Menopause

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Plan for today

- Definitions
- Pathophysiology
- Symptoms
- Treatment
  - WHI
- Practice management

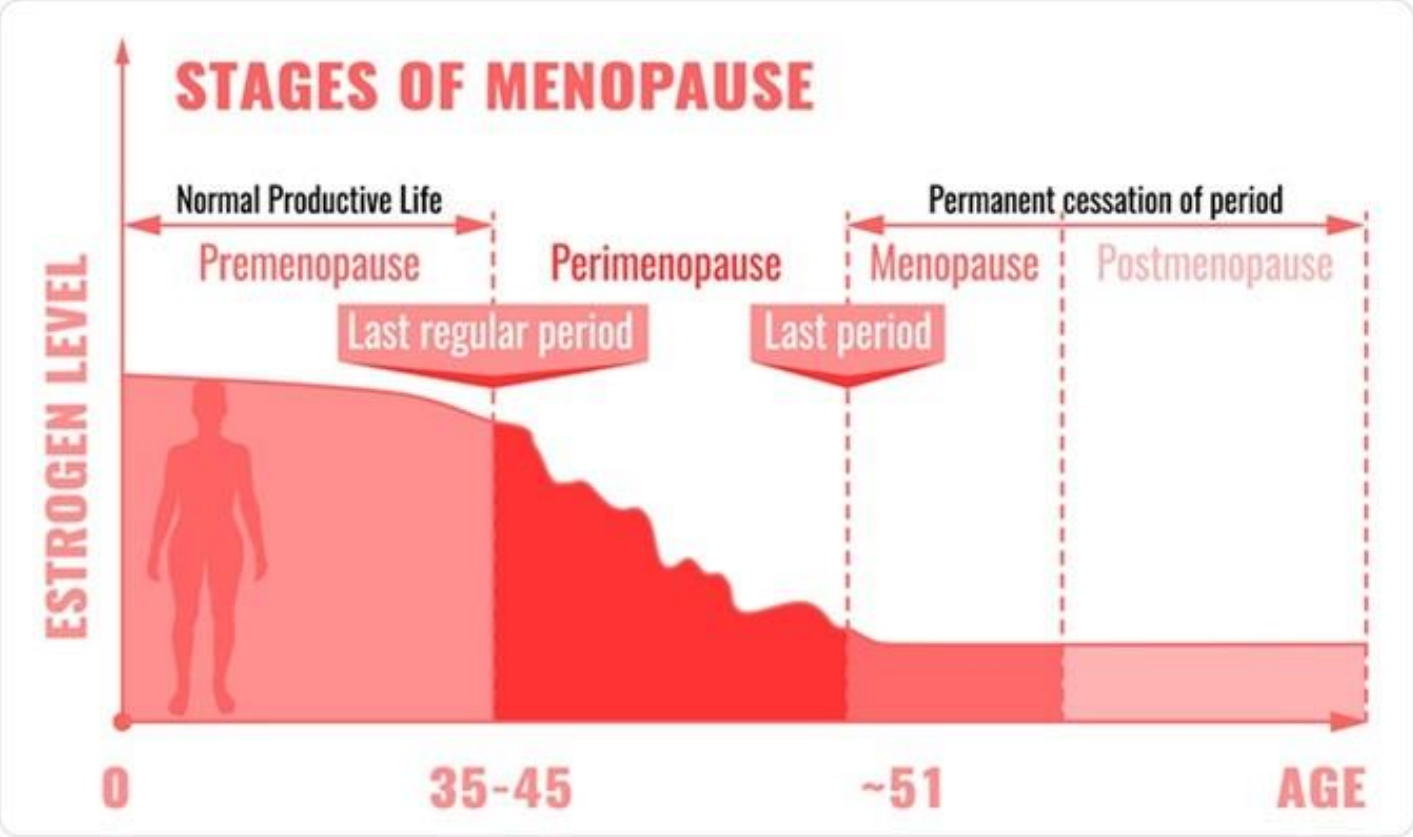
Definitions

- Natural Menopause: permanent stopping of menstrual periods (after 12 months of amenorrhea without any other obvious pathological or physiological cause)

