AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS, AMERICAN COLLEGE OF ENDOCRINOLOGY, AND ANDROGEN EXCESS AND PCOS SOCIETY DISEASE STATE CLINICAL REVIEW: GUIDE TO THE BEST PRACTICES IN THE EVALUATION AND TREATMENT OF POLYCYSTIC OVARY SYNDROME – *PART 2*

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EXECUTIVE SUMMARY

Polycystic ovary syndrome (PCOS) is recognized as the most common endocrine disorder of reproductive-aged women around the world. This document, produced by the collaboration of the American Association of Clinical Endocrinologists and the Androgen Excess Society aims to highlight the most important clinical issues confronting physicians and their patients with PCOS. It is a summary of current best practices in 2014.

Submitted for publication March 26, 2015
Accepted for publication August 6, 2015
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DOI: 10.4158/EP15748.DSCPT2
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The opinions represented in the AACE/ACE Disease State Clinical Review: Guide to the Best Practices in the Evaluation and Treatment of Polycystic Ovary Syndrome are the expressed opinions of the Reproductive Endocrinology Scientific Committee of the American Association of Clinical Endocrinologists and the Androgen Excess and PCOS Society. AACE/ACE Disease State Clinical Reviews are systematically developed documents written to assist health care professionals in medical decision making for specific clinical conditions, but are in no way a substitute for a medical professional's independent judgment and should not be considered medical advice. Most of the content herein is based on literature reviews. In areas of uncertainty, professional judgment of the authors was applied.

This review article is a working document that reflects the state of the field at the time of publication. Because rapid changes in this area are expected, periodic revisions are inevitable. We encourage medical professionals to use this information in conjunction with, and not a replacement for, their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision by practitioners to apply these guidelines must be made in light of local resources and individual patient circumstances.

- Insulin resistance is believed to play an intrinsic role in the pathogenesis of PCOS.
  The mechanism by which insulin resistance or insulin give rise to oligomenorrhea and hyperandrogenemia, however, is unclear.

  Hyperinsulinemic-euglycemic clamp studies have shown that both obese and lean women with PCOS have some degree of insulin resistance.
  Insulin resistance is implicated in the ovulatory dysfunction of PCOS by disrupting the hypothalamic-pituitary-ovarian axis.

- Given the association with insulin resistance, all women with PCOS require evaluation for the risk of metabolic syndrome (MetS) and its components, including type 2 diabetes, hypertension, hyperlipidemia, and the possible risk of clinical events, including acute myocardial infarction and stroke.

  Obese women with PCOS are at increased risk for MetS with impaired glucose tolerance (IGT; 31 to 35%) and type 2 diabetes mellitus (T2DM; 7.5 to 10%). Rates of progression from normal glucose tolerance to IGT, and in turn to T2DM, may be as high as 5 to 15% within 3 years.

  Data suggest the need for baseline oral glucose tolerance test every 1 to 2 years based on family history of T2DM as well as body mass index (BMI) and yearly in women with IGT.

  Compared with BMI- and age-matched controls, young, lean PCOS women have lower high-density lipoprotein (HDL) size, higher very-low-density lipoprotein particle number, higher low-density lipoprotein (LDL) particle number, and borderline lower LDL size.

  Statins have been shown to lower testosterone levels either alone or in combination with oral contraceptives (OCPs) but have not shown

improvement in menses, spontaneous ovulation, hirsutism, or acne. Statins reduce total and LDL cholesterol but have no effect on HDL, C-reactive protein, fasting insulin, or homeostasis model assessment of insulin resistance in PCOS women, in contrast to the general population.

There have been no long-term studies of statins on clinical cardiac outcomes in women with PCOS.

Coronary calcification is more prevalent and more severe in PCOS than in controls.

In women under 60 years of age undergoing coronary angiography, the presence of polycystic ovaries on sonography has been associated with more arterial segments with >50% stenosis, but the relationship between PCOS and actual cardiovascular events remains unclear.

- Therapies for PCOS are varied in their effects and targets and include both nonpharmacologic as well as pharmacologic approaches.

Weight loss is the primary therapy in PCOS—reduction in weight of as little as 5% can restore regular menses and improve response to ovulation-inducing and fertility medications.

Metformin in premenopausal PCOS women has been associated with a reduction in features of MetS.

Clamp studies using ethinyl estradiol/drosperinone combination failed to reveal evidence of an increase in either peripheral or hepatic insulin resistance.

Subjects with PCOS have a 1.5-times higher baseline risk of venous thromboembolic disease and a 3.7-fold greater effect with OCP use compared with non-PCOS subjects.

There is currently no genetic test to screen for or diagnose PCOS, and there is no test to assist in the choice of treatment strategies.

Persistent bleeding should always be investigated for pregnancy and/or uterine pathology—including transvaginal ultrasound exam and endometrial biopsy—in women with PCOS.

