Treatment of obesity in polycystic ovary syndrome: a position statement of the Androgen Excess and Polycystic Ovary Syndrome Society

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Objective: To summarize current evidence on lifestyle management (dietary, exercise, or behavioral interventions) of obesity in women with polycystic ovary syndrome (PCOS), to indicate gaps in knowledge, and to review the medical and surgical alternatives for weight management.

Design: Expert panel appointed by the Androgen Excess and PCOS Society (AEPCOS Society) to review the literature and draft the initial report after a consensus process via electronic communication. The initial report was reviewed and critiqued by all expert panel members and the AEPCOS Society Board of Directors and modified based on their comments.

Conclusion(s): Lifestyle management should be used as the primary therapy in overweight and obese women with PCOS for the treatment of metabolic complications. For reproductive abnormalities, lifestyle modification may improve ovulatory function and pregnancy. Data are preliminary for improvement in pregnancy and live-birth rates, and further research is needed. There is currently no evidence that modifying dietary macronutrient composition offers additional benefits over conventional dietary approaches for weight loss, and further research is needed. Emerging evidence suggests that exercise offers additional benefits to dietary energy restriction for reproductive features of PCOS. (Fertil Steril® 2009;92:1966–82. ©2009 by American Society for Reproductive Medicine.)

Key Words: Obesity, overweight, polycystic ovary syndrome, diet, exercise, lifestyle, weight loss

Polycystic ovary syndrome (PCOS) is a common endocrine condition affecting 5% to 10% of women of reproductive age (1). The diagnostic features include clinical or biochemical hyperandrogenism, oligoovulation or anovulation, and presence of polycystic ovaries on ultrasound (2). Polycystic ovary syndrome has serious clinical sequelae including reproductive manifestations (hirsutism, infertility, and pregnancy complications) (3), metabolic complications (insulin resistance, metabolic syndrome, impaired glucose tolerance, and type II diabetes mellitus [DM2], and risk factors for cardiovascular disease [CVD]) (4–9), and psychological problems (poor self-esteem, anxiety) (10). Polycystic ovary syndrome represents a major health and economic burden; in 2006, the estimated economic burden of PCOS in the United States was over $4 billion (menstrual dysfunction 31%, infertility 12%, and PCOS-associated DM2 40% of total costs) (11).

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Many women with PCOS (40% to 70%) have insulin resistance independent of obesity (12–15). This is a key factor in the etiology of PCOS through insulin-stimulating ovarian androgen production and decreasing hepatic sex hormone–binding globulin (SHBG) production leading to increased free androgens (16). It is estimated that 40% to 60% of women with PCOS are overweight or obese (17–19) with greater abdominal or visceral adiposity compared with weight-matched controls (20), which further worsens underlying insulin resistance and insulin resistance–associated reproductive (17, 18) and metabolic features (5, 21). There is widespread variability in the degree of adiposity in women with PCOS by geographic location and ethnicity. In studies in Spain, China, Italy, and the United States, 20%, 43%, 38%, and 69%, respectively, of women with PCOS were noted to be obese (22–24). Worldwide obesity prevalence is increasing, with the United States demonstrating the highest population prevalence of obesity at more than 30% (25). This likely influences the specific prevalence of obesity in PCOS.

Treatment of PCOS includes addressing reproductive, metabolic, and psychological features. With regards to reproductive features, reducing biochemical and clinical hyperandrogenism, regulating menstrual cycles, restoring ovulation and reproductive function, and improving reproductive

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outcomes are important. From a metabolic perspective, addressing insulin resistance and the metabolic syndrome are important in reducing long-term metabolic morbidity. From a psychological perspective, addressing factors including self-esteem and dysthymia is critical to improving motivation for effective lifestyle change (26).

In PCOS complicated by obesity and insulin resistance, lifestyle intervention has been adopted as an initial treatment strategy, either alone or combined with antiobesity pharmacologic options. The following statement summarizes the existing literature on lifestyle management, with or without antiobesity pharmaceutic or surgical treatment, in the management of reproductive and metabolic dysfunction in overweight and obese women with PCOS.

PROCESS OF REVIEW

The Committee chose to review lifestyle treatment and antiobesity pharmacologic and surgical treatment of PCOS based on knowledge of the content of existing literature. A review was conducted of the medical literature to identify studies evaluating the lifestyle treatment of PCOS (i.e., dietary, exercise, or behavioral treatment with the aim of inducing weight loss in overweight or obese women with PCOS). All uncontrolled and controlled studies on antiobesity drug use and antiobesity surgery in women with PCOS associated with dietary manipulation and/or lifestyle intervention were also considered. The search aimed to locate trials reported in all languages. Supplementary references were obtained from initial citations. Where unpublished data was identified, the investigators were contacted to request data inclusion. We did not define PCOS diagnosis before the search strategy and included each investigator's definition to include a range of diagnostic phenotypes. We searched the databases MEDLINE (1966 to October 2007), EMBASE (1980 to 2007 Week 43), CINAHL (1982 to October Week 3 2007), the Cochrane Menstrual Disorders and Subfertility Group Trials Register, and the Cochrane register of controlled trials. For PCOS, we searched for the keywords in all article text for the subject heading and keywords: polycystic ovary syndrome, PCOS, PCO, polycystic ovaries, hyperandrogenism, hirsutism, or anovulation with searches limited to females and humans. For lifestyle (dietary, exercise, or behavior modification), we searched for the keywords for the subject heading and keywords in all article text: diet, dietary, diet therapy, dietary intervention, weight loss, weight reduction, weight reducing, weight decreasing, energy restriction, or feeding behavior; or exercise, exercise therapy, exertion, physical fitness, physical performance, sports, strength training, resistance training, aerobic training, endurance training, or physical training; or lifestyle change, lifestyle intervention, lifestyle program, lifestyle, behavioral therapy, cognitive therapy, psychotherapy, behavior therapy, psychotherapy group, or social support; and combined this with the PCOS search. For antiobesity drugs and antiobesity surgery, we searched for the keywords for the subject heading and keywords in all article text: antiobesity drugs, sibutramine, orlistat, rimonabant, dexfenfluramine, topiramate, or bariatric surgery.

