Impact of Obesity on the Risk for Polycystic Ovary Syndrome

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Context: Although it is well established that adiposity increases the severity of the clinical features of polycystic ovary syndrome (PCOS), the data regarding the prevalence of PCOS in obese women and the change in body weight women presented with PCOS over time are scarce.

Objective: The objective of the study was to determine whether obesity increases the risk of PCOS and whether the degree of obesity of PCOS patients has increased, paralleling the rise in obesity in the population.

Design: We analyzed data from two consecutive populational studies assessing the prevalence of PCOS and a database containing all untreated PCOS patients evaluated at a university clinic between 1987 and 2002.

Setting: The study was conducted at a tertiary care center.

Patients or Other Participants: Participants included 675 women who participated in prevalence studies and 746 PCOS patients.

Main Outcome Measures: Populational prevalence of PCOS according to body mass index (BMI) and change in BMI of PCOS patients over time were measured.

Results: The prevalence rates of PCOS in underweight, normal-weight, overweight, and obese women were 8.2, 9.8, 9.9, and 9.0%, respectively. Prevalence rates reached 12.4 and 11.5% in women with BMI 35–40 kg/m^2 and greater than 40 kg/m^2 (P = NS). The mean BMI of PCOS patients diagnosed between 1987 and 2002 rose, beginning in 1997 and reaching 37.3 $\pm$ 9.9 kg/m^2 in 2000–2002, paralleling the change in BMI of the surrounding population (10–14% obesity rate in 1987, 15–19% in 1997, and 25% or greater in 2002).

Conclusion: Our results suggest that the risk of PCOS is only minimally increased with obesity, although the degree of obesity of PCOS patients has increased, similar to that observed in the general population. These data indicate that obesity in PCOS reflects environmental factors to a great extent. **(*J Clin Endocrinol Metab* 93: 162–168, 2008)**

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder of reproductive-aged women, with an estimated prevalence of 4–8% (1–4), and is the most frequent cause of oligoanovulatory infertility (5). About 50–70% of PCOS women have detectable insulin resistance and hyperinsulinemia, and PCOS is associated with increased risk of type 2 diabetes, dyslipidemia, cardiovascular disease, and endometrial carcinoma (6–8). Health care-related economic burden of PCOS

0021-972X/08/$15.00/0

Printed in U.S.A.

doi: 10.1210/jc.2007-1834 Received August 16, 2007. Accepted October 3, 2007.

First Published Online October 9, 2007

Abbreviations: A4, Androstenedione; BMI, body mass index; DHEAS, dehydroepiandrosterone sulfate; 17-HP, 17-hydroxyprogesterone; NCAH, nonclassic adrenal hyperplasia; P4, progesterone; PCOS, polycystic ovary syndrome; PRL, prolactin; T, testosterone; UAB, University of Alabama at Birmingham.

is significant in that the annual cost of evaluating and providing care to reproductive-aged women in the United States exceeds $4.3 billion (9). In turn, the incidence of obesity has increased dramatically worldwide (10) and most dramatically in the United States (11). The total cost attributable to obesity and its negative health consequences has been estimated to represent 2–7% of national health expenditures worldwide (12).

Obesity appears to be closely associated with PCOS. For example, in the United States, more than half of the patients with PCOS are either overweight or obese (4). It is well known that obesity influences the phenotypic expression of PCOS and might play a significant role in the pathophysiology of hyperandrogenism and chronic anovulation. Increased adiposity is associated with several abnormalities of sex steroid metabolism and results in increased androgen production and suppression of SHBG (13). Furthermore, obese patients with PCOS have more severe cardiometabolic risk factors, compared with their lean counterparts (14). Finally, it is noteworthy that even modest weight loss through diet interventions and increased physical activity has favorable effects on metabolic, endocrine, and reproductive outcome in PCOS (15, 16).

Despite these associations, it is unclear whether the increase in populational obesity has altered the prevalence of PCOS or whether the presence of obesity in PCOS simply reflects the populational prevalence of obesity. A recent study from Spain reported a 28.3% prevalence rate of PCOS among 113 overweight or obese women who were referred to an endocrinology clinic for weight loss, compared with a previously reported populational prevalence of 6.5% (3), suggesting that the prevalence of PCOS might be markedly increased in obesity (17). In the present study, we sought to determine whether obesity increases the risk of PCOS in the general population and whether the degree of obesity in PCOS patients has increased, paralleling the rise in obesity in the surrounding population.