- PCOS women can have difficulty conceiving. Those who become pregnant are at risk for gestational diabetes (which should be evaluated and managed appropriately) and the microvascular complications of diabetes.

Assessment of a woman with PCOS for infertility involves evaluating for preconceptional issues that may affect response to therapy or lead to adverse pregnancy outcomes and evaluating the couple for other common infertility issues that may affect the choice of therapy, such as a semen analysis.

Women with PCOS have multiple factors that may lead to an elevated risk of pregnancy, including a high prevalence of IGT—a clear risk factor for gestational diabetes—and MetS with hypertension, which increases the risk for pre-eclampsia and placental abruption.

Women should be screened and treated for hypertension and diabetes prior to attempting conception.

Women should be counseled about weight loss prior to attempting conception, although there are limited clinical trial data demonstrating a benefit to this recommendation.

Treatment for women with PCOS and anovulatory infertility should begin with an oral agent such as clomiphene citrate or letrozole, an aromatase inhibitor. **(Endocr Pract. 2015;21:1415-1426)**

Abbreviations:
AMH = anti-Müllerian hormone; **BMI** = body mass index; **BP** = blood pressure; **CIMT** = carotid intima media thickness; **CV** = cardiovascular; **GnRH** = gonadotropin-releasing hormone; **GWAS** = genome-wide association study; **HDL** = high-density lipoprotein; **HOMA-IR** = homeostasis model assessment of insulin resistance; **IGT** = impaired glucose tolerance; **LDL** = low-density lipoprotein; **LH** = luteinizing hormone; **MetS** = metabolic syndrome; **MI** = myocardial infarction; **NIH** = National Institutes of Health; **OCP** = oral contraceptive; **OGTT** = oral glucose tolerance test; **PCOM** = polycystic ovary morphology; **PCOS** = polycystic ovary syndrome; **RR** = relative risk; **SSPG** = steady-state plasma glucose; **T** = testosterone; **T2DM** = type 2 diabetes mellitus; **TG** = triglyceride; **VTE** = venous thromboembolic; **WHR** = waist to hip ratio

INTRODUCTION

The past decade of research into polycystic ovary syndrome (PCOS) has produced important new insights into the evaluation and treatment of this disorder. This document is intended as a guide, highlighting the most current clinical information that a health care provider can use in managing patients with this disorder. It is not intended as a guideline but is written in a question and answer format by experts in clinical practice.

INSULIN RESISTANCE AND PCOS

1. What Is the Role and Mechanism of Insulin Resistance in the Pathogenesis of PCOS?

Insulin resistance is believed to play an intrinsic role in the pathogenesis of PCOS. In vitro studies showing that insulin stimulates ovarian steroidogenesis suggest that the compensatory hyperinsulinemia in PCOS would promote hyperandrogenism and ovulatory dysfunction. The mechanism by which insulin resistance or insulin give rise to oligomenorrhea and hyperandrogenemia, however, is unclear. Women with PCOS are at increased risk of developing glucose intolerance and type 2 diabetes mellitus (T2DM) as a result of decreased insulin sensitivity or insulin resistance, in a manner independent of their degree of adiposity, body fat topography, and androgen levels. The insulin resistance of PCOS is most likely caused by post–insulin receptor defects, which may differ among both clinical and metabolic PCOS phenotypes (e.g., obese versus lean).

The following is a summary of the possible mechanisms whereby insulin resistance gives rise to a PCOS phenotype:

- Direct stimulation of ovarian androgen secretion.
- Augmentation of luteinizing hormone (LH)-stimulated androgen secretion by induction of steroidogenic enzymes.
- Enhancement of the amplitude and frequency of gonadotropin-releasing hormone (GnRH)-stimulated LH pulses, leading to ovarian dysfunction.
- Decreased hepatic production of sex hormone–binding globulin.
- Decreased ovarian insulin-like growth factor–binding protein 1α gives rise to increased free insulin-like growth factor 1, which in turn stimulates androgen production.
- Hyperinsulinemia may contribute to midantral follicular arrest by enhancing anti-Müllerian hormone (AMH).

2. What Are the Methods Used to Measure Insulin Resistance, and What Is Their Clinical Importance?

It is not clear what the most accurate method or markers are for clinical assessment of insulin resistance. The gold standards for measuring insulin sensitivity are the hyperinsulinemic-euglycemic clamp and steady-state plasma glucose (SSPG) or insulin suppression test. Studies using the clamp method have reported that both obese and lean women with PCOS have some degree of insulin resistance (1,2).

