Polycystic Ovary Syndrome and the Metabolic Syndrome

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Diabetologists have long recognized the comorbid diseases of obesity, hypertension, and hyperlipidemia in their type 2 diabetic patients, and the necessity of treating these conditions in order to improve outcomes. Cardiovascular disease (CVD) is the number-one cause of death among patients with diabetes, and its prevention is at the forefront of modern diabetes care. The clustering of insulin resistance, obesity, hypertension, and dyslipidemia has been termed "the metabolic syndrome."

As national attention is focused on the emerging epidemic of type 2 diabetes and obesity, more energy is being directed toward earlier detection, improved therapies, and potential prevention. One condition commonly detected in a younger age group and associated with a high risk of progression to diabetes is polycystic ovary syndrome (PCOS). Interestingly, many of the features of the metabolic syndrome, including insulin resistance, obesity, and dyslipidemias, are also present in PCOS. Is PCOS an early manifestation of the metabolic syndrome?

Recent Developments Regarding the Metabolic Syndrome

The metabolic syndrome is composed of abnormalities that increase cardiovascular risk. Although each constituent condition is associated with heart disease in its own right, the combination of these conditions far more powerfully augments cardiovascular risk.

The metabolic syndrome was recently codified in the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III) guidelines, but has long been the subject of extensive research and debate. The NCEP definition includes fasting glucose, waist circumference, blood pressure, and lipid criteria pertaining to triglycerides and HDL cholesterol.[1] An earlier definition by the World Health Organization (WHO) relied more heavily on insulin resistance as a necessary component of the metablic syndrome[2] and was thus closer to the original description of the "insulin resistance syndrome" or "syndrome X" within the diabetic population.[3] Definitions of the metabolic syndrome are summarized in Table 1.

A major advantage of the NCEP definition is its ease of application. For instance, while neither sensitive nor specific as an indicator of insulin resistance, fasting glucose testing identifies further developed abnormalities of glucose regulation and can readily be performed in clinical practice and large clinical trials. For the WHO definition, measurement of insulin resistance requires a cumbersome clamp study, which has confounded its use. Thus, major epidemiological studies such as the European Group for the Study of Insulin Resistance and the Botnia study in Finland and Sweden used widely applicable surrogate markers of insulin resistance, such as fasting glucose and insulin levels,[4] or glucose tolerance tests.[5] Additionally, newer data have allowed subtle refinements in cutoff criteria based on outcomes research. Just as the blood glucose level used to define diabetes was lowered in 1997 based on outcomes,[6] definitions of hypertension in the metabolic syndrome have recently been lowered.[7] Finally, waist circumference has replaced BMI as a marker of obesity because of its better correlation with intra-abdominal visceral adipose tissue and worsened cardiovascular outcomes.[8]

Using data from the Kuopio Finnish cohort, the NCEP ATP-III and the WHO modified definitions of the metabolic syndrome were both validated in a large epidemiological study that found up to fours times higher coronary heart disease (CHD) mortality in patients with the metabolic syndrome.[9]

The stated purposes of the NCEP ATP-III guidelines were to maintain the original ATP-I and -II goal of primary prevention of CHD in people with high LDL cholesterol with the new focus on people with multiple risk factors, such as those with the metabolic syndrome.[1] Women with PCOS are such a group.

IN BRIEF

Many patients with polycystic ovary syndrome (PCOS) also have features of the metabolic syndrome, including insulin resistance, obesity, and dyslipidemia, suggesting an increased risk for cardiovascular disease. Increased awareness of this overlap advocates therapies that improve insulin resistance and often ameliorate PCOS symptoms.

What is PCOS?

PCOS is familiar to internists and diabetologists because of its frequent occurrence as a precursor to diabetes. PCOS is clinically defined as oligomenorrhea associated with hyperandro-

