



Can Polycystic Ovarian Syndrome be cured? Unfolding the Concept of Secondary Polycystic Ovarian Syndrome!

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Abstract

Classic polycystic ovarian syndrome (PCOS) is one of the commonest endocrine metabolic disorders in women of reproductive years. It is very disappointing that we have still not been able to know the exact cause, and hence, we cannot completely cure this syndrome. With availability of effective drugs and lifestyle modification, it can only be controlled and symptoms can be reduced. There are some well-defined factors which lead to PCOS phenotype. A concept of secondary PCOS is being described recently. This condition, even though rare, is completely curable, as majority of these factors are treatable. Hence, it is advisable to actively look for these conditions and offer treatment in time. This editorial gives an account of various causes of secondary PCOS, gives broader view of PCOS phenotypes and aims for an insight into pathophysiological aspects of PCOS. The clinical categorization by HA-PODS nomenclature of both primary and secondary PCOS can minimize diagnostic and therapeutic pitfalls and will serve as a checklist to ensure the appropriate investigation is ordered and specific treatment is initiated as per diagnostic code. This will achieve uniformity in therapies offered and also enable better comparison of data and a smooth conduct of research which is much needed in this field.

Keywords Polycystic ovarian syndrome · HA-PODS · Secondary PCOS · Insulin resistance · Hyperprolactinaemia · Hyperandrogenaemia · Menstrual dysfunction · Hypothyroidism · Autoimmune thyroiditis · Congenital adrenal hyperplasia · Obesity

Introduction

Polycystic ovarian syndrome (PCOS) is a heterogeneous disorder with multiple phenotypes. Despite the fact that the condition was identified in 1935 [1], we have not succeeded in finding a cure! The reason is that we have still not zeroed down on the exact aetiology of this syndrome. We know all the possible symptoms it can produce, and we have

more recently understood that it has a lot of metabolic consequences, but disappointingly not understood the precise cause. Hence, we can only reduce or eliminate symptoms but not the pathology.

We have subsequently discovered that some hyperandrogenic conditions result in polycystic ovarian syndrome phenotype. The concept of secondary PCOS has emerged due to this fact that there are some well-defined conditions which induce PCOS-like syndrome. So clinicians can identify these causes and completely cure the consequent PCOS as most of them are treatable conditions.

Various diagnostic criteria have been proposed by different groups like NIH, Rotterdam group, and androgen excess and PCOS society for classic PCOS [2–5], and all of them have one common prerequisite, exclusion of the mimics. However, the core diagnostic features of PCOS [hyperandrogenism, persistent ovulatory dysfunction and polycystic ovarian morphology (PCOM)] have been variable in these diagnostic criteria. To prevent diagnostic and therapeutic pitfalls, a new nomenclature “HA-PODS (hyperandrogenism and persistent ovarian dysfunction syndrome)” was proposed

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which reflects exact clinico-pathological aspects [6]. After several years of experience, I am of the view that long-standing ovulatory dysfunction and long-standing hyperandrogenism perpetuate each other irrespective of the cause. This vicious cycle of one precipitating the other (Fig. 1) will eventually produce PCOS phenotype irrespective of the initiating mechanism. We have clearer understanding today that primary defects in HPO axis will lead to the classic PCOS, and factors other than the HPO axis will lead to the secondary PCOS. In my personal case series of 100 PCOS cases, I observed hyperprolactinaemia in 12% and thyroid disorders in 18% as the cause of persistent anovulation, and after treatment, many of them resolved and started getting regular cycles (unpublished data).

