

# Clinical Updates and Practical Considerations in Menopause Care

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

# Disclosures summary of relevant financial relationships

Financial Disclosures: While not pertinent to the content of this lecture, I have in the past 24 months or am currently serving as a consultant for Bayer and Astellas.

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.



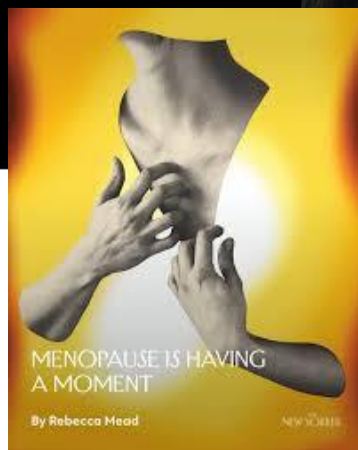
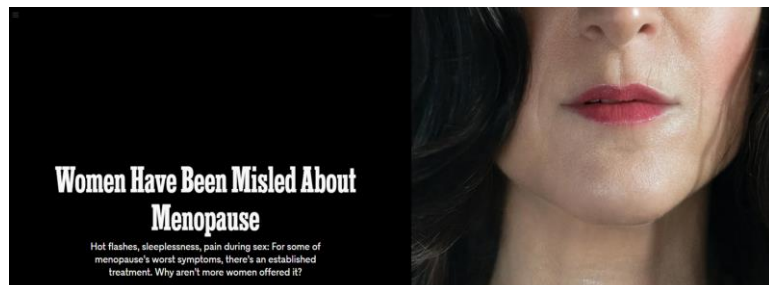
# Learning Objectives:

*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!



Consumer	Virtual + Hybrid Care	Biopharma
<p>Femarelle<sup>®</sup> Womaness</p> <p>Attn: Grace moona.</p> <p>MPowder<sup>®</sup></p> <p>MENOLABS<sup>®</sup> binto<sup>®</sup></p> <p>Tabu<sup>®</sup> Bonafide<sup>®</sup></p> <p>IB<sup>®</sup> PAUSE<sup>®</sup></p> <p>MIGHTY menopause<sup>®</sup> WILE</p> <p>KINDRA<sup>®</sup> issviva<sup>®</sup></p>	<p>MIDI gennev alloy</p> <p>Peppy STELLA E ELEKTRA HEALTH</p> <p>MyMenopauseRx alpha HerMD</p> <p>Modern Menopause WINONA EVERNOW upliv</p>	<p>OVIVA gameto</p> <p>celmatix MenoGenix</p>
Digital Technology	Medical Devices	
<p>PHENOLOGY</p> <p>HEALTH &amp; HER</p> <p>B-wom Olivia</p> <p>caria balance</p> <p>Mickday</p> <p>Peanut my SYSTERS</p>	<p>Embr Labs GRACE</p> <p>mira Amira</p> <p>Madorra thermaband</p>	

