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INVITED REVIEW

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Challenges in diagnosis and understanding of natural history of polycystic ovary syndrome

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Abstract

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy affecting 8%–13% of reproductive-aged women. The aetiology of the syndrome is complex, with genetic susceptibility, androgen exposure in early life and adiposity related dysfunction leading to perturbance in hypothalamic–ovarian function. PCOS clinical features are heterogeneous, with manifestations arising even in early adolescence, developing into multisystem reproductive, metabolic and psychological manifestations in adulthood. In this review, we will discuss challenges in the diagnosis of PCOS and understanding of the natural history of PCOS.

KEYWORDS
challenges, diagnosis, natural history, phenotypes, polycystic ovary syndrome

1 | INTRODUCTION

Polycystic ovary syndrome (PCOS) is a complex heterogeneous multisystem disorder affecting 8%–13% of reproductive-aged women[1] and 3%–11% of adolescent girls[2] depending on the diagnostic criteria used and the population studied. PCOS is characterized by oligo/amenorrhoea, clinical/biochemical hyperandrogenism (HA) and polycystic ovary morphology (PCOM) on ultrasound in adult women.[3] PCOS has significant metabolic (obesity, metabolic syndrome, impaired glucose tolerance, type 2 diabetes (T2DM),[4] cardiovascular risk factors), reproductive (anovulation, subfertility)[5] and psychological (depression, anxiety,[6] eating disorders,[7] impaired quality of life)[8,9] sequelae. Diagnosis of PCOS using the 2003 Rotterdam criteria is based on the presence of two of three features: oligo/amenorrhoea, clinical/biochemical HA and PCOM on ultrasound following exclusion of secondary causes. The Rotterdam criteria are recommended and endorsed by the 2018 international PCOS evidence-based guideline (EBG) for adult women.[10] This guideline with recommendations for PCOS diagnosis and management is underpinned by an extensive process of evidence synthesis involving 37 professional societies and consumer groups around the world, 71 experts in all aspects of PCOS, including consumers and extensive literature review with 40 systematic reviews and 20 narrative reviews detailed in the 1800 page guideline evidence document.[11–14]

2 | THE HISTORY OF PCOS AND ITS DIAGNOSTIC CRITERIA

In 1935, Drs Stein and Leventhal first published a case series of seven women with enlarged ovaries in association with menstrual disturbance and/or clinical HA.[15] The term Stein-Leventhal syndrome arose, but other names such as sclerocystic ovary syndrome and polycystic ovary disease were used interchangeably before the term polycystic ovary syndrome was finally settled on in the early 1990s. Nevertheless, there is ongoing advocacy for a name change for the condition as many clinicians, researchers and affected women consider the name PCOS a misnomer that does not reflect the true characteristics or complexity of the disorder.[16,17] Over and above renaming the disorder, the ideal diagnostic criteria for PCOS remains an ongoing and unresolved debate. Currently available diagnostic criteria and their phenotypes are presented in Table 1. Phenotypes A and B are considered 'classic' PCOS, Phenotype C is 'ovulatory PCOS' and Phenotype D is regarded as 'nonhyperandrogenic PCOS'.[18]

The first attempt to define PCOS occurred in an expert conference in 1990 sponsored in part by the National Institute of Child Health and Human Development of the United States (US) National Institutes of Health (NIH).[19] After a survey of all participants, mainly from US, regarding their perception of PCOS features, they concluded PCOS as an androgen-excess disorder of exclusion with ovarian consequences.[19] The 1990 NIH criteria therefore defines PCOS as the presence of both clinical and/or biochemical HA and ovulatory dysfunction (OD).[19] Using the criteria, PCOS prevalence is estimated to be between 5% and 8%, raising worldwide recognition for PCOS to be the most prevalent endocrinopathy in women of reproductive age.[1] While the diagnostic criteria were driven mainly by expert consensus rather than research evidence, it sets the scene for much of the subsequent literature, which contributes greatly to our current understanding of PCOS.

