Menopause Madness:

Breaking it down

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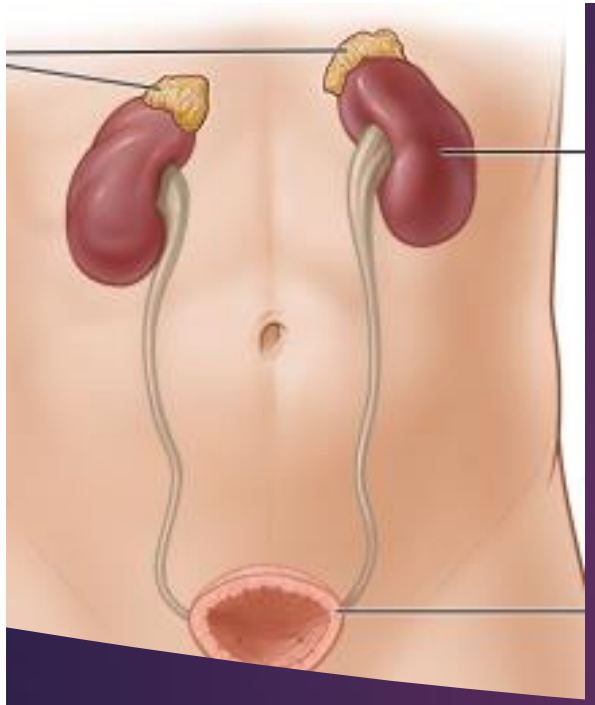
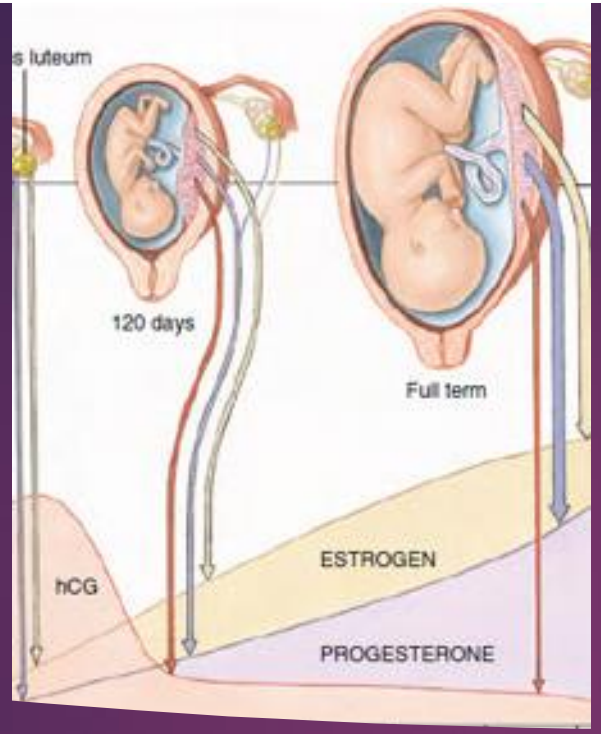
Estrogen

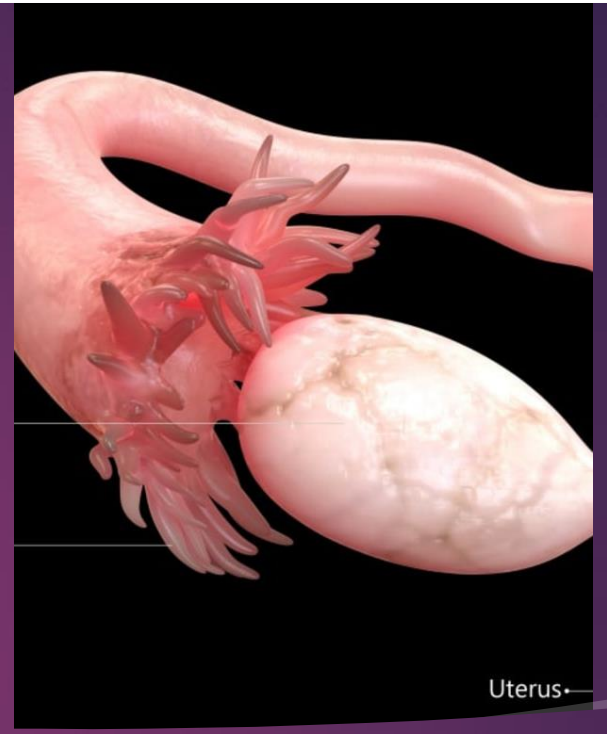
- Estrogen is one of 2 sex hormones commonly associated with AFAB, cis women, trans men and NB folx with vaginas/canals
- All genders have estrogen, although AFAB folx have the most
- Types
  - **Estrone** (E1)
    - Primary form made by bodies after menopause (found in adipose tissue)
  - **Estradiol** (E2)
    - Primary form in bodies during reproductive years
    - Most potent form
  - **Estriol** (E3)
    - Primary form during pregnancy
  - **Estetrol** (E4)
    - Normally produced by human fetal liver
- Estrogen peaks in the days leading up to ovulation
- It also thins the cervical mucous
- Maintains vaginal pH (3.5-4.5 – acidic) which makes penetration more comfortable, keeps vaginal walls robust and elastic and lubricated

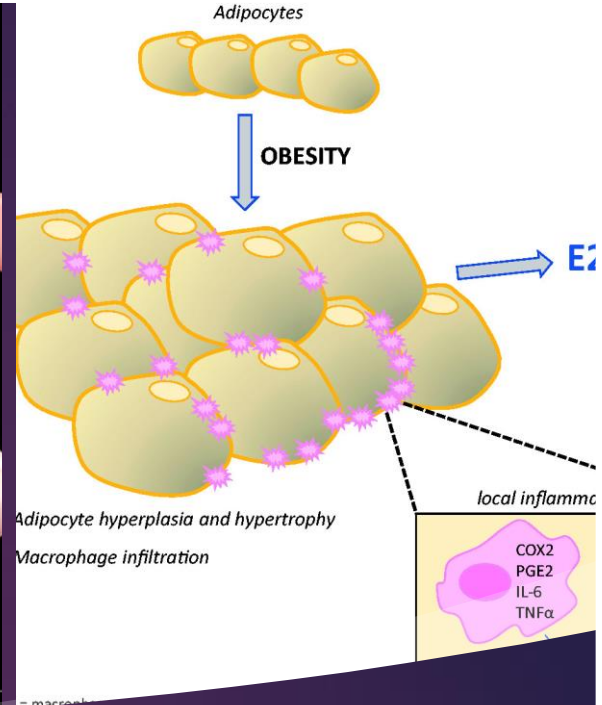
Estrogen affects:

Cholesterol	Blood sugar	Bone health	Muscle mass	Circulation and blood flow
Collagen production and moisture in skin	Brain/cognitive function/focus	Reproduction	Sexual function	Vasomotor symptoms
Sleep	Vaginal and urinary health	Skin, hair, nails	Joint health	Macular degeneration









Estrogen Origins

- Ovaries
- Adrenal Glands
- Adipose tissue
- Placenta
- Fetal liver

Estrogen levels

- **Too High**
  - Decreased libido
  - Weight gain (namely waist/hips)
  - Irregular periods (including light or heavy flow)
  - Worsening PMS/PMDD
  - Fibrocystic breasts/chest
  - Fatigue
  - Depression/anxiety
- **Too Low**
  - Breast tenderness
  - Weak/brittle bones
  - Hot flushes/night sweats
  - Irregular or no periods
  - HA's/trouble concentrating
  - Fatigue/drowsiness/trouble sleeping
  - Mood changes/lability
  - Vaginal dryness/dry skin
  - Decreased libido

