Metabolism Clinical and Experimental 92 (2019) 108–120

Contents lists available at ScienceDirect

Metabolism Clinical and Experimental

journal homepage: www.metabolismjournal.com

Characteristics of obesity in polycystic ovary syndrome: Etiology, treatment, and genetics☆

Charles J. Glueck *, Naila Goldenberg

The Cholesterol, Metabolism, and Thrombosis Research Center, 3906 Middleton Avenue, Cincinnati, OH 45220, United States of America

ARTICLE INFO

Keywords:
Obesity
Polycystic ovary syndrome
Genetics
Treatment

ABSTRACT

Polycystic ovary syndrome (PCOS) has multiple etiologies including ovarian and adrenal hyperandrogenism, neuro-endocrine and hypothalamic-pituitary dysfunction, and disorders of peripheral insulin resistance. Obesity is neither necessary nor sufficient for the PCOS phenotype, and the association of PCOS with obesity is not universal, with national, cultural, and ethnic differences. Obesity, particularly visceral adiposity which is common in obese and non-obese women with PCOS, amplifies and worsens all metabolic and reproductive outcomes in PCOS. Obesity increases insulin resistance and compensatory hyperinsulinemia, which in turn increases adipogenesis and decreases lipolysis. Obesity sensitizes thecal cells to LH stimulation and amplifies functional ovarian hyperandrogenism by upregulating ovarian androgen production. Obesity increases inflammatory adipokines which, in turn, increase insulin resistance and adipogenesis. Lifestyle interventions focused on diet-weight loss and concurrent exercise are central to therapy which also commonly subsequently needs to include pharmacologic therapy. PCOS symptoms commonly improve with 5% to 10% weight loss, but 25% to 50% weight loss, usually achievable only through bariatric surgery, may be required for morbid obesity unresponsive to lifestyle-medical treatment. Bariatric surgery is a valuable approach to weight loss in PCOS where BMI is ≥40 kg/m^2 when non-surgical treatment and/or induction of pregnancy have failed, and can be an initial treatment when BMI is ≥50 kg/m^2. Further research in PCOS is needed to better understand the fundamental basis of the disorder, to ameliorate obesity, to correct hyperandrogenism, ovulation, hyperinsulinemia, and to optimize metabolic homeostasis.

Contents

1. Introduction . . . 109
   1.1. Visceral Adiposity . . . 110
   1.2. Factors Promoting and Associated with Obesity in PCOS . . . 110
   1.3. PCOS Etiologies . . . 110
2. Heritability of PCOS and Related Obesity . . . 111
   2.1. Meta-analysis of Genetic Studies of PCOS . . . 111
   2.2. Individual Genetic Studies of PCOS . . . 111
3. Lifestyle Modification in PCOS . . . 111
   3.1. Systematic Review-Meta Analysis of Lifestyle Interventions . . . 111
   3.2. Individual Studies of Lifestyle Intervention . . . 112
      3.2.1. Maintaining Lifestyle Modification Before and During Pregnancy in PCOS . . . 112
4. Type of Diet . . . 112
   4.1. Individual Studies of Effects of Type of Diet in PCOS . . . 112
5. Diet-Exercise . . . 113
   5.1. Systematic Review and Meta-Analysis of Diet Combined with Exercise in PCOS . . . 113
   5.2. Individual Studies of Diet Combined with Exercise in PCOS . . . 113

☆ Supported in part by the Lipoprotein Research Fund of the Jewish Hospital of Cincinnati.
* Corresponding author.
E-mail address: sonar16@gmail.com (C.J. Glueck).

https://doi.org/10.1016/j.metabol.2018.11.002
0026-0495/

6. Drug Therapy to Reduce Obesity in Women with PCOS . . . 113
6.1. Metformin . . . 113
6.1.1. Systematic Review and Meta-analysis of Metformin Effect in PCOS . . . 113
6.1.2. Individual Studies of Metformin Effect in PCOS . . . 113
6.2. Liraglutide . . . 114
6.2.1. Meta-Analysis of Liraglutide Therapy in PCOS . . . 115
6.2.2. Individual Studies of Liraglutide Therapy in PCOS . . . 115
6.3. Saxenda-Exenatide . . . 115
6.4. Thiazolidinediones . . . 115
6.4.1. Meta-analysis of Thiazolidinediones in PCOS . . . 115
6.4.2. Individual Studies of Thiazolidinediones in PCOS . . . 115
6.5. Orlistat . . . 115
6.5.1. Systematic Review and Meta-analysis of Orlistat in PCOS . . . 115
6.5.2. Individual Studies of Orlistat in PCOS . . . 115
6.6. Acarbose . . . 116
6.6.1. Meta-analysis of Acarbose in PCOS . . . 116
6.6.2. Individual Studies of Acarbose in PCOS . . . 116
6.7. Bariatric Surgery . . . 116
6.7.1. Meta-analysis of Bariatric Surgery in PCOS . . . 117
6.7.2. Individual Studies of Bariatric Surgery in PCOS . . . 117
7. Summary . . . 117
Conflict-of-Interest/Financial Disclosure Statement . . . 117
References . . . 117

1. Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder among women of reproductive age, with a prevalence estimate of 6.6% 8% in black women, 4.8% in white women [1]. The prevalence of PCOS (Rotterdam diagnostic criteria) in a meta-analysis of 15 studies was 10% [2]. Approximately 50% of women with PCOS are overweight or obese [3]. As summarized in Fig. 1, obesity is neither necessary nor sufficient for the PCOS phenotype, and the association of obesity with PCOS is not universal, with national, cultural, and ethnic differences [4]. Women with PCOS often have visceral adiposity (when compared to age and BMI-matched controls [5]). Excess weight in PCOS, particularly in the presence of androgen excess [6], amplifies adverse metabolic outcomes, doubles the likelihood of type 2 diabetes (T2DM) and the relative risk of T2DM increases 4 fold [7].

Obesity further augments the adverse metabolic and reproductive outcomes of PCOS [8], Fig. 1. Obesity increases insulin resistance and compensatory hyperinsulinemia, which in turn increases adipogenesis and decreases lipolysis. Obesity sensitizes thecal cells to LH stimulation and amplifies functional ovarian hyperandrogenism by upregulating ovarian androgen production. Obesity increases inflammatory adipokines which, in turn, then promote hyperinsulinemia, which increases obesity, providing a vicious feedback cycle, Fig. 1. Obesity increases insulin resistance and compensatory hyperinsulinemia, glucose intolerance, dyslipidemia, and increases risk of pregnancy complications [8].

Obese women with PCOS have a more severe phenotype than those less obese, with more severe menstrual irregularity, infertility, miscarriage, pregnancy induced hypertension, gestational diabetes, prematurity, biochemical and clinical hyperandrogenism, glucose intolerance and/or T2DM, and metabolic syndrome [9–11].

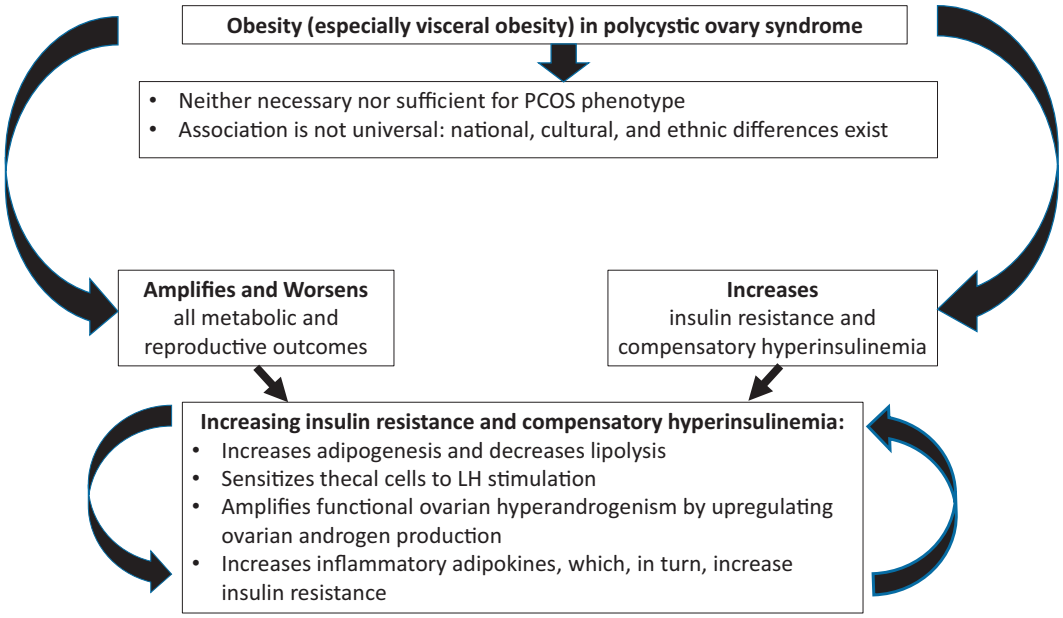

Fig. 1. Obesity, particularly visceral, in PCOS.

1.1. Visceral Adiposity

Women with PCOS are not only more likely to be obese than non-PCOS female controls, but are much more likely to have visceral adiposity and high visceral adiposity indices, associated closely with insulin resistance [5]. Enhanced visceral fat lipolysis of PCOS promotes hepatic insulin resistance by lipotoxicity of excess free fatty acids released into the portal circulation [12]. PCOS patients, whether obese or nonobese, have greater visceral adiposity than age- and BMI-matched controls [13].Testosterone promotes visceral fat accumulation and insulin resistance by inhibiting lipolysis and promoting lipogenesis [14]. Visceral adiposity index (VAI) levels are much higher in both obese and non-obese PCOS patients than in age- and BMI-matched controls [5]. Jena et al. [13] studied 58 women with newly diagnosed PCOS and 40 age- and BMI-matched controls, finding higher visceral abdominal fat thickness in cases vs controls ($p = .003$). Moreover, despite having normal BMI, non-obese women with PCOS had increased visceral adiposity and higher inflammatory markers vs matched nonobese controls. Cascella et al. [15] compared 200 overweight women with PCOS and 100 age-BMI matched controls, reporting increased visceral fat in cases ($p < .001$), directly related to insulin resistance, and to carotid intimal-media thickness. Tripathy et al. [16] compared 124 women with PCOS to 118 age-BMI-matched controls, reporting increased visceral fat and a strong association of visceral fat with carotid intimal medial thickness. Overall, screening for visceral adipose tissue appears to provide valuable information beyond other measures for obesity and for risk for the metabolic and cardiovascular complications of PCOS ([5,13,15,16].

1.2. Factors Promoting and Associated with Obesity in PCOS

There are many factors which are markers for PCOS and/or promote obesity in PCOS, Fig. 2. These include the following: small for gestational age (promoting insulin resistance and hyperinsulinemia) [17,18], large for gestational age [19], maternal PCOS [17,20], and intrauterine hyperandrogenism [20,21]. Precocious pubarche [18], associated with obesity in PCOS and also associated with small for gestational age, appears to be related to insulin resistance and hyperinsulinemia. Additional factors which promote obesity in this pathology included early (<age 10) and late (≥16) menarche [22] (increased insulin resistance and hyperinsulinemia), adolescent oligomenorrhea [23], and aboriginal origin with subsequent western diet and accretion of obesity and hyperinsulinemia [24]. The PCOS phenotype can be induced in otherwise normal subjects by valproic acid [25], apparently through induction of hyperinsulinemia.

1.3. PCOS Etiologies

The most likely etiology of PCOS is functional ovarian hyperandrogenism caused by dysregulation of steroidogenesis that sensitizes ovarian androgen production to LH, present in 90% of cases [14] Fig. 1. Insulin resistance (IR) and compensatory hyperinsulinemia play a central role in the pathogenesis of the pituitary-ovarian axis [26–29].

