Menopausal Hormone Therapy: Where Are We Now?

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Options pre-2014

- Hot flashes (+/- vaginal atrophy depending):
  - Oral HT
  - Combined estrogen + progestogen
  - Estrogen alone
  - Transdermal HT
  - Combo estrogen + progestin patch
  - Estradiol patch
  - Topical estradiol emulsion, gel, spray

- Vaginal atrophy
  - Vaginal estrogen creams
  - Vaginal estrogen tablet
  - Vaginal estrogen ring (higher dose approved for rx hot flashes also)

Objectives:

- 2 New SERMs approved in 2013
- New studies re existing medications
- Vaginal estrogens have systemic effects
- Adverse effects of oral menopausal hormone therapy

New SERM 1: CEE + Bazedoxifene

- Bazedoxifene is an estrogen agonist/antagonist
- Conjugated estrogens 0.45 mg and bazedoxifene 20 mg

- Indications in women with a uterus:
  - Treatment of moderate to severe vasomotor symptoms associated with menopause
  - Prevention of postmenopausal osteoporosis
  - dosage: 1 tablet daily

CEE + Bazedoxifene

- Contraindications:
  - Undiagnosed abnormal uterine bleeding
  - Known, suspected, or past history of breast cancer
  - Known or suspected estrogen-dependent neoplasia
  - Active or past history of venous thromboembolism
  - Active or past history of arterial thromboembolism
  - Known hepatic impairment or disease (not studied)
  - Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders
  - Pregnancy, women who may become pregnant, nursing

- Shortest duration consistent with treatment goals and risks for the individual woman

- Warnings/precautions:
  - Cardiovascular disorders (VTE, PE, stroke, retinal vascular thrombosis)
  - Malignant neoplasms —endometrial cancer, breast cancer, ovarian cancer)
  - Gallbladder dz
  - Monitor thyroid function, d/c if loss of vision, hyperTG, or cholestatic jaundice
**CEE + Bazedoxifene**

- Adverse rxns (≥ 5%):
  - Muscle spasms
  - Nausea
  - Diarrhea
  - Dyspepsia
  - Abdominal pain
  - Oropharyngeal pain
  - Dizziness
  - Neck pain

- Longest follow-up for safety:
  - Breast cancer: 1 yr (Pinkerton et al Obstet gynecol 2013)
  - BMD: 2 yr (Lindsay et al Fertil Steril 2009)
  - AEs general: 2 yrs (Lobo et al Fertil Steril 2009)
  - Endometrial biopsy: 2 yrs (Pickar et al Fertil Steril 2009)

- Bazedoxifene by itself (without CEE) in women with postmenopausal osteoporosis:
  - reduction in vertebral, not hip fx (Silverman J Bone Miner Res 2008 and 2012, Silverman Osteoporos Int 2012)

**New SERM 2: Ospemifene**

- Estrogen agonist/antagonist

**INDICATIONS AND USAGE:**
- Treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause
- One 60 mg tablet once daily with food
- Shortest duration consistent with treatment goals and risks for the individual woman.

(www.fda.gov)

**Ospemifene**

- Contraindications:
  - Undiagnosed abnormal genital bleeding
  - Known or suspected estrogen-dependent neoplasia
  - Active DVT, pulmonary embolism, history of these
  - Active arterial thromboembolic dz (stroke, myocardial infarction) or history of these
  - Known or suspected pregnancy

(www.fda.gov)

**Warnings:**
- Risk of DVT and PE
- Severe hepatic impairment
- Known, suspected, history of breast cancer
  - in uterus, estrogen agonist effects
  - Adding a progestin to estrogen therapy reduces risk of endometrial hyperplasia
  - Has not been adequately studied in women with h/o breast cancer

(www.fda.gov)

**Adverse rxns (<1%):**
- Hot flush
- Vaginal discharge
- Muscle spasms
- Genital discharge

(www.fda.gov)

**Longest f/u duration: 1 year!**
- endometrial biopsy (mostly atrophic), hot flashes (most common), vaginal bleeding 2%, no DVTs (Simon et al Menopause 2013):
Case:

- 51-year-old healthy woman with intact uterus describes bothersome symptoms of atrophic vaginitis.
- You prescribe vaginal estradiol ring.
- Does she need progestogen? Can ring cause breast cancer?

