Menopause & Hormone Therapy: A 2013 Update

Andrew M. Kaunitz, MD. FACOG, NCMP
Professor and Associate Chairman
Department of Obstetrics and Gynecology
University of Florida College of Medicine -
Jacksonville

Director, Menopause & GYN Ultrasound Services
UF Southside Women’s Health Specialists

Men.ht. 8.19.2013
Menopause & Hormone Therapy

- Our patients will likely spend more than one third of their lifespan as menopausal women...
  - We need to remain up to date as we help women make good choices regarding HT

- Abbreviations
  - HT = hormone therapy
  - ET = estrogen therapy
  - CE = conjugated equine estrogen,E2=estradiol
  - EPT = combination estrogen-progestin therapy
  = Women’s Health Initiative (WHI)
Learning Objectives: Review

- Identify vasomotor symptoms (VMS) and recommend appropriate hormonal/nonhormonal treatment
- Recognize the risks of HT, with emphasis on breast cancer, venous thromboembolism (VTE), and coronary heart disease (CHD)
- Evaluate the role of HT in dementia prevention/treatment
- Assess treatment considerations for early menopause
- Recognize the signs of genital atrophy and recommend appropriate treatment
<table>
<thead>
<tr>
<th>Clinical Trials</th>
<th>Consultant</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Funding to University of Florida Research Foundation):</td>
<td>• Actavis</td>
</tr>
<tr>
<td>• Bayer</td>
<td>• Bayer</td>
</tr>
<tr>
<td>• Endoceutics</td>
<td>• Teva</td>
</tr>
<tr>
<td>• Noven</td>
<td>• Teva</td>
</tr>
<tr>
<td>• Teva</td>
<td></td>
</tr>
<tr>
<td>• Trimel</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Royalties</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• UpToDate</td>
<td>I will refer to off-label use of SSRIs, SNRIs and gabapentin in the treatment of menopausal symptoms</td>
</tr>
<tr>
<td>NAMS</td>
<td></td>
</tr>
<tr>
<td>• Menopause editorial board</td>
<td></td>
</tr>
<tr>
<td>• Board of Trustees</td>
<td></td>
</tr>
<tr>
<td>• HT Position Statement writing group member</td>
<td></td>
</tr>
</tbody>
</table>
Vasomotor Symptoms (VMS)

- Spontaneous sensations of warmth, usually felt on chest, neck and face
  - may be called ‘hot flushes’ or ‘night sweats’
  - often associated with perspiration, palpitations and anxiety
  - may impair quality of life
- Variable in frequency, duration and severity
  - usually < 5 minutes
- Can be triggered by warm environments, hot drinks, emotional stress
- **VMS: Most common reason women seek care at time of menopausal transition**
VMS Etiology Poorly Understood

• Reduced estrogen levels cause decreased endorphin concentrations in the hypothalamus

• Leads to increased release of norepinephrine and serotonin
  – these neurotransmitters lower set point in the hypothalamic thermoregulatory nucleus
  – trigger inappropriate heat loss

RF Casper, SS Yen. Clin Endocrinol (Oxf) 1985
Prevalence and Timing of VMS

- Experienced by > 50% of menopausal women
- Substantial increase in frequency and severity during menopausal transition (perimenopause)
- For some women, VMS persist 6 months to several years, with ↓ frequency and intensity over time
- Mean duration bothersome VMS 10.2 years

EW Freeman, et al. Obstet Gynecol 2011
Factors That Affect Prevalence of VMS

- Increase
  - high BMI
  - induced menopause (surgery, chemotherapy, other)
  - African-American ethnicity
  - smoking
  - depression/anxiety

- Decrease
  - exercise
  - Japanese or Chinese ethnicity

Treatment of VMS

- Treatment appropriate when VMS disrupt daytime activities and/or sleep
- Estrogen used for many decades used to treat VMS
  - most effective treatment
    - numerous randomized, placebo-controlled trials
    - 75% reduction in VMS frequency
    - significant reduction in VMS severity
- Oral and transdermal estrogen have similar efficacy
- Progestin therapy, including DMPA and megestrol
  - also effective in treating VMS

HD Nelson. JAMA 2004
AH MacLennan, et al. Cochrane Database Syst Rev 2004
Hormone Therapy

