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Hormone therapy throughout the ages

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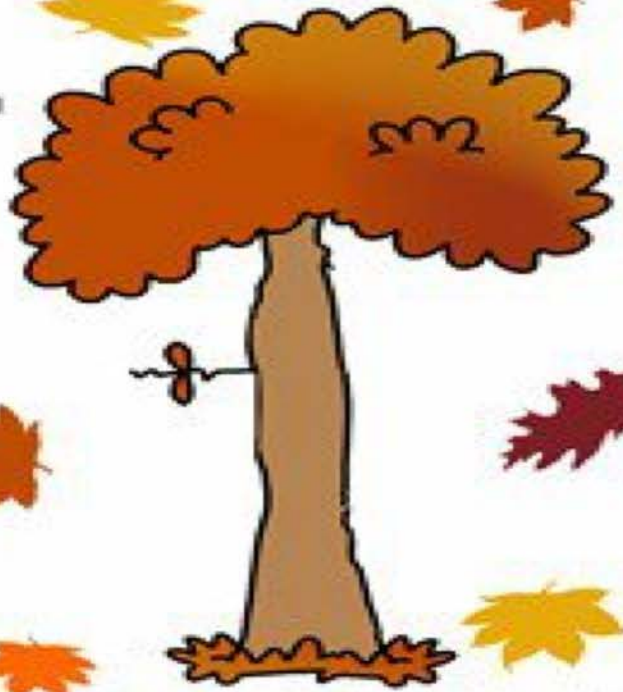
Objectives

- **Discuss risks and Benefits of Menopausal Hormonal Therapy (MHT)**
- **Explain how to prescribe and stop Menopausal Hormonal Therapy**

Menopause

- Menopause between ages of 45 to 55, mean age is 51
- Symptoms include hot flashes, vuvlovaginal atrophy causing dyspareunia.
- At menopause there is an increased risk of cardiovascular disease and osteoporosis.
- Menopausal Hormonal therapy appears to outweigh its risks for most symptomatic women who are either under age 60 or less than 10 years from menopause.

I kind of feel sorry for the trees in the Fall...



at least when I went through the change, nothing fell off!

Hormones: Estrogen

- Estradiol, E2(Main ovarian estrogen), Estriol E3(converted from DHEAS) and Estrone E1 (converted in peripheral fat).
- Builds a thick lining in the uterus (endometrium).
- Stimulates growth of breast tissue.
- Maintain vaginal blood flow and lubrication.
- Preserves bone density, cognitive function and cardiovascular health.

Hormones: Progesterone

- Stabilizes the lining of the uterus to get it ready for implantation in a pregnancy.
- Counteracts the effects of estrogen on the uterine lining.
- Helps in achieving deep (REM) sleep.
- Promotes bone density, lessens pms symptoms.

Hormones: Testosterone

- Factors into energy and libido.
- Maintains muscle and bone strength.
- Lessens joint pains.

Menopausal Symptoms:

- Vasomotor symptoms-hot flashes, inability to tolerate heat or cold (75 % of menopausal women report these).
- Lack of sleep-insomnia-trouble falling or staying asleep, poor sleep quality.
- Thin, dry vaginal mucosa, itching and burning of the vulvar tissue and painful intercourse (genito-urinary syndrome of menopause).
- Bone loss, cardiovascular disease, poorer cognitive function.
- Emotional changes-anxiety, depression, irritability (can't blame all of it on lack of hormones!!!!!).

Treatment for hormonal symptoms

- Vasomotor symptoms and sleep disturbances are the main reason women seek treatment.
- Replacing missing hormones is the main effective way to relieve these symptoms.
- Much controversy regarding using hormones for menopausal relief, but the latest evidence confirms that women who are symptomatic, and are candidates for hrt should use it as first line therapy with full informed consent.

