Beyond the Label: A Patient-Centred Approach to Polycystic Ovary Syndrome

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ABSTRACT

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting women of reproductive age. Importantly, it is not one disease with a single pathophysiology but is instead a heterogeneous syndrome with several underlying biological mechanisms. Careful diagnosis requires attention to the key symptom of androgen excess as well as the exclusion of similar disorders including hyperprolactinemia, late-onset congenital adrenal hyperplasia, and hypothalamic amenorrhea. A patient-centred approach to treatment requires further assessment of underlying drivers and mechanisms including neuroendocrine disturbance, insulin resistance, and adrenal hyperresponsiveness.

Key Words Overdiagnosis, neuroendocrine, hyperandrogenism, oral micronized progesterone

INTRODUCTION

The goal of health care is to alleviate symptoms and prevent negative health outcomes. To that end, medicine has become adept at categorizing and labelling constellations of symptoms in an attempt to deliver appropriate treatment. For some conditions, such an approach is highly effective, especially when there is a single and clearly identifiable underlying pathophysiology (e.g., infection). For other conditions, the approach is less effective, especially when there is multifactorial or heterogeneous pathophysiology (e.g., depression). If taken too far, enthusiastic diagnostic imaging and labelling of symptoms can result in overdiagnosis and overtreatment, as has been documented for depression, hyperlipidemia, and osteoporosis.[1,2] Polycystic ovary syndrome (PCOS) is, unfortunately, both 1) a syndrome with a heterogeneous pathophysiology and 2) subject to overdiagnosis and overtreatment, largely as a result of the expansion[3] of the Rotterdam diagnostic criteria to include non-androgenic PCOS.[4]

In this perspective article, I will outline how the current one-size-fits-all approach to diagnosing and treating PCOS can produce negative patient outcomes such as healthy women receiving an unnecessary disease label and the misdiagnosis of hypothalamic amenorrhea as PCOS. I will describe a more precise diagnostic approach which requires the key symptom of androgen excess and emphasizes the exclusion of disorders with similar clinical symptoms.

Furthermore, I will propose an individualized approach of "looking beyond the PCOS label" to identify the underlying physiological driver or drivers of hyperandrogenism in each patient. Such an approach will enable clinicians to mechanistically target the driver with evidence-based methods, such as myo-inositol, and deliver better patient-centred outcomes such as relieving androgen excess and a return to ovulatory cycles.

BACKGROUND

From the earliest descriptions in the medical literature, polycystic ovary syndrome (PCOS) was recognized as a condition of androgen excess, with high luteinizing hormone (LH) and testosterone levels generally regarded as key components of a diagnosis.[3] Although an abnormal ovarian appearance was observed in some patients, it was not required for diagnosis, in part because pelvic ultrasound was not yet available.

The first formal PCOS diagnostic criteria from the National Institutes of Health (NIH)[5] did not include ovarian morphology but, instead, characterized PCOS as *unexplained hyperandrogenic anovulation*. More precisely, the NIH criteria stated that PCOS can be diagnosed when *all* of the following criteria are present: symptoms of androgen excess (clinical or biochemical), infrequent ovulation, and exclusion of other disorders with similar clinical symptoms. This is consistent with the definition of "anovulatory androgen excess" later proposed by Canadian endocrinology professor Jerilynn C. Prior[6] and the criteria of the Androgen Excess and PCOS (AE-PCOS) Society Task Force, which state that "PCOS should be defined by the presence of hyperandrogenism (clinical and/or biochemical), ovarian dysfunction

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(oligo-anovulation and/or polycystic ovaries), and the exclusion of related disorders."[7]

Therefore, according to the NIH, Professor Jerilynn Prior, and the AE-PCOS Society, PCOS is, *by definition*, a condition of androgen excess. In simplest terms, PCOS is the symptom of androgen excess when all other causes of androgen excess have been ruled out.

That clear focus on androgen excess changed in 2004 with the introduction of the Rotterdam Criteria,[4] which proposed for the first time polycystic ovarian morphology (PCOM) as a stand-alone criterion, thus enabling a PCOS diagnosis to be made based on only two of the following three criteria:

1. rare ovulation or lack of ovulation,
2. symptoms of androgen excess (clinical or biochemical),
3. polycystic ovarian morphology.