● Clear
  – VMS: most common indication for HT
  – HT’s efficacy in treating VMS well-established

● Controversial
  – Our understanding of HT’s safety....
WHI: Women’s Health Initiative

- Multicenter, double-blind, placebo-controlled trial of women age 50-79 years at baseline, designed to assess HT’s impact on cardiovascular disease

- Mean age at screening 63-64 years

- Planned 10-year trial; stopped early
  - CEE/MPA v. placebo: N= 16,608 , stopped Summer ’02, mean follow-up 5.2 years
  - CEE v. placebo: N = 10,739 , stopped Spring ’04, mean follow-up 6.8 years

Writing Group WHI. JAMA 2002
WHI Steering Committee. JAMA 2004
WHI: 2002 Findings re EPT...
EPT: Breast Cancer

Invasive Breast Cancer

26% ↑*

Cumulative Hazard

Follow-Up Year

*95% nominal CI Hazard Ratio = 1.26 (1.00-1.59)

Adapted from: Writing Group WHI. JAMA 2002
EPT: Pulmonary Embolism

Follow-Up Year

Cumulative Hazard

Placebo

Estrogen + Progestin

0
0.01
0.02
0.03
0 1 2 3 4 5 6 7

Pulmonary Embolism

113%* ↑

*95% nominal CI Hazard Ratio = 2.13 (1.39-3.25)

Adapted from: Writing Group WHI. JAMA 2002
EPT: Coronary Heart Disease (CHD)

Initially, no analysis by age/years post-menopause presented…

Hazard Ratio = 1.29
*Statistically significant based on 95% nominal CI on Hazard Ratios

Adapted from: Writing Group WHI. JAMA 2002
EPT & Colorectal Cancer, Hip Fracture

Colorectal Cancer

37%↓*

Hip Fracture

34%↓*

*Statistically significant based on 95% nominal CI on Hazard Ratios

Adapted from: Writing Group WHI. JAMA 2002
WHI EPT Study: Findings at Early Interruption
Summer 2002

Risks
- VTE/PE
- MI
- CVA
- Breast Cancer

Benefits
- Fracture
- Colon Cancer

Adapted from: Writing Group WHI. JAMA 2002
WHI ET Initial Findings: Summary as of 2004

- ET component of study stopped early
  - after 6.8 years of follow-up
- ET not found to significantly impact risk of breast cancer, CHD, PE, or colorectal cancer
  - significant reduction in hip fracture risk
- Overall safety of ET appears greater than EPT
- Death rates not different in HT and placebo groups (EPT and ET studies)
- **11-year follow-up (JAMA 2011) findings...**
WHI’s Impact on Use of HT in US Women

- Since 2002, use of HT has decreased substantially
- Although the main conclusion of WHI is that HT not appropriate to prevent coronary heart disease, this study has resulted in many women with bothersome vasomotor symptoms, who could benefit from HT, discontinuing or avoiding treatment

J Shifren and I Schiff. Obstet Gynecol 2010
EPT & Breast Cancer: A Closer Look...

Invasive Breast Cancer

- Placebo
- Estrogen + Progestin

26%↑*

*95% nominal CI Hazard Ratio = 1.26 (1.00-1.59)

Follow-Up Year

Cumulative Hazard

Kaplan-Meier

Writing Group WHI. JAMA 2002
EPT & Risk of Breast Cancer

- Overall, increased risk becomes evident 3-5 years after initiating EPT
  - Elevated risk is modest: 8 additional cancers per 10,000 women using EPT for 5 or more years

- Increased risk of breast cancer with EPT may reflect promotion of preexisting cancers too small to be diagnosed by imaging studies or clinical examination.
  - These small cancers may never progress without the stimulation of EPT
  - The elevated risk of new diagnosis of breast cancer dissipates over the 3 years after cessation of EPT

RT Chelbowski et al. JAMA 2003, NEJM 2009
### WHI Trial of EPT: Breast Cancer Stage & Mortality at 11 Years Follow-up

<table>
<thead>
<tr>
<th>Hazard Ratio (95% CI) vs. Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Node positive tumors</td>
</tr>
<tr>
<td>Death from Breast Cancer</td>
</tr>
</tbody>
</table>

