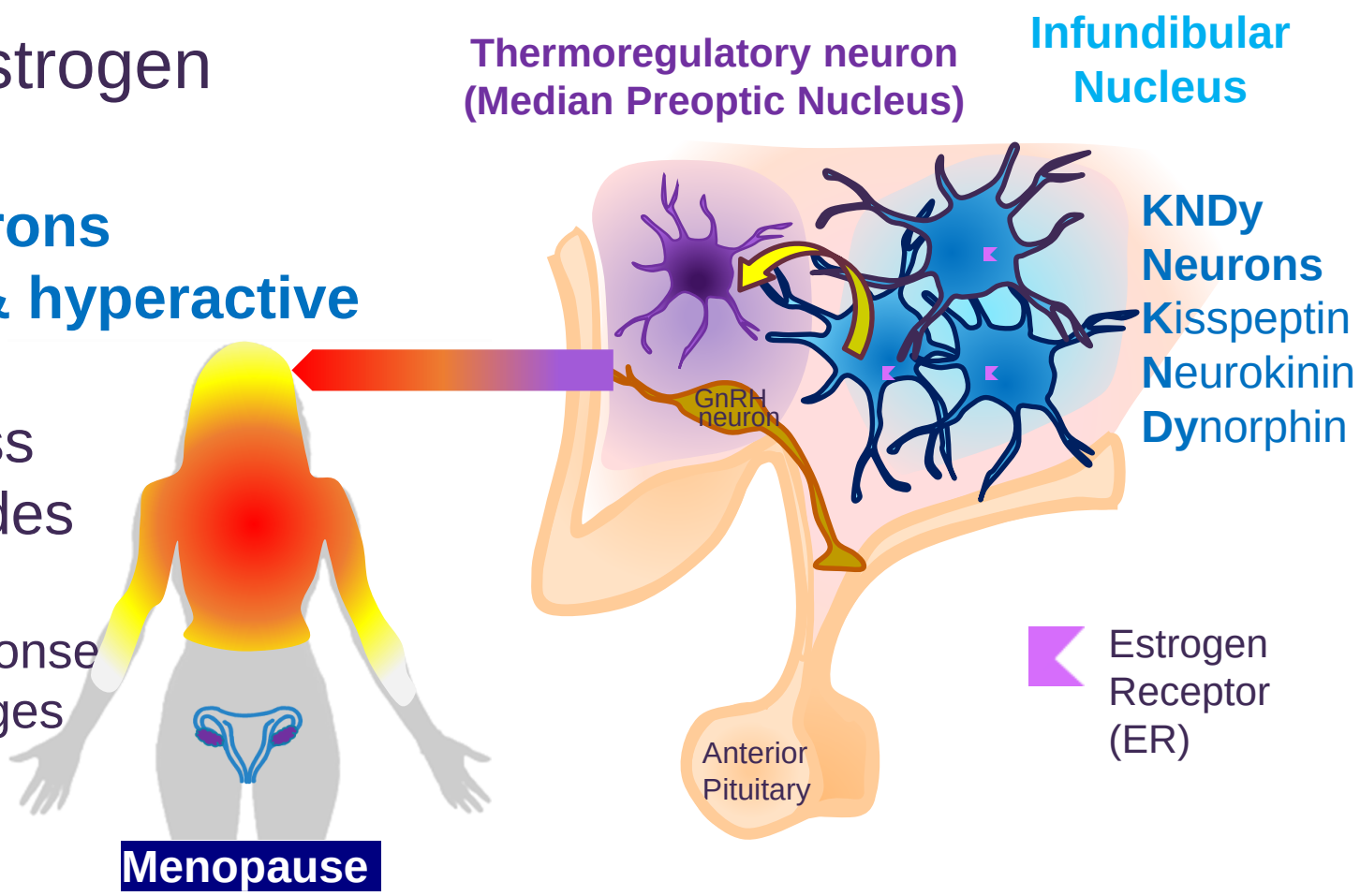
Thermoregulation Menopause

Loss of estrogen

KNDy neurons
Enlarged & hyperactive

Overexpress neuropeptides

Extreme response to temp changes



Adapted from, Christ et al., JAMA. 2023

Sleep Fragmentation – Additive

1

Fully Awake and Alert

Going to bathroom

Difficulty returning to sleep

2

Many mini-awakenings

Hours in bed “asleep”

Thurston RC, et al. *Menopause*. 2012

Waking up exhausted

- Changes in Mood
  - Irritability
  - Depression
  - Anxiety
  - Lack of Motivation
- Changes in Memory
- Reduced Attention
- Brain Fog and Fuzziness

White Matter Hyperintensities

- VMS, particularly VMS occurring during sleep, were associated with *greater*

  White Matter Hypersensitivities
- Identification of female-specific midlife markers of poor brain health later in life is critical to identify women who warrant early intervention and prevention
- VMS has long term implications for brain health

Thurston R.C., et al. Neurology. 2023

What does she need next?

