Evidence-based Patient Centered Care of Menopause Symptoms

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Disclosure Statement

- Jessica Pettigrew, CNM, MSN has no financial relationships with commercial interests to disclose
- Any unlabeled/unapproved use of drugs or products referenced will be disclosed
- I acknowledge my lived experience and intersectionality of my identity as a cis gender heterosexual woman of European descent
- Use of the term "woman" is not meant to exclude those with other gender identities however therapies discussed here are not validated in individuals on hormones for gender dysphoria

Objectives

- Explain the physiology of perimenopause, menopause and the physiology of menopause symptoms
- Describe the limitations of the WHI and how to use that data in practice
- Discuss how to counsel patients on appropriate hormonal and nonhormonal treatment options, including the consensus on providing hormone replacement using FDA-approved formulations

Start with "why"…

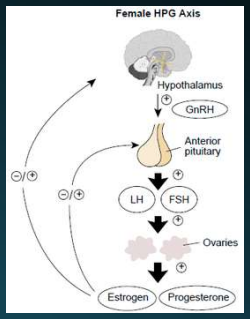
- "With women, for a lifetime."
- Why I menopause...

Perimenopause: The storm before the calm

- Lasts 2-8 years
- 90% of women note variability in menstrual cycles
- Initially shorter cycles due to shorter follicular phase
- Next, irregular ovulation and longer cycles

What is going on?

Review of normal menstrual cycle



Pathyphysiology: The biologic basis for disease in adults and children. 5th Ed. McCance and Huether 2006

Perimenopause

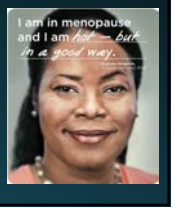
- Oocyte atresia requires higher levels of FSH secretion
- More follicles recruited (net follicular depletion)-->increased E2 and oligo-ovulation
- Lower follicular reserves
- E levels vary during this time
- P levels fluctuate depending on if ovulation occurs
- FSH varies depending on if ovulation occurs

42yo G2P2 comes to see you for an annual exam. Menses are becoming irregular, and heavier than normal 22-38 days. No bleeding between periods. "I want to get my hormones checked so I can see where I am and when I will be menopausal."

- Labs?
  - Estrogen?
  - Progesterone?
  - FSH
  - Anti-Mullerian Hormone
- Given that values fluctuate widely, measurement of serum hormone levels is not helpful.

Symptoms during perimenopause

- Hot flushes
- Mood/concentration changes
- Vaginal dryness
- Weight gain (changes to body composition)
  - Decrease in lean muscle
  - Increase in fat, particularly central fat



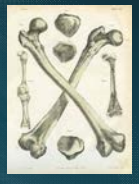
Diagnosis of menopause

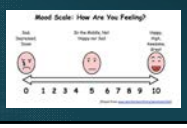
- One year with no bleeding.
- What if she has an IUD?
- What if she has had a hysterectomy?
- Salivary testing is not clinically validated
- FSH
  - Elevated FSH indicator of menopause
  - Not recommended to "see where I'm at"
  - Limitations: Perimenopausal may be elevated with period of anovulation but then she may ovulate

Following hysterectomy with BSO…

- Significant increase in all-cause mortality among premenopausal women NOT on estrogen
- We can improve their quality and length of life by recommending estrogen supplementation AT LEAST until age of natural menopause (early 50s)

Chronic health problems and menopause





Vasomotor symptoms

- Pathophysiology poorly understood
  - Related to dysregulation in the temperature regulating system in the hypothalamus
  - PMP women have lower body temperature overall than premenopausal women
- Often at night, disturbs sleep--->mood symptoms
- Documented increase in skin body temperature, sweating, sometimes accompanying anxiety

Treatment of Vasomotor symptoms

- Hormones
- Non-hormonal agents
- Novel/Emerging therapies
- Complementary/lifestyle

Not all estrogens are equal!

