The Importance of Diagnosing the Polycystic Ovary Syndrome

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The polycystic ovary syndrome (PCOS) is an extremely common disorder that occurs in 4% to 7% of women of reproductive age. Although PCOS is known to be associated with reproductive morbidity and increased risk for endometrial cancer, diagnosis is especially important because PCOS is now thought to increase metabolic and cardiovascular risks. These risks are strongly linked to insulin resistance and are compounded by the common occurrence of obesity, although insulin resistance and its associated risks are also present in nonobese women with PCOS. Women with PCOS are at increased risk for impaired glucose tolerance, type 2 diabetes mellitus, and hypertension. Cardiovascular disease is believed to be more prevalent in women with PCOS, and it has been estimated that such women also have a significantly increased risk for myocardial infarction. Many lipid abnormalities (most notably low high-density lipoprotein cholesterol levels and elevated triglyceride levels) and impaired fibrinolysis are seen in women with PCOS. Early diagnosis of the syndrome and close long-term follow-up and screening for diabetes and cardiovascular disease are warranted. An opportunity exists for preventive therapy, which should improve the reproductive, metabolic, and cardiovascular risks.

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Hyperandrogenism and insulin were linked as early as 1921, when Achard and Thiers (1) published their classic description of a bearded women with diabetes (1). Since then, researchers have realized that most women with hyperandrogenism show evidence of a disorder known as the polycystic ovary syndrome (PCOS), which is extremely common but heterogeneous. Most women with PCOS have some degree of insulin resistance, although it may be subtle. Abnormalities of insulin secretion and action have been implicated in the pathophysiology of PCOS. For this and other reasons, diagnosis of PCOS is important.

The polycystic ovary syndrome, then called the Stein–Leventhal syndrome, was first described in 1935. Originally, diagnosis required pathognomonic ovarian findings and the clinical triad of hirsutism, amenorrhea, and obesity (2). The next diagnostic milestone occurred 30 years later, when researchers in the late 1960s and early 1970s noted derangements in the hypothalamic–pituitary axis. This focused the diagnosis on endocrine criteria, such as elevated levels of serum luteinizing hormone or ratio of luteinizing hormone to follicle-stimulating hormone (3, 4).

With the advent of pelvic ultrasonography in the 1970s and 1980s (first, abdominal sonography and, later, vaginal sonography), the recognition of a characteristic polycystic ovary complicated the diagnosis. Some believed that ultrasonographic findings alone were sufficient to make a diagnosis. In this setting, it was misleading to call the disorder "polycystic ovary" (PCO) or polycystic ovarian disease (PCOD) because these terms completely ignored the well-accepted endocrine features. It was also quickly realized that polycystic ovaries can occur in some "normal" women and in women with well-defined endocrinopathies as varied as hypothalamic amenorrhea and congenital abnormal hyperplasia (5, 6). In normal ovulatory women with no other typical endocrine features, we prefer to call this finding as polycystic-appearing ovary (7) to distinguish it from the term "PCO," which is often used synonymously, but incorrectly, with PCOS.

The polycystic ovarian syndrome is extremely prevalent and is considered the most frequently encountered endocrinopathic condition. It has been suggested that the disorder occurs in 4% to 7% of women of reproductive age (8, 9). During the reproductive years, PCOS is associated with important reproductive morbidity, including infertility, abnormal bleeding, increased pregnancy loss, and complications of pregnancy (10). Because women with PCOS also have an increased risk for endometrial carcinoma because of long-standing unopposed estrogen stimulation, their menstrual function must be continually monitored (11).

In 1990, the National Institutes of Health formed a group to investigate PCOS. No consensus was reached regarding the naming of the disorder (12). However, in women who present with hyperandrogenism and chronic anovulation, a diagnosis of PCOS is considered reasonable after other endocrine disorders (for example, congenital adrenal enzymatic deficiencies and tumors) have been ruled out. Hyperandrogenism and chronic anovulation remain the two most characteristic clinical features of the disorder and are discussed separately. Criteria for the diagnosis of PCOS are presented in the **Table**.

Table. Criteria for Clinical Diagnosis of the Polycystic Ovary Syndrome

Hyperandrogenism with or without skin manifestations
Irregular menses (anovulation or oligo-ovulation)
Absence of other androgen disorders (adrenal hyperplasia or tumor)
Polycystic ovaries on ultrasonography*

* Not required for diagnosis but extremely prevalent.

Hyperandrogenism

Hyperandrogenism is a key feature of PCOS. Although the adrenal gland may contribute, hyperandrogenism is principally ovarian in origin among women with a primary diagnosis of PCOS. In various populations around the world (13), it has been found that most women with PCOS have elevated levels of serum androgens; however, normal levels may be found in some women. For a diagnosis of PCOS, it is sufficient to have elevated serum androgen levels or a biological expression of hyperandrogenism (acne or hirsutism).

