Menopause - An Update
Management Consensus & Controversies

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Reproductive Endocrinology
Learning Objectives

At the conclusion of this presentation, participants should be able to:

- Appreciate the spectrum of menopause related symptom burden and health concerns
- **Be familiar with the status of menopausal medicine**
- Identify unique needs & risks of women experiencing unnatural menopause (POI, iatrogenic)
- Compare & contrast the efficacy, safety & side effects of available therapies (hormonal & non-hormonal)
- **Individualize risk assessment & Rx strategies**
Aging Female Population Mortality

Mortality Rate per 100,000

Age (years)

- Heart Disease*
- Lung Cancer†
- Breast Cancer†
- Colon & Rectal Cancer†
- Stroke*
- Endometrial Cancer†

Menopausal Symptom Burden

Prevalence of Hot Flushes

- >75% of women report hot flushes within the 2-year period around menopause
- Primary reason women seek medical treatment
- 25% remain symptomatic for >5 years

Gold, Am J Epi. 2004; 159:1169
Sleep Disturbance in Peri/Postmenopausal Women

↑ reports of difficulty

% with difficulty sleeping

Waking up repeatedly

Falling asleep

1 Kravitz, Menopause 2003
2 Kravitz, Sleep 2008
Reproductive Aging Paradigm

<table>
<thead>
<tr>
<th>Puberty</th>
<th>Reproductive Yrs</th>
<th>Transition</th>
<th>Postmenopause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stages:</td>
<td>-5</td>
<td>-4</td>
<td>-3</td>
</tr>
<tr>
<td>Terminology:</td>
<td>Reproductive</td>
<td>Menopausal Transition</td>
<td>Postmenopause</td>
</tr>
<tr>
<td></td>
<td>Early</td>
<td>Peak</td>
<td>Late</td>
</tr>
<tr>
<td>Duration of Stage:</td>
<td>variable</td>
<td>variable 4 yrs</td>
<td>until demise</td>
</tr>
<tr>
<td>Menstrual Cycles:</td>
<td>variable to regular</td>
<td>regular 4 yrs</td>
<td>none</td>
</tr>
<tr>
<td>Endocrine:</td>
<td>normal FSH</td>
<td>↑ FSH</td>
<td>↑ FSH</td>
</tr>
</tbody>
</table>

Final Menstrual Period (FMP)

*Stages most likely to be characterized by vasomotor symptoms

↑ = elevated
HT...Pre-WHI Perceptions

Weighing Risks vs Benefits

Risks
- VTE
- Stroke
- Breast Cancer

Benefits
- Cognition
- CVD Risk
- QOL
- Skeletal Benefit
- Symptom Control

Annual Risks & Benefits after 7 years of E alone

- Breast cancer: Decrease of 7 per 10,000 woman-years
- CVD: Increase of 5 per 10,000 woman-years
- VTE*: Increase of 7 per 10,000 woman-years
- Stroke: Increase of 12 per 10,000 woman-years
- Hip fractures: Decrease of 6 per 10,000 woman-years
- Vertebral fractures: Decrease of 6 per 10,000 woman-years
- All fractures: Increase of 57 per 10,000 woman-years

n = 10,733
* = NS

Adapted from JAMA 2004;291:1701-12
MacLennan A, Sturdee D. Climacteric 2004
Menopause Hormone Therapy (MHT)...

- Is NOT risk free
- NOT cardioprotective
- CAN harm
  - Aged
  - Remote from last menstrual period
  - Overweight/obese
  - Existing pre morbidities

**Figure 1.** Trends in menopausal hormone therapy use in the U.S.A., 1967-2003. (Adapted from Beral V, et al. 1999 and Hersch AI, et al. 2004)
Timing Hypothesis

Relation of years since menopause to progression of atherosclerosis

<table>
<thead>
<tr>
<th>Years postmenopause</th>
<th>% of WHI enrollees</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5</td>
<td>17%</td>
</tr>
<tr>
<td>5 to &lt; 10</td>
<td>19%</td>
</tr>
<tr>
<td>10 to &lt; 15</td>
<td>21%</td>
</tr>
<tr>
<td>≥ 15</td>
<td>43%</td>
</tr>
</tbody>
</table>
To compare effects of low dose oral CEE (0.45mg) vs. transdermal estradiol (50 µg/d weekly patch) vs. placebo on surrogates for CVD:

1) Carotid IMT
2) Coronary artery calcium (CAC)

- 727 women aged 42-59 (mean age, 52.7, within 3 yrs of FMP)
- Trial Duration = 48 months
- Multi-center double-blinded placebo-controlled RCT
- Active Treatment Arms:
  - Cyclical micronized Premarin 200 mg/d x 12 days/month vs. placebo

Kronos Early Estrogen Prevention Study
Study Design

Inclusion criteria

• 42-59 years of age at randomization
• Final menses ≤3 years earlier
• Good general health
• Plasma FSH ≥ 35 mIU/ml and/or E2 levels <40 pg/ml
• Normal mammogram within one year before randomization

Exclusion criteria

• Prior h/o CVD or VTE
• Use of lipid-lowering med
• CAC score >50
• LDL >160 mg/dl
• Triglyceride >400
• Uncontrolled hypertension
• Smoking >10 cigarettes/day
• Severe obesity (BMI >35)
• Use of estrogen/SERM in past 6 mos.
• Hysterectomy
• Endometrial thickening (>5 mm) at baseline
• Chronic systemic illness
  • Renal failure
  • Hepatic failure
  • Dementia
  • Diabetes mellitus
### Baseline Characteristics*

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>52.7</td>
<td>2.6</td>
</tr>
<tr>
<td>Yrs since menopause</td>
<td>1.43</td>
<td>0.7</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.2</td>
<td>4.3</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>119</td>
<td>15</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>75.0</td>
<td>9.2</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>208</td>
<td>34</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>111</td>
<td>28</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)†</td>
<td>72.0</td>
<td>15 (p &lt;0.05)</td>
</tr>
</tbody>
</table>

* Unless otherwise noted, there were no differences between treatment groups at baseline.