Shared Decision Making

Education ✓

Discuss her goals and concerns ✓

Review treatment options

Help her get more sleep

Reduce incontinence

Improve Sexuality

Treating sleep problems

- **Treat Night sweats**
  - Down stream benefits to mood, cognition, energy
- Essential to do a complete evaluation
- Complex condition
- Sleep specialist instead of Sleep study
- Multi-disciplinary approach
  - CPAP not helpful if in the closet
  - CBT, mindfulness, treating anxiety
  - Avoid Addictive medication

VMS Treatment Options

Recommended
Supported by Clinical Evidence[1,2]

Level I:

- Hormone Therapy
- SSRI/SNRIs
- Gabapentin
- Fezolinetant
- Clinical hypnosis, CBT

Level I/II: Oxybutynin

Level II/III: Weight loss
Stellate ganglion block

Not Recommended[1]

Lifestyle: Cooling techniques, Avoiding triggers, Exercise, Yoga; Diet changes

Mind Body Techniques: Mindfulness. Paced respiration

Prescription Therapies: Pregabalin, clonidine, suvorexant

Supplements: Black cohosh, all supplements, soy foods & extracts, soy metabolite S- equol, cannabinoids

Acupuncture & chiropractic interventions

Level I: good and consistent scientific evidence;
Level II: limited or inconsistent scientific evidence
Level III: consensus and expert opinion.

[1] Menopause. 2023 Jun 1;30(6):573-590 [2] Menopause. 2022 Jul 1;29(7):767-794

Considerations for Hormones

- All Estrogens and Progestogens are NOT created equal
- Estrogen alone is associated with a decreased risk of breast cancer
- Bio-identical hormones ARE available in FDA-approved formulations
- Hormone testing is rarely needed
- Compounded and Pellet hormones have ZERO regulation and are not recommended
- Use what's on formulary unless GoodRx or other pharmacy can provide better pricing

Breast Cancer and HT

- On-going research has shown that estrogen-alone is *not* associated with an increased risk of breast cancer.
- Micronized progesterone is preferred over a synthetic progestin.

IF there is a risk with estrogen

it is equal to women who:

- have 2 or more drinks/day

- do not get at least 3 hours of exercise/week

Considerations for Hormones

- Systemic hormones treat the entire body
    - Alleviate hot flashes and night sweats
    - Improve sleep – improve QOL
    - Prevents bone loss
- Women with their Uterus *must also* take a progestin to protect the endometrium
- Transdermal preparations have no risk of VTE
- Bijuva is the only oral E + P preparation with no risk of VTE

Systemic Hormones

- Both Estrogen Treatment (ET) and Estrogen Progestin Treatment (EPT) may reduce total mortality by 30% when initiated in women younger than age 60
  - Reduction in osteoporotic fracture
  - Reduction in vasomotor symptoms
  - Improvement in quality of life
  - Reduction in musculoskeletal pain

NAMS position statement. *Menopause* 2017.

Systemic Estrogens

Oral Estrogens:

17β-estradiol
Conjugated estrogens Synthetic conjugated estrogens
Esterified estrogens
Estropipate

Transdermal Gel:

17β-estradiol

Transdermal Patch

17β-estradiol

Transdermal Spray:

17β-estradiol

Vaginal Ring:

Estradiol acetate

Progestogen Regimens

- Progesterone can *NOT* be absorbed through skin
- LNG-IUS – 52 mg Progesterone containing IUD (off label)
- Oral medications
  - Prometrium = Bio Identical
  - Provera = Medroxyprogesterone Acetate
  - Aygestin = Norethindrone – less BTB

Symptom Recurrence & HT Discontinuance

- 50% chance of vasomotor symptoms recurring when HT discontinued
- Decision to continue HT must be individualized
- Symptom recurrence similar whether tapered or abruptly discontinued
- Data conflicting regarding breast cancer incidence after discontinuance

Start: Woman with Uterus

- **Bio-identical E + P**
  - Transdermal Estrogen patch, spray or gel
    various dosages and timing
  - Oral Micronized Progesterone (*Prometrium*)
    (100 – 200 mg). Less BTB with 200 mg
- Bijuva – Oral 2 doses: 0.5 mg or 1.0 mg Estradiol/100 mg micronized progesterone

- **Natural E +P**
  - Oral CEE/MPA (*Prempro*) various dosages

- **Natural E + SERM**
  - Oral CEE/Bazedoxifene (*Duavee*) has the lowest incidence of BTB