There is no evidence that assessing insulin resistance determines the risk of diabetes or other aspects of metabolic syndrome (MetS) for an individual. Although surrogate markers of insulin resistance, such as the fasting glucose to insulin ratio (3) and homeostasis model assessment of insulin resistance (HOMA-IR), have shown high sensitivity and specificity in some studies, more extensive reports have demonstrated that these measurements lack accuracy for defining insulin resistance (4). HOMA-IR, the quantitative insulin sensitivity check index, and fasting insulin strongly correlate with one another but correlate more weakly with insulin sensitivity as measured directly by SSPG testing, and, as stated by Diamanti-Kandarakis et al (4), "none of the three surrogate markers can account for more than 40% of variability of difference in insulin mediated glucose disposal measured directly."

3. What Is the Association of Insulin Resistance with MetS?

Obese women with PCOS are at increased risk for MetS with impaired glucose tolerance (IGT; 31 to 35%) and T2DM (7.5 to 10%). A 2-hour oral glucose tolerance test (OGTT) (75-g glucose load) with baseline and 120-minute glucose and insulin levels determines the degree of glucose tolerance and hyperinsulinemia (5). Some studies report that rates of progression from normal glucose tolerance to IGT, and in turn to T2DM, may be as high as 5 to 15% within 3 years. These data further emphasize the need for baseline OGTT every 1 to 2 years based on family history of T2DM as well as body mass index (BMI), and yearly in women with IGT (6,7).

4. What Is the Role of Insulin Resistance in the Hyperandrogenemia of PCOS?

Insulin may act directly to stimulate ovarian androgen secretion and/or augment LH-stimulated androgen secretion or indirectly to enhance the amplitude of GnRH-stimulated LH pulses (8). Insulin resistance in PCOS is most likely caused by a post–insulin receptor defect, and the serine phosphorylation hypothesis suggests that a single kinase serine phosphorylates both insulin receptor β (causing insulin resistance) and P450c17 (causing hyperandrogenemia). An SSPG study of the effect of insulin sensitivity on androgen production in obese women with and without PCOS found that both PCOS and insulin resistance independently contribute to increased total testosterone (T) concentrations within each group (9). The ovaries of women with PCOS are hypersensitive to the ability of insulin to increase T production. With increasing insulin resistance, T concentrations increase, even in non-PCOS women with insulin resistance compared with insulin-sensitive individuals, and increased insulin acts through augmentation of LH-stimulated androgen secretion.

5. What Is the Role of Insulin Resistance in the Reproductive Disruption of PCOS?

Insulin resistance is also implicated in the ovulatory dysfunction of PCOS by disrupting the hypothalamic-pituitary-ovarian (HPO) axis (10). Hyperinsulinemia increases the amplitude and frequency of GnRH-stimulated LH

pulses, leading to increased production of LH and in turn to ovulatory dysfunction and amenorrhea. Moreover, hyperinsulinemia may contribute to midantral follicular arrest by enhancement of AMH production (11).

6. What Is the Role of Lifestyle Modification in the Treatment of PCOS?

As central obesity (increased waist to hip ratio [WHR]) is a surrogate marker of insulin resistance, MetS, and cardiovascular (CV) risk, weight loss is the primary therapy in PCOS. Moreover, weight loss can also improve ovarian function, supporting a role for insulin resistance in suppressing the HPO axis (12). Indeed, a reduction in weight of as little as 5% from initial body weight can restore regular menses and improve response to ovulation-inducing and fertility medications (13).

7. What Is the Role of Insulin-Sensitizing Drugs in the Treatment of PCOS?

The association of insulin resistance in the pathophysiology of PCOS has given rise to the use of insulin-sensitizing drugs in its treatment. Studies of metformin in both obese and lean PCOS women have documented a significant decrease in fasting insulin and androgen levels, as well as a restoration of menstrual cyclicity. Moreover, metformin may indirectly induce ovulation by reducing the concentration of circulating insulin, leading to normalization of the pulsatile production of GnRH and gonadotropins (14). Metformin has also been shown to improve hyperandrogenemia, even in nonobese women with PCOS who appear to have normal metabolic insulin sensitivity. Whether it is the correction of abnormal insulin action per se or the reduction of plasma insulin levels that is responsible for these beneficial effects of insulin sensitizers is currently unclear (15). In a small group of normal-weight PCOS women with normal insulin sensitivity established by OGTT and insulin area under the curve analysis, up to 75% of the metformin-treated PCOS women experienced a restoration of menstrual cyclicity in the absence of any significant modification in BMI, WHR, or glucoinsulinemic and lipid profiles (16).

Drugs in the insulin-sensitizing thiazolidinedione class have also been shown to be effective in the treatment of obese and lean PCOS (17). A systematic review of the pioglitazone literature in this area suggested that this drug is effective for treating hyperinsulinemia and insulin resistance in PCOS patients (18). This class of drugs is associated with potential serious side effects, however, and is not recommended for use in PCOS.

