Original Study

Effect of Weight Loss on Menstrual Function in Adolescents with Polycystic Ovary Syndrome

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A B S T R A C T

Study Objective: To compare the effects of a hypocaloric low-fat diet with those of a very low carbohydrate diet on body mass index (BMI), waist circumference (WC), and menstrual function in overweight adolescent females with polycystic ovary syndrome (PCOS).
Design: Randomized pilot trial of two diets in a prospective, 12-week study.
Setting: A hospital-based, academic adolescent medicine division.
Participants: 24 females, age 12-22 years (mean 15.8 $\pm$ 2.2), with PCOS and a BMI above the 85th percentile for age (mean 35.7 $\pm$ 6.0 kg/m^2).
Interventions: Nutrition counseling was given biweekly, and dietary compliance, menstrual history, and weight were recorded. WC was measured at the beginning and end of the study.
Main Outcome Measures: Changes in weight, BMI, WC, and improvement in menstrual function over the course of the study period.
Results: 16 participants completed the study. 12 completers menstruated during the study period, 8 with regularity. The number of periods over 3 months increased from 0.6 $\pm$ 0.6 pre-treatment to 1.6 $\pm$ 1.3 post-treatment ($P = 0.003$). Overall, weight loss averaged 6.5% ($P < 0.0001$) and the WC decreased by an average of 5.7 $\pm$ 7.7 cm ($P = 0.01$). Those who lost weight were 3.4 times more likely to have improved menstrual function ($P = 0.001$). There were no statistically significant differences between the two groups.
Conclusions: Weight loss is feasible in adolescents with PCOS and results in significant improvements in BMI, WC, and menstrual function. Weight management may be preferable as first-line treatment in adolescents, because it targets both the menstrual dysfunction and risk factors for long-term morbidity associated with PCOS.
Key Words: Polycystic ovary syndrome, Adolescents, Lifestyle modification, Weight loss, Treatment

Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous disorder, affecting 5–10% of women of reproductive age, and it often presents in the perimenarcheal period.[1] The characteristic features of this syndrome include biochemical and/or clinical hyperandrogenism (hirsutism, acne) and chronic anovulation leading to menstrual disturbances, e.g. oligo/amenorrhea, dysfunctional uterine bleeding, and often infertility. There are also associated metabolic abnormalities, including obesity, insulin resistance, and dyslipidemia, thereby also conveying risk for the early development of associated cardiovascular disease, independent of obesity. However, none of these are included in the most recent set of diagnostic criteria, known as the "Rotterdam" criteria.[1,2] Obesity, most notably in a truncal distribution, is seen in up to 50% of adult women with the syndrome and probably impacts the degree of insulin resistance seen, as well as the degree of reproductive dysfunction present.[3] Insulin resistance has been documented as a highly prevalent feature of the disorder for almost 30 years, and is seen in both obese and lean patients. It has been theorized that insulin resistance plays an early and central role in the pathogenesis of the ovarian and reproductive dysfunction in PCOS.[1] In one large prevalence study, approximately 40% of women with PCOS had glucose intolerance, including 7.5% with type 2 diabetes.[4] It has been shown that up to 30% of teenage girls with PCOS already have impaired glucose tolerance.[5] The progression toward type 2 diabetes begins at an early age, making adolescence the optimal time to intervene.[6]

Although there are no published guidelines for the treatment of PCOS in adolescents, many consider the use of combination oral contraceptives (COCs) to be first-line therapy. Although these can induce cyclical bleeding and possibly reduce some of the signs of androgen excess, they may potentially aggravate the associated metabolic abnormalities, including obesity, insulin resistance, and dyslipidemia, thereby making them a poor long-term solution. Insulin-sensitizing medications, e.g. metformin, have been studied and used in adolescents with PCOS as well, but they have had variable results.[7–14] They are also not without side effects, such as gastrointestinal disturbance, which is common, and rarely, lactic acidosis. Additionally, metformin is not approved by the Food and Drug Administration for this indication. Lifestyle modification, particularly targeted at weight loss, provides a nonpharmacologic mode of treatment, which may be especially appealing for adolescents. Overall, the existing evidence on lifestyle

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modification in adults with PCOS suggests that modest weight loss, even as little as 5% from baseline, can produce positive effects on hyperinsulinemia and hyperandrogenemia, as well as improve menstrual function.[15–26] However, many of these studies combined dietary treatment with metformin and used pregnancy as an outcome measure. There are no known studies to date in adolescents using lifestyle modification alone to treat PCOS.

