

# THE *Lipid Spin*

Clinical Feature:

## Omega 3 Fatty Acids in the Treatment of Dyslipidemia

—Ronald Goldberg, MD

Lowering triglycerides and reducing CVD risk

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## Polycystic Ovarian Syndrome, Insulin Resistance, and Lipids

Polycystic ovarian syndrome (PCOS), a disorder of androgen excess, is a highly prevalent disease affecting approximately 10% of reproductive-age women. The androgen excess appears to be driven by an underlying insulin-resistant state. Patients with PCOS have a high prevalence of the metabolic syndrome and as a result are at increased risk for type II diabetes as well as increased risk for cardiovascular disease. Impaired glucose tolerance (IGT) or overt type II diabetes develops by the age of 30 in 30–50 % of obese women with PCOS.<sup>1</sup>

This article will focus on the lipid abnormalities that are typical of PCOS, the role of advanced lipid testing in assessment of these abnormalities, and an updated treatment approach focusing on insulin resistance.

PCOS is a clinical diagnosis associated with chronic anovulation and clinical or biochemical signs of hyperandrogenism, and in some patients polycystic ovaries.<sup>2</sup> Complications of PCOS include infertility, menstrual dysfunction, hirsutism, acne and obesity. Some studies in PCOS patients show evidence of increased hsCRP,<sup>3</sup> increased PAI-1, endothelial dysfunction,<sup>4,5</sup> hyperhomocysteinemia, and increased carotid intimal medial thickness (CIMT), especially if age is above 45 years.<sup>6</sup> Studies using coronary calcium scores as a surrogate showed young, obese women with PCOS have a high prevalence of early asymptomatic coronary atherosclerosis compared to obese controls.<sup>7,8</sup>

The lipid abnormalities in PCOS patients are similar to metabolic syndrome patients and type II diabetics: low HDL-C (<50 mg/dL), low HDL2 subfraction, low Apo-A1, high triglycerides (>150 mg/dL), and increased small dense LDL particle concentration. The low HDL-C is independent of body weight.<sup>9,10</sup> Compensatory

hyperinsulinemia, often seen in these young patients, is frequently sufficient to keep glucose, even postprandial glucose levels, in the normal range. Insulin levels may be helpful to confirm insulin resistant state but may be normal as well. The American Association of Clinical Endocrinologists states “Because accurate assessment of insulin sensitivity is impossible in the clinical practice setting, it is prudent to regard all obese women with PCOS as likely having insulin resistance and being at risk for the insulin resistance syndrome (IRS) and to assume that most non-obese women with PCOS have the IRS as well.”<sup>11</sup>

Referral of PCOS patients to a cardiometabolic lipid clinic may be appropriate, especially if other risk factors for cardiovascular disease exist. Also, patients with PCOS frequently have a discrepancy between calculated LDL cholesterol (LDL-C) and LDL particle concentration (LDL-P), as measured by NMR, or Apo B. An example is Sarah, a 20-year-old woman referred to our lipid clinic by her gynecologist due to diagnosis of PCOS and strong family history of premature coronary artery disease. Her BMI is 33.3 kg/cm<sup>2</sup>, waist circumference 38.5 inches, blood pressure 130/84, fasting glucose 76 mg/dL, 2-hour glucose after 75 g glucose challenge 111 mg/dL. She had a normal comprehensive metabolic panel, and TSH was normal at 1.21 μIU/ml. Clinical

symptoms included fatigue, polydipsia, polyphagia, hirsutism and irregular menses. Her lipid panel revealed total cholesterol 167 mg/dL, LDL-C 69 mg/dL, HDL-C 64 mg/dL, triglycerides 174 mg/dL, and non-HDL-C 103 mg/dL. An NMR showed LDL-P 1794 nmol/L (optimal

LDL-P <1000), small LDL-P 1421 nmol/L (optimal <850), large VLDL-P 7.8 nmol/L (high risk >5 nmol/L), and small LDL particle size consistent with pattern B. The calculated LDL cholesterol of 69 mg/dL meets even the most aggressive goal for lipid management, yet the NMR unmask a severe dyslipidemia consisting of numerous small LDL particles.

