EDITORIAL

Polycystic Ovary Syndrome (PCOS): Making Sense of the Alphabet

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PCOS is the commonest endocrinopathy of reproductive years with a quoted prevalence of 5-11%, depending upon populations studied.[1] Despite being a liberally diagnosed, the disorder remains relatively poorly understood. The syndrome was first described in 1935 as a conglomeration of symptoms of menstrual irregularity and signs of hyperandrogenism (hirsutism) and of enlarged cystic ovaries. Currently, at least three nomenclatures are widely recognized for diagnosing PCOS, with a considerable overlap in the diagnostic criteria (Table 1).[2] It is imperative to appreciate the heterogeneity within the population diagnosed with PCOS and to recognize that PCOS remains a diagnosis of exclusion. The common systemic disorders that may mimic PCOS include hypothyroidism, hyperprolactinemia, late onset congenital adrenal hyperplasia, androgen secreting tumors, Cushing's syndrome and exogenous androgen exposure; these must be excluded prior to arriving at a diagnosis of PCOS.[1-2]

Symptomatology of PCOS includes menstrual irregularity, and symptoms of relative androgen excess (excessive facial and body hair, acne and occasionally androgenic alopecia). Menstrual irregularity may be acknowledged by almost 2/3rd, mostly presenting as oligomenorrhea (duration of cycles>35 days), or even amenorrhea. Bothersome hair and/or acne may similarly be acknowledged in up to 2/3 of the patient population; androgenic alopecia is the least common of the symptoms, and can be seen in less than 10% of women meeting criteria for PCOS. The majority of the patients with PCOS are overweight (BMI=25 and <30 kg/m^2) to obese (BMI=30kg/m^2), although almost a third may be of a lean body habitus.

While the pathophysiology is far from understood, significant strides have been made in elucidating the endocrine and metabolic profiles in women diagnosed with PCOS.[3] The endocrine profile of PCOS includes elevated serum levels of luteinizing hormone (LH). The hyperandrogenemia is commonly of ovarian origin (elevated testosterone) although elevations in serum levels of dehydroepiandrosterone sulfate (DHEAS) may additionally be seen identifying adrenal contributions to androgen excess in a subset. Mild elevations in prolactin may be observed in a proportion. Insulin resistance has emerged as a key player in the pathogenesis of the hypothalamo-pituitary dysfunction, and in the causation of hyperandrogenemia and hyperandrogenism.[4]

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Clinical concerns relating to the diagnosis of PCOS extend well beyond the presenting symptoms (1, 5). Menstrual irregularity and cosmetic issues dominate in the adolescent and the young, whereas anovulatory infertility adds to the patient's burden for the reproductive age population. The risk for endometrial pathology is independent of age; a spectrum of proliferative endometrial disorders has been described in women with PCOS, ranging from endometrial polyps to endometrial hyperplasia to adenocarcinoma. Chronic anovulatory cycles in the setting of obesity, hyperandrogenemia and insulin resistance are of pathophysiologic relevance in the context of endometrial pathology. Beyond the reproductive issues, women with PCOS are at an enhanced risk for chronic medical disorders, particularly type II diabetes. While longitudinal data are sparse to lacking in this population, cross-sectional studies and epidemiological data identify PCOS as a risk for cardiovascular and cereberovascular disease.[5] A disproportionally increased prevalence of depressive symptomatology is additionally noted in women with PCOS, adding to the burden of chronic disorders in this otherwise young population.[6] While the prognosis for reproductive success with fertility treatment is reassuring, women with PCOS are at an increased risk for iatrogenic concerns including risk for ovarian hyperstimulation syndrome, multiple pregnancy and spontaneous miscarriage. For those achieving pregnancy, either spontaneously or aided by therapy, the challenges may continue as pregnancies in women with PCOS are at an enhanced risk for gestational diabetes, pre-eclampsia and fetal macrosomia.[7]

Management strategies must be individualized to the patient's needs and risk profile. A recent review summarizes the spectrum of medical approaches to PCOS.[8] Menstrual regulation is commonly achieved through use of combined hormonal contraceptive formulations (pills/patch or vaginal ring); this strategy offers endometrial protection as well as holds benefit against symptoms of androgen excess. The dose of estrogen (higher estrogen dose confers potential for benefit against hyperandrogenemia by increasing the hepatic production of sex hormone binding globulin that binds and reduces the circulating free androgen levels) and the type of progestin (anti androgenic progestins such asdrosperinone offer potential for benefit whereas androgenic progestins such as levonorgestrel may worsen symptoms of acne for some) should be considered when deciding on the optimal hormonal contraceptive strategy. While oral contraceptive pills (OCP's) are commonly utilized as a first line strategy in the management of PCOS, a potential for detriment relating to an injudicious use of this approach must be kept in perspective, given that deterioration in serum triglyceride profile is not uncommon,