Contraindications to Hormones

- Known, suspected, or history of breast cancer
- Known or suspected history of other estrogen-based cancer (ie, uterine cancer)
- Active deep venous thrombosis (DVT) or a history of DVT or pulmonary embolism
- History of blood clotting disorder, the most common being Factor V Leiden mutation carriers
- Active or history of arterial thrombotic diseases (eg, myocardial infarction or stroke)
- Chronic liver disease or dysfunction
- Migraine with aura

NK3 receptor Antagonist – Fezolinetant (*Veozah*)

- Works directly at the level of the hypothalamus to inhibit the uptake of Neurokinin 3, a neuropeptide associated with thermoregulation
- Part of the KNDy neurons
- These neurons are overexpressed when Estrogen declines and lead to temperature dysregulation and VMS
- 80% reduction in HF and NS within 2 weeks
- Hormone Free
- Check LFTs prior to initiation, and at 3,6 & 9 months

NK3 receptor Antagonist – Fezolinetant (*Veozah*)

- Check LFTs prior to initiation, and at 3, 6 & 9 months due to rare occurrence of ALT elevations in the clinical trials
- Contraindicated in:
  - Known cirrhosis
  - Severe renal impairment or end-stage renal disease
  - Concomitant use with CYP1A2 inhibitors

Other Prescription Therapies

- Gabapentin 300 – 900 mg at hs (titrate dose)
- 50% reduction in HF & NS
  - Many adverse side effects – somnolence, dizziness

- Oxybutynin – 2.5 – 5.0 mg 1, 2, or 3 times/day
- 80% reduction in HF and NS
  - Also helps with OAB
  - Many adverse side effects – somnolence, dizziness,
  - Many Drug to drug interactions
  - Do NOT use in pts with narrow angle glaucoma

Other Prescription Therapies

- SSRI/SNRIs
- May work by increasing serotonin & by decreasing sympathetic response
  - 60% reduction in HF and NS
  - Improved sleep quality and other QOL
  - No sexual side effects or weight gain
- Venlafaxine & Desvenlafaxine – (*Effexor & Pristiq*)
- Paroxetine Mesylate (*Brisdelle*) – only FDA approved SSRI
  - Molecule, dose & side effects different from Paroxetine Hydrochloride (*Paxil*)

Estrogen and Serotonins

- E2 increases the production of tryptophan – the precursor to serotonin
- E2 increases the amount of time serotonin stays in the synapse
- E2 Increases density, distribution of serotonin receptors
- E2 increases serotonin transporter sites

What does she need next?

Shared Decision Making

Education ✓

Discuss her goals and concerns ✓

Review treatment options ✓

Help her get more sleep 🛏 ✓

Reduce incontinence

Improve Sexuality

GSM
GenitoUrinary Syndrome of Menopause

Vulvar, Vaginal & Urinary symptoms

Does This Look Familiar?

Things feel different

- Toilet paper sticking
- Irritated & itching
- Pain with sex
- Less natural lubrication
- Leaking urine
- Sense of urgency

