Hormone Replacement Therapy
Where are we in 2011

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Conflict of Interest

- Financial conflict – none
- Research conflict
  - Funded research: Kronos Early Estrogen Progestin Study (KEEPS)
- Off-label drug use
  - none

Problems in Peri-Postmenopausal Women

- Abnormal uterine bleeding
- Vasomotor symptoms
- Genital atrophy
- Decrease in skin collagen
- Rapid bone loss
- Increase in coronary heart disease
- Increase in Alzheimer’s disease

Today’s Random Medical News
Benefits of Menopausal HT: What We Thought We Knew before WHI

- Prevents or abolishes hot flashes
- Prevents or improves genital atrophy
- Prevents or slows bone loss
- Reduces risk of cardiovascular disease
- Improves cerebral blood flow
- May reduce risk of Alzheimer’s disease
- May reduce risk of colon cancer
- Improves overall quality of life

Risks of Menopausal HT: What We Thought We Knew before WHI

- Breast cancer, ?RR 1.1-1.5
- Endometrial cancer, RR 4.0-11.0 (unopposed estrogen)
- Venous thromboembolism
  - 2 additional cases per 10,000 women
  - Low mortality rate of 1%
- Gall bladder disease

Menopausal HT/CVD Why we thought we “knew” it

- Observational studies (e.g. Nurse’s Health Study) suggested ET/HT use associated with 50% reduction in CHD (Mikkola et al., Ann Med, 2004)
- The NIH Lipid Research Clinics Trial Reported that ET normalized CHD risk for women with a CHD history (Bush et al., Circulation, 1987)
- Angiographic studies suggested that women with the Most Severe CHD derived the Most Benefit from ET/HT (Sullivan et al, Arch Int Med, 1990)

Publication of Clinical Trials in July, 2002

- Heart & Estrogen/Progestin Replacement Study (HERS) II
  - JAMA 2002;288:49-66 (July 3)
- Women’s Health Initiative (WHI)
  - JAMA 2002;288:321-33 (July 17)
HERS: Conclusion

- HRT should not be used to reduce the risk of further CHD events in postmenopausal women with already established CHD.

Number of women needing to take HT for one extra adverse or protective event per year:

- 1100 for myocardial infarction
- 1200 for stroke
- 600 for serious thromboembolism
- 1300 for invasive breast cancer
- 2000 to prevent a hip fracture
- 1700 to prevent a colon cancer

The WHI Estrogen-Alone Trial
(JAMA 2004:291:1701-1712)

- Only strokes and hip fractures were significantly impacted in 10,739 postmenopausal women aged 50-79 over 6.8 years: There was an absolute excess risk of 12 additional strokes and 6 fewer hip fractures per 10,000 person-years.

- A possible reduction in breast cancer risk, inconsistent with other studies, “requires further investigation.”

- Preliminary analyses suggest lower hazard ratios (for CVD) in women aged 50 to 59 years.
Observations about the WHI Study

• 97.5% of subjects had no adverse events

• Were subjects not as healthy as thought at entry

Reconciling observational studies and clinical trials

What’s different?

• Methodological explanations:
  – Confounding
    • intrinsic biases of observational studies
  – Incomplete capture of early clinical events
    • attenuation of risk

• Biological explanations
  – Clinical characteristics of the populations
    • timing of initiation of treatment
  – Characteristics of hormone therapy
    • type and dosage

WHI vs. Observational studies

Manson JE, et al. 2006; 13:139
WHI vs. Observational studies
Cardiovascular Disease

• Biological explanations
  – Clinical characteristics of the populations
    • healthier users
    • timing of initiation of treatment
  – Characteristics of hormone therapy
    • type and dosage

WHI HRT Study: Patient Characteristics

- Mean age 63
- BMI 28.5 kg/m²

Hormone Use Prior to Study Entry

<table>
<thead>
<tr>
<th>Age</th>
<th>Never User 74%</th>
<th>Past User 20%</th>
<th>Current User 6%</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>N=5522</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>N=7510</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-79</td>
<td>N=3576</td>
<td></td>
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</tbody>
</table>

The Effect of Body Mass on the Risk of CHD: Putting the WHI Results in Perspective

- Median baseline levels of CRP and interleukin-6 (IL-6) were significantly higher in 304 women with incident CHD than in matched controls
- Both inflammatory markers were associated with a 2-fold increase in odds for CHD events
- HT use increased CRP but not IL-6
- Use or non-use of HRT had less importance as a predictor of cardiovascular risk than did baseline levels of either CRP or IL-6

