MAYO CLINIC | School of Continuous Professional Development

19TH ANNUAL

WOMEN'S HEALTH UPDATE 2023

March 23-25, 2023

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MENOPAUSE OVERVIEW

A DROP IN THE BUCKET

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DISCLOSURE OF RELEVANT FINANCIAL RELATIONSHIP(S) WITH INELIGIBLE COMPANIES

- Nothing to disclose

REFERENCES TO OFF-LABEL USAGE(S) OF PHARMACEUTICALS OR INSTRUMENTS

- Nothing to disclose

All relevant financial relationships have been mitigated.

LEARNING OBJECTIVES

- Review the definition, symptoms, and management of menopause
- Explore cases to highlight basic symptom management, individualized care, and shared decision making

STAGES OF REPRODUCTIVE AGING

- In 2001, the Stages of Reproductive Aging Workshop (STRAW) established a nomenclature for reproductive aging

- In 2011, STRAW+10 updated and modified the model

Harlow SD Menopause 2012;19:387-95

STRAW+10

Menarche — FMP (0)

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]

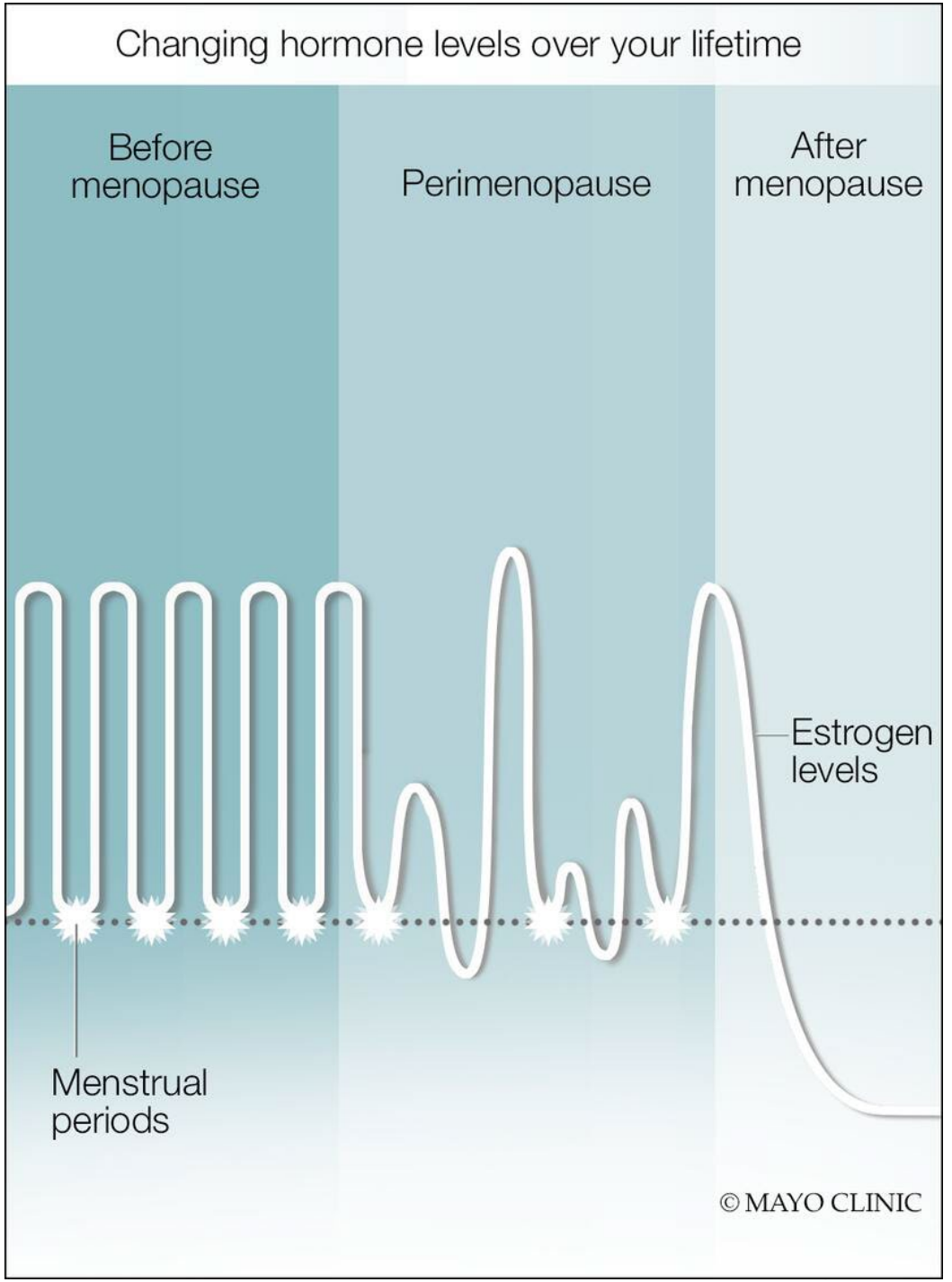
Harlow SD Menopause 2012; 19:387-95

WHEN I SAY MENOPAUSE, WHAT DO YOU ENVISION?

- Hot and Sweaty
- Lost Sex Drive
- New Tummy

MENOPAUSE TERMINOLOGY

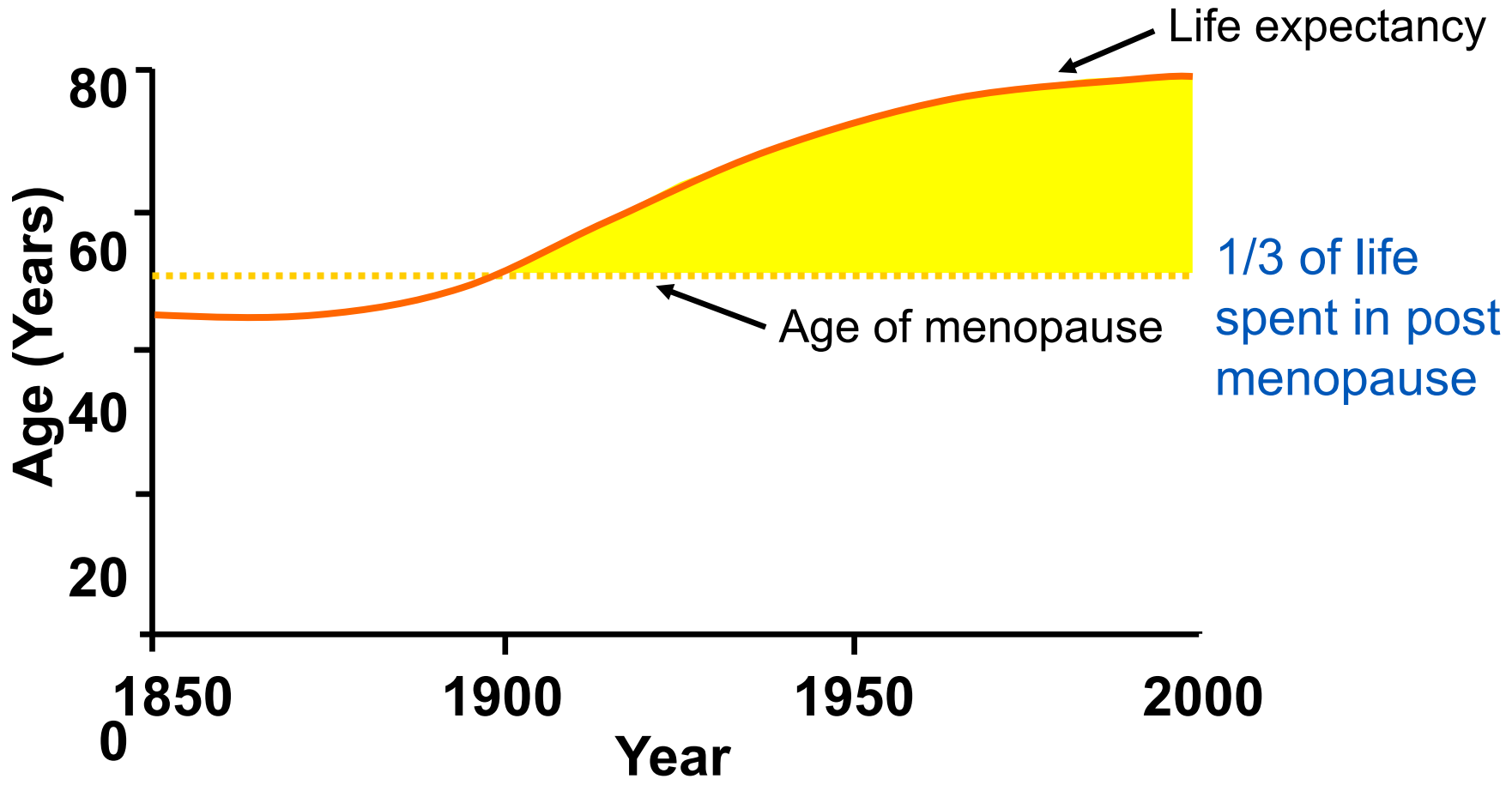
- Menopause- spontaneous, permanent ending of menstruation that is not caused by any medical intervention; confirmed after 12 consecutive months without a period.
- Perimenopause is the transitional phase up to 6 years or more immediately prior to menopause when changes begin, plus 1 year after menopause.
- Induced menopause is cessation of menstruation that follows bilateral oophorectomy (with or without hysterectomy), chemotherapy, or pelvic radiation
therapy