RT Chlebowski, et al. JAMA 2010
EPT: Pulmonary Embolism

Kaplan-Meier

Cumulative Hazard

Follow-Up Year

Pulmonary Embolism

113%\*↑

Placebo

Estrogen + Progestin

E+P

Placebo

*95% nominal CI Hazard Ratio = 2.13 (1.39-3.25)

Oral HT used in WHI - might transdermal HT be safer?
VTE & CVA Risk and Route of ET: Five Studies

- France: ESTHER case-control study and E3N cohort study
- UK: GP Research Database: VTE and CVA
- US: Claims-based cohort study
- Dutch (Leiden) case-control study

- **Oral estrogen therapy:** ↑ risk VTE & CVA
- **Transdermal ET:** no ↑ risk

ACOG Committee Opinion 556, April 2013

L Laliberté, et al. Menopause 2011
M Canonico, Arterioscler Thromb Vasc Biol 2010
C Renoux, et al. BMJ 2010
Combination HT and CHD: a Closer Look

**Coronary Heart Disease**

- **Estrogen + Progestin**
- **Placebo**

- **29%** *Statistically significant based on 95% nominal CI on Hazard Ratios*

**Follow-Up Year**

**Kaplan-Meier Cumulative Hazard**

- **Median age at screening:** -63-64 years
- **No analysis by age or years post-menopause presented in 2002**

**HR: 1.29**

Adapted from: Writing Group WHI. JAMA 2002
### Absolute Excess Risks (cases per 10,000 person-yrs) by Age in the Combined Trials (EPT and ET) of the WHI

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50-59</td>
</tr>
<tr>
<td>CHD</td>
<td>-2</td>
</tr>
<tr>
<td>Stroke</td>
<td>+2</td>
</tr>
<tr>
<td>Total mortality</td>
<td>-10*</td>
</tr>
<tr>
<td>Global index†</td>
<td>-4</td>
</tr>
</tbody>
</table>

*P<0.05

†Global index is a composite outcome of CHD, Pulmonary embolism, breast ca, colorectal ca, endometrial ca, hip fracture and mortality

HT, CHD and the ‘Timing Hypothesis’

- HT (ET, or EPT)
  - Does not increase CHD risk if initiated *early* in the menopausal transition
  - May have a beneficial effect on morbidity/mortality if initiated *early* in the menopausal transition
  - ‘Early’: Age 50-59 years, or < 10 years after menopause onset
  - Findings congruent with non-human primate data

JL Shifren, I Schiff. Obstet Gynecol 2010
JE Rossouw et al. JAMA 2007
Stram DO, et al. Menopause 2011
Overall (all ages), estrogen use not associated with significant impact on risk of CHD, CVA, DVT, hip fracture or total mortality

- However, initially noted reduced risk of breast cancer persisted (HR 0.77, P<.05)

Among women age 59 or younger at randomization, estrogen use HRs for CHD (0.59) and overall mortality (0.73) significantly decreased

## Estrogen-Alone Age-Specific Results

<table>
<thead>
<tr>
<th>Condition</th>
<th>50-59 years</th>
<th>60-69 years</th>
<th>70-79 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>↓</td>
<td>0</td>
<td>↑</td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>DVT/PE</td>
<td>0</td>
<td>↑</td>
<td>0</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>0</td>
<td>0</td>
<td>↑</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>↓</td>
<td>0</td>
<td>↑</td>
</tr>
<tr>
<td>Global index</td>
<td>↓</td>
<td>0</td>
<td>↑</td>
</tr>
</tbody>
</table>

ET Trial: 11 Years of Follow-Up Breast Cancer Mortality

- Estrogen
  - 23% lower risk of invasive breast cancer (P=0.02)
  - Lower risk persisted from intervention to f/u phase of study
  - Breast cancer prevention more pronounced (32%) in participants most adherent with study meds
  - Among women with breast cancer, overall and breast cancer-specific mortality significantly lower

Mortality Resulting from Estrogen Non-use in Hysterectomized Women

- Since 2002, ET post-hysterectomy for women in their 50s declined from ~90% to ~30%
- Given the higher mortality for post-hysterectomy women age 50-59 years who do not use ET, an estimated additional 19,000-92,000 women post-hysterectomy died prematurely due to ET non use in their 50s
- Above estimates underscore the need for clinicians and women to better understand
  - Differences between ET and EPT
  - How benefit-risk profile of HT varies by age

