MENSTRUAL PHYSIOLOGY

HHD 2015 PART 2

Paula J. Adams Hillard, MD
Professor,
Department of Obstetrics and Gynecology
OBJECTIVES

At the conclusion of this presentation, the student should be able to:

• Describe the physiology of the normal menstrual cycle with regard to events taking place in the hypothalamus, pituitary, ovary, and uterus/endometrium

• Draw a representation of pituitary and ovarian hormones throughout the normal menstrual cycle

• Describe the evidence-based “normal menstrual cycle” with regard to menarche, menstrual frequency, duration, menstrual volume, and menopause

• Describe the pathophysiology of reproductive dysfunction
Puberty

Pubertal events:

- In childhood, LH/FSH are suppressed (low levels of estrogen suppress gonadotropins= neg feedback)
- Escape from this suppression and decreased sensitivity to negative feedback of estrogen
- Increased amplitude and frequent of GnRH pulses provoke progressive enhancement of FSH and LH secretion and increasing estrogen secretion
- Sleep-associated LH release with increasing GnRH pulses
Puberty

Pubertal events:

- Adrenarche: increased adrenal androgen production
  - growth of pubic and axillary hair
  - control mechanisms likely separate from H-P-O maturation
- Decreasing repression of the “gonadostat”
- Gradual amplification of GnRH-gonadotropin and gonadotropin-ovarian steroid interactions leading to “gonadarche”
Sexual Maturity Rating / "Tanner Staging"
Puberty

- Menarche: mid-pubertal
- Menarche in relationship to pubertal development
- Pathways through puberty
  - Breast development first
  - PH first
PUBERTY

Earlier onset than previously thought

Racial differences—
  • AA girls earlier than Caucasians
  • Little data on other racial groups

Menarche ~ 12.2-12.8—little change in ~ 50 years for Caucasian girls

Wyshak and Frisch, NEJM 1982
Menarche—average 12.8 yo

• Precocious puberty—pubertal development prior to age 8
• Primary amenorrhea—no periods by age 16

Early cycles anovulatory and irregular

Typical menstrual cycles 28 days

Amenorrhea defined as 6 months no periods

Bleeding 2-7 d

Mean blood loss/cycle 30cc (20-60)

• Chronic loss > 80cc associated with anemia
MENSTRUATION: What’s Normal?
The REAL Answers, Evidence-Based

Menarche—average 12.8 yo FOR CAUCASIAN girls
  • AA girls slightly younger ~ 12.2 yrs
  • Mexican-American girls intermediate between Caucasian and AA

Changes in onset of puberty
  • At age 8, 48% of AA girls had pubertal development vs 15% Caucasian girls
  • ? Due to increasing obesity/BMI/overnutrition vs endocrine modulators

Primary Amenorrhea:
  • No periods by age 15;
  • No breast development by age 13
PUBERTAL DEVELOPMENT

• Precocious Puberty
  • Previous definition: <8 yo for girls, based on small non-diverse population
  • New large data set 17,000- PROS
• Peds Endocrine Society has proposed new guidelines

New guidelines propose that breast or pubic hair development should be evaluated only if
• 1 or both of these occur before age 7 in white girls or
• Before age 6 in AA girls.

MENSTRUATION: What’s Normal?  
The REAL Answers, Evidence-Based

Early cycles for adolescents are anovulatory and irregular
  – But not "anything goes"
  – Overall trend toward shorter and more regular cycles through adolescence

Normal Menstrual Cycle length
  – Adolescents ~19-45 days
  – Adult women 21-38 days

Amenorrhea defined as no periods for 90 days

Bleeding 2-7 days

Mean blood loss/cycle 30cc (20-60)
  – Chronic loss> 80cc associated with anemia

31,645 cycles reported by 656 women

<table>
<thead>
<tr>
<th>Clinical dimensions of menstruation and menstrual cycle</th>
<th>Descriptive terms</th>
<th>Normal limits (5th to 95th percentiles)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of menses (days)</td>
<td>Frequent</td>
<td>&lt;24</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>24–38</td>
</tr>
<tr>
<td></td>
<td>Infrequent</td>
<td>&gt;38</td>
</tr>
<tr>
<td>Regularity of menses (cycle to cycle variation over 12 months; in days)</td>
<td>Absent</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Regular</td>
<td>Variation ± 2 to 20 days</td>
</tr>
<tr>
<td></td>
<td>Irregular</td>
<td>Variation greater than 20 days</td>
</tr>
<tr>
<td>Duration of flow (days)</td>
<td>Prolonged</td>
<td>&gt;8.0</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>4.5–8.0</td>
</tr>
<tr>
<td></td>
<td>Shortened</td>
<td>&lt;4.5</td>
</tr>
<tr>
<td>Volume of monthly blood loss (ml)</td>
<td>Heavy</td>
<td>&gt;80</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>5–80</td>
</tr>
<tr>
<td></td>
<td>Light</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