MENOPAUSE

- Occurs 40-58 years old; average age 51
- Premature age… different than a natural menopause
- Smoking proven to effect age of onset; smokers approx. 2 years earlier than nonsmokers
- Genetic link suggested

GAP WIDENS BETWEEN LIFE EXPECTANCY AND MENOPAUSAL AGE

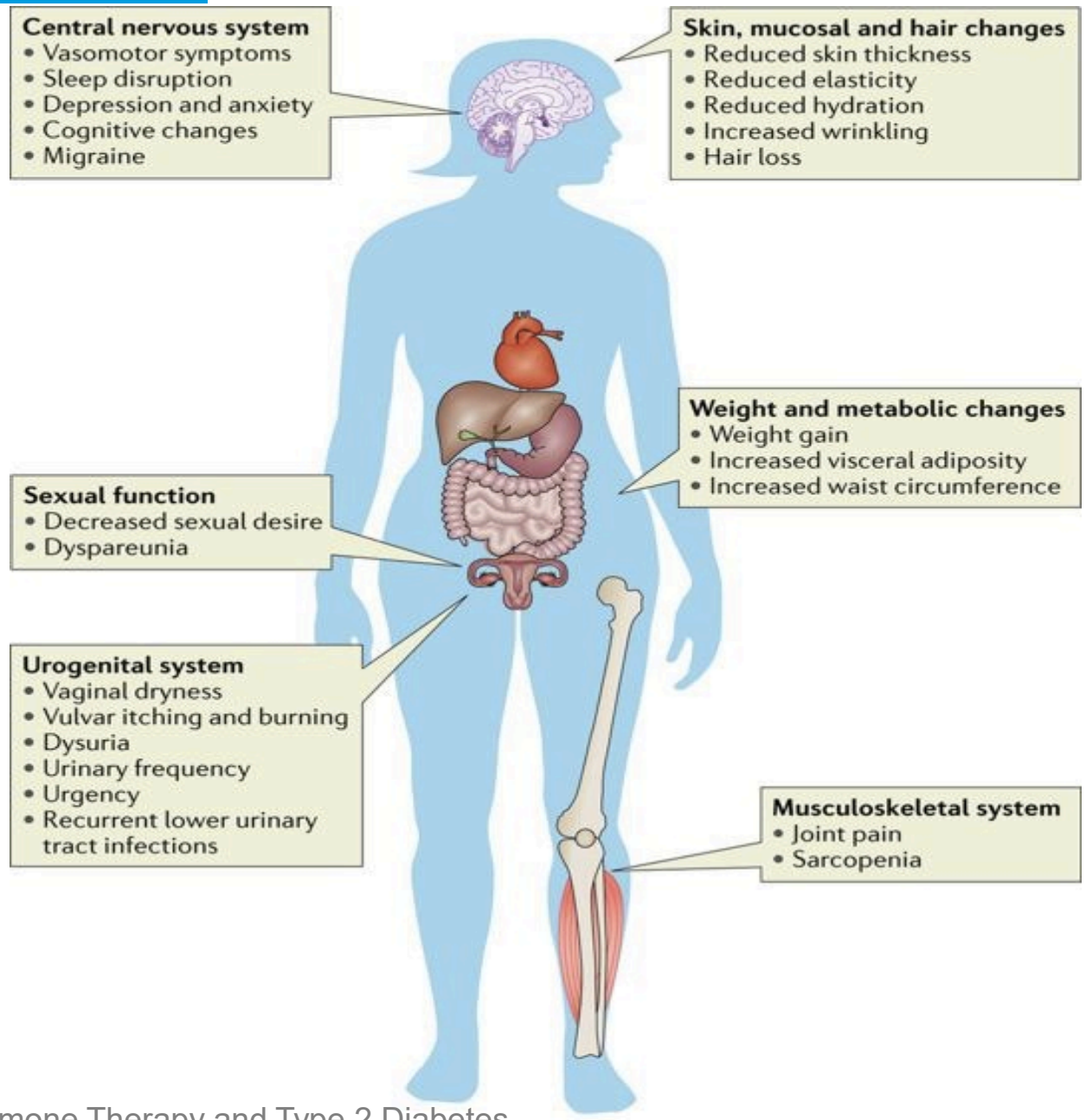


Soules MR, et al. *J Am Geriatr Soc.* 1982;30:547-561.

52 YR OLD WOMAN PRESENTS TO WOMEN'S HEALTH CLINIC:

- Difficulty with concentration, 'fuzzy thinking' over past year
- Mood labile, easily angered, quick-tempered
- Awakes easily at night, trouble getting back to sleep
- Vaginal dryness, painful intercourse, ↓ libido
- LMP 9 months prior
- PM/SH – hyperlipidemia, cx dysplasia
- Meds – niacin, multivit, calcium + D

Are her symptoms related to Menopause?



Mauvais-Jarvis et al. “Menopausal Hormone Therapy and Type 2 Diabetes Prevention: Evidence, mechanisms and clinical implications”. Endocr Rev. 2017, Jun;38 (3):173-188.

VASOMOTOR SYMPTOMS (VMS)

- Recurrent, feeling warm/hot, face/neck/upper and lower body, sweating
- 75% will experience
- Severe in 10%-15% of women
- Some persist for a lifetime but usually decrease in frequency and intensity over time
- May be more severe in smokers
- Estrogen level doesn’t predict severity of symptoms

PHYSIOLOGIC MECHANISMS

- Not completely understood
- Related to small fluctuations in core body temperature superimposed on an extremely narrow thermoneutral zone
- Triggered when core body temperature rises above upper (sweating) threshold
- Shivering occurs when core body temperature falls from elevated level to a level below the lower threshold of thermoneutral zone

Freedman RR *Fertil Steril* 2002;77487-90; Freedman RR *Menopause* 2005;12:156-9

VASOMOTOR SYMPTOMS TREATMENT

- VSM may begin during perimenopause, and frequent VMS may persist on average 7.4 years or longer. They affect quality of life and may be associated with cardiovascular, bone, and brain health.
- Hormone therapy remains the gold standard for relief of VMS
  - Estrogen-alone therapy can be used for symptomatic women without a uterus
  - For symptomatic women with a uterus, estrogen-progestogen therapy or a tissue-selective estrogen complex protects against endometrial neoplasia
- Shared decision-making should be used when considering formulation, route of administration, and dose of hormone therapy for menopause symptom management with adjustment tailored to symptom relief, adverse events and patient preferences.