75% of your patients
Starts in the 40’s

It feels like this

- Less estrogen
- Tissue shrinks
- Less ability to widen and stretch

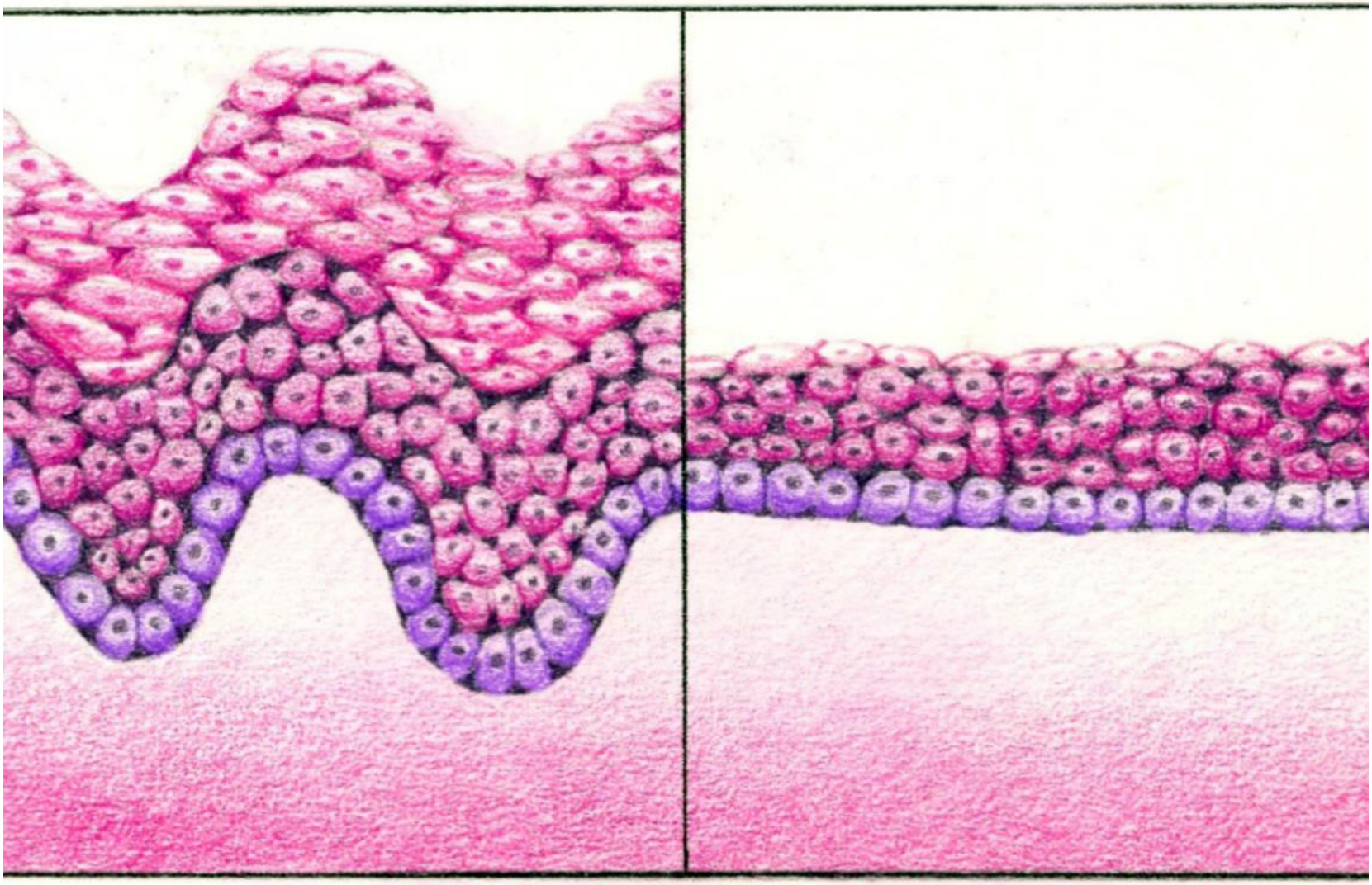
This does NOT improve on its own

GSM

- Physiology:
  - Early stages associated with thin dry, erythematous vaginal epithelium
  - Later, loss of labial fat pad, labia majora pendulous, labia minora less distinct
  - Prepuce covering clitoris decreases, clitoris may appear larger
  - Tissues of vulva become pallid, thin, dry
  - Increased tenderness of vestibule

