PCOS in Bipolar Women on Valproate

BY JANE SALODOF MACNEIL
Southwest Bureau

Women taking valproate for bipolar disorder are at significantly increased risk of developing features of polycystic ovary syndrome, according to a published study of 230 female patients in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) trial.

Investigators reported finding new-onset oligomenorrhea with hyperandrogenism in 9 (10.5%) of 86 women treated with valproate (Biol. Psychiatry 2006;59:1078-86).

Only 2 (1.4%) of 144 women on lithium or an anticonvulsant other than valproate developed these symptoms of polycystic ovary syndrome (PCOS).

In all cases, oligomenorrhea began within a year of the patient's starting valproate use. The investigators calculated the relative risk as 7.5 for women with bipolar disorder using valproate as a mood stabilizer.

Dr. Hadine Joffe, the lead author, is director of endocrine studies in the perinatal and reproductive psychiatry clinical research program at Massachusetts General Hospital in Boston.

She and her colleagues recommended warning women of PCOS risk before starting them on valproate.

Further, women on valproate should be evaluated for PCOS if they develop menstrual irregularities with hyperandrogenic symptoms. Along with PCOS treatment, the investigators suggested that "it may also be appropriate to consider alternative mood stabilizers if PCOS features develop on valproate."

In an address at a psychiatric symposium sponsored by the University of Arizona, Dr. Gary Sachs, senior author and principal investigator of STEP-BD, emphasized the need for vigilance during the first year a patient is on valproate.

"Before you start women on valproate, you absolutely have to warn them this is a risk," Dr. Sachs, founder and director of the bipolar clinic and research program at Massachusetts General Hospital, told psychiatrists at the Santa Fe, N.M., symposium, which was also sponsored by the University of Texas Southwestern Medical Center at Dallas and the University of New Mexico.

Sponsored by the National Institute of Mental Health, STEP-BD enrolled 4,361 patients in the largest clinical study to date on the treatment of bipolar disorder. Dr. Sachs said that Abbott Laboratories, which sells valproate under the brand name Depakote, was among the drug companies that supported the trial.

"They were very confident the risk wasn't there," he said. "It turned out that was wrong. There really was a risk. The risks are there and published."

To study the relationship in a nonepileptic population, the investigators sought out women aged 18-45 years in STEP-BD who were taking at least one mood stabilizer for at least 3 months.

Participants who had discontinued another mood stabilizer within the previous 3 months were not included in the substudy.

Of the 300 identified eligible women, 14 patients previously diagnosed with PCOS and three others with disorders involving oligomenorrhea were among those excluded from the sample. All told, 230 women were available for the analysis.

Of the valproate users, 12 developed oligomenorrhea, and 9 of them also had hirsutism, according to the report.

Among all patients with oligomenorrhea, valproate users had fewer menstrual cycles (median of 5 vs. 8.5 per year) than did nonusers.

Some had elevated total or free testosterone, moderate to severe acne, or male-pattern alopecia.

The valproate users who developed oligomenorrhea with hyperandrogenism had a higher median body mass index (kg/m^2) of 36 vs. 26—as well as a higher median homeostatic model assessment for insulin resistance (3.1 vs. 1.7)—than did valproate users who did not take on PCOS features.

"Our study raises the possibility that increased body weight, insulin resistance, PCO morphology, younger age of first valproate use, and polypharmacy may predispose to the development of PCOS features on valproate," the investigators concluded. ■

PCOS Daughters Have Altered Folliculogenesis

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

BOSTON — The daughters of women with polycystic ovary syndrome have elevated levels of antimüllerian hormone from infancy to the perimenarche, suggesting the underpinnings of PCOS may be present long before clinical symptoms develop.

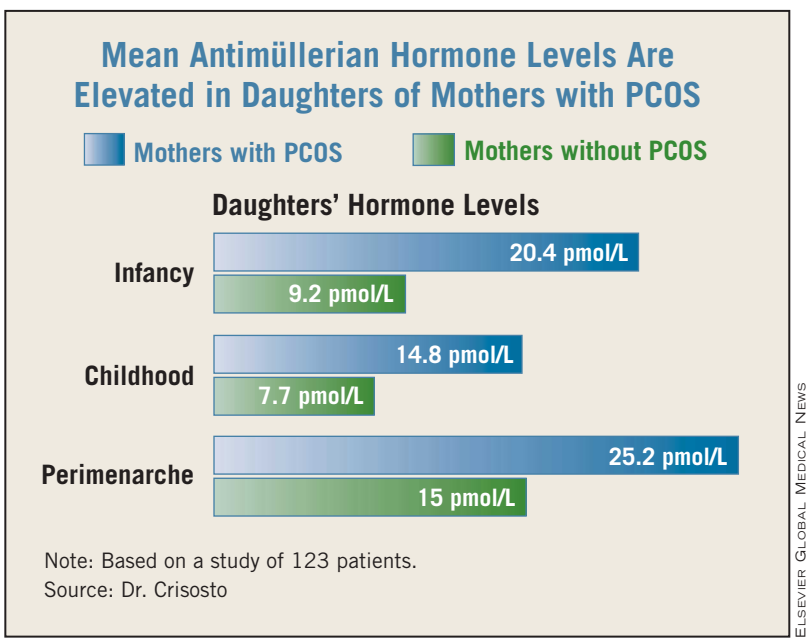
Folliculogenesis may be altered in these girls, said Dr. Nicolas Crisosto of the University of Chile, Santiago, at the annual meeting of the Androgen Excess Society. He compared anthropometric, hormonal, and metabolic parameters in 58 daughters of women with PCOS and in 65 daughters of control women at three time points: early infancy (2-3 months), childhood (4-7 years), and the perimenarchal period (8-15 years).