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VASOMOTOR SYMPTOMS TREATMENT CONT.

- Periodic assessment of the need for ongoing use of hormone therapy should be individualized on the basis of a woman's menopause symptoms; general health and underlying medical conditions; risks; treatment goals; and personal preferences.
- Micronized progesterone 300mg nightly significantly decreases vasomotor symptoms (VSM: hot flashes and night sweats) compared with placebo and improves sleep.
- Synthetic progestins have shown benefit fro VMS in some studies. No long-term study results are available, and use of progestogens without estrogen for either indication is off-label.

SLEEP DISTURBANCES

- During Menopause transition, women with VMS are more likely to report disrupted sleep
- Hormone therapy improves sleep in women with bothersome nighttime VMS by reducing nighttime awakenings.
- Estrogen may have some effect on sleep, independent of VMS.

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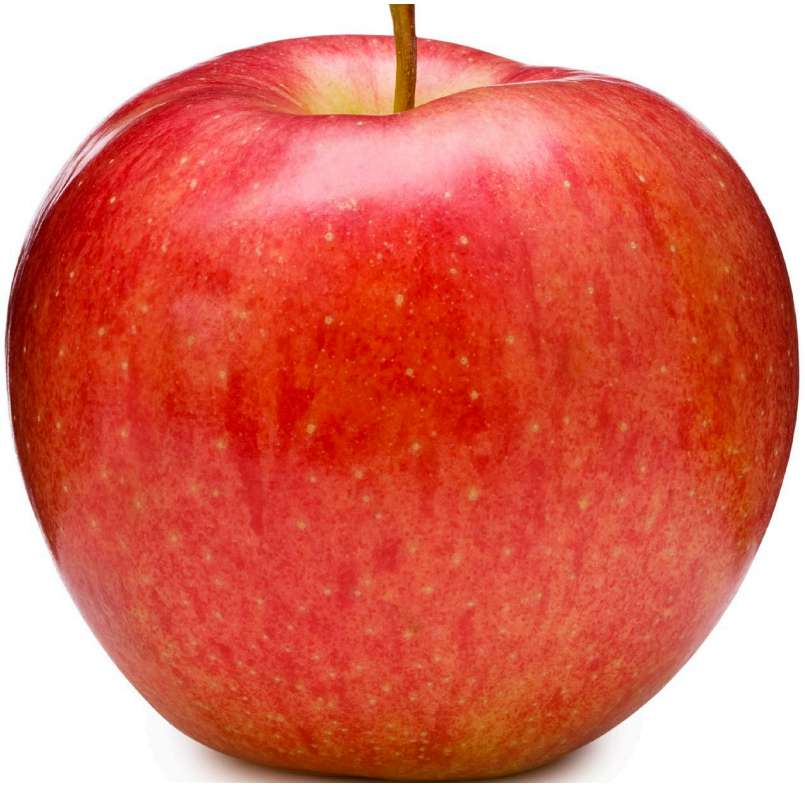
WEIGHT GAIN



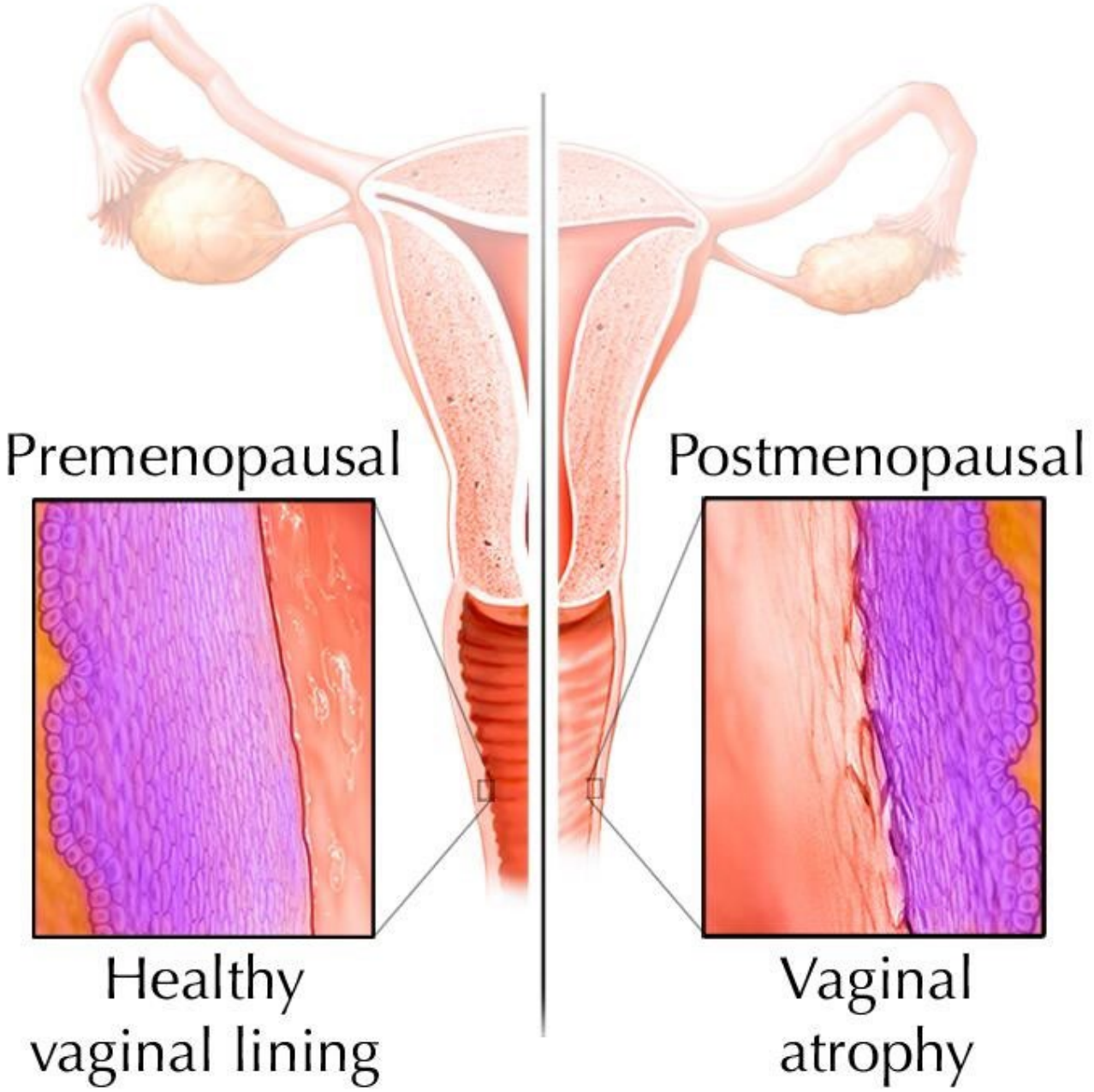
- Many women gain an average of 5 lb (2.27 kg) at midlife related mostly to aging and lifestyle, not menopause or hormone therapy (HT)
- Increase in body fat and a decrease in lean body mass
- Changes in fat distribution and decreased basal metabolic rate.
- What used to work- doesn’t seem to work anymore
- Hormone therapy isn’t a weight loss treatment plan