Well-estrogenized
Premenopausal State

Low-estrogen
Postmenopausal State



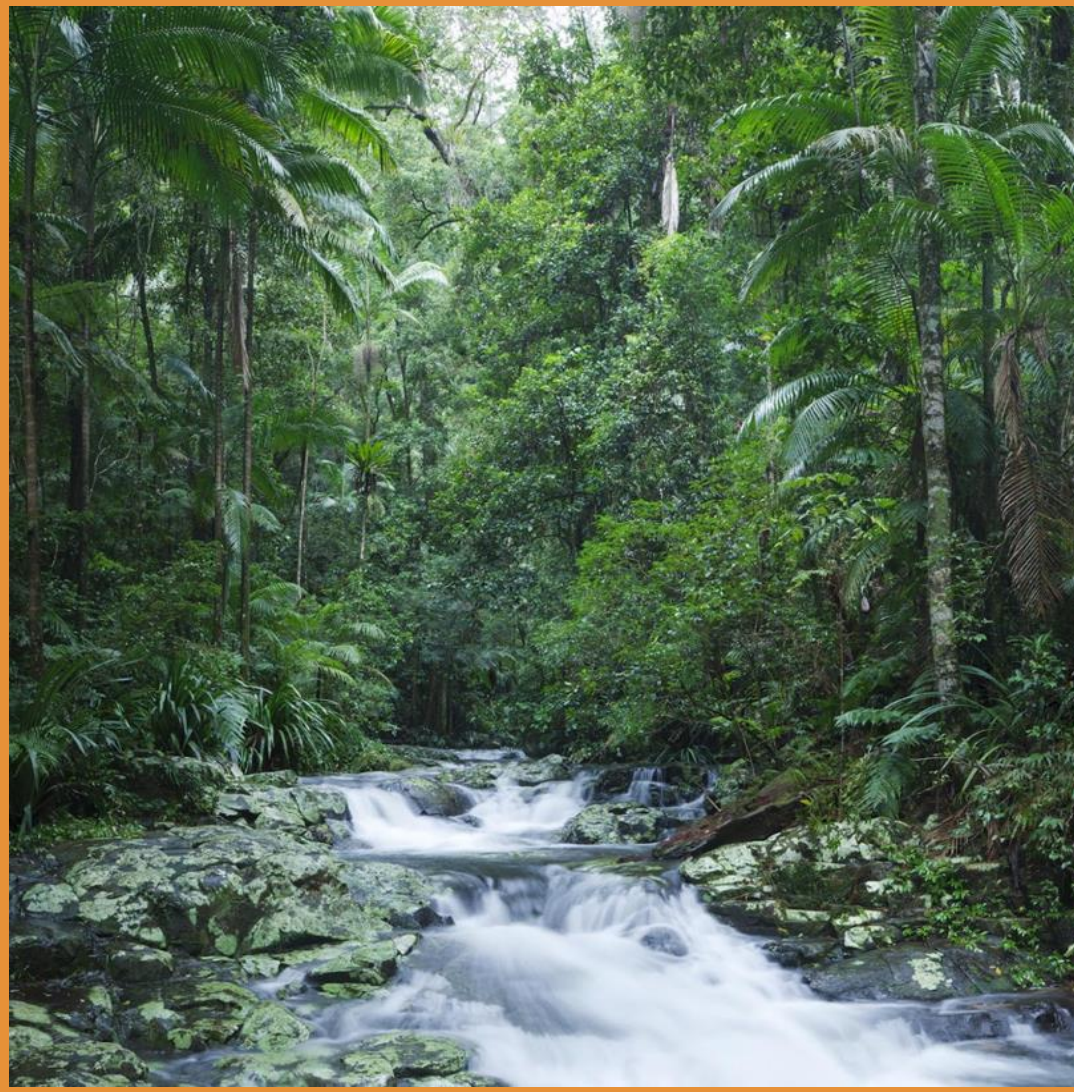
Courtesy of the Graphic Courtesy Dr. Diane Todd Pace NP from the North American Menopause Society

Loss of Estrogen

- Vagina loses elasticity, shortens, narrows, easily traumatized and irritated
- Loss of rugae, fornices become obliterated, cervix flush with vaginal vault
- Petechiae may be present
- pH greater than 5.0, parabasal cells dominate
- Repopulation with diverse vaginal flora leads to frequent UTIs
- Worse for women on chemo (tamoxifen, AIs)

The goal

- More moisture
- Improve aginal health
- Restore the vaginal biome
- Reduce all symptoms



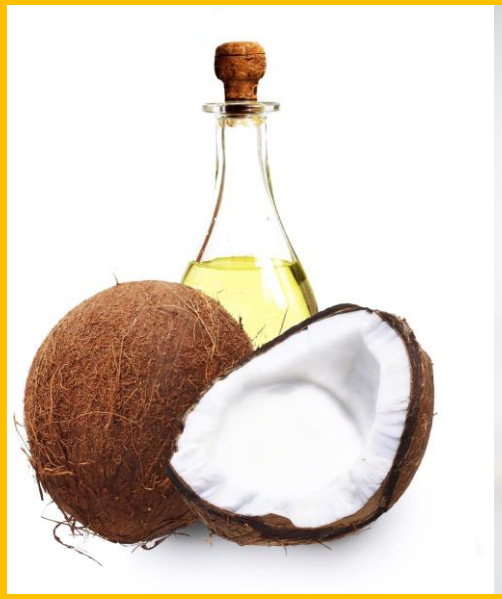
Vaginal moisturizers

- Hormone-free
- Attracts 60 times more moisture
- Best have hyaluronic acid
- These are NOT lubricants
- Ongoing treatment
- Use twice/week

Don’t stop or dryness returns

Lubricants:

Oil-based
Water-based
Silicone
Hybrid



Consider vaginal hormones

- Vaginal estrogen or DHEA
- Increases natural lubrication
- Reduces or eliminates pain with sex
- Helps restore the vaginal biome
- Helps reduce urinary symptoms
- Helps restore collagen to urethra and pelvic floor muscles

No risk of breast cancer

Vaginal hormones

Stays in the pelvis — localized
Healthier vaginal tissue within 2 weeks
Dyspareunia improves

ACOG now recommends for Breast Cancer survivors

Available as:

- Creams: apply externally and inside vagina
- Capsules and tablets: insert vaginally
- Vaginal ring: change every 90 days

Ospemifene – (*Osphena*)

- Selective Estrogen Receptor Modulator (SERM) taken orally q day to reduce dyspareunia
- The estrogen like effects in the vagina are unique from other SERMS
  - Increases vaginal epithelial cells, decrease in parabasal cells, improves vaginal maturation index and decreases pH
  - Does not stimulate the endometrium
  - Similar to tamoxifen, seems to be anti-estrogenic in breast, more studies needed

Soe, et al. International Journal of Women's Health, 2013.

