Exaggerated 17-hydroxyprogesterone response to intravenous infusions of recombinant human LH in women with polycystic ovary syndrome

Christopher R. McCartney, Amy B. Bellows, Melissa B. Gingrich, Yun Hu, William S. Evans, John C. Marshall, and Johannes D. Veldhuis

1The Center for Research in Reproduction, 2Division of Endocrinology, Department of Internal Medicine and 3Department of Obstetrics and Gynecology, University of Virginia Health System, Charlottesville, Virginia 22908

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McCartney, Christopher R., Amy B. Bellows, Melissa B. Gingrich, Yun Hu, William S. Evans, John C. Marshall, and Johannes D. Veldhuis. Exaggerated 17-hydroxyprogesterone response to intravenous infusions of recombinant human LH in women with polycystic ovary syndrome. Am J Physiol Endocrinol Metab 286: E902–E908, 2004.—Studies using pharmacological gonadotropin stimulation suggest that ovarian steroidogenesis is abnormal in the polycystic ovary syndrome (PCOS). We assessed ovarian steroid secretion in response to near-physiological gonadotropin stimuli in 12 ovulatory controls and 7 women with PCOS. A gonadotropin-releasing hormone-receptor antagonist (ganirelix, 2 mg sc) was given to block endogenous LH secretion, followed by dexamethasone (0.75 mg orally) to suppress adrenal androgen secretion. After ganirelix injection (12 h), intravenous infusions of recombinant human LH (0, 10, 30, 100, and 300 IU; each over 8 min) were administered at 4-h intervals in a pseudorandomized (highest dose last) manner. Plasma LH, 17-hydroxyprogesterone (17-OHP), androstenedione, and testosterone were measured concurrently. LH dose-steroid response relationships (mean sex-steroide

In vivo studies of PCOS demonstrate characteristically abnormal ovarian steroid responses to acute administration of either a potent gonadotropin-releasing hormone (GnRH) agonist (2, 7, 15, 31, 38) or a high dose of human chorionic gonadotropin (hCG; see Ref. 12, 15, 19). Specifically, these stimuli elicit exaggerated secretion of 17-hydroxyprogesterone (17-OHP) and, to a lesser degree, androstenedione (Δ4A), suggesting abnormal ovarian steroidogenesis. However, these paradigms involve pharmacological ovarian stimulation and do not reproduce physiological LH pulsatility. For instance, with acute GnRH agonist administration, plasma LH approaches or exceeds 100 IU/l within 4 h (2, 31) and remains elevated for several days. Similarly, hCG challenge protocols involve administration of 5,000–10,000 IU hCG (12, 15, 19), which effects potent and prolonged ovarian stimulation. In contrast, mean LH concentrations in women with PCOS approximate 5–35 IU/l (5, 26, 37). Thus these paradigms of supraphysiological gonadotropin stimulation evaluate maximal ovarian responses only. Moreover, supraphysiological gonadotropin stimuli may induce selective downregulation of ovarian steroidogenic enzymes. For instance, when gonadotropin stimulation of rodent or human Leydig cells is excessive, partial downregulation of 17-hydroxylase and 17,20-lyase ensues (7). Therefore, it is possible that abnormal 17-OHP and Δ4A responses in PCOS reflect abnormalities of steroidogenic enzyme downregulation in response to supraphysiological stimuli.

We hypothesized that near-physiological LH stimuli would effect greater ovarian secretion of androgens and their precursors in women with PCOS compared with controls. To test this supposition, we employed a paradigm of sequential GnRH-receptor antagonist administration to suppress endogenous LH concentrations, and intermittent (pulse-like) infusions of physiological amounts of recombinant human LH (rhLH) to stimulate ovarian steroidogenesis.

EXPERIMENTAL PROCEDURES

Subjects. We studied seven women with PCOS (ages 19–33 yr), diagnosed in accordance with criteria established at the 1990 NIH conference on PCOS (39). Specifically, these women had oligo- or amenorrhea; clinical and/or biochemical hyperandrogenism; and no evidence of other endocrine disorders. Thirty women (ages 19–34 yr) with regular menstrual cycles (every 28–33 days) and no biochemical hyperandrogenism served as controls. During a screening visit, all subjects were evaluated with determinations of LH, FSH, estradiol (E2), progesterone (P), total testosterone (T), sex hormone...

