Polycystic Ovarian Syndrome: Is It Time to Rename PCOS to HA-PODS?

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Abstract The term polycystic ovarian syndrome (PCOS) came into existence 80 years ago. Pathophysiology of PCOS remains ill understood despite extensive research in this field. It is now accepted that the manifestations of PCOS are not confined to the reproductive dysfunction, and there are endocrine–metabolic implications to PCOS with

several consequences to female health. PCOS is a misnomer as ovaries do not contain epithelial cysts, but they are actually antral follicles. Moreover, the name PCOS neither reflects the hyperandrogenism which is essential for diagnosis nor the metabolic derangements. While various authors have expressed the need for change of the name, a suitable new option has not yet been established. This review aims to analyse the current understanding of pathophysiology of PCOS and addresses to the controversies associated with its diagnosis and nomenclature. The name “Hyperandrogenic Persistent Ovulatory Dysfunction Syndrome or HA-PODS” is proposed here to overcome diagnostic pitfalls of previous nomenclature. This new name will help formulate appropriate treatment and promote consistency in research as well. Further categorizations of HA-PODS are also discussed in the article.

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Introduction

Polycystic ovarian syndrome (PCOS) is an enigmatic entity so far. The syndrome was first described in 1935 when American gynaecologists Stein and Leventhal associated the presence of ovarian cysts with anovulation [1]. For many years these factors were used as the diagnostic criteria of the syndrome. The scope of PCOS has expanded to an endocrine–metabolic disorder that implies several consequences to female health, including high rates of infertility, hyperandrogenism, insulin resistance (IR), and hyperinsulinemia as well as many cosmetic problems. Several comorbidities, including obesity, dyslipidaemia, hypertension and type 2 diabetes mellitus (DM2) are higher in women with PCOS. These features, along with other alterations such as endothelial dysfunction and a chronic low-grade inflammatory state, underlie the greater risk of developing cardiovascular disease and increased all-cause mortality observed in these subjects [2].

This review aims to discuss the controversies associated with its diagnosis and nomenclature. Due to its widened scope and various phenotypic presentations, the name “PCOS” seems to be incomplete.

What Goes Wrong in PCOS?

Normal ovulation requires three components, namely intact central hypothalamic–pituitary–ovarian axis, synchronized feedback signals, and normal local responses within the ovary [3].

Causes of anovulation like stress, anxiety, crash diet, pituitary disorders, and thyroid disorders, exist in many women. If these causes are not corrected, anovulation persists and leads to vicious cycle depicted in Fig. 1.

Hypothalamic–Pituitary–Ovarian Axis Disruption

Chronic deficiency of progesterone due to persistent anovulation caused by many genetic and environmental factors leads to vicious cycle (Fig. 1). This continues unless interrupted with treatment.

Abnormal Feedback Signals

Interestingly many important hormones act differently at different serum levels at different phases of cycle and hence have different feedback signals.

- Early follicular phase: Estradiol levels must fall sufficiently low for FSH action.

Fig. 1 Vicious cycle of persistent anovulation

- Late follicular phase: Estradiol levels must rise enough for LH surge and action.

Various disorders, like obesity, thyroid, and hepatic disease, can lead to inappropriate oestrogen levels. These factors lead to abnormal feedback signals.

Local Ovarian Conditions Preventing Selection of Dominant Follicle

Autocrine/paracrine activity and several other local factors may lead to persistence of many follicles and lack of development of single dominant follicle.

- Role of ovarian androgens secretion:
 - Androgens in low concentrations: Serving as substrate for FSH-induced aromatization, the androgens in low concentrations enhance aromatase activity and oestrogen production.
 - Androgens in high concentrations: At higher concentrations, the granulosa cells favour the conversion of androgens to more potent 5 α -reduced androgens, which cannot be converted to oestrogen and in addition, and are capable of inhibiting aromatase activity and FSH induction of LH receptors.

Thus, raised local androgen concentration above a critical level inhibits the emergence of a dominant follicle and leads to follicular atresia in non-dominant follicles. PCOD results as multiple follicles develop without the dominant follicular development.

- Role of anti-mullerian hormone (AMH) secretion:
 - AMH in low concentration: It is required for transition from the primordial to the primary stage,

dominant follicle selection, and progression to ovulation.

- AMH in high concentration: It exerts powerful inhibition of primordial follicle initiation and follicle sensitivity to follicle-stimulating hormone (FSH). There is disruption of ovarian physiology due to high levels.