Table 1. Definitions of the Metabolic Syndrome

NCEP	WHO	WHO modified*
Any three of the following criteria:		
Fasting plasma glucose ≥110 mg/dl	Insulin resistance (under hyperinsulinemic, euglycemic conditions)	Hyperinsulinemia: upper quartile of population **or** fasting plasma glucose ≥ 110 mg/dl
	Plus any two of the following criteria:	**Plus any two of the following criteria:**
Hypertension ≥ 130 mmHg systolic or ≥ 85 mmHg diastolic blood pressure	Hypertension > 160/90 mmHg or controlled with drug treatment	Hypertension ≥ 140/90 mmHg or controlled with drug treatment
Obesity Waist circumference > 40 inches for males, > 35 inches for females	Obesity BMI > 30 kg/m^2 **or** waist-to-hip ratio > 0.9 for males, > 0.85 for females	Obesity BMI ≥ 30 kg/m^2 **or** waist-to-hip ratio > 0.9 for males, > 0.85 for females
Elevated triglycerides ≥ 150 mg/dl	Elevated triglycerides ≥ 150 mg/dl	Dislipidemia with either or both: Elevated triglycerides ≥ 150 mg/dl
Low HDL cholesterol < 40 mg/dl for males, < 50 mg/dl for females	Low HDL cholesterol < 35 mg/dl for males, < 40 mg/dl for females	Low HDL cholesterol < 35 mg/dl for males, < 40 mg/dl for females
	Microalbuminuria > 20 µg/min or albumin-to-creatinine ratio ≥ 20 mg/g	

*Modified as described in the Kuopio study.[9]

genism. It has been described poetically as "the thief of womanhood"[10] because women with PCOS seek medical attention for infertility and hirsutism. Characteristics of PCOS are summarized in Table 2.

That PCOS also conveys significant risks for diabetes and endometrial cancer is a fact that has been clinically underrecognized. PCOS may also be associated with an increased risk for CVD; several studies have shown increased markers of CVD, usually in relation to features of the metabolic syndrome. Many women with PCOS have additional features of the metabolic syndrome, especially insulin resistance and obesity.

Women with PCOS have a higher prevalence and a greater degree of hyperinsulinemia[11,12] and insulin resistance[13–15] than weight-matched control subjects. Of women who have PCOS, as many as 30% have impaired glucose tolerance (IGT) and an additional 7.5% have diabetes.[16] Even among nonobese women with PCOS, 10.3% have IGT, and 1.5% have diabetes.[16] In long-term follow-up, 16% of women who had been treated for PCOS 20–30 years earlier had developed diabetes by the age of menopause.[17] The etiology of the insulin resistance is unclear, but suppression of the excess androgens does not alter the insulin resistance.[18,19]

Insulin resistance is worsened by the coexistence of obesity, which is also increased in the PCOS population.[20] More than 40% of PCOS patients are obese.[21,22] The insulin resistance is disproportionate to the obesity, however. Obese women with PCOS have greater insulin resistance than weight-matched control subjects or lean PCOS subjects.[13,14] This is associated with differences in fat distribution. Even in individuals with a nonobese BMI, a higher waist-to-hip ratio is seen in those with PCOS compared to those without PCOS.[23] This is supported by the higher proportion of visceral adiposity measured by ultrasound in lean PCOS patients compared to weight-matched control subjects.[24]

Obesity also exacerbates several other metabolic abnormalities in PCOS. In comparison to lean women with PCOS, obese women with PCOS have higher levels of testosterone and lower levels of luteinizing hormone.[25–27]

Obese women with PCOS also have a dyslipidemia. At least one abnormal lipid level is seen in 70% of women with PCOS.[28] The pattern of dyslipidemia found in the metablic syndrome, which features elevated triglycerides and low HDL cholesterol, has been reported in association with obesity in PCOS, but this has not been found to differ from weight-matched control subjects.[29] Studies controlling for insulin resistance have found that the low HDL cholesterol and high triglycerides are associated with

Table 2. Features of Polycystic Ovary Syndrome

By definition:
- Oligomenorrhea
- Hyperandrogenism: acne or hirsutism, or
- Hyperandrogenemia: elevated total or free testosterone or DHEA-S

Also frequently seen:
- Insulin resistance
- Hyperinsulinemia
- Elevated LH:FSH ratio
- Abdominal obesity
- Polycystic ovaries by ultrasound*
- Infertility

DHEA-S, dihydroepiandrosterone-sulfate; LH, luteinizing hormone; FSH, follicle-stimulating hormone.
*Polycystic ovaries are not part of the definition of PCOS because they are also found in 24% of normal cycling, nonhyperandrogenic women.[84]

insulin resistance rather than with the presence of PCOS.[30] Abnormalities of LDL cholesterol have not been found consistently in PCOS.[31] However, even in those with a normal LDL level, Pirwany et al.[32] have shown increased VLDL and small, dense LDL cholesterol in PCOS relative to control subjects, as is seen in the metabolic syndrome.[33]

The final facet of the metabolic syndrome, hypertension, is uncommon in PCOS.[31,34] However, this may be a matter of exposure. In a retrospective study, women treated 20–30 years for PCOS were found to have an increased prevalence of both hypertension and diabetes compared to weight-matched control subjects.[17,35] In addition, some studies of 24-hour ambulatory systolic blood pressure recordings in young women with PCOS show increases that are predictive of the development of hypertension later in life.[36] Thus, several features of the metabolic syndrome overlap with features of PCOS.

