Menopause

Caren Solomon, MD

A Sample Case
MF is a 50 yo woman who is wondering if she is menopausal. She had regular menses monthly until 2 years ago when she began to note cycle changes, with cycles sometimes shorter than 4 weeks, other times skipping cycles. Over the past 5 months she has had only 2 episodes of bleeding, most recently 2 months ago. She has had occasional hot flashes for the past 3 years.

Menopause
• Cessation of menses (no menses for 1 y+)
• Average age 51 y (earlier in smokers)
• Preceded by perimenopause
  Variable cycle length
  May be symptomatic despite ongoing menses
  FSH not useful in this setting

Menopausal Symptoms
• Hot flashes
  Up to 20% of women age 40-49
  Up to 75 % within 2 y of menopause
  Frequency varies with ethnicity, BMI, other factors
• Genitourinary symptoms
  Vaginal atrophy - dryness, pruritis, dyspareunia
  Urethral atrophy- stress incontinence, dysuria, urgency, frequency
• Mood changes
  Irritability, anxiety, depression, sleep disturbance

More on MF
At her initial visit, MF did not feel she needed any treatment. She returns one year later. She has not had menses for the past year. She has continued to have very bothersome hot flashes that interrupt her sleep. She is eager to reduce these symptoms, but understands that HRT is “dangerous.” What do you advise?
HRT and Menopausal Symptoms

- Significant reduction in hot flash frequency/severity
- Improvement in GU symptoms
- Short-term, lower dose HRT often adequate for symptom control

HRT and Quality of Life

- WHI: 16,608 postmenopausal women 50-79 y randomized to estrogen (CEE)/progestin (MPA)
- Quality of life measures collected at baseline, 1 y, and 3 y in a subgroup of 1511 women

Hays, NEJM, 2003

HRT

- Reasonable for symptoms in many women
- Long-term use (for chronic disease prevention) is another story

BEFORE WE HAD THE CLINICAL TRIAL DATA:

- Observational data suggested about a 50% reduction in MI risk among women who used postmenopausal estrogen therapy

- Physiologic studies indicated favorable metabolic effects of ERT/HRT including
  - ↓ LDL, ↑ HDL, ↓ lipoprotein(a), ↑ endothelium-dependent vasodilatation, ↑ insulin sensitivity…”
Heart and Estrogen/progestin Replacement Study (HERS)

- 2763 postmenopausal women with coronary heart disease, average age 67 years
- Randomized to combined estrogen/progestin (CEE 0.625 mg /Provera 2.5 mg) vs placebo
- Average follow-up 4.1 years

Hulley, JAMA, 1998

Longer Term HERS Results (HERS II)

- 2321 women (93% of surviving women) followed additional 2.7 years
- Open label HRT prescribed at discretion of personal physician
- NO apparent reduction in CHD events w/longer term HRT use (even when analyses restricted to adherent women)

Grady, JAMA, 2002

Potential explanations

- Adverse effects of progestin?
  - Known that medroxyprogesterone confers some adverse metabolic effects (eg blunts estrogen – induced rise in HDL)
- Women already had coronary disease

Women’s Health Initiative: HRT Trial

- ~27,500 women randomized to HRT or placebo with initial plan to continue for ~ 9 y
  - Intact uterus: Combined estrogen/progestin (Prempro) vs placebo
  - Prior hysterectomy: Estrogen (Premarin) alone vs placebo

BUT secondary prevention trials of estrogen alone not more promising ...

- Women with known CAD randomized to CEE w/or w/o medroxyprogesterone vs placebo; atherosclerosis progressed in all groups (no sig differences)
  Harrington, NEJM, 2000
- Estradiol alone did not reduce stroke risk in women with a history of cerebrovascular disease
  Viscosi, NEJM, 2001
WHI: Estrogen-Progestin versus Placebo

- 16,608 women with intact uterus (mean age 63 y)
- DSMB recommended stop trial 5/31/02 based on findings for invasive breast cancer and "global index" summarizing benefits and risks (CHD, breast CA, stroke, PE, endometrial CA, colorectal CA, hip fx, death)
- Mean 5.2 y follow up

HRT :CHD and Stroke

- **CHD** *(NEJM, 2003)*
  - Hazard ratio 1.24 (1.00-1.54) (or 0.97-1.60, adjusting for sequential testing)
  - at 1 year: hazard ratio 1.81 (1.09-3.01)

- **Stroke** *(JAMA, 2003)*
  - HR for stroke overall 1.31 (1.02-1.60)
  - for ischemic stroke 1.44 (1.09-1.90)

How can the clinical trial results be reconciled with observational studies?