# 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

	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<sup>67-69</sup>

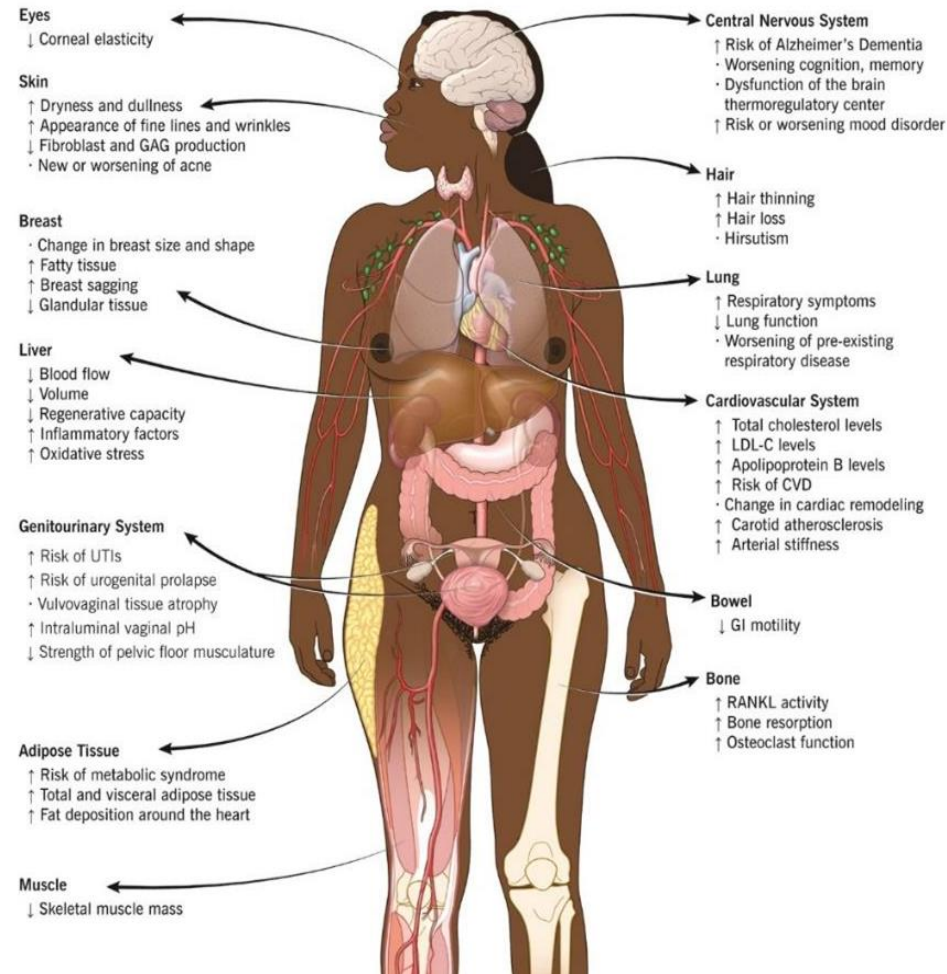
FIG. 2. The Stages of Reproductive Aging Workshop + 10 staging system for reproductive aging in women.





# 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



# Cardiometabolic changes during the menopausal transition independent of aging

- Given the established accelerating CVD risk in women undergoing the menopausal transition, there is a key role for clinicians to monitor and intervene on the cardiovascular health of their patients that is often overlooked
  - Increased carotid atherosclerosis and arterial stiffness
  - Adverse changes in body composition
    - Increased total and visceral adipose tissue
    - Reduction in lean muscle mass
  - Increased prevalence of metabolic syndrome
  - Worsening lipid profile
    - Increased total cholesterol
    - Increased LDL-C
    - Increased Apolipoprotein B





# 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	FMP	Postmenopause
<b>FSH</b>	Normal	↑	↑	↑		↑
<b>AMH</b>	Normal/↓	↓	↓	Undetectable		Undetectable
<b>Inhibin B</b>	Normal	↓	↓	Undetectable		Undetectable
<b>Estradiol</b>	Normal	Normal	Normal	↓		↓



## 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?



# What therapy is most effective to treat her 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



# 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 2x/week + 100 mg micronized progesterone nightly

Estrogen	Route	Typical dose range	Frequency	Equivalent dose
17- $\beta$ 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





