New Guidelines for Menopause

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Consultant/Advisory Board
Actavis, Agile, Bayer, ContraMed, Female Health, Merck, MicroCHIPS Biotech, PharmaNest

Learning Objectives
At the conclusion of this presentation, the participant will be able to:

- Describe the normal endocrinologic changes of menopause and their impact on menopausal women.
- List hormonal and nonhormonal therapies available for each of the major menopausal symptom complexes.
- Estimate the health risks associated with use of hormonal therapies to identify appropriate candidates.
Menopause Demographics

Approximately 4900 US women enter menopause each day.

1. North American Menopause Society
2. US Bureau of the Census

When Can IT Start?

- 43 year old healthy woman presents with monthly menses complaining of 2 months of what she now knows are hot flashes. She is confused. She thought hot flashes came with menopause.

- Does she need any tests?
- What is her diagnosis?
- What therapies can you offer her?

The Perimenopausal Transition

- Average age of onset: 46 years
- Age of onset for 95% of women: 39-51 years
- Average duration: 5 years
- Duration for 95% of women: 2-8 years
Endocrinology of Menopause

- Ovarian event
  - Depletion of number of follicles
  - Decreased sensitivity of the few remaining follicles
- Gonadotrophins elevated; FSH increasing more than LH
- Glandular secretion of estrogens decreased
  - Peripheral conversion of androstenedione to estrone increased: age and weight related
  - Testosterone secretion unchanged
- Over 95% of androstenedione is secreted by the adrenal

FSH and E₁ Variability in a Perimenopausal Woman

- FSH variability makes diagnosing menopause using a single FSH value unreliable
- Estrogen variability may account for perimenopausal menstrual irregularities

Menopause Neuroendocrinology: Animal Model

- Supporting evidence for hypothesis that neuroendocrine axis controls transition from regular cycles to irregular cycles but ovary determines ultimate cessation of cycles
  - Transplantation of old ovaries into reproductive-aged, previously oophorectomized animals results in follicular development and ovulation.
  - Grafting young ovaries into old animals does not restore cycling

Earlier and Better Understanding Needed of Perimenopause

- Perimenopause heralded by:
  - Decreased bone density
  - Decreased fertility
  - Poorer implantation
  - Increased spontaneous abortion
- Transition may start 10 years before any break in menstrual cycling -- in early 30’s

Length of Menstrual Cycle By Age

Perimenopausal Symptoms

- Vasomotor symptoms
  - Hot flashes
  - Night sweats
  - Insomnia
- Psychological symptoms
  - Anxiety
  - Emotional liability/irritability
  - Impaired memory, concentration
Hormonal Contraceptives for Vasomotor Treatment

- Cyclic estrogen-containing
  - Birth control pills
  - Vaginal ring
  - Transdermal patch
- Extended cycle birth control pills, vaginal rings
- Question: At what age do you stop them?

Diagnosing Menopause

- Surgical menopause can be diagnosed after bilateral oophorectomy
- Natural menopause:
  - After 12 consecutive months of amenorrhea with no other etiology
  - Trend toward diagnosis after 6 months of amenorrhea
  - No single biochemical test is a reliable guide to an accurate diagnosis before 6 to 12 months of amenorrhea
  - Elevated FSH (>30 mIU/mL) alone does not diagnose menopause
  - One measurement of E1 does not diagnose menopause
  - FSH and E2 levels are not reliable predictors of menopause
  - Variable in perimenopausal women

How Long Oh Lord?

- Duration of moderate to severe hot flashes

<table>
<thead>
<tr>
<th></th>
<th>Median Duration (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All women</td>
<td>10.20</td>
</tr>
<tr>
<td>Hot Flashes Started</td>
<td></td>
</tr>
<tr>
<td>Entry to transition</td>
<td>11.57</td>
</tr>
<tr>
<td>Early in transition</td>
<td>7.25</td>
</tr>
<tr>
<td>Late transition</td>
<td>3.84</td>
</tr>
</tbody>
</table>

- Most common age 45-49 years
- Median duration 8.1 years
- African American women had longer duration
- Lighter BMI: symptoms lasted longer

References:

Vasomotor Symptoms: Prevalence

- > 75% of women report hot flashes within the 2-year period surrounding their menopause
- Primary reason women seek medical treatment
- 25% remain symptomatic for > 5 years

Prevalence of Hot Flashes

Years Before | Years After
3 | 2 | 1 | 1 | 2 | 3


Prevalence, Frequency and Intensity of Hot Flushes in Older Postmenopausal Women

% with HF/NS
0 | 10 | 20 | 30 | 40 | 50 | 60 | 70
4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 22 | 24

