Some PCOS Therapies Cut Cardiovascular Risk

Data on cardiometabolic risk in PCOS treatment show cyproterone acetate to be a 'bad actor.'

BY SHERRY BOSCHERT

SAN FRANCISCO — Metformin, some oral contraceptives, and possibly statins used to treat polycystic ovary syndrome can decrease the associated cardiovascular risk, while other oral contraceptives increase cardiovascular risk, studies suggest.

Dr. Andrea Dunaif summarized the data on cardiometabolic risk in the treatment of polycystic ovary syndrome at a meeting sponsored by the American Diabetes Association.

"We treat women with PCOS with insulin sensitizing drugs, but we also frequently treat them to regulate their menstrual periods with oral contraceptives," explained Dr. Dunaif, professor of endocrinology at Northwestern University, Chicago.

Previous evidence that estrogen therapy can increase triglyceride levels and that certain oral contraceptives can exacerbate insulin resistance raised concern that oral contraceptives may have adverse metabolic consequences in women with PCOS.

One study randomized 48 hirsute women with polycystic ovary syndrome to 6 months of treatment with a common oral contraceptive (Yasmin, or Yaz) containing 3 mg of drospirenone and 20 mcg of ethinyl estradiol or the same therapy plus either metformin 1,500 mg/day or cyproterone acetate (12.5 mg/day, 10 days per cycle), a progesterone used in other countries, but not in the United States (Fertil. Steril. 2009 Nov. 19 [doi:10.1016.j.fertnstert.2009.10.016]).

Insulin sensitivity improved in patients on Yasmin alone or Yasmin plus metformin but significantly worsened with Yasmin plus cyproterone acetate in the open-label trial, Dr. Dunaif explained at the meeting.

A separate open-label trial randomized 100 overweight women with PCOS to 6 months of oral therapy with 35 mcg of ethinyl estradiol and 2 mg of cyproterone acetate (a formulation known in Europe as Diane-35), a low-dose oral contraceptive regimen (20 mcg of ethinyl estradiol and 100 mcg of levonorgestrel) plus the antiandrogen drug spironolactone 50 mg b.i.d., or metformin 1 g b.i.d.

Each of the treatment arms showed similar, significant improvements in PCOS symptoms and menstrual cycle length.

Insulin resistance improved significantly in the metformin group, but insulin resistance and arterial stiffness worsened in the ethinyl estradiol/cyproterone acetate group (Diabetes Care 2007;30:471-8).

"Cyproterone acetate looks to be a bad actor in these studies," Dr. Dunaif said.

Several studies of metformin therapy in women with PCOS have shown that the drug can improve risk factors for cardiovascular disease such as endothelial dysfunction, she noted.

Twelve weeks of metformin significantly decreased arterial stiffness and improved endothelial function in 30 women with PCOS in a randomized, double-blind trial.

Compared with placebo, 12 weeks of metformin significantly decreased arterial stiffness and improved endothelial function in 30 women with polycystic ovary syndrome in a randomized, double-blind crossover trial (J. Clin. Endocrinol. Metab. 2010; 95:722-30).

Most recently, "statins are showing promise" in women with polycystic ovary syndrome by decreasing androgen levels and improving insulin sensitivity, Dr. Dunaif added.

One prospective trial randomized 136 women with polycystic ovary syndrome to treatment with simvastatin, metformin, or a combination of the two drugs for 3 months.

Improvements in insulin sensitivity were greater with simvastatin than with metformin or with the combination, while testosterone levels decreased significantly and comparably in all groups (J. Clin. Endocrinol. Metab. 2009;94:4938-45).

"This is something to look out for in the future, to see more data on the role of statins in the treatment of women with PCOS," she said.

Polycystic ovary syndrome has been associated with multiple cardiometabolic risk factors, including increased risk for type 2 diabetes. Indirect evidence suggests that the relative risk for myocardial infarction may be increased sevenfold in women with PCOS, Dr. Dunaif said.

