AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS POSITION STATEMENT ON METABOLIC AND CARDIOVASCULAR CONSEQUENCES OF POLYCYSTIC OVARY SYNDROME

Polycystic Ovary Syndrome Writing Committee

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AACE Position Statement

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Abbreviations:
AACE = American Association of Clinical Endocrinologists; **ACE** = American College of Endocrinology; **BMI** = body mass index; **CRP** = C-reactive protein; **CVD** = cardiovascular disease; **ET-1** = endothelin-1; **HDL** = high-density lipoprotein; **IGT** = impaired glucose tolerance; **IRS** = insulin resistance syndrome; **LDL** = low-density lipoprotein; **PCOS** = polycystic ovary syndrome; **T2DM** = type 2 diabetes mellitus; **WHR** = waist-to-hip ratio

INTRODUCTION

Women with polycystic ovary syndrome (PCOS) constitute the largest group of women at risk for the development of cardiovascular disease (CVD) and diabetes. PCOS is the most common metabolic abnormality in young women today, occurring in 10% of female patients of reproductive age (1,2).

The purpose of this position statement is to inform health care professionals and the public about the need to identify women with PCOS and, once this diagnosis has been established, to search for metabolic and cardiovascular risk factors that may be associated with PCOS. Physicians should not regard these women as merely having cosmetic complaints, or primarily coping with infertility, but as having potential metabolic disorders that may be associated with type 2 diabetes mellitus (T2DM) and cardiovascular events. Although the patient's immediate problems and concerns necessitate sensitive attention and prompt therapy, they should also be seen as an opportunity to practice proactive preventive medicine. Early case finding and intervention are expected to result in a reduction of serious associated medical consequences. This report will review the available data from studies that attempt to analyze these risks and their clinical consequences (3).

DIAGNOSTIC CRITERIA FOR PCOS

A broad range of opinions prevails about the definition of PCOS. Most authorities in the field accept the following three criteria as a basis for diagnosis of the syndrome:

1. A history of irregular menstrual cycles and anovulation, with onset at puberty. Many investigators believe that 25% of women with PCOS, in fact, do have regular menstrual cycles, although these periods of menstrual bleeding may represent anovulatory cycles. (Clinical evidence of androgen excess, such as moderate or severe acne that persists into the late 20s or 30s, hirsutism, and alopecia, is often the initial presentation to the physician. When such symptoms are noted, the woman must be questioned regarding the presence of irregular menstrual cycles.)
2. The presence of chemically measurable hyperandrogenism, with documentation of high plasma levels of ovarian androgens, including total and free testosterone (4).
3. The exclusion of other hormonal disorders with similar clinical features, including adult-onset congenital adrenal hyperplasia, hyperprolactinemia, adrenal or ovarian androgen-producing adenomas, hyperthecosis, and Cushing's syndrome.

PATHOGENESIS OF PCOS

Genetic studies support the increased frequency of PCOS in first-degree relatives of affected women. Many candidate genes have been proposed. Most likely, several genes are involved in the development of this heterogeneous syndrome. Accordingly, many different hypotheses have been proposed for the pathogenesis of PCOS (5), including the following:

1. Hypothalamic-pituitary abnormalities that result in gonadotropin-releasing hormone and luteinizing hormone dysfunction
2. A primary enzymatic defect in ovarian or combined ovarian and adrenal steroidogenesis
3. A metabolic disorder characterized by insulin resistance in conjunction with compensatory hyperinsulinemia that exerts adverse effects on the hypothalamus, pituitary, ovaries, and, possibly, adrenal glands

CLINICAL EVALUATION OF PCOS

The history should include a detailed inquiry about growth and sexual development, menarche, and menstrual pattern, as well as information to exclude other potential causes of oligomenorrhea, hirsutism, acne, and infertility. Physical findings of acanthosis nigricans and a hyperpigmented area on the nape of the neck or other areas such as the axillae or groin are suggestive of insulin resistance. Measurements of blood pressure, body mass index (BMI), and waist circumference must be made. Defining the extent of hirsutism and the degree of acne or alopecia is also essential.