This small but important change dramatically increased the incidence of PCOS from 5% of women of reproductive age to an incredible 20%[8] and opened the door to the diagnosis of PCOS *in the absence of androgen excess*. According to the Rotterdam criteria, *non-androgenic* PCOS can be diagnosed based *only* on the symptoms of anovulation and polycystic ovaries, which equates to counting the same symptom twice because the polycystic (or more accurately, poly-follicular) appearance of the ovaries is merely an indicator of temporarily stalled follicle development and failure to ovulate in that cycle. In other words, anovulation (of any cause) is likely to correlate with PCOM, and the fact that anovulatory cycles are common (occurring in up to 30% of otherwise clinically normal menstrual cycles[9]) means that polycystic ovaries are common (occurring in up to 30% of women with normal cycles and hormones).[10]

The disconnect between the PCOM and androgen excess has been addressed in several papers including a 2010 commentary in *The Journal of Clinical Endocrinology & Metabolism*, which acknowledges that "an isolated PCOM in an ovulatory woman is not an indication for metabolic evaluation,"[11] and a 2022 paper about diagnostic criteria,[12] which notes that it is entirely possible to have the endocrine condition of androgenic PCOS but normal looking ovaries. The same paper goes on to say that "the presence of PCOM is neither necessary nor sufficient for diagnosis of PCOS" and concludes "there is no evidence that the presence of PCOM has any implications with regard to the endocrine or metabolic features of PCOS."

It's also worth noting that it is entirely possible to have androgenic PCOS but normal looking ovaries, especially in older women, who have fewer follicles.

So, polycystic ovaries occur in some (but not all) women with PCOS and in women with normal hormones. Polycystic ovaries also occur in women using hormonal birth control and women with any condition of oligo- or amenorrhea including the increasingly common scenario of hypothalamic amenorrhea or relative energy deficiency in sport (RED-s) as a result of undereating or underfueling. Of course, even under the Rotterdam Criteria, hypothalamic amenorrhea is supposed to be ruled out by asking patients about restricted eating. In practice, many clinicians do not ask about restricted eating, which means hypothalamic amenorrhea is frequently misdiagnosed as PCOS.[13]

The Problem of Misdiagnosis and Overdiagnosis

According to public health researcher Tessa Copp from The University of Sydney, the problem goes further than just misdiagnosis of hypothalamic amenorrhea as PCOS. In a recent *British Medical Journal* article titled "Driven by good intentions: Why widening the diagnostic criteria for polycystic ovary syndrome may be harming women,"[14] Copp argues that even the tightened diagnostic criteria of the 2018 International PCOS Guidelines[15] "still capture many women with few or mild symptoms," including women who would naturally *outgrow* their androgen symptoms.[16] Women who would naturally outgrow mild hyperandrogenism include young women and women experiencing what the author has clinically observed to be rebound hyperandrogenism upon discontinuation of androgen-suppressing medication such as cyproterone- and drospirenone-containing oral contraceptives.

Copp warns that in the case of mild or temporary PCOS, women are harmed by the unnecessary fear that "their condition will worsen, which threatens their perception of health and fertility."[14] As part of her research, Copp and her team conducted a qualitative study,[17] which found that "fear of infertility can result in adverse psychological and behavioural consequences including anxiety, depression, lower self-worth, altered life and education goals, risk-taking with contraception, and unintended pregnancies." In the same study, she called for "reducing the harms of unnecessarily labelling healthy women for whom the benefits of a diagnosis are small." Yet another paper[18] explored the subjective nature of assessing clinical hyperandrogenism (hirsutism) and warned that a "milder degree [of hirsutism] can be considered as normal patterns" for some ethnic groups and "not a reason for seeking medical care."

An additional concern is when a PCOS diagnosis is provided to patients seeking an explanation for pelvic pain. According to a 2017 study,[19] patients report pain as the most common symptom of PCOS. This is despite the fact that pain is not a symptom of PCOS.[15] The reason for this mismatch between what the patient needs (an explanation for pain) and what is provided (a possibly mistaken and unnecessary PCOS diagnosis) is that both PCOS and menstrual pain are common, so it's easy to have both a PCOS diagnosis and menstrual pain, including pain due to endometriosis.

Misdiagnosing hypothalamic amenorrhea and endometriosis as PCOS muddies the waters for both researchers and clinicians. In my own clinical practice, I commonly encounter patients who say: "I've tried everything for my PCOS but still have this pain." By which they mean they have tried metformin and a low-carb diet but still have pain, which is not surprising given that neither metformin nor a low-carb diet is a treatment for pelvic pain.

Finally, it's important to remember that PCOS is a "diagnosis of exclusion,"[20] with all formal diagnostic criteria (NHI, AE-PCOS, and Rotterdam) stipulating the exclusion of other disorders with similar clinical symptoms.[5,7,4] Clinicians should therefore take care to rule out other causes of anovulation and androgen excess

including thyroid disease, Cushing syndrome, nonclassical or late-onset congenital adrenal hyperplasia (CAH), hyperprolactinemia, hypothalamic amenorrhea, and side effects from medication, such as progestins with a high androgen index.

