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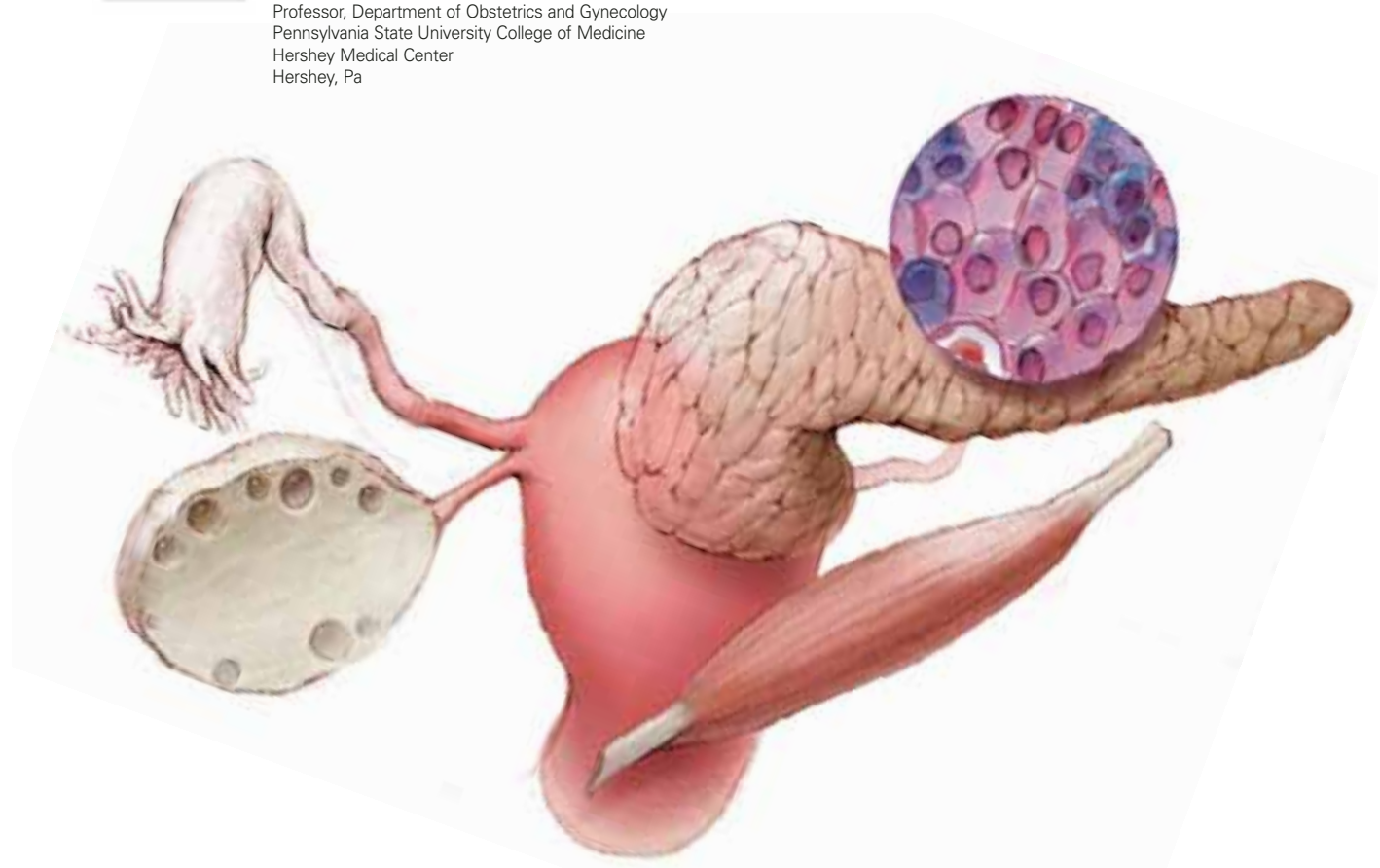

IMAGE: KIMBERLY MARTENS

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PCOS

Sizing up insulin resistance—one treatment doesn't fit all

There is no single best intervention for all women. It depends on the severity of glucose intolerance and metabolic abnormality in each patient.