Based primarily on [23–25].
MENOPAUSE--DEFINITION

Cessation of Menses-FMP (final menstrual period)

• X 1 year

Average age 50-51

Ethnicity:

• AA: 6-12 mos earlier than Caucasions?
• Mexicans: 1 year earlier than Caucasions
• Japanese: 5 months later
MENOPAUSAL TRANSITION

- Increased variability of cycles transition to Long Cycles
- Early age at menopause related to:
  - Smoking
  - Lower SES
- Older age at menopause related to:
  - Longer cycles throughout reprod life
  - Longer more variable cycles prior to menopause
  - Higher parity
  - Use of COC
DURATION OF MENOPAUSAL TRANSITION

• Median age at entry is 45.5
• Marker for FMP
  • Onset of 90 day cycle
    • Earlier onset of 90 d cycle predicts earlier FMP
    • 1-3 yrs from 90 d cycle to FMP
• Median duration of the transition is 4.8 years
• Range of 1-11 years

The Stages of Reproductive Aging +10 staging system for reproductive aging in women

<table>
<thead>
<tr>
<th>Stage</th>
<th>Menarche</th>
<th>FMP (0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminology</td>
<td>REPRODUCTIVE</td>
<td>MENOPAUSAL TRANSITION</td>
</tr>
<tr>
<td>Early</td>
<td>Peak</td>
<td>Late</td>
</tr>
<tr>
<td>Duration</td>
<td>variable</td>
<td>variable</td>
</tr>
</tbody>
</table>

**PRINCIPAL CRITERIA**

<table>
<thead>
<tr>
<th>Menstrual Cycle</th>
<th>Variable to regular</th>
<th>Regular</th>
<th>Regular</th>
<th>Subtle changes in Flow/Length</th>
<th>Variable Length Persistent ≥7-day difference in length of consecutive cycles</th>
<th>Interval of amenorrhea of ≥60 days</th>
</tr>
</thead>
</table>

**SUPPORTIVE CRITERIA**

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

**DESCRIPTIVE CHARACTERISTICS**

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

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

Harlow et al. STRAW +10 Staging Reproductive Aging Climacteric, Fertil Steril, JCEM, Menopause 2012
Population mean of hormone* vs. #Years around final menstrual period (FMP):

- FSH (IU/L)
- E2 (pg/mL)

Randolph et al, JCEM 2011;96:746-54
PATTERNS OF MENOPAUSAL TRANSITION

- Increasing variability followed by increasing cycle length—“typical”
- “Just stopped”
- History of long or irregular cycles
- Increased variability and long cycles and then “revert” to prior, less variable pattern

31,645 cycles reported by 656 women
CASES: Feedback

Age and Gonadotropins
CASE

• 16 yo girl
  • Primary amenorrhea
    • DDx:
    • Labs:
• 16 yo girl
  • Primary amenorrhea
  • High FSH
  • High LH
• Estradiol =
• Etiology =
• Therapy =
CASE

- 16 yo girl
  - Primary amenorrhea
  - Low FSH
  - Low LH
  - Estradiol =
  - Etiologies =
  - Therapy =
CASE

- 24 yo woman
  - Infrequent periods
  - Normal FSH
  - High LH
- Estradiol =
- Etiology =
- Therapies =
- Implications for future health =
CASE

- 29 yo woman
  - Secondary amenorrhea
  - Elevated FSH
  - Elevated LH
- Estradiol =
- Etiology =
- Therapy =
CASE

• 45 yo woman
  • Infrequent periods
  • Elevated FSH
• Estradiol =
• Etiology =
• Therapy =
CASE

- 45 yo woman
  - LMP 13 months ago
  - Elevated FSH
- Estradiol =
- Etiology =
- Therapy =