POSITION STATEMENT: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society Guideline

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Ricardo Azziz, Enrico Carmina, Didier Dewailly, Evanthia Diamanti-Kandarakis, Hector F. Escobar-Morreale, Walter Futterweit, Onno E. Janssen, Richard S. Legro, Robert J. Norman, Ann E. Taylor and Selma F. Witchel

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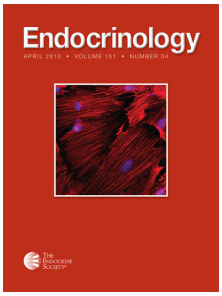

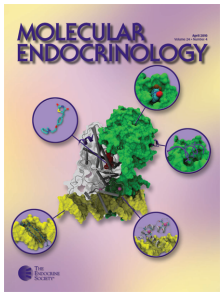

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POSITION STATEMENT:

CRITERIA FOR DEFINING POLYCYSTIC OVARY SYNDROME AS A PREDOMINANTLY HYPERANDROGENIC SYNDROME: AN ANDROGEN EXCESS SOCIETY GUIDELINE

Task Force on the Phenotype of the Polycystic Ovary Syndrome
of The Androgen Excess Society

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Abbreviated title: The AES criteria for defining PCOS

Words: 3633

ABSTRACT

Objective: The Androgen Excess Society (AES) charged a Task Force to review all available data and recommend an evidence-based definition for Polycystic Ovary Syndrome (PCOS), whether already in use or not, to guide clinical diagnosis and future research.

Participants: Expert investigators in the field.

Evidence: Based on 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.

Consensus Process: The Task Force drafted the initial report, following a consensus process via electronic communication, which was then reviewed and critiqued by the AES 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.

Conclusions: Based on the available data, it is the view of the AES Task Force on the Phenotype of PCOS that there should be acceptance of the original 1990 National Institutes of Health criteria with some modifications, taking into consideration the concerns expressed in the proceedings of the 2003 Rotterdam conference. A principal conclusion that PCOS should be firstly considered a disorder of androgen excess or hyperandrogenism, although 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.

61 **Abstract**: 245 words

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The disorder that eventually would be known as the polycystic ovary syndrome (PCOS) was initially described by Stein and Leventhal in 1935 (1). 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 features. However, establishing a clear, contemporaneous, and evidence-based definition for this syndrome has important clinical and investigational implications. Nonetheless, the definition of PCOS has continued to generate significant controversy (2-4).

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) (5). Furthermore, it has important familial implications, principally, but not exclusively, for her sisters and daughters (6-8). 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 also essential to guide current and future research. The inclusion of patients whose definition, characterization, and selection criteria are unclear continues to plague the PCOS scientific literature. This issue is becoming critical as the field moves to the establishment of larger clinical trials, and to studies of the molecular biology and genetic nature of the disorder. In addition, definitions not based on clear-cut evidence have the potential effect of discouraging future and needed research into the nature of the disorder, its breadth and its phenotype. Consequently, a contemporaneous definition based on what is currently known will benefit future investigation in this area.

The Androgen Excess Society (AES) 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, non-classic adrenal hyperplasia, idiopathic

hirsutism, and premature adrenarche. The Society was founded in 2000, and currently has over 200 members principally composed of investigators whose primary focus is the study of androgen excess disorders and polycystic ovary syndrome. The Board of Directors of the Society appointed the Task Force on the Phenotype of PCOS and charged it with reviewing all current data concerning the phenotype of PCOS to answer the query: 'What different component phenotypes (features) constitute PCOS, based on the available published and peer-reviewed data, assuming that long-term morbidity is the anchor?' The following summarizes the results of this Task Force's yearlong investigation.

1) PROCESS

The Board of Directors of the AES 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 (cross-references and those published in 2006) were also considered. Emphasis was placed on those studies which included greater than 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 in order to more clearly define common phenotypes or features irrespective of the definition used.

The Task Force drafted the initial report, following a consensus process via electronic communication, which was then reviewed and critiqued by the AES 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.