Treatment with oral contraceptives has been a traditional approach that helps correct the reproductive and menstrual abnormalities thus providing symptom relief. Hormonal therapy, however, may be associated with adverse metabolic consequences such as decreased insulin sensitivity, impaired glucose tolerance, increased triglycerides, and increased risk of thrombosis. An adjunctive approach would address the insulin resistance which is at the core of the cardiovascular pathophysiology of this disorder. Hyperinsulinemia is in part due to genetic predisposition and obesity. Excess insulin leads to decreased sex hormone binding globulin (SHBG) synthesis in the liver and therefore increased levels of circulating free testosterone. PCOS is also managed with therapies that address the altered androgen metabolism. Spironolactone, an androgen

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antagonist, may be used to treat the hirsutism but neither spironolactone nor hormonal contraceptives address the underlying insulin resistance which will persist.

The initial treatment of PCOS should be aimed at weight loss because even a small reduction of body weight by 2–5 % and loss of visceral fat can restore ovulation, lower insulin levels, increase insulin sensitivity, increase SHBG and reduce testosterone levels and acne. LDL-C and LDL-P will generally improve with the weight loss. Our approach has been to prescribe exercise in the form of pedometers and step counts. Exercise for 60–90 minutes/day is recommended for weight loss and weight maintenance; this includes a minimum of 10,000 steps/day plus at least 30 minutes of moderate exercise. Our diet recommendations focus on high fiber, whole-grain food and lower intake of simple carbohydrates. We also advise eliminating intake of trans fat (partially hydrogenated oil).

If lifestyle change alone fails to produce weight loss, we consider the addition of metformin or thiazolidinediones (TZDs). Although not FDA approved for treatment of PCOS, metformin is commonly used in PCOS. Many studies have demonstrated safety and efficacy in this patient population.<sup>12</sup> Metformin is a category B drug in pregnancy, and has no known fetal toxic effects, so it can be used fairly safely in young women. Metformin reduces plasma insulin levels, reduces blood pressure and reduces LDL-C. In our clinical experience, we see a more dramatic decrease in LDL-P than LDL-C with metformin than with lifestyle change alone. The Indian Diabetes Prevention program and US Diabetes Prevention program are major randomized trials that have shown that the use of metformin decreases relative risk of progression to diabetes among patients with IGT at baseline. There have been no randomized trials to date assessing the affect of metformin on the progression to type 2 diabetes in patients with PCOS specifically.<sup>13,14</sup> Appropriate starting dose is 500 mg twice daily with food or long-acting formulation once daily.

Multiple studies of thiazolidinediones (TZDs) (troglitazone,<sup>15,16</sup> Rosiglitazone,<sup>17,18,19</sup> and Pioglitazone<sup>20</sup>) have shown benefit in the treatment of metabolic abnormalities of PCOS. TZDs have also been shown to decrease androgen levels, improve ovulation, and reduce progression to overt type II DM in patients with PCOS and IGT. Lipids also improve with use of TZDs, although effects vary by specific TZD. Pioglitazone is more likely to produce a drop in triglycerides and an increase in HDL-C, whereas

all TZDs shift LDL particles to large buoyant particles. However, TZDs may cause increased body weight. TZDs are considered category C drugs in pregnancy and, therefore, need to be used with caution in women of child-bearing potential.

The Androgen Excess Society released a position paper recently recommending that all women with PCOS be screened with glucose tolerance test at diagnosis and every 2 years thereafter. They also state use of metformin to treat or prevent progression to impaired glucose tolerance may be considered but not mandated until randomized controlled trials demonstrate efficacy.<sup>21</sup> The American Association of Clinical Endocrinologists recommends metformin for initial intervention in most women with PCOS, particularly if overweight.<sup>11</sup>

In summary, PCOS is a syndrome of androgen excess that is driven by insulin resistance. This frequently results in impaired glucose tolerance, lipid abnormalities such as high triglycerides, low HDL-C, and increased LDL-P or Apo B, all easily evaluated in many patients by looking for an elevated non-HDL-C. These patients have an increased risk of cardiovascular disease in a manner similar to patients with the metabolic syndrome and diabetes. Patients with PCOS will therefore likely benefit from cardiovascular prevention efforts. Therapeutic lifestyle changes should be initiated but at times additional pharmacotherapy which addresses insulin resistance will help correct a large portion of the metabolic and dyslipidemic complications of this syndrome.

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