Criteria, prevalence, and phenotypes of polycystic ovary syndrome

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Polycystic ovary syndrome (PCOS) is a highly prevalent disorder effecting reproductive-aged women worldwide. This article addresses the evolution of the criteria used to diagnosis PCOS; reviews recent advances in the phenotypic approach, specifically in the context of the extended Rotterdam criteria; discusses limitations of the current criteria used to diagnosis, particularly when studying adolescents and women in the peri- and postmenopause; and describes significant strides made in understanding the epidemiology of PCOS. This review recognizes that although there is a high prevalence of PCOS, there is increased variability when using Rotterdam 2003 criteria, owing to limitations in population sampling and approaches used to define PCOS phenotypes. Last, we discuss the distribution of PCOS phenotypes, their morbidity, and the role that referral bias plays in the epidemiology of this syndrome. (Fertil Steril® 2016;106:6–15. ©2016 by American Society for Reproductive Medicine.)

Key Words: Phenotypes, polycystic ovary syndrome, prevalence, referral bias

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Polycystic ovarian syndrome (PCOS) is a highly prevalent disorder (1, 2) affecting multiple aspects of a women's overall health, with long-term effects that transcend well beyond the reproductive age (3, 4). The term "polycystic ovarian syndrome" does not fully or accurately reflect the complexity of this disorder (5) given its very broad spectrum of clinical manifestations and associated morbidities (6–13). Patients with PCOS demonstrate reproductive abnormalities (6, 7), marked insulin resistance (8), increased risk for type 2 diabetes mellitus (9), coronary heart disease (10), atherogenic dyslipidemia (11), cerebrovascular morbidity (12), and anxiety and depression (13). If pregnant, these women have substantially increased odds for the development of gestational diabetes, pre-eclampsia, fetal macrosomia, small-for-gestational age infants, and perinatal mortality (14–16). Hospital admissions for women with PCOS are twice as high as for the general population (17).

Over the last several decades, significant efforts have been made to classify PCOS; however, global consensus regarding a PCOS criterion remains controversial (18–20). Unfortunately, existing epidemiologic and/or basic research data have not been sufficient in providing the foundation needed to derive an evidence-based definition of the syndrome. Currently proposed criteria are predominantly based on expert opinion (18–20), thereby serving as a point of disagreement among researchers: some experts assert it is a disorder predominantly of androgen excess (21), whereas others believe that it has a broader spectrum of presentation (22).

Some progress has been achieved more recently with the introduction of a novel phenotypic approach to the diagnosis. A phenotypic approach to classifying PCOS avoids the drawbacks of currently existing criteria, which may be interpreted as "lumping" all phenotypes together, while providing a simple diagnostic instrument and avoiding the need to decide between multiple different PCOS definitions (23).

In the present article we review the controversy around the PCOS definition; the prevalence of the disorder on the basis of these definitions; the distribution and associated morbidity of the PCOS phenotypes; and important phenotypic differences in PCOS according to population source and referral bias.

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DIAGNOSTIC CRITERIA FOR PCOS

PCOS Criteria in Adult Women

Three sets of diagnostic criterion have been proposed over the past three decades (18–20, 23–25) (Table 1). The

first formal attempt to classify PCOS was carried out at a National Institute of Child Health and Human Development of the US National Institutes of Health (NIH) conference, April 1990 (18). A tabulation of participant impressions indicated that clinical or biochemical hyperandrogenism (HA) and chronic oligo-anovulation (OA), after the exclusion of related disorders were considered key diagnostic PCOS features. The second definition was based on the consensus opinion of 27 PCOS experts, who met in Rotterdam, the Netherlands, May 2003 (19, 20). The conference was partially sponsored by the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM). As a result of this meeting, ultrasound characteristics for polycystic ovarian morphology (PCOM) were added to the NIH 1990 definition, making it more complex. The ESHRE/ASRM 2003 PCOS criteria required the presence of two of the following three findings: [1] signs of clinical or biochemical HA; [2] chronic ovulatory dysfunction (OD); and [3] PCOM, after exclusion of secondary causes (19, 20) (Table 1). This definition essentially expanded the diagnosis of PCOS to include women who either had PCOM in combination with HA, or PCOM in combination with OD (OD is a slightly broader term than OA, and includes other forms of OD beyond just oligo-anovulation, possibly reflected in, e.g., polymenorrhea) (Table 2). Importantly, the introduction of Rotterdam criteria led to a substantial increase in the number of patients diagnosed with PCOS, as well as broadened the heterogeneity of PCOS phenotypes as compared with the NIH definition (26).

