Reproductive Care of Women During the Perimenopausal Years

Anita L. Nelson, MD
Professor Emeritus, Obstetrics & Gynecology, David Geffen School of Medicine at UCLA
Clinical Professor Obstetrics & Gynecology, University Southern California
Professor and Chair of Obstetrics & Gynecology, Western University of Health Sciences

University of Missouri School of Nursing & Health Studies
2018 National Reproductive Health Conference
Kansas City, MO – July 16, 2018
## Conflict of Interest Disclosure

**Anita L. Nelson, MD**

<table>
<thead>
<tr>
<th>Grants/Research</th>
<th>Agile Pharmaceutical, ContraMed, Estetra SPRL, Evofem Inc, FHI (MonaLisa), Merck</th>
</tr>
</thead>
<tbody>
<tr>
<td>Honoraria/Speakers Bureau</td>
<td>Allergan, Bayer, Merck</td>
</tr>
<tr>
<td>Consultant/Advisory Board</td>
<td>Agile, AMAG Pharma, Bayer, ContraMed, Merck, PharmaNest</td>
</tr>
</tbody>
</table>
Learning Objectives

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

- Counsel women about the endocrinologic changes that occur during perimenopause
- Describe how those changes can affect current symptomatology and long term health.
- Explain how differences among women (weight, ethnicity, etc.) impact on those changes
- Outline appropriate therapies to help women experiencing troublesome symptoms
- Discuss contraceptive options for women in these years
Common Reproductive Health Issues for Perimenopausal Women

- Vasomotor symptoms (FSH fluctuations)
- Hypo-estrogenic impacts – bone loss, GSM
- Abnormal uterine bleeding
- Contraception and/or fertility
- Cancer screening and prevention
# 10 Staging System for Reproductive Aging in Women

<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>
<th>+2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminology</td>
<td>REPRODUCTIVE</td>
<td>MENOPAUSAL TRANSITION</td>
<td>POSTMENOPAUSE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>Peak</td>
<td>Late</td>
<td>Early</td>
<td>Late</td>
<td>Early</td>
<td>Late</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Perimenopause**

| Duration | variable | variable | 1-3 years | 2 years (1+1) | 3-6 years | Remaining lifespan |

**PRINCIPAL CRITERIA**

| Menstrual Cycle | Variable to regular | Regular | Regular | Subtle changes in Flow/Length | Variable Length | Persistent ≥7- day difference in length of consecutive cycles | Interval of amenorrhea of >=60 days |

10 Staging System for Reproductive Aging in Women

<table>
<thead>
<tr>
<th>SUPPORTIVE CRITERIA</th>
<th>Endocrine</th>
<th>Antral Follicle Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>AMH</td>
<td>Variable*</td>
<td>Low</td>
</tr>
<tr>
<td>Inhibin B</td>
<td>Variable*</td>
<td>Variable*</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>&gt;25 IU/L**</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>Variable</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>Stabilizes</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>Very Low</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>Very Low</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DESCRIPTIVE CHARACTERISTICS</th>
<th>Symptoms</th>
<th>Vasomotor symptoms</th>
<th>Vasomotor symptoms</th>
<th>Increasing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>Likely</td>
<td>Most Likely</td>
<td>symptoms of urogenital atrophy</td>
</tr>
</tbody>
</table>

* Blood draw on cycle days 2-5  → = elevated
** Approximate expected level based on assays using current international pituitary standard

2 Stages of Perimenopause

- Early transition
  - Cycles mostly regular, few interruptions
  - Fertility still possible, but less likely
  - Ovarian reserve fluctuations
  - Smaller numbers of follicles ↓ AMH* and ↓ inhibin β
  - Less inhibin β leads to rise in FSH

*AMH = Antimullerian hormone

2 Stages of Perimenopause

- Late transition
  - Variation in menstrual cycle > 7 days
  - Amenorrhea lasts ≥ 60 days
  - FSH consistently high, AMH and inhibin ß critically low
  - High FSH causes folliculogenesis to be faster
  - Ovulation occurs at smaller sized follicles

Important Points

- Loss of ovarian reserve occurs before follicular failure
  - Failure is lack of granulosa cells to respond to FSH

