The Menopausal Transition

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Disclosures:
- I have no financial disclosures
- More than 13 years ago, I was on the Speaker’s Bureau for Eli Lilly and Merck promoting the importance of bone health in the menopause
- I have been an OB/GYN since 1991
- Prior to becoming a Permanente Physician, I had a busy private practice in a NW suburb in Illinois and Chaired the OB/GYN department of my hospital
- I am the current District Chair for Section 7(DC) of CA ACOG
- I am an active participant in the menopausal transition
- I have only 3 daughters

What are we going to talk about???
- Define some important terms
- Get a little historical on how thoughts/treatments of the Menopausal Transition have evolved
- Remind ourselves about the WHI and why it is important
- Review symptoms of the Perimenopause and what we can do to help our patients
- Touch on the roles of Bioidentical HRT, phytoestrogens, herbals
- Practice what we have learned on 3 different patients
- Answer questions
Let’s start at the very beginning…….

Definitions
Menopause versus Perimenopause

Menopause:
- One year with no menstruation, not a laboratory diagnosis
- Complete “Follicular Exhaustion”
- Characterized by low Estrogen levels, high Follicular Stimulating Hormone (FSH)
- On average occurs at 51.2 years of age. By age 56, menopausal 95% of the time
- Retrospective diagnosis
- If ablation or hysterectomy, 3 months require 2 FSH and E2 levels

Perimenopause:
- The time period leading up to the menopause
- Characterized by fluctuating ovarian function
- On average occurs at age of 40-49 years
- Diagnosis made by symptoms, primarily

The Historical Journey…….

- 18th and 19th century - Climacteric was used to refer to the wide variety of physiological changes occurring around the menopause
- The symptoms described have changed over time (a little) and differ by culture
- 18th Century England- “hysterical vapors”, “bleeding piles”
- 19th Century- list grows now with Hysteria, Epilepsy, and Diabetes
- Universally described were hot flashes, palpitations, lengthening of the menstrual cycle, vertigo, headaches, constipation, heartburn, insomnia, vaginitis
- Anxiety symptoms were thought to be due to coincident life changes occurring at that time in a women’s life (i.e., divorce, children moving out, parents moving in)
TREATMENTS:

- Most recommendations from 1900-1932 centered on women needing to do “community housekeeping”
- Rest, fresh air, a change in scenery
- Exercise
- Many women self medicated with liquor
- Sedatives like Phenobarbital 15 mg TID rx’d
- Products were marketed for “female complaints”
Birth of Hormone Replacement Therapy...

- 1898: In Berlin, ground cow ovary fed to young women after oophorectomy
- 1910: US started using ovarian preparations for combating the insufficiency of estrogen in menopause. Used fresh ground ovaries from farm animals, then moved to desiccated ovaries mixed with alcohol from mares, ewes and cows
- 1929: Dodd invents synthetic estrogen "Diethylstilbestrol" (DES). This drove costs down 3-8 cents per day
- 1943: Goodall extracted estrogen from pregnant mares. Concerns regarding risk of cancer with estrogen use. Use for a short time only
- 1950s: Benefits of estrogen on the bone, emotional stability, improved sleep

Revolution of interest...

- 1963: In Brooklyn, Dr. Wilson wrote an article, then a book, Feminine Forever. Untreated menopause "robs femininity" commits women to live as remnants of themselves. This estrogen deficiency need to be replaced
- 1962-1975 estrogen sales quadrupled (~28 million Rx's). Women wanted more and started the conversation regarding menopause. Women's liberation supported their plight for their condition to be respected
- 1975: Link of unopposed estrogen therapy and uterine cancer after ~7 years of use by researchers at Kaiser Permanente in LA and Washington University
- 1980: only 15 million Rx's
- 1989: progestosterone added for uterine protection and Rx's increased > 28 million
Women’s Health Initiative

- Randomized prospective study trial - multiethnic, age 50-79, 1993-1998 enrollment, 48 US centers, primary outcomes were CVD, Breast Cancer
- 27,347 women with mean age of 63.4 years
- Arms were CEE alone versus placebo or CEE + MPA versus placebo
- CEE+ MPA arm treated for 5.6 years - stopped due to breast cancer concerns
- CEE alone treated for 7.2 years
- 2003 Black Box warning got placed on estrogen containing products for HRT - increased risks of use (primarily CVD)

