Chapter 1
Diagnostic Criteria and Epidemiology of PCOS

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Key Points

- As of 2013, the *three* recognized sets of criteria for PCOS diagnosis include the NIH criteria, the Rotterdam criteria, and the Androgen Excess and Polycystic Ovary Syndrome Society criteria.
- The prevalence of PCOS depends upon the diagnostic criteria used. Rotterdam is most inclusive, followed by the Androgen Excess Society criteria. The NIH criteria are the most strict and account for the lowest detected prevalence of PCOS
- Women with PCOS have an increased rate of many major cardiovascular risks: obesity, insulin resistance, metabolic syndrome, dyslipidemia, and type 2 diabetes. An increased risk for cardiovascular disease and events is suggested in this population.
- Acne and hirsutism may be the presenting symptoms of PCOS and should prompt a thorough evaluation.
- Women with PCOS are at an increased risk for additional chronic disorders such as depression and endometrial cancer.

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Table 1.1 Diagnostic criteria and their associated phenotypes[a]

	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	√	√	√	√	√	√										
Rotterdam 2003	√	√	√	√	√	√	√	√	√	√						
AE-PCOS 2006	√	√	√	√	√	√	√	√	√							

[a]Adapted from Azziz et al. [4]

Diagnostic Criteria for Polycystic Ovary Syndrome

Since 1935, when Stein and Leventhal originally described the combination of oligo-ovulation and hyperandrogenism [1], the polycystic ovary syndrome (PCOS) has undergone multiple iterations of diagnostic criteria. Initially, description of the syndrome was based upon case reports in the literature. In the 1800s abnormal uterine bleeding was the most common symptom associated with the condition. Over time, as new and better evidence has become available, multiple efforts have been made to better characterize this syndrome to allow for better appreciation of this complex entity.

Clinicians worldwide may now choose between three major sets of *diagnostic criteria* to arrive at a diagnosis of PCOS (Table 1.1). The first set of relatively stringent criteria was outlined at the National Institutes of Health (NIH) in Bethesda, Maryland, in 1990, but has largely been replaced in clinical practice by the relatively recently proposed *Rotterdam criteria*. A task force sponsored by the European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) met in Rotterdam, The Netherlands, in 2003 to review the available data and proposed a revision to the 1990 NIH diagnostic paradigm, hence the inception of the Rotterdam criteria. More recently, in 2009, the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society outlined its own set of criteria. It is important to appreciate that the subtle heterogeneities within the various diagnostic criteria utilized by investigators impacts upon the reported prevalence of PCOS in a given population.

The NIH meeting in 1990 was the first international conference on PCOS, and the guidelines that resulted from this meeting were based largely on expert opinion of the attendees, rather than the results of analytic studies [2]. The criteria set forth included (1) chronic anovulation and (2) clinical or biochemical signs of hyperandrogenism. Both criteria *must* be present, and other diagnoses *must* be excluded to allow reaching a diagnosis of PCOS. Once this initial step was taken to clearly define the syndrome, in ensuing years, better analytic studies revealed additional information that was subsequently evaluated by The Rotterdam ESHRE/ASRM-Sponsored

PCOS Consensus Workshop Group to revise the original NIH proposed set of diagnostic criteria.

The Rotterdam consensus includes three diagnostic criteria, and states that *any two of the three* must be present in order to make the diagnosis [3]. The revised criteria include (1) oligo- or anovulation, (2) clinical or biochemical signs of hyperandrogenism, and (3) polycystic appearing ovaries (PCO) on imaging. Other disorders *must*, of course, be excluded, including 21-hydroxylase deficient non-classic congenital adrenal hyperplasia (NC-CAH), Cushing's syndrome, and androgen-secreting tumors as well as commoner entities such as thyroid dysfunction and hyperprolactinemia. The addition of morphological appearance of polycystic ovaries identifies two additional phenotypes not previously included in the diagnosis: women with ovulatory dysfunction and polycystic ovaries but without hyperandrogenism, and ovulatory women with hyperandrogenism and polycystic ovaries; deeper explorations reveal that these subcategories within PCOS identified based on the Rotterdam diagnostic criteria manifest subtle but distinct hormonal and metabolic milieu when compared to cases of PCOS identified based on the more stringent NIH criteria. The stated rationale for incorporating these additional phenotypes included the recognition that PCOS does not represent a single entity, but rather occurs on a spectrum, as well as the associated long-term health risks such as of type 2 diabetes mellitus and cardiovascular disease, commonly encountered in women diagnosed with PCOS. The Rotterdam consensus statement advocated widening the inclusion criteria to avoid missing patients with the potential for these increased health risks.

