

# Metformin Urged for PCOS, Despite Lack of Data

*Current knowledge of the risks of insulin resistance and the disadvantages of OCs deemed convincing.*

BY CHRISTINE KILGORE  
Contributing Writer

WASHINGTON — Insulin resistance is such an integral and dangerous feature of polycystic ovary syndrome that metformin should be favored over oral contraceptive pills for treatment of the syndrome, said physicians in annual scientific sessions of the American Diabetes Association meeting.

Although there is a paucity of “good, prospective outcomes data” on cardiovascular disease in patients with polycystic ovary syndrome (PCOS)—as well as the existence of only limited data on oral contraceptives’ (OCs) effect on insulin resistance—the speakers warned against waiting for definitive data to appear. Current knowledge of the risks of insulin resistance and the potential disadvantages of OCs is too convincing, they argued.

“Given everything [we know now], I believe we now must have the goals of preventing glucose intolerance and diabetes, and preventing atherosclerosis and acute coronary events” in addition to addressing the immediate symptoms of PCOS, said Dr. John Nestler, professor of medicine, ob.gyn., pharmacology, and toxicology at the Virginia Commonwealth University, Richmond.

“I will be provocative, because there aren’t a lot of studies, but I’m going to argue that there may be disadvantages to using OCs,” said Dr. Nestler, who also chairs the division of endocrinology and metabolism.

OCs may be better for treating symptoms such as acne and hirsutism (studies of metformin have not addressed these problems as primary end points), but studies indicate that OCs worsen insulin resistance and glucose intolerance and that they may increase triglycerides, worsening the risk of diabetes and cardiovascular disease, he said.

Metformin, on the other hand, targets insulin resistance, “what may well be the initiating abnormality in PCOS, and has been shown to normalize or improve the biochemical, clinical, and reproductive abnormalities of PCOS,” said Dr. Tessa Lebinger, a pediatric endocrinologist. The drug is effective whether or not insulin resistance can be documented, she added.

In most cases, Dr. Nestler agreed, it won’t be documented because insulin resistance is too difficult to accurately measure in a clinical setting. “Most women with PCOS are insulin resistant ... so an empiric trial of metformin in any woman with PCOS is reasonable as you long as you monitor her and make sure that her menses are improving,” he said.

Dr. Burton Sobel, who directs the Cardiovascular Research Institute at the University of Vermont, said during a symposium on PCOS that from his perspective as a cardiologist, “PCOS is a cardiovascular disease.”

“We know, from so many perspectives, that impaired sensitivity to insulin is a forerunner, and probably a determinant, of premature coronary disease,” Dr. Sobel said. “It may be years before we have prospective data and legitimacy for using insulin sensitizers [in PCOS patients], but if I had a daughter with PCOS, I’d use an insulin sensitizer beginning with my recognition of the problem regardless of whether she had abnormal glucose tolerance. ... I wouldn’t wait—to me this is a smoking gun.”

The relationship between hyperinsulinemia and hyperandrogenism—in particular, the question of which causes which—is still discussed, but these physicians said they’re convinced from available data that insulin resistance leads to hyperandrogenism and is likely a primary cause of PCOS.

Study results have shown that 30%-35% of women with PCOS have impaired glucose tolerance, and that 8%-10% have type 2 diabetes.

On the whole, Dr. Nestler said, 30%-50% of obese women with PCOS develop either impaired glucose tolerance or type 2 diabetes by age 30. Lean women with PCOS, on the other hand, are just as insulin resistant—if not more so—than obese women without PCOS, several speakers said.

Dr. Nestler said he and his colleagues found in a chart review of 50 consecutive PCOS patients treated with metformin that the incidence of impaired glucose tolerance was “dramatically” reduced.

At baseline, 78% of the 50 patients had normal glucose tolerance (NGT), and 22% had impaired glucose tolerance (IGT). At

follow-up (a mean of 43 months for NGT patients, and 29 months for IGT patients), 55% of the IGT patients had converted to normal, with 45% continuing to have IGT. Of the NGT patients, 95% continued to have NGT, and 5% converted to IGT.

“It needs to be verified in a prospective study, but our annual conversion rate to IGT of 1.4% with metformin treatment is a dramatic reduction from the 16%-19% annual conversion rates” reported in women with PCOS who are not treated with metformin, he said.

He and other physicians at the meeting pointed to the Nurses’ Health Study as the best of few studies that provides a look at the cardiovascular “outcomes” of PCOS.