- **Healthy User Effect**
  - Even prior to HRT use, subsequent HRT users (versus non-users) had:
    - Lower blood pressure
    - Lower BMI
    - Lower waist circumference
    - Higher physical activity levels
    - Higher SES
  - Rodstrom, BMJ, 1999

Observational Studies vs RCTs

<table>
<thead>
<tr>
<th>Observational</th>
<th>RCTs</th>
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<tbody>
<tr>
<td>Unopposed estrogen</td>
<td>Estrogen/progestin</td>
</tr>
<tr>
<td>Long-term use</td>
<td>Shorter-term use</td>
</tr>
<tr>
<td>Younger women</td>
<td>Older women</td>
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</table>

WHI: Estrogen alone

- 10,739 women aged 50-79 years with prior hysterectomy
- Followed on average 6.8 yrs
- Randomized to premarin 0.625 mg versus placebo
- Study stopped 2/04 based on increased risk of stroke in estrogen arm
WHI: Estrogen (CEE) Alone

Relative Risks for CVD:
- CHD: RR 0.91 (0.75-1.12) (376 cases)
- Stroke: RR 1.39 (1.10-1.77) (276 cases)
- All CVD*: RR 1.12 (1.01-1.24)

*CHD, stroke, DVT/PE

• What about younger menopausal women?

There is some evidence that age and time since menopause influence cardiovascular effects of HRT:
• Monkey data: Beneficial vascular effects of estrogen initiated soon after oophorectomy, but not later
• Re-analysis of Nurses’ Health Study data: Women initiating hormone therapy soon after menopause had significantly reduced CHD risk vs those initiating therapy 10 + y after menopause did not have significant reduction in CHD

However, data from WHI do not support significant differences in CV effects of HRT/ERT by age or time since menopause

- Relative risks for CHD by time since menopause
  < 10 y – 0.76 (0.50-1.16)
  10-19 y – 1.10 (0.84-1.45)
  20+ y – 1.28 (1.03-1.58) p trend 0.02 (did not meet criterion for significance)

-- Relative risks for CHD by age
  50-59 y – 0.93 (0.65-1.33)
  60-69 y – 0.98 (0.79-1.21)
  70-79 y – 1.25 (1.00-1.59) p trend 0.16

--RRs for stroke not significantly affected by time since menopause or age

Implications:
• Data are insufficient to support that postmenopausal hormones are cardioprotective in younger postmenopausal women, and they should not be prescribed for cardioprotection
• The data provide reassurance that short-term use for symptoms is still reasonable

Other Effects of HRT/ERT
WHI: HRT and Invasive Breast CA

- 349 cases overall
- Hazard ratio for HRT: 1.24 (1.01-1.54)
- Hazard ratios appeared higher in women who reported prior HRT use
- No significant interactions between HRT and other risk factors (eg age, race, parity, age at first birth, BMI, Gail model risk score)

*JAMA, 2003*

At diagnosis, the invasive cancers in the HRT (vs placebo) group were:
- Larger (mean 1.7 vs 1.5 cm, p = 0.04)
- More advanced (regional/metastatic 25.4% vs 16.0%, p = 0.04)

Abnormal mammograms more common in HRT group (At 1 y, 9.4% vs 5.4%, similar thereafter)

*JAMA, 2003*

WHI: HRT and Invasive Breast CA, Longer F/u

After total mean f/u of 11 y,
HR for invasive breast CA w/HRT 1.25 (1.1-1.5)
HR for breast CA death w/HRT 1.96 (1.0-4.0)

