Exenatide Plus Metformin Aids Ovulation in PCOS

BY MIRIAM E. TUCKER
Senior Writer

ROME — Treatment of polycystic ovary syndrome with exenatide plus metformin was more effective than either medication alone in improving menstrual cycle frequency and in ameliorating hormonal and metabolic derangements, a study has found.

The study findings were presented at the annual meeting of the European Association for the Study of Diabetes by Dr. Ted Okerson of Amylin Pharmaceuticals Inc. on behalf of the scheduled presenter, Dr. Rajat Bhushan of the Metabolic Center of Louisiana Research Foundation, Baton Rouge, who was unable to attend the meeting because of a hurricane. Dr. Karen Elkind-Hirsch of the same institution was the principal author of the study, which was published in the Journal of Clinical Endocrinology and Metabolism (2008;93: 2670-8).

Metformin has been shown to reduce insulin resistance and androgen levels while increasing ovulation in women with polycystic ovary syndrome (PCOS). However, metformin does not alter insulin secretion. Exenatide (Byetta), used to treat type 2 diabetes, has been shown to restore first- and second-phase insulin secretion, which is attenuated in women with PCOS, as well as promote weight loss, thereby potentially further improving insulin sensitivity, Dr. Okerson said.

An open-label, prospective 24-week pilot study of 60 obese oligo-ovulatory women with PCOS was funded by a grant from Amylin Pharmaceuticals and Eli Lilly & Co. In the study, 40 white and 20 African American women with PCOS were randomized to receive either 1,000 mg metformin twice daily, exenatide 10 mcg twice daily, or a combination of the two, for 24 weeks. All were aged 18-40, with a body mass index above 27 kg/m^2 and six or fewer menses per year. Forty-two patients (14 in each group) completed the study, with equal racial distribution across groups.

Menstrual cycle frequency, the primary study end point, was significantly increased in all treatment groups at 24 weeks and to a significantly greater degree with the combination, compared with metformin alone. The proportion of normal cycles in the group increased from a mean of 22% at baseline to 57% with exenatide alone, from 21% to 49% with metformin alone, and from 29% to 83% with both drugs. Ovulatory rates also improved with all three regimens, but significantly more so with the combination. Ovulation occurred in 12 of the combination patients (86%), compared with 7 who received exenatide alone (50%) and 4 (29%) with metformin alone.

Body weight changes were significant in both groups receiving exenatide, but not in those receiving metformin alone. At 24 weeks, mean weight loss was 6 kg in the combination group and 3.2 kg with exenatide alone, vs. just 1.6 kg with metformin alone. Similar reductions were seen in body mass index. Abdominal girth diminished slightly in both exenatide groups but increased slightly between weeks 12 and 24 among the metformin-alone patients, Dr. Okerson reported.

Total testosterone was significantly decreased from baseline in all treatment groups, by 10.2 ng/dL with exenatide alone, 3.6 ng/dL with metformin alone, and 18.4 ng/dL with the combination. The free androgen index was significantly more reduced with the combination, compared with metformin alone but not compared with exenatide alone. Levels of sex hormone–binding globulin were increased, but not significantly, with all treatments, while levels of dehydroepiandrosterone sulfate and thyroid-stimulating hormone were not significantly altered in any group.

Insulin sensitivity improved significantly with all treatments, and was significantly higher in the combination group than in the metformin group at 24 weeks. After therapy, the calculated mean insulin secretion sensitivity index was 516 with combination therapy, 395 with exenatide alone, and 232 with metformin alone. Total cholesterol and triglycerides decreased significantly with combination therapy vs. metformin monotherapy, which did not consistently improve those levels, while HDL and LDL cholesterol levels did not change significantly with treatment. Adiponectin levels increased significantly with all treatments, while other inflammatory markers did not change. ■

Testosterone Patch Boosts Sex In Women, but Safety Is Issue

BY MARY ANN MOON
Contributing Writer

The testosterone patch improves sexual function in postmenopausal women who have hypoactive sexual desire disorder, but the patch's long-term safety needs to be studied, according to a report.

The improvement in frequency of satisfying sexual episodes was "numerically modest," at 1.4 more such episodes per month, but this amount has been shown to be clinically meaningful in previous studies, said Dr. Susan R. Davis of Monash University, Prahran, Victoria, Australia, and her associates.

