Menopausal Transition

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Objectives

- Define the menopausal transition.
- Describe the hormonal changes and their consequences.
- Evaluation of the perimenopausal patient.
- Health maintenance.
- Therapies for perimenopausal women.
Disclosure

• I have no conflicts of interest regarding this presentation on the menopausal transition (but, I am menopausal and certainly may be biased by personal hot flashes!!!)

• I will be discussing off label uses of contraceptives.
Menopause Terminology: STRAW* Staging System

<table>
<thead>
<tr>
<th>Stages:</th>
<th>-5</th>
<th>-4</th>
<th>-3</th>
<th>-2</th>
<th>-1</th>
<th>+1</th>
<th>+2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminology:</td>
<td>Reproductive</td>
<td>Menopausal Transition</td>
<td>Postmenopause</td>
<td></td>
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<tr>
<td>Menstrual Cycles:</td>
<td>Variable to regular</td>
<td>Regular</td>
<td>Variable cycle length (&gt;7 days different from normal)</td>
<td>≥2 skipped cycles and an interval of amenorrhea (≥60 days)</td>
<td>Amen. X12 mos.</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Endocrine:</td>
<td>Normal FSH</td>
<td>↑FSH</td>
<td>↑FSH</td>
<td>↑FSH</td>
<td>↑FSH</td>
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</tbody>
</table>

*STRAW = Stages of Reproductive Aging Workshop
Defining Hormonal Status

• Premenopause
  – Menses in previous 3 months with no change in menstrual regularity in preceding year

• Early Perimenopause
  – Menses in previous 3 months and changes in regularity in past year

• Late Perimenopause
  – No menses in previous 3 months, but menses in previous 11 months

• Menopause
  – 12 or greater months of amenorrhea

Menopause 2009; 16: 860-869
The Perimenopause

Perimenopause  Menopause

47.5  51.3

Study of Women’s Health Across the Nation: SWAN

- Prospective, longitudinal multiethnic study of over 3000 premenopausal or perimenopausal women at 7 U.S. sites from 1995-2002 seen annually x 6 yrs
- Eligibility: uterus present, at least one ovary, not using hormones, menses in last 3 months, aged 42-52
- Numerous variables evaluated and reported in several publications
Change in HRQL in menopausal transition in a multiethnic cohort of middle-aged women:  
SWAN Menopause 2009; 16: 860-69

- Ethnic groups: 48% white, 27% black, Hispanic 7.5%, Chinese 8%, Japanese 9%
- Reduced physical functioning was significantly greater at late peri- and post menopause
- Changes in HRQL over the menopausal transition are largely explained by symptoms related to menopause and/or aging (VMS, vaginal dryness, urine leakage, trouble sleeping, health conditions, depressed mood and stress)
Depressive symptoms during the menopausal transition: SWAN
J Affect Disord 2007; 103: 267-72

• Most midlife women do not experience high depressive symptoms but those that do more likely to occur during peri- or postmenopause

• Health and psychosocial factors (difficulty paying for basics, negative attitudes, poor perceived health, stressful events) increased the odds of having a high depression score and in some cases was more important than menopausal status
Findings in Numerous SWAN Publications

- Higher % of body fat assoc. with increasing odds of VMS  
  Am J Epidemiol 2008; 167: 78-85
- VMS higher in: Blacks, increasing BMI, smokers, h/o anxiety, less educated, and particularly in late perimenopause  
  Am J Public Health 2006; 96: 1226-35
- Higher testosterone level sign. assoc. with higher depression scores during menopausal transition but no assoc. with other hormones (estradiol, FSH, DHEA-S)  
  Arch Gen Psychiatry 2010; 67: 598-607
Findings in Numerous SWAN Publications

• While Blacks reported sign. more VMS, Whites report sign. more psychosomatic symptoms.