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

The Road to Menopause

Pre-MT

Regular
Normal to low ovarian reserve

Median Age 47

Early MT

Skipped cycles
Reduced reserve
Brief bouts of amenorrhea

Median Age 49

Late MT

Prolonged Amenorrhea

Perimenopause As A Teaching Moment

- Signs and symptoms may alert woman to impending menopause
- Difficult transition for many women
  - Many women define themselves in terms of their fertility
- Impending menopause reminds them of their own mortality
- Use as opportunity to motivate for healthier lifestyle habits to promote health
Endocrinology of Menopause

- Ovarian event
  - Depletion of number of follicles
  - Decreased sensitivity of the few remaining follicles
- Gonadotropins 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
Inhibin-FSH Closed Loop

Pituitary → FSH → Ovary → E2 → Inhibin

Increases E₂ and Inhibin

Decrease FSH
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
  - Grafts of 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
  - Changes in menstrual cycling

- Transition may start 10 years before any break in menstrual cycling -- in early 30’s
Length of Menstrual Cycle By Age

# Hutterite Fertility

## Age At Last Pregnancy

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 34 years</td>
<td>11%</td>
</tr>
<tr>
<td>&lt; 40 years</td>
<td>33%</td>
</tr>
<tr>
<td>&lt; 45 years</td>
<td>87%</td>
</tr>
</tbody>
</table>

Vasomotor Symptom Prevalence

<table>
<thead>
<tr>
<th>Stage of Menopause</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premenopause</td>
<td>14-51%</td>
</tr>
<tr>
<td>Perimenopause</td>
<td>35-50%</td>
</tr>
<tr>
<td>Postmenopause</td>
<td>30-80%</td>
</tr>
</tbody>
</table>

- Risk factors: high BMI, younger age of onset of menopause
- 25% of WHI subjects resumed therapy after study terminated

Four Key Cardinal Symptoms of Menopausal Transition

1. Vasomotor symptoms
   - 39% early transition; 67% cumulative
   - Associated with elevated FSH

2. Poor Sleep*
   - Related to menopause (VMS?) or aging?
   - Insomnia, inability to stay asleep linked to hot flashes, hormone swings

3. Vaginal dryness/dyspareunia genitourinary syndrome of menopause (GSM)*
   - 60% central American vs 21% non-Hispanic whites

* Do not improve without treatment

Four Key Cardinal Symptoms of Menopausal Transition cont.

4. Adverse Mood

- Depressive symptoms peak in late transition
- Anxiety – worsening symptoms and new onset
- Depressive disorders increased 2.27 in perimenopausal
  - 3.57 in postmenopausal

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

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>$T_c$ 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, $E_2$, $P_4$ or skin fold thickness

# Impact of Ethnicity SWAN

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

### Other Factors Influencing Outcomes

<table>
<thead>
<tr>
<th>Economic Status</th>
<th>Depressive symptoms, menopausal symptoms, early menopause</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High BMI:</strong> Perimenopause</td>
<td>Worse vasomotor symptoms, lower gonadotropin and $E_2$ levels, metabolic syndrome, and lower levels, mood, symptoms, metabolic syndrome, greater CV risk</td>
</tr>
<tr>
<td><strong>High BMI:</strong> 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>

SWAN: Hot Flashes and Abdominal Adiposity

- 461 midlife women
  - 45-58 years
  - 65% Caucasian, 35% African American
  - Every standard deviation increase in total or subcutaneous abdominal adiposity increased odds of hot flashes by ≥ 25%
  - Risk not altered by hormonal levels or visceral adiposity

Hormonal Contraceptives for Vasomotor Treatment in Perimenopause

- 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?
Vasomotor Symptoms: FDA Approved Products

- Paroxetine (Brisdelle®) 7.5mg (sole source)
- 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 (TSEC)

- 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
- Improvements in HR QoL, sleep, treatment satisfaction
- Brand name: Duavee (sole source)

