51 IS GETTING YOUNGER EVERY DAY: MANAGING MENOPAUSAL PATIENTS IN 2016

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Disclosures

- Nothing to disclose
If all goes well, at the end of this talk you will:

- Understand the limitations of the Women’s Health Initiative in guiding menopause management
- Consider the “timing hypothesis” in your assessment of menopausal patients
- Know the recent revised global consensus position on risk/benefit profile of MHT
- Perhaps...be inspired to educate your colleagues!

Life Expectancy and Age at Menopause

*Projected estimate.
What Patients Experience

- Irregular bleeding
- Hot flashes/night sweats
- Vaginal discomfort
- Changes in sexuality
- Mood issues
- Insomnia
- Other body changes: weight gain, hair, skin, eyes, ears, teeth

What Patients Worry About

- Heart health
- Bone health
- Breast cancer risk
- Dementia risk
Menopause Management in the 1990s

The PEPI Trial
Metabolic Impact After 3 Years

n = 875.
CEE = conjugated equine estrogens, 0.625 mg/d; CEE/MPA (cyc) = CEE + 10 mg medroxyprogesterone acetate (MPA) for last 12 days each cycle; CEE/MPA (con) = CEE + 2.5 mg/d MPA;
CEE/MPA (cyc) = CEE + 200 μg micronized progesterone (MP) for first 12 days of each cycle.
Menopause Management in 2002

The Women’s Health Initiative

- Trial designed in 1991
- Total of 162,000 women
- 17,000 in the trial of E+P
- 11,000 w hysterectomy in E only group
- Most expensive trial in US history ($600 million+)
- Stopped in 2002 due to adverse effects in E+P group
WHI Results

Absolute and Relative Risk or Benefit of combined E/P HT

<table>
<thead>
<tr>
<th>Health Event</th>
<th>Relative Risk vs Placebo at 5.2 Years</th>
<th>Increased Absolute Risk per 10,000 Women/Yr</th>
<th>Increased Absolute Benefit per 10,000 Women/Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart attacks</td>
<td>1.29</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Strokes</td>
<td>1.41</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>1.26</td>
<td>8</td>
<td></td>
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<tr>
<td>VTEs</td>
<td>2.11</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>0.63</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Hip fractures</td>
<td>0.66</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Risks/benefits of E+P

- Pros:
  - It works—quickly!—for hot flashes
  - Decreased rates of colon cancer
  - Decreased rates of hip fractures

- Cons:
  - Increased rates of breast cancer
  - Increased rates of heart attack
  - Increased rates of stroke
  - Increased rates of VTE

Considerations

- Symptom relief not considered in original WHI trial data
- Average age of women in WHI was 63
- Only one form studied (CEE/MPA)

- Does decreased dose mean decreased risk, or is it all-or-none phenomenon?
- What about younger women?
- What about other delivery systems?

FDA guidelines after WHI

- MHT should be used for symptom management only
- It should not be used for CV or bone protection
- Lowest effective dose for shortest length of time
Headscratching...

- Dozens of observational studies consistently showed inverse associations between MHT and risk of CAD and death from any cause.

- BUT...null or adverse cardiovascular effects reported from randomized controlled trials.

The Plot Thickens

- The Timing Hypothesis
The Timing Hypothesis

- The effects of HT on atherosclerosis and CAD depend on when started relative to
  - Menopause
  - Age
  - Both

- Let’s look at some of the evidence in support of a critical window
Reanalysis of WHI 2011

- The E + P group was divided into women <10 years and >20 years from menopause
- Non-SS trend toward protection from CV disease seen in women < 10 years postmenopausal
- Elevated risk in women starting tx > 20 years after menopause


Other Studies that Support the Timing Hypothesis

- Estrogen in Prevention of Atherosclerosis Trial (EPAT)
  - 222 PMP women 45 y or older without preexisting CAD
  - Slowing of atherosclerosis progression w E tx compared to placebo

- Women’s Estrogen Lipid-Lowering Hormone Atherosclerosis Regression Trial (WELL-HART)
  - 226 women, mean age 63, with at least one coronary artery lesion
  - Showed no benefit of E or E+P tx on progression of existing CAD

Hodis H et al, NEJM 2003;349:535-45
ELITE Trial

- 643 healthy pm women
  - No diabetes
  - No clinical evidence of CAD
- Stratified according to early (<6 y) or late (>10 y) postmenopause
  - Mean age of early group = 55, late group = 63
- Oral 17B estradiol 1 mg (+ progesterone vaginal gel 45 mg) or placebo
- US carotid artery intima-media thickness (CIMT) at baseline and q 6 mo
- CT atherosclerosis measured at end of trial

Hodis H et al, NEJM 374;13:1221-1231

ELITE Trial: results

- Overall adherence to the study regimen was excellent (98%)
- Median 5 y intervention
- Early cohort
  - Less progression of subclinical atherosclerosis measured by CIMT
- Late cohort
  - No difference from placebo
- Results similar in E group and E+P group
- No difference in cardiac CT outcomes across groups (reflects existing disease)
Primate studies

- Many studies provide clear evidence that HT is effective in slowing the progression of CAD only when administered soon after surgical menopause.
- That benefit is lost if HT delayed.
- No evidence that HT has any beneficial effects on preexisting coronary artery atherosclerosis.

Clarkson TB et al, Menopause Mar 2013

Limitations of ELITE

- Studied surrogate markers, not cardiac events.
- Oral estrogen
- Progesterone gel
Importance of Dose?