*(n=25 in HRT group vs n=12 in placebo group)*

*JAMA, 2010*

WHI: Other Effects of HRT

<table>
<thead>
<tr>
<th>Effect</th>
<th>RR (95% CI)</th>
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<tbody>
<tr>
<td>DVT/PE</td>
<td>2.13 (1.39-3.25)</td>
</tr>
<tr>
<td>Stress incontinence</td>
<td>1.87 (1.61-2.18)</td>
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<tr>
<td>Ovarian CA</td>
<td>1.58 (0.77-3.24)</td>
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<tr>
<td>Endometrial CA*</td>
<td>0.81 (0.48-1.36)</td>
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<tr>
<td>Mortality</td>
<td>0.98 (0.82-1.18)</td>
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<tr>
<td>Hip fx</td>
<td>0.66 (0.45-0.98)</td>
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<tr>
<td>Any fx</td>
<td>0.76 (0.69-0.85)</td>
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<tr>
<td>Colorectal CA</td>
<td>0.56 (0.38-0.81)</td>
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</tbody>
</table>

*endometrial biopsies more common in HRT group (23% vs 6%, p < 0.001)*


WHI: Estrogen Alone

<table>
<thead>
<tr>
<th>Event</th>
<th>HRT</th>
<th>ERT</th>
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</thead>
<tbody>
<tr>
<td>CHD events*</td>
<td>+7</td>
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</tr>
<tr>
<td>Strokes</td>
<td>+8</td>
<td>+12</td>
</tr>
<tr>
<td>PE</td>
<td>+8</td>
<td></td>
</tr>
<tr>
<td>Invasive breast CA</td>
<td>+8</td>
<td></td>
</tr>
<tr>
<td>Colorectal CA</td>
<td>-6</td>
<td></td>
</tr>
<tr>
<td>Hip fractures</td>
<td>-5</td>
<td>-6</td>
</tr>
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</table>

*WHI, JAMA, 2002; JAMA 2004*
Absolute changes in event rates attributable to HRT: Systematic review (for US Preventive Services Task Force Recommendations update)

• Per 10,000 person years:
  - CHD events
  - Strokes
  - DVT
  - PE
  - Invasive breast CA
  - Lung CA death
  - Gallbladder disease
  - Dementia
  - Urinary incontinence
  - Fractures

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<tr>
<td>PE</td>
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<tr>
<td>Invasive breast CA</td>
<td>+8</td>
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<td>Lung CA death</td>
<td>+5</td>
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<tr>
<td>Gallbladder disease</td>
<td>+20</td>
<td>+33</td>
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<tr>
<td>Dementia</td>
<td>+22</td>
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<tr>
<td>Urinary incontinence</td>
<td>+872</td>
<td>+1271</td>
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<tr>
<td>Fractures</td>
<td>-42</td>
<td>-56</td>
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</table>


HRT and Dementia

• Observational studies suggested reduced risk of Alzheimer’s disease in estrogen users
• Randomized trials of estrogen for treating AD showed no benefit
• WHI Memory Study (women ≥ 65 y):
  Risk for probable dementia increased with HRT or ERT (RR 1.76 (1.19-2.60))

HRT: What about skin aging?

Data lacking from randomized trials to prove benefit

What about other regimens/preparations?

• ??patch, other estrogens/progestins, “natural” estrogens and progesterone??
• There are no long-term data to support these

Micronized 17ß Estradiol and Atherosclerosis

• 226 postmenopausal women with CAD
• Randomized to 17ß estradiol alone (1 mg), 17ß estradiol/sequential MPA (5 mg 12 days per month), or placebo; LDL reduced to < 130 mg/dl with diet and lipid lowering therapy X mean 3.3 y of flu; 169 had evaluable angiograms pre and post
• Atherosclerosis progressed in the majority, and there were NO significant differences between groups in the change in the percent stenosis

NEJM, 2003

FDA: Label for Estrogen and Estrogen/Progestin Products

• NOT approved for the prevention of heart disease
• Boxed warning re increased risks for coronary disease, stroke, breast cancer
• Only clear indication: vasomotor sx
• May be used for genitourinary atrophy or prevention of osteoporosis but other therapies should be considered.
• What happens to associated risks after women stop postmenopausal hormone therapy?