In its tracking of over 80,000 women for 14 years, the study found that women with abnormal menstrual cyclicity had a relative risk for cardiovascular disease of 1.5 and a relative risk of fatal MI of 1.9, compared with women with normal menses. (The NHS also found a twofold increased risk, independent of weight, of type 2 diabetes in women with oligomenorrhea.)

Dr. Holley Allen, a pediatric endocrinologist at Baystate Medical Hospital in Springfield, Mass., said that a metaanalysis of case-control studies published in 2005 showed a twofold increased risk of both MI and ischemic stroke in women who took OCs.

The risk may be higher in women with PCOS, because they likely start at a higher baseline risk and take OCs for long periods of time, she said.

Still, she said she views the concerns about OCs’ impact on insulin resistance and cardiovascular disease as “potential but unproven.”

And the “question is, whether she’ll take a pill for the next 30 years that does not make her lose weight, doesn’t do much for her facial hair or acne, and tastes like dead fish,” she said.

Dr. Lebinger, who spoke with Dr. Allen, acknowledged there are “inadequate data [on metformin use] in adolescents—only small studies and not many [that are] placebo controlled.”

Still, the literature consistently demonstrates either normalization or significant improvements in glucose intolerance, insulin resistance, and menstrual irregularities, said Dr. Lebinger, who practices in New Rochelle, N.Y.

Her adolescent patients on metformin also have improvements in their acne and

frequently lose weight. “We’re making recommendations based on what we know today. I present all the options—it’s the patient’s decision,” she said.

Regarding OCs and insulin resistance, “most of us observe that if you take a patient with type 1 diabetes and give them OCs, they usually require more insulin,” Dr. Lebinger said.

Dr. Nestler disclosed to the ADA that he is on the speakers’ bureau for Sanofi-Aventis and that he is a stock/shareholder of the Bristol-Myers Squibb Co. and of Pfizer Inc. ■

## Okay for Use in Infertile Patients

If time is not critical, metformin is also an appropriate front-line drug for patients with PCOS whose primary concern is infertility, Dr. Nestler said at the annual meeting of the American Diabetes Association.

“If a woman comes to me with PCOS and wants to get pregnant, I will usually tell her I’d like to put her on 3-6 months of metformin coupled with diet and exercise. In that way, we can try first for the singleton pregnancy [without clomiphene],” Dr. Nestler said. “If, at the end of 6 months, she doesn’t become pregnant, I will send her to the endocrinologist.”

The authors of a 2003 review by the Cochrane Collaboration concluded that women with PCOS who take metformin are almost four times as likely to achieve ovulation, compared with women receiving placebo, he said.

In a study of 68 infertile women treated at his institution with metformin, Dr. Nestler and his colleagues found that 78% had improvements in menstrual cyclicity and ovulation, with the frequency of cycles increasing threefold. Approximately 44% had normalized cycles—the “optimal” outcome, he said.

Results from a National Institutes of Health-sponsored, multicenter, randomized study of metformin, clomiphene, or both for treating infertility in PCOS patients will be announced in October, he mentioned.

## Liver Disease May Accompany Polycystic Ovary Syndrome

BY JOYCE FRIEDEN  
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CHICAGO — Women with polycystic ovary syndrome can have fairly advanced liver disease, Dr. Tracy L. Setji of Duke University, Durham, N.C., and colleagues said in a poster presentation at the annual meeting of the American Association of Clinical Endocrinologists.

At a university endocrinology clinic, charts were reviewed retrospectively for

275 PCOS patients with oligomenorrhea and clinical or biochemical evidence of hyperandrogenism.

Of these, 200 had no other causes of irregular menses and drank less than one alcoholic beverage daily. Aspartate aminotransferase and alanine aminotransferase levels greater than 60 U/L were seen in 15%. Patients with elevated aminotransferase levels had lower median HDL cholesterol levels (41 mg/dL vs. 50 mg/dL), higher median triglycerides (174 mg/dL

vs. 129 mg/dL), and higher median fasting insulin (21  $\mu$ IU/mL vs. 12  $\mu$ IU/mL), compared with patients without elevated aminotransferase levels.

Liver biopsies were performed in six women with persistently high aminotransferase levels, and they were diagnosed with nonalcoholic steatohepatitis (NASH) with fibrosis. These patients had lower median HDL levels and higher median triglyceride and fasting insulin levels than did patients who did not undergo biopsy.

The study was limited by the self-reporting of alcohol consumption. Additionally, normal liver enzyme values do not exclude the presence of liver disease, including NASH, the investigators said.

“The young age of many women with polycystic ovary syndrome and the relatively advanced stage of NASH seen on the biopsies of our patients suggest the possibility of significant risk for long-term complications from liver disease,” the authors concluded. ■