Menopause and the Impact of Estrogens and Vitamin D on Women’s Health

Rebecca D Jackson MD
Professor and Associate Dean
March 10, 2012
A Picture of Women’s Health

- Population
  - 151.9M women

- On average, women live longer than men and therefore experience more chronic conditions throughout their lifetime

- Health Status
  - 14% state they have fair or poor health
  - 13% report limitation in usual activities due to health

- Risk factors
  - 18% smoke
  - 62% overweight
  - 33% have hypertension
  - >70% are vitamin D insufficient
Top Ten Women’s Health Issues

- Bone and Joint Health
  - Osteoporosis, arthritis, autoimmune disease
- Heart Health
  - Coronary heart disease, CHF, atrial fibrillation
- Diabetes
- Breast Health
  - Fibrocystic breast disease, breast feeding, breast cancer
- Reproductive Health
  - Pregnancy, infertility, menopausal symptoms, pelvic pain, STD, cancer
- Mental Health
  - Depression, anxiety, stress, domestic violence
- Colorectal Health
  - Irritable bowel disease, colon cancer
- Eye and Ear Health
  - Macular degeneration, hearing loss
- Skin Health
  - Skin cancers, melanoma
- Oral Health
Postmenopausal women’s health

• Average age of menopause in US is 50-51 yrs
  – By age 55, 85% of women will have transitioned into menopause
• 50 y.o woman today can expect to spend 1/3 lifespan after menopause
• Changes in estrogen status modulates incidence of many chronic diseases
  • Cause major limitations in activities daily living for 1 in 10 American women
  • Cause significant racial/ethnic health disparities
  • Account for about 75% of annual U.S. medical care costs

What can a woman do to reduce her risks of health conditions after the menopause?

• Is there any role for postmenopausal HT?
• Could Vitamin D insufficiency/deficiency be contributing to this epidemic of chronic disease?
Case Study: 51 y.o white woman with menopausal symptoms

- Transitioned through menopause in last 18 months
- Vasomotor symptoms started 2 years prior to menopause but worsening
  - Hot flashes (> 20/day); irritability; significant sleep disturbance; and vaginal dryness
  - Unresponsive to layering clothes, using fan and avoiding caffeine
- Past history: modest hyperlipidemia (low fat diet) and hypothyroidism
- Family history of CHD in mother; no breast cancer
- Exam: Weight 63.5 kg; Height 165.1 cm.
  - Otherwise negative –modest vaginal dryness and normal breast exam

*Is she a candidate for postmenopausal HT?*
Vasomotor symptoms and menopause

- Constellation of symptoms
  - Hot flashes, night sweats, mood swings, sleep disturbance (including nocturnal awakenings)

- 75% of menopausal women are symptomatic
  - 14-51% of women prior to menopause; 35-50% during the transition; 30-80% after menopause
  - 15-20% severe enough to ↓QoL

- Mean duration 5.2 years
  - 12-15% persist into 60s; 9% after age 70

- Risk Factors
  - Differs by race and ethnicity
    - Most common in African Americans; less frequent Asian women
    - More common with obesity, trait anxiety and smoking
PHT and Vasomotor Symptoms

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<th>E+P vs. Placebo</th>
<th>CEE vs. Placebo</th>
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<td>Sample size (n)</td>
<td>1072 vs 974</td>
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<tr>
<td>Hot flashes</td>
<td>76.7% vs 51.7%</td>
<td>85.7% vs 57.7%</td>
<td>p&lt;.001</td>
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<td>Night sweats</td>
<td>71.0% vs 52.8%</td>
<td>77.6% vs 57.4%</td>
<td>p&lt;.001</td>
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- Synthetic conjugated estrogens (0.3 mg) effective at decreasing nocturnal awakening flushes
- Transdermal estrogens may be more effective
  - Square-waved pharmacokinetics-rapid attainment stable levels
  - 41% women decrease hot flashes by > 75% at dose of 14 mcg-equivalent to E2 10-20 pg/ml; 85% at 0.02 mg

*Ob Gyn 2012;119:78  
Clin Obstet Gyn 2008;51:539*
Estrogen Therapy Has Other Benefits and Risks

Hip and Clinical Fractures in E+P and E-alone

**E+P Trial**
- HIP: 33%
- Clinical Vertebral: 34%

**E-alone Trial**
- HIP: 39%
- Clinical Vertebral: 38%

JAMA 2002; 288:321-33
JAMA 2004; 291:1701-12
Estrogen Therapy Has Other Benefits and Risks