Progesterone

Class of hormones called Progestogens

- Progestins
  - Synthetic steroid hormones with progesterone-like properties

Secreted from the corpus luteum

- Produced by the body after ovulation

Progesterone prepares the endometrium for potential implantation after ovulation

Helps maintain early pregnancy

Placenta also releases progesterone so the body will not produce more eggs

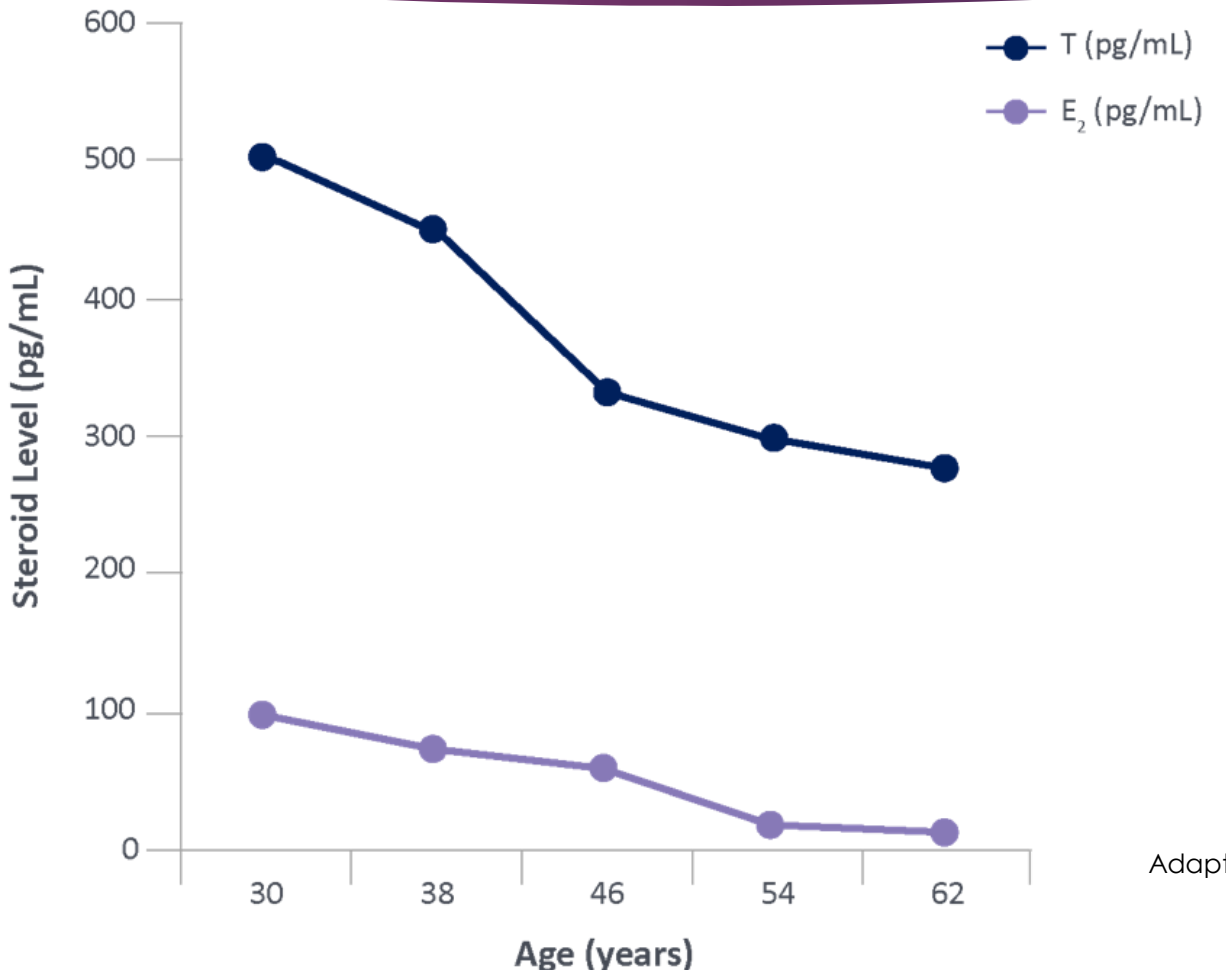
Helps prepare breasts/chest for milk production