Kronos Early Estrogen Prevention Study (KEEPS)

● 727 healthy women, intact uterus, within 3 years of menopause onset (age 42-58) randomized to:
  – CEE 0.45, TD E2 0.05 or placebo
  – Micronized P 200 12 days/month or placebo
  – Study medications x 4 years

● Study not powered to assess impact on clinical outcomes
  – MI, CVA, VTE, breast cancer

NAMS Annual Meeting, Orlando, FL, October 2012. Manson JE. Women’s Health 2013
Kronos Early Estrogen Prevention Study (KEEPS)

- Oral/transdermal estrogen:
  - No change in coronary artery calcium vs. placebo
  - No change in carotid intima medial thickness vs. placebo

- Oral CEE associated with evidence of mood benefits

- Findings overall not surprising but do provide additional reassurance regarding safety of HT in recently/young menopausal women

- Stay tuned for published reports, more analyses

NAMS Annual Meeting, Orlando, FL, October 2012. Manson JE. Women’s Health 2013
Interest in **Nonhormonal** Management of VMS Has Increased

- Since WHI/2002, use of menopausal HT has declined
- More women and clinicians interested in nonhormonal options
  - More and better quality trials are examining nonhormonal options
Nonhormonal Treatment of VMS: Nonprescription Options

- Best studied options:
  - Soy-extract and red clover isoflavones
  - Black cohosh
  - Chinese herbs also have been studied
- None of these options have consistently been found more effective than placebo
- In trials comparing efficacy of nonprescription agents to HT, HT substantially more effective
Nonhormonal Treatment of VMS: Prescription Options

- Until 2013, no nonhormonal medication FDA-approved for VMS: all such use had been off-label
- Although nonhormonal agents less effective than HT, the following are more effective than placebo:
  - Gabapentin
  - Antidepressants
    - SSRIs (paroxetine best studied)
    - SNRIs (venlafaxine, desvenlafaxine)
  - Side effect profile different than HT
- FDA failed to approve desvenlafaxine (2011) and gabapentin (2013) to treat VMS...
Low-dose Mesylate Salt of Paroxetine 7.5 mg (Brisdelle)

- In 12- and 24-week randomized, blinded, placebo-controlled trials, LDMP more effective than placebo in reducing frequency of VMS
  - 1-2 fewer flashes/day with paroxetine vs. placebo
  - Side effects more common with active drug vs. placebo:
    - Nausea, fatigue and dizziness (each < 4%)

- FDA approval to treat menopausal VMS June 2013

U.S. Food and Drug Administration. FDA approves the first non-hormonal treatment for hot flashes associated with menopause. FDA 2013 Jun 28; [e-pub ahead of print].
http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm359030.htm?source=govdelivery

HT and Dementia: Women >=65 Years

- WHIMS: HT increased dementia risk and cognitive decline and decreased brain volume on MR (cognitive decline likely vascular)
  - Data do not support using HT in elderly women
    - To prevent cognitive decline
    - To improve cognition in patients with dementia

HT and Dementia: Women 50-55 Years

● WHIMSY (WHI Memory Study in Younger Women): 1326 participants; cognition assessed mean 7.2 years after study meds halted
  – Cognitive function similar in women treated with ET/EPT compared with placebo
  – No substantive cognitive benefit noted with HT
● Reassuring that HT ‘cognitively safe’ in younger women
● Disappointing that no cognitive benefit noted in younger women

When Menopause Occurs Too Early

- Early menopause
  - Surgical (BSO, or impact of hysterectomy), chemotherapy or radiation therapy, heavy smoking history

- WHI did **not** enroll women younger than age 50

- Loss of ovarian function prior to age 50
  - Unless estrogen employed, increased risks of CAD, CVA, dementia, as well as all-cause mortality

CM Rivera et al. Menopause 2009
WA Rocca et al. Neurol 2007
PG Moorman et al. Obstet Gynecol 2011
MA Allison, JE Manson, et al. Menopause 2008
WH Parker et al. Obstet Gynecol 2013
Early Menopause: Treatment Considerations

