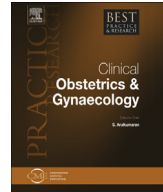




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Preface

Polycystic Ovarian Syndrome – Issue 30.8

Some 80 years ago, Drs. Irving Stein and Michael Leventhal reported a case series of seven women characterized by amenorrhea associated with hirsutism and bilateral polycystic ovaries [1]. This seminal description remains the basis for diagnosis of polycystic ovarian syndrome (PCOS), a condition that affects 5–15% of women. During the intervening decades, much has been elucidated but many aspects of the syndrome remain enigmatic. This volume brings together eminent scholars of PCOS to provide up to date reviews of the state of play and evidence-based treatment options for the practicing clinician.

Clinicians would readily recognise the full syndrome. However, a precise definition of PCOS remains elusive even after 8 decades. As *Dewailly, Chapter 1*, reminds us, this is because PCOS is a heterogeneous syndrome, not a disease. Patients with PCOS, more or less, have a set of phenotypic characteristics but lack a single defining element or “gold standard” on which the diagnosis could be anchored. According to the predominance of a particular symptom or clinical manifestation, patients are directed to various specialists who, therefore, have partial and oriented vision of the syndrome.

Nevertheless, as discussed by *Inthrani et al, Chapter 2* the discovery of molecular pathways modulating androgen biosynthesis and their relationship to insulin metabolism have enhanced our understanding of the pathophysiology of PCOS. Studies with ovarian theca cells taken from women with PCOS have demonstrated increased androgen production due to increased CYP17A1 and HSD3B2 enzyme activities. Furthermore, overexpression of DENND1A variant 2 in normal theca cells resulted in a PCOS phenotype with increased androgen production. Notably, cellular steroidogenesis models have facilitated the understanding of mechanistic effects of pharmacotherapies, including insulin sensitizers (e.g. pioglitazone and metformin) used for the treatment of insulin resistance in PCOS, on androgen production. In addition, animal models of PCOS have provided a critical platform to study the effects of therapeutic agents in a manner closer to the physiological state. Indeed recent breakthroughs have demonstrated that natural derivatives such as the dietary medium-chain fatty acid decanoic acid can restore oestrous cyclicity, and lower androgen levels in an animal model of PCOS thus laying the platform for novel therapeutic developments for treatment or even prevention of PCOS.

In the last decade, two developments in particular have forced a rethink of criteria for diagnosis of PCOS.

Firstly, as reviewed by *Zhu et al, Chapter 3*, the improvement in the resolving power of modern ultrasound machines is such that ovarian antral follicles, which have escaped detection previously, can now be visualized. This results in a major, but artificial increase, in the prevalence of polycystic ovarian morphology in normal populations. The criterion of more than 12 antral follicles per ovary for diagnosis becomes obsolete, necessitating a modern revision by increasing the threshold of follicle number per ovary.

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Secondly, recent data reviewed by *Bhida & Homburg, Chapter 4*, suggest that measurement of anti-müllerian hormone (AMH) may replace the relatively unpleasant and time-consuming transvaginal ultrasound procedure itself. AMH levels are significantly higher in women with polycystic ovary syndrome due to an increased number of antral follicles and also a higher production per antral follicle. AMH is postulated to have an inhibitory role in folliculogenesis and may play an important role in the pathophysiology of anovulation in PCOS. One school of thought suggests that serum AMH may be a useful test in the identification of PCOS and has been suggested as a diagnostic criterion. International standardisation of the AMH assay, large population based studies, and a global consensus is needed before its incorporation into routine diagnosis.

It is clear that PCOS is an ethnic, familial and polygenic condition. *Huang & Yong, Chapter 5*, examined the role of ethnicity. It is increasingly recognised that ethnic differences are likely contributors to the differing manifestations of the syndrome. Generally, rates of PCOS may be lower in East Asians. It is clear that East Asians are less hirsute compared to Caucasians. Despite population-adjusted scoring, Caucasians have higher hirsutism rates amongst patients diagnosed with PCOS. Rates of hyperandrogenaemia do not appear to differ among PCOS subjects of different ethnicities, although serum androstenedione appeared to be higher in Caucasians in one study. Interestingly, higher prevalence of the polycystic ovarian morphology has been reported in East Asian PCOS populations compared to Caucasian PCOS subjects.

Zhao et al, Chapter 6, assessed the contribution of genetics to our understanding of PCOS. More than 100 candidate genes, principally related to reproductive hormones, insulin metabolism, and chronic inflammation, are associated with PCOS. Recently genome-wide association studies have identified 11 risk loci. These are located in or near the candidate genes for PCOS such as FSHR and LHCR (gonadotropin action); INSR, HMG2 and THADA (type 2 diabetes); YAP1, SUMO1P1, HMG2 (cell proliferation) and RAB5B, SUOX and ERBB3 (type 1 diabetes). These studies provide new clues to understand the genetic components and pathways in PCOS pathophysiology.

Pitonen, Chapter 7 argues that women with PCOS present with several endometrial abnormalities possibly explaining some of the adverse endometrium-related outcomes in these women. PCOS and an increased miscarriage rate have been suggested to coincide, but the results are conflicting. Recent studies have also shown increased risks of pregnancy-induced hypertension, preeclampsia, and premature delivery that may be related to altered decidualization/placentation in affected women. In the long run, PCOS per se is associated with occurrence of endometrial cancer, with obesity aggravating the risk. Most investigated markers of endometrial abnormalities in women with PCOS are related to steroid hormone action (ERs, PRs, ARs, steroid receptor co-activators), endometrial receptivity/decidualization (HOXA10, integrin, IGFBP-1), glucose metabolism (IRs, glucose transporters, IGFs) and inflammation/immune cell migration (IL6, CCL2, u-NK-cells). Despite several endometrial abnormalities in women with PCOS, the clinical relevance of these findings still awaits future clarification and so far no common screening protocols/recommendations for women with PCOS are established.

Baskin & Balen, Chapter 8, considers the role of the hypothalamic-pituitary axis and gonadotropin abnormalities in the pathophysiology of PCOS. Neuroendocrine abnormalities include increased gonadotrophin-releasing hormone pulse frequency with consequential hypersecretion of luteinising hormone to impact ovarian androgen synthesis, folliculogenesis and oocyte development. Disturbed ovarian-pituitary and hypothalamic feedback accentuates the gonadotrophin abnormalities and there is emerging evidence putatively implicating dysfunction of the Kiss 1 system. Within the follicle subunit itself there are intraovarian paracrine modulators, cytokines and growth factors, which appear to play a role. Adrenally-derived androgens may also contribute to the pathogenesis of PCOS, but their role is less defined.

Lizneva et al, Chapter 9 reflects on the role of androgen excess and its contribution to the to the clinical phenotype of PCOS. While androgen excess will contribute to the ovulatory and menstrual dysfunction of these patients the most recognizable sign of hyperandrogenaemia includes hirsutism, acne and androgenic alopecia or female pattern hair loss. Evaluation not includes scoring facial and body terminal hair growth using the modified Ferriman-Gallwey method, but also recording and possibly scoring acne and alopecia. Assessment of biochemical hyperandrogenism is also necessary, particularly in patients with unclear or absent hirsutism, and will include assessing total and free testosterone, and possibly DHEAS and androstenedione, although these latter add a limited amount to

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