Brigham and Women's Hospital
Founding Member, Mass General Brigham

Clinical Updates and Practical Considerations in Menopause Care

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CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE

HARVARD MEDICAL SCHOOL
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Disclosures summary of relevant financial relationships

Financial Disclosures: While not pertinent to the content of this lecture, I have served as a consultant for Bayer and Astellas within the past 24 months and currently serve on the Medical Advisory Board of Amissa, Inc.

In compliance with the ACCME, when I discuss specific healthcare products or services, I will use generic names to the extent possible. If I need to use trade names, I will use trade names from several companies when available, and not just trade names from any single company.

I value and respect each individual's gender identity and aim to be inclusive of all patients in need of our care. I recognize the limitations of applying inclusive language when source materials use gender-binary terms and descriptors, and thus I primarily use the terms female and woman when discussing perimenopause, menopause, and the genitourinary syndrome of menopause.

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- Clinical and research foci: Perimenopause and Menopause, Obesity Medicine

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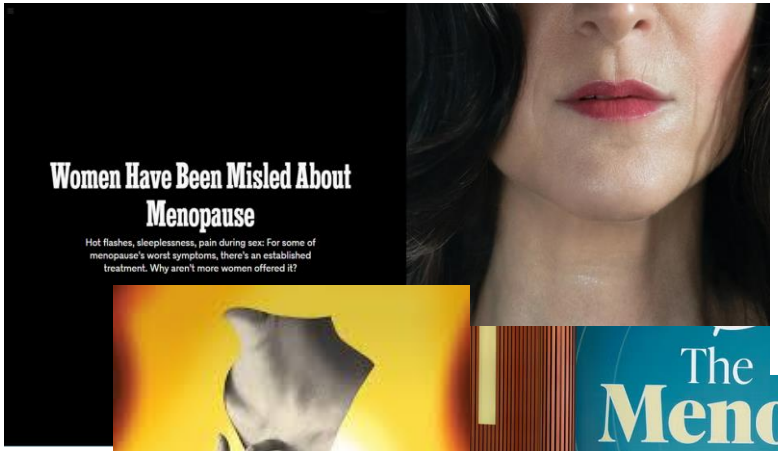
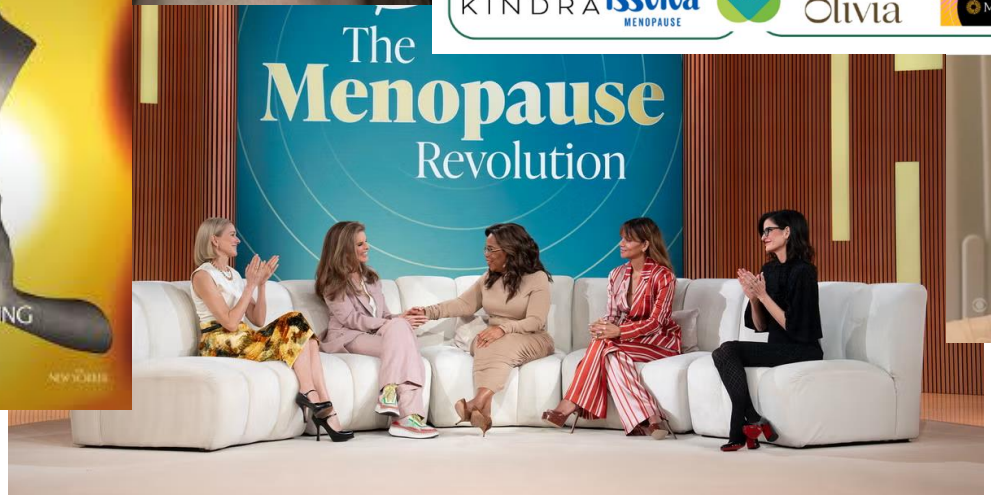
Learning Objectives:

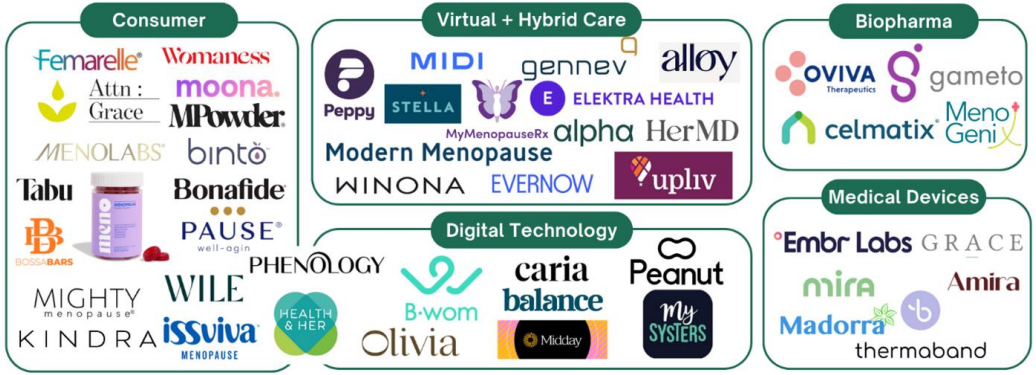
Upon completion of this activity, participants will be able to…

- Discuss the clinical evaluation of perimenopausal and menopausal patients
- Demonstrate knowledge of the appropriate use of hormone therapy and non-hormone medications in perimenopausal and menopausal women

Menopause is having a moment!







Terminology

- **Perimenopause:** The highly symptomatic time frame that exists from the first occurrence of menopause-related symptoms to one full year after the final menstrual period (FMP)
- **Natural Menopause:** Cessation of menses for 12 consecutive months after (FMP) due to loss of ovarian follicular activity
  - Early Menopause: < 45 yo
  - Late Menopause: > 55 yo
- **Induced Menopause:** Cessation of menses due to surgical or iatrogenic causes
- **Premature Ovarian Insufficiency (POI):** Menopause occurring < 40 yo