Role of Insulin

PCOS appears to result from combination of environmental and genetic factors; both factors favour the development of IR. IR leads to compensatory hyperinsulinemia, which substantially augments ovarian androgen synthesis by increasing LH pulse frequency at the pituitary by stimulating GnRH gene transcription in hypothalamic cells. Insulin also triggers hyperandrogenemia by directly activating mitogenic pathways in ovarian cells and increasing transcription of StAR and several key steroidogenic enzymes. Hyperandrogenemia is the key factor in disrupting ovarian physiology leading to typical clinical features of PCOS. Increased ovarian production of androgens may in turn worsen IR, thus precipitating a vicious cycle of IR–hyperinsulinemia–hyperandrogenemia (Fig. 1) Androgens also trigger lipolysis leading to raised free fatty acids in circulation, favouring IR. Leptin participates by creating a chronic systemic inflammatory state. Ultimately, both IR and chronic inflammation thrive on all endocrine–metabolic disturbances pertaining PCOS, predisposing patients to the development of comorbidities.

Role of Excess Body Weight

Obesity is associated with three alterations that interfere with normal ovulation, and weight loss improves all three:

1. Increased peripheral aromatization of androgens to oestrogens.
2. Decreased levels of sex hormone-binding globulin (SHBG), resulting in increased levels of free estradiol and testosterone.
3. Increased insulin levels that can stimulate ovarian stromal tissue production of androgens.

Various mechanisms leading to development of this syndrome are suggested, but exact pathophysiology is still poorly understood.

Currently Used Diagnostic Parameters of PCOS

Currently accepted core diagnostic criteria include hyperandrogenism and ovulatory dysfunction. Women without hyperandrogenism are less likely to have metabolic consequences [4].

Three different statements on diagnostic criteria have been described in the literature (Table 1). Most clinicians find these different definitions confusing and difficult to explain to the patients. As there are differences in criteria used by various studies, standardization has become difficult.

Agreements and Disagreements Amongst The Diagnostic Criteria

Table 2 depicts all phenotypes of PCOS possible with the four parameters essential for diagnosis used by all three statements. All the three statements are in concurrence for phenotypes ‘A to F’. However, phenotype ‘G, H and I’ are excluded from NIH statement of definition as oligo-ovulation is absent, perhaps we are looking at ovulatory PCOS, which is seen only in a minority group, and in presence of hyperandrogenism, the quality of this ovulation is less likely be good, and would fit in the term ovulatory dysfunction. Phenotype ‘J’ shows presence of oligo-ovulation and PCO morphology, but does not show hyperandrogenism. The Rotterdam 2003 definition includes this as PCOS, but NIH and AE-PCOS definitions both exclude this phenotype.

The Androgen Excess and PCOS Society [8] task force suggested that PCOS should be first considered a disorder of androgen excess or hyperandrogenism.

They identified nine phenotypes (Table 2) that could be considered as diagnostic of PCOS, and all show presence of hyperandrogenism.

Apart from core diagnostic criteria of hyperandrogenism and ovulatory dysfunction, a host of clinical, pathological, and biochemical abnormalities coexist with this syndrome. These are not essential for the diagnosis.

Clinical hyperandrogenism includes hirsutism, androgenic alopecia, acne, seborrhoea, onycholysis and onychorrhexis [9], but only hirsutism qualifies for the diagnosis. Associated conditions except obesity are less prevalent [10–25] but important to appreciate that these will have a bearing on the morbidity and prognosis. Hence, these parameters need to be incorporated in the diagnostic evaluation and nomenclature.

Differential Diagnosis

Diagnosis is often mistaken due to its apparent similarities with several other pathologies, like 21-hydroxylase-deficient non-classic adrenal hyperplasia, androgen-secreting neoplasms, androgenic/anabolic drug use or abuse, Cushing’s syndrome, the hyperandrogenic-insulin-resistant acanthosis nigricans syndrome, thyroid dysfunction [26] and hyperprolactinemia. Hence these must be excluded

Table 1 Diagnostic Parameters*NIH Statement (1990) [5]*

To include all of the following:

1. Hyperandrogenism and/or hyperandrogenemia
2. Oligo-ovulation
3. Exclusion of related disorders^a

ESHRE/ASRM Statement (Rotterdam 2003) [6]

To include two of the following, in addition to exclusion of related disorders^a:

1. Oligo-ovulation or anovulation (e.g., amenorrhoea, irregular uterine bleeding)
2. Clinical and/or biochemical signs of hyperandrogenism (e.g., hirsutism, elevated serum total or free testosterone)
3. Polycystic ovaries (by ultrasonography) polycystic ovary as having 12 or more follicles, measuring between 2 and 9 mm, and/or an ovarian volume >10 cc

AES Suggested Criteria for the Diagnosis of PCOS (2006) [7]

To include all of the following:

1. Hyperandrogenism: hirsutism and/or hyperandrogenemia
2. Ovarian dysfunction: oligo-ovulation and/or polycystic ovaries
3. Exclusion of other androgen excess or related disorders^a

