PART 2 OF A 4-PART E-SERIES

Polycystic ovary syndrome: How are obesity and insulin resistance involved?

Which of my patients with PCOS do I screen for insulin sensitivity? What screening tests are available, and which are most appropriate? Two experts continue to tackle a long list of questions that your clinician–colleagues have been posing.

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Polycystic ovary syndrome, or PCOS, is an enigmatic condition. It presents with varying levels of severity of those symptoms and conditions associated with it—clinical hyperandrogenism (hirsutism, acne, alopecia), obesity, and menstrual disturbance. Although its exact cause is unknown, at least half of all women with PCOS are overweight or obese. What does obesity and, more specifically, insulin resistance, contribute to the pathogenesis of PCOS, and why is it important to screen your patient with PCOS for insulin resistance?

In part 2 of this 4-part series, which will continue to be posted here on the OBG MANAGEMENT Web site, we address these questions. [*Editor's note*: As they are published, future installments of this series will continue to be collected on a single Web page for ease of access.]

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The roles of obesity and insulin resistance

Q Can you define obesity and explain how its associated insulin resistance comes into play in the pathology of PCOS?

Overweight: BMI ≥ 25 kg/m^2

Obesity: BMI ≥ 30 kg/m^2

Morbid obesity: BMI ≥ 40 kg/m^2

PCOS is associated with truncal fat distribution, manifesting as an increased waist-to-hip ratio. According to the Centers for Disease Control and Prevention (CDC), more than one-third of the population was obese in 2009 and 2010.[1] Approximately 50% to 65% of women with PCOS are overweight or obese, and most of them have the truncal fat distribution phenotype.[2]

Obesity is associated with an increase in insulin resistance (IR) and hyperinsulinemia. IR can be characterized as impaired action of insulin in the uptake and metabolism of glucose. Impaired insulin action leads to elevated insulin levels. Insulin synergizes with abnormally high secretion of luteinizing hormone (perhaps induced by hyperinsulinemia) to promote excess androgen production by intraovarian theca cells and an arrest of follicular development resulting in chronic anovulation.

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In addition, hyperinsulinemia causes a decrease in hepatic sex hormone binding globulin, resulting in free circulating androgens and, thus, hirsutism and acne issues. While this picture tends to be more pronounced in women who have PCOS and are obese, it is important to realize that a nonobese patient with PCOS also may have IR, which suggests that insulin plays a major role in the pathogenesis of this disease.[3,4]

Q Does hyperandrogenism cause the insulin resistance or does insulin resistance cause the hyperandrogenism?

Most of the evidence suggests that hyperinsulinemia causes hyperandrogenism and not the reverse. Weight loss and insulin sensitizers are associated with a reduction in androgens, particularly testosterone and androstenedione. Gonadotropin-releasing hormone–analogs, which reduce androgen secretion from the ovaries, do not result in a reduction in insulin.[3,4]

Screening for insulin resistance: The rationale

Q How prevalent are insulin resistance, impaired glucose tolerance, and diabetes in PCOS, and what is the best way to screen for them?

The documented prevalence of IR and type 2 diabetes mellitus (DM) in women with PCOS suggests that impaired glucose tolerance (IGT) is present in 31% to 35% of women with PCOS[5,6]—and DM, classified according to World Health Organization (WHO) criteria, is present in 7.5% to 10% of women with PCOS.

The prevalence of IR and DM are considerably lower in women without PCOS. According to the Third National Health and Nutrition Examination Survey, in US women of similar age, the prevalence of IR is 1.6%, and the prevalence of DM is 2.2%.[7]

2003 consensus: Screen for IGT in obese PCOS patients. In view of the high prevalence of IR and IGT, a 2003 PCOS consensus[8] established that obese women with PCOS should be screened for insulin sensitivity and undergo screening for the metabolic syndrome, including glucose intolerance. For nonobese women, the consensus recommended screening only if additional risk factors are present.

Unfortunately, IGT also occurs independent of obesity. In lean women with PCOS, 5% may have IGT, while 2% are frankly diabetic. Moreover, the conversion from normal glucose tolerance to IGT in patients with PCOS can be as high as 16% per year,[9] while the conversion rate from IGT to DM among women with PCOS has been reported to be as high as 2% per year.