- Surgical Menopause: removal of both ovaries

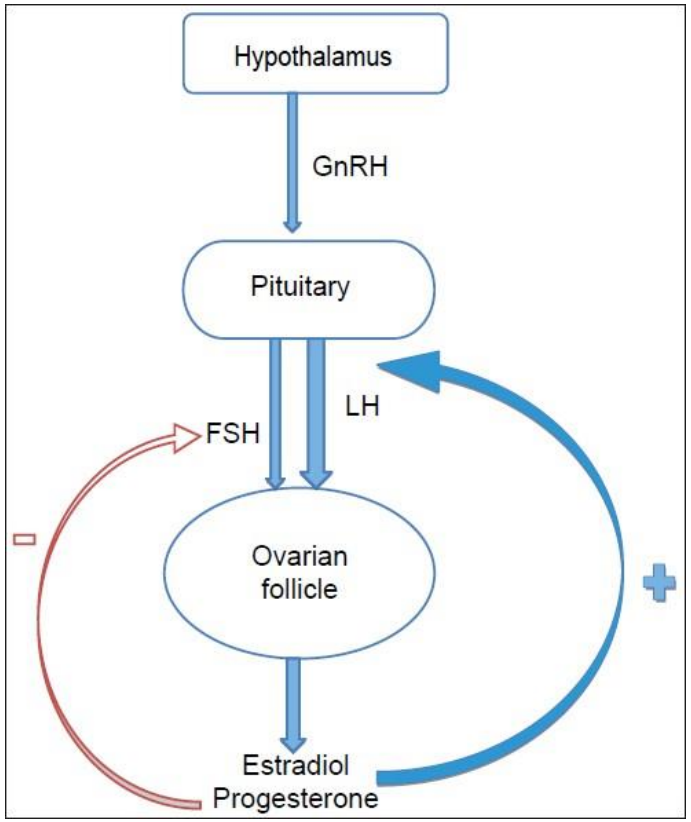
Definitions

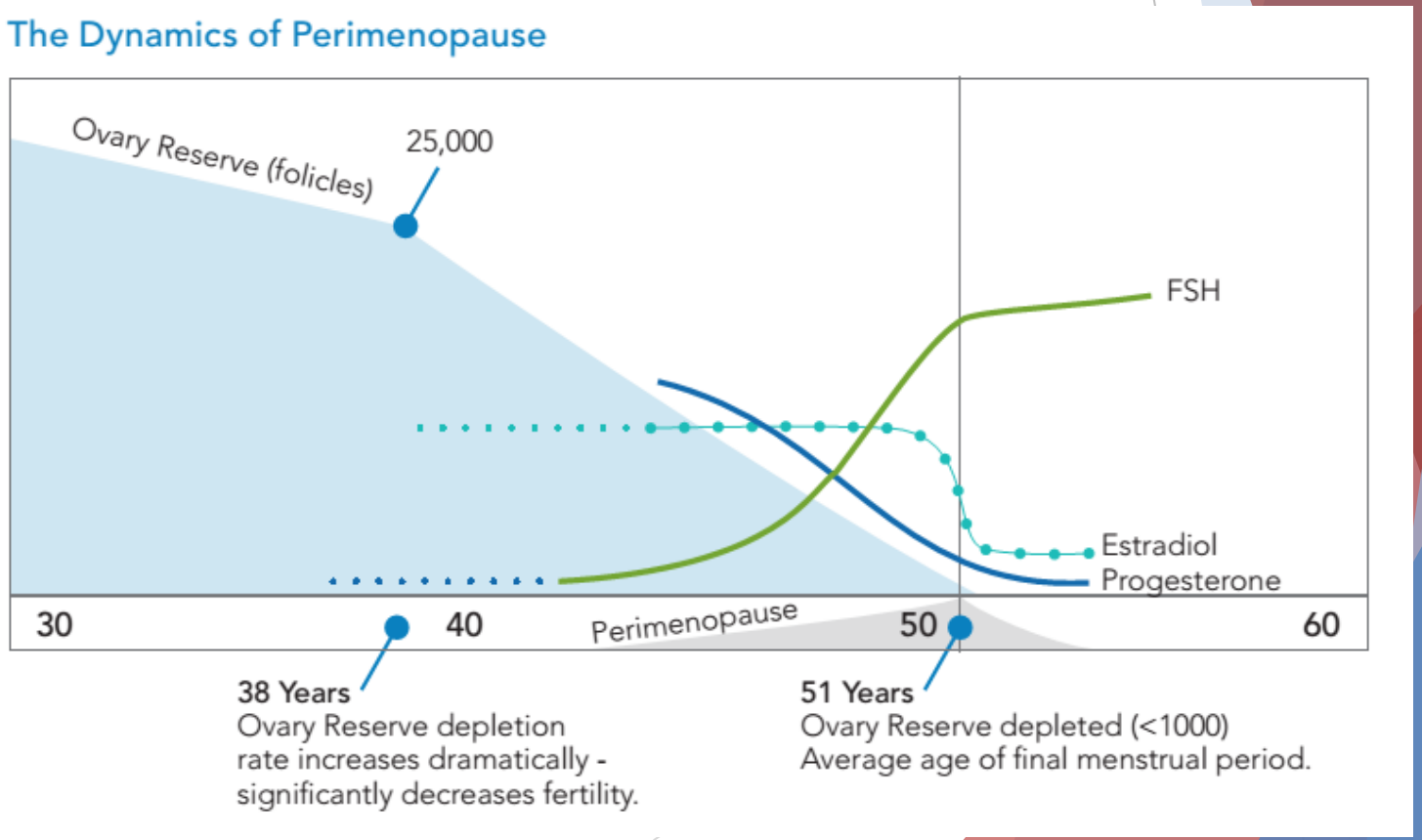
- Median age 51.4 years (95% between 45 – 55)
- Perimenopause ~ Menopause - Postmenopause
- If < 40 years of age, abnormal POI (primary ovarian insufficiency/failure)



Definitions

- Happens due to ovarian follicular depletion → hypoestrogenemia
- Estradiol and progesterone decrease (~ 80%)
- FSH levels increase (~50%)