LABORATORY ASSESSMENT OF POSSIBLE PCOS

No consensus exists among endocrinologists about the battery of laboratory tests that must be ordered in the assessment of women for PCOS. The following are the most commonly ordered laboratory tests, which are meant both to confirm the clinical diagnosis of PCOS and to evaluate for glucose intolerance and cardiovascular risk. Studies should be performed early in the morning, with the patient in a fasting state, and, in women with regular menses, sometime between days 5 and 9 of the menstrual cycle.

1. Several determinations of total and free testosterone levels or a free androgen index performed by a competent laboratory will help assess the status of androgens.
2. Serum levels of luteinizing hormone and follicle-stimulating hormone can be determined. An increased ratio of luteinizing hormone to follicle-stimulating hormone >2 is found in 60 to 70% of women with PCOS and is more likely to occur in nonobese than in obese women.
3. Measurement of serum sex hormone-binding globulin may reveal decreased levels in patients with PCOS.
4. Measurements of serum prolactin, dehydroepiandrosterone sulfate, and 17α-hydroxyprogesterone will provide useful information.
5. A lipid profile can be obtained, including serum high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol and triglycerides.
6. Plasma insulin may be measured; clinicians should remember that methodologic inconsistencies occur and that insulin levels are not necessary for the diagnosis of the insulin resistance syndrome (IRS).
7. The American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) recommend screening for diabetes by age 30 years in all patients with PCOS, including obese and nonobese women. The risk for diabetes is further heightened by a family history of diabetes, a personal history of gestational diabetes, and obesity, sedentary behavior, and ethnicity. Determination of a blood glucose level after challenge with a 75-g load of glucose may be performed. The usefulness of measuring insulin levels at baseline and 2 hours after administration of glucose is under study. Under some circumstances, earlier testing before the age of 30 years may be indicated. Because T2DM evolves over time, women with PCOS who initially test negative for diabetes should be periodically reassessed throughout their lifetime.
8. Pelvic ultrasonography, although nonspecific, affords a pretreatment view of the ovaries. The effect of treatment of PCOS can be monitored, in part, by noting ovarian size, follicle number, endometrial lining, and possible development of benign ovarian dermoids or other neoplasms (incidence of approximately 5 to 10%) (6). The finding of morphologic evidence of polycystic ovaries on pelvic ultrasonography in 23% of apparently normal women limits its specificity in the diagnosis of PCOS. Several other endocrine pathologic conditions may mimic the ovarian morphologic appearance in PCOS. Thus, a history of oligomenorrhea and evidence of ovarian hyperandrogenism are key elements in defining PCOS.

PCOS AND IRS

The IRS is defined as a cluster of abnormalities and clinical syndromes that are much more likely to occur in patients with insulin resistance than in others (7). It identifies patients at increased risk for T2DM and cardiovascular disease. The prevalence of insulin resistance and compensatory hyperinsulinemia is increased in women with PCOS. Most reports indicate that at least 75% of women with PCOS fulfill the criteria for IRS (8). Not all patients with insulin resistance have any or all of the abnormalities and clinical syndromes of the IRS, and these abnormalities and clinical syndromes can develop in the absence of insulin resistance. Nevertheless, the likelihood that a woman with PCOS will have insulin resistance or hyperinsulinemia is so substantial that all women with PCOS should undergo assessment for the adverse outcomes that constitute the IRS.

Each component of the IRS in the subsequent list is a risk factor for CVD, with greater risk for T2DM or CVD (or both) occurring in the presence of more abnormalities. The importance of this clustering of abnormalities recognized as the IRS prompted AACE to promote the institution of the International Classification of Diseases code 277.7 for IRS (dysmetabolic syndrome X).