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



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



## CASE #1 continued...

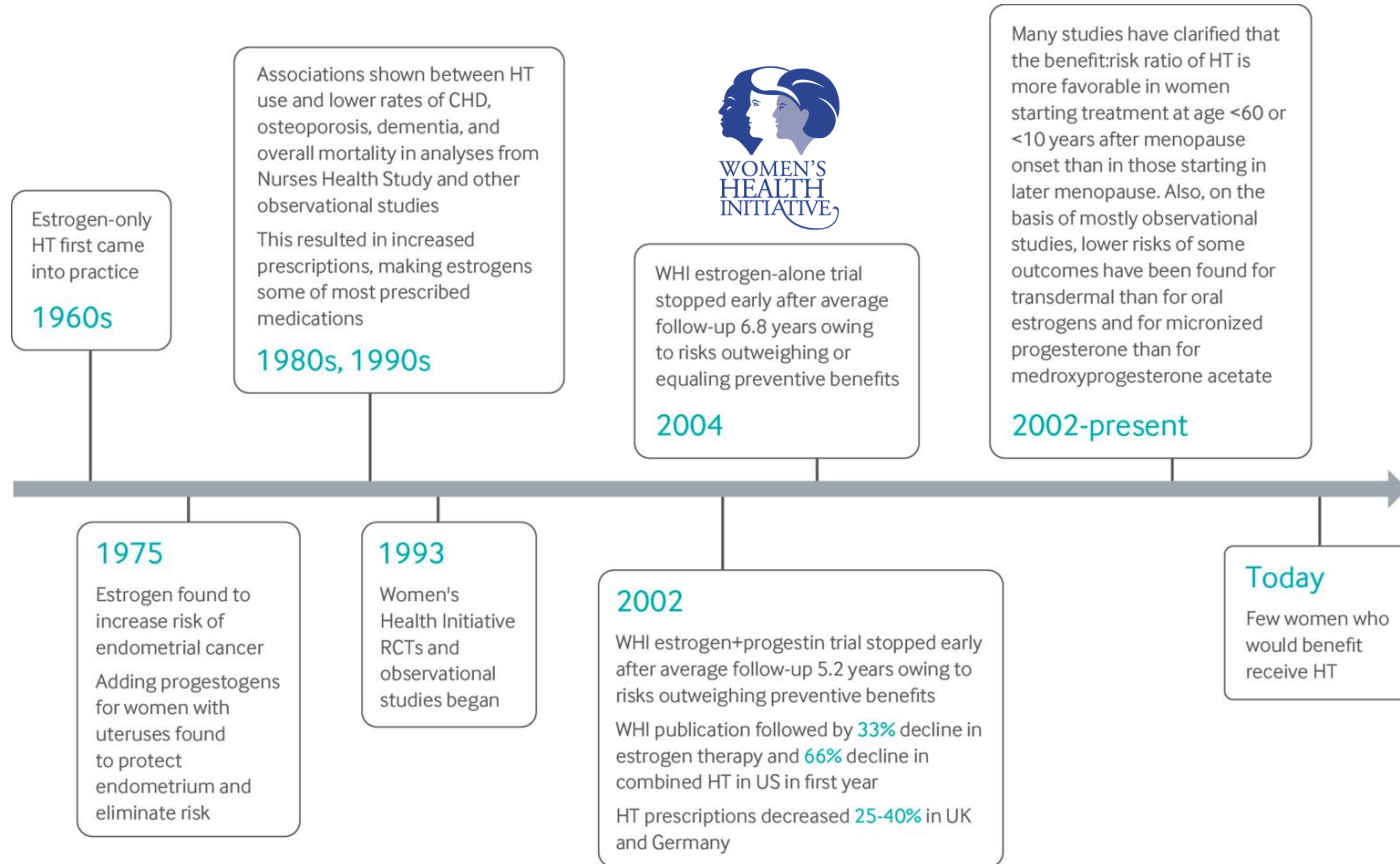
You recommend menopausal hormone therapy for this patient.

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?*



# Controversy over hormone therapy explained: a timeline



# 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, especially with respect to cardiovascular disease outcomes.

Long term benefits of MHT	Absolute risks of MHT
Reduction in all-cause mortality (including cancer and stroke mortality)	Absolute risks for HT use in healthy women after 50-59 are rare but can include VTE, stroke, breast cancer
Reduction in CVD incidence and mortality	
Reduction in risk of osteoporosis and osteoporotic fractures at the hip and the spine	
Reduction in incidence of colon cancer	