• Odds of developing metabolic syndrome increased during the menopausal transition. Increase in testosterone or a decrease in SHBG increased the odds.
  Arch Intern Med 2008; 168: 1568-75
SWAN Study: Reported Prevalence of Vasomotor Symptoms in Perimenopausal Women

Ages 40 to 55 Years

n = 12,357; SWAN = Study of Women's Health Across the Nation.
Hot Flushes May Continue Years After Menopause

*Ages 29 to 82 Years*

- Number of years women report having hot flushes as estimated by a survey of 501 untreated women who experienced hot flushes.

Mean age of natural menopause was 49.5 years; mean age of surgical menopause was 43.7 years. Kronenberg F. *Ann NY Acad Sci.* 1990;592:52-86. Used with permission.
Bone loss accelerates with menopause (~1%-2% per year)

Age-related bone loss (~0.5%-1.0% per year)
Symptoms/Sequele of Perimenopause

- Menstrual changes
- Vasomotor symptoms
- Mood alterations

- Infertility
- Declining bone mass
- ↑ risk for H.D.
Physiology of the Perimenopause

Progressive follicular depletion
(quantity/quality)

- Birth: 1 million follicles
- Constant rate of atresia, ? accelerated in late 30s secondary to elevated FSH
- Menopause: approx. 1000 follicles remaining
- Genetic factors: family history
- Environmental factors: smoking
Physiology of Perimenopause

- Reduced quality / quantity of aging follicles
- Reduced secretion of inhibin (granulosa cells); exerts negative feedback on FSH
- Increase in FSH: increased follicular response
- Increase in estrogen levels and inadequate luteal progesterone production
- Eventually ovarian follicular depletion and a hypoestrogenic state
Characterization of Reproductive Hormonal Dynamics in the Perimenopause

- Study comparing the hormonal dynamics of cycling women aged 47 and older, compared to women aged 43 to 47, and women aged 19-38.
- Measured LH, FSH, estrone conjugates, and pregnanediol glucuronide

Perimenopausal Hormonal Dynamics

- Shorter follicular phase of menstrual cycle
- Greater estrone conjugate excretion: hyperestrogenism
- Elevated FSH and LH levels
- Decreased luteal phase progesterone excretion

Perimenopausal Menstrual Patterns

- Shortened follicular phase of menstrual cycle (from an average 14 days to 11 days) → cycles every 24 days or less
- Increased estrogen throughout ovulatory cycles with decreased luteal progesterone → menorrhagia
- Anovulatory cycles → dysfunctional bleeding
- Hypoestrogenic cycles with elevated gonadotropins → menses further apart and lighter
### B. MENSTRUAL CYCLE RECORD

| Month | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 |
|-------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Jan   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |  S |  B |  B |  B |  S |    |    |
| Feb   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Mar   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |  B |  B |  B |  B |  S |    |    |    |    |    |  S |  B |  B |  B |  S |
| Apr   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |  S |  S |  B |  B |  S |    |    |    |    |    |    |    |    |
| May   |   |   |   |   |   |   |   |   |   |    |    |  B |  H |  S |  S |  S |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |  S |
| Jun   |   |   |   |   |   |   |   |   |  B |  B |  S |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Jul   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Aug   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Sep   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Oct   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Nov   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Dec   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |

*S—Spotting; B—Bleeding; H—Heavy*
Perimenopausal Transition

Hyperestrogenic Hypoprogesteronegenic State

Endometrial hyperplasia
Growth of fibroids
Menorrhagia
Dysfunctional bleeding
Perimenopause Hormone Transition

- In the early phase, most perimenopausal cycles are ovulatory but shortened follicular phase.
- Cycles of hyperestrogenism with luteal phase hypoprogesterone state.
- Progression to tonically elevated gonadotropin (FSH) secretion and persistently low estrone excretion as approach menopause.