3 endogenous Estrogens

- POTENCY
  - Estrone (E1)
  - Estradiol (E2)
  - Estriol (E3)

E2>>E3>>E1

Estrogen in OCPs

- Ethinylestradiol – most common E in any OCP in the US
- EE is 15-20 times more potent than Estradiol (E2)
- "Low dose" OCP has 20mcg EE.
- Starting dose for MHT is 0.5mg or 50mcg estradiol (E2)

Hormone preparations: Estrogen

Type	Daily Dosage
Conjugated estrogen (Premarin, Cenestin)	0.625 mg
Estradiol (Estrace)	1.0 mg
Transdermal estradiol (patches)	.05 mg (50 mcg)
Estropipate (Ogen, Ortho-Est)	1.25 mg
Esterified estrogen (Menest, Estratab)	0.625 mg
Tri-est/Bi-est	2.5 mg
Ethinyl estradiol	.01 to .015 mg (10 to 15 mcgs depending upon the source)

https://www.earlymenopause.com/hrt-equivalencies/

Progesterone? Progestogens? Progestin?

- Progestogens: Class of steroid hormone that bind to and activate the progesterone receptor
- Progesterone: major active progestogen in the body
- Progestin: synthetic progestogen used in medication

Hormone preparations: Progestogen

Type	Cyclical Dosage	Continuous Dosage
Medroxyprogesterone acetate (Provera)	5 mg	2.5 mg
Micronized progesterone (Prometrium)	200 mg	100 mg
Norethindron acetate (Aygestin)	5 mg	2.5 mg
Norethindrone (Micronor)	.7 mg	.35 mg
Progesterone gel (Prochieve 4%)	every other day for 12 days (delivers 45 mg of progesterone per application)	2 times weekly

https://www.earlymenopause.com/hrt-equivalencies/

Novel therapies: CEE 0.45mg + Bazedoxifene 20mg "Duavee"

- CEE + SERM
- Bazedoxifene: antagonist on breast/uterine tissue, agonist effect on bone
- Ideal patient: risk for osteoporosis, low bone density
- Intolerance to progestin

Hormones: Who? What? And WHI?

- For women with intact uterus, need E+P (for endometrial protection)
- Women without uterus may use E alone
- Various formulations:
  - Oral
  - Transdermal
  - Combined E+P PO/Transdermal
  - IUD (for P component)* Off label

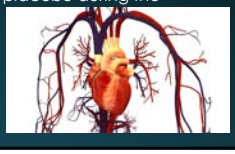
Women's Health Initiative (2009)

- Goal of study was to look at MHT use to **prevent** CAD
- Women aged 50-79
- Used CEE 0.625mg plus 2.5mg medroxyprogesterone acetate
- The study was stopped due to increased cardiovascular risk

Outcomes: Cardiovascular

- E+P: Increased risk of CHD first year, only slightly increased over entire treatment period.
  - For every 10,000 women taking MHT in their 50s, 5 extra dx CHD
  - For every 10,000 women taking MHT in their 70s, 19 extra dx CHD
- E alone: there was no difference in rates of heart disease for women taking estrogen versus placebo during the treatment period.

www.whi.org



Outcomes: Breast cancer

- E+P: for every 10,000 women taking estrogen-plus-progestin for one year, there were 9 *extra* cases of breast cancer.
- E alone: there was observed a **reduced risk** of breast cancer among women assigned to estrogen compared to placebo.
  - For every 10,000 women taking estrogen-alone for one year, there were 7 *fewer* cases of breast cancer.

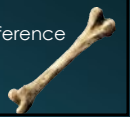
www.whi.org

Outcomes: Stroke/clot

- Both *E+P* and *E-alone* increased the risk of stroke by about one-third during the trial.
  - For every 10,000 women taking estrogen-plus-progestin, there were 9 extra cases of stroke and for estrogen-alone there were 11 extra cases of stroke.
- Both *E+P* and *E-alone* increased the risks of blood clots in the legs or lungs, but the risks were greater for estrogen-plus-progestin than for estrogen-alone.