Neuroendocrine abnormalities appear to play an important role in PCOS pathophysiology with an increase in frequency of GnRH pulses, with shorter pulses promoting luteinizing hormone (LH), resulting in a decrease in FSH [26,30–34]. In a mouse model, Caldwell et al. [32] reported that androgen receptor signaling was an important extra-ovarian mediator in development of PCOS traits. In a rat model, Chaudhari et al. [30] reported that increased GnRH and LH pulsatility in PCOS appeared to result from the "cumulative effect of altered GnRH stimulatory and inhibitory neurotransmitters in the hypothalamic-pituitary centre". Moore and Campbell [31] concluded that the brain played an important role in the ontogeny and pathology of PCOS.

Obesity is the most common cause of insulin resistance, and the global pandemic of obesity [35] promotes PCOS diagnosis and recognition. Obesity increases insulin resistance and generates testosterone from circulating androstenedione while suppressing gonadotropin production [14]. Obesity-associated compensatory hyperinsulinemia as a response to insulin resistance is associated with anovulation of PCOS [14]. Sufficient weight loss to reduce insulin sensitivity improves ovulation in PCOS [36,37].

Testosterone promotes visceral fat accumulation and insulin resistance by inhibiting lipolysis and promoting lipogenesis [14]. Abdominal adipocyte hypertrophy triggers an inflammatory response which is aggravated in PCOS by hyperandrogenism [38], priming mononuclear cells of adipose tissue to secrete proinflammatory cytokines in response to glucose and saturated fat ingestion [39]. Obesity is associated with suppressed ovulation and high LH levels [40]. Obesity by itself can account for excess peripheral formulation of testosterone independent of PCOS [41].

Given insulin resistance, all women with PCOS are at risk for metabolic syndrome, amplified by obesity, for impaired glucose tolerance (31–35%), and for T2DM [27]. Insulin resistant hyperinsulinism is an important aggravating factor in PCOS, and about 50% of PCOS women have an abnormal degree of insulin resistance, which may be independent of obesity. Obesity-associated compensatory hyperinsulinemia sensitizes ovarian theca cells to LH stimulation. Insulin excess, by stimulating adipogenesis and lipogenesis and inhibiting lipolysis, contributing to the obesity of PCOS. Obesity upregulates ovarian androgen production via insulin resistant compensatory hyperinsulinemia and by increasing inflammatory cytokines [14].

Cassar et al. carried out meta-analysis focusing on 28 articles on obesity, insulin resistance, and PCOS. Insulin sensitivity was 27% lower in PCOS than controls, and higher BMI exacerbated reduction in insulin resistance by 15%. BMI has greater impact on insulin sensitivity in PCOS than in controls [42]. Insulin resistance was also emphasized by Lim et al. [43] in a systematic review and meta-analysis of 30 studies of the metabolic consequences of obesity in PCOS. Overweight or obese women with PCOS (vs non-overweight PCOS women), had decreased sex hormone binding globulin (SHBG), increased testosterone (T), increased free androgen index (FAI), more hirsutism, higher fasting

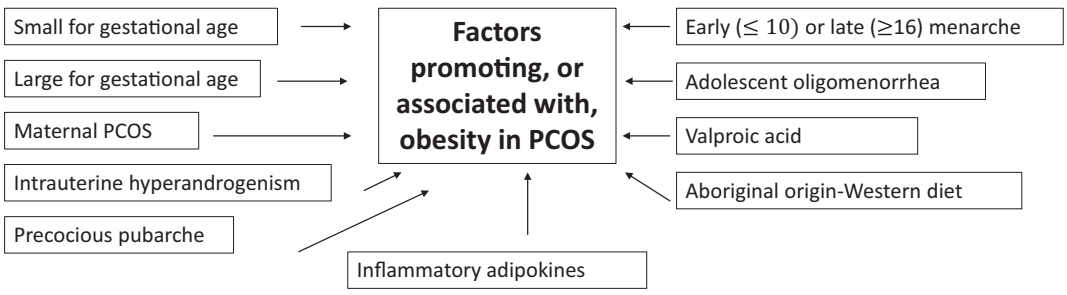

Fig. 2. Factors associated with and/or promoting development and severity of PCOS; small for gestational age [17,18], large for gestational age [19]; maternal PCOS [17,20]; intrauterine hyperandrogenism [20,21]; precocious pubarche [18]; menarche early, age (≤10), late (≥16) [22]; adolescent oligomenorrhea [23]; valproic acid [25,176,177]; aboriginal origin-western diet [24]; inflammatory adipokines [178].

glucose, and increased insulin resistance (IR). Obesity significantly worsened all metabolic and reproductive outcomes measured when compared to normal weight women with PCOS. Central obesity was associated with higher serum insulin levels [43].

Women with PCOS, both obese and non-obese, have an increased risk of cardiovascular disease (CVD), related to insulin resistance, T2DM, and metabolic syndrome [44]. In a Danish national registry study, Glintborg et al. [44] reported that the total CVD event rate was 22.6 per 1000 patient years in PCOS vs 13.2 per 1000 patient years in controls ($p < .001$). In the Nurses' health study, presence of very irregular menses, a surrogate for PCOS, was associated with a relative risk of 1.35 for non-fatal myocardial infarction (MI) and 1.88 for fatal MI [45]. In the Rancho Bernardo study, the relative risk for CVD in women with 3 or more components of PCOS was 1.3 [46].

2. Heritability of PCOS and Related Obesity

Currently, PCOS is thought to be a complex polygenic trait, with marked familial clustering of PCOS characteristics [47]. Heritability of PCOS, as assessed through monozygotic twin studies, may be as high as 70% [48]. Studies assessing single nucleotide polymorphisms (SNPS) have, overall, been inconclusive [49]. Genome wide (GWAS) studies of Chinese and European cohorts have identified 15 significant PCOS risk loci, but these loci have accounted for only a small percentage (<10%) of heritability [49–52].

Genetic studies of possible associations with PCOS and/or with obesity are summarized below, with the caveat that results differ by country of national origin and race, and, to date, have not provided new avenues to diagnosis or therapy. A broad and varied array of polymorphisms has been recognized without a single polymorphism or group of closely related polymorphisms uniformly accounting for major characteristics of PCOS.

2.1. Meta-analysis of Genetic Studies of PCOS

Meta-analyses of genetic studies have identified differing polymorphisms including DENND1A Rs10818854 and rs10986105, and significant associations between rs2479106 in Asian PCOS patients but not European [53]. In meta-analysis by Liu et al. [54], a different set of polymorphisms was identified, with the FTO gene rs9939609 A/T polymorphism differing between PCOS and controls. The A allele was a risk factor for PCOS susceptibility and was significantly associated with PCOS [54].

2.2. Individual Genetic Studies of PCOS

PCOS clusters in families, brothers, and sisters of probands with PCOS, and two genome wide association surveys have revealed insulin candidate genes related to insulin signaling, sex hormone function, and T2DM [50,51]. Two candidate genes were identified, THADA associated with T2DM, and DENND1A with endocytic trafficking in Caucasian populations [55,56]. Similarly, in a GWAS study by Cui et al. [57], DENND1A (rs2479106) was associated with elevated serum insulin 2 h after a glucose load ($p = .02$). DENND1A polymorphisms have also been associated in GWAS studies by Chen et al. [58] (rs346803513 on DENND1A). Additional studies have also focused on DENND1A variants; Dallel et al. [59] reported two DENND1A variants (rs10818854, rs 10986105) in 320 women with PCOS and 446 age and ethnically matched controls. Homozygous wild type genotype carriers of rs 10818854 and 10986105 were associated with increased risk for PCOS after controlling for covariates. Using GAT haplotypes as reference, AAG and GAG were positively, while GAT was negatively associated with PCOS.

Beyond DENND1A polymorphisms (as above), a broad variety of polymorphisms have been reported without uniform recognition of a single polymorphism or set of polymorphisms. An association between programmed cell death 4 (PDCD4) has been reported with the level of PDCD4 independently associated with odds of PCOS risk after controlling for E2 and insulin [60]. In GWAS studies in Koreans, Hwang et al. [61] found significant associations between GYS2 and BMI, and these findings were then later replicated in an obesity study in 482 children, and in 1710 women with gestational diabetes. The newly identified GYS2 was implicated as a gene as predisposing factor of PCOS.

In studies of a variant which predisposes to obesity and to increased susceptibility to PCOS via adiposity, Barber et al. [62] found significant associations between FTO genotypes and PCOS status, attenuated by adjustment for BMI. The effect of FTO polymorphisms on obesity related traits in PCOS were two times greater than the effect in large population-based studies as reported by Wojciechowski et al. [63]. There was a 3.3 kg/m^2 increase in BMI, and a 9.6 kg gain in body weight between TT and AA/CC homozygotes [63].

Hopefully, future GWAS and candidate gene studies will be able to more uniformly explain a larger percentage of variance in PCOS characteristics, thus opening up avenues to drug development.

3. Lifestyle Modification in PCOS

Multicomponent lifestyle intervention (diet, exercise, behavioral modification) is important in obese PCOS patients with a goal of ≥5% weight loss [64]. Overall, the older and more obese women are at the start of multicomponent therapy, the less the weight loss. There is no systematic data to indicate whether multicomponent lifestyle intervention has differential effects on visceral adiposity vs general adiposity, and whether anaerobic exercise is superior to aerobic for weight loss. A modest weight loss of 5–10% improves many of the features of PCOS [28,65,66]. From the data of Crosignani et al. [67], 25% of obese women with PCOS will not reach targeted weight loss of 5% of more with caloric restriction and exercise, and would be candidates for added pharmacologic therapy. Using caloric restriction (1200 cal/day) and aerobic exercise for 40 weeks in 33 anovulatory overweight patients with PCOS, Crosignani et al. [67] reported that 75% lost ≥5% body weight, and 33% ≥ 10%. Among 27 patients with oligo-amenorrhea, 67% had resumption of normal cycles, and 56% experienced spontaneous ovulation. Of the 25 patients with ≥5% weight loss, 40% had spontaneous pregnancies. Review of 12 months nonsurgical weight loss interventions summarizes the broad variations in the percentage of women achieving ≥5% weight loss with multicomponent lifestyle intervention [68], who then may subsequently need added pharmacologic intervention. Moreover, in women with a BMI ≥40 where lifestyle plus pharmacologic therapy has failed, and in those with a BMI ≥50 kg/m^2, bariatric surgery needs to be considered as an additional therapeutic option [69].

In face of the major amplifications of the metabolic and clinical abnormalities associated with obesity in women with PCOS, it is important to understand the efficacy of diet and lifestyle modification in reducing obesity in PCOS, as well as efficacy and side effects of pharmacologic and bariatric surgery approaches to treatment. An initial intervention of choice in PCOS involves lifestyle intervention with diet plus exercise plus behavioral programs, but there are few treatments, short of bariatric surgery, which result in permanent weight loss. Symptoms of PCOS may improve with 5–10% weight loss, but 25–50% weight loss (usually achievable only through bariatric surgery) may be required in the very obese [36,70].

In anovulatory women, >5% loss of body weight facilitates for resumption of ovulation [71–74]. In women with PCOS undergoing weight loss programs, loss of abdominal fat is associated with resumption of ovulation [73,74]. Conservative, non-operative weight loss efforts are difficult to sustain long term, and are associated with high rates of weight regain [75] or loss of improvement in endocrine function [76–78].

