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The Prevalence and Features of the Polycystic Ovary Syndrome in an Unselected Population

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Notwithstanding the potential public health impact of the polycystic ovary syndrome (PCOS), estimates regarding its prevalence are limited and unclear. Between July 1998 and October 1999, 400 unselected consecutive premenopausal women (18–45 yr of age) seeking a preemployment physical at the University of Alabama at Birmingham were studied (223 Black, 166 White, and 11 of other races). Evaluation included a history and physical examination, a modified Ferriman-Gallwey hirsutism score, and serum screening for hyperandrogenemia, hyperprolactinemia, and 21-hydroxylase-deficient nonclassical adrenal hyperplasia. PCOS was diagnosed by the presence of the following: 1) oligoovulation, 2) hyperandrogenemia and/or hirsutism (modified Ferriman-Gallwey score ≥ 6), and 3) the exclusion of related disorders. Confirmed PCOS was established in those individuals whose evaluation was complete and indicative of PCOS, and possible PCOS was established when the hormonal 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 assigned a weight based on the findings in similar subjects whose evaluation was complete, and the total number of PCOS cases arising from these individuals was calculated (*i.e.* individual probability of PCOS × total number of subjects in the group). The cumulative prevalence of PCOS in our population was 6.6% (26.5 of 400), including 15 subjects among the 347 women completing their evaluation and a calculated prevalence of 11.5 subjects among the remainder. The prevalence rates of PCOS for Black and White women were 8.0 and 4.8%, respectively, not significantly different. These data from a large representative unselected population support the concept that PCOS is the most common endocrine abnormality of reproductive-aged women in the United States. (*J Clin Endocrinol Metab* 89: 2745–2749, 2004)

POLYCYSTIC OVARY SYNDROME (PCOS) is a genetically complex endocrine disorder of women of uncertain etiology and is a common cause of anovulatory infertility, menstrual dysfunction, and hirsutism (1, 2). PCOS appears to be associated with an increased risk of metabolic aberrations, including insulin resistance and hyperinsulinism, type 2 diabetes mellitus, dyslipidemia, cardiovascular disease, and endometrial carcinoma (3–6).

For research purposes, many investigators define PCOS using the recommendations of a conference sponsored by the National Institutes of Health (NIH)/National Institute of Child Health and Human Development in April 1990 (7). The conference concluded that PCOS should be defined by the following (in order of importance): 1) hyperandrogenism and/or hyperandrogenemia, 2) ovulatory dysfunction, and 3) exclusion of related disorders such as hyperprolactinemia, thyroid disorders, and nonclassical adrenal hyperplasia (NCAH).

Notwithstanding its significant public health impact and associated reproductive, endocrine, and metabolic implications, estimates regarding the prevalence of PCOS are limited and unclear. We previously reported a prevalence of 4.0% among 277 unselected women of reproductive age (18–45 yr of age) seeking a preemployment physical, 4.7% among White and 3.4% among Black women (8). However, three studies from Europe have suggested prevalence rates 60–100% higher. Studying 192 random women recruited through the offer of a free medical examination on the island of Lesbos, Greece, Diamanti-Kandarakis *et al*. (9) reported a 6.8% prevalence of PCOS. In this study, women who were receiving hormonal medications were excluded. In another study, 230 women aged 18–25 yr were recruited from two universities and two general practice surgeries in Oxford, United Kingdom via a letter and information sheets for participation in "a study of women's health issues" (10). In this study, the prevalence of PCOS, endocrinologically defined, was 8%. Among 154 White women in Madrid, Spain reporting spontaneously for blood donation, 6.5% were found to have PCOS (11).

The recruitment process of the study population can significantly impact the characteristics and prevalence of the disorder under study (12–14). Unfortunately, two of the four currently available studies determining the prevalence of PCOS based their estimates on subjects recruited through the promise of a health evaluation (9, 10), potentially biasing the population toward disease-carrying individuals. The objective of the present study was to determine the prevalence of PCOS in a well-defined population of unselected reproduc-

Abbreviations: A4, Androstenedione; BMI, body mass index; DHEAS, dehydroepiandrosterone sulfate; 21-OH, 21-hydroxylase; 17-HP, 17-hydroxyprogesterone; mF-G, modified Ferriman-Gallwey; NCAH, nonclassical adrenal hyperplasia; PCOS, polycystic ovary syndrome; T, testosterone.