Pelvic Floor PT & Bladder Diary

- Bladder diary
- Bladder retraining
- Pelvic Floor PT is much more effective with vaginal estrogen
- At home exercisors


Our Sexuality

Flying Solo or Partnered

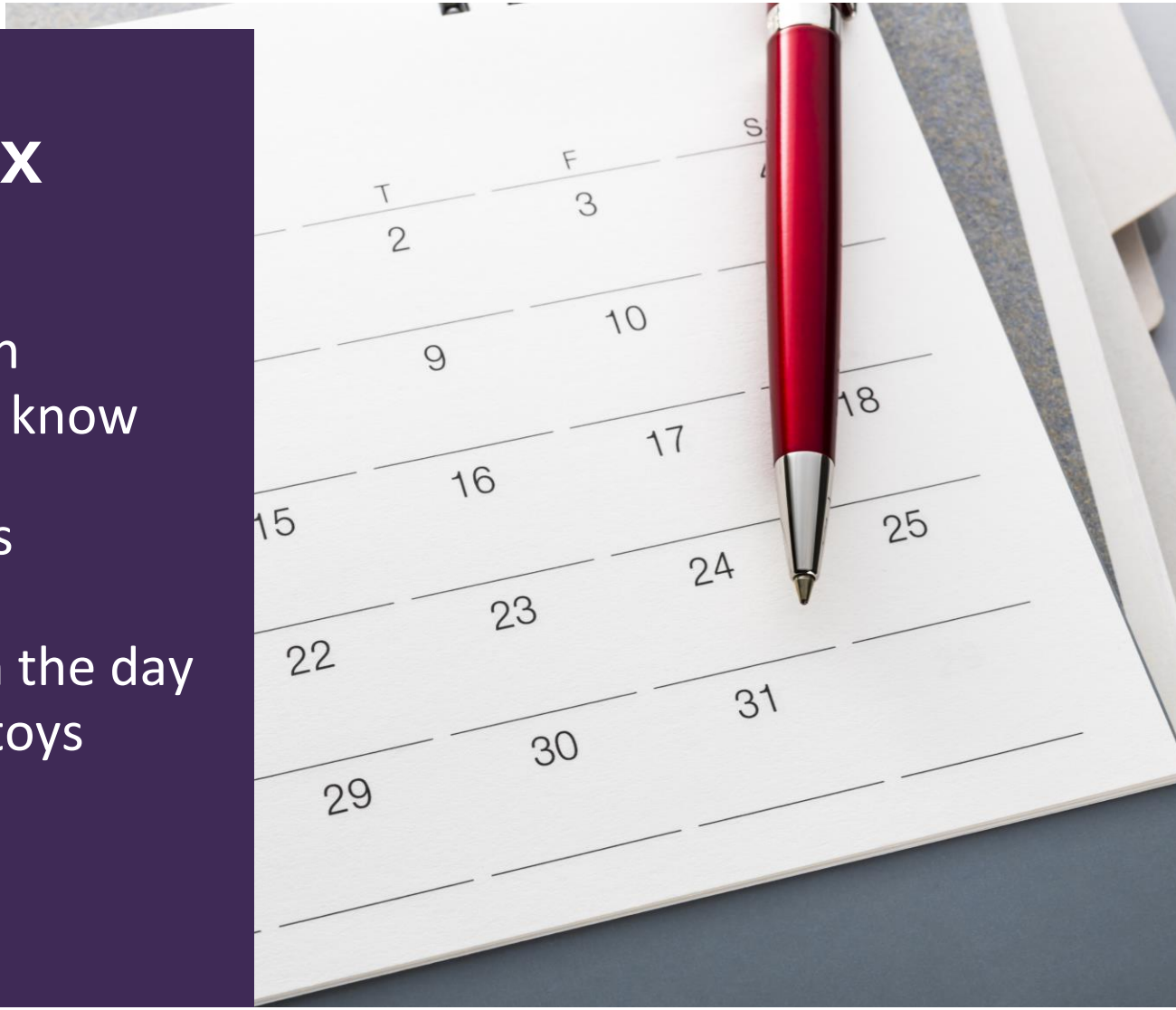
Changes in

- Our bodies/hormones
- Sex Drive
- Sexual response
- Our health/medications
- Relationships
- Stressors


Clitoral Stimulators
Warming lubricants
Vibrators
Zestra gel
Ristela

Calendar Sex

- Increase anticipation
- Helps both partners know what to expect
- Reduces distractions
- Set the mood
- Text or sext through the day
- Have lubricant and toys ready



Many couples are looking for ways to reconnect

- Drs John and Julie Gottman
- Small things often
- Gratitude for the little things
- Rituals of connection

Gottman.com

What does she need next?

