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Updates in Menopause Management

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Disclosures

I have no relevant financial relationships with ineligible companies

AI was used in the preparation of this presentation for limited research

What medical event…
affects half the population…
lasts decades…
impacts every organ system…

…and is barely taught in medical training?

Menopause

Key Learning Objectives

01

Describe rationale behind removal of Black Box Warning from Estrogen Products

02

Demonstrate knowledge of new data on the safety of estrogen therapy

03

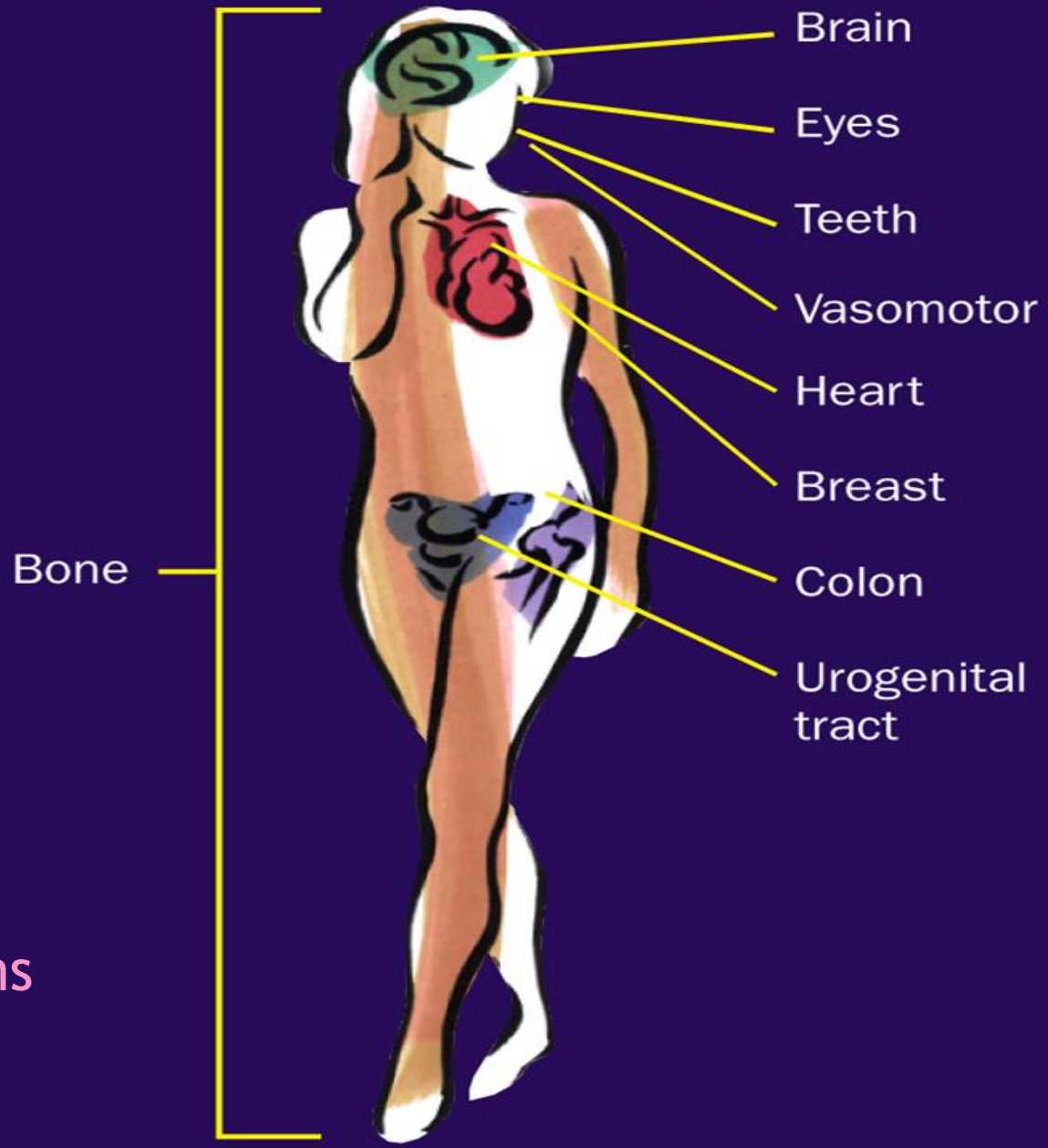
Define the Genito-urinary Syndrome of Menopause and new guidelines for therapy

Michelle 50 yo

Hot flashes
Fatigue
Poor Sleep
Pain with sex
LMP 3 months ago

“Should I try hormones?”