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tive-aged women in the United States, aiming to evaluate a large number of subjects and perform a complete phenotyping of the women involved. Secondarily, the impact of race (Black *vs.* White) on the prevalence of the disorder was determined.

Subjects and Methods

Subjects

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. Between July 1, 1998 and October 31, 1999, all consecutive premenopausal females, ages 18–45 yr, who were to undergo a preemployment physical examination were asked to participate. The study was approved by the Institutional Review Board of UAB, and all subjects entered gave written consent. None of the subjects in the present study have been previously reported on because our previous report included women recruited between March 1, 1996 and July 30, 1997 (8).

To minimize treatment bias, we included all women regardless of hormonal therapy, including oral contraceptive pills or continuous progestin, glucocorticoid, or insulin sensitizer therapy. This is particularly important because PCOS may predispose patients to the use of hormonal therapy. We excluded women younger than 18 yr of age or older than 45 yr of age, menopausal women, women who have undergone a previous hysterectomy or bilateral oophorectomy, and women who were pregnant at the time of the evaluation. Women with a diagnosis of hypothyroidism who were receiving adequate thyroid hormone replacement were included in the study.

All study subjects with abnormal findings were notified of the results of their evaluation, and those individuals with abnormal physical, historical, or biochemical findings were encouraged to undergo further investigation and/or therapy.

Study protocol

A standardized history form was completed, with emphasis on menstrual dating and regularity, hirsutism and acne, gynecological history, medications, and family history. Patients on hormonal therapy were questioned regarding their menstrual cyclicity before they started the medications. The amount of excess terminal hair growth was first assessed using a previously described modified Ferriman-Gallwey (mF-G) 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 (14a). To maximize the accuracy of hirsutism scoring, subjects with an initial mF-G score more than 3 per the study nurse were reexamined by a single physician (E.S.K.). The presence of acne was also recorded, although no specific scoring system was applied. 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 examination 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); if any of these was abnormal, the levels of prolactin and 17-hydroxyprogesterone (17-HP) were also assessed to exclude hyperprolactinemia and 21-hydroxylase (21-OH)-deficient NCAH, respectively.

3) In women with hirsutism only, serum was obtained on d 22–24 of the cycle for the measurement of progesterone (P4) to confirm ovulatory function; if the P4 level was less than 4 ng/ml, indicating anovulation, prolactin and 17-HP levels were determined.

4) In women with menstrual dysfunction and hirsutism, serum was obtained for the measurement of prolactin and 17-HP levels.

Any subject with a 17-HP level more 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; 21-OH-deficient NCAH, as previously described (15). We should note that androgen levels were not assessed in subjects receiving hormonal therapy.

Defining the presence of PCOS

The presence of PCOS in these unselected women was defined by the presence of ovulatory dysfunction and clinical hyperandrogenism (*i.e.* hirsutism) and/or hyperandrogenemia—and the exclusion of other known disorders, as previously described (8). Specifically, the individual criterion are as follows:

1) 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 more than 35 d in length; or a d 22–24 (midluteal) P4 level of less than 4 ng/ml in subjects with cycles 26–35 d in length.

2) Clinical hyperandrogenism. Clinical hyperandrogenism was diagnosed by the presence of hirsutism (*i.e.* mF-G score ≥6, see above).

3) Hyperandrogenemia. Hyperandrogenemia was defined as a total and/or free T, A4, and/or DHEAS level above the upper 95th percentile of 98 healthy nonhirsute eumenorrheic women, as previously reported (8). Specifically, the upper normal limits were total T = 84.7 ng/dl (2.94 nmol/liter), free T = 0.75 ng/dl (0.026 nmol/liter), A4 = 2496 pg/ml (8.73 nmol/liter), and DHEAS = 2459 ng/ml (6.64 μmol/liter).

4) 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 analyzed to exclude hyperprolactinemia and 21-OH-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 assigned a weight based on the findings in similar subjects whose evaluation was complete (*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).

Hormonal analysis

As indicated, serum samples were analyzed for total T, SHBG, DHEAS, A4, prolactin, TSH, 17-HP, and P4. Total T was measured by an in-house RIA method after serum extraction, as previously described (16). SHBG activity was measured by diffusion equilibrium dialysis, using Sephadex G-25 (Sigma-Aldrich Corp., St. Louis, MO) and [^{3}H]T as the ligand, and the free T was calculated as previously described (13). 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 (17, 18).

