Women's Health: Managing Menopause

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Disclosures

- I have no conflicts of interest

Learning Objectives

1. What is our current understanding of menopause
2. Learn how and when to treat menopausal symptoms with hormone therapy and with alternatives
3. Know the data showing the benefits and risks of menopausal hormone therapy

Menopause

- Definition: permanent cessation of menstrual periods, defined as no periods for one year
- Occurs at mean age of 51
- Reflects ovarian follicular depletion with resulting low estrogen levels and high FSH
- Menopause before age 40: considered to be abnormal, referred to as premature ovarian failure

Managing perimenopause

- On average, begins 4 years before final menstrual period
- The issues: hot flashes, possible irregular bleeding, possible vaginal atrophy, but still needs contraception
- Best option: low-estrogen oral contraceptive (OC): 20 mcg ethinyl estradiol
  - treats hot flashes and vaginal atrophy, controls bleeding and provides contraception
  - most women are between ages 40-50, still candidates for OCs

Contraindications to OC use in perimenopause

- Obesity: increased risk of thromboembolism
- Smoking
- Hypertension
- Migraines

Stopping OC use during perimenopause

- When woman reaches age 50 or 51, discuss stopping the pill or switching to a postmenopausal estrogen regimen
- As women this age often have hot flushes when estrogen stopped abruptly, taper the OC by 1 pill per week

General principles

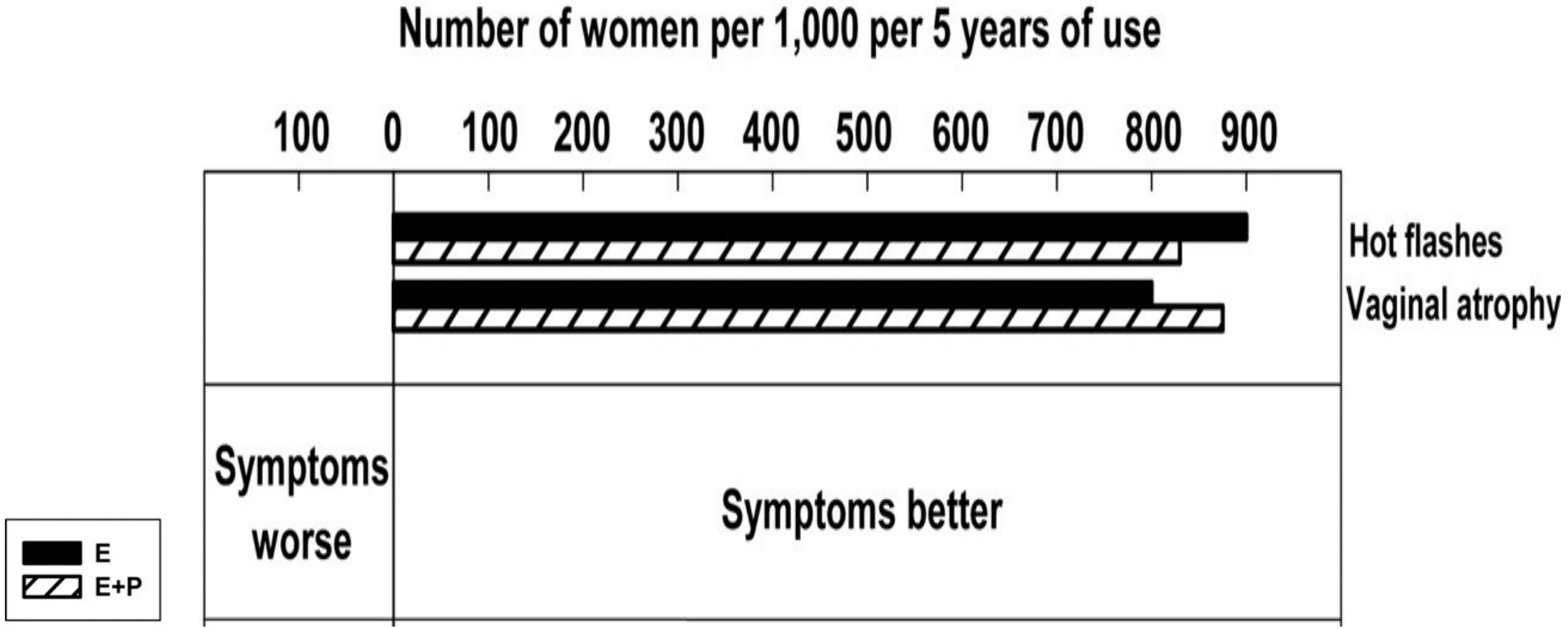
- Menopausal hormone therapy (MHT) is the broad term describing both unopposed estrogen use and combined estrogen-progestin therapy
- Unopposed estrogen therapy is known as ET
- Combined estrogen-progestin therapy is EPT