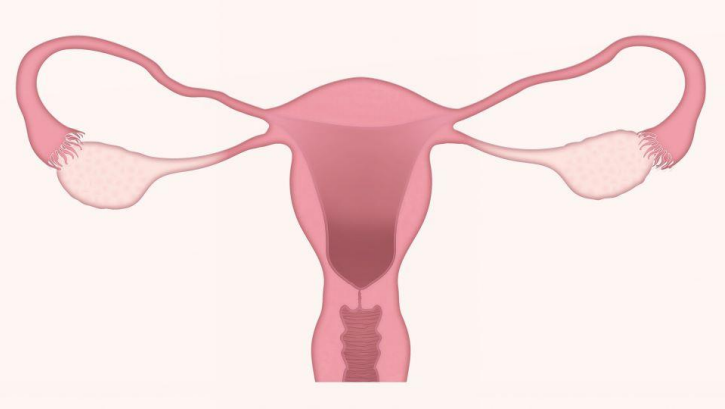
Effect of Estrogen in Target Tissues



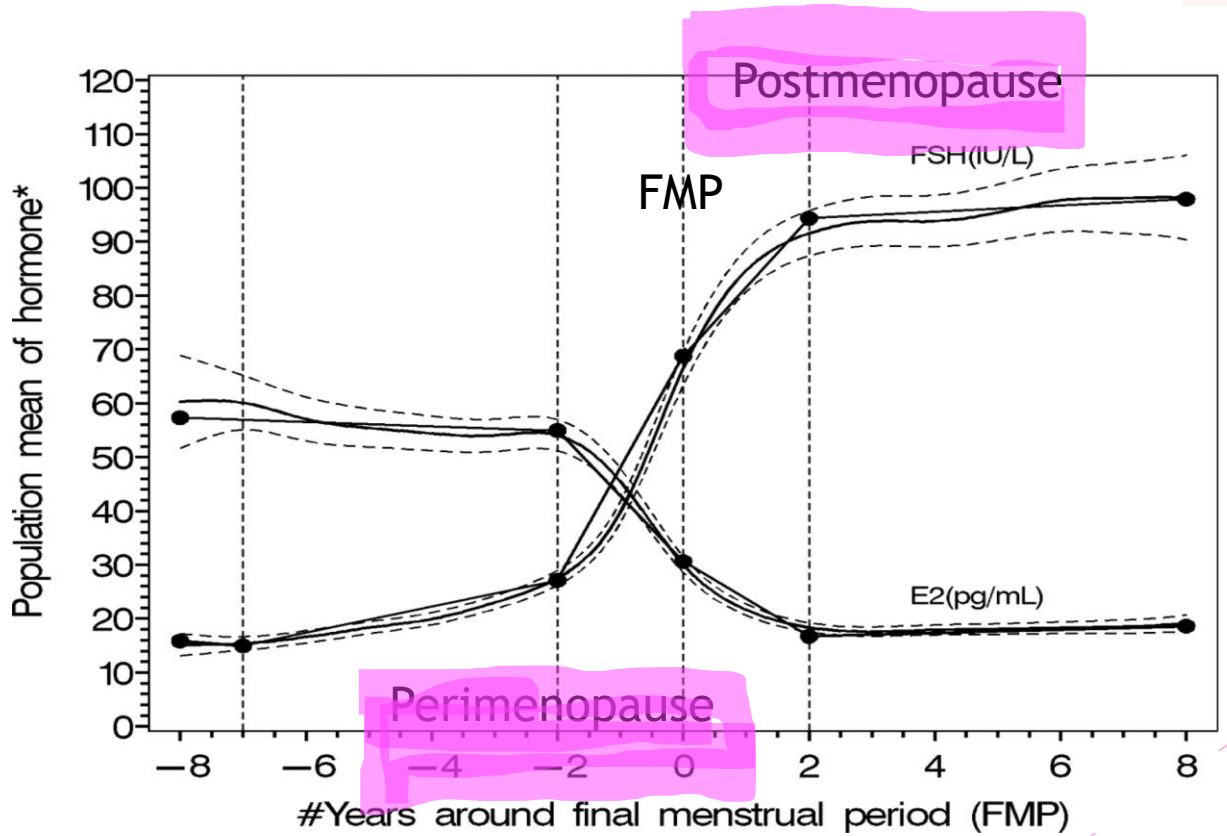
Estrogen receptors are found throughout the body

Effects beyond menopausal symptoms

The Menopausal Journey

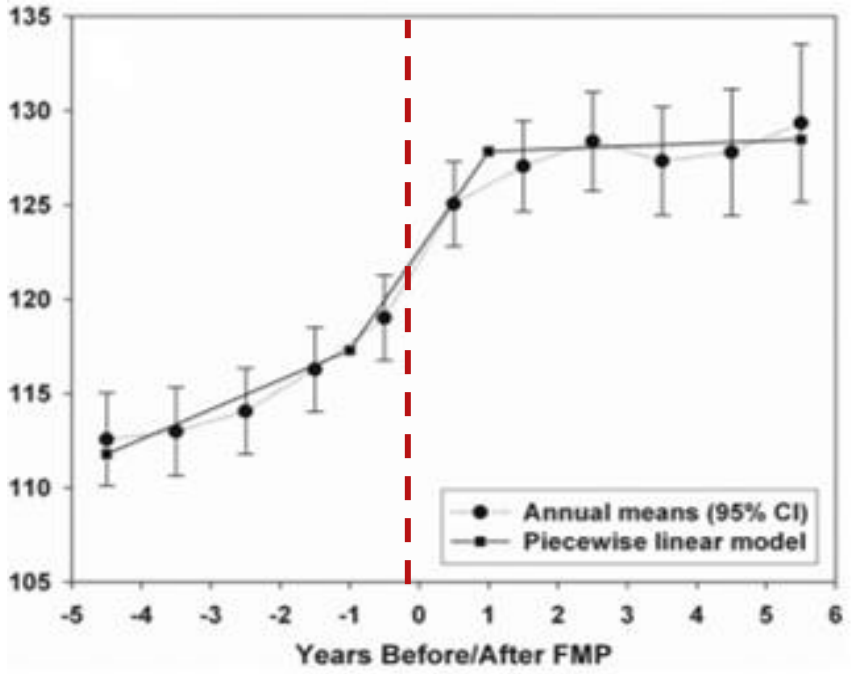


- Gradual loss of ovarian function (natural menopause)
- FMP Average 51-52
- 90% of women age 45-56.
- Premature Ovarian Insufficiency <40
- Early Menopause <45
- Bone loss

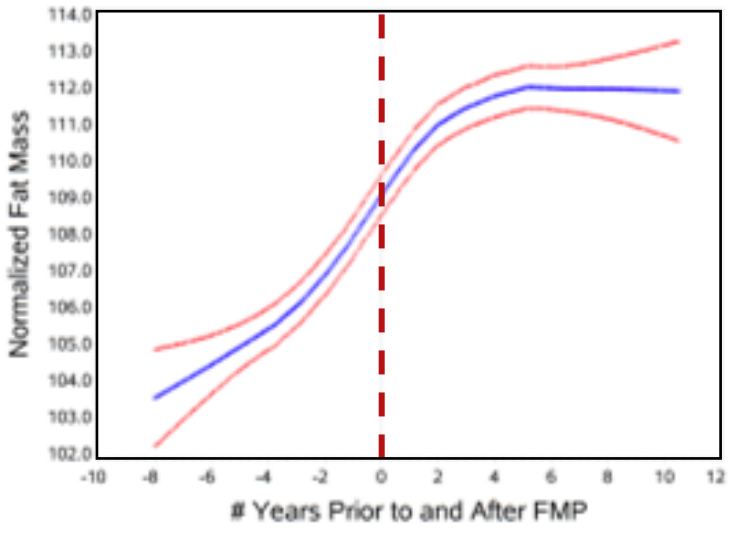


Women experience adverse changes in cardiometabolic health during the menopausal transition