The European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine partly sponsored another expert conference in Rotterdam in 2003.[3] Deliberately including international experts from Europe and US, the consensus workshop group recognized PCOM on ultrasound as a cardinal feature of PCOS and proposed to include it as another diagnostic criterion.[3] The 2003 Rotterdam criteria broaden the definition of PCOS as the presence of any two of the three features of HA, OD and PCOM, after the exclusion of other causes.[3] This definition recognized additional phenotypes not included in the 1990 NIH criteria and further increased the prevalence of PCOS to between 8% and 13%.[1] The NIH Evidence-based Methodology Workshop on PCOS later also recommended to endorse the 2003 Rotterdam criteria in 2012.

The latest addition of PCOS diagnostic criteria was proposed in 2006 by the Androgen Excess Society, now known as the Androgen Excess and PCOS Society (AEPCOS). The Task Force included seven international experts in the field and generated a consensus, supported by evidence from a systematic literature search to reinstate PCOS as primarily a hyperandrogenic disorder and defines PCOS to be the presence of HA with either OD or PCOM.[20] This definition is broader than the 1990 NIH criteria but slightly more restrictive than the 2003 Rotterdam criteria, and gives rise to an estimated PCOS prevalence of 7%–13%.[1] Acknowledging that multiple classifications of PCOS adds to the confusion around PCOS diagnosis and that the addition of yet another set of diagnostic criteria for PCOS may be futile, the AEPCOS Task Force highlighted the need for PCOS definition to be evidence-based and highlighted that the definition of PCOS will likely evolve over time with newer research findings.[20]

Currently, the 2003 Rotterdam criteria is the most widely used diagnostic criteria for PCOS and this is also the definition recommended by the 2018 international PCOS EBG to diagnose adult women.[10] Diagnosis in adolescents can be particularly challenging due to the overlap of PCOS diagnostic features with normal pubertal physiology. As such, the application of the Rotterdam criteria in adolescents is likely to over-diagnose adolescents with PCOS with potential detrimental long-term health implications.[21] With a lack of research on an accurate diagnostic approach in adolescents, based on evidence-informed consensus, the new PCOS guideline recommends modified diagnostic criteria in adolescents. The guideline recommends that the diagnosis of PCOS in adolescents requires menstrual cycle irregularity well defined according to time post menarche and clinical HA (severe acne and/or hirsutism)/biochemical HA as the two essential criteria.[10] It is recommended that PCOM should not be used as a criterion for PCOS diagnosis within 8 years of menarche.[10] Adolescents meeting one of the PCOS diagnostic criterion may be considered 'at risk' of PCOS and benefit from follow up, in addition to symptom management.

TABLE 1 PCOS diagnostic criteria and phenotypes

	1990 NIH criteria			
	AE-PCOS criteria			
	2003 Rotterdam criteria			
	Phenotype A	Phenotype B	Phenotype C	Phenotype D
Hyperandrogenism	+	+	+	−
Ovulatory dysfunction	+	+	−	+
Polycystic ovary morphology	+	−	+	+

Abbreviations: AE-PCOS, Androgen Excess and Polycystic Ovary Syndrome Society; NIH, National Institutes of Health; PCOS, polycystic ovary syndrome.

