Polycystic ovarian syndrome, type 2 diabetes mellitus and cardiovascular disease relationship

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Insulin resistance and polycystic ovarian syndrome (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 GnRHstimulated 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 insulinsensitizing 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.

Cardiovascular and metabolic risk in POCS

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 BMImatched 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 insulinresistant 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

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 highdensity lipoprotein (HDL) size, higher very-low-densitylipoprotein (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/m2, 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 notrelated 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/m2) 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 lowerrisk 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 nonPCOS 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/m2 versus 28.3 kg/m2; 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 (Rotterdamdefined) 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 eventfree survival of 78.9% in PCOS, compared with 88.7% for non-PCOS subjects. PCOS remained a significant predictor (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).

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