In women with obesity, there may be an adverse clinical synergy between features of both PCOS and the metabolic syndrome. Both of these conditions could predispose to CVD through common pathways.

The risk for CVD in the metabolic syndrome is well supported by large epidemiological studies. In PCOS, retrospective studies based on menstrual abnormalities (which would mostly, but not exclusively, be caused by PCOS) show increased cardiovascular and diabetes-related deaths.[37,38] One challenge of these studies is the time lag between reproductive symptoms heralding PCOS and much later development of CVD.

An assessment of women undergoing coronary angiography for chest pain found an excess of women with polycystic ovaries seen on ultrasound.[39] While neither endpoint—the need for angiography or the presence of polycystic-appearing ovaries—is specific, this has encouraged others to look more closely. Coronary artery calcification was increased when examined in small studies of women with PCOS.[40,41]

In classically defined PCOS, many risk factors, such as dyslipidemia and hypertension, and markers of CVD have been found. Models based on the combined risk factors of the metabolic syndrome in PCOS, such as obesity, diabetes, dyslipidemia, and hypertension, predict a sevenfold increased risk of myocardial infarction in women with PCOS compared to age-matched control subjects.[42] However, as carefully reviewed by Legro,[43] not all women with PCOS have the metabolic syndrome, and prospective data do not yet support an increased occurrence of CVD in all women with PCOS. These issues may be increasingly difficult to resolve because current therapies for PCOS also affect known metabolic risk factors.

Therapeutic Overlap

Is it important to identify women with PCOS and the metabolic syndrome in order to target early intervention? This question can best be addressed by considering separately two subsets of PCOS: those with diabetes and those with other metabolic features including standard symptoms of PCOS, such as infertility, oligomenorrhea, and hirsutism. In the former set, therapies for diabetes with dual effects in PCOS and the metabolic syndrome should be the first approach. In the latter patients, the chief complaint can be targeted using a broader range of therapeutics.

Women with PCOS features who already have diabetes

Up to 27% of premenopausal women with type 2 diabetes also have PCOS.[44] This is interesting for two reasons: first, it emphasizes the potential severity of the insulin resistance in PCOS, and second, it shows that insulin resistance itself does not lead to PCOS in the majority of women with type 2 diabetes.

For those women with both PCOS and diabetes, specific therapies can address features of both diseases, especially those exacerbated by insulin resistance. Reducing hyperinsulinemia and insulin resistance has been shown to improve the defining features of PCOS—increasing menstrual cyclicity and decreasing hyperandrogenism.

It is essential to identify those patients with both PCOS and diabetes not only to tailor their therapies, but also to introduce the appropriate preventive screening and treatment for known cancer risks. The risk of endometrial cancer is increased in type 2 diabetes and in PCOS.[35] In diabetes, epidemiological studies link this risk closely with obesity.[45–47] In PCOS, obesity, hyperinsulinemia, and anovulation have been associated with the increased risk.[48] In

addition to regular Pap smears, PCOS therapies have focused on increasing menstrual regularity to decrease this risk. Many mechanisms that decrease insulin resistance also improve menstrual function. This raises an important and as yet unanswered question: are any diabetes therapies better for women with PCOS?

Weight loss. The safest and cheapest therapy that has shown benefit both in diabetes and PCOS is weight loss by lifestyle modification. The observation that weight gain often preceded the development of hyperandrogenism and oligomenorrhea led to early approaches to treat PCOS by weight reduction. Many small studies have shown that even modest weight loss (10–20%) improves all symptoms of PCOS in obese patients: acne, hirsutism, and menstrual irregularities.[49–54] The improvements are likely a result of the reductions in insulin levels and insulin resistance also measured in these studies. Weight loss was accomplished by using hypocaloric diets, usually 1,000–1,200 kcal/day for as little as 8 weeks.