3.1. Systematic Review-Meta Analysis of Lifestyle Interventions

Lifestyle interventions in PCOS were examined by Moran et al. [79] including randomized controlled trials comparing lifestyle treatment

(diet, exercise, behavioral or combined treatments) to minimal or no treatment in women with PCOS. Three studies compared physical activity to minimal dietary and behavioral advice or no advice, and 3 compared combined dietary, exercise and behavioral interventions to minimal intervention. Moran et al. concluded that "…lifestyle intervention improves body composition, clinical and biochemical manifestations of hyperandrogenism and insulin resistance in women with PCOS." The benefit of lifestyle interventions to facilitate weight loss in obese women with and without PCOS were also examined by Kataoka et al. in a systemic review [80] which included 14 studies involving 933 women. Women with and without PCOS sustained comparable weight loss with lifestyle intervention. Domencq et al. [81] carried out a systematic review and meta-analysis of 9 lifestyle modification trials in women with PCOS, revealing significant decrements in insulin and glucose, with metformin having similar effects. Cumulative ovulation rates were 60% with lifestyle modification, and live birth rates were 26% [81].

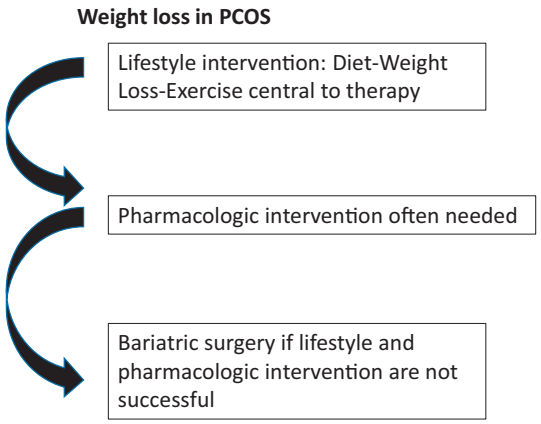

Fig. 3. Sequential treatment options in PCOS.

3.2. Individual Studies of Lifestyle Intervention

Pelletier et al. [82] retrospectively studied 117 women with PCOS, with mean BMI of 38.7 and mean age of 28.5, followed for median of 21.9 months. More than 40% of women lost >5% of initial weight after >6 months follow up, and ≥20% lost ≥10% after 1-year follow-up. These outcomes were retained for ≥4 years. Having T2DM or impaired glucose tolerance was associated with better weight loss sustainability. Tolino et al. also reported positive results from dietary weight loss intervention [83]. In 143 patients with PCOS and mean baseline BMI of 35, a 1000 kcal/day diet for 7 months resulted in a mean weight loss of 6 kg and improvement in markers of insulin resistance. Circulating androgens were reduced, with improvement in hirsutism, menses, and increased conception rate [83]. Moderate caloric restriction with loss of 2% to 5% of body weight has also been reported to reduce free testosterone, and to increase likelihood of regular cycles 50% [84]. In a study by Guzick et al. [71], 24 obese women with PCOS were maintained on a 1000 cal low fat diet for 6–7 months. Thirteen of the 24 lost >5% of body weight, and of these women, more than half had normalization of ovarian function. When given a very low calorie (600 kcal/day) commercial preparation for 12 weeks in a retrospective study by Nikokavoura et al. in 508 women with PCOS and 508 age-BMI-matched women without PCOS (entry BMI ≥28), women with PCOS lost 17.1 ± 5.6% of body weight and those without PCOS 18.2 ± 4.4% [85].

In aggregate, as summarized above, lifestyle modification is a key intervention in obese women with PCOS, resulting in weight loss and concurrent reduction of insulin resistance, circulating androgens, with improvement in menses and hirsutism. However, in a small group of women, lifestyle interventions along with subsequent pharmacologic therapy may not be enough, either because of the degree of obesity, or because there is no adherence to classical treatment. Therefore, the alternative that could be offered is bariatric surgery that has been shown to effectively optimize weight loss, reduce visceral adiposity, reduce insulin, circulating androgens, and inflammatory markers, to improve hirsutism and menstrual regularity, and to facilitate successful pregnancy [70,86–91] (Fig. 3).

3.2.1. Maintaining Lifestyle Modification Before and During Pregnancy in PCOS

Lifestyle modification to improve pregnancy outcomes appears to be particularly important pre-conception in women with PCOS and preconception obesity [92]. Legro et al. [92] carried out a randomized controlled trial of preconception and infertility treatment. Women were randomly assigned to receive either 16 weeks of 1) continuous oral contraceptive pills (OCPs) (ethinyl estradiol 20 μg/1 mg norethindrone acetate); 2) lifestyle modification including caloric restriction with meal replacements, weight loss medication (either sibutramine, or orlistat), and increased physical activity to promote a 7% weight loss ("Lifestyle"); or 3) combined treatment with both OCP and lifestyle modification ("Combined"). After preconception intervention, women underwent standardized ovulation induction with clomiphene citrate and timed intercourse for four cycles. Significant weight loss was achieved with both Lifestyle (mean weight loss, −6.2% and combined (mean weight loss, −6.4%) compared with baseline and OCP (both $p < .001$). Cumulative ovulation rates were superior after weight loss: OCP, 46%; Lifestyle, 60%; and Combined, 67% ($p < .05$). Preconception weight loss intervention eliminated adverse metabolic OCP effects and, compared with OCP pretreatment, led to higher ovulation rates [92]. Legro et al. [93] also reported improved ovulation and live births with delayed infertility treatment with clomiphene citrate when preceded by lifestyle modification with weight loss compared with immediate clomiphene treatment. Palomba et al. studied 40 obese PCOS patients with anovulatory infertility who followed a structured exercise and diet program (20 in each group). The frequency of menses of ovulation rate was higher in the structured exercise group but the increased cumulative pregnancy rate was not different [94]. Palomba et al. also reported that a 6-week intervention of structured exercise training and a hypocaloric diet was effective in increasing the probability of ovulation under clomiphene citrate treatment, $p = .008$ [95]. Weight reduction was also important when IVF was employed in women with PCOS: Einarsson et al. [29] evaluated 317 women where weight reduction and IVF and IVF alone were compared. There were more live births achieved through spontaneous pregnancies in the weight reduction and IVF group vs IVF alone 10.5% vs 2.6%, $p = .009$ [29].

4. Type of Diet

Irrespective of caloric restriction, an issue which has been repetitively examined is whether there is an optimal type of diet irrespective of caloric restriction in women with PCOS. Although various studies summarized below have suggested unique benefits from the type of diet, irrespective of caloric restriction, overall there is no uniform evidence that any unique type of diet optimizes weight loss or reproductive or metabolic changes in women with PCOS [66,68,96,97]. In obese women with PCOS any type of tolerable hypocaloric diet which can be maintained long-term should be used.

4.1. Individual Studies of Effects of Type of Diet in PCOS

Azadi-Yazdi et al. [98] carried out a randomized 3 months controlled clinical trial, where 60 women with PCOS were randomly assigned to one of two diets with energy restriction: the DASH diet and a control diet. The DASH and control diets consisted of 50–55% carbohydrate, 15–20% protein and 25–30% total fat. The DASH diet was designed to be rich in vegetables, fruits, whole grains and low-fat dairy products, as well as low in saturated fats, cholesterol, refined grains and sweets. The DASH diet compared to the control diet was associated with a

significant reduction in weight [−5.78 kg versus −4.34 kg, $p = .032$], BMI [−2.29 versus −1.69 kg/m^2, $p = .02$], fat mass [−3.23 versus −2.13 kg, $p = .008$] and serum androstenedione [−1.75 versus −1.02 ng/ mL, $p = .019$]. Mehrabani et al. [99] gave two diets to 60 obese women with PCOS, one a conventional hypocaloric diet with 15% of calories from protein, and the second, high protein, low glycemic index diet (30% of calories from protein. Weight loss did not differ between the two diets, but the higher protein diet was more effective in regarding insulin sensitivity and decrements in high sensitivity CRP. Moran et al. [100] gave a hypocaloric 1435 cal diet for 12 weeks, with 4 subsequent weeks of weight maintenance, either low protein (55% carb, 15% protein) or high protein (45% carb, 30% protein) to women with PCOS. Decrements in weight (7.5%) and abdominal fat (12.5%) occurred independently of diet composition. Moran et al. concluded that the high protein-weight loss diet might result in minor differential endocrine and metabolic improvements. Marsh et al. [101] compared changes in insulin sensitivity and clinical outcomes after similar weight losses after consumption of a low-glycemic index (GI) diet compared with a conventional healthy diet in 96 women with PCOS. Overweight and obese premenopausal women with PCOS were given either an ad libitum low-GI diet or a macronutrient-matched healthy diet and were followed for 12 months or until they achieved a 7% weight loss. The attrition rate was high in both groups (49%). Among completers, measures of insulin sensitivity after oral glucose tolerance testing improved more with the low-GI diet than with the conventional healthy diet. There was a significant diet-metformin interaction ($p = .048$), with greater improvement in insulin sensitivity among women prescribed both metformin and the low-GI diet.

5. Diet-Exercise

5.1. Systematic Review and Meta-Analysis of Diet Combined with Exercise in PCOS

Meta-analysis of lifestyle modification in PCOS reveals benefits on body composition, hyperandrogenism, and insulin resistance in women with PCOS [79]. Moran et al. [79] carried out meta-analysis with 6 studies with 164 women with PCOS. Three studies compared physical activity to minimal dietary and behavioral advice or no advice. Three studies compared combined dietary, exercise and behavioral interventions to minimal intervention. Lifestyle intervention provided benefits when compared to minimal treatment for anthropometric and reproductive outcomes. Benefits included reductions in testosterone, hirsutism, weight, waist circumference, and fasting serum insulin.

5.2. Individual Studies of Diet Combined with Exercise in PCOS

BMI and age of women with PCOS affects outcome of diet- aerobic and anaerobic exercise programs, with less weight loss associated with higher entry BMI and/or age. Structured exercise, when added to dietary caloric restriction, improves ovulation [94], glucose tolerance [102], resumption of ovulation [103], weight loss [104], and reduction in skinfold thickness [105]. Diet plus exercise interventions are often hard to maintain, as reported by Thomson et al. [106] who randomized 104 overweight PCOS patients into one of three 20-week lifestyle programs: diet only, diet + aerobic exercise, diet + combined aerobic-resistance exercise. There were no differences in outcomes (BMI, body weight) for the 3 groups [106]. Only 55% of the participants completed the study. Redman et al. [107] have reported that aerobic exercise for 16 weeks without weight loss improved insulin sensitivity and ovarian morphology in women with PCOS.

Any intervention which reduces excess weight can improve many of the metabolic abnormalities of obese women with PCOS, and lifestyle interventions which focus on diet-weight loss and exercise are very important [66,108]. The addition of exercise to dietary caloric restriction facilitates weight loss [109].

6. Drug Therapy to Reduce Obesity in Women with PCOS

Table 1 provides an overview of commonly used pharmacologic approaches to reduce obesity in women with PCOS. Weight loss effectiveness is graded on a relative scale of 1 (least) to 10 (most), based in part on network meta-analysis which has identified, in decreasing weight loss effectiveness, liraglutide, orlistat, and metformin [110]. Phentermine and sibutramine are FDA approved drugs for reduction of obesity in general populations, and sibutramine along with lifestyle modification-diet has been reported to facilitate weight reduction in PCOS patients beyond diet-placebo [111,112]. Teede et al. [64] have concluded "… anti-obesity medications in addition to lifestyle could be considered for the management of obesity in adults with PCOS after lifestyle intervention, as per general population recommendations." However, sibutramine has potential for increasing blood pressure [113], and given limited published data in women with PCOS for weight reduction drugs approved for obesity treatment in general obese populations, and limited published data on D-chiro-inositol in PCOS cohorts, these agents are not included in Table 1.