Samples were batched at regular intervals for analysis to minimize the impact of interassay variability while providing 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 (8).

Statistical analysis

All parameters were given as mean ± SD. Student's *t* test and χ^2 test were used when appropriate. $P < 0.05$ was considered statistically sig-

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nificant. Data analysis was performed using the SPSS 9.0 PC package (SPSS Inc., Chicago, IL).

Results

Study population characteristics

Between July 1, 1998 and October 31, 1999, 608 unselected consecutive premenopausal women at ages 18–45 yr seeking a preemployment physical at the UAB were invited to participate. Of these, eight were excluded due to either pregnancy or menopause, and 200 (33%) refused to participate, yielding a total of 400 subjects (66% of screened) available for study (223 Black, 166 White, 11 of other races). The 208 women who were excluded due to pregnancy or menopause or refusal to participate in the study did not differ from the 400 women agreeing to enter the study in racial composition (57% Black *vs.* 56% Black, respectively) or body mass index (BMI) (27.5 ± 6.6 kg/m^2 *vs.* 27.8 ± 7.7 kg/m^2 respectively), although they did slightly differ in mean age (31.2 ± 7.7 *vs.* 29.1 ± 7.2 yr, respectively; $P < 0.01$).

Of the 400 women included in the study, 24% were overweight (BMI, 25.0–29.9 kg/m^2), and 32% were obese (BMI ≥ 30.0 kg/m^2). Overweight and obesity prevalence rates for Black and White women were 25 and 42%, and 21 and 19%, respectively, a significant difference ($\chi^2 = 9.00$; $P < 0.004$). One hundred forty women (35%) were receiving hormonal therapy; 60% of these women were taking the medications primarily for contraceptive purposes.

Prevalence of menstrual dysfunction, hirsutism, and PCOS

The overall prevalence of menstrual dysfunction and hirsutism was 22.8% (91/400) and 6.8% (27/400), respectively. The prevalence rates of menstrual dysfunction in Black and White women were 25.1 and 20.5%, respectively ($\chi^2 = 0.6$; $P > 0.05$). Hirsutism was found in 8.1% of Black and 5.4% of White women ($\chi^2 = 0.57$; $P > 0.05$). Two of the 400 women included in the study were found to have undiagnosed hypothyroidism, and nine were already receiving thyroid hormone replacement for a total prevalence of hypothyroidism (diagnosed and undiagnosed) of 2.7% in our sample population. None of the patients had features suggestive of hypercortisolemia or were diagnosed with NCAH or hyperprolactinemia. A total of 86.7% (347 of 400) of subjects completed their evaluation (Table 1).

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:

1) Women without menstrual dysfunction or hirsutism. Of the 400 women studied, 293 were found to be nonhirsute and eumenorrheic, effectively excluding PCOS (Table 1).

2) Women with menstrual dysfunction only. Eighty women (20% of the total) had menstrual dysfunction without hirsutism (Table 1). Thirty-eight subjects had complete evaluations, and three of these had confirmed PCOS. The remaining 42 individuals with incomplete evaluations were designated as having possible PCOS. Their individual probability of PCOS was 0.08 (*i.e.* 3 of 38 in the group completing evaluation), and the total number of additional PCOS cases from this group was 3.4 (*i.e.* 0.08 × 42). The prevalence of PCOS in this phenotype was 8% (6.4 of 80).

3) Women with hirsutism only. Sixteen subjects had hirsutism in the absence of menstrual dysfunction (*i.e.* hirsute only), of which nine had a complete evaluation with six of these having confirmed PCOS (Table 1). The remaining seven hirsute-only women had possible PCOS, with an individual probability of PCOS of 0.67 (6 of 9) and a total of 4.7 (0.67 × 7) additional PCOS cases. The prevalence of PCOS in this group was 67% (10.7 of 16).

