Controversies in Menopause Management

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Objectives

- Review normal menopause transition and management options
- Discuss "Critical Window" hypothesis to explain clinical trials data
- Discuss risks, benefits and effect modifiers of hormonal therapy

Menopause

Diagnosis made in retrospect as definition is the absence of menses for 12 months
Natural depletion of ovarian follicles leads to decline in ovarian production of progesterone, estradiol and testosterone (in that order)

*The most reliable sign of the menopausal transition is menstrual irregularity*
Menopause

Eventually, follicles stop responding to FSH
Leads to gradual decline in estradiol secretion and amenorrhea
HAVOCs:
- Hot flashes
- Atrophy of the urogenital tract
- Osteoporosis
- Coronary artery disease
- Sleep disturbances

Atypical Symptomatology

In women with menstrual abnormality without other signs or symptoms of menopause, especially if < 45 years of age, consider:
- Pregnancy test, TSH, prolactin
- Serum androgens if exam and/or symptoms are suggestive of androgen excess
Menopause prior to age 40 y suggests primary ovarian Insufficiency
Which of the following statements about vasomotor symptoms is false?

A. 75% of women will experience vasomotor symptoms during the menopausal transition
B. Estrogen levels are always low in women experiencing vasomotor symptoms
C. Most women do not require medical management for vasomotor symptoms
D. Hot flashes are common in women who are still menstruating

Scope of the Problem

75% of perimenopausal and menopausal women will experience vasomotor symptoms (hot flashes and/or night sweats)
In 15% of women, symptoms are moderate-severe and may warrant treatment
Symptoms are common in women who are still menstruating
Symptoms are common in women with normal estrogen levels

Anatomy of a Hot Flash

Hormone Levels and Menstrual Status


<table>
<thead>
<tr>
<th>Menstrual Status</th>
<th>N</th>
<th>FSH</th>
<th>E2</th>
<th>INH</th>
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<tbody>
<tr>
<td>Normal Flow</td>
<td>53</td>
<td>13.0</td>
<td>249.3</td>
<td>187.4</td>
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<tr>
<td>Change in Flow</td>
<td>39</td>
<td>13.8</td>
<td>243.7</td>
<td>189.6</td>
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<tr>
<td>Change in Frequency</td>
<td>26</td>
<td>19.7</td>
<td>196.8</td>
<td>170.2</td>
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<tr>
<td>Change in Both</td>
<td>85</td>
<td>19.5</td>
<td>256.9</td>
<td>156.2</td>
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<tr>
<td>Amenorrhea &lt;3 m</td>
<td>65</td>
<td>69.2</td>
<td>81.4</td>
<td>98.9</td>
</tr>
<tr>
<td>Amenorrhea &gt;3 m</td>
<td>66</td>
<td>93.9</td>
<td>77.0</td>
<td>76.2</td>
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<tr>
<td>HRT</td>
<td>104</td>
<td>26</td>
<td>357.4</td>
<td>89.5</td>
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</table>

Newest Controversy-Hot Flashes and CVD

Are hot flashes predictive of, protective for, or have no impact on the risk of cardiovascular disease?

Recent data from WISE study (Thurston et al. Menopause 2017;24:126-132) suggest vasomotor symptoms are marker of abnormal endothelial dysfunction later in life.

Data from WHI and KEEPS did not find same association

Stay Tuned!

What is one explanation for the discrepancy in cardiac outcomes between observational and clinical trials of hormone therapy?

A. Clinical trials enrolled younger women than observational studies
B. Different hormones were used in clinical trials compared to observational studies
C. The timing of hormone therapy was different in clinical trials compared to observational studies
Timing Hypothesis

There is a “Critical Window” for benefit of HT (younger is better)
Helps explain discrepancy between observational studies and RCTs
Component 1: HT initiated early in menopausal transition will slow progression of early atherosclerosis
Component 2: Beneficial effects of HT will be lost in later menopause when atherosclerosis is more advanced

Timing Hypothesis

Nurses Health Study RR 0.61 for major coronary event (observational) in HT users
HERS no differences between groups in CAD or plaque progression (secondary intervention)
WHI no difference in CAD except in youngest women (benefit)