2) CURRENT DEFINITIONS OF PCOS

Currently, two definitions of PCOS are in widespread use. The first arose from the proceedings of an expert conference sponsored in part by the National Institute of Child Health and Human Disease (NICHD) of the U.S. National Institutes of Health (NIH) on April 16-18, 1990. During the meeting all participants were surveyed regarding their perception of what features formed part of PCOS, and Drs. Zawadski and Dunaif summarized these findings in the meeting proceedings (9). They concluded that the major criteria for PCOS "*should include (in order of importance) : i) hyperandrogenism and/or hyperandrogenemia, ii) oligo-ovulation, [and the] iii) exclusion of other known disorders".* This survey 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 (ESHRE) and the American Society for Reproductive Medicine (ASRM) (10, 11). 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 prior to assigning the diagnosis of PCOS.

Whether these definitions are consistent with currently available data, and whether they are overly narrow or unjustifiable broad, were explored by the Task Force.

3) THE ESSENTIALS 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 (12-21). A syndrome may be defined by: a) historical usage in medical practice and/or literature, b) expert knowledge and consensus processes, or c) evidence-based, via analysis of published data.

One evidence-based approach to establishing the limits of a syndrome is to determine whether the various phenotypes defined by the criteria behave in a manner suggestive that they are part of the same disorder. Firstly, all possible phenotypes generated by the definition of a syndrome are catalogued and examined. Secondly, a feature not included in the definition (i.e. the 'anchor') is chosen to serve as the common thread (e.g. inheritance pattern, morbidities, a response to intervention). Essentially, for the phenotypes to 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. The Task Force opted for this latter approach in determining what phenotypes (and hence, what criteria) reflected PCOS based on current data.

Essentially, the Task Force considered that PCOS was defined by all those component phenotypes which potentially signaled an increased risk for insulin resistance and the resulting metabolic abnormalities. This is not to say that all individuals with a component phenotype had to demonstrate metabolic abnormalities, but that the phenotype as a group should demonstrate an increased prevalence of markers for metabolic dysfunction. A similar approach has been taken when defining the limits of the metabolic syndrome (22).

4) THE FEATURES OF PCOS

The Task Force recognized four key features of PCOS: a) ovulatory and menstrual dysfunction, b) hyperandrogenemia, c) clinical features of hyperandrogenism, and d) polycystic ovaries. Clinically evident menstrual dysfunction, such as oligo-amenorrhea or abnormal uterine bleeding, can be observed in a majority of patients with PCOS.

a) Ovulatory and menstrual dysfunction: In large series of patients diagnosed with PCOS, approximately 75% have clinically evident menstrual dysfunction (23-37) **(Table 1)**. Current data also suggests that ~20% of women with PCOS will present with a history of apparent eumenorrhea (i.e. subclinical oligo-anovulation) (23, 25-39) **(Table 1)**. In clinical practice, the presence of anovulation in clinically hyperandrogenic (i.e. hirsute) eumenorrheic women may be determined by measuring a serum progesterone level sometime during days 20 through 24 of the cycle. If anovulation is present, it may be prudent to confirm this finding with a repeat study.

b) Hyperandrogenemia: Elevated circulating androgen levels are observed in approximately 60-80% of PCOS patients**(Table 2)** (35-37, 40-42). The vast majority of the abnormal values are in the form of free testosterone (T), with the sole measurement of total T adding a limited amount to the diagnosis (36).

The value of also measuring androstenedione is unclear, but it may increase the number of subjects identified as hyperandrogenemic by ~10% (43). Approximately 25% of patients with PCOS will demonstrate supranormal levels of the androgen metabolite DHEAS (44) which may be the sole abnormality in circulating androgens in ~10% of these patients (36, 43). Alternatively, measuring the level of DHEA, a weak androgen primarily of adrenal origin, has limited diagnostic value.

