Controversies in Menopause Management

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CONFLICT OF INTEREST DISCLOSURE STATEMENT

I don’t have financial interest or other relationships with the industry relative to the topics being discussed.
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
Discuss management of vulvovaginal symptoms

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

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
VMS may be a marker for increased risk of CAD

Anatomy of a Hot Flash

Which of the following is not a component of the “timing hypothesis”?

a) Hormone therapy initiated early will slow progression of atherosclerosis
b) Timing of menopause is important in atherosclerosis progression
c) Hormone therapy initiated late will not benefit atherosclerosis progression

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
Animal Studies

Clarkson et al, cynomolgus monkeys, showed beneficial effect of estrogen on atherosclerosis progression. Decrease in estrogen receptors (ER) seen 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.
Relation of Age Distribution in WHI to Stage of Progression of Coronary Artery Atherosclerosis

<table>
<thead>
<tr>
<th>Age Range</th>
<th>0% yrs</th>
<th>10% yrs</th>
<th>20% yrs</th>
<th>45% yrs</th>
<th>70% yrs</th>
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<tr>
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<td>55-59</td>
<td>60-69</td>
<td>70-79</td>
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Rossouw JE et al, 2007: Postmenopausal Hormone Therapy and Risk of Cardiovascular Disease by Age and Years Since Menopause

<table>
<thead>
<tr>
<th>Age Range</th>
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<th>CEE+MPA</th>
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<td>0.63</td>
<td>1.29*</td>
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<tr>
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<tr>
<td>70-79</td>
<td>1.26</td>
<td>1.13</td>
<td>1.48*</td>
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<table>
<thead>
<tr>
<th>Years since LMP</th>
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<th>CEE</th>
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<tr>
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<td>0.88</td>
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<td>10-19</td>
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<td>&gt;20</td>
<td>1.28</td>
<td>1.12</td>
<td>1.66*</td>
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</table>
Timing Hypothesis-Extended

Early benefit/late harm effects may also be true in other organ systems

Studies in mice show E2-induced down-regulation of proinflammatory cytokines (IL-6, TNF-alpha, MCP-1) in the CNS

E2 important in maintaining functioning mitochondria “one cannot re-estrogenize senescent mitochondria”

(Turner & Kerber. Menopause 2017;14;1086-1097)

The WHI was an attempt to re-estrogenize women after an average of 10-12 years post-menopause

Other factors (besides age) that modify the risk of estrogen therapy 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 P4 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

[Diagram showing M2 macrophage, adipocyte, CD4+ T cell, CD8+ T cell, M1 macrophage, adipocytokines, and anti-inflammatory and pro-inflammatory adipokines.]
Obesity and metabolic syndrome may also shift atherosclerosis progression to the left.

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**Estrogen Effects on Glucose Homeostasis**

In normal weight women, estrogen improves insulin sensitivity and decreases abdominal fat deposition by about 7%

Progestogens blunt this affect, especially synthetic progestins

Hormone therapy decreases incidence of new onset DM in younger PMP women

Estrogen has other anti-diabetogenic effects which cannot be overcome by exercise in animal models
HT and Health Outcomes, 2013

Manson JE et al; JAMA 2013;310:1353-1368
Extended outcomes data, 13y cumulative follow up, includes intervention and post-intervention phases
CHD: RR 1.18 for CEE/MPA; 0.94 for CEE
Breast Cancer: 1.24 for CEE/MPA; 0.79 for CEE
Age affected risk for CHD and stroke
Neither regimen affected all-cause mortality

Attributable risk of breast cancer in the WHI CEE/MPA clinical trial is similar to the risk related to:

a. Obesity
b. BRCA mutation carrier status
c. One glass of wine daily
d. Estrogen-only therapy
HT and Health Outcomes, 2017

Manson JE et al; JAMA 2017;318:927-938
Extended outcomes data, 18y cumulative follow up, includes intervention and post-intervention phases
All-cause mortality: HR 1.02 for CEE/MPA, 0.94 for CEE (compared to placebo)
Cardiovascular mortality: HR 1.00
Cancer mortality: HR 1.03
Comparing all-cause mortality for younger women (50-59) to older (70-79): HR 0.87

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
Transdermal Estrogen

Absorption of estrogen through the skin is high
Avoids first pass effect
No change in SHBG or other binding globulins
No change in E2:E1 ratio
Emerging data of lower risk for venous thromboembolism compared to oral therapy
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.”