Subsequently, an increasing body of evidence suggested that HA seemed to be the strongest determinant of the PCOS pathophysiology and a key predictor of the associated metabolic dysfunction (27–29). Therefore, it has been suggested that non-hyperandrogenic PCOS patients (i.e., those with chronic anovulation and PCOM) do not truly represent patients with the syndrome and are etiologically distinct from hyperandrogenic PCOS (24, 25). In 2006 a task force assembled by the Androgen Excess & PCOS Society (AE-PCOS), composed of five investigators from the United States and six from Europe and Australia, conducted a systematic review of published literature to identify the link between PCOS phenotypes and independent morbidity. They concluded that PCOS is a disorder predominantly of androgen excess and that a concise diagnosis of PCOS should be based on the presence of clinical or biochemical HA in combination with ovarian dysfunction (i.e., OD or PCOM), excluding other causes (24, 25). Therefore, the AE-PCOS 2006 criteria excluded the non-hyperandrogenic phenotype (i.e., phenotype D, including PCOM plus OD) that was proposed by the 2003 Rotterdam definition (19, 20) (Table 2).

The global use of varying PCOS diagnostic criteria raised issues of compatibility for PCOS research worldwide, which then resulted in confusion within clinical practice and a "delay in progress in understanding the syndrome" (23). Therefore, the NIH in 2012 undertook an Evidence-Based Methodology PCOS Workshop which, among other topics, addressed the "benefits and drawbacks" of existing diagnostic criteria (23). The meeting was organized in accordance with standard NIH criteria for Consensus Development Programs, and all available evidence was presented by 29 PCOS experts from different countries to four workshop panel members whose research expertise was not in PCOS (23). As a result the panel recommended the use of the broader ESHRE/ASRM 2003 criteria, but accompanied with a detailed description of the PCOS phenotype included (23). As previously proposed by Azziz et al. (24), the NIH consensus panel recommended use of the following phenotype classification: phenotype A: HA (clinical or biochemical presence) + OD + PCOM; phenotype B: HA + OD; phenotype C: HA + PCOM; and phenotype D: OD + PCOM (23). Table 2 summarizes these four PCOS phenotypes and their relationship to current criteria.

The proposed phenotypic approach is highly convenient for clinical practice and epidemiologic research. Notwithstanding the ongoing discussion about the validity of current PCOS criteria, phenotypic classification allows for the characterization of PCOS populations according to the presence and/or absence of key features. As long as the presence of HA, OD, and PCOM are considered the core PCOS features and are reported as such, the specific criteria (NIH 1990, ESHRE/ASRM

TABLE 1

Evolution of the diagnostic criteria for polycystic ovarian syndrome.

Parameter	NIH 1990 (18)	ESHRE/ASRM 2003 (19, 20)	AE-PCOS 2006 (24, 25)	NIH 2012 extension of ESHRE/ASRM 2003 (23)
Criteria	HA OA	HA OD PCOM	1. HA 2. Ovarian dysfunction (OD and/or PCOM)	1. HA 2. OD 3. PCOM
Limitations	1.Two of two criteria required	1. Two of three criteria required	1. Two of two criteria required	1. Two of three criteria required; and 2. Identification of specific phenotypes included: A: HA + OD + PCOM B: HA + OD C: HA + PCOM D: OD + PCOM
Exclusion of related or mimicking etiologies				

Note: AE-PCOS = Androgen Excess & PCOS Society; ASRM = American Society for Reproductive Medicine; ESHRE = European Society for Human Reproduction and Embryology; HA = hyperandrogenism; NIH = National Institutes of Health; OA = oligo-anovulation; OD = ovulatory dysfunction; PCOM = polycystic ovarian morphology.