Testosterone

Main sex hormone found in AMAB **and** AFAB folx

AFAB folx have 1/10th the circulating amounts of AMAB folx

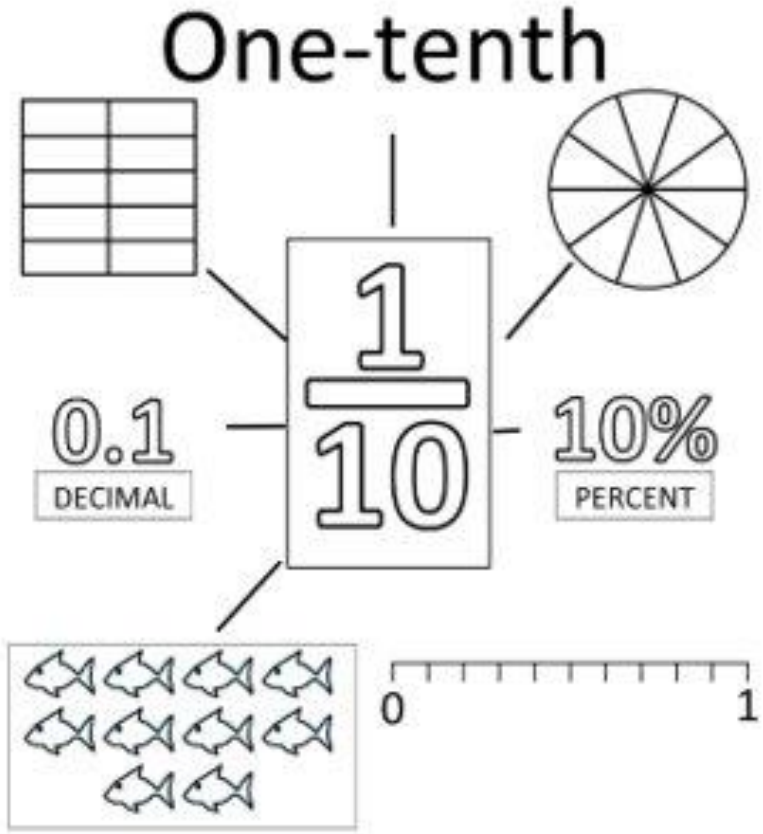
Testosterone/Estrogen ratio

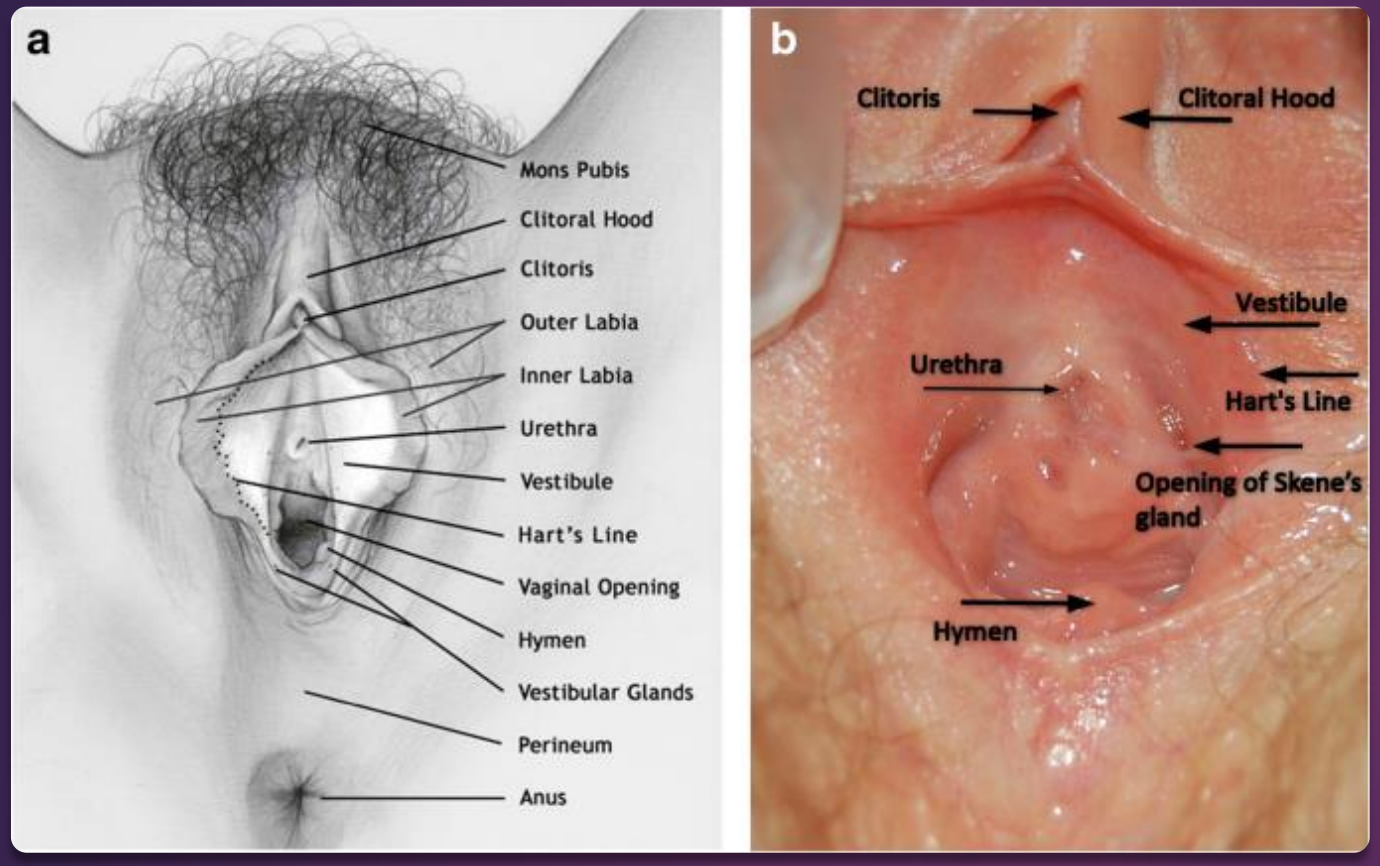


Adapted from: Glaser R, Dimitrakakis C. Maturitas. 2013; 74(3):230-234.

Key Messages for Testosterone Use

- Not yet FDA approved for AFAB folx
- Use 1/10th the dose as that for AMAB folx
- Oral, IM, Transdermal, Pellets, Troche
- Levels of endogenous androgens do not predict sexual function

