Polycystic Ovary Syndrome

François Pralong
Division of Endocrinology
Definition

Association of clinical and/or biochemical evidence of androgen excess with chronic anovulation

Heterogeneous condition with a spectrum of clinical/biochemical features

Estimated prevalence: 25% of all women, full blown syndrome in ~5% of women of reproductive age

Clinical presentation

- Hirsutism (95%), acne, alopecia
- Enlarged ovaries (95%)
- Sterility (75%)
- Amenorrhea (55%)
- Obesity (40%)
- Dysmenorrhea (28%)
- Chronic anovulation (20%)
Pathogenic hypothesis
Abnormal hormonal feedback mechanisms
PCOS: THE TEXTBOOK VIEW I

Hypothalamus

↓ LH Secretion
↓ FSH Secretion

↓ Plasma FSH Level

↓ Plasma LH Level

Ovaïre

↑ Stimulation of Stroma and Theca

Surrénale

↑ Ovarian Androgen Secretion

Tissu adipeux

↑ Extraglandular Aromatization

Obesity

↓ Cyclic Estrogen (Estradiol)

Androgen Excess

↓ Acyclic Estrogen (Estrone)
Pathogenic hypothesis

Obesity and insulin resistance
PCOS: A DEVELOPMENTAL VIEW

Adapted from S Franks, 2002

Puberty

LH

Insulin

↑ ANDROGENS

• Hirsutism
• Acne
• Alopecia

Adapted from S Franks, 2002
Gonadotropin Secretion in PCOS

*Increased LH secretion:*

- Ratio of LH/FSH: 2-3/1
- Prevalence: 30 to 90%

Importance of assessing LH secretion in relation to recent menses
GnRH

Pituitary

LH, FSH

GnRH

LH

FSH

E2, T
GnRH neurons

Facilitation

Gonadotrophs

Inhibition

Childhood years
Facilitation

Metabolic signals

GnRH neurons

Gonadotrophs

Inhibition

Post-pubertal Period

LH
Insulin

LH

ANDROGENS

• Hirsutism
• Acne
• Alopecia

Puberty

Adapted from S Franks, 2002
Possible Mechanisms of Abnormal LH Secretion in PCOS

Altered sex steroid feedback:

• Increased spontaneous LH pulse amplitude
• Increased LH response to GnRH
• Normal FSH response to GnRH

Inherent neuroendocrine abnormality
A CHRONOBIOLGIC ABNORMALITY IN LUTEINIZING HORMONE SECRETION IN TEENAGE GIRLS WITH THE POLYCYSTIC-OVARY SYNDROME

Barnett Zumoff, M.D., Ruth Freeman, M.D., Susan Coupey, M.D., Paul Saenger, M.D., Morri Markowitz, M.D., and Jacob Kream, Ph.D.

Study of 5 teenage, post-pubertal girls with PCOS, compared to age-matched controls

Diagnostic criteria:
• Chronic anovulatory syndrome
• Exclusion of other virilizing syndromes (Cushing, CAH...)
• Normal TFTs and PRL

NEJM 309, 1983
A CHRONOBILOGIC ABNORMALITY IN LUTEINIZING HORMONE SECRETION IN TEENAGE GIRLS WITH THE POLYCYSTIC-OVARY SYNDROME

Barnett Zumoff, M.D., Ruth Freeman, M.D., Susan Coupey, M.D., Paul Saenger, M.D., Morri Markowitz, M.D., and Jacob Kream, Ph.D.

Abnormality present in 4 of 5 patients
Hyperfunction of the Hypothalamic-Pituitary Axis in Women with Polycystic Ovarian Disease: Indirect Evidence for Partial Gonadotroph Desensitization*

JOANNE WALDSTREICHER, NANETTE F. SANTORO, JANET E. HALL†, MARCO FILICORI‡, AND WILLIAM F. CROWLEY, Jr.