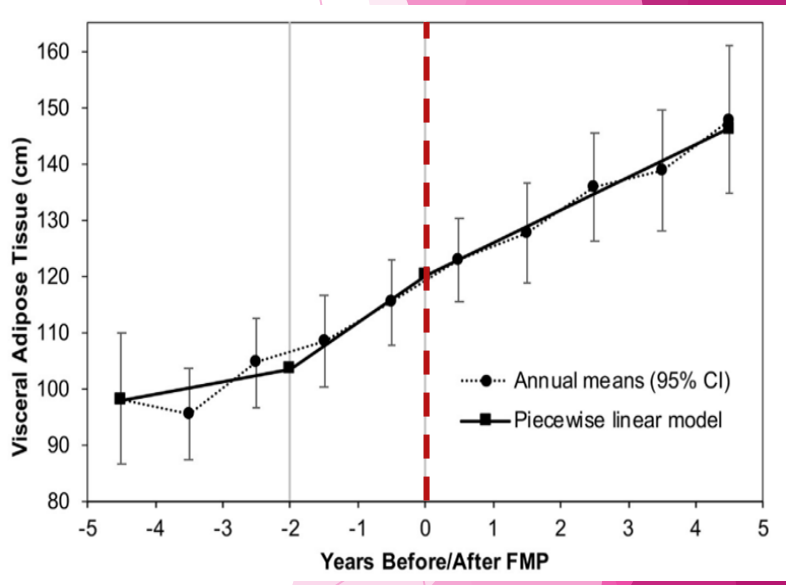
LDL-C



Fat mass



Visceral adipose tissue



Matthews et al., *J Am Coll Cardiol* 2009
El Khoudary SR et al., Circulation 2020

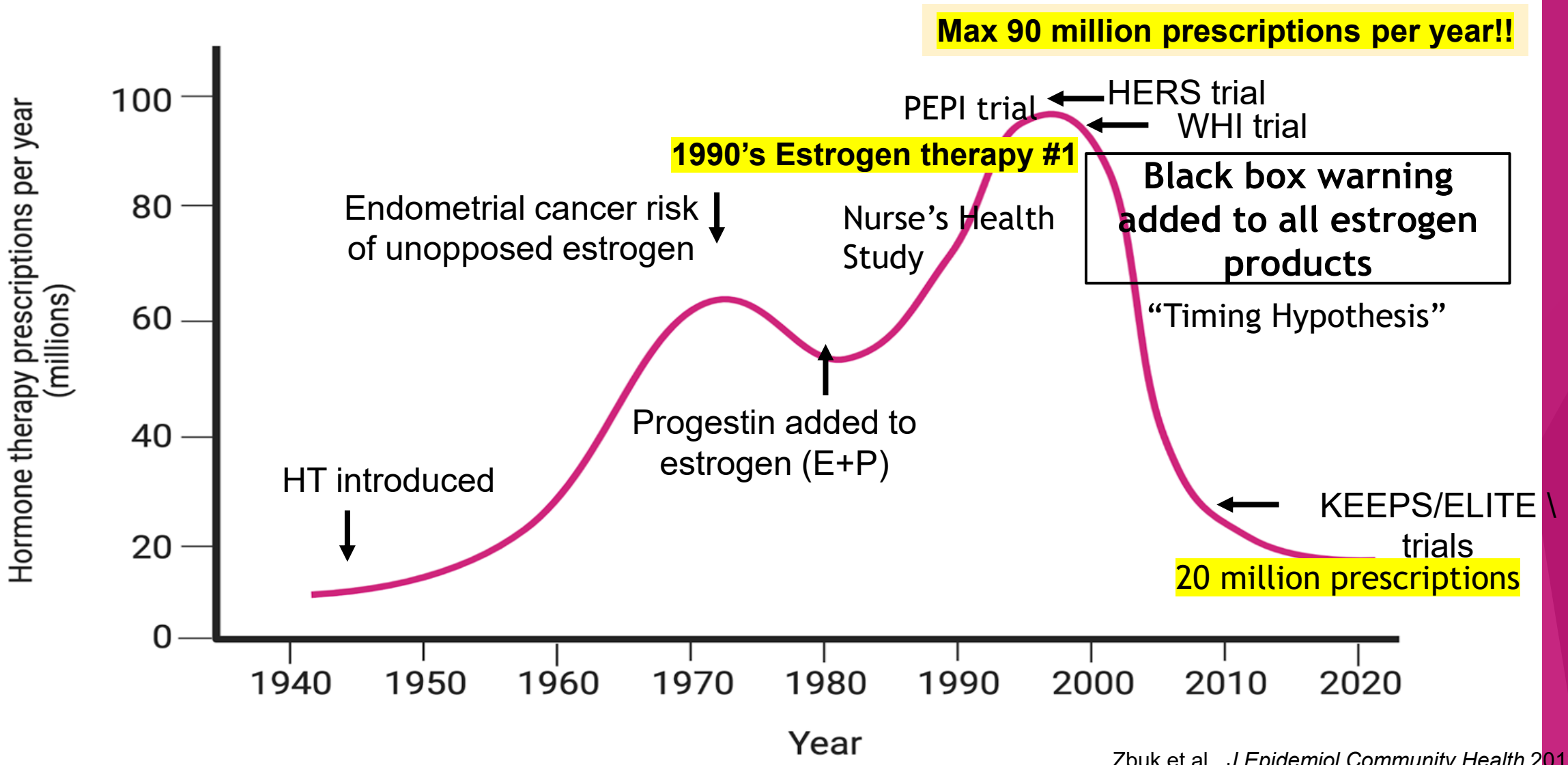
Benefits of Hormone Replacement Therapy: Then and Now

Treatment of VMS
Improved Sleep
Decreased Genitourinary Syndrome of Menopause
Improved Mood
50% reduction in CVD
50% reduction in Osteoporotic fractures
True replacement in women with early menopause

The Women's Health Initiative (WHI)

…changed everything

Hormone therapy: Annual prescriptions



Zbuk et al., *J Epidemiol Community Health* 2012


BLACK BOX
WARNING

ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER

Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of 'natural' estrogens results in a different endometrial risk profile than synthetic estrogens at equivalent estrogen doses. (See **WARNINGS, Malignant neoplasms, *Endometrial cancer.***)

CARDIOVASCULAR AND OTHER RISKS

Estrogens with or without progestins should not be used for the prevention of cardiovascular disease. (See **WARNINGS, Cardiovascular disorders**.)

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo. (See **CLINICAL PHARMACOLOGY, Clinical Studies**.)

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with oral conjugated estrogens plus medroxyprogesterone acetate relative to placebo. It is unknown whether this finding applies to younger postmenopausal women or to women taking estrogen alone therapy. (See **CLINICAL PHARMACOLOGY, Clinical Studies**.)

Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

ESTRACE® CREAM

(estradiol vaginal cream, USP, 0.01%)

Rx only

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JAMA 2002 Jul 17;288(3):321-33.
doi: 10.1001/jama.288.3.321.

Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial

Jacques E Rossouw[1], Garnet L Anderson, Ross L Prentice, Andrea Z LaCroix, Charles Kooperberg, Marcia L Stefanick, Rebecca D Jackson, Shirley A A Beresford, Barbara V Howard, Karen C Johnson, Jane Morley Kotchen, Judith Ockene; Writing Group for the Women's Health Initiative Investigators

WHI asked a prevention question

Should women 50-79 start hormones to prevent coronary disease?

What WHI studied

- Women aged 50–79 (mean 63)
- Years past menopause
- Oral Conjugated Equine Estrogen (CEE) ± Medroxyprogesterone (MPA)
- **Prevention-**not symptom treatment

Absolute risks were small

↑ venous thromboembolism (VTE)/ pulmonary embolism 8 cases
↑ stroke 8 cases
↑ breast cancer (combined) 8 cases
↓ fractures 5 cases
↓ colorectal cancer 6 cases

…per 10,000 person-years

WHI conclusion: reality

Oral CEE hormones should not be initiated to ALL women age 50-79 for the sole purpose of the prevention of Cardiovascular disease

“Timing Hypothesis”

<60 years of age or <10 years since menopause: CHD risk reduced by roughly half and all-cause mortality reduced by 30%

>60 years- 70 years or >10 -20 years after menopause showed no effect on CHD or mortality

Age >70 increased ASCVD risk- women should “think twice” per JoAnn Manson

JAMA Internal Medicine. 2025. Rossouw JE, Aragaki AK, Manson JE, et al
Circulation. 2020. El Khoudary SR, Aggarwal B, Beckie TM, et al.

Approach by Decade

Less than 40 yo: POI
Eval and replace estrogen

40's: premature menopause/ perimenopause
Replace estrogen

50's: perimenopause and postmenopause
Most okay for MHT

60's
Start systemic hormones with caution
okay to continue

Over 70
Vaginal hormones
Okay to continue MHT

Removal of Black Box Warning

- ✓ Nov 10, 2025
- ✓ Comprehensive FDA literature review,
- ✓ Expert panel deliberations, 60 day public comment
- ✓ Individual product inserts will contain appropriate risk and benefit information

Elimination of the Black Box Warning on Menopausal Hormone Therapy.
Obstetrics and Gynecology. 2026. Sriprasert I, Hodis HN, Mack WJ, et al.
Hormone Therapy for Postmenopausal Women.
The New England Journal of Medicine. 2020. Pinkerton JV.

Rationale for Removal

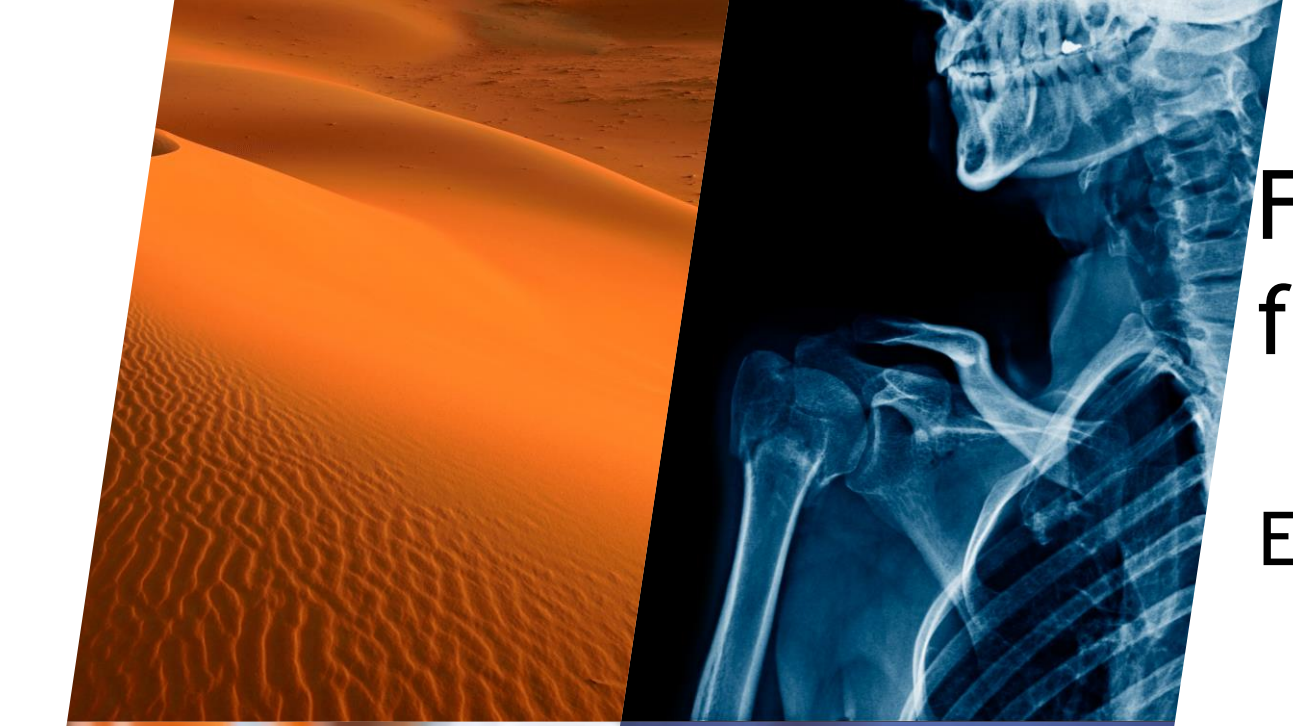
- Original warning inappropriately generalized WHI findings (specific to oral conjugated equine estrogens and medroxyprogesterone acetate) to all hormone therapy products
- Post-WHI evidence demonstrated substantial variation in risk based on patient age, timing of initiation, and product characteristics "Timing hypothesis" supported: estrogens may benefit cardiovascular health when started in early menopause but may be harmful when started late

Reference: Sriprasert I, Hodis HN, Mack WJ, et al. Elimination of the Black Box Warning on Menopausal Hormone Therapy. Obstet Gynecol. 2026;147(5):642-646.