Subjects and Methods

Assessing the prevalence of PCOS according to body mass index (BMI)

To determine the prevalence of PCOS in the general population according to BMI, we analyzed the data from two consecutive populational studies designed to assess the prevalence of PCOS in women undergoing a preemployment physical, conducted between 1995–1996 and 1998–1999 in Alabama (1, 4).

All prospective employees of the University of Alabama at Birmingham (UAB), from resident staff to environmental workers, undergo an entrance medical evaluation that includes a brief history and physical and blood sampling. It should be noted that UAB is the single largest employer in the city of Birmingham and the third largest employer in the state of Alabama, and its employees represent a cross-section of the population. We evaluated premenopausal females, aged 18–45 yr, who were to undergo a preemployment physical exam to determine the prevalence of PCOS between 1995–1996 and 1998–1999 in two consecutive populational studies (1, 4). We now assessed the combined data of these women to determine the prevalence of PCOS according to BMI.

The diagnosis of PCOS was made according to the National Institutes of Health (NIH) 1990 criteria (18), and the protocol for defining the prevalence of PCOS in the general population has been previously detailed (4). In brief, a standardized form including medical history and physical examination was completed, with an emphasis on menstrual regularity, hirsutism, and medications. Patients on hormonal therapy were asked about their menstrual cyclicity before the start of any medications. The amount of excess terminal hair growth was assessed using a modified Ferriman-Gallwey method, scoring the presence of terminal hairs over nine body areas (*i.e.* upper lip, chin, chest, upper and lower abdomen, thighs, upper and lower back, and upper arms) from 0 to 4. Blood was obtained for subsequent hormonal analysis. Serum was stored at −70 C until assayed.

For evaluation purposes, subjects were subdivided according to the presence or absence of menstrual dysfunction and hirsutism into four groups: 1) no hirsutism or menstrual dysfunction, 2) menstrual dysfunction only, 3) hirsutism only, and 4) menstrual dysfunction and hirsutism. The evaluation in each of these groups was planned as follows: 1) subjects determined to have no hirsutism or menstrual dysfunction by the history and physical exam were not further evaluated and were deemed to not have PCOS; 2) in women with menstrual dysfunction only, serum was obtained for the evaluation of total and free testosterone (T), androstenedione (A4), and dehydroepiandrosterone sulfate (DHEAS), and if any of these was abnormal, the levels of prolactin (PRL) and 17-hydroxyprogesterone (17-HP) were also assessed to exclude hyperprolactinemia and nonclassic adrenal hyperplasia (NCAH), respectively; 3) in women with hirsutism only who all have regular menstrual cycles between 26 and 35 d, serum was obtained on d 22–24 of the cycle for the measurement of progesterone (P4) to confirm ovulatory function, and if the P4 level was less than 4 ng/ml indicating anovulation, PRL and 17-HP levels were determined; and 4) in women with menstrual dysfunction and hirsutism, serum was obtained for the measurement of PRL and 17-HP levels.

Any subject with a 17-HP level greater than 2 ng/ml underwent an acute adrenal stimulation test, measuring 17-HP levels before and 60 min after the iv administration of 0.25 mg ACTH-(1–24) to exclude or diagnose 21-hydroxylase-deficient NCAH, as previously described (19). We should note that androgen levels were not assessed in subjects receiving hormonal therapy.

The presence of PCOS in these unselected women was defined by: 1) ovulatory dysfunction; 2) clinical hyperandrogenism (*i.e.* hirsutism) and/or hyperandrogenemia; and 3) the exclusion of other known disorders, as previously described (1). Specifically, these individual criteria are as follows:

Ovulatory dysfunction

Ovulatory dysfunction was surmised by a history of eight or fewer menstrual cycles in a year or menstrual cycles less than 26 d or > 35 d in length; or a d 22–24 (mid-luteal) P4 level of less than 4 ng/ml in subjects with cycles 26–35 d in length.

