MD CONFERENCE EXPRESS

Dyslipidemia in Polycystic Ovary Syndrome

Written by Rita Buckley

Dyslipidemia occurs in up to 70% of women with polycystic ovary syndrome (PCOS) in the United States. Tracy Lynn Setji, MD, Duke University Medical Center, Durham, North Carolina, USA, discussed the latest findings on the etiology, screening, and treatments for PCOS. Roughly 60% of women with PCOS are obese and insulin-resistant. At menopause, a woman with PCOS is likely to have had multiple cardiac risk factors for several decades [McGowan MP. *Curr Treat Cardiovasc Med* 2011].

PCOS is the most common endocrinopathy among women of reproductive age, impacting 5% to 10% of premenopausal American women. Up to 40% of women with the syndrome will develop diabetes by the age of 50 years, and many are dyslipidemic [McGowan MP. *Curr Treat Options Cardiovasc Med* 2011]. Beyond known alterations in triglycerides and high-density lipoprotein-cholesterol (HDL-C), women with PCOS have higher low-density lipoprotein-cholesterol (LDL-C) and non-HDL-C, regardless of their body mass index (BMI).

A recent systematic review and meta-analysis found that triglyceride levels were 26 mg/dL higher (95% CI, 17 to 35) and HDL-C concentrations 6 mg/dL lower (95% CI, 4 to 9) in women with PCOS than in controls. LDL-C and non-HDL-C concentrations were also higher in PCOS subjects by 12 mg/dL (95% CI, 10 to 16) and 19 mg/dL (95% CI, 16 to 22), respectively [Wild RA et al. *Fertil Steril* 2011].

Dr. Setji reported that the atherogenic lipoprotein profile is likely related to insulin resistance. The elevation in LDL-C also appears to be due in part to hyperandrogenemia. Free androgen index (FAI), which is associated with increased LDL-C, is improved with administration of flutamide [Gambineri A et al. *Clin Endocrinol (Oxf)* 2004].

Androgens are involved in the regulation of lipoprotein lipase and hepatic lipase activity (Table 1). While estrogens increase the rate of LDL-C clearance by inducing upregulation of LDL-C receptors, androgens attenuate this process, decreasing catabolic removal of LDL-C [Diamanti-Kandarakis E et al. *Trends Endocrinol Metab* 2007]. Testosterone administration has significant effects on lipid profiles but not on insulin resistance [Cupisti S et al. *Fertil Steril* 2010].

Table 1. Androgen Effects on LDL-C.

• Hyperandrogenemia may also play a role in LDL-C in women with PCOS
• Among postmenopausal women, FAI is associated with increased LDL-C
• In small studies of women with PCOS, flutamide has shown to lower LDL-C

Geographic, genetic, and lifestyle factors also affect the severity of dyslipidemia. Studies that compare women with PCOS from the Mediterranean region and the United States highlight these differences. Additionally, within the US, African-American women with PCOS have better lipid profiles than Caucasian women with the syndrome.

According to Wild et al. [Wild RA et al. *Fertil Steril* 2011], women with PCOS should have a complete lipid profile, with reassessment every 2 years if normal and sooner if significant weight gain occurs (Table 2).

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Table 2. Screening Recommendations.

• Check complete lipid profile • If normal, reassess every 2 years (sooner if significant weight gain occurs)	LDL-C	<130 mg/dL (3.37 mmol/L) if no other risk factors
		<70-100 mg/dL (1.81-2.59 mmol/L) if metabolic syndrome
		<70 mg/dL (1.81 mmol/L) if T2DM, overt vascular, or renal disease
	Non-HDL-C	30 mg/dL (0.77 mmol/L) higher than LDL-C goal
	Triglycerides	<150 mg/dL

Besides modest increases in LDL-C, with a higher concentration of small, dense LDL-C, dyslipidemia in PCOS is also associated with a reduction in subclass HDL_2. This category contains more cholesterol molecules per unit of alipoprotein than HDL_3 and may put women with the syndrome at higher risk for coronary artery disease [Demacker PN et al. *Atherosclerosis* 1986]. Some studies also show decreases in apoA-1.

Lifestyle modification is first-line therapy, with low-fat diet and regular moderate-intensity exercise. Even without weight loss, moderate-intensity exercise (at least 30 minutes) a day can improve dyslipidemia in PCOS [Brown AJ et al. *Med Sci Sports Exerc* 2009].

Oral Contraceptives and CV Health

Written by Rita Buckley

Oral contraceptives (OCs) are the most commonly used form of birth control worldwide [Blackmore KM et al. *BMC Womens Health* 2011]. Estrogen and progestins have been used by millions of women as effective combined oral contraceptives (COCs). Their safety has been documented by years of follow-up, and serious adverse events that may be related to their use are rare in the young population that is exposed to these agents. Nonetheless, COCs are not risk-free. Regine Sitruk-Ware, MD, Center for Biomedical Research, Population Council, New York, New York, USA, discussed the risks, benefits, and strategic initiatives in the quest for safer and more effective OCs.

Although the balance between the benefits and liabilities of contraceptive steroids is generally positive, in particular when compared with the risks of pregnancy (especially in women with risk factors), cardiovascular (CV) and venous risks have been associated with surrogate markers, such as lipoprotein changes (eg, total cholesterol, total triglycerides, apolipoproteins, and very low low-density lipoprotein cholesterol) and coagulation factors (eg, factor VII, protein C, endogenous thrombin potential-based activated protein C resistance, and free protein S levels), that are induced by the synthetic steroids that are used in contraceptives. Thus, the dose of synthetic estrogen in ethinyl estradiol COC pills has been reduced to minimize the likelihood of ischemic stroke, myocardial infarction, and venous thromboembolism [Archer DF and Lasa IL. *J Womens Health* 2011].

Ethinyl estradiol (EE) exerts a stronger effect than natural estradiol (E2) on hepatic metabolism, including estrogen-dependent markers, such as liver proteins. EE's more powerful hepatic impact has been related to its 17α-ethinyl group, which prevents the inactivation of the molecule. Due to the strength of its activity, the administration of EE via a nonoral route does not prevent its impact on liver proteins [Sitruk-Ware R and Nath A. *Rev Endocr Metab Disord* 2011].

To circumvent the metabolic changes that are induced by EE, newer products that use more natural compounds, such as estradiol (E2) and estradiol valerate (E2V), have been introduced, as well as new formulations, including extended-cycle and continuous-use COC. They may offer improvements over their predecessors [Archer DF and Lasa IL. *J Womens Health* 2011].

Over the last 50 years, there has also been intense interest in the type of progestin that is used in COCs in an attempt to exploit novel properties and minimize adverse risks. The synthetic progestins that are used for contraception are structurally related either to testosterone (estranes and gonanes) or to progesterone (pregnanes and 19-norpregnanes).

Several new progestins that are closer to progesterone have been designed to bind more specifically to the progesterone receptor and to minimize side effects that are related to androgenic, estrogenic, or glucocorticoid receptor interactions. Dienogest, drospirenone, and the 19-norpregnanes (eg, Nestorone®, nomegestrol acetate, and trimegestone) have been combined with low-dose estrogen—EE, E2, or E2V. E2 and E2V induce fewer changes in coagulation markers than EE. However, the relevance to venous risk is not established. It is important, though, to note that the limited thrombotic risk that is observed with OC use is lower than risk during pregnancy

Risks and benefits of the newer progestins that are used in contraceptives depend upon molecular structure, the type and dose of estrogen that is used, and the route of administration. The lower impact of estradiol-based combinations on metabolic surrogate markers may result