STRAW+10 Classification

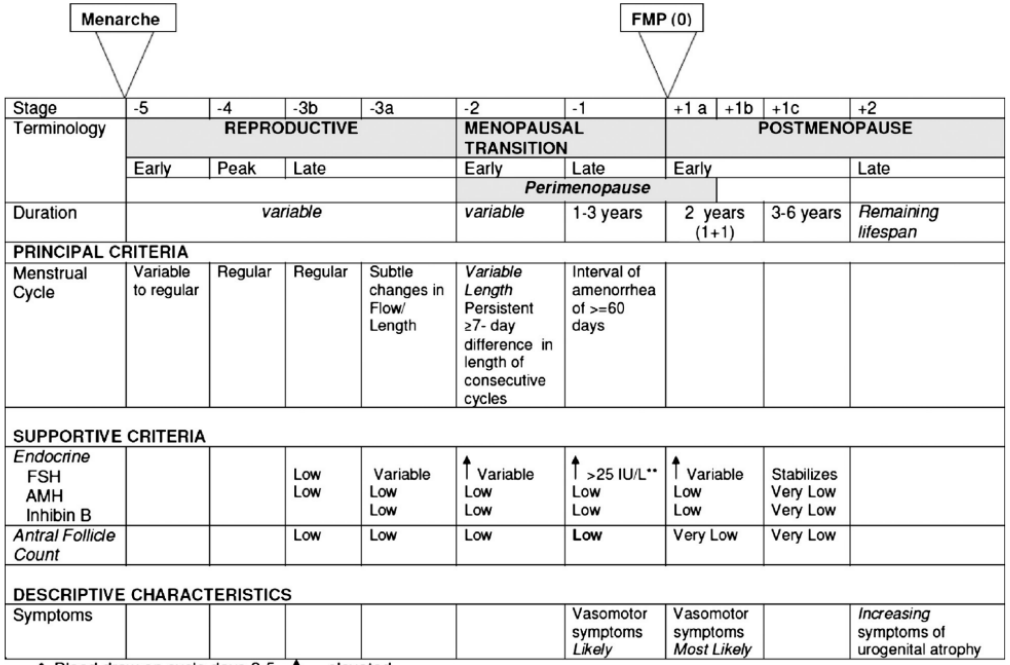
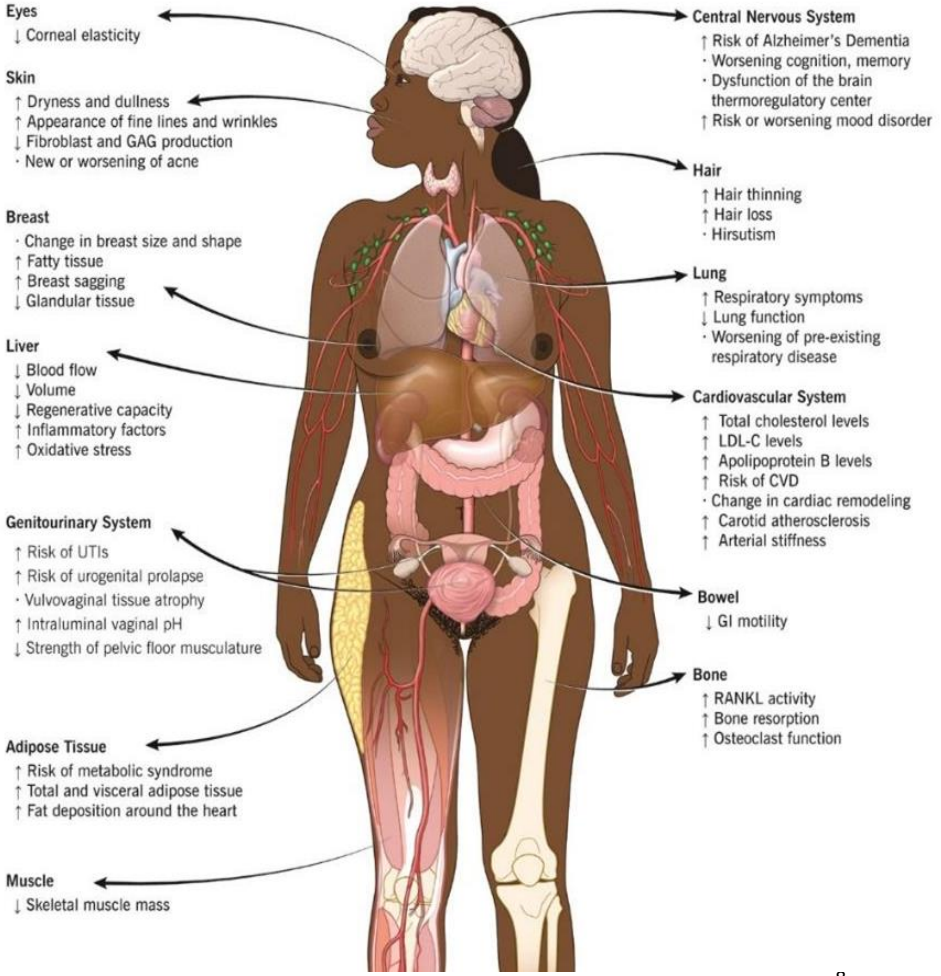


FIG. 2. The Stages of Reproductive Aging Workshop + 10 staging system for reproductive aging in women.

Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, Sherman S, Sluss PM, de Villiers TJ; STRAW+10 Collaborative Group. Executive summary of the Stages of Reproductive Aging Workshop +10: addressing the unfinished agenda of staging reproductive aging. Climacteric. 2012 Apr;15(2):105-14.

Perimenopausal and menopausal symptoms

- Estrogen affects every organ system in the body leading to a vast possible symptom profile
- Classic symptoms of the menopause transition
  - Change in bleeding patterns, vasomotor symptoms (VMS), genitourinary syndrome of menopause (GSM)
- Other symptoms associated with the menopause transition
  - Sleep disturbances
  - Cognitive concerns (brain fog, memory, concentration, word-finding difficulty)
  - Psychological symptoms
  - Musculoskeletal pain
  - Weight gain (esp. visceral distribution)
  - Headaches
  - Changes to skin, hair



Iyer TK, Thacker HL. "Menopause" In: Falcone T, Hurd WW. Editors. Clinical Reproductive Medicine and Surgery: A Practical Guide, 4th Edition Springer Nature; 2022.

Evaluation: perimenopause and menopause are both a clinical diagnosis!

- Clinical diagnosis
  - Perimenopause vs Menopause
- Utility of labs
  - FSH
  - 17-B-Estradiol
  - TSH
- Special considerations
  - Hysterectomy, endometrial ablation
  - Certain forms of contraception
  - Underlying menstrual disorders

Summary of hormones of reproductive aging by STRAW criteria

	Peak Reproductive	Late Reproductive	Early MT	Late MT		Postmenopause
FSH	Normal	↑	↑	↑		↑
AMH	Normal/↓	↓	↓	Undetectable	**FMP**	Undetectable
Inhibin B	Normal	↓	↓	Undetectable		Undetectable
Estradiol	Normal	Normal	Normal	↓		↓

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CASE #1

52 yo woman presenting with hot flashes, night sweats, mood swings, sleep disturbance, hair thinning and joint pain. It has been 14 months since her last menstrual period.

- PMHx: hypertension, overweight (BMI 29.7), hypothyroidism
- PSHx: none
- Medications: losartan, levothyroxine

What therapy is most effective to treat her symptoms?

Image from: https://www.health.harvard.edu/blog/menopause-related-hot-flashes-night-sweats-can-last-years-201502237745

What therapy is most effective to considered gold standard to treat her vasomotor symptoms?

A. Gabapentin 300 mg nightly
B. Venlafaxine 37.5 mg daily
C. Estradiol transdermal patch 0.0375 mg/day every 3.5 days + Progesterone 100 mg nightly
D. Lifestyle modification (weight loss, trigger avoidance, cooling techniques, mind-body techniques, etc.)

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Management of menopausal symptoms

- Gold standard of treatment: menopausal hormone therapy (MHT)
- FDA-approved for:
  - Vasomotor symptoms
  - Genitourinary syndrome of menopause
  - Prevention of bone loss/ fracture reduction in postmenopausal women
  - Mitigation of early estrogen loss in surgical menopause/ POI

Image from: https://news.cancerconnect.com/treatment-care/hormonal-therapy

Prescribing hormone therapy

- Hormone Therapy: FDA-approved for the treatment of menopausal symptoms
  - **Estrogen alone** – unopposed estrogen for women who are s/p hysterectomy; or can be used locally for GSM
  - **Estrogen + Progestogen** – for women with intact uterus to protect endometrial lining
    - Reasons to consider progestogen use in hysterectomized women
      - History of endometriosis with concern for remnant endometrial tissue
      - For significant sleep/nighttime anxiety issues
  - **Bioidentical HT** – chemically identical to those made in the body
    - Unregulated – unapproved and untested from various compounding pharmacies
    - Regulated – FDA approved and tested
- Important counseling points: route/dosing, duration of therapy, side effects, risks/benefits

Dosage ranges

Have a “go-to” prescription: Transdermal estradiol 0.0375 - 0.05 mg/24h patch 1-2x/week or estradiol gel 0.5-1 mg daily + 100 mg micronized progesterone nightly

Estrogen	Route	Typical dose range	Frequency	Equivalent dose
17-β estradiol	Oral	0.5-2 mg	Daily	1 mg
	Patch	0.014-0.1 mg	Once or twice weekly	0.05 mg
	Gel pouch	0.25-1.25 mg	Daily	1 mg
	Gel pump	1-4 pumps (0.52-0.75 mg/pump)	Daily	1-2 pumps
	Spray	1-3 sprays (1.53 mg /spray)	Daily	2-3 sprays
Conjugated equine estrogen	Oral	0.3-1.25 mg	Daily	0.625
Conjugated estrogen	Oral	0.3-1.25 mg	Daily	0.625 mg
Ethinyl estradiol	Oral	0.01-0.03 mg	Daily	0.01-0.015 mg
Esterified estrogen	Oral	0.3-2.5 mg	Daily	0.625 mg
Estradiol acetate	Vaginal ring	0.05 mg; 0.10 mg	90 days	0.05 mg

Table adapted from: Duralde ER, Sobel TH, Manson JE. Management of perimenopausal and menopausal symptoms. bmj. 2023 Aug 8;382.