Incident Diabetes in E+P and E-alone

- 3.5% (212/7352) of women receiving E+P reported treated diabetes compared to 4.2% (252/7352) of women receiving placebo
- 8.3% (397/4787) of women on E alone reported diabetes compared to 9.3% (455/4887) of women on placebo

- Both glucose and insulin reduced after one year on estrogen
- Mechanism may be related to estrogen effects on SHBG
Estrogen Therapy Has Other Benefits and Risks

Coronary Heart Disease and Stroke

**E+P Trial**
n=16,608; 5.6 yrs

- CHD: 24% (ns)
- Strokes: 31%

**E-alone Trial**
n=10,739; 6.8 yrs

- CHD: No effect
- Strokes: 39%

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JAMA. 2003; 289:2673-84.
Arch Intern Med 2006; 166:357-65
Estrogen Therapy Has Other Benefits and Risks

Venous Thromboembolism in E+P and E-alone

E+P Trial
n=16,608; 5.6 yrs

- PE: 113% increase
- DVT: 95% increase

E-alone Trial
n=10,739; 6.8 yrs

- PE: 34% (ns)
- DVT: 47%

JAMA 2004; 292:1573-80
JAMA 2004; 291:1701-12
Estrogen Therapy Has Other Benefits and Risks

Invasive Breast Cancer in E+P and E-alone

- **E+P**:
  - Invasive Breast Cancer
  - 24% increase

- **E-alone**:
  - Invasive Breast Cancer
  - 23% (ns) increase

References:
- JAMA 2003; 289:3243-53
- JAMA 2004; 291:1701-12
Estrogen Therapy Has Other Benefits and Risks: Probable Dementia

Pooled: E-Alone and E + P

- E-Alone or E + P
- Placebo

HR, 1.76
95% CI, 1.19-2.60
P = 0.005

Years Since Randomization

JAMA 2004; 291:2947-58
Does Timing Make A Difference? Estrogen and CHD risk by age groups

No increased CHD risk associated with E-alone in young women

*Arch Intern Med* 2006; 166:357-65
E-alone May Decrease Coronary Artery Calcification in Young Women

* Risk with CEE compared to placebo, adjusted for age, race/ethnicity, smoking, HTN, high chol, diabetes, family history of MI, BMI.
† Restricted to participants with ≥80% adherence to CEE or placebo for ≥5 years.
Stages of Atherosclerosis

Figure 2. Estrogen: beneficial and thrombogenic effects
From Mendelshon & Karas 2005 [20]
Stages of Atherosclerosis

- **Initiation** (endothelium, fatty streaks)
  - Younger adult
  - Estrogen may delay

- **Progression** (raised lesions)
  - Middle age
  - Estrogen has no effect

- **Complicated Lesions** (erosion or rupture of unstable plaque)
  - Older age
  - Estrogen triggers events
Timing Hypothesis and Risk for CHD

- Risk for CVA is not affected by timing
  - HR CVA 1.52 (1.11-2.08) in women < 55 yrs

- CVD mortality
  - Meta-analysis 16,000 women in 19 RCT (mean age 55 yrs)
  - RR of mortality 0.73 (0.52-0.96)

**KEEPS and ELITE should define HT CVD risks and benefits in younger women**
Timing Hypothesis and Breast Cancer Risk

Unlike CHD, early initiation of HT is associated with a greater risk.

**JNCI 2011;103:296-305**
Estrogen, Cognition and Risk for Cognitive Decline: A Window of Opportunity

Early initiation of HT may also be associated with no risk for cognition decline

Brain Res 2011;1379:188-198
Predicting Risk: Biomarker Interactions in HT Trials

Risk of CHD (OR)

- LDL Cholesterol (mg/dl)
  - <126
  - 126-155
  - >155

- C-reactive protein (mg/L)
  - <1.30
  - 1.30-3.59
  - >3.59

* interaction p< 0.01
* interaction p< 0.04

E + P Trial

E Alone Trial

NEJM 2003;349:523-34
Arch Intern Med 2006;166:1-9
Predicting Risk: Pharmacogenomics for Venous Thrombosis in E+P Trial