On the basis of the 2003 ACE position statement on IRS, the identifying features of this syndrome (7,9) are as follows:

1. Reduction of serum HDL cholesterol level to <50 mg/dL
2. Increase in serum triglyceride level to >150 mg/dL

3. Hypertension, as defined by a blood pressure >130/85 mm Hg
4. Insulin resistance and increased tendency to have T2DM
5. Fasting glucose level of 110 to 125 mg/dL
6. Glucose level of 140 to 199 mg/dL 120 minutes after challenge with 75 g of glucose

Both obesity and physical inactivity are major factors that work synergistically with the inherent postreceptor defect and lead to insulin resistance in patients with PCOS (10). Obesity increases the likelihood of occurrence of insulin resistance. Although not all obese persons have insulin resistance, obesity is associated with insulin resistance in the majority of women, and most nonobese women with PCOS and oligomenorrhea also have insulin resistance (11). Not all women with insulin resistance have PCOS (12); this finding may be related to genetic differences in susceptibility of the ovary and pancreas. Obesity is often the trigger that precipitates the symptoms of PCOS in association with biochemical and clinical hyperandrogenism.

Insulin resistance may be difficult to assess accurately in the absence of hyperinsulinemic-euglycemic clamp studies, particularly in the setting of basal insulin levels in the normal or high-normal range and in the nonobese subgroup of women with PCOS. Methods that measure only fasting glucose and insulin levels (including homeostasis model assessment and the quantitative insulin sensitivity check index) may be inaccurate in assessing insulin sensitivity in this group of women (13). Therefore, data are likely to underestimate the frequency of insulin resistance in patients with PCOS, who have a unique form of insulin resistance, and in those with mild insulin resistance and borderline normal fasting glucose and insulin levels. Perhaps other hormonal and genetic factors, as well as ethnicity, may influence the degree of insulin resistance and contribute to the conflicting reports of the incidence of insulin resistance in women with PCOS. Because accurate assessment of insulin sensitivity is impossible in the clinical practice setting, it is prudent to regard all obese women as likely having insulin resistance and being at risk for the IRS and to assume that most nonobese women with PCOS have the IRS as well (14).

TYPE 2 DIABETES MELLITUS

Impaired glucose tolerance (IGT) and frank diabetes occur in the presence of insulin resistance when the pancreatic beta cell is unable to compensate for the insulin resistance (15).

The incidences of IGT and T2DM are significantly increased in women with PCOS. In a study from the University of Pittsburgh, T2DM was noted in 12.6% of women with PCOS (who had a mean age of 42 years) in comparison with 1.4% of matched control subjects (16). Studies have indicated that, on initial evaluation with a 2-hour glucose tolerance test, 30 to 40% of patients with PCOS already have IGT or T2DM (17-19). These findings may prevail even in young teens with PCOS (18). A higher prevalence of IGT and T2DM occurs in obese women with PCOS, particularly those with a family history of T2DM.

Oligomenorrhea is a surrogate marker for probable PCOS and may predict a 2- to 2.5-fold increase in risk for T2DM, particularly in the presence of a family history of T2DM (20). In the Nurses' Health Study, more than 116,000 women 25 to 42 years old underwent follow-up for 8 years. A 2- to 2.5-fold increased incidence of T2DM was present in women with a history of oligomenorrhea (some of whom had severe cystic acne and hirsutism), in comparison with the women who had regular menses, although no physician-based diagnosis of PCOS was made. Obesity increased the frequency of diabetes in this population. Because approximately 80% of women with irregular menses have PCOS, these data are highly suggestive that PCOS is a strong risk factor for T2DM, independent of but exacerbated by the presence of obesity (16).

Because the presence of T2DM abolishes the "gender gap" in coronary artery disease (21) and because patients with concurrent diabetes and the IRS have the highest prevalence of coronary artery disease (22), women with PCOS, the IRS, and diabetes are likely to have not only an extremely high risk of coronary artery disease but also the microvascular consequences of uncontrolled diabetes.

Prevention trials have shown that identification of IGT is important because intensive lifestyle modification, with or without pharmacologic intervention, will prevent the progression to overt T2DM and its consequent risks (23,24). Therefore, AACE and ACE have already included PCOS as an important risk factor for diabetes and have recommended screening for diabetes by age 30 years in all patients with PCOS (25).