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TABLE 2

Classification of polycystic ovarian syndrome phenotypes.

Parameter	Phenotype A	Phenotype B	Phenotype C	Phenotype D
PCOS features	HA/OD/PCOM	HA/OD	HA/PCOM	OD/PCOM
HA	+	+	+	−
OD	+	+	−	+
PCOM	+	−	+	+
NIH 1990 criteria	X	X		
Rotterdam 2003 criteria	X	X	X	X
AE-PCOS 2006 criteria	X	X	X	

Note: AE-PCOS = Androgen Excess & PCOS Society; HA = hyperandrogenism; NIH = National Institutes of Health; OD = ovulatory dysfunction; PCOM = polycystic ovarian morphology. Modified from reference (24).

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2003, or AE-PCOS 2006) being used to define PCOS are of limited consequence, because essentially the PCOS phenotypes are the "building blocks" of all existing definitions.

The phenotypic approach to defining PCOS has a number of practical applications. For example, in routine clinical practice it would be helpful to identify those women with PCOS who are at the highest risk for metabolic dysfunction—those with "classic" PCOS phenotypes (i.e., phenotypes A and B) (24). Another important application of this approach is seen when conducting epidemiologic research and clinical trials (23), in which the use of this classification allows researchers to categorize their outcomes on a finite number of PCOS phenotypes, permitting comparisons with other well-defined PCOS populations.

PCOS Criteria in Adolescents

Although essentially the definition of PCOS in adolescents follows the general principles outlined for adult women, there are a number of caveats that need to be considered when evaluating this age group, particularly in girls whose presentation does not meet the full presentation seen in adults. Clinicians and researchers alike should keep in mind that this is a period of hormonal and reproductive transition, such that whereas some of these girls will present with clearly mature PCOS features, others will present with less clear and more subtle signs only suggestive of the disorder. However, by age 18 years, the vast majority of girls who have PCOS will have developed the phenotype clearly.

It is possible that PCOS may begin to manifest itself in adolescence but may not be readily diagnosable until adulthood. There is no general consensus on how PCOS should be defined in adolescents (30). Several features suggestive of PCOS are also common during the normal pubertal transition to adulthood. For example, multifollicular ovaries can be found in approximately 26% of adolescents (31). Moreover, during puberty ovarian volume is typically greater compared with adults (32). However, limited evidence suggests that 2 years after menarche the threshold for ovarian size is similar to that of adults (32). Despite the fact that menstrual dysfunction is a common feature of normal reproductive maturation (33), prolonged adolescent oligomenorrhea at age 14–19 years has been found to be predictive of persistent ovarian dysfunction later in life (34).

Total and free T levels in adolescents 1 to 2 years after menarche are generally comparable to those in adults (35, 36). Alternatively, there are no data documenting the progression of terminal hair growth over time from adolescence through adulthood, although it is likely that by age 18 years the modified Ferriman-Gallwey hirsutism scores are those of an adult. In a study of 633 unselected women presenting for a pre-employment physical examination, mostly aged 18 through 45 years, the modified Ferriman-Gallwey score was not associated with age (37). Therefore, it is likely that adult criteria for HA and ovarian volume, but not follicular count, could be used in adolescents that are 2 years after menarche (30).

Recently two sets of adolescent PCOS criteria were suggested, one by an ESHRE/ASRM working group (38) and the other by a clinical practice guidelines committee of the Endocrine Society (30) (Table 3). According to these recommendations, when PCOS is not clearly evident by adult standards, in adolescents the disorder could be considered on the basis of the presence of increased serum androgens levels and/or progressive hirsutism, in association with persistent oligo/amenorrhea for at least 2 years after menarche and/or primary amenorrhea by age 16 years, and/or an ovarian volume >10 cm^3, after exclusion of secondary causes. It should be

TABLE 3

Diagnostic criteria for polycystic ovarian syndrome in adolescents.