In diabetes and the metabolic syndrome, weight loss is also associated with improvements in other features of the metabolic syndrome, including dyslipidemia and hypertension.[55] Although dietary restriction-induced weight loss offers significant advantages as a treatment for both diabetes and PCOS, it is notoriously difficult to achieve.

Altered dietary composition is also useful. Fiber slows nutrient absorption after meals and reduces insulin secretion. Increased dietary fiber intake has been shown to improve insulin resistance in healthy adults[56] and in diabetes[57] but has not yet been separately assessed in PCOS. Reduction in digestible dietary carbohydrate, as in the popular Atkins diet, has been shown to be safe and effective in obese patients, with improvement in insulin response to glucose load, diastolic blood pressure, and dyslipidemia, increasing HDL cholesterol and decreasing triglycerides.[58,59] In PCOS, when low- and high-protein isocaloric diets were compared, both resulted in equal weight loss and improvement in insulin levels, insulin response to a meal, total cholesterol, triglycerides, and LDL, although HDL was slightly decreased on the low-protein diet.[60] Thus, the benefits derive from weight loss more than from the specific mechanism by which that loss is achieved.

Eating dynamics, such as binge eating, can increase insulin secretion and insulin resistance.[61] This is problematic because of the increased incidence of eating disorders in both diabetes and PCOS.[62–65] Eating disorders may contribute to difficulties with sustaining weight loss.

Given the significant effects of modest weight loss on features of both PCOS and the metabolic syndrome, it is tempting to consider more interventional approaches to weight loss when caloric restriction fails. In the subset of patients with diabetes and obesity, several other options have been proven effective.

Weight loss medications, including phenteramine (for short-term use) and sibutramine and orlistat (for long-term use), are recommended for individuals with a BMI > 30 kg/m^2 or lower if comorbidities such as diabetes are present. (Sibutramine must be used very carefully if hypertension is present.) In separate trials in diabetes or dyslipidemia, both sibutramine and orlistat caused weight loss with improvements in hyperinsulinemia and dyslipidemia, although sibutramine was associated with an increase in blood pressure.[66–68] Just as lifestyle modifications must be maintained to prevent weight regain, sibutramine and orlistat usually need to be continued. Neither drug has been studied yet in PCOS without these other comorbidities, though the improvement in insulin resistance suggests that they would be useful for obese women with PCOS.

For patients with diabetes and a BMI > 35 kg/m^2, bariatric surgery may also be an appropriate intervention. Weight loss after bariatric surgery also leads to improvements in insulin resistance, hypertension, and dyslipidemia. Again, while important for the management of diabetes and obesity, the effects on features of PCOS have not been examined.

Exercise. As a lifestyle modification, physical exercise helps sustain weight loss, but it also has benefits independent of weight loss. Exercise can increase glucose disposal and muscle sensitivity to insulin. In PCOS, women who self-reported 8 hours of sports activities per week had improvement in acne and menstrual irregularities.[69] Exercise as the primary intervention without attendant weight loss (< 5% weight loss) improved insulin sensitivity and free testosterone index and induced ovulation in 9 of 18 obese PCOS patients.[70] Clearly, a reasonable regimen of exercise (see the Diabetes Prevention Program [DPP] regimen below), in addition to modifications of diet, is a prudent recommendation for patients with PCOS.

Medical therapies for insulin resistance. Two major pharmacological approaches to the treatment of diabetes have also revolutionized the therapy of PCOS. These are the insulin sensitizers: the biguanide metformin and the thiazolidinediones troglitazone (no longer available), pioglitazone, and rosiglitazone. These agents improve not only glucose control, but also the reproductive abnormalities associated with PCOS.

Metformin increases peripheral glucose uptake and decreases hepatic glucose production. The major advantage in patients with diabetes and PCOS is that metformin is one of only two diabetes medications that do not cause weight gain.

Harborne et al.[71] have recently reviewed the seven randomized placebo-controlled trials (six of which were double-blinded) of metformin in PCOS. This analysis showed improvements in metabolic syndrome features that included weight loss (4%) and decreased insulin levels (27%). Several of these studies also noted improvements in dyslipidemia, with an increased HDL and a decreased LDL cholesterol. In terms of PCOS features, androgens decreased (21%), menstrual cyclicity improved

(50%), and acne decreased (in one study).[71] Notably, hirsutism improved significantly in only three of six trials that evaluated hirsutism, although most were too short to determine changes in hair growth. Major side effects were nausea and diarrhea, which are also seen with metformin therapy in diabetes.