Progestogen	Route	Dose range	Frequency	Side effects
Micronized progesterone	Oral	100-300 mg; 200-300 mg (300 mg rarely needed)	Daily; cycled	Somnolence, fatigue, bloating, abdominal pain, nausea, dizziness
Levonorgestrel	IUD	52 mg*†	5 years (approved in EU, off-label in US)	Pain with placement, pelvic pain, breast pain, irregular bleeding and spotting, acne, abdominal pain, nausea, dizziness, headache, fatigue
Drospirenone	Oral	4 mg*†	Daily	Acne, weight gain, nausea, headache, breast tenderness, low libido, hyperkalemia
Medroxyprogesterone acetate	Oral (depo unstudied)	2.5-5 mg; 5-10 mg	Daily; cycled	Bloating, weight gain, abdominal pain, dizziness, fatigue
Norethindrone‡	Oral	0.35-0.7 mg*†; 0.7 mg	Daily; cycled	Nausea, headache, breast tenderness
Norethindrone acetate	Oral	2.5 mg*† (lowest dose needed is 0.5 mg, but 2.5 mg is smallest dose available)	Daily; cycled	Edema, nausea, breast tenderness
Megestrol acetate	Oral	20-40 mg	Daily	Hypertension, rash, hot sweats, weight gain, diarrhea, nausea, insomnia, mood swings
Micronized progesterone	Capsule inserted vaginally†§	100-300 mg; 200-300 mg	Daily; cycled	As above for oral consumption, to a lesser degree
Progesterone	Vaginal gel†§	4-8% (45-90 mg); 8%	Daily; cycled	Same as oral micronized progesterone, to a lesser degree

Table adapted from: Duralde ER, Sobel TH, Manson JE. Management of perimenopausal and menopausal symptoms. bmj. 2023 Aug 8;382.

Combined estrogen-progestogen	Route	Dose range	Frequency
17-β estradiol + norethindrone acetate	Patch	0.05 mg+0.14 mg; 0.05 mg+0.25 mg	Twice weekly
	Oral	0.5 mg+0.1 mg; 1.0 mg+0.5 mg	Daily
17-β estradiol + levonorgestrel	Patch	0.045 mg+0.015 mg	Weekly
Conjugated equine estrogen + medroxyprogesterone acetate	Oral	0.625 mg+5 mg	CEE daily; CEE+MPA on days 15-28
		0.3 mg+1.5 mg; 0.45 mg+1.5 mg; 0.625 mg+2.5 mg; 0.625 mg+5 mg	Daily
17-β estradiol + norgestimate	Oral	1 mg+0.09 mg	Cyclic
17-β estradiol + micronized progesterone	Oral	0.5 mg+100 mg; 1 mg+100 mg	Daily
17-β estradiol + drospirenone	Oral	0.5 mg+0.25 mg; 1mg+0.5 mg; 1 mg+1 mg	Daily
Conjugated estrogens + bazedoxifene	Oral	20 mg+0.45 mg; 20 mg+0.625 mg	Daily
Ethinyl estradiol+NETA	Oral	2.5 µg+0.5 mg; 5 µg+1 mg	Daily

Table adapted from: Duralde ER, Sobel TH, Manson JE. Management of perimenopausal and menopausal symptoms. bmj. 2023 Aug 8;382.

CASE #1 continued…

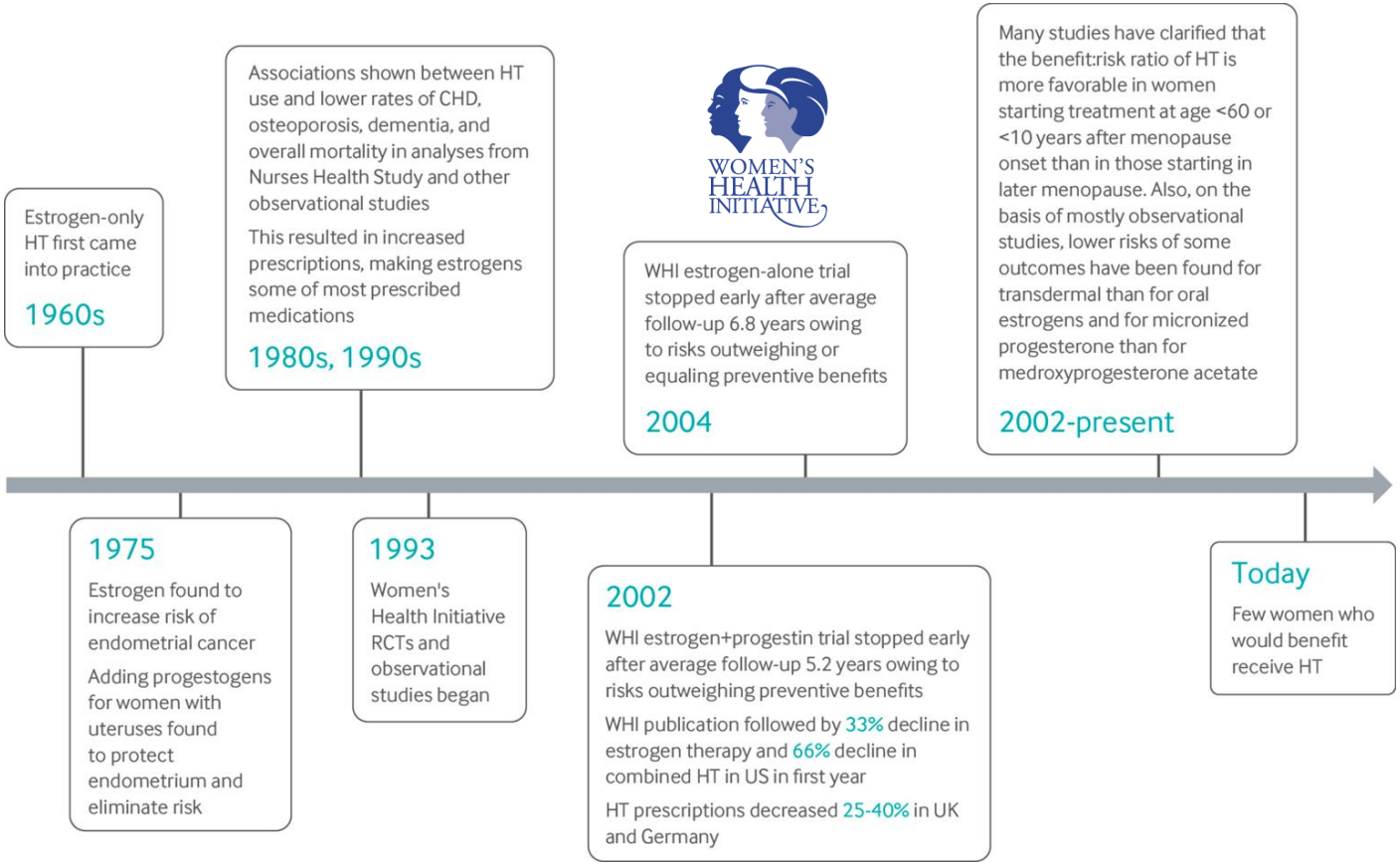
You recommend menopausal hormone therapy for this patient.

She is weary of taking hormones, reporting she has heard they can cause breast cancer and other health problems. She is also worried about side effects.

How would you counsel this patient?