Parameter	ESHRE/ASRM 2012 (38)	Endocrine Society 2013 (30)
Criteria	1. Clinical or biochemical hyperandrogenism[a] 2. Oligo-/anovulation[b] 3. Polycystic ovarian morphology[c]	1. Clinical or biochemical hyperandrogenism[a] 2. Persistent oligo-/anovulation[b]
Limitation	Three of three criteria required with exclusion of other etiologies	Two of three criteria required with exclusion of other etiologies

Note: ASRM = American Society for Reproductive Medicine; ESHRE = European Society for Human Reproduction and Embryology.
[a] Increased serum androgens and/or progressive hirsutism.
[b] Oligo-/amenorrhea for at least 2 years, or primary amenorrhea by age 16 years.
[c] Ovarian volume >10 cm^3.

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noted, however, that neither of the proposed criteria have yet to be validated.

PCOS Criteria in the Peri- and Postmenopause

Diagnosing PCOS in the peri- and postmenopause is challenging. The menopausal transition of women with PCOS is not well understood, although it seems that as women with PCOS age many gain menstrual cyclicity (39), experience a decrease in the ovarian volume and number of ovarian follicles (40, 41), and maintain serum androgen levels (42)—all of which can ameliorate the clinical presentation of PCOS. The measurement of androgenemia suffers from a lack of normative ranges during menopausal transition (43). However, androgen levels in women with PCOS tend to remain higher compared with similarly aged women without PCOS, and despite a generalized decrease in circulating androgen levels with age.

In 2013 an Endocrine Society–appointed committee of experts, on the basis of limited evidence, formulated the first presumptive PCOS definition for postmenopause (30) (Table 4). This recommendation suggested that the PCOS diagnosis in postmenopausal women could be based on a previous medical history of menstrual dysfunction and the presence of HA during the reproductive period (30). The presence of PCOM was considered a supportive sign; however, it was unlikely to be found owing to age-related changes in ovarian morphology (30).

GLOBAL PREVALENCE OF PCOS

Understanding the global prevalence and phenotype of PCOS is important, considering that geographic factors and ethnic/racial variations can shape the clinical presentation of the syndrome. The first studies to determine prevalence in a medically unselected (unbiased) population were initiated by Azziz and colleagues, who reported PCOS prevalences ranging from 4% to 6.6% using the NIH 1990 criteria among unselected reproductive-age women residing in the southeastern region of the United States (1, 44). Interestingly, no statistical significant differences were detected between black and white women in these studies (1, 44). A number of epidemiologic studies have subsequently reported PCOS prevalence in various populations using multiple PCOS definitions (1,2, 44–63). Worldwide prevalence of PCOS ranges from 4% to 21% (46, 49), depending on the diagnostic criteria used (Table 5). The prevalence of PCOS among different geographic regions ranges from 5% to 10% according to NIH 1990 criteria; from 10% to 15% according to the AE-PCOS 2006 criteria, and from 6% to 21% when the ESHRE/ASRM 2003 criteria were applied (Table 5). Greater estimates of PCOS prevalence with the Rotterdam 2003 and AE-PCOS 2006 criteria are largely attributed to their more expansive definition and inclusion of additional phenotypes, compared with NIH 1990 diagnostic criteria (64). Variations in the reported prevalence within the same definition across countries can in part be explained by ethnic differences, by the variety of approaches used to define study population(s), and the application of varying methods to evaluate key PCOS features.

Overall, the use of the NIH 1990 criteria for PCOS was associated with reduced variability in the prevalence across countries, with a few exceptions. For example, patients assessed via a questionnaire from subjects in the Mexican-American Coronary Artery Disease (MACAD) Project (13.0%) (63) and Australian Aborigines from Darwin Region Urban Indigenous Diabetes (DRUID) study (15.3%) (46) demonstrated a higher PCOS prevalence than other studies, whereas a lower prevalence was reported from one study in China (2.2%) (48). However, these differences could be explained in part by ethnic differences in the prevalence of hirsutism—with a higher prevalence among Australians (46) and a lower prevalence within the Chinese population (48), as well as some limitations in sampling (i.e., enrolling subjects from the trials originally designed to study diabetes [DRUID study] and coronary artery disease [MACAD project]).