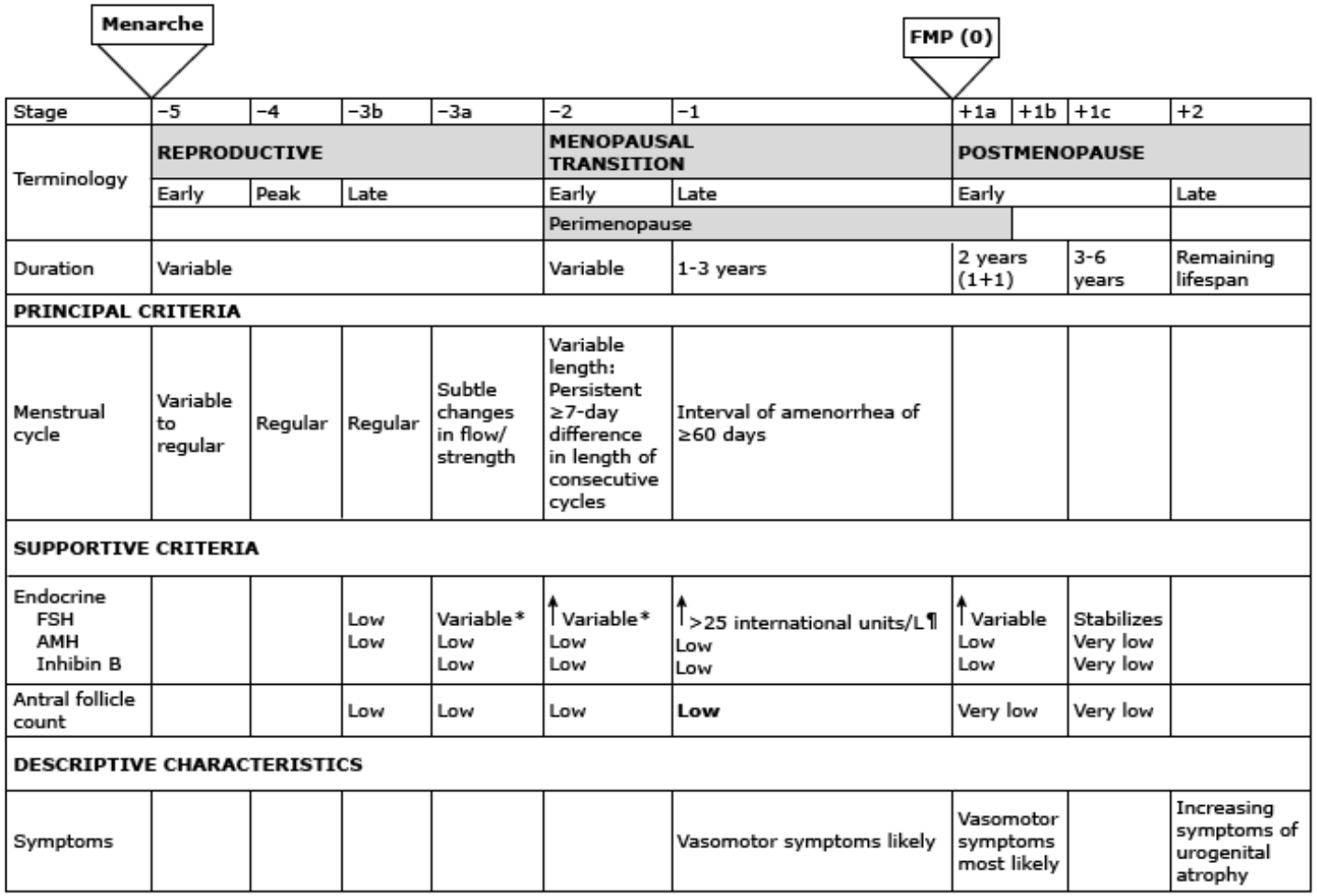
Evaluation

- HISTORY!!
  - Menstrual calendar
  - Menopausal symptoms
- Exam: look for vaginal dryness/atrophy, dyspareunia
- Labs (supportive criteria)
  - FSH elevated 50% higher > 15 – 25 IU/L seen menopausal transition
  - bHCG, TSH, Prolactin (in certain situations, especially if < 45 yrs)
- Differential diagnosis: Thyroid disorders, medications, pregnancy, hyperprolactinemia, POI

Special situations

- If on OCPs??
  - Stop the pill and measure FSH 2 – 4 weeks later if > 25 then likely in menopause
- If they have had a hysterectomy or endometrial ablation??
  - Check FSH

The Stages of Reproductive Aging Workshop +10 staging system for reproductive aging in women



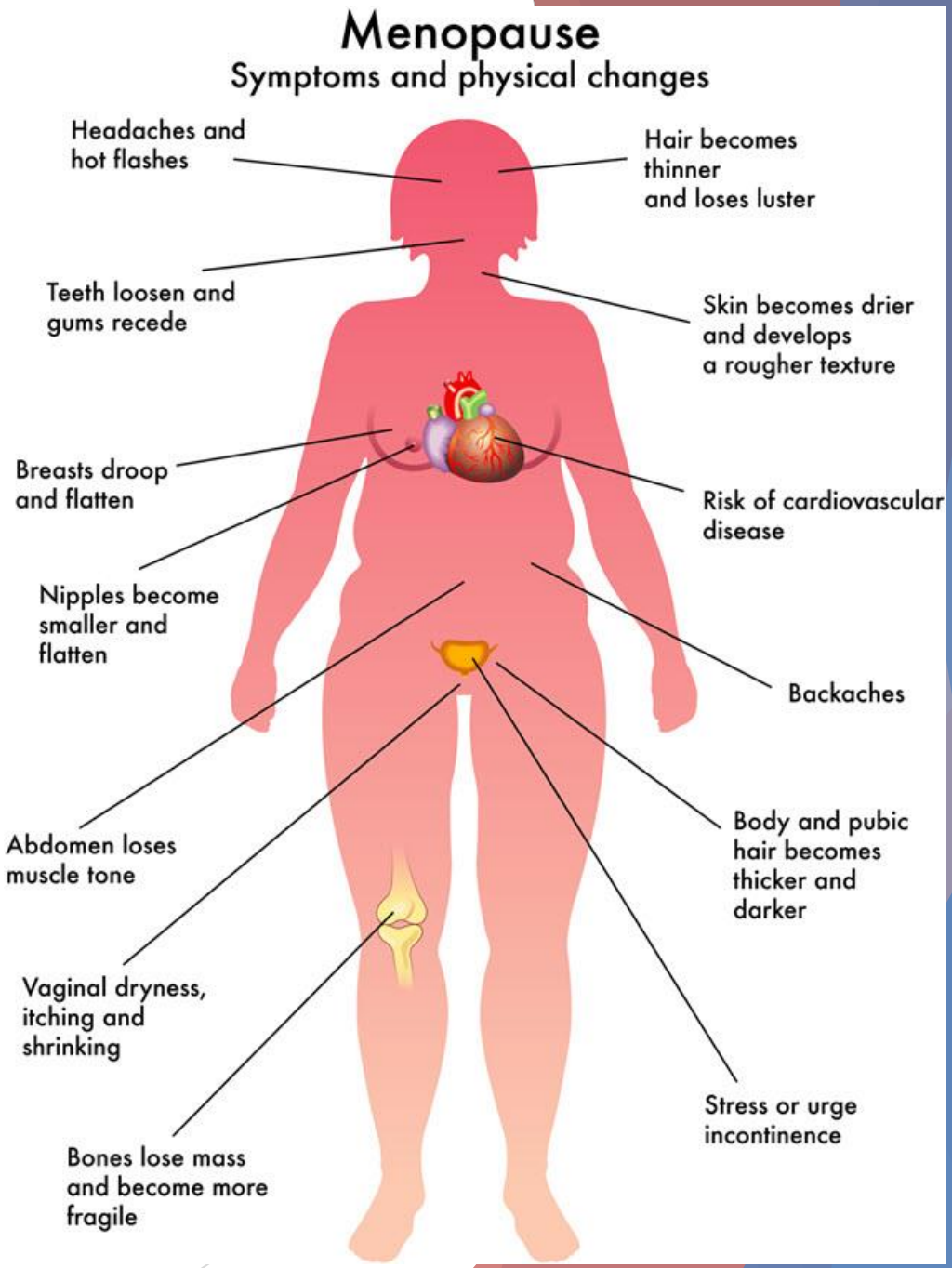
	Menarche					FMP (0)				
Stage	−5	−4	−3b	−3a	−2	−1	+1a	+1b	+1c	+2
Terminology	REPRODUCTIVE				MENOPAUSAL TRANSITION		POSTMENOPAUSE			
	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Duration	Variable				Variable	1-3 years	2 years (1+1)		3-6 years	Remaining lifespan
PRINCIPAL CRITERIA										
Menstrual cycle	Variable to regular	Regular	Regular	Subtle changes in flow/ strength	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 international units/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

