Managing Menopause amid Controversy

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Massachusetts General Hospital  
Harvard Medical School
From here…
How did we get here?

Menopause Management — Getting Clinical Care Back on Track
JoAnn E. Manson, M.D., Dr.P.H., and Andrew M. Kaunitz, M.D.

By 2020, more than 50 million U.S. women will be older than 51 years of age, the mean age when menopause occurs. During the late stages of the perimenopausal transition, almost three quarters of women report symptoms such as hot flashes or night sweats, and women with moderate-to-severe symptoms often for these symptoms and should be recommended for women with moderate-to-severe vasomotor symptoms, in the absence of contraindications. Such criteria apply to approximately 20% of women in early menopause, most of whom remain untreated despite having symptoms that adversely affect their daily life. The management of chronic disease in postmenopausal women who were on average 63 years of age at initiation of therapy (both of us serve as investigators and one of us [J.E.M.] as a Steering Committee member). But its results are now being used inappropriately in making decisions about treatment for women in their 40s and 50s.
What we know about menopausal symptoms

Clear relationship to menopause:
- Vasomotor symptoms
- Vaginal dryness
- Sleep disturbance
- Mood disturbance
- Joint pain
- Cognition: slight changes in memory, processing speed in late perimenopause

The Study of Women’s Health Across the Nation (SWAN)

Multicenter, multi-ethnic longitudinal study of menopause transition

3300 healthy women followed for 5 years
Vasomotor Symptoms: Duration and Risk Factors

Frequent hot flashes last > 7 years for more than half of women

Early onset predicts longer duration

Moderate to severe symptoms in 40% of women 60 to 65

Avis NE. JAMA Intern Med 2015;175:531.
Freeman EW. Menopause 2014;21:924.
Menopause and the Brain

Estrogen has multiple neurophysiologic effects

Transient changes in processing ability occur during late perimenopause, temporarily affecting learning ability\(^1\)

1 Greendale GA. Neurology 2009;72:1850
Menopause and Mood

Depressive symptoms increase in menopause transition
- 2- to 4-fold increase in depressive symptoms\textsuperscript{1,2,3,4}
- Incidence of depression is 1 in 4

Menopause transition is a “window of vulnerability” for some women\textsuperscript{5}

\begin{itemize}
\item 1 Schmidt PJ. Am J Psych 2004;161:2238
\item 2 Freeman EW. Arch Gen Psych 2006;63:375
\item 3 Cohen LS. Arch Gen Psych 2006;63:385
\item 4 Bromberger JT J Affect Disord 2007
\item 5 Freeman EW. Menopause 2010:17:823.
\end{itemize}
### Menopause and Sexual Function

<table>
<thead>
<tr>
<th></th>
<th>Premenopause</th>
<th>Post-menopause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low desire (&lt; once/week)</td>
<td>42%</td>
<td>65%</td>
</tr>
<tr>
<td>Pain w/ intercourse</td>
<td>15%</td>
<td>30%</td>
</tr>
</tbody>
</table>

Avis NE. Menopause 2009;16:422
Metabolic Changes at Menopause
Changes in bone density begin in late perimenopause

Finkelstein JS. J Clin Endocrinol Metab 2008;93:861
Management of Menopausal Symptoms

1. Hormone Therapy (HT)
   - Estrogen plus progestogen
   - Estrogen alone
   - Choice of therapy
   - Starting and stopping therapy

2. Nonhormonal Therapy
Case 1.

53 year old nurse
Menopause at 52
Recent BMD: femoral neck T score = -2.0
Otherwise healthy
No breast cancer risk factors

Severe hot flashes, insomnia, and vaginal dryness
Benefits and Risks of Two Hormone-Therapy Formulations
CEE/MPA and CEE Alone in Women 50-59

A CEE-MPA Trial

<table>
<thead>
<tr>
<th>Intergroup Difference in No. of Events per 1000 Women over 5 Yr</th>
<th>Risks</th>
</tr>
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<tbody>
<tr>
<td>Coronary Heart Disease</td>
<td>2.5</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.5</td>
</tr>
<tr>
<td>Deep-Vein Thrombosis</td>
<td>5.0</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>3.0</td>
</tr>
<tr>
<td>Colorectal Cancer</td>
<td>-0.5</td>
</tr>
<tr>
<td>All Cancers</td>
<td>-0.5</td>
</tr>
<tr>
<td>All Fractures</td>
<td>-12.0</td>
</tr>
<tr>
<td>Death from Any Cause</td>
<td>-5.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>-5.5</td>
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B CEE-Alone Trial