Outcomes after stopping WHI intervention

• CEE/MPA
  – At mean 2.4 y f/u post-intervention, risks not significantly different for intervention versus placebo group for CV events, fractures, mortality
  – Cancer risk was still higher in intervention group (annualized rates (1.56 vs 1.26)) *Heiss et al, JAMA, 2008*

• CEE alone
  – Post-intervention, risks not significantly different for intervention versus placebo groups for CHD, breast cancer, total mortality, stroke, hip fracture
  – DVT risk was lower in the intervention group *LaCroix, JAMA, 2011*

Breast CA Incidence and Trends in HRT Use

Implications

• Don’t start HRT for reasons other than planned short term use for symptoms
• For women who are longer term users of HRT, appropriate to discuss WHI findings and encourage cessation

Findings from clinical trials of HRT cannot be generalized to:

• Younger women using OCPs
• Younger women using HRT s/p premature menopause

MF: History

MF is in good health.
PMH: Hypertension.
Meds: HCTZ 25 mg po qd
SH: No cigs. 1-2 glasses of wine daily.
FH: Mother had hip fx at age 72. No breast cancer.
PE: Normal, including breast and pelvic exam
Labs: Total cholesterol 220. LDL 150
HDL 40 TG 150. Glucose 99.
PAP normal. Mammogram negative.
HRT: When Might Short-Term Use be Reasonable?

- Indications
  - Symptoms (particularly moderate to severe vasomotor symptoms)
- Contraindications
  - History of breast cancer or premalignant breast lesion
  - H/o endometrial CA or unexplained vaginal bleeding
  - H/o DVT/PE
  - Liver disease
  - CHD

HRT: Side Effects

- Estrogen-nausea, headaches, bleeding
- Progestin-breast tenderness, irritability, depression
- Vary with dose, regimen
- If progestin side effects, possible option is to give less frequently (eg q 2-3 months) though ??endometrial safety

MF wants to try HRT. You start her on Premarin 0.3 mg daily, and MPA 5 mg 14 days/month.
She reports marked improvement in her hot flashes and that she is sleeping better.
6 months later she returns with a new concern. Her 49 year old sister was just diagnosed with breast cancer, and she is worried about continuing to use HRT.
What are alternatives to HRT?

Selective Estrogen Receptor Modulators

- Bind to estrogen receptors
- Estrogen-like effects at some tissues
- Estrogen-antagonist effects at other tissues

Multiple Outcomes of Raloxifene Evaluation (MORE) Study

- Multicenter double blind trial comparing raloxifene 60 mg qd, raloxifene 120 mg qd, vs placebo among 7705 postmenopausal women with osteoporosis
- Primary endpoints: vertebral fracture, bone density
- Secondary endpoints included non-vertebral fracture, markers of cardiovascular risk, uterine stimulation, breast cancer

Effects of Raloxifene (MORE)

- 30-50% decrease in risk of vertebral fractures
- 2-3% increase in bone density
- No significant effect on non-vertebral fractures
- Decrease in LDL but no rise in HDL
- 76% decrease in invasive breast CA risk
- No increase in endometrial CA risk
- Three-fold increase in risk of DVT/PE
- Does not help (and may cause) hot flashes
- Does not affect cognitive function

Additional Findings re Raloxifene

- STAR trial: Raloxifene as effective as tamoxifen in reducing breast cancer risk in high risk women; less likely than tamoxifen to cause thromboembolic events and cataracts
  *JAMA, 2006*
- RUTH trial: Raloxifene (versus placebo) did not reduce the risk of coronary events in women at high coronary disease risk; reduced the risk of breast cancer but increased risks of thromboembolic events and fatal stroke  *NEJM, 2006*

Phytoestrogens

- Estrogenic and anti-estrogenic effects
- Plant-derived; sources include soy, chickpeas, red clover, lentils, many beans
- Population-based data suggest lower rates of hot flashes, CVD, breast and other cancers in populations with phytoestrogen-rich diets
- RCTs limited

Phytoestrogens and Hot Flashes

- Review of 31 RCTs of phytoestrogens, including dietary soy isoflavones (eg beverage, powder); soy isoflavone supplements/extracts, red clover extracts, other phytoestrogens in menopausal women
- Quality was rated independently by 2 reviewers; most rated as fair or poor
- Majority (including the 2 trials rated "good quality") did not show sig benefit of phytoestrogens vs placebo
  *Nedrow, Arch Intern Med, 2006*

