Menopause Update

SHELAGH LARSON, MS, RNC WHNP, NCMN
ACCLAIM, JPS HEALTH NETWORK

the only large, long-term RCT of HT in women aged 50 to 79 years,
Drug trial for HT on chronic diseases
WHI (HT oral, only)
- one formulation of estrogen (conjugated equine estrogens [CEE], 0.625 mg)
- one progestogen (medroxyprogesterone acetate [MPA], 2.5 mg)
limited enrollment of women with bothersome vasomotor symptoms (VMS; hot flashes, night sweats) who were aged younger than 60 years or who were fewer than 10 years from menopause onset—the group of women for whom HT is primarily indicated

Guide Updates

Benefits are most likely to outweigh risks for symptomatic women who initiate HT when aged <60 years or <10 years of menopause onset.

Change from previous position statement: The lowest dose used for the shortest duration needed to manage menopausal symptoms.

New statement: Management should be individualized and patient preference considered to identify the most appropriate: HT Type, Dose, Formulation, Route of Administration, Duration of Use.

Using the best available evidence to maximize benefits and minimize risks.

Periodic reevaluation of the benefits and risks of continuing or discontinuing HT.

The Women’s Health Initiative Randomized Trials: 2017 Update

- Among postmenopausal women, hormone therapy with
  - CEE plus MPA for a median of 5.6 years or
  - CEE alone for a median of 7.2 years
- HT was not associated with risk of all-cause, cardiovascular, or cancer mortality during a cumulative follow-up of 18 years.

So what does this mean…..

Estrogen alone showed a nonsignificant reduction in breast cancer risk after an average of 7.2 years of randomization, with 7 fewer cases of invasive breast cancer per 10,000 person-years, remained for up to a median 13 years.

The attributable risk of breast cancer (mean age, 63 y) randomized to CEE & MPA is less than 1 additional case of breast cancer diagnosed per 1,000 users annually.

- a risk slightly greater than that observed with one daily glass of wine, less than with two daily glasses,
- similar to the risk reported with obesity, low physical activity, and other medications.

The “Her-Mones”

HRT REGIMENS

Tips
- Estrogen, HRT vs COCP?
- Progestogens or micronised progesterone? Six months?
- Oral or transdermally.
- Mini- or combination pills?
- Supplemental progestogens?
- Vaginal progesterone regimens?
- Conjugated estrogens/base/diolene?
Difference CEE and E2

- Both CEE and estradiol are rapidly metabolized into weaker estrogens such as estrone.
- Meta-analysis of FDA-approved estrogen trials found no evidence of a significant difference in effectiveness between estradiol and CEE in treating VMS.
- Adverse events (AEs) were inconsistent, despite more hepatic protein production with CEE.
- There were differences in cognitive outcomes between types of estrogen and the brain serotonergic system, with estradiol providing more robust anxiolytic and antidepressant effects.

Estrogen

- Both CEE and estradiol are rapidly metabolized into weaker estrogens such as estrone.
- Meta-analysis of FDA-approved estrogen trials found no evidence of a significant difference in effectiveness between estradiol and CEE in treating VMS.
- Adverse events (AEs) were inconsistent, despite more hepatic protein production with CEE.
- There were differences in cognitive outcomes between types of estrogen and the brain serotonergic system, with estradiol providing more robust anxiolytic and antidepressant effects.

Estrogen Dosing

- 1st line: suggest transdermal 17-beta estradiol for many women starting HT.
- The appropriate, often lowest, effective dose of systemic ET consistent with treatment goals that provides benefits and minimizes risks for the individual woman should be the therapeutic goal.
- Conjugated estrogen 0.625 mg/day and 17-beta estradiol 0.05 mg/day appeared to be equally effective for the treatment of hot flashes.
- The appropriate dose of progestogen is added to provide endometrial protection if a woman has a uterus, unless CEE is combined with Bazedoxifene.

Progestogen indication: need for endometrial protection

- Primary menopause-related indication for progestogen use is to prevent endometrial overgrowth and the increased risk of endometrial cancer during ET use.
- Progestins commonly used include:
  - Medroxyprogesterone acetate (MPA)
  - Norethindrone acetate.
  - Micronized progesterone (MP)
  - Levonorgestrel.