The Task Force noted that the measurement of circulating androgen levels, including free T, was to be used only as an adjuvant for the diagnosis of hyperandrogenic disorders, and never as the sole criterion for diagnosis or in lieu of the clinical assessment. This recommendation reflects the fact that between 20% and 40% of women with PCOS will have androgen levels within the 'normal' range (36),and that assays for androgens, particularly total T, tend to be highly variable and inaccurate (45-47)

c) Hirsutism, acne and androgenic alopecia: Clinical features of hyperandrogenism frequently seen in PCOS include hirsutism, acne, and androgenic alopecia. Among women of White, Black, Southern Asia (Pakistani, Bengali, Gujarati, or Dravidian Indian), Maori, or Pacific Island descent, with PCOS defined by the NIH criteria, approximately 60% are found to be hirsute **(Table 2)** (24-26, 29-32, 35-37, 40-42, 48-50). We note that the degree of facial and body terminal hair growth in women represents a continuum, and that a value as low as three, using the modified Ferriman-Gallwey (mFG) score, may be considered abnormal (51). However, most investigators have used the 95th percentile of controls as the upper normal limit, which corresponds to an mFG score of 6-8 in the White or Black populations studied (51, 52).

Acne affects 15-25% of PCOS patients (38, 39, 53) although it is unclear whether the prevalence of acne is significantly increased in these patients over that observed in the general population (54-58). Finally, androgenic alopecia is a recognized sign of PCOS (39, 40, 59-61), although the prevalence of this abnormality in PCOS is unclear. In one study of 257 patients undergoing treatment for hyperandrogenic symptoms, only 5% complained of hair loss (39). Further studies are needed to better define the prevalence of acne and androgenic alopecia in PCOS.

d) Polycystic ovaries: Current data suggests that polycystic ovaries detected by transvaginal ultrasonography may be found in ~75% of women with a clinical diagnosis of PCOS (25, 26, 30-

32, 35, 37, 42, 49, 62-66) **(Table 3).** However, the Task Force also recognized that the false positive rate is relatively high, as evidenced by the high rate of polycystic ovaries in the general population (see above). The Task Force noted that the diagnosis of polycystic ovaries requires strict criteria (65, 67), and should not be assigned based solely on a 'polycystic' or 'multicystic' appearance of the ovary. The diagnosis of polycystic ovaries has been recently reviewed (68). The most commonly used criteria today are those proposed by Dewailly and colleagues (65), and reaffirmed in the Rotterdam 2003 consensus (10, 11), which indicate that polycystic ovaries can be established when at least one ovary demonstrates an ovarian volume of greater than 10 cm^3 (mL), or 12 or more follicles measuring 2-9 mm in diameter.

The Task Force noted that the diagnosis of polycystic ovaries should not be considered more or less objective than that of hirsutism or hyperandrogenemia. Witness the changing definition of 'polycystic ovaries' (67) and the 10% to 30% of women with PCOS who do not demonstrate polycystic ovaries on ultrasound (68). In addition, there are also technical limitations to this parameter, including the fact that at least 20% of women will refuse transvaginal ultrasonography (69) and that most clinicians (even gynecologists) do not perform their own ovarian ultrasonography, relying instead on the expertise of radiologists who may be less familiar with the diagnosis.

Finally a number of other features of PCOS have been recognized, including gonadotropic abnormalities, insulin resistance, and obesity. These features have not formed part of any of the recognized definitions to date, and the Task Force found no evidence to suggest that this should be otherwise.

6) PCOS: EXCLUSION OF OTHER ANDROGEN EXCESS AND RELATED DISORDERS

In addition to PCOS, there are a number of other disorders of androgen excess in women, including the adrenal hyperplasias (CAHs), the syndromes of severe insulin resistance, and androgen-secreting neoplasms (ASNs); that have the appearance of androgen excess (e.g. idiopathic hirsutism); or that have not yet been well characterized (e.g. idiopathic hyperandrogenism). There are also a number of other disorders that may result in ovulatory dysfunction, including hyperprolactinemia and thyroid abnormalities. These disorders account for approximately 5-10% of all patients with androgen excess (24, 26, 39-42, 60, 70-76) **(Table 4)**, and should be excluded when establishing the diagnosis of PCOS.

Although not a true disorder of androgen excess, idiopathic hirsutism (IH) should be excluded when assessing a hirsute patient for PCOS. Using the NIH 1990 criteria for PCOS, IH can be strictly defined as hirsutism, in the presence of regular ovulation and in the absence of hyperandrogenemia (77), such that approximately 5-7% of hirsute patients will have IH (27, 28, 77). It is possible that these patients may also need to demonstrate normal ovarian morphology on ultrasound, which would reduce their prevalence even further.