Animal Studies

Clarkson et al, cynomolgus monkeys, showed beneficial effect of estrogen on atherosclerosis progression
Decrease in estrogen receptors (ER) in endothelium affected by atherosclerosis
Estrogen may be anti-inflammatory with more ER and pro-inflammatory with fewer ER
Pro-inflammatory effect leads to activation of MMPs (matrix metalloproteinases) and plaque disruption
### Rossouw JE et al, 2007; Postmenopausal Hormone Therapy and Risk of Cardiovascular Disease by Age and Years Since Menopause

<table>
<thead>
<tr>
<th>Age</th>
<th>All</th>
<th>CEE</th>
<th>CEE+MPA</th>
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</thead>
<tbody>
<tr>
<td>50-59</td>
<td>0.93</td>
<td>0.63</td>
<td>1.29*</td>
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<td>60-69</td>
<td>0.98</td>
<td>0.94</td>
<td>1.03</td>
</tr>
<tr>
<td>70-79</td>
<td>1.26</td>
<td>1.13</td>
<td>1.48*</td>
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</table>

<table>
<thead>
<tr>
<th>Years since LMP</th>
<th>All</th>
<th>CEE</th>
<th>CEE+MPA</th>
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</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>0.76</td>
<td>0.48</td>
<td>0.88</td>
</tr>
<tr>
<td>10-19</td>
<td>1.10</td>
<td>0.96</td>
<td>1.23</td>
</tr>
<tr>
<td>&gt;20</td>
<td>1.28</td>
<td>1.12</td>
<td>1.66*</td>
</tr>
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### Pathogenesis of Coronary Artery Atherosclerosis of North American Human Females

Stage of Reproductive Life

- Premenopause
- Perimenopause
- Postmenopause

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### Relation of Age Distribution to Stage of Progression of Coronary Artery Atherosclerosis

- 0% yrs
- 10% yrs
- 20% yrs
- 45% yrs
- 70% yrs

- Adventitia
- Media/Intima/Endothelium
- Fibrous Cap
- Plaque
- Necrotic Core
- Necrotic Core

- 35-45 yrs
- 45-55 yrs
- 55-65 yrs
- >65 yrs
Other factors that modify the risks/benefits of estrogen include all of the following except?

A. Route of administration  
B. Metabolic syndrome  
C. Concurrent Progestin use  
D. Presence of vasomotor symptoms
Other Effect Modifiers

Age/Years from LMP (see previous slides)

Progestogen

WHI data suggest deleterious effect; other data conflicting: micronized progestrone may be safer than synthetic progestogens

Metabolic Disorder

Wild et al, 2013; nested case-control study within WHI in women without prior CHD

HR 2.26 for HT vs. placebo in women with MetS

HR 0.97 for HT vs. placebo in women without MetS

Dose

CHD benefit seen with even low doses

High doses may increase other risks

Obesity and Metabolic Dysfunction

Obesity and metabolic syndrome may also shift coronary disease to the left.
Estrogen Effects on Glucose Homeostasis

In normal weight women, estrogen improves insulin sensitivity and decreases abdominal fat deposition by about 7%
Progestogens blunt this effect, especially synthetic progestins
Hormone therapy decreases incidence of new onset DM in PMP women
Estrogen has other anti-diabetogenic effects

HT and Health Outcomes, WHI 2013

Extended outcomes data, 13y cumulative follow up
CHD: RR 1.18 for EPT; 0.94 for ET
Breast Cancer: 1.24 for EPT; 0.79 for ET
Age affected risk for CHD and stroke
Neither regimen affected all-cause mortality

Manson JE et al; JAMA 2013;310:1353-1368

Hormone Therapy—Can We Make it Safer?

Need to consider multiple factors:
Age
Years since LMP
Contraindications
Medical co-morbidities
Route of Administration
Need for and Choice of Progestogen
Which of the following is not a benefit of transdermal estrogen when compared to oral estrogen?

A. VTE risk  
B. Symptom relief  
C. Sexual function  
D. Improved HDL cholesterol

Transdermal Estrogen

Absorption of estrogen through the skin is very high  
Avoids first pass effect  
No change in SHBG or other binding globulins  
No change in E2:E1 ratio  
Allows for more convenient dose titration and weaning

Transdermal = Oral

Symptom relief  
Bone protection  
Blood pressure  
Breast tenderness  
Endometrial effects
Oral Better than Transdermal

HDL response
LDL response
Allergic skin reactions
Uterine fibroid growth

Route of Administration

Oral estrogen leads to increased fat mass, decreased IGF-1, increased GH and decreased lean body mass
Transdermal estrogen causes no change in body mass or leptin and increases adiponectin (that’s good!)

