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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