Retention of estradiol negative feedback relationship to LH predicts ovulation in response to caloric restriction and weight loss in obese patients with polycystic ovary syndrome

Eveline W. C. M. van Dam,1,6 Ferdinand Roelfsema,1 Johannes D. Veldhuis,7 Simone Hogendoorn,1 Jos Westenberg,5 Frans M. Helmerhorst,4 Marijke Frölich,3 H. Michiel J. Krans,1 A. Edo Meinders,2 and Hanno Pijl2

1Department of Endocrinology and Metabolic Diseases, 2Department of General Internal Medicine, 3Department of Clinical Chemistry, 4Department of Obstetrics, Gynaecology and Reproductive Medicine, and 5Department of Radiology, Leiden University Medical Center, Leiden, 2300 RC; 6Department of Internal Medicine, Vrije Universiteit Medical Center, Amsterdam, 1007 MB The Netherlands; and 7General Clinical Research Center, Mayo Medical and Graduate Schools of Medicine, Mayo Clinic, Rochester, Minnesota 55905

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Van Dam, Eveline W. C. M., Ferdinand Roelfsema, Johannes D. Veldhuis, Simone Hogendoorn, Jos Westenberg, Frans M. Helmerhorst, Marijke Frölich, H. Michiel J. Krans, A. Edo Meinders, and Hanno Pijl. Retention of estradiol negative feedback relationship to LH predicts ovulation in response to caloric restriction and weight loss in obese patients with polycystic ovary syndrome. Am J Physiol Endocrinol Metab 286: E615–E620, 2004. First published December 16, 2003; 10.1152/ajpendo.00377.2003.—The present study tests the hypothesis that specific endocrine, metabolic, and anthropometric features distinguish obese women with polycystic ovary syndrome (PCOS) who resume ovulation in response to caloric restriction and weight loss from those who do not. Fifteen obese (body mass index 39 ± 7 kg/m2) hyperandrogenemic oligoovulatory patients undertook a very low calorie diet (VLCD), wherein each lost ≥10% of body weight over a mean of 6.25 mo. Body fat distribution was quantitated by magnetic resonance imaging. Hormones were measured in the morning at baseline, after 1 wk of VLCD, and after 10% weight loss. To monitor LH release, blood was sampled for 24 h at 10-min intervals before intervention and after 7 days of VLCD. Responders were defined as individuals exhibiting two or more changes in LH secretion in the course of intervention, as corroborated by serum progesterone concentrations ≥18 nmol/l followed by vaginal bleeding. At baseline, responders had a higher sex hormone-binding globulin (SHBG) concentration but were otherwise indistinguishable from nonresponders. Body weight, the size of body fat depots, and plasma insulin levels declined to a similar extent in responders and nonresponders. Also, SHBG increased, and the free testosterone index decreased comparably. However, responders exhibited a significant decline of circulating estradiol concentrations (from 191 ± 82 to 158 ± 77 pmol/l, means ± SD, P = 0.037) and a concurrent increase in LH secretion (from 104 ± 42 to 140 ± 5 U·1−1·day−1, P = 0.006) in response to 7 days of VLCD, whereas neither parameter changed significantly in nonresponders. We infer that evidence of retention of estradiol-dependent negative feedback on LH secretion may forecast follicle maturation and ovulation in obese patients with PCOS under dietary restriction.

fertility; ovarian cycle; sex hormones; body fat distribution; gonadotropins

POLYCYSTIC OVARY SYNDROME (PCOS) is a heterogeneous disorder of female reproduction characterized by hyperandrogenism and chronic oligo- or anovulation in the absence of specific disease of the adrenal glands, ovaries, or pituitary gland (41). If these criteria are applied to establish the diagnosis, PCOS occurs in 4–8% of premenopausal women (2, 5, 19).