Although diet and lifestyle modification are the primary treatment modalities for overweight/obese PCOS women, weight reduction in these patients is difficult to both achieve and maintain. Accordingly, there is a place for insulin-sensitizing drugs, specifically metformin, which has no significant safety concerns and has demonstrated efficacy in improving weight loss. PCOS with MetS, specifically prediabetes and gestational diabetes, is a clear indication for metformin therapy because, as noted, metformin can prevent conversion of IGT to T2DM (19).

The use of metformin in reproductive dysfunction improves menstrual regulation and rates of ovulation and pregnancy. However, a recent randomized controlled trial (20) found no difference in live birth rates when clomiphene alone was compared to clomiphene plus metformin therapy. Another study found that the improved ovulation rate with metformin is correlated with weight loss independent of drug use (21). Although metformin has been shown to lower androgens in PCOS patients, there are no significant clinical studies that point to its efficacy in managing hyperandrogenism (i.e., hirsutism, acne, or alopecia).

The following is a summary of issues for consideration in the relationship between insulin resistance and PCOS:

- Using the gold-standard evaluation systems for insulin resistance/sensitivity, namely euglycemic clamp and SSPG, nearly all women with PCOS exhibit some degree of insulin resistance.
- There is evidence that insulin resistance directly affects androgen production and ovulatory function in PCOS through a variety of mechanisms, including direct effects of insulin on ovarian theca cells and adrenal tissue and disruption of GnRH signaling.
- Because surrogate markers do not accurately define insulin resistance, all PCOS women should be tested for components of MetS, including glucose intolerance, dyslipidemia, hypertension, BMI/waist circumference, and nonalcoholic fatty liver disease.
- The primary therapy of insulin resistance is lifestyle management, including weight reduction and exercise. The use of insulin-sensitizing drugs, which are limited to metformin due to potential risks from thiazolidinediones, has variable benefits in PCOS patients, including improved weight management and glucose tolerance, reduced androgen production, and improved menstrual cyclicity and fertility. The use of hormonal contraception can exacerbate insulin resistance and should be used with caution in PCOS women with MetS. Finally, menstrual regulation can be achieved with cyclic progestins.

CV AND METABOLIC RISK IN PCOS

1. What Is the Relationship Between PCOS and T2DM?

Abundant evidence, supported by multiple strong cross-sectional and longitudinal studies and powerful meta-analyses, indicates that diabetes is much more prevalent in PCOS women than in the general population. Early studies showed that even young women with PCOS are at

increased risk of diabetes. In adolescent obese PCOS girls, 50% reductions in peripheral insulin sensitivity and hepatic insulin resistance were demonstrated compared with obese age-matched controls (22). Even at a young age, these women also exhibit β-cell dysfunction (23), and IGT and T2DM have been observed in 30 to 40% of women with PCOS (24,25). Furthermore, a meta-analysis of multiple strong studies calculated an odds ratio for overt T2DM of 4.0 in PCOS women compared with age- and BMI-matched controls (26).

2. What Possible Mechanisms Link T2DM and PCOS?

It has been postulated that serine kinase phosphorylation of the insulin receptor plays an important—even primary—role in insulin resistance in PCOS. For example, an important study by Dunaif et al (27) found that 50% of PCOS subjects exhibit insulin-independent serine residue phosphate incorporation in the β subunit of insulin receptors in skin fibroblasts and skeletal muscle. In parallel, insulin-induced tyrosine phosphorylation is decreased, resulting in reduced tyrosine kinase activity. Moreover, no mutations were seen in the insulin receptor, and control insulin receptors mixed with lectin eluates from affected PCOS fibroblasts exhibited comparably increased rates of insulin receptor β subunit serine phosphorylation (27).

3. What Is the Relationship between MetS, Insulin Resistance, and PCOS?

Although it might be suggested that PCOS is the female phenotypic manifestation of insulin resistance and MetS, it is not clear that this is an obligate phenomenon. For example, when evaluated by SSPG, not all insulin-resistant women have elevated T levels. In fact, studies suggest that "insulin-sensitive" PCOS women have higher T levels than insulin-resistant non-PCOS women, implying that both the PCOS disease state, as well as insulin resistance, contribute to higher T levels. It has been postulated that the ovaries of women with PCOS are hypersensitive to insulin induction of T production (9). Women with MetS have been shown to have lower insulin sensitivity and a higher free androgen index (FAI), and in multiple regression analyses, FAI was shown to correlate with abdominal obesity and diastolic blood pressure (BP) (28). These data led the authors to conclude that a hyperandrogenic hormone profile is a typical feature of premenopausal female MetS, even without PCOS.

