American Association of Clinical Endocrinologists Position Statement on Metabolic and Cardiovascular Consequences of Polycystic Ovary Syndrome

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Women with polycystic ovary syndrome (PCOS) are the largest group of women at risk for the development of cardiovascular disease and diabetes. PCOS is the most common metabolic abnormality in young women today, occurring in 10 percent of women of reproductive age.

The purpose of this Position Statement is to inform health care professionals and the public of the need to identify women with PCOS and, once a diagnosis is established, to search for metabolic and cardiovascular risk factors which may be associated with PCOS. The physician should no longer regard these women as merely having annoying cosmetic complaints, or primarily suffering from 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 require sensitive attention and prompt therapy, they should also be seen as an opportunity to practice proactive preventive medicine. Early case finding and intervention will result in a reduction of serious medical consequences. This paper will review the available data from studies which attempt to analyze these risks and their clinical consequences[1].

What are the Criteria for a Diagnosis of PCOS?

There is a broad range of opinions of the definition of the syndrome. Most authorities in the field accept the following three criteria as a basis for diagnosis:

1. A history of irregular menstrual cycles and anovulation, with onset at puberty. Many authors believe that 25 percent of women with PCOS, in fact, do have regular menstrual cycles, although these menstrual bleeds may represent anovulatory cycles. (Clinical evidence of androgen excess such as moderate or severe acne which persists to the late 20's or 30's, hirsutism and alopecia are often the presenting symptom to the physician. When these occur, the woman must be questioned regarding the presence of irregular menstrual cycles.)

2. The presence of hyperandrogenism, with documentation of elevated plasma levels of ovarian androgens, including total and free testosterone.

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.

The Pathogenesis of PCOS

Genetic studies support the frequency of PCOS in first-degree relatives of affected women. Many candidate genes have been proposed and it is likely that a number of genes are involved in the development of this heterogeneous syndrome. In this regard, a number of different hypotheses have been proposed for the pathogenesis of PCOS. These include[2]:

1. Hypothalamic-pituitary abnormalities which result in gonadotropin-releasing hormone (GnRH) and luteinizing hormone dysfunction.

2. A primary enzymatic defect in ovarian or combined ovarian-adrenal steroidogenesis.

3. A metabolic disorder characterized by insulin resistance with compensatory hyperinsulinemia that exerts adverse effects on the hypothalamus, pituitary, ovaries, and, possibly, adrenal glands.

Clinical Evaluation

History should include a detailed history of development, menarche and menstrual pattern, as well as information to exclude other etiologies of oligomenorrhea, hirsutism, acne, and/or infertility. Physical findings of acanthosis nigricans, a hyperpigmented area in the nape of neck, and/or other areas such as the axillae, and groin are suggestive of insulin resistance. Analysis of blood pressure, BMI and waist measurement must be made. Defining the extent of hirsutism, the degree of acne or alopecia is also essential.

What Laboratory Tests Should be Performed in the Investigation of a Patient Suspected of having PCOS?

There is no consensus among endocrinologists on the set of laboratory tests which must be ordered in the evaluation 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 an affected woman for glucose intolerance and cardiovascular risk. Studies should be done early in the morning, in a fasting state, and in those with regular menses from days 5-9 of the menstrual cycle.

1. Several determinations of total and free testosterone or a free androgen index performed by a competent laboratory.

2. Serum LH and FSH. (An increased LH/FSH ratio > 2 is found in 60-70 percent of women with PCOS, and is more likely to occur in non-obese women)

3. Measurement of serum sex hormone-binding globulin

4. Measurement of serum prolactin, dehydroepiandrosterone sulfate, and 17 alpha-hydroxyprogesterone

5. Lipid profile, including serum HDL and LDL cholesterol, and triglycerides

6. Plasma insulin may be measured, remembering that methodologic inconsistencies occur and that insulin levels are not necessary for the diagnosis of the insulin resistance syndrome.

