Menopause Hormone Therapy: Where Are We Now?

SPEAKER
Martin A. Quan, MD

MHT: Reasons for Increase in Use

- "greying of America"
  - estimated 58 million American women over age 50 years
  - average life span: 79 years
- delay or prevention of osteoporosis, ? CHD, Alzheimer’s, colon cancer, diabetes

MHT: Nuts and Bolts

- MHT is not without risk
- 1995: 38 percent of postmenopausal women in the U.S. taking MHT

Estrogen Use in the United States

JAMA 2004;291:47
MHT: Nuts and Bolts

Contraindications
- known or suspected breast cancer
- active thromboembolic disease
- undiagnosed uterine bleeding
- active liver disease
- chronically impaired liver function
- endometrial cancer*

FDA-approved indications
- hot flashes: 80 to 90% reduction
- prevention of osteoporosis: maintains BMD, 50% reduction in fracture (WHI: 34-39% reduction)
- genitourinary atrophy: atrophic vaginitis, senile urethral syndrome

Non FDA-approved Indications
- dermatologic changes of aging, i.e. wrinkling
- psychological symptoms (e.g. depression, anxiety, mood swings)
- cardioprotective effect (?)

MHT and Depression
Fischer et al, Fertil Steril 2014;101:898
- 5 of 6 RCTs demonstrate benefit in in mood in menopausal women
- Soares et al1: 100 ug patch 17 β-E2 remission in 68% vs 20% controls (p=0.001) in perimenopause depression
- Gordon et al2: 0.1 mg patch E-2 + 200 mg micro P q 3 mo reduced depressed sx in perimenopausal women

1. Arch Gen Psych 2001;58:529
2. JAMA Psych 2018; 75:149
**MHT: Nuts and Bolts**

**Non FDA-approved Indications**
- dermatologic changes of aging, i.e. wrinkling
- psychological symptoms (e.g. depression, anxiety, mood swings)
- cardioprotective effect (?)

**Evidence for cardioprotective effect**
- 50 + epidemiological studies that supported a 50% reduction in risk *
- Biologically plausible:
  - favorable impact on lipids
  - antioxidant- reduced oxidized LDL
  - reversal of paradoxical vasoconstriction

* Grodstein & Stampfer, Maturitas 1998

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**MHT and CHD**

**Prevention of CHD**

- **HERS Study** - Heart & Estrogen Replacement Study - (JAMA 1998;280:605)
- **ERA Study** - Estrogen Replacement & Atherosclerosis - (NEJM 2000;343:522)
- **WHI** - Women’s Health Initiative (JAMA 2002;288:321; 2004;291:1701)

**Secondary prevention**
- **HERS** (Hulley et al, JAMA 1998)
  - no benefit (MI or CHD death) after 4.5 years in women with known CAD (mean age 66.7 yrs)
- **ERA** (Herrington et al, NEJM 2000)
  - no impact on angiographic progression of CAD in women with known disease after mean F/U 3.2 yr (mean age 65.6 yrs)
**MHT and CHD**

**Secondary prevention**

**HERS (Hulley et al, JAMA 1998)**
- no benefit (MI or CHD death) after 4.5 years in women with known CAD (mean age 66.7 yrs)

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**MHT- WHI: E + P**

**Primary prevention of CHD**

- RCT primary prevention (JAMA 2002:288:321)
- 16,608 women, 50 to 79 yr (avg 63 yrs)
- mean F/U 5.2 yrs in E + P arm
- increased risk of CHD in E+P users with HR=1.29 (CI 1.02-1.63)

**HR=1.24 (nominal CI 1.00-1.54; adjusted CI 0.97-1.60 )- Manson, NEJM 2003;349:523)**
MHT: WHI E + P Arm
C/V Events & Onset of Use

**E + P Start Time**  **RR of CHD**

- **< 10 yrs of menopause**  **0.89**
- **10 to 19 yrs of menopause**  **1.22**
- **> than 20 yrs of menopause**  **1.72**

Manson et al, NEJM 2003;349:523

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MHT- WHI: Unopposed E
Primary prevention of CHD

- RCT primary prevention (JAMA 2004:291:1701)
- 10,739 women, 50 to 79 yr (avg 63.6 yrs)
- mean F/U 6.8 yrs in unopposed E arm
- no increased risk of coronary heart disease with HR=0.91 (CI 0.75-1.12)

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WHI- Unopposed E
Primary prevention of CHD