When is menopausal hormone therapy indicated?

- Endocrine Society Clinical Practice Guideline:
  - For treatment of **hot flashes**
  - For treatment of **symptomatic vaginal atrophy**
  - NOT for prevention of cardiovascular disease, osteoporosis or dementia

Stuenkel CA, et al. J Clin Endocrinol Metab 2015; 100(1):3975-4011.

Hormone therapy for menopausal symptoms



Santen RJ, et al. J Clin Endocrinol Metab. 2010;95:S1-S66.

Importance of patient's age in using MHT

- WHI 2002: adverse effects of MHT in older postmenopausal women (over age 60): increased CV events and breast cancer
- However most women seeking therapy for menopausal symptoms are in their late 40s or 50s
- Women in this age group should be reassured that absolute risk of complications for healthy, young postmenopausal women taking MHT for five years is very low

WHI: Combined estrogen-progestin therapy

Number of cases per 1000 women aged <60 after 5 years of hormone use compared to placebo

- **Coronary heart disease (CHD): 2.5 additional cases**
- **Invasive breast cancer: 3 additional cases**
- **Stroke: 2.5 additional cases**
- **Pulmonary embolism: 3 additional cases**
- Colorectal cancer: 0.5 fewer cases
- Endometrial cancer: no difference
- Hip fracture: 1.5 fewer cases
- All-cause mortality: 5 fewer deaths

Stuenkel CA, et al. J Clin Endocrinol Metab. 2015;100(1):3975-4011.

WHI Estrogen-alone therapy: Number of cases per 1000 women aged <60 after 5 years of hormone use compared with placebo

- **CHD: 5.5 fewer cases**
- **Invasive breast cancer: 2.5 fewer cases**
- **Stroke: 0.5 fewer cases**
- **Pulmonary embolism: 1.5 additional cases**
- Colorectal cancer: 0.5 fewer cases
- Hip fracture: 1.5 additional cases
- All-cause mortality: 5.5 fewer deaths

Stuenkel CA, et al. J Clin Endocrinol Metab. 2015;100(1):3975-4011.

New meta-analysis: all types of MHT except vaginal estrogen are associated with increased breast cancer risk

- **Meta-analysis** of individual participants from 58 observational studies: 108,647 postmenopausal women who developed breast cancer; 55,575 (51%) had used MHT
- **Findings**: 5 years of MHT starting at age 50 increased breast cancer incidence at ages 50-69 by
  - 1 in every 50 users of estrogen plus daily progestogen
  - 1 in every 70 users of estrogen plus intermittent progestogen
  - 1 in every 200 users of estrogen only
- Increases from 10 years of MHT were twice as great

Lancet 2019; 394: 1159-68

Estrogen alone: why was breast cancer risk **decreased** in the WHI but **increased** in the meta-analysis?

- WHI: **randomized controlled trial**: both users and non-users underwent standardized mammographic screening
- **Observational studies:** women on MHT tend to undergo mammographic screening more frequently and consistently than non-users
  - The excess breast cancer risk could reflect increased mammographic detection of nonlethal cancers: overdiagnosis

NEJM Journal Watch – Women's Health, Oct. 2019; 24 (10): 78

Should this meta-analysis influence clinical practice?