4. Is MetS Only a Consequence of Obesity, or Is There a Unique Predisposition in PCOS?

Evidence gathered at both the cellular and clinical levels indicates that PCOS women have a unique predisposition to insulin resistance and its consequences (including glucose intolerance and other components of the MetS) that is independent of obesity. It is also clear, however, that obesity may compound this risk. The form or definition of PCOS, as well as the level of androgen, also contribute to the statistical probability of MetS (vide infra). Because androgen levels, lipid levels, and MetS appear to correlate, the extent to which the CV disease risk of PCOS is a direct result of higher androgen levels versus other factors is unclear.

5. What Is the Relationship Between the Definition of PCOS and the Likelihood of MetS?

Women with PCOS as a group demonstrate greater insulin resistance than controls, in both lean and obese subjects. The prevalence of MetS (as defined by several criteria, including the Adult Treatment Panel III, the World Health Organization, and the American Association of Clinical Endocrinologists) is increased in PCOS women, with at least 33% of nondiabetic PCOS women having one or more MetS criteria in a multicenter study. As anticipated, obesity amplifies the effect of PCOS, with 1 study finding a 13.7-fold difference in the incidence of MetS between the highest and lowest BMI quartiles and an absence of MetS in women with a BMI <27 kg/m^2 (29). Moreover, the same study found a strong correlation between the level of T and the likelihood of MetS, a correlation that has been upheld in subsequent studies.

This fact is extremely important, given the various definitions of PCOS. The Rotterdam criteria include women who may only have menstrual irregularity and polycystic ovary morphology (PCOM) without having clinical and or chemical hyperandrogenism, as is required in the National Institutes of Health (NIH) and Androgen Excess Society (AES) criteria for PCOS. If, therefore, the prevalence of MetS or its components is sought in this subset of women, the likelihood of finding significant differences (and hence greater CV risk) may be less than in classic PCOS.

Even in very young (age 14 to 17 years) adolescent females, the definition of PCOS determines the risk for MetS, with a prevalence of 35% in those defined by NIH criteria and 26% in those defined by the Rotterdam criteria. In this group, menstrual irregularity and high free T predict PCOS, whereas menstrual irregularity and PCOM are not predictive alone (30). In a Brazilian study, MetS was 3-times more common in classic PCOS women than in those with nonclassical or Rotterdam-defined criteria, even when corrected for BMI, and even when only obese subjects were considered. Moreover, HOMA-IR has been shown to correlate with T levels (31). In a Turkish series, hypertension, high triglycerides (TGs), and abdominal obesity were more likely to be present in NIH-defined PCOS, compared with Rotterdam or AES-defined syndrome (32).

6. What Is the Importance of Lipid Abnormalities in MetS and Their Treatment in PCOS?

Compared with BMI- and age-matched controls, young lean PCOS women have been shown to have lower high-density lipoprotein (HDL) size, higher very-low-density

lipoprotein (VLDL) particle number, higher low-density lipoprotein (LDL) particle number, and borderline lower LDL size, even after adjusting for ethnicity, alcohol and tobacco use, and exercise. In stepwise regression models, bioavailable T was the only predictor of LDL, TG, VLDL and LDL particle number, while SSBG was the only predictor of LDL and HDL size (33), which confirms other studies linking MetS parameters and androgen levels. A systematic review and meta-analysis of multiple studies confirmed the association between lower HDL, higher TGs, and MetS but also demonstrated that LDL is 12 mg/dL higher in PCOS patients compared with controls, with a 9 mg/dL difference with BMI matching. The differences were greater in the NIH-defined versus Rotterdam-defined group of PCOS women (34).

As statin therapy is well recognized as improving CV risk in subjects with hypercholesterolemia, particularly those with diabetes, statin use may be appropriate in patients with PCOS. A review of randomized controlled clinical trials comparing a statin versus placebo or a statin in combination with another drug versus another drug alone encompassed a total of 244 women with PCOS in 4 trials of between 6 and 12 weeks in duration utilizing simvastatin or atorvastatin. Although statins lowered T levels either alone or in combination with oral contraceptives (OCPs), there was no evidence for improvement in menses, spontaneous ovulation, hirsutism, or acne. As anticipated, there was a reduction in total and LDL cholesterol in response to treatment with statins, but there was no effect on HDL, C-reactive protein, fasting insulin, or HOMA-IR. In contrast to the general population, there have been no long-term studies to assess the effect of statins on clinical cardiac outcomes in women with PCOS (35).

7. What Surrogate Markers for CV Disease Have Been Studied in PCOS?

Coronary Calcification

In young (mean age, 38 years) women with an average BMI of 31 kg/m^2, significant coronary calcification scores were present in nearly 40% of PCOS women, compared with 20% of matched controls (36). In middle-aged women followed in a 10-year prospective study, coronary calcification was more prevalent and more severe than in controls and was related to obesity but could not be completely explained by either age or BMI (37). In PCOS women in the same study, coronary calcification was related to insulin resistance and MetS markers.

