Controversies in Menopause Management

Vanessa M. Barnabei, MD, PhD
Professor and Chair
Department of Obstetrics and Gynecology
Jacobs School of Medicine and Biomedical Sciences
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_
<table>
<thead>
<tr>
<th>Stage</th>
<th>-5</th>
<th>-4</th>
<th>-3b</th>
<th>-3a</th>
<th>-2</th>
<th>-1</th>
<th>+1 a</th>
<th>+1b</th>
<th>+1c</th>
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<tr>
<td>Terminology</td>
<td>REPRODUCTIVE</td>
<td>MENOPAUSAL TRANSITION</td>
<td>POSTMENOPAUSE</td>
<td></td>
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<tr>
<td>Menarche</td>
<td>FMP (0)</td>
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<tr>
<td>Duration</td>
<td>Variable</td>
<td>Variable</td>
<td>1-3 years</td>
<td>2 years (1+1)</td>
<td>3-6 years</td>
<td>Remaining lifespan</td>
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<td>PRINCIPAL CRITERIA</td>
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<td>Menstrual Cycle</td>
<td>Variable to regular</td>
<td>Regular</td>
<td>Regular</td>
<td>Subtle changes in Flow/ Length</td>
<td>Variable Length</td>
<td>Persistent ≥7- day difference in length of consecutive cycles</td>
<td>Interval of amenorrhea of ≥60 days</td>
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<td>SUPPORTIVE CRITERIA</td>
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<td>Endocrine</td>
<td>FSH</td>
<td>AMH</td>
<td>Inhibin B</td>
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<tr>
<td>Antral Follicle Count</td>
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<td>Low</td>
<td>Low</td>
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<td></td>
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<td>&gt;25 IU/L**</td>
<td>Variable</td>
<td>Stabilizes</td>
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<td>DESCRIPTIVE CHARACTERISTICS</td>
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<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td>Vasomotor symptoms Likely</td>
<td>Vasomotor symptoms Most Likely</td>
<td>Increasing symptoms of urogenital atrophy</td>
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<tr>
<td>* Blood draw on cycle days 2-5</td>
<td>= elevated</td>
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<tr>
<td>**Approximate expected level based on assays using current international pituitary standard&quot;67-69</td>
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</table>
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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</thead>
<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>165.2</td>
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<tr>
<td>Amenorrhea &gt;3,&lt;12 m</td>
<td>65</td>
<td>69.2</td>
<td>81.4</td>
<td>98.9</td>
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<tr>
<td>Amenorrhea &gt;12 m</td>
<td>66</td>
<td>93.9</td>
<td>37.9</td>
<td>76.2</td>
</tr>
<tr>
<td>HRT</td>
<td>104</td>
<td>26</td>
<td>357.4</td>
<td>89.5</td>
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</tbody>
</table>
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.
Pathogenesis of Coronary Artery Atherosclerosis of North American Human Females

Stage of Reproductive Life

- Premenopause (~5%)
- Perimenopause (~15%)
- Postmenopause

- 15-25 yrs: Benefits of Endogenous E₂
- 25-35 yrs
- 35-45 yrs: Primary Benefits of ERT/HRT
- 45-55 yrs
- 55-65 yrs: Deleterious Effects of ERT/HRT
- > 65 yrs: MMP-9
## Relation of Age Distribution in WHI to Stage of Progression of Coronary Artery Atherosclerosis

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Adventitia</th>
<th>Media</th>
<th>Internal Elastic Lamina</th>
<th>Fatty Streak/Plaque</th>
<th>Fibrous Cap</th>
<th>Plaque</th>
<th>Necrotic Core</th>
<th>MMP-9</th>
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<tr>
<td>35-45 yrs</td>
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<td>55-65 yrs</td>
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<td>&gt; 65 yrs</td>
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</table>

<table>
<thead>
<tr>
<th>Percent</th>
<th>0%</th>
<th>10%</th>
<th>20%</th>
<th>70%</th>
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<tr>
<td>Years</td>
<td>yrs</td>
<td>50-54</td>
<td>55-59</td>
<td>60-69</td>
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</table>

- Adventitia
- Media
- Internal Elastic Lamina
- Fatty Streak/Plaque
- Fibrous Cap
- Plaque
- Necrotic Core
- MMP-9
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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<tbody>
<tr>
<td>50-59</td>
<td>0.93</td>
<td>0.63</td>
<td>1.29*</td>
</tr>
<tr>
<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>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Years since LMP</th>
<th>All</th>
<th>CEE</th>
<th>CEE+ MPA</th>
</tr>
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<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>
</tbody>
</table>
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
Rossouw JE et al, 2007; Postmenopausal Hormone Therapy and Risk of Cardiovascular Disease by Age and Years Since Menopause