6.1. Metformin

6.1.1. Systematic Review and Meta-analysis of Metformin Effect in PCOS

In adults, recently published meta-analyses by Teede et al. [64] have provided the following information: In 3 randomized controlled studies in women with PCOS and BMI >25 kg/m^2, metformin was better than placebo for weight loss, and better for BMI reduction when 11 randomized controlled trials in women with BMI >25 kg/m^2 were subgrouped. Similarly, metformin and lifestyle modification compared to placebo-lifestyle modification lowered BMI (−0.73 kg/m^2) and reduced subcutaneous adipose tissue (−92.5 cm) after 6 months in a systematic review and meta-analysis by Nanderpoor et al. of 12 randomized controlled clinical [114]. There was also an increase in the number of menstrual cycles. There were no differences between metformin alone vs lifestyle alone. Similar results were reported by Nieuwenhuis-Ruifrok et al. [115] in a systematic review and meta-analysis where there was a significant decrease in BMI vs placebo (−0.68 kg/m^2), greater with high dose metformin >1500 u/day, and greater with longer duration of therapy. Moreover, the negative effect of combined oral contraceptives on BMI is blunted by concurrent metformin as reported in a meta-analysis by Luque-Ramirez et al. [116]. They focused on metformin, antiandrogens (AA) and combined oral contraceptives (COC) including 33 studies and 1521 women with PCOS. …" Differences between COC, AA, and metformin effects on the hirsutism score were not significant and the combination of COC and/or AA with metformin was similar to COC and/or AA therapy alone for the hirsutism score. The negative effect of COC therapy on BMI was blunted by its combination with metformin. Metformin also reduced HOMA-IR, compared to COC and/or AA. Adding metformin to COC and/or AA yielded a beneficial effect on fasting glucose levels. Although COC improves menstrual frequency in oligomenorrheic women with PCOS, metformin is needed to blunt the adverse metabolic effects on COC. ".

6.1.2. Individual Studies of Metformin Effect in PCOS

Metformin lowers serum insulin and androgen levels and promotes resolution of cyclicity abnormalities inducing ovulation by normalizing pulsatile production of GNRH and gonadotropins [117]. Metformin also improves hyperandrogenemia even in non-obese women with PCOS who appear to have normal metabolic insulin sensitivity. Whether it is the correction of abnormal insulin action or reduction of levels is unclear [118]. In obese women with PCOS, when accompanied by diet, metformin usually facilitates weight loss, and concurrently, with reduces serum androgens, increases ovulation, and improves menstrual frequency [64,119], Table 1. in additional to lifestyle change, metformin should be considered in adolescents with a definitive diagnosis of PCOS or with characteristics of PCOS before the diagnosis is made to attempt

Table 1
Pharmacologic [64,179] approaches to weight loss in polycystic ovary syndrome.

Drugs used in treatment of polycystic ovary syndrome in adjunct with lifestyle intervention to achieve weight loss
Weight loss effectiveness scale[a] (qualitative: 1 lowest–10 optimal best)

Metformin
- **Mode of action**: decreases hepatic glucose production, decreases intestinal absorption of glucose, improves insulin sensitivity by increasing peripheral glucose uptake and utilization
- **Dose**: 1.5–2.55 g/day, 1–2 g/day if XR, in divided doses with meals. Dose-response present, start with lowest dose
- **Use in pregnancy**: Increases live births, not teratogenic, reduces gestational diabetes
- **Contraindications**: creatinine clearance <40 mL/min
- **Use with caution**: creatinine clearance <60 mL/min moderate–severe heart failure, acute myocardial infarction, before major surgery
- **Rare side effects**: intractable nausea, gastritis, vomiting
- **Common side effects**: nausea, vomiting, diarrhea
- **Weight loss effectiveness**: 5, (8 when combined with Liraglutide)

Liraglutide
- **Mode of action**: long-acting glucagon-like peptide-1 receptor agonist, binding to the same receptors as does endogenous GLP-1, stimulates insulin secretion, central appetite suppression.
- **Dose**: 1.2–1.8 μg/once/day subcutaneously, dose response present. 3 mg/ once per day (Saxenda). Start with lowest dose.
- **Use in pregnancy**: not recommended
- **Contraindications**: History of medullary thyroid carcinoma, multiple endocrine neoplasia syndrome type 2, acute or chronic pancreatitis, gastroparesis.
- **Use with caution**: previous pancreatitis
- **Rare side effects**: intractable recurrent nausea, vomiting
- **Common side effects**: nausea, vomiting, headache
- **Weight loss effectiveness**: 7, (8 when combined with Metformin)

Thiazolidinediones
- **Mode of action**: PPAR-gamma agonists, reduce insulin resistance
- **Dose**: Pioglitazone (45 mg, up to 15 mg, three times/day with meals); Rosiglitazone (4–8 mg/day, divided doses with meals). Start with lowest dose.
- **Use in pregnancy**: not recommended
- **Contraindications**: congestive heart failure, peripheral edema
- **Use with caution**: safety during pregnancy not well understood
- **Rare side effects**: bladder cancer, bone fracture in women
- **Common side effects**: peripheral edema
- **Weight loss effectiveness**: 0–1, weight gain possible

Orlistat
- **Mode of action**: Reduces fat absorption. Inhibits gastric and pancreatic lipases, blocks hydrolysis of dietary triglycerides to absorbable fatty acids, triglycerides excreted unchanged.
- **Dose**: 120 mg up to 3 times/day with meals, restrict dietary fat to <30% of calories, add fat-soluble vitamin daily
- **Use in pregnancy**: contraindicated (fat soluble vitamin malabsorption)
- **Contraindications**: acute or chronic cholecystitis, obstructive bowel disease.
- **Use with caution**: pancreatic or liver disease
- **Rare side effects**: Oxaluria, kidney stones
- **Common side effects**: flatulence, steatorrhea, diarrhea, increased stool frequency.
- **Weight loss effectiveness**: 5

Acarbose
- **Mode of action**: Delayed glucose absorption with lowering of postprandial hyperglycemia, competitive-reversible inhibition of pancreatic alpha-amylase and membrane-bound intestinal alpha-glucoside hydrolase enzymes.
- **Dose**: 50 mg every 8 h if <60 kg; 100 mg every 8 h if >60 kg, take with first bite of meal
- **Use in pregnancy**: not recommended
- **Contraindications**: Reduced renal function (eGFR <25 mL/min/1.73 m^2). Inflammatory bowel disease, colonic ulceration, partial intestinal obstruction, predisposition to intestinal obstruction.
- **Use with caution**: eGFR <50 mL/min/1.73 m^2, previous small or large bowel partial resection
- **Common side effects**: Abdominal pain, diarrhea, flatulence
- **Weight loss effectiveness**: 5

[a] By network meta-analysis [110] including 23 trials with 941 women with PCOS, amount of weight loss in descending order was liraglutide, orlistat and Metformin.

to ameliorate obesity and to prevent development of morbid obesity in young adulthood [64].

Multiple individual studies have shown that when metformin is added to diet in women with PCOS, there is significant weight loss (often ~8%), reduction in the waist to hip ratio, reduction of insulin resistance and serum testosterone, and (usually) improvement in menstrual cyclicity [77,118,120–122]. Metformin therapy also has a role in women with PCOS who have normal weight and normal HOMA IR, where up to 75% have restoration of normal menses in absence of modification of BMI, waist to hip ratio, or glucose, insulin, or lipid profiles [123].

In contrast to estrogen-progestin oral contraceptives, Metformin is anti-thrombotic, promoting fibrinolysis. In a 1997 study by Velazquez et al. [124], in 16 nondiabetic women with PCOS before and after 8 weeks on metformin (1.5 g/day), metformin reduced the levels of the major inhibitor of fibrinolysis, antigenic plasminogen activator inhibitor type 1, and BMI decreased 1.3%. Metformin may be favored over combined oral contraceptives (COC) in PCOS due to increased thrombotic risk with COC vs metformin [125]. Burchall et al. [125] studied 60 overweight women with PCOS (mean age 34 years, mean BMI 37 kg/m^2) who were randomized to either metformin, higher-dose oral COC or low-dose COC + spironolactone. Aberrant coagulation was noted in both COC groups, but not with metformin.

Overall, metformin has been one of the initial drugs added to multicomponent lifestyle therapy in PCOS to facilitate weight loss and for its metabolic benefits in reducing insulin resistance. Combination of metformin with liraglutide (as below) has been particularly effective in facilitating weight loss.

6.2. Liraglutide

There is increasing evidence for effectiveness of liraglutide in treatment of obesity in PCOS, particularly when given in conjunction with metformin and lifestyle intervention and it appears to have the greatest weight loss potential [110] of the drugs listed in Table 1. However, genetic variability in the GLP-1 receptor is associated with inter-individual differences in the weight loss potential of liraglutide [126].

6.2.1. Meta-Analysis of Liraglutide Therapy in PCOS

Niafar et al. [127] performed a meta-analysis for 7 randomized clinical trials of liraglutide in PCOS for at least 90 days, including 178 women, and 172 post treatment measures. BMI dropped 1.65 kg/m^2 after 3 months, without change in waist circumference, fasting insulin, HOMA IR, or SHBG. Serum testosterone fell by 0.29 nmol/L in 88 women, $p = .00003$.

6.2.2. Individual Studies of Liraglutide Therapy in PCOS

Multiple individual studies have reported that liraglutide therapy usually reduces weight by 5% or more, reduces visceral adiposity, and serum testosterone [128–133]. Jensterle et al. [133] compared 12 weeks therapy with liraglutide 1.2 mg/day vs metformin 2 g/day for 12 weeks in 32 obese women with BMI 39.5 kg/m^2. There were significant decrements in BMI, waist circumference, and whole-body fat mass, without differences between liraglutide and metformin. However, in the subgroup with HOMA IR >2, severe obesity, and higher odds ratio for metabolic syndrome, BMI fell more on Liraglutide, 2.13 vs 0.62 kg/m^2.

Liraglutide is particularly effective for weight loss when combined with metformin [134,135]. Pre-conception liraglutide added to metformin optimizes pregnancy rates in infertile women with PCOS [136]. Salamun et al. [136] carried out a prospective, randomized, open label study in 28 infertile PCOS patients (mean age 31, BMI 36.7 kg/m^2) given metformin 2 g/day or metformin 2 g combined with liraglutide (1.2 mg/day) for 12 weeks. Patients on metformin lost 7.0 kg compared with 7.5 kg on combined therapy with no between group difference in weight loss. The IVF pregnancy rate per embryo transfer was higher in the combination group 85.7% vs 28.6%, $p = .03$. The cumulative pregnancy rate in 12 months was 69.2% in the combination group vs 35.7% in the metformin group. Preconception low dose liraglutide added to metformin was superior in increasing pregnancy rates in infertile obese women with PCOS, despite comparable weight reduction in both groups.

Liraglutide is very effective and in the first rank of drugs for weight loss in PCOS, particularly in concert with metformin. Overall, particularly with a metformin-liraglutide combination, when coupled with diet and exercise, weight loss of ~5–10% and improvement in insulin resistance and hyperandrogenemia can be expected in a majority of women with PCOS.

6.3. Saxenda-Exenatide

Elkind-Hirsch et al. [137] studied 60 overweight anovulatory women with PCOS (BMI >27 kg/m^2), ages 18–40, given metformin 2 g/day, exenatide 10 μg twice/day, or combined therapy for 24 weeks. Combined therapy was superior to monotherapy in improving menstrual cyclicity, ovulation rate, free androgen index, and insulin sensitivity measures and reducing weight and abdominal fat. Both exenatide arms were more effective in promoting weight loss than metformin ($p = .003$). Tzotzos et al. [138] emphasized that the beneficial effects of liraglutide 1.2 and 1.8 mg in weight loss in PCOS would be amplified with the use of the recently approved 3.0 mg/day dose (Saxenda) for weight loss.

