Prevalence and Characteristics of the Polycystic Ovary Syndrome in Overweight and Obese Women

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Background: Surprisingly, the prevalence of polycystic ovary syndrome (PCOS) in otherwise unselected overweight or obese women is unknown, despite obesity being frequent in patients with PCOS. We conducted the present study to obtain an unbiased estimate of the prevalence of PCOS in unselected overweight and obese premenopausal women from Spain.

Methods: All premenopausal women reporting to the Department of Endocrinology, Hospital Universitario Ramón y Cajal, for dietary treatment of overweight or obesity from May 2002 to December 2005 were prospectively recruited. Women referred for any other reason were automatically excluded to avoid selection bias. Diagnosis of PCOS relied on the presence of clinical and/or biochemical hyperandrogenism, oligo-ovulation, and exclusion of secondary causes. Anthropometric measurements, hirsutism scores, and androgen, gonadotropin, metabolic, and lipid profiles were obtained.

Results: Of a total of 113 consecutive women recruited, 32 (28.3%) were diagnosed as having PCOS (95% confidence interval, 20.0%-36.6%). The prevalence of PCOS was not different when considering the degree of obesity. Another 3 women presented with hyperandrogenemia without oligo-ovulation, 2 had idiopathic hirsutism, 2 had chronic oligomenorrhea without clinical or biochemical hyperandrogenism, and 2 had oligomenorrhea with hyperprolactinemia, precluding the diagnosis of PCOS. The remaining 72 women (63.7%) had no evidence of hyperandrogenism or reproductive abnormalities.

Conclusions: Our results demonstrate a 28.3% prevalence of PCOS in overweight and obese women from Spain, which is markedly increased compared with the 5.5% prevalence of PCOS in lean women of our country. Therefore, PCOS must be routinely ruled out in overweight and obese premenopausal women seeking advice for weight loss.

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The Polycystic Ovary Syndrome (PCOS) is one of the most common endocrine disorders in premenopausal women, presenting with an overall 6.5% prevalence in premenopausal women from Spain, including lean, overweight, and obese patients as a whole. Aside from its cutaneous symptoms and significant reproductive morbidity, PCOS is associated distinctly with an increased prevalence of sleep apnea, a substantial impairment in quality of life, an increased risk of type 2 diabetes mellitus, and a possible increase in risk of cardiovascular disease. The primary defect in PCOS appears to consist of an increased androgen synthesis and secretion by ovarian theca cells, which is favored in many patients by the hyperinsulinism that results from insulin resistance.

Obesity is present in more than half of patients with PCOS. This finding is not unexpected because obesity is a major contributor to insulin resistance, and secondary hyperinsulinism favors hyperandrogenism and PCOS. Together with the presence of insulin resistance, obesity contributes to the approximately 33% to 47% prevalence of the metabolic syndrome in PCOS patients recently described in the United States, a figure that is considerably higher than that reported for the general population. However, currently it is unclear if the frequency of PCOS is actually increased in premenopausal women with the metabolic syndrome.

Considering that insulin resistance is a major contributor to the pathogenesis of PCOS, it is likely that, being insulin resistant, a significant number of overweight and obese women would experience PCOS. Surprisingly, the prevalence of PCOS in otherwise healthy overweight or obese premenopausal women remains unknown, and screening for PCOS is not usually included in the clinical routine evaluation of overweight and obese women.

In this study we have obtained an unbiased estimate of the prevalence of PCOS, and its possible concurrence with the metabolic syndrome, in an adequately sized sample of otherwise healthy overweight or obese premenopausal women. As we show,
perandrogenism, and exclusion of hyperprolactinemia (serum prolactin level < 24 µg/L [1043 pmol/L]), nonclassic congenital adrenal hyperplasia (basal 17-hydroxyprogesterone levels less than 2 ng/mL [< 6.0 nmol/L]), and androgen-secreting tumors. Evidence for oligo-ovulation was provided by chronic oligomenorrhea (according to retrospective self-report and/or menstrual diary) or, in regularly menstruating women, by prospective detection of luteal phase progesterone below 4 ng/mL (< 12.7 nmol/L) and/or basal body temperature charts.

Other possible diagnoses included idiopathic hirsutism (hirsutism, androgen levels within the normal range, and evidence for regular ovulation), hyperandrogenemia without oligo-ovulation, hyperprolactinemia, and isolated chronic oligomenorrhea (no evidence of clinical or biochemical hyperandrogenism or hyperprolactinemia). Of note, because the study was designed and was already started before the revised criteria for the diagnosis of PCOS sponsored by the European Society for Human Reproduction and Embryology and the American Society of Reproductive Medicine were published in early 2004, ovarian morphologic features were not evaluated and not considered for the diagnosis of hyperandrogenic disorders.

