The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report

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Objective: To review all available data and recommend a definition for polycystic ovary syndrome (PCOS) based on published peer-reviewed data, whether already in use or not, to guide clinical diagnosis and future research.
Design: Literature review and expert consensus.
Setting: Professional society.
Patients: None.
Intervention(s): None.
Main Outcome Measure(s): A systematic review of the published peer-reviewed medical literature, by querying MEDLINE databases, to identify studies evaluating the epidemiology or phenotypic aspects of PCOS.
Result(s): The Task Force drafted the initial report, following a consensus process via electronic communication, which was then reviewed and critiqued by the Androgen Excess and PCOS (AE-PCOS) Society AE-PCOS Board of Directors. No section was finalized until all members were satisfied with the contents, and minority opinions noted. Statements were not included that were not supported by peer-reviewed evidence.
Conclusion(s): Based on the available data, it is the view of the AE-PCOS Society Task Force that PCOS should be defined by the presence of hyperandrogenism (clinical and/or biochemical), ovarian dysfunction (oligo-anovulation and/or polycystic ovaries), and the exclusion of related disorders. However, a minority considered the possibility that there may be forms of PCOS without overt evidence of hyperandrogenism, but recognized that more data are required before validating this supposition. Finally, the Task Force recognized and fully expects that the definition of this syndrome will evolve over time to incorporate new research findings. (Fertil Steril® 2009;91:456–88. ©2009 by American Society for Reproductive Medicine.)

Key Words: Polycystic ovary syndrome, hirsutism, menstrual dysfunction, phenotype, criteria

The Androgen Excess and PCOS Society (AE-PCOS, formerly the Androgen Excess Society) is an international organization dedicated to promoting knowledge, and original clinical and basic research, in every aspect of androgen excess disorders, such as the polycystic ovary syndrome, nonclassic adrenal hyperplasia, idiopathic hirsutism, and premature adrenarche. Members include basic and clinical scientists, and clinicians, whose major interest is the etiology, diagnosis, treatment, and prevention of androgen excess disorders. The Society disseminates information to the medical and scientific community, and the lay public. The Society appointed the Task Force on the phenotype of the polycystic ovary syndrome (PCOS) and charged it with reviewing all current definitions of PCOS, reviewing all published evidence, and recommending a definition, whether currently used or new, that would be based on currently available evidence.

A brief summary of the Task Force's year-long investigation and conclusions were previously published (1). In the following we present in greater detail the information and reasoning that resulted in the Task Force's conclusions, to allow individual investigators and practitioners to evaluate the data gathered and the rationale presented for themselves.

THE POLYCYSTIC OVARY SYNDROME

The disorder that eventually would be known as the polycystic ovary (or ovarian) syndrome (PCOS) was initially described by Stein and Leventhal in 1935 (2). However, the findings of polycystic (or cystic oophoritis or sclerocystic) ovaries dates back at least a century before that (3–5). Despite the difficulty in ascertaining the prevalence of this disorder among women there are convincing data today to suggest that it affects between 6% and 8% of women worldwide, using the National Institutes of Health (NIH) 1990 criteria (6–10), such that it can be considered one of the most common disorders of humans, and the single most common endocrine abnormality of women of reproductive age.

There is little disagreement that PCOS should be considered a syndrome, that is, a collection of signs and features, where no single test is diagnostic. In essence, the whole (or global assessment) is greater than the sum of the individual parts (or features). However, establishing a clear and contemporaneous definition for what this syndrome is has important clinical and investigational implications.

Clinically, diagnosing a woman as having PCOS implies an increased risk for infertility, dysfunctional bleeding, endometrial carcinoma, obesity, type 2 diabetes mellitus (DM), dyslipidemia, hypertension, and possibly cardiovascular disease (CVD). Furthermore, it has important familial implications, principally, but not exclusively, for her sisters and daughters. Finally, a diagnosis of PCOS may mandate life-long treatments (e.g., the use of insulin sensitizers), and may negatively affect her ability to access healthcare coverage, principally in capitalistic markets. Consequently, the diagnosis of PCOS should not be assigned lightly, and diagnostic criteria should be based on robust data.

A judicious definition of PCOS is essential to guide current and future research. The inclusion of patients whose definition, characterization, and selection criteria are unclear in studies purportedly of PCOS continues to plague the scientific literature. This is becoming particularly important as the field moves to the establishment of larger clinical trials, and to studies of the molecular biology and genetic nature of the disorder. Furthermore, definitions not based on clearcut evidence have the potential effect of discouraging future and needed research into the nature of the disorder, its breadth, and phenotype. Consequently, a contemporaneous definition based on what is currently known will benefit future investigations.

It is also understood, and actually hoped for, that the definition of this syndrome will be modified over time to incorporate new research findings. As understanding of the molecular and genetic aspects of the disorder increases, the definition will be expanded, contracted, or divided to incorporate these new findings. Consequently, the aim of this report is to yield diagnostic criteria for PCOS based on currently available data to guide research and clinical diagnosis, and future investigations.

PREVIOUS DEFINITIONS OF PCOS

Stein and Leventhal provided the first description of PCOS noting varying degrees of enlarged ovaries, obesity, hirsutism, and chronic anovulation (2). With the ability to measure hormone concentrations, the diagnostic criteria were revised to include inappropriate gonadotropin secretion and hyperandrogenemia (11). Development of ultrasonography shifted attention to ovarian morphology (12). However, with recognition of the role of insulin resistance/hyperinsulinemia in PCOS, the development of methods to measure insulin sensitivity in vivo, and awareness of the higher risk of these patients for abnormalities of carbohydrate metabolism, and possibly cardiovascular complications, focused attention on the metabolic abnormalities of the disorder.

Previously, two definitions of PCOS were in widespread use (Table 1). The first arose from the proceedings of an expert conference sponsored in part by the National Institute of

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TABLE 1

All possible phenotypes based on the presence or absence of oligo anovulation, hyperandrogenemia, hirsutism, and polycystic ovary syndrome (PCOS).

Features	Potential Phenotypes															
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
Hyperandrogenemia	+	+	+	+	−	−	+	−	+	−	+	−	−	−	+	−
Hirsutism	+	+	−	−	+	+	+	+	−	−	+	−	−	+	−	−
Oligo-anovulation	+	+	+	+	+	+	−	−	−	+	−	−	+	−	−	−
Polycystic ovaries	+	−	+	−	+	−	+	+	+	+	−	+	−	−	−	−
NIH 1990 criteria	√	√	√	√	√	√										
Rotterdam 2003 criteria	√	√	√	√	√	√	√	√	√	√						
AE-PCOS 2006 criteria	√	√	√	√	√	√	√	√	√							

Azziz. AE-PCOS Society report on PCOS phenotype. Fertil Steril 2009.

Child Health and Human Disease (NICHD) of the 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. Zawadzki and Dunaif summarized these findings in the meeting proceedings (13). They concluded that the major criteria for PCOS "should include (in order of importance): i) hyperandrogenism and/or hyperandrogenemia, ii) menstrual dysfunction, (and the) iii) exclusion of other known disorders." This survey identified PCOS as an androgen excess disorder of exclusion, with an ovarian etiology and/or consequences.

Another expert conference was convened in Rotterdam, The Netherlands, May 1–3, 2003 sponsored in part by the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine (14, 15). The meeting proceedings recommended that PCOS be defined when at least two of the following three features were present: [i] oligo and/or anovulation, [ii] clinical and/or biochemical signs of hyperandrogenism, and [iii] polycystic ovaries. These criteria also recognize that other androgen excess or related disorders should be excluded before assigning the diagnosis of PCOS. Whether these definitions are consistent with currently available data, and whether they are overly narrow or unjustifiably broad, will be explored in the following sections of this report. However, what is clear is that the impact of using a broader definition (e.g., Rotterdam 2003) compared with more restrictive criteria (e.g., NIH 1990) can lead to a significant increase in the population considered to be affected (16). Whether this expansion in the number of affected individuals more accurately reflects the true prevalence of the disorder or whether it is a gross overestimation remains to be determined, and was of concern to the AE-PCOS Society and its appointed Task Force.

THE ESSENTIALS OF DEFINING A SYNDROME

"Diagnosis is a system of more or less guessing; in which the end-point achieved is a name. These names applied to disease come to assume the importance of specific entities, whereas they are for the most part no more than insecure and therefore temporary conceptions."

Sir Thomas Lewis, 1944 (17)

Why is it important to define a syndrome? For centuries, physicians have used the patterns of associated signs and symptoms to identify the etiology, describe the natural history, predict the prognosis, and choose the appropriate therapeutic interventions for specific disorders. In this molecular genetic era, we strive to identify the molecular and genetic basis for disease. The discovery of molecular pathophysiologies and genetic markers will enable early detection and intervention, and the design and discovery of specific therapies. Molecular and genetic studies rely critically on the inclusion of well-characterized and homogenous populations. However, it is also clear that only a clear definition of the disorder

under study will allow us to develop the populations necessary for intensive molecular genetic analysis.

The Processes of Defining a Syndrome

The difficulties and intricacies of defining a syndrome is a challenge that many other organizations have and continue to struggle with. Witness the efforts to define fibromyalgia (18, 19), chronic fatigue syndrome (19, 20), irritable bowel syndrome (21), systemic lupus erythematosus (22, 23), antiphospholipid syndrome (24), and metabolic syndrome (25–27). For example, the Agency for Healthcare Research and Quality arrived at a definition of chronic fatigue syndrome by considering four contemporaneous definitions (28). Potential approaches to define a syndrome, include:

1. *Historic usage in medical practice and/or literature:* historic usage may be best reflected in the definitions presented in contemporaneous texts. However, it can be effectively argued that historic usage has limited value in yielding a contemporaneous definition of a disorder or syndrome, except to provide a reference point for the development of an updated definition.

2. *Expert knowledge and consensus processes:* it also may be effectively argued that science is not and should not be driven by a consensus process. It is educational to review the comments of investigator Michael Crichton, in presenting the Caltech Michelin Lecture, January 17, 2003. Crichton argues that ". . . the work of science has nothing whatever to do with consensus. Consensus is the business of politics. Science, on the contrary, requires only one investigator who happens to be right, which means that he or she has results that are verifiable by reference to the real world. In science consensus is irrelevant. What is relevant are reproducible results. The greatest scientists in history are great precisely because they broke with the consensus . . . There is no such thing as consensus science. If it's consensus, it isn't science. If it's science, it isn't consensus. Period" (29). He goes on to list a number of cases in which the process of consensus was used to override good scientific reasoning, with resulting public harm. Crichton argues that the number and importance of those holding an opinion have no impact in determining what is actually true, and that one good study can, and should, change the world. He concludes his discussion by noting that "Consensus is invoked only in situations where the science is not solid enough," and this may be the position that the PCOS investigator community finds itself in today . . .

3. *Based on analysis of available data:* in this setting, the available data is evaluated by a group of experts, generally under the auspices of an official organization(s), that is, such as being attempted in the present report. Alternatively, the available evidence may be evaluated, and a consensus statement written, by a group of independent experts. An example of such a process is that undertaken by the NIH Consensus Development

Program. The NIH Consensus Statements "are written by broad-based, independent panels of non-Federal, nonadvocate individuals knowledgeable in the field of medical or public health science under consideration. The makeup of each panel represents various sectors of professional and community life and typically includes research investigators, health care providers, methodologists, and a public representative. Following 1-1/2 days of scientific presentations and public testimony during the Consensus Development Conference sessions, the panel convenes in an executive session to write the draft consensus statement. On the third and final day of the conference, the statement is circulated to the conference audience for comment. The panel resolves any conflicting recommendations and releases a revised statement at the end of the conference" (30).

Defining a Syndrome by Using Phenotypic Features That Are NOT Part of the Definition

An evidence-based analysis could attempt to determine whether the various definitions in use, or the various phenotypes available, of a syndrome behave in a manner suggestive that they are part of the same disorder (i.e., they could have similar inheritance patterns, or similar morbidities, or similar patterns of affection, or respond similarly to the same molecular-based intervention). One way to address this is to determine all the possible phenotypes generated by the definition of the syndrome being examined. Essentially, for the phenotypes to actually be part of the same "syndrome" they should have a common thread above and beyond the commonality of their definition (which in itself may be arbitrary). For example, if the various phenotypes of PCOS have the same overall morbidity (e.g., insulin resistance and hyperinsulinism) then we could consider these phenotypes to reflect the same overall syndrome.

Despite considerable phenotypic heterogeneity in PCOS, and overlap with the normal population, several metabolic and hormonal markers may prove helpful in future attempts to identify the PCOS genes. For example, elevated dehydroepiandrosterone sulfate (DHEAS) concentrations have been found in brothers of women with PCOS and may serve as a hormonal phenotype (31). The finding that nearly 50% of sisters of women with PCOS had elevated total or bioavailable testosterone concentrations provides further support for genetic factors influencing androgen concentrations (32). Abnormalities of carbohydrate metabolism such as insulin resistance, impaired glucose tolerance, type 2 DM tend to cluster in families with PCOS (33, 34).

Defining a Syndrome by Using Heritability Traits or Inherited Features That Are NOT Part of the Definition

Another potential common thread to ascertain whether the various recognized phenotypes of PCOS are part of the same or different syndromes is to assess heritability patterns, that is, do the various phenotypes of PCOS have similar degrees of heritability or appear in the same families? Clearly, the familial pattern of PCOS with affected mothers and daughters implies a role for genetic factors (35). Approximately 35% of mothers and 40% of sisters of women with PCOS are affected (36). Yet, the phenotypic and genetic heterogeneity even in the same family confounds identification of the causative genes (37). Lack of a male phenotype, inconsistent diagnostic criteria, and relative infertility make linkage studies difficult because linkage analyses depend on definitive categorization of family members as "affected" or "unaffected."

Association and linkage analysis studies have been performed, largely utilizing a candidate gene approach. Despite difficulty identifying PCOS genes, current evidence indicates that PCOS is a multifactorial polygenic disorder. In addition to phenotypic heterogeneity, genetic heterogeneity likely exists. Disease susceptibility is presumably governed by genetic variation at a limited number of major and minor susceptibility loci. The disease phenotype reflects interactions between susceptibility genes, modifier genes, and environmental factors. Presumably, modifier genes do not affect disease susceptibility. Rather, modifier genes, in the presence of susceptibility genes, increase or decrease the risk to develop the disease. Obesity, with its metabolic consequences, that is, insulin resistance, compensatory hyperinsulinemia, dyslipidemia, and hypertension, is common among women with PCOS. Effects of environmental factors such as diet composition may differ depending on genetic variation at specific loci (38).