Insulin resistance. Some clinicians take it for granted, assuming every woman with polycystic ovary syndrome (PCOS) has it and treating her the same as every other patient with the syndrome.

Admittedly, some evidence supports this approach. For example, a recent meta-analysis[1] demonstrated that metformin improves ovulation and, in conjunction with clomiphene citrate, boosts pregnancy rates. That may be rationale enough to use the drug routinely for ovulatory-related infertility in women with PCOS.

But for the rest of our PCOS patients, measuring the degree of insulin resistance—by assessing the patient for metabolic syndrome and glucose intolerance—can yield a reasonably accurate view of long-term risk, as well as the optimal intervention for a given patient.

More good news: Effective treatment does exist, including lifestyle modification and pharmacologic therapy. And lest we assume drugs are the strongest medicine, consider this: Intensive lifestyle intervention reduces the risk of diabetes by as much as 58%—about twice the efficacy of medication.[2]

While many small reports implicate insulin resistance or hyperinsulinemia in a variety of reproductive disorders and even endometrial cancer, the quality and quantity of that evidence pale in comparison with data showing it can cause type 2 diabetes.[3] Anything we can do to slow the progression is bound to benefit the patient and, in the long run, help prevent cardiovascular disease as well.

TABLE

Is it metabolic syndrome or not?

3 or more risk factors make the diagnosis

RISK FACTOR	CUTOFF
Abdominal obesity (waist circumference)	>88 cm (>35 in)
Triglycerides	≥150 mg/dL
HDL cholesterol	<50 mg/dL
Blood pressure	≥130/≥85 mm Hg
Fasting and/or 2-hour glucose from a 75-g oral glucose tolerance test	110–126 mg/dL* and/or 2-hour glucose level of 140–199 mg/dL†

HDL = high-density lipoprotein

*As recommended by the Expert Panel on the Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults

†As recommended by ACOG and AACE

How to identify insulin resistance

The best way is to assess the patient for metabolic syndrome (**TABLE**) and then measure the 2-hour glucose level after a 75-g oral glucose load. The World Health Organization criterion for impaired glucose tolerance (IGT) after this test is a plasma glucose level of 140–199 mg/dL.[4]

Limitations of other tests

The problem with traditional research tests such as euglycemic clamp studies and intravenous glucose/insulin tolerance tests is that they are invasive, labor intensive, time-consuming, and require a skilled team to perform—all of which translate into a poor clinical test. And among the limitations of the homeostatic models devised to replace them—which use fasting glucose and insulin levels as surrogate measures of these dynamic tests—is poor sensitivity in patients with IGT.

These models also have shifting cut-off levels in different studies in different populations.

Clinical parameters are more practical

Rather than rely on these traditional and homeostatic tests, some experts focus on validated clinical parameters. For example, the Third Report of the National Cholesterol Education Program Expert Panel on the Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP-III) defined metabolic syndrome using biometric and biochemical measures of centripetal obesity, hypertension, fasting hyperglycemia, and dyslipidemia (**TABLE**).[5]

Metabolic syndrome is closely related to insulin resistance syndrome, or syndrome X, which is characterized by dyslipidemia (depressed high-density lipoprotein [HDL] cholesterol and elevated triglycerides), hypertension, and glucose intolerance.[6]

Other groups such as ACOG[7] and the American Association of Clinical Endocrinologists[8] recommend adding a modified glucose tolerance test to the fasting blood tests used to identify metabolic syndrome.

Although a 2-hour glucose level after dynamic challenge does not test insulin sensitivity, it is more likely to identify a pathological relationship between insulin sensitivity and compensatory insulin secretion—one that is less detectable using fasting measures of glucose and insulin. One reason: In most women with IGT, fasting glucose levels are in the normal range. Thus, the fasting test alone would provide little discriminatory information.

FAST TRACK

Intensive lifestyle modification reduces the risk of diabetes by 58%, versus 29% for drugs

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Is PCOS a way station on the road to diabetes?