Progestin “Pro Pregnancy”

- Primary menopause-related indication for progestogen use is to prevent endometrial overgrowth and the increased risk of endometrial cancer during ET use.
- Synthetic progestin.
- Long-term use may increase your risk of breast cancer, heart attack, stroke, or blood clots.
- Used to treat conditions such as absent or irregular menstrual periods, or abnormal uterine bleeding and to decrease the risk of endometrial hyperplasia.
- With CEE:
  - 0.025mg/0.5mg
  - 0.4mg/1.5mg
  - 0.4mg/0.5mg

Oral Micronized Progesterone

- First-line progestin because it is effective for endometrial hyperplasia, is metabolically neutral, and does not appear to increase the risk of either breast cancer or CHD.
- Flows through small blood vessels in a similar way as in pregnancy. It decreases blood pressure.
- Our basal body temperature to burn about 300 more calories a day.
- And it blocks the production of dihydrotestosterone, the male hormone that causes acne and unwanted facial hair growth.

Micronized Progesterone

- Natural progestogen:
  - In peanut oil.
  - Helps with hot flashes, insomnia, and bone health.
  - 200-400 mg HS.
  - Increased deep sleep by approximately 15%.
  - Stimulates formation of new bone.
  - Suggest off-label use of the lower dose levonorgestrel-releasing intrauterine device (IUD) when no other oral progestogen is tolerated.

Other

- Suggest off-label use of the lower dose levonorgestrel-releasing intrauterine device (IUD) when no other oral progestogen is tolerated.
- Flow through small blood vessels in a similar way as in pregnancy. It decreases blood pressure.
- Our basal body temperature to burn about 300 more calories a day.
- And it blocks the production of dihydrotestosterone, the male hormone that causes acne and unwanted facial hair growth.
Medroxyprogesterone Acetate (MPA)

- Long-term use of MPA may increase your risk of breast cancer, heart attack, stroke, or blood clot.

Progestosterone Dosing

- The appropriate formulation/dose/route of administration of progestogen is needed to counter the proliferative effects of systemic estrogen on the endometrium.
- EPT daily was associated with a risk of endometrial cancer = placebo
- A incidence of breast cancer was seen in the WHI for EPT compared with placebo, but a reduced incidence with ET alone.

- Progestogen dosing regimens options that provide for endometrial safety are dependent on the potency of the progestogen and vary with the estrogen dose.

Progesterone dosing (cont)

- Observational studies suggest the risk of breast cancer may be less with the use of micronized progesterone (MP) compared with synthetic progestogens.
- Different types and doses of progestogens, routes of administration, and types of regimen (sequential or continuous/combined) may have different health outcomes.
- Progestogen dosing regimens for endometrial safety are dependent on the potency of the progestogen and vary with the estrogen dose.

Tissue-selective estrogen complex: Bazedoxifene

- Selective estrogen receptor modulator (SERM) (Duavee).
- Estrogen-like effects on bone (increase bone density) and lipids (decrease LDL); antiestrogenic in uterus and breast (reduces risk of endometrial hyperplasia that can occur with conjugated estrogen).
- The combination provides endometrial protection without the need for a progestogen.
- Indicated for 1) vasomotor symptoms associated with menopause and 2) for prevention of postmenopausal osteoporosis.
- 20 mg/0.45 mg (1 tablet) PO daily. May take with or without food.
- If dose not satisfactory to relieve VMS, do not add additional estrogen. ****Change Rx*****.

Potential risks of HT JAMA, 2017

- A median of six to seven years were no more, nor less, likely to die of any cause over the study’s duration than were women who had been assigned to receive a placebo treatment.
- Women who got synthetic estrogen and progesterone hormones to replace their naturally declining levels were no more (nor less) likely than those who got a placebo to die of stroke or heart failure.
- And they were neither more nor less likely to die of cardiovascular disease or cancer.

Hot flashes

Initiation of HT

- The safety profile of HT is most favorable when it is initiated by women aged younger than 60 years or within 10 years of menopause onset.
- In general, initiation by older menopausal women aged >65 years requires careful consideration of all individual health benefits and risks.
- Vaginal estrogen (and systemic if required) or other non-estrogen therapies may be used at any age for prevention or treatment of GSM.