Table 1: Summary of commonly utilized diagnostic criteria for PCOS [2]

Criterion	NIH Criteria 1999	Rotterdam Criteria 2003	Androgen Excess Society Criteria 2006
Oligomenorrhea	+	±	±
Hyperandrogenism (Hirsutism/Acne)	±	±	±
Hyperandrogenemia	+	±	±
PCO appearing ovaries on pelvic ultrasound [a]	-	±	±
Diagnostic requisites	Oligomenorrhea plus androgen excess (hyperandrogenemia)	Any two criteria	Androgen excess (symptoms &/or hyperandrogenemia) plus ovulatory disturbance (oligomenorrhea or PCO [a])

[a] PCO-Polycystic appearing ovary on pelvic ultrasound: ovarian volume>10ml, &/or > 12 follicles <9mm in size in at least one ovary

especially with the use of higher estrogen dose OCP's. A risk for thrombo-embolic phenomenon must additionally be considered especially in the morbidly obese, and in those with existing hypertension. Insulin sensitizers, such as glucophage (metformin), offer a potential for improving reproductive physiology (menstrual regulation and improved androgen profile and symptoms of hyperandrogenism) in addition to their recognized metabolic benefits. Accruing data suggest that combining glucophage with hormonal approach may offer enhanced benefit than seen with the use of a single agent. Of interest are emerging data suggesting a promise of statins in improving the androgen profile in addition to the recognized facilitatory effects on lipids, and may offer a preferred strategy for those with significant dyslipidemia, especially in the setting of a strong family history of cardiovascular disease. Use of anti-androgens is of particular relevance for those with bothersome features of hyperandrogenism; adequacy of contraceptive coverage must however be ensured when prescribing anti-androgens, given their potential for teratogenecity. Topical therapies such as eflornithine (for management of hirsutism) and minoxidil (for alopecia) are adjuncts that may offer targeted benefit. Limited data suggest a relevance of vitamin D deficiency in the pathophysiology of PCOS;[9] ongoing studies may shed some light regarding potential for therapeutic efficacy of vitamin D in the management of PCOS.

To summarize, PCOS is a common disorder with a finite spectrum of manifestations; the diagnosis holds implications that extend well beyond the spectrum of presenting symptoms. Management strategies for PCOS should target not just the evident presenting complaint, but also the covert health burdens the individual patient is deemed at risk for. Beyond symptom control, management considerations must address endometrial protection, lifestyle modification to achieve target weight goals and risk reduction strategies to minimize future burden of cardiovascular risk and type II diabetes.

REFERENCES

1 Carmina E, Lobo RA. Polycystic ovary syndrome (PCOS) arguably the most common endocrinopathy is associated with significant morbidity in women. J Clin Endocrinol Metab 1999; 84:1897-9.

2 Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. Fertil Steril 2009; 91:456-88.

3 Guastella E, Longo RA, Carmina E. Clinical and endocrine characteristics of the main polycystic ovary syndrome phenotypes. Fertil Steril 2010; 94:2197-201.

4 Baptiste CG, Battista MC, Trottier A, Baillargeon JP. Insulin and hyperandrogenism in women with polycystic ovary syndrome. J Steroid Biochem Mol Biol 2009; 122:42-52 Epub 2009 Dec. 28.

5 Wild RA, Carmina E, Diamanti-Kandarakis E, Dokras A, Escobar-Morreale HF, Futterweit W, et al. Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society. J Clin Endocrinol Metab 2010; 95:2038-49.

6 Dokras A, Clifton S, Futterweit W, Wild R. Increased risk for abnormal depression scores in women with polycystic ovary syndrome: a systematic review and meta-analysis. Obstet Gynecol 2011; 117:145-52.

7 Homburg R. Pregnancy complications in PCOS. Best Pract Benchmarking Healthe 2006; 20:281-92.

8 Saha L, Kaur S, Saha PK. Pharmacotherapy of polycystic ovary syndrome - an update. Fundam Clin Pharmacol 2011; 1472-8206.

9 Selimoglu H , Duran C, Kiyici S, Ersoy C, Guclu M, Ozkaya G, et al. The effect of vitamin D replacement therapy on insulin resistance and androgen levels in women with polycystic ovary syndrome. J Endocrinol Invest 2010; 33:234-8.