Study of 12 women with PCOS, compared to 21 normal controls

Diagnostic criteria:

- Perimenarchal onset of oligo/amenorrhea
- Hirsutism and/or acne
- Raised LH/FSH ratio
- Raised T/androstenedione levels

- E2 lower than controls in MFP and LFP
- Estrone higher than controls in EFP and MFP, lower in LFP

J Clin Endocrinol Metab 66, 1988
Normal

EFP
Day -12
$E_2=41 pg/ml$

MFP
Day -8
$E_2=45 pg/ml$

LFP
Day -1
$E_2=84 pg/ml$

PCOS

A. $E_2=20 pg/ml$

B. $E_2=28 pg/ml$

C. $E_2=39.6 pg/ml$

J Clin Endocrinol Metab 66, 1988
Hyperfunction of the Hypothalamic-Pituitary Axis in Women with Polycystic Ovarian Disease: Indirect Evidence for Partial Gonadotroph Desensitization

A. LH PULSE AMPLITUDE

B. LH PULSE FREQUENCY

J Clin Endocrinol Metab 66, 1988
Accelerated 24-Hour Luteinizing Hormone Pulsatile Activity in Adolescent Girls with Ovarian Hyperandrogenism: Relevance to the Developmental Phase of Polycystic Ovarian Syndrome*

D. Apter†, T. Bützow, G. A. Laughlin, and S. S. C. Yen‡

Department of Reproductive Medicine, University of California-San Diego School of Medicine, La Jolla, California 92037-0802

Study of 13 women (aged 11-18) with hyperandrogenism, compared to 28 aged-matched normal controls

Patients from Adolescent Medicine/Repro Endo clinics, UCSD

Diagnostic criteria:
• Chief complaint: hirsutism
• No hormonal medication for 3 months

J Clin Endocrinol Metab 79, 1994
### Accelerated 24-Hour Luteinizing Hormone Pulsatile Activity in Adolescent Girls with Ovarian Hyperandrogenism: Relevance to the Developmental Phase of Polycystic Ovarian Syndrome*

#### Table 1. Clinical characteristics of the hyperandrogenic subjects

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>Age (yr)</th>
<th>Age at menarche (yr)</th>
<th>BMI</th>
<th>Menstrual pattern</th>
<th>Hirsutism scorea</th>
<th>Acne</th>
<th>Acanthosis nigricana</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11.6</td>
<td></td>
<td>21.8</td>
<td>Premenarche</td>
<td>10</td>
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<tr>
<td>2</td>
<td>11.9</td>
<td></td>
<td>34.6</td>
<td>Oligomenarche</td>
<td>7</td>
<td>+</td>
<td>Yes</td>
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<tr>
<td>3</td>
<td>12.8</td>
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<td>39.5</td>
<td>Oligomenarche</td>
<td>15</td>
<td>+</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>13.5</td>
<td></td>
<td>21</td>
<td>Oligomenarche</td>
<td>10</td>
<td>−</td>
<td>No</td>
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<tr>
<td>5</td>
<td>14.7</td>
<td></td>
<td>33</td>
<td>Oligomenarche</td>
<td>16</td>
<td>++</td>
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<tr>
<td>6</td>
<td>14.7</td>
<td></td>
<td>33.2</td>
<td>Regular</td>
<td>10</td>
<td>+</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>15.4</td>
<td></td>
<td>34.2</td>
<td>Oligomenarche</td>
<td>12</td>
<td>+</td>
<td>No</td>
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<tr>
<td>8</td>
<td>16.2</td>
<td></td>
<td>43.5</td>
<td>Amenorrhea</td>
<td>20</td>
<td>++</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>16.4</td>
<td></td>
<td>23.1</td>
<td>Oligomenarche</td>
<td>16</td>
<td>+</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>17.1</td>
<td></td>
<td>20.4</td>
<td>Regular</td>
<td>8</td>
<td>−</td>
<td>No</td>
</tr>
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<td>11</td>
<td>17.1</td>
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<td></td>
<td>21.7</td>
<td>Oligomenarche</td>
<td>17</td>
<td>−</td>
<td>No</td>
</tr>
<tr>
<td>13</td>
<td>18.1</td>
<td></td>
<td>26.4</td>
<td>Amenorrhea</td>
<td>21</td>
<td>++</td>
<td>No</td>
</tr>
</tbody>
</table>