Discontinuation of HT

- Considerations for long-term (or extended) use of HT include persistent VMS, QOL issues, or prevention of osteoporosis in women at elevated risk of fracture.
- Vasomotor symptoms persist on average 7.4 years and for many for more than 10 years.
- In a study of Swedish women aged older than 85 years, 16% reported hot flashes at least several times per week.
- HT does not need to be routinely discontinued in women >60 and can be considered for continuation beyond age 65 years for persistent VMS, QOL issues, or prevention of osteoporosis after appropriate evaluation and counseling of benefits and risks.

Contraindication

- Unexplained vaginal bleeding.
- Severe active liver disease.
- Prior estrogen-sensitive breast or endometrial cancer.
- Coronary heart disease (CHD).
- Stroke.
- Dementia.
- Personal hx or inherited high risk of thromboembolic disease.
- Hypertriglyceridemia.
- Concern that endometriosis might reactivate.
- Migraine headaches may worsen.
- Leiomyomas may grow.

Compounded bioidentical HT

- Should be avoided, given concern about safety, including the possibility of over or under dosing, lack of efficacy and safety studies, and lack of a label providing risks. (Level I)
- If compounded bioidentical HT is prescribed, concerns about safety should be discussed, and the indication for prescribing compounded rather than government approved bioidentical HT should be documented (allergy, medical need for lower-than-available dose, different preparation). (Level III)

Hormone therapy: type, dose, regimen, and duration of use

- The type of HT, specific options, dose, and regimen should be individualized, using shared decision-making and taking into account the risks and safety information.
- Lowering doses and/or changing to transdermal HT may be appropriate as women age or in those with metabolic syndromes such as hypertriglyceridemia with risk of pancreatitis or fatty liver. (Level III)
- Endometrial protection
- For women with a uterus using systemic estrogen, endometrial protection requires an adequate dose and duration of a progestogen or use of the combination CEE with bazedoxifene. (Level I)
- Progestogen therapy is not recommended with low-dose vaginal ET, but appropriate evaluation of the endometrium should be performed if vaginal bleeding occurs, given the limits of safety data. (Level I)
FDA-APPROVED INDICATIONS for HT

• VASOMOTOR SYMPTOMS (LEVEL I)
• PREVENTION OF BONE LOSS (LEVEL I)
• PREMATURE HYPOESTROGENISM (HYPOGONADISM, POI, OR PREMATURE SURGICAL MENOPAUSE WITHOUT CONTRAINDICATIONS) (LEVEL II)
• GENITOURINARY SYMPTOMS (LEVEL I)

Vasomotor symptoms

- Vasomotor symptoms persist on average 7.4 years in the SWAN and appear to be linked to cardiovascular (CV), bone, and cognitive risks.
- Lower doses of HT (oral: CEE 0.3 mg, 17b-estradiol 0.5 mg; or estradiol patch 0.025 mg) may take 6 to 8 weeks to provide adequate symptom relief.
- Compared with placebo, ET / EPT was found to significantly reduce symptom severity and take 6 to 8 weeks to provide adequate symptom relief.
- RCT and observational studies show that HT reduces postmenopausal osteoporotic fractures, including hip, spine, and all non-spine fractures.
- Women with early menopause and POI have health risks that may include persistent VMS, bone loss, VVA, mood changes, and increased risk of heart disease, dementia, stroke, Parkinson disease, opthalmic disorders, and overall mortality.
- Women with early menopause and POI have health risks that may include persistent VMS, bone loss, VVA, mood changes, and increased risk of heart disease, dementia, stroke, Parkinson disease, opthalmic disorders, and overall mortality.
- Health risks of early natural menopause and POI

Health risks of early natural menopause and POI

- Women with early menopause and POI have health risks that may include persistent VMS, bone loss, VVA, mood changes, and increased risk of heart disease, dementia, stroke, Parkinson disease, opthalmic disorders, and overall mortality.
- Hormone therapy such as transdermal estradiol in higher doses with adequate endometrial protection may be superior to oral contraceptive therapy to restore or maintain bone mineral density (BMD).
Genitourinary symptoms

- HT has been shown in RCTs to effectively
  - restore genitourinary tract anatomy,
  - increase superficial vaginal cells,
  - reduce vaginal pH,
  - treat symptoms of vulvovaginal atrophy (VVA).