- Dr. JoAnn Manson, director of WHI and Dr. Andrew Kaunitz, editor of NEJM Journal Watch – Women's Health:
  - No
  - Benefits will outweigh risks for many menopausal patients
  - Net effects of MHT are most favorable for recently menopausal women who have moderate to severe vasomotor symptoms and low or average risks for breast cancer, CV disease and venous thromboembolism
  - Women who are above average risk may want to avoid MHT and consider nonhormonal options

NEJM Journal Watch – Women's Health, Oct. 2019; 24(10): 78

Contraindications to MHT

- Hx of breast cancer
- CHD
- Previous venous thromboembolic event
- TIA or stroke
- Active liver disease
- Unexplained vaginal bleeding
- High-risk endometrial cancer

Choosing a candidate for MHT

- Safe option for healthy women within 10 years of menopause or younger than age 60 and without contraindications
- Endocrine Society 2015 clinical practice guideline presents individualized approach to treatment based on calculating a woman’ baseline cardiovascular and breast cancer risks

Stuenkel CA, et al. J Clin Endocrinol Metab 2015; 100(1):3975-4011

Endocrine Society recommendations for estrogen

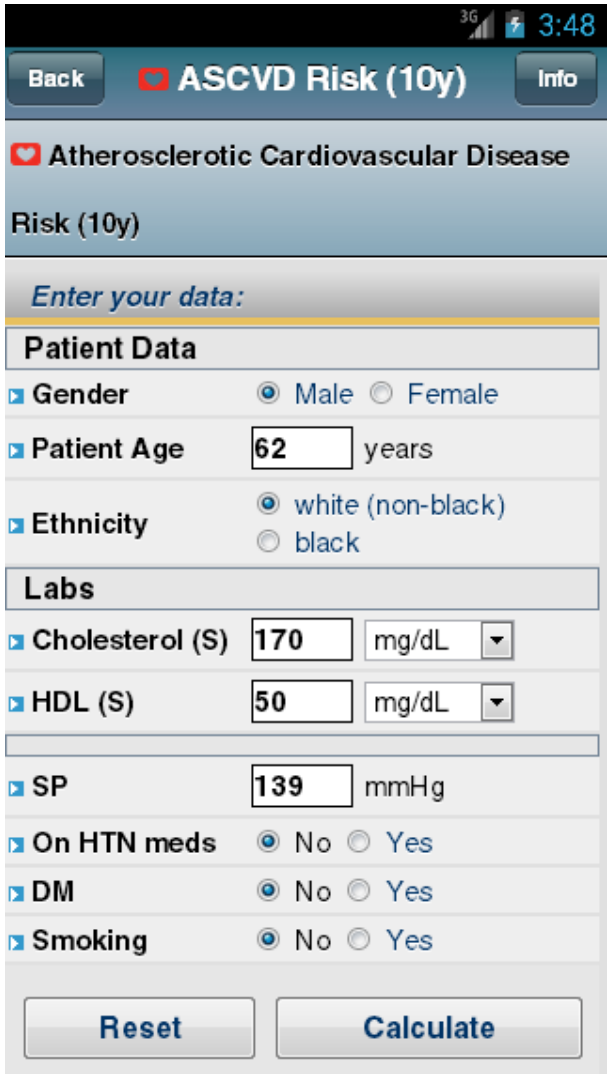
- **CVD**
  - **Low risk** (<5% ten-yr risk): transdermal or, if patient prefers, oral estrogen
  - **Moderate risk** (5-10% ten-yr risk): transdermal estrogen
  - **High risk** (>10% ten-yr risk): nonhormonal therapy
- **Breast cancer**
  - **Moderate risk** (1.67-5% five-yr risk): nonhormonal therapy
  - **High risk** (>5% five-yr risk): nonhormonal therapy

Stuenkel CA, et al. J Clin Endocrinol Metab. 2015;100(1):3975-4011.

