The diagnostic dilemma of Polycystic Ovarian Syndrome (PCOS)

Introduction

There is significant disagreement among experts on the presentation of Polycystic Ovarian Syndrome (PCOS) (1-4). By definition, a syndrome is a grouping of symptoms and for PCO, these symptoms are poorly defined with significant debate as to which should be included (4). This creates a lack of uniformity or consistency within research regarding the aetiology, prevalence, symptoms, risks, and treatments for PCOS, making it difficult to understand the epidemiology of the syndrome (1). Rather than provide contested and inconclusive epidemiological statistics, this paper will focus on the technical and ethical issues regarding the definition and diagnostic criteria for PCOS. The history of the diagnostic criteria, issues associated diagnostic testing measures, and most importantly, the larger consequences of these criteria will be discussed. Ultimately, there is a clear need for the revision and specification of PCOS criteria, both for the benefit of individuals suffering from PCOS and for the sake of advancing science.

Diagnostic Criteria History

PCOS was initially documented by Chereau and Rokitansky in the mid-1800s (5,6). In 1935, Stein and Leventhal's article became the first record of PCOS in medical literature (7). They associated amenorrhea with enlarged, polycystic ovaries along with symptoms of hirsutism, acne and obesity (3,7). 85 years later, PCOS is still characterized by these symptoms, but the scientific community has yet to agree on which ones are necessary versus secondary.

There are three, conflicting, proposed criteria [Table 1] (3). The NIH/NICH criteria, created in 1990, stipulated that hyperandrogenism and menstrual dysfunction are the relevant factors (1). In 2003, the ESHRE and ASRM created a new set of diagnostic metrics, known as the Rotterdam criteria, which was also amended in 2012 (8, 9). They asserted that two of three factors were required: hyperandrogenism, polycystic ovaries, and/or oligio-anovulation. Widening the diagnostic criteria increased the patient population who qualified as having a PCOS diagnosis and created more heterogeneity among those included (10). Specifically, this added women with androgen excess and polycystic ovaries, but normal ovulatory function (Table 1, Phenotype C) as well as those with oligio-anovulation and polycystic ovaries but not hyperandrogenism (Phenotype D) (4,8,10). The Androgen Excess Society then redefined the criteria again in 2006, requiring hyperandrogenism in tandem with ovarian dysfunction and/or polycystic ovaries, thus excluding Phenotype D (11,12).

While the Rotterdam criteria is the most commonly used, there is considerable variation across countries and medical specialties (15). Experts continue to argue as to whether androgen excess is necessary, as the NIH and AES criteria contend, or if the broader Rotterdam definition is better (4,8). The lack of consensus among the scientific research community leads to problems with determining the prevalence of the syndrome. When using the NIH criteria, global levels are about 5-9%, Rotterdam brings them up to 20% and the Androgen Excess Society criteria shows them to be 10-15% (14-16). Not only is there no agreement in defining the patient population, but the testing measures presented by all of these criteria lack clarity and specificity.

Diagnostic Testing Measures

Hyperandrogenism (HA)

Androgen excess is characterized by hirsutism, acne, and androgenic alopecia (2). Hirsutism is most commonly measured by a modified Ferriman-Gallwey (mFG) score (1,17,18). Yet, measuring hirsutism is variable due to the subjectivity of the clinician and the ethnicity of the patient, as well as a lack of consensus on which score is considered a positive hirsutism result (13, 15). Acne and alopecia are both measured completely subjectively, and androgen assays are also insensitive (15). A meta-analysis determined androgen assays as the weakest measurement among PCOS symptoms (13, 18). Which androgens should be measured is not unanimous across studies, with some simply testing total T and others testing a comprehensive panel (12,15).

