Managing Menopause with Hormones

Cynthia A. Stuenkel, MD
Clinical Professor of Medicine
Division of Endocrinology and Metabolism

No conflicts to disclose
Managing Menopause with Hormones
Presentation Objectives

- Acknowledge uniqueness of women with BRCA+
- Review basics of menopause
- Best available evidence overall for risks and benefits of menopausal hormone therapy
- Best available evidence for women with BRCA+ regarding risks and benefits of menopausal hormone therapy
- Expert recommendations and path ahead
## Cancer Risk in BRCA Carriers

<table>
<thead>
<tr>
<th></th>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast cancer</strong></td>
<td>55-70%</td>
<td>45-70%</td>
</tr>
<tr>
<td><strong>Peak age</strong></td>
<td>30-40 y</td>
<td>40-50 y</td>
</tr>
<tr>
<td><strong>Ovarian cancer</strong></td>
<td>40%</td>
<td>15%</td>
</tr>
</tbody>
</table>
## Management of Cancer Risk in BRCA Carriers

<table>
<thead>
<tr>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovariectomy</td>
<td>age 35-40 y</td>
</tr>
<tr>
<td>Breast risk</td>
<td>age 40-45 y</td>
</tr>
<tr>
<td>- Mastectomy</td>
<td>?</td>
</tr>
<tr>
<td>- Chemoprevention</td>
<td>?</td>
</tr>
<tr>
<td>- Surveillance</td>
<td>?</td>
</tr>
<tr>
<td>Endometrium</td>
<td>?</td>
</tr>
</tbody>
</table>

UpToDate Topic 758 Version 40.0; Last updated 9/4/18; accessed 9/30/18.
What is menopause?
The Menopausal Transition

20s  30s  40s  50s  60s  70s  80s+

Reproductive  Menopause transition  Postmenopause
The Menopausal Transition

20s       30s          40s         50s        60s      70s      80s+

Reproductive  Menopause transition  Postmenopause

Menopause
The Menopausal Transition

20s       30s          40s         50s        60s      70s      80s+

Reproductive  Menopause transition  Postmenopause

Menopause

The final menstrual period— diagnosed retrospectively after 12 months without a period
What causes menopause?
When does menopause occur?
Timing of Menopause

- 20s: Reproductive
- 30s: Menopause transition
- 40s: Menopause transition
- 50s: Postmenopause
- 60s: Postmenopause
- 70s: Postmenopause
- 80s+: Postmenopause

Menopause
Timing of Menopause

20s  30s  40s  50s  60s  70s  80s+
Reproductive  Menopause transition  Postmenopause

46-55
Menopause
Timing of Menopause

20s       30s          40s         50s        60s      70s      80s+
Reproductive Menopause transition Postmenopause

40-45 Early

46-55 Menopause
Timing of Menopause

20s  30s  40s  50s  60s  70s  80s+

Reproductive  Menopause transition  Postmenopause

< 40 years  40-45  46-55  Menopause

Premature  Early

Premature Menopause
What hormones change with menopause?
Hormones in Relation to FMP: Melbourne Women’s Midlife Health Project

FMP = final menstrual period
Hormones in Relation to FMP: Melbourne Women’s Midlife Health Project

FMP = final menstrual period
<table>
<thead>
<tr>
<th>Estrogen</th>
<th>Pre-</th>
<th>Post-</th>
<th>Surgical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol (E2) (pg/mL)</td>
<td>50-250</td>
<td>10-20</td>
<td>less!</td>
</tr>
<tr>
<td>Estrone (E1) (pg/mL)</td>
<td>50-125</td>
<td>30-35</td>
<td>“</td>
</tr>
</tbody>
</table>

Greenspan’s Textbook; 9th Ed, 2011; Table 13-6.
What are the consequences of menopause?
Consequences of Menopause
The Good News

Liberates women from:

- Inconvenience and discomfort of monthly menstrual cycles
- Associated mood swings
- Concerns with contraception and risk of unintended pregnancy
Consequences of Menopause
The Good News

Liberates women from:

- Inconvenience and discomfort of monthly menstrual cycles
- Associated mood swings
- Concerns with contraception and risk of unintended pregnancy
- Oophorectomy reduces ovarian and breast cancer risk substantially
Age Specific Incidence of Breast Cancer
Nurses’ Health Study

Consequences of Menopause
The Bad News: Symptoms

Decline in estrogen associated with:

- Vasomotor symptoms
- Depressive and anxiety symptoms, sleep disorders, memory complaints
- Genitourinary symptoms
What are concerns about early or premature menopause?
Potential Concerns about Early and Premature Menopause

- Menopause symptoms occur abruptly and in some cases, are more severe.
- There are some concerns that shortening the reproductive life span (puberty to menopause) might be associated with increased diseases of aging.
  - Heart disease, diabetes, osteoporosis, cognitive decline
- Studies are limited in women without BRCA+ and almost nonexistent in those positive for BRCA+.
- There are no randomized trials to assess benefits and risks of menopausal hormone therapy in either group.