Clinical hyperandrogenism

This was diagnosed by the presence of hirsutism (*i.e.* modified Ferriman-Gallwey score 6 or greater; see above).

Hyperandrogenemia

This was defined as total and/or free T, A4, and/or DHEAS level above the upper 95th percentile of 98 healthy nonhirsute eumenorrheic women, as previously reported (1). Although all control women were premenopausal, we did not select according to BMI; their mean BMI was 27.7 ± 7.5 kg/m^2 and mean age was 30.7 ± 7.3 yr. Specifically the upper normal limits were total T = 2.94 nmol/liter (84.7 ng/dl), free T = 0.026 nmol/liter (0.75 ng/dl), A4 = 8.73 nmol/liter (2496 pg/ml), and DHEAS = 6.64 -mol/liter (2459 ng/ml).

Exclusion of related disorders

After initial examination (and reexamination) and hormonal analysis, all subjects who potentially had PCOS (*i.e.* oligoovulation with hirsutism and/or hyperandrogenemia) had their serum sample further assayed for circulating PRL and 17-HP levels to exclude hyper-

prolactinemia and 21-hydroxylase-deficient NCAH, respectively. Serum TSH levels were not checked systematically in all subjects unless the subject had clinical symptoms suggestive of thyroid dysfunction or was currently on thyroid replacement. Twenty-four-hour urine free cortisol levels were measured if the subject had possible clinical features of hypercortisolemia.

Confirmed PCOS was established in those individuals whose evaluation was complete and met the criteria described above. Possible PCOS was defined when the evaluation was not complete or was unavailable, but the clinical phenotype was otherwise suggestive of the disorder. The individual probability of PCOS in women with possible PCOS was calculated based on the prevalence of individuals with confirmed PCOS in the population of all individuals having a complete evaluation in the same type of subject (*i.e.* number of confirmed PCOS in category/number of patients with complete evaluation). The total number of PCOS cases arising from these individuals was then calculated (*i.e.* individual probability of PCOS × total number of subjects in group). The strength of this methodology is that it allows for the more thorough estimation of affected subjects and does not penalize the estimate in those subjects whose confirmation of diagnosis requires a greater number of tests (*e.g.* hirsute eumenorrheic patients).

In all participants, weight and height were measured and BMI [weight in kilograms/(height in meters)^2] was calculated. The degree of obesity was classified as follows: 18.9 kg/m^2 or less was considered underweight; 19.0–24.9 kg/m^2 was considered normal weight; 25.0–29.9 kg/m^2 was considered overweight; 30.0–34.9 kg/m^2 was considered class 1 (mild) obesity; 35.0–39.9 kg/m^2 was considered class 2 (moderate) obesity; and 40.0 kg/m^2 or greater was considered class 3 (severe) obesity.

Assessing the change in BMI of the patients diagnosed with PCOS over time

To determine the change in BMI in PCOS patients over time, we analyzed a prospective database containing all untreated androgen excess disorder patients evaluated at a university clinic between 1987 and 2002. The protocol for this study has been previously described (20). In brief, all patients presenting for the evaluation of symptoms potentially related to androgen excess to the reproductive endocrinology clinic (to R.A.) at UAB between October 1987 and June 2002 were evaluated, including women presenting with oligo/amenorrhea, ovulatory dysfunction, excess hair growth, virilization, alopecia, or acne. The data were recorded and maintained prospectively in a computerized database (α Four, version 6.0; Alpha Software Corp., Burlington, MA). All untreated patients completing their initial evaluation and who were diagnosed with PCOS according to the NIH 1990 criteria (18) were included in this analysis. Both protocols were approved by the Institutional Review Board of UAB.

Hormonal analysis

Serum samples were analyzed for total T, SHBG, DHEAS, A4, PRL, TSH, 17-HP, and P4. Total T was measured by an in-house RIA method after serum extraction, as previously described (21). SHBG activity was measured by diffusion equilibrium dialysis, using Sephadex G-25 and [^{3}H]T as the ligand, and the free T was calculated as previously described (3). DHEAS, P4, A4, PRL, and 17-HP were measured by direct RIA, using commercially available kits (DHEAS and P4 from Diagnostic Products Corp., Los Angeles, CA; A4 from Diagnostics Systems Laboratories, Webster, TX; and PRL from Nichols Institute Diagnostics, San Juan Capistrano, CA) as previously described (22, 23).