The etiology of the disease remains uncertain. It is thought that various environmental factors interact with genes that predispose women to the development of PCOS (8, 21). A number of features that are often, but not always, present in PCOS may provide mechanistic clues: obesity, peripheral insulin resistance, and chronic hyperinsulinemia (6, 11). More than 50% of women with PCOS are obese (body mass index >30 kg/m2), reflecting primarily visceral adiposity (11). Intra-abdominal obesity is frequently accompanied by insulin resistance and compensatory hyperinsulinemia (3). Collective evidence suggests that hyperinsulinemia drives ovarian (over)production of androgens and simultaneously inhibits hepatic sex hormone-binding globulin (SHBG) synthesis, potentially enhancing androgen availability to target tissues (6, 32). The ensuing hyperandrogenism contributes to hyperestrogenemia and is accompanied by ovulatory dysfunction and apparent resistance to estrogen/progesterone-dependent feedback restraint of LH secretion, another typical feature of women with PCOS (1, 9, 17, 29, 35). In keeping with this association, insulin-lowering drugs tend to reduce circulating androgen concentrations and promote ovulation in this disorder (7, 24–26).

Caloric restriction and weight loss often ameliorate excessive androgen production and restore ovulatory cyclicity in 50–80% of obese PCOS patients (11, 28). The clinical postulate that concomitant reduction of circulating insulin and androgen concentrations in the course of weight loss presages ovulatory recovery in this setting was not affirmed in a controlled study (28). Accordingly, precise predictors of gonadal axis improvement in obese PCOS individuals undergoing weight reduction are not clear.

The present prospective intervention appraises the predictive value of total and regional adiposity, metabolic adaptations, and endocrine markers in defining resumption of ovulatory menses after a 10% diet-induced decrease in body weight.

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SUBJECTS AND METHODS

Subjects

Fifteen obese women with the diagnosis of PCOS participated; mean age was 29 (range: 20–38) yr and mean body mass index (BMI) was 39 (range: 30–54) kg/m². The diagnosis of PCOS was based on the presence of infertility due to an- or oligoovulation that is not secondary to a specific underlying disease of the pituitary, ovaries, or adrenal glands, with elevated serum concentrations of testosterone in the absence of hyperprolactinemia or thyroid disease. Late-onset adrenal hyperplasia was excluded by a morning plasma 17-hydroxyprogesterone concentration below 10 nmol/l. LH and testosterone concentration ratios were significantly higher than in a group of weight-matched control women with regular menses (data not shown; for details see Ref. 35). The mean intermenstrual interval was 138 ± 104 days; the median was 120 days. None of the subjects used any psychoactive medication or hormones (including oral contraceptives), and each had a stable body weight for ≥3 mo before the study. Written informed consent was obtained from all subjects. The study protocol was approved by the ethics committee of the Leiden University Medical Center.

Clinical Protocol

An- or oligoovulatory women with PCOS were studied at baseline (occasion 1), after 1 wk of a very low calorie diet (VLCD) (occasion 2), and after the loss of 10% baseline body weight (occasion 3) on a random day. Ovulation had not occurred before occasion 1 or 2, as evidenced by evaluation of serum progesterone concentrations measured 20 (range 9–25) days before the study and on those two occasions.

On occasions 1 and 2, subjects were admitted to the Clinical Research Center just before 0800, after a 10-h overnight fast. On the morning of admission, body weight, waist and hip circumferences, and body composition were measured. A single venous blood sample was withdrawn ≥30 min after insertion of an intravenous cannula at 0800 to allow later measurement of serum insulin, glucose, 17-hydroxyprogesterone, progesterone, testosterone, estradiol, SHBG, FSH, and LH. Subsequently, blood was sampled in heparinized tubes at 10-min intervals for 24 h for LH assay. Samples were centrifuged within 1 h of sampling, and plasma was stored at −20°C. Body fat distribution was quantitated by MRI ≤4 wk before baseline study.

On occasion 3, the foregoing biochemical parameters were repeated after an overnight fast. Body weight and MRI estimates of fat distribution were made again within 1 wk of the admission.

For 3 days before admission for occasion 1, all subjects were fed a liquid diet [total of 8.3 MJ (1,970 kcal)/day] consisting of Modifast [2 MJ (471 kcal)/day in three equal proportions, with macronutrient composition: 43% protein, 15% fat, and 42% carbohydrate; Novartis Nutrition Benelux, Breda, The Netherlands] plus Nutridrink [6.3 MJ (2 MJ (471 kcal)/day in three equal proportions, with macronutrient composition as described above]. Modifast and Nutridrink were served as meals at 0900 (300 kcal Nutridrink and 157 kcal Modifast), 1400 (600 kcal Nutridrink and 157 kcal Modifast), and 1900 (600 kcal Nutridrink and 157 kcal Modifast). Subjects refrained from napping or drinking caffeinated beverages during each occasion. They were allowed to walk around inside the research center during the day. Lights were put out at 2300.