Here we are today, the WHI turns 18

- JAMA 9/13/2017 - looking now at ALL cause and cause SPECIFIC mortality from HRT
- Cause Specific mortality divided into CVD, Cancer, and “Other”
- CVD: 8.9% with HT: 9% with placebo
- Cancer: 6.8% with HT: 8.1% with placebo
- Other Causes of mortality: 10% with HT: 10.7% with placebo

Thus, no increased all cause mortality after 18 years with hormone therapy

SWAN STUDY Updated in 2011

- Study of Women Across the Nation - diverse communities
- Endocrine and clinical manifestations of menopausal transition
- 3000 women aged 42-52 followed for 15 years
- Hormone assays were used to access ovarian ageing
- Resulted in a STAGING primarily used in research:
  - Reproduction
  - Menopausal/Transition
  - Postmenopausal
Symptoms of the Menopausal Transition

- Hot flashes, with or without sweating
- Irregular vaginal bleeding
- Insomnia
- Mood changes (anxiety, depression)
- Mastodynia
- Headaches
- Vaginal dryness

Perimenopause

Make sure no other medical factors are playing a role in signs and symptoms

- PCOS
- Endocrine disorders: hypothalamic conditions
- Rule out endometrial pathology as cause of AUB
- Medications: chemotherapeutics, antipsychotics
- Chronic illness or acute stress (emotional and/or physical, surgery)
- Dramatic acute weight loss, loss of body fat
- Tobacco use
What is happening physiologically??

- Shorter follicular phase (from 14 to 10 days) thus shorter intervals between cycles. Fertility is declining.
- Luteal phase progesterone decreases
- Anti mullerian hormone (AMH) begins declining
- Inhibin levels decline
- Variable estradiol levels and mild elevations of FSH but variable
- Cortisol increases as well as DHEAS and other adrenal hormones
- Later, FSH increases with low AMH, inhibin and decreased follicular count with increased intervals between menses

Vasomotor symptoms

- Most common symptom, 80% of women have them- last 2-4 min, from the chest up.
- Palpitations or anxiety may accompany.
- Last on average 4-7 years, commonly up to 2 years after the last menses
- 9% of women have vasomotor sx intermittently for many years
- Triggers: ETOH, hot temperature fluids, spicy food, caffeine, abrupt temperature changes

Most effective treatments include Estrogen. Progestins alone may help a little

Sleep Disturbance

- Chronic insomnia causes a decreased overall sense of well being and an increased risk for depression and anxiety
- Increased incidence of sleep apnea, restless leg
- Decreased productivity at work
- May require sleep studies if medical interventions do not help
- Inadequate sleep may have a role in decreasing our immune response to insults, as well as prohibiting effective cellular repair thus increasing our risk for abnormal cell proliferation

Treatments may include treating night sweats, OAB, or anxiety
Mood

- Mood swings
- Transition occurring at the same time as other life stressors

Treatments include anti-depressants, anti-anxiety medications, HRT, cognitive behavior and lifestyle modifications.

Urogenital Changes

- 70% of women report vaginal dryness-decreased vaginal lubrication with intercourse
- So worse about 3 years after last menses. FRICTION SYMPTOMS
- Can lead to vaginal discomfort and itching or burning. PH changes and this alters the normal ecosystem
- The decrease in blood flow to vaginal and vulvar tissues causes skin changes. Less hair, less elasticity, moistness and vaginal narrowing as well as architectural changes in vagina and labia minora
- Rule out vulvar dystrophies, STDs and BV
- Treatment includes vaginal lubricants and moisturizers, increased sexual activity, topical estrogens, oil water based or silicon based products
- New medications= Ospemifene orally and DHEA suppositories, 8 laser therapy with MonaLisa Touch

Atrophic Vaginitis

- Up to 60% of Perimenopausal/ Menopausal patients experience
- Easy to address with topical estrogen therapy- 17B Estradiol ( Estrace, Vagifem) or Conjugated estrogens(Premarin)
- There is very little systemic absorption- no progestrone needed
- Can be used in Breast Cancer patients with caution
Sexual Dysfunction