Inflammatory Biomarkers, HT, and Coronary Heart Disease (CHD) in the WHI
(Pradhan et al., JAMA 2002;288:980)
**Metalloproteinase and Gelatinolytic Activity of Human Coronary Artery Atherosclerotic Plaques**

From Galis et al, J Clin Invest, 1994

**Plasma Expression of Matrix Metalloproteinase-9 (MMP-9) and Gelatinolytic Activity of Postmenopausal Women (Av. Age 66 yrs) Treated Either with Placebo or HT (0.625 mg CEE and 2.5 mg MPA per day)**

Modified from Zanger et al, J Am Coll Cardiol, 2000

**Effect of Statin Treatment on Plasma MMP-9 of Patients with Coronary Heart Disease**

From Koh et al, Cor Artery Dis, 2004
Estrogen Effects on the Natural History of Atherosclerosis

Estrogen Effects in Atherogenesis
↓LDL oxidation ⇒ ↓LDL atherogenicity
↓LDL binding/accum ⇒ ↓lesion progression
↓CAMs ⇒ ↓monocyte adhesion/↓macrophage accumulation
↓SMC proliferation ⇒ ↓lesion progression
↑Endothelial function ⇒ ↑vasodilation

Benefits of estrogen on atherosclerosis prevention

Estrogen Effects in Established Plaques
↑Inflammation ⇒ ↑PQ instability
↑Lesion progression
↑MMP expression ⇒ ↑PQ instability/rupture
↑Neovascularization ⇒ ↑PQ hemorrhage

Loss of Estrogen Benefits
↓Expression of estrogen receptors
↓Vascular responsivity

Adverse effects of estrogen on atherosclerosis/CHD

Patient Characteristics: Age

- 27 Hydroxycholesterol
- “SERM”
  - Competitive inhibitor of the estrogen receptor
  - Accumulates in vessels in low estrogenic state


Patient Characteristics: Age

- Grodstein et al. J Womens Health 2006
  - Nurse’s Health Study: evaluating time from menopause – women near menopause reduced CV risk (RR 0.66 CI: 0.54-0.80)
- Manson et al. NEJM 2007
  - WHI: coronary calcium – women 50-59, coronary calcium score lower in women on ET vs. placebo (OR 0.69 CI: 0.48-0.98)

HYPOTHETICAL RATIONALE FOR KEEPS

Early Intervention (KEEPS) No MHT Late Intervention (HERS, WHI)

HYPOTHETICAL RATIONALE FOR KEEPS

35-45 45-55 55-65 >65

Years Post-menopause
Risk of Invasive Breast Cancer by Duration of ET Use Among All Postmenopausal Women Who Had Undergone Hysterectomy and Those With ER+/PR+ Cancers Only*

<table>
<thead>
<tr>
<th>Duration (y)</th>
<th>All</th>
<th>Screened/Current</th>
<th>All</th>
<th>Screened/Current</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>Risk</td>
<td>Cases</td>
<td>Risk</td>
<td>Cases</td>
</tr>
<tr>
<td>Current</td>
<td>275</td>
<td>1.00</td>
<td>124</td>
<td>1.00</td>
</tr>
<tr>
<td>&lt;5</td>
<td>168</td>
<td>0.66(0.49-1.03)</td>
<td>54</td>
<td>0.66(0.25-1.70)</td>
</tr>
<tr>
<td>5-9</td>
<td>130</td>
<td>0.52(0.25-1.09)</td>
<td>45</td>
<td>0.52(0.25-1.09)</td>
</tr>
<tr>
<td>10-14</td>
<td>100</td>
<td>1.35(0.57-3.29)</td>
<td>44</td>
<td>1.35(0.57-3.29)</td>
</tr>
<tr>
<td>&gt;15</td>
<td>84</td>
<td>1.50(0.82-2.75)</td>
<td>38</td>
<td>1.50(0.82-2.75)</td>
</tr>
</tbody>
</table>

*Cases are reported as number of cases; data are reported as odds ratios (95% CI), controlled for age (and sex), age at menopause (continuous), oral hormone therapy (continuous), BMI (continuous), history of breast cancer (age 40-49 in first degree relative), smoking status (current vs. non-smoker), and menopausal status (current vs. postmenopause). Odds ratios adjusted for all other variables.