Recommendations: Menopausal Hormone Therapy for Early and Premature Menopause

- For young women with primary ovarian insufficiency, premature or early menopause (not BRCA carriers)
- Without contraindications
- We suggest taking menopause hormone therapy
- Until the time of natural menopause
- When the advisability of continuing can be reassessed

The Endocrine Society, 2015
North American Menopause Society, 2017
American College of Obstetricians and Gynecologists, 2014
What are vasomotor symptoms?
Treatments of Menopause-Associated Vasomotor Symptoms

Estrogen

Prescription Rx

Nonprescription Therapy

Mind-Body and Behavior

Lifestyle Modifications

Treatments of Menopause-Associated Vasomotor Symptoms

- Estrogen
- Prescription Rx
- Nonprescription Therapy
- Mind-Body and Behavior
- Lifestyle Modifications

Estrogen therapy is the most effective treatment of hot flashes (systemic) and vaginal dryness (local therapy). It prevents bone loss, osteoporosis, and fractures (2 sx studies in BRCA carriers)*

Estrogen has been in use since the 1940’s when conjugated equine estrogens (Premarin) was approved.

Women with a uterus require endometrial protection with progestogen or bazedoxifene (a selective estrogen-receptor modulator) because estrogen alone increases uterine cancer risk

What evidence is available to inform us of the risks and benefits of hormone therapy?
Hierarchy of Evidence

- Meta-Analysis of Randomized Controlled Trials
- Systematic Review of RCTs
- Primary and Secondary Analyses
  - Subset Analyses
- Cohort and Case-Control Studies
- Test Tube, Animal, Human Physiology
- Expert Opinions, Consensus Opinions

Strong

Oxford Centre for Evidence Based Medicine; May 2001.
Hierarchy of Evidence

- Meta-Analysis of Randomized Controlled Trials
  Systematic Review of RCTs
  Primary and Secondary Analyses
  Subset Analyses
  Cohort and Case-Control Studies
  Test Tube, Animal, Human Physiology
  Expert Opinions, Consensus Opinions

Oxford Centre for Evidence Based Medicine; May 2001.
## Hierarchy of Evidence

<table>
<thead>
<tr>
<th>Strong</th>
<th>Weak</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meta-Analysis of Randomized Controlled Trials</td>
<td>Test Tube, Animal, Human Physiology</td>
</tr>
<tr>
<td>Systematic Review of RCTs</td>
<td>Expert Opinions, Consensus Opinions</td>
</tr>
<tr>
<td>Primary and Secondary Analyses</td>
<td>Cohort and Case-Control Studies</td>
</tr>
<tr>
<td>Subset Analyses</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Oxford Centre for Evidence Based Medicine; May 2001.
Hormone Therapy for Menopause Symptom Relief

- No adequately powered RCTs with clinical outcomes have been specifically conducted with younger, symptomatic women
- The best available evidence in women 50 to 59 years or age of < 10 years since menopause comes from subgroup analyses of WHI data
- This data provide trends but few statistically significant differences

WHI 2013 Update: Intervention and Extended Poststopping Phases

- **CEE + MPA**
  - Intervention: 5.6 y
  - Postintervention: 13 y
  - Cumulative: 13 y

CEE, conjugated equine estrogens, 0.625 mg; MPA, medroxyprogesterone acetate, 2.5 mg
WHI 2013 Update: Intervention and Extended Poststopping Phases

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Postintervention</th>
<th>Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CEE + MPA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.6 y</td>
<td></td>
<td>13 y</td>
</tr>
<tr>
<td><strong>CEE-alone</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.2 y</td>
<td></td>
<td>13 y</td>
</tr>
</tbody>
</table>

CEE, conjugated equine estrogens, 0.625 mg; MPA, medroxyprogesterone acetate, 2.5 mg
Benefits and Risks of MHT
Events per 1000 women age 50-59 per 5 y

Manson JE and Kaunitz AM. N Engl J Med 2016; 374:803-806; intergroup difference in number of events
Age Specific Incidence of Breast Cancer Nurses’ Health Study