Women's Health Initiative (WHI)

- WHI Trial composed of two hormone therapy (HT) trials - unopposed estrogen and continuous, combined estrogen-progestin therapy vs placebo. Conjugated equine estrogen and medroxyprogesterone orally.
- 27,000 postmenopausal women (mean age of 63 years old)
- Showed number of adverse outcomes, including an excess of CHD, stroke, venous thromboembolism (VTE), and breast cancer.
- As a results United States Preventive Services Task Force (USPSTF) did meta-analysis of 22 studies including WHI and recommends against use of HRT for prevention of chronic conditions.

Women's Health Initiative

- Started in fall of 1997 and supposed to conclude in 2005.
- Estrogen/progestin arm terminated after 5.2 years in July of 2002 when risks outweighed benefits ,increase in breast cancer and cardiovascular disease.
- Estrogen only arm terminated after 7 years in march 2004 also early because increase risk of stroke, but no increase in breast cancer.

Women's Health Initiative

- **Use of hormone therapy for younger postmenopausal women with moderate to severe symptoms is not contraindicated.**
- **Some experts advise that HT be limited use to five years however hot flashes can last a decade or more in many women. Therefore, longer therapy is reasonable in select women with persistent symptoms.**
- **Counseling women should include absolute risks and benefits for up to five years of treatment in young postmenopausal women (<10 years of menopause or under age 60 years). In this age group risk is very low.**

WHI Data-Combined Estrogen-Progestin therapy

- Number of cases per 10,000 women per year
  - Breast cancer-8 additional cases
  - Cardiac events-6 to 8 additional cases
  - Strokes -8 additional cases
  - Venous thromboembolism-18 additional cases
  - Colorectal- 6 fewer cases
  - Hip fractures-5 fewer cases (34% reduction in hip and vertebral and 23% reduction in other osteoporotic fractures)
  - Overall no difference in mortality or cause of death reported between the treatment and placebo group.

WHI estimated risks with Estrogen-Progestin therapy in women 50 to 59 years

- Number of cases per 1000 women per five years of hormone use when compared with placebo.
  - Coronary heart disease -2.5 additional cases
  - Invasive breast cancer-3 additional cases
  - Pulmonary embolism-3 additional cases
  - Endometrial Cancer-no difference
  - Stroke-2.5 additional cases
  - Colorectal Cancer-0.5 fewer cases
  - Hip fracture-1.5 fewer cases
  - All-cause mortality-5 fewer cases

WHI estimated risks with Estrogen-alone therapy in women 50 to 59 years

- Number of cases per 1000 women per five years of hormone use when compared with placebo.
  - Coronary heart disease -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 fewer cases
  - All-cause mortality-5.5 fewer cases

Women's Health Initiative Data

- **Overall risks of HT in younger postmenopausal women are considerably lower than those for older women.**
- **Major explanation for the difference in absolute excess risk between older and younger postmenopausal women is the lower baseline risk of CHD, stroke, VTE and breast cancer in younger postmenopausal women.**
- **Combined therapy was associated with a higher risk of CHD and breast cancer than unopposed estrogen.**

Women's Health Initiative-Cardiovascular Effects

- **WHI reported that many of the apparent benefits of HT seen in epidemiologic studies were not found in the randomized trials. Rather than reduction in risk of CHD events there was an increase was seen probably due older age of study population and timing of initiation of therapy--8/10,000 (combined HT).**
- **In unopposed HT did not affect the incidence of CHD events over an average follow-up of 6.8 years --3/10,000 fewer cases.**

Women's Health Initiative-Stroke

- **In WHI 31 % increase in stroke risk with combination HT vs placebo. Increase in ischemic but not hemorrhagic stroke. Excess risk seen in all age groups. Also seen in unopposed HT**
- **Stroke risk appears to be lower with transdermal compared with oral estrogen preparations.**

Women's Health Initiative-Venous thromboembolism.

- VTE in WHI increased with comibned HT (34 vs 16 per 10,000 person-years)
- Similar for both DVT and PE
- Risk of VTE lower with transdermal compared with oral estrogen. Risk may vary by type of progestin.
- For women age 50-59 VTE was 4.7/1000 with combination HT vs 1.3/1000 in estrogen only users.