From this perplexing situation, can the underlying pathophysiology and genetic factors ever be identified? Phenotypic heterogeneity, inconsistent diagnostic criteria, temporal variation in symptoms, and incomplete penetrance plague ongoing research to identify the genes in other disorders as well, including inflammatory bowel disease (IBD), systemic lupus erythematous, and functional gastrointestinal disorders (21, 23).

Recent progress in identifying the genetic loci involved in IBD may provide a map on an approach on elucidating the PCOS genes. Similar to PCOS, IBD is a complex genetic disorder involving multiple low-risk genetic factors and environmental influences for clinical manifestations (39). Linkage analyses identified several loci associated with genetic susceptibility for IBD; some loci are specific to either Crohn's disease or ulcerative colitis whereas other loci confer increased susceptibility to either form of IBD (40). Using genome wide scans of multiply affected pedigrees with Crohn's disease, the IBD1 locus at *NOD2/CARD15* was identified (41–44). This association has been strengthened by independent replications and biologic relevance of the gene product to the disease process. However, existence of many unaffected individuals homozygous for *NOD2/CARD15* mutations emphasizes the importance of environmental influences and genetic interactions (epistasis) with modifier genes in manifestation of clinical disease (45).

Identification of *NOD2/CARD15* as a Crohn's disease gene has provided encouragement that the challenges posed by complex genetic disorders can be surmounted. Factors that contributed to this success in IBD include classification of patients into accurately defined clinical subgroups, family studies, and collaboration of many investigators. The challenges to clarify the sequence of events involved in the pathophysiology of PCOS and to find the "PCOS genes" stands before us—but can we prevail? Can we use the same roadmap as the IBD investigators to characterize homogenous patient groups (and controls) for metabolic and molecular studies? Will we find one or more molecular genetic markers common to women with PCOS? Will these studies lead to the development of specific therapies, perhaps considering the emerging field of pharmacokinetics?

MATERIALS AND METHODS

The Board of Directors of the AE-PCOS appointed a seven member Task Force of experts in the field, intentionally including international investigators. Members of the Task Force and the Board of Directors constituted the Writing Committee. No external funding was accepted for this project. The evidence gathered was based on a systematic review of the published peer-reviewed medical literature to identify studies evaluating the epidemiology or phenotypic aspects of PCOS, by querying MEDLINE databases. The Medical Subject Headings (MeSH) heading used was "polycystic ovary syndrome" <C04.182.612.765>, with the following limitations: Major topic AND adolescent (13–18 years) OR Adult (19–44 years) AND English AND Publication Date from 1980 to 2005 AND Core Clinical Journals AND Female AND Humans). A total of 527 articles were initially available for this review, although additional studies (crossreferences and those published in 2006) were also considered. Emphasis was placed on those studies which included >100 subjects, although in some areas no studies of this size were available, and the paucity of data was noted. Studies in which epidemiologic (e.g., prevalence) data could not be ascertained or calculated, or which reported on the same parameter in mostly the same population as a larger study, were eliminated from consideration. Unpublished data or personal communications were not included. Although only studies where the criteria for PCOS were clearly stated were included, we did not define the disorder a priori, and rather used each individual investigator's own definition. In essence, we allowed PCOS to have a variety of definitions to more clearly define common phenotypes or features irrespective of the definition used.

Above we drew on the distinction between the value of conclusions generated by consensus (limited) versus those that are "evidence based" (better). However, it should be noted that although we have attempted to analyze what available evidence there is, this does not necessarily indicate that our conclusions are "evidence based." Rather, the data for these analyses flows primarily from the selection of patients by the investigators of the various published studies employing whatever diagnostic criteria that were chosen at the time,

resulting in a comprehensive pooling of the likelihood of the cardinal phenotypic manifestations of PCOS. In addition, we should note that although an attempt was made to evaluate all available data, partiality was given to those data published in peer-reviewed journals. We made a deliberate decision not to include preliminary data presented in abstract form or personal communications, although it is understood that such a choice carries with it the potential for publication bias (i.e., data that are positive are more likely to be published).

The Task Force drafted the initial report, following a consensus process via electronic communication, which was then reviewed and critiqued by the AE-PCOS board of directors. No section was finalized until all members were satisfied with the contents, and minority opinions noted. Statements were not included that were not supported by peer-reviewed evidence. Approval by the respective Institutional Review Board for Human Use, or equivalent, was not sought or obtained, as the study entailed a review of the publicly available literature.

THE POTENTIALLY AFFECTED PATIENT POPULATIONS

Several populations of women are at greater risk for having PCOS. These include reproductive-aged women with clinical evidence of hyperandrogenism (i.e., hirsutism, acne, or alopecia), with menstrual and/or ovulatory dysfunction, with polycystic ovaries, or with insulin resistance and metabolic abnormalities. Another potential population includes those women with overweightness or obesity. We should note that most the following studies regarding the epidemiology of PCOS have used the NIH 1990 criteria, unless otherwise indicated.

Women with Clinical Hyperandrogenism

Clinically hyperandrogenism can manifest itself in the form of unwanted hair growth or hirsutism, seborrhea, and/or acne, and androgenic alopecia or male pattern balding. Alternatively, clinical experience has indicated that virilization (i.e., masculinization of body musculature, severe or extreme male-pattern balding or hirsutism, clitoromegaly, and so forth) is rarely a sign of PCOS. Rather, significant virilization suggests disorders of severe insulin resistance (i.e., mutations in the insulin receptor gene), androgen-secreting tumors, and androgenic substance abuse. In a large study of patients with clinical hyperandrogenism, 72.1% of 950 patients were diagnosed with PCOS according to Rotterdam 2003 criteria (46). Of these, 538 (56.6% of the total number of patients) were anovulatory and were considered affected by classic PCOS (NIH criteria), whereas 147 (15.5% of the total number of patients) were ovulatory and were considered affected by mild ovulatory PCOS.

Women with hirsutism and unwanted hair growth In a study of over 1,000 patients with androgen excess, 78.4% of 659 hirsute patients evaluated were diagnosed with PCOS according to the NIH 1990 criteria (47). Similar data have been presented by other investigators (46). However, it is important to

note that the sole complaint of "unwanted hair growth," in the absence of frank hirsutism on physical examination, may also signal the presence of PCOS. Approximately 50% of 288 women complaining of unwanted excess facial or body hair growth, with minimal hair growth on examination (i.e., a modified Ferriman-Gallwey [mFG] score of 5 or less) demonstrated PCOS on further evaluation (48).

Women with acne The prevalence of PCOS among women with acne only (excluding patients with hirsutism) is somewhat less. In one study of 29 patients having treatment-resistant acne without menstrual disturbance, alopecia, or hirsutism, 36% had PCOS (49). Rates ranging from 19% to 37% have been reported by others (50, 51). Overall, it seems that 20% to 40% of patients with acne may suffer from PCOS. However, most studies of acne patients have simply reported selected features (e.g., polycystic ovaries on ultrasound, androgen levels, degrees of menstrual dysfunction, and so forth), and have not carefully addressed the prevalence of PCOS using contemporaneous criteria. Large population studies of acne patients, particularly those without other evidence of hyperandrogenism (e.g., hirsutism), are still needed to better define this prevalence.

Women with alopecia The prevalence of PCOS among women with alopecia is also unclear. One study of 89 women with androgenic alopecia and 73 controls indicated that the prevalence of polycystic ovaries by ultrasonography was 67% and 27%, respectively (52). Women with alopecia (with or without polycystic ovaries) had higher androgen index levels than controls, although few had frankly abnormal androgens and there was no significant difference in the prevalence of menstrual irregularity (24% vs.15%, respectively). More specifically, in a report of 109 consecutive premenopausal women whose presenting complaint was alopecia, with or without hirsutism, the incidence of PCOS was found to be 36.5% (53). Of the 40 women with PCOS, nine (22.5%) had no other sign of hyperandrogenism at the time of presentation, despite the presence of oligo-amenorrhea and bilaterally enlarged ovaries on ultrasonography. Correlation between the alopecia and biochemical hyperandrogenemia was also poor, probably secondary to varying androgen sensitivity of the skin and hair follicles.

However, combining patients with alopecia only and those with alopecia and hirsutism will tend to increase the prevalence of PCOS, as this disorder is present in a high proportion of patients with hirsutism (see above). In a study of 110 patients with alopecia and no other clinical signs of hyperandrogenism, Vexiau and colleagues observed that only 10% had PCOS (54). Overall, it would appear that the proportion of women with alopecia only who have PCOS is considerably less than that of women with hirsutism, with or without alopecia.

Overall, current data would suggest that a majority of patients with hirsutism (75%–80%) have PCOS, based on the 1990 NIH definition; alternatively, between 20 and 40% of patients with persistent acne only, and 10% of those women with alopecia only will have PCOS.

Women with menstrual and ovulatory dysfunction Oligomenorrhea can be defined as menstrual cycles (or more accurately vaginal bleeding episodes) at ≥35-day intervals or <10 bleeds per year, and polymenorrhea as ≤25 days (55, 56). The prevalence of PCOS among women with menstrual dysfunction can be estimated from four studies evaluating the prevalence of PCOS in the general population using the NIH 1990 criteria (6, 7, 9, 10). In these studies, examining a combined population of over 1,000 unselected women, it was noted that the overall prevalence of menstrual dysfunction was 18.0% (14.6%–22.8%) of the populations studied, very similar to the rate of 22.9% reported by 101,073 women participating in the Nurses' Health Study II for cycles ≥32 days in length (57). Of the women complaining of menstrual dysfunction 27.1% (17.4%–46.4%) had PCOS as defined.

Overall, these data suggest that between one-quarter to one-third of all women with oligo-amenorrhea or menstrual dysfunction have PCOS.

Women with polycystic ovaries The Rotterdam 2003 guidelines for diagnosis of PCOS included the sonographic finding of polycystic ovaries among the criteria. However, we should note that the sole presence of polycystic ovaries should not be considered as the *sine qua non* for PCOS because polycystic ovaries are common in young healthy women (58). Overall, polycystic ovaries are observed in 20% to 30% of the population. In a study of 257 volunteers who considered themselves to be normal and who had not sought treatment for menstrual disturbances, infertility, or hirsutism, 23% had polycystic ovaries (58). Other groups have confirmed this observation. The prevalence of polycystic ovaries in English women 20 to 25 years old was 22% (59) and 33% (8), 21.6% in Finish women of <36 years of age (60), 21% in New Zealand (61), and 23% in Australia (62). The prevalence pf polycystic ovaries may be less if determined by transabdominal versus transvaginal ultrasonography, although the former is better tolerated and accepted by study subjects (63) The prevalence of polycystic ovaries in the general population appears to decrease with age, and was observed to be only 7.8% in women older than 35 years, compared with 21.6% in women younger than this age (60).

In turn, polycystic ovaries can be observed during pubertal development, and in patients with hypothalamic amenorrhea and hyperprolactinemia (64, 65). The prevalence of PCOS among women with polycystic ovaries is unknown. From the estimates of the prevalence of polycystic ovaries in the general population and of the prevalence of polycystic ovaries in women with a diagnosis of PCOS, it may be estimated that about 20% of women with polycystic ovaries have PCOS, a prevalence threefold higher in these women than that found in the general population.

The sole presence of polycystic ovaries has limited clinical implications. In most studies, apparently normal women with polycystic ovaries do not present with alterations in fertility

(59, 66, 67). Women with polycystic ovaries by ultrasound and regular menstrual cycles had cycle lengths, gonadotropins, estradiol, and progesterone levels that completely overlapped those of women with regular cycles and normal ovaries (68), although another study observed slightly reduced progesterone secretion during luteal phase in these women (69). Clayton et al. (59), found that proven prior fertility was similar in apparently normal women with or without polycystic ovaries, and Hassan and Killick (66) reported that the appearance of polycystic ovaries in asymptomatic women is not associated with a reduction of fecundity or fertility. Polycystic ovaries are also commonly observed in ovum donors with proven prior fertility (67).

Nonetheless, asymptomatic women with polycystic ovaries may have some mild abnormalities of androgen secretion and insulin sensitivity. In fact, although an initial report found no differences in mean androgen levels (59), other studies have found that a significant proportion of asymptomatic women with polycystic ovaries have hyperandrogenism (70, 71) and some others have found an increase of mean androgens (60, 68, 72). LH secretion and pulsatility was normal in these women (68).

A mild reduction in insulin sensitivity may also be found in asymptomatic women with polycystic ovaries (68, 72, 73). In addition, in a study from India where the subjects were patients attending a diabetes unit a higher prevalence of polycystic ovaries was found (52%) (74). Other investigators have also found that 52% of women with a history of gestational diabetes present with polycystic ovaries (73), suggesting a link between altered glucose metabolism and the appearance of polycystic ovaries.

Taken together these data suggest that in asymptomatic women:

i) Polycystic ovaries are common in young age but become less common with age.
ii) The sole presence of polycystic ovaries is not associated with a reduction in fertility.
iii) The presence of polycystic ovaries may be associated with mild alterations in insulin sensitivity, glucose metabolism, and androgen secretion.
iv) Too few data are available to be able to predict whether women with regular ovulation and polycystic ovaries have an increased cardiovascular risk.
v) Although it can be estimated that approximately one-fifth of unselected reproductive aged women with polycystic ovaries may have PCOS when evaluated more thoroughly, this remains to be confirmed in prospective studies.

Women with insulin resistance and/or metabolic abnormalities No study to date has examined the prevalence of PCOS among women with insulin resistance or hyperinsulinemia. However, it may be useful to examine the prevalence of PCOS among women with disorders strongly associated with insulin resistance, such as those with the metabolic syndrome and type 2 DM.

Metabolic syndrome is a common disorder whose presence primarily predicts an increased risk for CVD, and features variably include visceral obesity, hypertension, dyslipidemia, insulin resistance, and glucose intolerance. It is commonly diagnosed using the criteria suggested by Expert Panel on the Detection, Evaluation, and Treatment on High Blood Cholesterol in Adults (Adult Treatment Panel III or ATP III) (75), although a number of other organizations have proposed different definitions. The prevalence of the metabolic syndrome, at least as diagnosed by ATP III, increases with age in the US population ranging from ~5% in women age 20–29 to ~15% in women age 30–39 years (76, 77).