The diagnosis of the metabolic syndrome was established according to the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, when 3 or more of the following criteria were present: waist circumference greater than 88 cm, serum triglycerides level of at least 150 mg/dL (1.7 mmol/L), high-density lipoprotein cholesterol level below 50 mg/dL (1.3 mmol/L), blood pressure of at least 130/85 mm Hg, or serum glucose level of at least 110 mg/dL (6.1 mmol/L).

HORMONE PROFILES

Clinical and anthropometric variables, including a modified hirsutism score,22 clinical blood pressure, body mass index, and waist-hip ratio, were determined in all the patients. Serum and plasma sampling and an oral glucose tolerance test were performed as previously reported.23 In brief, between 8 AM and 9 AM and after a 12-hour overnight fast, an indwelling intravenous line was placed in a forearm vein, and after 15 to 30 minutes baseline blood samples were obtained for the measurement of serum triglycerides, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, prolactin, total testosterone, sex hormone-binding globulin, gonadotropins, 17-hydroxyprogesterone, androstenedione, and dehydroepiandrosterone sulfate. A standard 75-g oral glucose tolerance test was performed, and blood samples were obtained after 0, 30, 60, 90, and 120 minutes for glucose and insulin determinations. The women received a 300-g carbohydrate diet for 3 days before sampling. All samples were immediately centrifuged, and serum and plasma were separated and frozen at −30° until assayed.

The technical characteristics of the assays used for hormone measurements have been reported elsewhere.24–26 The free-testosterone concentration was calculated from total testosterone and sex hormone-binding globulin concentrations.28 In non-diabetic women, homeostasis model assessment (HOMA) was used to estimate insulin resistance in the fasting state (HOMA-IR) and β-cell function (HOMA-β)17 and the composite insulin sensitivity index was calculated from the insulin and glucose levels obtained during the oral glucose tolerance test.28

STATISTICAL ANALYSIS

Sample size was predetermined using the Ene2.0 program (http: //www.ene-ctm.com). Considering that 5.3% of lean women

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**METHODS**

**STUDY DESIGN**

All the premenopausal women referred by their general physicians to the Department of Endocrinology of Hospital Universitario Ramón y Cajal, for weight loss from May 1, 2002, through December 31, 2005, were prospectively evaluated. Inclusion criteria required being referred exclusively for weight loss as the main complaint, having a body mass index (calculated as weight in kilograms divided by the square of height in meters) above 25, being younger than 50 years, and not having classic menopausal symptoms such as hot flushes. Overweight and obese women referred for any other reasons were automatically excluded to avoid overestimation of the prevalence of PCOS because of selection bias.

Women taking medications that might interfere with hormone profiles, such as contraceptives or insulin sensitizers, were also excluded, even at the risk of underestimating the prevalence of PCOS in the sample, because these drugs might interfere with the correct evaluation of ovulatory function and clinical and biochemical hyperandrogenism. The ethics committee of the Hospital Universitario Ramón y Cajal approved the protocol, and informed consent was obtained from all the women.

**CRITERIA FOR HEALTH AND DISEASE**

The diagnosis of PCOS was established according to the criteria derived from the 1990 National Institute of Child Health and Human Development conference.29 Specifically, PCOS was defined by oligo-ovulation, clinical and/or biochemical hy-
(body mass index, 18.0-25.0 kg/m²) from the general population of Madrid have PCOS, and hypothesizing a conservative 20% prevalence of PCOS in overweight or obese women from our country, for an α of .05 and a power (1-β) of 0.995, a sample size of 104 women should be included in the study.

Continuous variables are expressed as mean±SD unless otherwise stated. The Kolmogorov-Smirnov statistic was applied to continuous variables; logarithmic or square root transformations were applied as needed to ensure a normal distribution of the variables. Age and body mass index between patients and nonhyperandrogenic control women were compared using the unpaired t test. Because PCOS patients were older than nonhyperandrogenic control women, other continuous variables were submitted to a general linear model introducing PCOS or control status as the independent variable and age as a covariate. Discontinuous variables were analyzed by Pearson χ² or Fisher exact tests. Analyses were performed using SPSS for Macintosh, version 10 (SPSS Inc, Chicago, Ill). P<.05 was considered statistically significant.

**RESULTS**

**PREVALENCE OF PCOS**

Of a total of 113 consecutive women evaluated, 32 were diagnosed as having PCOS for a 28.3% prevalence of this syndrome in overweight or obese women (95% confidence interval, 20.0%-36.6%). The number of patients who met the individual criteria for PCOS definition are given in Table 1.