Samples were batched at regular intervals for analysis to minimize the impact of interassay variability and provide study subjects with timely information. The intra- and interassay variations for total T, SHBG, DHEAS, A4, PRL, TSH, 17-HP, and P4 have been previously reported (1).

Statistical analysis

All parameters were given as mean ± SD. Newman-Keuls multiple-comparison, Student's *t*, and χ^2 tests were used when appropriate. A $P < 0.05$ was considered statistically significant. Data analysis was performed using the SPSS 9.0 PC package (SPSS Inc., Chicago, IL).

Results

Prevalence of PCOS in unselected women

Combined data from 675 women who participated in the two prevalence studies of PCOS (mean age 29.1 ± 7.1 yr, and mean BMI 27.4 ± 7.6 kg/m^2) were analyzed. For the determination of PCOS, subjects were subdivided according to the presence or absence of menstrual dysfunction and hirsutism into four groups: 1) no hirsutism or menstrual dysfunction, 2) menstrual dysfunction only, 3) hirsutism only, and 4) menstrual dysfunction and hirsutism, as follows (Table 1).

Women without menstrual dysfunction or hirsutism

Of the 675 women studied, 506 were found to be nonhirsute and eumenorrheic, effectively excluding PCOS.

Women with menstrual dysfunction only

One hundred ten women (16% of the total) had menstrual dysfunction without hirsutism. Eighty-one of those had menstrual cycles longer than 35 d, whereas the remaining 29 women had menstrual cycles less than 26 d. Fifty-six subjects in this group had complete evaluation, and three of these had confirmed PCOS. The remaining 54 individuals with an incomplete evaluation were designated as having possible PCOS. Nineteen individuals in this group had hyperandrogenemia missing only TSH, PRL, and 17-HP. Their individual probability of PCOS was assigned as 0.95 based on our previous studies, indicating that approximately 0.7% have abnormal TSH, approximately 0.3% have abnormal PRL, and approximately 1.6% have NCAH (20). The remaining 35 individuals who had no androgen measurements had individual probability of PCOS of 0.05 (*i.e.* three of 56 in the group completing evaluation), and the total number of additional PCOS cases from this group was 19.8 [*i.e.* (19 × 0.95) + (35 × 0.05)]. The calculated prevalence of PCOS in this phenotypic group was 21% (22.8 of 110).

Women with hirsutism only

Forty-four subjects had hirsutism in the absence of menstrual dysfunction (*i.e.* hirsute only) of which 17 had a complete evaluation with six of these having confirmed PCOS. The remaining 27 hirsute-only women had possible PCOS. Twenty-one women in the latter group had low P4 levels missing only TSH, PRL, and 17-HP measurements with an individual probability of PCOS of 0.95 (20), whereas six hirsute-only women had missing P4 levels with an individual probability of PCOS of 0.35 (*i.e.* six of 17 in the group completing evaluation). Total number of additional cases of PCOS was 22.5 [*i.e.* (21 × 0.95) + (6 × 0.35)]. Hence, the calculated prevalence of PCOS in this group was 65% (28.5 of 44).

Women with menstrual dysfunction and hirsutism

Fifteen women had menstrual dysfunction and hirsutism, seven of which had a complete evaluation with six having confirmed PCOS. One subject was found to have an elevated TSH level (20.0 mIU/liter) but did not return for further testing or reassessment after therapy and consequently could not be properly designated as having PCOS. The remaining eight also were designated as having possible PCOS, with an individual probability of PCOS of 0.85 (six of

TABLE 1. Number of individuals with PCOS among 675 unselected reproductive-aged women

Initial presentation[a]	n	No. with complete evaluation	No. with confirmed PCOS[b]	No. with possible PCOS[c]	Probability that patients with possible PCOS have PCOS[d]	No. additional calculated PCOS[e]
Eumenorrhea without hirsutism	506	506	0	0	0	0
Menstrual dysfunction only	110	56	3	19	Menstrual dysfunction + hyperandrogenemia with missing only TSH, PRL, 17-HP 0.95[f]	19.8
				35	Menstrual dysfunction with missing androgens 0.05 (three of 56)	
Hirsutism only	44	17	6	21	Hirsutism and oligoovulation with missing only TSH, PRL, 17-HP 0.95[f]	22.5
				6	Hirsutism with missing progesterone 0.35 (six of 17)	
Menstrual dysfunction + hirsutism	15	7	6	8	0.85 (six of seven)	6.8
Total	675	586	15	89		49.1

[a] The initial presentation is based on the clinical features evident prior to the hormonal evaluation.