This is the first large-scale, phase III clinical trial of testosterone therapy that involved postmenopausal women who were not taking concomitant estrogen.

Testosterone without concomitant estrogen may have adverse effects on the breast and endometrium.

In this study, four cases of breast cancer occurred in women on active treatment, compared with no cases in women taking placebo, and vaginal bleeding also was significantly more common with active treatment.

The study involved women aged 20-70 years who had surgically induced menopause of at least 1 year's duration, and women aged 40-70 years who had natural menopause of at least 2 years' duration. The women all had hypoactive sexual desire and were treated at 65 medical centers in the United States, Canada, Australia, the United Kingdom, and Sweden between 2004 and 2006 (N. Engl. J. Med. 2008;359:2005-17).

The study was sponsored by Procter & Gamble Pharmaceuticals Inc., which also was involved in study design and data collection, and conducted the data analysis. Procter & Gamble makes Intrinsa, a testosterone patch that has been approved by the European Medicines Agency for treatment of hypoactive sexual desire.

A Food and Drug Administration advisory committee recommended against approval of the drug for the U.S. market in 2004.

In the study, 814 women were randomly assigned to use a 150-mcg testosterone patch, a 300-mcg testosterone patch, or a placebo patch every day for 1 year.

The efficacy analysis was performed at 24 weeks, after which the effect of testosterone tends to plateau; the safety analysis was performed at 1 year. A total of 71% of the women completed 24 weeks, and 57% completed the full year.

Compared with the placebo group, both groups on active treatment reported significant increases in sexual desire and frequency of satisfying sexual episodes, as well as decreases in personal distress related to sexual function.

The overall incidence of adverse effects was similar among the three groups.

The most common reasons for withdrawal from the study were patch-site reactions and androgenic events, principally the growth of facial hair.

Dr. Davis reports receiving consulting or lecture fees, and grant support, from Procter & Gamble Pharmaceuticals and other firms. ■

Metformin No Aid to IVF Success In Polycystic Ovaries Sans PCOS

BY SHARON WORCESTER
Southeast Bureau

SAN FRANCISCO — Metformin treatment before and during in vitro fertilization does not improve the chance of pregnancy in women with ovaries of polycystic morphology who do not have anovulation or hyperandrogenism, according to a study of 134 women.

Study participants treated with metformin before oocyte collection were no more likely to become pregnant or have a clinical pregnancy than were patients given placebo, Dr. Alex G. Swanton of John Radcliffe Hospital in Oxford, England said at the annual meeting of the American Society for Reproductive Medicine.

In the multicenter study, women with ovaries of polycystic morphology but no other manifestations of polycystic ovary syndrome (PCOS), such as anovulation or hyperandrogenism, were randomized to receive 1.5 g metformin (62 patients) or placebo (62 patients) starting 7 weeks before oocyte retrieval. The women were younger than 39 years and undergoing their first or second cycle of IVF (with or without intracytoplasmic sperm injection). IVF was performed using the long protocol. One 500-mg capsule of metformin was taken every morning for 1 week, increasing to two capsules daily and then three daily until the day of oocyte collection.

Polycystic ovaries were diagnosed by the ultrasound presence of at least 12 follicles measuring 2-9 mm in diameter and/or increased ovarian volume greater than 10 mL in at least one ovary. Severe ovarian hyperstimulation syndrome was defined as the presence of clinical ascites and hemoconcentration requiring hospital admission.

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The study relates to 33% of fertility clinic patients, Dr. Alex G. Swanton noted.

There were no statistically significant differences between the two groups in baseline characteristics.

The study was prompted by several factors. "Firstly, polycystic ovaries are very common, affecting about 33% of patients attending fertility clinics," Dr. Swanton said in an interview. "Secondly, women with polycystic ovaries, who have regular cycles and no symptoms of acne or hirsutism (that is, no features of polycystic ovary syndrome) may have underlying biochemical abnormalities similar to [those of] women with polycystic ovary syndrome. Thirdly, there is good evidence that women with polycystic ovary syndrome undergoing IVF treatment benefit from metformin treatment, as it increases pregnancy rates and decreases ovarian hyperstimulation syndrome rates." ■