Another 3 women presented with hyperandrogenemia without oligo-ovulation, 2 had idiopathic hirsutism, 2 had isolated chronic oligomenorrhea without clinical or biochemical hyperandrogenism, and 2 had oligomenorrhea and hyperprolactinemia, precluding the diagnosis of PCOS. The remaining 72 women (63.7%) had no evidence of hyperandrogenism or reproductive abnormalities and were considered as the nonhyperandrogenic control group for further comparisons. The prevalence of PCOS was not statistically different when considering the degree of obesity, as classified according to the guidelines published by the National Institutes of Health²⁹ (Table 2).

**Characteristics of Women Diagnosed as Having PCOS**

The PCOS and nonhyperandrogenic control groups had similar mean body mass index values, but PCOS patients were significantly younger than the nonhyperandrogenic controls (Table 3). Therefore, we included age as a covariate in the general linear model to correct for this difference when studying the possible differences between PCOS patients and nonhyperandrogenic controls in other variables.

Compared with nonhyperandrogenic controls, PCOS patients presented with increased hirsutism scores; increased triglycerides, fasting insulin, total and free-testosterone, 17-hydroxyprogesterone, androstenedione and luteinizing hormone levels; increased HOMA-IR and HOMA-β values; and reduced composite insulin sensitivity index values (Table 3). The other clinical and biochemical variables studied were not different among the PCOS and nonhyperandrogenic control groups.

**PREVALENCE OF THE METABOLIC SYNDROME AND ITS INDIVIDUAL CRITERIA IN WOMEN WITH OR WITHOUT PCOS**

The prevalence of the metabolic syndrome and individual criteria was similar in the PCOS patients and in nonhyperandrogenic controls (Table 4); conversely, PCOS was equally frequent in women with (27.6%) or without (28.6%) the metabolic syndrome (χ²=0.01; P=.99), despite patients being significantly younger compared with the nonhyperandrogenic control group (Table 4).

When considering the influence of the degree of obesity on the prevalence of the metabolic syndrome, the prevalence of this syndrome and several of its individual criteria, including a fasting glucose level of at least 110 mg/dL (6.1 mmol/L), blood pressure of at least 130/85 mm Hg, and waist circumference greater than 88 cm, was increased in the subgroups with higher degrees of obesity compared with the subgroup of overweight women (Table 2).

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**Table 2. Prevalence of the Polycystic Ovary Syndrome and the Metabolic Syndrome and Its Individual Criteria in Unselected Consecutive Overweight and Obese Women From Spain**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Overweight (BMI of 25.0-29.9) (n = 25)</th>
<th>Grade 1 Obesity (BMI of 30.0-34.9) (n = 35)</th>
<th>Grade 2 Obesity (BMI of 35.0-39.9) (n = 30)</th>
<th>Grade 3 Obesity (BMI &gt;40) (n = 23)</th>
</tr>
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<tr>
<td>Polycystic ovary syndrome</td>
<td>10 (40)</td>
<td>8 (23)</td>
<td>8 (27)</td>
<td>6 (26)</td>
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<tr>
<td>Metabolic syndrome</td>
<td>2 (8)</td>
<td>4 (11)</td>
<td>12 (40)</td>
<td>11 (48)</td>
</tr>
<tr>
<td>Waist circumference &gt;88 cm</td>
<td>7 (28)</td>
<td>18 (51)</td>
<td>24 (80)</td>
<td>23 (100)</td>
</tr>
<tr>
<td>Triglycerides &gt;1.7 mmol/L (≥150 mg/dL)</td>
<td>3 (12)</td>
<td>3 (9)</td>
<td>7 (23)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>HDL-C &lt;1.3 mmol/L (≥50 mg/dL)</td>
<td>12 (48)</td>
<td>23 (66)</td>
<td>24 (80)</td>
<td>18 (78)</td>
</tr>
<tr>
<td>Blood pressure ≥130/85 mm Hg</td>
<td>3 (12)</td>
<td>10 (29)</td>
<td>11 (37)</td>
<td>13 (57)</td>
</tr>
<tr>
<td>Fasting glucose ≥6.1 mmol/L (≥110 mg/dL)</td>
<td>0</td>
<td>1 (3)</td>
<td>3 (10)</td>
<td>5 (22)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>No. (%) of Patients</th>
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<td></td>
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<tr>
<td></td>
<td>χ²</td>
<td>P Value</td>
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Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); HDL-C, high-density lipoprotein cholesterol.

*Values are raw numbers (percentages).
†P² values were obtained by combining categories to maintain below 20% the percentage of categories with expected values less than 5 and to eliminate all categories with expected values less than 1.
COMMENT

To our best knowledge, the present study is the first to address the prevalence of PCOS in unselected premenopausal overweight and obese women seeking advice for weight loss, showing a 5-fold increase with respect to the prevalence in lean women from the general population living in the same city (28.3% vs 5.5%, respectively). Aside from being hyperandrogenic, PCOS patients were more insulin resistant compared with nonhyperandrogenic controls, despite having similar body mass indexes and degrees of obesity, and were as a group substantially younger.