In a population-based study of unselected women from a town in central Finland, 84 women with the metabolic syndrome were compared with 50 lean and 58 obese age-matched healthy controls (78). The group with metabolic syndrome had the highest free testosterone concentrations and greatest prevalence of oligomenorrhea, especially in those with more severe symptoms (46.2%, compared with 25.4% and 15.1% in obese and lean controls, respectively). However, polycystic ovaries were detected by transvaginal ultrasonography with similar frequency (13.1%, 15.3%, and 13.2% in women with metabolic syndrome, obese women, and lean women, respectively), and there were no differences between the groups regarding parity, infertility problems, or obstetric outcome. Thus, although women with the metabolic syndrome had a slightly higher rate of oligomenorrhea, it is unclear whether this is directly related to a greater prevalence of PCOS or to other unrelated factors.

Conn and colleagues (79) studied 38 premenopausal women with type 2 DM recruited from a hospital diabetes clinic. Eighty-two percent of these women had polycystic ovaries on ultrasonography, and among these women 32% had hirsutism, 6% had moderate to severe acne, and 26% had oligo-amenorrhea. Peppard and colleagues (80) studied 30 women with type 2 DM and observed PCOS in 26.7%. Escobar-Morreale and colleagues (81) also reported a high prevalence of ovarian hyperandrogenism and PCOS among women with type 1 DM, and suggested that it is not insulin resistance that is primarily responsible for the ovarian hyperandrogenism, but rather hyperinsulinemia (82). Patients with type 1 DM may experience exogenous hyperinsulinism because the insulin is not being delivered directly into the portal circulation, but through a less physiologic subcutaneous route.

Overall, it would appear that women with hyperinsulinism, at least as observed in diabetes, are at greater risk for developing PCOS. This association is less certain for women with the metabolic syndrome, and additional studies are needed.

THE FEATURES OF PCOS

We generally recognize four key features of PCOS: [i] ovulatory and menstrual dysfunction, [ii] hyperandrogenemia, [iii] clinical features of hyperandrogenism, and [iv] polycystic ovaries. For each of these features, we should review

current definitions, pitfalls, and limitations in their definition, and how predictive each is in defining women with PCOS. Stated differently, what is the fraction of women with the particular feature, and what is the fraction of women with the particular feature that have PCOS. Obtaining these estimates would essentially allow us to determine the positive and negative predictive value of each feature for PCOS.

Ovulatory and Menstrual Dysfunction

Clinically ovulatory dysfunction may present with obvious disruption of the menstrual flow pattern, often resulting in oligo-amenorrhea or abnormal uterine bleeding. Ovulatory dysfunction can also present subclinically, with no obvious disruption in the regularity of vaginal bleeding. It should be noted that having regular menses might not always be indicative of ovulatory cycles. Although many patients and some practitioners refer to these cyclic bleeding episodes as "menses" or "periods," strictly speaking "menstruation" and "menstrual cycle" actually refers to the cyclic vaginal bleeding that results from the decline (withdrawal) in circulating estrogen and progestogen occurring at the end of the luteal phase of an ovulatory cycle in females who are not pregnant. Following, we will address these associations of vaginal bleeding and ovulatory dysfunction separately.

Overt menstrual dysfunction Obvious menstrual dysfunction can be observed in a majority of patients with PCOS. In a large series of patients diagnosed with PCOS, approximately 75% to 85% have clinically evident menstrual dysfunction (Table 2) (46, 65, 83–100). However, as many women with potential PCOS do not seek medical care (101), and women with overt abnormalities of vaginal bleeding may be more likely to seek medical care, more accurate estimates of the prevalence of menstrual dysfunction in PCOS may be determined from prospective studies of unselected women. In a prospective study of 400 unselected women being evaluated for an employment physical,

TABLE 2

Prevalence of menstrual dysfunction in the polycystic ovary syndrome (PCOS).

Study	Reference	Total No. PCOS	No. of PCOS patients with oligo-amenorrhea	% of PCOS patients with oligo-amenorrhea	No. of PCOS patients with eumenorrhea	% of PCOS patients with eumenorrhea
Ferriman & Purdie, 1983	83	280	237	84.60%	43	15.40%
Conway et al., 1989	84	556	395	71.00%	139	25.00%
Kiddy et al., 1990	85	263	203	77.20%	60	22.80%
Ardaens et al., 1991	65	144	105	72.90%	39	27.10%
Rajkhowa et al., 1995	86	153	129	84.30%		
Balen et al., 1995	87	1741	1043	59.90%	517	29.70%
Falsetti & Eleftheriou, 1996	88	240	207	86.30%	24	10.00%
Khoury et al., 1996	89	112	112	100.00%	0	0.00%
Talbott et al., 1998	90	244	229	93.90%	15	6.10%
Carmina et al., 1998	91	332	290	87.30%	42	12.70%
Alborzi et al., 2001	92	371	371	100.00%	0	0.00%
Williamson et al., 2001	93	162	144	88.90%		
Haddad et al., 2002	94	146	120	82.20%	26	17.80%
Amer et al., 2002	95	161	149	92.50%	12	7.50%
Glueck et al., 2003	96	138	138	100.00%	0	0.00%
Orio et al., 2003	97	100	100	100.00%	0	0.00%
Chang et al., 2005	98	316	265	83.90%	51	16.10%
Hahn et al., 2005	99	200	200	100.00%	0	0.00%
Carmina et al., 2006	46	685	538	56.60%	147	15.50%
Diamanti-Kandarakis & Danidis, 2007	100	634	545	85.90%	89	14.10%
Total		6978	5520	79.11%[a]	1204	17.25%

[a] Difference in percentage between patients with oligo-amenorrhea and eumenorrhea and anovulation is composed of patients with polymenorrhea or menometrorraghia.

Azziz. AE-PCOS Society report on PCOS phenotype. Fertil Steril 2009.

approximately 60% of PCOS patients detected, using the NIH 1990 criteria, had clinically evident menstrual dysfunction, whereas the remaining 40% had oligoanovulation but apparently "regular cycles" (see below) (10).

The menstrual dysfunction of PCOS is generally characterized by infrequent or absent menstrual bleeding. Alternatively, polymenorrhea (i.e., excessively frequent cycles, generally defined as occurring at intervals of <26 days in length) is relatively rare, present in only 1.5% of 716 consecutive untreated patients with PCOS (47). Menstrual irregularity may start at menarche. Some patients may give a history of regular cycles for a short period of time following menarche, followed by the onset of oligomenorrhea.

We should note that the prevalence of menstrual dysfunction in PCOS changes with age, decreasing as the patient approaches menopause (102); correlating with the decrease in androgen levels also occurring in PCOS women as they age (103). These age-related changes may confound the prevalence of oligomenorrhea in PCOS if age is not noted carefully controlled for in studies.

These data suggest that between 20% and 30% of women with PCOS will present with a history of eumenorrhea, despite evidence of oligoanovulation; the remainder will present with overt oligoamenorrhea.

Subclinical ovulatory dysfunction A history of "regular" menses does not exclude the presence of ovulatory dysfunction. This phenomenon is uncommon in the general population (104) but may be relatively common in some particular conditions (105, 106) including hyperandrogenism. In fact, 20-50% of hyperandrogenic women with normal menses have chronic anovulation and may be considered to be affected by PCOS (91, 107, 108). In a report of 316 untreated consecutive women diagnosed as having PCOS by the NIH 1990 criteria, 16% had apparent eumenorrhea (cycles every 27–34 days in length) despite having oligo-anovulation (98). In eumenorrheic women with PCOS the absence of premenstrual symptoms (e.g., bloating, mood changes, or breast fullness) may also suggest anovulation.

As noted above, studies of large populations of PCOS patients, or PCOS diagnosed prospectively in the general population suggests that between 15% and 40% of oligo-ovulatory PCOS patients may present with apparent eumenorrhea. This estimate is consistent with prospective studies of women with overt or clinical evidence of hyperandrogenism (e.g., hirsutism), which indicate that between 14% (91) and 40% (107) of hirsute eumenorrheic women are oligo-ovulatory. The proportion of PCOS patients with eumenorrhea would undoubtedly increase if the Rotterdam 2003 criteria were used, as patients with normal ovulation (but polycystic ovaries and clinical hyperandrogenism) are included.

In clinical practice, the presence of anovulation in eumenorrheic women may be determined most easily by measuring a serum progesterone level day 20 to 24 of the cycle. If progesterone level is below 3 to 4 ng/mL, depending on the laboratory, then the cycle is deemed to be oligo-anovulatory. Of course, it may be argued that in a patient with a long-term history of regular "menses" a single anovulatory cycle is not sufficient to make the diagnosis of chronic oligo-anovulation. Consequently, it may be prudent, in the event the first cycle monitored is anovulatory, that one more cycle be studied; chronic oligo-anovulation is established if this second cycle is also anovulatory.

Overall, 60% to 85% of patients with PCOS and oligo-ovulation demonstrate overt menstrual dysfunction, primarily oligomenorrhea; the remainder present with apparent eumenorrhea. Patients who present with clinical evidence of hyperandrogenism but apparent eumenorrhea should have their ovulatory function evaluated further; this is generally done by measuring a progesterone level in the latter part of the menstrual cycle (i.e., days 20–24 of the cycle).

Hyperandrogenemia

Hyperandrogenemia refers to the finding of supranormal levels or estimates of circulating endogenous androgens. The most frequent androgen measured is testosterone (T), total, unbound, or free. Androstenedione (A4) and dehydroepiandrosterone (DHEA), and the DHEA metabolite DHEAS, may also be measured.

An important consideration for the measurement of androgen levels is the proper establishment of normal ranges or limits. These can be established by measuring androgens in a large population of well-characterized normal women, in whom the presence of menstrual/ovulatory dysfunction and hirsutism, among other factors, has been excluded. However, it may also be argued that a more appropriate method for establishing a normal range is to assess unselected women from the general population, particularly if a percentile cutoff value (e.g., 95th or 97.5th percentile) is used, which would take into account any outliers within the population studied. Which approach to take is not clear, as the prevalence of PCOS among unselected women is at least 7% (9, 10), greater than the fraction allowed to be abnormal under cutoff values using the 95th or 97.5th percentile. Perhaps an approach that combines the use of women from the general population, but that excludes women with overt abnormalities, may be preferable (6). Following we discuss the use of total and free or unbound T, A4, and DHEA and DHEAS for the diagnosis of PCOS.

Total and free T, Sex Hormone Binding Globulin (SHBG) Serum T is possibly the most important androgen in women. Testosterone circulates bound to SHBG and other proteins such as albumin, and only the unbound or free fraction enters into target tissues. It appears that assessments of free T levels are much more sensitive than the measurement of total T for the diagnosis of hyperandrogenic disorders (Table 3) (83–90, 92, 93, 95, 97–99, 109, 110). However,

TABLE 3

Prevalence of hyperandrogenemia and hirsutism in the polycystic ovary syndrome (PCOS).

Study	Reference	Total No. PCOS	No. with elevated Total T	% with elevated Total T	No. with elevated Free T	% with elevated Free T	No. with elevated DHEAS	% with elevated DHEAS	No. with Hirsutism[c]	% with Hirsutism[c]
Ferriman & Purdie, 1983	83	280							230	82.14%
Conway et al., 1989	84	556	110	22.30%[a]					320	57.55%
Kiddy et al., 1990	85	263							129	49.05%
Rajkhowa et al., 1995	86	153							123	80.39%
Balen et al., 1995	87	1741	503	28.90%					1153	66.23%
Norman et al., 1995	109	122							103	84.43%
Falsetti & Eleftheriou, 1996	88	240							92	38.33%
Khoury et al., 1996	89	112							20	17.86%
Talbott et al., 1998	90	244							105	43.03%
Alborzi et al., 2001	92	371							300	80.86%
Williamson et al., 2001	93	162							147	90.74%
Amer et al., 2002	95	161							53	32.92%
Orio et al., 2003	97	100	33	33.00%			27	27.00%	100	100.00%
Azziz et al., 2004	47	873							517	72.20%
Chang et al., 2005	98	316	122	38.60%	216	68.40%	71	22.50%	224	70.89%
Hahn et al., 2005	99	200	162	81.00%			76	38.00%	129	64.50%
Legro et al., 2006	110	626	373	60.80%[b]					505	80.67%
Diamanti-Kandarakis & Danidis, 2007	100	634	535	84.38%			70	11%	441	69.55%
Total		6281	1838	29.26%	216	3.44%	244	3.88%	4691	74.69%

Note: Abbreviations: T is testosterone, DHEAS is dehydroepiandrosterone sulfate.
Subjects included are mostly of White and Black race.
[a] Based on 494 patients who underwent androgen measurements.
[b] Based on 613 subjects who underwent androgen measurements.
[c] Hirsutism defined variously as mFG scores of 5-9.

Azziz. AE-PCOS Society report on PCOS phenotype. Fertil Steril 2009.

we should note that the practice of measuring total or free T directly has several limitations:

- Measurement of free T by direct radioimmunoassay (RIA) (analogue method) is highly inaccurate and does not reflect the actual free or unbound T levels (111–113).
- Alternatively, methods of directly assessing the quantity of free T in serum, such as equilibrium dialysis, are more accurate, correlating well with mass spectrometry (114). However, this method is not widely available given its relative technical complexity and high economic cost.
- Direct assays for total T are highly variable, especially in the lower range found in most women, and in women with lower SHBG levels such as patients with PCOS (115). A high-quality direct double antibody RIA assay for total T might be useful clinically, as long as the interassay coefficients of variation are below 10% as determined by the lab conducting the assays, and the normal ranges are determined in-house in a carefully selected healthy nonhyperandrogenic control female population. Alternatively, a greater degree of accuracy, particularly for clinical research, will be obtained by measuring total T concentration using extraction and chromatography (115), or gas (GC-MS) or liquid (LC-MS) chromatography-mass spectrometry (116–118).
- Assays for T have relatively large intra- and interassays coefficients of variation (approximately 7%–10%) when compared with other analytical procedures such as plasma glucose by the glucose-oxidase method (below 3%).
- Testosterone and dihydrotestosterone (DHT), formed by the 5α-reduction of T, both bind to the androgen receptor. However, the duration of action is longer for DHT than T causing it to be more "active" within target cells than T. Serum T concentrations, therefore, do not necessarily correlate with the biologic activity in target tissues.