Cardiac risk

- Use the ACC/AHA ASCVD risk calculator

  www.cvriskcalculator.com

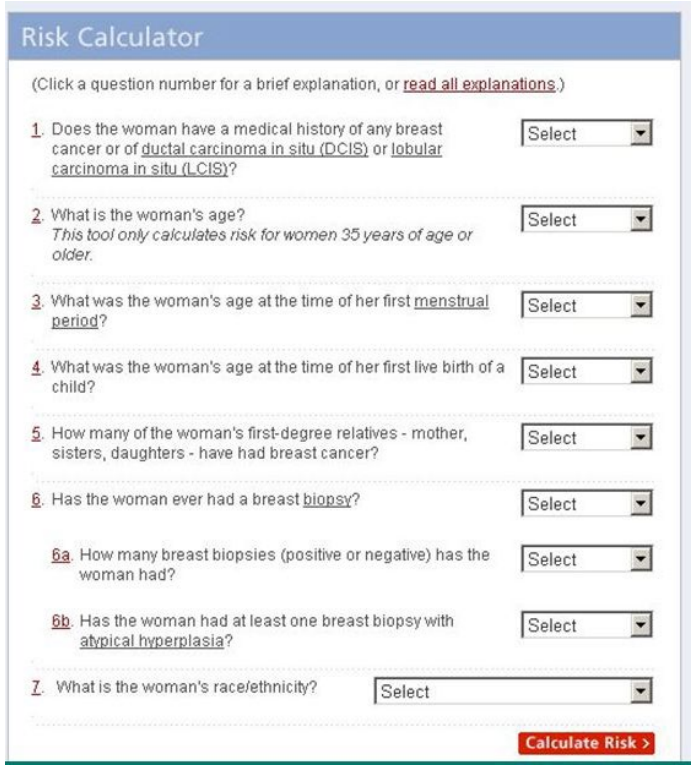


Breast cancer risk

- Use online tool such as the National Cancer Institute Breast Cancer Assessment Tool

  www.cancer.gov/bcrisktool

- Calculates patient's 5-year and lifetime risk



Caveat

- Formal CVD calculation may not be necessary in a thin, healthy, nonhypertensive, nondiabetic patient well known to the clinician

Vaginal estrogen

- Not associated with increased risk of CV events or breast cancer
- Assessment of CV and breast cancer risk not needed when low-dose vaginal estrogen is used

Useful tool for patients and clinicians: **MenoPro** App

- Evidence-based free mobile app created by the North American Menopause Society about therapies for menopause symptoms
- Downloadable to mobile iPhone/iPad
- Designed for women ≥ 45 years old and for clinicians

Manson JE, et al. Menopause 2015;22(3):247-253.

MenoPro App

- Includes:
  - Contraindications
  - Cardiac risk calculator
  - Breast Cancer Risk Assessment tool
  - Recommendations based on patient's CV risk and breast cancer risk
  - Handout on benefits/risks of hormone therapy

Manson JE, et al. Menopause 2015;22(3):247-253.

Case

- 54 yo woman in menopause since age 52 who is suffering from severe hot flashes.
- No known contraindications to hormone therapy.
- Calculated 10 year cardiac risk is 6%.
- You and she decide that she should try hormone therapy to treat her symptoms.

What would be the best treatment to start her on?

The best answer is:

A. Conjugated equine estrogen 0.625 mg po qd plus medroxyprogesterone acetate 2.5 mg po qd

B. Conjugated equine estrogen 0.3 mg po qd plus medroxyprogesterone acetate 2.5 mg po qd

C. Transdermal estradiol 0.025 mg qd plus micronized progesterone 200 mg po for 12 days a month

D. Transdermal estradiol 0.025 mg qd plus micronized progesterone for 12 days every 6 months

Starting estrogen

- Need to think about:
  - Type of estrogen
  - Route
  - Need for progestin
  - Most appropriate progestin

UK evaluation of hormone replacement and VTE found decreased risk with **estradiol** and **transdermal** preparations