DEFINITION OF LIFESTYLE MANAGEMENT

Dietary management of obesity consists of reducing body weight, maintaining a lower long-term body weight, and preventing further weight gain (27). In the general population, guidelines for obesity management in women recommend an initial weight loss of greater than or equal to 5% to 10% for reduction of obesity-related risk factors with long-term goals of achieving and maintaining a reduction in weight of 10% to 20% and waist circumference of less than 88 cm (27, 28). Although weight loss may be possible in the short term through dietary energy restriction, many patients will eventually regain the weight (29, 30). The success of a weight loss strategy will be further increased with incorporation of additional principles including regular physical activity and attention to psychological adjustment, including behavior modification and stress management strategies (27, 28).

In the general population, there is some evidence that the success of weight management programs can be predicted by dietary or exercise self-efficacy and readiness to change, highlighting the importance of addressing psychosocial factors (26, 31). These strategies can be implemented into longer term weight maintenance regimes through use of lifestyle modification techniques. These consist of a multifaceted approach of dietary, exercise, and behavior therapy with the aim of teaching principles and techniques for achieving dietary and exercise goals for long-term weight management (32).

EVIDENCE FOR LIFESTYLE MANAGEMENT

Management of obesity in PCOS is multifactorial, and initial nonrandomized uncontrolled trials have included diet or exercise alone and combined diet, behavioral, and/or exercise modification (lifestyle therapy). The specifics of each approach to weight loss in PCOS are detailed in subsequent sections.

Evidence for Dietary Interventions without Exercise and Behavioral Advice

The overall impact of weight reduction through diet alone in PCOS in uncontrolled intervention studies is reviewed here. There are now a multitude of uncontrolled intervention studies in weight reduction for women with PCOS with subject numbers ranging from 6 to 143 and durations of 1 week to over 1 year. Most of these studies employ various forms of dietary restriction with resultant weight reduction of $<5\%$ to $>15\%$ over the starting body weight (Table 1).

With respect to androgens, most studies demonstrated reduction in either total or free testosterone (33–43), and some demonstrated reduction in adrenal androgens (38, 39). Levels of SHBG were improved in all of the longer term studies (34–36, 39, 41, 44, 45), with only one short-term intervention failing to show improvement (40). Clinically, improvements in hirsutism were documented in a number of studies (42, 43, 46). Menstrual function and ovulation improved in all the studies reporting this end point (35, 36, 42, 43, 47, 48–50). Pregnancy or conception was measured in

TABLE 1

Trials of dietary intervention and impact on key features in overweight/obese women with polycystic ovary syndrome (PCOS).

Study	Patients	Duration	Intervention	Weight loss	Hormones, metabolism, and reproduction
Bates and Whitworth 1982 (33)	n = 18 BMI: 29.0 kg/m^2	Variable	Uncontrolled intervention study Dietary restriction	>15% decrease in body weight in 13/18	48% decreased T, 77% spontaneous conception in those with weight loss >15%
Pasquali et al., 1986 (48)	n = 7 BMI >28 kg/m^2	3 months	Uncontrolled intervention study 1000–1200 kcal/day	8.5% decrease in BMI	3/7 improved menstrual function Increased glucose:insulin ratio No change in androgens
Kiddy et al., 1989 (34)	n = 5 BMI: 36.1 kg/m^2	4 weeks	Uncontrolled intervention study Very low calorie diet	NA	Twofold increased SHBG, decreased free T
Pasquali et al., 1989 (43)	n = 20 BMI: 32.1 kg/m^2	6–12 months	Uncontrolled intervention study 1000–1500 kcal/day	9.7 kg	8/20 increase in menstrual cyclicity 55% decreased hirsutism 4/20 pregnancies Decreased total T, OGTT glucose, insulin, fasting insulin
Dessole et al., 1990 (42)	nn = 11 BMI: 28.4 kg/m^2	6–12 months	Uncontrolled intervention study 1200–1800 kcal/day	8.5 kg	Hirsutism improved 7/11 10/11 improved menstrual function Decreased T
Kiddy et al., 1992 (35)	n = 24 BMI: 34.1 kg/m^2	6–7 months	Uncontrolled intervention study 1000 kcal diet	13/24 lost >5% body weight	54% increased SHBG, 31% decreased T, decreased fasting insulin, 11/13 improved menstrual function
Hamilton-Fairley, et al., 1993 (44)	n = 6 BMI: 34.2 kg/m^2	1 month	Uncontrolled intervention study Very low calorie diet	5.6 kg	Increased SHBG, decreased OGTT insulin.
Nicolas, et al., 1993 (36)	n = 23 BMI: 29.9 kg/m^2	4 months	Uncontrolled intervention study 1500 kcal diet	2.7 kg/m^2 decrease in BMI	23% increased SHBG, 22% decreased Free T, 13/23 improved menses

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TABLE 1

Continued.