Michelle 50

Hot flashes
Fatigue
Poor Sleep
Pain with sex

“I would like to try hormone therapy”




FDA-approved Indications for Estrogen Therapy

Estrogen deficiency (age <50-52)

Vasomotor symptoms

Genitourinary Syndrome of Menopause

Prevention of Osteoporosis

Menopause Society position paper 2022

Hormone Therapy Truths/ Myths

- MHT has 25% the potency of COC pills
- MHT is replacing hormones at the level of a healthy premenopausal woman in her 40s
- MHT is extremely safe, and even beneficial when started before age 60 or within 10 years of menopause
- MHT can be started before the LMP for symptoms
- Topical Estrogen therapy is often combined with systemic MHT
- Antidepressants are not highly effective for hot flashes

Estradiol levels

Reference:

30-400pg/ml

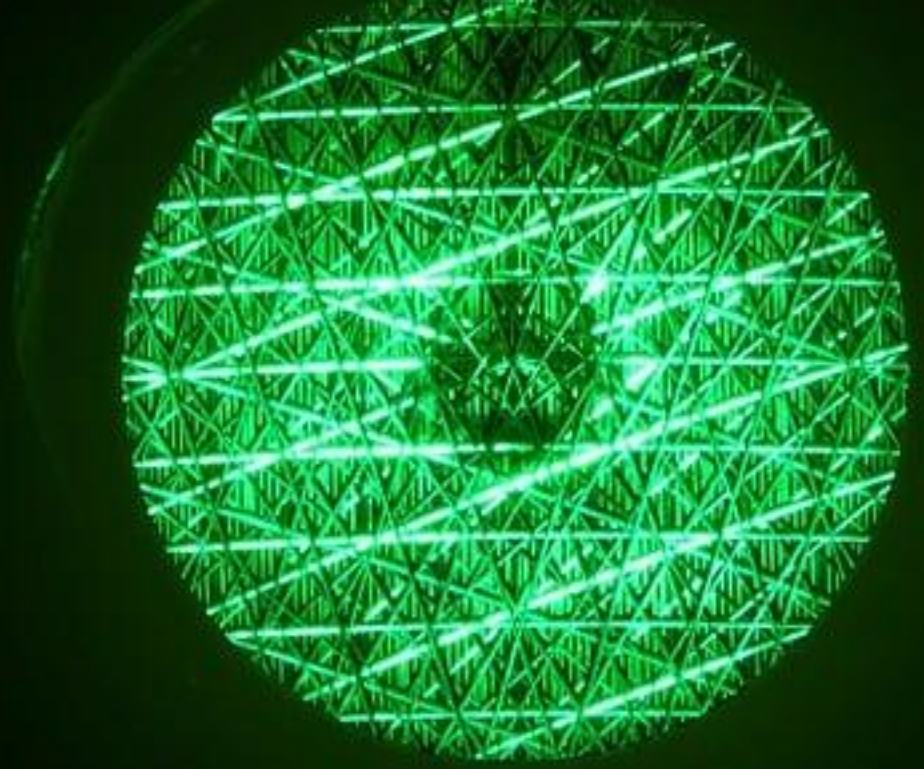
29,000 pregnancy

- **Baseline postmenopausal estradiol:**
  Without MHT, estradiol levels are usually **<20 pg/mL**, often closer to 5–10 pg/mL.
- **On oral estradiol (1–2 mg daily):**
  - 1 mg oral estradiol → average serum estradiol around **60–70 pg/mL**
  - 2 mg oral estradiol → average serum estradiol around **100–110 pg/mL** nature.com
- **On conjugated estrogens (0.45–0.625 mg):**
  - 0.45 mg → ~60 pg/mL
  - 0.625 mg → ~75–80 pg/mL nature.com
- **Transdermal estradiol (patches, gels, sprays):**
  These often produce steadier levels, generally **40–80 pg/mL**, depending on patch strength (e.g., 0.05 mg/day patch often yields ~50 pg/mL).
- **Vaginal estrogen (cream, ring, tablet):**
  Used for local symptoms, systemic absorption is minimal, so estradiol levels usually remain **within the postmenopausal range (<20 pg/mL)**.

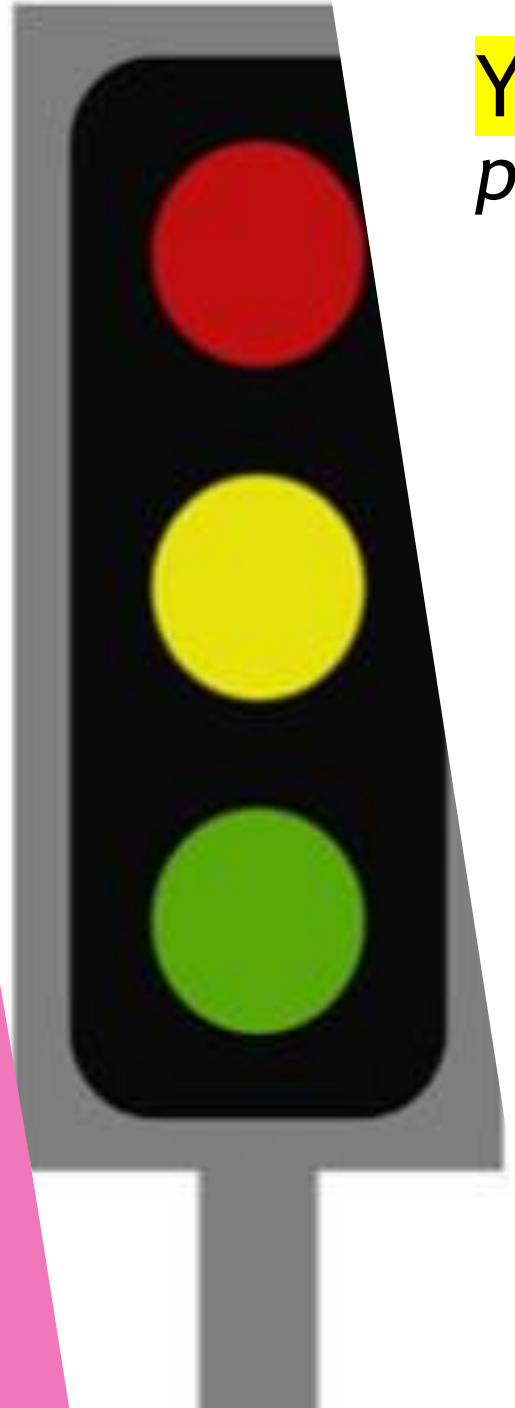
Menopause Society Statement 2022

- Hormone therapy (HT) remains the most effective treatment for vasomotor symptoms (VMS) and the genitourinary syndrome of menopause (GSM)
- HT prevents bone loss and fracture.
- 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 favorable for treatment of bothersome VMS and prevention of bone loss.
- For women who initiate hormone therapy more than 10 years from menopause onset or who are aged older than 60 years, the benefit-risk ratio appears less favorable.
- Longer durations of therapy should be for documented indications such as persistent VMS, with shared decision-making and periodic reevaluation.