THE ETIOLOGY OF OVARIAN HYPERANDROGENEMIA in the polycystic ovary syndrome (PCOS) remains enigmatic. Previous studies have emphasized the relative roles of neuroendocrine abnormalities leading to persistent and excessive LH secretion (11, 14, 20, 30, 34) and the ovarian actions of hyperinsulinemia, a consequence of insulin resistance (4, 27, 35, 40). Additional evidence suggests that anomalous ovarian steroidogenesis is a primary abnormality in PCOS. For example, theca cell cultures derived from women with PCOS secrete androgens excessively (13), even after propagation for three to four passages in LH-free media (22).

Address for reprint requests and other correspondence: C. R. McCartney, Center for Research in Reproduction, Box 800391, Univ. of Virginia Health System, Charlottesville, VA 22908 (E-mail: cm2h@virginia.edu).

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binding globulin (SHBG), dehydroepiandrosterone sulfate, fasting glucose, HbA1c, prolactin, TSH, thyroxine, and β-estradiol. Subjects had not taken any hormonal medications for at least 90 days before the study screening, and none of the women was taking medications known to affect the reproductive axis.

Study protocol. The study was approved by both the Human Investigation Committee and the General Clinical Research Center (GCRC) Advisory Committee of the University of Virginia Health System. Informed consent was obtained from all study volunteers. Ganirelix (Antagon; Organon, West Orange, NJ) and rhLH (Luveris; Serono, Aubonne, Switzerland) were used in the protocol under an investigator-initiated Food and Drug Administration Investigational New Drug application.

All study participants were admitted to the GCRC for study over 2 nights and the intervening day. Women with PCOS were studied at least 60 days after last menses. Recent ovulation was excluded in these women by a plasma P concentration <1 ng/ml at the time of study, the absence of vaginal bleeding within 1 mo of study completion, or both. Normal controls were studied between days 3 and 2 of the follicular phase to approximate the hormonal milieu of PCOS (e.g., E2, P, LH pulse frequency). Pregnancy was excluded in all participants with a β-hCG measured on arrival to the GCRC.

The GCRC protocol is shown in Fig. 1. At 8 AM, an intravenous catheter was placed in an antecubital vein and used exclusively for sampling purposes. At 10 PM, 2 mg ganirelix, a GnRH-receptor antagonist, was given subcutaneously. Ganirelix lowers plasma LH over 2–6 h, with maximal suppression occurring in 8–12 h and continuing for at least 24 h (21, 29). In the last five subjects studied (3 controls, 2 PCOS), blood samples for later LH assay were obtained every 10 min for 1 h before ganirelix administration. At 12 AM, subjects took 0.75 mg dexamethasone orally to suppress adrenal androgen secretion. At 7 AM, a second intravenous catheter was placed in a contralateral antecubital vein and used for later hormone infusion.

Beginning at 8 AM and continuing for 22 h, blood samples were withdrawn as follows; LH every 10 min; 17-OH, Δ4A, and T every 30 min. At 10 AM (12 h after ganirelix), we began pseudorandomized (i.e., highest dose last) intravenous doses of rhLH. In the initial 10 controls and 5 PCOS subjects, administered doses included 0 (saline), 10, 30, and 100 IU rhLH. Evaluation of these patients revealed the 10 IU dose to be ineffectual; therefore, the last five subjects studied (3 controls, 2 PCOS) received 0, 30, 100, and 300 IU rhLH. The highest rhLH dose was always administered last to obviate sequence artifact. All rhLH doses were given as 8-min square wave infusions at 4-h intervals via a Harvard infusion pump; this method of rhLH administration produces plasma LH profiles that are essentially indistinguishable from endogenous LH pulses. In the initial five women with PCOS and nine controls, 500 µg GnRH were administered intravenously at 2 AM on the second night.