- Multifactorial with large contribution from outside stressors. Look at medications, lifestyle, acute onset of new stressors.
- Anorgasia is not always synonymous with Decreased Libido.
- ArginMax: proprietary nutritional supplement (Ginko, Gingseng, Damiana, L-Arginine, and minerals). 73% improved sexual desires, orgasms, coital frequency; no reported side effects.
- Zestra: botanical massage oil. Apply to vulva prior to coitus. Improves arousal, genital sensation, ability to orgasm.
- Eros Therapy: FDA cleared, hand held with cup over clitoris and genitalia restores blood flow to clitoris and genitalia, vaginal lubrication and sexual satisfaction.
- Scream Cream: made in a compound pharmacy. Apply 15 min prior.
- Aminophylline, Ergoloid mesylates, Isosorbide dinitrate, L-Arginine, Pentoxifylline, Sildenafil Citrate, Testosterone.

Headaches

- Hormonally related migraines will increase during transitions and then will decrease (may even disappear) after menopause.
- Migraines with aura have increased risk for CVA especially in tobacco users. Minimal improvement in menopause. AVOID ESTROGENS.
- If a woman > 50 has new onset headaches, needs a work up.

Treatments include: NSAID, TCA for tension headaches, non-cyclical hormonal therapies (continuous or progestrone only OCPs, Patches, Depo-Provera).

Bone Health

- We all start bone loss in our 30's.
- Accelerated bone loss in the menopause due to increased resorption, more of trabecular bone than cortical. Up to 20% of all loss occurs in late menopause.
- Joint pain in perimenopause: noted to have us improved with ERT in WHI.

Treatments: Always optimize calcium, vitamin D and weight bearing exercise. Estrogen maintain bone density and decrease fracture risks. Other treatments include bisphosphonates, SERMs, Calcitonin, Bazedoxifene with estrogen.
Cognition

- During the menopause transition it is common for poor memory to be reported. Normalizes with menopause
- Exacerbated by decreased sleep, life stressors, medications
- Role of estrogen is complex. It may minimize decline in memory function
- In WHI, those in early menopause or use in early menopause (< first 10 years) may decrease risk of dementia later in life. No role in treatment of dementia. Later use of estrogen (> 65) associated with increased risk Alzheimer’s.

Cardiovascular Disease

- Leading cause of death in women in the menopause
- WHI taught us that HRT does not prevent CVD. However, CV mortality was no different in the HRT versus the placebo group
- Estrogens increase HDL, lower LDL, improves endothelial function in coronary vasculature

Breast Cancer

- Role of ERT is controversial
- WHI: CEE alone had decreased risk. CEE+MPA had increased risk. Unclear still why this was seen. Is it related to formulations?
- Annual Mammography
- Self Breast Awareness
Venous Thrombotic Events (VTE)

- Use of any estrogen increases the risk 2-3 fold
- Combination of estrogen and progesterone increases risk higher than estrogen alone
- Transdermal preparations of estrogen carry lower risks—need studies
- Vaginal estrogens have no increased VTE risk

Skin and Nails

- Decreased skin thickness, elastin, and collagen matrix in menopause resulting in wrinkles, skin laxity. Effects exacerbated by sun, environment, smoking and genetics
- In early menopause there is a RELATIVE increased androgen to estrogen ratio due to drop in estrogen and that contributes to hair loss on the head and hirsutism of lip and chin
- Be sure to check thyroid and iron levels.

Eyes, Ears and Teeth

- Menopause causes increased dry eyes, cataracts. Treated with lubricants and anti-inflammatories
- Hearing loss increases after age 50, multifactorial in cause. Keeping estrogen at physiologic levels may preserve hearing. Possible negative effect with estrogen + progesterone.
- Teeth decreased estrogen causes recession of the gums, increased periodontal disease and loss of bone density is seen with increased tooth loss.
**Gall Bladder Disease**

- All estrogens increase potential for gall bladder disease.
- Risk is greater with estrogens given orally than those given trans dermally

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**Epilepsy**

- Earlier age at the time of menopause
- Lability of the estrogen may results in more seizures

Treatments: natural progesterones, Depo-Provera, Gonadotropin releasing hormone agonist, Gabapentin

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**Approaching Management of the Menopausal Transition**

- Ask yourself and your patient:
  - What are the goals of our interventions?
  - Is contraception needed?
  - Are there medical issues for this patient that may influence our available options?
Contraception in the Menopausal Transition