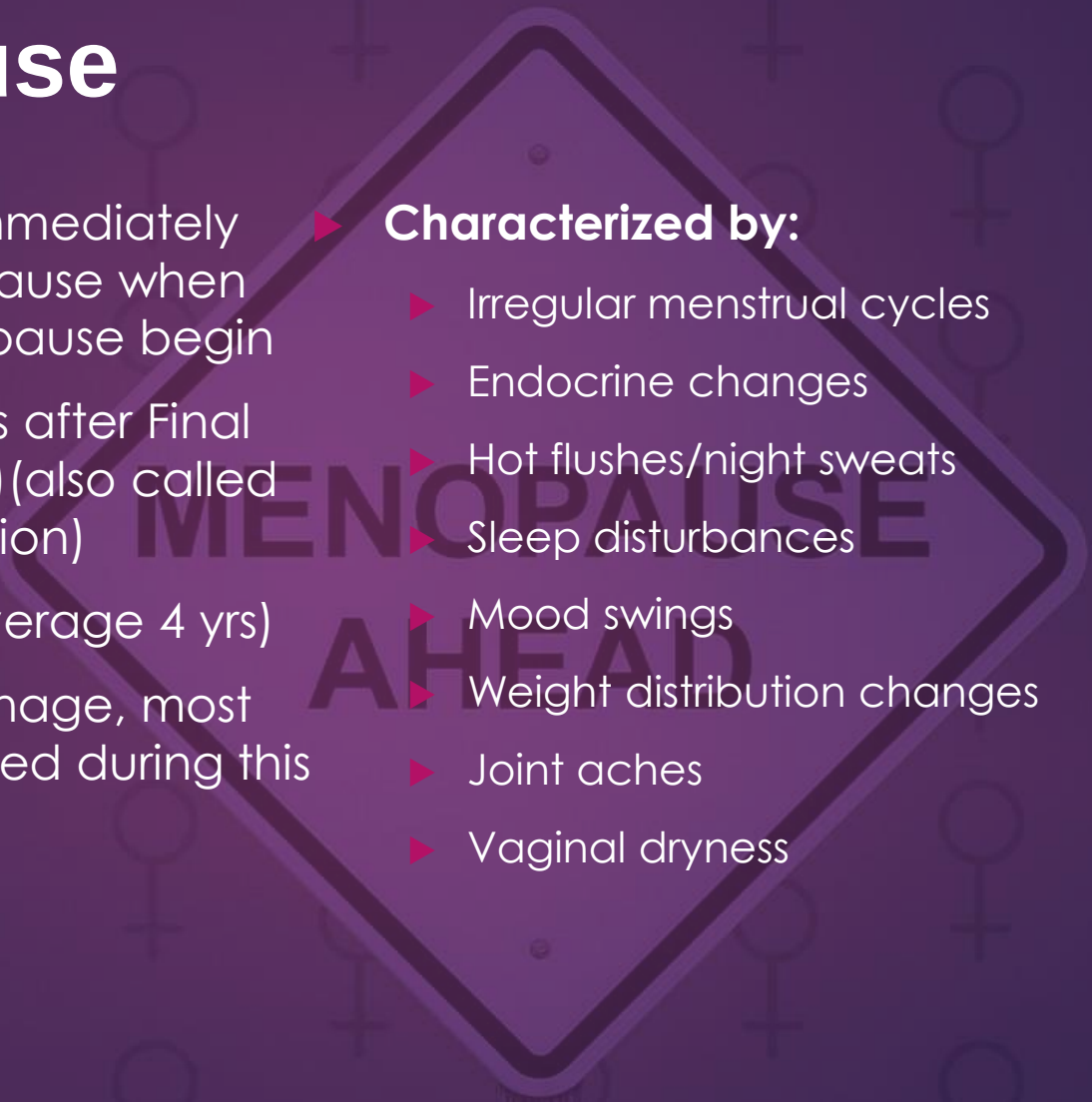




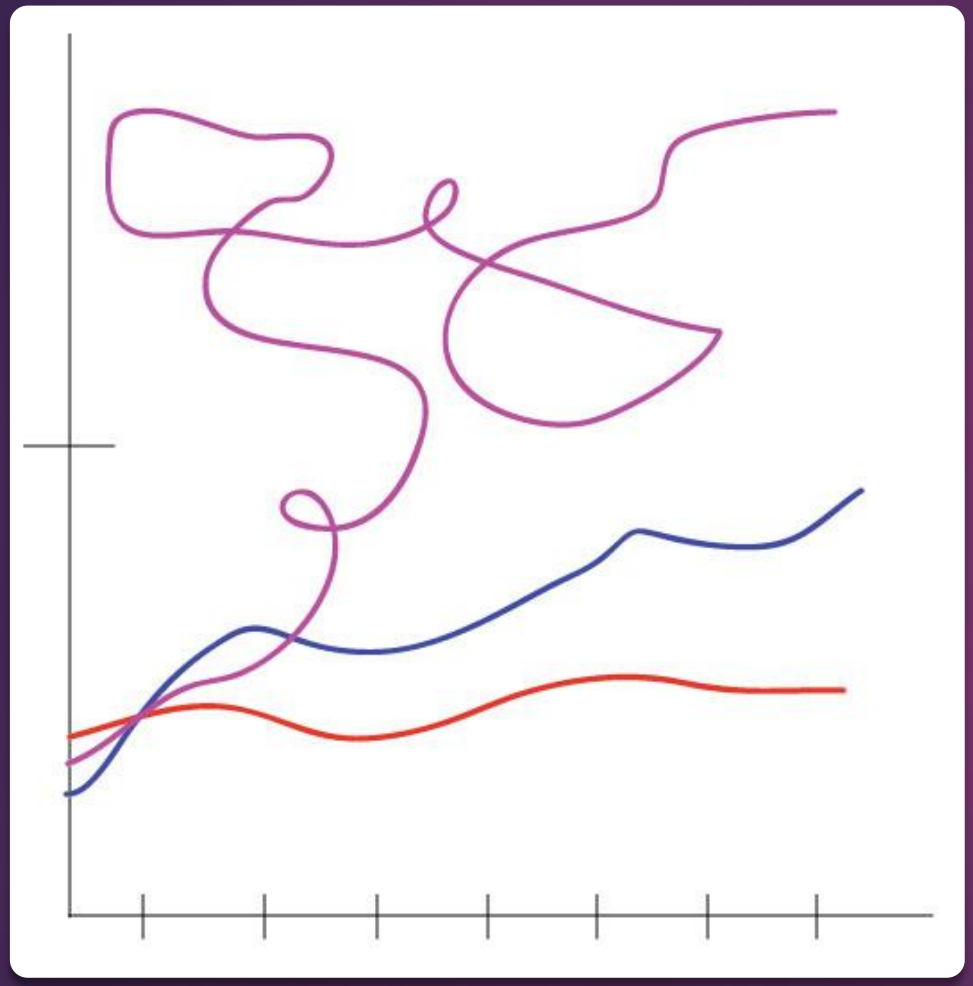
Testosterone at the vestibule

Perimenopause

- The transitional time immediately before natural menopause when the changes of menopause begin
- Includes the 12 months after Final Menstrual Period (FMP)(also called the menopause transition)
- Can last 2-12 years (average 4 yrs)
- Can be difficult to manage, most want hormones checked during this time frame!



- **Characterized by:**
  - Irregular menstrual cycles
  - Endocrine changes
  - Hot flushes/night sweats
  - Sleep disturbances
  - Mood swings
  - Weight distribution changes
  - Joint aches
  - Vaginal dryness



Fluctuations!

Contraception during Peri

- Contraindications to oral contraceptive (OC) use in peri:
  - Smoking
  - Hypertension
  - Migraines
- Ethinyl Estradiol → ↑SHBG → ↓testosterone
- Discuss stopping OC ~ age 50-51
  - TAPER!!
    - By 1 pill per week
    - May need to recommend condom use during this time
- LNG IUD/Etonogestrel implant
  - Can then add transdermal estradiol if/as needed

Grace

- Education about peri
- Help understand the changes that are happening to help empower folx to create an environment of healing/acceptance
- Anxiety in the unknown
- Set realistic expectations and help them advocate for themselves

Menopause

- Confirmed after 12 months without a period/bleeding
- Or when both ovaries are removed or permanently damaged
- Average age is 51.4 yrs (range 40-58)
- May have an elevated FSH level (but you would only know **IF** you checked!)
- Postmenopause is defined as all the years beyond menopause

Diagnosis of Menopause

- Currently – no single test of ovarian function that will predict or confirm menopause
- Usually confirmed based on symptoms and medical/menstrual history
- Non-ovarian hormone tests sometimes necessary to r/o other causes for symptoms (ex: TSH)
- Patients often ask for baseline and/or intermittent hormone testing based on insistence from some compounding pharmacists, clinicians, partners
  - No scientific basis for baseline hormone levels or intermittent checks
  - Recommended practice is to titrate med doses based on patient's report of symptom relief and AEs

Clinical Presentation

Hot flushes – affects up to 80%, only 20-30% seek medical treatment

2-4 minutes often w/ profuse sweating and occasionally palpitations, sometimes followed by chills and shivering and feeling of anxiety

Untreated typically resolve spontaneously within 4-5 years (9% report>70yrs)

Sleep disturbances – even in the absence of night sweats

~32-46% of women affected starting in early transition

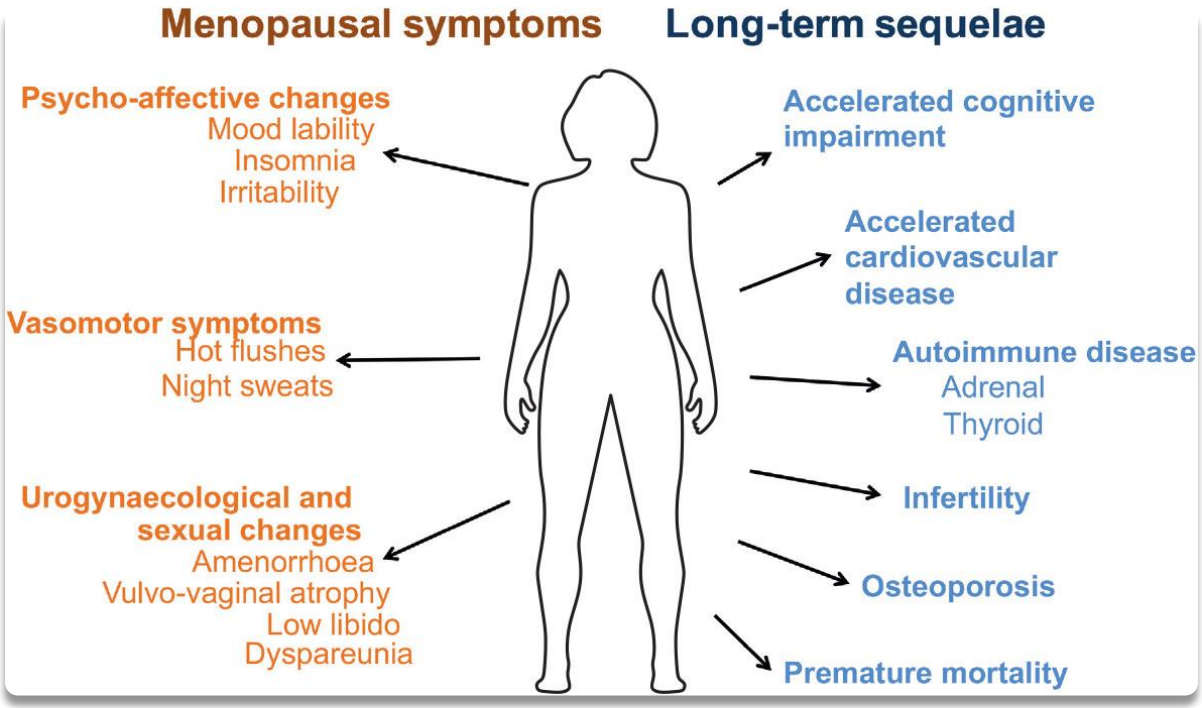
>50% have sleep apnea, RLS, or both

Mood swings – significant increased risk of new-onset depression during menopausal transition