3 | CONTROVERSIES REGARDING INDIVIDUAL DIAGNOSTIC CRITERION

3.1 | Ovulatory dysfunction

Women with PCOS commonly present with irregular menstrual cycles and anovulation, although neither of the criteria are mandatory for the diagnosis of PCOS according to the Rotterdam consensus.[3] As follicle development is slowed down by low action of follicle-stimulating hormone partly due to high anti-Mullerian hormone (AMH) levels, menstrual cycles tend to be longer in women with PCOS, thus resulting in oligomenorrhea. In cases with a more severe PCOS phenotype, women may also experience amenorrhoea. Indeed, a previous study showed that women with anovulation present more often with amenorrhoea (23.6%) compared to women with oligoovulation (10.3%).[22] The cycle length on average is 60 days for women with anovulation and 43 days for women with oligoovulation.[22] The women with anovulation and amenorrhoea also have higher androgen levels and waist circumference.[22] In line with this, another study reported cycle length reflects the severity of the syndrome, with the women with amenorrhoea representing a more severe phenotype.[23] Even though longer cycle length seems to predict anovulation, normal cycles may also present with anovulation. Interestingly, a study with over 3700 spontaneously menstruating women, aged 20–49.9 years and regular cycles, showed that as high as 26%–37% of cycles were anovulatory when validated against serum progesterone <3 ng/ml during the luteal phase.[11] In clinical practice, measuring luteinizing hormone surge that occurs one to one and a half days before expected ovulation (ovulation occurring 14 days before expected menses) or luteal phase serum progesterone (≥3 ng/ml 7 days prior expected menses and ±3 days) can assist in cases where ovulation is uncertain despite normal cycle length. Moreover, a previously published clinical review suggests cycle length >35 days being indicative for chronic anovulation, whereas in cases of cycle length that is slightly longer than normal (32–35 days) or slightly irregular (32 to 35–36 days), assessment for OD should be evaluated if only one other signs of the syndrome is present.[11,12] It has to be noted though, that when establishing the diagnosis, ovulation assessments are quite rarely needed as usually other characteristics (PCOM and HA) are present (Phenotype C). There are also some challenges in diagnosing anovulation and irregular menses especially in adolescents and young women as OD may persist long after menarche. The international guideline, therefore, calls for caution in diagnosing PCOS in young women less than 8 years from menarche.[13] It has to be noted also that affected women gain regular cycles with ageing.[14] Whether this results in more frequent ovulation or increased likelihood of spontaneous pregnancies is unclear and needs to be determined in future studies. The international PCOS EBG supports retrospective diagnosis if the woman has a history of irregular cycles in the presence of other diagnostic PCOS features (e.g., clinical/biochemical HA, PCOM).[10] Considering this, regular cycles in an older woman may not prevent establishing the diagnosis.

3.2 | Hyperandrogenism

Biochemical HA is probably more useful in establishing the diagnosis of PCOS as the assessments of clinical HA are highly subjective. Measurable circulating androgens include testosterone (T), dihydrotestosterone, androstenedione, dehydroepiandeosterone (DHEA) and its sulphated form DHEAS; however, it is agreed that total T and free T levels best correlate with HA. The accuracy and precision of T assays can vary widely depending on the method used. Mass spectrometry or radioimmunoassay (RIA) after extraction and chromatography are more accurate than direct assays (simple RIA, enzyme-linked immunosorbent assay or chemiluminescent immunoassay),[3,20,24] It is also important to note that normative range for T levels in women has not been well established as T levels are affected by ethnicity, age and body mass index (BMI).[24] The timing of testing also contributes to variability as T follows a diurnal pattern, and demonstrates variation across the menstrual cycle where T levels increase at mid-cycle.[24] Variation is also seen throughout a woman's lifespan where T levels peak after puberty and decline with age.[24] Ideally, the assessment of biochemical HA would best be performed in the morning and during the early follicular phase or after a withdrawal bleed, but the extent to which this improves accuracy remains uncertain.

Clinical manifestations of HA include hirsutism, acne and androgenic alopecia, all of which may be present in the absence of biochemical HA, partly due to altered sensitivity of target tissues to circulating androgens.[25] However, clinical acne and androgenic alopecia, which are estimated to be present in 12%–14% and 5%–50% of women with PCOS, are generally thought to be less accurate markers for HA not only because there is a lack of unified scoring system but also due to other contributing etiologies.[3,20] The PCOS phenotype varies over time. Androgen production decreases over time,[26] with a lower prevalence of acne and hirsutism as women age. Hirsutism, defined as the presence of excessive terminal hair in androgen-dependent areas of the female body, is the primary indicator of clinical HA and is estimated to be present in 65%–75% of women with PCOS.[20] The international PCOS EBG recently recommended a modified Ferriman–Gallwey score of 4–6 as being indicative of clinical HA.[10] Even though the modified Ferriman–Gallwey score is widely used to assess hirsutism, the cut-off values for ethnic variation across the lifespan have not been well established.[20,25]