In type 2 diabetes, as well as polycystic ovary syndrome (PCOS), a main component is peripheral insulin resistance,[20] although women with PCOS have somewhat better beta cell function than diabetic women, with initial hypersecretion and compensation. Over time, dysfunction develops, leading to inadequate insulin secretion, beta cell exhaustion, fasting hyperglycemia, and frank type 2 diabetes.

Just what is insulin resistance?

Insulin is the primary anabolic hormone in the body, acting in diverse ways in different tissues. Yet insulin resistance is usually defined as a single action: decreased insulin-mediated glucose uptake by peripheral tissues (largest utilizer: skeletal muscle).

Most research tests, such as euglycemic clamp studies, focus on glucose uptake—or its disappearance from the circulation—during dynamic challenge tests. The higher the glucose uptake, the greater the insulin sensitivity and the lower the eventual risk of developing diabetes.

Signs of insulin resistance in PCOS patients

In women with PCOS, the picture is complicated by selective tissue sensitivity to insulin and/or selective actions within tissues that are either sensitive (adrenal or ovary) or resistant (skeletal muscle) to insulin.[21]

Women with PCOS are profoundly resistant to insulin at the level of skeletal muscle, where 85% to 90% of insulin is utilized. This is comparable to the resistance in women with type 2 diabetes.[22]

In the target tissues of women with PCOS, compensatory hyperinsulinemia is thought to create aberrant states, suggesting that these tissues are differentially responsive to insulin's action. For instance, hyperinsulinemia drives excess ovarian and adrenal androgen production, stimulates the proliferation of the pilosebaceous unit (worsening acne and hirsutism), and suppresses hepatic sex hormone binding globulin production, thus increasing the bioavailable androgen load.

Insulin resistance is not always a disorder

Determining precisely who is insulin-resistant, and assigning clinical cutoffs, are complicated tasks. We lack standardized assays for insulin, and results vary from lab to lab. Normal insulin sensitivity varies widely and is influenced by age, gender, ethnicity, diet, and obesity. Simply put, not all people with impaired insulin sensitivity are necessarily suffering from a disorder. Pregnancy, a temporary condition of markedly diminished insulin sensitivity, is one example.

Thus, establishing limits for normal degrees of insulin sensitivity is arbitrary; often the bottom 10% to 25% of a population is labeled "insulin-resistant."

Why glucose intolerance is important

Impaired glucose tolerance is a strong risk factor for diabetes, and recent studies show it is possible to delay progression to diabetes in women with IGT using lifestyle and, when appropriate, pharmacotherapy.[2,9,10] IGT also identifies excess risk for mortality, especially in women.[11] This is important because in obese women with PCOS, IGT approaches 40%.[12–14] And the incidence of type 2 diabetes among women with PCOS is 11.9%, compared with only 1.4% in healthy controls.[15]

Managing impaired glucose tolerance

Diet and exercise double risk reduction

In a recent trial by the Diabetes Prevention Program Research Group, which offers excellent guidelines for intervention,[2] both metformin and lifestyle intervention reduced diabetes risk, although lifestyle was far more effective (58% reduction versus 29%).

That trial randomized 3,234 men and women with IGT to 3 treatments: conventional lifestyle recommendations, intensive and active lifestyle intervention, or insulin sensitization with metformin.

Intensive lifestyle intervention involved a case manager to ensure compliance with the study's goals: at least a 7% loss in body weight maintained over the life of the study, and at least 150 minutes of exercise weekly.

Exercise was key. Individuals who complied with intensive lifestyle intervention exercised an average of 6 hours weekly over the 4 years of the trial. The other groups exercised on average less than 2 hours weekly.

