

Estrogenic ovulatory dysfunction or functional female hyperandrogenism: an argument to discard the term polycystic ovary syndrome

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Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders seen among reproductive-age women, with a prevalence of 4%–9% depending on the criteria used to define the syndrome. The diagnostic criteria for PCOS have been surprisingly controversial and confusing for patients, clinicians, and researchers. We believe that the confusion surrounding PCOS arises almost entirely because its name refers to a trait that is inconsistently present and irrelevant to both the etiology and the treatment of the disorder. We suggest that merely abandoning the term PCOS will cure much of what has ailed us for decades and allow us to focus on the etiology and treatment of the causes of what the experts in this field have come to recognize as functional female hyperandrogenism. (*Fertil Steril*® 2006;86:1292–5. ©2006 by American Society for Reproductive Medicine.)

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Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders seen among reproductive-age women, with a prevalence of 4%–9% depending on the criteria used to define the syndrome. Polycystic ovarian syndrome was first described by Stein and Leventhal in 1935 as a syndrome that included polycystic ovaries, male pattern hair growth (hirsutism), irregular periods, and infertility (1). Since then, the diagnostic criteria for PCOS have been surprisingly controversial and confusing for patients, clinicians, and researchers. We believe that the confusion surrounding PCOS arises almost entirely because its name refers to a trait that is inconsistently present and irrelevant to both the etiology and the treatment of the disorder. It has become a syndrome that is easy to recognize but paradoxically difficult to define, because we continue to hold on to an historical misconception. Several unsuccessful attempts have been made to obtain a consensus on the definition of PCOS (2, 3). In the present article, we suggest that merely abandoning the term PCOS will cure much of what has ailed us for decades and allow us to focus on the etiology and treatment of the causes of what the experts in this field have come to recognize as functional female hyperandrogenism.

HISTORICAL LEGACY

The use of the term polycystic ovary syndrome is deeply rooted in history and tradition. The clinical entity was first described in 1935 by Stein and Leventhal as a cluster of symptoms in seven women that included hirsutism, irregular or absent menses, infertility (sterility), and even pelvic pain (1). However, only one of these variables was shared by all seven women: the presence of bilateral enlarged polycystic-appearing ovaries, which were observed by transabdominal pneumoperitoneum. The focus on the ovaries was reinforced when it was observed that a large wedge resection of the polycystic ovaries resulted in the return of regular predictable menses. Because the cystic ovaries appeared to be linked to the diagnosis and the treatment of the disorder, the name PCOS seemed appropriate.

However, this observation has not stood the test of time. It has become increasingly clear that the ovarian cysts are not the cause of the syndrome. They are merely “one of many” inconsistent manifestations of this disorder. We have learned that the plethora of small subcortical ovarian cysts associated with this syndrome represents an unusually large number of follicles that have entered the FSH-responsive pool. With this knowledge, the therapy shifted away from treating the cysts surgically and toward ovulation induction. Furthermore, the benefits of ovarian surgery, although real, are short lived at best and do not extend to other aspects of the disorder, such as correction of hyperandrogenism (hirsutism or acne) (4). As our knowledge of this syndrome and

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our armamentarium of pharmacologic options have progressed, our focus has shifted away from the ovarian cysts to medical treatment of hyperandrogenism and ovulatory dysfunction. Unfortunately, the term PCOS is a constant reminder of a historical misconception, which continues to distract patients, clinicians, and researchers from focusing on the cause and treatment of hyperandrogenism.

OVARIAN MORPHOLOGY

Several studies have demonstrated that the polycystic morphology of the ovary is not the most reliable marker for PCOS. Not only is it an inconsistent finding in women with estrogenic ovulatory dysfunction, but many normal ovulatory women may have also polycystic-appearing ovaries, particularly in the early follicular phase of the menstrual cycle (5). These small cysts appear to represent the pool of recruitable follicles which may be found in women with or without any other evidence of PCOS.

