



What to do about insulin resistance in **PCOS**

By R. Hugh Gorwill, MD, FRCSC

In this article:

1. What are treatment options for polycystic ovary syndrome (PCOS)?
2. How prevalent is PCOS?
2. How is metformin used in PCOS?
3. What are the secondary risks of PCOS?

A clearer understanding of polycystic ovary syndrome (PCOS) began in 1935, with a study of seven patients, aged 20 to 33, with “a distinct tendency to masculinizing changes”.¹

Treatment with wedge resection produced good results in menstrual function and fertility. It was noted that the disorder was “likely the result of hormonal influences.”¹

Another study in 1980 showed that those with PCOS—based on the presence of oligomenorrhea/amenorrhea, obesity, hirsutism, hyperandrogenism, elevated luteinizing hormone to follicle-stimulating hormone ratios, and in some patients, ovarian biopsy—had elevated androgens, insulin, and glucose as compared to obese controls.² The study concluded that hyperandrogenism correlates with hyperinsulinism.²

These studies raised the issue of insulin insensitivity, also known as insulin resistance. These terms had first been used in describing poor glucose response to exogenous insulin in obese patients with diabetes. Currently, insulin resistance is defined as a state in which a given concentration of insulin produces a subnormal response in respect to blood sugar.

In 1981, Swanson et al. described, on ultrasound, the characteristic cysts in polycystic ovaries as 2 mm to 6 mm in diameter, and arranged in the periphery of an ovary or throughout the parenchyma.³ These cysts were not only seen in those with the syndrome, but also in those with no disorder.

Table 1

Some treatment options for PCOS

- Diet modifications
- Exercise
- Weight loss (which is linked to two options above)
- Use of antiandrogens
- Use of oral contraceptives
- Ovulation induction
- Surgical intervention

What is PCOS?

In his recent review, Stephen Franks defines PCOS as “the association of hyperandrogenism with chronic anovulation in women without specific underlying diseases of the adrenal or pituitary glands.”⁴ The latter exclusions include androgen secreting tumours, Cushing’s syndrome, hypothyroidism, hyperprolactinemia, and non-classical 21 hydroxylase deficiency.⁵ Franks notes that in PCOS, obesity is common but not

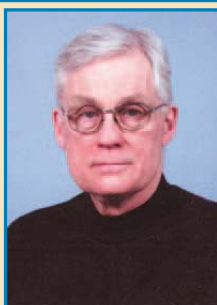
universal. Ovarian cysts are not part of his definition. Therefore, PCOS is a heterogeneous syndrome. The result of any clinical study, and particularly of PCOS, depends on the criteria chosen for inclusion/exclusion of study subjects.

Nestler and Jakubowicz, in 1996, found that elevated insulin levels in PCOS induced increased ovarian androgen synthesis, and therefore contribute, along with increased weight, to increased androgen effects.⁶ Increase in adrenal androgen secretion has also been demonstrated. Techniques for the clinical assessment of insulin resistance are difficult, and not often carried out in clinical practice. In clinical practice, it has been assumed that all PCOS patients, to varying degrees, have insulin resistance. This is another source of patient heterogeneity.

How prevalent is PCOS?

PCOS has been reported as affecting 5% to 10% of women of reproductive age in the U.S. Conservatively stated, 60% of those with PCOS are obese, and 40% have impaired glucose intolerance or frank diabetes. Forty per cent of all infertility is due to anovulation; PCOS is among the most common causes of anovulation. Its effect, therefore, on infertility is substantial. If only for these reasons, management of PCOS is a public health issue.

Until recently, treatment has been based on symptom management. Some of these treatments are listed in Table 1. Data showing that hyperinsulinemia plays an important role in PCOS has led to the possibility that reduction in circulating insulin may improve endocrine function. This possibility has been tested and found to be valid.



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What is metformin?

Metformin, an insulin sensitizing agent, was developed in the ‘50s and marketed for the treatment of Type 2 diabetes.⁷ Its glucose lowering effect is attributed mainly to decreased hepatic glucose out-

Table 2

Unwanted side effects of metformin

Gastrointestinal problems

- abdominal discomfort
- anorexia
- diarrhea
- metallic taste

Lactic acidosis (rare, but serious and possibly fatal)*

*Those with liver or kidney disease or hypoxia are at higher risk.

Bailey CJ, Turner RC: Metformin. N Engl J Med 1996; 334(9):574-9.

Practice Pointer

Consideration should be given to discontinuation of metformin before surgery or use of intravenous radiographic contrast agents.

put, and enhanced peripheral glucose uptake. It improves insulin sensitivity, and, therefore, decreases insulin resistance.⁷ If taken alone, metformin rarely causes hypoglycemia. Some unwanted effects are listed in Table 2. Particular risk has been reported in those with renal impairment, liver disease, or risk of hypoxia.⁷ Consideration should be given to discontinuation of treatment before surgery or the use of intravenous radiographic contrast agents. The use of metformin in PCOS is an off label use.

In 1994, Velazquez et al. reported on the use of metformin, in 26 women with PCOS in an eight-week, uncontrolled study; insulin sensitivity improved, androgen levels fell, menstrual function improved, and pregnancies occurred.⁸ Many small studies have followed and most have confirmed the findings of the first.