7. AACE recommends screening for diabetes in all patients with PCOS by age 30 in both obese and non-obese women. Risk for diabetes is further heightened by a family history, a history of gestational diabetes, and obesity, sedentary behavior and ethnicity. Post-challenge blood sugar with a 75 gm load of glucose may be performed. The usefulness of measuring the baseline and two-hour post-glucose insulin level is under study. Under some circumstances, earlier testing before the age of 30 may be indicated. Since type 2 diabetes evolves over time, women who initially test negative should be periodically reassessed over their lifetimes.

8. Pelvic ultrasonography, although nonspecific, affords a pretreatment view of the ovaries. The effect of treatment 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 ~ 5-10%)[3]. The finding of morphologic evidence of polycystic ovaries on pelvic ultrasonography in 23 percent of apparently normal women limits its specificity in the diagnosis of PCOS. A number of other endocrinopathies may mimic the ovarian morphology; thus, a history of oligomenorrhea and evidence of ovarian hyperandrogenism are key elements in defining PCOS.

PCOS and the Insulin Resistance Syndrome

The Insulin Resistance Syndrome (IRS) is defined as a cluster of abnormalities and clinical syndromes that are much more likely to occur in insulin resistant individuals[4]. It identifies individuals at increased risk for T2DM and cardiovascular disease. The prevalence of insulin resistance/compensatory hyperinsulinemia is increased in women with PCOS. Most reports indicate that at least 75 percent of women with PCOS fulfill the criteria for IRS[5]. Not all insulin resistant individuals develop any or all of the abnormalities and/or clinical syndromes of the IRS and these abnormalities and/or clinical syndromes can develop in the absence of insulin resistance. However, the likelihood that a woman with PCOS will be insulin resistant/hyperinsulinemic is so substantial that all women with PCOS should be evaluated for the adverse outcomes that comprise the IRS.

Each component of the IRS listed below is a risk factor for CVD, with greater risk of T2DM and/or CVD occurring in the presence of more abnormalities. The importance of this clustering of abnormalities recognized as the insulin resistance syndrome underlies the institution by AACE of the IRS Code 277.7 (Dysmetabolic Syndrome X).

According to the AACE Position Statement (2003), the identifying features of the Insulin Resistance Syndrome[4,6] are:

1. Reduction of serum HDL cholesterol below 50 mg/dL
2. Increase in serum triglycerides > 150 mg/dL
3. Hypertension as defined by a blood pressure > 130/85mm Hg.
4. Insulin resistance (IR) and increased tendency to type-2 diabetes mellitus
5. Fasting glucose of 110-125 mg/dL
6. 120 minute post-(75 gram) glucose challenge of 140-199 mg/dL

Both obesity and physical inactivity are major factors which synergize with the inherent post-receptor defect leading to IR in PCOS. Obesity increases the likelihood of an individual being insulin resistant. Although not all obese people are insulin resistant, obesity is associated with insulin resistance in the majority of women, and most non-obese oligomenorrheic women with PCOS are insulin resistant[7]. Not all women with insulin resistance have PCOS[8] and this may be related to genetic differences of the ovary and pancreas. Obesity or the development of obesity often is a synergistic trigger that promotes the symptoms of PCOS associated with biochemical and clinical hyperandrogenism.

IR may be difficult to assess accurately in the absence of hyperinsulinemic-euglycemic clamp studies, particularly, when the basal insulin levels are in the normal or high normal range and in the non-obese subgroup of PCOS women. Methods that only measure fasting glucose and insulin levels (including homeostasis model assessment (HOMA) and the quantitative insulin sensitivity check index (QUICKI)) may be inaccurate in assessing insulin sensitivity in this group of women[9]. It is likely, therefore, that data may underestimate the frequency of insulin resistance in PCOS, who have a unique form of IR, and where mild IR may be present with borderline normal fasting glucose and insulin levels. Perhaps other hormonal and genetic factors, as well as ethnicity, may influence the degree of IR, and contribute to the conflicting reports of the incidence of IR in women with PCOS. Since it is impossible to accurately assess insulin sensitivity in the clinical practice setting, it is prudent to regard all obese women as likely suffering from insulin resistance and being a risk for the insulin resistance syndrome and to assume that most non-obese women with PCOS have the syndrome as well.