- ✓ Symptomatic, healthy women
- ✓ Age <60 and/or less than 10 years post menopause
- ✓ 10-year ASCVD risk <5%, low VTE risk
- ✓ AVERAGE risk of breast cancer



GREEN LIGHT



Yellow light- *transdermal estrogen preferred over oral- consider referral*

- Age more than 60 yo or greater than 10 years post-menopause
- Migraine headaches (aura or not)
- HTN
- DM
- Smoking
- Obesity/ Metabolic Syndrome
- Hypertriglyceridemia (for orals)
- 10-year ASCVD risk 5-10%
- Calculated 5-year risk of breast cancer >3-5%
- Low risk thrombophilia

Initiating MHT: Contraindications
Use non-hormonal treatments

- h/o Cardiovascular Disease/PAD/MI
- 10-year ASCVD risk >10%
- h/o DVT, Pulmonary Embolism, or high-risk thrombophilia
- h/o Stroke/TIA
- Unexplained Vaginal Bleeding/High Risk Endometrial cancer
- Breast Cancer- ER positive
- Severe liver disease/ Cirrhosis

https://doi.org/10.1161/CIRCULATIONAHA.122.061559

Circulation. 2023;147:597–610Lundberg G and Wegner N. *J Am Coll Cardiol* 2019

Leslie C…Lau ES et al., *Circulation* 2023, Shifen J et al., *JAMA* 2019

- ✓ Safety of transdermal MHT in terms of thrombosis. New hope for “red light” contraindications

New England Journal of Medicine Review 2026

VTE Risk by Route of Administration:

Transdermal estradiol alone: No increase in thrombotic risk when used alone

Transdermal estrogen combined with progestogen: When combined with transdermal estrogen, micronized progesterones and most pregnane progestogens do not appear to carry thrombotic risk, but other progestogen formulations may increase risk

Recurrent VTE in Women with Prior VTE:

Oral estrogen: Significantly increased risk of recurrent VTE (adjusted HR 7.2, 95% CI 1.6-31.2)

Transdermal estrogen: No increased risk of recurrent VTE (adjusted HR 0.9, 95% CI 0.9-3.0)

A randomized trial comparing oral estradiol and norethisterone with placebo in postmenopausal women with previous VTE was stopped early due to increased VTE risk with oral hormone therapy (10.7% vs 2.3%; RR 7.8, 95% CI 1.0-60.5)

Clinical Recommendations:

Continuing hormone therapy during anticoagulation: Data support the safety of continuing hormone therapy after VTE in cisgender women while receiving anticoagulant therapy

After anticoagulation discontinuation: In patients with strong VTE risk factors or previous VTE in whom anticoagulant therapy has been discontinued, hormone therapy should be stopped or switched to a nonthrombotic formulation (i.e., transdermal)

The New England Journal of Medicine. 2026. Skeith L, Bates SM.

Therapeutic Options:

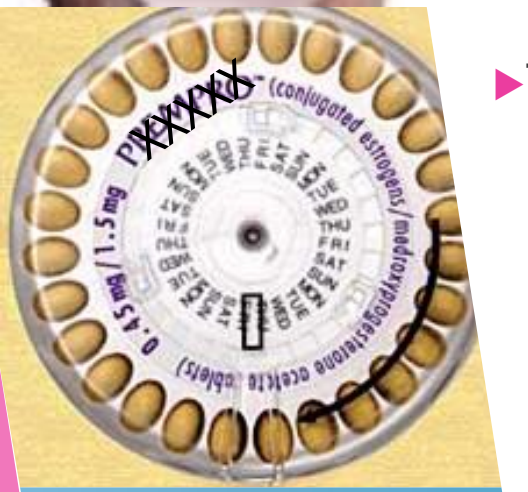
MHT: Estrogen and Progestogen
Estrogen and IUD
Duavee: CEE and SERM

SSRI/ SNRI
Gabapentin
Oxybutynin

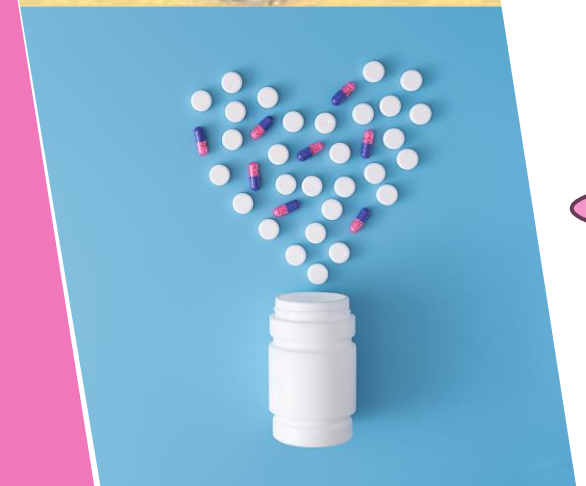
Fezolinetant NK-3 antagonist
Elinzanetant NK-1/ NK-3 receptor antagonist

Systemic HT- starting treatment

- **Estrogen therapy** (ET): when uterine protection not needed
- **Estrogen-progestogen therapy** (EPT): For women with a uterus
- **CEE and SERM** (CEE/bazedoxifene): option to avoid progestogen



- Types of Estrogen and Progestogens:
  - **Estradiol (E2- 17 ß- estradiol)** “bioidentical”-Patch
  - Conjugated equine estrogens (CEE) – Premarin/ Prempro ® used in WHI
  - Ethinyl Estradiol (used in OCPs)
  - Esterified estrogens (used alone or in combo with testosterone e.g Estratest®)
  - Estetrol (E4) Newly available “bioidentical”



Micronized progesterone “bioidentical”- Oral

- MPA- Medroxyprogesterone
- Progestins used in OCPs, MHT combination patches and pills