- Avoid incidental oophorectomy with hysterectomy unless ovarian cancer risk high
- HT risk-benefit profile more favorable in menopausal women < 50 years of age
  - HT should be considered unless contraindications present
  - Higher doses of HT may be appropriate
Genital Atrophy: an Estrogen-deficiency state

- Women report vaginal dryness, pruritis, bleeding, dyspareunia, urinary urgency, recurrent UTIs
- Clinicians may note introital narrowing, loss of labia minora tissue and pigmentation, vaginal shortening, loss of mucosal rugal folds, petechiae, friability and elevated vaginal pH
- Unlike vasomotor symptoms, genital atrophy **worsens** over time unless treatment instituted...**long-duration** treatment often appropriate
Treatment of Genital Atrophy (VVA)

- Behavioral
  - Stop smoking
  - Regular sexual activity

- Nonhormonal vaginal therapy
  - Moisturizers, Lubricants

- Systemic estrogen therapy

- Vaginal (local) estrogen therapy
  - Creams (conjugated equine estrogen, estradiol)
  - Ring (2 mg estradiol): q 3-months
  - Tablets (estradiol: 25 mcg–10 mcg) start qHS x 2 weeks, then twice weekly
Advantages of Locally-Administered Estrogen

- Improves genital atrophy
  - Also reduces urgency incontinence, UTIs
- Minimizes/avoids systemic impact
- In general, progestin protection of endometrium not needed
  - However, clinical trials have generally been for one year only
Ospemifene 60 mg tablets: Oral Medication to Treat VVA

- Tissue-selective estrogen agonist/antagonist
- Effectively treats dysparunnea, VVA
- Most common AEs: hot flushes, vaginal leukorrhea, muscle spasms
- Contraindications: similar to estrogen
- May appeal to women with symptomatic VVA who prefer not to use vaginal medications
- Consider endometrial monitoring, particularly with long-term use

DJ Portman, et al. Menopause 2013
Menopausal Hormone Therapy: A Clinician’s Evidence-based 2013 Perspective

Summary & Conclusions
Helping Menopausal Women Make Sound Choices
Re HT (1)

- Menopausal symptoms impair quality of life, and are undertreated
  - HT safe for most younger/recently menopausal women
  - HT: Most effective treatment for bothersome vasomotor symptoms
  - HT also effective for fracture prevention and treatment of genital atrophy
Helping Women Make Sound Choices Re EPT: Coronary Heart Disease (2)

- No increased risk when started by women within 10 years of menopause (< age 60)
  - Although possible cardioprotection, HT should not be Rxed for this indication

- Modest elevated risk in women who start HT more than 10 years post menopause
Helping Women Make Sound Choices re **EPT**: Breast Cancer (3)

- Increased risk breast cancer becomes evident 3-5 years after initiating EPT

- Elevated risk
  - modest
  - increases with longer term use
  - dissipates 3+ years after stopping EPT

- Tumors with E+P use more likely node-positive

- Breast cancer mortality marginally increased at 11 years f/u
Helping Women Make Sound Choices Re ET (4)

- Persistent reduction in risk of invasive breast cancer
  - Lower breast cancer mortality

- No increase in CHD when initiated in young menopausal women; cardioprotection likely
  - Also, reduced mortality in this subgroup of users

- In women with or w/o uterus, oral EPT and ET increases VTE & CVA risk
  - Use of transdermal ET may avoid the elevated VTE & CVA risk associated with oral therapy
Helping Menopausal Women Make Sound Choices
Re HT (5)

- For women with **symptomatic genital atrophy** free of vasomotor symptoms and bone health concerns, *vaginal* estrogen preferred
Helping Menopausal Women Make Sound Choices
Re HT: Final Thoughts

- Risk of breast cancer increases after 3-5 years of EPT, and cardiovascular risks increase with age
  - Symptomatic women using HT should periodically (e.g. annually) review their therapy with their clinician, with goal of reducing systemic HT dose or discontinuing systemic HT over time
  - Selectively, some well-counseled menopausal women may elect long-term systemic HT use
    - Risk:benefit profile of ET more favorable than EPT
    - Risk:benefit profile of transdermal and lower dose HT may be more favorable

JL Shifren, I Schiff. Obstet Gynecol 2010

menopause.org

- Menopause 2012; 19: 257-271
THANK YOU!