At each of the time points, the girls received a physical exam that included assessment of weight, height, waist-to-hip ratio, and sexual development. A panel of tests was performed for serum hormone levels (gonadotropins, sex steroids, sex hormone–binding globulin, and antimüllerian hormone). The girls in perimenarche also had a transabdominal ultrasound of their ovaries.

There were no significant anthropometric differences between the two groups at any of the exams, Dr. Crisosto said. Antimüllerian hormone levels were significantly increased in the PCOS group at all three stages. Free androgen level was elevated in the PCOS group at the perimenarchal exam.

The mean antimüllerian hormone levels in infants were 20.4 pmol/L in the girls born to women with PCOS vs. 9.2 pmol/L in girls born to women without PCOS. In childhood, the values for the two groups were 14.8 pmol/L and 7.7 pmol/L. In the perimenarchal period, the respective values were 25.2 pmol/L vs. 15.0 pmol/L. The results of the transabdominal ultrasound showed slightly higher ovarian volume (8.8 cm^3 vs. 6.8 cm^3) in the daughters of women with PCOS.

The findings, recently published in the Journal of Clinical Endocrinology and Metabolism (DOI:10.1210/jc.2005-2693), led the investigators to conclude that serum antimüllerian hormone levels seem to be correlated with the development of preantral and small antral follicles, from puberty to the end of reproductive life. Elevated serum antimüllerian hormone concentrations in daughters of PCOS women during childhood, at a time when the gonadal axis is relatively quiescent and other hormonal markers of ovarian function are very low, suggests that antimüllerian hormone may be used as an early marker of ovarian follicular development. ■



ELSEVIER GLOBAL MEDICAL NEWS

Glycemic Values May Be Low in Early Pregnancy

BY JEFF EVANS
Senior Writer

PRAGUE — Normative values for mean blood glucose levels during the first trimester may be much lower than what has been reported previously, Dr. Yariv Yogev reported at the 20th European Congress of Perinatal Medicine.

This lower-than-expected glycemic profile may suggest new targets for glycemic control during pregnancy complicated by diabetes, said Dr. Yogev of the department of obstetrics and gynecology at Rabin Medical Center, Petah Tikva, Israel.

Before this study, there was little information on the definition of normal blood glucose levels during pregnancy, especially during the first trimester, he said. Most of the previous information had come from "very limited studies" of 10-25 patients, mostly in the third trimester, who were placed on a strict diet and hospitalized to evaluate their glycemic profile.

The current study included 62 healthy, nondiabetic women in their first trimester of pregnancy (average of 10 weeks' gestation). The investigators fit the women with continuous glucose monitoring devices that measured their blood glucose levels every 5 minutes for 72 hours. Patients were asked not to modify their lifestyles or nutritional habits.

Because of the difficulty of performing continuous glucose monitoring in nondiabetic women with a normal pregnancy, the study did not involve a specific cohort of patients but instead mostly included doctors' wives, midwives, and nurses.

The women's overall mean blood glucose (79.3 mg/dL) and mean fasting blood glucose levels (75 mg/dL) were "much, much lower than was previously reported by others" Dr. Yogev said.

Mean nighttime blood glucose levels (66 mg/dL) "almost represented hypoglycemia," but such values may actually represent "normal physiology during the first trimester in nondiabetic patients," he said.

The postprandial glycemic profile of the women was the same after each meal. Mean blood glucose values started at 79 mg/dL just before a meal and rose to 106 mg/dL 60 minutes after the meal; it reached a high of 112 mg/dL 74 minutes after the meal. The values reached 99 mg/dL at 2 hours and 82 mg/dL at 3 hours.

The fasting and overall mean blood glucose levels were similar in 18 obese (defined as a body mass index greater than 27.3 kg/m^2) and 44 nonobese women. Compared with nonobese women, however, those who were obese had significantly higher mean preprandial blood glucose levels (73 mg/dL vs. 88 mg/dL) and significantly lower mean nighttime blood glucose concentrations (69 mg/dL vs. 60 mg/dL).

The obese patients were characterized by a higher postprandial peak value, a longer time interval to reach the postprandial peak value, and higher mean blood glucose levels during the 3 hours after each meal, Dr. Yogev said. ■