The results of epidemiologic studies of PCOS largely depend on how the study population and the PCOS phenotypes were defined. For example, in some studies a population-based model was used to identify the study population, whereby subjects were randomly selected from a certain geographic area (50, 55, 65). These studies overall are highly representative of the reference population and are considered standard for the evaluations of true relationships among variables of interest, even if those were not prespecified in the original study hypothesis (50, 56, 61, 65).

In addition, the results of studies assessing the prevalence of PCOS also suffer from the fact that the assessment of the PCOS phenotype is a complex multistep process, which requires multiple clinical and laboratory assessments, pelvic ultrasound, and possibly several visits for some subjects. Thus, these studies may suffer from underreporting of PCOS, because these patients require more intensive study and follow-up compared with unaffected individuals. Furthermore, the fact that detecting PCOS in a study population requires greater effort than diagnosing unaffected subjects means that population-based studies are the most difficult to complete and suffer from significant incomplete data (45, 65).

Another common model used to determine the prevalence of PCOS is the institution-based study, wherein subjects are undergoing a physical and medical assessment for nonmedical reasons, for example a pre-employment or yearly employment assessment (1, 2, 44). In this approach the study cohort is less likely to be truly representative of the

TABLE 4

Suggested diagnostic criteria for polycystic ovarian syndrome in postmenopausal women.

Parameter	Endocrine Society 2013 (30)
Criteria	Clinical or biochemical hyperandrogenism[a] Prolonged oligo-amenorrhea[a]
Limitation	Two of two criteria required with exclusion of other etiologies

[a] Based on well-documented long-term previous medical history.

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TABLE 5

Prevalence of polycystic ovarian syndrome in different countries.

Country	Population	N	PCOS criteria used: NIH 1990	ESHRE/ASRM 2003	AE-PCOS 2006	First author, year (reference)
Australia	Birth registry in a single hospital	728	8.7	11.9	10.2	March, 2010 (45)
Australia	Indigenous women, DRUID[a] study	248	15.3	21.3	–	Boyle, 2012 (46)
Brazil	Women undergoing cervical cancer screening	859	–	8.5	–	Gabrielli, 2012 (47)
China	Routine physical examination, South China	915	2.2	–	–	Chen, 2008 (48)
China	Stratified sample of women in Beijing	2,111	–	6.11	–	Ma, 2010 (49)
China	Residences from 10 provinces	15,924	–	5.6	–	Li, 2013 (50)
China	Residents of Chengdu	1,645	7.1	11.2	7.4	Zhuang, 2014 (51)
Denmark	Employees at Copenhagen University	447	–	16.6	13.9	Lauritsen, 2014 (52)
Greece	White women, general population recruited via offer of a free medical evaluation	192	6.8	–	–	Diamanti-Kandarakis, 1999 (53)
Iran	Four random provinces of different geographic regions	929	7.1	14.6	11.7	Tehrani, 2011 (64)
Iran	Females attending pre-marriage clinic in Isfahan	820	7.0	15.2	7.92	Mehrabian, 2011 (55)
Iran	Randomly selected women from southwest Iran	602	4.8	14.1	12	Rashidi, 2014 (56)
Italy and Spain	Blood donors from Madrid and Bologna	592	5.4	–	–	Sanchon, 2012 (57)
Mexico	Hospital employees Volunteers	150	6.0	–	–	Moran, 2010 (58)
Palestine	Students from Najah National University-Palestine	137	7.3	–	–	Musmar, 2013 (59)
Spain	Blood donors in Madrid	154	6.5	–	–	Asuncion, 2000 (60)
Sri Lanka	Four areas in Gampaha region	2,915	–	6.3	–	Kumarapeli, 2008 (61)
Turkey	Pre-employment medical assessment in General Directorate of Mineral Research and Exploration	392	6.1	19.9	15.3	Yildiz, 2012 (2)
UK	Volunteers in Oxford	224	8.0	–	–	Michelmore, 1999 (62)
USA	Pre-employment medical assessment in the Southeastern USA	277	4.0	–	–	Knochenhauer, 1998 (44)
USA	Pre-employment medical assessment in the Southeastern USA	400	6.6	–	–	Azziz, 2004 (1)
USA	Mexican American Women, MACAD[b] Project, by questionnaire	156	13.0	–	–	Goodarzi, 2005 (63)

Note: AE-PCOS = Androgen Excess & PCOS Society; ASRM = American Society for Reproductive Medicine; ESHRE = European Society for Human Reproduction and Embryology; NIH = National Institutes of Health.