Serum testosterone level is the best marker for ovarian hyperandrogenism, and dehydroepiandrosterone sulfate is the best adrenal marker. It is recommended that these analytes be measured. The measurement of free testosterone provides a higher diagnostic yield for ovarian hyperandrogenism because levels of sex-hormone binding globulin are decreased. However, clinical assays used to test this measure vary considerably, affecting its reliability. It is important to point out that hyperandrogenemia is not synonymous with hirsutism or acne. Some ethnic groups (for example, Asians) have substantial hyperandrogenism (elevated levels of testosterone and dehydroepiandrosterone sulfate) without any significant skin manifestations (13, 14).

Anovulation

Anovulation in PCOS is usually chronic and presents as oligomenorrhea or amenorrhea of perimenarchial onset. Nevertheless, a history of regular menses is also possible. Because the degree and chronicity of self-reported menstrual irregularity vary, it has been the most difficult aspect of the diagnosis to define. Some women who report normal menses may be anovulatory. In a recent prospective survey of hyperandrogenic women who reported "normal" menses, we found that 21% experienced anovulation despite reporting regular menstrual cycles (15). It is important to note, however, that PCOS is extremely heterogeneous and that a small number of affected women may have ovulatory function. Although this contradicts our definition of PCOS, it is now accepted that a subset of women with the syndrome who have typical polycystic ovaries on ultrasonography also experience ovulation.

The Ovarian Diagnosis

The polycystic ovary is easily diagnosed. It is enlarged, usually greater than 9 mL with more than 8 mL peripherally oriented cystic structures (<10 mm) in a sonographic plane surrounded by an increased stromal mass (>25% of the ovarian volume) (16). However, although we and others have insisted on these strict criteria, a sonographic spectrum exists. Polycystic ovaries may sometimes be absent in women with all of the other classic clinical characteristics of PCOS. This may be related to the particular resolution of the ultrasonographic technique (for example, vaginal scans are much more sensitive than abdominal scans). We again emphasize that although the ultrasonographic diagnosis of polycystic ovaries is most common in women with PCOS, it may occur in women with other disorders and in healthy women. Ultrasonographic diagnosis alone is not sufficient to diagnose PCOS.

Test for Gonadotropin-Releasing Hormone Agonists

Some investigators believe that PCOS can be diagnosed by performing a test for gonadotropin-releasing hormone agonists and demonstrating an exaggerated ovarian response (17). This test is helpful because it can show that the ovary is producing more androgen in response to luteinizing hormone, but it is our view that it should be considered an adjunctive test. It is not specific enough to pinpoint the diagnosis, and it is impractical to perform.

Insulin Resistance

Many of the late complications of PCOS seem to be related to insulin resistance (18). Burghen and coworkers (19) first reported this observation in 1980, and we and many other groups later confirmed it (20, 21). Although severe insulin resistance, which is often associated with acanthosis nigricans (22), may be present in PCOS, most patients have only a mild form with slightly elevated fasting serum insulin levels. A ratio of fasting glucose to insulin is usually sufficient to diagnose insulin resistance (23), although this ratio is not valid in patients with overt glucose intolerance. It has been suggested that with more sophisticated techniques (for example, an intravenous glucose tolerance test

or clamps), insulin resistance may be diagnosed in almost all women with PCOS.

Although insulin resistance is associated with obesity, it is also found in normal-weight women with PCOS (13, 21, 24) and in women with PCOS from different ethnic groups (13). It has been suggested that anovulation is a major determinant of insulin resistance in women with PCOS. We recently confirmed this and have found that although all women with PCOS may have evidence of insulin resistance, it is more pronounced in those with chronic anovulation than in those who have ovulatory cycles.

The pathogenesis of insulin resistance remains unclear. However, it has been reported that insulin resistance may be related to excessive serine phosphorylation of the insulin receptor in at least 50% of women with PCOS (25). Dysfunction of β cells may also occur in women with PCOS, making them susceptible to type 2 diabetes mellitus (26). More recently, it was suggested that women with PCOS exhibit decreased action of chiroinositol, which is important for insulin signaling. Some patients have been successfully treated with D-chiroinositol (27).

Impaired Glucose Tolerance and Diabetes

Because of insulin resistance, all women with PCOS have increased risk for impaired glucose tolerance and overt type 2 diabetes mellitus. A recent study found that 31% of obese, reproductive-age women with PCOS had impaired glucose tolerance and that 7.5% had overt diabetes (28). In addition, 10.3% of nonobese women with PCOS had impaired glucose tolerance and 1.5% had diabetes, a rate almost three times that of the general population (28). In another study, longitudinal follow-up of women who had been treated with wedge resection showed that 16% developed type 2 diabetes mellitus by menopause (29).

These and other data (30) show that women with PCOS have a high risk for diabetes and that this risk is similar in different populations and ethnic groups (28). Because of the known long-term morbidity associated with diabetes, even young women with PCOS should be followed closely for impaired glucose tolerance and diabetes. In our view, women should be screened for glucose intolerance with an oral glucose tolerance test. We suggest that this be done in obese women with PCOS before pregnancy is attempted and in all affected women with PCOS after 40 years of age.