- **Method:** 2 case-control studies of 80,396 women with diagnosis of VTE between 1998 and 2017 matched to 391,494 controls
- **Results:**
  - **Oral estradiol** had lower risk of VTE than conjugated equine estrogen (CEE) when used as estrogen alone and as estrogen + progestin
  - CEE with medroxyprogesterone acetate had highest risk
  - **Transdermal** estradiol: NO increased risk of VTE

Vinogradova Y, et al. BMJ 2019; 364:k4810

Recommendations to minimize risk of VTE

- Consider estradiol as estrogen **preparation** of choice
- Consider transdermal as estrogen **route** of choice
- If patient prefers oral route, ok if her 10-year risk of CV disease is low (less than 5%)

Transdermal estrogen

- Available as patch, gel, spray
- I recommend the patch
- Be careful with the spray
  - Contact with the spray by small children and pets can cause breast enlargement, not always reversible

Estrogen dose – start low, titrate up if hot flashes persist

Preparation	Initial dose	After 1 month	After 2nd month
Transdermal estradiol	0.025 mg patch	0.0375 mg patch	0.05 mg patch
Oral estradiol	0.5 mg qd	0.75 mg qd	1 mg qd
CEE	0.3 mg qd	0.45 mg qd	0.625 mg qd

Adding a progestin

- All women with **intact uterus** need a progestin in addition to estrogen to prevent endometrial hyperplasia
  - Endometrial hyperplasia and cancer can occur after as little as 6 months of unopposed estrogen
- Women who have had **hysterectomy** do not need a progestin

WHI showed small increased risk of breast cancer with **medroxyprogesterone acetate**

- Estimated additional risk of breast cancer: three additional cases per 1000 women in their 50s for five years of combined conjugated estrogen-MPA use

Stuenkel CA, et al. J Clin Endocrinol Metab 2015: 100(11):3975

E3N study showed no increased risk of breast cancer with estrogen plus **progesterone**

- Prospective cohort of 80,377 postmenopausal women followed for average of 8 years
  - 70% used HRT
- Relative risks of invasive breast cancer varied between the progestogens
  - **Estrogen-progesterone**: no or non-significant increase in risk
  - All other estrogen-progestogen combinations (MPA, other synthetic progestins): associated with increased risks

Fournier A, et al. Breast Cancer Res Treat (2008); 107:103-111

My recommendation:
Oral micronized progesterone

- **For < 2 years post menopause**
  - Cyclic progesterone 200 mg: days 1-12/month
  - Will have regular withdrawal bleed after the 12 days of progesterone
  - Decreases likelihood of irregular, unscheduled bleeding
- **≥ 2 years post menopause:** continuous dose
  - Has endometrial atrophy, less risk of irregular bleeding
  - Progesterone 100 mg daily

Progestin side effects

- Mood symptoms
- Bloating
- Worse with cyclic dosing
- What to do: switch to continuous

Options for women who can't tolerate any oral progestin

- **New combination pill:** conjugated estrogen 0.45 mg qd and bazedoxifene, a selective estrogen receptor modulator (SERM), 20 mg qd
  - Prevents endometrial hyperplasia
  - Risk of VTE increased with bazedoxifene
  - To date, no additive risk of VTE noted with bazedoxifene plus estrogen
- **Levonorgestrel IUD:** off-label use
  - High uterine, low systemic levels of levonorgestrel

Pinkerton JV, et al. Obstet Gynecol 2013;121(5):959-968.

Monitoring with mammography

- Routine mammograms and breast exams are recommended in women taking MHT
- WHI
  - Risk of breast cancer with combined EPT did not increase till 4^{th} year
  - Abnormal mammograms were more common with both ET and EPT: most were requests for additional views

When to stop menopausal hormone therapy

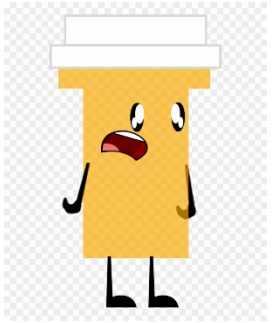
- Individualize
- Usual recommendation: try to stop after 5 years
- No evidence supports routine discontinuation of MHT at a specific age

The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. Menopause 2017 Jul;24(7):728-753.