Carotid Intima Media Thickness (CIMT)

In a group of very young (mean age, 24 years) women, CIMT was significantly greater in PCOS subjects compared with controls, in lean, overweight, and obese individuals (38). CIMT directly correlated with androgen levels and inversely correlated with insulin sensitivity but was not related directly to BMI. In multiple stepwise linear regression models, serum androgen level was found to be the only independent predictive variable (38). An intervention study in adolescent PCOS women showed that lifestyle modification with significant weight loss (BMI reduction from 32 to 28 kg/m^2) improved CIMT, without significant differences in BP, lipids, HOMA-IR, or blood sugar (39). Note that androgen levels were not reported in this study.

Aortic Calcification

In a 10-year prospective study, Talbot et al (37) found that the incidence of aortic calcification was higher in PCOS women compared with controls, with a strong association between aortic calcification and T level. In contrast, in the Dallas Heart Study, aortic plaque was not significantly higher in a group of PCOS women aged 35 to 49 years, compared with controls. Although PCOS was defined using the Rotterdam criteria, with over 49% having only oligomenorrhea and PCOM, there was also no difference from controls, even among the subset of women with oligomenorrhea and hyperandrogenism. It should be noted, however, that in this nested case-cohort study, there was a relatively low rate of dysglycemia, MetS, and hyperlipidemia in women of Hispanic ethnicity, compared with other studies (40).

Coronary Angiography

In women under the age of 60 years undergoing coronary angiography, the presence of polycystic ovaries on sonography has been associated with more arterial segments with greater than 50% stenosis, when controlled for other coronary risk factors (41).

8. What Is the Relationship Between PCOS and Actual CV Clinical Events?

There are conflicting data regarding the relationship between PCOS and actual CV events. Such discrepancies have been attributed to differences among study populations, the definition of PCOS used, study methodology, and ethnic and geographic differences. Although firm conclusions cannot be reached at this time, it is certainly safe to state that the presence of obesity, hyperandrogenism, lipid and glycemic abnormalities, MetS, and family history of CV disease in a young woman with PCOS should raise concern and lead to appropriate screening, counseling, and preventive care. It is also reasonable to assume that those women with PCOS defined by the more liberal Rotterdam criteria and who do not have any of the risk factors listed above should be carefully watched and at least counseled in maintaining a healthy lifestyle to minimize the risk of diabetes and CV complications. Pharmacologic intervention (see below) may be individualized in the absence of strong evidence that macrovascular complications will occur and can be prevented with medication in the lower-risk population.

Negative Clinical Studies

Negative studies include a report of no difference in all-cause mortality or CV mortality in PCOS women compared with controls, despite more CV disease risk factors, even after BMI adjustment (42). The same study calculated a hazard ratio of 2.8 for nonfatal cerebrovascular accident. Using the Rotterdam criteria to define PCOS, a Mayo Clinic group compared 309 PCOS women with 343 non-PCOS women between 1966 and 1988. The women had an average age of 25 years at first diagnosis and were followed for a mean period of 23.7 years. Other than a slightly higher BMI (29.4 kg/m^2 versus 28.3 kg/m^2; $P = .01$), there was no difference in the prevalence of T2DM, hypertension, total cholesterol, HDL cholesterol, LDL cholesterol, or TGs between the 2 groups, nor was there any increase in CV events, including myocardial infarction (MI) (43). In a 21-year prospective Swedish study of lean (Rotterdam-defined) PCOS women compared with controls, despite higher LDL, TGs, and fibrinogen levels in the PCOS population, the incidence of CV events was comparable between the 2 groups (44). Interestingly, in the same study, the difference in diabetes prevalence in younger PCOS women and their controls disappeared over time.

Positive Clinical Studies

A positive association of PCOS with clinical CV disease was found as early as 1992 in a prospective study controlling for age, BMI, WHR, TGs, BP, and T2DM, which reported relative risks (RRs) for myocardial infarction (MI) in PCOS of 4.2 in women aged 40 to 49 years and 11.0 in women aged 50 to 61 years, compared with controls (45). Furthermore, a comparison of 28 PCOS women aged 45 to 60 years with a population of 752 women matched for BMI, WHR, family history, and smoking found a 4-fold higher incidence of T2DM and MI in the PCOS group but no difference in the rate of hypertension (46). Moreover, in the large prospective cohort Nurses Health Study, the presence of very irregular menses, a surrogate marker for PCOS, was associated with RRs of 1.35 for nonfatal MI and 1.88 for fatal MI in multivariate analyses (47). In addition, the Rancho Bernardo study found a RR of 1.3 for CV disease and coronary artery disease in women with three or more components of the PCOS syndrome (48). A retrospective (1998-2009) chart review of 2,301 PCOS (defined as hyperandrogenism and oligomenorrhea with other causes excluded) subjects at an English endocrinology clinic, with a mean age of 29 years at outset, found highly significant hazard ratios for T2DM, angina, and MI (49).

