Hot Flash: safety of menopause hormone therapy

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Disclosures

- None
Objectives

- Provide background on menopause hormone therapy
- Review the Women's Health Initiative
- Introduce “timing hypothesis”
- Identify risk stratification tools
- Help providers make informed decisions about hormone therapy
Agenda

- Primary focus
  - Oral hormone therapy for vasomotor symptoms
- What won’t be discussed
  - Non-hormonal medications
  - Special populations
  - Types of hormones
Abbreviations

- MHT = menopausal hormone therapy
- E+P = estrogen + progestin (e.g., Prempro)
- E = estrogen only (e.g., Premarin)
  - pregnant mares’ urine extraction = Premarin
Benefits from HRT 'outweigh the risks': After years of conflicting advice, now a major study finds it is safe. Oct 18, 2015

2002: US Women's Health Initiative study claims long term use of HRT is linked to higher risk of heart disease, strokes and cancer

2003: Cancer Research UK Million Women Study claims HRT users are at double the risk of breast cancer

2004: Second MWS report says the breast cancer risk for women in their 50s using HRT for five years is 50 per cent higher. Doctors are advised by the government's Medicines and Healthcare Products Regulatory Agency (MHRA) to prescribe the 'lowest effective dose for shortest possible time'

2007: WHI researchers publish analysis showing women on HRT are not more at risk of heart problems - and could be less at risk than non-users. MHRA says HRT should only be used to prevent osteoporosis in women who cannot take other medicines

2011: MWS report says the increased risk of breast cancer from HRT reverts to level of non-users two years after stopping it

2012: Danish study finds HRT can protect against heart disease

2013: The British Menopause Society says potential benefits of HRT outweigh harm

Oct 18, 2015

Hormone Replacement Therapy Seems Safe, Study Finds July 28, 2014 THE WALL STREET JOURNAL
Why is this important? *

- ~6,000 women/day reach menopause in US (> 2 million/yr!)
- Distressing symptoms
- Estrogen is most effective tx for vasomotor symptoms
- Conflicting messages in the media have clouded the picture

"Menopause really isn’t that bad"  
...said no woman ever.
Clinical question

- Do the benefits of MHT outweigh the risks for [young, healthy] menopausal women with moderate-to-severe vasomotor symptoms?
Some history on estrogen

- **Early 1960s:** first prescribed for vasomotor sx
- **Late 1960s:** heralded as a fountain of youth
- **Mid 1970s:** a/w uterine cancer
- **Early 1980s:** back in favor w/progestin
- **Late 1980s:** used for prevention of fractures and CHD
- **1993:** Women’s Health Initiative (WHI)
  - Randomized, double blind, placebo-controlled trial
  - 68,132 postmenopausal women in hormone therapy trial
  - Purpose: evaluate efficacy of hormone therapy for chronic disease prevention
- **Early 2000s:** Hormone therapy plummets
WHI, 2002

Statistics reported in the media:
- 26% more breast cancer
- 41% more strokes
- 29% more heart attacks
- 50% more blood clots
- 76% increase in dementia
- 37% less colorectal cancer
- 33% fewer hip fractures

80% decrease in MHT
A closer look at the WHI

- Did not evaluate menopausal sx
- Relatively high dose of hormones
- Women in the study were older
  - Avg. age in the study for initiating hormones: 63yo
  - Avg. age of menopause onset: 51yo
  - Common symptom range: 48-55yo
- Outcomes varied by hormone type and age
  - e.g., fewer cases of breast cancer in E only group
  - e.g., mortality benefit in 50-59yo

www.whi.org
Timing is everything

- “Timing hypothesis”
  - Effects of MHT depend on when started relative to age & menopause onset
    - Lower baseline risk of chronic disease
    - More estrogen receptors
- Target population:
  - Within 10 yrs of menopause (50-59yo)
  - No CI to hormone therapy
Support for “timing hypothesis”

- WHI, 1993-2015
  - Risk of MI in 50-59yo -> 40% lower than placebo
  - Risk of severe coronary artery calcium -> 40% lower than placebo
  - Effect not seen in women >60yo

- Early versus Late Intervention Trial with Estradiol (ELITE), 2004-2013
  - Single-center, randomized, double blind, placebo-controlled trial
  - Less progression of subclinical atherosclerosis vs placebo when initiated within 6 yrs of menopause
  - Effect not seen when initiated >10 yrs after menopause

- Danish Osteoporosis Prevention Study, 1990-2010
  - Cohort study of young women ~ 50yo
  - Significantly lower risk of CHD at 10 and 16 yrs of f/u

Support for ‘timing hypothesis’

- 2015 Cochrane review of 19 RCTs of oral hormone therapy initiated <10 yrs since menopause:
  - Lower mortality: RR 0.70 (CI 0.52 to 0.95)
  - Lower CHD: RR 0.52 (CI 0.29-0.96)
  - No increased risk of stroke

- Initiated > 10 years:
  - No mortality or CV benefit
  - Increased stroke: RR 1.21 (CI 1.06 to 1.38)

Cochrane Database Syst Rev 2015; 3:CD002229
WHI: Benefits and risks of MHT in women 50-59yo

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Number of women per 1000 per 5 years of use

- Coronary heart disease
- Invasive breast cancer
- Stroke
- Pulmonary embolism
- Deep vein thrombosis
- Colorectal cancer
- Endometrial cancer
- Lung cancer
- All fractures
- Hip fractures
- All-cause mortality
- Diabetes

Risks vs. Benefits

Postmenopausal women (50-59 years of age)