Cognitive changes – substantial evidence points to importance of estrogen to cognitive function

Joint pain – 50-60% - many note relief with estrogen and/or progestin therapy

Clinical Presentation



- Vaginal dryness – as opposed to vasomotor symptoms (VMS), genitourinary syndrome of menopause (GSM) symptoms are progressive and worsen
  - Labial pallor, vestibular pallor or erythema, lack of nml rugae, scarce pubic hair, diminished elasticity and turgor of vulvar skin, introital narrowing, decreased moisture, fusion or resorption of labia minora
- Sexual function – partially due to GSM, shortening or narrowing of the vaginal vault and introitus. Systemic hormonal influences as well as body image, fatigue
- Breast pain – common in early transition but diminish in late transition. Likely due to estradiol fluctuations
- Menstrual migraines – may worsen in frequency and intensity

Factors determining age at Menopause

- Genetics
  - Genetic variation in the estrogen receptor gene
- Family history
  - Earlier in those with a family history of early menopause
- Ethnicity
  - Compared to white women, menopause occurs earlier in Hispanic women, and later in Japanese American women
- Smoking
  - ~ 2 yrs earlier in those who smoke
- Reproductive hx
  - Earlier if nulliparous or shorter cycle length during adolescence

Meno stats

- Average age 51.4 yrs (range 46-54 yrs)
  - US life expectancy for women 81.2 yrs
- African American women have the most severe VMS
  - Followed by Hispanic, White, then Asian

Long term consequences of estrogen deficiency

- Cardiovascular disease – risk increases after menopause
- Lipid profile - begins to change during perimenopause
- Bone loss – begins during menopausal transition, greatest during 1 yr before FMP through 2 yrs after
- Dementia – role of estrogen here is yet unclear
- Osteoarthritis – estrogen deficiency may contribute, but data limited
- Body composition – gain fat mass and lose lean mass
- Skin changes – estrogen deficiency decreases collagen content in skin and bones
- Balance – impaired balance may be a central effect of decreased estrogen

Here's why we don't use FSH to diagnose menopause

- Generally accepted that someone has reached menopause if they have consistently elevated levels of FSH > 30 mIU/mL
- FSH levels in the postmeno range can return to premeno ranges a few days, weeks, or months later
- FSH levels in perimeno folx are often normal, or can be elevated, while estradiol levels paradoxicaly remain in a premeno range
- Elevated early follicular FSH is enough only to put someone in the late reproductive stage
- LH elevation occurs much later than FSH elevation in the menopausal transition

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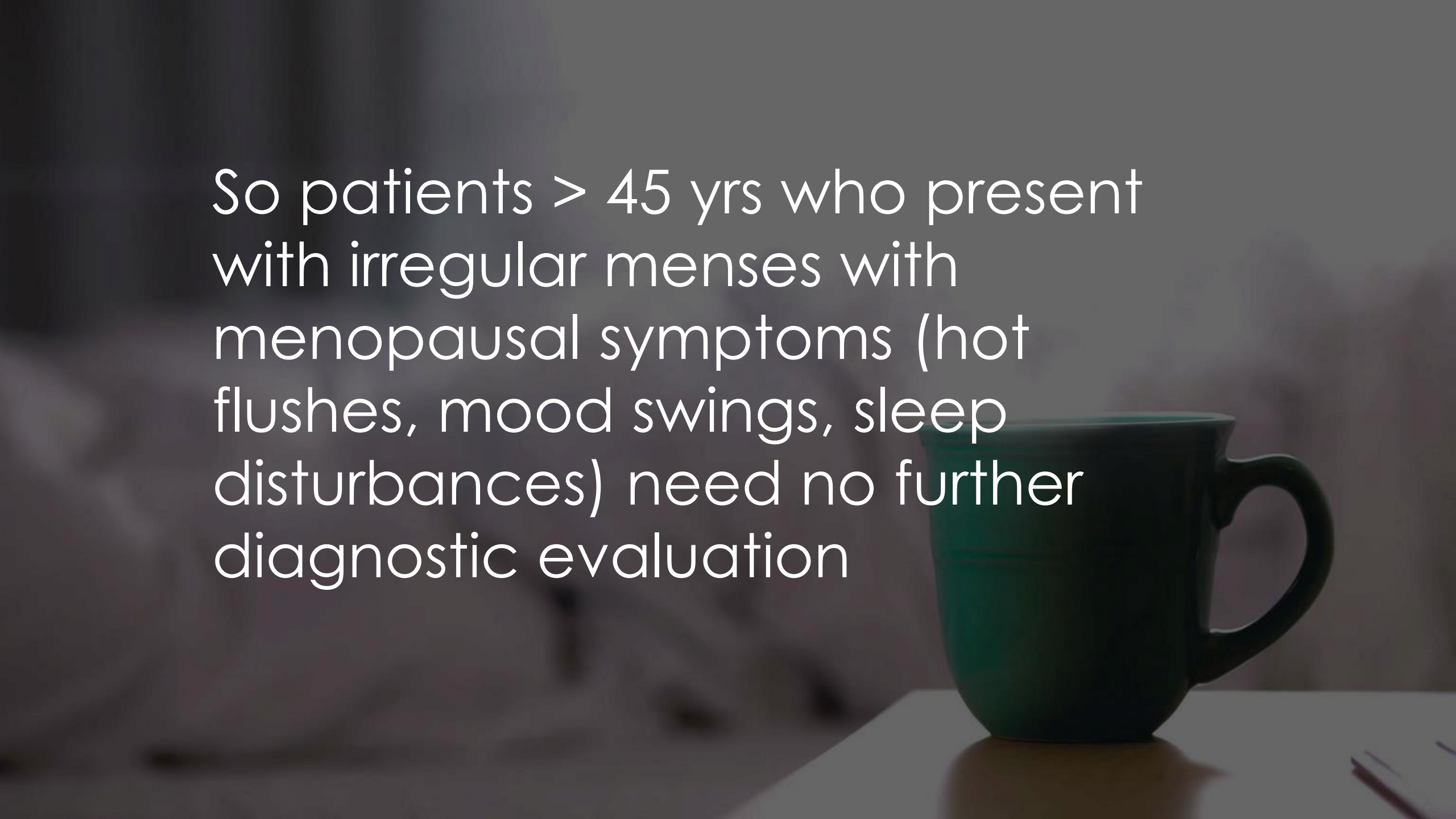


So patients > 45 yrs who present with irregular menses with menopausal symptoms (hot flushes, mood swings, sleep disturbances) need no further diagnostic evaluation

Menopausal Hormone Therapy (MHT)

- Goal
  - Relieve menopausal symptoms/vasomotor symptoms
  - Prevent osteoporosis
  - Treat GSM
  - Emotional lability/depression, GSM, dyspareunia, insomnia, joint pains have all been shown to also respond to estrogen therapy (ET)
- Treat vasomotor symptoms with systemic estrogen (if MHT is chosen)
- Treat Genitourinary Syndrome of Menopause (GSM) with low-dose topical therapy or oral ospemifene (Osphena)
- Alternative therapies are available if hormones are not desired or contraindicated
  - Treat the symptom

Contraindications to hormone therapy

- h/o breast ca
- CHD (caution if risk >8-10%)
- h/o blood clot or stroke/TIA
- Active liver disease (mostly for oral)
- Unexplained vaginal bleeding
- High risk endometrial cancer

- Should be avoided in:
  - Hypertriglyceridemia
  - Active gallbladder disease
  - Known thrombophilias (ex: Factor V Leiden (FVL))

Transdermal estrogen is <u>preferred</u> for those with migraines with aura

Things to consider

All routes of estrogen appear to be equally effective for symptom relief (and bone density), but their metabolic effects differ

- VTE/stroke risk lower with transdermal vs oral
- Oral estrogens increase SHBG

Select initial treatment agent based upon main concern

- Depression is main concern with mild hot flushes – consider SSRI
  - Some SSRIs help vasomotor symptoms in low doses as well
- Hot flushes are main concern with mild mood swings – consider MHT

Things to consider

HT is considered safe to initiate for healthy, symptomatic folx within 10 yrs of menopause or younger than 60 yrs of age without CIs

Vaginal estrogen is not associated with an increased risk of dementia, CV events or breast ca

Still has class effect black box warning!

