Effect of sibutramine on weight reduction in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial

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Objective: To examine the efficacy of sibutramine together with brief lifestyle modification for weight reduction in obese women with polycystic ovary syndrome (PCOS).
Design: Investigator-initiated, multicenter, double-blind, randomized, parallel-group clinical trial.
Setting: Departments of Obstetrics and Gynecology in primary care, referral centers, and private practice.
Patient(s): Forty-two patients with confirmed PCOS were included in the study, and 34 patients completed the study.
Intervention: Sibutramine 15 mg once daily together with brief lifestyle modification was compare with placebo together with brief lifestyle modification.
Main Outcome Measure(s): The primary endpoint was to assess weight loss. Secondary endpoints included the efficacy of sibutramine for treatment of menstrual pattern and cardiovascular risk factors.
Result(s): After 6 months the sibutramine group had lost 7.8 ± 5.1 kg compared with a weight loss of 2.8 ± 6.2 kg in the placebo group. Sibutramine treatment resulted in significant decreases in apolipoprotein B, apolipoprotein B/apolipoprotein A ratio, triglycerides, and cystatin C levels.
Conclusion(s): Sibutramine in combination with lifestyle intervention results in significant weight reduction in obese patients with PCOS. In addition to the weight loss, sibutramine seems to have beneficial effects on metabolic and cardiovascular risk factors. (Fertil Steril® 2008;89:1221–8. ©2008 by American Society for Reproductive Medicine.)

Key Words: Polycystic ovary syndrome, sibutramine, randomized clinical trial, obesity

Polycystic ovary syndrome (PCOS) is a complex and heterogeneous clinical condition characterized by hyperandrogenism and chronic oligo-ovulation or anovulation. It is estimated that approximately 6.5% of fertile women have PCOS, although no precise determinations have been possible to obtain (1–3).

Long-term follow-up studies of women 50 to 59 years old with a diagnosis of PCOS (Stein-Leventhal syndrome) have indicated that these women more often have type 2 diabetes mellitus and hypertension and that they have an increased risk of the development of myocardial infarction during the menopause (4, 5). Likewise, irregular menses, presumably most likely due to PCOS, are associated with increased risk of fatal coronary heart disease (6).

Already at a young age, the prevalence of impaired glucose tolerance and type 2 diabetes mellitus is higher than expected in women with PCOS (5, 7, 8). During their reproductive years, these women also have an increased risk of subclinical atherosclerosis (9–12) together with a number of independent risk factors for cardiovascular disease such as obesity (13), changes in lipid profile (14–16), decreased fibrinolytic capacity (17, 18), and a labile control of blood pressure (19).

Weight reduction is the primary target for intervention in obese patients with PCOS and, although difficult to achieve in many patients, its beneficial effects have been documented in a number of studies (20, 21). Metformin, which is one of the most widely used drugs for treatment of PCOS, has been proved to have positive effects on a number of metabolic parameters such as insulin resistance, fasting insulin levels, blood pressure, and low-density lipoprotein (LDL) levels (22). However, the effect of metformin as a weight-reducing agent in obese subjects with PCOS has been discouraging (22–24). The negative results from recent randomized

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clinical trials on metformin treatment in patients with PCOS, together with the need for weight reduction in obese patients with PCOS, point to the need to evaluate other antiobesity drugs in this group of patients.

Sibutramine is a Food and Drug Administration–approved antiobesity drug that acts by inhibiting the reuptake of serotonin and norepinephrine, thus increasing satiety and adrenergic activity (25). Compared with placebo, sibutramine induces a more pronounced body weight reduction, ranging between 5% and 10%, in obese patients (26–30). As with other antiobesity drugs, the combined effect of lifestyle modification and sibutramine treatment is more effective than sibutramine treatment alone (26). Sibutramine previously has been evaluated in two open-label studies in patients with PCOS with promising results (31, 32).

The aim of this prospective, double-blind, multicenter, placebo-controlled study was to examine the efficacy of sibutramine together with brief lifestyle modification in overweight and obese women with PCOS. The primary endpoint was to assess weight loss, whereas secondary endpoints included the efficacy of sibutramine for treatment of menstrual pattern and cardiovascular risk factors.

