Estrogen Therapy After Postmenopausal Hysterectomy: Issues, Challenges, Risks/Benefits

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“Truth is ascertained only when sufficient numbers of appropriate studies are conducted and no one study or one study design has a monopoly on the truth.”

Trudy Bush
Int. J. Fert. 2001:46:56

Definitions

• Hormone Therapy (HT)
  – Use of an estrogen and progestin taken cyclically or in a combined E + P mode taken on a daily basis.

• Estrogen Therapy (ET)
  – Use of an estrogen-only preparation daily

• Estrogen-Progestin Therapy (EPT)
  – Use of estrogen and progestin therapy (cyclic and continuous combined)
  – For the Women’s Health Initiative, E+P was used on a daily basis

Disclosure

• Advisory Boards
  – Pfizer
  – Actavis
  – Charter Venture
  – Sermonix
  – Nuelle

• Clinical Trials
  – AbbVie
  – NIH
  – Actavis
  – Palatin
  – Pharmacos
Is What We Know About Hormone Therapy a Delusion? HT Then and Now

Key Findings of WHI-E Trial From 2004

- Small decrease in breast cancer risk
- No change in cardiovascular risk
- Known DVT risk
- Increase risk of stroke
- Increase in urinary incontinence
- Reduce fractures

So What Does this Elephant Look Like Now?

Issues: Causes of Death Among U.S. Women

- Heart Disease (45%)
- Other (25%)
- Pneumonia (4%)
- COPD (4%)
- Ovarian Cancer (<2%)
- Breast Cancer (4%)
- Lung Cancer (5%)
- Other Cancer (11%)

Issues: Extended WHI Trial Results and Now the Post Treatment Follow-up

- Not publicized
- Lack of interest by clinicians as “old news”
- Too new to percolate into practice guidelines and recommendations
Vertical dotted lines represent quintiles of duration of intended intervention and follow-up in the study population (elapsed time from randomization until the end of the intervention on February 29, 2004). CEE indicates conjugated equine estrogens.

aIncludes events from randomization to August 14, 2009.
bIncludes events from March 1, 2004, to August 14, 2009.

Figure Legend:

The “Timing Hypothesis” for Cardiovascular Risk and Hormone Therapy: A Window of Opportunity (50-59yrs) Estrogen-Alone

- CEE versus placebo had significant reductions in CHD (HR 0.59; 0.38-0.9)
- CEE versus placebo had significant reductions in MI (HR 0.54; 0.34-0.86)
- CEE versus placebo had significant reductions in overall mortality (HR 0.73; 0.53-1.00)
Challenges: Fear of Breast Cancer

- The fear of breast cancer is unlike any other health condition.
- Breast cancer is common, yet death from breast cancer is 4% among all other causes.
- Public is ill informed regarding breast cancer risks.

Issues: WHI CEE alone - Breast Cancer Risk

Issues: WHI CEE alone - Breast Cancer Deaths

Challenges: Why Would Estrogen Inhibit Breast Cancer in This Age Group?

- Decrease in breast cancer in CEE group runs counter to perceived notion of role of E in breast carcinogenesis.
- Did you know that high dose estrogen (DES) was used to treat metastatic breast cancer in the 1940-60’s?
- Concept of estrogen-induced apoptosis.
Challenges: Counseling Breast Cancer Risk and Hormone Therapy: Overall Perspective

- Increased breast density
- High serum E2
- Obesity
- E+P
- E alone

Challenges: Recurrence of Endometriosis with Estrogen Therapy

- Over 100,000 hysterectomies are performed for endometriosis.
- Use of hormone therapy is associated with recurrence of pelvic pain in 3.5% of cases.
- Malignant transformation of residual endometriosis foci into endometrioid cancer is rare.

Issues: Estrogen Dosing Options

- Local Vaginal Estrogen
  - Vagifem
  - Premarin cream
  - Estrace cream
  - Estrting

- High Systemic Dose E
  - 50 µg per day E2 Transdermal
  - 0.625 mg CEE, E1, SO4, esterified E

- Low Systemic Dose E
  - 14 µg, 25 µg, 37.5 µg per day E2 Transdermal
  - 1.0 mg oral E2
  - 0.3 mg, 0.45 mg CEE, E1, SO4, esterified E

ET and VTE* in French Menopausal Women

<table>
<thead>
<tr>
<th>ESTHER Study: 1999–2005</th>
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<tbody>
<tr>
<td>Case n = 259</td>
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<tr>
<td>OR</td>
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<tr>
<td>None</td>
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<tr>
<td>Oral ET</td>
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<td>Transdermal ET</td>
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VTE = venous thromboembolism.
Mean concentrations of E1 and E2 in plasma of postmenopausal women following administration of E2 by the transdermal and oral route.

**Take Home Away Points**

- For CHD (1st endpoint), the HR was NULL in CEE vs Placebo during and post-interval
  - HR for the 50-59yo group favored CEE
- For Breast CA (1st endpoint), the CEE risk was LOWER during the treatment and post-interval
- Stroke risk is higher with CEE but the risks dissipated during the post-interval for CEE
- Rates of total mortality and the global index of chronic diseases were the same in both groups overall.

**Issues: NAMS Position Statement on Hormone Therapy in Older Women**

The decision to continue or discontinue HT should be made jointly by the woman and her healthcare provider that the woman has been advised of the increase in risk associated with continuing HT beyond age 65 and has clinical supervision, extending HT use with the lowest effective dose is acceptable under some circumstances, such as for the woman who has persistent bothersome menopausal symptoms and for whom her clinician has determined that the benefits of menopause symptom relief outweigh the risks. Use of HT should be individualized and not discontinued solely based on a woman age.

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