- RCT primary prevention (Arch Int Med 2006:166:357)

<table>
<thead>
<tr>
<th>Age</th>
<th>CEE</th>
<th>Placebo</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>46</td>
<td>70</td>
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</tr>
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<td>60-69</td>
<td>186</td>
<td>194</td>
<td>0.98 (0.80-1.21)</td>
</tr>
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WHI- Unopposed E
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<td>141(1.58)</td>
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</table>
MHT: WHI  CEE  Arm
Coronary artery calcification

Ancillary study of 1064 women (50-59 yrs) 8.7 yrs after randomization (mean 7.4 yrs of Rx and 1.3 yrs post- trial)

<table>
<thead>
<tr>
<th></th>
<th>CEE</th>
<th>Placebo</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean score</td>
<td>83.1</td>
<td>123.1</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Manson et al, NEJM 2007;356:2591

KEEPS and CHD:

Kronos Early Estrogen Prevention Study
- RCT 727 women (42-58 yrs)* w/o CHD and CAC <50
- 3 groups- 0.45 mg CEE vs t-E2 0.05 patch vs placebo + 200 mg micro P x 12 days
- No impact on CIMT or CAC after 48 mo

*within 6-30 mo from LMP

CAC- coronary Ca++ score      CIMT- carotid intima media thickness

ELITE and CHD:
Primary prevention of CHD
ELITE (Early vs Late Intervention Trial With Estradiol)
- RCT launched in 7/04 by Nat’l Institute of Aging
- oral micronized estradiol (1 mg/d with intravaginal progesterone) given to women less than 6 yrs vs 10 or more yrs from menopause
- primary outcomes: carotid artery intima- media thickness, coronary Ca+

ELITE and CHD:
Support for the “Timing Hypothesis”

After median F/U of 5 years
- CIMT progression in early menopause
  (+) estrogen: 0.0044 mm/yr
  placebo: 0.0078 mm/yr (p<0.008)
- no difference in CIMT progression in late menopause women
- no difference in coronary Ca+ in any group

Hodis et al, NEJM 2016;374:1221-31
MHT: ? Cardioprotective effect

Bottom Line

- no role in the secondary prevention of coronary artery disease
- evidence points against significant role in the primary prevention of coronary artery disease

Possible Benefits of MHT

- reduced risk of colon cancer
  - 35 to 40% reduction (Grodstein, Ann Intern Med 1989)
  - 19% reduction (WHI, JAMA 2013) with E + P
  - 14% reduction with unopposed E (WHI, JAMA 2013)

Potential Benefits of MHT

- reduced risk of diabetes
  - WHI- E+P: HR=0.81 (CI 0.70-0.94)
  - E: HR= 0.86 (CI 0.76-0.98)

Manson, Fertil Steril 2014;101:916-21
ERT and Endometrial Cancer

- link between unopposed estrogen and endometrial cancer established
- 10 to 15% annual incidence of adenomatous hyperplasia, 3-fold increased risk of cancer
- dose-duration effect: 8 X after 8 yrs

Concerns allayed re endometrial ca

- ERT-associated cancer tends to be localized and well-differentiated at time of diagnosis
- increased risk greatly offset by concomitant use of progestin agent

ERT and Breast Cancer

- most feared cancer among women
- most common cancer
- typical American female 50+ yrs
  - 12% lifetime risk of developing it
  - 3% lifetime probability of dying from it

<table>
<thead>
<tr>
<th></th>
<th>RR(any use)</th>
<th>RR(long-term)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Armstrong (1988)</td>
<td>0.96</td>
<td>1.04</td>
</tr>
<tr>
<td>DuPont (1991)</td>
<td>1.08</td>
<td>--</td>
</tr>
<tr>
<td>Grady (1992)</td>
<td>1.00</td>
<td>1.25</td>
</tr>
<tr>
<td>Sternberg (1993)</td>
<td>1.00</td>
<td>1.30</td>
</tr>
<tr>
<td>Sillero-Arenas (1992)</td>
<td>1.06</td>
<td>1.23</td>
</tr>
<tr>
<td>Colditz (1993)</td>
<td>1.02</td>
<td>1.23</td>
</tr>
<tr>
<td>Collaborative Grp (1997)</td>
<td>--</td>
<td>1.35</td>
</tr>
</tbody>
</table>

* 3.5 X risk if (+) fam hx
MHT and Breast Cancer: WHI: E + P Arm and Breast Cancer