[a] From the Darwin Region Urban Indigenous Diabetes (DRUID) study.

[b] From the Mexican-American Coronary Artery Disease (MACAD) Project.

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general population as compared with population-based cohorts, because individuals who are undergoing a pre-employment or employment assessment may be of higher socioeconomic and educational status than the general population (1, 2). However, using this approach is usually makes it easier to obtain a complete phenotype assessment in the majority of subjects (1, 2).

A final approach used in establishing the epidemiology of PCOS is the recruitment of volunteers seeking an unspecified medical evaluation (53). However, this approach can possibly cause selection (volunteer) bias (i.e. women seeking a free medical evaluation may be more likely to have health issues and are more likely to be affected by the symptoms of PCOS than the general population). However, in the one study that used this

TABLE 6

Distribution polycystic ovarian syndrome phenotypes in studies reported from unselected populations by countries.

			Phenotype				
Country	Study type	N	(A) HA/OA/PCOM (%)	(B) HA/OA (%)	(C) HA/PCOM (%)	(D) PCOM/OA (%)	First author, year, (reference)
Denmark	Cross-sectional	Total N: 447 PCOS: 86	4.7	4.7	72.1	18.6	Lauritsen, 2014 (52)
China	Cross-sectional	Total N: 15,924 PCOS: 886	28.7	19.0	37.3	15.0	Li R, 2013 (50)
China	Cross-sectional	Total N: 2,111 PCOS: 129	31.0	16.3	27.1	25.6	Ma, 2010 (49)
Australia	Cross-sectional	Total N: 728 PCOS: 129.5	21.2	27.5	18.9	32.5	March, 2010[a] (45)
Mexica	Cross-sectional	Total N: 150 PCOS: 10	70	20	0	10	Moran, 2010 (58)
Iran	Cross-sectional	Total N: 929 PCOS: 136	8.8	39.7	31.6	19.9	Tehrani, 2011 (64)
Iran	Cross-sectional	Total N: 602 PCOS: 85	12.9	22.4	49.4	15.3	Tehrani, 2014 (54)
Turkey	Cross-sectional	Total N: 392 PCOS: 78	25.6	5.1	46.2	23.1	Yildiz, 2012 (2)

Note: HA = hyperandrogenism; OA = oligo-anovulation; PCOM = polycystic ovarian morphology.
[a] Including imputed data.

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approach the prevalence of PCOS obtained was similar to that of other, less-biased studies (53).

Several limitations in the definition of the outcomes (PCOS and its compounds) could be another possible source of heterogeneity in prevalence estimates (e.g., the lack of population-defined normative ranges), androgen measures based on total T only, use of insensitive/inaccurate circulating androgen assays, involvement of multiple observers for the evaluation of hirsutism with unknown interobserver variation, the definition of OD based solely on the presence of menstrual dysfunction, and the absence of standardization in the evaluation for the exclusion of mimicking disorders (24). Recent data also suggest that an effect of transvaginal ultrasound transducer frequency on the cut-off value for antral follicle count can also contribute to heterogeneity in the phenotype and prevalence, particularly when using the Rotterdam 2003 criteria for diagnosing PCOS (66).

Moreover, the effects of sociodemographic factors and environmental and psychological determinants of health were not generally taken into account in the epidemiologic studies of PCOS to date. However, despite all discussed limitations, the prevalence of PCOS by the NIH 1990 criteria is relatively similar among different ethnic and geographic populations, possibly suggesting that, at least for the "classic" PCOS phenotype, the disorder seems to have originated before the separation of *Homo sapiens* into racial groups (67).