Age Specific Incidence of Breast Cancer
Nurses’ Health Study

Age Specific Incidence of Breast Cancer
Nurses’ Health Study

Age Specific Incidence of Breast Cancer
Nurses’ Health Study

What do we know about HT in women with BRCA mutations?
Observational Studies Evaluating Hormone Therapy in Women with BRCA+

- Prevention and Observation of Surgical Endpoints\(^1\)
  - 462 BRCA carriers; 114 took HT
  - No impact on breast cancer risk with HT among those who underwent a BSO

- Matched case-control study\(^2\)
  - 472 postmenopausal women with BRCA1 mutations
  - Inverse (beneficial) relationship between E-alone and breast cancer
  - No significant association with combined E+P

- Decision analysis\(^3\)
  - HT after BSO and mastectomy taken until age 50 improved life expectancy

What steps are involved to check whether hormone therapy makes sense for me?
Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline

Cynthia A. Stuenkel, Susan R. Davis, Anne Gompel, Mary Ann Lumsden, M. Hassan Murad, JoAnn V. Pinkerton, and Richard J. Santen

University of California, San Diego, Endocrine/Metabolism (C.A.S.), La Jolla, California 92093; Monash University, School of Public Health and Preventive Medicine (S.R.D.), Melbourne 03004, Australia; Université Paris Descartes, Hôpitaux Universitaires Port Royal-Cochin Unit de Gynécologie Endocrinienne (A.G.), Paris 75014, France; University of Glasgow School of Medicine (M.A.L.), Glasgow G31 2ER, Scotland; Mayo Clinic, Division of Preventive Medicine (M.H.M.), Rochester, Minnesota 55905; University of Virginia, Obstetrics and Gynecology (J.V.P.), Charlottesville, Virginia 22908; and University of Virginia Health System (R.J.S.), Charlottesville, Virginia 22903

Position Statement

The 2017 hormone therapy position statement of The North American Menopause Society

Abstract

The 2017 Hormone Therapy Position Statement of The North American Menopause Society (NAMS) updates the 2012 Hormone Therapy Position Statement of The North American Menopause Society and identifies future research needs. An Advisory Panel of clinicians and researchers expert in the field of women’s health and menopause was recruited by NAMS to review the 2012 Position Statement, evaluate new literature, assess the evidence, and reach consensus on recommendations, using the level of evidence to identify the strength of recommendations and the quality of the evidence. The Panel’s recommendations were reviewed and approved by the NAMS Board of Trustees.

Hormone therapy (HT) remains the most effective treatment for vasomotor symptoms (VMS) and the genitourinary syndrome of menopause (GSM) and has been shown to prevent bone loss and fracture. The risks of HT differ depending on type, dose, duration of use, route of administration, timing of initiation, and whether a progestogen is used. Treatment should be individualized to identify the most appropriate HT type, dose, formulation, route of administration, and duration of use, using the best available evidence to maximize benefits and minimize risks, with
Goals of the Guideline

- Focus on **treatment of symptoms** of menopause
- Emphasize **individualized clinical approach**
  - Patient symptoms
  - Personal preferences
  - Overall health status
- Suggest **baseline risk assessments**
  - Contraindications to medical therapies
  - Cardiovascular risks
  - Breast cancer risks
Approach to Patient with VMS Considering MHT

Assess Patient Criteria
- Symptomatic woman?
  - Age < 60 y or
  - < 10 y since menopause
- Interested in MHT?

If age ≥ 60 y or ≥ 10 y since menopause

CONSIDER OTHER OPTIONS

YES

Consider circumstances where MHT should not be used:
- Contraindications
- Cautions
Contraindications to Hormone Therapy

- Possibility of pregnancy
- Undiagnosed vaginal bleeding
- Estrogen sensitive cancers (breast/endometrium)
- History of stroke or MI
- History of deep vein thrombosis or pulmonary embolism
- Liver dysfunction or disease
Approach to Patient with VMS Considering MHT

- Evaluate Cardiovascular Risk
- Acceptable
- High *
- Consider Other Options

* Includes known CHD, CVD, PAD, etc.

Approach to Patient with VMS Considering MHT

- EVALUATE BREAST CANCER RISK
  - HIGH to MODERATE *
    - CONSIDER OTHER OPTIONS

* Includes calculated level of risk that would qualify for risk-reducing medications

ACCEPTABLE

Approach to Patient with VMS Considering MHT

UTERUS PRESENT?

- ESTROGEN plus PROGESTOGEN
- ESTROGEN combined with BAZEDOXIFENE
- TIBOLONE where available

NO

ESTROGEN ALONE
The MenoPro app from The North American Menopause Society (NAMS) has 2 modes: one for clinicians and one for women/patients, to support shared decision making.