Dietary Intervention

After occasion 1, the patients were prescribed a VLCD [Modifast, 2 MJ (470 kcal)/day, with macronutrient composition as described above]. They were instructed not to change their physical activity for the first 7 days. On occasion 2, the VLCD was served as meals in three equal portions (157 kcal each) at 0900, 1400, and 1900. Thereafter, the subjects continued to use the VLCD until the end of the study.

Definition of Responders

Patients were classified as responders only if ovulation occurred at least twice during follow-up, on the basis of a serum progesterone concentration >18 nmol/l and vaginal bleeding. Intermenstrual intervals before intervention were similar in responders [120 ± 51 (SD) days, median 120 days] and nonresponders (165 ± 158 days, median 105 days).

Follow-Up

Mean (±SD) follow-up duration was 29 (±13) wk for the whole group, 29 (±15) wk in responders and 29 (±10) wk in nonresponders. Serum progesterone concentrations, the occurrence of genital bleeding, and body weight were assessed every 2 wk until the end of the study.

Assays

Androstenedione, testosterone, progesterone, and 17-OH-progesterone were measured by solid-phase RIA (Diagnostic Products, Los Angeles, CA). Estrone and SHBG were quantitated by coated-tube RIA and immunoradiometric assay (IRMA), respectively (Spectria, Espoo, Finland). Estradiol was determined by RIA (Diagnostic Systems Laboratory, Webster, TX). LH and FSH were measured with a time-resolved immunofluorometric assay (Wallac, Turku, Finland) (30). Insulin was measured with IRMA (Biosource, Nivelles, Belgium) and glucose by automated chemianalyzer (Hitachi 747; Hitachi, Tokyo, Japan).

Anthropometric Measures and Body Composition

The waist-to-hip ratio, or WHR, was calculated as waist circumference divided by hip circumference. The waist circumference (cm) was measured halfway between the lower costal margin and the iliac crest.

Table 1. Effects of calorie restriction on anthropometric parameters

<table>
<thead>
<tr>
<th></th>
<th>Responders</th>
<th>Nonresponders</th>
<th>P Value by ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>at 1 wk</td>
<td>at 10% WL</td>
</tr>
<tr>
<td>No.</td>
<td>9</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Age, yr</td>
<td>30 ± 2.5</td>
<td>30 ± 1.8</td>
<td>33.4 ± 1.6*</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>37.5 ± 1.6</td>
<td>36.5 ± 1.6*</td>
<td>33.4 ± 1.6*</td>
</tr>
<tr>
<td>Body fat, kg</td>
<td>52.5 ± 3.5</td>
<td>49.6 ± 3.5*</td>
<td>38.7 ± 3.7*</td>
</tr>
<tr>
<td>Fat, cm²</td>
<td>138 ± 17</td>
<td>ND</td>
<td>91 ± 18</td>
</tr>
<tr>
<td>Visceral abdominal</td>
<td>660 ± 46</td>
<td>ND</td>
<td>530 ± 40</td>
</tr>
<tr>
<td>Subcutaneous abdominal</td>
<td>565 ± 37</td>
<td>ND</td>
<td>462 ± 38</td>
</tr>
</tbody>
</table>

Values are means ± SE. BMI, body mass index; WL, weight loss; ND, not done. Post hoc significance vs. baseline: *P < 0.0001; †P < 0.001.
The hip circumference was measured at the maximal circumference of the hip, with the subjects in a standing position.

Body fat mass was estimated by bioelectrical impedance analysis (Bodystat; Douglas, Isle of Man, UK). Impedance measurements were obtained in the morning after subjects had voided and were resting in bed.

Magnetic resonance imaging (MRI) scans were made using a multislice fast-spin echo sequence (Gyroscan-T5 whole body scanner; Philips Medical Systems, Best, the Netherlands). Visceral and subcutaneous adipose tissue areas (mm²) were assessed by transverse abdominal (at the level of L₄-₅) and femoral scans, as previously described (20).