- Need to use it until 12 months of amenorrhea. After age 40, 75% of pregnancies are unintended.
- Sterilization is most commonly employed method (either partner).
- With increased age, poorer obstetrical outcomes, increased risk for genetic and congenital anomalies, thus increased risk for SAB and still birth. Also increased risk for GDM, PIH, Eclampsia.
- Increased risk for maternal mortality if >45 y/o: 32.3/100,000 live birth versus 7.12/100,000 live birth when younger.
- Condoms to be used for STD prevention.
- Availability for Emergency Contraception.
  - Good options: Levonogestrel IUD, Continuous OC, Depo-Provera, OC.

Hormone Replacement Therapy

- Individualized treatment with shared decision making and periodic reevaluations.
- Appropriate dose for the appropriate duration in the appropriate regimen and route.
- Formulations and timing of initiation of therapy may matter.
- For those <40 y/o within 10 years of the menopause, favorable data on ERT for treatment of bothersome sx of perimenopause.
- For those >40 y/o or 10-20 years after menopause, less favorable for ERT due to increase risk for CVD, VTE and CVA.

What are Bioidentical Hormones?

- “Bioidentical” is a marketing term not a medical term. No standard definition.
- Endocrine Society defines “bioidentical” as a compound that has chemical and molecular structure identical to that produced in our body.
- Included FDA and non-FDA products.
- No reflection on the source of the product or delivery method - FDA and US Pharmacopoeia both usually extract Drosperin from plants and then chemically convert it to make progesterone and then the make the estrogen and androgens.
- “Natural” is not always “Bioidentical.”
- Term is sometimes used to refer to customized mixed products not FDA regulated or tested or approved.
**Bioidentical Estrogen**

- We make 3 estrogens: Estrone and 17β Estradiol (made in ovaries), Estriol (weakest, made from conversion of Estrone and E2).
- Pre-menopause Estradiol (E2) is primary estrogen. In menopause, Estrone is highest. Estriol is high during pregnancy, made by placenta.
- 17β Estradiol in Bi products is derived from plant sources.
- 17β Estradiol is 80% more potent than Estradiol. E2 goes to both receptors. Estrone goes to Alpha > Beta receptors.
- Pills, patches, sprays, creams, gels, vaginal tablets.
- FDA approved - manufactured with strict standards.
- Estrogens activity depends on which estrogen receptors interact:
  - Alpha in breasts, uterus, ovary, cancer cells
  - Beta in bone, kidney, lung, endothelial tissue.

**Bioidentical Progesterone**

- Ovaries and adrenal glands usually make progesterone.
- Use in HRT is aimed at preventing endometrial cancer.
- Sedative quality thus used QHS.
- Some data suggests a decreased risk for breast cancer with use of micronized progesterone use.
- Topical preparation not shown to protect endometrium.
- Compounding can be done so it is not in peanut oil. Watch for varied bioactivity or availability.
- Mexican Yams-progesterins in these are not bioavailable to humans.

**Compounded Products**

- Most common ERT= Biest- E2+Estriol.
- The mg dose listed is the combined mg of all estrogens.
- "Work horse" is the higher potency 17β E2 but it comprises only 20% of the total mg.
- Compounding often advocates for salivary testing - results are not reproducible or reliable. Very based on assay used, time of day, diet, and pharmacokinetics of prescribed compounded HRT.
- FDA, NAMS, ACOG - do not advocate for salivary testing for treatment. Use symptom control as endpoint.
- If compounded hormone is applied to the skin it is considered a supplement. No efficacy or safety trials or regulations.
Current Safety Concerns with Compounding

- Oversight for compounding is done at the state level. In 2001 a limited FDA survey of 12 compound pharmacies demonstrated that 34% of the products failed quality testing.
- Compounding pharmacies do not have safety, efficacy testing, and regulations and there is a wide variation in active versus inactive ingredients.
- These are not safer or more effective drugs, in general.

What about Phytoestrogens?