The thiazolidinedione class works at the level of the peroxisome proliferators–activated receptor gamma to directly improve insulin action. These drugs decrease insulin resistance and hyperinsulinemia and improve dyslipidemia and blood pressure in patients with diabetes or IGT.[72] Troglitazone, which has now been withdrawn from the market because of reports of hepatotoxicity, was studied extensively in nondiabetic PCOS patients.[73] It improved ovulation, hirsutism, hyperandrogenemia, and insulin resistance despite an average 1-kg weight gain. The newer congeners pioglitazone and rosiglitazone are effective for the metabolic syndrome and diabetes and in small studies have worked well for PCOS symptoms of menstrual irregularity and hyperandrogenism.[74–76]

Antiabsorptive therapy such as acarbose should be considered second-line because, although it reduces insulin requirements by decreasing absorption of ingested carbohydrate, it does not decrease insulin resistance. It also does not affect obesity. Acarbose has been tested in one small study of hyperinsulinemic women with PCOS and has demonstrated effectiveness in reducing hirsutism and acne scores as well as postprandial glucose and insulin responses.[77]

Insulin does not improve chronic insulin resistance. Therefore, there is no apparent benefit to this therapy for women with PCOS who do not have diabetes, although the use of insulin specifically in PCOS has not been studied. Its use should be limited to women with diabetes and PCOS whose diabetes does not respond to the above oral agents (or who cannot tolerate them). As in any diabetic patient with extremely high blood glucose levels, in women with PCOS and diabetes, the short-term use of insulin may be necessary for immediate safety concerns to avoid dehydration and related complications. Insulin use also causes weight gain and therefore is not the best therapy for such women with early diabetes who are still producing excess insulin.

As with insulin, sulfonylureas act by augmenting insulin secretion rather than treating the primary pathology of insulin resistance. Therefore, they are not an appropriate therapy for women with both diabetes and PCOS.

Pregnancy concerns. The risks of these therapies in relation to their benefits for PCOS must be considered, especially in pregnancy. Because PCOS patients are by definition premenopausal, pregnancy is a significant issue, and in many cases, infertility is the chief complaint. Metformin increases ovulation rapidly (as early as 3 months), modestly (increasing from one to two ovulations per 5 months), and without weight loss.[71] It has also improved spontaneous pregnancy rates, and contraception is recommended for women who do not wish to become pregnant.

Women must be informed about this increased probability of conception and the risk of continuing metformin during pregnancy. Data about the safety of metformin in early pregnancy are conflicting regarding possible protection from early pregnancy loss. There is no evidence of animal or human teratogenicity (pregnancy category B). In mothers with diabetes, metformin has been used in the second and third trimesters without conclusive evidence of increased perinatal morbidity, although Coetzee et al.[78] reported an increase in neonatal jaundice. Another study comparing metformin to sulfonylurea treatment in pregnancy did show a modest increase in perinatal mortality and pre-eclampsia, but these results were confounded by a higher BMI and age in the metformin group. Thus, further studies of metformin in pregnancy are needed, and current recommendations are to discontinue use as soon as pregnancy is established.

Thiazolidinediones, on the other hand, are known teratogens that exhibit profound effects on cellular differentiation with documented teratogenicity and lethality in animal studies (pregnancy category C). They have the additional disadvantage of a slow metabolic clearance and may take months to be eliminated from the body. Despite the controlled setting of a major study of troglitazone, 5.9% of subjects had unexpected pregnancies in the treatment arms, highlighting the need for counseling and contraception.[73] Therefore, the thiazolidinediones must be stringently avoided in women who might become pregnant. Most insulins are safe for use and are the preferred therapy for diabetes in pregnancy.

An important but overlooked consideration is the medical risk of facilitating pregnancy in women with severe diabetes or obesity. The intending mother must be made aware of the increased risk of pregnancy to her health and that of her baby based on the severity of her diabetes, obesity, or hypertension. Having said this, most women with PCOS can have successful pregnancies without a dramatic increase in health risk, and the risks of pregnancy from diabetes and obesity can be minimized with good prepregnancy counseling and care.