Younger patients after surgical menopause often require higher doses for the 1st 1-3 yrs after surgery

Newly menopausal or perimenopausal folx can expect breakthrough bleeding (BTB) due to occasional ovarian "surge" of endogenous hormone

Vaginal estrogen

- 2023 study compared 1,262 women with early ER+ breast cancer, given vaginal estrogen, with 12,620 women who did not use vaginal estrogen.
- All participants were being treated with either tamoxifen or aromatase inhibitor therapy
- All were followed up for 13 yrs
- Vaginal estrogen DID NOT INCREASE the risk of death from breast cancer.

Sund M, Garmo H, Andersson A, Margolin S, Ahlgren J, Valachis A. Estrogen therapy after breast cancer diagnosis and breast cancer mortality risk. Breast Cancer Res Treat. 2023 Apr;198(2):361-368. doi: 10.1007/s10549-023-06871-w. Epub 2023 Feb 11. PMID: 36773184; PMCID: PMC10020306.

Duration of MHT

- Short term use is suggested
  - Insurances might send letters after 5 years or after age 60-65
- Hot flushes persist an average of 7.4 years
- Many will continue to have them for > 10 yrs
- Those with persistent symptoms may choose longer term therapy
- "Critical Window"
  - *Recommendation* to start within 10 years from menopause
  - Within 5 yrs for preservation of neurologic function/dementia benefit is best

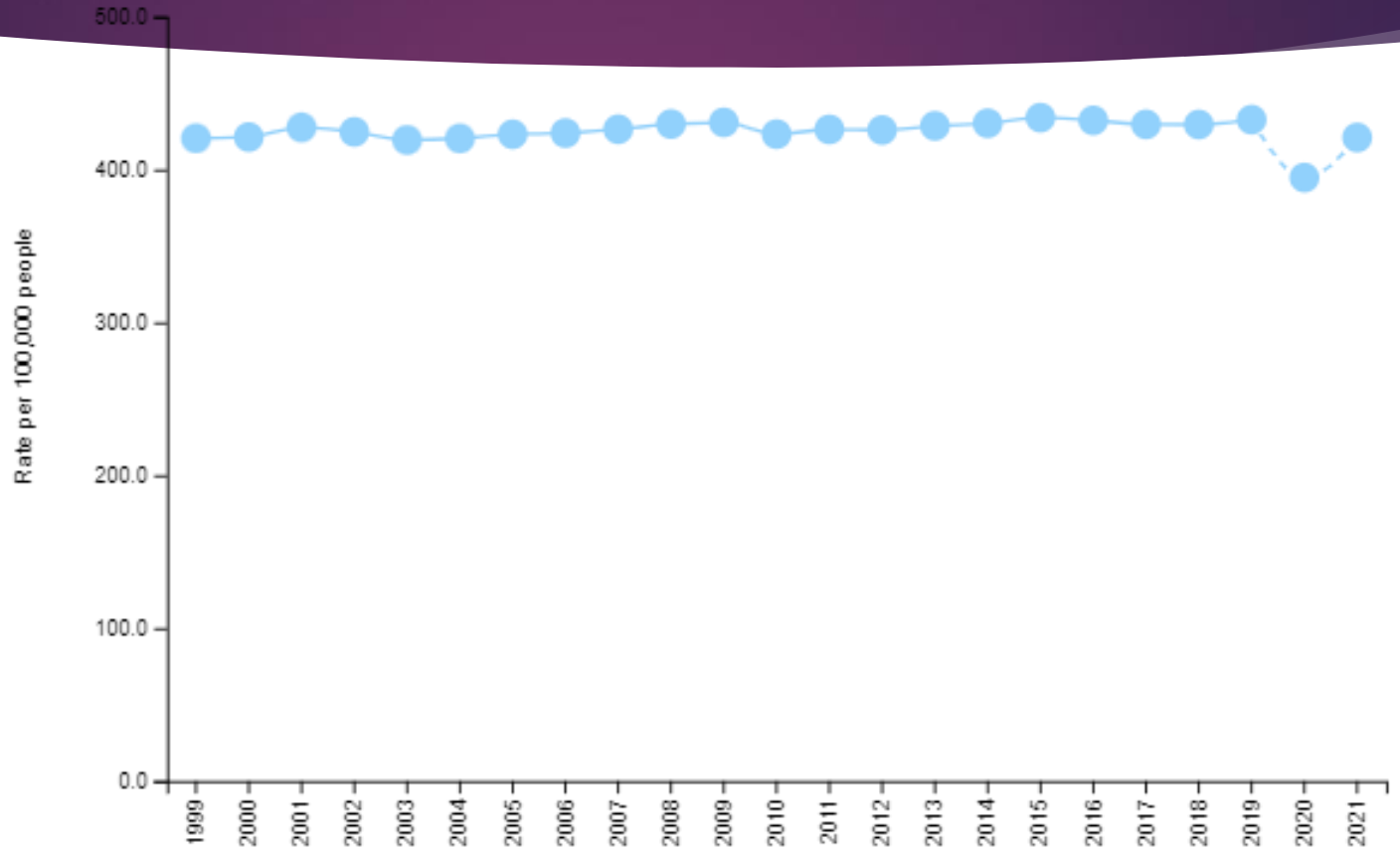
Women's Health Initiative (WHI)

- Mean age of women enrolled ~63 yrs
- ~27,000 postmenopausal women
- Risk of breast cancer with combined estrogen and progestin therapy did not increase until the 4th year
- Breast cancer risk:
  - 3 additional cases per 1,000 women per 5 years of hormone use with ***combined*** estrogen/progestin therapy
    - Higher incidence, but no difference in mortality
    - Need to understand the difference between relative and absolute risk (not 25% more women will get breast cancer, but 25% risk from baseline)
  - 2.5 fewer cases per 1,000 women per 5 years of hormone use with ***estrogen alone*** therapy