Type 2 Diabetes Mellitus

Impaired glucose tolerance and frank diabetes occurs in the presence of insulin resistance when the pancreatic beta-cell is unable to compensate for the IR[10].

There is a significant increase in the incidence of impaired glucose tolerance (IGT) and T2DM in women with PCOS. In a study from the University of Pittsburgh, T2DM was noted in 12.6 percent of PCOS women with a mean age of 42 years compared to 1.4 percent in their matched controls[11]. Studies indicated that on the initial evaluation with a 2-hour GTT, 30-40 percent of PCOS already have IGT or T2DM[12-14]. These findings may even occur in younger teens with PCOS[13]. A higher prevalence of IGT and T2DM occurs in obese women with PCOS, particularly, those with a positive family history of T2DM.

Oligomenorrhea is a surrogate marker for probable PCOS and may predict a 2 to 2.5 percent increased risk for T2DM, particularly, in the presence of a family history of T2DM[15]. In the Nurses' Health Study, a cohort of over 116,000 women ages 25-42 years old were followed for eight years. A 2-2.5 fold increased incidence of T2DM was present in women with a history of oligomenorrhea, (some of whom had severe cystic acne and hirsutism), compared to the women with regular menses, although no physician based diagnosis of PCOS was made. Obesity increased the frequency of diabetes in this population. Since approximately 80 percent of women with irregular menses have PCOS, this data is highly suggestive that PCOS is a strong risk factor for T2DM, independent of, but exacerbated by the presence of obesity[11].

Since the presence of T2DM abolishes the "gender gap" in coronary artery disease[16] and since people with concurrent diabetes and the insulin resistance syndrome have the highest prevalence of coronary artery disease[17], women with PCOS, insulin resistance syndrome and diabetes are burdened with not only an extremely high risk of coronary disease but also the microvascular consequences of uncontrolled diabetes.

Prevention trials have shown that identification of impaired glucose tolerance is important because intensive lifestyle modification with or without pharmacologic intervention will prevent the progression to overt type 2 diabetes with its consequent risks[18,19]. It is for this reason that AACE has already included PCOS as an important risk factor for diabetes mandating screening by the age of 30[20].

Dyslipidemia

Women with PCOS are frequently found to have atherogenic lipid abnormalities which may reflect underlying insulin resistance, as well as the effects of genetics, ethnicity, obesity and lifestyle factors. Low HDL[21] and high triglyceride (TG) levels are found in both obese and non-obese hyperinsulinemic women with PCOS[22-23]. 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 seen in these individuals. A ratio of triglycerides to HDL of greater than 3.0 appears to effectively predict insulin resistance[24]. Obesity has a synergistic effect on the elevated TG levels in women with PCOS.

Atherogenic modifications of LDL cholesterol toward smaller more dense particles has been demonstrated[25] in 31 women with PCOS whose mean age was 26 years, compared to controls.

The combination of a low HDL and increased LDL cholesterol level in women with PCOS is often present. In a study of 153 obese or overweight (BMI > 27 kg/m2) and 42 non-obese non-Hispanic Caucasian women with PCOS having a mean age of 28 years, lipids were compared to BMI and waist-to-hip ratio (WHR) matched controls of the same ethnicity in central Pennsylvania[26]. The women with PCOS had higher LDL levels compared to controls, independent of obesity.

A large-scale epidemiological study of 244 women with PCOS[27] demonstrated elevated levels of LDL and reduced HDL cholesterol levels compared in PCOS women under the age of 45 years compared with matched controls. After the age of 45 years, there were no significant lipid differences between women with PCOS and controls. This early prolonged exposure to hyperlipidemia is a significant cardiovascular risk factor in women with PCOS compared to their normal menstruating peers.

Endothelial Dysfunction

Women with PCOS have impaired endothelial function due to altered insulin regulation of endothelial nitric oxide synthesis which leads to impaired NO-dependent vasodilatation. The arterial consequences of metabolic dysregulation leads to reduced large vessel vascular

compliance, as well as reduced vasodilatation. An abnormal vasodilatory response correlates with long-term risk for CVD[28].