Hormonal measurements. All samples from each individual were analyzed in duplicate in the same assay for each hormone. Plasma LH and FSH were measured by chemiluminescence (assay sensitivities 0.01 and 0.2 IU/l, intra-assay CVs ≤5.4 and 9.5%, and interassay CVs ≤15.1 and 14.4%, respectively; Nichols Institute Diagnostics, San Juan Capistrano, CA). Steroids were measured by RIA (Diagnostic Systems Laboratories, Webster, TX). For 17-OH, Δ4A, and T, sensitivities were 0.01 ng/ml (0.03 nmol/l), 0.03 ng/ml (0.1 nmol/l), and 0.08 ng/ml (0.28 nmol/l), respectively; intra-assay CVs ≤7.9, 7.5, and 11.5%, respectively; and interassay CVs ≤18.6, 18, and 18.9%, respectively. For E2 and P, sensitivities were 4.7 pg/ml (17.3 pmol/l) and 0.12 ng/ml (0.38 nmol/l), respectively; intra-assay CVs ≤10.6 and 11%, respectively; and interassay CVs ≤15.9 and 17.4%, respectively. SHBG was measured by immunoradiometric assay (assay sensitivity 3 nmol/l, intra-assay CV ≤9.4%, interassay CV ≤15%; Diagnostic Systems Laboratories). Samples with measured values below assay sensitivity were assigned the value of the assay’s sensitivity.

Data and statistical analysis. Data from one normal control was excluded because of failure to administer the highest (100 IU) rhLH dose; the final analysis for this report is thus based on 12 controls and 7 women with PCOS. All data are reported as means ± SE.

Screening data were compared using Wilcoxon rank-sum tests. Average plasma LH, 17-OH, Δ4A, and T concentrations were calculated from 0800 to 1000 (i.e., beginning 10 h after ganirelix administration and ending immediately before the first rhLH infusion) and designated as baseline hormone concentrations; these were compared (PCOS vs. controls) using Wilcoxon rank-sum tests.

Average LH and ovarian steroid concentrations over the 4-h intervals after each dose of rhLH were also calculated. Missing values, which represented <0.1% of the total, were ignored. For each steroid and each individual, linear regression models were estimated to characterize the relationship between the mean steroid concentration over each 4-h period (the dependent variable) and the corresponding 4-h mean LH concentration (the independent variable). In this way, we estimated an LH dose-steroid response relationship for each woman with PCOS and each control. Mean LH was chosen as the measure of ovarian stimulus because this incorporated possible disparity between the relative contributions of endogenous LH (because suppression with ganirelix could have differed) between PCOS and controls. We chose the mean 4-h steroid concentration, instead of steroid pulse mass, as the dependent variable largely because clear steroid pulses were rarely observed (see below). To determine whether mean steroid concentration changed significantly with increasing mean LH concentration (i.e., if estimated regression line slopes were different from 0) within the PCOS group and within the control group, Wilcoxon signed-rank tests were used. To determine whether the association between steroid and LH concentrations was the same (i.e., the apparent LH dose-steroid response relationship) differed between PCOS and controls, estimated regression line slopes were compared using Wilcoxon rank-sum tests. For all Wilcoxon signed-rank and rank-sum tests, statistical testing was based on exact permutation tests (32). All hypothesis tests were two-sided and conducted at the 0.05 level of significance.

Because 300 IU rhLH produced supraphysiological LH pulses, linear regression models were also estimated while disregarding this highest dose only. Differences in results were negligible, and we therefore report results including all rhLH doses, unless otherwise specified.

RESULTS

A trend was observed toward higher body mass index in women with PCOS (34.8 ± 3.3 kg/m²) compared with controls (27.5 ± 1.6 kg/m²), but this difference was not statistically
concentrations associated with each rhLH dose are the average of 10-min plasma values for the 4 h after rhLH or GnRH infusion. LH amplitude is de... equilibrium constant for T binding to SHBG (1.6...PCOS 2.80...

Mean LH concentrations and LH amplitudes after LH or GnRH infusions are shown in Table 3, and representative LH and...