FMP: final menstrual period; FSH: follicle-stimulating hormone; AMH: anti-müllerian hormone; Arrow: elevated.
* Blood draw on cycle days 2 to 5.
¶ Approximate expected level based on assays using current international pituitary standard.

Reproduced with permission from: Harlow SD, Gass M, Hall JE, et al. Executive Summary of the Stages of Reproductive Aging Workshop + 10: Addressing the Unfinished Agenda of Staging Reproductive Aging. J Clin Endocrinol Metab 2012.

Symptoms

- Hot flashes
  - most common symptom
  - 87% of women report symptoms
- Vaginal symptoms
  - 10-40% of women
  - Vaginal atrophy, dryness, dyspareunia
- Sleep disturbance, mood symptoms - depression



Hot flash “hot flush”

- Sudden sensation of extreme heat in upper body, neck, face, chest
- Last 1 – 5 minutes
- Chills, clamminess, anxiety, heart palpitations
- Causes:
  - Narrow thermoregulatory zone
  - Hormonal changes
  - neurotransmitters, norepinephrine, adrenalin
  - Genetics
- Risk factors
  - Race (African American highest), culture (diet), smoking
- Can persist for years after final menstrual periods

Vaginal symptoms

- Loss of estrogen
  - Lose superficial epithelial cells
  - Thinning of tissue, decrease elasticity, increase friability
  - Narrowing of vagina → dyspareunia

Treatment

- Lifestyle modification
- Medication

Lifestyle modifications

- Lower room temperature
- Layering of clothing
- Avoid alcohol and caffeine – associated with increased frequency of vasomotor symptoms
- Fans, ect

Hormone replacement – most effective therapy

- Estrogen alone or combined with progesterone
- Contraindications: breast cancer, CHD, h/o VTE, CVA, TIA, active liver disease, unexplained vaginal bleeding

Hormone replacement

- Treat with the lowest effective dose for the shortest amount of time (specific situations may be different – young patient – surgical menopause)
- Estrogen: PO, transdermal, topical or vaginal
- Progesterone continuous versus cyclic

Estrogen

- Oral, transdermal, topical, or vaginal
  - Oral less expensive
  - Transdermal decrease VTE and CVA – avoid first pass through liver
  - Vaginal, do not need to use progesterone if have uterus
- Conjugated Estrogen (CEE) from pregnant mare's urine

Vaginal Estrogen

- For women with vaginal symptoms
  - Cream, ring, tablet form
  - Give for 1 – 2 weeks daily then weekly maintenance therapy – tablet/cream
  - Ring usually placed every 3 months
  - Does not require a progesterone
  - Contraindicated in women with history of hormone sensitive breast cancer – because of possible systemic absorption