3.3 | Polycystic ovary morphology

Identification of PCOM on ultrasonography requires an assessment of the number of antral follicles per entire ovary (FNPO) and ovarian volume (OV) to gauge the presence of follicle excess and/or ovarian enlargement. Characteristics of the ovarian stroma (area and brightness) or follicle arrangement may be helpful in corroborating the presence of PCOM but have less diagnostic accuracy for PCOS and are not recommended in the diagnostic

evaluation.[27] Transvaginal ultrasonographic (TVUS) imaging is the preferred approach to evaluate PCOM if sexually active and if acceptable to the patient. Using TVUS whose bandwidth includes 8 MHz, the PCOS EBG recommend a threshold on either ovary of FNPO ≥ 20 and/or OV ≥ 10 ml, ensuring no corpora lutea or dominant follicles are present.[13] The threshold for ovarian enlargement is consistent with previously proposed criteria based on expert opinion,[28,29] diagnostic test studies[30] and consideration of the upper limits of normal in healthy women with regular cycles and normal androgens.[31] However, the threshold for follicle excess is lower than the 25 follicles proposed by the AEPCOS Society[31] and substantially higher than the definition of PCOM previously supported by the Rotterdam consensus (i.e., FNPO ≥ 12).[29,32] Similar to that of the AEPCOS Society definition of follicle excess,[33] the EBG threshold for FNPO may result in the exclusion of a subset of patients (~20%) that would otherwise have met the Rotterdam criteria for PCOS status.[34] The excluded patients would now be judged to have solely HA or oligo-anovulation yet may display greater metabolic risk compared to eumenorrhoeic controls.[33,34] While the poorer metabolic profiles of the excluded patients could be interpreted as evidence for retention of the more conservative Rotterdam definition of PCOM, the EBG recommendations reflect a need to base diagnostic thresholds on data from the most unbiased populations available worldwide, as well as re-evaluation of the appropriateness of the 95th percentile to judge the upper limit of normal. Further, they acknowledge the need to account for the higher detection rates of small antral follicles which are possible owing to advances in image technology since the Rotterdam consensus.[31] The guideline recommends a focus on ovarian enlargement (OV ≥ 10 ml) when using older technology or transabdominal ultrasonography.[13] However, if adequate visualization of follicles in the largest cross-sectional slice of the ovary is available, a threshold of 9 or 10 follicles in a single slice (FNPS) can be used in combination with OV to increase diagnostic accuracy for PCOS.[27,28] Ultimately, these most recent EBG recommendations corroborate follicle excess as the most predictive marker for PCOS, followed by ovarian enlargement. Consistent with existing convention, identification of PCOM in one ovary is still considered sufficient. Data on the rates of unilateral versus bilateral PCOM are sparse. Yet, recent findings of left-right differences in PCOM support prioritizing the use of FNPO, over FNPS and OV as this metric showed the strongest correlation between ovaries and had no differences in the probability of unilateral versus bilateral PCOM unlike the other markers.[35] The guideline encourages more research in order to determine the biological relevance of PCOM and their association with short- and long-term health outcomes in PCOS.[36] Accurate criteria for PCOM that hold up across the reproductive lifespan are needed and we can expect revisions to criteria for PCOM as advances in imaging technology emerge, and cross-validation with serum markers (i.e., AMH) enable identification of surrogate or adjuvant measures for PCOM on ultrasonography.