Sleep disturbances

- HT in the form of low dose estrogen or progestogen could improve chronic insomnia in menopausal women, with 14 of the 23 studies reviewed showing positive result
- Oral progestrone has mildly sedating effects, reducing wakefulness without affecting daytime cognitive functions

Breast cancer and vaginal therapy

- Because of the potential risk of small increases in circulating estrogens, the decision to use low-dose vaginal ET in women with breast cancer should be made in conjunction with their oncologists
- although no increased risk was seen in an observational trial of survivors of breast cancer on tamoxifen or aromatase inhibitors (AIs) with low-dose vaginal ET during 3.5 years’ mean follow-up.
Sexual function

- Both systemic HT and low-dose vaginal estrogen increase lubrication, blood flow, and sensation of vaginal tissues.
- Systemic HT generally does not improve sexual function, sexual interest, arousal, or orgasmic response in women without menopause symptoms.
- If sexual function or libido are concerns, transdermal ET may be preferable over oral ET because of less effect on sex hormone-binding globulin and free testosterone levels.
- Low-dose vaginal ET improves sexual function in postmenopausal women with GSM (symptomatic VVA).

Osteoporosis

- Hormone therapy prevents bone loss in healthy postmenopausal women, with dose-related effects.
- Unless contraindicated, women with premature menopause who require prevention of bone loss are best served with HT or oral contraceptives (which are less effective than HT) rather than other bone-specific treatments until the average age of menopause, when treatment may be reassessed.
- Hormone therapy effectively prevents postmenopausal osteoporosis and fractures.
- Some formulations of ET, EPT, and CEE combined with bazedoxifene are approved for this indication.

Osteoporosis (cont)

1. Woman in the ET and EPT cohorts in the WHI intervention trial overall had significant reductions in hip fractures.
2. For women with VMS aged <60 years or <10 years of menopause onset, HT (ET, EPT, or CEE combined with bazedoxifene) is probably the most appropriate bone-active therapy in the absence of contraindications.
3. When alternate osteoporosis therapies are not appropriate or cause AEs, the extended use of HT is an option for women at high risk of fracture.
4. The decision to stop HT should be made on the basis of extraskeletal benefits and risks.

GALLBLADDER AND LIVER

- Cholelithiasis, cholecystitis, and cholecystectomy occur more frequently in women who take oral estrogen, presumably because of the first-pass hepatic effect after oral ingestion.
- Lower risk with transdermal HT than with oral
- An association of HT with slower fibrosis progression in hepatitis C and with fatty liver has been observed, but randomized trials are needed.

DIABETES MELLITUS, METABOLIC SYNDROME, AND BODY COMPOSITION

- Combined HT (EPT) reduced type 2 DM incidence almost 40%, with lower fasting glucose levels and levels of hemoglobin A1c, but it is not US-government approved for this purpose.
- CEE-alone cohort, there was a reduction of 14% in onset of DM
- The EPT either has no effect on weight or is associated with less weight gain in women who are using it than in women who are not.

MOOD, DEPRESSION, & COGNITION

- HT cannot be recommended at any age to prevent or treat a decline in cognitive function or dementia.
- ET was effective in improving clinical depression in perimenopausal but not postmenopausal women.
- Timing of HT initiation is a significant determinant of Alzheimer disease risk, with early initiation lowering risk and later initiation associated with increased risk.
- Progestins may contribute to mood disturbance.
MOOD, DEPRESSION, AND COGNITION

- HT does not improve memory or other cognitive abilities and that CEE + MPA may be harmful for memory when initiated in women >65.
- CEE + MPA doubled the risk of all-cause dementia (23 cases per 10,000 women) when initiated in women aged 65 years or older whereas CEE alone did not significantly increase the risk of dementia.
- ET may have positive cognitive benefits when initiated immediately after early surgical menopause, but HT in the early natural postmenopausal period may have neutral effects on current cognitive function.

CARDIOVASCULAR DISEASE AND ALL-CAUSE MORTALITY

- For healthy symptomatic women aged 60 years <10 years of menopause onset, the more favorable effects of HT on CHD and all-cause mortality should be considered against potential rare increases in risks of breast cancer, VTE, and stroke.
- Hormone therapy is not FDA indicated for primary or secondary cardioprotection.

CORONARY HEART DISEASE

- HT represents a safe and effective option for the treatment of menopause symptoms when initiated in healthy postmenopausal women aged younger than 60 years or are within 10 years of menopause onset.
- However, the effects of HT on CHD may vary depending on when HT is initiated in relation to a woman’s age and/or time since menopause onset. Studies suggest reduced risk of CHD in women who initiate HT when <60 years and/or <10 years of menopause onset.