-- NOT AN ORDERLY PROGRESSION --
Menopause

- Discontinuous, erratic, unpredictable process
- Can begin in late 30s
- Each cycle is an independent event
- FSH is constantly fluctuating and does not help predict when menopause will occur
Assessing Ovarian Reserve in Infertility Patients

- Chronological age
- Day 3 FSH, estradiol, inhibin B, AMH
- Stimulation tests with clomiphene citrate, gonadotropin agonist, exogenous FSH
- Ovarian volume measurement
- Antral follicle number
Hormonal Roller Coaster

- Hyperestrogenic Ovulatory Cycles
- Anovulation
- Hypergonadotrophic hypoestrogenic cycles
- Decreased luteal phase progesterone secretion
- Shorter menstrual cycles

-- Constantly fluctuating hormonal state --
Hormonal Management of the PERIMENOPAUSE
Factors To Consider in Hormonal Management of Perimenopause

• What is the hormonal status of the patient?
• What are you treating?
• Which products/how much are we going to prescribe?
What is the Hormonal Status?

- Estrogen deficient only
- Progesterone deficient only (estrogen excess)
- Estrogen and progesterone deficient
What is the Hormonal Status?

**Estrogen Deficient Only:**

**Example:** Still menstruating every 21-35 days (not heavy) but c/o hot flashes. If menstruating regularly, still producing progesterone.

**Treatment:** Low dose estrogen only, very carefully as needed; add progestin when patient ceases regular menses; discontinue if heavy menses; combination OCs in healthy nonsmokers.
What is the Hormonal Status?

Progesterone Deficient Only:

**Example:** Perimenopausal (overweight) with LMP 3 months ago; denies hot flashes, night sweats, mood alterations; anovulatory with continued estrogen production.

**Treatment:** Progestin only; can add estrogen when no withdrawal bleeding occurs after progestin and/or develops estrogen deficiency symptoms.
What is the Hormonal Status?

**Progesterone Deficient Only:**

**Example:** Perimenopausal with regular but heavy menses (hyperestrogenic, hypoprogestational state)

**Treatment:** Progestins (high dose)

- NSAIDS with menses
- OCs in healthy nonsmokers
- Levonorgestrel IUD
- Antifibrinolytic agent (Lysteda)
What is the Hormonal Status?

**Estrogen & Progesterone Deficient:**

*Example:* c/o estrogen deficiency symptoms with menses every 2-4 months.

*Treatment:* Estrogen and progestin can be initiated if patients desires, but replace carefully only in amounts needed.
What are we treating?

- **Symptoms**: hot flashes, vaginal dryness, mood alterations, abnormal bleeding.
- **Risk Factors**: osteoporosis, ?heart disease?, endometrial cancer
? Which Products/How Much ?

• Estrogen only -- how much?
• Progestin only -- how much/when?
• Estrogen & Progestin: cyclic vs. combined HRT; combination OCs
Hormonal Management of Perimenopause

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<tr>
<th></th>
<th>OCs</th>
<th>HRT</th>
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<tbody>
<tr>
<td>Treat Menorrhagia</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Treat Anovulatory Bleeding</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Contraception</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Prevention of bone loss</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Treat vasomotor symptoms</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>↑ risk DVT/PE</td>
<td>✔</td>
<td>✔</td>
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ACOG Bulletins
Beneficial Effects of Perimenopausal Oral Contraceptive Use

- Contraception
- Menstrual cycle control
- Cancer protection
- Prevention of bone loss
- Treat vasomotor symptoms
- Beneficial effects on breast
- Possible decrease in fibroid growth, endometriosis, and ovarian cysts

Oral Contraceptives  ACOG Bulletin
Beneficial Effects of Perimenopausal Oral Contraceptive Use

Reduced Need for Surgical Procedures

- Sterilization
- Endometrial Biopsy
- Hysteroscopy
- Fx D&C
- Endometrial ablation
- Hysterectomy
- Sonohysterography
HORMONE THERAPY

Hormone Therapy  ACOG Bulletin
Perimenopause: Preventive Healthcare

- Smoke cessation
- Maintenance of IBW
- Exercise

- Caloric restriction
- Calcium supplements
- Low dose aspirin ??
Perimenopause: Screening Tests

• Pap Smear
• Mammogram
• Lipid profile
• FBS and/or glucola
• TSH
• Colon CA screening

If risk factors: Bone mineral density