Michelle 50

All symptoms

-Improved with systemic MHT

Except continued pain with sex

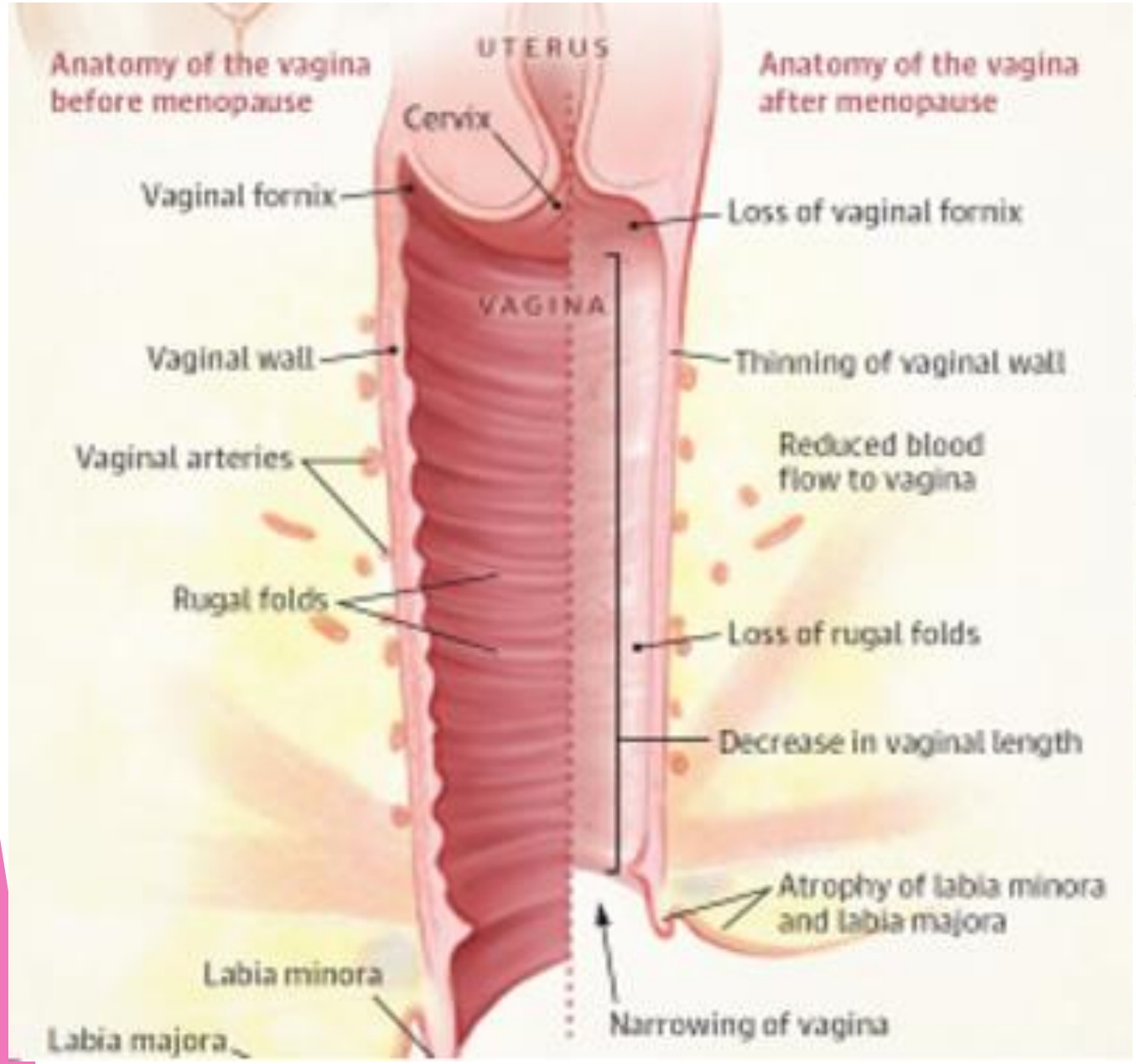
The Genitourinary Syndrome of Menopause (GSM)

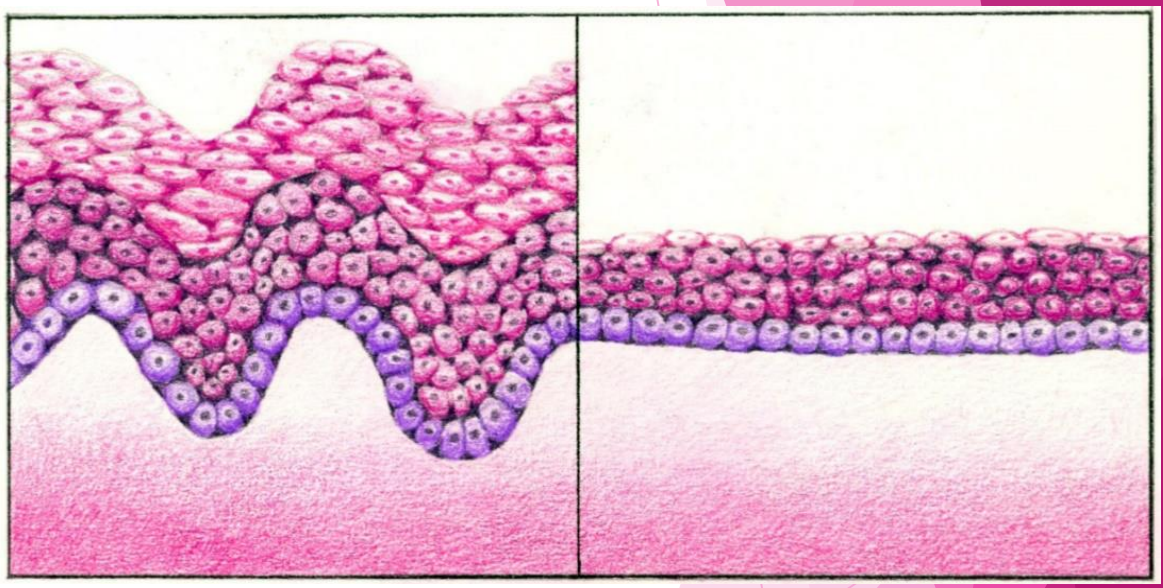
Genitourinary syndrome of menopause (GSM)

defined as a collection of symptoms and signs associated with **decreased estrogen and other sex steroids** involving changes to the labia majora/minora, clitoris, vestibule/introitus, vagina, urethra, and bladder. The term was formally endorsed in 2014 by the International Society for the Study of Women's Sexual Health (ISSWSH) and the North American Menopause Society (NAMS) to replace the older, narrower term "vulvovaginal atrophy."

- **Genital symptoms**: vaginal/vulvar dryness, burning, irritation, loss of vaginal rugae, introital narrowing, decreased tissue elasticity, resorption of the labia minora
- **Sexual symptoms**: dyspareunia, lack of lubrication, discomfort or pain with intercourse, impaired sexual function
- **Urinary symptoms**: urgency, frequency, dysuria, nocturia, recurrent urinary tract infections

Genitourinary Syndrome of Menopause





Well-estrogenized

Low-estrogen

Genitourinary Syndrome of Menopause: AUA/SUFU/AUGS Guideline (2025)

USING AUA GUIDELINES

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Endorsed by The International Society for the Study of Women's Sexual Health (ISSWSH), The Sexual Medicine Society of North America (SMSNA), and The Menopause Society (TMS).