Brown WJ Obes Res 2005;13:1431-41; Milewicz A Climacteric 2004;4:273-83; Crawford SI Menopause 2000;7:96-104

GENITOURINARY SYNDROME OF MENOPAUSE

Results in:

- Less cells - less lubrication
- Fragile cells - discomfort
- Change in pH
- Risk of UTI
- Decrease in blood flow
- Loss of elasticity



GENITOURINARY SYMPTOMS TREATMENT

- Low-dose vaginal estrogen therapy (ET) preparations are effective and generally safe for the treatment of genitourinary syndrome of menopause, with minimal systemic absorption, and are preferred over systemic therapies when ET is used only for genitourinary symptoms.
- For women with breast cancer, low-dose vaginal ET should be prescribed in consultation with their oncologists.
- Progestogen therapy is not required with low-dose vaginal estrogen, but randomized, controlled trial data are lacking beyond 1 year.
- Nonestrogen prescription FDA-approved therapies that improve vulvovaginal atrophy in postmenopausal women include ospemifene and intravaginal dehydroepiandrosterone.

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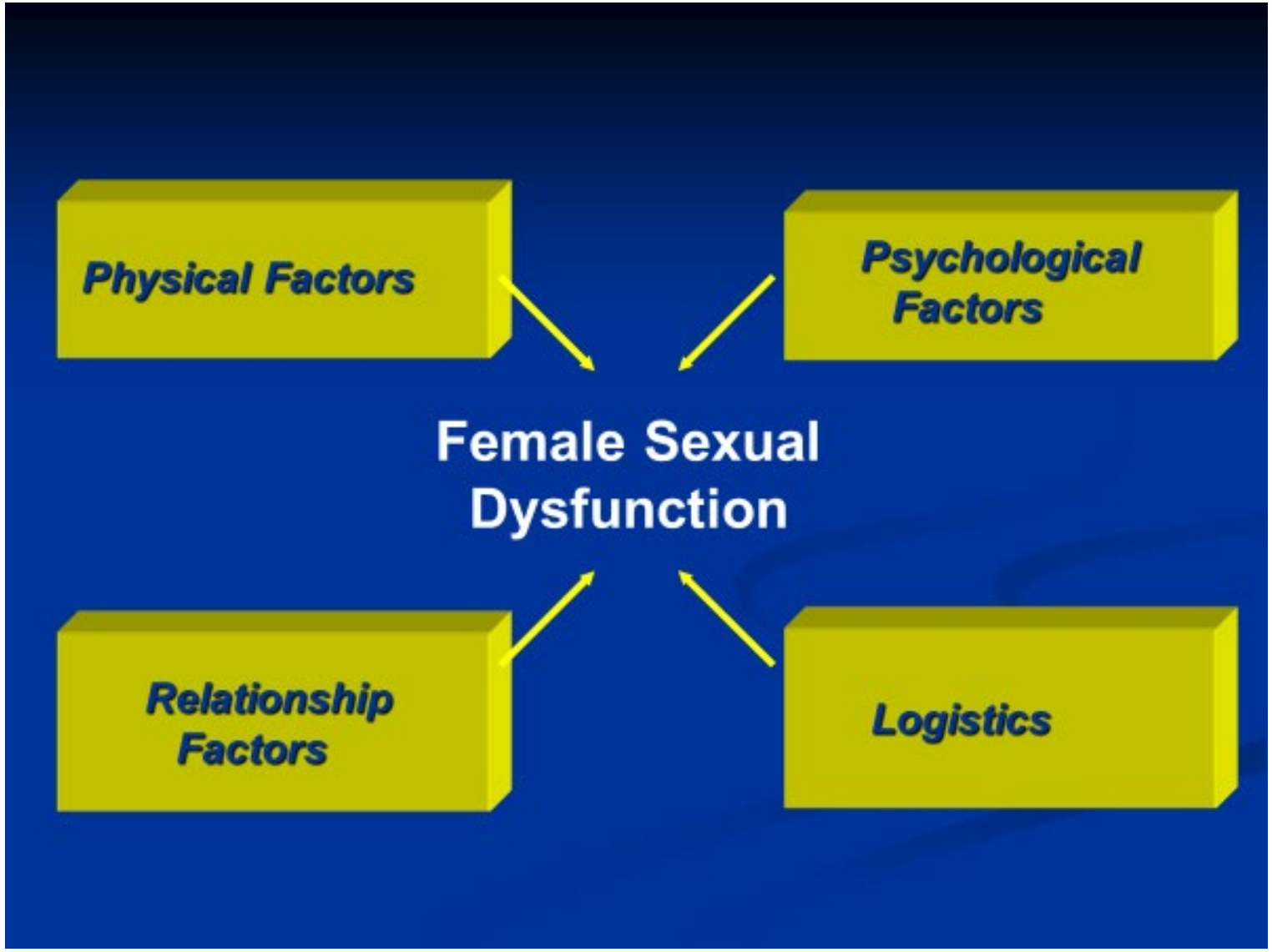
SEXUAL DYSFUNCTION

- Hormonal loss
- Fatigue
- Medications
- Stress/Anxiety
- Self-image
- Communication
- Expectations