Fortunately, the diagnostic performance of measuring serum T may be enhanced easily by the concomitant measurement of SHBG, such that:

- The calculation of free T concentration from the total T and SHBG levels only requires solving a second degree equation (112), which can be introduced in a spreadsheet for easy automatic calculation of this parameter.
- Calculated free T has a fairly good concordance and correlation with free T as measured by the equilibrium dialysis method (111, 112).
- Serum SHBG may be a surrogate marker of insulin resistance in women (119), and therefore its measurement may be useful per se.
- Single determinations of serum SHBG and free T levels, when using accurate methods of measurement have a high predictive value for PCOS diagnosed according to the NIH 1990 criteria in epidemiologic studies, with receiver operating characteristic curve values above 0.830 (120).

Androstenedione Although A4 may be used to diagnose hyperandrogenemia, few studies of its prospective value are available. Androstenedione can be synthesized in the adrenal cortex and in ovarian theca cells. In one study of 277 women undergoing a preemployment physical and who had measurements of A4, 2 of the 11 women (18%) diagnosed with PCOS had supranormal A4 levels (6). In one of these women the supranormal A4 level was the only androgen abnormality, suggesting that 9% of PCOS patients may have been missed by not measuring this androgen. Clearly, further studies of the value of A4 are required.

Dehydroepiandrosterone and DHEAS Adrenal androgen production is exaggerated in a fraction of patients with PCOS (120, 121). The principal C19 steroid distinguishing adrenal from ovarian androgen production is DHEA, of which 95% to 97% of the circulating amount is secreted by the adrenocortical zona reticularis. However, the measurement of DHEA for the diagnosis of PCOS has limited diagnostic use, principally because of its diurnal variation, its relatively low concentration, which requires the development of accurate and sensitive assays, its wide intersubject variation (122), and the fact that any degree of stress, including anticipation of blood drawing, can result in spurious increases in circulating levels.

Measurement of the principal DHEA metabolite DHEAS has been the preferable method of assessing adrenal androgen production (123). Clinically, the measurement of circulating levels of the metabolite DHEAS has been traditionally used as the marker for adrenal androgen excess (123–125), because this hormone is: [i] 97% to 99% of adrenocortical origin (126–128), [ii] the most abundant steroid, [iii] relatively stable throughout the day and the menstrual cycle (127, 129–131) because of its relatively long-half life (132–136), and [4] is easily measured.

Increased circulating DHEAS levels are sufficient to indicate the existence of the condition of hyperandrogenism. Although PCOS is considered a syndrome with a prevalent ovarian androgen secretion, serum DHEAS is also elevated in many of these patients. In different studies increased serum DHEAS levels were found in about 50% of women with PCOS (137, 138). However, because DHEAS levels decrease with age, the use of age-adjusted normative values may result in a somewhat lower prevalence of DHEAS excess. For example, in a study of 213 women with PCOS and 182 age-matched healthy eumenorrheic nonhirsute controls (88 Black and 94 White) the prevalence of supranormal DHEAS levels was 33.3% and 19.9% of Black (n = 27) and White (n = 186) women with PCOS, respectively (139). Overall, 25% to 35% of women with PCOS will demonstrate elevated DHEAS levels (Table 3).

In PCOS, increased DHEAS is generally associated with increases in other circulating androgens (98). Furthermore, we should note, however, that DHEAS levels might not always reflect the status of adrenocortical steroidogenesis. Serum DHEAS concentrations reflect DHEA biosynthesis,

as well as the activity of DHEA sulfotransferase (140). Hence, DHEAS should be used with caution as a marker of adrenal androgen secretion, particularly in PCOS, as DHEAS levels may not always reflect alterations in adrenocortical steroidogenesis. For example, DHEAS levels are often normal in patients with inherited adrenocortical dysfunction, such as those with 21-hydroxylase (21-OH) deficient nonclassic congenital adrenal hyperplasia (NC-CAH). For example, we studied 13 patients with untreated 21-OH deficient NC-CAH and observed that 92.3% and 100% of NC-CAH patients had A4 and DHEA basal levels, and 100% had ACTH-stimulated levels of A4 and DHEA, above normal. Alternatively, only 53.8% of patients with NC-CAH had DHEAS levels above normal (141). As such, even in patients with genetically evident NC-CAH the circulating DHEAS level is not a good predictor.

Some patients with PCOS present with an isolated increase in serum DHEAS. In these instances a pattern suggestive of deficiency in 3β-hydroxysteroid dehydrogenase (3β-HSD) function may be found, suggested by an increased Δ^5 to Δ^4 metabolite ratio in response to (ACTH) (139). However, in patients who develop this form of hyperandrogenism during adult life, no specific genetic defect has been detected, and it has been suggested that these patients may have a functional enzymatic deficiency (143, 144). In practice, these patients may be considered affected by PCOS because they generally have anovulation and menstrual irregularities and have similar phenotypic features, including insulin resistance and LH hypersecretion, as patients of classic PCOS (142, 144).

In summary, elevated free T levels are observed in approximately 70% of PCOS patients, at least those diagnosed by the NIH 1990 criteria. The vast majority of the abnormal values are in the form of free T, with the sole measurement of total T adding little to the diagnosis. The present recommendation is to measure free T concentration either directly by equilibrium dialysis, or to calculate free T based on the total T measured accurately (e.g., by RIA using column chromatography, or by LC-MS or GC-MS) and SHBG (e.g., measured using competitive binding or a high quality immune-based assay). As with any other analytical procedure, it is highly recommended that each laboratory establish its own analytical performance and the normal ranges. The value of also measuring A4 is unclear, but it may increase the number of subjects identified as hyperandrogenemic by ~10%.

Approximately 20% to 30% of patients with PCOS will demonstrate supranormal levels of DHEAS, which may be the sole abnormality in circulating androgens in ~10% of these patients. Nonetheless, we should note that DHEAS levels might not always reflect the status of adrenocortical steroidogenesis, and overinterpretation of DHEAS levels should be avoided. Circulating levels of DHEA have limited diagnostic value. For all the reasons outlined above, serum measurements of androgens, including free T, should be used only as an adjuvant tool for the diagnosis of hyperandrogenic disorders, and never as the sole criterion for diagnosis

or in lieu of the clinical assessment. This latter recommendation reflects that fact that between 20% and 40% of women with PCOS will have androgen levels within the "normal" range, and assays for androgens, particularly total T, are highly variable and inaccurate.

Clinical Hyperandrogenism

Clinical features of hyperandrogenism frequently seen in PCOS include hirsutism, acne, and androgenic alopecia. Here, we review the prevalence of these features in this disorder.

Hirsutism Hirsutism is the presence of terminal hairs on the face and/or body in a female in a male-type pattern. The most common method of determining the presence of hirsutism uses a visual score. Various methods have been proposed (145, 146). The most commonly used method is a modification of a method originally reported by Ferriman and Gallwey (148, 149). Nine body areas, including the upper lip, chin, chest, upper back, lower back, upper and lower abdomen, upper arm, and thigh, are assigned a score of 0–4 based on the density of terminal hairs. A score of 0 represented the absence of terminal hairs, a score of 1 minimally evident terminal hair growth, and a score of 4 extensive terminal hair growth. The cutoff value should be established after the study of a large population of unselected women. Using this approach, cutoff values for defining hirsutism have been variously reported to be a score of 6 or greater (6), 7 or more (150), and 8 or more (149).

In a study of 716 subjects with PCOS, 72% were found to have hirsutism, defined as a modified Ferriman-Gallwey (mFG) score of ≥6 (150). However, we should note that the prevalence of hirsutism in PCOS will vary according to the race and ethnicity of the population being studied. These data suggest that the degree of body and terminal hair growth and the prevalence of hirsutism (6, 150) are not significantly different between unselected White and Black women. Consequently, it is likely that there will be little difference in the prevalence of hirsutism between Black and White PCOS women, although this remains to be confirmed.

Consistent with the lower population prevalence of hirsutism observed in East Asian women, a comparative study of patients with PCOS from the United States (primarily Mexican Americans), Italy, and Japan noted that Japanese women had a significantly lower mean hirsutism score than their non-Asian counterparts (150). However, the lesser prevalence of hirsutism among East Asian PCOS patients may not extend to all groups in the region. For example, Wijeyaratne and colleagues (152) observed that hirsutism was more prevalent and more severe among PCOS patients of Southern Asian extraction (Pakistani, Bengali, Gujarati, or Dravidian Indian) than Whites. Likewise, among women of Indian descent in New Zealand, about two-thirds of women with PCOS presented with clinical evidence of hirsutism, similar to the prevalence found in women of European, Maori, and Pacific Island descent (93). Although it is clear that there is racial variation in hair growth patterns,

race-specific normative ranges have not been well established, which is required to determine whether a particular woman has excessive amounts of body of facial hair.

Overall, hirsutism is an important feature of PCOS, affecting approximately 65% to 75% of patients with PCOS (Table 3), including women of White, Black, and Southeast Asian race. The prevalence of hirsutism in PCOS is likely to be less among women of East Asian extraction.

Acne Acne affects approximately 12% to 14% of White PCOS patients (10, 47, 152) although the prevalence of this dermatologic abnormality varies with ethnicity: it is reportedly higher in Asian Indians (152) and lower in Pacific Islanders (93). In a study of 248 women with PCOS in Italy, acne alone in the absence of other pilosebaceous features was present in 23.4% (153). Among 716 patients with PCOS, 14.5% presented with acne, either alone or in combination with hirsutism (47). In a prospective study of women presenting for blood donation, Asuncion and colleagues (9) noted that of the 10 women diagnosed with PCOS, four (40%) had acne, three without associated hirsutism.

However, various surveys have noted a relatively high prevalence of acne in the general population, particularly among younger women. Approximately 20% of individuals in their midteens and ~15% of those in their early 20s complain of acne; even 10% of women in their 30s and ~5% of women 40 to 60 years old will complaint of, albeit mild, acne (154–158). Consequently, the degree to which PCOS increases the risk of acne above the general population prevalence is unclear. The variability in the prevalence of acne is compounded by the fact that there is no single scoring system used.

Overall, although acne affects 15% to 25% of PCOS patients, it is unclear whether the prevalence of acne is significantly increased in these patients over that observed in the general population.

Androgenic alopecia Scalp hair loss in women is a distressing complaint with significant psychologic morbidity. It usually represents the pilosebaceous unit response to endogenous androgens and may be associated with acne and hirsutism. Androgen sensitivity of the pilosebaceous unit varies, and there is poor correlation between clinical features and evidence of biochemical hyperandrogenism (159, 160). The presence of DHT, formed from the 5α-reduction of T in the dermal papilla, is associated with a higher 5α-reductase activity in the hairs plucked from a scalp presenting with androgenic alopecia (161). In addition to androgen excess, other potential etiologies of alopecia or diffuse scalp hair loss in any woman may be genetic (i.e., familial premature scalp follicular loss), environmental (e.g., damage following the use or abuse of hair cosmetics), and nutritional (e.g., poor protein intake, zinc deficiency, iron-deficient anemia).

Androgenic alopecia is a recognized sign of PCOS (47, 52, 53, 84, 162, 163). However, the prevalence of this abnormality in PCOS is unclear. Although we previously noted that

PCOS patients may account for ~10% to 40% of all women with alopecia, literature defining the incidence of alopecia in either normal women or women with PCOS is sparse. In a study of 257 patients who were compliant with treatment and follow-up, only 12 (4.7%) complained of hair loss (47).

The pattern of hair loss in PCOS generally involves thinning of the crown with preservation of the anterior hairline (53, 162). Androgenic related alopecia in women with PCOS tends to seen in the anterior midvertex area extending to the crown. The anterior hairline remains intact in women with PCOS and significant a bitemporal scalp hair recession is unusual except in virilizing syndromes. Unfortunately, a loss of at least 25% of scalp hair is needed before a woman becomes aware of thinning of her scalp hair (162).

The sole presence of alopecia or diffuse scalp hair loss in women may be the sole dermatologic sign of PCOS. However, estimates regarding the prevalence of alopecia in PCOS vary widely, from 5% to 50%, and further studies are needed to better define this prevalence.

Polycystic Ovaries

Polycystic ovaries were first described by Stein and Leventhal (2) in 1935 in their eponymous case report, linking ovulatory dysfunction with morphologic changes of the ovaries to define the PCOS. After the 1990 NIH sponsored conference (13), which defined PCOS as anovulation and hyperandrogenism and absence of other ovarian, adrenal, or pituitary disease, it has become appreciated that the syndrome encompasses a broader spectrum of signs and symptoms (12, 164, 165), resulting in the 2003 Rotterdam definition of PCOS (14, 15). PCOS is thus understood as a functional disorder; polycystic ovaries need not be present to make the diagnosis (166), and conversely, their presence in the absence of other signs and symptoms does not establish the diagnosis (8, 58).

Three features are generally assessed to define polycystic ovaries, including ovarian size and volume, stromal volume, and follicle size and number. Based on the available literature (167–169), the Rotterdam criteria defines polycystic ovaries solely on total follicle number, defined as the presence of 12 or more follicles throughout the ovary measuring 2 to 9 mm in diameter (as opposed to prior criteria that counted the number of follicles in the largest single plane) and/or increased ovarian volume >10 mL, in at least one ovary, respectively. However, in some recent studies, it has been found that normal limits of ovarian size are <7–7.5 cm³, and therefore, values higher than these limits may be used to indicate increased ovarian size (170, 171).

The Rotterdam definition of polycystic ovaries cannot be used in women taking oral contraceptives, as these modify ovarian morphology (172). Evidence of a dominant follicle (>10 mm) or a corpus luteum necessitates examination during the next cycle and presence of an abnormal cyst or ovarian asymmetry further investigation (14, 15). Although

increased stromal volume is a common feature of polycystic ovaries (173), it was not included in the definition for lack of a simple means of quantification and because ovarian volume has been shown to be a good surrogate (174).

The prevalence of polycystic ovaries appears to be relatively high among patients with androgen excess or PCOS (Table 4) (86, 88, 89, 92, 93, 95, 97, 99, 110, 168, 175, 176). In a study of 173 women with anovulation or hirsutism, polycystic ovaries by ultrasound was found in 92% of women with hirsutism with regular menstrual cycles, 87% of women with oligomenorrhea, 57% of anovulatory women, and 26% of women with amenorrhea (12). Using transvaginal ultrasound, 60% of 226 women with PCOS diagnosed by NIH criteria had increased ovarian size and another 35% had polycystic ovaries with normal ovarian size (171). When assessing the ovaries ultrasonographically, it is preferable to use transvaginal rather than transabdominal sonography, although some patients are resistant to undergoing the transvaginal procedure (63).