Women's Health Initiative-Mortality

- Data from 18 year follow-up from WHI of unopposed estrogen or estrogen-progestin vs placebo. All-cause mortality was similar in women taking HT vs placebo. CHD and Cancer mortality rates were also similar HT vs placebo.
- BUT fewer hip fractures in all ages!

Women's Health Initiative-Cancer

- **Breast Cancer-with combined HT increase in invasive breast cancer seen over 5.6 years.**
- **In unopposed estrogen trial slightly lower risk of breast cancer. This comparison narrowly missed statistical significance (p=.06).**
- **Ovarian Cancer-a nonsignificant increase in the risk of ovarian cancer was observed in the WHI with combined HT. The excess risk was not statistically significant and would be approximately 0.75 cases per 1,000 treated for five years.**
- **Endometrial hyperplasia and carcinoma -Within one year, endometrial hyperplasia can be demonstrated in 20 to 50 percent of women receiving unopposed estrogen.**

Women's Health Initiative-Cognitive function and dementia

- **WHI Memory Study (WHIMS) an ancillary study of WHI assessed annual cognitive function scores in 4532 postmenopausal women who were over age 65 and free of probable dementia at baseline.**

- **Unopposed estrogen and combined HT had no global cognitive benefits in older, nondemented postmenopausal women and led to accelerated cognitive decline.**

Women's Health Initiative-Osteoporotic Fracture

- **The risk of osteoporotic fracture with combined HT and unopposed HT vs placebo was reduced at the hip and at the vertebrae and wrist.**
- **Women ages 50 to 59 years there were 4.9 and 5.9 fewer fractures per 1000 women per five year use of HT.**

Elite Trial: Early vs. Late intervention Trial with estradiol 2016

- >600 healthy postmenopausal women who had hysterectomy stratified according to time since menopause.
- Either 17 B-estradiol or placebo
- Primary outcome: rate of change of carotid artery intima-media thickness.
- Secondary outcome: assessment of coronary atherosclerosis by cardiac Ct.

Elite Trial (Early vs Late Interventional Trial with Estradiol

- In 2016 primary finding of ELITE demonstrated that oral estrogen administered to women who were less than 6 years post menopause slowed progression of subclinical atherosclerosis as assessed by carotid artery intima-media thickness but has neutral or adverse effects in women who are at least a decade past menopause onset.

Hormone Therapy Benefits

- **Vaginal estrogen decreased urinary tract infection(normalize vaginal flora increases lactobacilli and decrease e coli vaginal colonization).**
- **Decrease in falls estrogen improved balance and reduce tendency to fall.**
- **Estrogen improves skin due to ability to preserve the thickness and the collagen content of skin.**
- **Decrease in cataract formation noted in estrogen users 60% reduction if used over 10 years.**
- **No change in weight noted with HT use.**
- **May increase seizure activity.**
- **May stir up leiomyoma.**

Contraindications of Postmenopausal Hormonal Therapy

- **History of Breast Cancer**
- **Coronary Heart Disease**
- **Previous Venous Thromboembolic event or stroke**
- **Active liver disease**
- **Unexplained vaginal bleeding**
- **High risk endometrial cancer**
- **History of Transient ischemic attack**

Hormone Therapy

- **Estrogen -oral, transdermal, topical, gels, emulsions and lotions, intravaginal creams and tablets, and vaginal rings.**
- **Vaginal estrogen is most commonly used in very low doses for the management of genitourinary syndrome of menopause.**
- **Estrogen orally has a greater effect on the liver due to the first-pass effect because intestinal absorption leads to portal vein concentrations that are initially substantially higher than those after transdermal administration.**
- **Most oral preparations except conjugated equine estrogens are derived from plant sources(soy and yams). No evidence that plant derived estrogens have safety and efficacy advantages over those from pregnant mare urine .**

Choosing Hormonal Therapy

- **Route - start with transdermal 17-beta estradiol because of lower risk of VTE, stroke and hypertriglyceridemia than oral estrogen.**
- **Oral estrogens have favorable effects on lipids but can increase c- reactive protein and triglycerides.**