DYSLIPIDEMIA

Women with PCOS are frequently found to have atherogenic lipid abnormalities that may reflect underlying insulin resistance, as well as the effects of genetics, ethnicity, obesity, and lifestyle factors. Low HDL (26) and high triglyceride levels are found in both obese and nonobese women who have hyperinsulinemia and PCOS (27,28). The reciprocal relationship of triglycerides and HDL is strongly associated with insulin resistance in most populations and is one factor contributing to the accelerated atherogenesis detected in these patients. A ratio of triglycerides to HDL of greater than 3.0 appears to predict insulin resistance effectively (29). Obesity exacerbates the elevated triglyceride levels in women with PCOS.

Atherogenic modifications of LDL cholesterol toward smaller, more dense particles have been demonstrated (30) in 31 women with PCOS, whose mean age was 26 years, in comparison with LDL cholesterol particles in control subjects.

The combination of low HDL and increased LDL cholesterol levels is often present in women with PCOS. In a study in central Pennsylvania of 153 obese or overweight (BMI >27 kg/m^2) and 42 nonobese non-Hispanic white women with PCOS having a mean age of 28 years, lipids were compared with those in control subjects of the same ethnicity and matched for BMI and waist-to-hip ratio (WHR) (31). The women with PCOS had higher LDL levels than did the control subjects, independent of obesity.

A large-scale epidemiologic study of 244 women with PCOS (32) demonstrated elevated levels of LDL and reduced HDL cholesterol levels in the women with PCOS younger than age 45 years in comparison with matched control subjects. Beyond 45 years of age, no significant lipid differences were found between women with PCOS and control subjects. This early prolonged exposure to hyperlipidemia is a significant cardiovascular risk factor in women with PCOS in comparison with their peers who had normal menstruation.

ENDOTHELIAL DYSFUNCTION

Women with PCOS have impaired endothelial function due to altered insulin regulation of endothelial nitric oxide synthesis, which leads to impaired nitric oxide-dependent vasodilatation. The arterial consequences of metabolic dysregulation lead to reduced vascular compliance of large vessels as well as reduced vasodilatation. An abnormal vasodilatory response correlates with long-term risk for CVD (33).

Diminished alteration in vascular compliance in response to insulin in brachial arteries, suggesting impaired insulin action (that is, insulin resistance), was demonstrated in studies of brachial arteries of young women with PCOS (mean age, 26 years) in comparison with control subjects. This finding links insulin resistance in vascular tissue with endothelial dysfunction, decreased arterial compliance, and possible later development of CVD in patients with PCOS (33,34). Increased endothelin-1 (ET-1) levels, a marker for vasculopathy in patients with insulin resistance (35), have been noted in patients with PCOS. Plasma ET-1 levels were increased 5-fold in obese and nonobese subjects with PCOS over those in control subjects. These increased ET-1 levels may be an early sign of abnormal vascular reactivity induced by this vasoconstrictor polypeptide. Administration of 1,700 mg of metformin daily for 6 months reduced ET-1 and testosterone levels; this result suggests that insulin resistance and hyperandrogenemia potentially contribute to endothelial injury (35).

HYPERTENSION

As patients with PCOS age, they have a higher incidence of hypertension than do matched control subjects (36-38). Increased systolic blood pressure has been noted in patients with PCOS. When blood pressure was monitored for 24 hours, women with PCOS had higher daytime systolic blood pressure, even after adjustment for BMI, insulin sensitivity, and body fat distribution, in comparison with that in matched control subjects (39). The association with hyperinsulinemia in both the obese and the nonobese subjects in that study was of interest.

PROINFLAMMATORY AND ATHEROGENIC MARKERS

In comparison with control subjects, patients with PCOS have decreased fibrinolytic activity, higher levels of plasminogen activator inhibitor-1 (17,40), and increased C-reactive protein (CRP) levels, all of which are markers for inflammation and correlate well with an increased risk for CVD in epidemiologic studies (41-43). Elevated CRP levels have been found in both obese and nonobese women with PCOS (42). Treatment directed toward reduction of cardiovascular risk (smoking cessation, diet, aspirin, statins, and possibly metformin and thiazolidinediones) should probably be more aggressive in those women with PCOS who have increased CRP levels (7,44).