GSM Pre and post 6 weeks of treatment with topical hormones

Photos courtesy of Rachel Rubin, MD

Vaginal Estrogen 2025 Guidelines

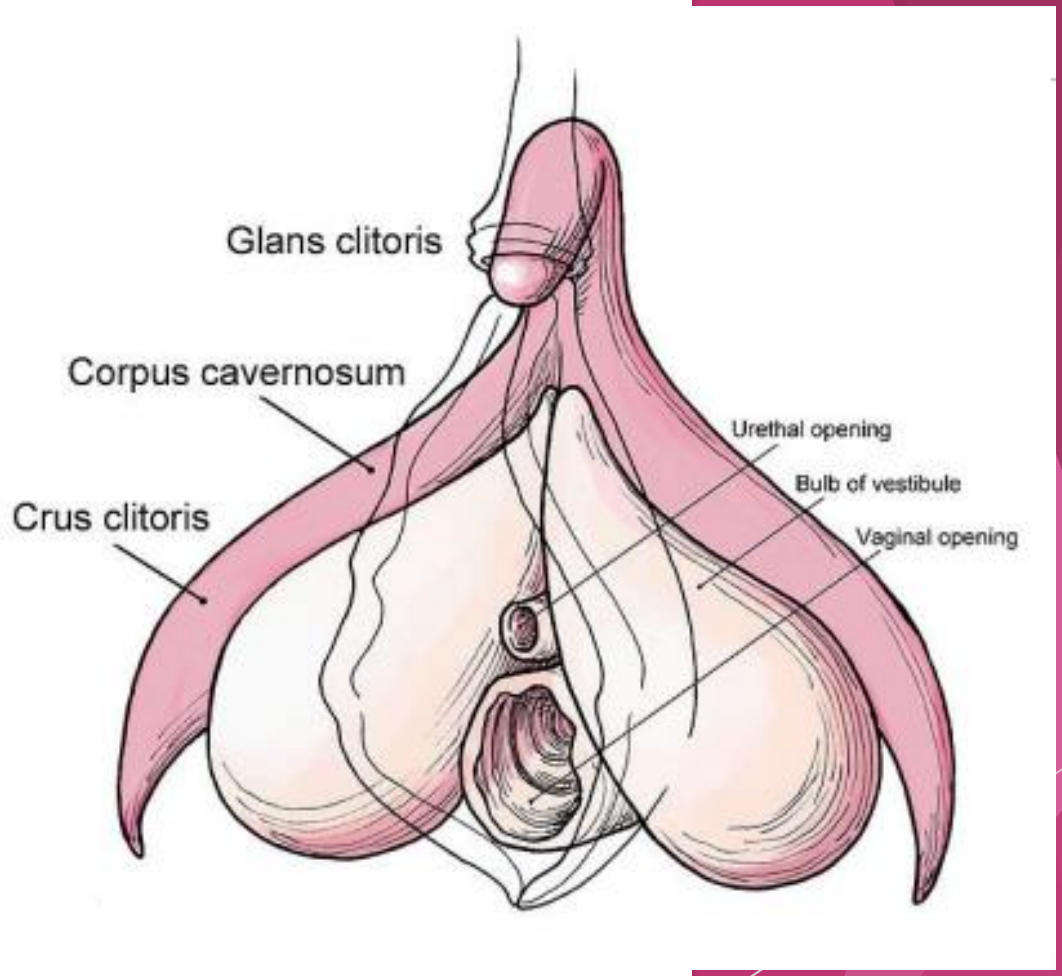
- **Diagnosis: GSM is diagnosed based on symptoms (with or without physical findings)** after ruling out other etiologies or co-occurring pathologies

- **Treatment approach: Low-dose vaginal estrogen has the most robust evidence base among all treatment options**

- **Recurrent UTI prevention: Local vaginal estrogen** is effective for preventing recurrent urinary tract infections in postmenopausal women

Discoveries about women's sexual health

- Clitoris has been ignored
- Same structure as the penis
- 10,000 nerve fibers
- Role of hormones in genital health
- Estrogen, Testosterone, DHEA
- Testosterone for libido
- Shrinkage and scaring of genital tissue without hormonal support
- **Sexual symptoms**: dyspareunia, lack of lubrication, discomfort or pain with intercourse, impaired sexual function



Treatment Guidelines

- ✓ Over-the-counter vaginal lubricants and moisturizers
- ✓ Low-dose vaginal estrogens, vaginal DHEA (prasterone), systemic estrogen therapy, or oral ospemifene are effective treatments.
- ✓ **Progestogen not required:** When low-dose vaginal estrogen, vaginal DHEA, or ospemifene is used, concurrent progestogen is not indicated
- ✓ **Endometrial safety limitation:** Endometrial safety has not been studied in clinical trials beyond 1 year

- ✓ Improved urge incontinence
- ✓ Prevention of recurrent urinary tract infections

- ✓ Low-dose vaginal estrogen has minimal systemic absorption:
- ✓ Vaginal estradiol ring (7.5 mcg daily) and vaginal estradiol tablets (4 mcg daily) have the least systemic absorption
- ✓ Vaginal tablets (10 mcg twice weekly) and creams (0.5 mg daily) also have very low absorption
- ✓ RCTs show low-dose vaginal estrogen tablets do not significantly increase serum estradiol levels
- ✓ No evidence that vaginal estrogen increases risk of breast cancer, endometrial cancer, coronary heart disease, stroke, or venous thromboembolism

Prevention- use lifelong and regularly. Like brushing your teeth…

Key Points and Next Best Steps

- MHT safe for most women! Best **start** less than age 60.
- Black box warning removed.
- No age limit or time limit for HT Rx
- Transdermal safest- no increased clot risk
- Look out for early and premature menopause= needs hormone replacement
- Use topical estrogen for GSM
- Sexual health complex and can improve greatly with hormone support

Next steps:

Help dispel myths of MHT being dangerous- Don't be stuck in 20-year-old thinking/data.

Resources:

- Menopause.org
- HMS CME: Update in Women's Health and Menopause March 15-19, 2027. Special discounts available

https://WHAM-cme.org

Menopause and Midlife Clinic

Thank you!

Questions?

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