**Analytical Techniques**

Cluster, a largely model-free computerized peak detection algorithm, was used to quantify statistically significant LH peaks in the hormone concentration series in relation to dose-dependent measurement error, as described previously (37). Multiparameter deconvolution analysis was applied to compute basal, pulsatile, and total 24-h LH secretion (36). The homeostasis model assessment-insulin resistance index (HOMA-IRI) was calculated by the formula described by Matthews et al. (23).

**Statistical Analysis**

The effects of intervention were analyzed by repeated-measures two-way ANOVA in two or three (intervention cycle) × two (responders and nonresponders) factorial design. Within-subject comparisons were made with one-way ANOVA for repeated-measure design, followed by post hoc contrasts vs. basal by use of the appropriate C matrix. Values are means ± SE, unless otherwise noted. The significance level was set at 5%. Calculations were performed using Systat (Systat, Richmond, CA).

**RESULTS**

**Baseline Characteristics**

**Anthropometric, hormonal, and metabolic parameters.** The baseline anthropometric, metabolic, and hormonal characteristics of women who responded favorably to intervention and of women who did not are shown in Tables 1, 2, and 3, respectively. All women, except one, lost ≥10% body weight after 9 ± 8 wk (median 8 wk). Responders did so in 8 ± 2 wk (median 8 wk) and nonresponders in 11 ± 7 wk (median 8 wk); P = not significant (NS). The BMI of responders declined to 32 ± 5 kg/m² and that of nonresponders to 35 ± 5 kg/m² (P = NS). Total body fat and the adipose depots were reduced to a similar extent in both groups. Plasma glucose and insulin concentrations increased significantly in both groups. The plasma estradiol concentration declined by 42% in responders and nonresponders exhibited a rise in SHBG in response to VLCD in responders, whereas there was no change in nonresponders (Fig. 1). After the loss of 10% of initial body weight, estradiol concentrations returned to baseline in both groups. The ratio of estradiol to mean LH,

**Table 2. Effects of calorie restriction on metabolic markers**

<table>
<thead>
<tr>
<th></th>
<th>Responders</th>
<th>Nonresponders</th>
<th>P Value by ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>at 1 wk</td>
<td>at 10% WL</td>
</tr>
<tr>
<td>Fasting glucose, mmol/l</td>
<td>5.5±0.3</td>
<td>4.5±0.2</td>
<td>4.6±0.2b</td>
</tr>
<tr>
<td>Fasting insulin, pmoI/l</td>
<td>21.3±4.4</td>
<td>11.2±2.4</td>
<td>14.0±2.5</td>
</tr>
<tr>
<td>HOMA-IRI</td>
<td>5.0±0.9</td>
<td>2.3±0.5</td>
<td>2.9±0.6</td>
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</tbody>
</table>

Values are means ± SE. HOMA-IRI, homeostasis model assessment-insulin resistance index. Post hoc significance vs. baseline: *P = 0.002; bP = 0.005; cP = 0.0013; dP = 0.03; eP = 0.02; fP = 0.05.

**Response to Treatment**

**Occurrence of ovulation.** Nine of the 15 obese PCOS women could be classified as responders. One volunteer ovulated despite failure to achieve the required 10% weight loss. Six women did not show any sign of ovulation (nonresponders), despite achieving the target 10% weight loss.