Years since LMP


Recorded Changes in Finger and Core Temperatures and Skin Resistance During a Hot Flash Episode in a Postmenopausal Patient

Different Hot Flash Related Thermoregulatory Thresholds

<table>
<thead>
<tr>
<th></th>
<th>Symptomatic Women</th>
<th>Asymptomatic Women</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T_s sweat threshold (°C)</td>
<td>36.88±0.06</td>
<td>37.42±0.06</td>
<td>0.001</td>
</tr>
<tr>
<td>Basal rectal (°C)</td>
<td>36.82±0.09</td>
<td>37.12±0.07</td>
<td>0.023</td>
</tr>
<tr>
<td>Maximum sweat rate (mg/cm²/min)</td>
<td>0.200±0.015</td>
<td>0.128±0.020</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

No difference in BMI, E₂, P₄ or skin fold thickness


Impact of Ethnicity
SWAN

<table>
<thead>
<tr>
<th></th>
<th>More Likely To:</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American</td>
<td>Report heavy bleeding</td>
</tr>
<tr>
<td></td>
<td>Have hysterectomy</td>
</tr>
<tr>
<td></td>
<td>Have high BMI</td>
</tr>
<tr>
<td></td>
<td>Report high rates of hot flashes</td>
</tr>
<tr>
<td>Hispanic:</td>
<td></td>
</tr>
<tr>
<td>Puerto Rico</td>
<td>Develop metabolic syndrome, Type 2 DM, anxiety, depression, vasomotor symptoms</td>
</tr>
<tr>
<td>Central America</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic Caucasian</td>
<td>Low bone density</td>
</tr>
</tbody>
</table>


Other Factors Influencing Outcomes

<table>
<thead>
<tr>
<th>Economic Status</th>
<th>Worse depressive symptoms, menopausal symptoms, early menopause</th>
</tr>
</thead>
<tbody>
<tr>
<td>High BMI: Perimenopause</td>
<td>Worse vasomotor symptoms, lower gonadotropin and E₂ levels increased metabolic syndrome, CVD risk and mood symptoms</td>
</tr>
<tr>
<td>High BMI: Postmenopause</td>
<td>No increase in hot flashes</td>
</tr>
<tr>
<td>Obesity related to</td>
<td>Higher androgens, low SHBG, surgical menopause</td>
</tr>
<tr>
<td>Timing</td>
<td>Late perimenopause most symptomatic</td>
</tr>
</tbody>
</table>

Nelson: New Guidelines for Menopause

Impression of Hormone Therapy

- All women 45 to 60
- Women currently experiencing symptoms

Positive Neutral Negative
11% 47% 49%
10% 20% 40%


Menopause Relief

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% Who Used</th>
<th>% Helped a Lot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescription medication</td>
<td>36%</td>
<td>63%</td>
</tr>
<tr>
<td>Black cohosh</td>
<td>22%</td>
<td>21%</td>
</tr>
<tr>
<td>Over-the-counter medications</td>
<td>35%</td>
<td>18%</td>
</tr>
<tr>
<td>Multivitamins</td>
<td>35%</td>
<td>9%</td>
</tr>
<tr>
<td>Calcium supplements</td>
<td>34%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Consumer Reports National Research Center, 2010 Annual Questionnaire

Hot Flush Count During 6-month Trial of Oral Conjugated Equine Estrogens and Placebo

NAMS Position Statement 2012
Benefits and Risks of Hormone Therapy

- Vasomotor symptoms (VMS)
  - HT/ET most effective therapy
  - Also helps sleep quality, irritability, difficulty concentrating
  - Progestogen alone also reduces VMS but to lesser extent
- Quality of life
  - HT/ET can improve health-related quality of life in symptomatic women


Doses of Estrogens Used in HT

<table>
<thead>
<tr>
<th>Estrogens</th>
<th>Conventional</th>
<th>Low Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral conjugated equine estrogen</td>
<td>≥ 0.625mg</td>
<td>0.3mg</td>
</tr>
<tr>
<td>Oral estradiol valerate, 17 β-estradiol</td>
<td>2.0mg</td>
<td>≤ 1.0mg</td>
</tr>
<tr>
<td>Percutaneous 17 β-estradiol gel</td>
<td>150mcg</td>
<td>&lt; 100mcg</td>
</tr>
<tr>
<td>Patch 17 β-estradiol</td>
<td>50mcg</td>
<td>&lt; 50mcg</td>
</tr>
<tr>
<td>Intranasal estradiol</td>
<td>300mcg</td>
<td>&lt; 300mcg</td>
</tr>
</tbody>
</table>