Altered Serum Lipid Profiles and Impaired Fibrinolysis

Women with PCOS have many abnormalities in lipid and lipoprotein profiles, including elevated levels of cholesterol, triglyceride, and low-density lipoprotein cholesterol and low levels of high-density lipoprotein (HDL) cholesterol and apolipoprotein A-I (31, 32). These findings vary and depend on body weight, diet, and ethnicity. Conway and colleagues (33) reported that the most characteristic lipid alteration in PCOS is decreased levels of HDL2. Hyperandrogenism probably plays some role in these abnormalities, but hyperinsulinemia (insulin resistance) seems to be the more dominant influence (34). In our experience, it is common to find lipid abnormalities (mostly low levels of HDL cholesterol) in young women with PCOS. We believe that HDL cholesterol should be measured during routine cholesterol screening in women with PCOS. Women with PCOS often have impaired fibrinolytic activity, as assessed by circulating levels of plasminogen activator inhibitor (35, 36). This finding is closely associated with insulin resistance and the risk for vascular lesions (37).

Although there is no consensus, we believe that because of the high prevalence of abnormal lipoprotein levels in U.S. women with PCOS, cholesterol, low-density lipoprotein cholesterol, HDL cholesterol, and triglyceride levels should be measured in all affected women at 35 years of age. Women with normal results should be tested again every 3 to 5 years.

Obesity

Forty percent to 50% of women with PCOS are obese (38, 39). This obesity is usually of the android type, with increased waist-to-hip ratios. When present, obesity worsens insulin resistance and increases the risk for diabetes and cardiovascular disease. The treatment of obesity should be a major focus of preventive health care for women with PCOS. However, weight loss in such patients is difficult to achieve. This may be due in part to an impairment of adipocyte lipolysis, which in turn is linked to insulin resistance (40).

Cardiovascular Disease in Women with the Polycystic Ovary Syndrome

Hypertension is uncommon in young women with PCOS, but its prevalence increases by the time of perimenopause. One study showed this increase to be approximately 40%, which confirms the need to monitor patients carefully from the time of diagnosis (29).

Because of the prevalence of risk factors, women with PCOS are thought to have an increased incidence of cardiovascular disease (33, 41–43). It has

been shown that atherosclerosis is more prevalent in women with PCOS (42, 43). The major contributing factor to the risk for cardiovascular diseases is probably dysglycemia. Women with PCOS have an estimated sevenfold increased risk for myocardial infarction (44), although more studies are needed. A recent study showed that patients with PCOS have an increased cardiac risk profile and that this risk is principally related to insulin resistance (45). Because cardiovascular disease is the leading cause of death in women, clinicians should take advantage of opportunities for early intervention. The polycystic ovary syndrome should be considered a risk factor for cardiovascular disease.

How Does This Relate to Pathophysiology?

A detailed discussion of pathophysiology is not possible in this review. However, because 16% to 25% of "normal" women have the isolated finding of polycystic ovaries (5–7), development of PCOS seems to require additional factors (46). It has been suggested that certain women have a genetic propensity for PCOS and that PCOS has an autosomal dominant mode of inheritance (47). The male counterpart of PCOS is thought to be premature baldness.

Future Directions

Diagnosis of PCOS is extremely important because it in turn identifies risk for potential metabolic and cardiovascular diseases. Although women who present with characteristic PCOS usually seem healthy, most have evidence of insulin resistance and hyperinsulinemia, abnormal lipid and lipoprotein levels, and altered fibrinolysis. Recently, we identified subtle abnormalities (increased fasting insulin levels and low levels of HDL cholesterol) in young, healthy, ovulatory women who did not qualify for a diagnosis of PCOS because their only symptom was altered ovarian sonography (48). Some of these women may eventually develop more defined features of the syndrome and may receive a diagnosis of PCOS in later years. Although more research in this area is needed, we believe that because the risks associated with PCOS are severe, women with ovarian morphologic findings require close follow-up for clinical features of the disorder (such as anovulation and hyperandrogenism).

Conclusion

Diagnosis of PCOS, particularly at an early age, has important consequences besides those associated with reproduction. An opportunity for preventive health care exists and may alleviate risks for metabolic and cardiovascular disease. Reduction in insulin resistance should be a mainstay of any long-term strategy. Although diet and exercise are an important first-line approach, insulin-sensitizing agents are considered beneficial because they have been shown to improve risk factors (27, 49–51). However, a consensus regarding the use of these agents to reduce health risks in women with PCOS has not been reached, and a full discussion is beyond the scope of this article. Low-dose oral contraceptives can be used to treat the characteristic menstrual irregularity and are known to reduce the risk for endometrial as well as ovarian cancer. Although oral contraceptives have a neutral effect on insulin resistance, they lower androgen profiles; newer formulations increase HDL cholesterol levels (52). It is important to monitor glucose intolerance in obese women before pregnancy and in all women after 40 years of age. Because abnormal lipid and lipoprotein levels are prevalent, we recommend monitoring them every 3 to 5 years in women older than 35 years of age.

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