Study	Patients	Duration	Intervention	Weight loss	Hormones, metabolism, and reproduction
Andersen, et al., 1995 (51)	n = 9 BMI: 33.6 kg/m^2	4 + 20 weeks	Uncontrolled intervention study Very low calorie diet followed by 1000–1500 kcal diet	13% reduction in body fat	Decreased TC and TG, 6% decreased FBS and 20% decreased FAI, 54% decreased PAI-1, 2/9 spontaneous pregnancy
Holte, et al., 1995 (45)	n = 13 BMI: 32.3 kg/m^2	14.9 months	Uncontrolled intervention study Dietary intervention	12.4 kg	Improved insulin sensitivity, 35% increased SHBG, decreased truncal fat, decreased free fatty acids
Hollmann et al., 1996 (49)	n = 35 BMI: 34.6 kg/m^2	32 weeks	Uncontrolled intervention study Not specified weight reducing program	10.2 kg	Decreased fasting insulin, fasting glucose; 80% improvement in menstrual function, 29% pregnancy
Jacubowicz and Netser et al., 1997 (37)	n = 12 BMI: 32.0 kg/m^2	8 weeks	Uncontrolled intervention study Hypocaloric diet	7.5% decrease in BMI	Decreased fasting insulin, decreased 17-OHP, decreased T 37% and free T 34%
Wahrenberg et al., 1999 (52)	n = 9 BMI: 37.9 kg/m^2	8–12 weeks	Uncontrolled intervention study Very low calorie diet	8.0 kg	50% reduction in basal lipolysis rate, improved insulin sensitivity
Hernadez-Garcia et al., 1999 (38)	n = 30 Initial weight: 86.6 kg	Variable	Uncontrolled intervention study Not specified	9.5 kg	86% resumed ovulation, decreased T, DHEAS, improved glucose tolerance in 9/12
Pasquali et al., 2000 (47)	n = 9 BMI: 39.6 kg/m^2	7 months	Uncontrolled intervention study 1200–1400 kcal/day	5.0 kg	Improved menstrual cyclicity Decreased fasting insulin No change in androgens, SHBG, hirsutism
Butzow et al., 2000 (39)	n = 10 BMI: 37.1 kg/m^2	6 week + 4 week	Uncontrolled intervention study Very low calorie diet followed by maintenance	8% reduction in body fat	Increased SHBG 46%, Decreased fasting insulin 38%, Decreased leptin 37%, decreased testosterone 20%, DHEAS 13%

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TABLE 1

Continued.

Study	Patients	Duration	Intervention	Weight loss	Hormones, metabolism, and reproduction
Van Dam et al., 2002 (40)	n = 15 BMI: 39.0 kg/m^2	1 week	Uncontrolled intervention study Very low calorie diet	1.0 kg.m^2 decrease in BMI	75% decreased fasting insulin, 18% decreased fasting glucose, 25% decreased T, no change in SHBG
Crosignani et al., 2003 (50)	n = 33 BMI: 32.1 kg/m^2	Variable	Uncontrolled intervention study 1200 kcal diet	25/33 lost 5% 11/33 lost 10% body weight	18/33 resumed regular menses, 10 spontaneous pregnancies
Van Dam et al., 2004 (41)	n = 15 BMI: 39.0 kg/m^2	6.25 months	Uncontrolled intervention study Very low calorie diet	10% body weight reduction	Increased SHBG, decreased free T, increased LH secretion
Tolino et al., 2005 (46)	n = 143 BMI: 35 kg/m^2	7 months	Uncontrolled intervention study 1000 kcal/day diet	6.0 kg	24/114 improved hirsutism 30/54 conceptions 54/66 improved menstrual cyclicity Decreased fasting insulin and OGTT insulin, free T Increased SHBG
Moran, et al., 2007 (53)	n = 15 BMI: 35.6 kg/m^2	8 weeks	Uncontrolled intervention study Energy restrictive diet with meal replacements	3.9 kg	Decreased TG, postprandial glucose, fasting and postprandial insulin, T, free T, FAI, increased SHBG, no change in hsCRP

Abbreviations: BMI = body mass index; DHEAS = dehydroepiandrosterone sulfate; FAI = free androgen index; hsCRP = highly sensitive C-reactive protein; OGTT = oral glucose tolerance test; 17-OHP = 17-hydroxyprogesterone; PAI-1 = plasminogen-activator inhibitor-1; SHBG = sex hormone–binding globulin; T = testosterone; TC = total cholesterol; TG = triglycerides; LH = luteinizing hormone.

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TABLE 2

Trials of exercise interventions and combined lifestyle interventions and impact on key features in overweight/obese women with polycystic ovary syndrome (PCOS).

Study	Patients	Duration	Intervention	Weight loss	Hormones, metabolism, and reproduction
Palomba et al., 2008 (55)	n = 40 BMI: 33 kg/m^2 n = 20 diet, n = 20 exercise	6 months	RCT Structured exercise (SET) 3 × 30-minute sessions/week, treadmill supervised, titrated to VO2max vs. High-protein, low-calorie diet: 35% P, 45% C, 20% F	Divided into ovulatory and nonovulatory	Exercise: increased menses, ovulation and pregnancy rate vs. diet. In ovulators (responders)— Exercise: greater increases in SHBG, decreases in FAI, HOMA Diet: greater decreases in weight, adrenal androgens
Vigorito et al., 2007 (54)	n = 90 BMI: 29 kg/m^2 n = 45 exercise n = 45 no exercise	3 months	RCT Structured supervised exercise program vs. controls	Decreased BMI and waist circumference in exercise group only	Exercise: Decreases in blood pressure, fasting insulin, OGTT Insulin and CRP Control group: No changes No change in androgens in either group
Bruner et al., 2006 (56)	n = 12 BMI: 36 kg/m^2 n = 5 diet alone BMI = 37 kg/m^2 n = 7 Exercise + diet	3 months	RCT Nutrition session all participants 1 hour per week Exercise supervised, monitored, 3 times per week, 40 minutes to 75% max HR	No significant change in weight or BMI Greater decrease in fat mass (skinfolds) for exercise + diet	Both groups reduced insulin levels
Randeva et al. 2002 (60)	n = 21 BMI: 35 kg/m^2 n = 12 exercisers, n = 9 non exercisers	6 months	Uncontrolled intervention study 5 walks per week for 20–60 minutes, self monitored and reported	Weight: no change, WHR improved with exercise	Lower homocysteine, no change in fasting insulin, free T
Guzick et al., 1994 (63)	n = 6 diet BMI: 32.3 kg/m^2 n = 6 no diet BMI: 34.2 kg/m^2	12 weeks	RCT Diet versus no diet Behavior modification training around eating behaviors, 1000–1200 kcal/day diet	16.2 kg weight loss for diet group	4/6 diet and 1/6 no diet improved menstrual function Increase SHBG, decreased free T for diet group

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TABLE 2

Continued.