Vaginal lubricants and moisturizers

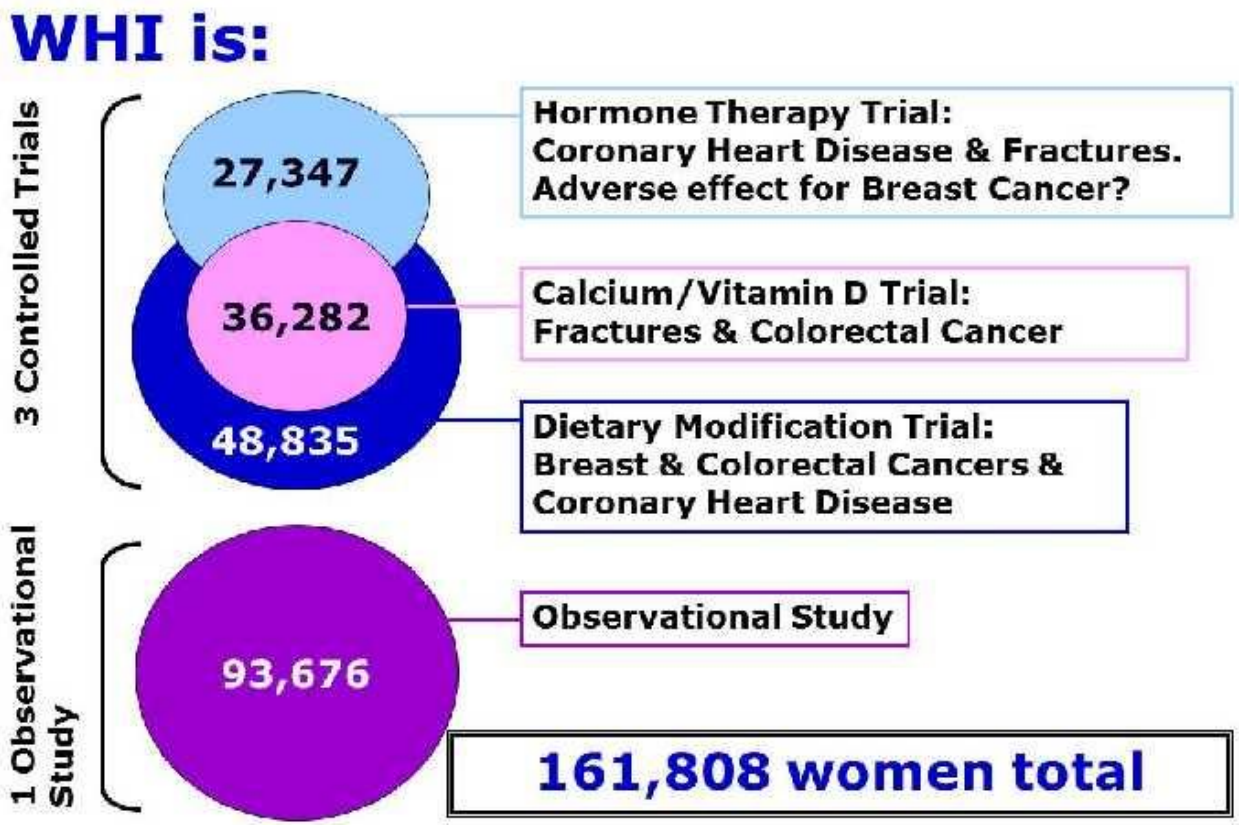
- Use especially in women contraindication to vaginal estrogen (h/o of breast cancer)
- Silicone based
- Water based
- Vagisil
- Replens

Progestin

- Used to protect endometrium
- Medroxyprogesterone acetate (used in WHI)
  - Cyclic or daily
- Micronized progesterone
- Mirena IUD can be used off label

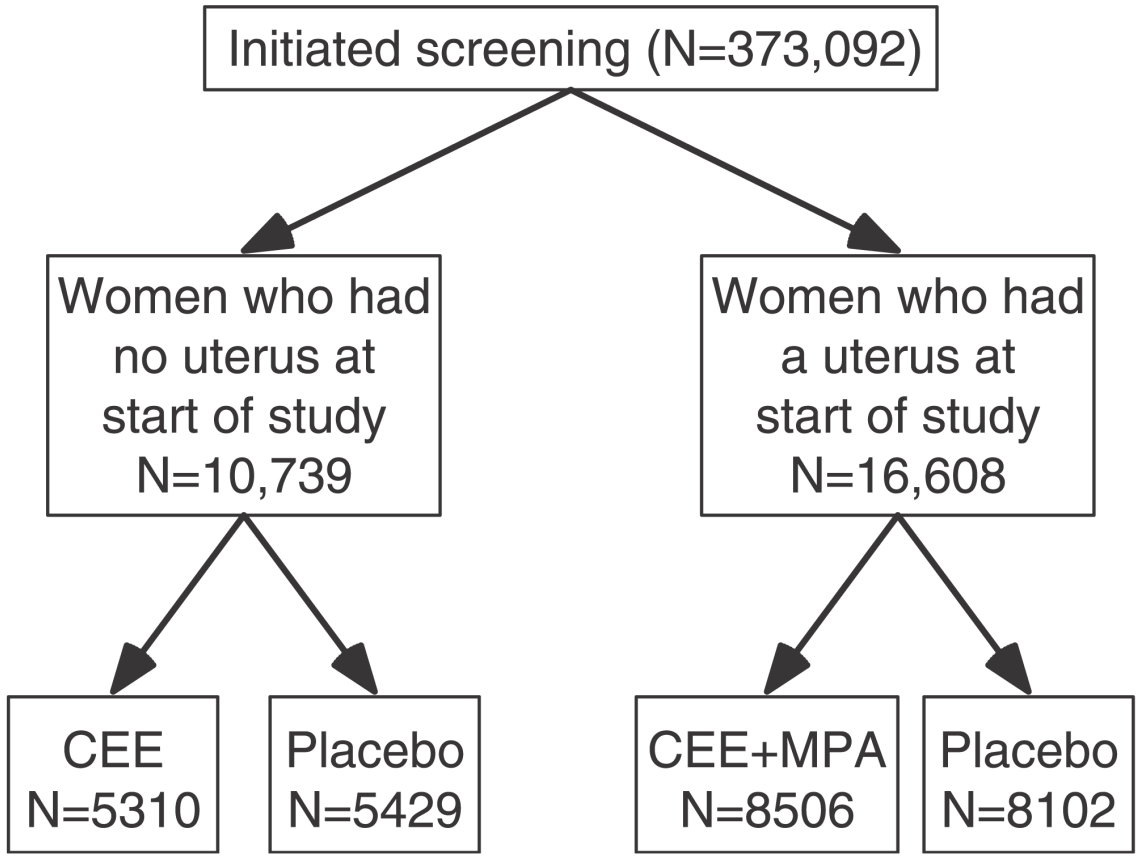
Women's Health Initiative (WHI)

