Post-Menarchal Adolescent Girls Demonstrate Multi-Level Reproductive Axis Immaturity

Bob Z. Sun, BA1,2; Tairmae Kangarloo, BS3; Judith M. Adams, RN, DMU3; Patrick M. Sluss, PhD3; Corrine K. Welt4; Donald W. Chandler, PhD5; David T. Zava, PhD6; John A. McGrath, MA7; David M. Umbach, PhD1; Janet E. Hall, MD, MSc1,3; and Natalie D. Shaw, MD, MMSc1,3

1National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC; 2Cleveland Clinic Lerner College of Medicine, Case Western Reserve University, Cleveland, OH; 3Harvard Reproductive Sciences Center and Reproductive Endocrine Unit, Massachusetts General Hospital, Boston, MA; 4Department of Endocrinology, Metabolism, and Diabetes, University of Utah School of Medicine, Salt Lake City, UT; 5Endocrine Sciences, Calabasas Hills, CA; 6ZRT Laboratory, Beaverton, OR; 7Social & Scientific Systems, Inc., Durham, NC

Introduction

Irregular menstrual periods are very common in the first few years after menarche due to reproductive axis immaturity. While acquisition of estradiol positive feedback (E2+FB) has been proposed as the last step in reproductive development, even premenarchal girls have normal, spontaneous mid-cycle surges (MCS). We hypothesized that delayed maturation of other reproductive axis components explain menstrual irregularity in adolescent girls.

Research Protocol

Participants
- 23 adolescent girls, 12.8 – 17.6 years old
- BMI percentile 41st – 99th; 58% overweight/obese
- 0.4 – 3.5 years post-menarchal
- No excessive exercise, eating disorders, or smoking

Measures
- Monitoring during 2 consecutive menstrual cycles
- Reproductive hormone measurements, each method 2-5x/wk:
  - serum: LH, FSH, E2, progesterone (P)
  - dried urine strips: E2, pregnanediol (Pd)
- Pelvic ultrasounds to document follicle growth and luteinization
- Early Follicular Phase (EFP)
- Mid-cycle (MC) where midcycle surge = day 0
- Luteal Phase (LP)

Menstrual Cycle Classification

- Short OV: ovulatory with short (<10d) luteal phase
- Normal OV: ovulatory with normal luteal phase length
- ANOV: anovulatory

Hormone Dynamics by Cycle Phase

Cycle 1
- Late Follicular Phase (LFP)
- Mid-cycle (MC) where midcycle surge = day 0
- Luteal Phase (LP)
Cycle 2
- Early Follicular Phase (EFP)

Statistical Methods

Standardization of Hormone Measurements
- Passing-Bablok regression to determine conversion from DBS (LH, FSH) and urine (E2) to serum

Menstrual Cycle Classification
- Short OV: ovulatory with short (<10d) luteal phase
- Normal OV: ovulatory with normal luteal phase length
- ANOV (no luteinization)

Hormone Dynamics by Cycle Phase

Cycle 1
- Late Follicular Phase (LFP)
- Mid-cycle (MC) where midcycle surge = day 0
- Luteal Phase (LP)
Cycle 2
- Early Follicular Phase (EFP)

Hormones compared between each adolescent sub-group and 65 ovulatory historic adult controls using mixed models to account for repeated measures

The mid-cycle LH surge adjusted for pre-ovulatory (days #3 to 0) E2 taken as index of E2+FB

 Adolescents Demonstrate Diminished LH and FSH Secretion and Luteal Insufficiency Compared with 65 Ovulatory Adult Women

Characteristics of Adolescent Groups

<table>
<thead>
<tr>
<th>Measures</th>
<th>Normal OV</th>
<th>Short OV</th>
<th>ANOV (luteinization)</th>
<th>ANOV (no luteinization)</th>
<th>Difference among groups, p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>11</td>
<td>5</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>BMI percentile</td>
<td>79.8 ± 9.3</td>
<td>78.0 ± 5.7</td>
<td>88.7 ± 9.7</td>
<td>69.8 ± 28.8</td>
<td>0.91</td>
</tr>
<tr>
<td>Chronologic age (yrs)</td>
<td>14.8 ± 0.8</td>
<td>14.0 ± 0.3</td>
<td>14.1 ± 0.4</td>
<td>13.7 ± 0.1</td>
<td>0.48</td>
</tr>
<tr>
<td>Age at menarche (yrs)</td>
<td>12.6 ± 0.2</td>
<td>12.9 ± 0.3</td>
<td>12.3 ± 0.3</td>
<td>12.8 ± 0.1</td>
<td>0.58</td>
</tr>
<tr>
<td>Gynecologic age (yrs)</td>
<td>1.9 ± 0.3</td>
<td>1.9 ± 0.5</td>
<td>1.8 ± 0.5</td>
<td>0.8 ± 0.4</td>
<td>0.68</td>
</tr>
<tr>
<td>Cycle length (days)</td>
<td>39.4 ± 3.9</td>
<td>25.2 ± 1.1</td>
<td>38.8 ± 5.8</td>
<td>26.5 ± 8.5</td>
<td>0.10</td>
</tr>
<tr>
<td>Follicular phase length (days)</td>
<td>27.8 ± 4.0</td>
<td>37.4 ± 1.2</td>
<td>---</td>
<td>---</td>
<td>0.11</td>
</tr>
<tr>
<td>Luteal phase length (days)</td>
<td>11.6 ± 0.4</td>
<td>7.8 ± 0.8</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Peak serum progesterone (ng/mL)</td>
<td>7.1 ± 1.3</td>
<td>3.4 ± 0.4</td>
<td>1.8 ± 0.5</td>
<td>0.4 ± 0.2</td>
<td>---</td>
</tr>
<tr>
<td>Peak urine pregnanediol (mcg/g Cr)</td>
<td>12767.7 ± 153.9</td>
<td>588.0 ± 89.0</td>
<td>377.0 ± 81.5</td>
<td>165.0 ± 35.0</td>
<td>---</td>
</tr>
</tbody>
</table>

All values presented as mean ± SE.

ANOV girls with and without luteinization combined; †Used in definition of adolescent groups.

Conclusions

- E2+FB is intact in normal OV but remains impaired in short OV and ANOV girls
- Normal OV girls have immature FSH dynamics and follicle growth; they also show luteal insufficiency and decreased ovarian responsiveness to FSH
- These findings suggest the final stage of reproductive axis maturity entails coordinated development of brain and ovary


Funding: NIH 5T32-HL007384-26, R01-ES016115-01.