These data suggest that morphologic ovarian alteration may be found in >80% of women with a clinical diagnosis of PCOS, although we should recognize that the false positive rate is relatively high.

Other Features of PCOS

A number of other features of PCOS have been recognized, although they have not formed part of any of the recognized definitions to date. These include, among others, gonadotropic abnormalities, insulin resistance, and obesity.

Gonadotropic abnormalities (LH/FSH) The existence of abnormalities in the secretion of gonadotropins in patients with PCOS has been recognized for >40 years. These abnormalities consist of an increased secretion of LH, resulting from an accelerated GnRH/LH pulse frequency, whereas FSH levels are normal or even decreased.

Adequate studies using frequent blood sampling and accurate gonadotropin assays demonstrate that >75% of PCOS patients present with a dysregulation in gonadotropic function (177–179). Typically, GnRH/LH pulsatility is increased (179). In fact, it is lean PCOS women that primarily have an increased LH pulse amplitude, explaining in part the finding that in many obese women with PCOS basal LH levels are within the normal range and the ratio of LH to FSH is not increased (84).

Conceptually, the increased secretion of LH, and an increase in the ratio of serum LH to FSH during the follicular phase of the menstrual cycle, has been considered as a marker of PCOS (180). However, the cutoff value for the LH/FSH ratio is quite dependent on the assay used to measure these gonadotropins (181), making difficult its broad application in clinical practice. In addition, the high proportion of obesity in PCOS (see below) may confound the measurement, explaining the normal LH/FSH ratio found in many patients, particularly if the assessment is based on a single LH and FSH determination.

TABLE 4

Prevalence of polycystic ovaries (PCO)[a] by transvaginal ultrasonography in the polycystic ovary syndrome (PCOS).

Study	Reference	Total No. PCOS	No. PCOS with PCO	% PCOS with PCO
Rajkhowa et al., 1995	86	153	141	92.20%
Falsetti & Eleftheriou, 1996	88	240	180	75.00%
Khoury et al., 1996	89	112	77	68.80%
Van Santbrink et al., 1997	168	198	148	74.70%[b]
Laven et al., 2001	175	190	154	81.10%
Alborzi et al., 2001	92	371	211	56.90%
Williamson et al., 2001	93	162	161	99.40%
Amer et al., 2002	95	161	93	57.80%
Jonard et al., 2003	176	214	160	74.80%
Orio et al., 2003	97	100	33	33.00%
Hahn et al., 2005	99	200	166	83.00%
Legro et al., 2006	110	626	573	91.50%
Diamanti-Kandarakis & Danidis, 2007	100	634	383	60%
Total		3361	2480	73.79%

[a] Excluding multicystic or multifollicular ovaries.
[b] PCOS defined as oligo-amenorrhea with either increased androgens and/or high LH.

Azziz. AE-PCOS Society report on PCOS phenotype. Fertil Steril 2009.

For the reasons outlined above, basal gonadotropin measurements are not generally helpful for the diagnosis of PCOS. We should note that these measures may provide information supportive for a PCOS diagnosis if the LH level, or the LH/FSH ratio, were elevated; alternatively, they provide little information if not elevated, although in patients presenting with menstrual dysfunction, FSH levels may be useful to exclude ovarian failure.

Insulin resistance, hyperinsulinemia, and the metabolic syndrome It is a common assumption that all women with PCOS are insulin resistant. However, not all women with PCOS have documented insulin resistance by invasive dynamic tests such at the euglycemic clamp (182), the frequently sampled intravenous glucose tolerance test (183), the insulin tolerance test (151), and baseline indices (184). The prevalence of insulin resistance is greater in obese than nonobese patients. Overall, between 50% and 70% of women with PCOS have demonstrable insulin resistance.

Insulin resistance results in a compensatory increase in insulin secretion by the islet cells of the pancreas to maintain normal glucose homeostasis. In fact, it is the secondary hyperinsulinemia that drives many of the phenotypic features of the disorder including the associated ovarian hyperandrogenism and acanthosis nigricans. The hyperinsulinemia results in increased ovarian theca androgen production (185, 186) and decreased production of SHBG by the liver (187, 188). Because most women with PCOS are young with relatively healthy pancreatic function, they tend to develop significant hyperinsulinemia, and this fact underlies the relative insensitivity of basal glucose measures for detecting glucose intolerance, as impaired glucose tolerance becomes manifest only when these individuals are stressed by an oral or intravenous glucose load (189).

Although most women with PCOS have normal or even an exaggerated insulin secretory response, many of these women actually demonstrate impaired beta cell function when taking into account the degree of insulin resistance present. This is most evident by the fact that in many women with PCOS the disposition index (i.e., the relation between first-phase insulin secretion and insulin sensitivity) is lower than in normals (190), and the ability of the beta cells to respond to oscillations in plasma glucose (191) or to dexamethasone-induced insulin resistance (192) is reduced. However, we should note that although β-cell dysfunction appears to be prevalent in PCOS, the severity of the abnormality is closely tied to a family history of type 2 DM (193).

There is substantial controversy regarding the methods for assessing insulin resistance in PCOS, clinically and investigationally. Although beyond the scope of this position article, a few general principals may be stated. For larger epidemiologic studies detection of insulin resistance may be accomplished using surrogate measures, such as the homeostatic model assessments (HOMA-IR assessing insulin resistance and HOMA-%B assessing the percent β-cell function or insulin secretion) or the quantitative insulin sensitivity check index (QUICKI), this latter measure essentially the log transformation of HOMA-IR (193, 194), although there are more limitations with the use of the glucose to insulin ratio (195).

Some studies have attempted to determine the cutoff values for HOMA or QUICKI, which may be useful in epidemiologic studies or in clinical practice (184, 196). Generally, normal ranges have been established using the upper 95th percentile or the lower 5th percentile of values (normality tested) in a group of age, race, and gender-matched lean controls. Based on 95% confidence limits, normal limits were as follows: QUICKI: >0.332 (196) or HOMA-IR <3.90 mol*μU/L2 (150). However, it is important to recognize that all these calculations are strongly influenced by the insulin values, and hence, by the quality of the insulin assays used. Many commercial assays for insulin give values higher than those reported in these studies, a fact that should be taken into account when using these cutoff values.

Alternatively, research studies of insulin resistance, particularly those involving a smaller number of subjects, should strive to use the clamp, the frequently sampled intravenous glucose tolerance test, the insulin suppression test, or oral glucose tolerance test techniques (197–200). Clinically, in PCOS the standard 2-hour oral glucose tolerance test (OGTT) measuring both insulin and glucose yields the highest amount of information for a reasonable cost and risk, providing an assessment of both the degrees of hyperinsulinemia and glucose tolerance (188). To date, there are no accepted standards for clinically estimating the degree of hyperinsulinemia (even as a surrogate for insulin resistance) from the OGTT. In general, peak insulin levels at either 1 or 2 hours during a standard 75-g OGTT that exceed 80 to 100 μIU/mL are consistent with hyperinsulinemia, and levels >300 mIU/mL are indicative of severe hyperinsulinemia (and marked insulin resistance). However, considering the current variability in insulin assays (201), each laboratory should set its own normal range and establish a method for periodically reevaluating the acceptability of their results.

Establishment of normative range for detecting hyperinsulinemia during an OGTT usually entails studing sufficient numbers of well-characterized healthy controls (>50), with body mass indices (BMIs) similar to that of the PCOS being evaluated. Levels of insulin should be obtained at 1 and 2 hours, as peak insulin may occur at either time. Values are log-transformed (to normalize the data) and the cutoff value selected based on the percentage expected abnormal; although most investigators use the upper 5% or even 2.5%, as the cutoff, recognizing the high frequency of metabolic abnormality in the general population suggests that a lower cutoff, such as the upper 10%, or even the upper quintile (20%) or quartile (25%), may be more indicated. Cluster analysis and related statistical testing, if a population studied is large enough, may also be used to determine the "natural" cutoff value.

Notwithstanding the lack of universality regarding insulin resistance in PCOS, the prevalence of the metabolic

syndrome, a disorder highly associated with insulin resistance, is substantially higher in women with PCOS, ranging in the United States from 33% to >50% (202). Likewise, for the prevalence of type 2 DM, which appears to affect 4% to 10% of young women with PCOS (188, 192, 203). However, in some other countries, the prevalence of metabolic syndrome and type 2 DM among patients with PCOS is lower than that observed in United States (99, 204), most likely because of differences in body weight and environmental factors affecting the prevalence of metabolic disturbances in PCOS.

We should understand that the clinical quantification of insulin resistance remains an imprecise science with no generally acknowledged guidelines or criteria (76, 205). In addition to obesity and family history of diabetes, ethnicity adversely affects the prevalence of insulin resistance, and generally minority populations with PCOS tend to be more insulin resistant than Caucasians (206). Presumably, many diverse factors contribute to the molecular basis of insulin resistance among women with PCOS.

In summary, between 50% and 70% of patients with PCOS have insulin resistance and hyperinsulinism, although this is not a universal feature of the disorder. Metabolic complications of insulin resistance, including the metabolic syndrome, dyslipidemia, and type 2 DM are higher among women with PCOS.

Dyslipidemia Dyslipidemia may be the most common metabolic abnormality in PCOS, although the type and extent of the abnormalities have varied. Prevalence of at least one abnormal lipid level (borderline or high) by National Cholesterol Education Program guidelines approaches 70% (207). However many women with PCOS still have a completely normal circulating lipid profile and in larger published series of lipid levels in women with PCOS, mean levels, for the most part, fall within normal limits as determined by National Cholesterol Education Program cutoffs (208–211). Insulin resistance and compensatory hyperinsulinemia have been associated with other distinct patterns of dyslipidemia (212). These include decreased levels of high-density lipoprotein cholesterol (HDL-C), increased levels of small dense low density lipoprotein (LDL-C), and elevated levels of triglyceride. Multiple studies have reported similar findings of decreased HDL-C/increased triglycerides in the lipid profiles in PCOS women (208, 213, 214). The larger studies (often compared with weight matched controls) have however noted elevations in LDL-C in women with PCOS (207, 209–211), a finding not usually noted in insulin resistant states. This may be related to elevations in circulating androgens, or possibly given that elevated LDL-C levels have also been noted in first-degree relatives of women with PCOS (215–217), a genetic or environmental (i.e., common diet) influence. The LDL-C levels in PCOS women appear to remain elevated but stable over time into the menopause (90, 209).

Obesity Obesity frequently accompanies PCOS and about 50% of women with PCOS are obese (47). It may be argued that the degree of obesity in PCOS is a uniquely American characteristic, and may be directly related to the larger obesity epidemic in the United States. For example, women with PCOS from other countries tend to be leaner, with mean BMIs of 25 kg/m^2 in England (87), 28 kg/m^2 in Finland (218), 31 kg/m^2 in Germany (99), and 29 kg/m^2 in Italy (204). Contrast this with a recent multicenter trial at 22 sites in the United States in PCOS, where the BMI in the four treatment arms (total n = 305) ranged from 35 to 38 kg/m^2 (219). Likewise, data arising from studies in the general population suggests that obesity is more prevalent in women with PCOS diagnosed in the United States. In the largest prevalence study of PCOS in the United States that examined 400 unselected females applying for employment at a university hospital in Alabama, 24% were found to be overweight (BMI 25.0–29.9 kg/M^2) and 42% were obese (BMI >30 kg/M^2) (10). Alternatively, in a study of blood donors in Spain, 30% of the women were overweight, but only 10% were obese (9).

It appears that the risk of PCOS increases with obesity. Escobar-Morreale and colleagues (220) studied 113 consecutive women reporting for dietary treatment of overweightness or obesity. Of these, 28.3% were diagnosed as having PCOS, a prevalence markedly higher then the 5.5% reported among lean women by the same investigators (220). However, the effect of obesity on the prevalence of PCOS may be more modest if unselected women from the general population are studied. Studying 675 unselected women seeking a pre-employment exam, Azziz and colleagues (221) observed that the prevalences 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 BMIs of 35 to 40 kg/m^2 and >40 kg/m^2, a nonsignificant difference. Alternatively, the mean BMI of 746 PCOS patients diagnosed over a 15-year period of time rose steadily, paralleling the increase in the prevalence of obesity in the surrounding population. These data suggest that although the prevalence of PCOS is affected only modestly by the presence of obesity, the degree of obesity of PCOS patients has increased, similar to that observed in the general population, lending support to the concept that obesity in PCOS reflects to great extent environmental factors.

Even acknowledging differences in the periods of ascertainment and diagnostic criteria for PCOS between countries, this represents a large weight gap tipping the scales against American women with PCOS. The reasons for this supersizing of PCOS in the United States may be because of reductions in activity or differences in diet, and especially composition of diet (222). Nonetheless, weight gain after adolescence and abdominal obesity are associated with an increased prevalence of PCOS symptoms in non-US population studies (223).

Obesity further exacerbates metabolic and reproductive abnormalities in women with PCOS, and may bring out the PCOS phenotype in a susceptible population as family

studies suggest (224). For example, risk factors for glucose intolerance in women with PCOS include a family history of diabetes, age, obesity, and especially a centripetal fat distribution (188, 194, 209). One mechanism for this is that elevated insulin levels suppress hepatic production of SHBG levels. Thus, both obesity and insulin resistance lead to lower SHBG levels and higher bioavailable levels of androgens (185). Adipose tissue also is a source of aromatase, and may convert androgens into estrogens (including estrone and estradiol leading to inappropriate gonadotropin secretion and unopposed estrogen effects on the endometrium (225).

Overall, the prevalence of obesity in PCOS varies according to ethnicity and geographic location, and even in the United States, in the midst of an obesity crisis, between 40% and 50% of PCOS may be nonobese.

POLYCYSTIC OVARY SYNDROME: EXCLUSION OF OTHER ANDROGEN EXCESS AND RELATED DISORDERS

In addition to PCOS, there are numerous other disorders of androgen excess in women, including the adrenal hyperplasias (CAHs), syndromes of severe insulin resistance, and androgen-secreting neoplasms (ASNs); and disorders that have not been well identified (e.g., idiopathic hyperandrogenism) or that have the appearance of androgen excess (e.g., idiopathic hirsutism). These disorders account for approximately 10% to 30% of all patients with androgen excess (47, 91, 162, 226). There are also a number of other disorders that may result in ovulatory dysfunction, including hyperprolactinemia and thyroid abnormalities. Consequently, although PCOS has specific diagnostic criteria, other disorders associated with androgen excess and/or menstrual irregularities should be excluded (Table 5) (46, 47, 83, 84, 87, 89, 110, 226–231). In the following we review the specific disorders that may require exclusion when defining PCOS.