Outcomes: Colorectal cancer and fracture

- Effects on hip fracture were similar for both groups.
  - Fewer hip fractures (about a 33% reduction or 6 fewer cases for every 10,000 women treated for one year).
- Over the 13-year follow-up, rates were still lower in women who had taken E+P than in the placebo group
  - rates in women who had taken E-alone were similar to those in the placebo group.
- Colorectal cancer: E+P slightly lower risk, no difference with E alone



Outcomes: Overall death

- For women taking E-alone in their 50s, there were **reduced risks** of overall illness and death, whereas for women in their 70s there were **increased** risks of overall illness and death.
- During the trial, the rates per year showed **19 fewer illnesses and deaths** per 10,000 women in their 50s taking E-alone
- Compared to **51 extra illnesses and deaths** per 10,000 women in their 70s taking estrogen-alone.

Limitations of the WHI

- Used a single oral synthetic form and dose of E and P
  - Unknown if all are equal
- Women were young and old, with preexisting conditions
- 2/3 of participants were ≥ age 60
- Just 30% of participants had a normal BMI
- 30% were obese
- 36% were had or were being treated for hypertension
- Women were randomized **regardless of symptoms** and prior hormone use
- Half of women were current or past smokers

What does this tell us?

- "HRT initiated several years after menopause increases the risk of CVD in a population of older women with a high frequency of obesity and hypertension."

Anette Tønnes Pedersen, Bent Ottesen, Issues to debate on the Women's Health Initiative (WHI) study. Epidemiology or randomized clinical trials—time out for hormone replacement therapy studies?, *Human Reproduction*, Volume 18, Issue 11, November 2003, Pages 2241–2244, https://doi.org/10.1093/humrep/deg435

Where do we go from here?

Clot/Stroke/DVT

Breast cancer

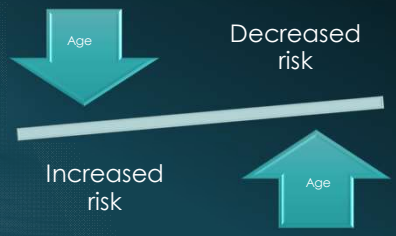
Heart attack

Bone health

The Nurses Health Study

- Enrolled women 1980-1994, followed until 2002
- Participants aged 50-59 at time of initiation
- Similar to WHI used single formula of single dosage CEE 0.625 +/- MPA (<10mg/d)
- Primary outcomes: CVD, cancer, all-cause mortality
- Overall, results mirrored WHI **except** when evaluating risk for heart attack where observed decrease in risk was noted.

Timing hypothesis: Cardiovascular risk



Emerging therapies: Fezolinetant

- For treatment of moderate/severe VMS
- MOA: Neurokinin 3 receptor antagonist (nonhormonal)
- 52wk Randomized placebo controlled double blind trial (N=1800)
- Negligible effect on endometrium
- 82-94% response to treatment relative to placebo

Emerging therapies: E4, estetrol

- Favorable for selective action on tissues
- No effect on liver health, clot risk, triglycerides, breast tissue

E4 RELIEF Trial (Gaspard et al, 2020)
Double-blind placebo-controlled multi-center RCT
n= 257 aged 40-65 (32 s/p hysterectomy)
All had moderate to severe VMS as defined by ≥7 hot flushes daily
Aim: determine dosage needed to treat VMS
Safety outcomes: adverse events, endometrial thickening, bleeding
Findings: dose of 15mg was minimum effective daily dose

Special populations: Women s/p hysterectomy +/- BSO

- Robust data shows increase in mortality for young (premenopausal) women s/p hysterectomy who are NOT on Estrogen
- No uterus, no risk for uterine cancer
- Estimates that between 18-91K women have died prematurely from 2004-2009 due to iatrogenic estrogen deficiency
- Replace until age of natural menopause, then re-evaluate based on sx.
- Counsel women on increased risk for morbidity/mortality if menopausal at young age

Indications for MHT

- MHT may be used in appropriate patients to treat MODERATE TO SEVERE vasomotor symptoms of menopause
- Treatment must be patient-specific and clinicians must use ***shared decision making***
- ***In my practice:*** I look at age, comorbidities (HTN, DM, obesity, smoker), family history (stroke, CVD), and symptom severity. Then, we discuss all options and risks/benefits associated with each

Local therapy for local symptoms

- Ask all PMP women about vaginal dryness
- Vaginal estrogen is locally absorbed
  - One exception: Fem ring
  - Virtually no contraindications to local vaginal E
- Recurrent UTIs-->try vaginal E
- Local vaginal estrogen preparations:
  - vaginal cream
  - tablets
  - Estradiol vaginal ring (think giant nuvaring)

Emerging therapies: CO2 Laser

Metaanalysis 2020 (Li et al.)