To understand how polycystic ovaries develop, it may be helpful to review what we know about normal folliculogenesis. Generally, hundreds of oocytes begin the recruitment process each month. Of these, 1 to 40 oocytes may reach the gonadotropin-responsive phase of development. Therefore, multifollicular ovaries could result from either a physiologic or a pathologic process (6). The prevalence of polycystic ovarian morphology is approximately 17%–33% among all women of reproductive age (7–9). In 1999, Kousta et al. (10) reported the prevalence of polycystic-appearing ovaries in 289 women presenting with infertility. They found polycystic-appearing ovaries present in 83% of anovulatory patients, 53% of patients with male factor, 50% of those with tubal disease, and 44% of patients with unexplained infertility. The prevalence in each of these groups was higher than in a control group of 67 parous volunteers, among which only 28% had PCOS.

Polycystic appearance of ovaries can often be a sign of other endocrine abnormalities, particularly those associated with excess androgen production, such as congenital adrenal hyperplasia and Cushing's syndrome. Other clinical scenarios associated with multifollicular ovaries include normal puberty, central precocious puberty, hyperprolactinemia, hypothalamic anovulation, and use of certain drugs (5, 11, 12). Several studies have shown the association between anovulation and/or hyperandrogenism and polycystic-appearing ovaries (16–18). However, there is also evidence that ovulatory women with and without hyperandrogenemia can have the polycystic ovarian morphology as well (13, 14, 19). Therefore, the presence of polycystic ovaries is not a reliable indicator of PCOS.

LACK OF CONSENSUS

Attempts to obtain an international consensus on the definition of PCOS were made in 1990 and in 2004. At both meetings, there was controversy over the importance of

ovarian morphology to the diagnosis. At the 1990 National Institutes of Health (NIH) international conference in Bethesda, MD, experts were given a questionnaire about the diagnostic criteria and nomenclature for PCOS (2). Their recommendations evolved to include only clinical or biochemical evidence of hyperandrogenism, chronic anovulation, and exclusion of other disorders causing androgen excess. These findings were felt to be definitive of the disorder, without regard for the ovarian morphology (20). It is clear however that there was not a consensus on excluding ovarian morphology from the diagnosis, because a second attempt at reaching a consensus was held at a joint European Society for Human Reproduction and Embryology (ESHRE)/American Society for Reproductive Medicine (ASRM) meeting in Rotterdam in 2004 (3). Here it was determined that no single set of diagnostic criteria exist for PCOS, and it is therefore merely a diagnosis of exclusion. We believe that this is further support for abandoning the term completely. The outcome, however, of the Rotterdam conference was to elevate the importance of ovarian morphology. The diagnostic criteria for PCOS were revised to include two out of the following three findings; oligo- or anovulation, evidence of hyperandrogenism (clinical or biochemical), or polycystic ovaries (3). However, we believe that this diagnostic definition is still inadequate, because an ovulatory woman with polycystic-appearing ovaries and hyperactive 5-alpha-reductase activity, causing hirsutism and acne, would meet the 2004 Rotterdam criteria for PCOS diagnosis without truly having the disorder. Meanwhile, inconsistency and confusion in the diagnostic criteria and definition of PCOS have been perpetuated in the literature as studies define the syndrome differently. Recent studies vary greatly in their choice of definition for the disorder, some having adopted the 2004 consensus and others maintaining support for the 1990 diagnostic criteria.

Another area of inconsistency is the specific ultrasound guidelines for diagnosis of polycystic ovaries (13–15). There are several imaging criteria and measurement guidelines for ovaries and accompanying cysts that supposedly define PCOS. Regardless, these imaging diagnostic criteria have not been universally used, because it is not necessarily clinically relevant in the absence of other signs or symptoms that characterize PCOS. The syndrome cannot be diagnosed by ultrasound imaging criteria alone, and there is no proven advantage in identifying ovarian morphology in patients without other signs or symptoms of the disorder (7). In addition, depending on the expertise of the transvaginal sonographer, multifollicular ovaries due to other etiologies, including the immature hypothalamic-pituitary-ovarian axis in early puberty to recovering hypothalamic amenorrhea, may be difficult to distinguish from the classic form of polycystic ovaries (15).

Some authors have hypothesized that the detection of polycystic ovarian morphology alone may be a risk factor for the subsequent development of PCOS. It is suggested that these women may have a subclinical form of the disorder and

require close follow-up (20). However, this theory has not been proven, and presumptive treatment of these patients has not been shown to affect the long-term outcome. Thus, sonographic detection of polycystic-appearing ovaries always requires correlation with clinical presentation to determine their significance and subsequent management.