Thyroid Dysfunction

Thyroid disorders may have a profound impact on reproductive health in women (232, 233) and have been shown to adversely affect child development (234, 235). Overt thyroid dysfunction may induce menstrual dysfunction, yet thyroid disorders are less frequently associated with menstrual abnormalities than was previously believed (236, 237).

In one study of 873 consecutive untreated patients with androgen excess, containing 716 women with PCOS, only five were on thyroid replacement for hypothyroidism at the time of their initial visit, and one additional patient was diagnosed with hypothyroidism during the initial evaluation, for a total prevalence of thyroid dysfunction of 0.7% (47). Likewise, Carmina and colleagues (46) reported that only three (0.32%) of 950 patients with clinical hyperandrogenism had hypothyroidism.

Thyroid dysfunction was also found to be relatively uncommon among 467 hirsute women studied by Ferriman and Purdie (83). This prevalence is similar or less than that reported by other investigators in the general population of women of similar age, that is, 0.46% to 7.3% for clinical or subclinical hyper and hypothyroidism (238–242). Alternatively, one study found a higher prevalence of elevated thyroperoxidase or thyroglobulin antibodies in PCOS (27% of 175 patients compared with 8% of 168 controls) and eight patients compared with one control required thyroxine supplementation because of hypothyroidism (230). Whether the increased prevalence of autoimmune thyroiditis observed in this study will be confirmed in other populations remains to be demonstrated.

This data suggest that the prevalence of thyroid disorders is relatively rare, so exclusion of hypo- or hyperthyroidism may not be mandatory to make a diagnosis of PCOS in absence of other symptoms or signs of thyroid dysfunction.

Hyperprolactinemia

Hyperprolactinemia is a frequent cause of amenorrhea and infertility in clinical endocrinology and has been found in up to 30% of women with secondary amenorrhea. Beside the well-characterized prolactin secreting adenomas (representing up to 50% of secretory pituitary tumors), a large spectrum of functional hyperprolactinemia exists, some being secondary to known causes and others idiopathic. The different etiologies include physiologic situations (stress, exercise, pregnancy, lactation, stimulation of the breast and nipples), medication interfering with dopamine (representing the most common cause of hyperprolactinemia, including neuroleptics, antidepressants, sequential contraceptives, and antihypertensives), primary hypothyroidism, chronic renal failure, and even PCOS. In addition, hyperprolactinemia is associated with excess production of adrenal androgens in vivo and in vitro (243, 244), suggesting a potential mechanism whereby it may promote hyperandrogenism.

Early studies suggested a high prevalence of abnormalities in prolactin secretion in PCOS, although the abnormalities detected frequently required multiple sampling (227) or dynamic testing (245). Escobar-Morreale (229) reported on 109 consecutive PCOS patients of whom eight (7.3%) presented with supranormal serum prolactin levels on at least two different occasions. In four of these women, the hyperprolactinemia was because of macroprolactinemia, which occurs when the predominant form of prolactin in serum is a 150- to 170-kDa complex (macroprolactin, or big big prolactin), usually composed of prolactin and an IgG autoantibody. Although macroprolactin exhibits limited bioactivity in vivo, it retains immunoreactivity. Macroprolactinemia is estimated to account for 10% of hyperprolactinemia. Effective laboratory tests, based on polyethylene glycol precipitation, are available to detect macroprolactin. Testing for macroprolactin is generally reserved for those subjects with elevated serum prolactin levels, but whose clinical features or a response to treatment are not typical of true hyperprolactinemia, or

TABLE 5

Prevalence of thyroid dysfunction, hyperprolactinemia (Hi-Prl), androgen secreting neoplasms (ASNs), 21-hydroxylase deficient nonclassic adrenal hyperplasia (NCAH), and Cushing's Syndrome (CS) in patients with hyperandrogenism or polycystic ovary syndrome (PCOS).

Study	Reference	Total No. PCOS	No. with thyroid dysfunction	% with thyroid dysfunction	No. with Hi-Prl	% with Hi-Prl	No. NCAH	% NCAH	No. CS	% CS	No. ASN	% ASN
Ferriman and Purdie 1983	83	467	0	0.00%	4	0.90%[a]						
Conway et al., 1989	84	556			58	11.00%	10	1.80%[e]				
Luciano et al., 1984	227	150			25	16.70%						
O'Driscoll et al., 1994	162	350			1	0.30%	3	0.90%	0	0.00%	2	0.60%
Moran et al., 1994	226	250					5	2.00%	1	0.40%	2	0.80%
Balen et al., 1995	87	1871	0	0.00%	25	1.30%	19	1.00%			0	0.00%
Khoury et al., 1996	89	112			17	15.20%						
Romaguera et al., 2000	228	100					1	1.00%				
Azziz et al., 2004	47	873	6	0.70%	3	0.30%	18	16.50%	0	0.00%	2	1.83%
Escobar-Morreale et al., 2004	229	109			4	3.70%[b]						
Janssen et al., 2004	230	175	36	20.60%[c]								
Glintborg et al., 2004	231	340			6	1.80%[d]	2	0.60%	1	0.29%	1	0.29%
Carmina et al., 2006	46	950					41	4.30%			2	0.21%
Legro et al., 2006	110	626	45	7.20%								
Diamanti-Kandarakis & Danidis, 2007	100	634	4	0.60%	69	10.80%[f]	0	0%	0	0%	0	0%
Total		7563	87	1.15%	212	2.80%	99	1.31%	2	0.03%	9	0.12%

[a] 4 of 467 subjects had amenorrhea and galactorrhea suggestive of hyperprolactinemia.
[b] Another 3.7% also demonstrated macroprolactinemia.
[c] 11 of 168 controls (6.5%) also had thyroid dysfunction.
[d] 7 of 8 hyperprolactinemic PCOS patients demonstrated normalization of prolactin levels during extended follow-up.
[e] Denominator is entire androgen excess population (n = 711).
[f] All subjects with PRL>25ng/ml; mean value and SD was 31 ± 6.1 ng/mL.

Azziz. AE-PCOS Society report on PCOS phenotype. Fertil Steril 2009.

in those individuals who demonstrate wide variations in prolactin levels from one assay to another in a single patient (246). However, macroprolactinemic patients cannot always be differentiated from true hyperprolactinemic patients on the basis of clinical features alone, and a high degree of suspicion is required (247).

However, although subtle abnormalities of prolactin secretion may exist in PCOS, the more important issue at hand is whether patients with hyperandrogenic symptomatology should be screened for overt hyperprolactinemia, particularly in those patients with ovulatory dysfunction. In one large study of 873 consecutive untreated patients with androgen excess only two patients were found to be receiving bromocriptine for a previous diagnosis of hyperprolactinemia and one additional patient was diagnosed during her evaluation, for a total prevalence of hyperprolactinemia in this population of 0.3% (47). Similarly, in a study of 340 Caucasian women referred for hirsutism, supranormal values of prolactin were observed in eight; however, only one (0.3%) had prolactinoma, and the remaining were observed to normalize their prolactin levels in the following months (231). These prevalences are similar to that found by other investigators in hyperandrogenic women (87, 162, 226, 248–250).

Overall, although subtle abnormalities of prolactin secretion can be observed in a variable proportion of PCOS, its implications remain unclear. Furthermore, the prevalence of frank abnormalities among large populations of women presenting with hyperandrogenic symptoms is relatively low, generally <1%. Like thyroid dysfunction, the value of routinely screening all patients with suspected PCOS in the absence of other clinical symptomatology (e.g., galactorrhea, chronic headaches, and visual disturbances) may be questioned. However, as not all PCOS patients present with clinically obvious hyperandrogenism (e.g., hirsutism) and hyperprolactinemia may lead to secondary adrenal androgen excess, combined with the relatively low cost of the test, would suggest that the screening of patients with suspected PCOS for frank hyperprolactinemia may be cost-effective. Macroprolactinemia may need to be excluded in those PCOS patients with persistent elevations in prolactin.

The Congenital Adrenal Hyperplasias

The CAHs comprise a group of autosomal recessive disorders characterized by impaired cortisol biosynthesis because of inactivating mutations in the genes coding for steroidogenic enzymes. In these disorders, decreased cortisol biosynthesis leads to loss of negative feedback inhibition, increased ACTH secretion, and subsequent excessive adrenal androgen secretion. The clinical manifestations vary depending on the specific steroidogenic enzyme gene mutation, the severity of the inactivating mutation, and age at presentation (251). Typically, the classical forms present in childhood and are readily distinguished from PCOS. However, the clinical presentations for nonclassical CAH (NC-CAH) and PCOS share many features including oligo-amenorrhea, hirsutism, hyperandrogenemia, acne, and infertility (252). LH hypersecretion

and polycystic ovaries on ultrasound are considered to be laboratory features of PCOS. Nevertheless, women with NC-CAH may have one or both findings (252). Because of the nature of the symptoms, males with NC-CAH are usually asymptomatic and usually identified through family studies.

One major phenotypic difference between NC-CAH and PCOS revolves around insulin resistance and other features of the metabolic syndrome. Depending on the method used to ascertain insulin sensitivity, insulin resistance/hyperinsulinemia can be detected in approximately 50% to 75% of women with PCOS. However, it has been suggested that in women with CAH, the hyperandrogenemia also leads to a decrease in insulin sensitivity (253, 254), making distinction more difficult. In general, clinical assessment cannot be relied upon to distinguish PCOS from NC-CAH patients.

The most common form of CAH is 21-hydroxylase deficiency, secondary to mutations in the 21-OH (*CYP21*) gene. *CYP21* is located in the class III HLA region on the short arm of chromosome 6 where it lies in close proximity to a nonfunctional highly homologous pseudogene, *CYP21P*. Most mutations associated with CAH are gene conversion events in which the functional gene, *CYP21*, has acquired deleterious sequences from *CYP21P*. Although over 40 mutations have been reported, approximately 10 mutations account for most affected alleles. Mutations typically associated with NC-CAH are P30L, V281L, and P453S. About two-thirds of patients with 21-OH-deficient NC-CAH carry an allele for a severe mutation (i.e., are "compound heterozygotes"), and, in general, the phenotype correlates loosely with the specific *CYP21* mutations (255, 256). Many NC-CAH patients carry a severe mutation on one allele and a mild mutation on their other. Although commonly we define these individuals as "compound heterozygotes," genetically this term refers to individuals who carry two different types of mutations on each allele. Consequently, patients with NC-CAH can be also be "compound heterozygotes" if they carry two different mild mutations, such as V281L on one allele and P453S on their other.

Twenty-one hydroxylase-deficient CAH is endocrinologically recognized by the exaggerated secretion of the immediate Δ^4 precursor 17-hydroxyprogesterone (17-HP), either basally or more commonly after ACTH stimulation. When classical CAH is suspected in infants and toddlers, random hormone concentrations may be sufficiently elevated to confirm the diagnosis and often exceed 100 ng/mL (10,000 ng/dL). However, stimulation with synthetic ACTH, 0.25 mg administered by intravenously or intramuscularly, may be helpful to establish or exclude the diagnosis of NC-CAH. In 21-OH-deficient NC-CAH, correlation of stimulated 17-HP responses with molecular genotype has defined responses >10 ng/mL to 12 ng/mL (1,000–1,200 ng/dL) as consistent with NC-CAH, 5 to 10 ng/mL (500–1,000 ng/dL) as suggestive of heterozygosity for *CYP21* mutations, and <3 to 5 ng/mL (300–500 ng/dL) to be within normal limits (257). However, 50% of *CYP21* mutation carriers (heterozygotes) demonstrate ACTH-stimulated responses within the normal

range (258). ACTH-stimulated 17-HP values >200 ng/mL (>20,000 ng/dL) are generally consistent with classical CAH, and not NC-CAH. However, we should note that the diagnosis of NC-CAHl versus classical CAH is clinical and based on the age at presentation. Children with classical forms of CAH (salt-losing and simple virilizing) generally present at the birth or early infancy with varying signs of genital ambiguity, whereas NC-CAH present later in life, generally at the puberty but sometimes decades later.

Screening for 21-OH-deficient NC-CAH can be accomplished by a basal serum 17-HP level, which, if >2 ng/mL or 3 ng/mL (depending on the desired sensitivity and false positive rate), suggests the possibility of NC-CAH. An acute ACTH stimulation test measuring the 17-HP response is then required to establish the diagnosis. The screening 17-HP should be obtained in the follicular or preovulatory phase, as 50% of normal subjects will have basal 17-HP levels above the cutoff value when measured in the luteal (postovulatory) phase. This screening method detects about 90% of 21-hydroxylase deficient NC-CAH patients (259, 260).

Decreased activity of 3β-HSD because of mutations in the *HSD3B2* gene, mapped to chromosome 1p11–13, is a second type of CAH. This enzyme converts steroids in the Δ^5 pathway to those in the Δ^4 pathway. It has been recognized that women with PCOS often manifest increased ACTH-stimulated responses of steroids in the Δ^5 pathway, that is, 17-hydroxypregnenolone (17-PREG) and DHEA (267, 268). This finding led to the speculation that NC-CAH due to 3β-HSD deficiency was common among women with hyperandrogenism (261–264). With the identification of the *HSD3B2* gene, phenotype–genotype correlation established that NC-CAH, because of *HSD3B2* mutations, is rare (143, 265). Correlation of molecular genotype analyses with ACTH-stimulated hormone concentrations indicated that patients with mutations on both *HSD3B2* alleles have ACTH-stimulated 17-PREG and DHEA concentrations >10 standard deviations above the range observed for healthy control subjects (265, 266). Mildly elevated ACTH-stimulated 17-PREG and DHEA concentrations (>2–3 standard deviations) are often found among women who fulfill the diagnostic criteria for PCOS (144).

The least common form of CAH due to mutations of the 11β-hydroxylase (*CYP11B1*) gene located in the chromosome 8q24.3 region. This enzyme converts 11-deoxycortisol to cortisol. Nonclassical CAH because of a mutation in the *CYP11B1* gene is extremely rare (267).