MATERIALS AND METHODS

Patients

The study was a multicenter study involving the gynecologic departments at Sunderby Hospital, Umeå University Hospital, Uppsala University Hospital, Läkarhuset Björnen, Piteå, and Lund University Hospital in Sweden. The study was conducted during 2005.

Fifty patients with PCOS were screened for inclusion in the study. Subjects were included among patients seeking care for oligomenorrhea and/or hirsutism at the outpatient wards of the participating clinics and from newspaper advertisement. Of these, eight patients did not fulfill the inclusion or exclusion criteria for participation in the study. Hence, 42 patients with confirmed PCOS were included in the study.

Polycystic ovary syndrome was defined according to the Rotterdam criteria (33). Two of the following three features had to be present for the PCOS diagnosis: [1] oligomenorrhea with eight or fewer menstruations in the previous 12 months or amenorrhea; [2] clinical and/or biochemical signs of hyperandrogenism such as T >2.7 nmol/L, elevated DHEAS, free androgen index $\geq$1.0, or hirsutism (>7 on the Ferriman and Gallway scale); and [3] polycystic ovaries on ultrasound examination (>12 follicles 2 to 9 mm in diameter and/or increased ovarian volume (>10 mL). Diagnosis of PCOS also implied that no evidence of thyroid disease (normal serum-TSH level), adrenocortical dysfunction (normal 17-hydroxyprogesterone level), or hyperprolactinemia (prolactin <30 μg/mL) was present. In addition, subjects had normal fasting levels of glucose, creatinine, aspartate aminotransferase, and alanine aminotransferase before inclusion.

Inclusion criteria for the study was confirmed PCOS, age 18 to 40 years, body mass index (BMI) >27 kg/m^2, and consent to participation after written and oral information. The limit for BMI was chosen on the basis of prior studies indicating increased insulin resistance already at BMI 27 kg/m^2 in patients with PCOS (34).

Exclusion criteria for the study were obesity due to organic disorder, psychiatric disorder in need of medical treatment, pregnancy or lactation, use of hormonal treatments 6 months before inclusion in the study (oral contraceptives, gestagens, ovulatory stimulants, antidiabetic agents [including metformin], cortisone, antiandrogens), history of serious eating disorder (anorexia nervosa and/or bulimia nervosa), use of drugs with a central nervous system effect later than 2 weeks before study start (antidepressants, benzodiazepines, and antipsychotic drugs), history of coronary heart disease, heart failure, arrhythmia, tachycardia, peripheral arterial disease, history of stroke or a transient ischemic attack, uncontrolled hypertension (>140/90 mm Hg), severe renal or hepatic insufficiency, impaired liver function, Gilles de la Tourette's syndrome, pheochromocytoma, glaucoma, and abuse of drugs (illegal or otherwise) or alcohol.

The patients gave a written informed consent and the Independent Ethical Review Board at Uppsala University, Sweden, and the Medical Products Agency of Sweden approved the study.

Protocol

The study was an investigator-initiated, multicenter, double-blind, randomized, parallel-group clinical trial during which subjects were treated with either sibutramine 15 mg once daily (Abbott Scandinavia, Sollentuna, Sweden) or placebo (Apoteket Production and Laboratories, Tillverkningsenheten, Stockholm, Sweden) during 24 weeks. Apoteksbolaget Production and Laboratories (the National Corporation of Swedish Pharmacies) in Stockholm prepared identical-looking capsules containing either sibutramine or placebo. The packing and randomization were done by Apoteket Production and Laboratories, Stockholm, Sweden. During the study, the subjects and study personnel were not informed about which treatment the patient received. Randomization codes were kept secret at the pharmacy at Uppsala University Hospital until completion of the study. Compliance was assessed by counting the remaining capsules at each visit.

Study visits took place at baseline and at weeks 2, 6, 10, 14, 18, 22, and 24. At each visit weight, blood pressure, and heart rate were assessed, as well as reports on adverse effects from treatment and concomitant medication. Lifestyle modification advice was given at the start of the study, but diet and physical activity were discussed with the patient at each visit as well. Urinary hCG was measured in each subject before the start of the study, at week 14, and at the end of the study to exclude pregnancy. Every woman was also advised to use nonhormonal contraception throughout the study.