Combined Trials

- CHD
  - 50-59 y: -2
  - 60-69 y: -1
  - 70-79 y: -19
- Stroke
  - 50-59 y: 2
  - 60-69 y: 14
  - 70-79 y: 12
- Total Mortality
  - 50-59 y: -10
  - 60-69 y: -4
  - 70-79 y: 16
- Global Index
  - 50-59 y: -4
  - 60-69 y: 15
  - 70-79 y: 43

Trial of CEE

- CHD
  - 50-59 y: -10
  - 60-69 y: -4
  - 70-79 y: 11
- Stroke
  - 50-59 y: -2
  - 60-69 y: 19
  - 70-79 y: 12
- Total Mortality
  - 50-59 y: -11
  - 60-69 y: 1
  - 70-79 y: 27
- Global Index
  - 50-59 y: -21
  - 60-69 y: 2
  - 70-79 y: 50

Trial of CEE+MPA

- CHD
  - 50-59 y: 5
  - 60-69 y: 1
  - 70-79 y: 28
- Stroke
  - 50-59 y: 4
  - 60-69 y: 9
  - 70-79 y: 11
- Total Mortality
  - 50-59 y: -9
  - 60-69 y: 4
  - 70-79 y: 8
- Global Index
  - 50-59 y: 9
  - 60-69 y: 25
  - 70-79 y: 39

Estimated Absolute Excess Risk/10,000 Person-Years
Rossouw JE et al, 2007; *Postmenopausal Hormone Therapy and Risk of Cardiovascular Disease by Age and Years Since Menopause*

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**Combined Trials**

<table>
<thead>
<tr>
<th>Condition</th>
<th>&lt;10 y</th>
<th>10 - 19 y</th>
<th>≥20 y</th>
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<tbody>
<tr>
<td>CHD</td>
<td>-6</td>
<td>4</td>
<td>17</td>
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<tr>
<td>Stroke</td>
<td>9</td>
<td>7</td>
<td>11</td>
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<tr>
<td>Total Mortality</td>
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<td>-1</td>
<td>14</td>
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<tr>
<td>Global Index</td>
<td>5</td>
<td>20</td>
<td>23</td>
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**Trial of CEE**

<table>
<thead>
<tr>
<th>Condition</th>
<th>&lt;10 y</th>
<th>10 - 19 y</th>
<th>≥20 y</th>
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<tbody>
<tr>
<td>CHD</td>
<td>-14</td>
<td>-2</td>
<td>8</td>
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<tr>
<td>Stroke</td>
<td>16</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Total Mortality</td>
<td>-11</td>
<td>-4</td>
<td>15</td>
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<tr>
<td>Global Index</td>
<td>-6</td>
<td>-9</td>
<td>17</td>
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**Trial of CEE+MPA**

<table>
<thead>
<tr>
<th>Condition</th>
<th>&lt;10 y</th>
<th>10 - 19 y</th>
<th>≥20 y</th>
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<tr>
<td>CHD</td>
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<td>32</td>
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<tr>
<td>Stroke</td>
<td>8</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>Total Mortality</td>
<td>-5</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Global Index</td>
<td>8</td>
<td>29</td>
<td>36</td>
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</tbody>
</table>

Estimated Absolute Excess Risk/10,000 Person-Years
Other Effect Modifiers

Age/Years from LMP (see previous slides)

Progestogen

WHI data suggest deleterious effect; other data conflicting; micronized progesterone 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

Lean with normal metabolic function
- Inflammation
- Metabolic control
- Vascular function

Obese with mild metabolic dysfunction
- Inflammation
- Metabolic control
- Vascular function

Obese with full metabolic dysfunction
- Inflammation
- Metabolic control
- Vascular function

M2 macrophage
Adipocyte
CD4+ T cell
CD8+ T cell
Blood vessel

Anti-inflammatory adipokines
- Adiponectin
- SFRP5

Pro-inflammatory adipokines
- Leptin
- ANGPTL2
- CCL2
- Resistin
- TNF
- CXCL5
- RBP4
- IL-6
- NAMPT
- Lipocalin 2
- IL-18

Nature Reviews | Immunology
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 affect, 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

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<tr>
<th></th>
<th>Oral E2</th>
<th>TD E2</th>
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<tbody>
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<td>CRP</td>
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<td>⇧</td>
</tr>
<tr>
<td>MMP</td>
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<td>⇧</td>
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<tr>
<td>VTE</td>
<td>↑</td>
<td>⇧</td>
</tr>
<tr>
<td>HDL</td>
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<tr>
<td>TG</td>
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<td>⇧</td>
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<tr>
<td>Adiponectin</td>
<td>↓</td>
<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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</tbody>
</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
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 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.
Summary-2

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.