Study	Patients	Duration	Intervention	Weight loss	Hormones, metabolism, and reproduction
Clark et al., 1995 (65)	n = 13 (8/13 PCOS) BMI: 38.7 kg/m^2	6 months	Uncontrolled intervention study Behavioral change, weekly diet and exercise class and advice	6.3 kg No change in WHR	12/13 resumed ovulation 11 became pregnant, Decreased fasting insulin and T Increased SHBG
Clark et al., 1998 (66)	n = 67 (53/67 PCOS) BMI: 37.4 kg/m^2	6 months	Uncontrolled intervention study Behavioral change, weekly diet and exercise class and advice	10.2 kg	60/67 resumed ovulation 52 pregnancies (18 spontaneous) 45 live birth
Huber-Buchholz et al., 1999 (67)	n = 19 BMI: 27–45 kg/m^2	6 months	Uncontrolled intervention study Behavioral change, diet and exercise	2–5% reduction in body weight	115 decreased in central fat 71% improvement in insulin sensitivity 33% decreased fasting insulin No change in androgens
Hoeger et al., 2004 (68)	n = 15 adolescents BMI: 35.9 kg/m^2	6 months	RCT Lifestyle vs. no lifestyle Lifestyle: Group format with one adult family member, Behavioural change, aim for 5–7% weight loss, exercise (150 minutes exercise/week)	Lifestyle: –3.0 kg/m^2 versus no lifestyle +1.8 kg/m^2, insignificant change for both.	Lifestyle: decreased in FAI, PAI-1, DBP, increased in SHBG, trend for improvement in OGTT insulin No lifestyle: No changes in any parameter
Hoeger et al., 2004 (69)	n = 6 Lifestyle BMI: 40.0 kg/m^2 n = 7 no lifestyle BMI: 37.1 kg/m^2	48 weeks	RCT Lifestyle vs. no lifestyle Lifestyle: Behavioural change, dietary (500–1000 kcal deficit/day) and exercise (150 minutes exercise/week) advice	Lifestyle –6.8 kg versus no lifestyle +0.2 kg	Lifestyle: no change in androgens, SHBG, insulin, glucose, hirsutism. 3.5 documented ovulations No lifestyle: no change in hirsutism, androgens, SHBG, OGTT glucose, insulin, fasting glucose 2.7 documented ovulations

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TABLE 2

Continued.

Study	Patients	Duration	Intervention	Weight loss	Hormones, metabolism, and reproduction
Tang et al., 2006 (64)	n = 66 BMI: 37.6 kg/m^2	6 months	Uncontrolled intervention study Lifestyle modification: dietary and exercise advice 500 kcal deficit/day	1.5 kg	58.1% improved menstrual function 2/68 pregnancy No change in androgens, SHBG, insulin, glucose, TC, TG

Abbreviations: BMI = body mass index; C = carbohydrate; DBP = diastolic blood pressure; F = fat; HOMA = homeostasis assessment of insulin resistance; OGTT = oral glucose tolerance test; P = protein; RCT = randomized controlled trial; SHBG = sex hormone–binding globulin; T = testosterone; TC = total cholesterol; TG = triglycerides; WHR = waist-to-hip ratio.

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six studies, but all without controls (33, 43, 46, 49–51). Metabolic improvements in fasting insulin, glucose, and glucose tolerance were seen in all studies in which they were measured (35, 37–40, 43–45, 47–49, 51–53). Lipids and other cardiovascular measures were infrequently reported, but total cholesterol and triglycerides were improved with weight reduction, as were plasminogen activator inhibitor-1 (51) and free fatty acids (45), while C-reactive protein did not change (53).

Evidence on the Effects of Exercise

In overweight women with PCOS, most lifestyle studies focus on dietary management. These often face the issue of high dropout rates and modest weight loss, and sustainable weight maintenance remains a challenge. Incorporating structured exercise as a fundamental component of lifestyle studies may improve their efficacy, feasibility, sustainability, and consequent effect on clinical outcomes in PCOS (54, 55). Furthermore, given the mechanisms of action of exercise and improvement in insulin resistance and metabolic syndrome demonstrated in other insulin-resistant states, exercise independent of weight loss offers significant potential benefits in PCOS (56–58).

Exercise where incorporated in lifestyle studies in PCOS is usually unstructured or unsupervised or does not meet current guidelines of 30 minutes of activity daily (59). Very few studies have focused on exercise specifically. Palomba et al. (55) recently completed a prospective, 6-month, nonrandomized study of structured, supervised, individual, 30-minute treadmill sessions, 3 times per week, titrated to fitness levels (n = 20) versus dietary energy restriction alone (n = 20). With exercise versus diet, greater improvements were noted in ovulation rate (65% vs. 25%, respectively) and a trend to increased pregnancy rate (6.2% vs. 1.7%, respectively). In an analysis of responders (those who ovulated, 3 out of 20 with exercise and 5 out of 20 with diet), responders in both groups showed improvement in weight, androgens, fasting glucose, and insulin resistance. Diet induced greater weight loss (10% vs. 5%) and a fall in adrenal androgens, and exercise induced a greater rise in SHBG, and a fall in testosterone, free androgen index, and insulin resistance (9% vs. 41%, respectively) (Table 2). This is the first study to suggest that exercise alone significantly improves insulin resistance and clinical outcomes in PCOS compared with diet alone and that it does so through mechanisms other than weight loss (55).