[b] Confirmed PCOS was established by the presence of oligoovulation (cycles less than 26 d or longer than 35 d in length; anovulation demonstrated by a midluteal progesterone level less than 4 ng/ml if cycles were 26–35 d in length), with hyperandrogenemia and/or hirsutism (modified Ferriman-Gallwey score 6 or greater), after the exclusion of related disorders (thyroid dysfunction, hyperprolactinemia, and 21-hydroxylase-deficient NCAH) in individuals whose evaluation was complete.

[c] Possible PCOS was defined when the evaluation was not complete or was unavailable, but the phenotype was suggestive of the disorder.

[d] Women with possible PCOS were assigned a weighted prevalence value based on the findings in similar subjects whose evaluation was complete were available.

[e] The number of additional calculated PCOS = number of women with possible PCOS × probability that patients with possible PCOS have PCOS.

[f] Weighted prevalence values in this group were assigned based on our previous studies (see text and Ref. 15).

seven) and a total number of additional PCOS cases of 6.8 (8 × 0.85). The calculated prevalence of PCOS in this phenotypic group was then estimated to be 85% (12.8 of 15).

Overall, the cumulative number of PCOS subjects in the study population included 15 subjects among women completing their evaluation and 49.1 estimated subjects among the remainder, with a calculated cumulative prevalence of 9.4% (*i.e.* 64.1 of 675).

Prevalence of PCOS in the general population according to BMI

Of the 675 women included in the study, 5.3% were underweight, 41.8% were normal weight, and 52.9% were overweight or obese (Table 2). No significant differences in the prevalence of PCOS were observed between the obesity classes (Table 2). Furthermore, although the prevalence of PCOS was 11.97% among the 110 women with either moderate or severe obesity, compared with 9.02% among the 565 women who were of lesser BMI, this difference also did not reach significance.

TABLE 2. Prevalence of PCOS according to BMI among 675 unselected reproductive-aged women

Obesity class	n (%)	Estimated no. (%) of PCOS in obesity class
Underweight (≥18.9 kg/m^2)	36 (5.3)	2.95 (8.2)
Normal (19.0–24.9 kg/m^2)	282 (41.8)	27.64 (9.8)
Overweight (25.0–29.9 kg/m^2)	160 (23.7)	15.84 (9.9)
Class I (mild) obesity (30.0–34.9 kg/m^2)	87 (12.9)	4.52 (5.2)
Class II (moderate) obesity (35.0–39.9 kg/m^2)	57 (8.5)	7.07 (12.4)
Class III (severe) obesity (≥40.0 kg/m^2)	53 (7.8)	6.10 (11.5)

Change in BMI of PCOS patients across time

A total of 746 untreated PCOS patients were diagnosed between 1987 and 2002. The mean BMI of patients diagnosed with PCOS rose, beginning in 1997. The prevalence of obesity (*i.e.* a BMI 30 kg/m^2 or greater) among patients diagnosed with PCOS was 51, 59, and 53% between 1987–1990, 1991–1993, and 1994–1996, whereas the prevalence was, 70, and 74% between 1997–1999 and 2000–2002, respectively (Table 3). These data possibly reflected the change in the prevalence of obesity in the surrounding population during that time (10–14% obesity rate in 1987, 15–19% in 1997, and 25% or greater in 2002). However, the mean age of PCOS patients at presentation did not change between 1987 and 2002.

