

Polycystic Ovarian Syndrome

Insights into the Enigma That Is PCOS Today

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Introduction

Polycystic ovary syndrome (PCOS) is an endocrine condition with both reproductive and metabolic implications. It affects 6–10% of reproductive aged women making it the most common endocrinopathy in this group of women. It is a frequent cause of infertility, has potential for serious long-term complications, and represents a major cost burden on the health care system. Although PCOS is a heterogeneous condition and many research challenges remain, it is imperative that clinicians are aware of the recent advances in the area. This special section reviews the current literature on PCOS including controversies in diagnostic criteria, etiology, metabolic and cardiovascular implications, and the debate over ideal therapies focusing on lifestyle modification, insulin sensitisers, and infertility therapy.

Until recently there was no generally accepted clinical definition for PCOS. Original descriptions of PCOS were based on crude appearances of the ovary at surgery combined with clinical features of the syndrome. Research over the last 30 yr has demonstrated a profound heterogeneity in the condition, which has sparked ongoing speculations regarding appropriate diagnostic criteria and etiology. In 1990 a NIH-sponsored meeting proposed new diagnostic criteria for PCOS. Although this may be too narrow, the more recent Rotterdam criteria may be over inclusive. A considered discussion of the controversies over international views on diagnostic criteria in PCOS is presented here. The current consensus is for the use of anovulation with menstrual disturbance, clinical or biochemical hyperandrogenism, and polycystic ovaries at ultrasound as the key diagnostic criteria. Obesity, insulin resistance, and the metabolic syndrome are also related. The application of this information to the assessment of a woman with PCOS is discussed.

This series of reviews also covers the etiology of PCOS focusing on the role of genes and environment. Complex polymorphic genetic abnormalities combined with environmental factors primarily mediated through obesity (affecting approx 70% of sufferers), both contribute to the underlying increased insulin resistance (IR) in PCOS. The evidence for genetic linkage in PCOS is reviewed here; however, the phenotype confusion that has characterized PCOS also adds complexity to the literature on genotype. Although several loci have been proposed as PCOS genes, the evidence supporting linkage for most of these is not overwhelming. The most likely candidates are in the region near the insulin receptor gene; however, the specific responsible gene remains to be identified. To date, no gene has been identified that causes or contributes substantially to the development of the PCOS phenotype.

Although the search for the candidate genotype for PCOS continues, the role of insulin resistance in the etiology has been extensively researched in the past decade. IR, secondary to both genetic and lifestyle factors, is integrally involved in the pathogenesis, the metabolic and clinical features, and the long-term sequelae of PCOS with profound IR noted in the majority of obese and lean PCOS patients. IR, hyperinsulinemia, and beta-cell dysfunction are all very common in PCOS, but are not currently required for the diagnosis. The underlying mechanisms involved in IR are explored here as well as the role of IR in the clinical presentation of PCOS. The impact of the discovery of IR in PCOS including contributions to the understanding of the clinical features, the metabolic components, and the broader health implications of these issues are also discussed.

The traditional concept of PCOS as a reproductive disorder (hyperandrogenism, ovulatory disturbance, and infertility) has evolved to include the endocrine aspects of the disorder encompassing the metabolic syndrome (IR, dyslipidemia, obesity), with a high risk of diabetes and potentially increased cardiovascular disease. The underlying IR, metabolic implications, high risk of diabetes (four- to seven-fold) and evidence for premature accelerated cardiovascular disease are covered in this special section. An understanding

Received March 20, 2006; Revised March 20, 2006; Accepted July 6, 2006.
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of these components of PCOS has important implications for screening for diabetes and cardiovascular risk as well as affecting decisions on suitability of long-term treatment options in this condition.

Therapy is generally targeted to specific clinical presentations or to IR. Therapy is somewhat determined by the subspeciality of the practitioner, reflecting in part the current controversies in therapy. Targeting IR, lifestyle including weight loss is first line therapy for the majority of women; however, it is often challenging to attain and sustain. The literature in this area is discussed as well as the use of insulin-sensitizing agents in the treatment of PCOS. Lifestyle changes can significantly modulate the phenotype of the disease with diet, exercise, smoking, stress, and other factors adversely affecting reproductive outcomes in PCOS. These influences can be modulated by behavioral change, and lifestyle choices should be discussed in this group of patients. The role of insulin sensitizers, including metformin, are also reviewed but are yet to be clarified.

One of the prime focuses for therapy for PCOS has been on improving fertility. Infertility is a major clinical complication accounting for more than 75% of cases of anovulatory infertility. The mechanism of anovulation is uncertain, but there is evidence that arrested antral follicle develop-

ment is related to insulin resistance and hyperinsulinemia. A comprehensive review of the treatment of infertility is included in this special section. The use of lifestyle, insulin sensitizers, as well as antiestrogens are covered; however, the focus of the review of infertility therapy is on the difficult challenge of resistant subjects. Conventional doses of gonadotropins are associated with high complication rates, whereas low-dose gonadotropin therapy may offer a viable alternative with lower complications rates.

Given the prevalence of PCOS, the serious and costly short-term and long-term implications of the condition, and the controversies that still surround important aspects of the condition, it is vitally important that research continue. Specifically, clarification of the etiology, as well as exploration of ideal therapies, including effective implementation strategies for lifestyle change, are needed. The role of insulin sensitizers in PCOS including determining the long-term risks and benefits of these therapies remains a focus of research as does establishing the safest and most effective infertility therapies. In this setting, this series of comprehensive reviews outlines current knowledge and future directions for research.

In conclusion, we would like to thank the authors, the Senior Editor, and the Publisher for making this issue possible.