Because the CAHs are autosomal recessive disorders, family history is often negative. This contrasts to the family history obtained from PCOS women where approximately 35% of mothers and 40% of sisters are also affected (36).

The prevalence of NC-CAH, particularly that because of 21-OH deficiency, differs according to locale and ethnicity. Among American White and Hispanic hyperandrogenic women, prevalence is reported to be 1% to 2%, whereas prevalences reported from France, Italy, and Canada range from 4% to 6% (268). Studies from Israel, India, and Jordan have reported prevalences of 6% to 10%. Using results of quantitative hormone concentrations and HLA-B genotype results, the prevalence of 21-OH-deficient NC-CAH was 3.7% among Ashkenazi Jews, 1.9% among Hispanics, 1.6% among Yugoslavs, and 0.3% among Northern Italians (269). Specific mutations demonstrate a higher prevalence in certain ethnic groups. For example, large deletion is prevalent in the Anglo-Saxons; the V281L mutation associated with NC-CAH is prevalent in Ashkenazi Jews, the R356W mutation is prevalent in the Croatians, the intron 2 splicing mutation is prevalent in the Iranians and Yupik-speaking Eskimos of Western Alaska, and the Q318X mutation is prevalent in East Indians (270). Overall, NC-CAH appears to be uncommon among African Americans.

Overall, 21-OH-deficient NC-CAH is one of the most common autosomal recessive disorders of man, affecting between 1% and 10% of hyperandrogenic women. Clinical features do not distinguish PCOS and NC-CAH patients. Routine screening for 21-OH-deficient NC-CAH using a basal 17-HP level is recommended, more so in high-risk populations (e.g., Ashkenazi Jews and Europeans of Latin descent). Alternatively, 3β-HSD and 11β-hydroxylase-deficient NC-CAH are very rare, and should not be screened for routinely in patients with suspected hyperandrogenism or PCOS.

Cushing's Syndrome

Cushing's syndrome may be ACTH dependent (e.g., pituitary Cushing's and ectopic ACTH-secreting tumors) or independent (adrenal neoplasms). Cushing's syndrome, secondary to adrenal neoplasms, is discussed further in the next section (see below). Overall, in women with Cushing's syndrome menstrual irregularities are seen in 80% to 100%, hirsutism in 60% to 100%, and acne is present in 40% to 50% (271–274). In patients with Cushing's syndrome hirsutism arises either from the exaggerated secretion of adrenal androgens in response to excess ACTH stimulation, which usually results in mild hair growth, or because of direct excessive secretion of adrenal androgens by an adrenocortical carcinoma, if which case hair growth may be more severe (275).

Consequently, when considering the presence of rapid weight gain, oligo-amenorrhea, signs of hyperandrogenism and possible impaired glucose tolerance and hypertension, one should exclude the possibility of Cushing's syndrome and other sources of androgen excess secretion from the ovaries and adrenal glands (274, 276, 277). If these are present in association with hypertension, myopathy, thinned skin, easy bruisability, moon-facies, and myopathy, a diagnosis of cortisol excess should be considered (278). Nonetheless, the prevalence of Cushing's syndrome in hyperandrogenic women appears to be very low, well below 1% (46, 47, 162, 204, 226). Other than maintaining a high degree of clinical suspicion, routine screening for Cushing's syndrome is not warranted in patients presenting with probable PCOS, because of the very low incidence of the disorder.

Ultrasonographic studies have noted that the morphologic appearance of the ovary in premenopausal women with Cushing's syndrome may be either normal or bilaterally polycystic (274). A report noted that 6 of 13 women with Cushing's syndrome, including one with an ectopic ACTH syndrome, and two with adrenal adenomas, had ovarian ultrasonographic morphology consistent with polycystic ovaries with a smaller mean ovarian volume than that seen in concurrently studied women with PCOS. All 13 women with Cushing's syndrome had features of hyperandrogenism while 70% had menstrual irregularity (274). Unlike women with PCOS, many women with Cushing's syndrome have hypothalamic–pituitary suppression of gonadotropin secretion, often leading to a reduction of serum estradiol, LH, and FSH levels (279, 280). An elevation of T in the blood has been reported in one half of patients with Cushing's syndrome (279, 280).

The clinical and biochemical diagnosis of suspected Cushing's syndrome is often a challenge to clinicians. The low-dose dexamethasone suppression test has been found to be of value in only 70% of patients in a large study of 80 patients with Cushing's syndrome (281). Biochemical screening including measurement of the 24-hour urinary free cortisol should take into account that some patients have episodic increases in cortisol secretion (278). Midnight salivary cortisol determinations may be helpful (282). The presence of atypical presentations in Cushing's syndrome including those seen in PCOS and pseudo-Cushing's should alert the endocrinologist to carefully evaluate any woman with PCOS who have developed some of the features seen in Cushing's syndrome, other than menstrual dysfunction and hyperandrogenism (281, 282).

Overall, the low rate of Cushing's syndrome in the population as a whole, and particularly among patients with suspected PCOS, precludes recommending the routine screening for Cushing's syndrome as part of the standard evaluation of these patients. However, screening for Cushing's syndrome, such as by measurement of a 24-hour urine free cortisol level, should be used liberally to study those patients with specific and suggestive symptomatology.

Androgen-Secreting Neoplasms

Although rare, ASNs of the adrenal or ovary may initially mimic the hyperandrogenism and menstrual dysfunction seen in PCOS. A rapidly progressive onset of hyperandrogenism, particularly in the postmenopause, and/or the development of frank virilization or masculinization, however, suggests a neoplastic process. This latter may include severe hirsutism or acne, temporal or male pattern balding, laryngeal hypertrophy, increased muscle mass, decreased breast size, and loss of feminine body contours, increased libido, and the hallmark of virilization, that is, clitoral hypertrophy. A diagnosis of a virilizing neoplasm may at times also be suggested by noting the clinical history in association with the finding of a palpable abdominal or pelvic mass.

Ovarian androgen-secreting neoplasms occur in approximately 1/300 to 1/1,000 of hyperandrogenic patients (47,

161, 226, 249). They are usually palpable on pelvic exam and/or are associated with a unilateral ovarian enlargement on ultrasound. Functional ovarian tumors may include Sertoli-Leydig cell tumors, which are 95% unilateral, and which rarely metastasize. Some granulosa cell tumors (<10%) may also produce excessive androgens (283), and a useful marker may be the measurement of inhibin. Although large ovarian dermoid cysts may be easily palpable and present in increased frequency in PCOS, they are unlikely to cause virilization (284).

Androgen-producing tumors of the adrenal are less common than ovarian neoplasms, and include adenomas and carcinomas (248). Adrenal carcinomas are usually associated with the development of Cushingoid features, and can be diagnosed as a large (>6 cm) irregular adrenal mass on adrenal computerized tomography (CT) scanning. Unfortunately, the prognosis of patients with adrenocortical carcinomas is poor. Although most virilizing adrenal adenomas are localized with these imaging studies, the finding of an isolated adrenal nodule or incidentaloma (1.7% population) may occasionally necessitate selective venous catheterization for diagnosis (285, 286).

Diagnosis of an ASN is frequently suggested by biochemical evidence of markedly increased levels of serum total T (>150–200 ng/dL); an associated elevated DHEAS level >600–700 μg/dL is found in most T-secreting ASNs. However, it should be noted that basal androgen levels are of limited predictive value. As many as 50% of ASNs do not have levels of total T or DHEAS above these cutoff values (147, 248, 287, 288). In turn, in one study of 478 consecutive hyperandrogenic patients, over 90% of women with persistently elevated total T levels (two values >250 ng/dL) did not have an ASN (289). Furthermore, many patients with persistently and severely elevated levels of circulating total T may actually suffer from a syndrome of severe insulin resistance (see below). The utilization of adrenal and gonadal stimulation and suppression tests has been found to be unreliable as a means of differentiating an ASN from a functional etiology, and an ovarian versus an adrenal source, in the instance of small or occult neoplasms (248, 288).

Overall, all patients presenting with hyperandrogenic symptomatology should be screened for ASNs, albeit screening is primarily clinical. If history or physical exam suggests rapid onset or virilization, or androgen levels are persistently and markedly abnormal, further diagnostic testing, primarily radiologic or sonographic, may be instituted. It should be noted that overreliance on androgen levels as a screening tool will lead to significant false positive rates.

Syndromes of Severe Insulin Resistance and Hyperandrogenism

Insulin resistance is associated with a wide variety of markedly heterogeneous clinical disorders, either inherited or acquired, which may result in acanthosis nigricans, ovarian hyperandrogenism, and ovulatory dysfunction. These include

the type A insulin resistance syndrome (primarily affecting lean women and resulting from defects of the insulin receptor), type B (resulting from an autoimmune process affecting the insulin receptor), and type C (a variant of type A, characterized by the presence of marked acanthosis, hyperandrogenism, insulin resistance, obesity, and the absence of insulin receptor defects) insulin resistance syndromes. More rare syndromes include leprechaunism, the Rabson-Mendenhall Syndrome, and a heterogeneous group of lipodystrophic syndromes (290).

Hyperandrogenic patients with the type C insulin resistance syndrome, are also described as suffering from the hyperandrogenic-insulin resistant-acanthosis nigricans (HAIR-AN) syndrome. In addition, some patients with types A and B may also present with phenotypic features suggestive of the HAIR-AN syndrome. Although there is controversy concerning the differentiation between PCOS and many patients with the HAIR-AN syndrome, most investigators recognize a distinct subgroup of hyperandrogenic patients with severe metabolic abnormalities (291, 292). In a recent study, approximately 3% of hyperandrogenic women were observed to suffer from this disorder (47).

Patients with syndromes of severe insulin resistance often demonstrate ovarian hyperthecosis, a pathologic finding characterized by islands of hyperplastic luteinized theca cells located throughout the stroma and the presence of relatively few and small atretic follicles (293), and circulating LH and FSH levels may be normal to low (4–8 mIU/mL) because of negative feedback from the extremely high circulating levels of T. Consequent to the presence of ovarian hyperthecosis many patients with syndromes of severe insulin resistance are severely hyperandrogenic, and may even present with a moderate degree of virilization. It should be noted that previously ovarian hyperthecosis was considered a separate disease entity; however, current evidence suggests that this pathologic finding is most frequently observed in hyperandrogenic patients with significant degrees of hyperinsulinemia, such as those with the HAIR-AN syndrome. These patients also exhibit extensive acanthosis nigricans, a velvety hyperpigmented change of the crease areas of the skin, and achrocordons (skin tags). Some of these patients may also demonstrate variable degrees of lipodystrophy.

Because of the severe degree of insulin resistance many of these patients demonstrate at the time of the initial evaluation, or will develop, glucose intolerance or type 2 DM, hypertension, and dyslipidemia, particularly suppressed HDL-C and hypertriglyceridemia, and CVD. Overall, both morbidity and mortality in these patients is quite significant, and these women require intensive counseling, follow-up, and treatment of both their hyperandrogenic and metabolic abnormalities.

Although exact diagnostic guidelines have yet to be elucidated, it appears that the disorder can be diagnosed by the presence of extremely high circulating levels of insulin, generally >80 μU/mL in the fasting state, and/or >300 μU/mL following a 2- or 3-hour oral glucose tolerance test (291, 292). In the early stages of the disorder, particularly in children or adolescents, their glucose levels are relatively normal. Nonetheless, over time many of these patients will develop progressive islet cell failure with the development of type 2 DM.

In summary, some hyperandrogenic patients, possibly as high as 3%, suffer from the HAIR-AN syndrome, primarily characterized by extreme degrees of insulin resistance and hyperinsulinism. Patients also exhibit extensive acanthosis nigricans and may also demonstrate varying degrees of lipodystrophy. These patients should be distinguished from women with PCOS, a disorder that is also associated with insulin resistance, although to a much lesser degree than that of patients with the HAIR-AN syndrome. Diagnosis can be achieved by measuring fasting or postprandial insulin levels.

Idiopathic Hirsutism

Using the NIH 1990 criteria for PCOS, idiopathic hirsutism (IH) can be strictly defined as the presence of hirsutism, in the presence of regular ovulation and in the absence of hyperandrogenemia (294). Using this definition approximately 5% to 7% of hirsute patients will have IH (46, 47, 91, 107). Using the Rotterdam 2003 criteria IH patients have the above features and including the absence of polycystic ovaries. Undoubtedly this will reduce the prevalence of IH further.

Practically speaking, IH is a diagnosis of exclusion, as is PCOS, and often it is difficult to fully differentiate the two disorders. The diagnosis of IH requires assessment of androgen levels, and it is assumed that some or all of women with IH demonstrate excessive 5α-reductase activity of the hair follicle, which results in hirsutism despite "normal" circulating androgens (295). In evaluating the hirsute apparently eumenorrheic patient for IH (or PCOS) it is also critical to confirm the presence of normal ovulatory function (e.g., by using a basal body temperature chart and/or luteal progesterone measurements). Up to 40% of these individuals are actually oligo-ovulatory if studied more carefully (46, 47, 91, 107, 296).

When strictly defined, IH is present in 5% to 7% or less of all hirsute patients seen. Patients with IH should demonstrate normal long-term ovulation, normal androgen levels, and normal ovarian morphology.

SUMMARY

A thorough review of current data, emphasizing larger epidemiologic and phenotypic studies has indicated the following:

1) 1. *At-risk populations:* the "at-risk" populations for PCOS include women with:
   a) *Androgenic dermatologic signs*, most notably hirsutism. Current data would suggest that although a majority of patients with hirsutism have PCOS, only between 20% and 40% of patients with

persistent acne-only and 10% of those with alopecia-only will demonstrate the disorder.

b) *Menstrual dysfunction*, such that between one-quarter and one-third of all women with oligo-amenorrhea or menstrual dysfunction have PCOS.

c) *Oligo-ovulatory infertility.*

d) *Polycystic ovaries*, with about one-fifth of unselected reproductive-aged women with this morphologic finding having PCOS.

e) *Insulin resistance and hyperinsulinism*, who are at greater risk for developing the disorder, at least as observed in diabetic populations; this association is less certain for women with the metabolic syndrome.