2007 position statement: Screen for IGT in all PCOS patients. A position statement by the Androgen Excess–PCOS Society on glucose intolerance and PCOS recommends screening for IGT in all PCOS women, regardless of BMI, at least once every 2 years.[10]

Screening for insulin resistance: The methods

There are two ways to determine insulin sensitivity:

- direct infusion of IV glucose and/or insulin
- indirect assessment using surrogate markers (such as fasting glucose and insulin, or C-peptide, and oral glucose tolerance test [OGTT]).

Direct infusion of IV glucose or insulin reveals how insulin disposes of glucose from the blood stream; however, this method is expensive, time consuming, and potentially dangerous due to possible hypoglycemia. Indirect assessments are less complex to perform and correlate reasonably well with the results of the more invasive direct measures.

Q What are the current direct-infusion methods to measure insulin sensitivity?

Direct infusion of glucose and insulin

The hyperinsulinemic euglycemic clamp is the gold standard, but drawbacks relegate it to medical research only. This method measures the amount of glucose necessary to compensate for an increased insulin level without causing hypoglycemia. Numerous blood samplings (every 5 to 10 minutes) are taken to monitor serum glucose so that a

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Screen for impaired glucose tolerance in all PCOS women, regardless of BMI, at least once every 2 years

steady "fasting" level can be maintained. The degree of insulin resistance is measured by the amount of glucose that is taken up by tissues during the procedure.[11–14]

The "clamp" technique is the most scientifically sound method for measuring insulin sensitivity, and it's the standard against which all other tests are usually compared. Because the clamp technique is expensive, time consuming (about 2 hours), and labor intensive, however, it is not practical and is rarely performed in clinical care. It is primarily used in medical research.

Frequently sampled IV glucose tolerance tests: "minimal model." The frequently sampled IV glucose tolerance test estimates insulin sensitivity through a computer-based mathematical analysis of the glucose-insulin dynamics. Though this test still requires 11 to 34 blood samples over a 3-hour period, it is less labor intensive than the clamp technique. However, in contrast to the clamp, it does not distinguish between peripheral and hepatic glucose utilization.[15]

Direct infusion of insulin

Insulin sensitivity test. This test involves IV infusion of a set glucose load and a fixed-rate infusion of insulin over approximately 3 hours. The mean plasma glucose concentration over the last 30 minutes of the test reflects insulin sensitivity. Although lengthy, the insulin sensitivity test is less labor intensive and requires fewer blood samples than the clamp technique.[16]

Insulin tolerance test. This test is a simplified version of the insulin sensitivity test, as it measures the decline in serum glucose after an IV bolus of insulin is administered. Several insulin and glucose levels are sampled over the following 15 minutes. In contrast to the clamp and the minimal model, the insulin tolerance test primarily measures insulin-stimulated uptake of glucose into skeletal muscle, and insulin sensitivity values reflect the rate of decline of log transformed glucose values.[17]

Direct infusion of glucose

Continuous infusion of glucose with model assessment. This method utilizes a constant IV glucose infusion; samples for glucose and insulin are drawn at 50, 55, and 60 minutes. A mathematical model is then used to calculate insulin sensitivity. The results are correlated with clamp techniques; however, few laboratories have used this continuous-infusion method for insulin sensitivity testing in women with PCOS.[18]

Unfortunately, all of these methods require IV access and multiple venipunctures, making them relatively impractical for office assessment. To overcome these obstacles, alternative tests have been developed including fasting methods and the OGTT, the latter of which does not require IV access and does correlate reasonably well with dynamic clamp techniques.

Q What are the current indirect assessments to measure insulin sensitivity?

Fasting methods

Fasting insulin. The measurement of fasting serum insulin is simple and inexpensive. Generally, a fasting level of 30 µU/mL indicates greater insulin resistance in a diabetic individual than in a normoglycemic patient. However, fasting insulin levels may be in the "normal" range in up to 40% of PCOS patients who have impaired glucose tolerance diagnosed by the OGTT. It has been suggested by some investigators that a fasting insulin greater than 20 µU/mL in white women and greater than 23 µU/mL in Mexican-American women probably indicates insulin resistance in women with PCOS. Some have also advocated averaging two or three readings to account for day-to-day variability.[19–21]

Fasting plasma glucose. This is a simple blood test taken after 8 hours of fasting. Fasting plasma glucose (FPG) levels are considered normal up to 100 mg/dL (or 5.5 mmol/L). Levels between 100 and 125 mg/dL (5.5 to 7.0 mmol/L) are considered *impaired fasting glucose* or *prediabetes*. These levels are considered to be risk factors for DM and its complications. DM is diagnosed when FPG levels are 126 mg/dL (7.0 mmol/L) or higher. A "normal" result on the FPG test is not