**Anthropometric, hormonal, and metabolic parameters.** Anthropometric, metabolic, and hormonal responses to caloric restriction in both cohorts with PCOS (responders and nonresponders) are shown in Tables 1, 2, and 3, respectively. All women, except one, lost ≥10% body weight after 9 ± 8 wk (median 8 wk). Responders did so in 8 ± 2 wk (median 8 wk) and nonresponders in 11 ± 7 wk (median 8 wk); P = not significant (NS). The BMI of responders declined to 32 ± 5 kg/m² and that of nonresponders to 35 ± 5 kg/m² (P = NS). Total body fat and the adipose depots were reduced to a similar extent in both groups. Plasma glucose and insulin concentrations increased significantly in both groups. The plasma estradiol concentration declined by 42% in responders and nonresponders exhibited a rise in SHBG in response to VLCD in responders, whereas there was no change in nonresponders (Fig. 1). After the loss of 10% of initial body weight, estradiol concentrations returned to baseline in both groups. The ratio of estradiol to mean LH.
A conspicuous finding in this study is the amplification of pulsatile LH secretion (assessed by deconvolution analysis) under short-term VLCD only in patients with PCOS destined to ovulate in subsequent weeks. This outcome is remarkable, in that mean LH concentrations and the amplitude of LH pulses are elevated in the majority of women with PCOS (1, 9, 29, 33, 35). Although the exact role of hypergonadotropism in the pathogenesis of anovulation in this syndrome is not clear, excessive LH drive presumptively contributes to intraovarian and systemic hyperandrogenism and follicular growth arrest (17, 40). On the other hand, several means of ovulation induction in PCOS increase pulsatile LH and FSH secretion, i.e., clomiphene citrate and pulsatile GnRH administration (12, glucose and insulin concentrations; and the HOMA-IR decreased comparably in response to caloric restriction and weight loss in responders and nonresponders. In contrast, the plasma concentration of estradiol and the FTI fell, and plasma LH rose significantly, only in women who ovulated in the course of dietary intervention. The latter reciprocal relationship is consistent with a hypothesis that preserved negative feedback control of pulsatile LH release (that is, pulse amplitude) by estrogen forecasts ovarian cyclicity in response to dietary restriction in PCOS patients. However, other mechanistic explanations for our findings cannot be excluded on the basis of our data set.

Fig. 1. Estradiol-to-mean LH ratio before and after 7 days of calorie restriction in individual women who regained ovulation in the course of treatment (responders) and in women who did not (nonresponders). Short horizontal lines represent means.

Table 4. Effects of short-term calorie restriction on LH secretion

<table>
<thead>
<tr>
<th></th>
<th>Responders</th>
<th>Nonresponders</th>
<th>P Value by ANOVA</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>at 1 wk</td>
<td>Baseline</td>
</tr>
<tr>
<td>Cluster analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean LH, U/l</td>
<td>6.3±0.9</td>
<td>7.9±0.9</td>
<td>6.2±1.1</td>
</tr>
<tr>
<td>Pulse no./24 h</td>
<td>22±0.8</td>
<td>20±1.3</td>
<td>21±0.9</td>
</tr>
<tr>
<td>Pulse area, U/l·min</td>
<td>49±6.5</td>
<td>89±20.8</td>
<td>42±5.5</td>
</tr>
<tr>
<td>Incremental pulse amplitude, U/l</td>
<td>1.7±0.2</td>
<td>2.6±0.4</td>
<td>1.5±0.2</td>
</tr>
<tr>
<td>Deconvolution analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal secretion, U/l·day⁻¹</td>
<td>40.6±5.6</td>
<td>52.0±6.8</td>
<td>42.2±7.2</td>
</tr>
<tr>
<td>Pulsatile secretion, U/l·day⁻¹</td>
<td>63.6±8.8</td>
<td>87.0±12.2</td>
<td>57.9±9.1</td>
</tr>
<tr>
<td>Total secretion, U/l·day⁻¹</td>
<td>104±13.9</td>
<td>140±18</td>
<td>100±15.6</td>
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</table>

Values are means ± SE.

as a measure of estrogen negative feedback activity within the gonadal ensemble, declined significantly in response to caloric restriction in responders, whereas it did not change in nonresponders (Fig. 2, Table 3).

**DISCUSSION**

The current prospective dietary interventional study in obese patients with PCOS delineates several endocrine features that correlate specifically with ovulatory recovery. At baseline, a significantly higher plasma SHBG concentration was the sole characteristic that identified women who subsequently regained ovulation during intervention. However, the baseline FTI was similar in both groups. Anthropometric parameters: total, subcutaneous, and visceral abdominal fat mass; plasma glucose and insulin concentrations; and the HOMA-IR declined comparably in response to caloric restriction and weight loss in responders and nonresponders. In contrast, the plasma concentration of estradiol and the FTI fell, and plasma LH rose significantly, only in women who ovulated in the course of dietary intervention. The latter reciprocal relationship is consistent with a hypothesis that preserved negative feedback control of pulsatile LH release (that is, pulse amplitude) by estrogen forecasts ovarian cyclicity in response to dietary restriction in PCOS patients. However, other mechanistic explanations for our findings cannot be excluded on the basis of our data set.