In the prospective NIH-sponsored WISE trial of 390 postmenopausal women undergoing coronary angiography for stable angina, 104 subjects were identified as having PCOS based on a history of previous irregular menses and a top quartile current androgen level. PCOS was associated with more diseased coronary segments, hazard ratios of 2.0 for overt diabetes and 1.5 for CV-associated death, and a highly significant reduced cumulative 5-year CV event-free survival of 78.9% in PCOS, compared with 88.7% for non-PCOS subjects. PCOS remained a significant predictor ($P<.01$) in prognostic models, including diabetes, waist circumference, hypertension, and angiographic coronary artery disease as covariates (50).

9. What Is the Cardiometabolic Risk of Therapies Used to Treat PCOS in Pre- and Postmenopausal Women?

As the goals of treatment of PCOS women vary by age and individual, it is important to evaluate therapeutic options for the management of oligomenorrhea, hirsutism, alopecia, acne, and infertility and their possible impact, both positive and negative, on the CV and metabolic risks to the patient.

Metformin

Although it is beyond the scope of this document to review all critical data relating to the therapeutic risks of metformin for various aspects of PCOS, it seems clear that there is no increased CV or metabolic risk in its use. For example, in premenopausal PCOS women, there was a reduction in features of MetS, from 35 to 21% of subjects (51).

OCPs

It has been suggested that estrogen/progestin therapy in PCOS is associated with increased insulin resistance and IGT (52). Although the type and dose of each of these hormones is important in determining its risk to benefit ratio, recent studies may be reassuring (53). For example, clamp studies using an ethinyl estradiol/drosperinone combination failed to reveal evidence of an increase in either peripheral or hepatic insulin resistance (54).

Venous Thromboembolic (VTE) Disease

OCPs are known to increase the risk of VTE disease, an effect largely attributed to the dose of estrogen employed but also perhaps influenced by the specific progestagen involved. It should be noted that at least in one study, subjects with PCOS had a 1.5-times higher baseline risk of VTE and a 3.7-fold greater effect of OCP use, compared with non-PCOS subjects (55).

REPRODUCTIVE AND GENETIC ISSUES IN PCOS

1. What Is Known Regarding the Genetic Causes of PCOS?

PCOS is a heterogeneous disorder that clusters in families, and brothers and sisters of women with PCOS have been found to have an increased prevalence of reproductive (hyperandrogenism) and metabolic (insulin resistance and dyslipidemia) abnormalities associated with

PCOS (56-61). That said, PCOS does not appear to have a Mendelian pattern of inheritance (i.e., recessive or dominant) but rather resembles a complex genetic disorder, in which probably a large number of genes contribute small but significant input. Such disorders are best investigated using a genome-wide association study (GWAS), which compares the prevalence of genetic markers between controls and cases affected by a disorder. To date, there have been 2 major GWAS reports in PCOS published by the same Chinese group investigating a total of 8 loci (62,63). Candidate genes identified in these studies were related to insulin signaling, sexual hormone function (including the LH/human chorionic gonadotropin, and follicle-stimulating hormone receptors), T2DM, calcium signaling, and endocytosis. Some of these associated genes, including *THADA* (which has also been associated with T2DM) and *DENND1A* (which is involved in endocytotic trafficking), have also been identified in a Caucasian population of European origin (64,65). Although further GWASs are ongoing in Caucasian cohorts, there is currently no genetic test to screen for or diagnose PCOS, nor are any tests available to assist in the choice of treatment strategies.

2. How Should Oligomenorrhea Be Assessed, and What Are the Risks of This Symptom?

Oligomenorrhea, also described as oligo-ovulation, is a cornerstone symptom of PCOS that is included in all diagnostic schema, and it remains the only symptom that is primarily diagnosed by menstrual history. Because anovulation and oligo-ovulation can be associated with a variety of menstrual bleeding patterns, from complete amenorrhea to menometrorrhagia, a menstrual history can sometimes be confusing to interpret in women with PCOS. Whereas regular anovulatory bleeding is likely a rare phenomenon among women with PCOS, anovulation can be diagnosed with a timed midluteal progesterone level, which should be elevated (>3 ng/mL) if the patient has ovulated. Further persistent spotting or vaginal bleeding is also suggestive of a potential unknown pregnancy or uterine pathology, which may range from a polyp to endometrial hyperplasia or cancer. Persistent bleeding should therefore always be investigated further for pregnancy and/or uterine pathology—including transvaginal ultrasound exam and endometrial biopsy—in women with PCOS.