Similar finding not noted for CEE

JAMA 2004; 292:1573-80
Reducing Risk: All Estrogens May Not Be Equal

Transdermal estrogens may be associated with less risk for stroke

- Oral (high dose): 1.48 (1.16, 1.90)
- Oral (low dose): 1.25 (1.12, 1.40)
- Oral: 1.28 (1.15, 1.42)
- Transdermal (> 50 mcg): 1.89 (1.15, 3.11)
- Transdermal (< 50 mcg): 0.81 (0.62, 1.05)
- Transdermal: 0.95 (0.75, 1.20)

Overall HR Transdermal vs. Oral E2: 0.74 (0.58, 0.96)

*Lancet Neurol 2012;11:82-91*
Case study

- Our subject was placed on low dose transdermal estradiol (0.025 mg) plus micronized progestin daily
  - Symptoms lessened but were still persistent-doses increased with prompt resolution of symptoms

- Lab evaluation normal except:
  - Elevated LDL 150 mg/dl
  - Low 25(OH) vitamin D 14 ng/ml

- After 3 yrs, given that she is at higher risk for adverse risk for CVD effects due to the elevated LDL, she discontinued her HT
  - Hot flashes subsequently return

- She is now interested in alternatives for:
  - Management of vasomotor symptoms
    - Role for bioidentical hormones
    - Alternative treatments for menopausal symptoms
  - Prevention of chronic diseases of aging in women
    - Role for vitamin D on non-skeletal aspects of women’s health
Women more likely to have hot flashes after stopping if:
- had symptoms at baseline: OR = 5.4 (95% CI = 4.5-6.4)
- were randomized to E+P: OR = 5.8 (95% CI = 4.9-6.9)
- were current smokers: OR = 1.5 (1.2-2.0)
Effect of E+P Discontinuation on Risk for CHD

Coronary Heart Disease

Overall

HR = 1.11
(0.94 - 1.31)

After Intervention

HR = 0.95
(0.73 - 1.26)

No. at Risk
- CEE + MPA: 8506, 8299, 8112, 7837, 3966
- Placebo: 8102, 7926, 7747, 7496, 3689
Effect of E+P Discontinuation on Risk for CVA

HR = 1.28
(1.05 - 1.58)

HR = 1.16
(0.83 - 1.61)

No. at Risk
CEE + MPA 8508 8328 8136 7888 7568 3974
Placebo 8102 7939 7788 7622 7308

Overall
Stroke
After Intervention
Effect of E+P Discontinuation on Risk for Breast Cancer

Invasive Breast Cancer

Overall

HR = 1.27
(1.06 - 1.51)

After Intervention

HR = 1.27
(0.91 - 2.78)

No. at Risk
CEE + MPA
Placebo

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Effects of Discontinuation of E-alone

Coronary heart disease

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Stroke

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Pulmonary embolism

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Invasive breast cancer

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Bioidentical Hormone Therapy

- Contain 2-3 plant-based or chemically converted estrogens
  - Tri-estrogen (8:1:1 estriol:estrone:estradiol)
  - Bi-estrogen (8:2 or 9:1 estriol: estradiol)
  - Most of estrogenic activity is 17β estradiol

- Progestin usually micronized progestin

- May include testosterone

- Lack of efficacy or safety data from RCT
  - No RCT supporting enhanced safety (E2 may have lower breast cancer risk)
  - 34% failed quality testing and 90% potency testing
  - Salivary testing to individualize dose-poor reproducibility and large intra-individual variability

Bioidentical HT and Menopausal Symptoms

**Graph:**
- Proportion with moderate to severe symptoms over baseline and 3 to 6 months.
- Emotional Lability (n=57): Baseline 53%, 3 to 6 Months 28%, *p<0.01*
- Irritability (n=57): Baseline 58%, 3 to 6 Months 33%, *p<0.01*
- Anxiety (n=55): Baseline 49%, 3 to 6 Months 27%, *p=0.01*
- Night Sweats (n=56): Baseline 46%, 3 to 6 Months 32%, p=0.09
- Hot Flashes (n=60): Baseline 48%, 3 to 6 Months 42%, p=0.50

**Notes:**
- *p<0.01 indicates statistically significant difference.

**Source:** BMC Women’s Health 2011;11:27
Non-Hormonal Treatment of Hot Flashes

- Clonidine
  - Meta-analysis demonstrated <50% RCT showed reduction in vasomotor sx

- SSRI/SNRI
  - Paroxetine and venlafaxine reduced hot flashes by 50% in RCT - more effective than sertraline and fluoxetine
  - Effective in women with concurrent mood disturbance
  - Desvenlafaxine effective within 1 week