Oligio-Anovulation (OA)

Oligio-anovulation is currently defined by menstrual dysfunction. While this may seem like a clear-cut assessment, there is debate as to how this should be measured (15). Older epidemiologic studies use >35-day cycles as the metric of abnormal, while new studies use >45 days (2,15). Anovulation can also create shorter periods, but literature on what should be considered abnormal here as it relates to PCOS is absent. One suggestion to consider is defining oligio-anovulation as cycles <22 or >42 days per year (19).

Polycystic Ovaries (PCO)

The presence of polycystic ovaries (PCO) is the second metric that is utilized to diagnose ovulatory dysfunction. Cysts signify halted development of a dominant follicle, which curtails ovulation (20). However, PCO are commonly found in women, with studies showing 20-30% of normal women have evidence of PCO (21-24). None of the criteria see the presence of PCO alone as sufficient for diagnosis, though many patients are not made aware of this (1). The Rotterdam criteria defines PCO as 12 or more follicles measuring 2-9 mm in diameter or increased ovarian volume greater than 10 cm in one ovary (1,4,13). However, with newer technology, many experts believe a higher threshold should be utilized, as the devices available make this definition “now obsolete” (25-27). A Task Force Report from the AES recommends a threshold of 25 follicles or greater, or in the absence of newer technology, using only ovarian volume and excluding these results from research (11). One other new school of thought is to shift from testing PCO to AMH, which is considered to be a valuable tool for future use, however this debate cannot be covered in the scope of this paper (28-37).

Timing

One final problem with testing is the issue of transitionary findings. There are not established metrics to determine abnormal androgen levels for adolescents (38). Oligio-anovulation is common in pubertal development and adolescents have higher numbers of ovarian follicles as well (39-43). Therefore, younger woman would be more likely to meet the Rotterdam criteria simply because it utilized studies of women in their late twenties and early thirties (29, 36). For

women between 18-27 who are not on hormonal contraception, the prevalence of PCO is as high as 66-84% (29, 44). Some experts have suggested that an adolescent diagnosis must include all three measures in the Rotterdam criteria, but there is little, high-quality evidence on this specification and thus no consensus on how to account for adolescents (2, 39,40,45). A second timing problem is the influence of hormonal contraception. The fact that many contraceptive options suppress androgens is well established, given that it is a method of treatment for androgen excess (46). However, a "rebound" effect has been noted when patients terminate contraception use (47). Therefore, timing in relation to contraceptive use could highly influence the outcome of testing for the presentation of androgens and ovulatory dysfunction as well.

The Diagnostic Criteria Debate

While testing is problematic, there are larger consequences of these broad and widely contested criteria. Scientific discourse mainly centres around which PCOS phenotypes deserve to be included in the criteria [Table 1], specifically, whether Phenotype C should be included and most contentiously in regard to the inclusion of Phenotype D (48). However, when analysing this argument, it is vital to first consider the aim of syndrome diagnosis. The purpose of diagnosing a syndrome is to provide an awareness of associated risks and potentially a path for treatment options, as well as to create an organized foundation on which to conduct further research (13). When assessing all three criteria by these two measures, it is evident they are insufficient in their current form.

Criteria Flaws for Risk Assessment

Risk Discrepancy

PCOS has multiple health implications across the lifespan, including a higher risk of detrimental metabolic, cardiovascular, reproductive, and psychosocial outcomes (2,13). However, it is important to consider which criterion, or combination of criterion, are relevant for associated risks. The current criteria options cast a wide net for who is considered to have the syndrome, and thus PCOS presentation has considerable variability, translating to variable risk profiles among patients. Women who have a "classic" PCOS presentation – Phenotypes A and B – must understand that they are at high risk of developing associated diseases. Women in these categories have greater menstrual dysregulation, increased insulin levels, more severe dyslipidaemia and higher prevalence of obesity, rates of insulin resistance, BMI, cardiovascular risk and risk for metabolic syndrome (3,49-55). Phenotypes A and B account for about two-thirds of PCO patients overall, and patients with greater symptom severity are often used in research studies (56). Despite ample research that Phenotypes C and D lack the same long-term risks, they are often grouped under the PCOS umbrella without accounting for these differences (2-4,11,55,57). This status quo is a disservice to all phenotypes. The inclusion of less-severely affected phenotypes should be clearly demarcated and strictly based on which combinations of symptoms would benefit from being grouped in this syndrome.