STUDIES OF CVD IN WOMEN WITH PCOS

Data Suggesting Subclinical CVD Risk

Two major surrogate markers for cardiovascular risk factors in PCOS are coronary calcifications, identified by electron beam tomography, and carotid intima-media thickness, determined by ultrasonography.

A Mayo Clinic study of coronary calcification with use of electron beam tomography in 36 nondiabetic women with PCOS, who were 30 to 45 years old, revealed a mean 3-fold higher level of coronary artery calcification than in population control subjects (45). In comparison with obese control subjects, women with PCOS had a 2-fold increase in coronary artery calcification. A correlation was found between coronary artery calcification score and BMI, visceral adiposity, and elevated levels of serum triglycerides in women with PCOS.

The electron beam tomographic technique for coronary calcium scoring was also used by Talbott et al (46) to study 102 middle-aged women with PCOS (ages 40 to 61 years; mean age, 46.9) in comparison with 118 control subjects (mean age, 48.5 years). The mean coronary artery calcification score for women with PCOS and control subjects was 25.2 and 4.1, respectively. These investigators found that the presence of PCOS, age, BMI, smoking status, increased fasting insulin levels, and low HDL levels were associated with increased coronary artery calcification scores and consequent risk of coronary events. In a subsequent prospective case-control study, Talbott et al (47) found that women with PCOS had a higher prevalence of both coronary artery calcification and aortic calcification in comparison with control subjects and had an increased risk for the metabolic cardiovascular syndrome.

Carotid intima-media thickness measured by carotid ultrasonography is a surrogate marker for coronary risk. This technique was used to study 125 white women with PCOS and 142 age- and BMI-matched control subjects (48). No significant difference in carotid intima-media thickness was found between control subjects and women with PCOS who were younger than age 44 years. In contrast, women with PCOS who were 45 years of age or older had a mean carotid intima-media thickness of 0.78 mm in comparison with 0.70 mm in matched control subjects ($P = 0.005$). The absence of a significant difference between younger women with PCOS and control subjects suggests that metabolic alterations in younger women with PCOS translate into measurable increases in intima-media thickness by middle age. This occurs despite the well-known narrowing difference in lipid levels between control subjects and women with PCOS at the approach of menopause.

Defined Actual CVD Event Studies

A risk factor model analysis has calculated that patients with PCOS have a 4-fold to 7-fold higher risk of myocardial infarction in comparison with age-matched control subjects (49). This risk factor model analysis was based on 33 women with PCOS and 132 age-matched control subjects who underwent assessment in a prospective population study of 1,462 women in Göteborg, Sweden. Factors evaluated included age, hypertension, diabetes mellitus, central obesity, and serum triglyceride concentration.

A profound increase in cardiovascular risk factors is present in women with PCOS. The aforementioned cohort of 33 women with PCOS, who had a mean age of 50 years and a history of a prior ovarian wedge resection, were compared with 132 age-matched control subjects (37). Postmenopausal women constituted 30% of the patients with PCOS and 56% of the control subjects. In comparison with the control subjects, the women with PCOS had the following:

1. A 7-fold increased prevalence of T2DM (15% versus 2.3% in control subjects)
2. A 3-fold increased incidence of treated hypertension
3. A significantly higher WHR
4. A significant increase in plasma insulin levels and decrease in sex hormone-binding globulin levels

In a study from the Czech Republic (50), 28 women with PCOS, who had undergone prior ovarian wedge resection, were compared with 752 female control subjects who were 45 to 54 years old. The mean age of both groups was 51 years, and the groups were matched for BMI, WHR, hypertension, lipid profiles, and smoking. The following findings in the women with PCOS were reported:

1. An increased frequency of T2DM—32% versus 8% of control subjects
2. An increased frequency of coronary artery disease—21% versus 5% of control subjects

PCOS was detected by pelvic ultrasonography in 42% of 143 women younger than age 60 years, who were undergoing cardiac catheterization for chest pain or valvular disease (51)—double the frequency in the general population (52). Patients with PCOS exhibited more coronary artery segments with >50% stenosis and significantly greater clinical heart disease than did women with normal ovaries ultrasonographically. Ultrasound evidence of PCOS was associated with clinical hirsutism, elevated testosterone levels, and a higher incidence of dyslipidemia.