- Kronos Early Estrogen Prevention Study (KEEPS)
  - 772 women, mean age 53, mean time from LMP 1.5 years
  - Oral or patch lower dose (0.5 mg) E + oral P in women with low baseline CAD risk had no effect on CIMT progression
  
  Harman SM et al Climacteric 2005;8:3-12

- ELITE trial used 1 mg

MHT and Fracture Prevention
MHT and Fracture Prevention

- WHI was the first RCT evidence that HT reduced risk of fractures even in low risk women
- Average T scores
  - hip -0.94
  - spine -1.3
- Vertebral and radiologically-detected not included in global index

Bagger et al, Bone 2004; 34:728-735

Bagger et al, Bone 2004; 34:728-735
PERF Study

- 347 healthy women with normal BMD who had participated in one of four placebo-controlled trials of E+P (1985, 89, 95, 96)
  - 263 received HT for 2-3 years then stopped
  - 84 prolonged or current use of HT
- Measured spine BMD, radiologically-detected vertebral, and clinical non-vertebral fractures at 5, 11, and 15 years post treatment
  - Average age 65 at followup
- E+P treated women in all studies showed
  - Normal rates of PMP bone loss after stopping treatment
  - Higher spine BMD (>5%) than placebo
  - 52% decreased RR of all fractures
  - Highest BMD in longterm/current users
- Since WHI, increasing reports of risks of alternative drugs
  - Bisphosphonates
  - SERMS

“lowest effective dose”

- Treats vasomotor symptoms
  - 30 pg/mL
- Protects bone health
  - 40 pg/mL
- Cardioprotection
  - 50-80 pg/mL
- Serum assays are an advantage of estradiol over conjugated estrogens
Use of systemic MHT has decreased by 80% since WHI. WHI designed to address risks and benefits of longterm use of HT for prevention of chronic illness in women in their 60s. Results being used inappropriately to make decisions about women in their 40s and 50s. New generation of providers are not being trained. Burgeoning market of unregulated potions.

2015 NAMS survey: 35% of women on MHT are using a compounded product.

Resident Training in Menopause Management

- 2013 study of 100 US internal medicine residents
  - 75%+ considered care of menopausal women to be very important
  - 50% reported a low comfort level managing menopausal symptoms
  - 75%+ reported limited training opportunities
  - 33%+ reported no management of menopausal patients in the past 6 months

Hsieh E et al, J Women’s Health 2013;22:667-72

Menopause Management in 2016
June 2016: IMS and NAMS joint statement

Climacteric

Revised Global Consensus Statement on Menopausal Hormone Therapy

T. J. de Villiers, J. E. Hall, J. V. Pinkerton, S. Cerdas Pérez, M. Rees, C. Yang & D. D. Pieroz

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Benefit/risk profile of MHT

- MHT is most effective treatment for vasomotor symptoms at any age
  - Benefits more likely to outweigh risks before age 60 or within 10 years of menopause
- SSRIs/SNRIs best alternative; gabapentin third-line
- MHT may improve quality of life, sexual function, joint/muscle pain, mood changes, sleep disturbance
- MHT is effective in prevention of bone loss and significantly lowers risk of osteoporosis-related fractures
- MHT is the only therapy w/ RCT-proven efficacy of fracture reduction in low risk women w normal-to-low T scores
  - Can be initiated in women at risk of fracture before age 60 or within 10 years of menopause
  - Initiation after age 60 for fracture prevention is considered second-line tx and must be individualized
Benefit/risk profile of MHT

- Local low-dose ET is preferred for symptoms limited to vaginal dryness, dyspareunia, or for prevention of UTI
- E-alone MHT may decrease risk of MI and all-cause mortality when initiated in women < 60 yo or within 10 years of menopause
- E + P MHT shows less-compelling trend for mortality benefit; cardioprotective effect less robust
- Risk of VTE and stroke is increased w MHT but rare in <60 yo; risk decreased w/ transdermal forms
- Risk of breast ca is complex; decreased w/ E-alone, possibly increased w/ E + P related to duration of use
  - Risk of breast ca <1.0 per 1000 women per year, similar or lower than sedentary lifestyle, obesity, alcohol consumption

Benefit/risk profile of MHT

- MHT started at age of menopause has no substantial effect on cognition but may prevent Alzheimer’s dz in later life
- MHT started at 65 or older has no substantial effect on cognition and increases risk of dementia
- MHT may improve mood in early postmenopausal women w/ depression and/or anxiety
- MHT may improve mood in perimenopausal women w/ major depression
  - Antidepressant therapy remains first-line
- MHT reduces symptoms and preserves bone density in women with early menopause from all causes, and is advised at least until age of natural menopause
General principles

- Evidence regarding differences in risk/benefits between different products and routes of administration is limited.
- Benefit/risk profile should be assessed annually.
  - Especially important in light of new data indicating longer duration of vasomotor sx in some women.
- CEE/BZA is alternative to systemic P.
- Testosterone therapy is supported in carefully selected women with interest/arousal disorder in countries where approved.
- Custom-compounded MHT not recommended due to lack of regulation.
- Current data do not support use of systemic MHT in breast cancer survivors but may be individualized after alternative treatment failure in selected women for compelling reasons.

Summary

- Assess your patients’ risk/benefit ratio for hormone therapy.
- Keep in mind the limitations of WHI for younger women.
- Do not withhold treatment in appropriate patients.
- Educate patients regarding ineffective potions.
- It is our responsibility to educate our colleagues.
Thank you!

References

- Bagger YZ et al. Two to three years of hormone replacement treatment in healthy women have longterm preventive effects on bone mass and fractures: the PERF Study. Bone. 2004; 34:728-735.