Route of Administration Matters

<table>
<thead>
<tr>
<th></th>
<th>Oral E2</th>
<th>TD E2</th>
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<tbody>
<tr>
<td>CRP</td>
<td>↑</td>
<td>⬇</td>
</tr>
<tr>
<td>MMP</td>
<td>↑</td>
<td>⬇</td>
</tr>
<tr>
<td>VTE</td>
<td>↑</td>
<td>⬇</td>
</tr>
<tr>
<td>HDL</td>
<td>↑</td>
<td>⬇</td>
</tr>
<tr>
<td>TG</td>
<td>↑</td>
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<tr>
<td>Adiponectin</td>
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<tr>
<td>IGF-1</td>
<td>↑</td>
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<tr>
<td>Abd Fat</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>BP</td>
<td>⬇</td>
<td>⬇</td>
</tr>
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</table>
Transdermal vs. Oral Estrogen

Data emerging that thromboembolism risk is modified by mode of administration
Non-oral administration avoids first-pass effect
ESTHER study 2007; no change in coag factors
Synthetic progestogens may also increase VTE risk
ACOG Committee Opinion April 2013:
“When prescribing estrogen therapy, the gynecologist should take into consideration the possible thrombosis-sparing properties of transdermal forms of estrogen therapy.”

Progesterone and Progestogens

Progestogen is recommended for all women with a uterus who are receiving systemic estrogen therapy. Includes women s/p endometrial ablation.
Transdermal, intravaginal, intrauterine
Risk for breast cancer, VTE and CVD varies with type of progestogen
  Bioidentical P4 lowest risk
  WHI: combined therapy (CEE with MPA) showed increased risk for CVD and breast cancer vs. CEE alone
BZA-CEE option may alleviate progestogen issues but not risks of oral estrogen

All of the following are helpful in the treatment of Vulvovaginal Atrophy symptoms except?

A. Raloxifene
B. Estrogen
C. Ospemifene
D. Long-acting moisturizers
**Management of Vulvovaginal Atrophy (VVA), aka Genitourinary Syndrome of Menopause (GSM)**

Up to 45-50% of PMP women symptomatic from VVA
75% report negative consequences on sex life
Symptoms and Treatment options often not discussed by PCPs and gynecologists
Delay in recognition and treatment can lead to loss of structure and function

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**Management of VVA**

Very few absolute contraindications for vaginal estrogen use
Most effective therapy for urogenital atrophy
Estradiol works better than estriol
Minimal absorption once vagina is re-epithelialized
Absorption: cream > tablet > ring
Ring has highest acceptability and fewest side effects

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**Management of VVA**

Serum E2 with vaginal administration:
- Vaginal ring: 5-10 pg/ml (may be higher during first week of use)
- Vaginal tablets: 3-11 pg/ml
- Vaginal E2 cream: up to 80 pg/ml!
- CEE cream: no change in E2 but may still have systemic estrogenic effect
Use in breast cancer patients still controversial but not absolutely contraindicated; consult with patient’s oncologist before prescribing
Alternatives to Local E2

Vaginal DHEA (dehydroepiandrosterone) 0.5% (6.5 mgm/gram)
- Precursor to all sex hormones
- Binds to estrogen receptors but not acted on by aromatase
- No stimulation of the endometrium
- Improves vaginal pH, maturation index, dyspareunia
- No change in serum hormone levels

Labrie et al. Menopause 2016;23:243-256

Alternatives to Local E2

Laser or radiofrequency energy therapy to vaginal mucosa: stimulates collagen remodeling
- Fractional CO2 laser (MonaLisa Touch approved 2014)
- Erbium laser
- Effects may last months-years

SERMS
- Ospemifene-effective in relief of symptoms but has similar VTE risk profile as oral estrogen

Summary-1

All women transition through menopause, although some more easily than others
- Primary indication for HT is treatment of moderate-severe menopausal symptoms
- HT is not indicated for the treatment or prevention of disease (except maybe osteoporosis)
- Risks and benefits of HT are modified by age, years from LMP, obesity/MetS, progestogen, route of administration and dose
- Transdermal estrogen may be safer than oral
Vulvovaginal atrophy and symptoms tend to worsen with time.
Local estrogen use is safe for the vast majority of PMP women and should be offered to many.
DHEA used vaginally may be a safe alternative to local estrogen.