7) A PHENOTYPIC APPROACH TO DEFINING PCOS: TASK FORCE RECOMMENDATIONS

The Task Force considered all data published and summarized above, emphasizing larger epidemiologic and phenotypic studies, in arriving to its conclusions and recommendations regarding the phenotype of PCOS. These include the following:

a) <u>That PCOS is a hyperandrogenic disorder:</u> The Task Force concluded 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 cannot be established without evidence of either clinical or biochemical hyperandrogenism. While the exact measures for these may vary, the Task Force felt that the single most reliable indices of this feature included

hirsutism and free T levels. Nonetheless, the Task Force recognized that the methods for measuring androgens in the circulation were frequently inaccurate and insensitive, and that determination of hirsutism using visual scales was subjective, with significant inter-observer variation (78), and whose cut-off level may be unclear (51). Finally, the Task Force also noted that while many patients with PCOS may have evidence of acne or androgenic alopecia, these features could not be used reliably as clinical signs of hyperandrogenism. The Task Force also noted that support for this criteria is based on the risk for metabolic morbidity in the disorder, not on whether hyperandrogenism per se is present or not.

b) <u>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:</u> The Task Force recognized that ~75% of women with PCOS will demonstrate a polycystic ovarian morphology on transvaginal ultrasonography, 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 (6.a) above, the Task Force felt strongly that in 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) <u>That ovulatory dysfunction is a prominent, but not universal feature, of PCOS</u>: The Task Force recognized that some patients with PCOS may demonstrate regular ovulation at the time of their evaluation, the so-called “ovulatory PCOS” (79, 80). However, it was 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. It was also recognized that there exists little data regarding the long-term maintenance of ovulation in

women with “ovulatory PCOS”. Nonetheless, the Task Force recognized that there were persuasive, albeit limited, data to suggest that hyperandrogenic ovulatory women with polycystic ovaries had some degree of metabolic dysfunction, and were amenable to the inclusion of this phenotype as a form of PCOS.

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: A history of regular predictable vaginal bleeding in a patient without clinical signs of hyperandrogenism can be used as strong evidence of normal ovulation. Alternatively, a history of ‘regular’ menstrual cycles in patients who demonstrate hyperandrogenic features (e.g. hirsutism) could not be relied upon as evidence of normal ovulation, since up to 40% of these women have oligo-anovulation when examined more carefully. 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: Although the Task Force recognized that specific androgen excess or other endocrine disorders needed to be excluded when establishing the diagnosis of PCOS, they also recognized the validity of tailoring testing to reflect the prevalence of these disorders in the population being studied.

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.

8) MINORITY REPORT:

Notwithstanding the above recommendations, the Writing Committee acknowledged that two of its members considered the possibility that there are forms of PCOS without overt evidence of hyperandrogenism, and which may be associated with metabolic abnormalities and morbidity. However, these investigators also recognized, as did the Committee as a whole, that more data are 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 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) (81).

9) CONCLUSIONS

Based on the above review of the available data, it is the view of the AES Task Force on the Phenotype of PCOS 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 (**Figure 1**). Considering the four features of ovulatory dysfunction, hirsutism, hyperandrogenemia, and polycystic ovaries, the Task Force identified nine different phenotypes that could be considered as being PCOS with currently available evidence (**Table 5**).

The Task Force noted that there was ample data to support an increased risk of metabolic dysfunction in women with the following phenotypes: a) hirsutism and/or hyperandrogenemia, and oligo-ovulation with and without polycystic ovaries (phenotypes A-F in **Table 5**) and b) hyperandrogenemia and/or hirsutism, and normo-ovulation with polycystic ovaries (phenotype G and H in **Table 5**) (7, 34, 36, 37, 82-94). Current evidence generally did not support an

increased metabolic dysfunction among women with polycystic ovaries only, with or without oligo-ovulation (phenotype J in **Table 5**) (95, 96), although not all agreed (97). As expected, the incidence of metabolic dysfunction in PCOS is also significantly increased by the concomitant presence of obesity). However, the Task Force recognized that clinical features may not be constant even in a single patient and can be modified by changes in body weight and lifestyle choices, and age. In addition, the Task Force also recognized 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 firstly 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 do not have PCOS.