**HA**b

<table>
<thead>
<tr>
<th></th>
<th>Age (yr)</th>
<th>Age at menarche (yr)</th>
<th>BMI</th>
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</tr>
</thead>
<tbody>
<tr>
<td>HAb</td>
<td>15.1 ± 0.6</td>
<td>12.3 ± 0.2</td>
<td>28.0 ± 1.6(c)</td>
<td>13.1 ± 1.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normalb</td>
<td>14.8 ± 0.3</td>
<td>12.4 ± 0.3</td>
<td>22.1 ± 1.2(c)</td>
<td>&lt;7.0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* According to Ferriman and Gallwey (12).

b Mean ± s.e. for group.

\(c\) \(P = 0.005\) vs. normal.

J Clin Endocrinol Metab 79, 1994
Accelerated 24-Hour Luteinizing Hormone Pulsatile Activity in Adolescent Girls with Ovarian Hyperandrogenism: Relevance to the Developmental Phase of Polycystic Ovarian Syndrome*

J Clin Endocrinol Metab 79, 1994
Determinants of Abnormal Gonadotropin Secretion in Clinically Defined Women with Polycystic Ovary Syndrome*

ANN E. TAYLOR*, BRIAN MCCOURT, KATHRYN A. MARTIN, ELLEN J. ANDERSON, JUDITH M. ADAMS, DAVID SCHOPENFELD, AND JANET E. HALL
Reproductive Endocrine Unit and National Center for Infertility Research, Massachusetts General Hospital, Boston, Massachusetts 02114

Study of 61 women with PCOS, compared to 24 normal controls (EFP)

Diagnostic criteria:
• Chronic oligoamenorrhea (<9 cycles/yr) or amenorrhea
• Hyperandrogenism (clinical or biochemical)
• Exclusion of late-onset CAH
• Normal TFT and PRL
• Off all medication for at least 2 months

J Clin Endocrinol Metab 82, 1997
Determinants of Abnormal Gonadotropin Secretion in Clinically Defined Women with Polycystic Ovary Syndrome*

<table>
<thead>
<tr>
<th></th>
<th>Anovulatory PCOS patients (n = 52)</th>
<th>Post-ovulatory PCOS patients (n = 9)</th>
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<th>P for ANOVA</th>
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<tr>
<td></td>
<td>Median</td>
<td>Range</td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>29</td>
<td>16–42</td>
<td>28</td>
<td>19–37</td>
</tr>
<tr>
<td>Cycle/ day</td>
<td>49&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4–862</td>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>−5–6</td>
</tr>
<tr>
<td>BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>33.8&lt;sup&gt;c&lt;/sup&gt;</td>
<td>17.0–60.2</td>
<td>26.2</td>
<td>21.5–40.1</td>
</tr>
<tr>
<td>Hirsutism score</td>
<td>11&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0–29</td>
<td>13.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8–18</td>
</tr>
<tr>
<td>Ovarian volume (cm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>14.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.7–44.8</td>
<td>14.6</td>
<td>9.7–21.5</td>
</tr>
<tr>
<td>LH pool (IU/L)</td>
<td>15.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.3–112.9</td>
<td>8.0&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.1–10.8</td>
</tr>
<tr>
<td>FSH pool (IU/L)</td>
<td>9.5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4.0–29.1</td>
<td>9.1</td>
<td>2.0–16.4</td>
</tr>
<tr>
<td>LH/FSH ratio</td>
<td>1.58&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.70–15.68</td>
<td>1.05&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>0.40–1.82</td>
</tr>
<tr>
<td>LH pulse amplitude (IU/L)</td>
<td>7.1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.6–50.7</td>
<td>8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.3–66.5</td>
</tr>
<tr>
<td>LH pulse frequency (#/24 hr)</td>
<td>18&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4–28</td>
<td>8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2–13</td>
</tr>
<tr>
<td>Testosterone (ng/mL)</td>
<td>1.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.4–4.2</td>
<td>0.8&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>0.7–1.0</td>
</tr>
<tr>
<td>Androstenedione (ng/mL)</td>
<td>3.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.5–12.6</td>
<td>2.4</td>
<td>1.0–5.0</td>
</tr>
<tr>
<td>17-OH progesterone (ng/mL)</td>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.3–3.6</td>
<td>0.8</td>
<td>0.5–2.7</td>
</tr>
<tr>
<td>DHEAS (μg/dL)</td>
<td>148</td>
<td>20–455</td>
<td>150</td>
<td>50–592</td>
</tr>
<tr>
<td>Estradiol (pg/mL)</td>
<td>83</td>
<td>16–235</td>
<td>80</td>
<td>34–178</td>
</tr>
<tr>
<td>Estrone (pg/mL)</td>
<td>82</td>
<td>14–606</td>
<td>65</td>
<td>28–298</td>
</tr>
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</table>