Moreover, the increased prevalence of PCOS was found in overweight and obese women irrespective of the degree of obesity and independently from the presence or absence of the metabolic syndrome and its individual criteria, a finding that is in conceptual agreement with a previous population-based study that showed that the prevalence of PCOS is not actually increased in women who present with the metabolic syndrome. This particular finding suggests that obesity and insulin resistance may be important contributors to the development of PCOS but are not the major etiologic defects leading to this disorder.

As stated herein, the primary defect in steroidogenesis characteristic of PCOS is probably the major factor that determines which overweight or obese women develop the syndrome, with the hyperinsulinism resulting from insulin resistance playing a favoring role. Furthermore, we might also speculate that hyperandrogenism could contribute to a more android distribution of body fat in PCOS patients because androgen excess favors abdominal adiposity, an effect that can be reversed by treatment with the antiandrogen drug flutamide, explaining at least in part the higher insulin resistance found in our PCOS patients when compared with the nonhyperandrogenic controls. However, only a statistically borderline trend toward a higher waist-hip ratio was observed in PCOS patients compared with the nonhyperandrogenic controls, casting some doubt on the plausibility of this explanation.

In contrast, the metabolic syndrome and its individual components are much more dependent on the degree of obesity, their prevalence rising markedly in women presenting with grade 2 and 3 obesity, supporting the finding that insulin resistance plays an essential role in the development of the metabolic syndrome. However, although the prevalence of the metabolic syndrome was...
not higher in PCOS patients compared with nonhyperandrogenic controls, PCOS patients were significantly younger, and therefore the health burden of the metabolic syndrome and its components may be especially important in women with PCOS, considering that this syndrome appears earlier in life.

Dietary treatment for overweight or obesity is one of the commonest complaints in endocrinology outpatient clinics such as ours because endocrinology and nutrition are a single medical specialty in Spain, and dietitians and other health care workers who are involved in the management of obesity work in endocrinology departments. This explains why most persons demanding dietary intervention because of overweight or obesity are referred directly to endocrinologists by their general physicians, irrespective of whether other health complaints are present at baseline. Because our recruitment procedure carefully avoided positive selection biases that might have occurred because of our research interest in PCOS, we are reasonably convinced that the population studied herein was representative of the general population of Spain, where 26.3% of premenopausal women are overweight (20.0% and 6.3%, respectively).32

Similarly, the relatively unexpected distribution of the prevalence of PCOS that depends on the degree of obesity, showing no statistically significant difference with increasing obesity grades, merits a further comment because it might result from an inadvertent and unavoidable referral bias. On the one hand, the suspicion of PCOS among general physicians is more likely when frank obesity is present, and our experimental design automatically excluded women in whom hyperandrogenism or PCOS was suggested as a possible diagnosis by their referral physicians to avoid a positive selection bias. Therefore, this might have resulted in an underrepresentation of PCOS patients in women with higher degrees of obesity.

On the other hand, women with overweight and milder degrees of obesity are more likely to seek medical advice if they notice any kind of symptom, such as those resulting from hyperandrogenism, and this might justify a tendency toward an overrepresentation of less obese women among the PCOS patients recruited in our sample in case the women or their physicians did not report these symptoms when referring these women for treatment. Other than this, we are reasonably sure that our recruitment of overweight and obese women did not include any significant positive bias that might affect the overall prevalence of PCOS in this population. Furthermore, the exclusion of women taking oral contraceptives or insulin sensitizers might even have led to an underestimation of the prevalence of PCOS in overweight and obese women in our present study. Some limitations of our study preclude the full extrapolation of the present results to the general population. First, the study was conducted in a clinical setting and based on women referred for weight loss, whereas we relied on a historical control group for the rate of PCOS in lean patients used for sample size analysis. Second, although the latter demonstrated a high statistical power, the number of women recruited was relatively small. Third, despite our best efforts to the contrary, there is still a possibility of unavoidable selection biases, as discussed earlier.

In summary, we report that the prevalence of PCOS is markedly increased in unselected overweight and obese women seeking medical advice for weight loss, independent of the degree of obesity or the presence or absence of the metabolic syndrome and related disorders. We conclude that physicians treating overweight and obese patients should be aware of the high prevalence of PCOS among these women and that screening for PCOS, at least
by obtaining a detailed menstrual history and a careful clinical evaluation of hyperandrogenic symptoms, should be conducted routinely to diagnose PCOS and ameliorate the health burden distinctly associated with this prevalent disorder.

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Analysis and interpretation of data: Álvarez-Blasco, Botella-Caretero, and Escobar-Morreale.

Drafting of the manuscript: Escobar-Morreale.

Critical revision of the manuscript for important intellectual content: Álvarez-Blasco, Botella-Caretero, San Millán, and Escobar-Morreale.


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