Table 1. Screening hormonal data

<table>
<thead>
<tr>
<th>Age, yr</th>
<th>BMI, kg/m²</th>
<th>LH* IU/L</th>
<th>FSH, IU/L</th>
<th>T* ng/dl</th>
<th>SHBG, nmol/l</th>
<th>Calculated Free T* pmol/l</th>
<th>E₂, pg/ml</th>
<th>P, ng/ml</th>
<th>DHEA-S, µg/dl</th>
<th>Glucose, mg/dl</th>
<th>Hba₁c*, %</th>
<th>Prolactin, ng/ml</th>
<th>TSH, µIU/ml</th>
<th>Thyroxine, µg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Controls</td>
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<td></td>
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<tr>
<td>Mean ± SE</td>
<td>27.2 ± 1.5</td>
<td>27.5 ± 1.6</td>
<td>5.96 ± 1.8</td>
<td>4.56 ± 0.6</td>
<td>34.0 ± 5.5</td>
<td>78.7 ± 10.6</td>
<td>12.0 ± 2.7</td>
<td>86.9 ± 15.4</td>
<td>4.33 ± 1.4</td>
<td>251 ± 42</td>
<td>78.6 ± 22</td>
<td>5.0 ± 0.1</td>
<td>11.6 ± 1.6</td>
<td>1.6 ± 0.2</td>
</tr>
<tr>
<td>SD</td>
<td>5.3</td>
<td>5.4</td>
<td>6.1</td>
<td>2.1</td>
<td>18.9</td>
<td>36.8</td>
<td>9.5</td>
<td>53.3</td>
<td>4.8</td>
<td>145</td>
<td>7.5</td>
<td>0.3</td>
<td>5.6</td>
<td>0.64</td>
</tr>
<tr>
<td>Median</td>
<td>29</td>
<td>27</td>
<td>4.0</td>
<td>4.4</td>
<td>32</td>
<td>75</td>
<td>10.5</td>
<td>79</td>
<td>2.9</td>
<td>233</td>
<td>79</td>
<td>5.0</td>
<td>9.5</td>
<td>1.6</td>
</tr>
</tbody>
</table>

PCOS

Mean ± SE | 26.6 ± 1.6 | 34.8 ± 3.3 | 10.0 ± 1.4 | 4.50 ± 0.8 | 63.1 ± 9.6 | 28.2 ± 4.6 | 28.2 ± 4.6 | 78.2 ± 16.3 | 0.096 ± 0.2 | 234 ± 92 | 93.0 ± 5.1 | 5.5 ± 0.2 | 8.6 ± 1.7 | 2.4 ± 0.5 | 7.5 ± 0.6 |
| SD | 4.2 | 8.8 | 3.7 | 2.1 | 25.5 | 12.0 | 12.0 | 39.9 | 0.5 | 244 | 13.4 | 0.5 | 4.4 | 1.2 | 1.6 |
| Median | 27 | 36 | 10.6 | 4.1 | 57 | 52 | 26.5 | 70 | 0.8 | 154 | 87 | 5.4 | 6.6 | 2.6 | 8.2 |

In 6 of 12 controls, screening laboratory tests were obtained during the luteal phase. BMI, body mass index; T, testosterone; SHBG, sex hormone binding globulin; E₂, estradiol; P, progesterone; DHEA-S, dehydroepiandrosterone sulfate; PCOS, polycystic ovary syndrome. *P < 0.05 controls vs. PCOS.

Table 2. Mean LH concentrations and LH amplitudes after LH or GnRH

<table>
<thead>
<tr>
<th>Mean LH over 4 h, IU/L</th>
<th>LH Amplitude, IU/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>rhLH dose</td>
<td>GnrH</td>
</tr>
<tr>
<td>0</td>
<td>10³</td>
</tr>
<tr>
<td>Normal Controls</td>
<td>2.24 ± 0.35</td>
</tr>
<tr>
<td>PCOS</td>
<td>2.80 ± 0.45</td>
</tr>
</tbody>
</table>

Data are means ± SE; n = 14 subjects (a), 5 subjects (b), or 13 subjects (c). rh, recombinant human; GnRH, gonadotropin-releasing hormone. Mean LH concentrations associated with each rhLH dose are the average of 10-min plasma values for the 4 h after rhLH or GnRH infusion. LH amplitude is defined as the peak increment within 30 min of rhLH infusion.
Table 3. Mean 17-OHP, Δ4A, and testosterone concentrations after rhLH or GnRH