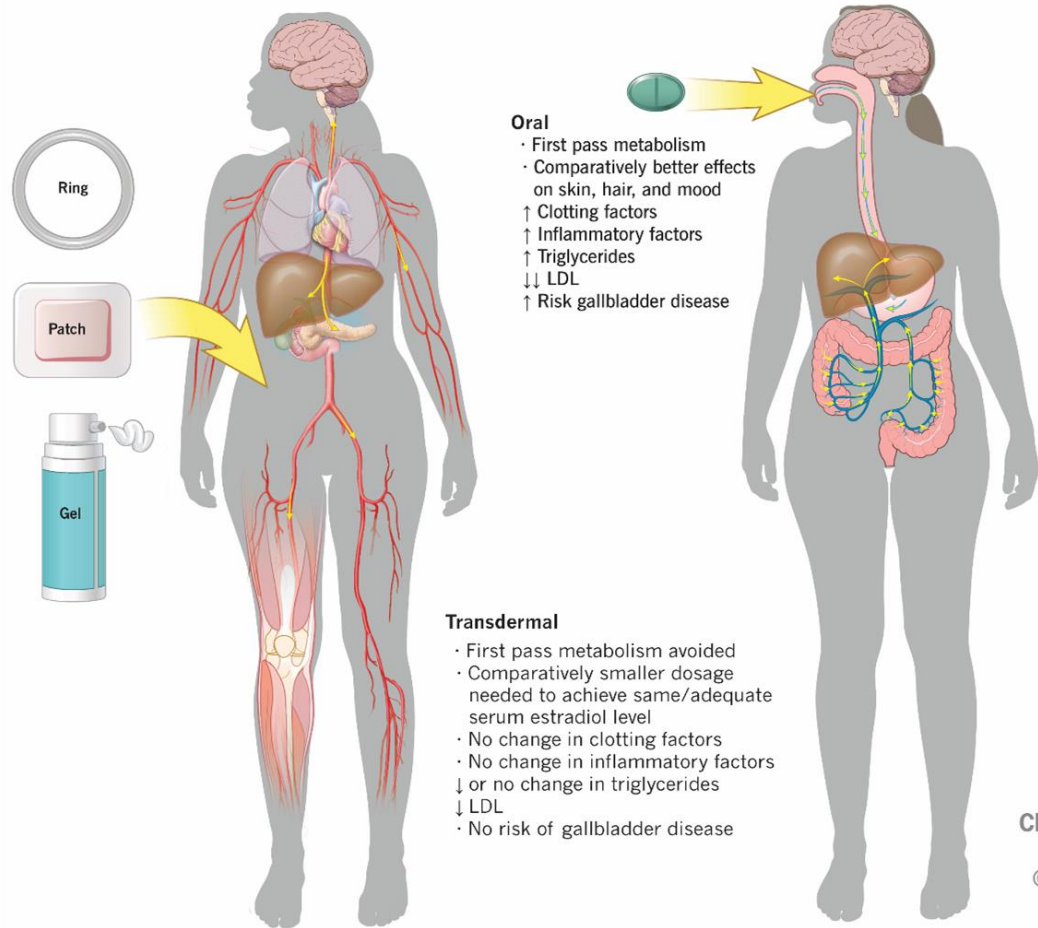
# What do we know today? Breast cancer data

- Evidence from the WHI:
  - The risk of breast cancer (BC) related to HT use is rare (less than one additional case per 1,000 women per year of HT use or three additional cases per 1,000 women when used for 5 years with CEE+MPA)
  - No increased risk of breast cancer mortality
  - CEE-only users experienced a reduction in breast cancer incidence and mortality compared to controls
- 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 (i.e. alcohol consumption, obesity, smoking, etc.)



## VTE/Stroke risk: TD vs oral MHT

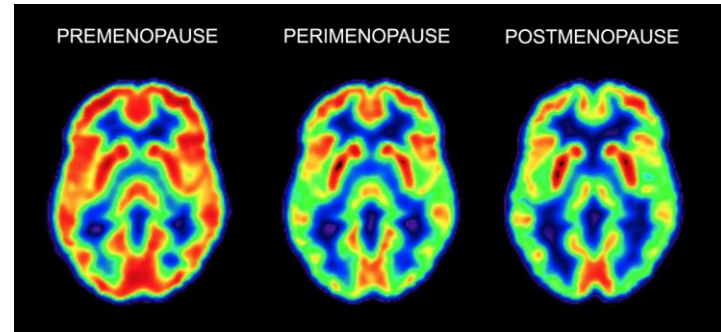
- Large two nested case control study 2019: Transdermal HT was NOT associated with any increased risk of VTE and consistent among various regimens
- Transdermal HT has not been associated with VTE/stroke risk in multiple observational studies; though limited observational data and a systematic review suggest less risk(as opposed to no risk) with transdermal HT than oral





# Menopausal Hormone Therapy, Cognition, and Dementia

- The effect of hormone therapy may be modified by baseline cognitive function, with more favorable effects in women with normal cognitive function before hormone therapy initiation
- HRT may have cognitive benefits when initiated immediately after TAH/BSO in surgical menopause patients
- HT in the early natural postmenopausal period has likely neutral or positive effects on cognitive function, but detrimental effects when initiated after age 65
  - Data is mixed, though most observational data points to a reduced risk of AD when HT is initiated in early menopause
  - Risk of dementia was increased in women who started hormone therapy at age 65 or later in the WHI trials, however, hormone therapy use was not associated with increased mortality from Alzheimer's disease or dementia at 18 year follow-up



# MHT and the Musculoskeletal Syndrome of Menopause

~70%

Prevalence of midlife women will experience the musculoskeletal syndrome of menopause

**Table 1.** Musculoskeletal syndrome of menopause: processes and signs.

<i>Process</i>	<i>Signs</i>
Inflammation	Arthralgia, joint pain, joint discomfort, frozen shoulder
Sarcopenia	Poor balance, falls, decreased muscle mass, loss of stamina, walking slowly
Decreased satellite cell proliferation	Decreased muscle mass, inability to gain muscle
Osteoporosis	Loss of height, back pain, stooped posture, low-impact fracture
Arthritis	Arthralgia, joint pain, joint stiffness

- Two RCTs (WHI, 2008 Australian RCT) demonstrated modest, but significant, reductions in joint pain and stiffness with HT use compared to controls
- Data is mixed with regard to effects of MHT on osteoarthritis prevalence
- Research is limited and more must be done!