Are you a Health Care Provider or Woman/Patient?
“As the impact of severe menopausal symptoms on quality of life may be substantial, however, there are instances in which a woman with a history of coronary heart disease or breast cancer, for example, will choose to accept a degree of risk that might be considered to outweigh the benefits of MHT.

An accepted philosophy is that a fully informed patient should be empowered to make a decision that best balances benefits to that individual when weighed against potential risks.”
What do expert groups say about BRCA carriers and HT?
**Recommendations: Menopausal Hormone Therapy for BRCA+ Women after Oophorectomy**

- For women at high risk of breast cancer considering MHT for menopausal symptom relief, we suggest nonhormonal therapies over MHT to relieve symptoms (Endocrine Soc, 2015)

- Limited observational evidence suggest that MHT use does not further increase risk of breast cancer in women after oophorectomy for BRCA 1 or 2 gene mutations (NAMS, 2017)

- Menopausal symptoms are common in women who have undergone risk-reducing BSO. For women without a history of breast cancer, MHT can mitigate symptoms (ACOG, 2017)
Recommendations: Menopausal Hormone Therapy for BRCA+ Women after Oophorectomy

Up-to-Date: Shared Decision Making

- Suggest nonhormonal options initially. If MHT is elected,
  - Limit the duration of MHT
    - Start after surgery and taper after several years
    - Or stop at 51 years, average age of menopause
  - Use of unopposed estrogen
    - Concurrent hysterectomy (no need for progestins to protect)
    - Use ultra-low transdermal estrogen with progestins at 6 & 12 mo
- Prophylactic mastectomy

UpToDate Topic 758 Version 40.0; Last updated 9/4/18; accessed 9/30/18.
What do prominent oncologists advise?
Recommendations: Menopausal Hormone Therapy for BRCA+ Women after Oophorectomy

- The use of HRT should follow the overall recommendations to relieve vasomotor symptoms and improve urogenital symptoms and osteoporosis as needed.
- Also consider the increased risk of breast cancer associated with long-term use of estrogen-progestogens.
- For women with BRCA1 and/or BRCA2 mutations after BSO, HRT <50 years of age for short periods of time seems safe.

Recommendations: Menopausal Hormone Therapy for BRCA+ Women after Oophorectomy

- Limited data suggest that HRT is not unreasonable in women with a BRCA mutation who undergo a BSO for surgical cancer prevention.
- However, the lack of data makes it difficult to make definitive conclusions.
- Larger observational prospective studies are needed to better evaluate the safety of HRT in this population.

Anything new since these recommendations?
Hormone Replacement Therapy After Oophorectomy and Breast Cancer Risk Among \textit{BRCA1} Mutation Carriers

Joanne Kotsopoulos, PhD; Jacek Gronwald; Beth Y. Karlan, MD; Tomasz Huzarski, MD; Nadine Tung, MD; Pal Moller, MD; Susan Armel; Henry T. Lynch, MD; Leigha Senter; Andrea Eisen, MD; Christian F. Singer, MD, MPH; William D. Foulkes, MBBS, PhD; Michelle R. Jacobson, MD, MHS; Ping Sun, PhD; Jan Lubinski; Steven A. Narod, MD; The Hereditary Breast Cancer Clinical Study Group
Breast Cancer Incidence among BRCA1 Carriers by HRT Use

- Prospective, longitudinal cohort study
- BRCA carriers from 80 centers/17 countries
- Mean follow up of 872 women 7.6 years
- Included BRCA1 age 43.4 years with BSO
- Questionnaire every 2 years with 92 ca
- HRT use overall did not increase breast ca
- After 10 years, E-alone, 10% incidence
  E+P, 22%; p< .04

Kotsopoulos J, et al. JAMA Oncology, 2018 Aug 1
Breast Cancer Incidence among BRCA1 Carriers by HRT Use

- Prospective, longitudinal cohort study
- BRCA carriers from 80 centers/17 countries
- Mean follow up of 872 women 7.6 years
- Included BRCA1 age 43.4 years with BSO
- Questionnaire every 2 years with 92 ca
- HRT use overall did not increase breast ca
- After 10 years, E-alone, 10% incidence
- E+P, 22%; \( p < .04 \)

Kotsopoulos J, et al. *JAMA Oncology*, 2018 Aug 1
Breast Cancer Incidence among BRCA1
E versus E+P (oophorectomy < age 45)

10-y risk:
9% on E

24% on E+P

Kotsopoulos J, et al. *JAMA Oncology*, 2018 Aug 1
Breast Cancer Incidence among BRCA1 E versus E+P (oophorectomy < age 45)

What does it all mean?