† p=0.0497
Effects of Low Dose Oral vs. Transdermal E on Carotid Intima Thickness in Early Menopause ...

KEEPS Trial

Ultrasound Measurement of CIMT

Changes in Imaging Endpoints, CIMT - KEEPS Trial

Thickness of the common carotid artery intima-media layers measured by ultrasound (CIMT).

Gray's Anatomy, 1910, fig. 307
Effects of Low Dose Oral vs. Transdermal E on Coronary Artery Calcification (CAC) in Early Menopause ...KEEPS Trial
Effects of Low Dose Oral vs. Transdermal E on CVD Risk in Early Menopause ...KEEPS Trial
Effects of Low Dose Oral vs. Transdermal E on CVD Risk in Early Menopause ...KEEPS Trial

Blood Pressure Changes - KEEPS Trial

Changes in Fasting Blood Sugar & Insulin Resistance - KEEPS Trial
Placing HT Related Risks in Perspective
Effects of Low Dose Oral vs. Transdermal E in Early Menopause ...KEEPS Trial

Hot Flashes

Night Sweats

727 postmenopausal women within 3 years of final menses, mean age
Effects of Low Dose Oral vs. Transdermal E in Early Menopause ...KEEPS Trial

Dyspareunia

Vaginal Dryness

%

Months

%

Months

OCEE

t-E2

PBO

OCEE

t-E2

PBO
Effects of Low Dose Oral vs. Transdermal E in Early Menopause Symptoms ...KEEPS Trial

Female Sexual Function Index, Pain

Female Sexual Function Index, Lubrication

*P<0.05
MHT & Breast Cancer Risk

Current Understanding:
• Estrogen alone Rx in hysterectomized population is deemed relatively safe for breast tissue
• Type of progesterone (natural progesterone preferred over synthetic) and regimen (cyclic preferred over continuous) merit consideration.
Current Understanding:

- Advancing age, obesity and individualized profile should be considered when assessing risks for TE in patient being considered for HT.
Stroke Risk & HT in Nurses Health Study (1980-2004)
Risk for *current* versus *never* users by dose of CE

**CEE Dose**

0.3mg/day  
*(33,391 women yr, n=25)*

0.625mg/day  
*(233,249 women yr, n=268)*

1.25mg/day  
*(59,373 women yr, n=60)*

Reference: No estrogen (452,957 women-years; n=349)

*Adjusted: age, BMI, high cholesterol, high BP, DM, smoking, husband’s education, FH MI*

VTE Risk: Drug & Route

Route of HT & Progestin  Oral vs. Transdermal E

**Current Understanding:**
- Choice of progestin (progesterone preferred to synthetic progestins) and both dose & route of E (low dose transdermal preferred over oral route) can confer risk reduction against TE.
The *art* of medicine must not be a victim to our overzealous pursuit of *evidence based* approach.

Therapeutic benefits of HT far exceed purported risks for a substantial proportion of the most symptomatic population, i.e. early menopausal women.

It is my/our responsibility to ensure that I/we minimize risks while helping alleviate symptom/s.
MHT Decision Should Be Based upon Individualized Assessment

THERE IS NO ROLE OF HORMONE THERAPY FOR CARDIAC PROTECTION OR COGNITIVE BENEFIT
## Future of MHT

<table>
<thead>
<tr>
<th>Target</th>
<th>E+P</th>
<th>SERMs</th>
</tr>
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<tbody>
<tr>
<td>Breast</td>
<td>😫zing</td>
<td>😎</td>
</tr>
<tr>
<td>Uterus</td>
<td>😫zing</td>
<td>🤔</td>
</tr>
<tr>
<td>Hot Flush</td>
<td>🧠💡💡💡</td>
<td>😫zing</td>
</tr>
<tr>
<td>Vagina</td>
<td>🧠💡💡💡</td>
<td>😫zing</td>
</tr>
<tr>
<td>Bone</td>
<td>🧠💡💡💡</td>
<td>😎</td>
</tr>
</tbody>
</table>

*Note: The table uses emojis to indicate the level of satisfaction.*
Take Home Points

- Management strategies **MUST** be individualized to:
  - address nature and severity of symptoms
  - while maintaining individualized risk/s in perspective
- For early menopausal women, MHT is the **MOST** efficacious of available strategies.
- Non-hormonal therapies **SHOULD** be 1st line Rx for symptomatic women who are deemed “at risk” for MHT related adverse effects.
- Estrogen dose reduction, TD administration, choice of progestin & regimen **CAN** offer risk reduction.