# Hormone therapy (HT), weight, and metabolic outcomes

- Women's Health Initiative 3 year trial:
  - HT does not prevent weight gain, but it may minimize lean body mass loss and central adiposity redistribution
- Menopausal Hormone Therapy Is Associated With Reduced Total and Visceral Adiposity: The OsteoLaus Cohort
  - MHT is associated with significantly decreased visceral adipose tissue, BMI, and android fat mass
  - The benefits are not preserved in past users, suggesting caution when MHT is discontinued
- Estrogen and progestogen hormone replacement therapy for peri-menopausal and post-menopausal women: weight and body fat distribution
  - Hormone therapy regimens do not cause extra weight gain in addition to that normally gained at menopause



## Direct Effects of Aging

- Decrease in lean muscle mass
  - Decrease in total energy expenditure



## Direct Effects of Hormonal Changes

- Increase in visceral adiposity
- Decrease in lean muscle mass
- Decrease in fat oxidation
- Increase in appetite

## Indirect Effects of Aging and Hormonal Changes

- Increased environmental stressors/factors and disruptive menopausal symptoms (hot flashes/night sweats, sleep disruption, etc.) may negatively impact lifestyle and behaviors



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

Severe active liver disease
<b>History of estrogen-sensitive malignancy</b>
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



# Counseling on side effects

- Abnormal uterine bleeding can be common in the first 3-6 months and can even occur up to 1 year
  - Can be due to an estrogen-progestogen imbalance
    - Consider decreasing estrogen or increasing progestogen
  - If despite making medication changes bleeding persists, must evaluate the endometrium (transvaginal US +/- endometrial biopsy)

**Table 15.** Potential Adverse Events of Estrogen Therapy or Estrogen-Progestogen Therapy

- Uterine bleeding (starting or returning)
- Breast tenderness (sometimes enlargement)
- Nausea
- Abdominal bloating
- Fluid retention in extremities
- Changes in the shape of the cornea (sometimes leading to contact lens intolerance)
- Headache (sometimes migraine)
- Dizziness
- Mood changes with EPT, particularly with progestin
- Angioedema
- Gallstones, pancreatitis

Abbreviations: EPT, estrogen-progestogen therapy; ET, estrogen therapy



# 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





# 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?**



# 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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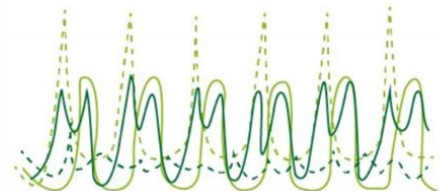


# Perimenopause hormone treatment options

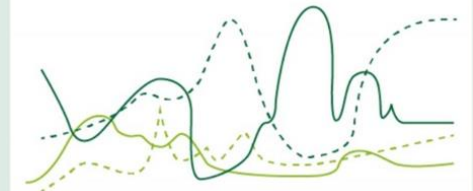
- Combined hormonal contraception
  - Consider PMHx, safety, symptoms
  - Do they need contraception? Do they have heavy bleeding?
  - Do they have PMDD or menstrual migraines (with or without aura)?
  - Do they have ovulatory or hyperestrogenic symptoms?

## HORMONE FLUCTUATIONS DURING MENOPAUSE

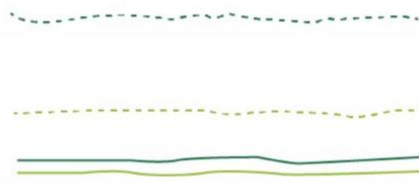
### Premenopause (180 days)



### Perimenopause (180 days)



### Postmenopause (180 days)



— estrogen — progesterone - - - FSH - - - LH

Changes in Hormone Level patterns over Six Months - Graph based on data from Dr. Nanette Santoro -> Harvard Women's Health Watch, 1999