A further 6-month, randomized controlled trial in 90 overweight women with PCOS noted that structured, supervised exercise improves insulin resistance and reduces body mass index (BMI) compared with women with PCOS randomized to no exercise (54). Two studies with inadequate sample size and insensitive measures of insulin resistance (fasting insulin) demonstrated either no improvements or equivalent changes in insulin resistance with diet versus diet and exercise (56, 60). Greater reductions in fat mass occurred for exercise and dietary counseling compared with diet alone, despite no changes in weight for either group (56).

TABLE 3

Trials of modification of dietary macronutrient composition in lifestyle programs and impact on key features in overweight/obese women with polycystic ovary syndrome.

Study	Subjects	Duration	Intervention	Weight loss	Hormones, metabolism, and reproduction
Moran et al., 2003 (72)	n = 28 BMI: 37.4 kg/m^2	4 month (3 month ER, 1 month WM)	RCT 12 weeks: 6000 kJ/day 4 weeks: WMD HP: 30% P, 40% C, 30% F HC: 15% P, 55% C, 30% F	HP –8.5 ± 1.1 kg vs. LP –6.9 ± 0.8 kg (NS)	All patients: Insulin, HOMA, TC, LDL-C, TG, total T similarly decreased SHBG similarly increased, Menstrual cyclicity similarly improved Diet comparison, postprandial glucose decreased for HP, HDL-C decreased ER for LP, TC/HDL-C decreased ER for HP, FAI increased during WM for LP
Stamets et al., 2004 (73)	n = 26 BMI: 37–38 kg/m^2	4 week	RCT Energy deficit 4200 kJ/day HP: 30% P, 40% C, 30% F HC: 15% P, 55% C, 30% F	HP 3.7 ± 1.9 kg vs. LP 4.4 ± 1.5 kg (NS)	All patients: Insulin, OGTT insulin, glucose/insulin ratio, total T, free T similarly decreased, SHBG similarly increased, menstrual cyclicity similarly improved
Hays et al., 2003 (74)	n = 15 BMI: 36.1 kg/m^2	24 week	Uncontrolled intervention study High saturated fat, low starch (very low C), 7200 kJ/day No control group comparison	Weight: –14.3% BMI: –3.7 kg/m^2	Insulin decreased
Mavropoulos et al., 2005 2006 (75)	n = 5 BMI: 38.5 kg/m^2	6 month	Uncontrolled intervention study Ketogenic (<20 g C/day) No control group comparison	Weight: –5 kg, 12%	Insulin, free testosterone decreased
Moran et al., 2006 (76)	n = 23 BMI: 35.4 kg/m^2	2 months ER 6 months WM	RCT 2-month meal replacements: All patients 6 months: High GL or low GL education	Weight: high GL 5.9 ± 2.1 kg vs. low GL 4.4 ± 0.7 kg	All patients: Insulin, total T, FAI similarly decreased, menstrual cyclicity similarly improved

Abbreviations: BMI = body mass index; C = carbohydrate; ER = energy restriction; F = fat; FAI = free androgen index; GL = glycemic load; HC = high carbohydrate; HDL-C = high-density lipoprotein cholesterol; HOMA-IR = homeostasis assessment of insulin resistance; HP = high protein; P = protein; LDL-C = low-density lipoprotein cholesterol; NS = not statistically significant; OGTT = oral glucose tolerance test; T = testosterone; RCT = randomized controlled trial; SHBG = sex hormone–binding globulin; TC = total cholesterol; WMD = weight-maintenance diet.

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TABLE 4

Effect of adjuvant pharmacologic treatment added to a lifestyle program in overweight women with polycystic ovary syndrome (PCOS).

Study	Subjects	Duration	Intervention	Weight loss	Hormones, metabolism, and reproduction
Sabuncu et al., 2003 (87)	n = 40	6 months	RCT 14 EE-CA vs. 12 Sib (10 mg) vs. 14 EE-CA + Sib added to a 1200 kcal LCD	BMI: 37.8 to 36.8 37.5 to 31.7 37.7 to 33.2 NS	Androgens similarly decreased SHBG similarly increased WHR, triglycerides and DBP significantly reduced only in Sib
Jayagopal et al., 2005 (91)	n = 21	3 months	RCT Orlistat (120 mg t.i.d.) vs. Metformin 50 mg t.i.d. on WM	Weight: -4.7 ± 1.2 kg vs. -1.0 ± 0.9 kg $P<.01$	Both treatments reduced testosterone No significant changes in insulin resistance and lipids
Lindholm et al., 2008 (86)	n = 42 34 completers	6 months	RCT Sib (15 mg) vs. placebo, plus lifestyle modification	-7.8 ± 5.1 kg vs. -2.8 ± 6.2 kg ($P<.01$)	3 pregnancies on sib and 1 on placebo Waist < more on Sib ($P<.01$) Menses improved in both treatments Sib significantly reduced ApoB, triglycerides, and FAI
Florakis et al., 2008 (88)	n = 59	6 months	RCT Sib (10 mg) + LCD vs. LCD alone	Weight: 15.4 ± 1.1 vs. $-11.1 \pm 1.9\%$ ($P<.05$)	% change in testosterone, FAI, SHBG, glucose–AUC significant only in Sib. % change in triglycerides > in Sib
Diamanti-Kandarakis et al., 2007 (89)	n = 29 PCOS n = 18 controls	6 months	Uncontrolled intervention study Orlistat (120 mg t.i.d.) added to a LCD (BMR 600 kcal/day)	BMI, PCOS: 35.4 to 31.5 BMI, controls: 36.4 to 32.1 NS	Similar decrease in WHR Testosterone decreased in PCOS SHBG increased, fasting insulin and insulin resistance improved and advance glycated end products reduced in both groups
Panidis et al., 2008 (90)	n = 18 PCOS n = 14 controls	6 months	Uncontrolled intervention study Orlistat (120 mg t.i.d.) added to a LCD (BMR 600 kcal/day)	BMI, PCOS: 36.0 to 30.4 BMI, controls: 36.1 to 30.1 NS	Similar decrease in waist and WHR Testosterone and FAI decreased in PCOS, whereas andostenedione did not significantly change SHBG increased in both groups, Fasting insulin and insulin resistance improved in both groups

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TABLE 4
Continued.