The Writing Committee also acknowledged that some of its members considered the possibility that there are forms of PCOS without overt evidence of hyperandrogenism, 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. Finally, while the aim of this report was to yield criteria based on currently available data to guide research and clinical diagnosis, and future investigations, the Task Force recognized that the definition of this syndrome will evolve over time to incorporate new research findings.

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Table 1. Prevalence of menstrual dysfunction in 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	(24)	280	237	84.6%		43	15.4%
Conway et al, 1989	(40)	556	395	71.0%		139	**25.0%**
Kiddy et al, 1990	(48)	263	203	77.2%		60	**22.8%**
Ardaens et al, 1991	(62)	144	105	72.9%		39	**27.1%**
Rajkhowa et al, 1995	(49)	153	129	84.3%			
Balen et al, 1995	(41)	1741	1043	59.9%		517	**29.7%**
Falsetti & Eleftheriou, 1996	(25)	240	207	86.3%		24	**10.0%**
Khoury et al, 1996	(26)	112	112	100.0%		0	**0.0%**
Talbott et al, 1998	(29)	244	229	93.9%		15	**6.1%**
Carmina et al, 1998	(28)	332	290	87.3%		42	**12.7%**
Alborzi et al, 2001	(30)	371	371	100.0%		0	**0.0%**
Williamson et al, 2001	(31)	162	144	88.9%			
Haddad et al, 2002	(33)	146	120	82.2%		26	**17.8%**
Amer et al, 2002	(32)	161	149	92.5%		12	**7.5%**
Glueck et al, 2003	(34)	138	138	100.0%		0	**0.0%**
Orio et al, 2003	(35)	100	100	100.0%		0	**0.0%**
Chang et al, 2005	(36)	316	265	83.9%		51	**16.1%**
Hahn et al, 2005	(37)	200	200	100.0%		0	**0.0%**
Total		**5659**	**4437**	**78.4%**	[a]	**968**	**18.1%**

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

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Table 2. Prevalence of hyperandrogenemia and hirsutism in 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	(24)	280								230	82.14%
Conway et al, 1989	(40)	556	110	22.3%	[a]					320	57.55%
Kiddy et al, 1990	(48)	263								129	49.05%
Rajkhowa et al, 1995	(49)	153								123	80.39%
Balen et al, 1995	(41)	1741	503	28.9%						1153	66.23%
Norman et al, 1995	(50)	122								103	84.43%
Falsetti & Eleftheriou, 1996	(25)	240								92	38.33%
Khoury et al, 1996	(26)	112								20	17.86%
Talbott et al, 1998	(29)	244								105	43.03%
Alborzi et al, 2001	(30)	371								300	80.86%
Williamson et al, 2001	(31)	162								147	90.74%
Amer et al, 2002	(32)	161								53	32.92%
Orio et al, 2003	(35)	100	33	33.0%				27	27.0%	100	100.00%
Chang et al, 2005	(36)	316	122	38.6%		216	68.4%	71	22.5%	224	70.89%
Hahn et al, 2005	(37)	200	162	81.0%				76	38.0%	129	64.50%
Legro et al, 2006	(42)	626	373	60.8%	[b]					505	80.67%
Total		**5647**	**1303**	**36.8%**		**216**	**68.4%**	**174**	**28.2%**	**3228**	**57.16%**

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

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Table 3. Prevalence of polycystic ovaries (PCO)[a] by transvaginal ultrasonography in PCOS

Study	Reference	Total No. PCOS	No. PCOS with PCO	% PCOS with PCO	
Rajkhowa et al, 1995	(49)	153	141	92.2%	
Falsetti & Eleftheriou, 1996	(25)	240	180	75.0%	
Khoury et al, 1996	(26)	112	77	68.8%	
Van Santbrink et al, 1997	(63)	198	148	74.7%	[b]
Laven et al, 2001	(64)	190	154	81.1%	
Alborzi et al, 2001	(30)	371	211	56.9%	
Williamson et al, 2001	(31)	162	161	99.4%	
Amer et al, 2002	(32)	161	93	57.8%	
Jonard et al, 2003	(65)	214	160	74.8%	
Orio et al, 2003	(35)	100	33	33.0%	
Hahn et al, 2005	(37)	200	166	83.0%	
Legro et al, 2006	(42)	626	573	91.5%	
Total		**2727**	**2097**	**76.9%**	

