Diagnostic criteria for polycystic ovary syndrome: A reappraisal

Ricardo Azziz, M.D., M.P.H., M.B.A.a,b,c

a Department of Obstetrics and Gynecology, Cedars-Sinai Medical Center, Los Angeles, California; and b Departments of Obstetrics and Gynecology and c Medicine, the David Geffen School of Medicine, the University of California at Los Angeles, Los Angeles, California

New diagnostic criteria for polycystic ovary syndrome (PCOS) were proposed in Rotterdam in 2003, which expanded the previous definition that arose from an expert conference sponsored by the National Institutes of Health (NIH) in 1990. However, these newer criteria give rise to phenotypes that may not actually represent PCOS, and a simple modification of the 1990 NIH/National Institute of Child Health and Human Disease diagnostic criteria may be more consistent with currently available data. (Fertil Steril® 2005;83:1343–6. ©2005 by American Society for Reproductive Medicine.)

Few disorders have generated as much debate, passion, and confusion in their definition as polycystic ovary (or ovarian) syndrome (PCOS), with the possible exception of insulin resistance and the metabolic syndrome, with which it is mechanistically associated. A critical issue remains the definition of the disorder, which not only has an important impact on the scientific investigation of the syndrome, but also implies significant consequences for individual patients. Diagnosing a woman as having PCOS has life-long implications for her health and well-being and suggests an increased risk for diabetes, dyslipidemia, hypertension, endometrial carcinoma, infertility, and possibly cardiovascular disease, in her, her relatives, and her offspring and has the potential of negatively impacting on her ability to access health care coverage. Consequently, the diagnosis of PCOS should not be assigned lightly, and diagnostic criteria should be based on sound data.

Two principal definitions of PCOS are in widespread use today. The first arose from the proceedings of an expert conference sponsored in part by the National Institute of Child Health and Human Disease (NICHD) of the United States National Institutes of Health (NIH) on April 16-18, 1990. During the meeting, all participants were surveyed regarding their perception of what features formed part of PCOS, and Drs. Zawadski and Dunaif summarized the findings in the meeting proceedings (1). They concluded that the major criteria for PCOS “should include (in order of importance): i) hyperandrogenism and/or hyperandrogenemia, ii) oligo-ovulation, [and the] iii) exclusion of other known disorders.” This survey had the clarity of identifying PCOS as an androgen excess disorder of exclusion, with ovarian consequences.

Under the NIH/NICHD criteria, clinical hyperandrogenism has generally been interpreted as hirsutism, since >70% of hirsute women are hyperandrogenemic (2). Consequently, three principal phenotypes are generally recognized: [1] women with hirsutism, hyperandrogenemia, and oligo-ovulation; [2] women with hirsutism and oligo-ovulation; or [3] women with hyperandrogenemia and oligo-ovulation. The NIH/NICHD criteria have proven extremely useful to begin to define and understand, among other features, the extraordinarily high prevalence of the disorder (3–6) and the accompanying high frequency of insulin resistance (7, 8) and considerable risk for developing type 2 diabetes mellitus (9, 10).

At the time of the 1990 NIH/NICHD meeting, and possibly because of the relative paucity of non-U.S. speakers, most participants felt that the presence of polycystic ovaries by ultrasound was suggestive, but not diagnostic, of PCOS. However, it is now clear that many patients with PCOS do demonstrate ultrasound evidence of polycystic ovaries (7, 11–17). Consequently, another expert conference was convened in Rotterdam, The Netherlands, on May 1–3, 2003, sponsored in part by the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine (18, 19). The meeting proceedings recommended that PCOS be defined when at least two of the...
following three features were present: [1] oligo- and/or anovulation, [2] clinical and/or biochemical signs of hyperandrogenism, and [3] polycystic ovaries. These criteria again recognize that PCOS is a diagnosis of exclusion.

Polycystic ovaries as defined by the 2003 Rotterdam criteria referred to the presence of at least one ovary exhibiting 12 or more follicles measuring 2–9 mm in diameter, regardless of location, and/or a total volume >10 mL, as determined by transvaginal ultrasound. This definition differs somewhat from that originally proposed by Adams and colleagues using transabdominal ultrasound, where polycystic ovaries were defined as those containing at least 10 follicles between 2 and 8 mm in diameter in one plane, arranged either peripherally around a dense core of ovarian stroma or scattered throughout an increased amount of stroma. These latter investigators have more recently modified their definition to consider as polycystic those ovaries containing at least eight follicles 2–8 mm in diameter. However, preliminary data suggest that the number of women who are misclassified by using the modified Adams et al. criteria versus the Rotterdam criteria is relatively small.

It should be noted that the 2003 Rotterdam criteria define a population of patients that is inclusive of those women previously diagnosed as having PCOS according to the 1990 NIH/NICHD criteria. In other words, the 2003 Rotterdam criteria has expanded, not replaced, the NIH 1990 criteria. In essence, the population of potential patients with the disorder has increased through the creation of two new phenotypes of PCOS, namely, patients who have polycystic ovaries, hirsutism, and/or hyperandrogenemia but normal ovulation and women who have polycystic ovaries and irregular ovulation but no sign of androgen excess. A valid and critical question is whether these newer phenotypes actually represent patients with PCOS. Here we briefly examine the available data to help assess the validity of these new criteria.

First, there is some, albeit limited, evidence that the sole presence of polycystic ovaries in women who otherwise are not hirsute and have normal ovulation is associated with the presence of features reminiscent of those observed in patients with PCOS. These include mild elevations in circulating LH and androgen levels, and in insulin resistance assessed using the homeostatic assessment (HOMA-IR) calculation or the insulin tolerance test, and in the LH, 17-hydroxyprogesterone, and T response to acute long-acting GnRH-analog stimulation. However, not all investigators agree, with some investigators reporting no differences in basal androgen levels or in gonadotropin dynamics in these women.