Study	Subjects	Duration	Intervention	Weight loss	Hormones, metabolism, and reproduction
Sathyapalan et al., 2008 (92)	n = 20	3 months	RCT Rimonabant (20 mg) vs. Metformin 500 mg t.i.d.	BMI: −6.0 ± 1.1% vs. −1.6 ± 1.0%, *P*=.02	Significant decreased waist, WHR, total testosterone and FAI, and HOMA-IR during rimonabant. No significant change on metformin

Abbreviations: AUC = area under curve; BMR = basal metabolic rate; BMI = body mass index; CA = cyproterone acetate; DBP = diastolic blood pressure; EE = ethinyl-estradiol; FAI = free androgen index; HOMA-IR = homeostasis model assessment–estimated insulin resistance; LCD = low-calorie diet; NS = no statistically significant difference; RCT = randomized controlled study; SHBG = sex hormone– binding globulin; Sib = sibutramine; t.i.d. = three times a day; WHR = waist-to-hip ratio; WM = weight-maintenance diet.

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Evidence on the Effects of Lifestyle Programs

Experience from treatment of populations at high risk for DM2 indicates lifestyle intervention is the most effective form of treatment for [1] improving insulin sensitivity, [2] reducing weight, [3] decreasing DM2 and metabolic syndrome incidence, and [4] improving risk factors for CVD, being superior to insulin-sensitizing drugs or placebo (61, 62). Guzick et al. (63) conducted a randomized controlled trial examining weight loss through dietary restriction in conjunction with behavioral modification in overweight women with PCOS. The diet and behavior group had reductions in weight, improvements in menstrual function, increases in SHBG, and decreases in free testosterone compared with the control group. In an uncontrolled study, Tang et al. (64) combined dietary restriction and exercise advice with resultant improvements in menstrual function, although the weight loss was minor (1.5 kg) and no changes in levels of insulin, androgens, or lipids occurred (see Table 2).

A small number of studies implemented a multifactorial lifestyle intervention (exercise, diet, and behavioral modification) in overweight adolescents or women with PCOS (65–67). Reductions in androgens and increases in SHBG were reported in one study in association with a 6.3-kg weight loss (65) or a 3.0 kg/m^2 insignificant BMI reduction (68), and no changes in androgens were noted with a 2% to 5% (67) or 6.8 kg (69) reduction in body weight. Metabolic improvements in fasting insulin, glucose, glucose tolerance, plasminogen activator inhibitor-1, diastolic blood pressure, or insulin resistance (measured by the euglycemic hyperinsulinemic clamp) were observed (65, 67, 68). Menstrual function and ovulation improved in most of the studies (65–67). Spontaneous and assisted-reproduction pregnancies were reported (65, 66), and Clark et al. (66) reported a not statistically significant reduction in miscarriage rates from 75% before treatment to 18% after treatment.

Current Controversies in Lifestyle Treatment of PCOS: Evidence on Dietary Macronutrient Composition

An area of increasing focus in PCOS is the macronutrient composition of the dietary component of a lifestyle program. A low fat (~30% of energy, saturated fat ~10%, <300 mg cholesterol daily), moderate protein (~15%), and high carbohydrate intake (~55%) in conjunction with moderate regular exercise is recommended for the management of obesity and related comorbidities (27, 28, 70). However, a recent Cochrane review reported similar weight loss and compliance for a low fat diet compared with other approaches (71). Alternative dietary approaches are increasingly being studied that may have more favorable hormonal or metabolic effects or may be more effective in achieving and sustaining long-term weight loss.

There has been limited research assessing the effect of modifying dietary macronutrients in PCOS (Table 3). Two small randomized controlled trials compared short-term reduced energy, high protein, or low protein diets and reported

TABLE 5

Key points from research studies assessing lifestyle modification in polycystic ovary syndrome (PCOS).

Research trials	Key points
Dietary intervention without exercise or behavioral advice	• A large number of uncontrolled intervention studies have been conducted examining the effect of weight loss through dietary restriction alone in overweight or obese women with PCOS. • Study durations range from 4 weeks to 15 months, study sample sizes are generally small, there are no randomized controlled trials comparing dietary intervention to no structured dietary intervention. • The studies demonstrate fairly uniform improvements in many key features of PCOS with modest weight loss (5% to 15%), with the majority of studies showing improvements in biochemical hyperandrogenism, menstrual cyclicity, ovulation, and fasting insulin and glucose as well as glucose tolerance. Fewer studies reported on clinical hyperandrogenism, pregnancy, or conception.
Exercise	• Limited studies examining the effects of exercise in PCOS suggest that exercise improves reproductive (reproductive hormones, menstrual cyclicity or ovulation) and metabolic features. • Eemerging evidence suggests that exercise offers additional benefits to dietary weight loss for reproductive and metabolic features of PCOS. • Remaining research questions include the effects of structured exercise with diet as well as the optimal amount, type, duration, and mechanisms of action of exercise.
Lifestyle programs	• In overweight women with PCOS, a small number of randomized controlled trials or uncontrolled intervention studies comparing dietary/behavioral and/or exercise programs with no lifestyle intervention report improvements in hyperandrogenism and menstrual function with modest weight loss. • A small number of studies report pregnancies and reduced miscarriage rates with modest weight loss (2% to –5% or $\sim$ 6 kg) • There are no data on the effect of lifestyle modification on pregnancy outcomes (live-birth rate).
Modifying dietary macronutrient composition in weight loss	• High-protein moderate-carbohydrate diets have similar effects to moderate-protein high-carbohydrate diets regarding weight management and reproductive and metabolic features. • Very low carbohydrate diets have been shown to reduce weight, insulin, and androgens but have not been directly compared with conventional approaches. • There are no data on the effect of modifying the glycemic index independent of changing the dietary carbohydrate amount on weight management and reproductive and metabolic outcomes in PCOS.
Antiobesity pharmacologic agents or bariatric surgery	• In a small number of studies, sibutramine decreased body weight and improved metabolic and reproductive parameters (reproductive hormones or spontaneous pregnancies) in PCOS. • There are limited data on the effects of orlistat, rimonabant, or metformin on weight management and reproductive or metabolic features of PCOS. • Antiobesity pharmacologic agents and bariatric surgery are potential future options for the management of overweight and obese women with PCOS but require further research.