NIH National Institutes of Health, *ESHRE* European Society for Human Reproduction and Embryology, *ASRM* American Society for Reproductive Medicine, *AES* Androgen Excess Society

^a Related disorders to be excluded: 21-hydroxylase-deficient non-classic adrenal hyperplasia thyroid dysfunction, hyperprolactinemia, neoplastic androgen secretion drug-induced androgen excess, the syndromes of severe insulin resistance, Cushing's syndrome, and glucocorticoid resistance

Table 2 All possible phenotypes of PCOS

Features	Diagnostic statements	Potential phenotypes															
		A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
Hyperandrogenemia		+	+	+	+	–	–	+	–	+	–	+	–	–	–	+	–
Hirsutism		+	+	–	–	+	+	+	+	–	–	+	–	–	+	–	–
Oligo-Ovulation		+	+	+	+	+	+	–	–	–	+	–	–	+	–	–	–
Polycystic Ovaries Ultrasound		+	–	+	–	+	–	+	+	+	+	–	+	–	–	–	–
	NIH, 1990 [5]	y ^a	y	y	y	y	y	n ^b	n	n	n	n	n	n	n	n	n
	Rotterdam, 2003 [6]	y	y	y	y	y	y	y	y	y	y	n	n	n	n	n	n
	AEPCOS, 2006 [7]	y	y	y	y	y	y	y	y	y	n	n	n	n	n	n	n

Adopted from AZIZ et al. [8]

^a y = diagnostic of PCOS

^b n = not diagnostic of PCOS

before making a diagnosis of PCOS and there is no disagreement about this amongst various criteria.

Why the Name “The Polycystic Ovary” Requires to be Changed?

Journey of nomenclatures has been interesting. Various nomenclatures like Stein–Leventhal syndrome [1], polycystic ovarian disease, sclerocystic disease [27], PCO HA IR syndrome, PCOS are used over last few years. The name PCOS causes confusion in minds of patients and

treating physicians and is certainly a hurdle to conduct research. The name PCOS is clearly a misnomer as it misleadingly focuses on ovarian cysts. The “cysts” noted in PCOS are actually antral follicles whose growth and maturation have been inhibited and are not true epithelial-lined cysts [28] In fact ovarian cysts are neither necessary nor sufficient for the diagnosis of this syndrome.

Another contradictory observation shows that there are polycystic ovaries with ovulatory cycles and normal looking ovaries can coexist with classic PCOS of anovulation and hyperandrogenism. If PCO morphology is

associated with hyperandrogenism, then it is diagnostic of PCOS, but in absence of hyperandrogenism, PCO loses its diagnostic significance. If finding of the polycystic morphology of ovaries is not essential for diagnosis of this syndrome, why retain the name PCOS?

The name of a condition should be accurate, should reflect pathology, should lead to both recognition and understanding by health professionals. Because the name “Polycystic ovary syndrome” is a misnomer, with no true epithelial-lined cysts on the ovary, the need for a name change is clear. This need for change is supported by the NIH [29] and by primary care physicians and women with PCOS as reported by Teede et al. [30]. AES Task force has observed that a minority of the PCOS population has “ovulatory PCOS” and has less severe androgenic and metabolic features than anovulatory women with PCOS [31, 32].

Giving consideration to the above contradictory observations, a revision of the name “Polycystic ovary syndrome” is needed to reflect the condition’s broader clinical features.

Appropriate alternative name for the condition is yet to be established. Lobo [33] proposed changing the name of the disorder to “hyperandrogenic chronic anovulation”. Behera et al. [34] suggested changing the name of PCOS to “oestrogenic ovulatory dysfunction” or “functional female hyperandrogenism”. These are too general to be useful. “Metabolic reproductive syndrome” has been suggested by Teede et al. [30]. But this does not reflect criteria of hyperandrogenism which is essential for diagnosis.

Dunaif et al. [35] suggested that there should be two names for the PCOS phenotypes: those with primarily reproductive consequences should continue to be called PCOS, and those with important metabolic consequences should have a new name. This perhaps may diversify the condition and add to confusion further.

Hence the name ‘Hyper Androgenic Persistent Ovulatory Dysfunction or “HA-PODS” is proposed here.

Why HA-PODS is a Better Terminology?

To avoid confusion, and disagreement amongst currently used diagnostic criteria, terminology “HA-PODS” is proposed here. The name has two parts: HA and POD, both are essential for diagnosis [8]. HA or hyperandrogenism includes either or both of hirsutism and hyperandrogenemia whereas POD or Persistent ovulatory dysfunction includes either or both oligo-ovulation <4/year, and PCO morphology.

It is not necessary to document biochemical hyperandrogenemia in presence of hirsutism and vice versa.

POD includes frequent or persistent anovulation, and/or polycystic morphology of ovaries. One of the two is essential for diagnosis.

