Reproductive Hormonal Changes with Aging

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Ovarian Aging--Modifying Factors

Midreproductive years: Ovarian function stable

Critical Follicle Depletion (c. 25K)

Subsequent Progress: modified by genetics, Lifestyle, exposures

Final Menses
### Stages: -5, -4, -3, -2, -1, 0, +1, +2

<table>
<thead>
<tr>
<th>Stages:</th>
<th>-5</th>
<th>-4</th>
<th>-3</th>
<th>-2</th>
<th>-1</th>
<th>0</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>
<td></td>
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<tr>
<td>Duration of Stage:</td>
<td>variable</td>
<td>variable</td>
<td>until demise</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Menstrual Cycles:</td>
<td>variable to regular</td>
<td>regular</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></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>none</td>
<td></td>
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<tr>
<td>Endocrine:</td>
<td>normal FSH</td>
<td>↑ FSH</td>
<td>↑ FSH</td>
<td>↑ FSH</td>
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</tbody>
</table>

*Stages most likely to be characterized by vasomotor symptoms

↑ = elevated

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Recommendations of Stages of Reproductive Aging Workshop (STRAW) Park City, Utah, USA, July 2001
The Inhibin Hypothesis
E2 and Inhibin Changes in Relation to FMP

My Early Career

- Obsessed with POF—etiology and treatment
- K08 award to describe endocrine characteristics of women with POF, perimenopause and postmenopause
- Urinary hormone measurement: non-invasive and appropriate for long-term longitudinal hormonal assessments
Perimenopausal Woman – urinary hormones x 6 mo

Days: 0, 20, 40, 60, 80, 90, 110, 130, 150, 170

Graph showing changes in LH (mIU/mgCr), FSH (mIU/mgCr), E1 (ng/mgCr), and PDG (µg/mgCr) over 200 days.
DOR: Sentinel Diagnosis

- May herald entry into POF/POI or early menopause
- May be a harbinger of genetic disease
- May be a harbinger of future health challenges
- Diagnosis goes beyond fertility concerns
Change of Focus

- New insight into physiology and symptomatology
  - The transition is NOT uniformly hypoestrogenic
  - The transition is NOT gradual—it’s saccadic
  - Hormone patterns explained symptoms/cycles

- Re-oriented to ‘go where the money is’
  - Re-evaluation of hormonal changes and influences
Strategy for Further Study

- Mechanistic models
  - Physiologic probing of the system
  - Animal models

- Epidemiological models
  - Large scale studies
  - Detect associations and inform causal inference
Opportunity Knocks 1994

- SWAN, the Study of Women’s Health Across the Nation
  - RFA issued in 1994
  - Independent assessment of the need for epidemiologic investigation of the menopausal transition
  - Longitudinal study cohort assembly
  - Long-term follow up planned from the start
Strategy for SWAN

- Develop a local cohort
- Assess gynecologic/endocrine outcomes
- Nothing proceeded as originally planned or expected
How Epidemiology Helps

- SWAN: Daily Hormone Study
  - Volunteer subcohort (n=990) collected daily urine for one cycle or up to 50 days (whichever came first)
  - All samples measured for LH, FSH, E1c Pdg and creatinine

- Initial analyses yielded previously unappreciated findings
Serum FSH and E2 Decrease with Increasing BMI in Women

Daily urinary hormones in women with BMIs <25 kg/m², 25-29.9 kg/m², and >30 kg/m²

What About the Mechanisms?

- Animal models
  - Difficult to establish
  - Currently being worked on in basic science labs (Gore, Neal-Perry, Rance)

- Physiologic probing in humans
  - Difficult to probe CNS mechanisms
  - Reproductive hormonal aberrations do not seem to lead to increased bleeding—Hypothesis not correct
  - Regrouping
Figure 2. Daily Urinary E1c Levels in Anovulatory Older Reproductive-Age Women With Estrogen Increases

Comparison of E1c levels (estrone conjugates) in women who had an LH surge (group 1) (left panel) vs those who did not (group 2) (right panel). E1c levels (mean [SEM]) for women with both estrogen increases and LH surges are shown here, where day 0 is the day of maximum E1c.
K24 Mid-Career Award

- Most productive grant I’ve ever had
- 27 publications in first funding period
- 27 proteges trained on the proposal
- Must have primary NIH grant as PI to qualify
- Renewable x 1
Opportunity Knocks 2004

- Link between reproductive hormones and obesity beginning to be appreciated
- Fertility severely compromised in obese women (Gesink-Law, Polotsky)
- Obesity epidemic gaining major attention
- Exploratory grant to examine effects of weight loss on hormone profiles
Representative LH Pattern in Normal Weight vs Obese Woman
Role of Estrogen Feedback

- Local estradiol may be responsible for blunting of LH pulsatility in obesity
- If so, then aromatase inhibition may be an ideal way to ‘query’ the system
### Participants

<table>
<thead>
<tr>
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<th>Letrozole n=5</th>
<th>Control n=12</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>32.3 ± 5.7</td>
<td>24.9 ± 4.8</td>
<td>0.07</td>
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<tr>
<td>BMI, kg/m²</td>
<td>20.6 ± 0.6</td>
<td>20.8 ± 1.7</td>
<td>0.82</td>
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<tr>
<td>Menstrual Cycle Length</td>
<td>29.5 ± 3.1</td>
<td>n/a</td>
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LH pulses per 4 hours

LH Pulse Frequency

\[ p = 0.4 \]

**Letrozole**

\[ 2.0 \pm 0.6 \]

**Control**

\[ 2.4 \pm 0.5 \]
LH Pulse Amplitude

- Letrozole: 5.1 ± 1.2
- Control: 1.6 ± 0.2

$p < 0.01$
Mean Serum LH

\[ p < 0.01 \]

**LH, IU/Liter**

- Letrozole: 8.7 ± 0.7
- Control: 3.4 ± 0.2
New Challenges/ New Opportunities

- Clinical Research
  - Regulatory burden
  - Role of CTSA
  - Need to collaborate

- Funding Situation
  - Will get worse before it gets better
  - Need to find alternative ways to support research
  - Need to distinguish ‘physiologic’ research from ‘epidemiologic’ research