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TABLE 6

Lifestyle modification principles suggested for obesity management in polycystic ovary syndrome (PCOS).

Guidelines for dietary and lifestyle intervention in PCOS

1. Lifestyle modification is the first form of therapy, combining behavioral (reduction of psychosocial stressors), dietary, and exercise management.
2. Reduced-energy diets (500–1000 kcal/day reduction) are effective options for weight loss and can reduce body weight by 7% to 10% over a period of 6 to 12 months.
3. Dietary pattern should be nutritionally complete and appropriate for life stage and should aim for <30% of calories from fat, <10% of calories from saturated fat, with increased consumption of fiber, fibre, whole-grain breads and cereals, and fruit and vegetables.
4. Alternative dietary options (increasing dietary protein, reducing glycemic index, reducing carbohydrate) may be successful for achieving and sustaining a reduced weight but more research is needed in PCOS.
5. The structure and support within a weight-management program is crucial and may be more important than the dietary composition. Individualization of the program, intensive follow-up and monitoring by a physician, and support from the physician, family, spouse, and peers will improve retention.
6. Structured exercise is an important component of a weight-loss regime; aim for >30 minutes per /day.

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equivalent retention rates, reductions in weight (3.6% to 7.5%), fasting insulin, reproductive hormones, and improvements in reproductive parameters for both approaches (72, 73). Minor benefits were observed for a higher protein intake with a greater reduction in postprandial glucose, a sustained reduction in the free androgen index in weight maintenance, and no decrease in high-density lipoprotein cholesterol in weight loss (72). In two small uncontrolled studies, very low carbohydrate diets led to reductions in weight, fasting insulin, and free testosterone over 24 weeks in overweight women with PCOS (74, 75). However, the effect of these approaches on reproductive outcomes was not reported, and the comparative success of these strategies is unknown as a standard control diet was not used.

One study assessed the effect of modifying the carbohydrate type or glycemic index and glycemic load in overweight women with PCOS. A high or low glycemic-load educational strategy (moderate fat or carbohydrate restriction in conjunction with low glycemic-index foods) produced equivalent weight maintenance and improvements in menstrual cyclicity, insulin resistance, and hyperandrogenism (76). However, the dietary strategy was unsuccessful in achieving a sustained difference in glycemic load between the diet groups. There has been no research assessing the effect of modifying the glycemic index independent of modifying carbohydrate amount in PCOS.

Some concern exists regarding the potentially detrimental effects of an increased protein intake on bone turnover and renal function. The evidence surrounding these claims has been recently reviewed and suggests no adverse effects of a moderately increased protein intake in weight loss in healthy individuals (77, 78). With regards to a very low carbohydrate approach, additional safety concerns relate to potential nutritional inadequacy; a potential increase in cardiovascular risk factors (particularly low-density lipoprotein) (79); effect of the low fiber intake on constipation and long-term cancer and diverticular disease; the effect of low magnesium, potassium, and vitamin C intakes on calciuria and osteoporosis; and elevated uric acid levels and effects on gout (80).

It has also been suggested that women with PCOS could choose foods that worsen their presentation. Lean women with PCOS consume less total energy than weight-matched women without PCOS, suggesting that women with PCOS may need to follow more stringent dietary restrictions to maintain weight (81). Conversely, no differences in total energy, macronutrient, micronutrient intake or intake of high fat, carbohydrate, or glycemic-index foods was observed between lean or overweight women with or without PCOS (81, 82) although the women with PCOS consumed higher amounts of specific high glycemic-index foods (white bread, fried potatoes) than the women without PCOS (82). The evi dence for specific macronutrient consumption predisposing to obesity or reproductive and metabolic abnormalities in PCOS is unclear.

CURRENT CONTROVERSIES IN LIFESTYLE TREATMENT OF PCOS: USE OF LIFESTYLE INTERVENTION IN ADDITION TO PHARMACOLOGIC TREATMENT OR BARIATRIC SURGERY

Although even modest weight loss can produce hormonal, metabolic, and fertility benefits, lifestyle intervention programs are difficult to maintain in the long term (83). Alternative approaches to the treatment of obesity and insulin

resistance are increasingly being studied and recommended clinically, including use of pharmacologic agents or bariatric surgery.

Pharmacologic Treatment

Available antiobesity drugs are orlistat, sibutramine, and rimonabant (84). Orlistat is a potent inhibitor of digestive gastric and pancreatic carboxylester lipase, reducing digestion of dietary triglycerides and lipid absorption. Sibutramine is a centrally acting drug inhibiting the reuptake of serotonin and norepinephrine, thus increasing satiety and energy expenditure. Rimonabant is a cannabinoid receptor-1 (CB1) antagonist that works as an anorectic drug and also modulates lipid and glucose metabolism as well as adipose tissue function. Long-term trials in obese and obese-diabetic patients have shown greater weight loss (30% to 50%), long-term weight maintenance, and metabolic as well as cardiovascular benefits compared with placebo and/or lifestyle treatment (85).