6.4. Thiazolidinediones

Thiazolidinediones (TZDs) have little weight loss effectiveness, but are effective in treating hyperinsulinemia and insulin resistance in both lean and obese women with PCOS [139–141], Table 1. Thiazolidinediones can be used as alternatives to metformin in PCOS, primarily in patients who cannot tolerate metformin or do not respond to metformin [142]. TZDs can effectively reduce insulin and fasting blood glucose levels in patients with PCOS, but TZDs may not effectively reduce the Ferriman-Gallwey score or androgen levels and may increase body weight [140,143].

6.4.1. Meta-analysis of Thiazolidinediones in PCOS

Du et al. [143] carried out meta-analysis of 6 thiazolidinedione trials, pioglitazone vs metformin, including 278 women with PCOS. Pioglitazone was better than Metformin at reducing insulin $p = .002$, and improving HOMA IR $p = .024$, but was less effective in reducing BMI, $p = .038$.

6.4.2. Individual Studies of Thiazolidinediones in PCOS

Glueck et al. studied 13 women with PCOS who failed to respond optimally to metformin [144]. When pioglitazone (45 mg/day) was added, insulin, glucose, insulin resistance, insulin secretion, and DHEAS fell. Sex hormone-binding globulin rose, and menstrual regularity improved, without adverse side-effects [144]. A second thiazolidinedione, rosiglitazone, has also been shown to be effective in PCOS. Du et al. [140,143] evaluated two studies using rosiglitazone (100 women, 4 mg once or twice/day) and two studies of pioglitazone (70 women, 30 mg/day). Menstrual cycle regularity improved with rosiglitazone and pioglitazone vs placebo.

In women unable to tolerate metformin (usually because of GI side effects), or in those who do not optimally respond the metformin, thiazolidinediones offer a reasonable alternative for reducing insulin resistance and hyperandrogenism, but they do not promote any weight loss.

6.5. Orlistat

6.5.1. Systematic Review and Meta-analysis of Orlistat in PCOS

Graff et al. [145] carried out a systematic review and meta-analysis of orlistat in PCOS. Three randomized control trials were included in the fixed effects model meta-analysis for a total of 121 women with PCOS. Orlistat and metformin had similar positive effects on BMI (−0.65%), HOMA-IR (−3.60%), testosterone (−2.08%), and insulin (−5.51%). Wang et al. [110] recently evaluated 23 trials reporting on 941 women in a network meta-analysis comparing liraglutide, orlistat, and metformin for weight loss. The amount of weight lost differed significantly among the drugs (in descending order): liraglutide, orlistat and metformin. Liraglutide alone, liraglutide + metformin, and metformin alone significantly reduced waist circumference, but no change was found with orlistat.

6.5.2. Individual Studies of Orlistat in PCOS

Several studies have suggested that orlistat is as good as metformin [145–149] in promoting weight loss and reducing insulin resistance. Panidis et al. [149] studied 101 women with PCOS, mean age 26.2 and BMI 34.5, and 29 BMI matched women with normal ovulation. Orlistat (120 mg three times/day) was given for 6 months along with low calorie diet and exercise. There was a reduction in BMI in both PCOS women and controls ($p < .05$). Markers of HOMA IR improved ($p < .05$), and to comparable degree in treated PCOS vs controls. Serum T and the free androgen index (FAI) fell in treated patients and not in controls. Metformin and Orlistat were also found to have similar beneficial results in a study by Kumar et al. [147] who evaluated 90 women, orlistat vs metformin with lifestyle, or controls with lifestyle alone. Orlistat and metformin were more effective than lifestyle in reducing weight, BMI, waist circumference, and waist/hip ratio. Side effects were less with orlistat. Conception rates were 40% orlistat, 16.7% metformin, and 3.3% in controls $p = .003$. Orlistat was as effective as metformin in reducing weight and achieved similar ovulation rates in obese PCOS patients. Orlistat was better tolerated than metformin in this study.

The use of orlistat is limited by gastrointestinal side effects, with 15% to 30% experiencing oily stool, fecal urgency, or oily spotting, and 7% fecal incontinence, especially at the initiation of treatment [150].

When orlistat can be tolerated, and if metformin and/or liraglutide have been ineffective in promoting weight loss, then orlistat offers an alternative treatment, but one which is limited by gastrointestinal side effects.

Table 2
Bariatric surgery approaches to treatment of polycystic ovary syndrome.

Bariatric surgery
- **Mode of action**: Increases endogenous secretion of incretin and GLP-1 with subsequent reduction in hyperinsulinemia and reduced insulin resistance. Reduction of caloric intake by mechanically limiting food intake. Malabsorption of dietary fats.
- **Use in pregnancy**: surgical procedure should be completed and weight loss stable for 12–24 months before attempting conception. Malabsorption of fat-soluble vitamins needs to be monitored
- **Contraindications**: Severe heart failure, unstable coronary artery disease, cirrhosis with portal hypertension, esophageal varices, chronic stomach or esophageal ulcer, Crohn's disease
- **Use with caution**: congenital or acquired esophageal narrowing, chronic pancreatitis, chronic long-term steroid use, severe pulmonary dysfunction
- **Common side effects**: Long term hypovitaminosis, secondary hyperparathyroidism, fetal malnutrition if pregnancy <1.5 years after surgery, gastric erosion. Long term hypovitaminosis, increased bone fracture
- **Weight loss effectiveness**: 10

6.6. Acarbose

6.6.1. Meta-analysis of Acarbose in PCOS

Zhang et al. [151] carried out meta-analysis of 3 studies of acarbose in PCOS. Changes in the Ferriman-Gallwey score or BMI were not significant. There were no significant differences between acarbose and metformin with respect to improvements in ovulation rate, menstrual patterns, or changes in serum levels of testosterone, adverse events, or BMI. Acarbose was superior to placebo or no treatment in reducing serum levels of testosterone ($p = .01$), but acarbose caused a significantly higher incidence of side effects, such as abdominal distention and diarrhea ($p < .0001$).

Kircher [152] reviewed 3 randomized controlled trials and 1 prospective study of acarbose in PCOS. Compared to metformin, acarbose induced greater weight loss and comparable menstrual regularity. In contrast, in an individual study, Hanjalic-Beck et al. [153], in 75 women in a prospective, randomized, blinded placebo-controlled trial, using metformin 2550 ($n = 37$) or acarbose 300 ($n = 38$) for 12 weeks, found a significant decrease in BMI only on metformin. At the end of treatment there was no difference in metabolic or hormonal variables between the two drugs. Flatulence and diarrhea were lower for acarbose than metformin 38% vs 80%, $p < .001$.

6.6.2. Individual Studies of Acarbose in PCOS

Penna et al. [154] studied 30 obese hyperinsulinemic women with PCOS comparing 150 mg acarbose/day vs placebo. Acarbose reduced BMI from 35.9 to 33 kg/m^2. No parameters changed in the placebo group. The lowest dose of acarbose which lowered glycemia in diabetic patients was 150 mg/day.

Because of the frequent side effects of abdominal distention and diarrhea, and (overall) lesser weight-loss capability than metformin, acarbose has not widely been used in treatment of PCOS.

In a small group of women where previous diet-exercise and pharmacologic therapies (summarized above) fail or are not able to ameliorate obesity and its associated metabolic consequences, bariatric surgery is an effective, successful, non-pharmacologic approach, but more complex, particularly for ensuring successful long-term follow-up.

6.7. Bariatric Surgery

In women with morbid obesity and PCOS, without adequate response to weight loss, diet, exercise, and pharmacologic intervention (Fig. 3), bariatric surgery is one of the last sequential recommendations for weight loss intervention and metabolic improvement in PCOS, but has considerably greater complexity. For the morbidly obese, bariatric surgery is a first-line therapy, indicated (by NIH criteria) when BMI is >40, or >35 with a concurrent serious co-morbidity [155] including, in some studies, PCOS [37,156]. Bariatric surgery is superior to medical therapy controlling hyperglycemia in type II diabetes [157], increasing incretin and glucagon-like peptide-1 (GLP-1), reducing hyperinsulinemia, and improving insulin sensitivity [158,159], all optimal for PCOS. Refraining from pregnancy for 12–24 months after bariatric surgery reduces risk for small-for-gestational-age babies and shorter pregnancies [160].

Candidates for bariatric surgery procedure include adults with BMI ≥40 kg/m^2 without comorbid illness or adults with BMI 35 to 39.9 kg/m^2 with at least one serious comorbidity [161], but it has been estimated that <1% of all subjects (irrespective of PCOS) who are candidates for bariatric surgery have had the surgery. The extraordinary obesity of women with PCOS having bariatric surgery is documented as follows: mean age and BMI levels in bariatric surgery studies of women with PCOS were 32 years and 52.8 kg/m^2 (Jamal et al. [70]), 36 years and 44.2 kg/m^2 (Christ and Falcone [86], 34 years and 59 kg/m^2 (Eid et al. [156, and]), and 31 years and 46 kg/m^2 (Sklubleny et al. [88]).

Bariatric surgery has an important role in treatment of morbid obesity in women with PCOS [70,86,90,91,162,163]. However, when considering the major benefits of bariatric surgery in morbidly obese women with PCOS, long term medical [164–166] and surgical [167] complications of the surgery need to be balanced against the benefits of weight loss and obesity related comorbidities. When comparing 6.5 year (median) follow-up of bariatric surgery vs specialized medical treatment, benefits included greater remission of hypertension and lower likelihood of new hypertension, greater likelihood of diabetes remission, and adverse outcomes included greater risk of new onset depression, greater use of opioids, and greater risk for undergoing at least 1 additional gastrointestinal surgical procedure (31.3% vs 15.5% [164]. Short term postoperative complications included bleeding 0.7%, wound infection 0.5%, urinary tract infection (0.3%), venous thromboembolism (0.3%) and leak (0.2%) [167]. Long term hypovitaminosis and secondary hyperparathyroidism persist at 5-year follow-up after gastric bypass [166]. In a retrospective cohort study using Swedish national databases, 38,971 obese patients undergoing gastric bypass were identified, 7758 with diabetes and 31,213 without. An equal number of well-balanced controls were identified through multivariable 1:1 propensity score matching. During a median follow-up time of 3.1 years, gastric bypass was associated with increased risk of any fracture in patients with and without diabetes, and this risk appeared to increase with time [168]. Fracture risk was not associated with the amount of weight loss or calcium and vitamin D supplementation following surgery. There was also an increased risk of fall injury after surgery, which could contribute to the increased fracture risk [168].

The multiple surgical approaches to bariatric surgery remain under review without any consensus optimal procedure [163,169–172]. The optimal bariatric surgical procedure for morbidly obese women with PCOS is unknown. Gastric banding, where the band could be loosened to allow larger caloric intake during pregnancy, was previously thought to be optimal, but band erosion is a serious long-term complication. Historically Roux-en-Y Gastric Bypass (RYGB) was the most common procedure and is associated with greater weight loss than gastric banding. Recently, vertical sleeve gastrectomy (VSG) has increasingly been used, which has lower operative and long-term morbidity due to the lack of bowel re-anastomosis in RYGB. VSG offers long term weight loss slightly less than RYGB [173].

An outline for bariatric surgery use in PCOS is provided in Table 2.

6.7.1. Meta-analysis of Bariatric Surgery in PCOS

In a meta-analysis by Skubleny et al. [88] of 13 studies with 2130 women, the incidence of PCOS preoperatively was 45.6%, falling, after 12 months to 6.8% ($p < .001$). Menstrual irregularity and hirsutism both fell at 12 month and study end follow-up. Butterworth et al. [91], pooling 6 studies, reported that post- surgical contraception rates varied from 33% to 100%.

Garb et al. [174], in a meta-analysis of bariatric surgery outcomes for morbidly obese subjects, reported percent excess weight loss of 62.6% for laparoscopic gastric bypass and 49.4% for laparoscopy banding.