Image from: https://www.health.harvard.edu/blog/menopause-related-hot-flashes-night-sweats-can-last-years-201502237745

Controversy over hormone therapy explained: a timeline

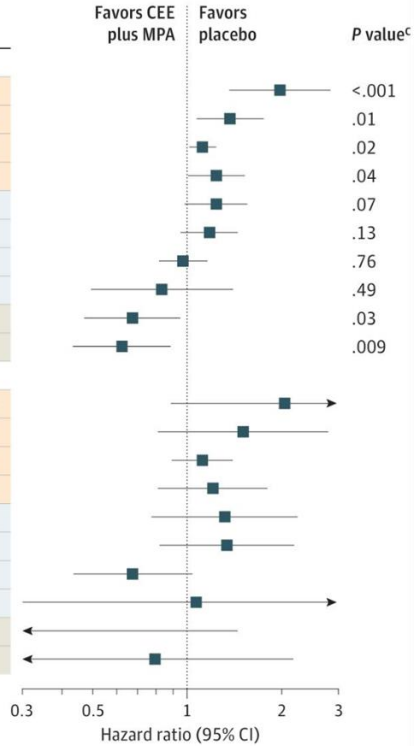


Duralde ER, Sobel TH, Manson JE. Management of perimenopausal and menopausal symptoms. bmj. 2023 Aug 8;382.

Women's Health Initiative (WHI) Data: CEE+MPA

A CEE plus MPA

Health outcomes	Annualized rate, No. (%)[a] CEE plus MPA	Placebo	Difference per 10 000 person-years[b]	Hazard ratio (95% CI)
CEE plus MPA trial, full cohort (N = 16 608)				
Pulmonary embolism[d]	87 (0.18)	41 (0.09)	+9	1.98 (1.36-2.87)
Stroke[d]	159 (0.33)	109 (0.24)	+9	1.37 (1.07-1.76)
Global index[d]	876 (1.89)	736 (1.68)	+20	1.12 (1.02-1.24)
Invasive breast cancer[e]	206 (0.43)	155 (0.35)	+9	1.24 (1.01-1.53)
Myocardial infarction[d]	168 (0.35)	129 (0.29)	+6	1.24 (0.98-1.56)
Coronary heart disease[e]	196 (0.41)	159 (0.35)	+6	1.18 (0.95-1.45)
All-cause mortality[d]	250 (0.52)	238 (0.53)	-1	0.97 (0.81-1.16)
Endometrial cancer[d]	27 (0.06)	30 (0.07)	-1	0.83 (0.49-1.40)
Hip fracture[d]	53 (0.11)	75 (0.17)	-6	0.67 (0.47-0.95)
Colorectal cancer[d]	50 (0.10)	75 (0.17)	-6	0.62 (0.43-0.89)
CEE plus MPA trial, age 50-59 y (n = 5520)				
Pulmonary embolism[d]	18 (0.11)	8 (0.05)	+6	2.05 (0.89-4.71)
Stroke[d]	26 (0.15)	16 (0.10)	+5	1.51 (0.81-2.82)
Global index[d]	170 (1.03)	141 (0.91)	+12	1.12 (0.89-1.40)
Invasive breast cancer[e]	55 (0.33)	42 (0.27)	+6	1.21 (0.81-1.80)
Myocardial infarction[d]	32 (0.19)	23 (0.15)	+4	1.32 (0.77-2.25)
Coronary heart disease[e]	38 (0.23)	27 (0.17)	+5	1.34 (0.82-2.19)
All-cause mortality[d]	35 (0.21)	48 (0.31)	-10	0.67 (0.43-1.04)
Endometrial cancer[d]	6 (0.04)	5 (0.03)	0	1.07 (0.33-3.53)
Hip fracture[d]	1 (0.01)	5 (0.03)	-3	0.17 (0.02-1.45)
Colorectal cancer[d]	7 (0.04)	8 (0.05)	-1	0.79 (0.29-2.18)

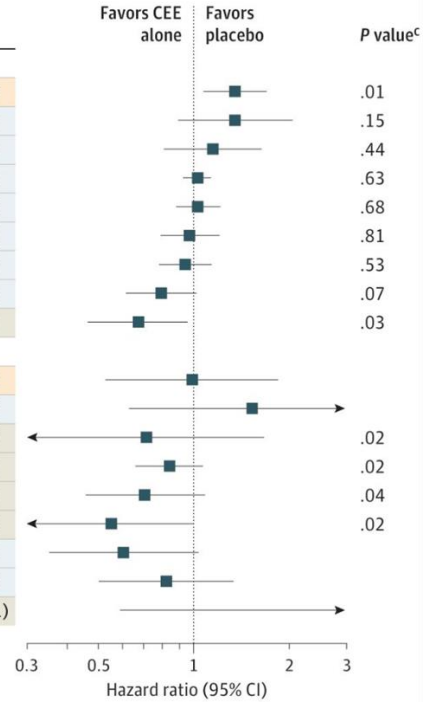


Manson JE, Crandall CJ, Rossouw JE, et al. The Women's Health Initiative Randomized Trials and Clinical Practice: A Review. *JAMA*. 2024;331(20):1748–1760. doi:10.1001/jama.2024.6542

WHI data: CEE alone

B CEE alone

Health outcomes	Annualized rate, No. (%)[a] CEE alone	Placebo	Difference per 10 000 person-years[b]	Hazard ratio (95% CI)	P value[c]
CEE-alone trial, full cohort (N = 10 739)					
Stroke[d]	169 (0.45)	130 (0.34)	+11	1.35 (1.07-1.70)	.01
Pulmonary embolism[d]	52 (0.14)	39 (0.10)	+4	1.35 (0.89-2.05)	.15
Colorectal cancer[d]	65 (0.17)	58 (0.15)	+2	1.15 (0.81-1.64)	.44
Global index[d]	753 (2.08)	755 (2.04)	+4	1.03 (0.93-1.13)	.63
All-cause mortality[d]	301 (0.80)	299 (0.77)	+3	1.03 (0.88-1.21)	.68
Myocardial infarction[d]	164 (0.44)	173 (0.45)	-1	0.97 (0.79-1.21)	.81
Coronary heart disease[e]	204 (0.55)	222 (0.58)	-3	0.94 (0.78-1.14)	.53
Invasive breast cancer[e]	104 (0.28)	135 (0.35)	-7	0.79 (0.61-1.02)	.07
Hip fracture[d]	48 (0.13)	74 (0.19)	-6	0.67 (0.46-0.96)	.03
CEE-alone trial, age 50-59 y (n = 3313)					
Stroke[d]	19 (0.16)	21 (0.17)	−1	0.99 (0.53-1.85)	
Pulmonary embolism[d]	12 (0.10)	8 (0.06)	+3	1.53 (0.63-3.75)	
Colorectal cancer[d]	9 (0.07)	13 (0.10)	-3	0.71 (0.30-1.67)	.02
Global index[d]	117 (0.98)	142 (1.17)	-19	0.84 (0.66-1.07)	.02
All-cause mortality[d]	35 (0.29)	50 (0.40)	-11	0.70 (0.46-1.09)	.04
Myocardial infarction[d]	17 (0.14)	31 (0.25)	-11	0.55 (0.31-1.00)	.02
Coronary heart disease[e]	21 (0.17)	35 (0.28)	-11	0.60 (0.35-1.04)	
Invasive breast cancer[e]	29 (0.24)	36 (0.29)	-5	0.82 (0.50-1.34)	
Hip fracture[d]	5 (0.04)	1 (0.01)	+3	5.01 (0.59-42.91)	



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The Timing Hypothesis

When initiated under the age of 60 years old or within 10 years from menopause in otherwise healthy women, hormone therapy demonstrates greater benefits than risks.