- RCT primary prevention of 16,608 women- ages 50-79 (avg 63 yr) mean F/U 5.2 yrs
- HR = 1.26 (CI 1.00-1.59)
- risk did not begin until after 4 yrs
- no effect of pre-existing risk factors: age, (+) family history, ethnicity, or BMI

MHT and Breast Cancer: WHI: Unopposed E and Breast Ca

Stefanick et al, JAMA 2006;295:1647

- RCT primary prevention of 10,739 women- ages 50-79 (avg 63.6 yr) mean F/U 7.1 yrs
- HR = 0.80 (CI 0.62-1.04)

Breast Cancer and E + P Studies Suggesting Increased Risk

<table>
<thead>
<tr>
<th>Study</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colditz (1995)</td>
<td>1.41 (1.15-1.74)</td>
</tr>
<tr>
<td>Persson (1999)</td>
<td>1.7 (1.1-2.6)</td>
</tr>
<tr>
<td>Magnusson (1999)</td>
<td>1.68 (1.39-2.03)</td>
</tr>
<tr>
<td>NCI Study (2000)</td>
<td>1.4 (1.1-1.8)</td>
</tr>
<tr>
<td>Olsson (2003)</td>
<td>2.45 (1.61-3.71)</td>
</tr>
<tr>
<td>E3N (2008)</td>
<td>1.66</td>
</tr>
</tbody>
</table>

MHT and Breast Cancer: WHI: Health outcomes after stopping ERT

Manson et al, JAMA 2017;318:927-38

- RCT primary prevention of 10,739 women- intervention 7.2 yrs, cumulative F/U 18 yrs
- HR = 0.55 (CI 0.33-0.92) for breast cancer mortality
MHT and Breast Cancer: Take-Home Lessons

- HRT (E+P) users appear to be at higher risk of breast cancer
- risk appears confined to specific subsets:
  - extended use - RR=1.25-1.40 (WHI RR=1.26 after 4 yrs of use)
- risk not reduced by progestin

MHT: Nuts and Bolts

Other potential risks

- 2-4 X risk DVT prior to WHI: WHI finding- 2 X (3.5 vs 1.7 per 1000 person-yrs)
- 2 X risk gallstones
- 1.5 to 2 X risk ovarian cancer (NCI study, JAMA 2001;285:1460)
- 1.37 X risk of stroke with E + P (WHI, JAMA 2013); 1.35 X risk with unopposed E (WHI, JAMA 2013)

MHT: Nuts and Bolts

2017 NAMS MHT Guidelines

- HT has clear benefits for the treatment of VMS, GSM, and bone loss prevention
- benefits > risks among women with sx < 60 yrs & within 10 yrs of menopause onset and have no contraindications
- less favorable benefit/risk ratio in women > 60 yrs who initiate HT > 10 years of menopause onset because of elevated risks of CHD, stroke, VTE, & dementia.

MHT: Nuts and Bolts

2017 NAMS MHT Guidelines

- risks of HT varies on the HT type, duration of use, administration route, timing of initiation, and whether a progestogen is needed (note: ET more favorable than EPT with longer use)
- for sx of GSM, use low-dose vaginal ET
- HT should be individualized and evaluated periodically to maximize benefits as well as minimize the risks
MHT Case Study

JJ is a 55 y/o white G1P1 female seen for frequent, increasingly severe HF and night sweats, dyspareunia, fatigue, joint pains, and poor sleep. LMP 1.5 years ago. PMHx and Fam Hx is unremarkable.

ROS menarche age 13; childbirth age 32. PE notable for BMI=27 and BP 110/82 and urogenital atrophy.

Labs reveal TC 225, LDL 130 mg/dl, HDL 65 mg/dl, TG 80 mg/dl.

OTC drugs, including Estroven® (black cohosh extract, soy isoflavones, cissus quadrangularis extract) and Vitamin E have not provided relief.