Phenotype C and Metabolic/Cardiovascular Factors

One factor that changes the risk profile of a PCOS patient is the existence or absence of insulin resistance, which is found in 50-70% of women with PCOS and associated with an increased risk of type 2 diabetes and possibly cardiovascular disease (1,2,15,22). Evidence points to the idea

that hyperandrogenism, specifically, is most closely linked with high insulin levels and metabolic risk, irrespective of BMI (Q 55, 58,59). The combination of luteinising hormone and excess insulin increases androgen production and decreases SHBG, creating higher concentrations of free androgens (60). Interestingly Phenotype C is often found with insulin resistance (61). This demonstrates that despite Phenotype C's different risk profile from Phenotype A or B, it may still have PCOS-related risks *when insulin resistance is considered.* Given the common finding of polycystic ovaries, there is very little evidence of how Phenotype C without insulin resistance differs from "idiopathic hyperandrogenism", which is currently, yet oddly, placed in the category of androgen disorders to exclude in a PCOS diagnosis (1). However, when hyperandrogenism and insulin resistance are both present, there is support for including this as an individually defined, but associated, subcategory.

Phenotype D and Reproductive/Psychological Factors

Conversely, there is little data to demonstrate how Phenotype D is related to these other subgroups in any other way aside from having a factor (PCO) that shares a name with the syndrome. Without hyperandrogenism, patients do not have the same long-term risks (13). Even those who are obese have lower rates of hyperglycaemia than those with hyperandrogenism, weakening the metabolic connection as well (62). This subgroup is associated with PCOS only in that it shares the risk of infertility and other risks associated with anovulation, such as endometrial carcinoma (15,63). While PCOS is known to be the most common cause of infertility, there is little evidence that PCOS-specific factors are related to infertility for Phenotype D. Women with PCOS are predisposed to obstetric issues such as gestational diabetes, pre-eclampsia, foetal macrosomia, and perinatal morbidity and mortality, but these factors are related to hyperandrogenism and/or insulin resistance (3,12, 64-68). Without hyperandrogenism or insulin resistance, the remaining reproductive risk is simply infertility. Thus, grouping someone without hyperandrogenism and insulin resistance under the umbrella of PCOS, when they do not share the risks, seems to lack utility. Moreover, a diagnosis of PCOS may be potentially harmful if the issue is actually hypothalamic amenorrhea. There is support in the research that that the presence of polycystic ovaries often leads to this misdiagnosis, especially when considering the outdated thresholds and subjective analysis of PCO testing (3,11,69-72). This misdiagnosis can have severe consequences, as PCOS patients are emphasized the importance of diet and hypothalamic amenorrhea is worsened by dieting, potentially exacerbating reproductive risks to detrimental effects.

There are also psychological risks to consider. Women with less severe phenotypes are often unaware of the evidence for differences in risk profiles (4,11). A PCOS diagnosis can generate fear and anxiety due to the associated fertility issues, necessity for further screening, and diet or lifestyle changes (40,73). One study found that women who were given a PCOS diagnosis in a hypothetical situation had lower confidence and perceived their condition to be more serious than those not given the label (2). Particularly given the limitations of PCOS research, the risks of not providing a diagnosis must be weighed against the risks of overdiagnosis, such as impairing well-being, quality of life, and socio-economic expenditures (74). Overall, the additional risks for Phenotype D beg the question of what purpose grouping this phenotype under PCOS serves, given the distinctly different risk profile and little connection to the other subgroups. Thus, there seems to be limited value, and considerable harm, in the inclusion of this phenotype under the current criteria.