6.7.2. Individual Studies of Bariatric Surgery in PCOS

Bariatric surgery, after conventional diet, weight loss, exercise, and pharmacologic intervention have failed in morbidly obese women with PCOS, effectively attenuates the major metabolic and functional abnormalities of PCOS and its clinical symptomatology [88–91,175], and facilitates regularization of menstrual function and improves conception rates. Weight loss 1 year after sleeve gastrectomy was 36% [87], and weight fell one year after surgery from 126 ± 38 kg to 97 ± 23 kg in studies by Christ and Falcone [86]. In 31 women treated with Roux-en-Y gastric bypass by Kjaer et al. [175], average weight loss in the first postoperative year was 39.6 kg, and 85% of women with oligo-amenorrhea gained regular menstrual cycles.

Increased conception rates in women with PCOS after bariatric surgery may be related to changes in AMH. Nilsson-Condori et al. [89] prospectively studied 48 women (PCOS not specified). Median AMH levels were 30.0 pmol/L at baseline and were 19 and 18 at 6 and 12 months after RYGB, $p < .001$. Chiofalo et al. [90] studied 14 women with PCOS. AMH levels in obese and non-obese PCOS women were high preoperatively 5.84, 7.35 ng/mL, and fell 1 year after surgery ($p < .02$). Bhandari et al. [162] reported that morbidly obese patients with PCOS benefitted from bariatric surgery both in regularization of menstrual function and normalization of serum AMH levels. In 31 morbidly obese women with PCOS treated with Roux-en-Y gastric bypass, menstruation corrected in 82%, and hirsutism resolved in 29%. Of those women with diabetes, 78% had complete remission of the diabetes. Most women with PCOS resume normal menstrual cycles after bariatric surgery. Eid [156] retrospectively studied 24 women with PCOS who had laparoscopic gastric bypass surgery, whose mean age was 35, and mean preoperative body weight was 306 lb, with a mean BMI of 50 kg/m^2. All patients were oligomenorrheic and 23 were hirsute. The mean follow-up period was 28 months. The mean excess weight loss at 1 year of follow-up was 56.7% ± 21.2%. All women resumed normal menstrual cycles. 52% of women had resolution of hirsutism. Five women were able to conceive after surgery without the use of clomid.

In morbidly obese women with PCOS who fail to satisfactorily achieve targeted weight loss, and remain oligo-amenorrheic, hyperandrogenemic, and have difficulty conceiving despite diet-exercise and pharmacologic treatment, bariatric surgery remains a last and effective intervention.

7. Summary

Obesity, particularly visceral adiposity, is one of the defining characteristics of PCOS, and from adolescence through adulthood, and requires continuing monitoring and intervention. Obesity amplifies and worsens all metabolic and reproductive outcomes in PCOS. Obesity increases insulin resistance and compensatory hyperinsulinemia, which in turn increases adipogenesis and decreases lipolysis. Obesity increases inflammatory adipokines which, in turn, increase adipogenesis. Lifestyle intervention focused on weight loss and concurrent exercise are central to therapy, but pharmacologic therapy often needs to be added, and if therapeutic goals are still not reached, bariatric surgery can often provide good outcomes for weight loss, amelioration of T2DM, resolution of hyperandrogenism, and resumption of ovulation and pregnancy. PCOS symptoms commonly improve with 5% to 10% weight loss, but 25% to 50% weight loss, usually achievable only through bariatric surgery, may be required for the morbidly obese when other interventions fail.

Conflict-of-Interest/Financial Disclosure Statement

The authors have no conflicts of interest. The study was supported in part by the Lipoprotein Research Fund of the Jewish Hospital of Cincinnati.

References

[1] Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. J Clin Endocrinol Metab 2004;89:2745–9.
[2] Bozdag G, Mumusoglu S, Zengin D, Karabulut E, Yildiz BO. The prevalence and phenotypic features of polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod 2016;31:2841–55.
[3] Hoeger KM. Obesity and lifestyle management in polycystic ovary syndrome. Clin Obstet Gynecol 2007;50:277–94.
[4] Ding T, Hardiman PJ, Petersen I, Wang FF, Qu F, Baio G. The prevalence of polycystic ovary syndrome in reproductive-aged women of different ethnicity: a systematic review and meta-analysis. Oncotarget 2017;8:96351–8.
[5] Durmus U, Duran C, Ecirli S. Visceral adiposity index levels in overweight and/or obese, and non-obese patients with polycystic ovary syndrome and its relationship with metabolic and inflammatory parameters. J Endocrinol Invest 2017;40:487–97.
[6] Glueck CJ, Dharashivkar S, Wang P, Zhu B, Gartside PS, Tracy T, et al. Obesity and extreme obesity, manifest by ages 20–24 years, continuing through 32–41 years in women, should alert physicians to the diagnostic likelihood of polycystic ovary syndrome as a reversible underlying endocrinopathy. Eur J Obstet Gynecol Reprod Biol 2005;122:206–12.
[7] Norman RJ, Masters L, Milner CR, Wang JX, Davies MJ. Relative risk of conversion from normoglycaemia to impaired glucose tolerance or non-insulin dependent diabetes mellitus in polycystic ovarian syndrome. Hum Reprod 2001;16:1995–8.
[8] Legro RS. Obesity and PCOS: implications for diagnosis and treatment. Semin Reprod Med 2012;30:496–506.
[9] Baillargeon JP, Nestler JE. Commentary: polycystic ovary syndrome: a syndrome of ovarian hypersensitivity to insulin? J Clin Endocrinol Metab 2006;91:22–4.
[10] Glueck CJ, Goldenberg N, Pranikoff J, Khan Z, Padda J, Wang P. Effects of metformin-diet intervention before and throughout pregnancy on obstetric and neonatal outcomes in patients with polycystic ovary syndrome. Curr Med Res Opin 2013;29:55–62.
[11] Zeng XL, Zhang YF, Tian Q, Xue Y, An RF. Effects of metformin on pregnancy outcomes in women with polycystic ovary syndrome: a meta-analysis. Medicine (Baltimore) 2016;95:e4526.
[12] Samuel VT, Petersen KF, Shulman GI. Lipid-induced insulin resistance: unravelling the mechanism. Lancet 2010;375:2267–77.
[13] Jena D, Choudhury AK, Mangaraj S, Singh M, Mohanty BK, Baliarsinha AK. Study of visceral and subcutaneous abdominal fat thickness and its correlation with cardiometabolic risk factors and hormonal parameters in polycystic ovary syndrome. Indian J Endocrinol Metab 2018;22:321–7.
[14] Rosenfield RL, Ehrmann DA. The pathogenesis of polycystic ovary syndrome (PCOS): the hypothesis of PCOS as functional ovarian hyperandrogenism revisited. Endocr Rev 2016;37:467–520.
[15] Cascella T, Palomba S, De Sio I, Manguso F, Giallauria F, De Simone B, et al. Visceral fat is associated with cardiovascular risk in women with polycystic ovary syndrome. Hum Reprod 2008;23:153–9.
[16] Tripathy P, Sahu A, Sahu M, Nagy A. Ultrasonographic evaluation of intra-abdominal fat distribution and study of its influence on subclinical atherosclerosis in women with polycystic ovarian syndrome. Eur J Obstet Gynecol Reprod Biol 2017;217:18–22.
[17] Melo AS, Vieira CS, Barbieri MA, Rosa ESAC, Silva AA, Cardoso VC, et al. High prevalence of polycystic ovary syndrome in women born small for gestational age. Hum Reprod 2010;25:2124–31.
[18] Ibanez L, Potau N, Francois I, de Zegher F. Precocious pubarche, hyperinsulinism, and ovarian hyperandrogenism in girls: relation to reduced fetal growth. J Clin Endocrinol Metab 1998;83:3558–62.
[19] Mumm H, Kamper-Jorgensen M, Nybo Andersen AM, Glintborg D, Andersen M. Birth weight and polycystic ovary syndrome in adult life: a register-based study on 523,757 Danish women born 1973–1991. Fertil Steril 2013;99:777–82.
[20] Puttabyatappa M, Cardoso RC, Padmanabhan V. Effect of maternal PCOS and PCOS-like phenotype on the offspring's health. Mol Cell Endocrinol 2016;435:29–39.
[21] Sir-Petermann T, Maliqueo M, Angel B, Lara HE, Perez-Bravo F, Recabarren SE. Maternal serum androgens in pregnant women with polycystic ovarian syndrome: possible implications in prenatal androgenization. Hum Reprod 2002;17:2573–9.
[22] Glueck CJ, Morrison JA, Wang P, Woo JG. Early and late menarche are associated with oligomenorrhea and predict metabolic syndrome 26 years later. Metabolism 2013;62:1597–606.
[23] Glueck CJ, Woo JG, Khoury PR, Morrison JA, Daniels SR, Wang P. Adolescent oligomenorrhea (age 14–19) tracks into the third decade of life (age 20–28) and predicts increased cardiovascular risk factors and metabolic syndrome. Metabolism 2015;64:539–53.