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Criteria for diagnosis of diabetes

	Venous plasma glucose (mg/dL)	
	Fasting Level*	2-hour postglucose load**
Normal/Low risk	≤99	≤139
Prediabetes/Increased risk	100–125	140–199
Diabetes	≥126	≥200

*Fasting is defined as no caloric intake for at least 8 h

**OGTT using a glucose load or 75 g as described by the World Health Organization

SOURCE: American Diabetes Association. Standards of medical care in diabetes—2012. Diabetes Care. 2012;35 (suppl 1):s11–s63. doi:10.2337/dc12-s011.

always reliable. Repeat testing with the OGTT is recommended if risk factors are suggestive for the presence of DM or a prediabetic condition.

Glucose/insulin ratio

The glucose/insulin (G/I) ratio has become very popular since its first description in 1998 as an accurate index of insulin sensitivity in women with PCOS. The ratio of glucose to insulin is easy to calculate, with lower values depicting higher degrees of insulin resistance. A G/I ratio of less than 4.5 has been shown to be sensitive (95%) and specific (84%) for insulin resistance in women with PCOS, compared with a control group. The normal range for G/I ratios may vary in different ethnic groups and have not been fully validated in nonobese patients.[22–25]

Homeostatic model assessment

First described in 1985, homeostatic model assessment (HOMA) has been used widely in clinical research to assess insulin sensitivity. Rather than using fasting insulin or a G/I ratio, the product of the fasting values of glucose (expressed as mg/dL) and insulin (expressed as μU/mL) is divided by a constant: I0 x G0 ÷ 405.

The constant 405 should be replaced by 22.5 if glucose is expressed in SI units (mmol/L). Unlike fasting insulin and the G/I ratio, the HOMA calculation compensates for fasting hyperglycemia. The HOMA value correlates well with clamp techniques and has been used frequently to assess changes in insulin sensitivity after treatment. HOMA also has been used to study insulin resistance among PCOS patients of differing ethnic origins.[12,24–26]

Quantitative insulin sensitivity check index

Like HOMA, quantitative insulin sensitivity check index (QUICKI) can be applied to normoglycemic and hyperglycemic patients. It is derived by calculating the inverse of the sum of logarithmically expressed values of fasting glucose and insulin: $1 \div [\log(I0) + \log(G0)]$.

Many investigators believe that QUICKI is superior to HOMA as a way of determining insulin sensitivity, although the two values correlate well. As the SI decreases, QUICKI values decrease.[27]

Oral glucose tolerance test

As OGTT does not require IV access, it is the current standard in practice for diagnosis of IGT and DM. It provides a better assessment of IGT and DM than fasting techniques because these patients may have normal fasting glucose values despite abnormal 2-hour fasting levels. The OGTT uses a 50-, 75-, or 100-g glucose load and measures glucose and insulin at various intervals over 1 to 3 hours. The WHO currently recommends a 75-g oral dose in all adults. A 50-g dose is used to screen for gestational diabetes over an hour, and the 100-g load over 3 hours if abnormal.[28] See **TABLE** for normal and abnormal values. Insulin sensitivity has been assessed by calculating insulin area under the curve (AUC insulin), AUC glucose/AUC insulin, and by an insulin sensitivity index (ISI) that applies only the glucose and insulin values from 0 and 120 minutes into a complex mathematical formula.[13,25,29–31]

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Oral glucose tolerance test is the current standard in practice for diagnosis of impaired glucose tolerance and diabetes mellitus

In the next installment: The authors begin by addressing recent data that have drawn attention to the long-term metabolic risks of PCOS by answering:

- *"What is metabolic syndrome and what are the current diagnostic criteria?"*
- *"We know metformin is used to treat insulin resistance…but what about hyperandrogenism, anovulation, infertility, weight loss, and early pregnancy loss?"*

Test for glycosylated hemoglobin

Tests for blood levels of glycosylated hemoglobin, also known as hemoglobin A_{1c} (HbA_{1c}) are not currently used for an initial diagnosis because normal HbA_{1c} levels do not necessarily rule out diabetes, but they are strongly associated with complications of diabetes. The test is not affected by food intake so it can be taken at any time. A normal HbA_{1c} level is below 7%.

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