4) Women with menstrual dysfunction and hirsutism. Eleven women had menstrual dysfunction and hirsutism, seven of which had a complete evaluation with six having confirmed PCOS (Table 1). 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 four also were designated as having possible PCOS, with an individual probability of PCOS of 0.86 (6 of 7), and a total number of additional PCOS cases of 3.4 (0.86 × 4). The

TABLE 1. Number of individuals with PCOS among 400 unselected women of reproductive age

Initial presentation[a]	n	Complete evaluation	No. of confirmed PCOS[b]	No. of possible PCOS[c]	Probability that patients with possible PCOS have PCOS[d]	No. of additional calculated PCOS[e]
Eumenorrhea without hirsutism	293	293	0	0	0	0
Menstrual dysfunction only	80	38	3	42	0.86 (3/38)	3.4
Hirsutism only	16	9	6	7	0.08 (6/9)	4.7
Menstrual dysfunction and hirsutism	11	7	6	4	0.67 (6/7)	3.4
Total	400	347	15	53	—	11.5

[a] The initial presentation is based on the clinical features evident before the hormonal evaluation.
[b] Confirmed PCOS was established by the presence of oligoovulation (cycles <26 d or >35 d in length; or anovulation demonstrated by a midluteal progesterone level <4 ng/ml if cycles were 26–35 d in length), with hyperandrogenemia and/or hirsutism (mF–G score ≥ 6), after the exclusion of related disorders (hyperprolactinemia and 21-OH-deficient NCAH), in individuals whose evaluations were 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 evaluations were complete and were available.
[e] The number of additional calculated PCOS is equal to the number of women with possible PCOS × probability that patients with possible PCOS have PCOS.

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prevalence of PCOS in this phenotypic group was 85% (9.4 of 11).

Overall prevalence and characteristics of PCOS patients diagnosed in unselected reproductive-aged women

The cumulative number of PCOS subjects in the study population included 15 subjects among 347 women completing their evaluation, and 11.5 subjects among the remainder, with a cumulative prevalence of 6.6% (*i.e.* 26.5 of 400). Eighteen (8.0%) of the 223 Black women studied and eight (4.8%) of the 166 White women studied were classified as having PCOS, a difference that was not statistically significant ($\chi^2 = 1.61$; $P > 0.05$). The prevalence of overweightness (BMI, 25.0–29.9 kg/m^2) in PCOS was 24% and similar to that of the general population; alternatively, the prevalence of obesity (BMI $\geq$ 30.0 kg/m^2) in these patients was 42%, significantly higher than that of the overall population under study ($\chi^2 = 35.91$; $P < 0.001$).

Discussion

In this prospective study of an unselected sample of 400 reproductive-aged women, the estimated prevalence of PCOS was 6.6%. This rate is very similar to those reported by other investigators in Greece, United Kingdom, and Spain (9–11). Alternatively, it is 65% higher than the rate we reported previously studying 277 consecutive unselected women (*i.e.* 4%) (8). The difference may rest on the larger number of subjects included in the present study and the fact that our previous study only included women with confirmed PCOS who completed their evaluation. Of women presenting with both menstrual dysfunction and hirsutism, 86% (and 68% of women with hirsutism but apparent eumenorrhea) had PCOS. Alternatively, in this populational study only 8% of patients with menstrual dysfunction alone (*i.e.* without hirsutism) had PCOS, raising questions regarding the high proportion of PCOS suggested to affect women with oligoovulatory infertility (1).

The prevalence rate of reported menstrual dysfunction in our population was 22.8%, very similar to the rate of 22.9% reported by 101,073 women participating in the Nurses' Health Study II for cycles 32 d or more in length (19). The prevalence of menstrual disorders was also similar to that observed in the studies of PCOS prevalence in Greece and Spain (9, 11). Alternatively, we observed an overall hirsutism rate of 6.8%, higher than the 2.4% rate of physician-diagnosed hirsutism reported by the participants of the Nurses' Health Study II (19). The lower rate reported in the latter study is consistent with the fact that many hirsute women do not seek physician evaluation (20), either because they are ignorant of the medical etiology of this cosmetic anomaly or, less likely, because they find hirsutism personally not distressing. Alternatively, the prevalence of hirsutism in our study was similar to that observed in a smaller population of Spanish women seeking to voluntarily donate blood (7.1%), but lower than that observed in a study on the Greek island of Lesbos (29%). The higher rate observed in this latter study may reflect ethnic differences or may be due to selection bias because these women were responding to an offer of a free medical evaluation.