4 | CURRENT UNDERSTANDING OF THE NATURAL HISTORY OF PCOS

4.1 | Genetics/epigenetics and heritability traits

PCOS is a heritable condition where daughters of affected women have 50%–60% risk and twin sisters 70% risk for the syndrome. Even though almost 30 loci have been identified in association with PCOS they explain less than 10% of the cases. Interestingly, the genetic traits seem to be similar among women with clinical and self-reported diagnosis.[37] Moreover, not all common traits, like BMI or mental distress, are causal from PCOS, thus other mechanisms may be involved.[38] Recent animal and human work have suggested epigenetic mechanism behind PCOS pathogenesis.[38] Epigenetic modifications can result from exposure to factors such as high levels of androgens or AMH in utero and they have been shown to carry over generations.[39] Future studies may also target epigenetic factors, opening new avenues for preventive strategies. Interestingly, not all women with predisposition to PCOS seem to develop the syndrome and it seems likely that postnatal triggers, such as early weight gain or environmental stress may in some cases be required.[40] Sensitive time windows and early triggers for PCOS should be revealed in future studies.

4.2 | Obesity

A large proportion of women (up to 88%) with PCOS have overweight or obesity.[41,42] Moreover, women with PCOS also have a higher risk of weight gain compared to those without PCOS.[43] Extensive evidence confirms a strong link between obesity and PCOS,[42] and the impact of weight gain on the development of PCOS.[41] Further findings from the 1966 Northern Finland Birth Cohort (NFBC) demonstrated an association between early adiposity rebound in childhood and PCOS diagnosis along with obesity during adulthood.[40] The NFBC study provides major highlights related to obesity and the natural history of PCOS from adolescence to adulthood.[40] However, other similar high-quality longitudinal studies to corroborate the findings and unravel the natural history of PCOS are needed.

An ongoing systematic review of longitudinal cohort studies indicates that in adult women, change in BMI over time does not seem to differ significantly between women with and without PCOS as observed by the majority of investigators.[44,45] Studies in adolescents suggest that increases in BMI are apparent during adolescence in girls who may develop PCOS, as shown by the consistent BMI increase from age 10 years onwards[46] and which may precede PCOS diagnosis.[47] However, assessment of BMI over time was not routine in most longitudinal studies and the current literature has inadequate data from community-based cohorts and adolescents. More research is needed to explore the natural history of BMI and/or weight gain in PCOS across the life course using standard and uniform indicators for changes in BMI over time.

4.3 | Metabolic outcomes

Core metabolic outcomes in PCOS include waist circumference, T2DM, insulin resistance, impaired glucose tolerance, hypertension, coronary heart disease, lipid profile, and venous thromboembolic disease.[48] Substantial evidence demonstrates PCOS to be associated with a higher risk for cardiometabolic diseases including T2DM, myocardial infarction and stroke, which are the major causes of mortality in women.[49] Understanding the natural history of the metabolic outcomes in PCOS is therefore vital and a key priority in PCOS research. This requires data from high quality long-term longitudinal studies, but most of the evidence regarding the association of PCOS with cardiometabolic outcomes such as dyslipidaemia, hypertension and hyperglycaemia is from cross-sectional studies.[50]

A recent review of longitudinal studies demonstrated a higher quantified risk of metabolic disease in women with PCOS compared to their counterparts.[51] It is important to evaluate data from longitudinal studies that have compared metabolic risk factors and outcomes over time in women with and without PCOS to establish natural history. Findings from longitudinal cohort studies suggest that the risk of developing T2DM is significantly higher in women with PCOS aged 15–69 years compared to those without PCOS.[45,52,53] The risk of cardiovascular disease (CVD) on the other hand, does not seem to vary significantly over time in adult women with PCOS compared to those without PCOS.[54,55] However, in most of the studies, participants studied were in a younger age group and therefore less likely to have CVD. Differences in other metabolic outcomes including dyslipidaemia[52,53,56] hypertension,[45,52,53,56] impaired glucose tolerance[57] and insulin resistance[44,45,52] remain unclear with conflicting and/or insufficient longitudinal data. These data demonstrate existing inconsistencies and limited quality of longitudinal studies in PCOS, including variations in outcome measures and time of follow-up.[58]