Hot flashes last longer than we used to think

- Begin in up to 80% of women during perimenopause
- Penn Ovarian Aging Study[1]
  - Mean duration: 4.9 years
  - 1/3 of women: moderate to severe hot flashes for 10 years after final menstrual period
- 9% of women: still having hot flashes at age 72[2]
- 8% of women still having hot flashes $\geq$ 20 years after menopause[3]

1. Menopause 2014;21:924 2. Menopause 2002;9:156 3. Arch Intern Med 2008; 168:840



How to stop

- Hot flashes recur in approx. 50% of women when HT is stopped
- No consensus re whether stopping “cold turkey” or tapering is preferable
- **My recommendation:** taper
  - Oral estrogen: 6 pills/wk x 2 wks -> 5 pills/wk x 2 wks, etc.
  - Transdermal estrogen: gradual dose reduction
  - Progestin: taper
  - If severe recurrent symptoms, taper more slowly

Brunner RL. Menopause. 2010;17:946-954.

Alternatives if symptoms recur

- SSRI/SNRI:
  - Citalopram, escitalopram 20 mg: minimal side effects
  - Paroxetine 7.5 mg: FDA approved, avoid in women on tamoxifen
  - Venlafaxine
    - More acute toxicity: nausea, vomiting
    - Use sustained release: 37.5 mg qd x 1 wk, then increase to 75 mg qd
- Gabapentin at night: 100 mg, increase by 100 mg q 3d up to 900 mg qhs

The North American Menopause Society, Menopause 2015; 22:1155

Continuing hormone therapy after age 65

- North American Menopause Society (NAMS) position statement:
  - Continuing past age 65 is acceptable IF:
    - Patient continues to have bothersome symptoms
    - Unable to use any other appropriate medication
    - Her clinician has determined that benefits outweigh risks
    - Patient has been advised of increased risks after age 60

The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. Menopause. 2017 Jul;24(7):728-753.

Compounded bioidentical hormone therapy

- Often contains multiple hormones
  - Untested, unapproved combinations, doses, routes: sublingual, subdermal, suppositories
- Endocrine Society Statement
  - No randomized trials show efficacy or safety
  - No regulatory oversight
  - When tested, highly variable potencies
  - Don’t use it

Santoro N, et al. J Clin Endocrinol Metab 2016 Apr;101(4):1318-43.

Role of androgen therapy

- Known decrease in ovarian androgen production in menopause
- Studies: no significant correlation between libido and serum estradiol or testosterone concentration
- Trials of testosterone replacement suggest modest benefit to libido
- BUT androgen replacement has risks and no approved commercially available product for women
- Would not routinely recommend this

Stop MHT before moderate or high risk surgery

- Because MHT is associated with increased risk of VTE
- Recommendation: stop it 4-6 weeks before moderate or high-risk surgery
- Patient may require alternative treatment for vasomotor symptoms (e.g. SSRI, gabapentin)

Surgery (Oxford) 2019 August; 37(8): 435-440

Complementary and alternative therapies for hot flashes

- **Promising:** CBT, hypnosis, stellate ganglion block, weight loss
- **Inconsistent evidence of efficacy:** plant-based therapy (phytoestrogens), herbal therapy (black cohosh)
- **Ineffective:** acupuncture, evening primrose oil, flaxseed, exercise

Case

- 53 year old woman is having severe pain on intercourse
  - Had her last menstrual period more than 1 year ago
  - Is not troubled by hot flashes

What is the most appropriate treatment for this woman with severe pain on intercourse?