<sup>a</sup> P < 0.001 vs. normal.
<sup>b</sup> P < 0.004 vs. anovulatory PCOS.
<sup>c</sup> P < 0.05 vs. normal.
Determinants of Abnormal Gonadotropin Secretion in Clinically Defined Women with Polycystic Ovary Syndrome*

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<th>P for ANOVA</th>
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</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>Median: 29, Range: 16–42</td>
<td>Median: 28, Range: 19–37</td>
<td>Median: 26, Range: 18–42</td>
<td>0.335</td>
</tr>
<tr>
<td>Cycle day</td>
<td>40, 4–862</td>
<td>2, −5–6</td>
<td>3, 1–7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>33.8, 17.0–60.2</td>
<td>26.2, 21.5–40.1</td>
<td>25.4, 19.6–50.9</td>
<td>0.022</td>
</tr>
<tr>
<td>Hirsutism score</td>
<td>11, 0–29</td>
<td>13.5, 8–18</td>
<td>5, 0–9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ovarian volume (cm³)</td>
<td>14.4, 5.7–41.8</td>
<td>14.0, 9.7–21.5</td>
<td>9.8, 2.7–16.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LH pulse (IU/L)</td>
<td>15.4, 5.3–112.9</td>
<td>8.0, 2.1–10.8</td>
<td>5.8, 2.0–12.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FSH pulse (IU/L)</td>
<td>9.3, 4.0–29.1</td>
<td>9.1, 2.0–16.4</td>
<td>10.8, 6.7–16.4</td>
<td>0.110</td>
</tr>
<tr>
<td>LH/FSH ratio</td>
<td>1.58, 0.70–15.68</td>
<td>1.05, 0.40–1.82</td>
<td>0.51, 0.21–1.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LH pulse amplitude (IU/L)</td>
<td>7.1, 2.6–50.7</td>
<td>8, 5.3–66.5</td>
<td>4.5, 2.0–14.9</td>
<td>0.004</td>
</tr>
<tr>
<td>LH pulse frequency (#/24 h)</td>
<td>18, 4–28</td>
<td>8, 2–13</td>
<td>15, 6–21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Testosterone (ng/mL)</td>
<td>3.9, 0.4–4.2</td>
<td>0.8, 0.7–1.0</td>
<td>0.6, 0.4–1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Androstenedione (ng/mL)</td>
<td>3.7, 1.5–12.6</td>
<td>2.4, 1.0–5.0</td>
<td>2.6, 0.9–5.0</td>
<td>0.004</td>
</tr>
<tr>
<td>17-OH progesterone (ng/mL)</td>
<td>1, 0.3–3.6</td>
<td>0.8, 0.5–2.7</td>
<td>0.7, 0.3–2.3</td>
<td>0.052</td>
</tr>
<tr>
<td>DHEAS (µg/dL)</td>
<td>148, 20–455</td>
<td>150, 50–592</td>
<td>158, 20–395</td>
<td>0.866</td>
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<tr>
<td>Estradiol (pg/mL)</td>
<td>83, 16–235</td>
<td>80, 34–178</td>
<td>84, 40–142</td>
<td>0.845</td>
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<td>Estrone (pg/mL)</td>
<td>82, 14–606</td>
<td>65, 28–298</td>
<td>64, 23–119</td>
<td>0.075</td>
</tr>
</tbody>
</table>