4.4 | Reproductive outcomes

It has been commonly thought that women with PCOS have poor reproductive outcomes. This may be true for pregnancy outcomes, however, not for parity. Indeed, recent register studies from Finland and Denmark, both countries with affordable and equally available health care covering fertility treatments, show even higher parity for women with PCOS compared to non-PCOS controls (at least one child Finland 49.2 vs. 41.1%; Denmark: 19.5 vs. 13.2%).[59] Given that potential infertility is a significant source of worry to many women with PCOS, this information should be disseminated and translated in clinical practice especially if the women have access to assisted reproductive technology (ART). Given that women with PCOS reach menopause later than non-PCOS women,[60] it is still not clear whether this translates into an extended fertility window for affected women. As for pregnancy outcomes, there is emerging evidence that PCOS presents a 2–3 fold risk factor for miscarriage, pregnancy-induced hypertension, pre-eclampsia, gestational diabetes mellitus (GDM) and prematurity independent of BMI.[61] Many of the studies are based on hospital registers and this may also explain some discrepancy from population-based data where BMI seems to play more significant role, especially for GDM.[62] Some of the data also points towards hyperandrogenic phenotypes being at higher risk especially for miscarriage and pre-eclampsia whereas ART does not seem to promote the risk.[61] It has been suggested that androgens may promote androgen resistance in PCOS endometrium, thus contributing to higher miscarriage rate and shallow placentation thus suggesting impaired luteal phase among affected women.[63,64] Indeed, some women with more severe phenotypic expression of PCOS may have impaired decidualization response, with metabolic dysfunction most likely also playing a role.[65,66] Lifestyle management is recommended for all women with PCOS as the first-line treatment and prepregnancy weight management should be aimed to optimize fertility outcomes for the patients.

4.5 | Psychological comorbidity in PCOS

Psychological comorbidity is the most recently understood association of PCOS with abundance of evidence showing increased prevalence of psychological distress, sexual dysfunction, mood disorders, eating disorders, personality disorders and even frank psychiatric disorders in women with PCOS.[7,8,67] Potential aetiologies included psychosocial (adverse childhood trauma), hormonal (insulin resistance, HA, hypothalamic–pituitary–adrenal axis disturbances), genetic and epigenetic (prenatal androgen exposure) factors but the interplay of their relationships are difficult to decipher.[8,68] Furthermore, studies on PCOS-related symptoms (hirsutism, obesity, infertility) predictive of negative psychological outcomes also reported conflicting findings.[67,69] Other major barriers to the understanding of the natural history of developing psychological comorbidities in PCOS are the lack of longitudinal research and the paucity of unselected community-based study populations which include their childhood or adolescent years.

The natural history of psychological comorbidities of PCOS during childhood may be postulated from studies exploring the neuropsychiatric development in offspring of women with PCOS given that PCOS is highly heritable. Several studies have now reported a link of anxiety, depression, conduct disorder, attention-deficit/hyperactivity disorder, autism spectrum disorder and Tourette's disorder in offspring of mothers with PCOS thought to be related to in utero androgen exposure.[70,71] Longer-term longitudinal evidence is only available for depression and/or anxiety in PCOS. Combined data indicate that depression and/or anxiety symptoms were increased in women with PCOS during their reproductive years when compared to women without PCOS.[72] However, a steady decline in depression and/or anxiety scores in women with PCOS over time was observed in a trajectory similar to women without PCOS.[72]

4.6 | Controversies in PCOS natural history

There are limited large community-based studies exploring PCOS prevalence, the impact of body weight and the natural history of PCOS related metabolic, reproductive and psychological sequelae. Many existing studies have been in selected clinic populations, limiting interpretation, and often with conflicting results. The 2018 international PCOS EBG summarized the data in the existing literature on the natural history of PCOS and also identified clear research gaps and the need for additional studies in these areas.[1] There are many cross-sectional cohort studies in PCOS; however, cross-sectional studies limit interpretation of results to only associations between the variables of interest and cannot establish causation. Large community-based studies, especially those with a longitudinal approach, are expensive, time-consuming and laborious; however, they provide an invaluable source of information for researchers on the natural history of a condition.