STROKE

- RCTs of women who initiate HT <60 <10, found no risk of stroke in women whereas observational study findings are mixed.
- In women on CEE alone who were within 10 years of menopause onset.
- A meta-analysis of RCTs found an rare, absolute risk of stroke risk in women who initiate HT when >60 /10+
- Studies suggest that compared with standard-dose oral HT, lower-dose oral and lower-dose transdermal therapy has less effect on risk of stroke, although RCT data are lacking.

CHD/VENOUS THROMBOEMBOLISM

- Initiation 10+ years from menopause onset, and clearly by 20 years, there is potential for a risk of CHD.
- Both ET & EPT risk of CHD, with potentially greater risk with CEE + MPA, which was significant when initiated in women who were 20+ years from menopause.

Risks of VTE with oral ET and EPT, with higher risk seen in the first 1 to 2 years.

- For women who initiated HT when aged <60 years, the absolute risk of VTE was rare but significantly increased.

CANCERS

- BREAST CANCER
- ENDOMETRIAL CANCER
- OVARIAN CANCER
- COLORECTAL CANCER
- LUNG CANCER
BREAST CANCER
- The effect of HT on breast cancer risk may depend on the type of HT, dose, duration of use, regimen, route of administration, prior exposure, and individual characteristics.
- ET alone showed a nonsignificant reduction in breast cancer risk after an average of 7.2 years of randomization, with 7 fewer cases of invasive breast cancer per 10,000 than placebo remained up to a median 13 years’ cumulative follow-up.
- EPT: in increased risk of breast cancer (a rare absolute risk of breast cancer), with 9 additional breast cancer cases per 10,000.

Other Cancers
- Colon:
  - Observational studies suggest a reduced incidence of colorectal cancer with HT, particularly if initiated early in menopause.
  - The use of EPT across all ages reduced colorectal cancer incidence during treatment.
  - Further analysis of the WHI data and postintervention data found no strong evidence of a protective effect of ET or EPT risk of colorectal cancer.
- Lung
  - In the WHI, after a median 13 years’ cumulative follow-up, the incidence of lung cancer did not differ significantly between placebo and treatment with either ET or EPT.

Cancer
Breast
- HT use alone further increases risk of breast cancer in women with a family history of breast cancer or in women after mastectomy for BRCA 1 or 2 gene mutation.
- Use of ET may be considered in combination, women with surgically treated, early-stage endocrine-responsive breast cancer. EPT is not recommended for women with early-stage endometrial cancer.
- Treat in postmenopausal women with breast cancer and in women with untreated breast cancers.

Endometrial
- Use of HT is associated with increased risk of endometrial hyperplasia or cancer. EPT is not indicated for women with endometrial hyperplasia or cancer.

OVARIAN
- If an association between HT and ovarian cancer exists, the absolute risk is likely to be rare (<1/1,000) or very rare (<0.01/1,000) and more likely with longer durations of use.
- Limited observational data have not found an increased risk of ovarian cancer in women with a family history or a BRCA 1 or 2 gene mutation.
- Concerns have been raised regarding HT in tumors that are likely to contain ERs, but data are limited.
- No increased risk of recurrence or death in women receiving HT after treatment for ovarian cancer.

Other Cancers
- Colon:
  - Observational studies suggest a reduced incidence of colorectal cancer with HT, particularly if initiated early in menopause.
  - The use of EPT across all ages reduced colorectal cancer incidence during treatment.
  - Further analysis of the WHI data and postintervention data found no strong evidence of a protective effect of ET or EPT risk of colorectal cancer.
- Lung
  - In the WHI, after a median 13 years’ cumulative follow-up, the incidence of lung cancer did not differ significantly between placebo and treatment with either ET or EPT.

Take Home
- HT does not need to be routinely dc’d in women aged >60 or 65 years and can be considered for continuation beyond age 65 years for persistent VMS, QOL issues, or prevention of osteoporosis after appropriate evaluation and counseling of benefits and risks.
- Decisions about duration of HT require individualization, including consideration of personal preferences, balancing potential ongoing benefits and risks, and decisions to continue HT for preventive and/or QOL purposes. (Level III)

2017 Hormone Therapy Position Statement of the North American Menopause Society
  - Vol. 24 (7)
  - DOI: 10.1097/GME.0000000000000921