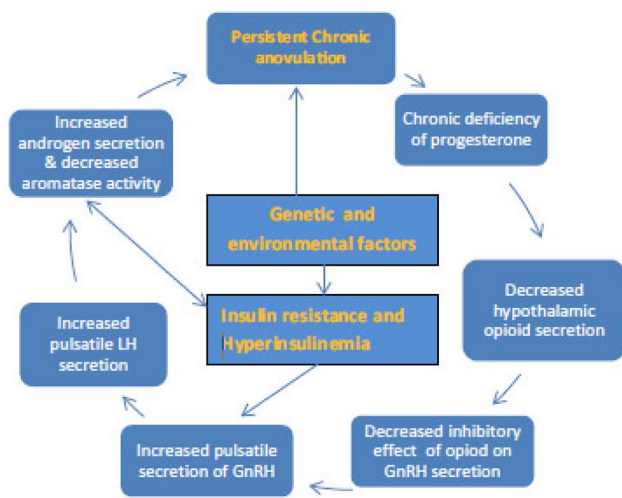


Fig. 1 Vicious cycle of persistent anovulation. Reproduced with permission [6]

Aetiological Classification of PCOS

Primary PCOS: Primary PCOS is the most common variety of PCOS without any known cause. Proposed theory suggests that there is functional ovarian hyperandrogenism (FOH) along with disturbance of hypothalamo-pituitary–ovarian axis function.

Secondary PCOS: The PCOS arising due to well-defined causes other than HPO axis dysfunction is labelled as secondary PCOS.

Causes of secondary PCOS are listed in Table 1.

Clinical Categories as Per Core Features and Comorbidities

As per AE-PCOS society definition [5] at least one from each group must be present: clinical or biochemical evidence of hyperandrogenism and clinical, biochemical or sonographic evidence (PCOM) of persistent ovulatory dysfunction.

Author described new nomenclature, “HA-PODS”—“hyperandrogenic persistent ovulatory dysfunction syndrome” [6]. With unfolding the concept the secondary PCOS, the nomenclature has added secondary PCOS categories (Table 2).

In my practice, this nomenclature is extremely useful to prevent diagnostic pitfalls and to plan the management. All patients get a diagnostic code at the end of complete investigations, depending on which of the above abnormalities are detected. For example, if there are insulin resistance and hypertension, the patient’s diagnostic code is HA-PODS-IR-HT; if patient also has endometrial hyperplasia, then the diagnostic code is written as HA-PODS-IR-HT-EH. If

Table 1 Secondary causes mimicking PCOS

Adipose tissue and Skin	Thyroid	Pituitary	Adrenal	
Obesity	Hypothyroidism	Prolactinoma	Glucocorticoid-suppressible FAH	Glucocorticoid-non-suppressible FAH
Lipodystrophy syndromes	Autoimmune thyroiditis	Hyperprolactinaemia	CAH: classic and non-classic 21-hydroxylase deficiency	Cushing’s syndrome
SSIR		ACTH secreting tumour, Cushing’s disease	Other less common enzymes deficiency ^a	Androgen-secreting tumours
Idiopathic Hirsutism		Acromegaly		Glucocorticoid resistance
Ovaries			Neuroendocrine	Drug induced
DSD			Epilepsy	Androgenic drugs
Androgen-secreting tumours {sertoli leydig cell tumour}				Valproic acid

FAH functional adrenal hyperandrogenism, DSD disorders of sex development, SSIR syndrome of severe insulin resistance, CAH congenital adrenal hyperplasia

^a11Beta-hydroxylase, cortisone reductase deficiency, DHEA sulphotransferase deficiency

Table 2 Clinical and aetiological categories of PCOS

HA-PODS-primary		HA-PODS-secondary	
IR	Insulin resistance	PRL	Hyperprolactinaemia
O	Obesity	THY	Thyroid disorders
DM	Diabetes mellitus	CAH	Congenital adrenal hyperplasia
D	Dyslipidaemia	SSIR	Syndrome of severe insulin resistance
C-EH	Cancer/endometrial hyperplasia	LD	Lipodystrophy
HT	Hypertension	AST	Androgen-secreting tumour
SA	Sleep apnoea	Cush	Cushing's syndrome
CV	Cardiovascular disease	DI	Drug (Valproic acid) Induced
FL	Fatty liver		
MS	Metabolic syndrome		

secondary cause is detected, diagnostic code specifies the same along with causative factor; for example, if there is thyroid disorder, then it will be labelled as secondary HA-PODS-THY. If any co-morbidity is also present then the respective diagnostic code can be added and then the code-specific treatment can be started for each factor. HA-PODS or PCOS phenotype gets completely resolved in case of treatable causes.