- Launched in 1993 enrolled 161,808 women ages 50 -79 into RCT looking at HT, DM, and or calcium and Vitamin D supplementation or observation



WHI - HT

Women's Health Initiative Hormone Trials



Primary Outcome: prevention coronary heart disease (nonfatal MI, CHD, death), risk of breast cancer (primary adverse outcome)
Other outcomes: CVA, PE, endometrial cancer, colorectal cancer, hip fracture
death due to other causes
- Planned follow up 9 years

WHI – Study stopped early

2002 - Combo ended early
5.2 years

2004 -E2 ended early
6.8yrs

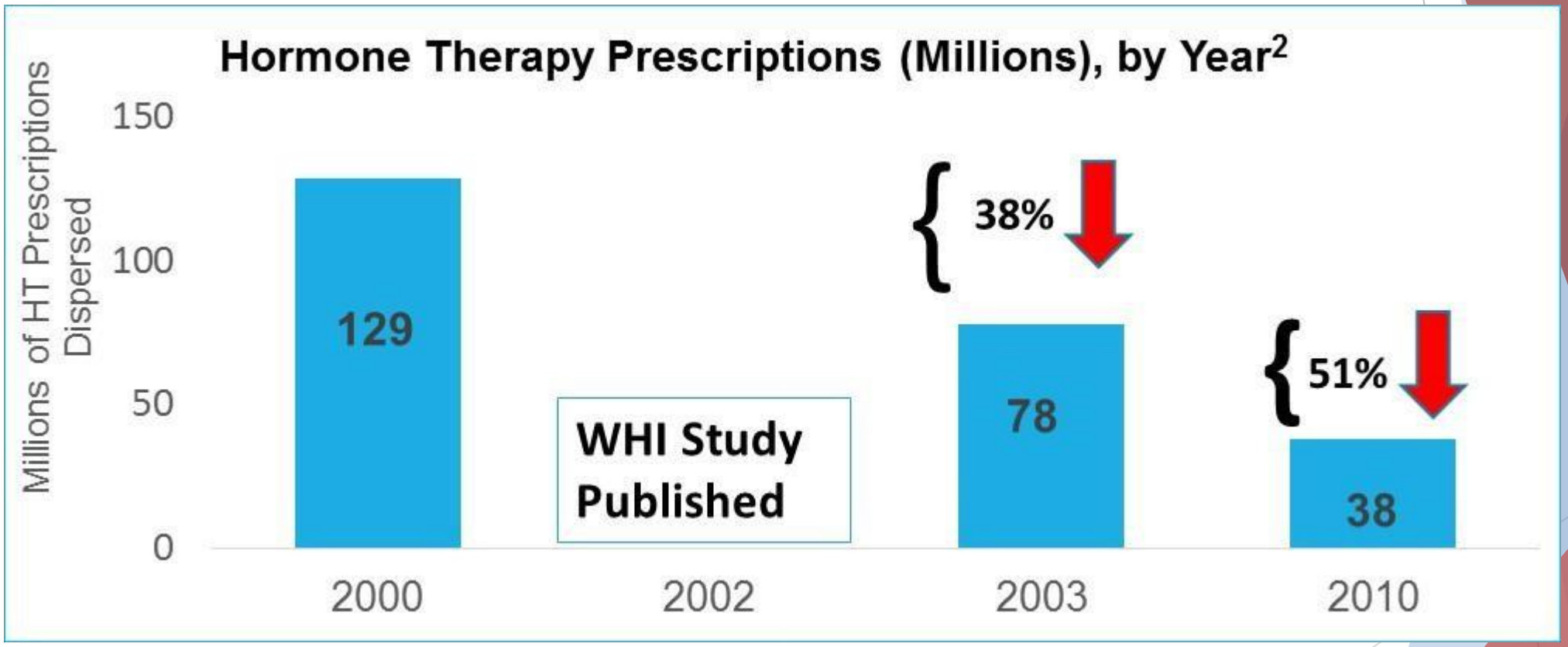
WHI results in 2002 found that post-menopausal women taking combination (estrogen and progestin) hormone therapy for menopause symptoms had an increased risk for breast cancer, heart disease, stroke, blood clots

	E+P v placebo	Number of persons	Absolute risk/10,000 persons	E only v placebo	Number of persons	Absolute risk/10,000 persons
CHD	+29%	37 vs 30	+7	-9%	49 vs 54	-5
CVA	+41%	29 vs 21	+8	+39%	44 vs 32	+12
VTE	+200%	34 vs 16	+18	+33%	28 vs 21	+7
Breast cancer	+26%	38 vs 30	+8	-23%	26 vs 33	-7
Colorectal cancer	-37%	10 vs 16	-6	0%	17 vs 16	+1
Hip fracture	-33%	10 vs 15	-5	-39%	11 vs 17	-6