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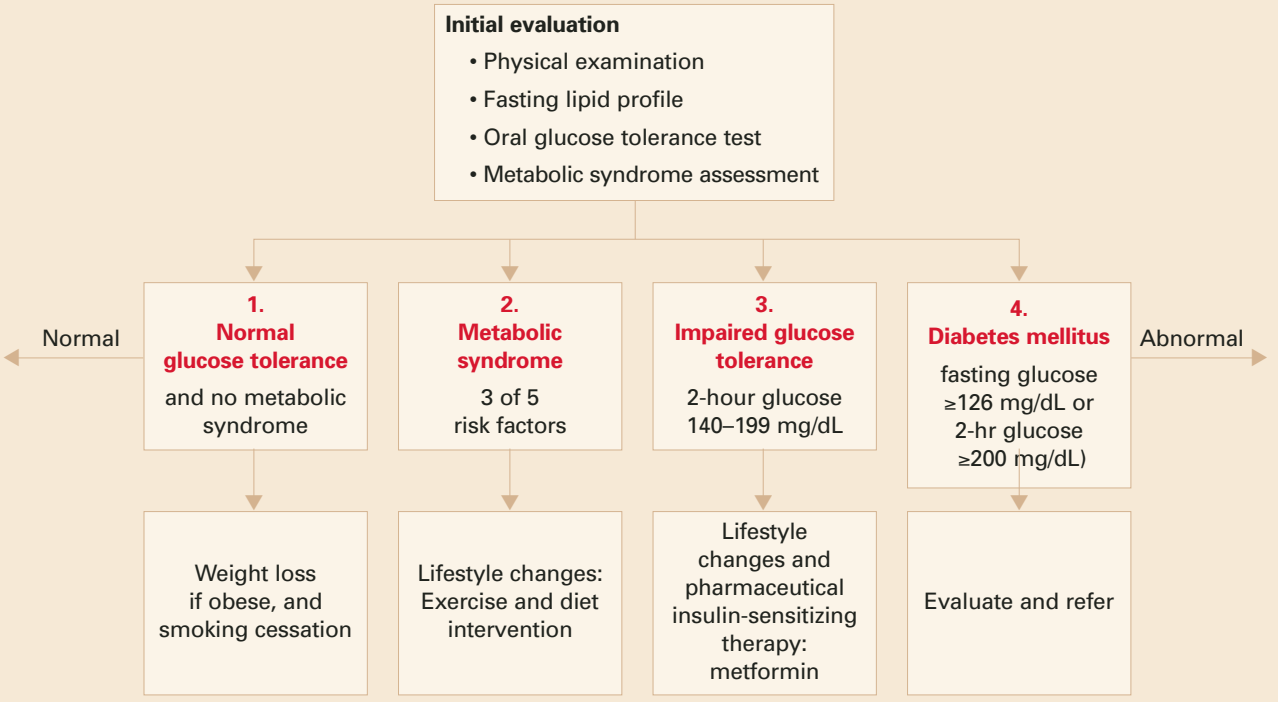
FIGURE

Treatment based on 4 degrees of insulin resistance



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Monitor treatment by measuring waist circumference, as well as BP, fasting lipids, and glucose tolerance

For metabolic abnormalities, start with lifestyle

With this information, it is possible to devise an algorithm for women with PCOS, depending on their degree of metabolic abnormality (**FIGURE**).

All individuals—even those taking medication—should be counseled about the importance of a healthy lifestyle, including staying physically active and quitting smoking. In addition:

- **In women with metabolic syndrome,** intensive lifestyle intervention is warranted, preferably supervised (ie, by a registered dietician and exercise trainer). This may involve out-of-pocket expense, but expert advice in these areas requires a professional. Obese, metabolically challenged women should also avoid overstrenuous exercise programs.
- **Impaired glucose tolerance** arouses further concern; insulin sensitization with metformin may be appropriate.
- **If type 2 diabetes is diagnosed,** repeat the blood tests to confirm the diagnosis and then evaluate the patient for sequelae and refer her for more intensive management.

Monitor response to therapy by following waist circumference and blood pressure, obtaining a fasting lipid profile with HDL cholesterol and triglyceride levels, and performing glucose tolerance testing.

If metabolic syndrome progresses, or if individual parameters change for the worse, additional therapy may be warranted, such as altering the dose or the choice of insulin sensitizer.