Common Conditions Mimicking PCOS

Obesity

Whether obesity is the cause, effect or incidental comorbidity is not very clear. It has been reported that if significant weight loss happens in women with extreme obesity, the PCOS-like picture undergoes complete remission in large number of women. And likewise excessive weight gain at or after puberty produces PCOS-like condition. The weight loss can occur because of diet, exercise and lifestyle changes, or severe weight loss can occur due to bariatric surgery. Whatever is the cause of weight loss, many women undergo complete remission as long as weight is under control [7].

One study reported 36.9% complete recovery from all features of PCOS with weight reduction, and only 15.4% had persistent PCOS features [8].

Impact of bariatric surgery on weight loss is well documented [9]. A recent meta-analysis showed that preoperative incidence of PCOS (45.6%) significantly decreased to 6.8% ($p < 0.001$), menstrual irregularities, hirsutism also reduced significantly, and many of them achieved complete remission at 12-month follow-up after bariatric surgery [10].

So obesity could be an independent secondary causal association of PCOS.

Thyroid Disorders and PCOS

Hypothyroidism and Hashimoto thyroiditis are commonly found associated in women with PCOS. It is certainly more

prevalent than in general population. General gynaecologist gets confused whether such patients are to be diagnosed as PCOS or no because this is contrary to recommendation that we must rule out thyroid disorders before diagnosing PCOS. The most logical explanation is that thyroid disorders particularly hypothyroidism often leads to persistent anovulation or ovulatory dysfunction. Longer the duration of the dysfunction, more sustained is the impact of anovulation. The resultant lack of progesterone triggers the vicious cycle of PCOS (Fig. 1), thereby leading to hyperandrogenism. But this does not happen in all women with thyroid disorders. It happens more commonly in genetically susceptible individuals. Common genetic predisposition exists for the development of both the diseases. The three genetic polymorphisms such as FBN3, GnRHR and CYP1B1 play a role in both the diseases [11].

Apart from genetic susceptibility, there are other common pathways which lead to both the diseases. The role of transforming growth factor beta (TGF- β) a multifunctional cytokine is implicated in the pathogenesis of both disorders. High levels of TGF- β are more prone to develop autoimmune diseases.

High oestrogen levels during intrauterine life interfere with the thymus development hence could cause both hypothyroidism and PCOS. Women with PCOS have imbalance between various sex steroids.

Unopposed oestrogen in the presence of high androgens stimulates autoimmunity. Hence, PCOS could lead to autoimmune thyroiditis. To sum up long-standing thyroid disorders leads to ovulatory dysfunction and lead to PCOS, whereas PCOS could lead to autoimmune thyroid disorder. Vitamin D deficiency is also proposed to be the common predisposing factor for both the disorders [12].

Polycystic appearance of ovaries sometimes referred to as soap bubble appearance on ultrasound is common with frank hypothyroidism, and milder forms may mimic polycystic morphology. We have effective therapy for thyroid disorders; hence, the progression of the disease could be halted with LT4. Vitamin D deficiency can also

be treated effectively today. Remission therefore is likely in this coexistence [13].

Hyperprolactinaemia

Elevated prolactin levels are found in 6% of women with hirsutism [14]. The exact reason why elevated prolactin levels are associated with androgen excess is not very clear. Direct action of prolactin on adrenal cortex is hypothesized. In my view, hyperprolactinaemia leads to chronic persistent ovulatory dysfunction with sustained lack of progesterone which may trigger the vicious cycle of PCOS and hyperandrogenism (Fig. 1). Fortunately, we have very effective treatment of this condition like cabergoline and dopamine agonists. The reversal of PCOS phenotype after treatment is quite common [14].