A conspicuous finding in this study is the amplification of pulsatile LH secretion (assessed by deconvolution analysis) under short-term VLCD only in patients with PCOS destined to ovulate in subsequent weeks. This outcome is remarkable, in that mean LH concentrations and the amplitude of LH pulses are elevated in the majority of women with PCOS (1, 9, 29, 33, 35). Although the exact role of hypergonadotropism in the pathogenesis of anovulation in this syndrome is not clear, excessive LH drive presumptively contributes to intraovarian and systemic hyperandrogenism and follicular growth arrest (17, 40). On the other hand, several means of ovulation induction in PCOS increase pulsatile LH and FSH secretion, i.e., clomiphene citrate and pulsatile GnRH administration (12,
Moreover, women with PCOS who respond favorably to pulsatile GnRH therapy tend to exhibit a more pronounced increase of LH release in response to this intervention, whereas the FSH response appears similar (in comparison with women who fail to ovulate) (12). Also, from a metabolic perspective, BMI is inversely associated with LH concentration in PCOS (1, 34), and obesity appears to hamper ovulation in this syndrome, albeit via unknown mechanisms. We hypothesize that heightened LH secretion during caloric restriction denotes less severe neuroendocrine disruption in such patients, as defined by expected physiological unleashing of LH secretion under estrogen withdrawal (15, 18, 22). Where physiological normalization is enacted primarily in this setting is not readily inferable. For example, one plausible clinical postulate is that an ovarian response of declining estradiol secretion is the proximate initiating factor, which secondarily elevates LH.

An unexpected metabolic outcome was that the degree of reduction in adiposity and parameters of insulin resistance were comparable, whether or not patients resumed ovulation. This finding implies that amelioration of metabolic anomalies, which are typical of PCOS (6), is not sufficient to restore menstrual cyclicity in all subjects. Insulin-sensitizing drugs, which also reduce hyperinsulinemia, facilitate ovulation in many (30–60%) but not all obese PCOS patients (14, 27). Other in vitro and in vivo evidence indicates that insulin drives theca-cell androgen production and possibly theca-cell hypertrophy (8, 38, 40, 42). Accordingly, the FTI and plasma insulin concentrations declined concurrently under dietary restriction and weight loss (although not significantly in nonresponders), as observed in other studies (4, 13, 16, 28). However, neither response appears to forecast subsequent ovulation, which was also reported earlier (28). Thus the change in androgenic milieu is not likely to be (solely) responsible for the resurgence of ovulation. Rather, hyperinsulinemia and hyperandrogenemia interact to impede ovulation in PCOS. However, the relatively small number of subjects included in this study does not allow multivariate analyses, which could be further informative in suggesting concerted or synergistic predictors of axis recovery. Moreover, the small number of participants may have hampered statistical detection of differences in BMI, visceral fat mass, and/or measures of insulin resistance in responders vs. nonresponders. In particular, at baseline and after 7 days of caloric restriction, nonresponders appear somewhat heavier and their visceral fat area seems larger than that of responders, but the difference was not statistically significant (Table 1). In addition, the HOMA index is not the most accurate measure of insulin action and may have failed to detect a subtle difference in insulin sensitivity between both groups. Obviously, any statistically undetected difference in insulin action could also contribute to the endocrine distinctions between responders and nonresponders we describe here.

It is important also to recognize a historical limitation of this study. Although the frequency of vaginal bleeding before intervention was similar in responders and nonresponders, we cannot rule out the possibility that some women who responded favorably to caloric restriction had more spontaneous ovulatory cycles even before intervention. If so, the present data would suggest that reciprocal elevation of LH and suppression of estradiol under caloric restriction, but not at baseline, provides a marker of greater ovulatory potential in the calorically replete state as well.

In conclusion, the present study reveals that obese women with PCOS who resume ovulation in response to caloric restriction and weight loss do not differ at baseline from those who do not, except in higher mean SHBG concentrations. However, women who respond favorably exhibit a decline in estradiol concentrations and elevation of pulsatile LH secretion in the early phase of caloric restriction. These data allow the hypothesis that preservation of estrogen-dependent negative feedback in obese patients with PCOS predicts greater ovulatory capacity.

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