[24] Boyle JA, Cunningham J, Norman RJ, Dunbar T, O'Dea K. Polycystic ovary syndrome and metabolic syndrome in Indigenous Australian women. Intern Med J 2015;45:1247–54.
[25] Hu X, Wang J, Dong W, Fang Q, Hu L, Liu C. A meta-analysis of polycystic ovary syndrome in women taking valproate for epilepsy. Epilepsy Res 2011;97:73–82.
[26] Doi SA. Neuroendocrine dysfunction in PCOS: a critique of recent reviews. Clin Med Res 2008;6:47–53.
[27] Anagnostis P, Tarlatzis BC, Kauffman RP. Polycystic ovarian syndrome (PCOS): long-term metabolic consequences. Metabolism 2018;86:33–43.
[28] Goodman NF, Cobin RH, Futterweit W, Glueck JS, Legro RS, Carmina E, et al. American Association of Clinical Endocrinologists, American College of Endocrinology, and Androgen Excess and PCOS Society disease state clinical review: guide to the best practices in the evaluation and treatment of polycystic ovary syndrome - part 2. Endocr Pract 2015;21:1415–26.
[29] Einarsson S, Bergh C, Friberg B, Pinborg A, Klajnbard A, Karlstrom PO, et al. Weight reduction intervention for obese infertile women prior to IVF: a randomized controlled trial. Hum Reprod 2017;32:1621–30.
[30] Chaudhari N, Dawalbhakta M, Nampoothiri L. GnRH dysregulation in polycystic ovarian syndrome (PCOS) is a manifestation of an altered neurotransmitter profile. Reprod Biol Endocrinol 2018;16:37.
[31] Moore AM, Campbell RE. Polycystic ovary syndrome: understanding the role of the brain. Front Neuroendocrinol 2017;46:1–14.
[32] Caldwell ASL, Edwards MC, Desai R, Jimenez M, Gilchrist RB, Handelsman DJ, et al. Neuroendocrine androgen action is a key extraovarian mediator in the development of polycystic ovary syndrome. Proc Natl Acad Sci U S A 2017;114:E3334–43.
[33] Blank SK, McCartney CR, Helm KD, Marshall JC. Neuroendocrine effects of androgens in adult polycystic ovary syndrome and female puberty. Semin Reprod Med 2007;25:352–9.
[34] Blank SK, McCartney CR, Marshall JC. The origins and sequelae of abnormal neuroendocrine function in polycystic ovary syndrome. Hum Reprod Update 2006;12:351–61.
[35] James WP. WHO recognition of the global obesity epidemic. Int J Obes (Lond) 2008;32(Suppl. 7):S120–6.
[36] Turkmen S, Ahangari A, Backstrom T. Roux-en-Y gastric bypass surgery in patients with polycystic ovary syndrome and metabolic syndrome. Obes Surg 2016;26:111–8.
[37] Escobar-Morreale HF, Botella-Carretero JI, Alvarez-Blasco F, Sancho J, San Millan JL. The polycystic ovary syndrome associated with morbid obesity may resolve after weight loss induced by bariatric surgery. J Clin Endocrinol Metab 2005;90:6364–9.
[38] Rosen ED, Spiegelman BM. What we talk about when we talk about fat. Cell 2014;156:20–44.
[39] Gonzalez F. Nutrient-induced inflammation in polycystic ovary syndrome: role in the development of metabolic aberration and ovarian dysfunction. Semin Reprod Med 2015;33:276–86.
[40] Roth LW, Allshouse AA, Bradshaw-Pierce EL, Lesh J, Chosich J, Kohrt W, et al. Luteal phase dynamics of follicle-stimulating and luteinizing hormones in obese and normal weight women. Clin Endocrinol (Oxf) 2014;81:418–25.
[41] Taponen S, Martikainen H, Jarvelin MR, Laitinen J, Pouta A, Hartikainen AL, et al. Hormonal profile of women with self-reported symptoms of oligomenorrhea and/or hirsutism: Northern Finland birth cohort 1966 study. J Clin Endocrinol Metab 2003;88:141–7.
[42] Cassar S, Misso ML, Hopkins WG, Shaw CS, Teede HJ, Stepto NK. Insulin resistance in polycystic ovary syndrome: a systematic review and meta-analysis of euglycaemic-hyperinsulinaemic clamp studies. Hum Reprod 2016;31:2619–31.
[43] Lim SS, Norman RJ, Davies MJ, Moran LJ. The effect of obesity on polycystic ovary syndrome: a systematic review and meta-analysis. Obes Rev 2013;14:95–109.
[44] Glintborg D, Rubin KH, Nybo M, Abrahamsen B, Andersen M. Cardiovascular disease in a nationwide population of Danish women with polycystic ovary syndrome. Cardiovasc Diabetol 2018;17:37.
[45] Solomon CG, Hu FB, Dunaif A, Rich-Edwards JE, Stampfer MJ, Willett WC, et al. Menstrual cycle irregularity and risk for future cardiovascular disease. J Clin Endocrinol Metab 2002;87:2013–7.
[46] Krentz AJ, von Muhlen D, Barrett-Connor E. Searching for polycystic ovary syndrome in postmenopausal women: evidence of a dose-effect association with prevalent cardiovascular disease. Menopause 2007;14:284–92.
[47] Legro RS, Driscoll D, Strauss III JF, Fox J, Dunaif A. Evidence for a genetic basis for hyperandrogenemia in polycystic ovary syndrome. Proc Natl Acad Sci U S A 1998;95:14956–60.
[48] Vink JM, Sadrzadeh S, Lambalk CB, Boomsma DI. Heritability of polycystic ovary syndrome in a Dutch twin-family study. J Clin Endocrinol Metab 2006;91:2100–4.
[49] Day FR, Hinds DA, Tung JY, Stolk L, Styrkarsdottir U, Saxena R, et al. Causal mechanisms and balancing selection inferred from genetic associations with polycystic ovary syndrome. Nat Commun 2015;6:8464.
[50] Shi Y, Zhao H, Shi Y, Cao Y, Yang D, Li Z, et al. Genome-wide association study identifies eight new risk loci for polycystic ovary syndrome. Nat Genet 2012;44:1020–5.
[51] Chen ZJ, Zhao H, He L, Shi Y, Qin Y, Shi Y, et al. Genome-wide association study identifies susceptibility loci for polycystic ovary syndrome on chromosome 2p16.3, 2p21 and 9q33.3. Nat Genet 2011;43:55–9.
[52] Hayes MG, Urbanek M, Ehrmann DA, Armstrong LL, Lee JY, Sisk R, et al. Genome-wide association of polycystic ovary syndrome implicates alterations in gonadotropin secretion in European ancestry populations. Nat Commun 2015;6:7502.
[53] Gao J, Xue JD, Li ZC, Zhou L, Chen C. The association of DENND1A gene polymorphisms and polycystic ovary syndrome risk: a systematic review and meta-analysis. Arch Gynecol Obstet 2016;294:1073–80.
[54] Liu AL, Xie HJ, Xie HY, Liu J, Yin J, Hu JS, et al. Association between fat mass and obesity associated (FTO) gene rs9939609 A/T polymorphism and polycystic ovary syndrome: a systematic review and meta-analysis. BMC Med Genet 2017;18:89.
[55] Goodarzi MO, Jones MR, Li X, Chua AK, Garcia OA, Chen YD, et al. Replication of association of DENND1A and THADA variants with polycystic ovary syndrome in European cohorts. J Med Genet 2012;49:90–5.
[56] Welt CK, Styrkarsdottir U, Ehrmann DA, Thorleifsson G, Arason G, Gudmundsson JA, et al. Variants in DENND1A are associated with polycystic ovary syndrome in women of European ancestry. J Clin Endocrinol Metab 2012;97:E1342–7.
[57] Cui L, Zhao H, Zhang B, Qu Z, Liu J, Liang X, et al. Genotype-phenotype correlations of PCOS susceptibility SNPs identified by GWAS in a large cohort of Han Chinese women. Hum Reprod 2013;28:538–44.
[58] Chen L, Hu LM, Wang YF, Yang HY, Huang XY, Zhou W, et al. Genome-wide association study for SNPs associated with PCOS in human patients. Exp Ther Med 2017;14:4896–900.
[59] Dallel M, Sarray S, Douma Z, Hachani F, Al-Ansari AK, Letaifa DB, et al. Differential association of DENND1A genetic variants with polycystic ovary syndrome in Tunisian but not Bahraini Arab women. Gene 2018;647:79–84.
[60] Ding L, Gao F, Zhang M, Yan W, Tang R, Zhang C, et al. Higher PDCD4 expression is associated with obesity, insulin resistance, lipid metabolism disorders, and granulosa cell apoptosis in polycystic ovary syndrome. Fertil Steril 2016;105:1330–7 [e3].
[61] Hwang JY, Lee EJ, Jin Go M, Sung YA, Lee HJ, Heon Kwak S, et al. Genome-wide association study identifies GYS2 as a novel genetic factor for polycystic ovary syndrome through obesity-related condition. J Hum Genet 2012;57:660–4.
[62] Barber TM, Bennett AJ, Groves CJ, Sovio U, Ruokonen A, Martikainen H, et al. Association of variants in the fat mass and obesity associated (FTO) gene with polycystic ovary syndrome. Diabetologia 2008;51:1153–8.
[63] Wojciechowski P, Lipowska A, Rys P, Ewens KG, Franks S, Tan S, et al. Impact of FTO genotypes on BMI and weight in polycystic ovary syndrome: a systematic review and meta-analysis. Diabetologia 2012;55:2636–45.
[64] Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, et al. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Hum Reprod 2018;86:33–43.
[65] Teede H, Deeks A, Moran L. Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. BMC Med 2010;8:41.
[66] Moran LJ, Pasquali R, Teede HJ, Hoeger KM, Norman RJ. Treatment of obesity in polycystic ovary syndrome: a position statement of the Androgen Excess and Polycystic Ovary Syndrome Society. Fertil Steril 2009;92:1966–82.
[67] Crosignani PG, Colombo M, Vegetti W, Somigliana E, Gessati A, Ragni G. Overweight and obese anovulatory patients with polycystic ovaries: parallel improvements in anthropometric indices, ovarian physiology and fertility rate induced by diet. Hum Reprod 2003;18:1928–32.
[68] Moran LJ, Brinkworth G, Noakes M, Norman RJ. Effects of lifestyle modification in polycystic ovarian syndrome. Reprod Biomed Online 2006;12:569–78.
[69] Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, et al. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Fertil Steril 2018;110:364–79.
[70] Jamal M, Gunay Y, Capper A, Eid A, Heitshusen D, Samuel I. Roux-en-Y gastric bypass ameliorates polycystic ovary syndrome and dramatically improves conception rates: a 9-year analysis. Surg Obes Relat Dis 2012;8:440–4.
[71] Guzick DS, Wing R, Smith D, Berga SL, Winters SJ. Endocrine consequences of weight loss in obese, hyperandrogenic, anovulatory women. Fertil Steril 1994;61:598–604.
[72] Clark AM, Ledger W, Galletly C, Tomlinson L, Blaney F, Wang X, et al. Weight loss results in significant improvement in pregnancy and ovulation rates in anovulatory obese women. Hum Reprod 1995;10:2705–12.
[73] Holte J, Bergh T, Berne C, Wide L, Lithell H. Restored insulin sensitivity but persistently increased early insulin secretion after weight loss in obese women with polycystic ovary syndrome. J Clin Endocrinol Metab 1995;80:2586–93.
[74] Huber-Buchholz MM, Carey DG, Norman RJ. Restoration of reproductive potential by lifestyle modification in obese polycystic ovary syndrome: role of insulin sensitivity and luteinizing hormone. J Clin Endocrinol Metab 1999;84:1470–4.
[75] Solomon CG, Dluhy RG. Bariatric surgery—quick fix or long-term solution? N Engl J Med 2004;351:2751–3.
[76] Norman RJ, Davies MJ, Lord J, Moran LJ. The role of lifestyle modification in polycystic ovary syndrome. Trends Endocrinol Metab 2002;13:251–7.
[77] Pasquali R, Gambineri A, Biscotti D, Vicennati V, Gagliardi L, Colitta D, et al. Effect of long-term treatment with metformin added to hypocaloric diet on body composition, fat distribution, and androgen and insulin levels in abdominally obese women with and without the polycystic ovary syndrome. J Clin Endocrinol Metab 2000;85:2767–74.
[78] Kiddy DS, Hamilton-Fairley D, Bush A, Short F, Anyaoku V, Reed MJ, et al. Improvement in endocrine and ovarian function during dietary treatment of obese women with polycystic ovary syndrome. Clin Endocrinol (Oxf) 1992;36:105–11.
[79] Moran LJ, Hutchison SK, Norman RJ, Teede HJ. Lifestyle changes in women with polycystic ovary syndrome. Cochrane Database Syst Rev 2011, Jul 6;7:CD007506.
[80] Kataoka J, Tassone EC, Misso M, Joham AE, Stener-Victorin E, Teede H, et al. Weight management interventions in women with and without PCOS: a systematic review. Nutrients 2017;9.
[81] Domecq JP, Prutsky G, Mullan RJ, Hazem A, Sundaresh V, Elamin MB, et al. Lifestyle modification programs in polycystic ovary syndrome: systematic review and meta-analysis. J Clin Endocrinol Metab 2013;98:4655–63.
[82] Pelletier L, Baillargeon JP. Clinically significant and sustained weight loss is achievable in obese women with polycystic ovary syndrome followed in a regular medical practice. Fertil Steril 2010;94:2665–9.
[83] Tolino A, Gambardella V, Caccavale C, D'Ettore A, Giannotti F, D'Anto V, et al. Evaluation of ovarian functionality after a dietary treatment in obese women with polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol 2005;119:87–93.