Long term benefits of MHT	Absolute risks of MHT
Reduction in all-cause mortality in pooled WHI trials	In women aged 50-59 years, the absolute risks of MHT are rare (<10 cases/10,000/y), but include increased: ● Breast cancer incidence (no increased mortality risk) ● Blood clot (VTE/Stroke/PE) with oral estrogen therapy ● Gallbladder disease primarily with oral estrogen therapy
Reduction in risk of osteoporotic fractures	
Reduction in incidence of colon cancer	
Reduction in incidence of Diabetes Mellitus	

Manson JE, Crandall CJ, Rossouw JE, et al. The Women's Health Initiative Randomized Trials and Clinical Practice: A Review. *JAMA*. 2024;331(20):1748–1760. doi:10.1001/jama.2024.6542

Contextualizing breast cancer data for patients

- Women should be counseled about the risk of breast cancer with hormone therapy, putting the data into perspective, with risk similar to that of modifiable risk factors
  - Relative risk of breast cancer incidence with MHT is similar to:
    - Moderate alcohol consumption
    - High fat diet
- Recognize patient confusion: the data is complex, there are still many gaps, and even experts do not fully agree
  - Breast cancer risk may vy by MHT type, formulation, route, and duration of use

Faubion SS, Crandall CJ, Davis L, El Khoudary SR, Hodis HN, Lobo RA, Maki PM, Manson JE, Pinkerton JV, Santoro NF, Shifren JL. The 2022 hormone therapy position statement of The North American Menopause Society.

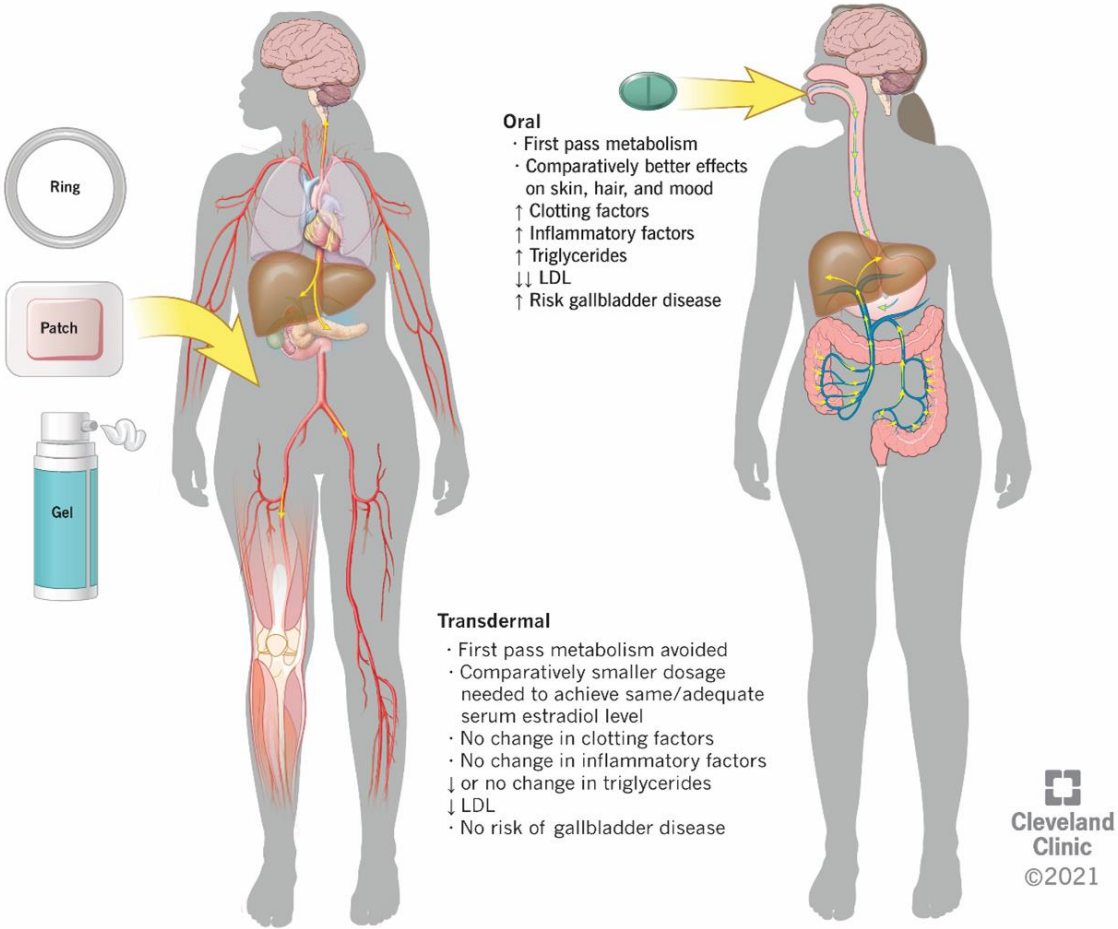
Formulation considerations in BC risk: CEE vs estradiol

- CEE-only users experienced a reduction in breast cancer incidence and mortality compared to controls
  - Intervention phase only (7.2 years): Nonsignificant reduction, 0.28% vs 0.35% (HR 0.79; 95% CI, 0.61-1.02)
  - 10.7-year cumulative follow-up: Statistically significant, HR 0.77 (95% CI, 0.62-0.95)
  - 12- and 20-year cumulative follow-up: **Statistically significant reductions persisted**
- Estradiol formulations
  - No large randomized trial has evaluated estradiol alone for breast cancer outcomes
  - A meta-analysis of 5 smaller RCTs using estradiol formulations showed a non-significant trend toward reduced risk (RR 0.63; 95% CI, 0.34-1.16; P=0.15)

Manson JE, Crandall CJ, Rossouw JE, et al. The Women's Health Initiative Randomized Trials and Clinical Practice: A Review. *JAMA*. 2024;331(20):1748–1760. doi:10.1001/jama.2024.6542
Chlebowski RT, Aragaki AK, Pan K, Mortimer JE, Johnson KC, Wactawski-Wende J, LeBoff MS, Lavasani S, Lane D, Nelson RA, Manson JE. Randomized trials of estrogen-alone and breast cancer incidence: a meta-analysis. Breast Cancer Res Treat. 2024 Jul;206(1):177-184. doi: 10.1007/s10549-024-07307-9. Epub 2024 Apr 23. PMID: 38653905.

VTE/Stroke risk: TD vs oral MHT

- Large (n=80,396) two nested case control study 2019: Transdermal HT was NOT associated with any increased risk of VTE and consistent among various regimens
- Transdermal HT has not been associated with VTE/stroke risk in multiple observational studies; though no RCTs have been specifically designed to compare transdermal vs. oral estrogen for clinical VTE or stroke endpoints



Iyer TK, Thacker HL. “Menopause” In: Falcone T, Hurd WW. Editors. Clinical Reproductive Medicine and Surgery: A Practical Guide, 4th Edition Springer Nature; 2022.
Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. bmj. 2019 Jan 9;364.

Menopausal hormone therapy and CVD prevention

- Current guidelines recommend against the use of MHT for prevention of CVD at this time (TMS, ACOG, Endocrine Society, AACE) based on available evidence
- A cochrane systematic review evaluating RCTs of MHT for preventing CHD in postmenopausal women showed:
  - Among women initiating MHT at <60 years of age or <10 years since menopause showed:
    - CHD risk was reduced by roughly half (RR, 0.52 [95% CI, 0.29–0.96])
    - All-cause mortality by 30% (RR, 0.70 [95% CI, 0.52–0.95])
    - Venous thromboembolism was increased (RR, 1.74 [95% CI, 1.11–2.73])
  - Among women initiating MHT at >60 years of age or >10 years since menopause
    - High quality evidence demonstrating MHT had no effect on CHD or all-cause mortality
    - Risks for stroke and venous thromboembolism were increased
- Long term RCT data on transdermal estradiol and micronized progesterone is lacking

El Khoudary SR, Aggarwal B, Beckie TM, Hodis HN, Johnson AE, Langer RD, Limacher MC, Manson JE, Stefanick ML, Allison MA; American Heart Association Prevention Science Committee of the Council on Epidemiology and Prevention; and Council on Cardiovascular and Stroke Nursing. Menopause Transition and Cardiovascular Disease Risk: Implications for Timing of Early Prevention: A Scientific Statement From the American Heart Association. Circulation. 2020 Dec 22;142(25):e506-e532. doi: 10.1161/CIR.0000000000000912. Epub 2020 Nov 30. PMID: 33251828.