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Vaginal estrogen systemic effects

- 40 menopausal women 40-60 y/o with vulvovaginal sx
- 1 g CEE vaginal cream (CEE 0.625 mg) once daily x 12 weeks (continuous phase), then 2x/wk for 12 weeks.
- Bone turnover markers were sig. affected at 24 wks vs. baseline:
  - Resorption and formation both decreased
- Estradiol levels were significantly increased after 12 and 24 weeks vs. baseline. (Luengratsameerung et al Climacteric 2013)
- Early studies by Naessen et al showed increased BMD and cholesterol changes comparable to oral CEE with vaginal E2 ring.

Vaginal estrogens: sample label for low dose ring

- Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. (See WARNINGS, Malignant neoplasms, Endometrial cancer.)
- (www.fda.gov)

Vaginal estrogens: sample label for low dose ring

- In the absence of comparable data, these risks should be assumed to be similar for other doses of CEE and MPA and other combinations and dosage forms of estrogens and progestins.
- CARDIOVASCULAR AND OTHER RISKS
  - Estrogens with or without progestins should not be used for the prevention of cardiovascular disease or dementia. (www.fda.gov)
  - Etc re MI, stroke, breast ca, PE, DVT, dementia in WHI.....

Vaginal estrogens: sample label for low dose ring

- Lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.
- Breast cancer is a contraindication.
- An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in women with a uterus.
- Most studies show no significant increased risk associated with use of estrogens for less than 1 year. (www.fda.gov)
- I ask: Who uses it for less than 1 year???
Vaginal estrogen: Cochrane systematic review

- Creams, pessaries, tablets and the estradiol vaginal ring equally effective for vaginal atrophy symptoms.
- 1 trial: significant side effects following cream (conjugated equine estrogen) compared with tablets-uterine bleeding, breast pain and perineal pain.
- 1 trial: significant endometrial overstimulation following use of conjugated equine estrogen cream vs. ring.
- Women favored the estradiol vaginal ring for ease of use, comfort of product and overall satisfaction.
  - (Suckling et al, Cochrane Database of Systematic Reviews 2010)

- Although not statistically significant, there were cases of hyperplasia and endometrial overstimulation with the ring, cream and tablets (17B-oestradiol).
- This raises the question of whether women need progestogenic protection from possible vaginal absorption of estrogen from the ring, cream or tablets when used beyond six months.
- This question cannot be answered by the presently available data. (Suckling et al, Cochrane Database of Systematic Reviews 2010) –longest study 6 months!

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Oral menopausal hormone therapy and endometrial hyperplasia

- Unopposed estrogen increases risk of endo. hyperplasia:
  - at all doses of therapy
  - at all durations of therapy after 1 year.
- The risk of endometrial hyperplasia is not different from placebo with use of low dose estrogen continuously combined with a minimum of:
  - 1 mg norethisterone acetate or
  - 1.5 mg medroxyprogesterone acetate

  (Furness et al, Cochrane Database of Systematic Reviews 2009, Issue 2. Art. No.: CD000402)

Menopausal hormone therapy and sexual function

- Estrogens alone or in combination with progestogens:
  - small to moderate improvement in sexual function, particularly in pain.
- No important effect of SERMs alone or combined with estrogens on sexual function.
  - (Nastri et al, Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD009672.)
- No hormonal preps are U.S. FDA-approved for decreased libido in women.

Estrogen and CVD

- Single and combination HT in both primary and secondary prevention conferred no protective effects for all cause mortality, CVD death, non-fatal MI, or angina.

  (Knight et al Cochrane Database of Systematic Reviews 2013, Issue 4. Art. No.: CD002229.)
### Estrogen and CVD
- Increased risk (versus placebo):
  - stroke: RR 1.26 (95% CI 1.11-1.43)
  - venous thromboembolism, RR 1.89 (95% CI 1.58-2.26)
  - pulmonary embolism RR 1.84 (95% CI 1.42-2.37).
- Numbers needed-to-harm:
  - stroke 164
  - venous thromboembolism 109
  - pulmonary embolism 243
(Main et al, Cochrane Database of Systematic Reviews 2013, Issue 4. Art. No.: CD002229.)