Discussion

In this report we determined whether the populational prevalence of PCOS increased with the degree of obesity and whether the degree and prevalence of obesity among PCOS patients changed over a 15-yr period of time. Our data indicate that whereas the prevalence of PCOS was approximately 30% higher

TABLE 3. Age and BMI of patients diagnosed with PCOS between 1987 and 2002

Years	n	Age (mean ± SD, yr)	BMI (mean ± SD, kg/m^2)	No. (%) of obese individuals among patients with PCOS[a]
1987–1990	142	27.8 ± 6.5	31.3 ± 8.2	51%
1991–1993	146	27.7 ± 8.0	32.0 ± 9.1	59%
1994–1996	156	26.9 ± 7.5	31.9 ± 8.8	53%
1997–1999	177	27.8 ± 7.6	35.7 ± 9.3[b]	70%[b]
2000–2002	125	27.3 ± 6.9	37.3 ± 9.9[b]	74%[b]

[a] Obesity was defined as a BMI 30 kg/m^2 or greater.

[b] Years 1997–1999 and 2000–2002 different from all others ($P < 0.001$).

among unselected reproductive-aged women from the general population with moderate to severe obesity (~12 *vs.* 9%), this difference did not reach significance. These data indicate that whereas prevalent obesity may increase the risk of PCOS in a population, this effect is relatively modest. These results stress the fact that PCOS is likely due to intrinsic or inherited factors, with only a limited role played and not primarily the result of environmental factors.

Various data also support the conclusions of the present study. For example, the populational prevalences of PCOS reported in two other studies in Greece (2) and Spain (3) were very similar to those of our group (4) (~6.5%), despite the much higher mean BMI of the U.S. population. In addition, Diamanti-Kandarakis (2), studying 192 women of reproductive age (17–45 yr) living on the Greek island of Lesbos, did not observe a difference in mean BMI between unaffected women (*i.e.* without hirsutism or menstrual dysfunction) *vs.* women with hirsutism only, menstrual dysfunction only, or hirsutism and menstrual irregularities (2).

Our data, however, contrast with the study of Escobar-Morreale and colleagues (17), who studied a total of 113 consecutive premenopausal women referred for dietary treatment for overweight or obesity. They observed a prevalence of PCOS of 40, 23, 27, and 26% among 25, 35, 30, and 23 women who were overweight or had mild, moderate, or severe obesity, respectively. These investigators (3) noted that these prevalences were significantly higher than those reported by their group in a series of 154 Caucasian women of reproductive age reporting spontaneously for blood donation (5.5–6.55%).

The difference between our results and those of Escobar-Morreale (17) is likely due to a number of factors. First, the population studied by Escobar-Morreale and colleagues (17) was significantly smaller than that of the present report (which included 113 *vs.* 357 overweight or obese individuals, respectively). Second, their comparison group was distinct from the population of individuals included in their study (*i.e.* volunteer blood donors *vs.* women seeking medical care for excess weight), whereas in our study all individuals included were unselected women seeking a preemployment physical from the same population. Finally, the principal reason for the difference rests likely is referral bias, *i.e.* patients included in the study of Escobar-Morreale *et al.* (17) were those women specifically seeking care for excess weight. It is probable that these women were more likely to have menstrual dysfunction and other features of PCOS, which encouraged them or their practitioners to refer for medical weight management.

Additional support for an incidental role of obesity in PCOS comes from our data, indicating that the mean BMI of women diagnosed with PCOS rose by approximately 5–6 kg/m^2 over a 15-yr span. This increase was observed primarily after 1997 and is similar to the increased prevalence of obesity observed in the surrounding population (state of Alabama) during that time (10–14% obesity rate in 1987, 15–19% in 1997, and 25% or greater in 2002) (24). This finding is also consistent with data indicating that the mean BMI of PCOS subjects diagnosed in different countries varies widely, concordant with the prevalence of obesity in the home population. For example, women with PCOS from countries other than the United States tend to be leaner, with mean BMIs of 25 kg/m^2 in England (25), 28 kg/m^2 in Finland (26), 31 kg/m^2 in Germany (27), and 29 kg/m^2 in Italy (28). In contrast, in a multicenter trial at 22 sites in the United States, the mean BMI of PCOS women assigned to four treatment groups (total n = 305) ranged from 35 to 38 kg/m^2 (29). Likewise, data from the U.S. multicenter Pregnancy in PCOS trial noted that the mean BMI among the 626 patients included was 35.2 kg/m^2 (30).