The most recent set of diagnostic criteria to be released was compiled by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society in 2009 [4]. Their expert review reexamined the key recognized features of PCOS, including menstrual dysfunction, hyperandrogenemia, clinical signs of hyperandrogenism, and polycystic ovarian morphology. Each feature was examined for its appropriateness for inclusion as a defining criterion, based on a thorough review of existing literature. A slightly modified version of the criteria for the diagnosis of PCOS emerged in this process: (1) hyperandrogenism, including hirsutism and/or hyperandrogenemia, (2) ovarian dysfunction, including oligo-anovulation and/or polycystic appearing ovaries, and (3) exclusion of other androgen excess or related disorders. The AE-PCOS criteria also acknowledge that related disorders of hyperandrogenism must be excluded, but allow that the clinician may take into account the prevalence of these differential diagnoses when deciding what tests to order. Disorders to consider in the differential diagnosis of PCOS include androgen-secreting neoplasms, Cushing's syndrome, 21-hydroxylase deficient congenital adrenal hyperplasia, thyroid disorders, hyperprolactinemia, and premature ovarian failure. Similar to the NIH criteria, androgen excess is a necessary component of the diagnosis by AES criteria. Therefore, the phenotype of ovulatory dysfunction and PCO alone—permissible under Rotterdam—does not qualify for a diagnosis of the syndrome by AES criteria. The combination of menstrual dysfunction and PCO, in the absence of features of hyperandrogenism or evidence of hyperandrogenemia has, in fact, been shown to have the most similar anthropometrics,

hormonal profile, and metabolic risks to the control subjects. The AES consensus criteria for defining PCOS are thus more inclusive than the NIH version but less so than the Rotterdam criteria.

Anti-Müllerian hormone (AMH) has recently been proposed as a parameter to replace ultrasonographic assessment of PCO morphology, with specificity and sensitivity of 97.1 and 94.6 % when using the Rotterdam criteria, or 97.2 and 95.5 % using the NIH criteria [5]. Indeed, AMH levels correlate independently with both PCO morphology and androgenic profile [6]. Another parameter proposed as an adjunct to PCO morphology is an assessment of the ovarian stromal volume, measured as a ratio of the stromal area to total area of the ovary (S/A ratio). Although this S/A ratio performed well when discriminating between women with and without PCOS, and correlated with androgen levels, it has not been adopted as part of any of the existing diagnostic criteria [7, 8].

Determination of hyperandrogenism in females can be problematic, both during clinical and biochemical assessment. Laboratory assays for androgens were initially designed for detection in males and have been calibrated accordingly. For example, total testosterone assays are typically calibrated for normal male levels, the lower end of which is 250 ng/dL. The upper end of normal female total testosterone ranges between 55 and 80 ng/dL (inter-laboratory differences exist and clinicians should familiarize themselves with the assay range for the laboratories serving their patient population). Both the above specified values are well below the fifth percentile for the assay detection range, where assay results may become unreliable; notably, calibration studies have not been done to develop a commercial female assay. An additional diagnostic dilemma is that the reporting of clinical hyperandrogenism is examiner-dependent and can be subjective. While a standardized tool such as the Ferriman-Gallwey score can objectify evaluation, this method has been shown to have good intra-observer reliability but poor inter-observer reliability [9]. Furthermore, a universal application of such tools across all ethnic groups may discount the normal ethnic variability in the appearance of body hair.

Inclusion of ultrasonographic evidence of PCO morphology into the definition of PCOS is controversial. The various sets of criteria place different degrees of emphasis on an isolated phenotypic PCO component not uncommonly encountered in the general reproductive age population; the NIH criteria do not address ovarian morphology, the Rotterdam criteria in 2003 include PCO as a phenomenon distinct from menstrual irregularities, and the AES lumps ovarian morphology into an "ovarian dysfunction" category along with oligo-anovulation and requires only one or the other to suffice as a diagnostic criterion. It is important to appreciate that PCO morphology is not specific to PCOS and can be found in 20–30 % of the general population of women 20–25 years of age; isolated PCO therefore should not be considered an indication of the syndrome in the absence of menstrual irregularities, infertility, or complaints of hirsutism [10].

In some ways, efforts to agree on diagnostic criteria are artifactual. There continues to be controversy and lack of complete agreement for what elements constitute optimal criteria for PCOS diagnosis, in part because of the natural clinical desire to move to discreet categorical criteria for the ease of diagnosis. In truth, there is a

Table 1.2 Relative population prevalence of PCOS (%) based on individual diagnostic criteria

	Diagnostic criteria		
	NIH[a]	Rotterdam[b]	AES[c]
March et al. [11]	8.7	17.8	12.0
Yildiz et al. [12]	6.1	19.9	15.3
Mehrabian et al. [13]	7.0	15.2	7.9

[a]National Institutes of Health international conference 1990
[b]Task force sponsored by the European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM), 2003
[c]Androgen Excess Society diagnostic criteria 2009

continuum of presentation from those persons minimally affected, with regular menses and only mild excess of androgens to those who have a unilateral PCO, to those who manifest more severe grades of androgen excess. Efforts to include hyperandrogenemia as diagnostic criteria will remain inadequate until the sensitivity of androgen assays is better refined because of our current inability to accurately quantify circulating androgens in women.