# Perimenopause hormone treatment options (continued)

- Micronized progesterone with or without transdermal ET
  - Prometrium 200 mg days 1-12 of each calendar month or 100-200 mg daily
    - Take at night, it is relaxing and can help sleep
    - Still need to consider contraception
    - Micronized in peanut oil so cannot be allergic to peanuts
    - Micronized progesterone, especially the higher doses, can also reduce hot flashes
- Mirena IUD with or without transdermal ET
  - Great option for endometrial protection, HMB, 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?**



# 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





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Class	Medication	Dosing for VMS <sup>a</sup>	Clinical pearls
SSRIs	Paroxetine salt <sup>10,11,23,24</sup>	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 <sup>10,11,23,24</sup>	10–25 mg daily	
	Fluoxetine <sup>11,23,24,26</sup>	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 <sup>11,23,24,27</sup>	25–100 mg daily	
	Citalopram <sup>10,11,23,24</sup>	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 <sup>10,11,23–25</sup>	10–20 mg daily	Sertraline has a moderate effect on the CYP2D6 enzyme Citalopram and escitalopram may cause QT prolongation
SNRIs	Desvenlafaxine <sup>10,11,23,24</sup>	100–150 mg daily	SNRIs may increase blood pressure, use with caution in patients with hypertension
	Venlafaxine <sup>10,11,23,24</sup>	37.5–75 mg daily	Venlafaxine is the most well studied SNRI in combination with tamoxifen
	Duloxetine <sup>11,23,25</sup>	30–60 mg daily	Duloxetine has a moderate effect on the CYP2D6 enzyme
Gabapentinoid	Gabapentin <sup>10,11,28–31</sup>	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 <sup>11,24,31,32</sup>	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 <sup>11,32,33</sup>	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

# Nonhormone Medications for VMS: How To Choose?

# 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: may become available 2025
  - OASIS 1,2 → Elinzanetant is a dual NK1/NK3 receptor antagonist is effective in the treatment of vasomotor symptoms
    - Most common side effects: headache, fatigue
    - OASIS 2 did not demonstrate concern for hepatotoxicity



# 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)



## 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



# 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





# 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



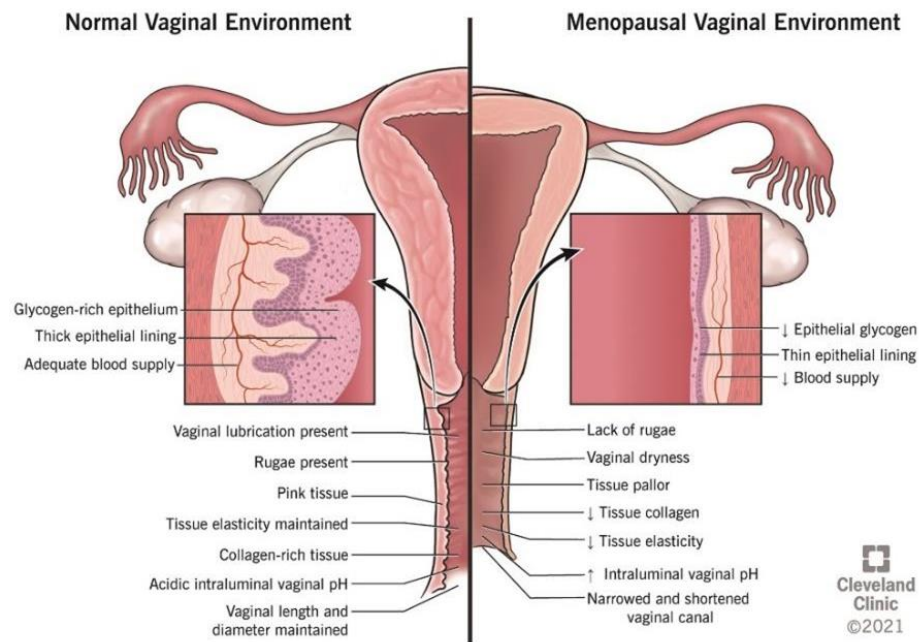
# GSM: practical considerations for prescribers

- 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





# Genitourinary Syndrome of Menopause



Labial atrophy

Vaginal dryness

Introital stenosis

Clitoral atrophy

Phimosis of the prepuce

Reduces mons pubis and labia majora bulk

Reduced labia minora tissue and pigmentation

Prominence and erythema of the urethral meatus

Urethral caruncle

Vaginal pallor

Lack of vaginal rugae

- “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**, also apply peri-urethrally if hx of recurrent UTIs
- 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



# 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**