Persistent ovulatory dysfunction, a broader terminology, is more appropriate than chronic anovulation. It covers

infrequent ovulation and ovulatory PCOS as well. This comprehensive terminology encompasses various stages of ovulatory dysfunction before it reaches the final stage of persistent anovulation (Fig. 2).

Should the Name Reflect Associated Metabolic Disorders?

The answer to this question is a definite yes! The associated metabolic disorders, when present, have a bearing on prognosis and management of patients. The clinical presentation can give indication of the presence of co morbid factors. For example, recently it was observed that the presence of clinically evident menstrual dysfunction can predict the presence and the degree of insulin resistance in women with PCOS [36]. It is proposed that the syndrome should be labelled as HA-PODS+ first letters of whichever metabolic syndrome [MS] factor is present, i.e., +IR, +O, DM, +D, +C, +SA, +CV +H: insulin resistance, obesity, diabetes mellitus, dyslipidaemia, cancer, sleep apnoea, cardiovascular morbidity, hypertension, respectively (Fig. 2). Such a uniform terminology will facilitate consistency in research.

Why is It So Important to Define and Diagnose PCOS?

PCOS has long-term consequences (RCOG 2014) [37]. Risks like gestational diabetes, type II diabetes, insulin resistance, obstructive sleep apnoea, cardiovascular disease, health-related poor quality of life, endometrial cancer, obesity and obesity-related risks are known to be associated in these women. Most of these are grouped under metabolic syndrome, and if present they indicate long-term nature of the disorder and require immediate intervention. If there is no uniformity in defining and diagnosing PCOS, these health risks cannot be assessed appropriately leading to increased morbidity and inherent mortality risks with these diseases.

PCO morphology by ultrasound is commonest occurrence with this syndrome. The question is whether this poses a health risk? Simply the morphology does not cause any direct risk to health. But PCO morphology by ultrasound (12 or more follicles, measuring between 2 and 9 mm, and/or an ovarian volume >10 cc as described by Rotterdam criteria) will subject the patient to higher risk of fatal hyperstimulation syndrome only when ovulation inducing drugs are used.

Conclusion and Recommendation

Syndrome name “HA-PODS” (hyperandrogenism-persistent ovulatory dysfunction syndrome) is proposed here. The term PCO should be restricted only to the morphological

Ovulatory status	Poly cystic ovarian morphology (PCO)	Regularity of Cycles	Hyper androgenism (clinical/biochemical) (HA)	Insulin Resistance (IR)	Obesity (O)	Dyslipidemia (D)	Diabetes Mellitus (DM)	Cardio vascular morbidity (CV)	Hyperertension (H) Sleep apnoea (SA)
Regular ovulation	+/-	Regular Cycles	-	-	-	-	-	-	-
Sporadic Anovulation (1-3 times/year)	+/-	Regular Cycles	-	-	-	-	-	-	-
Oligoovulatory (Anovulation >8 times/year)	+/-	Regular Cycles Irregular Cycle (poly / oligo/ amenorrhoea)	-	+/-	+/-	+/-	+/-	+/-	+/-
Regular ovulation/ Sporadic anovulation	+	Regular Cycles Irregular Cycle (poly or oligo or amenorrhoea)	+	+	+	+	+	+	+
Oligoovulatory (Anovulation >8 times/year)	+/-	Regular Cycles Irregular cycles	+						
Persistently Anovulatory	+/-	Irregular Cycle Oligomenorrhoea (<9cycles /year) Amenorrhoea	+						
				HA-PODS+ IR	HA-PODS+ O	HA-PODS+ D	HA-PODS+ DM	HA-PODS+ CV	HA-PODS+H HA-PODS+SA

Normal Dysfunction HA-PODS

Diagnostic Parameters Associated Parameters:

(HA-PODS+MS when > 1 comorbid factors present)

Fig. 2 From normalcy to full blown HA-PODS

feature of ovaries by ultrasound and is not necessary for the diagnosis of this syndrome. However, when present, the PCO morphology indicates ovulatory dysfunction. When other metabolic parameters are deranged in addition to the HA-PODS, the syndrome may be called “HA-PODS+”, the plus sign indicating co-morbidity present. Further categorization can be indicated by adding the first letter of comorbidity to + sign. If more than one factors present then can be labelled as HA-PODS + MS.

Proposed nomenclature will be useful for diagnosing and instituting appropriate therapies without delay. It will also enable researchers to attain consistency in research.

Uniformity in diagnosis and nomenclature is the need of the hour. Hence the condition must be diagnosed and labelled correctly to prevent health risks and improve quality of life for women with PCOS.

Compliance with Ethical Standards

Conflict of interest The author declares that she has no conflict of interest.

Ethical Statements Author has not received any funds for this paper.

Ethical Approval This article does not contain any studies with human participants performed by the author.

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