In a study in Holland, increased prevalences of hypertension, diabetes mellitus, and cardiac symptoms were found in 346 lean (BMI, 24.4 kg/m^2) women with PCOS, who had a mean age of 38.7 years, in comparison with a population database (53). The prevalence of diabetes mellitus in this lean group of women with PCOS was 2.3%, and the prevalence of hypertension was 9%. Cardiac symptoms occurred in 3.1% of women with PCOS who were 45 to 54 years old in comparison with 0.9% in the control population.

A 10-year follow-up study of a cohort of 127 white women with PCOS who were older than age 40 years revealed that 5 of these women had had 8 coronary events, in comparison with none in a matched control population of 142 women (54). Cardiac function may be impaired, as determined by echocardiographic indices, even in young women (less than 30 years old) with PCOS, independent of weight (55).

Clinical androgen excess in women may signal a risk for coronary artery disease. Hirsutism, acne, and an increased WHR were associated with more severe coronary artery disease on angiography in 102 women older than age 60 years (56), in comparison with age-matched nonhirsute women.

Oligomenorrhea is a good surrogate marker for the potential development of CVD; more than 80% of women with oligomenorrhea have been thought to have PCOS. The prospective Nurses' Health Study of more than 101,000 women linked a history of menstrual irregularity not only to a 2- to 2.5-fold increase in risk of diabetes mellitus (20) but also to an increased risk of mortality due to fatal coronary artery disease. When 82,439 nurses in this study underwent surveillance during a mean follow-up period of 14 years (57), a history of oligomenorrhea (at ages 20 to 35 years) was associated with a 100% increased incidence of fatal and 50% increased incidence of nonfatal coronary artery disease, after adjustment for age, cigarette smoking, and BMI.

The two following studies did not find an increase in cardiovascular risk or death rate in women with PCOS, but the predictive power of these studies may be limited by methodologic issues.

In the United Kingdom, 786 women diagnosed with PCOS (in most cases by undergoing a wedge resection of

the ovaries) between 1930 and 1979 were identified from hospital records and followed for a mean of 30 years (58). On analysis of the data, diabetes mellitus was found to be commonly mentioned as contributing to mortality in this group with PCOS. The standardized mortality ratio (observed/expected deaths) for women with PCOS was 0.83 in comparison with the national average of 0.90. The conclusion was that women with PCOS do not have a higher-than-average mortality from circulatory disease, despite the numerous risk factors for CVD.

In a retrospective UK study of 319 women with PCOS, most of whom had a tissue diagnosis by ovarian wedge resection (mean age, 57 years; range, 38 to 98), the incidence of coronary artery disease was not higher than that among women in the general population (36). Nonetheless, a 2.5-fold higher incidence of T2DM and nonfatal cerebrovascular events was noted in comparison with that in the age- and BMI-matched population-based control subjects. In this UK study, only 26% of patients demonstrated obesity (BMI, >30 kg/m^2), the mean BMI of the study subjects being 26 kg/m^2. The incidence of obesity in the United States is higher, ranging from 50 to 60%.

Summary and Synthesis of Data on Cardiovascular Risk

In summary, several lines of evidence strongly support the concept that women with PCOS are at high risk for cardiovascular and metabolic disease.

1. The prevalences of both T2DM, a myocardial infarction-equivalent state, and IGT, a condition associated with increased cardiovascular risk, are substantially increased in patients with PCOS. Accordingly, the AACE and ACE recommend screening for diabetes in all patients with PCOS by age 30 years.
2. Multiple recognized cardiovascular risk factors are present in excess in women with PCOS (often several simultaneously). The result is a higher-than-usual prevalence of the Adult Treatment Panel III- and AACE-defined metabolic IRS in patients with PCOS.
3. Imaging studies in women with PCOS have uniformly identified a higher prevalence of anatomic and functional abnormalities indicative of existing underlying cardiovascular disease or dysfunction in comparison with findings in age-matched control subjects.