Other Proposed Non- Prescription Treatments

- Black Cohosh (eg Remifemin)
  - Conflicting data regarding benefit; May have estrogenic effects, hepatotoxicity
- Other agents that have appeared generally ineffective for hot flashes (based on limited data) include:
  - Vitamin E, DHEA, topical progesterone, Dong quai, evening primrose oil, ginseng, melatonin
  *Obstet Gynecol 2004; Arch Internal Med, 2006*

Current status of alternative/complementary therapies for menopausal symptoms:

- Benefits and risks uncertain
- Long-term well done trials needed

Lifestyle Approaches to Vasomotor Symptoms

- Lower temperature: cool room, fan, cold foods/beverages
- Avoid smoking
- Weight control
- Regular physical activity*
- Relaxation techniques**

*2 small RCTs: 1 showed improved QOL; **Limited data to suggest benefit
Other Possible Pharmacologic Treatments for Vasomotor Symptoms

• SSRIs/SNRI
  – eg paroxetine (12.5 to 25 mg daily), fluoxetine (20 mg daily), venlafaxine (37.5-75 mg daily), escitalopram (10-20 mg daily)*
  – Some but not all RCTs show significant reductions in frequency/severity of hot flashes vs placebo
  - Adverse effects: insomnia, reduced appetite, nausea, sexual dysfunction. (for venlafaxine-also increased blood pressure)
  - Not FDA approved for this indication

* In recent RCT (JAMA, 2011), escitalopram (vs placebo) resulted in mean 1.41 fewer hot flashes/d, reduced severity at 8 wks

Limited data support benefits of:

• Gabapentin
  – studies used 900 mg up to 2700 mg daily
  – Adverse effects: drowsiness, dizziness, fatigue, weight gain, nausea, dry mouth, constipation

• Progestational agents
  – eg Depomedroxyprogesterone 400 or 500 IM, megestrol 20-40 mg/d
  – Adverse effects: thromboembolism, breast tenderness, dizziness, insomnia; concern re possible breast cancer risk

• Clonidine
  – 0.05 to 0.15 mg daily
  – Adverse effects: dry mouth, constipation, insomnia, headache, drowsiness, dizziness; hypotension, rebound hypertension

These are NOT FDA approved for vasomotor symptoms

Limited data support benefits of:

Other Approaches to Symptoms of Vaginal Atrophy

• Topical estrogen (CEE; applicator 1.25 mg)

• Vaginal estradiol ring (Estring 2 mg)

• Lubricants (eg Replens)

Other Approaches To Reduce Fracture Risk

• Adequate calcium 1200 mg daily

• Vitamin D 800 IU+ daily

• Weight bearing exercise

• Avoid cigarettes and excess EtOH

• Assess risk factors to identify women at increased risk; Evaluate bone density

• Medications where indicated: Alendronate, Risedronate, Ibandronate, Raloxifene, parathyroid hormone (Forteo)

Other Approaches To Reduce CHD Risk

• Lifestyle: Avoid cigarettes and excessive EtOH; exercise; control weight; healthy diet

• Assess and treat cardiac risk factors (lipids, bp, diabetes, cigs…)

Summary

• Still reasonable to use HRT (ERT) short-term for symptoms in absence of contraindications (though local therapy should be considered for genitourinary atrophy).

• HRT (ERT) should not be used for the prevention of heart disease or other chronic diseases

• Alternative approaches may be used to reduce vasomotor symptoms, although data currently are limited to support various alternative therapies.

• Other proven therapies are appropriate to prevent/treat osteoporosis, and to reduce the risk of CHD.
QUESTION 1
Which of the following was reported in the WHI with use of combined estrogen/progestin in postmenopausal women?
1) About 2 fold increase in breast cancer risk
2) About 25% increase in risk of coronary events
3) About 25% reduction in urinary incontinence
4) No reduction in fracture risk

QUESTION 2
Raloxifene treatment results in all of the following except:
1) 30 to 50% reduction in vertebral fracture risk
2) No increase in risk of endometrial hyperplasia
3) 25% reduction in hip fracture risk
4) More than 2-fold increase in risk of DVT/PE