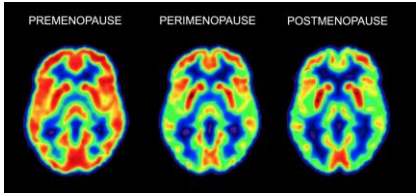
Boardman HM, Hartley L, Eisinga A, Main C, Roque I Figuls M, Bonfill Cosp X, Gabriel Sanchez R, Knight B. Hormone therapy for preventing cardiovascular disease in post-menopausal women. Cochrane Database Syst Rev. 2015CD002229. doi: 10.1002/14651858.CD002229.pub4

Menopausal hormone therapy and dementia: Mixed outcomes!

Study	Design / Population	Main Finding	Reference
WHIMS: CEE + MPA	RCT; women ≥65 yrs	↑ **Dementia risk:** HR 2.05 (1.21–3.48)	Shumaker et al., JAMA, 2003
WHIMS: CEE alone	RCT; women ≥65 yrs	↑ **Dementia/MCI:** HR 1.38 (1.01–1.89)	Shumaker et al., JAMA, 2004
RCT meta-analysis	RCTs, older women	↑ Dementia overall (RR 1.38); driven by EPT (RR 1.64); ET neutral	Nerattini et al., Front Aging Neurosci, 2023
Danish nationwide study	Nested case-control; midlife	↑ **Dementia with EPT:** HR 1.24; dose-response with longer use	Pourhadi et al., BMJ, 2023
UK QResearch/CPRD	Large population case-control	No overall increased risk; **ET ≥10 yrs ↓ risk**; EPT ↑ AD risk slightly	Vinogradova et al., BMJ, 2021
Observational meta-analysis	45 studies, >5M women	↓ **AD risk:** RR 0.78; ↓ all-cause dementia: RR 0.81; strongest with ET	Nerattini et al., Front Aging Neurosci, 2023
2025 meta-analysis (observational)	Large pooled observational data	↓ Dementia/AD risk -11% overall; greater with midlife ET	Mosconi et al., 2025

Menopausal hormone therapy and dementia

- Evidence is conflicting and not definitive
  - RCTs (older women ≥65) → consistently show increased dementia risk, especially with estrogen + progestogen
    - WHI data: HT use was not associated with increased mortality from AD or dementia at 18 year follow-up
  - Observational data (midlife initiation) → suggest neutral to reduced risk, particularly with estrogen-only therapy
  - Timing likely matters, but remains unproven and debated
  - Long term RCT data on transdermal estradiol and micronized progesterone is lacking
- Formulation may play a role:
  - ET → more favorable signal
  - EPT → more consistently associated with harm or no benefit with progesterone formulations more favorable than progestin formulations
- Current guidelines recommend against the use of MHT for prevention of Dementia at this time (TMS, ACOG, Endocrine Society, AACE) based on available evidence



Faubion SS, Crandall CJ, Davis L, El Khoudary SR, Hodis HN, Lobo RA, Maki PM, Manson JE, Pinkerton JV, Santoro NF, Shifren JL. The 2022 hormone therapy position statement of The North American Menopause Society. Menopause. 2022 Jul 1;29(7):767-94

Relative contraindications to HT: Menopause Society 2022 Hormone Therapy Position Statement

Severe active liver disease
History of estrogen-sensitive malignancy
Porphyria Cutanea Tarda
History of deep vein thrombosis
History of pulmonary embolism
History of stroke
Coronary Heart Disease
Unexplained vaginal bleeding that has not been evaluated

Faubion SS, Crandall CJ, Davis L, El Khoudary SR, Hodis HN, Lobo RA, Maki PM, Manson JE, Pinkerton JV, Santoro NF, Shifren JL. The 2022 hormone therapy position statement of The North American Menopause Society. Menopause. 2022 Jul 1;29(7):767-94.

Duration of use for systemic hormone therapy

- Hormone replacement therapy is gold standard of care in patients < 45 years old to mitigate deleterious effects of early estrogen loss and should be continued at least until the average age of menopause (~52 years old)
- Per Menopause Society Guidelines, hormone therapy does not need to be routinely discontinued in women aged older than 60 or 65 years
- Longer durations or extended use beyond age 65 years should be considered with periodic reevaluation (at minimum annually) considering severity of symptoms, comorbid conditions, periodic trials of lowering or discontinuing hormone therapy, effectiveness of alternative nonhormone interventions, patient preferences and response to hormone therapy, and underlying risk for osteoporosis, CHD, cerebrovascular accident, VTE, and breast cancer
- As women age, it is recommended to consider risk mitigation using lowest effective dose, nonoral therapy

Faubion SS, Crandall CJ, Davis L, El Khoudary SR, Hodis HN, Lobo RA, Maki PM, Manson JE, Pinkerton JV, Santoro NF, Shifren JL. The 2022 hormone therapy position statement of The North American Menopause Society. Menopause. 2022 Jul 1;29(7):767-94.

CASE #2

A 48 year old woman presents for an annual exam.

She reports her periods have become irregular. Her LMP was 15 days ago and her period was very heavy lasting 9 days. Prior to this month she had not had a period in 2 months. She also endorses intermittent hot flashes/night sweats, sleep changes, and recent weight gain despite no changes to her diet or exercise regimen.

PMHx: Brief hx of tobacco use as a teenager, but has not smoked since she was 19

PSHx: none

Contraception: Husband with vasectomy

What treatment options should you discuss with her?

Image from: https://atriumhealth.org/dailydose/2020/03/09/every-woman-goes-through-menopause-at-some-point-know-how-to-manage

Which of the following is a treatment option for this patient?

A. Cycled progesterone 200 mg days 1-12 of the month
B. Estradiol transdermal patch 0.0375 mg every 3.5 days + Progesterone 100 mg nightly
C. Combined hormonal contraceptives
D. Levonorgestrel IUD with estradiol transdermal patch
E. Only A and C
F. All of the above

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Image from: https://atriumhealth.org/dailydose/2020/03/09/every-woman-goes-through-menopause-at-some-point-know-how-to-manage

Perimenopause hormone treatment options

- Combined hormonal contraception
  - Consider PMHx, safety, symptoms
  - Do they need contraception? Do they have heavy bleeding?
  - Do they have PMDD or menstrual migraines (with or without aura)?
  - Do they have ovulatory or hyperestrogenic symptoms?

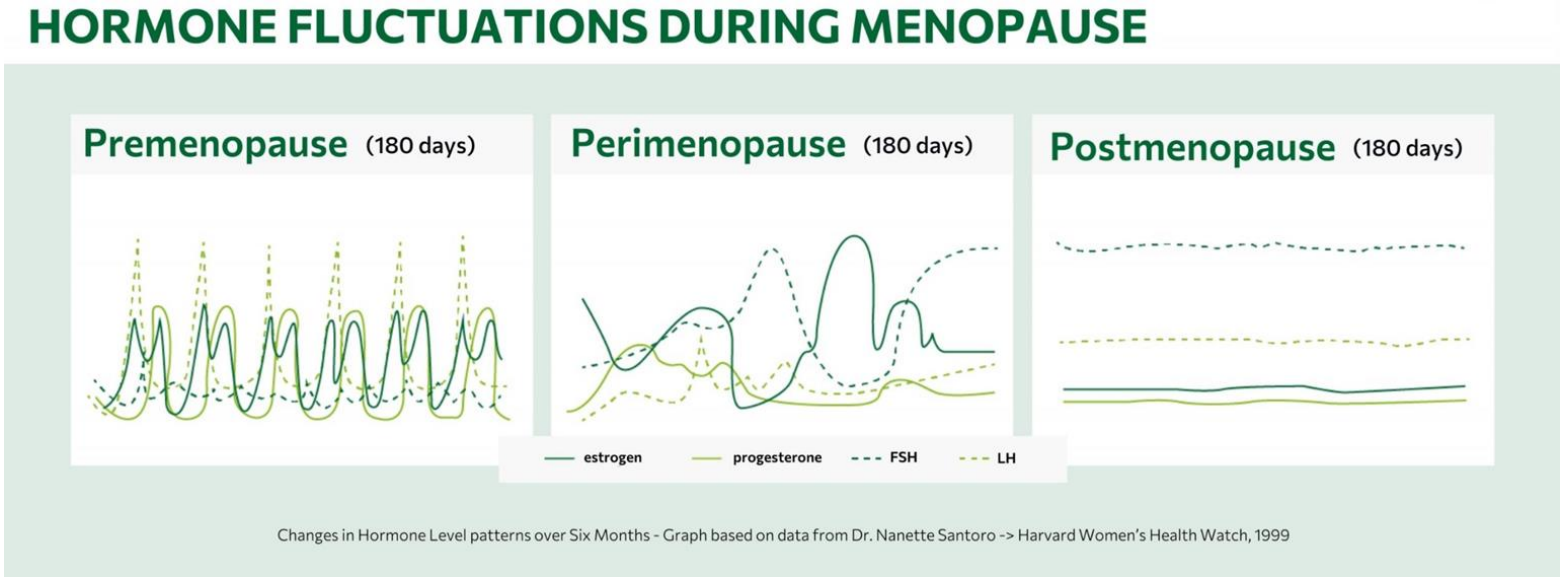

Image obtained from: https://alkmene.de/en/ratgeber/menopausal-skin-problems/

Perimenopause hormone treatment options (continued)