* indicates significance level: a P < 0.001 vs. normal.

b P < 0.004 vs. anovulatory PCOS.
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<tbody>
<tr>
<td>Age (yr)</td>
<td>Median 29, Range 16–42</td>
<td>Median 28, Range 19–37</td>
<td>Median 26, Range 18–42</td>
<td>0.335</td>
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<tr>
<td>Cycles/day</td>
<td>Median 40, Range 4–862</td>
<td>Median 9, Range 6–6</td>
<td>Median 5, Range 1–7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>Median 33.8, Range 17.0–60.2</td>
<td>Median 26.2, Range 21.5–49.1</td>
<td>Median 25.4, Range 19.6–50.9</td>
<td>0.022</td>
</tr>
<tr>
<td>Hirsutism score</td>
<td>Median 11, Range 0–29</td>
<td>Median 13.0, Range 8–18</td>
<td>Median 9, Range 0–9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ovarian volume (cm³)</td>
<td>Median 14.4, Range 5.7–44.8</td>
<td>Median 14.6, Range 9.7–21.5</td>
<td>Median 9.8, Range 2.7–16.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LH pool (IU/L)</td>
<td>Median 15.4, Range 5.3–112.9</td>
<td>Median 8.0, Range 2.1–10.8</td>
<td>Median 5.8, Range 2.0–12.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FSH pool (IU/L)</td>
<td>Median 9.1, Range 4.0–29.1</td>
<td>Median 9.4, Range 2.0–16.4</td>
<td>Median 10.8, Range 6.7–16.4</td>
<td>0.110</td>
</tr>
<tr>
<td>LH/FSH ratio</td>
<td>Median 1.58, Range 0.70–15.68</td>
<td>Median 1.05, Range 0.40–1.82</td>
<td>Median 0.51, Range 0.21–1.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LH pulse amplitude (IU/L)</td>
<td>Median 6.1, Range 2.6–50.7</td>
<td>Median 8.1, Range 5.3–66.5</td>
<td>Median 4.5, Range 2.0–14.9</td>
<td>0.004</td>
</tr>
<tr>
<td>LH pulse frequency (#/24 h)</td>
<td>Median 18, Range 4–28</td>
<td>Median 8.6, Range 2–13</td>
<td>Median 15, Range 6–21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Testosterone (ng/mL)</td>
<td>Median 1.3, Range 0.4–4.2</td>
<td>Median 0.89, Range 0.7–1.0</td>
<td>Median 0.6, Range 0.4–1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Androstenedione (ng/mL)</td>
<td>Median 3.7, Range 1.5–12.6</td>
<td>Median 2.4, Range 1.0–5.0</td>
<td>Median 2.6, Range 0.9–5.0</td>
<td>0.004</td>
</tr>
<tr>
<td>17-OH progesterone (ng/mL)</td>
<td>Median 1, Range 0.3–3.6</td>
<td>Median 0.8, Range 0.5–2.7</td>
<td>Median 0.7, Range 0.3–2.3</td>
<td>0.052</td>
</tr>
<tr>
<td>DHEA-S (µg/dL)</td>
<td>Median 148, Range 20–455</td>
<td>Median 150, Range 50–592</td>
<td>Median 158, Range 20–395</td>
<td>0.866</td>
</tr>
<tr>
<td>Estradiol (pg/mL)</td>
<td>Median 83, Range 16–235</td>
<td>Median 80, Range 34–178</td>
<td>Median 84, Range 40–142</td>
<td>0.845</td>
</tr>
<tr>
<td>Estrone (pg/mL)</td>
<td>Median 82, Range 14–606</td>
<td>Median 65, Range 28–298</td>
<td>Median 64, Range 23–119</td>
<td>0.075</td>
</tr>
</tbody>
</table>

*a P < 0.001 vs. normal.