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<tr>
<td>Colorectal Cancer</td>
<td>-1.5</td>
</tr>
<tr>
<td>All Cancers</td>
<td>-4.0</td>
</tr>
<tr>
<td>All Fractures</td>
<td>-8.0</td>
</tr>
<tr>
<td>Death from Any Cause</td>
<td>-5.5</td>
</tr>
<tr>
<td>Diabetes</td>
<td>-13.0</td>
</tr>
</tbody>
</table>
Risks and benefits of combined hormone therapy in women ages 50-59

For every 1,000 women taking E +P for 5 years:

- 2.5 more coronary events
- 2.5 more strokes
- 5 more DVT
- 3 more breast cancers
- 0.5 fewer colon cancer
- 0.5 fewer all cancers
- 12 fewer fractures
- 5.5 fewer diabetes
- 5 fewer deaths

Manson JE. JAMA 2013:310:1353; Manson JE NEJM 2016;374:9
HT in early postmenopause and cardiovascular risk:
The Timing Hypothesis
HRT and cardiovascular events in recently postmenopausal women: randomised trial

Danish Osteoporosis Prevention Trial

1006 healthy women age 45-58, recently menopausal, 16 years follow-up

Randomized to triphasic estradiol (2 mg/1 mg) + norethisterone (estradiol alone if s/p hyst)

10 years on Rx; then additional 5 year f/u

Schierbeck LL. BMJ 2012;245;e6409
Danish trial of HRT in recently menopausal women: results after 10 years

<table>
<thead>
<tr>
<th></th>
<th>HRT</th>
<th>Placebo</th>
<th>HR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>n = 502</td>
<td>n = 504</td>
<td></td>
</tr>
<tr>
<td>MI, heart failure, or death</td>
<td>16</td>
<td>33</td>
<td>0.48 (.26 - .87)</td>
</tr>
</tbody>
</table>

Schierbeck LL. BMJ 2012;245;e6409
HT within 10 years of menopause and risk of CVD

Boardman HT. Cochrane Database of Systematic Reviews 2015

### Review: Hormone therapy for preventing cardiovascular disease in post-menopausal women

**Comparison:** Subgroup analysis of timing hypothesis (<10 years versus >10 years since menopause)

**Outcome:** Coronary heart disease (death from cardiovascular causes and non-fatal myocardial infarction)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>HT n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hormone therapy commenced &lt;10 years after menopause</td>
<td>DOPS 2012 6/502</td>
<td>22/504</td>
<td>0.27 (0.11, 0.67)</td>
<td>25.2%</td>
</tr>
<tr>
<td>ERT II 1979 1/84</td>
<td>3/84</td>
<td>0.33 (0.04, 3.14)</td>
<td>6.4%</td>
<td></td>
</tr>
<tr>
<td>WHI II 2002 31/2762</td>
<td>35/2712</td>
<td>0.86 (0.53, 1.40)</td>
<td>41.5%</td>
<td></td>
</tr>
<tr>
<td>WHI II 2004 8/826</td>
<td>16/817</td>
<td>0.49 (0.21, 1.15)</td>
<td>26.8%</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>4194</strong></td>
<td><strong>4117</strong></td>
<td><strong>0.52 (0.29, 0.96)</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

Total events: 46 (HT), 76 (Control)

Heterogeneity: Tau² = 0.17; Chi² = 5.64, df = 3 (P = 0.13); I² = 47%

Test for overall effect: Z = 2.10 (P = 0.036)
Vascular effects of HT in early vs late postmenopausal women: recent trials

Effect on carotid intimal media thickness

1. KEEPS (Kronos Early Estrogen Prevention Study)
   conjugated estrogen 0.45 or estradiol 50 mcg patch with cyclic oral progesterone

2. ELITE (Early vs Late Intervention Trial with Estradiol)
The KEEPS Study

Randomized trial of 727 healthy women < 3 years from last menses
Oral conjugated estrogen .45 mg OR transdermal estradiol 50 mcg, plus oral progesterone 12 d/month
Duration 4 years
NO effect on carotid atherosclerosis or coronary artery calcium score
The ELITE study: Design

Randomized trial of 643 healthy postmenopausal women in 2 groups:
  < 6 years from menopause
  > 10 years from menopause

Oral estradiol 1 mg/day plus progesterone 45 mg vaginal gel for 10 days/month (if uterus intact) vs placebo

Median duration 5 years

The ELITE study: Results

Results:

Less progression of subclinical atherosclerosis with estradiol <6 years from menopause vs placebo

No effect in those >10 years from menopause

HT in early postmenopause and breast cancer risk
Conjugated estrogens plus medroxyprogesterone and breast cancer risk over time

At 3 yrs: increase in risk becomes statistically significant
What have we learned about HT and breast cancer risk in early postmenopause?