Specifically characterizing ovulatory women with polycystic ovaries who are clinically hyperandrogenic, Carmina and Lobo prospectively evaluated 62 hirsute ovulatory women by determining their baseline hormonal profiles, ovarian responses to gonadotropin-releasing hormone agonist, and ovarian morphology by ultrasound. Of these women, eight had normal androgen levels and were considered to have idiopathic hirsutism, although there was no mention of their ovarian morphology. Of the remaining 54 hyperandrogenemic patients, 22 (41%) had polycystic ovaries on ultrasound. Hyperandrogenemic ovulatory women with and without polycystic ovaries did not have significantly different androgen levels and LH/FSH ratios, although the former had higher fasting insulin levels, lower glucose-insulin ratios, and a higher 17-hydroxyprogesterone response to leuprolide. Taken together, these data suggest that hirsute hyperandrogenemic ovulatory women with polycystic ovaries, whether hirsute or not, tend to have mild insulin resistance and mild evidence of ovarian dysfunction, although significantly less than women with anovulatory PCOS.

There is considerably less evidence that women with polycystic ovaries and ovulatory dysfunction, but without clinical or biochemical evidence of hyperandrogenism, have features suggestive of PCOS. Norman and colleagues compared 21 women without clinical or biochemical signs of hyperandrogenism who demonstrated polycystic ovaries on transvaginal ultrasound with 97 women with polycystic ovaries who also had increased androgens and a clinical presentation normally associated with PCOS. These investigators found that fasting and glucose-stimulated insulin and glucose levels or gonadotropin levels were similarly altered in nonhyperandrogenic women with polycystic ovaries and in patients with PCOS. In both groups, menstrual irregularity was associated with significantly higher concentrations of serum fasting and stimulated insulin levels, independent of androgens and degree of obesity, compared with those women with normal menstrual cycles.

Alternatively, Michelmore et al. studied ovarian morphology by transabdominal ultrasound in 224 young women recruited as normal volunteers and observed polycystic ovaries in 33%. Surprisingly, and in contrast to the study by Norman and colleagues, these latter women had higher mean insulin sensitivity, as assessed by the HOMA-IR calculation. Many patients with nonandrogenic disorders also demonstrate a polycystic ovarian morphology. For example, most patients with bulimia and other eating disorders demonstrate polycystic ovaries on ultrasound in addition to having menstrual and ovulatory abnormalities. At least 50% of patients with hyperprolactinemia or hypothalamic amenorrhea also demonstrate polycystic ovaries. Finally, many adolescents transiently demonstrate polycystic ovaries.

Overall, when the available data are critically reviewed it would appear that ovulatory women with hirsutism and/or hyperandrogenemia and polycystic ovaries may have a mild form of PCOS, although it should be recognized that differences from normal are modest at best and that additional studies are needed to confirm these findings. In addition, acceptance of this presentation as a phenotype of PCOS in turn indicates that idiopathic hirsutism must be defined more
strictly and should be diagnosed only in hirsute patients who have no evidence of ovulatory dysfunction, hyperandrogenemia, or polycystic ovaries. Alternatively, there are significantly less data to support the concept that isolated polycystic ovaries in oligo-ovulatory women without clinical or biochemical evidence of hyperandrogenism represent PCOS, particularly considering that patients with other ovulatory disorders may also demonstrate this ovarian morphology.

Consequently, while it is clear that polycystic ovaries are a frequent feature of PCOS, the widespread adoption of the diagnostic criteria proposed in the 2003 Rotterdam meeting proceedings should be considered premature, particularly considering available data. While undoubtedly additional research is needed to more clearly determine the entire spectrum of PCOS, the publication of these guidelines should not be interpreted as an indication that the data are already available to support the phenotypes proposed. Based on current evidence, a new set of criteria for the diagnosis of PCOS can be proposed, which take into consideration the high prevalence of polycystic ovaries observed in the disorder (Table 1). These criteria simply represent a modification of the 1990 NIH/NICHD criteria and consider the two principal features of the disorder: [1] androgen excess (clinical and/or biochemical) and [2] ovarian dysfunction (functional and/or morphologic). While ovulatory patients who have polycystic ovaries with clinical and/or biochemical evidence of androgen excess would be considered to have PCOS, oligo-ovulatory patients without evidence of hyperandrogenism would not be diagnosed with the disorder, regardless of the presence of polycystic ovaries, until further data are made available.

REFERENCES

8. Legro RS, Finegood D, Dunai A. A fasting glucose to insulin ratio is a useful measure of insulin sensitivity in women with polycystic ovary syndrome. J Clin Endocrinol Metab 1998;83:2694–8.
19. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term

### TABLE 1

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androgen excess</td>
<td>Clinical and/or biochemical hyperandrogenism</td>
</tr>
<tr>
<td>Ovarian dysfunction</td>
<td>Oligo-anovulation and/or polycystic ovarian morphology</td>
</tr>
<tr>
<td>Exclusion</td>
<td>Other androgen excess or ovulatory disorders</td>
</tr>
</tbody>
</table>

a Such as hirsutism.
b Hyperandrogenemia, such as elevated levels of total or free T.
c Defined by either the number of intermediate follicles (>8–12 follicles each 2 to 8–9 mm in diameter) and/or an increased ovarian volume (e.g., >10 mL)2. d Including, but not limited to, 21-hydroxylase deficient nonclassic adrenal hyperplasia, thyroid dysfunction, hyperprolactinemia, neoplastic androgen secretion, or drug-induced androgen excess.