<table>
<thead>
<tr>
<th>rhLH dose, IU</th>
<th>0</th>
<th>10</th>
<th>30</th>
<th>100</th>
<th>300</th>
<th>GnRH 500 μg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean 17-OHP over 4 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal controls</td>
<td>0.26±0.06</td>
<td>0.17±0.03</td>
<td>0.26±0.06</td>
<td>0.31±0.08</td>
<td>0.45±0.11</td>
<td>0.33±0.06</td>
</tr>
<tr>
<td>PCOS</td>
<td>0.30±0.05</td>
<td>0.24±0.02</td>
<td>0.37±0.07</td>
<td>0.51±0.08*</td>
<td>0.68±0.11</td>
<td>0.78±0.10†</td>
</tr>
<tr>
<td>Mean Δ4A over 4 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal controls</td>
<td>0.83±0.09</td>
<td>0.80±0.09</td>
<td>0.90±0.09</td>
<td>0.97±0.12*</td>
<td>1.11±0.23</td>
<td>1.09±0.11</td>
</tr>
<tr>
<td>PCOS</td>
<td>1.18±0.14</td>
<td>1.25±0.16*</td>
<td>1.18±0.08</td>
<td>1.18±0.07</td>
<td>1.30±0.15</td>
<td>1.36±0.10</td>
</tr>
<tr>
<td>Mean T over 4 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal controls</td>
<td>0.37±0.04</td>
<td>0.31±0.05</td>
<td>0.39±0.05</td>
<td>0.36±0.06</td>
<td>0.51±0.10</td>
<td>0.32±0.06</td>
</tr>
<tr>
<td>PCOS</td>
<td>0.68±0.11*</td>
<td>0.73±0.12*</td>
<td>0.70±0.10*</td>
<td>0.75±0.08†</td>
<td>0.60±0.08</td>
<td>0.86±0.06†</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 14 subjects (a), 5 subjects (b), and 13 subjects (c). 17-OHP, 17-hydroxyprogesterone; Δ4A, androstenedione. Mean steroid concentrations are the average of 30-min plasma values for the 4 h after rhLH or GnRH infusion. *P < 0.05 and †P < 0.01, PCOS vs. controls. To convert 17-OHP, Δ4A, and T (ng/ml) to nmol/l, multiply by 3.03, 3.49, and 3.47, respectively.

DISCUSSION

With this study, we aimed to determine whether near-physiological ovarian stimulation produces abnormal steroid response profiles in women with PCOS. Prior studies involving pharmacological ovarian stimulation (i.e., acute administration of a GnRH agonist or a high dose of hCG) demonstrated exaggerated 17-OHP, and to a lesser degree Δ4A, responses in PCOS compared with controls. We similarly observed heightened 17-OHP secretion in response to near-physiological ovarian stimulation with rhLH in patients with PCOS, suggesting abnormalities of the early steps of ovarian steroidogenesis (i.e., conversion of early precursor steroids, such as pregnenolone and P, to the weak androgen Δ4A). Notably, the results were similar regardless of whether responses to the 300 IU dose were included in analysis, confirming that these findings were not driven by supraphysiological LH stimulation. The increased 17-OHP responses in PCOS observed in our study may reflect exaggerated acute steroidogenic responses that parallel escalating doses of rhLH. However, an alternative explanation is that the 17-OHP increase in PCOS reflects abrupt (compared with normal) rhLH-induced resumption of early steroidogenic steps after temporary removal of physiological LH stimulation.

In our research paradigm, LH dose-ovarian steroid responses were not observed in normal women, as the slopes for all steroids regressed on LH were indistinguishable from zero. Furthermore, acute ovarian steroid responses to rhLH infusions were not commonly apparent when reviewing individual steroid time series. It remains possible that ovarian steroid responses could have occurred after our surveillance had ended. Nonetheless, these observations suggest that ovarian steroidogenesis during the normal follicular phase is influenced by...
Fig. 3. Mean 17-OHP, Δ4A, and T regressed on mean LH. □, Data (4-h mean steroid concentration vs. 4-h mean LH) for control subjects; ■, data for patients with PCOS. To convert 17-OHP, Δ4A, and T (ng/ml) to nmol/l, multiply by 5.03, 3.49, and 3.47, respectively.

integrated LH stimulation and does not vary acutely with changes in LH pulse mass. This contrasts with acute P responses to endogenous LH pulses during the luteal phase (9).

The flat slopes of Δ4A and T regressed on LH observed in our study might be expected in light of steroid responses to GnRH agonist administration. For instance, with acute GnRH agonism, Δ4A does not increase above baseline in PCOS for ~12–24 h (2); likewise, T does not increase above baseline rapidly, even in response to maximal ovarian stimulation. Also, baseline T concentrations (i.e., 10–12 h after ganirelix) in our study were higher in PCOS than in controls despite similar LH levels, suggesting that increased T production in PCOS is maintained during short-term reduction of plasma LH. Taken together, these findings suggest that acute changes in gonadotropin stimulation result in more rapid alterations in the early steps of steroidogenesis, reflected by changes of 17-OHP concentrations, compared with later steps, reflected by changes in Δ4A and T. It is also possible that there is a time delay between rhLH administration and Δ4A and T responses, or that more rhLH doses, or a different pattern (frequency) of intermittent rhLH stimulation, are required to elicit a Δ4A and T response.