Shared Decision Making

Education ✓

Discuss her goals and concerns ✓

Review treatment options ✓

Help her get more sleep 🛏 ✓

Reduce incontinence ✓

Improve Sexuality ✓

Thank You

Barb Dehn WHNP-BC, MSCP, FAANP

Iowa NP Conference

@NurseBarbDehn

Questions

References

- Baker FC, Lampio L, Saaresranta T, Polo-Kantola P. Sleep and Sleep Disorders in the Menopausal Transition. Sleep Med Clin. 2018 Sep;13(3):443-456. doi: 10.1016/j.jsmc.2018.04.011. PMID: 30098758; PMCID: PMC6092036.
- Caufriez, A *et al.* Progesterone Prevents Sleep Disturbances and Modulates GH, TSH, and Melatonin Secretion in Postmenopausal Women *Clin Endocrinol Metab* 2011;96:E614-23.
- Christ JP, Navarro VM, Reed SD. Nonhormonal Therapies for Menopausal Vasomotor Symptoms. JAMA. 2023 Oct 3;330(13):1278-1279. doi: 10.1001/jama.2023.15965. PMID: 37713186.
- Geller, S. E., & Studee, L. (2005). Botanical and Dietary Supplements for Menopausal Symptoms: What Works, What Doesn't. *Journal of Women's Health (2002)*, *14*(7), 634–649.
- Gold EB, Sternfeld B, Kelsey JL, Brown C, Mouton C, Reame N, Salamone L, Stellato R. Relation of demographic and lifestyle factors to symptoms in a multi-racial/ethnic population of women 40-55 years of age. Am J Epidemiol. 2000 Sep 1;152(5):463-73. doi: 10.1093/aje/152.5.463. PMID: 10981461.

References

- Green R, Santoro N. Menopausal symptoms and ethnicity: the Study of Women's Health Across the Nation. Womens Health (Lond). 2009 Mar;5(2):127-33. doi: 10.2217/17455057.5.2.127. PMID: 19245351; PMCID: PMC3270699.
- Hale GE, Burger HG. Hormonal changes and biomarkers in late reproductive age, menopausal transition and menopause. Best Pract Res Clin Obstet Gynaecol. 2009 Feb;23(1):7-23. doi: 10.1016/j.bpobgyn.2008.10.001. Epub 2008 Dec 1. PMID: 19046657.
- Hale GE, Robertson DM, Burger HG. The perimenopausal woman: endocrinology and management. J Steroid Biochem Mol Biol. 2014 Jul;142:121-31. doi: 10.1016/j.jsbmb.2013.08.015. Epub 2013 Oct 14. PMID: 24134950.
- Harlow SD *Menopause* 2012;19:387-95 (reproduced with permission from Randolph JF *JCEM* 2011;96:746-54).
- Joffe H, White DP, Crawford SL, et al. Adverse effects of induced hot flashes on objectively recorded and subjectively reported sleep: results of a gonadotropin-releasing hormone agonist experimental protocol. *Menopause*. 2013;20(9):905–914.

References

- Kamp E, Ashraf M, Musbahi E, DeGiovanni C. Menopause, skin and common dermatoses. Part 1: hair disorders. Clin Exp Dermatol. 2022 Dec;47(12):2110-2116. doi: 10.1111/ced.15327. Epub 2022 Oct 28. PMID: 35796569; PMCID: PMC10092469.
- Kim G, Bahl M. Assessing Risk of Breast Cancer: A Review of Risk Prediction Models. J Breast Imaging. 2021 Feb 19;3(2):144-155. doi: 10.1093/jbi/wbab001. PMID: 33778488; PMCID: PMC7980704.
- Kronenberg F. Hot flashes: epidemiology and physiology. Ann N Y Acad Sci 1990;592:52–86; discussion 123–33.
- Lee MS, Shin BC, Ernst E. Acupuncture for treating menopausal hot flushes: a systematic review. *Climacteric. 2009 Feb; 12(1):16-25.*
- *Manson JE*, *Chlebowski RT*, *Stefanick ML* et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA* 310, 1353–1368 (2013).
- Marsh ML, Oliveira MN, Vieira-Potter VJ. Adipocyte Metabolism and Health after the Menopause: The Role of Exercise. Nutrients. 2023 Jan 14;15(2):444. doi: 10.3390/nu15020444. PMID: 36678314; PMCID: PMC9862030.
- Mei Z, Hu H, Zou Y, Li D. The role of vitamin D in menopausal women's health. Front Physiol. 2023 Jun 12;14:1211896. doi: 10.3389/fphys.2023.1211896. PMID: 37378077; PMCID: PMC10291614.