Abnormal vascular compliance to insulin in brachial arteries suggesting impaired insulin action (i.e., IR) was demonstrated in studies of brachial arteries of young mean aged 26-year old women with PCOS when compared to controls. This links IR in vascular tissue with endothelial dysfunction, decreased arterial compliance and possible later development of CVD in PCOS[28,29]. Increased Endothelin-1 (ET-1) levels, a marker for vasculopathy in IR patients with IR[30], have been noted in PCOS patients. Plasma ET-1 levels were increased 5-fold in obese and non-obese subjects with PCOS over those of controls. This may be an early sign of abnormal vascular reactivity induced by the vasoconstrictor polypeptide. Administration of 1700 mg metformin a day for 6 months reduced ET-1 and T levels suggesting a link of IR and hyperandrogenemia with endothelial injury.

Hypertension

As patients with PCOS age they have a higher incidence of HBP than matched controls[31-33]. Increased systolic blood pressure has been noted in PCOS. There is increased daytime systolic BP in PCOS women determined by 24-hour blood pressure monitoring, albeit in the normal range persisting after adjustment for BMI, insulin sensitivity and body fat distribution when compared to matched controls[34]. The association with hyperinsulinemia in both the obese and non-obese subjects in that study was of interest.

Proinflammatory and Atherogenic Markers in PCOS compared to controls include decreased fibrinolytic activity, higher PAI-1 levels[12,35], and increased C-reactive protein (CRP) levels, all of which are markers for inflammation and correlate well in epidemiologic studies with an increased risk for CVD[36-38]. Elevated CRP levels are found in both obese and non-obese women with PCOS[37]. Treatment directed to reduce cardiovascular risk (smoking cessation, diet, aspirin, statins and possibly metformin and/or thiazolidenediones) should probably be more aggressive in those women with PCOS with an increased CRP[4,39].

Real Events Studies of CVD in PCOS

Suggestive Data Indicative of Subclinical CVD Risk in Women with PCOS

Two major surrogate markers for cardiovascular risk factors in PCOS are coronary calcifications identified by electron beam tomography (EBT) and carotid intima media thickness.

A Mayo Clinic study of coronary calcifications with EBT in 36 non-diabetic women with PCOS aged 30-45 years revealed a mean 3-fold higher level of coronary artery calcification (CAC) than population controls[40]. When compared to obese controls there was a 2-fold increase in CAC in PCOS subjects. A correlation was found between CAC score and BMI, visceral adiposity, and elevated levels of serum triglycerides in PCOS women. The EBT technique for coronary calcium scoring was also used to study 102 middle-aged women with PCOS (age 40-61, mean=46.9 years) compared to 118 controls (mean=48.5 years)[41]. The mean coronary calcium for PCOS

women and controls were 25.2 and 4.1, respectively. The authors found that the presence of PCOS, age, BMI, smoking status, increased fasting insulin and low HDL levels were associated with increased coronary artery calcification scores and consequent risk of coronary events.

Carotid intima media thickness (IMT) measured by carotid ultrasonography is a surrogate marker for coronary risk. One hundred twenty-five Caucasian women with PCOS and 142 age and BMI-matched controls[42] were studies with this technique. There was no difference from controls in the younger PCOS women under age 44, but, women over the age of 45 with PCOS had a mean IMT of 0.78mm as compared with 0.70mm in controls. The absence of a significant difference between younger PCOS women and controls suggests that metabolic alterations in younger PCOS women translate into measurable IMT by middle age. This occurs despite the well known narrowing differences in lipid levels compared to controls at the approach of menopause in women with PCOS.