In large population-based studies, it is often not possible or feasible to screen for PCOS by means of physical or laboratory assessments due to the limitation of available resources to facilitate this. Often self-reported PCOS status or self-report of symptoms consistent with PCOS[11] or self-report of physician-diagnosed PCOS are used instead as an alternative approach and permits the study of larger populations with repeated measurements over long periods of time. The symptom-based PCOS diagnosis has been used in the Northern-Finland Birth Cohort 1966 studies since 1997. The validity of this symptom-based approach has also been confirmed by a recent study which demonstrated that 82.5% of women who self-reported hirsutism and irregular menses fulfilled the Rotterdam diagnostic criteria for PCOS when assessed clinically by a medical professional in comparison to 14.4% of women meeting Rotterdam criteria who reported neither symptom.[14] The sensitivity of self-report in predicting PCOS using the Rotterdam criteria was 89% with a specificity of 78%, thereby offering a time-efficient, practical and financially sustainable approach to identifying women with PCOS for larger population studies.[14] Self-report of physician-diagnosed PCOS has been used in the Australian Longitudinal Study on Women's Health and self-reported PCOS has been validated in this cohort against menstrual irregularity, which is a key feature and diagnostic criteria for PCOS.[43] Indeed, genome-wide association (GWAS) studies in PCOS seeking to identify candidate genes in PCOS have found that despite the diagnostic criterion used for PCOS, whether it is Rotterdam, NIH and also self-reported, women with PCOS share a similar genetic architecture, supporting the validity of self-reported PCOS.[15]

While the thresholds for menstrual cycles, HA and hirsutism (modified Ferriman–Gallwey scores) have been defined, these current normative cut-offs are based on arbitrary 95th centiles in variably defined populations. Diagnostic features can vary across the reproductive lifespan and often represent a continuum across the lifespan.[73] Androgen levels are often dependent on specific laboratory ranges as defined by the assay manufacturer.[10] There is significant ethnicity related variation regarding hirsutism, with recommendations for suggested cut-offs for the modified Ferriman–Gallwey score according to the 95th percentile in different unselected populations of premenopausal women, varying from a score of 2 in women of Chinese ethnicity to a score of 10 in women of Mediterranean ethnicity.[25] All these factors make it extremely difficult to distinguish between women with PCOS and those without, due to overlapping features and a lack of population-specific definitions for normative values.

The definition of PCOM has also posed challenges, with updated recommendations on the definition of PCOM. Factors contributing to the revision of the definition of PCOM include inadequate evidence informing initial criteria, poorly defined cut-offs between normal ovaries and PCOM, recent advances in ultrasound technology with greater resolution, the operator-dependent nature of ultrasound with operator skill level contributing to variation, lack of standardized reporting, the impact of approach (transvaginal vs. transabdominal), body habitus and age.[10] The FNPO threshold was recently overturned by the 2018 PCOS EBG with a recommendation for FNPO changing to ≥20 follicles, but the OV threshold held following a robust evaluation of the available evidence.[10] PCOM is detected in upto 70% of adolescents (using original criteria for PCOM); therefore, the PCOS EBG does not recommend the use of PCOM for diagnosis of PCOS in adolescents until 8 years postmenarche[10] due to the overlap of PCOM in healthy adolescents and adolescents with PCOS, as it may lead to overdiagnosis of PCOS in this cohort.