Adrenal Hyperandrogenic Disorders

a. Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) is a group of disorders arising due to deficiency of enzymes of steroidogenesis. All forms of CAH, including 21-hydroxylase deficiency, are transmitted as autosomal recessive disorders. Women carrying a classic mutation will transmit this to next generation which will be affected with severe disease. Conversion of 17-hydroxyprogesterone to 11-deoxycortisol and cortisol is blocked (CYP21A2); hence, there is hypocortisolism. Cortisol has a negative feedback on ACTH secretion, so hypocortisolism results in excessive secretion of ACTH which brings about hyperplasia and hyperactivity of all the three zones of adrenal gland, and high levels of 17-hydroxyprogesterone levels and androstenedione.

Female newborns when referred for ambiguous genitalia, with more serious form of salt wasting type and less risky virilising forms of CAH, are examples of classical 21-hydroxylase deficiency, but this form is mostly diagnosed in infancy. The “non-classical” form of 21-hydroxylase deficiency does not become apparent until adolescence or early adulthood, when abnormally high androgen levels cause hirsutism, menstrual abnormalities, premature pubarche and a phenotype that mimics polycystic ovary syndrome (PCOS). Prevalence of non-classic 21-hydroxylase deficiency ranges from 1 to 3% in general [15] but may be higher in tertiary referral centres.

Severe forms may require prednisolone treatment, but non-classic variety generally does not require any treatment till they become symptomatic. They will require ovulation induction and antiandrogen therapy to control the symptoms. Follicular phase 17-hydroxyprogesterone estimation must be done in all hyperandrogenic adolescents to rule out CAH. ACTH stimulation test may be done though not mandatory

to confirm diagnosis of CAH. This well-defined secondary cause of PCOS is non-curable as it is a congenital disorder, but this can certainly be effectively controlled and symptoms may be relieved.

b. Cushing's Syndrome

Cushing's syndrome is defined as hypercortisolism due to primary adrenal pathology often associated with obesity, hypertension and type II diabetes. If this results from primary pathology in pituitary gland secreting excess ACTH, it is termed as Cushing's disease. It gives rise to PCOS phenotype. In fact many a times, they are simply treated as PCOS cases which are resistant to standard treatment. PCOS is very common presentation, but Cushing's syndrome is relatively rare. However, we must remember that if diagnosed early, Cushing's syndrome will be completely cured unlike PCOS. So suspecting diagnosis is very important. Suspicion should arise when clinical features like plethoric round faces, supraclavicular fat pads and abdominal purple striae are found in addition to classic features of PCOS, i.e. central obesity, hirsutism, acne, baldness and irregular menstruation. These clinical indicators justify diagnostic tests like low-dose dexamethasone suppression test, 24 h urinary free cortisol and midnight salivary cortisol estimation, to diagnose Cushing's syndrome. One survey reported that only 6% of gynaecologists screened PCOS referrals for Cushing's syndrome [16]. Treatment in the form prednisolone medication, or surgery like laparoscopic adrenalectomy or transsphenoidal resection of ACTH secreting pituitary tumour may lead to complete cure of this condition.

Syndrome of Severe Insulin Resistance Syndrome (SSIR)

Severe insulin resistance syndrome (SSIR) is a group of disorders based on severe insulin resistance irrespective of whether patient is obese or non-obese. SSIR can be subclassified by the type of defect that leads to the severe insulin resistance. Type of defects includes autoantibodies, mutations and defects in signalling pathways of insulin receptors. A defect in the adipose tissue function leads to different types of lipodystrophies [17, 18]. There are several lipodystrophic phenotypes. These occur because of loss of subcutaneous fat which can be partial or complete. This varies as per different aetiologies [19]. Lipodystrophy may be accompanied by metabolic disorders, including insulin resistance, diabetes mellitus, fatty liver and dyslipidaemia.

Other manifestations of metabolic derangements can include acanthosis nigricans due to SSIR, and eruptive xanthomas as a result of severe hypertriglyceridaemia and PCOS [20, 21]. PCOS secondary to SSIR states is not very

uncommon. The prevalence of 1.5% of all PCOS phenotypes has been reported [22].