In the past decade or so, there has been renewed popularity in the use of low carbohydrate (LC) and very-low carbohydrate diets (e.g., Atkins, South Beach, Sugar Busters) by the general public. These types of diets have also been studied for various medical conditions.[27] A prior study conducted in this division demonstrated the effectiveness, safety, and acceptability of a LC diet in obese adolescents, without underlying medical pathology.[28] We conducted a similar randomized, controlled, prospective pilot trial in overweight and obese adolescents with PCOS. There are theoretical advantages to a LC diet, including decreased stimulation of insulin secretion, which could prove beneficial in reducing baseline insulin resistance in PCOS.

The purpose of this study was to compare the effects of lifestyle modification on menstrual function in overweight adolescents with PCOS. Furthermore, we sought to compare a hypocaloric National Cholesterol Education Program (NCEP) II diet (LF) with a very low-carbohydrate, high protein diet without fat or caloric restriction, designed to minimize insulin response (LC).[28] We hypothesized that weight loss would improve menstrual function and that the LC diet would be superior to the LF diet for weight loss, as well as improvement in BMI, WC, and menstrual function.

Materials and Methods

Participants

Participants were recruited from a population of patients referred for menstrual dysfunction to the Division of Adolescent Medicine. The inclusion criteria were: females between the ages of 12 and 22 years, at least two years postmenarche, diagnosed with PCOS clinically and/or biochemically, and with a body mass index (BMI) $>85^{th}$ percentile for age, which is considered overweight.[29] Diagnosis of PCOS was based on the complaint of oligomenorrhea or amenorrhea (fewer than six menstrual cycles over the one year preceding enrollment) combined with laboratory analysis consistent with hyperandrogenemia and/or features of androgen excess, e.g. hirsutism based on the Ferriman-Gallwey system[30] and acne. Exclusion criteria were: use of medications known to cause menstrual dysfunction or to affect insulin secretion or action (e.g., hormonal contraception, systemic steroids, antipsychotics, valproic acid); endocrinopathies, including non-classic 21-hydroxylase deficiency, thyroid dysfunction, Cushing's syndrome, hyperprolactinemia, and diabetes mellitus (type 1 or type 2); androgen-producing tumors; renal or hepatic disease; and pregnancy. Potential participants under treatment with COCs were enrolled after a two-month washout period.

Intervention

After obtaining informed written consent, as well as assent from those under 18 years of age, 24 participants were randomized to one of two diet treatment groups (LC or LF) for a 12 week pilot trial. The participants in the LC group were prescribed a diet that consisted of a daily intake of no more than 20 g/day of carbohydrate and an ad libitum intake of protein, fat, and energy for the initial two weeks. For weeks 3 through 12, carbohydrate was increased to 40 g daily by adding additional low glycemic index foods, such as nuts, fruits, and whole grains. This dietary plan was designed to minimize insulin response. Participants were advised to consume a minimum fluid intake of 50 oz per day, a multivitamin supplement containing 100% of the recommended dietary allowances for age, and a potassium chloride table salt substitute to avoid hypokalemia. Fiber supplements were prescribed if symptoms of constipation occurred.

The LF group was instructed to eat a hypocaloric diet consisting of less than 40 g per day of fat, with five servings of starch per day and an ad libitum intake of fat-free dairy foods, fruits, and vegetables for 12 weeks. A serving of starch was defined as a portion containing 15 g of carbohydrate per serving, and the consumption of whole grains was encouraged. Juices and sweetened beverages were omitted from the meal plan. A multivitamin supplement containing 100% of the recommended dietary allowances of vitamins and minerals for age and sex was also recommended.

Both diets shared a "stoplight" meal plan design with three categories of foods, as suggested by Epstein and Squires.[31] The contents of the food categories were designed by the investigators to correspond to the desired macronutrient content of each respective meal plan. Both groups were instructed to monitor urinary ketones daily with urine reagent strips, and these logs were reviewed biweekly with an investigator. Subjects in both groups were recommended to perform 30 minutes of aerobic exercise three times per week, although they were not required to record this activity.

Measures

At the first study visit, assessment included: menstrual history, diet history, measurements of seated blood pressure (BP), height, weight, BMI calculation, measurement of waist circumference (WC), and Ferriman-Gallwey score. Dietary compliance was monitored biweekly by one of the Registered Dietitians in our division, with review of self-reported consecutive three-day interval diet histories, as well as 24-hour recall, which is valid as a clinical tool.[32] In addition, urinary ketone logs were reviewed as another indirect measure of dietary compliance. Height, weight, and BP were recorded by a physician at each visit, as well as assessment of interval menstrual bleeding. Weights were obtained on a tared triple-beam balance scale and recorded to the nearest 0.1 kg, and heights were measured using a fixed stadiometer with right angle headpiece and recorded to the nearest tenth of a cm, with subjects gowned and