The most rigorous protocol (randomized, double blind, placebo-controlled, and later, an open, long-term study) with 37 subjects is that of Moghetti et al.⁹ It showed reduction of hyperinsulinemia and hyperandrogenemia and, in many subjects, sustained improvement in menstrual function and ovulation. The researchers concluded that higher plasma insulin, lower serum androstenedione, and less severe menstrual abnormalities are baseline predictors of clinical response to metformin. This experience has resulted in the widespread use of metformin in PCOS in doses of 500 mg to 1700 mg per day.

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Table 3

The Diabetes Prevention Program Research Group study

Group	Group description	Diabetes incidence
1	Control	11 cases/100 person-years
2	Lifestyle modification (<i>i.e.</i> , weight reduction of at least 7%, low-calorie, low-fat diet, and moderate physical activity for 150 min./week)	4.8 cases/100 person-years
3	Metformin-treated	7.8 cases/100 person-years

Diabetes Prevention Program Research Group: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; 364:393-03.

Table 4

Disorders linked to PCOS

- Central obesity
- Glucose intolerance/Type 2 diabetes
- High triglycerides
- Hyperandrogenism
- Hyperinsulinism
- Low high-density lipoprotein cholesterol

Wild RA: Obesity, lipids, cardiovascular risk, and androgen excess. *Am J Med* 1995; 98(1A):27S-32S.

Metformin in PCOS for infertility

Metformin use in initial management of PCOS, particularly along with lifestyle change, leads to positive effects on menstrual function and weight loss, along with more frequent ovulation. These observations have led to subsequent studies in infertility management in PCOS, which demonstrate increased frequency of ovulation with the addition of metformin to the clomiphene regimen.¹⁰ There seems to be a benefit in using gonadotropin induction of ovulation and in vitro fertilization.¹⁰

Metformin in PCOS during pregnancy

The literature has not suggested metformin teratogenicity.¹¹ Metformin is identified as Food and Drug Administration category B. Its use in pregnancy is increasing following its antecedent use in achieving the pregnancy. Early data suggests a decrease in early pregnancy loss, as compared to PCOS patients not using metformin.^{11,12} In view of the incidence of glucose intolerance in PCOS, an increased rate of gestational diabetes is expected. A recent small study showed a lower rate of gestational diabetes in those patients using metformin in PCOS pregnancy.¹³ This study yielded similar results to the Diabetes Prevention Program Research Group study, where a large, older population (mean age 51) at risk of Type 2 diabetes was randomized into three groups. The incidence of diabetes in each group after an average of 2.8 years is listed in Table 3.¹⁴

Take-home message

- The rate of diabetes is high in patients with PCOS.
- Metformin can decrease insulin resistance in PCOS patients, but side effects include gastrointestinal problems and lactic acidosis.
- In the Diabetes Prevention Program Research Group study, the incidence of diabetes in high risk patients was found to decrease most in patients who modified lifestyle habits, including diet and physical activity.

What are the secondary risks of PCOS?

Women with PCOS have long been thought to be at high risk for endometrial carcinoma, and at an earlier age than the general population. The suggested pathogenesis for this has been decreased frequency of ovulation with subsequent unopposed estrogen stimulation, although there are other possibilities. The data is far from clear due to lack of precision in the diagnosis of PCOS, and the small number of studies.

Women with PCOS have a high incidence of various other disorders (Table 4). All of these are seen as risk factors for coronary artery disease, although, at this time, it is not possible to prove the link.¹⁵ However, one study has noted that these patients are prime candidates for preventive medicine. The results of the studies in PCOS pregnancy, and in high-risk, older subjects suggest that metformin, or a metformin-like intervention may, in the long term, decrease morbidity in this population. Currently, the Diabetes Prevention Program Research Group study identifies



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PCOS

the possibly that weight loss, low-calorie, low-fat diet, and physical activity comprise an even more effective strategy. Finally, the frequency of Type 2 diabetes recommends appropriate screening to minimize the significance of this morbidity.

In summary, PCOS is a lifelong problem. Better management of reproductive problems may be on the horizon. Problems in later life, some not yet proven, must be considered, and methods for prevention must be articulated. CME

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Caution should be exercised when prescribing Xenical to patients with a history of hyperoxaluria or calcium oxalate nephrolithiasis and patients with pre-existing disease of the large bowel or rectum.

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Insulin Resistance in Polycystic Ovary Syndrome

1. Polycystic ovary syndrome (PCOS) seems uncommon. Why should I worry about it?

PCOS occurs in 5% to 10% of the adult female population. It is one of the most common causes of anovulation.

2. What causes anovulation in those with PCOS?

In addition to the same general causes as seen in other women, a combination of insulin resistance and hyperandrogenemia in women with PCOS may cause anovulation.

3. Isn't PCOS only a problem for those who are trying to achieve pregnancy?

Not really. PCOS is associated with a high incidence of glucose intolerance and Type 2 diabetes. As well, there is concern that it is a precursor of early coronary artery disease.

As presented at Queen's University

Presented at the 25th Annual Memorial Program, October 18, 2002.

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4. Isn't metformin only for the management of Type 2 diabetes?

Metformin is marketed for Type 2 diabetes, but an increasing off-label use is to decrease insulin resistance in PCOS patients.

5. Is metformin teratogenic?

There is no evidence in clinical studies that metformin is teratogenic when given during pregnancy.

For an in-depth article on Insulin Resistance in PCOS, please go to page 71.