Severe insulin resistance contributes to PCOS-like phenotype due to both central and peripheral mechanisms. Compensatory hyperinsulinaemia acts directly on pituitary and affects LH pulsatility. Higher LH production leads to excess androgen production from theca cells (CYP45017 α activity). Excess androgens are produced by non-LH-mediated mechanisms as well. High insulin levels directly act on liver to reduce SHBG secretion, thus increasing proportion of free active androgens. FSH response of granulosa cells is also altered. All these metabolic changes lead to antral follicular arrest and PCOM.

Suspected cases should be referred to endocrinologist. Suspicion must arise when a fasting insulin level is more than 20.9 $\mu\text{g/mL}$, and a peak insulin value after glucose load is above 209 $\mu\text{g/mL}$ in a non-diabetic women with BMI less than 30 kg/m^2 ; likewise, suspicion must arise when insulin requirement is more than 3 units/kg per day in diabetic women with BMI < 30 [17–21].

Diet control as well as insulin sensitizers, like thiazolidinediones specially pioglitazone [23–25], can be more helpful than metformin. However, therapeutic effect will be achieved only when adequate adipose depots are present. Low levels of serum leptin in patients with lipodystrophy and recombinant human leptin therapy may be highly effective in improving all metabolic derangements.

Androgen-Secreting Tumours

Classic PCOS is generally insidious in onset and presents with milder hirsutism, without much virilizing effects. If presentation is rather acute, with the rapid development of severe hyperandrogenism symptoms, virilization and menstrual irregularity, one must suspect an androgen-secreting tumour. Usually, the serum testosterone levels are more than 200 ng/mL . This condition will be certainly a differential diagnosis of PCOS. Sertoli Leydig cell tumours are known to cause this picture; however, any other ovarian tumour may also present with signs of hyperandrogenism.

Androgen-secreting tumours are less commonly found arising from adrenal gland. Patients usually present with features of Cushing's syndrome as well as virilization.

This condition is also completely curable, and surgical treatment resolves all the symptoms.

Drug-Induced PCOS

Epilepsy in young girls is more susceptible to lead to PCOS when treated with valproic acid. This antiepileptic drug activates the transcription of P450c17 and other enzymes involved in steroidogenesis [26, 27]. One meta-analysis suggested that in women treated with valproic acid for epilepsy,

the incidence of PCOS is 1.95-fold higher than in women treated with other drugs [28]. Valproic acid leads to weight gain; hence, this could be contributory factor in the development of PCOS phenotype. Most logically, the PCOS-like picture will regress after withdrawal of these drugs.

In addition to valproic acid effects, intrinsic neuroendocrine alterations in different types of epilepsy also may be responsible for PCOS phenotype.

Some androgenic drug therapy is associated with hirsutism and menstrual irregularities mimicking PCOS.

The exact cause of epilepsy is not well understood; hence, PCOS associated with this may not be completely curable.

Conclusion

Classic PCOS can be only controlled, and symptoms can be reduced. Many of them have recurrence of symptoms on cessation of therapy, and many others go on to develop comorbidities and health risks. Secondary causes of PCOS, even though rare, are completely curable. In clinical practice, it is worth searching for all these causes with appropriate investigations to rule out or confirm the same. If they are detected, then it will certainly be rewarding when patient gets completely cured of the undesirable symptoms. In complicated secondary cause, referral to concerned specialists will be more appropriate.

This account of various causes of secondary PCOS gives the broader view of PCOS phenotypes and gives an insight into pathophysiological aspects of PCOS [29]. The clinical categorization by HA-PODS nomenclature of both primary and secondary PCOS can minimize diagnostic and therapeutic pitfalls and will serve as a checklist to ensure that appropriate investigation is ordered and specific treatment is initiated as per diagnostic code. This will go a long way in establishing uniformity in diagnosis, treatment and research, which is the need of the hour. I hope and expect that further research may unfold some more unrevealed aspects of this condition towards better understanding of PCOS.

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