Defined Real CVD Event Studies in Women with PCOS

A risk model analysis calculates that patients with PCOS have a 4 to 7-fold higher risk of myocardial infarction compared to age-matched controls[43]. This risk factor model analysis was based on 33 women with PCOS and 132 age-matched controls studied in a prospective population study of 1,462 women in Goteborg, 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. A cohort of 33 PCOS women with a mean age of 50 years and a history of a prior wedge resection were compared with 132 age-matched controls[32]. Postmenopausal women comprised 30 percent of women with PCOS and 56 percent of controls. Compared with controls, women with PCOS had:

1. 7-fold increased prevalence of T2DM (15 vs. 2.3 percent in controls)
2. 3-fold increased incidence of treated hypertension
3. significant higher waist-to-hip circumference
4. significant increase of plasma insulin, and decrease in SHBG

In a study from Czechoslovakia, 28 women with PCOS with ovarian wedge resection of the ovaries were compared with 752 control women aged 45 to 54 years[44]. The mean age of both groups was 51 years and they were matched for BMI, WHR, hypertension, lipid profiles and smoking. Their findings included:

1. 32 percent of PCOS women had T2DM, vs. 8 percent of controls.
2. 21 percent of PCOS women had coronary heart disease vs. 5 percent in controls.

PCOS was detected in 42 percent of women on pelvic ultrasonography[45] in 143 women under the age of 60 undergoing cardiac catheterization for chest pain or valvular disease, double that of the general population[46]. Patients with PCOS exhibited coronary artery segments with > 50 percent stenosis and significantly greater clinical heart disease than women with normal ultrasonographic

ovaries. Ultrasound evidence of PCOS was associated with clinical hirsutism, elevated testosterone levels and a higher incidence of dyslipidemia.

An increased prevalence of hypertension, diabetes mellitus and cardiac symptoms were found in 346 lean (BMI 24.4) PCOS women with a mean age of 38.7 years in Holland compared with a population data base[47]. The incidence of diabetes mellitus in this lean group of women with PCOS was 2.3 percent, while that of hypertension was 9 percent. Cardiac symptoms occurred in 3.1 percent of women in the 45-54 year old PCOS group compared to 0.9 percent in the control data.

A 10-year follow-up study of a cohort of 127 Caucasian women over 40 years of age with PCOS revealed that 5 women had 8 coronary events compared to none in a matched control population of 142 women[48]. The 5 cardiovascular events consisted of one myocardial infarction with bypass surgery, one angina pectoris with bypass surgery and three medically treated PCOS women with angina pectoris.

Cardiac function may be impaired even in young women under the age of 30 with PCOS, independent of weight as measured by echocardiographic indices[49].

Clinical androgen excess in women may signal a risk for coronary artery disease, since hirsutism and acne and an elevated WHR were associated with more severe coronary disease on angiography in 102 women over the age of 60[50].

Oligomenorrhea is a good surrogate marker for the potential development of cardiovascular disease (CVD), since it is estimated that over 80 percent of these women with oligomenorrhea have PCOS. The prospective Nurses' Health Study of over 101,000 women linked a history of menstrual irregularity, not only to an increased 2-2.5 fold risk of diabetes mellitus[15], but to an increased risk of mortality due to fatal coronary heart disease. In the prospective Nurses' Health Study of 82,439 nurses, with an average follow-up of 14 years,[51] a history of oligomenorrhea (at ages 20-35 years) was associated with a 100 percent increased incidence of fatal and 50 percent increase of nonfatal coronary heart disease after adjustment for age, cigarette smoking and BMI.

Two studies do not indicate an increase in cardiovascular risk or death rate in women with PCOS, but both of these are limited by methodologic considerations which limit their predictive power.

Seven hundred eighty-six women diagnosed with PCOS (mostly by having had a wedge resection of the ovaries) in the UK between 1930 and 1979 were traced from hospital records and followed for an average of 30 years[52]. There were 59 deaths prior to the age of 79 years: 15 deaths from circulatory disease, 13 of who were from ischemic heart disease, and 2 from other circulatory diseases. Diabetes mellitus was found to be more commonly mentioned in analysis of data and contributing to mortality in the PCOS group. The standardized mortality rate for women with PCOS was 0.83 compared to the national average of 0.90. They concluded 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, 319 PCOS women most of who had a tissue diagnosis by wedge resection (mean age 57 years, with a range of 38-98 years), there was no significantly higher incidence of coronary heart disease than women in the general population[31]. However, a 2.5-fold higher incidence of T2DM and non-fatal cerebrovascular events was noted than in their age and BMI-matched population-based controls. It should be noted that the UK study only had 26 percent of patients demonstrate obesity (mean BMI was 26 kg/m2), while the incidence in the USA is higher, and may range between 50-60 percent.