PCOS PHENOTYPES

The distribution and morbidity associated with specific PCOS phenotypes has been the object of extensive research, as reported by studies conducted in Europe (68–71), the Middle East (54, 72), Asia (50, 73), the Americas (74, 75), and Australia (45). As noted above, the presentation of PCOS can be subdivided into four phenotypes: phenotype A: HA + OD + PCOM; phenotype B: HA + OD; phenotype C: HA + PCOM; and phenotype D: OD + PCOM (Table 2), and each phenotype will be discussed below. Overall it seems that the presence of HA (76), body mass index (BMI) (76), and degree of menstrual irregularity (77), but not ovarian morphology (78), are independent predictors of metabolic dysfunction. However, we should note that the majority of studies reporting clinical outcomes among PCOS cohorts were determined in subjects identified in the clinical setting, and very little information exists regarding the characteristics or phenotype of PCOS in subjects identified in the general population.

"Classic" PCOS (Phenotypes A and B)

Data derived from clinical populations suggest that women with "classic" PCOS (phenotypes A and B) are associated with more pronounced menstrual dysfunction (73, 79); increased insulin levels (80), higher rates of insulin resistance (79, 81, 82), and risk for metabolic syndrome (72, 83); body mass index (80) and prevalence of obesity (82); and more severe forms of atherogenic dyslipidemia (29, 79), as compared with women diagnosed with nonclassic or nonhyperandrogenic PCOS phenotypes (phenotypes C and D). There is also some evidence that women with the PCOS phenotypes A and B have an increased risk of hepatic steatosis as compared with women with PCOS with the nonhyperandrogenic phenotype and compared with healthy controls (83, 84). The highest antimüllerian hormone levels are also found in patients with classic PCOS (85–87). Data from 1,297 women with PCOS from Greece have shown that menstrual cycle pattern is more irregular in these women as compared with phenotype D but seems to normalize with ageing (88).

"Ovulatory PCOS" (Phenotype C)

Patients with "ovulatory PCOS" generally demonstrate intermediate levels of serum androgens, insulin, atherogenic lipids, hirsutism scores, and prevalence of metabolic syndrome, as compared with patients with "classic" and the nonhyperandrogenic PCOS phenotypes (29, 71, 89, 90). An interesting observation was made in an Italian cohort: higher socioeconomic status was related to a higher prevalence of the ovulatory phenotype (91). Differences in ovulation patterns between the social groups could in part be explained by differing insulin levels and fat tissue distribution (91).

"Nonhyperandrogenic PCOS" (Phenotype D)

In the majority of studies, patients with nonhyperandrogenic PCOS had the mildest degree of endocrine and metabolic dysfunction and the lowest prevalence of metabolic syndrome (51, 71, 80, 83, 90, 92) as compared with healthy controls (51, 93). These women had lower LH to FSH ratios, lower total and free T levels, and higher sex hormone-binding globulin levels, as compared with subjects with classic PCOS (87). Besides that, the number of women with regular cycles alternating with irregular cycles was highest in women with phenotype D (88). However, not all investigators agree.

Cupisti et al. (70) did not observe any significant difference in insulin resistance, BMI, and dyslipidemia between the various PCOS phenotypes in German patients, as did another study from Greece (94). However, in the latter study insulin resistance was observed only in those women with a BMI >25 kg/m^2 (94). Likewise, Wijeyaratne et al. (95) and Melo et al. (75) did not observe any difference in the prevalence of metabolic syndrome between the various PCOS phenotypes in women from Sri Lanka and Brazil, respectively. In a Turkish cohort, nonhyperandrogenic women with PCOS had levels of low-density lipoprotein–cholesterol that were actually higher compared with patients with ovulatory PCOS, but not compared with women with classic PCOS (96).

We should note, however, that the use of poor-quality androgen assays in the majority of these studies could have resulted in the misclassification of patients who actually have HA (i.e., with classic PCOS) as "nonhyperandrogenic" (43).

Distribution of PCOS Phenotypes

Understanding the distribution of PCOS phenotypes is essential in defining the epidemiology of PCOS in a population. Multiple studies from different regions around the world have reported the distribution of phenotypes in clinical cohorts of PCOS patients (70–75, 79, 81, 90, 93, 97). Overall, published data indicate that more than half of PCOS patients identified within the clinical setting demonstrate phenotype A, whereas the other three phenotypes (i.e., B, C, and D) have almost equal prevalence. Overall, it seems that the classic form of PCOS (i.e., phenotypes A and B) constitutes approximately two-thirds of the total of PCOS patients identified within the clinical setting (98).