Table 4 reports studies in overweight or obese PCOS patients. Sibutramine added to a reduced-energy diet resulted in more spontaneous pregnancies and greater decreases in body weight (86), triglycerides (86, 87), lipoprotein ApoA (86), and androgens (86, 88) compared with placebo and diet (86), diet alone (88), or ethinyl-estradiol plus cyproterone acetate (87). The effects of orlistat (120 mg, three times a day) added to a reduced-energy diet were investigated in obese women with or without PCOS. Although changes in weight, waist-to-hip ratio, and insulin resistance were similar in both groups, androgens decreased only in women with PCOS (89, 90). A weight maintenance study comparing orlistat and metformin in obese PCOS women reported similar decreases in testosterone for both drugs and no statistically significant changes in glucose, lipids, and insulin resistance for either drug (91). In a comparison of rimonabant (20 mg/daily) and metformin (1500 mg daily) in obese women with PCOS, rimonabant significantly reduced body weight, waist circumference, hyperandrogenism, and insulin resistance with no changes in these parameters reported for metformin. These promising preliminary data support the need for further randomized large studies on CB1-antogonists in obese PCOS women (92). An additional future area of interest is the use of metformin, an insulin sensitizer, in weight management. Although not proven to decrease weight in PCOS, its use has been reported to be associated with prevention of weight gain over time, observed in longer term trials in insulin resistant states (e.g., DM2) (93). Further research over the longer term may be warranted given the metabolic and reproductive benefits of metformin in PCOS.

Bariatric Surgery

A meta-analysis of the effects of bariatric surgery in more than 22,000 procedures found an average weight loss of more than 50% was associated with complete resolution or improvement of DM2, hyperlipidemia, hypertension, and obstructive sleep apnea in more than 60% of patients (94). These data are supported by a long-term, large, prospective study confirming that weight loss, metabolic and cardiovascular benefits, and a significant decrease in all-cause mortality was maintained 10 years after surgery (95). An uncontrolled study assessing the effect of bariatric surgery in morbidly obese women with PCOS reported sustained weight loss and complete resolution of all features defining PCOS, including hirsutism, hyperandrogenism, menstrual irregularity, anovulation, insulin resistance, and metabolic abnormalities (96). In another study examining gastric bypass in overweight women with PCOS, a 56.7% weight loss over 1 year improved menstrual cyclicity, hirsutism, and natural conception (97). This opens new perspectives on the pathophysiologic impact of obesity on PCOS.

Unfortunately, the criteria for adopting pharmacologic treatment or performing bariatric surgery are still largely debatable. Long-term trials using different drugs simply demonstrate that each drug adds independent benefits of weight loss and metabolic improvements, but no particular strategy on drug selection or routine use (including patient selection and definition of responsiveness) is available. According to the World Heath Organization, currently approved drug therapy is best used in conjunction with hypocaloric diet and lifestyle management and should require constant medical supervision; unfortunately, when drug therapy is discontinued, weight regain reoccurs (98). In addition, metformin, the most common insulin sensitizer used in PCOS, has often been administered alone. This contrasts with its recommended use, which should always be added to lifestyle modification in patients with DM2 or obesity. Conversely, the higher the weight loss, the greater the benefit achieved, as documented by the surgical studies. Current U.S. National Institutes of Health clinical recommendations advise bariatric surgery when BMI is greater than 40 kg/m^2 or greater than 35 kg/m^2 in patients with a high-risk obesity-related condition after failure of other treatments for weight control (99).

RESEARCH QUESTIONS

A large number of uncontrolled studies have demonstrated reproductive and metabolic improvements accompanying weight losses of 5% to 10% achieved through dietary weight-loss interventions, reinforcing the positive effects of modest weight loss in the treatment of overweight and obese women with PCOS. There are limited data comparing the relative efficacy of different types of lifestyle interventions in PCOS, but one recent study noted greater reproductive benefits with structured exercise than energy restriction, highlighting the importance of exercise in PCOS. On the whole, improvements with weight loss (clinical or biochemical reproductive parameters and surrogate markers of insulin resistance and other metabolic risk factors) appear to occur on a continuum, and no specific level of energy restriction or energy expenditure emerges as necessary, provided that modest weight loss is achieved. There is currently little evidence for one diet composition being optimal in obesity treatment in PCOS, with overall energy restriction being the most critical

factor, provided that a dietary regime is safe and sustainable (Table 5). Further well–designed, adequately powered comparative studies are needed to address the issues of exercise and dietary macronutrient modification, focusing on feasible, cost-effective exercise programs combined with dietary changes.

Translating evidence into practice suggests dietary advice based upon current recommendations for obesity management, targeting a 5% to 10% weight loss in combination with structured exercise and behavioral modification techniques (Table 6). There is no evidence regarding the optimum amount or type of exercise specifically for PCOS, but current national guidelines are advised, such as 3 to 5 hours/week or 30 minutes/day (28, 59).

Although it is clearly demonstrated that weight loss improves the reproductive and metabolic presentation of PCOS, the most pressing clinical question is how to increase program retention and long-term weight maintenance. There are no studies on long-term weight regain after lifestyle intervention with or without antiobesity drugs or surgery in overweight or obese PCOS patients. This remains an open question that should be investigated.

With regards to pharmacologic and surgical treatment of obesity, although the efficacy of orlistat and sibutramine has been substantially proved in simple obesity, available data in obese PCOS women need to be reevaluated and supported by larger long-term controlled trials (see Table 5). More scientific attention should be paid to therapeutic strategies including antiobesity drugs or bariatric surgery in obese women with PCOS.

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