- Micronized progesterone 200 mg days 1-12 of each calendar month or 100-200 mg daily with or without ET
  - Still need to consider contraception
  - Micronized in peanut oil so cannot be allergic to peanuts
- Oral progestin (drospirenone, norethindrone acetate, medroxyprogesterone acetate) with or without ET
  - Favorable in women who would benefit from ovulatory suppression
- Mirena IUD with or without ET
  - Great option for endometrial protection, heavy menstrual bleeding, and contraception
- Symptom-specific nonhormone medications (ex. SSRIs/SNRIs for mood symptoms, anti-obesity medications for weight disorders)

CASE #3

48 yo postmenopausal woman with a history of ER+/PR+/HER2- breast cancer currently being treated with tamoxifen with presenting with hot flashes, night sweats, increasing anxiety, depressive symptoms, and diffuse arthralgias.

She reports she went through menopause at age 47, and only had mild symptoms, but now after starting tamoxifen it feels like her previous symptoms have “returned, but in full force.”

What therapies may be options for her?

Image from: https://www.morelandobgyn.com/blog/perimenopause-symptoms-relief-how-to-find-a-perimenopause-doctor

Of the listed options, what therapy is most appropriate to treat her symptoms?

A. Paroxetine mesylate 7.5 mg nightly
B. Venlafaxine 37.5 mg daily
C. Estradiol transdermal patch 0.0375 mg/day every 3.5 days + Progesterone 100 mg nightly
D. Fluoxetine 20 mg daily

Image from: https://www.health.harvard.edu/blog/menopause-related-hot-flashes-night-sweats-can-last-years-201502237745

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Nonhormone Medications for VMS: How To Choose?

Class	Medication	Dosing for VMS[a]	Clinical pearls
SSRIs	Paroxetine salt[10,11,23,24]	7.5 mg daily at bedtime	Potent cytochrome P450 CYP2D6 enzyme inhibitors; do not use with tamoxifen as SSRIs reduce tamoxifen bioavailability and efficacy
	Paroxetine[10,11,23,24]	10–25 mg daily	
	Fluoxetine[11,23,24,26]	10–30 mg daily	Paroxetine mesylate 7.5 mg was the first and only US Food and Drug Administration–approved nonhormone medication for moderate to severe menopausal VMS until the development of neurokinin-receptor antagonists
	Sertraline[11,23,24,27]	25–100 mg daily	
	Citalopram[10,11,23,24]	10–20 mg daily	Fluoxetine and sertraline are not recommended for VMS reduction owing to inconsistent data regarding efficacy in hot flash frequency and severity reduction
	Escitalopram[10,11,23–25]	10–20 mg daily	
			Sertraline has a moderate effect on the CYP2D6 enzyme
			Citalopram and escitalopram may cause QT prolongation
SNRIs	Desvenlafaxine[10,11,23,24]	100–150 mg daily	SNRIs may increase blood pressure, use with caution in patients with hypertension
	Venlafaxine[10,11,23,24]	37.5–75 mg daily	Venlafaxine is the most well studied SNRI in combination with tamoxifen
	Duloxetine[11,23,25]	30–60 mg daily	
			Duloxetine has a moderate effect on the CYP2D6 enzyme
Gabapentinoid	Gabapentin[10,11,28–31]	300–2,400 mg daily (divided doses)	Consider for patients with a history of neuropathic pain or sleep concerns
			Consider nightly dosing (starting dose of 100–300 mg at bedtime) to minimize any adverse effects of daytime fatigue
Antimuscarinic	Oxybutynin[11,24,31,32]	2.5–5 mg twice a day (immediate release), up to 15 mg/day (extended release)	Consider for patients with concurrent overactive bladder or hyperhidrosis
			Use caution in older adults (≥ 65 years); avoid altogether in patients ≥ 65 years taking concomitant anticholinergic medications
Alpha-2 adrenergic agonist	Clonidine[11,32,33]	0.05–0.1 mg once or twice a day	Consider for patients with hypertension, especially if improved blood pressure control is desired
			Avoid in older adult patients (≥ 65 years)
			Less often used and no longer recommended by the Menopause Society owing to modest efficacy vs placebo and side-effect profile

Iyer TK, Fiffick AN, Batur P. Nonhormone therapies for vasomotor symptom management. Cleve Clin J Med. 2024 Apr 1;91(4):237-244. doi: 10.3949/ccjm.91a.23067. PMID: 38561208.

Neurokinin-targeted therapies (NKTs): NK3R and NK1/3R antagonists

- The thermoregulatory center in the hypothalamus is stimulated by neurokinin 3 receptor (NK3R) activation and inhibited by estrogen-negative feedback
  - This balance is disrupted in menopause, producing vasomotor symptoms
- Fezolinetant: approved by FDA 5/2023
  - SKYLIGHT → Fezolinetant 45 mg was efficacious for the treatment of moderate-to-severe VMS associated with menopause
  - Caution with certain medications (CYP1A2 inhibitors, including caffeine)
  - Check liver function tests at baseline, 1, 2, 3, 6, and 9 months
  - Most common side effect: headache, GI disturbances
- Elinzanetant: approved by FDA 10/2025
  - OASIS 1,2 → Elizanetant is a dual NK1/NK3 receptor antagonist is effective in the treatment of vasomotor symptoms
    - Most common side effects: headache, fatigue/somnolence
    - OASIS 2 did not demonstrate concern for hepatotoxicity, though still recommended to get baseline and 3 mo LFTs

Lederman, Samuel MD; Shapiro CM, Marla MD; Stute, Petra MD; Lee, Misun PhD; Wang, Xuegong PhD; Neal-Perry, Genevieve PhD. Phase 3 Study of Fezolinetant for Treatment of Moderate-to-Severe Vasomotor Symptoms Associated With Menopause [A132]. Obstetrics & Gynecology: May 2022 - Volume 139 - Issue - p 39S doi: 10.1097/01.AOG.0000825808.38519.3b
Pinkerton JV, Simon JA, Joffe H, Maki PM, Nappi RE, Panay N, Soares CN, Thurston RC, Caetano C, Haberland C, Haseli Mashhadi N, Krahn U, Mellinger U, Parke S, Seitz C, Zuurman L. Elinzanetant for the Treatment of Vasomotor Symptoms Associated With Menopause: OASIS 1 and 2 Randomized Clinical Trials. JAMA. 2024 Aug 22;332(16):1343–54. doi: 10.1001/jama.2024.14618. Epub ahead of print. PMID: 39172446; PMCID: PMC11342219.

Evidence-based non-pharmacologic interventions

- Weight loss
- Mind-body techniques
  - Cognitive behavioral therapy (CBT) → literature demonstrates slight reduction in VMS symptoms and benefits in mood, QOL, and overall functioning
  - Clinical hypnosis → RCTs demonstrated it to be effective in reducing VMS in survivors of breast cancer and in postmenopausal women
- Inconclusive or lack of robust evidence: yoga, acupuncture, s-equol, paced respiration, OTC/herbal supplements (including black cohosh)

The North American Menopause Society. Menopause Practice: A Clinician's Guide, 6th ed. 2019, p 49-51.