PROBLEMS WITH INACCURATE DIAGNOSIS

Despite decades of disagreement among experts regarding the diagnostic criteria for PCOS, there has been a strong concordance for the necessity of a universal and consistent concept for this disorder. Currently, various clinicians and investigators use diverse defining criteria, resulting in inconsistency and confusion surrounding the diagnosis, management, and underlying etiology and pathogenesis for the disease (21–23). The lack of uniformity evident in the literature makes study data interpretation and patient selection criteria difficult. The discrepancy in definitions also causes problems in the clinical management of affected patients (24). Because of the phenotypic heterogeneity and the reliance on ovarian morphology, some normal women are given the diagnosis and some women with estrogenic ovulatory dysfunction are not.

Receiving the label wrongly can have significant adverse consequences for the patient. The internet is filled with information about the health implications of PCOS, including subfertility and the risk of developing long-term complications such as endometrial carcinoma and cardiovascular disease, which may be unnecessarily frightening for women who are wrongly classified with this disorder. In addition, the diagnosis could have negative implications on obtaining health insurance. On the other hand, missing the diagnosis of PCOS may also be harmful, because the concern for intervening and modifying long-term health risks may be overlooked. Therefore, changing the focus from ovarian morphology to the real clinical problems and symptoms of each individual would enhance patient care. A problem-based or etiology-oriented approach would guide our goals for treatment toward relevant issues, such as irregular bleeding, hirsutism or acne, infertility, or preventative health care.

SHIFTING FOCUS TO REFLECT PATHOPHYSIOLOGY

Functional Female Hyperandrogenism

Most experts today agree that hyperandrogenism is the single most important diagnostic criteria for making the diagnosis of PCOS. This has been consistently true since the consensus conference held by NIH in 1990 (20, 25–26). Studies have repeatedly shown that most of the features characteristic of the PCOS phenotype can be linked to androgens, including hirsutism, acne, alopecia, ovulatory dysfunction, and even polycystic ovarian morphology (27–29). Given the problems with reference to ovarian morphology, it may be more accurate to refer to this syndrome as functional female hyperandrogenism (FFH).

Insulin Resistance

Some authors have stressed the importance of the contribution of abnormal insulin metabolism as one cause of hyperandrogenism (30). It has been shown that elevated insulin levels contribute to increased LH levels and subsequent ovarian androgen secretion (31). Insulin resistance is found in 25%–60% of women diagnosed with PCOS, most often relative to their body weight (26). Insulin resistance has also been implicated as an integral contributor to ovulatory dysfunction, based on the influence of insulin on gonadotropins (32). This is also implied in the improved ovulation with the use of medications to control insulin resistance.

Estrogenic Ovulatory Dysfunction

There is increasing evidence linking hyperandrogenism to estrogenic ovulatory dysfunction, which results in a spectrum of problems ranging from infertility to endometrial hyperplasia and endometrial adenocarcinoma. Therefore, changing the nomenclature to focus on androgens and its consequences once again helps physicians and their patients understand this disorder.

Overall, the critical issues in the management of patients with FFH includes the treatment of current symptoms and prevention of the long-term sequelae of unopposed estrogen, anovulation, hyperandrogenism, lipid abnormalities, and insulin resistance. These health consequences include cardiovascular disease, hypertension, and diabetes mellitus (33). Regardless of which theory is adopted to explain the metabolic and clinical symptomatology, treatments aimed at the affected patient's individual problems are of greatest importance. The principal objective is to figure out what is being evaluated for treatment and avoid being misled by the name.

Time for Change

It is time to recognize that the term polycystic ovary syndrome has outlived its usefulness and that its importance only resides in history. Experts around the world have not been able to agree on a definition of this disorder for decades, and although we may never be able to reach a consensus on a new name, it is important that we find some way to be more consistent and clear in the way that we describe female hyperandrogenism. If we perpetuate the confusion surrounding the definition of PCOS among physicians, scientists, and patients, we will continue to hinder the progress of scientific research and thus our understanding and treatment of this common disorder. We believe that the only way that this is going to happen is by eliminating all references to ovarian morphology. We can promote progress and gain a wider understanding of this common disorder by placing the emphasis on hyperandrogenism and its manifestations rather than remaining distracted by the outdated nomenclature.

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