HT Impact on Cardiovascular Risk Factors in Healthy Premenopausal Women: Meta-Analyses

- 28 trials with 3,360 patients
- Low dose HT vs. conventional dose or placebo
  - No effects on weight, BMI, blood pressure, C-reactive protein, HDL-C
- Low dose HT vs. placebo
  - Lower total cholesterol (-12.16 mg/dL)
  - Lower LDL-C (-12.16 mg/dL)
- Low dose vs. conventional dose HT
  - Higher total cholesterol (5.05 mg/dL)
  - Higher LDL-C (4.49 mg/dL)
  - Lower triglycerides (-14.09 mg/dL) (oral HT)

Hormone Therapy and Heart Disease

Menopausal hormone therapy should not be used for the primary or secondary prevention of coronary heart disease at the present time. Evidence is insufficient to conclude that long-term estrogen therapy or hormone therapy use improves cardiovascular outcomes. Nevertheless, recent evidence suggests that women in early menopause who are in good cardiovascular health are at low risk of adverse cardiovascular outcomes and should be considered candidates for the use of estrogen therapy or conjugated equine estrogen plus a progestin for relief of menopausal symptoms.

Hormone Therapy and Heart Disease

There is some evidence that lends support to the “timing hypothesis,” which posits that cardiovascular benefit may be derived when estrogen therapy or hormone therapy is used close to the onset of menopause, but the relationship of duration of therapy to cardiovascular outcomes awaits further study. Clinicians should encourage heart-healthy lifestyles and other strategies to reduce cardiovascular risk in menopausal women. Because some women aged 65 years and older may continue to need systemic hormone therapy for the management of vasomotor symptoms, the American College of Obstetricians and Gynecologists recommends against routine discontinuation of systemic estrogen at age 65 years. As with younger women, use of hormone therapy and estrogen therapy should be individualized based on each woman’s risk–benefit ratio and clinical presentation.

NAMS Position Statement 2012
Benefits and Risks of Hormone Therapy: Cardiovascular Effects

- HT started < 10 years after menopause
  - No increase in CHD risk
- Coronary artery calcium
  - Women < 60 with ET for 7 years had lower levels than placebo

NAMS Position Statement 2012: Venous Thromboembolism (VTE)
- WHI entire cohort addition VTE in women < 60
  - HT 14/10,000 women per year
  - ET 4/10,000 women per year
- VTE risk emerges in first 1-2 years
  - Decreases in time
- Obese women – baseline risk 3 fold higher
  - With HT – risk doubles again
- Limited observational studies suggest lower VTE risk with transdermal estrogen
- Lower doses of oral ET may lower risk


NAMS Position Statement 2012
Benefits and Risks of Hormone Therapy: Breast Cancer
- Estrogen + progestin therapy
  - Overall increase: 8 cases/10,000 ≥ 5 years use if started near menopause
  - Risk dissipated 3 years after cessation
  - Breast cancer mortality increased for 11 years
  - Increase avoided if HT initiation delayed 5 years


Estrogen + Progestin
Breast Cancer in WHI Observation Arm
- Mean follow-up 11.3 years, 2,236 invasive breast cancers diagnosed
- Women in E+P arm entered with 5.3 years prior use

<table>
<thead>
<tr>
<th></th>
<th>E + P</th>
<th>No E</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annualized rate</td>
<td>0.60%</td>
<td>0.42%</td>
<td>1.55(1.41-1.70)</td>
</tr>
<tr>
<td>Mammo ≤ Q2 years</td>
<td>0.63%</td>
<td>0.39%</td>
<td>1.61(1.46-1.77)</td>
</tr>
<tr>
<td>BMI &lt; 25</td>
<td></td>
<td></td>
<td>1.70(1.48-1.95)</td>
</tr>
<tr>
<td>BMI 25-30</td>
<td></td>
<td></td>
<td>1.50(1.29-1.75)</td>
</tr>
<tr>
<td>BMI &gt; 30</td>
<td></td>
<td></td>
<td>1.34(1.11-1.62)</td>
</tr>
</tbody>
</table>

- Decreased risk when time from menopause increased

### WHI E-Alone Substudy

**Attributable Risk for Breast Cancer**

Annualized attributable risk per 1,000 women

<table>
<thead>
<tr>
<th>Invasive Breast Cancer</th>
<th>In situ Breast Cancer</th>
<th>Localized Disease</th>
<th>Ductal Carcinoma</th>
<th>Lobular Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.6</td>
<td>-0.7</td>
<td>-0.7</td>
<td>0.2</td>
<td></td>
</tr>
</tbody>
</table>

* Nominal P<0.05 vs. placebo

Stefanick ML, et al. JAMA 2006;295:1647-1657

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### Vasomotor Symptoms: Newly Approved Products (Divigel)