Androgenic PCOS is a Heterogeneous Syndrome

Even when properly diagnosed, androgenic PCOS is still an "umbrella diagnosis," which means a set of symptoms (i.e., a syndrome) resulting from one or more *different* underlying biological drivers or mechanisms. For context, another well-known umbrella diagnosis is irritable bowel syndrome (IBS), which is a set of digestive symptoms resulting from different underlying mechanisms including dysbiosis, food intolerances, altered intestinal motility, and more.[21]

The umbrella or heterogeneous nature of the PCOS diagnosis was acknowledged almost from the beginning, with a 2002 paper stating that "a single cause [of PCOS] is unlikely."[22] The Public Library of Science (PLOS) took it further in 2020, when they said that "PCOS is, in fact, a heterogeneous disorder with *different underlying biological mechanisms*" [emphasis mine] and that "grouping women with PCOS under a single diagnosis may be counterproductive because distinct disease subtypes will likely benefit from different interventions."[23]

Treat the Individual

When treating a heterogeneous syndrome like PCOS, the best clinical strategy is to look beyond the diagnostic label of PCOS to possible underlying biological drivers and treat those. By doing so, androgen excess can be relieved and ovulatory cycles restored.

Documented physiological drivers of hyperandrogenism include neuroendocrine disturbance, insulin resistance, and adrenal hyperresponsiveness, all of which may be present simultaneously and interact.

Neuroendocrine Disturbance

In our paper, "The central role of ovulatory disturbances in the etiology of androgenic polycystic ovary syndrome,"[24] my co-authors Professor Jerilynn Prior and Sonia Shirin and I build the case that the central disturbance in many cases of androgenic PCOS is abnormally rapid pulsatility of gonadotropin-releasing hormone (GnRH). Such a disturbance is downstream from various origins including chronic inflammation[25] and genetic polymorphisms such as polymorphisms of the genes for FSH and LH receptors,[26] and 17-α-hydroxylase/17–20 lyase,[27] which is the rate-limiting step of androgen biosynthesis. Developmental factors are also important, especially *in utero* exposure to androgens,[28] which causes epigenetic changes to the genes associated with GnRH pulsatility and steroidogenesis[29] and creates a five-fold increased risk of androgenic PCOS in daughters of mothers with PCOS.[30]

Rapid GnRH pulsatility, in turn, promotes further impairment of the hypothalamic-pituitary-ovarian (HPO) axis by suppressing follicle-stimulating hormone (FSH) and stimulating LH resulting in stalled follicle development and high thecal cell androgen production, leading to aromatization and tonically high estrogen levels.[24] The resulting ovulatory disturbance and progesterone deficiency further deprive the system of the progesterone feedback that normally slows GnRH pulsatility, creating a vicious cycle,[24] as illustrated in Figure 1.

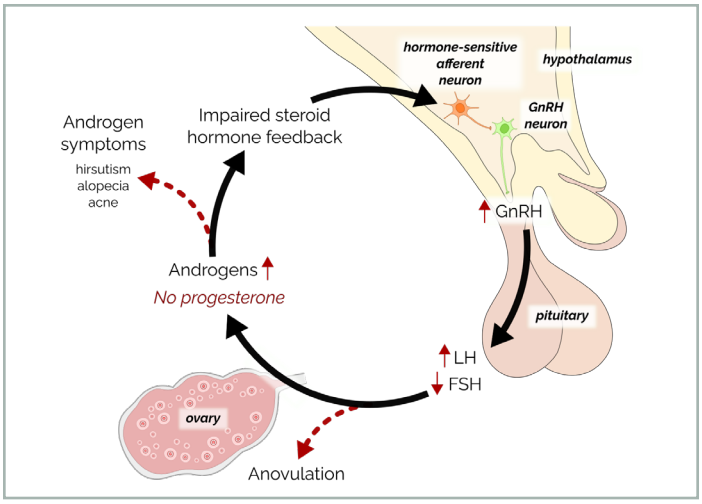

FIGURE 1 A model of the neuroendocrine disturbance causing androgen excess in some cases of androgenic PCOS. Dysregulation of the neural circuit of the GnRH/LH pulse generator leads to anovulation, absent progesterone, and consequent hyperandrogenism, creating a vicious cycle of impaired steroid feedback and further dysregulation of the neural circuit.