Summary and Synthesis of the 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. Prevalence of both type 2 diabetes mellitus, a myocardial infarction-equivalent state, and impaired glucose tolerance, a condition associated with increased cardiovascular risk, are substantially increased in PCOS. The American College of Endocrinology/American Association of Clinical Endocrinologists recommends screening patients with PCOS for diabetes at age 30.

2. Multiple recognized cardiovascular risk factors are present in excess in women with PCOS, often several simultaneously resulting in a higher prevalence of the ATP III and AACE-defined metabolic insulin resistance syndrome in PCOS.

3. Imaging studies in women with PCOS have uniformly identified a higher prevalence of anatomic and functional abnormalities indicative of extant underlying cardiovascular disease or dysfunction compared to age-matched controls.

These observations are remarkable for their abundance, uniformity and consistency, and predict an increased risk for adverse cardiovascular events in PCOS. However, to date, no prospective longitudinal study has assessed cardiovascular outcomes specifically in PCOS. Nonetheless, it is notable that a prospective large-scale study that followed women with oligomenorrhea for a decade and a half reported a 2-fold increased risk for fatal myocardial infarction in this population. It is likely that a large proportion of these women had PCOS, yielding indirect confirmation of increased adverse cardiovascular outcomes in PCOS.

In the absence of prospective longitudinal studies, retrospective epidemiologic studies have been performed to assess cardiovascular outcomes in PCOS. Unfortunately, the quality of these studies has been variable, 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, the majority of these studies, but not all, have confirmed an increased risk for adverse cardiovascular outcomes in PCOS.

Collectively, the above evidence substantively indicates that women with PCOS are at high risk for cardiovascular disease. Even in the absence of definitive outcome studies, the evidence

supports a strong recommendation that women with PCOS should be comprehensively evaluated for recognized cardiovascular risk factors and treated appropriately.

Treatment

There are well-defined data indicating a high risk for development of T2DM and cardiovascular disease in women with PCOS. In view of the lack of protective effect of female gender on CVD risk in diabetics[16,53], the associated risks of cardiovascular disease are magnified in diabetic women with PCOS. Clearly, this means that PCOS is a general health disorder of young women, with potential to reverse some of the risk with early diagnosis and treatment [39]. Lifestyle modification with weight loss and exercise, avoidance of tobacco, correction of lipid abnormalities, and use of metformin may be of value. The latter not only reduces hyperinsulinism, and improves steroidogenic dysfunction[54], but is helpful in achieving more regular menses and fertility potential[55]. Thaizolidenediones have also been shown to reduce androgens, improve ovulation and reduce progression to overt type 2 diabetes in patients with PCOS and impaired glucose tolerance[56-58].

In view of the potential and presence of a number of cardiovascular and metabolic risk factors present in the majority of women with PCOS, the role of the clinical endocrinologist is essential in:

1. Early recognition of the syndrome.

2. Lifestyle modification, emphasizing the need for controlled eating patterns and exercise, with encouragement 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, using appropriate medication such as statin, fibrate, niacin, and/or ezetimibe, as necessary.

5. Careful attention to and treatment of blood pressure abnormalities.

6. Measurement of atherogenic markers (CRP, fibrinogen and possibly homocysteine.

7. Metformin should be considered in most women with PCOS as initial therapy particularly when they are overweight or obese. Metformin improves many metabolic abnormalities in PCOS and may improve menstrual cyclicity and the potential for pregnancy. It should be noted that metformin is not FDA approved for use in PCOS, although abundant literature supports its efficacy.

8. The use of non-androgenic birth control pills (BCP) and an antiandrogen such as spironolactone for the skin manifestations of the disease. The presence of hair thinning requires the maximum dose of spironolactone with BCP. Ancillary use of electrolysis and laser therapy may also be required.

9. The use of thiazolidenediones in patients with impaired glucose tolerance or frank diabetes. The use of these agents to improve hyperandrogenism and ovulation is considered only investigational at this time. Thiazolidene drugs are Category C drugs and are contraindicated during pregnancy.

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