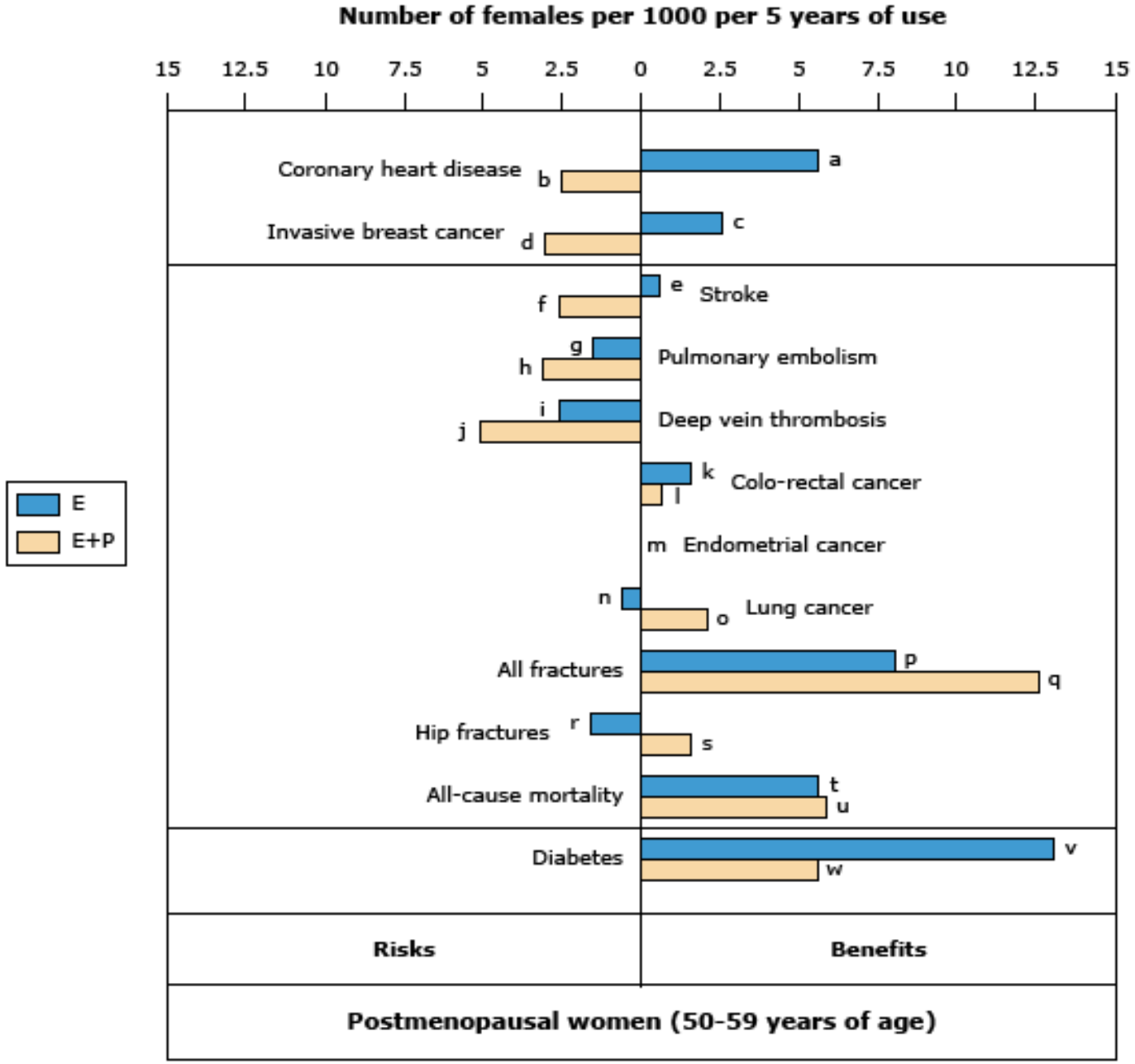
Decline in MHT use

- In women > 40 use decreased from: *(National Health and Nutrition Examination Survey (NHANES))*
  - 22% in 1999-2002
  - 12% in 2003-2004
  - 4.7% in 2009-2010
- Despite reassuring data that the benefits of MHT outweigh the risks for most young postmenopausal women
  - Those within 10 years of menopause or age < 60 yrs
- Largest declines in initiation reasons were for reducing osteoporosis and heart disease
- Largest increases in discontinuation reasons were for media reports and provider advice (SWAN – Study of Women's Health Across the Nation)

Annual Rates of New Cancers, 1999-2021
United States, All Types of Cancer, Female, All Races and Ethnicities



Source - U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; https://www.cdc.gov/cancer/dataviz, released in June 2024.



1.Reference:Santen RJ, Stuenkel CA, Burger HG, Manson JE. Competency in menopause management: whither goest the internist? J Womens Health (Larchmt) 2014; 23:281. Republished with permission of The Endocrine Society, from: Stuenkel CA, Davis SR, Gompel A, et al. Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2015. Copyright © 2015; permission conveyed through Copyright Clearance Center, Inc.

Estrogens

- **Transdermal**
  - Estradiol patch
  - Estradiol gel (Estrogel, Elestrin, Divigel)
    - Packets or pump
  - Estradiol spray (Evamist)
  - Estradiol vaginal ring
    - Femring (not Estring!)
  - Combination patches
    - Estradiol/LNG (Climara)
    - Estradiol/NE (Combipatch)
- **Oral**
  - Micronized 17-beta estradiol
  - Estradiol/progesterone (Bijuva)
  - Conjugated equine estrogen (Premarin/Prempro)
  - Estradiol/NE acetate (Activella, Mimvey)
  - Estradiol/drosperinone (Angeliq)
- **IM**
  - Cypionate: 1-5mg IM q3-4 wks
  - Valerate: 10-20mg IM q 4 wks

SERMs

- **Conjugated estrogen/Bazedoxifene** (Duavee)
  - VMS mod-severe menopausal
  - Osteoporosis prevention postmeno
  - Estrogen antagonist in uterus
  - Option for those who cannot tolerate progestins
- **Ospemifene** (Osphena)
  - Dyspareunia, mod-severe postmeno
  - Vaginal dryness, mod-severe
- **Raloxifene** (Evista)
  - Osteoporosis prevention and tx
  - Breast cancer prevention
  - Lower efficacy than bisphosphonates in reducing nonspine and hip fractures
  - Reduces risk of breast ca

Progestins

- The type of progestin may also affect breast ca risk
- Prospective cohort study of ~80K women, menopausal hormone regimens containing:
  - Estrogen plus progestin ⟶ excess breast ca risk
  - Estrogen plus progesterone ⟶ no increased risk

Fournier A, Berrino F, Clavel-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. Breast Cancer Res Treat. 2008 Jan;107(1):103-11. doi: 10.1007/s10549-007-9523-x. Epub 2007 Feb 27. Erratum in: Breast Cancer Res Treat. 2008 Jan;107(2):307-8. PMID: 17333341; PMCID: PMC2211383.

Progestogen therapy

- Progestins are synthetic progestogens
- Progesterone is a single chemical entity and the primary progestogenic hormone synthesized by the human body
- Oral micronized progesterone is 1st line
  - Necessary if intact uterus only
  - Natural progesterone may be safer for CV system (no adverse lipid effects) and possibly the breast
  - WHI studied Medroxyprogesterone acetate
    - Showed increased risk CHD and breast ca when given with conjugated estrogen
- May use LNG IUD for uterine protection
- May cause mood SEs and bloating if taken orally
- Perimenopausal folx will often have less BTB with cyclic progesterone due to endogenous hormone activity
- Options:
  - Oral micronized progesterone (check peanut allergy, can compound)
  - Medroxyprogesterone acetate
  - LNG IUD
  - POP

Discontinuation

- Taper Taper Taper!!
- Per WHI, ~55% of women will have recurrent VMS if MHT is stopped abruptly
- For transdermal, gradual dose reduction over 3-6 months
- For oral, decrease by 1 pill per week every 2-4 weeks
- ACOG and NAMS agree that MHT use should be individualized and not d/c'd based solely on age
- Use > 60-65 yrs may be reasonable when clinician and patient agree that benefits of symptom relief outweigh risks