Dr. Dunaif has been a consultant for Bristol-Myers Squibb Co., which makes metformin. ■

Removal of Ovaries Raises Heart, Osteoporosis, Cancer Risk

BY MICHELE G. SULLIVAN

Bilateral oophorectomy at the time of hysterectomy may do more harm than good, increasing the risk of death, cardiovascular disease, osteoporosis, and even lung cancer for a minimal trade-off in preventing ovarian cancer, according to an examination of available data.

An analysis of observational studies suggests that physicians and patients should fully discuss the issue before making a decision about which way to go at the time of hysterectomy.

"Prudence suggests that a detailed informed consent process covering the risks and benefits of oophorectomy and ovarian conservation should be conducted with women faced with this important decision," Dr. William H. Parker wrote (J. Min. Invas. Gyn. 2010;17:161-6).

Dr. Parker, of the John Wayne Cancer Institute at Saint John's Health Center, Santa Monica, Calif., plumbed numerous studies to examine the long-term health implications of premenopausal bilateral oophorectomy.

The surgery is usually recommended at the time of hysterectomy because it eliminates any later risk of ovarian cancer, which kills approximately 15,000 women every year in the United States.

However, Dr. Parker said, less than 1% of women who have a hysterectomy with ovarian conservation go on to develop ovarian cancer.

On the other hand, the Nurses' Health Study (NHS) and a recent Canadian study found that bilateral oophorectomy is associated with a 26% increased risk of lung cancer; the risk is even higher when patients don't take postsurgical estrogen. "Further studies are needed to confirm these unexpected findings," he wrote.

The NHS also provided information about all-cause mortality in women who had both ovaries removed.

Over a 24-year follow-up period, oophorectomy was associated with a 12% increase in all-cause mortality and significant increases in the risk of death from coronary artery disease (28%), lung cancer (31%), and all cancers (17%). The risk of death was highest for women who had the surgery before they turned 50; they had a 40% increase in the risk of all-cause mortality.

The NHS also found that women who had oophorectomy without estrogen replacement had twice the risk of myocardial infarction compared with age-matched premenopausal women. The surgery was associated with an 85% increase in the risk of stroke in women who didn't use hormones after menopause.

'Given that the data do not support widespread oophorectomy at the time of hysterectomy, it is problematic that so many patients have oophorectomy.'

Whether women used estrogens or not, oophorectomy was associated with a 28% increased risk of death from coronary artery disease in all women.

Dr. Parker found several studies that explored the relationship between oophorectomy and osteoporosis and hip fracture.

One study of 340 postmenopausal women who had the surgery (median age, 62 years) found that these women had 54% more osteoporotic fractures than women with intact ovaries. Two other studies, however, found no such association.

The Mayo Clinic Cohort Study of Oophorectomy and Aging, which followed more than 3,400 women for 25 years, found significant relationships between bilateral oophorectomy and Parkinson's disease (80% increased risk in women who had the surgery compared with women with intact ovaries), anxiety (greater than 200% increased risk), depression (54% increased risk), and cognitive impairment or dementia (70% increased risk).

Other studies suggest that bilateral oophorectomy throws women into a sudden, unnatural menopause that negatively affects mood, thought, memory, energy, libido, and sexual response.

Dr. Parker noted that a randomized trial is underway to examine the short-term associations of bilateral oophorectomy with cardiovascular, bone, and sexual health, as well as health-related quality of life.

"Until these and other data are available, removing the ovaries at the time of hysterectomy should be approached with caution," he said.

In an accompanying editorial, Dr. G. David Adamson of Palo Alto, Calif., agreed with Dr. Parker's assessment.

"Oophorectomy is not necessarily the wrong decision for many women, but assessment of these data leads to the conclusion that more women are undergoing oophorectomy than should be the case," he noted.

The reason for this remains unclear, Dr. Adamson wrote (J. Min. Invas. Gyn. 2010;17:141-2). "Given that the data do not support widespread oophorectomy at the time of hysterectomy, it is problematic that so many patients have oophorectomy.

"This implies that the data don't support ovarian conservation in most situations, which is not true, or that physicians are not giving patients a balanced rendition of the literature evidence, for whatever reason, or that women are choosing on their own to have oophorectomy, which does not seem likely," he noted.

Neither Dr. Parker nor Dr. Adamson reported any conflicts of interest. ■