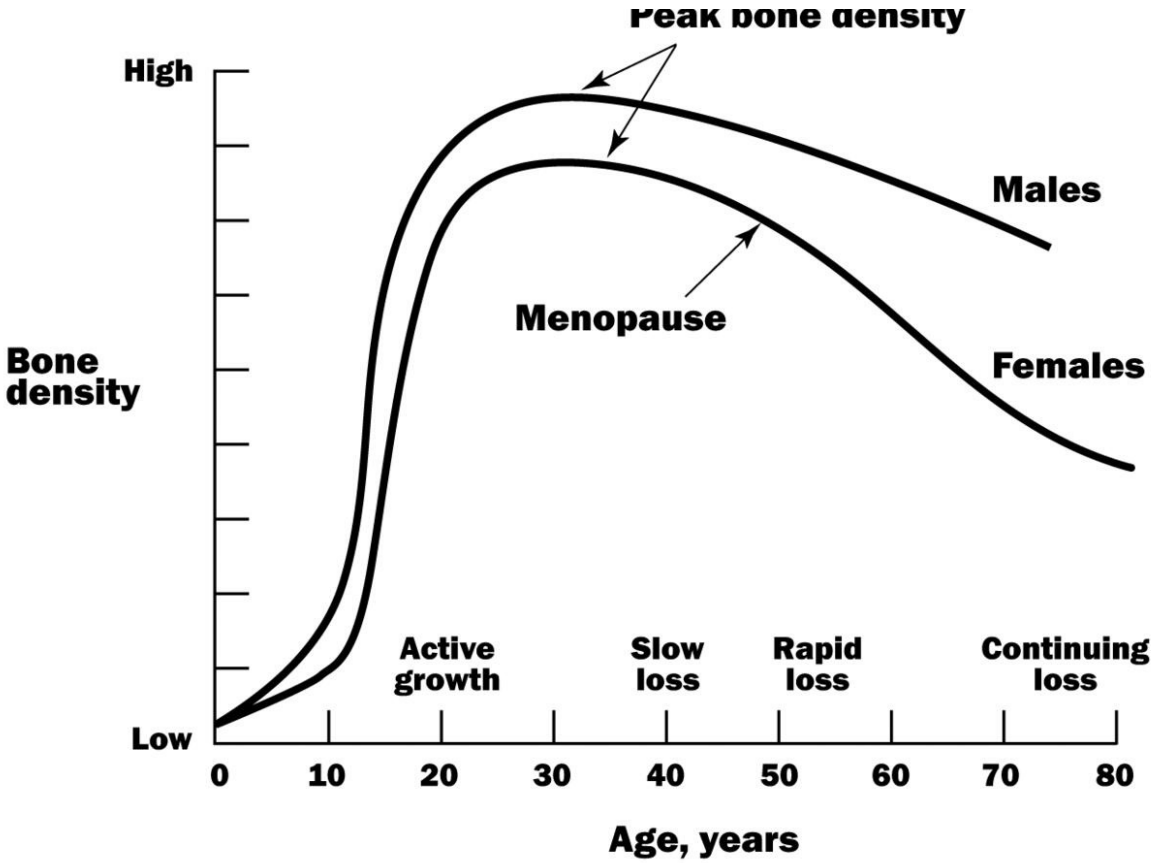
HAIR CHANGES

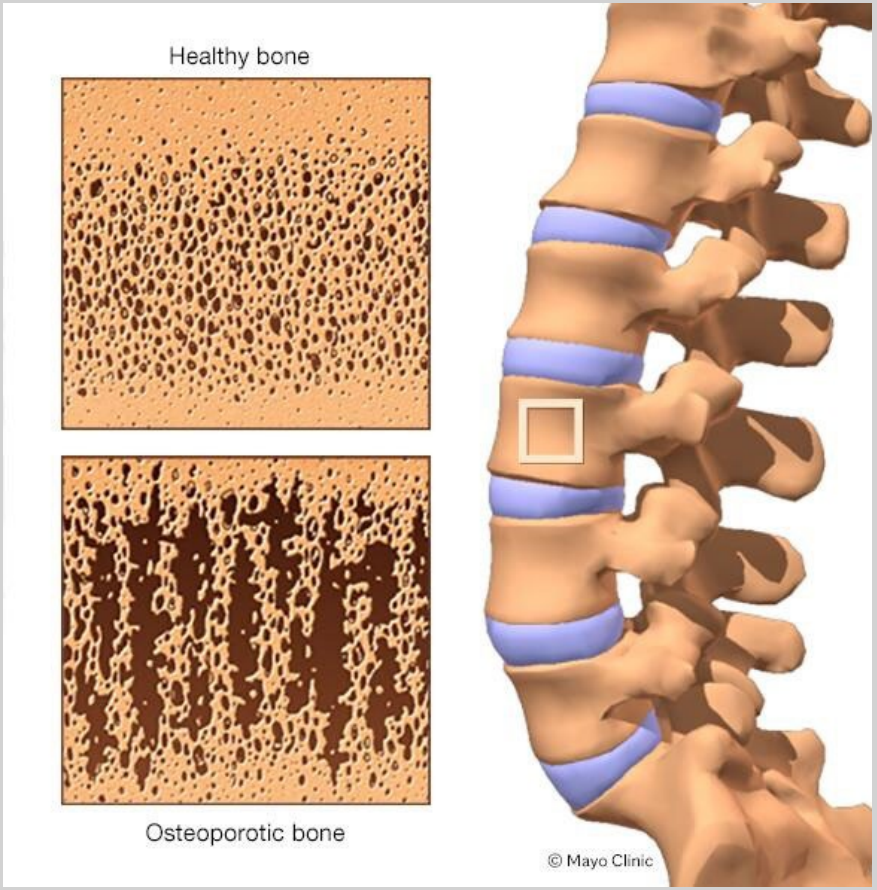
- Increase in the ratio of androgen to estrogen during the menopause transition may influence hair changes in some women
- Female pattern hair loss (thinning on crown) most common diagnosis
- Large “rogue hairs” can appear on the chin around menopause

Georgala S *Int J Dermatol* 1992;31:858-9; Olsen EA *J Am Acad Dermatol* 2005;52:301-11; Riedel-Baima A *Endocr Regul* 2008;42:14-16

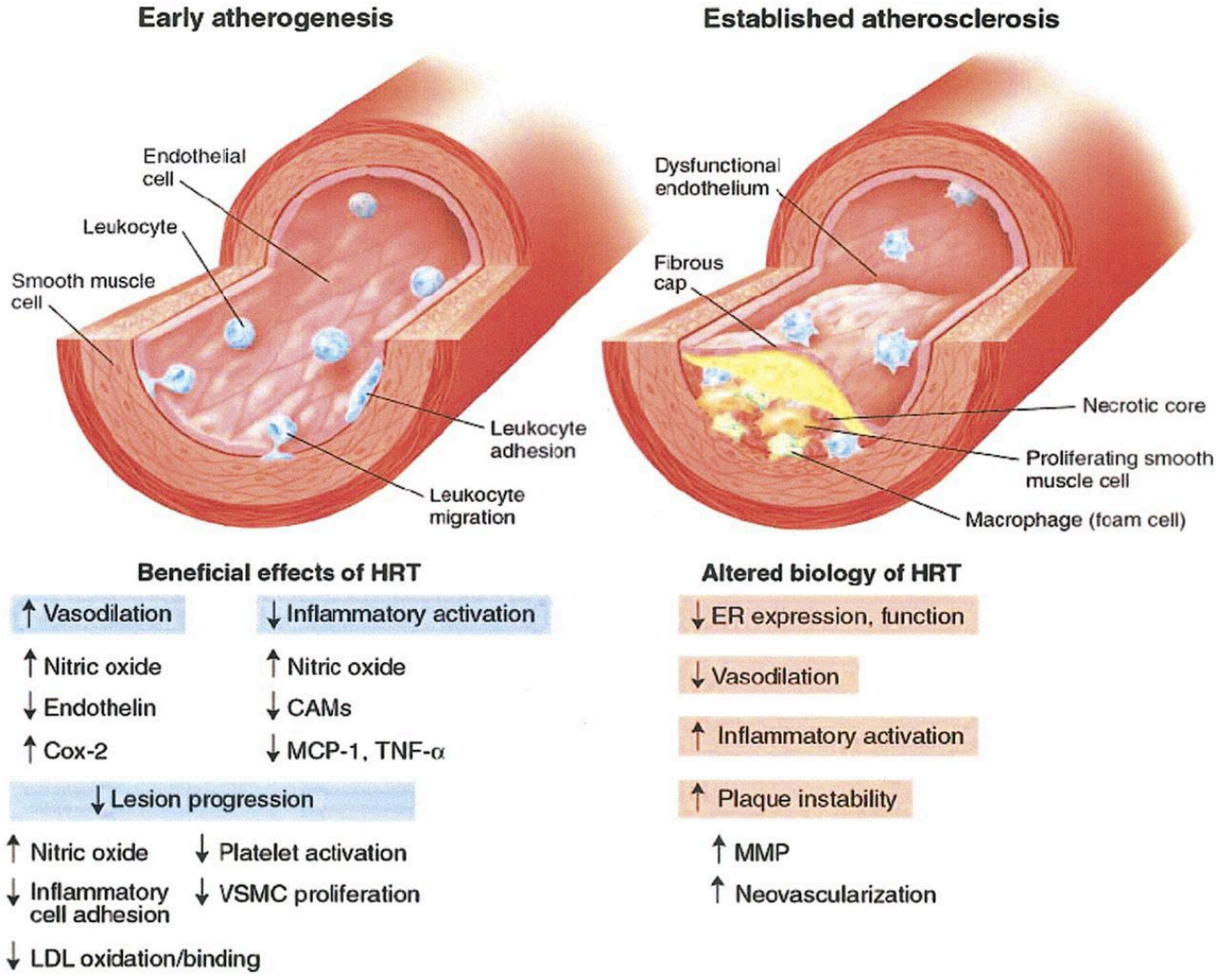
WHAT ABOUT, WHAT YOU CAN’T FEEL OR SEE?