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Bioidentical hormones

This means something different to each person

Often they mean compounded hormones

Asking reasoning will help you educate

"What is it about bioidentical hormones that is appealing to you"

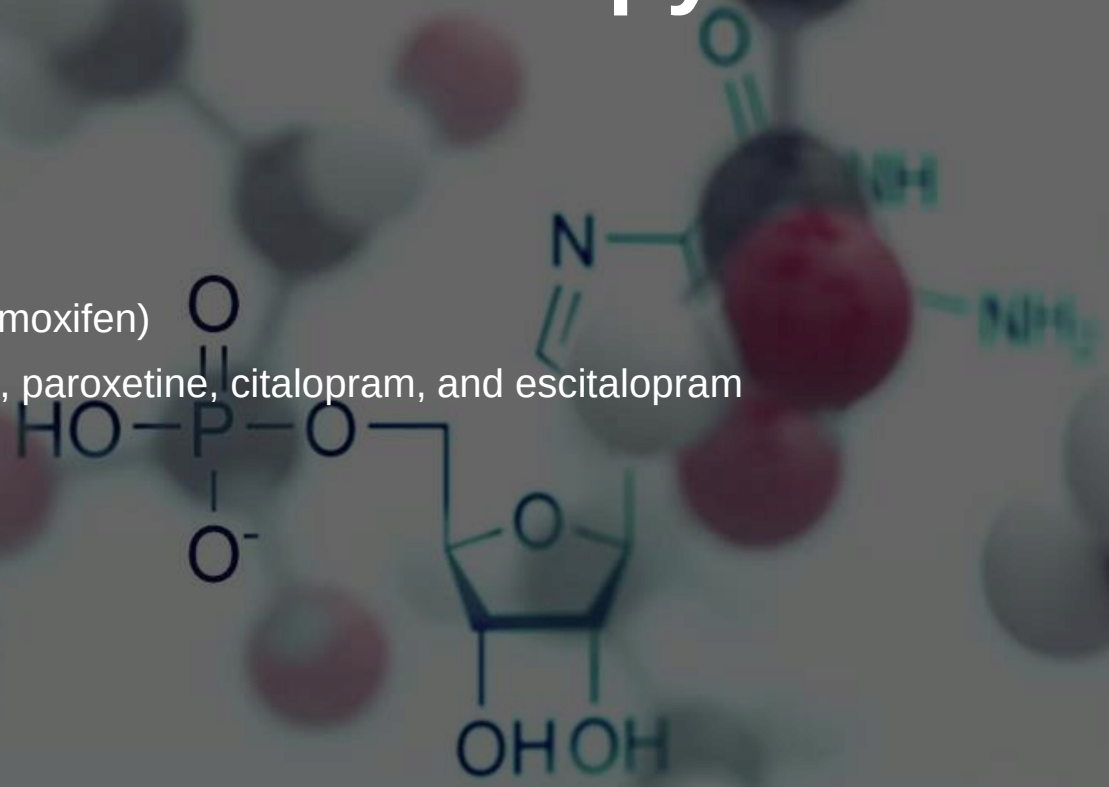
Often reply is "It's more natural" "It's safer" "There is less risk"

NAMS, ACOG, Endocrine Society have all issued scientific statements advising against the use of custom-compounded hormones

They are not required by law to include a Package Insert, however this does not render them without risk

Non hormonal approaches to therapy

- SSRI/SNRI
  - Paroxetine (Brisdelle) 7.5mg qhs (avoid with tamoxifen)
  - Venlafaxine XR up to 75mg qd, desvenlafaxine, paroxetine, citalopram, and escitalopram
- Gabapentin 300-900mg qhs (titrate up)
- Clonidine transdermal or oral
- Pregabalin 300mg
- Fezolinetant – NK3 receptor antagonist
- In development
  - Other NK receptor blockers
  - Anti-inflammatory tx
  - Estrogen mimic molecules



Integrated Health

- Mind-Body Practices
  - Hypnosis
  - CBT
  - Biofeedback
  - Meditation
  - Yoga
  - Acupuncture (conflicting data)
  - Reiki
  - Paced respiration
- Natural/OTC Products
  - Phytoestrogens and Isoflavones
  - Vitamins
  - Essential oils
  - Flaxseed
  - Supplements
    - Black cohosh
    - Soy proteins
    - Evening primrose

Patient FAQs

"I've always enjoyed sex and I'm worried that my vagina will change after menopause"

"My husband and I are in our late 60s. We have a loving marriage and snuggle a lot, but we haven't had sex in years. Is this abnormal?"

"I've had vaginal dryness and pain with intercourse since menopause. We use lubricants and I've even tried vaginal moisturizers, but sex is still uncomfortable. I'm nervous about using estrogen. Should I be?"

"I've been experiencing bothersome hot flushes for the past year, and I wake up almost every night sweaty and then get cold. My sex life was fine until menopause, but I'm just not interested any more. Could the hot flashes be affecting my libido?"

"My libido has slowly decreased since menopause, and I've heard that testosterone cream will really improve my sex life. Is this true?"

menopause.org

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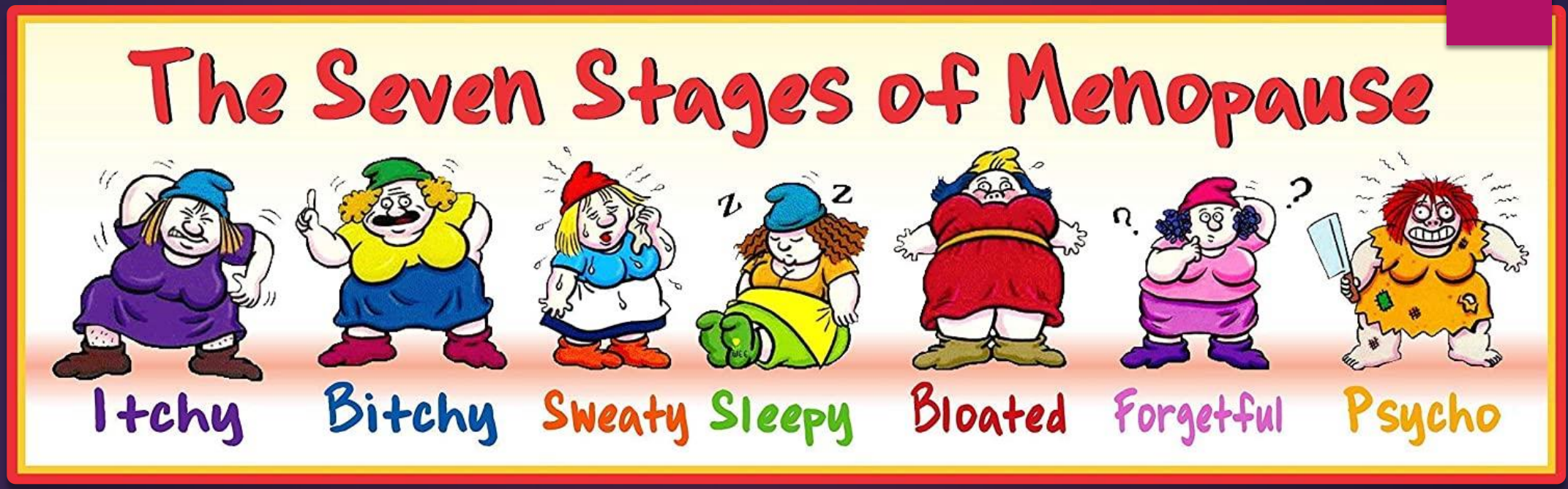

Questions/Cases?