### Women's Health Initiative (WHI) extended follow-up
- Women aged 50 - 79 years at 40 US centers.
- hysterx: conjugated equine estrogens (CEE; 0.625 mg/d) alone (n = 5310) or placebo (n = 5429).
- intact uterus: CEE + medroxyprogesterone acetate (MPA; 2.5 mg/d) (n = 8506) or placebo (n = 8102).
- Intervention lasted median of:
  - 5.6 years in CEE + MPA trial
  - 7.2 years in CEE alone trial
- Extended post-intervention follow-up (13 yrs)
  (Manson et al JAMA 2013)

### Women's Health Initiative extended follow-up: CEE + MPA
- **Intervention phase**, (vs. placebo) increased risk:
  - invasive breast cancer (HR, 1.24; 95%CI, 1.01-1.53).
  - stroke, pulmonary embolism, dementia (≥65 years), gallbladder disease, and urinary incontinence
  - No sig. increase in CHD
  - Benefits: decreased hip fractures, diabetes, vasomotor symptoms.
- **Cumulative long-term follow-up**:
  - Most risks and benefits dissipated post-intervention,
  - breast cancer risk persisted 1.28 [95%CI, 1.11-1.48]).
  (Manson et al JAMA 2013)

### Women's Health Initiative extended follow-up: CEE alone
- **During intervention phase**:
  - Increased stroke risk HR 1.35 (1.07-1.70), DVT (HR 1.48)
  - No increase in CHD or invasive breast cancer
- **During cumulative long-term follow-up**:
  - breast cancer HR,0.79; 95%CI,0.65-0.97.
  - Results for other outcomes were similar to CEE plus MPA.
(Manson et al JAMA 2013)

### Women’s Health Initiative extended follow-up
- Mortality: Neither regimen affected all-cause mortality.
- Global index of absolute risks of adverse events per 10,000 women annually (higher is bad):
  - CEE + MPA: ranged from 12 excess cases for ages of 50-59 years to 38 for ages of 70-79 years;
  - CEE alone: ranged from 19 fewer cases for ages of 50-59 years to 51 excess cases for 70-79 years.
- Findings do not support use of this therapy for chronic disease prevention, although it is appropriate for symptom management in some women.
  (Manson et al JAMA 2013)

### USPSTF 2012 Guideline HT and Chronic Conditions
- Recommends against the use of combined estrogen and progestin for the prevention of chronic conditions in postmenopausal women. (Grade D).
- Recommends against the use of estrogen for the prevention of chronic conditions in postmenopausal women who have had a hysterectomy. (Grade D).
- Does not apply to:
  - women considering HT for management of menopausal symptoms, such as hot flashes or vaginal dryness.
  - surgically menopausal women younger than 50 years.
  (Moyer et al Ann Intern Med online 23 Oct 2012)
- See also: Marjoribanks et al, Cochrane Database of Systematic Reviews 2012, Issue 7. Art. No.: CD004143
FDA re compounded hormones

- Estriol has not been proven safe and effective for any use.
- Compounded drugs are not reviewed by the FDA for safety and effectiveness.
- FDA encourages patients to use FDA-approved drugs whenever possible.
  (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116832.htm)
- Myth: “Bio-identical” hormones are safer and more effective than FDA-approved MHT drugs.
  (http://www.fda.gov/forconsumers/consumerupdates/ucm049311.htm)

Parting words

- 75% reduction in frequency (95% CI 64.3 to 82.3) for HT vs. placebo.
- In women who were randomized to placebo treatment, a 57.7% reduction in hot flushes was observed between baseline and end of study(!)
- Therapies purported to reduce such symptoms must be assessed in blinded trials against a placebo or a validated therapy because of the large placebo effect in well conducted RCTs
  (MacLennan et al Cochrane Database of Systematic Reviews 2004, Issue 4. Art. No.: CD002978)