10-yr AHA CVD risk score 1.4 %

Lifestyle Interventions for Hot Flashes

- avoid tobacco
- wear layered, cotton clothing
- regular exercise
- maintain cool ambient temperatures (e.g. use of fans, ice pack under pillow)
- avoid triggers: hot drinks, caffeine, hot or spicy foods, stress
- mind-body techniques (CBT, clinical hypnosis)

Alternative Rx

- Black cohosh: mixed results
- Isoflavones: mixed results
- Dong quai root: no benefit
- Red clover: no benefit
- Kava: no benefit
- Evening primrose oil: no benefit
- Ginseng: no benefit
- Vitamin E: no benefit

Trial with clonidine*

Pandya, Ann Intern Med 2000;132:78
- oral clonidine 0.1 mg BID- 40 % reduction in hot flashes*

Laufer al, Ob Gyn 1982;60:583
- transdermal patch 0.05-0.1 mg/week- 46 % reduction

Nelson et al, JAMA 2006;295:2057
- meta-analysis – “modest” benefit
- side effects: drowsiness, dry mouth

* off-label use
Trial with gabapentin*

- **Guttiuso et al**: RCT of 59 post-menopausal women- gabapentin 900 mg/d produced 45% reduction in hot flashes
- **Butt et al**: RCT of 197 women- gabapentin resulted in 51% reduction in hot flash scores
- **Reddy et al**: RCT of 60 women- gabapentin 2400 mg/day comparable to 0.625 mg CEE

* off-label use

Trial with SSRI* or SNRI*

- venlafaxine XR 75 mg/d produced 61% reduction in hot flashes*
- paroxetine CR 12.5 to 25 mg/d produced 62 to 65% reduction*
- desvenlafaxine 100 mg/d- 64% reduction*
- FDA approved 6-28-13: Paroxetine mesylate 7.5 mg daily

* off-label use

Initiate Menopause Hormone Rx

**WHI: CHD risk and EPT Timing**

<table>
<thead>
<tr>
<th>E + P Start Time</th>
<th>RR of CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10 yrs of menopause</td>
<td>0.89</td>
</tr>
<tr>
<td>10 to 19 yrs of menopause</td>
<td>1.22</td>
</tr>
<tr>
<td>&gt; than 20 yrs of menopause</td>
<td>1.72</td>
</tr>
</tbody>
</table>

Manson et al, NEJM 2003;349:523

CVD Risk Counseling and MHT

**Endocrine Society**

<table>
<thead>
<tr>
<th>10 yr CVD Risk</th>
<th>Low (&lt; 5%)</th>
<th>Intermediate (5 to 10 %)</th>
<th>High (&gt; 10 %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5 years from Menopause</td>
<td>OK</td>
<td>OK (choose transdermal)</td>
<td>Avoid</td>
</tr>
<tr>
<td>6 to 10 years from Menopause</td>
<td>OK</td>
<td>OK (choose transdermal)</td>
<td>Avoid</td>
</tr>
</tbody>
</table>

J Clin Endocrinol Metab 2015;100:3975-4011
Breast Cancer Risk: Gail Model Score

- 7-question tool for assessing 5-yr risk for breast cancer: age, ethnicity, menarche, age at first birth, fam history, hx breast bx, and hx ductal CIS or lobular CIS
- low-average risk = < 1.66 %
- case study score: 1.6 %

Estrogen Replacement Regimens

- Unopposed estrogen
- Continuous estrogen/cyclic progestin
- Continuous combined HRT
**PROGESTIN THERAPY**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Proprietary</th>
<th>cyclic (days 1 to 12-14 d)</th>
<th>continuous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medroxyprogesterone acetate</td>
<td>Provera, Amen</td>
<td>5 to 10 mg/d</td>
<td>2.5-5 mg/d</td>
</tr>
<tr>
<td>Norethindrone</td>
<td>Micronor, NorOD</td>
<td>0.7-1.4 mg/d</td>
<td>0.35-0.7 mg/d</td>
</tr>
<tr>
<td>Drospirenone</td>
<td>Ovestro</td>
<td>0.5 mg/d</td>
<td>0.075-0.15</td>
</tr>
<tr>
<td>Norgestrel</td>
<td>Ovestro</td>
<td>0.3 mg/d</td>
<td></td>
</tr>
</tbody>
</table>

**Micronized progesterone Prometrium**

- 200 mg qhs,
- 100-200 mg qhs
- 100 mg q am + 200 mg q pm

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**Low Dose Estrogen**

**Benefits:**
- reduced risk for thrombosis
- effective for reducing hot flashes
- effective for genitourinary atrophy
- prevents loss of BMD
- reduced likelihood of bleeding

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**MHT: Nuts and Bolts**

**Potential Estrogen Side Effects**
- nausea, vomiting
- breast tenderness
- edema, fluid retention
- bloating
- headache

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**Low Dose MHT**

**Low-dose systemic ET:**
- 0.3 mg oral CE
- 0.5 mg oral micronized 17β-estradiol
- 0.014-0.025 mg 17β-estradiol patch
- 0.25 mg 1% estradiol gel