Subset Analysis of WHI

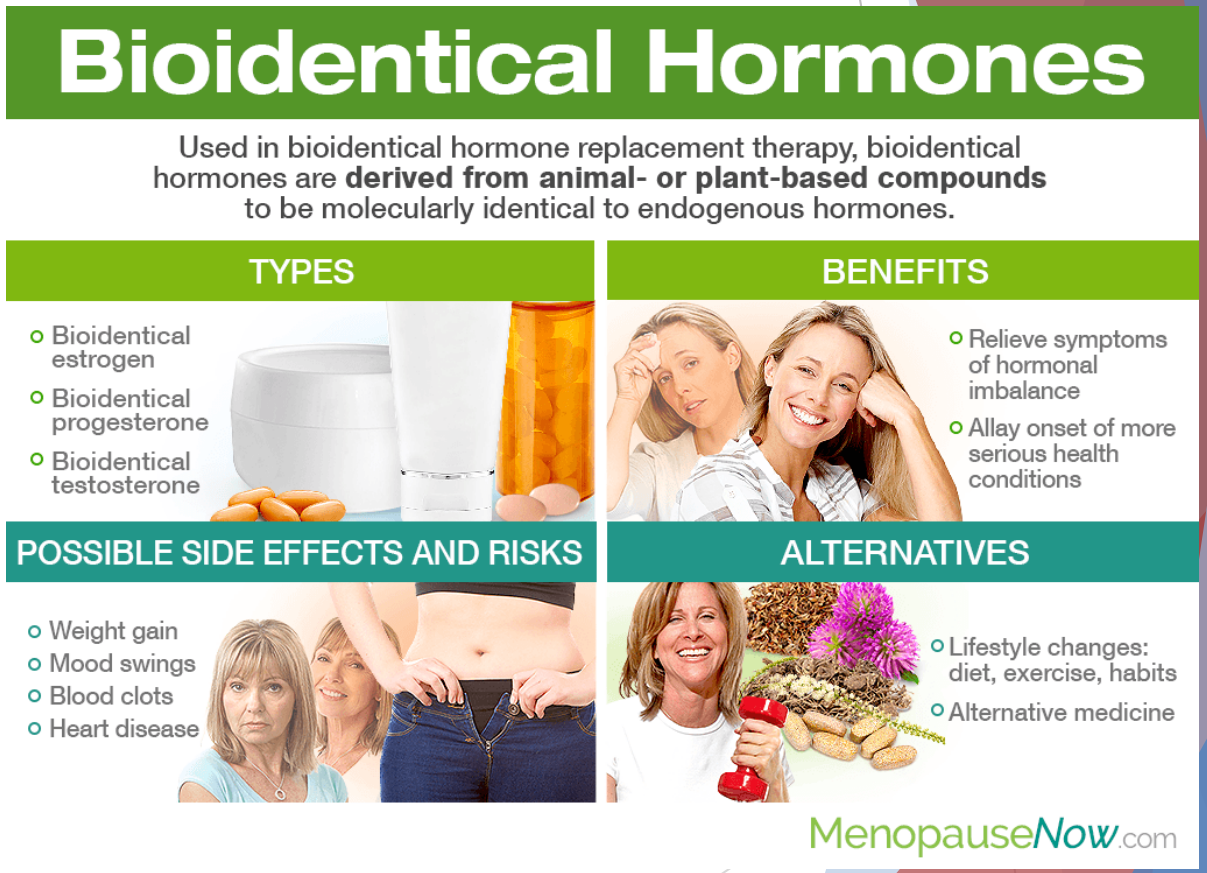
- Women <60yo and within 10yrs menopause
- Suggests possible cardiac benefit
- 50-59yo all cause mortality improved with HRT
- Women receiving estrogen only, no increased risk of cardiovascular events or breast cancer, but increase risk of VTE

Results of WHI



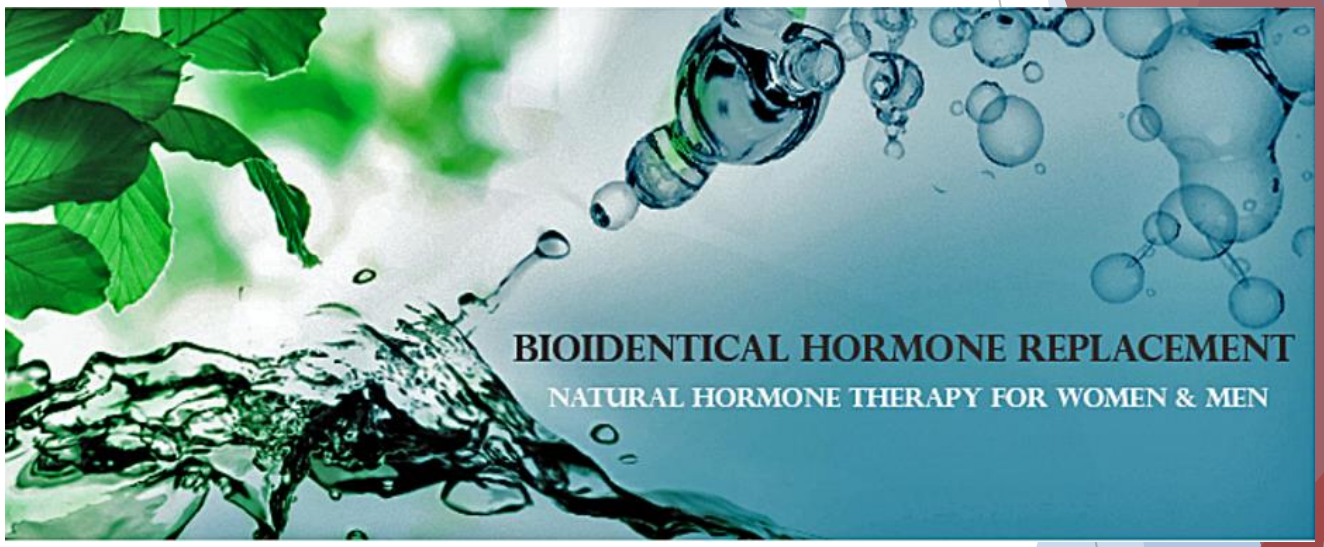
Bioidentical Hormone Therapy

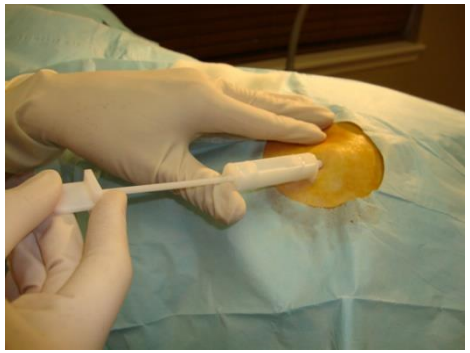
- Bioidentical hormones are chemically similar or structurally identical to
- Some are plant or animal derived
- Compounds lack oversight, so purity, potency, and quality of compounded preparations differ
- Risk of under-dosage and over-dosage