CASE #4

A 72 year old woman presents to for an annual exam.

LMP: age 50, no further episodes of bleeding, but having persistent vaginal dryness and discomfort, dyspareunia, and some urinary leakage issues

Genitourinary exam demonstrates frank vulvovaginal atrophy

Image from: https://www.forbes.com/sites/debgordon/2021/07/13/73-of-women-dont-treat-their-menopause-symptoms-new-survey-shows/?sh=42774104454f

Which of the following is a safe, effective treatment option for this patient?

A. Estradiol acetate vaginal ring 0.1 mg/day
B. Estradiol transdermal patch 0.0375 mg/day every 3.5 days + Progesterone 100 mg nightly
C. Estradiol vaginal ring 2 mg (7.5 mcg/day)
D. Over the counter vaginal lubricants

Image from: https://www.forbes.com/sites/debgordon/2021/07/13/73-of-women-dont-treat-their-menopause-symptoms-new-survey-shows/?sh=42774104454f

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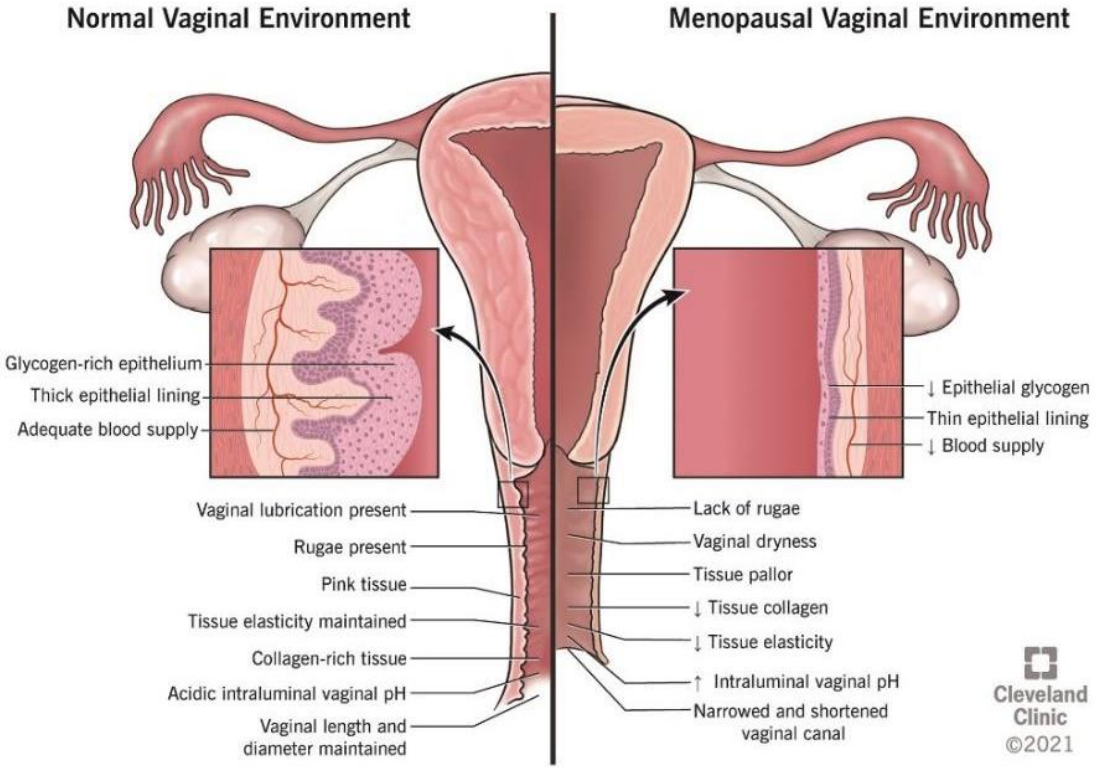
Image from: https://www.forbes.com/sites/debgordon/2021/07/13/73-of-women-dont-treat-their-menopause-symptoms-new-survey-shows/?sh=42774104454f

Genitourinary Syndrome of Menopause



- "Go-to" prescription: Vaginal estradiol cream → First 2 wks: Draw up 1 gram with applicator OR create a fingertip to middle knuckle length ribbon of cream. Insert into the vagina, spreading cream around inside and opening of vagina NIGHTLY. After 2 wks: same instructions 2-3 nights a week
  - Target lower ½ of vaginal canal **and introitus**
- No strict contraindications for vaginal estrogen except for possibly for history of uterine sarcomas and ensure appropriate counseling and transparency for breast cancer patients on aromatase inhibitors

Iyer TK, Thacker HL. "Menopause" In: Falcone T, Hurd WW. Editors. Clinical Reproductive Medicine and Surgery: A Practical Guide, 4th Edition Springer Nature; 2022.

GSM: practical considerations for prescribers

- Estradiol Vaginal Ring
  - Vaginal ring (Insert just like nuvaring)
  - One ring q every 3 months
  - Great for patients with incontinence as gives some bladder lift and patients with arthritis/obesity/chronic back pain – where frequent application may be difficult
- Conjugated Estrogen Vaginal Cream
  - Insert via applicator (fill applicator tube with cream then insert) or can use finger to apply to lower 1/2 of vagina
  - Likely only get 1 applicator so need to wash after every use with unscented soap and water
  - Use nightly x 2 weeks then 2-3x/week for maintenance
- Estradiol Vaginal Cream
  - Insertion similar to PVC
  - Use nightly 1-2 g/d x 2 weeks then 1g 2-3x/week
- Estradiol Vaginal Pearls
  - Suppository of estradiol and coconut oil that looks like elongated pearl
  - Less messy than creams because oil is a good bioadhesive
  - Insert into vagina up to knuckles length
  - Nightly x 2-3 weeks then 2x/week for maintenance
- Estradiol Vaginal Suppositories
  - Estradiol inserts placed with an applicator -> insert to knuckle length
  - Nightly x 2 weeks then 2x/week for maintenance
- Vaginal DHEA
  - Precursor hormone to both estrogens and androgens -> may lead to improved sexual and urinary outcomes
  - Stored at room temp or refrigerated
  - Brand name: Intrarosa 6.5 mg vaginal inserts nightly
- Ospemifene
  - FDA-approved for moderate to severe dyspareunia secondary to VVA
  - Oral tablet 60 mg take daily with food
  - SERM with estrogenic effects on vaginal mucosa and bone, no endometrial effects
- Fractional CO2 Vaginal Laser Therapy
  - Requires multiple sessions
  - Typically not covered by insurance
  - Recent double-blind, randomized, sham-controlled trial by Fiona et al. 2021 did not show significant improvement with fractional carbon dioxide laser vs sham treatment after 12 months
- Non-prescription therapy: regular sexual activity, lubricants, moisturizers

Summary and Key Points

- Age at menopause is a significant health indicator and an independent risk factor for cardiovascular disease
- HT is the gold standard of treatment for menopausal symptoms in healthy women aged younger than 60 years or within 10 years of menopause onset with no contraindications
    - Absolute risks for HT use in healthy women after 50-59 are rare but can include VTE, stroke, breast cancer
    - Evidence demonstrates improved bone health, cognition, GSM, QOL, CVD risk, all-cause mortality
    - Risks of hormone therapy differ for women, depending on type, dose, duration of use, route of administration, timing of initiation, and whether a progestogen is needed → consider each patient's own risks prior to starting HT
- There are effective non-hormonal options for the treatment of vasomotor symptoms for patients with contraindications or who cannot tolerate or do not want HT
- GSM should be assessed in all postmenopausal women and treated accordingly with one of several effective, safe therapeutic options
- Treatment of menopausal symptoms should be individualized using the best available evidence to maximize benefits and minimize risks, with periodic reevaluation

Questions?

Mass General Brigham