In our population, 74% of women with hirsutism were estimated to suffer from PCOS, and 76% (20.1 of 26.5) of women diagnosed with PCOS demonstrated hirsutism, consistent with our findings in studies of women seeking care for hirsutism (20). We should note that the prevalence of hirsutism in PCOS varies by ethnicity. In comparative studies, the rate of hirsutism in Japanese patients was lower than in Hispanic and Italian women living in the United States (21). Alternatively, the prevalence of hirsutism was higher among South Asian patients living in the United Kingdom, compared with PCOS women of European descent living in the same locale (22). In the present study, there was no difference in the prevalence of hirsutism between Black and White patients with PCOS.

In our overall study population, 24% of subjects were overweight, and 32% were obese, a rate that was higher among Black than White patients. These rates are similar to those observed in the 1999–2000 National Health and Nutrition Examination Survey in similarly aged U.S. women (23). The prevalence of obesity, but not overweightness, was higher in PCOS women than in our overall study population (*i.e.* 42%) and higher than Spanish patients similarly identified (*i.e.* 30%) (11). However, the prevalence of obesity in our PCOS patients was similar to the rate observed in Greek women (*i.e.* 38%) (9). These data suggest that there are significant ethnic differences in the prevalence of obesity in PCOS and that obesity *per se* is not a universal feature of the syndrome.

We have tried to minimize selection bias in the inclusion of subjects in this study. All subjects were undergoing a mandated preemployment physical examination, which includes all medical, nursing, clerical, and support staff seeking employment at UAB. Furthermore, racial and socioeconomic bias is minimized because UAB is the single largest employer in the city of Birmingham. Nonetheless, a few potential confounders remain. First, it is possible that the prevalence of PCOS may have varied if we had been able to include all those women refusing to participate (33%), although we have no evidence of a significant difference between those women agreeing and those refusing to participate. Second, it may be argued that it is possible that we underestimated the prevalence of PCOS when we assumed that those women presenting with regular menstrual function and without hirsutism did not have PCOS. However, a recent report evaluating 550 consecutive couples seeking pregnancy indicated that only 3.7% of eumenorrheic women had anovulation (24). Hence, it is likely that few, if any, patients with PCOS were present in the population of eumenorrheic nonhirsute women.

Most importantly, our study design may have biased against the diagnosis of PCOS because a negative evaluation was easier to complete than a positive one. For example, in the case of the patient with eumenorrhea and no hirsutism, only the completion of a history and physical examination was required. Alternatively, the diagnosis of confirmed PCOS required that all blood testing be completed, possibly including returning for a midluteal P4 level and/or an acute ACTH stimulation test. Hence, individuals not completing their evaluation, but whose phenotypes were suggestive of

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PCOS, were assigned a weighted prevalence value based on findings in similar subjects whose evaluation was complete.

Finally, we should note that a recent conference on the subject cosponsored by the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine was held May 1–3, 2003, in Rotterdam, The Netherlands. Conference participants suggested that the diagnostic criteria for PCOS be revised such that the disorder would be diagnosable if two of the following three criteria were present, after the exclusion of other etiologies: 1) oligo- and/or anovulation, 2) clinical and/or biochemical signs of hyperandrogenism, and 3) polycystic ovaries on ultrasonography (25, 26). The definition used in the current study is consistent with those proposed in Rotterdam. Nonetheless, per this newer definition, we may have further underestimated the prevalence of PCOS because our subjects did not undergo transvaginal sonography, and hence, we did not identify two additional potential phenotypes, *i.e.* women solely with oligoovulation and polycystic ovaries, or with hyperandrogenism and polycystic ovaries but normal ovulation.

We conclude that the estimated prevalence of endocrinologically defined PCOS in an unselected population of reproductive-aged women in the United States is 6.6%. This prevalence is higher than our previous estimate studying a smaller population of unselected women (8) and consistent with studies in random women seeking a free physical examination on the island of Lesbos, Greece (9) and in female blood donors in Madrid, Spain (11). Although PCOS is a complex heterogeneous disorder presenting with a spectrum of diverse phenotypes, it seems likely that even in different populations with varying genotypic and phenotypic characteristics, agreement on the definition of the syndrome eliminates an important source of variation in prevalence estimates and gives rise to consistent results. Among the PCOS patients diagnosed from our general population, approximately 75% were hirsute and 42% were obese. There did not appear to be a significant phenotypic difference between Black and White women with PCOS. Overall, PCOS is one of the most common and important endocrine abnormalities of women.

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