Bioidentical Hormone Therapy

- much more expensive
- not FDA regulated
- quality may be substandard
- no evidence for higher efficacy
- safety has not been established





SERM (Selective Estrogen Receptor Modulators)

- Estrogen agonist/antagonist – selective stimulate or inhibit estrogen receptors in different tissues
- Bazedoxifene
  - vasomotor symptoms and to prevent osteoporosis in postmenopausal women
- Ospemifene
  - Used for dyspareunia and vaginal atrophy
  - Does not stimulate endometrium
- Not first line, because increase risk of VTE

Non-hormonal medication

- SSRI/SNRI: most effective are venlafaxine (Effexor), desvenlafaxine, paroxitine, citalopram, escitalopram
  - Paroxetine only one that is FDA approved
  - RCT 62% of women treated had decrease in symptoms
- Gabapentin -off label use
  - RCT showed 45% reduction in hot flashes
- Clonidine – alpha 2 agonist
  - Systematic review showed a small benefit compared to placebo

Other Therapies

- Herbal therapies
  - Black Cohosh (plant) and Evening Primrose oil and Ginseng
  - Efficacy not proven but reported by women to help
- Soy products
- Vitamin E
- Reflexology

Table 1. Treatment Options for Menopausal Vasomotor Symptoms

Treatment	Dosage/Regimen	Evidence of Benefit*	FDA Approved
	Hormonal		
Estrogen-alone or combined with progestin			
• Standard Dose	Conjugated estrogen 0.625 mg/d	Yes	Yes
	Micronized estradiol-17β 1 mg/d	Yes	Yes
	Transdermal estradiol-17β 0.0375–0.05 mg/d	Yes	Yes
• Low Dose	Conjugated estrogen 0.3–0.45 mg/d	Yes	Yes
	Micronized estradiol-17β 0.5 mg/d	Yes	Yes
	Transdermal estradiol-17β 0.025 mg/d	Yes	Yes
• Ultra-Low Dose	Micronized estradiol-17β 0.25 mg/d	Mixed	No
	Transdermal estradiol-17β 0.014 mg/d	Mixed	No
Estrogen combined with estrogen agonist/antagonist	Conjugated estrogen 0.45 mg/d and bazedoxifene 20 mg/d	Yes	Yes
Progestin	Depot medroxyprogesterone acetate	Yes	No
Testosterone		No	No
Tibolone	2.5 mg/d	Yes	No
Compounded bioidentical hormones		No	No
	Nonhormonal		
SSRIs and SSNRIs		No	No
Paroxetine	7.5 mg/d	Yes	Yes
Clonidine	0.1 mg/d	Yes	No
Gabapentin	600–900 mg/d	Yes	No
Phytoestrogens		No	No
Herbal Remedies		No	No
Vitamins		No	No
Exercise		No	No
Acupuncture		No	No
Reflexology		No	No
Stellate-ganglion block		Yes	No

Abbreviations: FDA, U.S. Food and Drug Administration; SSRIs, selective serotonin reuptake inhibitors; SSNRIs, selective serotonin norepinephrine reuptake inhibitors.

*Compared with placebo.

Healthcare – Postmenopausal women

- PE, breast exam, pelvic exam yearly
- Mammogram every year starting age 40

Breast Cancer Screening Guidelines – Comparison

	ACR/SBI	ACS	ACOG	AMA	NCCN	USPSTF
Age to Start Mammography*	40	45 Option to start at age 40	Offer at 40, not later than 50	40	40	50
Age to Stop Mammography	No age limit; tailor to individual health status	When life expectancy is < 10 years	Age 75, then shared decision	Not stated	Not stated	74 years
Mammography Interval	Annual	Annual 45-54; Every 1 or 2 years 55 and older	Every 1 or 2 years	Annual	Annual	Every 2 years
View on Tomosynthesis (3D) Mammography	Improves cancer detection, reduces recall rates	Improvement in detection, lower chance of recall	Not stated	Not stated	Improves cancer detection, reduces recall rates	Insufficient evidence to support routine use; grade "I"

Rev. March 2018

* In a 2018 analysis from Harvard*, not considered in the current guidelines, black, Hispanic, and Asian women have peak incidence of breast cancer in their 40s and should begin screening at least by age 40. *Stapleton SM, Oseni TO, Bababekov YJ, Hung Y, Chang DC. Race/Ethnicity and Age Distribution of Breast Cancer Diagnosis in the United States. *JAMA Surg*. Published online March 7, 2018. doi:10.1001/jamasurg.2018.0035

- Dexa Scan – start at age 65 years in low risk women
  - Start earlier in high risk women – calculate based on FRAX score – predicts the risk of osteoporotic fracture in the next 10 years.

The 2017 hormone therapy position statement of The North American Menopause Society.

“Treatment should be individualized to identify the most appropriate HT type, dose, formulation, route of administration, and duration of use, using the best available evidence to maximize benefits and minimize risks, with periodic reevaluation of the benefits and risks of continuing or discontinuing HT.

For women aged younger than 60 years or who are within 10 years of menopause onset and have no contraindications, the benefit-risk ratio is most favorable for treatment of bothersome VMS and for those at elevated risk for bone loss or fracture. For women who initiate HT more than 10 or 20 years from menopause onset or are aged 60 years or older, the benefit-risk ratio appears less favorable because of the greater absolute risks of coronary heart disease, stroke, venous thromboembolism, and dementia.”

Questions?