These observations are remarkable for their abundance, uniformity, and consistency, and they predict an increased risk for adverse cardiovascular events in patients with PCOS. To date, however, no prospective longitudinal study has assessed cardiovascular outcomes specifically in women with PCOS. Nonetheless, it is notable that a prospective large-scale study of women with oligomenorrhea who underwent follow-up for 1½ decades reported a 2-fold increased risk for fatal myocardial infarction in this population (20). Most likely, a large proportion of these women had PCOS. Hence, this study provides indirect confirmation of increased adverse cardiovascular outcomes in patients with PCOS.

Despite the absence of prospective longitudinal studies, retrospective epidemiologic studies have been performed to assess cardiovascular outcomes in PCOS. Unfortunately, these studies have been of variable quality, and they have differed from one another with respect to diagnostic criteria, anthropometric and phenotypic characteristics, duration of follow-up, therapeutic intervention with bilateral wedge resection of the ovaries, and other factors. Nonetheless, most of these studies have confirmed an increased risk for adverse cardiovascular outcomes in patients with PCOS.

Collectively, the foregoing substantive evidence indicates that women with PCOS are at high risk for CVD. Even in the absence of definitive outcome studies, the evidence supports a strong recommendation that women with PCOS should undergo comprehensive evaluation for recognized cardiovascular risk factors and receive appropriate treatment based on findings.

TREATMENT OF PCOS

Well-defined published data indicate a high risk for development of T2DM and CVD in women with PCOS. In view of the lack of protective effect of female sex on CVD risk in patients with diabetes (21,59), the associated risks of CVD are magnified in women with diabetes who have PCOS. Clearly, this situation means that PCOS is a general health disorder of young women, with potential for reversal of some of the associated risk with early diagnosis and treatment (44). Lifestyle modification with weight loss and exercise, avoidance of tobacco, correction of lipid abnormalities, and use of metformin may be of value. Metformin therapy not only reduces hyperinsulinism and improves steroidogenic dysfunction (60) but also is helpful in achieving better regularity of menses and fertility potential (61). Thiazolidinediones have also been shown to decrease androgen levels, improve ovulation, and reduce progression to overt T2DM in patients with PCOS and IGT (62-64).

In view of the potential for and actual presence of numerous cardiovascular and metabolic risk factors in most women with PCOS, the role of the clinical endocrinologist is essential in the following:

1. Early recognition of the syndrome.
2. Lifestyle modification, with emphasis on the need for controlled eating patterns and regular aerobic exercise. Encouragement should be offered by an empathic physician, who will monitor the patient carefully during the course of treatment.
3. Measurement of glucose (and possibly insulin levels). An oral glucose challenge may be considered, particularly in obese women with PCOS and those with a family history of T2DM.

4. Detection and treatment of lipid abnormalities, with dietary measures first and then use of appropriate medications, such as a statin, fibrate, niacin, or ezetimibe (or some combination of these agents), as necessary.
5. Careful attention to and treatment of blood pressure abnormalities.
6. Measurement of atherogenic markers (CRP, fibrinogen, and possibly homocysteine).
7. Consideration of metformin therapy as the initial intervention in most women with PCOS, particularly in those who are overweight or obese. Metformin improves many metabolic abnormalities in PCOS and may improve menstrual cyclicity and the potential for pregnancy. Of note, metformin has not been approved by the US Food and Drug Administration for use in PCOS, although abundant medical literature supports its efficacy.
8. The use of a nonandrogenic oral contraceptive agent and an antiandrogen such as spironolactone for the skin manifestations of PCOS. The presence of hair thinning requires the maximal dose of spironolactone in conjunction with an oral contraceptive agent. Ancillary use of electrolysis and laser therapy may also be helpful.
9. The use of thiazolidinediones in patients with IGT or frank diabetes. The use of these agents to improve hyperandrogenism and ovulation is considered only investigational at this time. Thiazolidinediones are category C drugs; their use is contraindicated during pregnancy.

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