Gabapentin vs Estrogen vs Placebo

- Gabapentin up to 2400mg a day
  OR
- CEE 0.625 once a day
- Inclusion criteria 50 moderate-to-severe hot flashes a week
- Hot flash composite score reduction (ITT)
  - Estrogen: 72%
  - Gabapentin: 71%
  - Placebo: 54%
- Gabapentin: 25% complain of headaches, dryness or disorientation
  - Slow titration may lessen side effects

Genitourinary Syndrome of Menopause (GSM)

- Symptoms develop in 80-85% of women in 4-5 years
- 25% seek medical help
- Problems:
  - Dysuria*
  - Urgency*
  - Frequency*
  - Recurrent UTI
  - Urinary incontinence*

* Improved with vaginal estrogens

## Vaginal Dryness Prevalence

<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

Without Estrogen – Atrophic

- High concentration of estrogen receptors\(^2,3\)
- Most efficient response with local application\(^3,4\)

With Estrogen\(^1\)

6 weeks of estrogen

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

NORA: Fracture Rates, Population T Score Distribution, and Number of Fractures

WHO FRAX Model

- Estimates fracture risk due to osteoporosis/osteopenia in next 10 years
  - Based on DEXA T-score and risk factors
  - Individualizes to different US ethnic groups
- Identifies osteopenic people for whom treatment would be cost effective
  - >3% chance of hip fracture in the next 10 years
  - >20% chance of major osteoporotic fracture (clinical spine, forearm, hip or shoulder) in the next 10 years
- Applies only to previously untreated adults
## Selected Leading Causes of Death
Women Age 45-54 Years, 2013

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>% of Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>33.3%</td>
</tr>
<tr>
<td>Heart disease</td>
<td>14.8%</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>4.2%</td>
</tr>
<tr>
<td>Stroke</td>
<td>3.4%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3.2%</td>
</tr>
<tr>
<td>Suicide</td>
<td>3.2%</td>
</tr>
</tbody>
</table>

http://www.cdc.gov/women/lcod/2013/index.htm
Perimenopausal Obesity
Women 40-59 Years

- Cross-sectional data show obesity rates highest in perimenopause group
- % with abnormal normal weight varies by ethnicity
  - Non-Hispanic black 88.0%
  - Mexican American 79.7%
  - Non-Hispanic white 65.3%

Blood Loss by Age

- 77 healthy women aged 21-55, 2 consecutive cycles with colorometric measurement of hemoglobin

<table>
<thead>
<tr>
<th>Reproductive Stage</th>
<th>N</th>
<th>Anovulatory Cycles</th>
<th>Median Blood Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mid reproductive</td>
<td>21</td>
<td>2</td>
<td>30 mL</td>
</tr>
<tr>
<td>Late reproductive</td>
<td>17</td>
<td>0</td>
<td>33 mL</td>
</tr>
<tr>
<td>Early transition</td>
<td>16</td>
<td>1</td>
<td>55.7</td>
</tr>
<tr>
<td>Late transition</td>
<td>23</td>
<td>9</td>
<td>68.9</td>
</tr>
</tbody>
</table>

- Highest blood losses seen in late menopausal transition with ovulatory cycle and high E_2_ levels

How Bad Can It Get?

- 148 women with 168 episodes of admission for hemoglobin <5 mg/dL from HMB 2008-13
  - Hemoglobin range: 1.6-4.9 mg/dL
  - 77% were in 40’s; 44% obese
  - 25% had reactive thrombocytosis placing them at higher risk for VTE
  - 26.9% multiple subsequent transfusions

Chronic Heavy Menstrual Bleeding: Medical Therapies

- Prostaglandin normalization: NSAIDs
  - Inhibiting cyclooxygenase
    - Converts arachidonic acid to prostaglandin
  - Binding to prostaglandin receptors
  - Metaanalysis shows no one NSAID superior to another

- Decrease fibrinolysis
  - Antifibrinolytics

Unintended Pregnancy in Perimenopausal Women

- Reported sterility rates by age are:
  - Age 40: 17%
  - 45: 55%
  - 50: 92%

- One of most significant risk factors for nonuse of contraception is a woman’s belief that she is not at risk for pregnancies.

- Contraception should be provided until diagnosis of menopause can be made with confidence.