References

- Munro MG, et al. The flexible FIGO The Flexible classification concept for underlying causes of abnormal uterine bleeding. Semin Reprod Med. 2011 Sep;29(5):391-9.
- NAMS 2011 isoflavones report. The role of soy isoflavones in menopausal health: report of The North American Menopause Society. Menopause. 2011;18(7):732–753.
- NAMS 2017 Position Statement on Hormone Therapy
- National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: Genetic/familial high-risk assessment—breast, ovarian and pancreatic cancer. Version 2.2024. http://www.nccn.org, 2024.
- Nur U, El Reda D, Hashim D, Weiderpass E. A prospective investigation of oral contraceptive use and breast cancer mortality: findings from the Swedish women's lifestyle and health cohort. BMC Cancer. 2019 Aug 14;19(1):807. doi: 10.1186/s12885-019-5985-6. PMID: 31412822; PMCID: PMC6694621.
- Reed, S. D., et al. Incidence of Endometrial hyperplasia *American Journal of Obstetrics and Gynecology*, *2009*(6), 678.e1–678.
- Polo-Kantola P, Erkkola R, Helenius H, Irjala K, Polo O. When does estrogen replacement therapy improve sleep quality? Am J Obstet Gynecol. 1998 May;178(5):1002-9. doi: 10.1016/s0002-9378(98)70539-3. PMID: 9609575.

References

- Pruthi, S., Qin, R., Terstreip, S. A., Liu, H., Loprinzi, C. L., Shah, T. R. C., … Barton, D. L. (2012). A Phase III, Randomized, Placebo-Controlled, Double-Blind Trial of Flaxseed for the Treatment of Hot Flashes:NCCTG N08C7. *Menopause (New York, N.Y.)*
- Nappi, RE, Kokot-Kierepa, M. Vaginal Health: Insights, Views & Attitudes (VIVA) - results from an international survey. Climacteric. 2012 Feb;15(1):36-44
- Parry, BL. Sleep disturbances at menopause are related to sleep disorders and anxiety symptoms. Menopause. 2007 Sep-Oct;14(5):812-4.
- Prairie BA, Klein-Patel M, Lee M, Wisner KL, Balk JL. What Midlife Women Want from Gynecologists: A Survey of Patients in Specialty and Private Practices. *Journal of Women's Health*. 2014;23(6):513-518.
- Prairie BA, et al. Symptoms of Depressed Mood, Disturbed Sleep, and Sexual Problems in Midlife Women: Cross-Sectional Data from the Study of Women's Health Across the Nation. *Journal of Women's Health*. 2015;24(2):119-126.
- Rinaldi F, Trink A, Mondadori G, Giuliani G, Pinto D. The Menopausal Transition: Is the Hair Follicle "Going through Menopause"? Biomedicines. 2023 Nov 14;11(11):3041. doi: 10.3390/biomedicines11113041. PMID: 38002043; PMCID: PMC10669803.
- Sitka, CS, Atrophic vaginitis. Dermatol Ther. 2010 Sep-Oct;23(5):514-22.
- Smrekar K, Lodise NM. Combined Oral Contraceptive Use and Breast Cancer Risk: Select Considerations for Clinicians. Nurs Womens Health. 2022 Jun;26(3):242-249. doi: 10.1016/j.nwh.2022.01.003. Epub 2022 Feb 5. PMID: 35134383.

References

- Thurston RC, Santoro N, Matthews KA. Are vasomotor symptoms associated with sleep characteristics among symptomatic midlife women? Comparisons of self-report and objective measures. *Menopause*. 2012;19(7):742–748
- Thurston RC, Wu M, Chang YF, Aizenstein HJ, Derby CA, Barinas-Mitchell EA, Maki P. Menopausal Vasomotor Symptoms
- and White Matter Hyperintensities in Midlife Women. Neurology. 2023 Jan 10;100(2):e133-e141.
- Verdier-Sévrain, et al. Biology of estrogens in skin: implications for skin aging. Exp Dermatol. 2006 Feb;15(2):83-94.
- Tandon VR, Sharma S, Mahajan A, Mahajan A, Tandon A. Menopause and Sleep Disorders. J Midlife Health. 2022 Jan-Mar;13(1):26-33. doi: 10.4103/jmh.jmh_18_22. Epub 2022 May 2. PMID: 35707298; PMCID: PMC9190958.