Prevalence of Polycystic Ovary Syndrome

The prevalence of PCOS in any specified population is dependent upon the diagnostic criteria used, but does have some regional and ethnic variation. While most reports on the prevalence of PCOS range between 2 and 20 %, the chosen diagnostic criteria are recognized to influence the determined prevalence. A retrospective birth cohort in Australia found a prevalence of 8.7 % using NIH criteria, 17.8 % using Rotterdam criteria, and 12.0 % using AES criteria [11] (Table 1.2). A similar prevalence pattern was found in Turkey, where 6.1 % met NIH criteria, 19.9 % met Rotterdam criteria, and 15.3 % met AES criteria [12]. In Iran the estimated prevalence of PCOS was 7 % based on the NIH criteria, 15.2 % using Rotterdam criteria, and 7.92 % using AES criteria [13]. In North America, most estimates of the general population in the United States range from 4 to 8 % in the literature, although most of this information comes from an unselected population of white and black women in the southeast region [14, 15]. Mexican-American women have a higher prevalence, reportedly as high as 13 % [16]. Interestingly, the estimated prevalence of PCOS among women in Mexico is 6 %, only half of that found in their counterparts in the United States [17]. These discrepancies highlight not just an ethnic diversity in the prevalence of the disorder but also the significance of lifestyle in the occurrence of PCOS.

In India, PCOS is reported among 9 % of adolescents [18]. Among Indian women 15–35 years of age evaluated at a rural gynecology clinic, 13 % presented with menstrual irregularities, half of which were found to have PCOS, estimating the prevalence to be around 6.5 % [19]. In Sri Lanka, a similar prevalence of 6.3 % was

noted among women age 15–39 [20]. In Iran, the prevalence of PCOS is reported as 8.5 % out of a sample of reproductive-aged women selected for participation in the Tehran Lipid and Glucose Study [21]. A Greek study on the island of Lesbos found a prevalence of 6.8 % [22]. The overall prevalence of PCOS among a population of urban indigenous Australian women, using NIH criteria, was 15.3 % [23]. A study in the United Kingdom found the prevalence to be 8 % using stricter NIH criteria, while 26 % of their population met Rotterdam criteria, illustrating the differences seen when using different diagnostic criteria. In Spain, a population of Caucasian women presenting spontaneously for blood donation was found to have a prevalence of 6.5 % [24]. By any measure, PCOS is one of the most prevalent endocrine disorders worldwide, with obvious regional and ethnic variation.

Excess in facial and body hair and intractable acne are common reasons for women to seek evaluation with subsequent unmasking of PCOS. Rates of hirsutism vary among ethnic groups. In the United States, the rates are similar between black and white women (around 5 %) [25], but in Kashmir, India, the prevalence is much higher at 10.5 % [26]. Among women with hirsutism, up to one-third have an underlying diagnosis of PCOS. Around 27 % of women presenting with acne were found in one study to have undiagnosed PCOS, compared to 8 % of controls [27]. Patients presenting with acne resistant to standard treatment have an even higher rate, near 50 % [28]. Among adolescents with irregular menses, after a 6-year follow-up period, 62 % continued to have irregular menses, 59 % of whom were diagnosed with PCOS. In other words, approximately one-third of the original adolescent population with irregular menses was diagnosed with PCOS within the study period [29].

Summary

PCOS is considered as the most common endocrine disorder amongst reproductive-age women and is characterized by a chronic course, with features that suggest varying combinations of reproductive functional deficits (such as ovulatory dysfunction or PCO morphology) and androgen excess (such as acne and hirsutism). The diagnosis of PCOS is based on well-defined criteria, and currently there are three major sets of diagnostic criteria available for utilization in clinical practice. Regional prevalence of PCOS can vary depending on the diagnostic criteria utilized as well as the ethnicity studied. Women with isolated symptoms of acne, hirsutism, and irregular menstrual cycles should be offered targeted screening. Beyond the symptom burden relating to PCOS that adversely impacts quality of life, and perhaps more clinically significant, is the higher prevalence of several medical comorbidities in the PCOS population that have been extensively covered in additional chapters in this text. Identifying PCOS and screening for these adjunct disorders will allow for timely institution of preventive strategies aimed at minimizing the overall health risk in this population.

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