BONE HEALTH

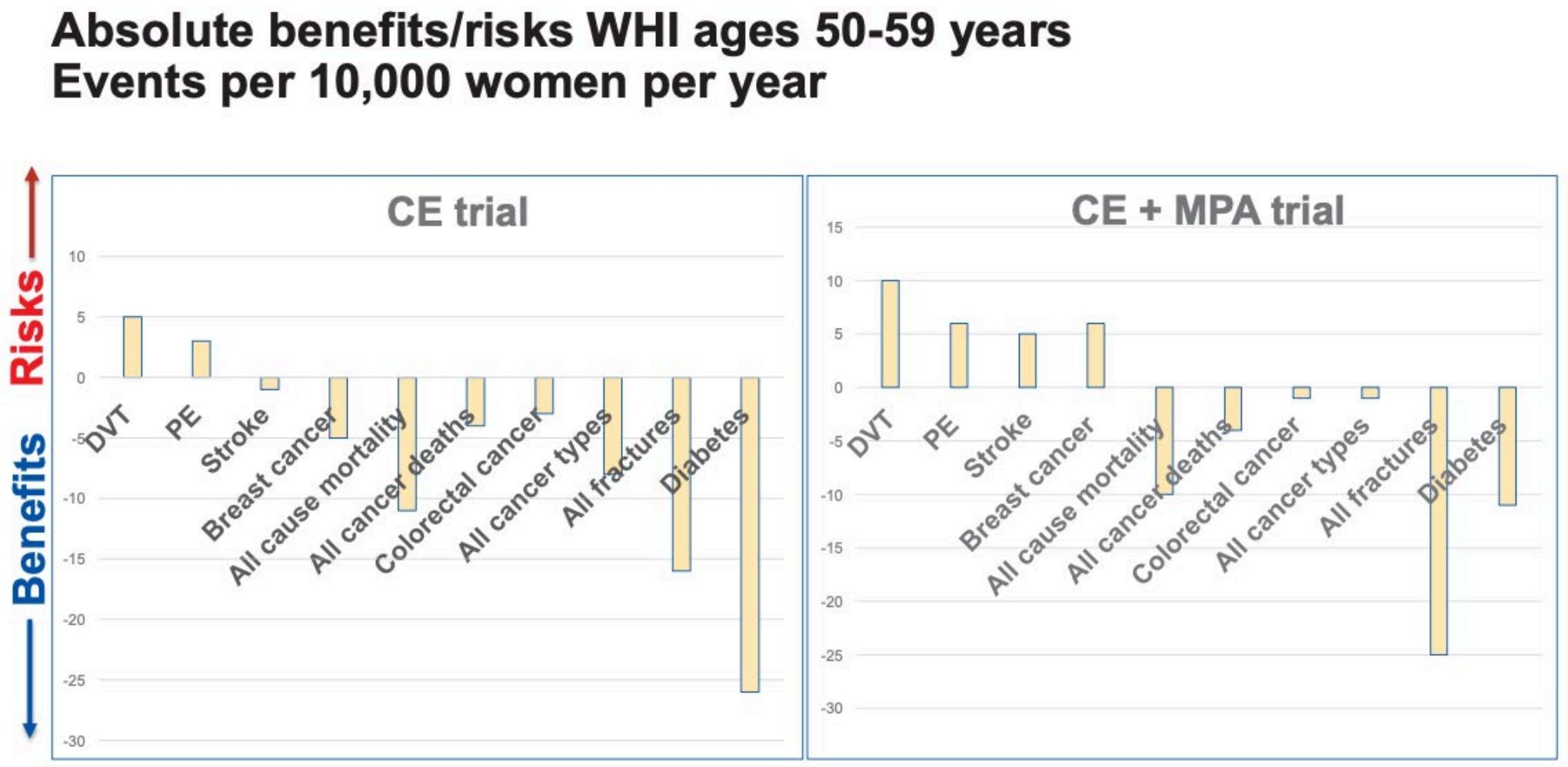




VASCULAR EFFECT OF ESTROGEN

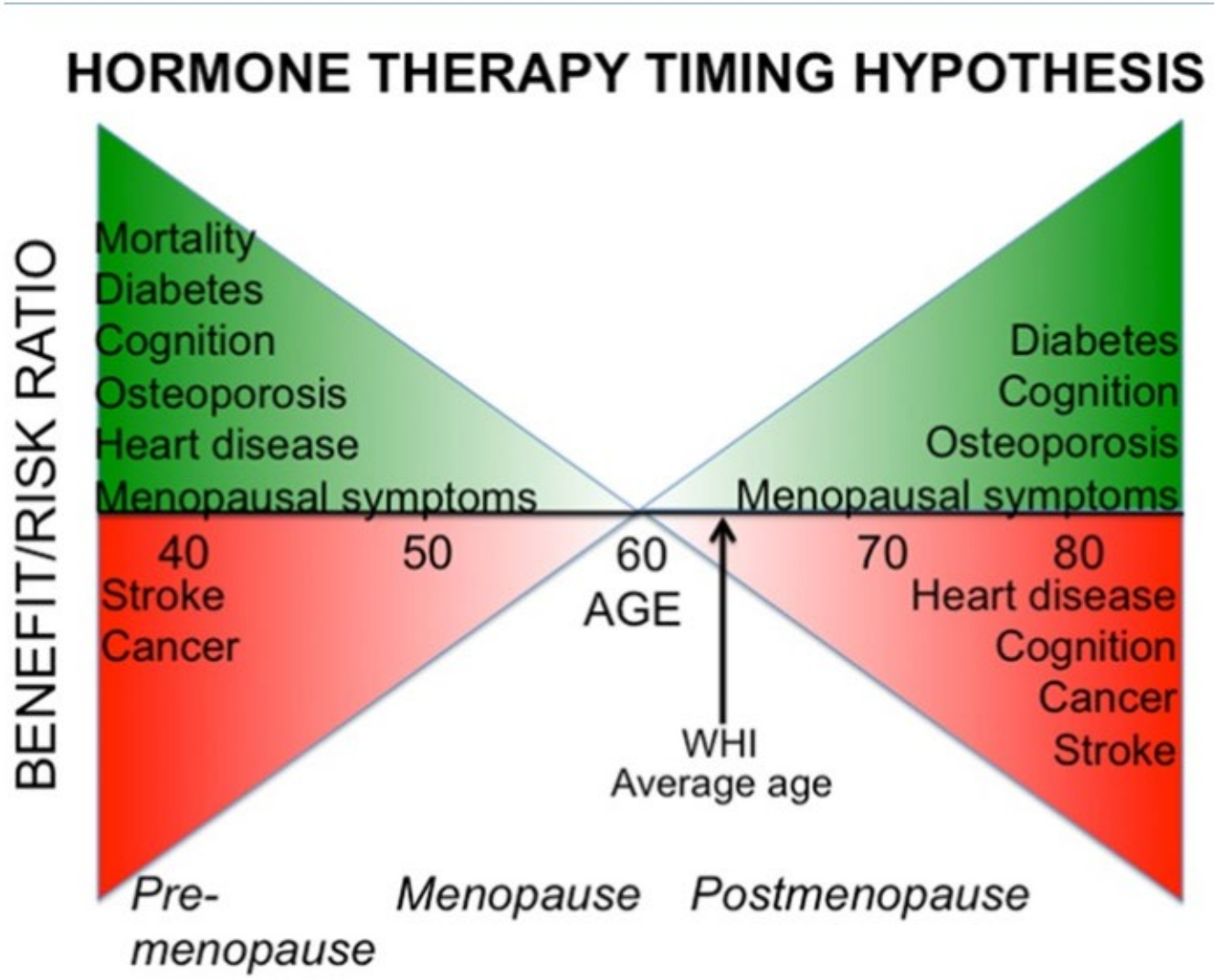


RECAP- WHI



Recreated from Lobo et al. Atherosclerosis 2016 Nov; 254:282-290

TIMING HYPOTHESIS



Bolton et al. Chem Res Toxicol. 2016; 29, 1583-1590.