Dosing Hormonal Therapy

- **It's not one size fits all anymore ie CEE 0.625mg equivalent to 17-beta estradiol (1mg/day) transdermal (.05mg).**
- **New approach start low and increase on each of above preparations. Start with .5mg day or 0.025mg transdermal then titrate up based on patient's symptom relief. Exception if patient is younger and severe symptoms or surgical menopause.**
- **Should be administered continuously.**
- **If patient has a uterus need to add progestin to protect lining of uterus from developing endometrial hyperplasia.**

Dosing Hormonal Therapy

- **When adding progestin oral micronized progesterone as first line start with 200mg for 12 days/month or 100mg daily.**
- **For newly menopausal women start with 200mg for 12 days/month because continuous administration in this population is associated with irregular unscheduled bleeding due to exogenous hormones and the continued endogenous ovarian function. If menopause more than 2 to 3 years should use 100 mg daily continuous.**
- **Some women may still bleeding irregularly for first 2 to 3 months it will eventually taper off.**
- **Conjugated estrogen/Bazedoxifene (selective estrogen receptor modulator). It's called DUAVEE commercially.**
- **Bioidentical hormone therapy is not recommended as their safety or efficacy when compared with approved and available products. The contents, dose, quality, and sterility of these products are not subject to regulatory oversight. When tested potencies and patterns of absorption of compounded estrogens have been highly variable.**

Stopping or continuing Hormonal Therapy

- **Abrupt withdrawal of exogenous estrogen results in return of menopausal symptoms therefore tapering is recommended.**
- **North American Menopause Society and the American college of obstetrics and Gynecology agree that use of menopausal hormone therapy should be individualized and not discontinued solely based upon patient age. They suggest that extended use of HRT(beyond 60 or 65) may be reasonable when the clinician and the patient agree that the benefit of symptom relief outweigh the risks.**

How to chose treatment

- If the symptoms are only vaginal, treat vaginal symptoms
  - Vagifem and Yuvafem 10mcg tabs
  - Estrogen cream use 1 gm nightly for 14 nights then twice weekly
  - Imvexxy 10 or 4 mcg one tab for 2 weeks then 1 tab twice weekly
  - Osphena-S.E.R.M 60 mg po q day
  - Estring vaginal ring every 3 months consider adding progesterone for 10-14days monthly
  - Vaginal DHEA-intrarosa 6.5 mg vaginally q hs
  - Lubricants, ph correctors, moisturizers
  - CO2 laser to vagina, vulva

Non Hormonal Options for Vasomotor symptoms

- SSRI, Brisdelle, Paxil, Venlafaxine
- Catapres: anti-hypertensive, patch or a pill
- Vit C: some success with 250mg 3 X day
- Relizen: Swedish flower Pollen, with some studies supporting it
- Gabapentin 300mg TID

Osteoporosis Treatments-non hormonal

- Bisphosphonates-Fosamax, Boniva, Actonel, Reclast
- SERM-Raloxifene (Evista)
- Calcitonin
- Bone Rebuilders-Forteo, Tymlos
- Biologics-Prolia, Evenity

Alternatives to HRT

- Cognitive Behavioral Therapy
- Yoga, Mindfulness, Stress reduction, Exercise
- Vitamin D3 and Calcium
- Soy products, Iso-flavones, supplements made from plants like Rhubarb root or Swedish flower Pollen are generally considered to be safe.

Articles to Review

- Journal of the North American Menopause Society-Vol 22 #7 2015. NAMS HRT recommendation statemen.
- Journal of the North American Menopause Society -Vol 23 #3 2015. Comparative Efficacy and Safety of Estradiol Transdermal Preparations.
- Hot Flash Havoc. Thanksgiving newsletter: 11/15/2012. www.redhotmamas.org.
- HRT May Reduce Atherosclerosis When Taken in Early Menopause March 30,2016 www.medscape.com
- NYTimes.com, in their Private Lives series, “All Praise The Women of Menopause” by Sharen Mesmer

The Seven Dwarves of Menopause

Itchy, Bitchy, Sweaty, Sleepy, Bloated, Forgetful & Psycho