We should note that the overall prevalence of PCOS detected in the population studied (9.4%) is somewhat higher than others and we have reported previously (~6.5%) (2–3), although similar to that of others (31), using the NIH 1990 diagnostic criteria. This is likely the result of a more complete inclusion of all women affected by PCOS in the present report. Furthermore, an increase in the prevalence of obesity over time could also have resulted in a subtle increase in the prevalence of PCOS. Finally, it is important to note that the use of more expansive diagnostic criteria for PCOS, *i.e.* the use of the Rotterdam 2003 criteria, would have increased the number of individuals diagnosed as having PCOS, possibly even doubling their number (32).

As detailed in our most recent populational study (4), we developed a methodology to allow us to estimate the prevalence of PCOS in a population that includes individuals who have both completed and have not completed their full assessment, according to a preset evaluation tree. In essence, this method allows us to assign a diagnostic probability or weight to an individual who has not completed her evaluation, based on the results obtained in similar women who have completed their evaluation. This is critical because it is those individuals with the greatest proba-

bility of PCOS who have to complete the greatest number of tests because PCOS is a diagnosis of exclusion. Hence, the result is a more complete assessment of the prevalence of PCOS in a population. Using this methodology, we previously observed that the prevalence of PCOS among unselected women seeking a preemployment exam increased by approximately 60%, compared with including only those women completing the full evaluation, *i.e.* 4.0 *vs.* 6.5% (1, 4).

The role of obesity in the development of PCOS, albeit modest, may stem from the endocrine function of adipose tissue. Adipose tissue is an endocrinologically active organ, producing a number of products including adipokines, peptides that are or act as cytokines, chemokines, growth factors, and neurally active hormones. To date, more than 50 adipokines have been identified, some unique to adipose tissues (*e.g.* adiponectin and leptin) and others that are also produced in nonadipose tissues (*e.g.* cytokines). More specifically to the development of PCOS, it is possible that adipokines including IL-6, leptin, monocyte chemoattractant protein-1, resistin, and TNF-α, alter and diminish insulin sensitivity (33–39). The exact role that adipokines play in the development of PCOS remains to be determined.

A limitation of our study is that the observed increase in BMI of PCOS patients over time might possibly reflect an unknown referral bias. Nevertheless, a similar rise in the prevalence of obesity in the surrounding population supports our hypothesis that the BMI change in PCOS parallels the BMI change in the population at large. Another limitation is the fact that we have introduced a category of probable PCOS, which includes patients for whom no complete information is available. Using similar patients for whom complete information is available, the diagnostic probability of PCOS is calculated. Although this technique is useful, its validity remains to be fully determined. It is also possible that we may have missed a few patients with PCOS who did not present with hirsutism or overt menstrual dysfunction.

Finally, another possible limitation is that we might have failed to detect a significant increase in the prevalence of PCOS in moderate and severe obesity due to our small sample size. However, a *post hoc* power analysis indicated that we would need at least 1000 individuals in each group to attain a power of 80%, suggesting that an effect, if present, is quite modest.

Overall, these data indicate that obesity only modestly increases the risk of PCOS, if at all, and that the prevalence of obesity in PCOS most strongly reflects environmental factors. In this study we have not assessed the potential contribution of any specific environmental factor. However, it is likely that changes in the quantity, type, and quality of dietary intake and in the degree and type of physical activity over time may have had significant influence on the prevalence of obesity among PCOS women, as they have in the general population (40). Finally and notwithstanding our observation that the role of obesity in altering the development or prevalence of PCOS appears to be modest, it is also clear that the concomitant presence of obesity will worsen the phenotypic and metabolic presentation of the disorder (41) and that weight loss and lifestyle management offers a beneficial effect on the ovulatory and metabolic dysfunction of obese women with PCOS (42).

Acknowledgments

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This work was supported by National Institutes of Health Grants RO1-HD29364 and K24-HD01346 (to R.A.).

Disclosure Statement: R.A. is a consultant for Procter & Gamble, Merck & Co., Pfizer, and Quest Diagnostics; E.S.K. and B.O.Y. have nothing to disclose.

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