- Estradiol gel in 3 doses
  - 1mg/day, 0.5mg/day, 0.25mg/day*
- Hot flash reductions at 12 weeks:
  - 70%, 79%, 86.6% (placebo 38.9%)
- Once daily on skin of upper thigh (5x7")
  - Alternate sides every other day
  - Allow to dry before dressing
  - Don’t wash site for 1 hour
  - Sunscreen and other lotions may change systemic exposure

* Delayed impact (week 7)

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### Vasomotor Symptoms: Newly Approved Products

- Paroxetine (Brisdelle®) 7.5mg
- Reduced hot flashes in two 12 week studies
  - 57-59% reduction
- Placebo at 12 weeks
  - 40-48% reduction
- Side effects: headaches, fatigue, nausea, reduced sex drive, possible bone loss
- Appropriate for women who want/need no hormones
Tissue Selective Estrogen Complex

- SERM: Bazedoxifene 20 mg
- Estrogen: conjugated estrogens
  - 0.45 mg, 0.625 mg
- Reduces hot flash frequency and intensity
- Prevents bone loss
- No uterine or breast stimulation
- Improves in HRQoL, sleep, treatment satisfaction
- Brand name: Duavee


Menopausal Symptoms
Cognitive Function

- Scores in late perimenopause vs. premenopause
- Decrements seen in most scores
  - Processing speed most affected
  - Vasomotor symptoms and sleep disturbances did not account for decrease
  - Concurrent depression decreased processing speed
  - Anxiety decreases memory test
- Treatments of symptoms will probably not improve cognitive function

Skin Quality at Menopause: Importance of Early Intervention

- 30% of skin collagen lost in first 5 years after menopause
- Many women experience sudden onset of skin aging symptoms several months after menopause
- Degenerative changes in connective tissue content that occur at time of menopause are preventable
- Improved skin tone:
  - Protective against infection and injuries


Prevalence of Vaginal Dryness

<table>
<thead>
<tr>
<th>Stage of Menopause</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premenopause</td>
<td>4-22%</td>
</tr>
<tr>
<td>Perimenopause</td>
<td>7-39%</td>
</tr>
<tr>
<td>Postmenopause</td>
<td>17-30%</td>
</tr>
</tbody>
</table>

Effects of ET on Vaginal Epithelium

- High concentration of estrogen receptors
- Most efficient response with local application


Ospemifene: Dyspareunia with Postmenopausal Atrophy (GUMS)

- Nonsteroidal, nonhormonal selective estrogen receptor modulator (SERM)
- Food intake increases absorption by 2-3 fold
- Endometrial biopsy: no hyperplasia at 12 months
- Clinical trial outcomes
  - Increase in epithelial cells
  - Decrease in parabasal cells
  - Increase in vaginal pH
- Future research: Bone protection? Breast cancer reduction?

Epidemiology of Osteoporosis

- >75 million Americans, Europeans, and Japanese are osteoporotic
- 80% of whom are women
- Costs $14 billion per year in the US
  - These costs will triple by 2040
- 50% of Caucasian women in the US will experience a fracture at some time in their lives

Sources: WHO, 1996; NOF, 1999

Osteoporosis Treatment

- Lifestyle measures:
  - Stop smoking
  - Stop/slow alcohol intake
  - Adequate calcium and vitamin D
  - Regular exercise
  - Prevent falls
- Medications that stop bone loss (slow osteoclasts)
  - Hormonal therapy, other anti-reabsorptive agents
- Medications that increase bone formation (stimulate osteoblasts)

NAMS Position Statement 2012
Benefits and Risks of Hormone Therapy: Osteoporosis

- HT reduces postmenopausal osteoporotic fractures; hip, spine, non-spine, even in women without osteoporosis
- Low doses are effective in maintaining or improving BMD
- Benefits dissipate rapidly after cessation

Compounded Bioidentical Hormonal Therapy Drawbacks

- No pharmokinetic studies for different delivery systems
  - Different emollients affect absorption
  - Interconversion of estrogens
- No efficacy data
- No FDA oversight; no labeling requirements


Compounded Bioidentical Hormonal Therapy Drawbacks

- In FDA testing, 34% of bioidentical hormone products failed
  - FDA standard is ≤ 2% failure
- No safety data
  - Lack of reports of problems ≠ safe
- FDA now under legal action to block sales unless regulations instituted


The Aging Population

- By 2015, approximately 45% of the US population will be older than 45 years of age
Common Misconception About Change in Life Expectancy

Human Survival Curves: US, 1900-1980

The Rectangular Survival Curve