2. *Features of PCOS:* PCOS remains a heterogeneous syndrome, with multiple and variable features, which may include:

a) *Menstrual and ovulatory dysfunction*, with overt oligomenorrhea present in 60% to 75% of affected women, although this prevalence may be lower if the Rotterdam 2003 rather than NIH 1990 diagnostic criteria are used. Because some PCOS patients may have a history of "regular menses" despite being oligo-ovulatory, patients who present with clinical evidence of hyperandrogenism but apparent eumenorrhea should have their ovulatory function evaluated further.

b) *Hyperandrogenemia*, with approximately 70% of PCOS patients demonstrating elevated free T levels, at least when high-quality assay methods are used and patients are diagnosed by the NIH 1990 criteria. The measurement of total T, A4, and DHEAS add a limited incremental amount to the diagnostic value of the androgen screen. The serum measurements of androgens, including free T, should be used only as an adjuvant tool for the diagnosis of hyperandrogenic disorders, and never as the sole criterion for diagnosis or in lieu of the clinical assessment. Basal gonadotropin measurements are of little value for the routine diagnosis of PCOS.

c) *Hirsutism,* which affects approximately 65% to 75% of affected patients of the White, Black, and Southeast Asian races, although likely to be less among women of the Mongolian or Far East extraction. Less prevalent is the sole presence of acne or alopecia, although more accurate studies are required to define the prevalence of these features in PCOS patients.

d) *Polycystic ovaries*, with this morphologic ovarian alteration found in 75% to 90% of women with the clinical diagnosis of the disorder.

e) *Insulin resistance and hyperinsulinism*, which is present in 50% to 70% of patients.

3. *Disorders to exclude:* Consistent with the fact that PCOS is a syndrome, no single test is available to establish its diagnosis, and various disorders may present in a similar fashion, the diagnosis of this disorder may require exclusion of the following:

a) *Hypo- or hyperthyroidism or hyperprolactinemia*; although this is not mandatory to make a diagnosis of PCOS in the absence of other symptoms or signs of thyroid dysfunction. However, despite their low prevalence the low cost of these tests would suggest that the screening of patients with suspected PCOS for thyroid dysfunction or hyperprolactinemia may still be cost-effective.

b) *21-hydroxylase-deficient NC-CAH*, with routine screening using a basal 17-hydroxyprogesterone level recommended in all patients presenting with signs or symptoms suggestive of androgen excess, and particularly in high-risk populations (e.g., Ashkenazi Jews and Europeans of Latin descent). Alternatively, the routine screening for 3β-HSD or 11β-hydroxylase deficient NC-CAH is not recommended.

c) *Cushing's syndrome*, although its very low rate among patients with suspected PCOS precludes recommending the routine screening for this disorder as part of the standard evaluation of these patients.

d) *Androgen-secreting neoplasms*, such that all patients presenting with hyperandrogenic symptomatology should be screened for these tumors, although the initial screening should be primarily clinical.

e) *The HAIR-AN syndrome*, characterized by severe insulin resistance and hyperinsulinism, possibly affecting up to 3% of androgen excess patients.

f) *Idiopathic hirsutism*, which is present in 5% to 7% or less of all hirsute patients seen, and should be diagnosed using strict criteria including normal long-term ovulation, normal androgen levels, and normal ovarian morphology.

g) Hyperandrogenic patients who do not fulfill the criteria for PCOS or for other well-known androgen excess disorders (e.g., women with the so-called "idiopathic hyperandrogenism") remain to be better characterized, and may represent a form of PCOS.

A Phenotypic Approach to Defining PCOS: Task Force Recommendations

The Task Force considered all data summarized above in arriving to its conclusions and recommendations regarding the phenotype of PCOS. These include the following:

a) *That PCOS is a hyperandrogenic disorder*: the Task Force felt that PCOS was above all a disorder of androgen biosynthesis, utilization, and/or metabolism in women. As such, with currently available evidence the diagnosis of PCOS should not be established without evidence of either clinical or biochemical hyperandrogenism. Although the exact measures for these may vary, the Task Force felt that the most reliable indices of this feature included hirsutism and free T levels.

Nonetheless, the Task Force also recognized that for hirsutism the cutoff value is unclear (6) and the interobserver variation, at least when using visual scales, significant (297). Likewise, the methods for measuring free T levels vary significantly, with column chromatography and immune assay, GC-MS or LC-MS, or equilibrium dialysis preferred, but not guaranteeing accuracy. Finally, the Task Force also recognized that although many patients with PCOS would have evidence of acne or androgenic alopecia, these could not be used reliably as clinical signs of hyperandrogenism.

b) *That the ovarian morphology should be considered when establishing the diagnosis*, as polycystic ovaries are found in the majority, although not all, women with PCOS: the Task Force recognized that 70% to 90% of women with PCOS would demonstrate a polycystic ovarian morphology on ultrasound, although they also recognized that the false positive rate is high with up to one-quarter of unselected reproductive aged women demonstrating this ovarian morphology. The Task Force also noted that the diagnosis of polycystic ovaries required the use of clear and strict criteria. Consistent with recommendation a) above, the Task Force felt that those women with polycystic ovaries, but no evidence of clinical or biochemical hyperandrogenism, the diagnosis of PCOS is less certain, regardless of the presence of concomitant ovulatory dysfunction.

c) *That ovulatory dysfunction is a prominent, but not universal feature, of PCOS:* the Task Force recognized that some patients with PCOS may demonstrate regular ovulation at the time of their evaluation, the so-called "ovulatory PCOS" (71, 108). However, the Task Force noted that patients with "ovulatory PCOS" constituted a minority of the PCOS population, and had less severe androgenic and metabolic features than anovulatory women with PCOS. The Task Force also recognized that there exists little data regarding the long-term maintenance of ovulation in women with ovulatory PCOS, whether these patients were intermittently anovulatory to a greater degree than normal, and that ovulatory function in PCOS often improved as patients neared the perimenopause.

d) *That eumenorrhea in the presence of dermatologic features suggestive of hyperandrogenism (e.g. hirsutism) could not reliably be used to establish the presence of normal ovulation:* the Task Force recognized that in patients with no clinical signs of hyperandrogenism a history of regular predictable vaginal bleeding could be used as strong evidence of normal ovulation. Alternatively, a history of "regular" menstrual cycles in patients who demonstrated hyperandrogenic features (e.g., hirsutism) could not be relied upon as evidence of normal ovulation, with up to 40% of these women having oligo-anovulation. In these patients, confirmation of ovulatory function by more objective means is required.

e) *That other well-defined disorders that could result in ovulatory dysfunction, polycystic ovaries, or clinical or biochemical hyperandrogenism had to be excluded:* the Task Force recognized that the initial screening for ASNs and Cushing's syndrome is primarily clinical, and that the prevalence of thyroid dysfunction, hyperprolactinemia, or premature ovarian failure among patients with frank hyperandrogenism, or of 21-hydroxylase-deficient NC-CAH in certain ethnic groups (e.g., those of Anglo-Saxon descent) was relatively low. Consequently, the Task Force recognized the validity of considering the prevalence of these disorders in the population being studied, and potentially limiting the disorders excluded.

f) *Recognition of associated abnormalities:* the Task Force noted that the presence of obesity, insulin resistance, and hyperinsulinism, and increased LH levels or an LH/FSH ratio, while observed in a significant fraction of patients, should not be used as part of the definition of PCOS.

PRINCIPAL RECOMMENDATIONS OF THE AE-PCOS TASK FORCE

It is the view of the AE-PCOS PCOS Phenotype Task Force that there should be acceptance of the original NIH/NICHD criteria of 1990 with some modifications, taking into consideration the opinion expressed in the proceedings of the 2003 Rotterdam conference (see Figure 1). Considering the four features of ovulatory dysfunction, hirsutism, hyperandrogenemia, and polycystic ovaries, the Task Force identified nine phenotypes that could be considered as being PCOS considering current evidence (Fig. 1). However, the Task Force recognizes that clinical features may not be constant even in a single patient and can be modified by changes in body weight and lifestyle choices. In addition, the Task Force also recognizes that there may be a number of women who have features suggestive of PCOS, but who do not fulfill the criteria; clearly, these women and their symptoms should be treated accordingly, regardless of whether a diagnosis of PCOS is established or not.

A principal conclusion of this report is that PCOS should be first considered a disorder of androgen excess or hyperandrogenism. The absence of clinical or biochemical hyperandrogenism in the untreated state, or in women under the age of 40 years, makes a diagnosis of PCOS less certain, regardless of the presence of ovulatory or menstrual dysfunction or the presence of polycystic ovaries. Overall, at the present time, in the Task Force's assessment, women with oligo-amenorrhea and polycystic-appearing ovaries on ultrasonography but no evidence of hyperandrogenism may not have PCOS and should be considered as having a different disorder. However, the Writing Committee acknowledged that some of its members considered the possibility that there are forms of PCOS without overt evidence of hyperandrogenism (see Minority Report below), but recognized that more data are required before validating this supposition. Alternatively, the diagnosis of PCOS in women who have evidence of hyperandrogenism and polycystic ovaries, in the presence of ovulatory cycles, appears justified based on current data.

Proposed criteria for the diagnosis of the PCOS. [a]Possibly including 21-hydroxylase deficient nonclassic adrenal hyperplasia, androgen-secreting neoplasms, androgenic/anabolic drug use or abuse, Cushing's syndrome, the Hyperandrogenic-Insulin Resistance-Acanthosis Nigricans syndrome, thyroid dysfunction, and hyperprolactinemia.

ANDROGEN EXCESS AND POLYCYSTIC OVARY SYNDROME SOCIETY: CRITERIA FOR THE DIAGNOSIS OF THE POLYCYSTIC OVARY SYNDROME

1- Hyperandrogenism: Hirsutism and/or hyperandrogenemia

and

2 – Ovarian Dysfunction: Oligo-anovulation and/or polycystic ovaries

and

3 - Exclusion of other androgen excess or related disorders[a]

Azziz. AE-PCOS Society report on PCOS phenotype. Fertil Steril 2009.

The aim of this report was to yield criteria based on currently available data to guide research and clinical diagnosis, and future investigations. In addition, the Task Force recognizes that the definition of this syndrome will evolve over time to incorporate new research findings. As our understanding of the molecular and genetic aspects of PCOS advances, it is unlikely that the definition of PCOS will remain unchanged, but will be expanded, contracted, or divided to incorporate new findings. The Task Force also recognizes that there may be a number of women who have features suggestive of PCOS, but who do not fulfill the criteria; clearly, these women and their symptoms should be treated accordingly, regardless of whether a diagnosis of PCOS is established or not. In addition, the Task Force recognizes that need to potentially modify the syndrome we define as PCOS as new data is made public. The Task Force felt that the diagnosis of PCOS should not be made lightly in view of its potential life-long health and insurability implications.

Finally, the Task Force recognized that the applicability or value of the specific definition of PCOS could vary according to the specific concerns being addressed in an individual study or by individual practitioners. For example, the definition proposed by the AE-PCOS Society relies heavily on the relationship of hyperandrogenism with metabolic dysfunction. Thus, if the ultimate clinical or investigational concern were to be the long-term metabolic or cardiovascular morbidities of patients with PCOS, defining the disorder using the NIH 1990 or the AE-PCOS Society criteria would seem more appropriate. If the interest were to determine the genetics underlying this complex trait, then a more restrictive criteria, such as the NIH 1990, or even more limited to one or tow specific phenotypes (see Table 1) may be necessary to maximize homogeneity of the population. Alternatively, if

the interest is determining the risk for anovulatory infertility and or hyperstimulation during ovulation induction, then broader criteria such as that proposed by Rotterdam 2003 may be appropriate (298).

Although it may seem to some of the readers futile to propose a third criteria for defining PCOS, considering the current climate of controversy, it is important to note that we believe that the sole exercise of considering all published data and rationally presenting each of the different phenotypic features separately encourages the development of a clearer and more logical approach to uncovering the true nature of this pervasive disorder, based on the individual phenotypic features. This is in line with the emerging field of "phenomics," increasingly used in the study of complex genetic traits such as the metabolic syndrome and lipodystrophy (299, 300). Phenomics can be defined as integrated multidisciplinary research to understand the complex consequences of genomic variation through systematic evaluation and cataloguing of standardized phenotypes. This approach, and the use of increasingly sensitive phenomic tools, has the additional potential for uncovering "early" or "intermediate" phenotypes that may be valuable in establishing the natural history and predictability of the disorder. Alternatively, insensitive, qualitative, subjective, and vaguely defined phenotypes are important barriers to the development of a greater understanding of the molecular biology and genetics underlying these disorders, including PCOS (301).

MINORITY REPORT

Notwithstanding the above recommendations, the Writing Committee acknowledged that some members of the Task Force disagreed with the strong emphasis placed on

hyperandrogenism in the report. For example, these investigators recognized the high degree of inaccuracy of many currently and clinically available androgen assay systems. Numerous studies have shown that routine platform assays for T and other androgens do not correlate with gold standard assays such as equilibrium dialysis and LC-MS (302). The vast majority of clinical practitioners do not have access to reliable assays of T, the correlation between different commercial assays is extremely poor, and correction with measurement of androgen binding proteins such as SHBG does not overcome the errors introduced. Therefore, one of the cardinal measures on which the AE-PCOS Society definition is based is unreliable in standard clinical practice and may exclude patients with PCOS because the assay results are reported to be in the "normal" range, or alternatively may include unaffected patients because of overestimation of T levels. Even in optimal circumstances, the relationship between the ovarian production of androgens and their circulating levels is largely unexplored.

Use of hirsutism as an alternate to T is unreliable in East Asians and other ethnic groups, whereas reliance on the finding of hirsutism in women of particular ethnic groups may include women who do not have PCOS. The assessment of hyperandrogenism is therefore at least as subjective and unreliable as ovarian ultrasound scanning in the current environment. As a result, some women with PCOS, and who may be at risk for metabolic disturbances, may be missed by overreliance on measures of hyperandrogenism. Consequently, some members of the Task Force considered women with oligo-ovulation and polycystic ovaries, but without overt evidence of hyperandrogenism (phenotype J in Table 1) to most likely represent a form of PCOS, reverting the criteria to that already recognized by the Rotterdam 2003 definition. However, these investigators also recognized, as did the Task Force as a whole, that more data was required before validating this supposition. For example, a recent study noted that women with oligo-anovulation and polycystic ovaries, but without evidence of hyperandrogenism (n = 66) had basal insulin levels, the principal metabolic parameter assessed, similar to controls (n = 118) and lower than patients with hyperandrogenemia and oligo-anovulation, with (n = 246) or without (n = 27) polycystic ovaries, or those with hyperandrogenemia and polycystic ovaries but without oligo-anovulation (n = 67) (303).

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