CURRENT TREATMENT OPTIONS

Non-Hormonal

Lifestyle modifications

CAM treatments

Antidepressants/
Gabapentin/ Clonidine

Hormonal

Conventional HRT

Bioidentical hormones (BHRT)

Compounded vs FDA approved

Treatment of menopause-associated vasomotor symptoms: position statement of The North American Menopause Society. Menopause. 2004 Jan-Feb;11(1):11-33.

2022 NAMS POSITION STATEMENT

- Hormone therapy is FDA approved for four indications:
  - Moderate to severe VMS
  - Prevention of osteoporosis in postmenopausal women
  - Treatment of hypoestrogenism caused by hypogonadism, bilateral oophorectomy or primary ovarian insufficiency
  - Treatment of moderate to severe vulvovaginal symptoms
- FDA guidance for treatment of genitourinary symptoms related to menopause in the absence of indications for systemic estrogen therapy (ET) suggests the use of low-dose topical vaginal ET (Level I)

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2022 NAMS POSITION STATEMENT
HORMONE THERAPY & CVD

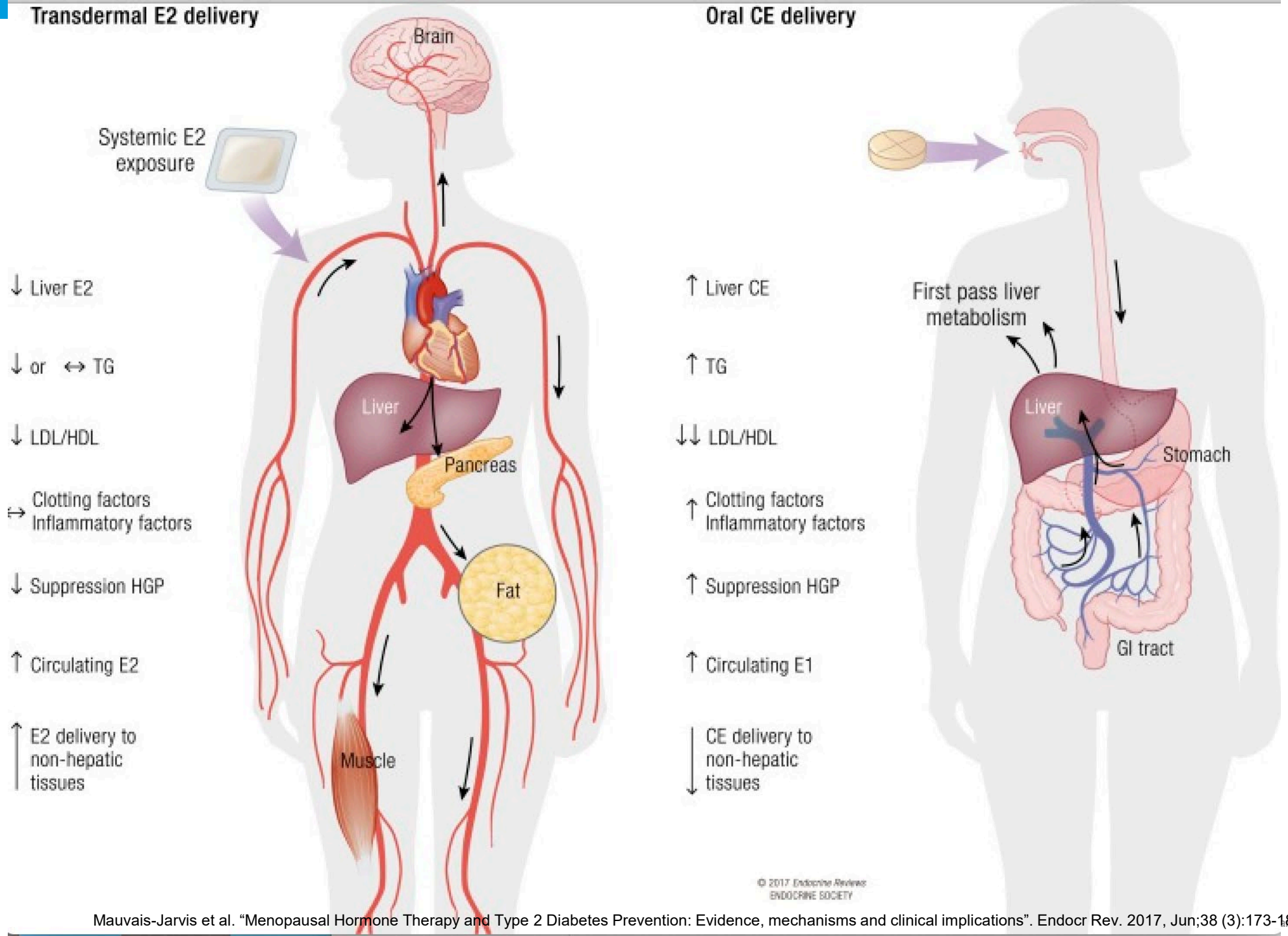
- For healthy symptomatic women within 10 years of menopause onset or less than 60 years of age, there are favorable effects on CHD and all-cause mortality.
- MHT not recommended for CVD prevention
- The potential increase in risk of VTE and stroke is low in this population
- Observational evidence: lower risk with transdermal estradiol

HORMONE THERAPY RISK OF VTE

- Observational studies and RCTs show an increased risk of VTE with oral HT
- The WHI demonstrated
  - 18 additional cases of VTE per 10,000 women on oral estrogen-progestin compared to nonusers
  - 7 additional cases per 10,000 women on oral estrogen alone compared to nonusers

TRANSDERMAL ET

Oral ET



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- Vaginal dryness, painful intercourse, ↓ libido
- LMP 9 months prior
- PM/SH – hyperlipidemia, cx dysplasia
- Meds – niacin, multivit, calcium + D

Join: **vevox.app** ID: **XXX-XXX-XXX**

POLL OPEN

CAN I STILL GET PREGNANT?

1. Yes, but the chance is so low no contraception is needed.

2. Yes, so you will need to use contraception until you have gone a full 12 months without a period.

3. No, don’t worry, be happy!

4. Maybe, so avoid penetration.

CAN I STILL GET PREGNANT?

1. Yes, but the chance is so low no contraception is needed.
2. **Yes, so you will need to use contraception until you have gone a full 12 months without a period.**
3. No, don’t worry, be happy!
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49 YO FEMALE

- She has noticed bothersome hot flashes. Her menstrual cycles have been regular although occasionally a few days later than expected. She is tired and hasn't been sleeping well. She has no history of sleep apnea or anxiety.
- LMP: 2 weeks prior
- PM/SH: G2 P2; Hypothyroidism
- Meds: multivitamin, levothyroxine
- Vitals: 120/70; BMI 24

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POLL OPEN

WHAT SHOULD I DO OR SAY?

1. Don’t worry, you are perimenopausal and your periods will go away within 6 months
2. This is common with perimenopause, and we must wait until your hot flashes are worse to treat with hormone therapy.
3. Check her CBC and TSH
4. Offer her a follow-up appointment in 6 months.