Contraceptive Risks for Perimenopausal Women

- Generally focus on cardiovascular risks associated with use of estrogen
  - Contraceptive and noncontraceptive benefits weighed against risks in the context of alternative options
- Historically
  - COCs offered cycle control, reduction of ovarian and endometrial cancer risk, reduction in heavy menses, and vasomotor symptom control
  - Women had only limited options
    - Permanent contraception
    - Barrier methods
- Current situation: more effective options available often with noncontraceptive benefits; more women have risk factors
Copper IUD

- Only top tier nonhormonal method
  - Women with breast cancer
- Menstrual blood loss can be returned to baseline levels with NSAIDs, but what if . . .
  - Baseline excessive?
  - NSAID contraindicated?
- Able to detect menopause
- Most effective method of emergency contraception
Implants and Hormonal IUDs

- Top tier contraceptive efficacy
- Few medical contraindications
  - Breast cancer
  - Drug-drug interaction (implant only)
  - Obesity does not affect efficacy, but...
- Provide progestin for endometrial suppression
- Treatment for heavy bleeding, adenomyosis, endometriosis (LNG-IUS-52 mg)
- Prevent unopposed estrogen (anovulatory cycles, postmenopausal estrogen therapy)
Other Contraceptive Options

- **DMPA**
  - Few contraindications
  - Many benefits
  - Detection of menopause difficult

- **POPs**
  - Go-to-method
  - Transition method

- **CHCs**
  - More medical contraindications
  - Many noncontraceptive benefits
Who Has Average Risk for Breast Cancer?

- No personal history of breast cancer
- No confirmed or suspected genetic mutation known to increase risk of breast cancer
- No history of radiotherapy to the chest at a young age
- No significant family history of breast cancer
- No prior diagnosis of benign proliferative breast disease
- No significant mammographic breast density

What Should We Be Doing?

- Personalize screening\(^1\)
  - Stop screening women with no benefit\(^2\)
    - 48% of primary care physicians said they would recommend breast cancer screening for women diagnosed with terminal lung cancer
  - Calculate patient’s individual breast cancer risk
    - Use estimate to determine screening frequency and modality
- Provide chemoprevention or other interventions when appropriate

Sensible Approach: Individualize: Calculate Personal Risk

- Utilize standard, online breast cancer risk assessment tools
  - [https://www.cancer.gov/bcrisktool/](https://www.cancer.gov/bcrisktool/)
- If lifetime risk greater than general population
  - Support earlier mammographic screening
- If 5-year risk for breast cancer
  - > 1.66% offer chemoprevention
  - > 3.0% for Caucasian women  Or
  - > 6.0% for African-American women
  - Encourage chemoprevention
Chemoprevention Candidates

- 15% of women in US eligible for tamoxifen
- Caucasian > Black or Hispanic
- Number needed to treat = 42 for breast cancer
  - NNT = 86 for BP to prevent stroke, MI
- Number needed to screen women in 40’s = 1904

Breast Cancer Risk Reduction Therapies

- Chemoprevention benefits outweigh risks
  - Caucasian women in 50’s
    - Gail score ≥ 3%
  - Afro-American women in 50’s
    - Gail score ≥ 6%*
- Premenopausal women with menses – tamoxifen
- Postmenopausal women with osteoporosis – raloxifene
- Newer approaches – aromatase inhibitors

* VTE risks higher

# Gynecological Cancer Actions in Perimenopause

<table>
<thead>
<tr>
<th></th>
<th>Screening</th>
<th>Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical</td>
<td>Dual testing Q5 year until 65 unless . . .*</td>
<td>Vaccine, condoms</td>
</tr>
<tr>
<td>Endometrial</td>
<td>N/A except highest risk</td>
<td>COCs, Progestin-only contraception</td>
</tr>
<tr>
<td>Ovarian</td>
<td>CA-125+, TVU only for high risk women**</td>
<td>COC’s, salpingectomy</td>
</tr>
<tr>
<td>Vulvar</td>
<td></td>
<td>Smoking cessation, safer sex practices</td>
</tr>
</tbody>
</table>

* New guideline, new approaches soon
** Search for new markers ongoing