- Plant derived chemicals structurally similar or functionally similar to estrogens. 100-1000X less active than human estrogens.
- In menopause we primarily talk about the ISOFLAVONE class used for VMS and vaginal dryness.
- Foods = Legumes (soy beans, chick peas, alfalfa, red clover)
- Diet and Genotype
- Meta analysis: favored improved sx with phytoestrogens but small difference from placebo, dose related improvement.
- Studies all small with different products. May help sleep.
- Lifelong phytoestrogen exposure may decrease breast cancer. Not the same as a Western menopausal woman taking soy or red clover in the menopausal transition.
- Soy protein may lower cholesterol.
- Phytoestrogen in the menopause may improve endothelial function.
- No increased breast cancer or uterine cancer risks. No VTE data. No adverse effects with 2 y follow up.
- ACOG: Data does not demonstrate any benefit of phytoestrogens, herbs or lifestyle changes on VMS.

Complimentary and Alternative Medicine (CAM)

- National Center for Complimentary and Integrative Health- use with western medicine.
- Alternative Health used instead of conventional medicine. In 2009, 34 billion out of pocket expense to CAM providers and products.
- Mind/Body- yoga, acupuncture, exercise, hypnosis
  - Exercise with multiple benefits may improve QOL.
  - Improves sleep quality.
  - Aids in VMS.
  - Increase endorphins.
  - Possible dose related response with yoga.
  - Hypnosis demonstrated decrease in VMS.
- Acupuncture, reflexology- no benefit.
- Diet and lifestyle changes- avoid triggers, layers of clothing, lower room temperatures.
Herbal Products

- Botanicals are not regulated by FDA, no safety or efficacy data. "Nutritional Supplements". Insufficient data to support
- Black Co hash- works on dopamine, serotonin, and gaba receptors. Dose dependent reduction in VMS. Concern is liver toxicity, GI sx, breast tenderness, vaginal bleeding
- St. John’s Wort- for depression sx. Mechanism of action is unclear but works like a SSRUI. May interact with other medications.
- Valerian Root- sedation, anti-anxiety, anti-depression. 300 mg BID improved sleep by 30%. One study demonstrated that 250 mg TID decreased severity of VMS.
- Ginseng, Ginkgo biloba, Dong Qai- no better than placebo for VMS
- Chinese Herbs + acupuncture as effective as hormones in one study
- Vitamin E- 800 IU/d- 1 less VMS per day

"Others"

- Testosterone- in studies no benefits for VMS. Not FDA approved. Safety concerns: elevates lipid profile, clitoromegaly, hirsutism. Possible increased breast cancer risk
- Tibolone- SERM synthetic steroid. Benefits to bone density, VMS, vaginal sx. No effect on breast or uterus. Not FDA approved. In Europe
- SSRUI Paroxetine 7.5 mg- the only one FDA approved for VMS
- SSNRI- most commonly used is Venlafaxine 75-150 mg/d (divided)
- Clonidine- 0.1 mg/d- anti hypertensive, not FDA indicated. Less effective than HRT. No b/p changes at this dose. Do not stop abruptly
- Gabapentin- 600-900 mg/d. 45% reduction in VMS in a RCT. Not FDA approved. Side effects for all of these include somnolence, dizziness, nausea, sexual dysfunction, nervousness, dry mouth

Patient #1

- 46 y/o G2P2 married female, mutually monogamous. BMI= 29
- No current contraception
- Full time work, stress with deadlines and down-sizing of company
- Cycles q21-55 days for the last 18 months with occasional intermenstrual bleeding. Heavy flow sometimes noted
- Intermittent hot flashes, fatigue, low libido, and irritability
- Admits to interrupted sleep patterns and insomnia
- Mom had breast cancer at age 70
Patient #2

- 52 y/o G1P1 CEO for international company. BMI=19
- Divorced but “online” dating. Concerned about sexual function
- s/p Tubal Ligation with her elective primary cesarean section at 40y/o
- Menses q 4-8 months for the past 3 years. No intermenstrual bleeding
- History of menstrual migraines but dissipating
- Insomnia, decreased concentration, hot flashes with sweats all day and night
  insomnia
- How does this change if she had no tubal ligation?
- How does this change if she had a previous hysterectomy for benign pathology?

Patient #3

- 44 y/o female, new to KP requesting her hormone levels and refill of her bioidentical hormone therapy
- Therapy started due to increased anxiety with palpitations intermittently, depression, decreased libido
- Still has monthly menses
- Monthly menstrual cycles that are heavy, occasional post coital spotting or spotting after working out hard
- No contraception on board but not interested in future fertility

Thank You !!