Women with PCOS but without diabetes

The metabolic syndrome by definition is associated with an increased risk of CVD. Treatment of the individual components of the syndrome, including dyslipidemia, obesity, and hypertension, clearly decrease CVD. Data from the DPP have demonstrated the powerful effects of treating insulin resistance in patients at high risk of developing diabetes.[79] Should women with PCOS be treated for insulin resistance alone (when infertility, oligomenorrhea, and hirsutism do not require treatment)? In this situation, the risks must be balanced with potential side effects and the need for monitoring in this young population. PCOS patients have distinct worsening

with obesity and should be especially counseled not to gain excess weight. Lifestyle alterations and weight loss when indicated reduce insulin resistance and offer multiple benefits. Medical therapies are not only less effective, but also carry risks.

As the DPP has recently shown, the most effective method to prevent progression from IGT to overt diabetes is lifestyle modification through exercise and diet.[79] The lifestyle arm of the DPP included dietary education, weight loss counseling, and 150 minutes of exercise per week, resulting in a net loss of 7% body weight and a 58% reduction in the progression to diabetes.[79] The metformin arm, while effective, only reduced the progression to diabetes by 21%.[79]

Metformin has also been used to treat the metabolic syndrome in the absence of diabetes. Landin et al.[80] used metformin in patients with insulin resistance and hypertension and found improvements in both as well as in dyslipidemia. Metformin is also effective in the treatment of some PCOS features. It modestly increases menstrual regularity and ovulation and decreases weight without clearly improving hirsutism.[71] Lean women with PCOS also improve insulin resistance and hyperandrogenism without changing BMI on metformin.[81] Because of these benefits and its relative safety before pregnancy, metformin is a useful adjunct to lifestyle changes for women with complaints of menstrual irregularity or infertility, but not for those complaining of hirsutism.

Except in women who are sterile, the thiazolidinediones must be used cautiously. As noted above, these medications are very effective for PCOS symptoms and insulin resistance, and improvement in these parameters may lead to increased ovulation. In the Azziz study of 305 women with PCOS, there were 16 unexpected pregnancies despite counseling to avoid pregnancy and the requirement for contraception.[73] No excess of elevated liver function test results were seen among these women.

The newer thiazolidinediones have not been studied as extensively in PCOS without diabetes. Pioglitazone reduced hyperandrogenism but was more effective at increasing ovulation in women with PCOS who were obese and insulin resistant than in those with obesity and normal insulin sensitivity.[75] Rosiglitazone has also been shown to increase ovulation and decrease hyperandrogenism.[74,76]

For women at risk for unplanned pregnancy who complain of irregular periods or hirsutism, combination estrogen/progestin contraceptives are the safest treatment and will also ameliorate hyperandrogenism without affecting insulin resistance. Anti-androgen therapy, such as spironolactone, can be added for further treatment of hirsutism.

New agents under investigation for use in PCOS include pramlintide and D-*chiro*-inositol. Pramlintide is an analog of amylin, a β-cell hormone that is normally cosecreted with insulin; it complements the effects of insulin in postprandial glucose control, in part by suppressing glucagon secretion. In type 1 and late type 2 diabetes, pramlintide improves postprandial glucose excursions, but its use so far has been in insulin- and amylin-deficient settings.[82] D-*chiro*-inositol is an insulin sensitizer that has preliminarily been shown to increase ovulation in PCOS.[83] Ovulation induction is the major area of PCOS treatment for which more effective therapies are needed.

Summary

Unlike the metabolic syndrome with its largely asymptomatic risk factors, PCOS presents with overt symptoms of infertility, hirsutism, and acne. Although these are the problems that bring women to health care providers' attention, their presence affords providers the opportunity to intervene early with counseling and, if needed, medications to alter the risk profile for later development of the metabolic syndrome or CVD.

However, there is also a deficit of long-term outcome information, and certainly risk factors do not always progress to disease. Therefore, the prudent approach requires emphasis on the modification of lifestyle factors such as diet and exercise to modify risk factors not yet reaching clinical disease.

In the subset of patients with PCOS and diabetes, tailored therapies that target the multiple abnormalities, particularly insulin resistance, are indicated. The role of medical therapy for insulin resistance or the metabolic syndrome in nondiabetic patients with PCOS is presently unclear.

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