Metformin May Reverse PCOS in Some Girls

Two randomized trials show improvement in weight, lipid profiles of prepubertal patients.

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

NEW ORLEANS — Metformin appeared to reverse the features of polycystic ovary syndrome when given to prepubertal girls with a history of low birth weight and precocious puberty in two small randomized studies.

When metformin was withdrawn from these girls after puberty, however, the beneficial changes were reversed within 6 months, Lourdes Ibanez, M.D., said at the annual meeting of the Endocrine Society.

Dr. Ibanez of the University of Barcelona, Spain, reported on two small randomized studies of metformin treatment in girls with a combined history of low birth weight and precocious puberty. The first study randomized 33 prepubertal girls to either no therapy or to 425 mg of metformin daily for 6 months. The second was a randomized crossover trial: 24 postpubertal girls received either no therapy or 850 mg metformin daily for 12 months, after which the groups switched treatments for 6 months.

In the first study, all girls were 8 years old and prepubertal. Birth weight averaged 2.4 kg and BMI, 18.5. All had precocious puberty secondary to exaggerated adrenarche, high circulating levels of interleukin-6 and dehydroepiandrosterone sulfate (DHEAS), and low adiponectin.

In untreated girls, these parameters continued to diverge from normal levels during the 6-month study, Dr. Ibanez said. Their DHEAS levels rose from about 105 g/dL to 115 g/dL; interleukin-6 rose from about 1,050 femtogram/mL to 1,100 fg/mL, and adiponectin decreased from about 10.5 g/mL to 9 g/mL. The girls continued to increase their abdominal fat over the 6 months, gaining an average of about 300 g.

All these parameters improved in the treated girls, Dr. Ibanez said. In this group, the DHEAS levels remained stable, the interleukin-6 level dropped from about 1,000 fg/mL to abut 800 fg/mL, and the adiponectin increased from about 10 g/mL to about 11 g/mL. Abdominal fat decreased in these girls by an average of 300 g.

The crossover trial contained 24 girls who were 6-12 months beyond menarche at the study outset. These girls were also low birth weight (average 2.4 kg). Their average age was 12 years and their average BMI was 21.

All of these girls showed precursor features of polycystic ovary syndrome (PCOS): They had hyperinsulinemia, hyperandrogenemia, increased truncal fat, decreased lean body mass, and dyslipidemia

The girls were randomized to either no treatment or 850 mg of metformin daily for 12 months. At the end of that period, the treated girls stopped therapy, and the untreated girls began therapy.

After 12 months, the untreated girls experienced increases in markers associated with incipient PCOS, Dr. Ibanez said. Their BMI increased from 21 to 21.6; their insulin sensitivity declined; and levels of testosterone, androstenedione, and DHEAS all increased. Their LDL cholesterol and triglycerides increased, while their HDL cholesterol decreased. The girls gained about 2 kg of truncal fat and lost about 1 kg of lean body mass.

Although not fully normalized by the end of 12 moths, these parameters all improved in the treated girls. BMI stayed stable, but the girls lost 0.5 kg of truncal fat and gained about 2 kg of lean body mass. Their insulin sensitivity increased, while their testosterone and androstenedione levels decreased. There was no significant effect on DHEAS.

The girls' lipid levels improved as well, with decreases in LDL cholesterol and triglycerides and an increase in HDL cholesterol.

After 12 months, the groups switched treatments. Within 6 months, the girls who stopped therapy lost almost all of their improvements in weight, hormones, and lipids, while the girls who began therapy made significant gains in these areas.

After 6 months of stopping metformin, the previously treated girls experienced a drop in insulin sensitivity (100% to about 65%) and adiponectin (from 14 g/mL to 12 g/mL) and an increase in interleukin-6 (from about 900 fg/mL to 1,300 fg/mL).

After 6 months of treatment, the previously untreated girls experienced an increase in insulin sensitivity (from 60% to about 85%) and adiponectin (from about 12 fg/mL to 13 fg/mL), and a decrease in interleukin-6 (from about 1,400 fg/mL to about 900 fg/mL). ■

Estrogen Used to Suppress Growth in Adolescence Linked to Later Infertility

BY CHRISTINE KILGORE
Contributing Writer

High-dose estrogen therapy for tall stature in adolescent girls appears to reduce fertility later in life, according to a retrospective cohort study.

Estrogen has been used for years in the United States, Europe, and Australia to limit the adult height of tall girls, but little has been known about its long-term effects, said Alison Venn, Ph.D., of the Menzies Research Institute at the University of Tasmania in Australia, and associates.