Unfortunately, few data exist regarding the distribution of phenotypes in women with PCOS identified in medically unbiased (i.e., unselected) populations, which would more accurately reflect the distribution of phenotypes in PCOS in the "natural" state. The few studies that recently reported the distribution of PCOS phenotypes according to Rotterdam (2, 45, 49, 50, 52, 54, 58, 65) suggest that approximately two-thirds of PCOS patients identified among unselected populations could be classified as having phenotypes B and C, whereas phenotype A and phenotype D are almost equally prevalent (Table 6). Interestingly, these early data suggest that the least prevalent phenotypes are the most (phenotype A) and least (phenotype D) metabolically severe phenotypes.

Referral Bias in Defining the PCOS Phenotype

The difference in the distribution of PCOS phenotype between patients identified in clinical vs. unselected populations suggests that the clinical PCOS cohort may not be truly representative of the disorder in its natural, medically unbiased, state in the general population. This concept has been confirmed by the results of three independent studies from different regions. Ezeh et al. compared two prospective cohorts of patients with PCOS from the southeastern region of the United States: one PCOS cohort was referred for medical care (referral cohort), and the second cohort consisted of patients identified through routine pre-employment medical screening (unselected cohort) (99). Both cohorts lived in the same geographic area and were evaluated at the same institution. The investigators found that the referral cohort of PCOS patients had a higher prevalence of the more severe PCOS phenotypes, greater BMI, more severe hirsutism, and more pronounced hyperandrogenemia, compared with women with PCOS identified in the unselected population (99). Referral PCOS patients were also more likely to be non-Hispanic white, a possible reflection of the limitations to accessing medical care for some ethnic/racial groups (99).

A more recent study from Spain confirmed these findings in part. Luque-Ramírez et al. (100) reported on patients with female functional hyperandrogenism and PCOS. They observed that patients with functional hyperandrogenism who sought medical care were more hirsute, had more pronounced clinical and biochemical HA, were more frequently obese, and had a higher prevalence of PCOS, as compared with patients identified in the general population.

Data from China are also supportive of the concept that significant referral bias exists in the studies of PCOS currently. Ma et al. (49) observed a higher prevalence of PCOS phenotype A and a higher rate of menstrual dysfunction in hospitalized patients with PCOS compared with PCOS subjects identified through general community screening.

These data raise important questions regarding the validity of epidemiologic research using clinical PCOS cohorts. Subjects with PCOS identified in the general population have less severe manifestation of the disorder, higher prevalence of milder phenotypes, and are different socioeconomically and racially, reflecting the ability to access medical care (99). Therefore, the use of clinical cohorts for epidemiologic research could possibly produce falsely elevated odds ratios and pseudo-significant associations (101). For

example, today almost all available data linking PCOS with long-term morbidities are derived from patients referred for medical care.

SUMMARY

Polycystic ovary syndrome is a common (4% to 21%) disorder among reproductive age women. Depending on diagnostic criteria, PCOS's prevalence was approximately 4%–6.6% in accordance with NIH 1990 criteria and approximately 4%–21% when Rotterdam 2003 criteria were applied. Despite meaningful limitations of published prevalence studies relevant to sampling and outcome definitions, PCOS prevalence by NIH 1990 criteria remains relatively constant. Over the last decade some progress has been achieved in the formal definition of the syndrome. Of the various PCOS criteria, NIH's 2012 phenotypic extension of the Rotterdam definition has been shown to be the most convenient approach when conducting research and clinical practice. This approach permits comparisons in epidemiologic studies among different populations and allows researchers to identify high-risk individuals in clinical practice. Despite some progress in understanding PCOS phenotype among female adolescents and peri- and postmenopausal women, more studies are needed. Recent evidence demonstrates a significant difference in phenotype, ethnicity, and morbidity among PCOS patients identified in the clinical setting vs. the general population. More epidemiologic data are required among medically unbiased PCOS populations to better understand the natural course of this syndrome, as well as validate any strengths of true associations with comorbid disorders.

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