Assessing for Neuroendocrine Disturbance

The simplest way to clinically assess for rapid GnRH pulsatility is to measure serum LH and FSH on day two or three of the menstrual cycle, or, in the case of amenorrhea or no cycle, on a random day, taking care to not misinterpret a normal ovulatory surge of LH as elevated baseline LH. Androgenic PCOS with neuroendocrine disturbance typically presents with a high ratio (>2:1) of baseline serum LH to FSH.[31] Hypothalamic amenorrhea typically presents with a normal to low ratio of baseline serum LH to FSH.[31]

Treatments or Interventions for Neuroendocrine Disturbance

The nutrient myo-inositol amplifies intracellular FSH signalling and promotes ovulation[32]; it can therefore help to correct the rapid GnRH pulsatility of androgenic PCOS. Myo-inositol is one of the evidence-based PCOS treatments included in the 2018 "Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome."[15]

Cyclic progesterone therapy using oral micronized progesterone (OMP) given in a cyclic pattern for 14 days to mimic the luteal phase can also improve neuroendocrine disturbance by exerting beneficial negative feedback on GnRH pulsatility,[24] as illustrated in Figure 2. Oral micronized progesterone induces withdrawal bleeds, slows the GnRH pulse generator, suppresses LH, lowers androgens, and eventually promotes ovulatory cycles.[24] Mechanisms by which progesterone lowers androgens include 1) slowing of the GnRH pulse generator, thereby reducing the LH stimulation of thecal cells and 2) competing for the enzyme 5 alpha-reductase, thereby reducing dihydrotestosterone (DHT), which is the active

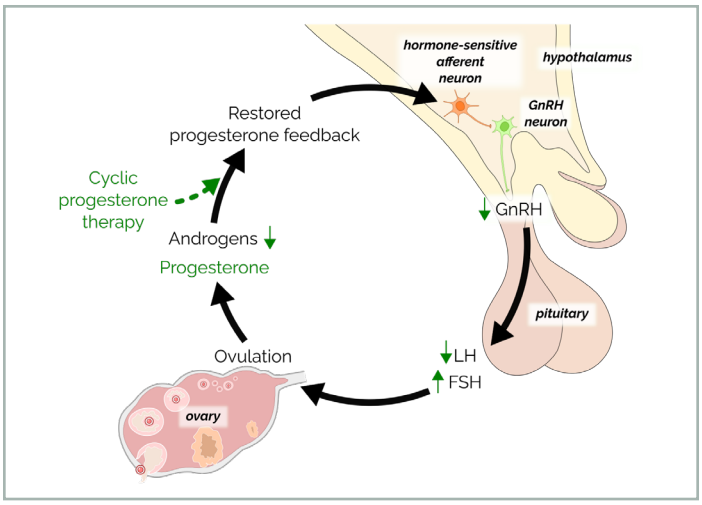

FIGURE 2 Treatment of androgenic polycystic ovary syndrome with cyclic oral micronized progesterone therapy. Oral micronized progesterone (OMP) given in a cyclic pattern for 14 days to mimic the luteal phase acts centrally to restore the healthy function of the GnRH pulse generator, suppress LH, and reduce androgen excess, promoting ovulation.

form of testosterone. Cyclic progesterone therapy is currently undergoing a clinical trial for PCOS.[33]

Insulin Resistance

A second driver of androgenic PCOS is insulin resistance or hyperinsulinemia, which contributes to androgen excess by:

- Directly stimulating ovarian thecal cells to produce androgens,[34] possibly by acting as a co-gonadotropin with LH[35]
- Increasing unbound or free testosterone by decreasing sex hormone-binding globulin (SHBG)
- Contributing to neuroendocrine disturbance by increasing GnRH pulsatility.[36]

Thus, hyperinsulinemia contributes to the vicious cycle of the first biological driver (neuroendocrine disturbance) to a greater or lesser degree depending on the severity. Severe hyperinsulinemia can even produce androgen excess in the absence of neuroendocrine disturbance or other source of hyperandrogenism.[37]

Hyperinsulinemia is, however, unlikely to be the primary initiating driver for most women with androgenic PCOS. Instead, insulin resistance is likely to be secondary to neuroendocrine anovulatory hyperandrogenism based on the findings that the androgenic anovulatory PCOS phenotypes have worse insulin sensitivity than do ovulatory phenotypes[38,39,40,41] and that increasing androgen burden often leads to a deterioration of insulin sensitivity.[42] Anovulatory hyperandrogenism was further demonstrated to be causal by a prospective study of a random sample of adolescents, which found that PCOS by age 18 was best predicted by oligomenorrhea at age 14, and not by obesity or insulin resistance.[43] In other words, androgen excess probably comes first and promotes insulin resistance,[44,45] via several mechanisms, including deposition of visceral fat,[46,47] the "masculinization" of adipose tissue,[48] decreased muscle glucose uptake,[49] decreased thermogenesis and energy expenditure,[50] and lipid accumulation in liver.[51]