Studies with self-reported PCOS do not usually offer enough detail about PCOS diagnostic criteria to be able to define PCOS phenotypes. Some large cohort studies have been able to conduct clinical assessments to establish PCOS diagnosis; however, this approach requires substantially greater resources to achieve this.[25,31–33] Studies with clinically validated PCOS diagnosis are often able to collect information regarding each diagnostic criteria, thereby providing the ability to be able to distinguish between the different PCOS phenotypes and thus contribute more widely to the pathogenesis and clinical questions related to the syndrome. Approximately two-thirds of women with PCOS present with the classic form of PCOS (Phenotypes A and B). In this subgroup of women, obesity is often present, but its prevalence does vary greatly among populations. There is an increased risk of metabolic syndrome, impaired glucose tolerance, T2DM, and increased cardiovascular risk factors, but their prevalence is influenced greatly by body weight and obesity.[18] Phenotype C often has a milder form of PCOS with less severe insulin resistance and hyperinsulinemia and with a lower prevalence of metabolic and cardiovascular risk factors compared to women with classic PCOS.[18] In these patients, body weight is often normal or only slightly increased, and changes in body weight may exacerbate reproductive and metabolic features of PCOS and may move patients to a more severe phenotype.[74] Phenotype D, normoandrogenic PCOS, is present in women with chronic anovulation and PCOM but normal androgen levels.[18] There is a paucity of data in this subgroup of women and more studies are needed to understand the natural history of PCOS in this group.

There is substantial clinical heterogeneity in PCOS seen in studies. Key factors that contribute to this heterogeneity are ethnicity and geographical variation.[75] Casarini and Brigante[76] reported women from Asia and America to more often be represented by the metabolic phenotype of PCOS, which is typically characterized by central obesity, high BMI, insulin resistance and increased risk of T2DM.[76] However, women from Europe and the Middle East often have the more hyperandrogenic phenotype, which is typically characterized by HA, hirsutism and androgenic alopecia.[76] A recent systematic review examining dysglycaemia in women with PCOS found that there was substantial heterogeneity and that ethnicity explained a significant amount of this heterogeneity. The review found that there was a higher risk of dysglycaemia in women from Asia and America and a moderate risk in women from Europe. This ethnic difference was even independent of obesity among women who developed impaired glucose tolerance, suggesting that there is a genetic predisposition contributing to this risk. Women with PCOS from Asia often express a higher metabolic risk[77] than women from other parts of the world. GWAS in Chinese, Korean and European populations have helped towards the understanding of the novel and genetic susceptibility loci for PCOS and reported single-nucleotide polymorphism which have demonstrated some variation between different racial and ethnical groups.[78] There is still much more that remains to be understood in the development and pathophysiology of PCOS, which may also in part explain the ethnicity related variation observed among women with PCOS.

5 | CONCLUSION

PCOS is a complex heterogeneous multisystem disorder. A key factor contributing to this complexity is the PCOS diagnostic criteria that have evolved over time. The diagnostic features of PCOS can vary significantly over the reproductive lifespan, based on BMI and also on ethnicity. PCOM can be dependent on the sensitivity of the transducer used and testosterone levels can vary depending on the assay used and the timing of testing. Many of the normative cut-offs for the existing PCOS diagnostic criteria are based arbitrarily on a 95th percentile cut off with little understanding of the true normative range in populations, with little data based on large unselected community-based populations with geographic and ethnic diversity. The currently accepted Rotterdam diagnostic criteria give rise to four distinct PCOS phenotypes, with much of the existing literature not reporting on PCOS phenotypes and grouping women with PCOS as a whole. Many studies in PCOS are cross-sectional and there are very few large longitudinal community-based studies to help understand the natural history of PCOS and its associated metabolic, reproductive and psychological features. Much of the existing longitudinal epidemiological studies use self-reported PCOS status, with no clinical or biochemical confirmation of PCOS status. Large longitudinal community-based studies across different ethnic populations can add substantially to new knowledge in the natural history of PCOS and support other data approaches. The ability of such longitudinal population studies to have clinically and biochemically validated data on individual PCOS diagnostic features, thereby providing data on PCOS phenotypes, would help make substantial and significant advances in improving PCOS diagnosis and understanding PCOS natural history. More resources are needed to conduct such well-constructed longitudinal studies across various ethnic populations.

AUTHOR CONTRIBUTIONS

All authors contributed and approved the final draft of this manuscript.

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The authors declare no conflict of interest.

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