J Clin Endocrinol Metab 2015
WHI data for women 50-59yo

**E+P**
- CHD – 2.5 more cases
- Invasive breast cancer – 3 more cases
- Stroke – 2.5 more cases
- Pulmonary embolism – 3 more cases
- Colorectal cancer – 0.5 fewer cases
- Endometrial cancer – no difference
- Hip fracture – 1.5 fewer cases
- **All-cause mortality – 5 fewer events**

**E**
- CHD – 5.5 fewer cases
- Invasive breast cancer – 2.5 fewer cases
- Stroke – 0.5 fewer cases
- Pulmonary embolism – 1.5 more cases
- Colorectal cancer – 0.5 fewer cases
- Hip fracture – 1.5 more cases
- **All-cause mortality – 5.5 fewer events**

No. of cases per 1,000 women per five years of hormone use vs placebo
WHI statistics in perspective

- 26% more breast cancer on E+P
  - 31 cases per 10,000 women/yr in placebo group
  - 39 cases per 10,000 women/yr in E+P group
  - Excess risk of 8 cases per 10,000 = RARE
- 2-3 drinks/day associated with similar risk of breast cancer
- Being overweight carries more (30-60%) risk of breast cancer

Very common: > 1 in 10
Common: > 1 in 1,000 and < 10 in 100
Uncommon: > 1 in 1,000 and < 10 in 1,000
Rare: > 1/10,000 and < 10 in 10,000
Very rare: < 1/10,000

Council of International Organizations of Medical Sciences
WHI statistics in perspective

- Excess breast cancer risk of 8/10,000 unacceptable for primary prevention of chronic disease
  - NNH = 1,250
- Same risk may be acceptable to symptomatic women seeking short term treatment for menopause.
  - 80% reduction in vasomotor sx
What does this mean?

- The **absolute risk** of complications in healthy, recently postmenopausal women taking **E+P** for 5 yrs is **low**.
- The **absolute risk** of complications in healthy, recently postmenopausal women taking **E only** for 5 yrs is **neutral, possibly favorable**.
Risk stratification

- Endocrine Society Guidelines
- Calculate 10 year CV risk and 5 year breast cancer risk before initiating MHT
  - MenoPro app

<table>
<thead>
<tr>
<th>Risk</th>
<th>Tx</th>
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<tbody>
<tr>
<td>Low CV risk (10 yr risk &lt;5%)</td>
<td>E+P – uterus</td>
</tr>
<tr>
<td>Low breast ca risk (5 year risk &lt; 1.67%)</td>
<td>E – no uterus</td>
</tr>
<tr>
<td>Moderate CV risk (10 yr risk 5-10%)</td>
<td>Transdermal E  + micronized P</td>
</tr>
<tr>
<td>Moderate breast ca risk (5yr risk 1.67-5%)</td>
<td>Caution</td>
</tr>
<tr>
<td>High CV risk (10yr risk &gt;10%)</td>
<td>Nonhormonal</td>
</tr>
<tr>
<td>High breast ca risk (5 yr risk &gt;5%)</td>
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Endocrine Society Guidelines, 2015
Hormone variations

- Oral vs transdermal E
  - Lower risk of VTE, stroke, and hypertriglyceridemia with transdermal
  - First pass metabolism
- Progestin vs progesterone
  - Synthetic (e.g. medroxyprogesterone): vaso-constrictive, affects lipids
  - Natural: vaso-relaxant, lipid neutral
- Intrauterine levonorgestrel
- Micronized
Treatment – many permutations

**Uterus: E+P**
- Oral
  - Prempro: 0.3mg CEE/1.5mg medroxyprogesterone daily
  - Estradiol + progesterone
- Patch
  - Combi-Patch: 0.05mg estradiol + 0.14mg norethindrone twice weekly
- Estrogen patch + LNG

**No uterus: E**
- Oral
  - Estrace: 0.5mg estradiol qd
  - Premarin: 0.3mg CEE qd
- Patch
  - Alora: 0.025mg estradiol twice weekly

CEE - conjugated equine estrogen
The MenoPro app from The North American Menopause Society (NAMS) has 2 modes: one for clinicians and one for women/patients, to support shared decision making.

Are you a Health Care Provider or Woman/Patient?

Does the patient have moderate-to-severe hot flashes and/or night sweats, defined as bothersome symptoms that interfere with daily activities, impair quality of life, and/or interrupt sleep?

- [ ] Yes
- [ ] No

Patient’s CVD Risk Score is 1.9% (low risk) over 10 years.

Patient appears to be a candidate for either oral or transdermal estrogen therapy. Women with hysterectomy are candidates for estrogen-alone therapy.

- Estrogen Therapy options and dosages
- Duration of treatment
- Recommendation if patient has metabolic syndrome
- Handout on risks/benefits of HT
- Email summary and handout to patient and/or yourself
Vulvovaginal sx

- Affect up to 45% of postmenopausal women
- Oral therapy efficacy: ~75%
- Vaginal therapy efficacy: ~80-90%
  - Tablet, ring or cream
  - ACOG supports use in breast cancer survivors
  - No endometrial hyperplasia or cancer after 3 years of use

ACOG Committee Opinion, No 659, Feb 2016.
Shared decision-making

- Risk stratify
- Give absolute risks with up to 5 yrs of tx
- Put the risk in perspective
- Caution
  - Prolonged use (>5 years)
  - Use by women with minimal symptoms
  - Special populations
Take home point

- The **benefits** of MHT likely **outweigh the risks** for young, healthy menopausal women with moderate-to-severe vasomotor symptoms.
References

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Questions