Assessing for Insulin Resistance

Signs and symptoms of insulin resistance include a high waist measure, acanthosis nigricans, low HDL cholesterol, and high serum triglycerides. Other possible laboratory findings include high HbA1C, high fasting insulin,[52] and, most accurately, a high HOMA-IR index (homeostatic model for insulin resistance), which is a calculation of fasting glucose and insulin concentrations, defined as fasting plasma glucose (mmol/L) × fasting plasma insulin (μU/mL/22.5).[53] A recent study of HOMA-IR and insulin resistance concluded that "monitoring insulin may have clinical relevance," including in patients with normal fasting glucose.[54] And in a study of girls with PCOS, fasting insulin was identified as a simple blood test that can be used clinically to guide treatment.[55] Of note, a positive response to insulin-sensitizing medication has been observed in normal-weight women with PCOS,[56] suggesting that mild insulin resistance is a factor even in so-called "lean PCOS."

Treatment or Intervention for Insulin Resistance

Conventional treatment for insulin resistance includes diet, exercise, and insulin-sensitizing medication, such as metformin. Nutritional supplements that have been clinically trialled for insulin resistance include magnesium,[57] myo-inositol,[58] and the phytonutrients berberine[59] and silymarin.[60]

Adrenal Hyperresponsiveness

Most women with PCOS have an elevation of all types of androgens: testosterone from the ovaries, androstenedione from the ovaries and adrenal glands, and DHEA-S (dehydroepiandrosterone sulfate) from the adrenal glands. When only DHEA-S is elevated but testosterone and androstenedione are normal, it may be classified as the adrenal subtype of PCOS,[61] which researchers have described as "a subclinical form of micronodular bilateral adrenal hyperplasia,"[62] and which accounts for about 10% of PCOS diagnoses.[7] Adrenal PCOS is driven by hyperresponsiveness of the adrenal cortex and stress response system,[63] and may be the result of stress or trauma around the time of puberty.[64]

Assessing for Adrenal PCOS

The adrenal PCOS sub-type is suggested by elevated serum DHEA-S, together with normal testosterone and androstenedione. A similar condition of nonclassical or late-onset CAH should be ruled out by screening for elevated follicular phase 17-OH progesterone, followed by an adrenocorticotropic hormone (ACTH) stimulation test and genetic testing. Late-onset CAH accounts for up to 9% of cases of androgen excess and can be misdiagnosed as PCOS.[65]

Treatment or Intervention for Adrenal Hyperresponsiveness

Adrenal PCOS may benefit from nutrients and herbal medicines that support the stress response system, particularly pantothenic

acid, which helps to modulate the response of the adrenal cortex to ACTH.[66] Androgen symptoms can also be improved with progesterone, either by taking cyclic progesterone therapy or by promoting ovulatory cycles and robust luteal phases. Finally, adrenal androgens can be downregulated with hydrocortisone[67] and the herbal medicine licorice (*Glycyrrhiza glabra*), which slows the activity of 17-α-hydroxylase, thereby lowering androgens[68] and "could be considered as an adjuvant therapy for hirsutism and polycystic ovary syndrome."[68]

CONCLUSION

The first step in a patient-centred approach to PCOS is careful diagnosis, with attention to the key symptom of hyperandrogenism and exclusion of disorders with similar clinical symptoms such as hyperprolactinemia, thyroid disease, and hypothalamic amenorrhea. By focussing on hyperandrogenism, and avoiding *non-androgenic* PCOS phenotypes, clinicians can avoid the harms of labelling healthy women or women with hypothalamic amenorrhea with an unnecessary (and possibly inaccurate) PCOS diagnosis.

The next step in a patient-centred approach is to recognize that PCOS is not a single disease but is instead a heterogeneous syndrome with multiple underlying physiological drivers, including neuroendocrine disturbance, insulin resistance, and adrenal hyperresponsiveness. By looking beyond the disease label to the underlying physiological driver, clinicians can mechanistically target the driver with evidence-based methods such as myo-inositol and cyclic progesterone therapy. Such an approach can produce the desirable patient outcomes of relieving androgen excess and a return to ovulatory cycles.

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CONFLICTS OF INTEREST DISCLOSURE

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