*b P < 0.001 vs. anovulatory PCOS.

*c P < 0.05 vs. normal.
Determinants of Abnormal Gonadotropin Secretion in Clinically Defined Women with Polycystic Ovary Syndrome*

High prevalence of gonadotropin secretion abnormalities in PCOS patients

Important associations between the elevated LH secretion and recent ovulation or LH pulse frequency, but NOT sex steroids

Strong association between LH pulse frequency and pool LH levels or LH/FSH ratio may suggest an etiologic relationship

J Clin Endocrinol Metab 82, 1997
CONCLUSIONS

Rapid GnRH pulse frequency probably has a role in the abnormal LH secretion pattern in PCOS

Marshall and Eagleson, 1999
CONCLUSIONS

Rapid GnRH pulse frequency probably has a role in the abnormal LH secretion pattern in PCOS

The defect in hypothalamic GnRH secretion seems to be intrinsic to PCOS patients

Could there be a role of elevated insulin levels/insulin resistance in this abnormal GnRH secretion pattern?
Role of Brain Insulin Receptor in Control of Body Weight and Reproduction

Brüning et al., Science 289, 2000
Role of Brain Insulin Receptor in Control of Body Weight and Reproduction

Brüning et al., Science 289, 2000
Euglycemic hyperinsulinemic clamp studies in mice

Insulin infusion

Glucose 15 % infusion

Glycemia
Insulin Stimulates GnRH Secretion In Vivo

Burcelin et al, Endocrinology 2003
Insulin Stimulates GnRH Secretion In Vitro

Burcelin et al, Endocrinology 2003
Insulin stimulates the expression of the GnRH gene

Burcelin et al, Endocrinology 2003
Hypothalamic GnRH neurons express a functional insulin receptor

Vollenweider et al, Bern 2003
Insulin signaling and GnRH transcription

Insulin receptor

Grb2
Sos
Ras
Raf

IRS
P85
P110

PI3 Kinase

Akt

Shc

ERK 1/2

GnRH

Hypothalamic neurons
ERK1/2 activation (Phospho ERK) in primary hypothalamic cells

![Graph showing ERK1/2 activation over time]

- **Time**: 2 min, 5 min, 10 min, 30 min
- **p-ERK/total ERK (% over basal)**
- **n = 5-6**

* indicates significant difference.
PI-3 kinase activation

**IP IRS-1**
- PI3-kinase activity (% over basal)

**IP IRS-2**
- PI3-kinase activity (% over basal)

**Time (min)**
- Basal
- 5 min
- 15 min
- 30 min
- 60 min
- 120 min

* indicates significant difference from basal.
ERK1/2 (Phospho ERK) and Akt (Phospho-Akt) activation in GnV-3 cells

**ERK 1/2**

- **p-ERK1/2/ERK (% over basal)**
  - 1 min
  - 5 min
  - 10 min
  - 30 min

**n = 5-6**

**Akt**

- **p-Akt/Akt (% over basal)**
  - Basal
  - 5 min
  - 15 min
  - 60 min

* * **
The insulin effect on GnRH gene expression is dependent upon Erk1/2 activation in primary hypothalamic neurons.
The insulin effect on GnRH gene expression is independent of PI3-kinase activation in primary hypothalamic neurons.
Treatment options

• Oral contraception: reestablish menstrual cycles, decrease hyperandrogenism

• Association with an anti-androgen

• Insulin sensitizers: metformin, thiazolidinediones

Usually good clinical response to clomiphene citrate when seeking fertility