Estrogen and Breast Cancer

Breast Cancer Reanalysis

Current/recent use HT: 2.3%/year
Delay in menopause: 2.8%/year

Breast Cancer Impact of change in HT use

- From 2001-2 to 2005-6
- reductions up to 20%
- strongest for women 50-60 years old
- strongest for ER+/PR+ cancers
- accelerated growth with attendant earlier detection
- by 3-5 years after stopping – no increased risk

Verkooijen HM, et al, 2009 Maturitas

Breast Cancer Risk Factors

- Starting close to menopause
- Low body weight
- High mammographic breast density
- 2 years after stopping HRT – risk equivalent to never users
Breast Cancer
Risk Factors

• Was there truly a “protective” effect of estrogen in the E-only arm – WHI?

• Estrogen
  – Role of estrogen deprivation
    • Whether natural or via anti-estrogens (tamoxifen/aromatase inhibitors)
  – Estrogen as a pro-apoptotic

Breast Cancer
The ‘Gap’ Hypothesis

• Starting estrogen remote from menopause decreases risk while treatment within 2 years increases breast cancer risk

• The ‘gap hypothesis’ and the ‘timing hypothesis’ are thus in conflict

The “Menopausal Syndrome”

• Almost all signs and symptoms result from decreased circulating estrogen

• Symptoms: Hot flushes, paresthesias, cold hands and feet, headache, vertigo, irritability, anxiety, nervousness, depression, fatigue, weight gain, insomnia, night sweats, forgetfulness

• Signs: Depressed menstrual bleeding, relocation of fat deposits, decreased skin elasticity, osteoporosis in 25%, genital tract atrophy

• Some signs and symptoms may begin before menopause - and last long after

Symptoms and the Menopausal Transition

• Hot flushes and night sweats

• Stiff or painful joints

• Difficulty sleeping

• Poor/fair self-rated health

• Depression

• Headache

**Estrogen and the Brain**

- **Direct effects**
  - Enhances synaptic plasticity, neurite growth, hippocampal neurogenesis and long-term potentiation (memory)
  - Protects against apoptosis and neural injury
  - Stimulates acetylcholine (memory), serotonin, noradrenaline
  - Decrease deposition of β-amyloid
  - Promotes morphological and electrophysiological correlates of learning and memory

- **Indirect effects**
  - Vasculature
  - Immune system

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**Estrogen and the Brain**

- **Natural menopause**
  - Does not seem to be associated with decreased memory

- **Surgical menopause**
  - Estrogen administration improves episodic memory

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**Estrogen and the Brain**

- **Alzheimer Disease**
  - Early and consistent symptom – loss of episodic memory (failing to recall appointments and events)
  - In the laboratory: estrogen reduces the formation of β-amyloid formation and diminishes hyperphosphorylation of tau protein

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**Estrogen and the Brain**

- Observational studies suggest protection
- Meta-analyses suggest risk reduction of approximately 1/3
- Contradicted by the WHIMS trial (ages 65-79)
  - Risk of dementia increased two-fold with combined HRT
  - Impact noted within a few years, suggesting impact primarily on the vasculature
  - Past history of use associated with lowered incident risk of dementia (including Alzheimer Disease)
- Initiation in older women WITH disease is no beneficial
HRT/ET and Neuroprotection

- **WHIMS** (Shumaker et al., JAMA 2003;289:2651-62; Rapp et al., JAMA 2003;289:2663-72)
  - increased cognitive impairment and dementia in the oldest population

- Observational/animal studies
  - role of timing, type
  - improvement in certain skills (memory and verbal fluency)
  - impact of smoking

HRT/ET and Neuroprotection

- Impact of timing
  - Suzuki et al. PNAS 2007
  - Mouse model
  - Estradiol exerted a profound neuroprotective action when administered immediately upon ovariectomy (attenuating proinflammatory cytokines)
  - Benefit lost is given remote from ovariectomy

Estrogen, Menopause, and the Aging Brain: How basic neuroscience can inform hormone therapy in women

- Disconnect with WHI and WHIMS
  - Animal and pre-clinical data supporting benefit
  - Timing of treatment
  - Administration formulations

- HT/ET at the menopausal transition and afterward could have beneficial effects on neurological symptoms

Morrison, Brinton, Schmidt, Gore: J Neuroscience: 26:10332

Estradiol and Depressive Disorders (Soares et al., Arch Gen Psychiatry 2001;58:529)

- 50 perimenopausal women aged 40-55 with irregular menstrual periods and FSH > 25 IU/L meeting criteria for major depressive, dysthymic, or minor depressive disorder by DSM-IV blindly randomized to transdermal estradiol (0.1 mg) or placebo for 12 wks
- Remission of depression observed in 17 of 25 (68%) on E₂ and 5% on placebo
- Regardless of DSM-IV diagnosis, subjects responded similarly to E₂
Route of Estrogen Therapy