The best answer is:

A. Vaginal moisturizer

B. Vaginal lubricant

C. Low-dose vaginal estrogen

D. Ospemifene

E. Oral estrogen

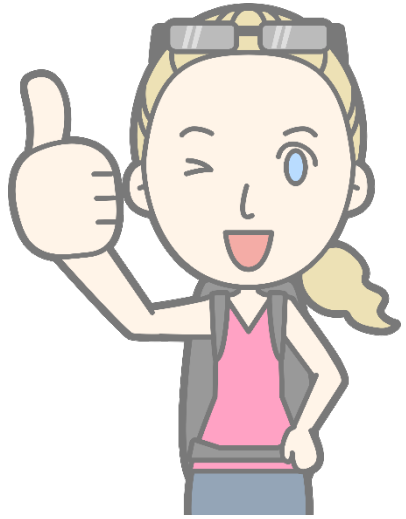
The genitourinary syndrome of menopause (GSM)

- New name for vaginal atrophy
- Due to estrogen deficiency affecting vagina, labia, urethra, bladder
- Symptoms may include:
  - **genital:** dryness, burning, irritation
  - **sexual:** decreased lubrication and pain
  - **urinary:** urgency, dysuria, recurrent UTIs
- Estrogen is the most effective treatment

First line treatment: vaginal moisturizers and lubricants

- Helpful for mild symptoms
- Use of moisturizer 2-3 times a week: Replens
- Use of lubricant before sexual activity: Astroglide
- All are OTC

Vaginal estrogen (VE)



- For moderate-severe symptoms
- **More effective** than systemic therapy
- Low-dose recommended: minimizes systemic estrogen effects
- Inserts, rings, creams: similarly effective

Cardozo L, et al. Obstet Gynecol 1998; 92(4 Pt 2):722-727.
Lethaby A, et al. Cochrane Database Syst Rev 2016;CD001500

Low-dose vaginal estrogen options

- **Estradiol insert:**
  - 10 mcg, or new 4 mcg dose
  - Insert in vagina daily x 2 weeks, then twice a week
- **Vaginal ring:** Releases estradiol 7.5 mcg qd into vagina x 90 days
- **Low-dose vaginal cream:**
  - 0.5 gm of conjugated estrogen (CE) cream = 0.3 mg CE
  - 0.5 gm of estradiol cream = 50 mcg estradiol
  - Daily x 2 weeks, then twice a week

www.imvexxy.com/pi.pdf

Serum estradiol levels

- Average level for postmenopausal woman: 5 pg/ml
- 10 mcg estradiol insert: 5-11 pg/ml
- Vaginal ring: 5-10 pg/ml
- Creams: hard to quantify
  - 0.5 gm of conjugated estrogen cream: made up of many compounds. Serum estradiol level doesn't reflect total absorption
  - 0.5 gm of estradiol cream: approx. 10 pg/ml

Eugster-Hausmann M, et al. Climacteric 2010; 13(3):219-227.

How long to continue low-dose vaginal estrogen (VE)

- Can be continued indefinitely due to low risk of adverse effects[1]
- Concomitant progestin not recommended
- New Nurses' Health Study findings: VE (mean duration of use, 36 months) NOT associated with higher risk of CV disease or cancer[2]

1. Menopause 2017;24:728-753 2. Menopause 2019;26(6):00 (pub online)

NEW: Ospemifene

- Selective estrogen receptor modulator (SERM)
  - Estrogen **agonist** in vagina: treats atrophy
  - No estrogen effect on breast or endometrium
- One 60 mg pill daily
- Good for women who can't or don't want to use a vaginal product
- Side effects
  - Hot flashes
  - Potential for thromboembolic events: no data yet

Bachmann GA, et al. Menopause 2010 May; 17(3):480-486.

NEWEST: Prasterone

- Approved 11/17/2016: 1st FDA approved product containing dehydroepiandrosterone (DHEA)
- Once-daily vaginal suppository
- **Efficacy:** Reduced pain during intercourse compared to placebo in two 12-week RCTs
- **Adverse reaction:** vaginal discharge: 14%

Kaufman, M. P&T 2017;42(2):90-91.

Take home points

- The **benefits** of menopausal hormone therapy are greater than the risks in many women < age 60 or < 10 years since menopause
- Systemic estrogen is the most effective treatment for relief of **hot flashes**
- Vaginal estrogen is the most effective treatment for **moderate-severe menopausal vaginal symptoms**