Breast cancer risk increases with combined HT use beyond 3 to 5 years

Breast density is a marker for the increased risk on HRT\(^1,2\)

Increased risk gradually attenuates after stopping combined HT\(^3\)

1 Hou N. JNCI 2013;105:1365; 2 Byrne C. JNCI 2017;109:djx001
3 Manson JE. JAMA 2013:310:1353
Progestin in combined HT increases risk

No increase in breast cancer risk after 7 years of estrogen alone

Hazard ratio (CI)

Breast cancer  0.77 (0.62 - 0.95)

LaCroix AZ  JAMA 2011;305:1305
HT in early postmenopause and effects on cognition
The ELITE study: Design

Randomized trial of 643 healthy postmenopausal women in 2 groups:
- < 6 years from menopause
- > 10 years from menopause

Oral estradiol 1 mg/day plus progesterone 45 mg vaginal gel for 10 days/month (if uterus intact) vs placebo

Median duration 5 years

Henderson VW. Neurology 2017;87:699.
The ELITE study: Results

Results:
No difference in cognitive function between women treated with estradiol vs placebo, regardless of time from menopause.

Estradiol neither benefits nor harms cognitive function regardless of time since menopause.

Henderson VW. Neurology 2017;87:699.
Risks and Benefits After Stopping Estrogen: Cognitive Function

Women 50-55 years, 7 years after stopping either E/P or E alone:

No effect (positive or negative) of either regimen on cognitive function

Espeland MA. JAMA Intern Med 2013;173;1429
Summary of menopausal hormone therapy

Hormone therapy has a complex pattern of benefits and risks.
Use in symptomatic early menopausal women is appropriate.
Long-term continuation of hormone therapy requires shared decision-making and periodic risk reassessment.
Treatment of menopausal symptoms with HT

What are benefits and risks of estrogen in early postmenopause?

What preparation and dosage?
Transdermal Estrogen

Available in patch, gel, emulsion, spray
Less adverse effects on:
  - Triglycerides
  - Cardiac biomarkers (e.g. CRP)
  - Clotting
  - Liver function
  - Sex hormone binding globulin

Sexual function improved compared to oral CEE¹

Less risk of venous thrombosis²,³
Less risk of cholecystectomy

1. Taylor HS.  JAMA Intern Med 8/28/17  online  
3. Racine A.  CMAJ 2013;185:555
Transdermal Estrogen

What is a good starting regimen?

- Estradiol
  - 14 mcg *ultra low dose*
  - 25 mcg *low dose*
  - 37.5 mcg
  - 50 mcg *average dose*

- Micronized progesterone cyclic or continuous (for women with uterus)
Estradiol Levels during Menopause Transition

$E_2$ (pg/ml)

FMP

# yrs around FMP

Graph showing the decline of estradiol levels around the time of menopause (FMP).
Transdermal estrogens and serum estradiol levels

pg/ml

Premenopausal level

Postmenopausal level

50 ug patch

37.5 patch

25 ug patch
When is a progestogen required?

Use with **systemic** doses of estradiol 25 mcg/day or higher

Not necessary to use progestin with standard doses of **vaginal** estrogen
<table>
<thead>
<tr>
<th>Progestogen Regimen</th>
<th>Typical Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micronized progesterone (Prometrium)</td>
<td>100 - 200 mg qd or cyclic</td>
</tr>
<tr>
<td>Medroxyprogesterone</td>
<td>1.5 mg qd</td>
</tr>
<tr>
<td>Norethindrone</td>
<td>1.0 mg qd</td>
</tr>
<tr>
<td>Drospirenone</td>
<td>0.5 mg qd</td>
</tr>
</tbody>
</table>

**Mirena IUD***

* not FDA approved for postmenopausal women
A new drug class: tissue-selective estrogen complexes

Combined estrogen agonist/antagonist (SERM)

45 mg conjugated estrogens
20 mg bazedoxifene

FDA approved as Duavee

Indications:
- Treatment of mod-severe hot flashes
- Prevention of osteoporosis
Conjugated estrogens and bazedoxifene

Relief of hot flashes
Preservation of bone density
Maintenance of normal endometrium
Reduces vulvovaginal atrophy symptoms
No adverse effects on lipids
Venous thromboembolism risk similar to estrogen alone

Treatment of Vulvovaginal Symptoms: Topical Therapy

Conjugated estrogen 0.5 gm or estradiol vaginal cream 1 gm pv 2x/w

Estring **
  - delivers estradiol 7.5 ug/day

Estradiol vaginal tablets** Vagifem/Yuvafem
  - estradiol 10 ug 2x/w

COST barrier – decreased formulary coverage?
Vaginal Prasterone (Intragosa) for genitourinary syndrome of menopause