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POLL OPEN

TSH AND CBC ARE NORMAL. WHAT DO YOU CONSIDER NEXT STEPS? (CHOOSE ALL THAT APPLY)

Vote for up to 6 choices

1. Offer her OCPs — 0%
2. Consider Mirena IUD with or without transdermal estradiol — 0%
3. Consider starting low dose escitalopram — 0%
4. Refer her to Gynecology for total hysterectomy — 0%
5. Start estradiol with cyclic progesterone — 0%
6. Do nothing — 0%

(% = Percentage of Voters)

WON'T HORMONE THERAPY CAUSE BREAST CANCER?

- Rare absolute risk of breast cancer (<1 additional case/1,000 person-years of use) was seen in CEE + MPA
  - Less than risk with 2 glasses of wine/day
  - Similar to risk with obesity, sedentary lifestyle
- Observational evidence: progesterone safer than MPA
- Durations of HT may be important (risk ↑ after 5 years)

CONSIDERATIONS WHEN CHOOSING TREATMENT

- Level of bother
- Age
- Patient’s preferences
- Past medical history
- Family history
- Finances
- ~~Hormone level~~

OLD: “lowest dose for shortest period of time”

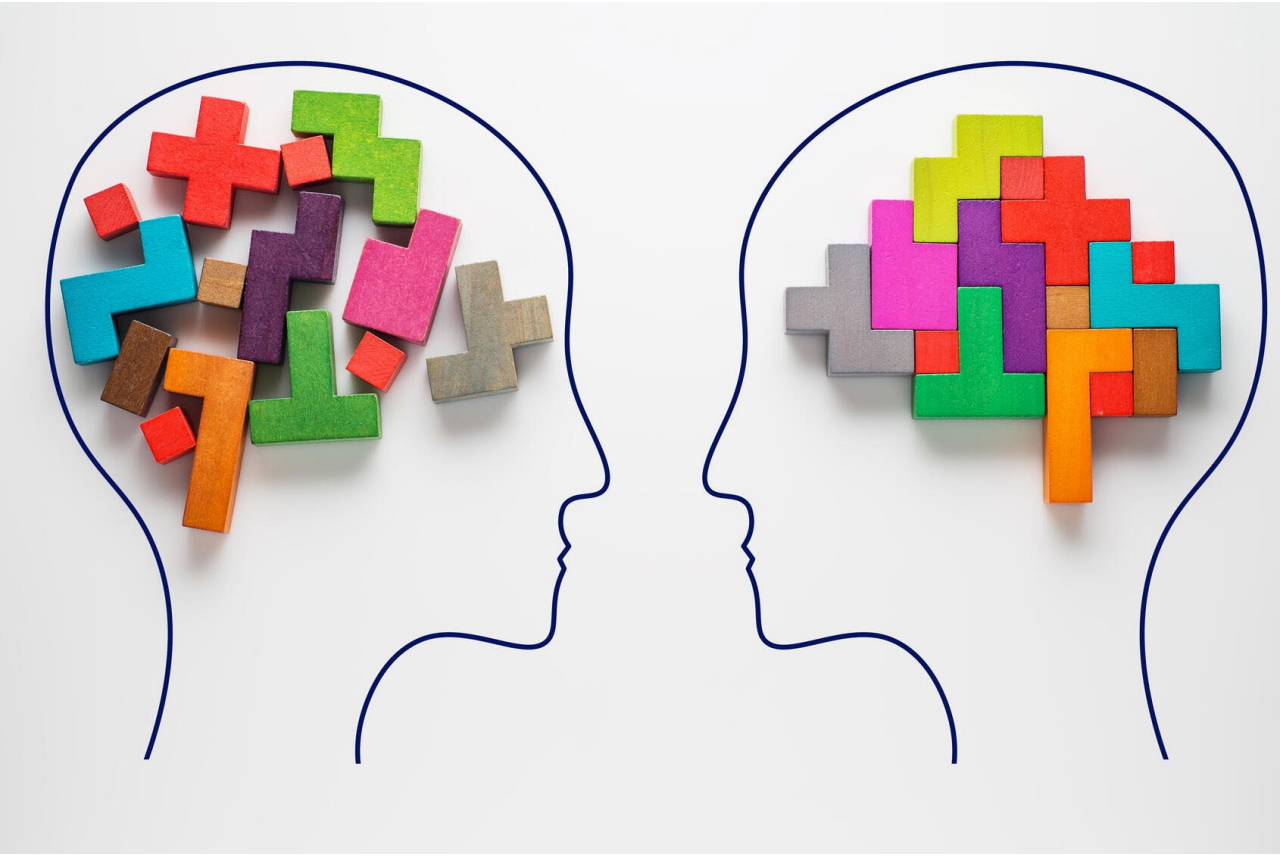
NOW: “appropriate MHT type, dose, formulation, route of administration and duration” to meet treatment objectives

HT should be individualized and reevaluated periodically to maximize the benefits as well as minimize the risks of use

FUTURE…

- Hot flashes symptom or troublemaker?
- Role of estrogen loss in diseases such as CVD, diabetes or dementia
- Expanding our understanding of hormonal loss in young women
- New nonhormonal prescriptions to treat hot flashes

FINAL THOUGHTS



- Menopause is not just a moment in time
- Estrogen deficiency has impact from head to toe
- Treatment is driven by symptoms….with exceptions
- Focus on individualized care
- Seek out a specialist as needed

RESOURCES

Faubion, S. Long-term health consequences of premature or early menopause and considerations for management, Climacteric. 2015 ; 18(4): 483–491. doi:10.3109/13697137.2015.1020484.

Kapoor, E. Weight Gain in Women at Midlife: A Concise Review of the Pathophysiology and Strategies for Management, Mayo Clin Proc. 2017;92(10):1552-1558

Santoro, N. Management of the Perimenopause, Clinical Obstetrics and Gynecology, Volume 61, Number 3, 419–432

Shoback, D. Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society Guideline Update; The Journal of Clinical Endocrinology & Metabolism, Volume 105, Issue 3, March 2020, Pages 587–594, https://doi.org/10.1210/clinem/dgaa048

The 2022 hormone therapy position statement of The North American, Menopause: The Journal of The North American Menopause Society, Vol. 29, No. 7, pp. 767-794, DOI: 10.1097/GME.0000000000002028

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THANK YOU.

THIELEN.JACQUELINE@MAYO.EDU

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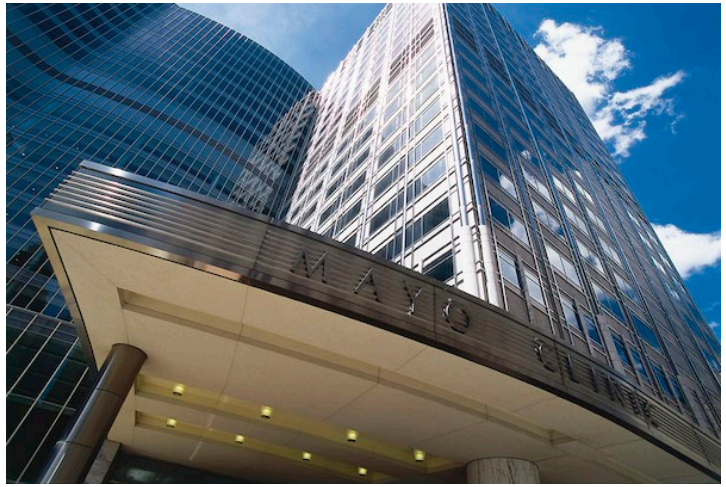
THANK YOU FOR JOINING US IN THIS COURSE



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Jacksonville, Florida