989 studies pulled

3 compared laser with local hormone and were included in analysis

Results: No difference between the two therapies

Conclusion: "Although prospective data continue to show promising outcomes, without strong evidence from well-powered, double-blind placebo-controlled trials to determine the efficacy of treatment compared with placebo, the use of energy-based treatments should continue to be undertaken in research studies only, with high-quality studies essentially free from bias "

Compounded Bioidentical Hormone Therapy (cBHT)

National Academies of Sciences, Engineering, and Medicine. 2020. The clinical utility of compounded bioidentical hormone therapy: A review of safety, effectiveness, and use

- FDA-Approved bioidentical MHT products on the market
  - Bijuva (estradiol/progesterone)
  - Estrace (estradiol)
  - Prometrium (progesterone)
  - Vagifem (estradiol)
  - All E products that are not conjucated equine estrogen (Premarin)
- "Given the lack of high quality, well-controlled data, the committee could not draw definitive overall conclusion on the safety or effectiveness of cBHT preparations"

FDA U.S. Food and Drug Administration Protecting and Promoting Your Health

Rationale for using compounded medications in general practice

- Allergy to ingredient
- No medication is available for the indication
  - HSDD, gender dysphoria
  - Recommendation: Use FDA approved male formulations at appropriate dosing
- Patient preference
  - Marketing as superior, not required to carry FDA labeling as other MHT products

"In the absence of safety and effectiveness data patient preference should not be the sole drive for use."

Expert Panel Recommendations

Restrict the use of cBHT preparations	Review cBHT therapies as candidates for FDA difficult to compound list	Improve education for prescribers and pharmacists who prescribe, compound, and dispense cBHT preparations
Describe potential conflicts of interest that exist within the industry	Implement federal and state oversight to address public health and clinical concerns regarding effectiveness and safety of cBHT	Provide patient information like that required with FDA approved medications

National Academies of Sciences, E., Medicine, Health, Medicine. (2020)

Vasomotor symptoms: Non-hormonal treatment

- SSRIs/SNRI at low doses:
  - Paroxitine 7.5mg "Brisdelle" (ie: low dose paxil)
  - Citalopram 20mg qd*
  - Venlafaxine 30mg*
- Clonidine patch*
- Gabapentin titrate up to 300mg TID*
- CBT, hypnosis
- Weight loss, mindfulness
- Lots of supplements and OTCs, little data showing help/harm

Caution in women on tamoxifen

- Avoid CYP2D6 inhibitors such as: paroxitine, buproprion, fluoxetine
- Preferred: Venlafaxine, gabapentin
- Take into consideration other symptoms: mood, sleep, etc

Discontinuing MHT

- The calm...
- Once menopausal, many women's symptoms abate naturally as their ovaries become quiet.
- After 5 or so years, she should be past "the transition". Discuss tapering off or discontinuing altogether
- If her symptoms persist, evaluate individual risk: consider lipid panel, monitor HTN, annual mammo.
  - Doubling of breast cancer risk after 10 yrs of E+P
- Ultimately, shared decision making should be employed with careful documentation. Risks of "taking away her hormones" are real.

Take aways:

- PREPARE women for the changes to multiple organ systems/metabolic changes that accompany peri/menopause
- ANTICIPATE what concerns might be
  - Many women in their mid 40s notice some changes in their cycles, their bodies, and their sexual desire, have you had any concerns?
- ADVOCATE for evidence-based care: MHT is safe for many women and it is EFFECTIVE!
  - Hormone pellets are not evidence-based, safe, or effective
  - KNOW non-hormonal treatments available
- CONSIDER screening for other diseases that can accompany menopause

Thank you!

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