FDA approved 11/16

DHEA
6.5 mg daily intravaginally

Adverse effects:
- Vaginal discharge (14%)
- Minor Pap smear abnormalities (2%)
Oral Ospemifene (Osphena) for vaginal atrophy

SERM
60 mg daily

Adverse effects:
- Hot flashes (9% vs 3%)
- Very rare DVT, stroke (1:1000)

Bachmann G. Menopause 2010 17:480
Hormone Therapy and Urinary Symptoms

**Urge incontinence:** vaginal ET may help

**Overactive bladder:** vaginal ET helps\(^1\)

**Stress incontinence:** systemic HT may worsen; effect of local ET varies

**Recurrent UTI:** vaginal ET reduces recurrence

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1 Nelken RS. Menopause 2011;18:962
Cochran Database of Systematic Reviews 2010
Hormonal therapy for sexual dysfunction after menopause

Vaginal dryness, pain  
Topical estrogen

Decreased libido  
???

Transdermal testosterone shows some evidence for benefit\textsuperscript{1-3}, but no long-term safety data; not approved by FDA

Topical testosterone 1\% (off-label): monitor testosterone levels

1 Shifren J et al. Menopause 2008;13:770  
“Bioidentical” hormone therapy

No good evidence for greater safety with custom-compounded formulations

Standardization is uncertain

Salivary and blood testing is difficult to interpret

No safety data on topical progesterone for endometrial protection: use not recommended
Treatment of menopausal symptom with HT

What are benefits and risks of estrogen in early postmenopause?
What preparation and dosage?

How long should treatment be continued?
Stopping HRT

Duration of therapy
- Combined HT: < 5 years recommended
- Estrogen alone: up to 7 years\(^1\)
- Duration should be individualized; longer duration may be appropriate for informed patients with persistent symptoms
- 1 in 4 women have difficulty stopping

Reassess risk annually
Monitor breast density on mammography

Taper gradually

1 US Preventive Services Task Force 2012
Management of Menopausal Symptoms

1. Hormone Therapy (HT)

2. Nonhormonal Therapy
Case 2.

55 year old postmenopausal woman with stage 1 breast cancer on tamoxifen bothered by hot flashes and sleep disturbance

Case 3

49 year old, missed 2 periods in past 6 months
Hot flashes, insomnia, anxiety
Does not want to use estrogen
Effectiveness of treatment options for hot flashes

% Reduction

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen</td>
<td>-90</td>
</tr>
<tr>
<td>SSRI</td>
<td>-80</td>
</tr>
<tr>
<td>Clonidine</td>
<td>-70</td>
</tr>
<tr>
<td>CAM</td>
<td>-60</td>
</tr>
</tbody>
</table>
Alternatives to hormone therapy for vasomotor symptoms

Relaxation techniques and mindfulness meditation
Exercise
Yoga
Clinical hypnosis¹
Acupuncture²

² Cochrane Review 2013
Yoga decreases insomnia in postmenopausal women: a randomized clinical trial


Reduced:
- menopausal symptoms
- insomnia severity

Improved:
- quality of life
- stress resistance
Plant-based therapies and menopausal symptoms

Phytoestrogens (dietary soy, soy supplements, red clover)
- Modest reduction in hot flashes and vaginal dryness
- No significant effect on night sweats

Black cohosh, Chinese medicinal herbs: no effect

Nonhormonal Therapy for Vasomotor Symptoms

SSRIs and SNRIs

- Fluoxetine 20 mg qd
- Venlafaxine SR 37.5 – 75 mg qd
- Desvenlafaxine 100 mg qd
- Paroxetine 7.5 mg * to 20 mg qd
- Citalopram 10 – 30 mg qd
- Escitalopram 10 - 20 mg qd

*FDA approved

- Avoid fluoxetine and paroxetine in women on tamoxifen
Nonhormonal Therapy for Vasomotor Symptoms

Gabapentin\textsuperscript{1,2}
  \begin{itemize}
    \item 300 mg tid – 800 mg tid
  \end{itemize}

Clonidine
  \begin{itemize}
    \item 0.1 - 0.2 mg bid po or 0.1 mg qd patch
  \end{itemize}

1 Reddy SY. Obstet Gynecol 2006;108:41
Summary

Ask about symptoms, especially vaginal dryness, depression, sexual concerns

Anticipate metabolic changes; use menopause as opportunity to address behavioral risk factors for CVD

Estrogen has an important role in treatment of symptoms in early postmenopausal women and can be used safely for short term

Shared decision-making is key
Resources

North American Menopause Society
www.NAMS.org

Useful patient education materials on menopause, treatments, sexuality