Guidelines into action

SUZANNE'S CASE

Suzanne is a 32-year-old mother of twins who presents with PCOS at a new-patient appointment, seeking advice about long-term care. She has a history of irregular

How to code PCOS-related exams and tests

Diagnostic phase. Polycystic ovary syndrome (PCOS) signs and symptoms are reported as such until you identify PCOS. For example, if the patient has excessive body hair, use hirsutism code ICD-9-CM 704.1; for obesity, code for unspecified obesity (278.00), morbid or severe obesity (278.01), or obesity of endocrine origin (259.9). If she has irregular menstrual periods, use the code for that condition (626.4).

Use the code for polycystic ovaries and PCOS (ICD-9-CM 256.4) once you have a diagnosis, during management, or when additional metabolic studies are done to rule out coexisting problems.

Link tests to suspected condition. A battery of laboratory tests will usually be part of diagnosis. Because many payers do not reimburse for routine screening tests, it is important to indicate that these tests are being performed to diagnose a suspected condition.

When screening women for metabolic syndrome and glucose intolerance, you may consider:

- **Lipid panel (CPT 80061)**, linked to a diagnosis of obesity or a family history of cardiovascular disease (V17.4).
- **Diabetes screening (CPT 82947** for fasting glucose plus 82950 for the 2-hour post glucose specimen) linked to a history of gestational diabetes (V13.29, other genital system and obstetric disorders) or family history of diabetes (V18.0), and possibly obesity.

After diagnosis, use E/M codes. Once you confirm PCOS and determine that management of affected systems is required, most follow-up care will be reported using evaluation and management (E/M) codes (99212–99215 for the established patient). Also use the E/M codes for initial physician encounters for diagnosis: consultation codes if another provider sends the patient to you for evaluation, or new/established patient codes if not.

Document counseling time. Some visits may entail counseling, so it is important to document counseling time (as well as total face-to-face time) with the patient. This allows you to select the E/M code based on total time, rather than on 2 of the 3 key components of history, examination, and/or medical decision-making.

The linking diagnosis during the management phase will be PCOS (256.4), along with any supporting diagnosis related to coexisting problems being managed at the time of the visit.

—Melanie Witt, RN, CPC, MA

menses; she conceived her twins on clomiphene 6 years ago, and now is being treated with an oral contraceptive (OC) containing 30 µg ethinyl estradiol, which she has taken for 4 years. She does not desire fertility.

Although Suzanne has a history of hirsutism, and occasionally plucks chest hair, she has been satisfied with her response to the OC. She has no other medical problems and does not smoke. Although she has a strong family history of type 2 diabetes, with both parents now on oral agents, there is no family history of premature heart disease.

She is 5 ft 9 inches tall and weighs 200 lb, with a body mass index of 29.5 kg/m^2 (a BMI of 25 to 30 is overweight). Her blood pressure is 110 mm Hg systolic, 70 mm Hg diastolic, and her waist circumference is 90 cm. She has mild hirsutism. Other physical examination findings, including breast and pelvic examinations, are normal.

A fasting lipid profile reveals that Suzanne's HDL cholesterol is 55 mg/dL, triglycerides are 175 mg/dL, and total and low-density lipoprotein (LDL) cholesterol are normal. A modified oral glucose tolerance test (OGTT) shows a fasting glucose level of 95 mg/dL and a 2-hour glucose level of 180 mg/dL, consistent with IGT.

Consider overall risk, modifiable factors

Besides the IGT, this patient has other risk factors for diabetes, including her BMI, strong family history, and several stigmata of metabolic syndrome, although she does not meet the ATP-III criteria for the syndrome. Nevertheless, the IGT merits attention.

While small case series suggest OCs can worsen glucose tolerance in women with

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Because many payers do not reimburse for routine screening, indicate that these tests are to screen for a suspected condition

PCOS, the overall evidence is conflicting. The Nurses Health Study[16] found no association between type 2 diabetes and OC use.

One treatment option would be to discontinue the OC and see whether glucose tolerance normalizes, but Suzanne expresses a desire to continue the OC, given her overall satisfaction with its contraceptive benefit and control of hirsutism. Another factor to consider is the profound lifetime benefit OCs offer in protection against endometrial cancer.