- May be a possible protective effect for E-alone (like WHI)
- Increased risk of E+P (similar to that in the WHI)
- Not shown here, this group reported increased risk of uterine cancer with E+P (opposite of WHI)
- Should women undergoing BSO before age 45 also consider hysterectomy and just use E-alone?
- Future studies are necessary to confirm these findings

Kotsopoulos J, et al. *JAMA Oncology*, 2018 Aug 1
What options are available for hormone therapies?
Low Dose Estrogen for Treatment of Vasomotor Symptoms

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORAL</strong></td>
<td></td>
</tr>
<tr>
<td>Conjugated equine estrogens</td>
<td>0.3 mg</td>
</tr>
<tr>
<td>Micronized 17-(B)-estradiol</td>
<td>0.5 mg</td>
</tr>
<tr>
<td><strong>TRANSDERMAL</strong></td>
<td></td>
</tr>
<tr>
<td>17-(B)-estradiol patch*</td>
<td>25 mcg</td>
</tr>
<tr>
<td>Cutaneous gel*</td>
<td>1-1.25 g</td>
</tr>
<tr>
<td>Estrogen lotion</td>
<td>1 packet</td>
</tr>
<tr>
<td><strong>VAGINAL</strong></td>
<td></td>
</tr>
<tr>
<td>Silastic ring estradiol acetate</td>
<td>3 months</td>
</tr>
</tbody>
</table>

* 14 mcg patch and .25 g gel effective at 12 weeks

Tailoring Hormone Therapy

- Progestogen administration
  - Synthetic preparations or progesterone
  - Prevents endometrial hyperplasia and cancer
  - Options: oral, transdermal by patch, vaginally, or intrauterine device

- Bazedoxifene* in combination with estrogen (CEE) is another option for endometrial protection

* Bazedoxifene is a SERM, a Selective Estrogen Receptor Modulator
There is insufficient evidence regarding the safety and efficacy of compounded “bioidentical” hormone therapy for treatment of menopausal symptoms.

Unable to identify any clinical trials comparing compounded hormone therapy for menopausal symptoms that met our criteria.

Limitations in the evidence base emphasizes the priority that should be given to future research.

“Are you experiencing vaginal dryness or discomfort with intercourse?”
Genitourinary Syndrome of Menopause (GSM)

- A collection of symptoms and signs associated with decreased estrogen levels that can involve the labia majora, labia minora, vestibule, introitus, clitoris, vagina, urethra, and bladder.
- Treatment indicated if symptoms are bothersome.
- Treatment should be individualized based on severity of symptoms and the woman’s preference after discussion of treatment options and risks/benefits.

Treatments of Menopause-Associated Vaginal Symptoms

- Vaginal E2 or DHEA
- Systemic HT or SERM Ospemifene
- Nonprescription Remedies
- Lifestyle Modification

Vaginal Symptoms: Estrogen preparations

Vaginal creams
- Conjugated equine estrogens (Premarin)
- 17-B-estradiol (Estrace)

Vaginal rings
- 17-B-estradiol (Estring)*

Vaginal tablets
- Estradiol hemihydrate (Vagifem)

Vaginal inserts
- 17-B-estradiol (IMVEXXY) (approved 5/30/18)

Progestogen is generally not indicated when low-dose estrogen is administered locally. *Serum E2 level = 7 pg/mL
FDA Approves Prasterone for Dypareunia Associated with Menopause

November 17, 2016  (*Intrarosa*)

- Prasterone, 6.5 mg, once-daily qHS vaginal insert
- Active ingredient: dehydroepiandrosterone (DHEA)
- Metabolized to estrogen and testosterone (+ 20%)
- Contraindication: undiagnosed abnormal genital bleeding
- Warning and precaution: current or past breast cancer

What’s the bottom line?
The concept of “lowest dose for the shortest period of time” may be inadequate or even harmful for some.

A more fitting concept is “appropriate dose, duration, regimen, and route of administration.”

Individualization with shared decision making remains key, with periodic reevaluation to determine an individual’s benefit-risk profile.
Managing Symptoms of Menopause

Summary
1. Reviewed physiology of menopause
2. Described the most common symptoms of menopause
3. Listed the key components of patient assessment for appropriateness of hormone therapy
4. Described risks and benefits of hormone therapy, and explain the pros and cons of different types, doses, and routes of administration
5. Emphasize need to individualize approach, particularly when evidence is controversial or inadequate.