Medical record reviews and interviews with women who were assessed for height from 1959 on showed that women who were treated with estrogen as growth-suppressant therapy were significantly more likely to have experienced infertility and were more than twice as likely to have ever taken fertility drugs than were women who were not treated (Lancet 2004;364:1513-8).

Women treated with estrogen as a growth suppressant were more likely to have experienced infertility and to have taken fertility drugs.

The number of girls treated in recent years is lower than in the 1960s to 1980s, the investigators said. However, growth-suppressant therapy is still prescribed. A survey of U.S. pediatric endocrinologists published in 2002 found that 96 (23%) of 411 respondents had treated tall girls in the preceding 5 years. Most said they had treated fewer than five girls.

The practice is based on the knowledge that in healthy pubertal development, estrogen leads to the epiphyseal fusion of the long bones. There have been no randomized controlled trials of treatment effectiveness, but height reductions of 2-10 cm have been reported, the investigators said.

Study participants were identified mainly from the medical records of Australian pediatric endocrinologists who assessed tall girls from 1959 to 1993; other participants self-referred in response to publicity about the study.

A cohort of 1,432 eligible women was identified; 1,243 were located and invited to participate. Of the women who were contacted, 780 completed interviews.

Women who had been treated (371 women, mean age of 40 years) and those who were assessed but not treated (409 women, mean age of 38 years) were similar in terms of socioeconomic status, sexual history, and other characteristics.

The type of estrogen treatment was unknown for 25 women, but in all other cases the treated women had been prescribed diethylstilbestrol (DES) or ethinyl estradiol; DES was in use before 1971.

Women treated with DES and ethinyl estradiol were similar in terms of their age at the start of treatment (approximately 13 years), the estimated mature height predicted before treatment (approximately 182 cm), and the duration of treatment (26 months for DES, 24 months for ethinyl estradiol).

Treated women were 80% more likely to have tried for at least 12 months to become pregnant without success; 36% of treated women and 19% of untreated women reported such difficulties.

Treated women were also 80% more likely to have ever seen a doctor because of trouble becoming pregnant, and they were more than twice as likely to have ever taken fertility drugs; 18% of treated women and 8% of untreated women reported taking the drugs.

An analysis of the reported time to first pregnancy showed that the treated group was 40% less likely to conceive in any given menstrual cycle of unprotected intercourse.

Investigators found the same associations when self-referred women were excluded from the analyses. ■

Growth Hormone Increases Adults' Exercise Capacity

NEW ORLEANS — Physiologic doses of growth hormone can increase exercise capacity in adults with growth hormone deficiency, as well as improve their body composition and lipid levels, Jostein Hallen, M.D., said at the annual meeting of the Endocrine Society.

The 7% increase in exercise capacity that he found in his placebo-controlled study "is similar to what you would see if you put a similar population on a training program," said Dr. Hallen of Norwegian University of Sport and Physical Education, Oslo.

The small study included 55 patients with adult-onset growth hormone deficiency; 96% had multiple pituitary hormone deficiencies; 4% had isolated growth hormone deficiency. Mean body mass index for men was 29; the mean BMI for women was 26. Average subject age was 48.5 years.

As many patients were already taking growth hormone, the study began with a 4-month washout period. Then, subjects were randomized to 9 months of placebo or growth hormone. Subjects' therapy was titrated to acheive an insulin-like growth factor–1 (IGF-1) level within the upper normal range for their age and sex. Final mean daily dose was 0.4 mg for men and 0.6 mg for women.

At outset, subject exercise capacity was determined by treadmill, increased until exhaustion occurred. Body composition was measured by dual-energy x-ray absorptiometry. Three quality-of-life scales were completed.

In men who took growth hormone, the mean IGF-1 levels increased from 95 mg/L to 216 mg/L; in women, the mean level increased from 68 mg/L to 186 mg/L. Subjects in the study group lost an average of 1.9 kg of fat and gained 1.8 kg of lean body mass. Their total and LDL cholesterol levels both dropped an average of 0.5 mmol/L.

Compared with placebo, growth hormone treatment increased the subjects' maximal oxygen uptake by 6%. Endurance increased by 7% over baseline in the study group.

There were no significant effects on quality of life, Dr. Hallen said, who is an investigator for Pfizer Inc. The company funded the study and supplied the drug.

—Michele G. Sullivan