Critical Flaws for Scientific Research

The absence of standardized, more specific methodology creates a delay in scientific progress in understanding PCOS (15). The current diagnostic criteria imply an understanding of these different phenotypes, but data for the classic presentation is muddled while the non-classical presentations are simultaneously overshadowed (4). Rather than publishing papers that argue for or against the validity of the Rotterdam criteria, experts should consider specifying or reorganizing groups based on explicit factors that influence PCOS risks and treatment. One doctor in New Zealand has proposed a novel approach, with four PCOS subgroups that are broken down by specific biochemical profiles as opposed to different variations of the Rotterdam criteria [Table 2]. By separating PCOS groups by different forms of hyperandrogenism, new considerations come to light, such as potential links to inflammation and adrenal dysfunction (75-82). While this is a rudimentary model that requires far more research, it conveys how a more clearly systematized framework could benefit patients through specifying biochemical pathways that clarify risks and treatment, as well as provide organizational structure for advancing scientific research.

Concluding Recommendations

In the words of Michael Crichton, "there is no such thing as consensus science. If it's consensus, it isn't science…consensus is invoked only in situations where the science is not solid enough" (83). PCOS, in its current form, cannot even be understood to be consensus science, as there is little consensus, much less, scientific evidence, for many factors associated with the syndrome. There is no question that more research is required to understand PCOS and the current diagnostic criteria hinders both current utility and future research. There are four recommendations that can be useful for approaching this dilemma. First, criteria must account for transitionary changes in symptomology, such as adolescence or hormonal contraception use. Second, insulin should be accounted for in some capacity, both to specify Phenotype C from general idiopathic hyperandrogenism, and to provide better indications of differences in risk among subgroups. Third, the AES criteria that calls for denouncing Phenotype D is seen as a valid amendment, given the dangerous overlap with hypothalamic amenorrhea, the unnecessary psychological risks, and the lack of relevance as a PCOS subgroup. Finally, PCOS desperately requires a new name. One would not call TMJ syndrome "teeth grinding syndrome", as many teeth grinders do not have the symptoms or risks of TMJ. Using the common finding of polycystic ovaries to label a syndrome is detrimental to the general understanding of the syndrome, particularly as PCO becomes an increasingly outdated measure. Overall, PCOS criteria desperately needs to be iterated upon.

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Table 1:

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			

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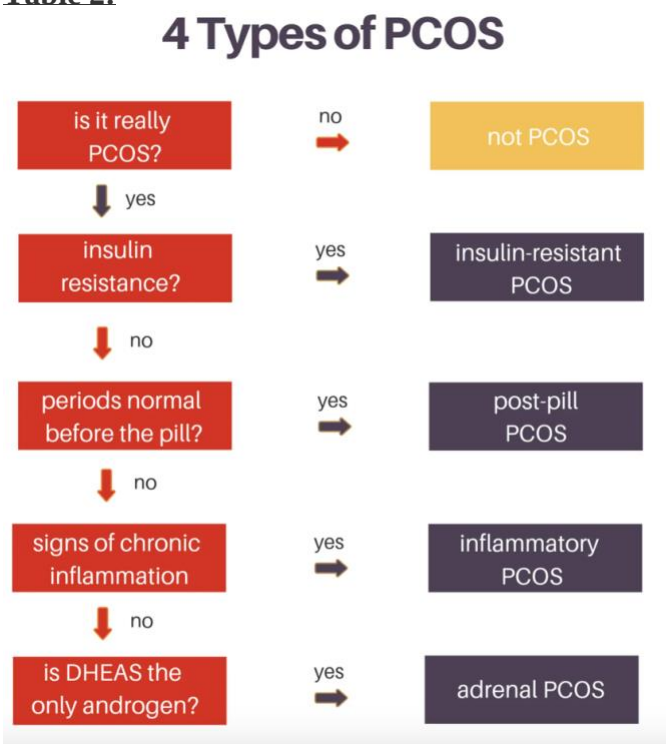
Table 2:



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