Route of Administration Matters

<table>
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<tr>
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<th>Oral E2</th>
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<tbody>
<tr>
<td>CRP</td>
<td>↑</td>
<td>⇓</td>
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<tr>
<td>MMP</td>
<td>↑</td>
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<tr>
<td>VTE</td>
<td>↑</td>
<td>⇓</td>
</tr>
<tr>
<td>HDL</td>
<td>↑</td>
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<tr>
<td>TG</td>
<td>↑</td>
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<tr>
<td>Adiponectin</td>
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<td>↑</td>
</tr>
<tr>
<td>IGF-1</td>
<td>↑</td>
<td>⇓</td>
</tr>
<tr>
<td>Abd Fat</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>BP</td>
<td>⇓</td>
<td>⇓</td>
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</table>
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 some progestogen issues but not risks of oral estrogen

HT Alternatives

SSRI/SSNI: many studies support benefit, off-label
Low-dose mesylate salt of paroxetine 7.5 mg (+FDA)
Gabapentin and Pregabalin, off-label
SERMS “estrogen agonist/antagonist with tissue selective effects”:
Ospemifene: approved for VVA, may make VMS worse; probable breast/endometrial safety
CEE+bazedoxifene, may relieve need for progestogen but still has risks of oral estrogen
Tibolone: endorsed by Spanish Menopause Society for VVA and VMS
Clonidine: still effective, still off-label
Emerging Treatment Options

Neurokinin 3 receptor (NK3R) antagonist
Reported but unpublished data of placebo-controlled trial of 87 women
Showed 93% reduction in moderate-severe hot flashes compared with 23% for placebo
May work by lowering core-body temperature (in animal models)

Which of the following is not an FDA-approved indication for HT?

a. Vasomotor symptoms
b. Prevention of osteoporosis
c. Prevention of cardiovascular disease
d. Hypogonadism
North American Menopause Society 2017 Hormone Therapy Position Statement

“For women aged younger than 60 years or who are within 10 years of menopause onset and have no contraindications, the benefit-risk ratio is most favorable for treatment of bothersome VMS and for those at elevate risk for bone loss or fracture”

“Treatment should be individualized to identify the most appropriate HT type, dose, formulation, route of administration, timing of initiation, and duration of use, using the best available evidence to maximize benefits and minimize risks...”

Which of the following is not an FDA-approved treatment for symptoms of Vulvovaginal Atrophy?

a) Raloxifene
b) Estrogen
c) Ospemifene
d) Vaginal DHEA
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

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
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; consult with patient’s oncologist before prescribing

Alternatives to Local E2

Vaginal DHEA (dehydroepiandrosterone) 0.5% (6.5 mgm)
- Precursor to all sex hormones
- Under conditions of low serum E2, intracellular conversion of DHEA to E2 is tightly controlled to have local effect only (in all tissues)
- No stimulation of the endometrium
- Improves vaginal pH, maturation index, dyspareunia
- No change in serum hormone levels

Now FDA approved
Alternatives to Local E2

Laser or radiofrequency energy therapy to vaginal mucosa
Sokol ER & Karram MM. Menopause 2017;24:810-814

1-year follow of CO₂ laser Rx (3 treatments q 6 weeks) in 30 women; improvement in dryness, dyspareunia which persisted at 1 year
Minimal data available on radiofrequency therapy

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 cardiovascular disease
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
Summary-2

Emerging data support the “timing hypothesis” of early benefit and late harm for cardiovascular disease and possibly other systems. NAMS has updated its position statement to reflect that benefits may outweigh risks in younger, perimenopausal women with moderate-severe VMS. NAMS also supports an individualized approach to prescribing HT.

Summary-3

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.