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*Obstet Gynecol* 2014;123(1):202
*Fertil Steril* 2014;101:905–15
Low Dose MHT

Low-dose progestin agent
- 1.5 mg oral MPA
- 0.1 mg oral norethindrone acetate
- 0.5 mg oral drospirenone
- 50-100 mg micronized progesterone

MHT: Nuts and Bolts
Potential Progestin Side Effects
- depression, fatigue
- anxiety, irritability
- weight gain
- breast tenderness
- headache
- reduction HDL, increase LDL

Switch to Conjugated Estrogen/Bazedoxifene
- Combination product
- FDA approved in 2013 for treatment of VMS and osteoporosis
- Bazedoxifene is a SERM
  - Preserves BMD, reduces vertebral and non-vertebral fractures
  - Increased risk of DVT
  - Reduces endometrial thickness

Switch to LNG-IUS
- Represents off-label use in U.S.
- Studied in Europe
- Both LNG-IUS (52 mg) and LNG-IUS (13.5 mg) effective but more data for the former
Postmenopausal Symptoms

<table>
<thead>
<tr>
<th>Yrs since menopause</th>
<th>Hot flashes %</th>
</tr>
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<tbody>
<tr>
<td>Less than 5 years</td>
<td>45</td>
</tr>
<tr>
<td>5 to 9 years</td>
<td>20</td>
</tr>
<tr>
<td>10 to 19 years</td>
<td>12</td>
</tr>
<tr>
<td>More than 20 years</td>
<td>8</td>
</tr>
</tbody>
</table>

Arch Intern Med 2008;168:940

Risk of CHD After 70 yrs
WHI: Use of MHT for severe VMS

<table>
<thead>
<tr>
<th>MHT regimen</th>
<th>HR of CHD</th>
</tr>
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<tbody>
<tr>
<td>CEE + 2.5 mg MPA</td>
<td>5.79 (CI 1.29-25.97)</td>
</tr>
<tr>
<td>CEE unopposed</td>
<td>4.34 (CI 1.43-13.14)</td>
</tr>
</tbody>
</table>

Manson et al, JAMA 2013;310:1353-68

Tapering MHT

- VMS recur in 50% and 1 of 10 develop severe and persistent sxs
- bone resorption accelerates, vaginal atrophy returns
- risks and benefits decline rapidly except for breast cancer
- “dose” taper vs “day” taper
- attempt q 6-12 months after 5 yr with E+P, 7 yr with unopposed E

Fertil Steril 2014;101:905-15, 916-21
JAMA 2002;287:2130

WHI Mortality Outcomes
18 Years Cumulative Follow Up

- observational F/U of 27,347 women participating in WHI
- CEE + MPA(n=8506) for 5.6 yrs (median) vs placebo (n=8102) or CEE alone (n=5310) vs placebo (n=5429) for 7.2 years (median)
- deaths: 1,088 during intervention phase, 6,401 during post-intervention F/U

Manson , JAMA 2017; :318(10):927-938
<table>
<thead>
<tr>
<th></th>
<th>ALL CAUSE MORTALITY HR (95% CI)</th>
<th>CVD MORTALITY HR (95% CI)</th>
<th>CANCER MORTALITY HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CEE + MPA vs PLACEBO</strong></td>
<td>1.02 (0.96-1.08)</td>
<td>1.03 (0.92-1.15)</td>
<td>1.06 (0.95-1.18)</td>
</tr>
<tr>
<td><strong>CEE alone vs PLACEBO</strong></td>
<td>0.94 (0.88-1.01)</td>
<td>0.94 (0.88-1.01)</td>
<td>0.99 (0.86-1.13)</td>
</tr>
</tbody>
</table>

"Opinion is like a pendulum and obeys the same law. If it goes past the centre of gravity on one side, it must go a like distance on the other; and it is only after a certain time that it finds its true point at which it can remain at rest."

Schopenhauer
ELITE TRIAL: E2 levels and CIMT progression

Estimates of CIMT rate by E2 Level:
Early Postmenopause

- 25th percentile: 6.8 pg/ml
- 50th percentile: 6.6 pg/ml
- 75th percentile: 6.2 pg/ml

Late Postmenopause

- 25th percentile: 10.4 pg/ml
- 50th percentile: 11.6 pg/ml
- 75th percentile: 13.6 pg/ml

Sriprasert et al, JCEM 2018 DOI: 10.1210/jc.2018-01600