- Gabapentin
  - 900 mg/d 54% reduction (vs 31% placebo) for hot flash composite score
  - 2400 mg/d comparable to estrogen (more AE)

- CAM
  - Phytoestrogens and Black cohosh-RCT and meta-analysis showed they are ineffective relative to placebo
  - No conclusive benefit of accupuncture or Yoga
Vitamin D May Modulate Many Common Women’s Health Conditions

Vitamin D: Biologic Functions

Vitamin D → 25(OH)D → Prostate Gland, Breast, Colon, Lung, Keratinocytes

1,25(OH)₂D → Regulation of Cell Growth and Differentiation (cancer prevention)

Vitamin D → 25(OH)D → 1,25(OH)₂D → Prostate Gland, Breast, Colon, Lung, Keratinocytes

1,25(OH)₂D → Calcium Homeostasis, Muscle Health, Bone Health

1,25(OH)₂D → Blood Pressure Regulation, Cardiovascular Health

1,25(OH)₂D → Immunomodulation, prevention of autoimmune diseases

Vitamin D and Risk for CVD

<table>
<thead>
<tr>
<th>25 (OH) D Level</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 15 ng/mL</td>
<td>1 (Referent)</td>
</tr>
<tr>
<td>10 - &lt; 15 ng/mL</td>
<td>1.53 (1.05 - 3.08)</td>
</tr>
<tr>
<td>&lt; 10 ng/mL</td>
<td>1.80 (1.00 - 2.36)</td>
</tr>
</tbody>
</table>

Vitamin D Deficiency

- ↑ PTH
- ↑ Insulin Resistance
- ↑ Pancreatic Beta Cell Dysfunction
- ↑ Inflammation
- ↑ RAAS
- ↑ Hypertension and Hypertrophy
- ↑ Diabetes and Metabolic Syndrome
- ↑ Atherosclerosis
- ↑ Adverse Cardiovascular Events
Diabetes and Vitamin D

**Type I DM and Vit D in Women**

- Patients
- Controls

**CaD and Risk for Type II DM in Women**

- Ca <600
- Ca 600-1200
- Ca >1200

Diabetologia, 2006; 49:2847

Diabetes Care, 2006; 29:650
Vitamin D and Breast Cancer

- Vitamin D is involved in
  - anti-proliferation
  - terminal differentiation
  - cell-cycle protein regulation
    - P27, p21, p17, ?p53

- Difference in risk of breast cancer not related to vitamin D
Depression and Vitamin D

- Inconclusive data regarding D status and depression
  - 25 (OH) vitamin D inversely correlated with Beck Depression Index (cognitive-affective scale)
  - inversely correlated with CES-D

![Vitamin D Treatment and Depression](image)
Vitamin D Repletion

- No one right way to increase vitamin D
  - 50,000-100,000 units for 8-12 weeks in severe vit D deficiency
  - Very high dose associated with greater risk for fracture
  - Vitamin D increases by 1 ng/ml for every 100 units
Genomics Predict Likelihood for Being Vitamin D Insufficient

Vitamin D Insufficiency According to Quartile of Genotype Score for Vitamin D Transport

$OR$ for vit D $<$ 75 nmol

$p = 2.3 \times 10^{-48}$
Case Study

- Short-term use of SSRI improved sleep and reduction of hot flashes
  - Tapered after 6 months and did well after 3-4 months of minor symptoms

- Correct vitamin D deficiency
  - Vitamin D intake increased to 1000 units daily
  - Repeat levels still 20 mg/ml
  - Vitamin D genotyping showed GC score 3-D dose increased to 2000 units

- Correct hyperlipidemia
  - Diet and statin

- Health monitoring
  - DXA performed-normal BMD
    - Ensure 1200-1500 mg total daily calcium and resistance training
Summary

- Menopause is associated with an increased risk for a number of chronic health conditions

- Hormone therapy (estrogen with or without a progestin) is effective for managing menopausal symptoms
  - Lowest dose for the shortest period time should be prescribed
  - Transdermal estrogens may offer lower risk for CVA
  - Although the timing hypothesis is biologically plausible, changes in prescribing behavior should await results of RCTs (ELITE and KEEPS)

- When HT is not appropriate, SSRI/SNRIIs are reasonable alternatives

- When HT is stopped, risks diminish (except for E+P where breast cancer and CVA risk persist)

- Vitamin D may have effect on reducing risk for chronic diseases associated with menopause