[a]Excluding multicystic or multifollicular ovaries

[b]PCOS defined as oligo-amenorrhea with either increased androgens and/or high LH

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Table 4. 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

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	(24)	467	0	0.0%	4	0.9%	[a]							
Conway et al, 1989	(40)	556			58	11.0%		10	1.8%	[e]				
Luciano et al. 1984	(70)	150			25	16.7%								
O'Driscoll et al. 1994	(60)	350			1	0.3%		3	0.9%		0	0.0%	2	0.6%
Moran et al, 1994	(71)	250						5	2.0%		1	0.4%	2	0.80%
Balen et al. 1995	(41)	1871	0	0.0%	25	1.3%		19	1.0%				0	0.00%
Khoury et al, 1996	(26)	112			17	15.2%								
Romaguera et al, 2000	(72)	100						1	1.0%					
Azziz et al, 2004	(39)	873	6	0.7%	3	0.3%		18	16.5%		0	0.0%	2	1.83%
Escobar-Morreale et al, 2004	(73)	109			4	3.7%	[b]							
Janssen et al, 2004	(74)	175	36	20.6%			[c]							
Glintborg et al, 2004	(75)	340			6	1.8%	[d]	2	0.6%		1	0.29%	1	0.29%
Carmina et al, 2006	(76)	950						41	4.3%				2	0.21%
Legro et al, 2006	(42)	626	45	7.2%										
Total		**5353**	**42**	**1.2%**	**143**	**4.3%**		**99**	**2.3%**		**2**	**0.14%**	**9**	**0.21%**

[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)

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Table 5. All possible phenotypes based on the presence or absence of oligo-anovulation, hyperandrogenemia, hirsutism, and polycystic ovary syndrome.

	POTENTIAL PHENOTYPES															
FEATURES	**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	√	√	√	√	√	√	√	√	√	√						
AES 2006 criteria	√	√	√	√	√	√	√	√	√							

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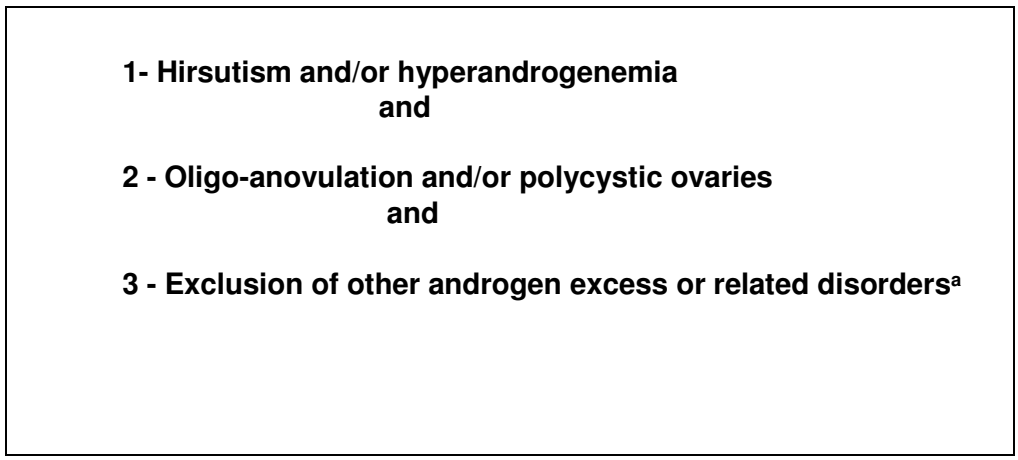
Figure 1
ANDROGEN EXCESS SOCIETY: SUGGESTED CRITERIA FOR THE DIAGNOSIS OF THE POLYCYSTIC OVARY SYNDROME



[a]Possibly including 21-hydroxylase deficient non-classic adrenal hyperplasia, androgen-secreting neoplasms, androgenic/anabolic drug use or abuse, Cushing's syndrome, the syndromes of severe insulin resistance, thyroid dysfunction, and hyperprolactinemia.