I recommend a structured lifestyle intervention and would refer her to an exercise physiologist and dietician, because I am concerned about her other risk factors for diabetes, including her weight and strong family history.

When to add metformin

This patient also may benefit from concomitant use of metformin. Although we lack evidence that the combination of intensive lifestyle intervention and metformin is superior to lifestyle intervention alone, there is suggestive evidence from a small pilot clinical trial in women with PCOS.[17]

In Suzanne's case I would treat the IGT more aggressively, given her strong family history of diabetes and her overweight status, by recommending that she add metformin to her regimen.

Higher doses may be more effective. Although the Diabetes Prevention Program study recommends a metformin dose of 850 mg twice a day, I prefer 2,000 mg a day in 2 divided doses. A dose-ranging study for type 2 diabetes found this to be the most effective dose for improving glycemic parameters.[18] I use a step-up regimen of 500-mg doses over 5 to 7 days until the 2,000-mg dose is attained, and will plateau the patient at a lower dosage if she does not tolerate the higher amount, most commonly due to gastrointestinal side effects.

Monitor at least annually

This patient warrants visits at least yearly to monitor her condition. The visits should include a lipid profile and, every few years, an OGTT. A glycosylated hemoglobin in lieu of the OGTT may be another option.

It also is prudent to monitor renal function at baseline and at least annually, given the renal clearance of metformin.

In addition, I would continue the OC, as there are no known interactions between OCs and metformin, and at least 1 randomized study[19] suggests the combination of the 2 is metabolically superior to an OC alone.

Scant evidence suggests that metformin alone improves hirsutism or results in eumenorrhea, and there are no data on endometrial cancer protection. ■

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2,000 mg metformin daily in 2 divided doses may improve glycemic values more effectively than 850 mg twice a day

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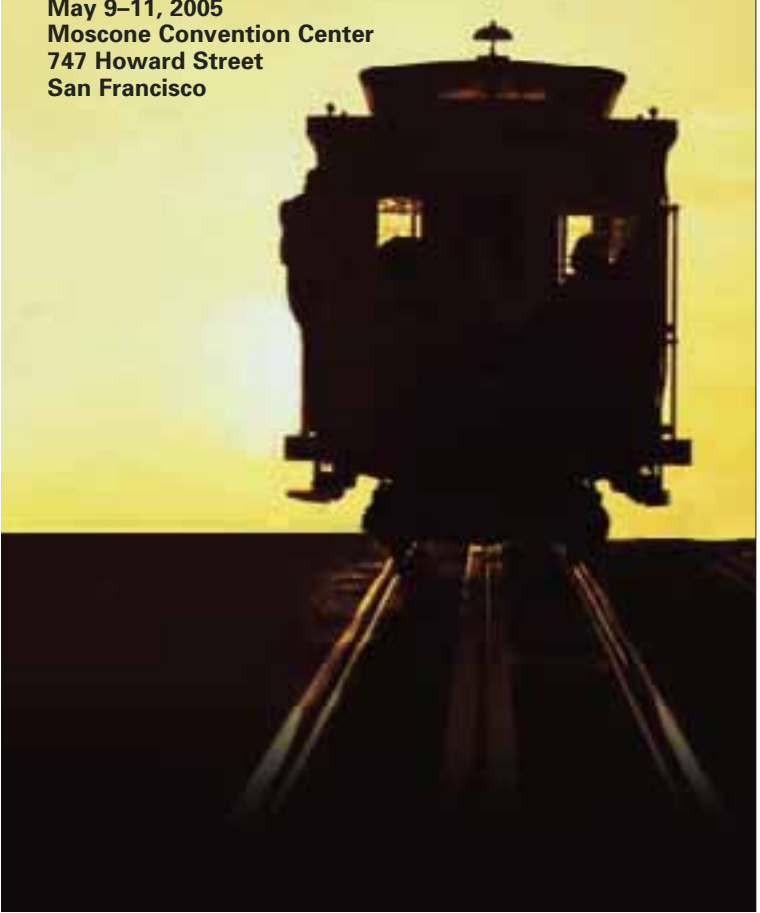

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