In a number of ways, ovarian stimulation in the present study differed from that achieved with either acute GnRH agonist or high-dose hCG administration. First, the magnitude of the LH stimulus is more physiological, as is the intermittent nature of the stimulus. Second, rhLH infusions do not elevate FSH in contrast to GnRH agonist administration; the absence of accompanying FSH stimulation, as in hCG stimulation protocols, may (19) or may not (15) mitigate abnormal ovarian responses to acute gonadotropin challenge. Third, rhLH differs from native LH in its posttranslational glycosylation and may have different biological potency from endogenous LH (3). Finally, it is possible that GnRH agonists and antagonists have differential effects on ovarian steroidogenesis, since GnRH receptors have been demonstrated in the human ovary (25).

In PCOS, steroidogenic response patterns after acute challenge with GnRH agonists, high-dose hCG, or intermittent rhLH stimulation are consistent with excessive 17-hydroxylase and 17,20-lyase activity (7). Ehrmann and colleagues (7) hypothesized that these patterns reflect a failure of appropriate steroidogenic downregulation in response to excessive gonadotropin drive. The patterns are also compatible with a global increase in ovarian steroidogenic activity, with pronounced accumulation of 17-OHP being secondary to the relative inefficiency with which 17,20-lyase uses 17-OHP as a substrate (10). Indeed, some investigators find no evidence of 17,20-lyase activity in the Δ4 pathway (i.e., converting 17-OHP to Δ4A) in humans (28).

The etiology of putative ovarian steroidogenic abnormalities in PCOS is unknown. They may reflect a primary ovarian abnormality, such as genetic mutations leading to increased steroidogenic enzyme activity. In vitro studies have demonstrated that PCOS theca cells cultured through three to four passages in LH-free media retain excessive steroidogenic activity (22), suggesting that abnormalities of steroidogenesis are inherent. Alternatively, steroidogenic abnormalities may reflect the prevailing hormonal milieu in PCOS. For instance, altered enzymatic activity may result from insulin excess. Insulin has potent trophic actions on ovarian theca cells in vitro, and high insulin doses stimulate androgen production, whereas lower doses augment LH-induced androgen secretion (4, 27, 35, 40). Additionally, insulin reduction in vivo is associated with reduced steroidogenic responses to GnRH agonist or hCG testing in most (6, 16–18, 23, 24, 36) but not all (33) PCOS studies.

Chronic exposure to excessive LH could also induce qualitative steroidogenic abnormalities in PCOS, but definitive evidence is lacking. 17-OHP responses to acute hCG challenge remain elevated 4 wk after GnRH agonist (leuprolide) administration (12), arguing against a role for LH. However, GnRH agonists initially stimulate gonadotropins, and pituitary desensitization and a fall in LH may not occur for 2–3 wk. Thus compelling evidence to exclude a role for LH awaits effective removal of LH drive for longer periods of time before acute stimulation of steroidogenesis using a physiological LH challenge.

Other factors may also contribute to abnormal steroidogenic response patterns in PCOS, including FSH deficiency, growth factors (e.g., insulin-like growth factors), and other autocrine and paracrine influences (7). An intriguing possibility is that abnormal steroidogenic activity may reflect early androgen exposure, since exaggerated 17-OHP and T responses to hCG occur in prenatally androgenized monkeys (8).

In summary, we conclude that near-physiological ovarian stimulation via intermittent (pulse-like) rhLH administration produces exaggerated 17-OHP secretion in patients with PCOS, supporting earlier studies of pharmacological ovarian stimulation. Delineating the mechanisms underlying heightened precursor responsiveness to LH in PCOS will require further clinical investigation.

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Present address for J. D. Veldhuis: Division of Endocrinology, Department of Internal Medicine, Mayo Medical and Graduate Schools, General Clinical Research Center, Mayo Clinic, Rochester, MN 55905.

GRANTS

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