Treatment of oligomenorrhea or amenorrhea in women with PCOS is indicated due to the probable long-term increased risk for developing endometrial cancer and its endometrial precursors, such as hyperplasia (66). Many of the signs and symptoms of PCOS overlap with risk factors for endometrial cancer, including prolonged unopposed estrogen exposure, oligomenorrhea, nulliparity, and obesity (67). Accordingly, preventive treatment with hormonal contraceptives or periodic progestin therapy is recommended to achieve regular withdrawal bleeding. The primary evidence supporting a benefit of hormonal contraception are the epidemiologic data that demonstrate a prolonged, time-related decrease in the prevalence of endometrial cancer among women who have taken OCPs (68,69). Although periodic progestin challenge to induce a withdrawal bleed is recommended in women with oligomenorrhea and unopposed estrogen, the optimal progestin or the most favorable number of induced cycles per year remain unknown.

The clinical role of metformin therapy in correcting oligomenorrhea is currently limited. Metformin has been associated with increased menstrual frequency (70), and there is increasing interest in its potential benefits in preventing or treating a number of malignancies (71,72). That said, there are few data indicating the efficacy of metformin in the prevention or treatment of endometrial hyperplasia or cancer in women with PCOS and, accordingly, this is certainly an area ripe for further investigation (73).

3. How Should a Woman With PCOS Be Assessed and Treated for Infertility?

The assessment of a woman with PCOS for infertility involves, firstly, evaluating the patient for preconceptional issues that may affect response to therapy or lead to adverse pregnancy outcomes, and secondly, evaluating the couple for other common infertility therapies that may affect the choice of therapy. Infertility involves a couple both in terms of evaluation and treatment. Subfertile couples frequently have multiple correctable infertility therapies that may not be immediately evident from a history and physical, and there may often be a significant male factor. For instance, in a large multicenter trial treating anovulatory infertility, 10% of women with PCOS were with a male with unknown severe oligospermia or azoospermia, and fallopian tube patency testing identified bilateral tubal blockage in a further 5% (74). This would suggest that further evaluation of a couple is indicated, involving a semen analysis at a minimum, before treatment of the female with ovulation-inducing drugs is initiated. With regard to the first issue, women with PCOS have multiple factors that may lead to an elevated risk of pregnancy, including a high prevalence of IGT—a clear risk factor for gestational diabetes—and MetS with hypertension, which increases the risk for pre-eclampsia and placental abruption (75). Accordingly, women should be screened and treated for frank hypertension and diabetes prior to attempting conception. Furthermore, obesity is a risk factor both for a high-risk pregnancy (including an increased risk for gestational diabetes mellitus, gestational hypertension, and preterm labor and delivery) and a lack of response to ovulation-induction therapy. Women should therefore be fully counseled about the potential benefits of weight loss prior to attempting conception, although there is unfortunately a paucity of clinical trials that demonstrate a benefit to this recommendation (76).

First-line treatment for women with PCOS and anovulatory infertility (without a male factor or tubal occlusion) should begin with an oral agent such as clomiphene citrate (70), although a recent large multicenter trial has shown a greater benefit in terms of live birth rate with letrozole, an aromatase inhibitor (77). Oral drugs are typically given after inducing a withdrawal bleed with progestin, though recently this practice has come into question as potentially harmful in the context of infertility treatment (78). Given concerns about the teratogenicity of both clomiphene and letrozole (79), serum hormonal assays are recommended to rule out pregnancy or ovulation prior to giving the drugs. Although metformin is inferior to clomiphene in achieving a live birth in women with PCOS (70), it may be useful as an adjuvant therapy in certain subgroups of women with PCOS, such as obese women (20,80). Although clomiphene and letrozole have increased rates (in the range of 4 to 7%) of multiple pregnancy compared with metformin (<4%), the trade-off is the markedly decreased efficacy of metformin, which is approximately 30% of that of clomiphene. Whereas second-line therapy in women with PCOS and anovulatory infertility is the subject of debate, in the U.S., it is most commonly low-dose gonadotropin therapy (81,82).

4. Is There a Role for AMH in the Diagnosis or Treatment of Women With PCOS?

Although AMH is classically associated with involution of the Müllerian tract during embryogenesis in males, it is also produced by the granulosa cells of ovarian follicles and is highly correlated with excess pre-antral follicles in women with PCOS (83,84). Indeed, some investigators have suggested substituting an elevated (≥5 ng/mL) level of circulating AMH as a means of diagnosing PCOM in lieu of an ovarian ultrasound (85). Given the expense and inconvenience of an ultrasound (especially in adolescents), such avenues of investigation are very promising. The predictive value of a baseline AMH level in terms of achieving a live birth with women with PCOS is also a topic of current investigation. Interestingly, there are data to suggest that higher baseline AMH levels may identify women with PCOS who are less likely to ovulate and conceive on clomiphene therapy (86). Accordingly, although AMH appears promising as both a diagnostic and prognostic indicator for women with PCOS, it is too soon to recommend its routine use in clinical care.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

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