- Blood pressure – impaired endothelial function
  - Small impact of oral; no impact for transdermal
  - Beneficial impact suggested with estradiol and drospirenone

- Metabolic syndrome – menopause diabetogenic
  - Reduced DM and insulin resistance with estrogen
  - Advantage of natural progesterone/non-androgenic progestins (drospirenone, dydrogesterone)

Route of Estrogen Therapy

- CVD
  - CRP – increased with oral and not transdermal; worsening affect with MPA
  - “first pass” effect on the liver (lipids)
  - Endothelial function - improved with both (inhibited by MPA and NET)
  - MMP-9 – increased by oral and not by transdermal

- Thromboembolic events
  - Increased risk with oral
  - No increase with transdermal

Route of Estrogen Therapy

- Neuroprotection
  - No differences available between oral and transdermal

- Breast cancer
  - No differences available between oral and transdermal
  - Increased risk with combined progestational agent

Route of Estrogen Therapy

- Breast cancer
  - RR 1.1-1.5 (all forms of estrogen) - 8 add’l/10,000 women
  - Increased with progestogen (especially continuous)
  - No increased risk with estrogen > 2 years post-menopause

- Endometrial cancer
  - R 4.0-11.0 (unopposed estrogen)
  - Reduced by progestin

- Venous Thromboembolism (oral therapy)
  - 2 additional cases per 10,000
  - Mortality low, 1%

- Gall bladder disease

- CVD
  - Increased risk with existing disease and remote from menopause

Risks of Menopausal HT: What We Think We Know Now

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- CVD
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Current “Truths” Regarding Menopausal HT and CVD

- The public is largely unaware that CVD is the primary cause of mortality in women.
- Women should not take estrogen to prevent CVD.
- Women with known CVD should not begin HT for treatment of heart disease.

Current “Truths” Regarding Menopausal HT and Breast cancer

- Estrogen-alone (greater than 5 years post-menopausally) lowers breast cancer risk
- 2 years post-cessation of HRT/ET – breast cancer risk is no greater than never-users

Current “Truths” Regarding Menopausal HT

- The “timing hypothesis” suggests CVD protection MAY be possible if started near the onset of menopause (KEEPS/ELITE)
- The “gap hypothesis” suggests breast cancer risk is HIGHEST when started near menopause.

Endocrine Society 2010
**Endocrine Society 2010**

**Assessment of Perimenopausal women**

- BP
- Fasting lipid profile
- Fasting glucose
- TSH
- Assess for metabolic syndrome (decrease in insulin sensitivity; increase in central obesity)
- Counsel re: maintenance of healthy weight
- Assess sleep quality
- Screen for depression
- Vitamin D deficiency

**IMPORTANCE OF LIFESTYLE**

**Current “Truths” Regarding HRT and CVD**

- A **statin** is the drug of choice for any woman with hypercholesterolemia
- **First-line therapies for women with known CVD disease** include risk-factor modification, aspirin, β-blockers, statins and angiotensin-converting enzyme inhibitors - *just as in men*

**Benefits of Menopausal HT: What We Think We Know Now**

- Prevents or abolishes hot flashes – *still the most effect treatment*
- Prevents or improves genital atrophy
- Prevents or slows bone loss
- May reduce risk of Alzheimer’s disease
- May reduce risk of colon cancer
- May improve overall quality of life
So Just When Is Menopausal HT Indicated Now?

• For symptomatic women
• For prevention of osteoporosis in those where other drugs may be contraindicated
• ?In women with new onset depression
• ?For those who feel better taking estrogen

Alternatives and Future Directions for Research

• Estrogen/Progestin Therapy
  – progestagen-IUD for uterine protection
  – transdermal estrogen
  – lower dosages
  – new progestational agent
• Raloxifene
  – no change in CRP
  – lowers homocysteine
  – increased VTE
• New SERMs
  – neurospecific action
  – bone specific action
  – anti-estrogenic at breast and uterus

Case 1

• 34 y/o stops oral contraceptive pills to attempt conception. She fails to menstruate and ultimately is diagnosed with premature ovarian failure.
• She is started on hormone replacement therapy and ultimately adopts a child.
• She presents for her well woman visit at age 40 having been on HRT for 5 years. How would you advise her re: continuing treatment at this time?
Case 2

• 46y/o woman presents with complaints of difficulty sleeping and premenstrual migraines. She has noted some increased irregularity in her cycles, but continues to bleed. Her last period was 3 months before this visit.

• What would be your evaluation?

• If the evaluation is negative, would you offer any treatments