[84] Guzick DS. Polycystic ovary syndrome. Obstet Gynecol 2004;103:181–93.
[85] Nikokavoura EA, Johnston KL, Broom J, Wrieden WL, Rolland C. Weight loss for women with and without polycystic ovary syndrome following a very low-calorie diet in a community-based setting with trained facilitators for 12 weeks. Diabetes Metab Syndr Obes 2015;8:495–503.
[86] Christ JP, Falcone T. Bariatric surgery improves hyperandrogenism, menstrual irregularities, and metabolic dysfunction among women with polycystic ovary syndrome (PCOS). Obes Surg 2018;28(8):2171–7.
[87] Abiad F, Khalife D, Safadi B, Alami R, Awwad J, Khalifeh F, et al. The effect of bariatric surgery on inflammatory markers in women with polycystic ovarian syndrome. Diabetes Metab Syndr 2018;12:999–1005.
[88] Skubleny D, Switzer NJ, Gill RS, Dykstra M, Shi X, Sagle MA, et al. The impact of bariatric surgery on polycystic ovary syndrome: a systematic review and meta-analysis. Obes Surg 2016;26:169–76.
[89] Nilsson-Condori E, Hedenbro JL, Thurin-Kjellberg A, Giwercman A, Friberg B. Impact of diet and bariatric surgery on anti-Mullerian hormone levels. Hum Reprod 2018;33(4):690–3.
[90] Chiofalo F, Ciuoli C, Formichi C, Selmi F, Forleo R, Neri O, et al. Bariatric surgery reduces serum anti-mullerian hormone levels in obese women with and without polycystic ovarian syndrome. Obes Surg 2017;27:1750–4.
[91] Butterworth J, Deguara J, Borg CM. Bariatric surgery, polycystic ovary syndrome, and infertility. J Obes 2016;2016:1871594.
[92] Legro RS, Dodson WC, Kris-Etherton PM, Kunselman AR, Stetter CM, Williams NI, et al. Randomized controlled trial of preconception interventions in infertile women with polycystic ovary syndrome. J Clin Endocrinol Metab 2015;100:4048–58.
[93] Legro RS, Dodson WC, Kunselman AR, Stetter CM, Kris-Etherton PM, Williams NI, et al. Benefit of delayed fertility therapy with preconception weight loss over immediate therapy in obese women with PCOS. J Clin Endocrinol Metab 2016;101:2658–66.
[94] Palomba S, Giallauria F, Falbo A, Russo T, Oppedisano R, Tolino A, et al. Structured exercise training programme versus hypocaloric hyperproteic diet in obese polycystic ovary syndrome patients with anovulatory infertility: a 24-week pilot study. Hum Reprod 2008;23:642–50.
[95] Palomba S, Falbo A, Giallauria F, Russo T, Rocca M, Tolino A, et al. Six weeks of structured exercise training and hypocaloric diet increases the probability of ovulation after clomiphene citrate in overweight and obese patients with polycystic ovary syndrome: a randomized controlled trial. Hum Reprod 2010;25:2783–91.
[96] Moran LJ, Noakes M, Clifton PM, Wittert GA, Williams G, Norman RJ. Short-term meal replacements followed by dietary macronutrient restriction enhance weight loss in polycystic ovary syndrome. Am J Clin Nutr 2006;84:77–87.
[97] Morley LC, Tang T, Yasmin E, Norman RJ, Balen AH. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. Cochrane Database Syst Rev 2017;11:CD003053.
[98] Azadi-Yazdi M, Karimi-Zarchi M, Salehi-Abargouei A, Fallahzadeh H, Nadjarzadeh A. Effects of Dietary Approach to Stop Hypertension diet on androgens, antioxidant status and body composition in overweight and obese women with polycystic ovary syndrome: a randomised controlled trial. J Hum Nutr Diet 2017;30:275–83.
[99] Mehrabani HH, Salehpour S, Amiri Z, Farahani SJ, Meyer BJ, Tahbaz F. Beneficial effects of a high-protein, low-glycemic-load hypocaloric diet in overweight and obese women with polycystic ovary syndrome: a randomized controlled intervention study. J Am Coll Nutr 2012;31:117–25.
[100] Moran LJ, Noakes M, Clifton PM, Tomlinson L, Galletly C, Norman RJ. Dietary composition in restoring reproductive and metabolic physiology in overweight women with polycystic ovary syndrome. J Clin Endocrinol Metab 2003;88:812–9.
[101] Marsh KA, Steinbeck KS, Atkinson FS, Petocz P, Brand-Miller JC. Effect of a low glycemic index compared with a conventional healthy diet on polycystic ovary syndrome. Am J Clin Nutr 2010;92:83–92.
[102] Hollmann M, Runnebaum B, Gerhard I. Effects of weight loss on the hormonal profile in obese, infertile women. Hum Reprod 1996;11:1884–91.
[103] Kuchenbecker WK, Groen H, van Asselt SJ, Bolster JH, Zwerver J, Slart RH, et al. In women with polycystic ovary syndrome and obesity, loss of intra-abdominal fat is associated with resumption of ovulation. Hum Reprod 2011;26:2505–12.
[104] Vigorito C, Giallauria F, Palomba S, Cascella T, Manguso F, Lucci R, et al. Beneficial effects of a three-month structured exercise training program on cardiopulmonary functional capacity in young women with polycystic ovary syndrome. J Clin Endocrinol Metab 2007;92:1379–84.
[105] Bruner B, Chad K, Chizen D. Effects of exercise and nutritional counseling in women with polycystic ovary syndrome. Appl Physiol Nutr Metab 2006;31:384–91.
[106] Thomson RL, Buckley JD, Lim SS, Noakes M, Clifton PM, Norman RJ, et al. Lifestyle management improves quality of life and depression in overweight and obese women with polycystic ovary syndrome. Fertil Steril 2010;94:1812–6.
[107] Redman LM, Elkind-Hirsch K, Ravussin E. Aerobic exercise in women with polycystic ovary syndrome improves ovarian morphology independent of changes in body composition. Fertil Steril 2011;95:2696–9.
[108] Bates GW, Legro RS. Longterm management of Polycystic Ovarian Syndrome (PCOS). Mol Cell Endocrinol 2013;373:91–7.
[109] Hall KD, Sacks G, Chandramohan D, Chow CC, Wang YC, Gortmaker SL, et al. Quantification of the effect of energy imbalance on bodyweight. Lancet 2011;378:826–37.
[110] Wang FF, Wu Y, Zhu YH, Ding T, Batterham RL, Qu F, et al. Pharmacologic therapy to induce weight loss in women who have obesity/overweight with polycystic ovary syndrome: a systematic review and network meta-analysis. Obes Rev 2018;19(10):1424–45.
[111] Florakis D, Diamanti-Kandarakis E, Katsikis I, Nassis GP, Karkanaki A, Georgopoulos N, et al. Effect of hypocaloric diet plus sibutramine treatment on hormonal and metabolic features in overweight and obese women with polycystic ovary syndrome: a randomized, 24-week study. Int J Obes (Lond) 2008;32:692–9.
[112] Lindholm A, Bixo M, Bjorn I, Wolner-Hanssen P, Eliasson M, Larsson A, et al. Effect of sibutramine on weight reduction in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. Fertil Steril 2008;89:1221–8.
[113] Jordan J, Scholze J, Matiba B, Wirth A, Hauner H, Sharma AM. Influence of Sibutramine on blood pressure: evidence from placebo-controlled trials. Int J Obes (Lond) 2005;29:509–16.
[114] Naderpoor N, Shorakae S, de Courten B, Misso ML, Moran LJ, Teede HJ. Metformin and lifestyle modification in polycystic ovary syndrome: systematic review and meta-analysis. Hum Reprod Update 2015;21:560–74.
[115] Nieuwenhuis-Ruifrok AE, Kuchenbecker WK, Hoek A, Middleton P, Norman RJ. Insulin sensitizing drugs for weight loss in women of reproductive age who are overweight or obese: systematic review and meta-analysis. Hum Reprod Update 2009;15:57–68.
[116] Luque-Ramirez M, Nattero-Chavez L, Ortiz Flores AE, Escobar-Morreale HF. Combined oral contraceptives and/or antiandrogens versus insulin sensitizers for polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update 2017 Dec 27. https://doi.org/10.1093/humupd/dmx039.
[117] De Leo V, la Marca A, Petraglia F. Insulin-lowering agents in the management of polycystic ovary syndrome. Endocr Rev 2003;24:633–67.
[118] Moghetti P, Castello R, Negri C, Tosi F, Perrone F, Caputo M, et al. Metformin effects on clinical features, endocrine and metabolic profiles, and insulin sensitivity in polycystic ovary syndrome: a randomized, double-blind, placebo-controlled 6-month trial, followed by open, long-term clinical evaluation. J Clin Endocrinol Metab 2000;85:139–46.
[119] Legro RS. Evaluation and treatment of polycystic ovary syndrome. In: De Groot LJ, Chrousos G, Dungan K, Feingold KR, Grossman A, Hershman JM, et al, editors. Endotext; 2000 (South Dartmouth (MA)).
[120] Velazquez EM, Mendoza S, Hamer T, Sosa F, Glueck CJ. Metformin therapy in polycystic ovary syndrome reduces hyperinsulinemia, insulin resistance, hyperandrogenemia, and systolic blood pressure, while facilitating normal menses and pregnancy. Metabolism 1994;43:647–54.
[121] Trolle B, Flyvbjerg A, Kesmodel U, Lauszus FF. Efficacy of metformin in obese and non-obese women with polycystic ovary syndrome: a randomized, double-blinded, placebo-controlled cross-over trial. Hum Reprod 2007;22:2967–73.
[122] Glueck CJ, Aregawi D, Agloria M, Winiarska M, Sieve L, Wang P. Sustainability of 8% weight loss, reduction of insulin resistance, and amelioration of atherogenic-metabolic risk factors over 4 years by metformin-diet in women with polycystic ovary syndrome. Metabolism 2006;55:1582–9.
[123] Romualdi D, Giuliani M, Cristello F, Fulghesu AM, Selvaggi L, Lanzone A, et al. Metformin effects on ovarian ultrasound appearance and steroidogenic function in normal-weight normoinsulinemic women with polycystic ovary syndrome: a randomized double-blind placebo-controlled clinical trial. Fertil Steril 2010;93:2303–10.
[124] Velazquez EM, Mendoza SG, Wang P, Glueck CJ. Metformin therapy is associated with a decrease in plasma plasminogen activator inhibitor-1, lipoprotein(a), and immunoreactive insulin levels in patients with the polycystic ovary syndrome. Metabolism 1997;46:454–7.
[125] Burchall GF, Piva TJ, Ranasinha S, Teede HJ. Differential effects on haemostatic markers by metformin and the contraceptive pill: a randomized comparative trial in PCOS. Thromb Haemost 2017;117:2053–62.
[126] Jensterle M, Pirs B, Goricar K, Dolzan V, Janez A. Genetic variability in GLP-1 receptor is associated with inter-individual differences in weight lowering potential of liraglutide in obese women with PCOS: a pilot study. Eur J Clin Pharmacol 2015;71:817–24.
[127] Niafar M, Pourafkari L, Porhomayon J, Nader N. A systematic review of GLP-1 agonists on the metabolic syndrome in women with polycystic ovaries. Arch Gynecol Obstet 2016;293:509–15.
[128] Frossing S, Nylander M, Chabanova E, Frystyk J, Holst JJ, Kistorp C, et al. Effect of liraglutide on ectopic fat in polycystic ovary syndrome: a randomized clinical trial. Diabetes Obes Metab 2018;20:215–8.
[129] Frossing S, Nylander M, Kistorp C, Skouby SO, Faber J. Effect of liraglutide on atrial natriuretic peptide, adrenomedullin, and copeptin in PCOS. Endocr Connect 2018;7:115–23.
[130] Nylander M, Frossing S, Clausen HV, Kistorp C, Faber J, Skouby SO. Effects of liraglutide on ovarian dysfunction in polycystic ovary syndrome: a randomized clinical trial. Reprod Biomed Online 2017;35:121–7.
[131] Nylander M, Frossing S, Kistorp C, Faber J, Skouby SO. Liraglutide in polycystic ovary syndrome: a randomized trial, investigating effects on thrombogenic potential. Endocr Connect 2017;6:89–99.
[132] Lamos EM, Malek R, Davis SN. GLP-1 receptor agonists in the treatment of polycystic ovary syndrome. Expert Rev Clin Pharmacol 2017;10:401–8.
[133] Jensterle M, Kravos NA, Pfeifer M, Kocjan T, Janez A. A 12-week treatment with the long-acting glucagon-like peptide 1 receptor agonist liraglutide leads to significant weight loss in a subset of obese women with newly diagnosed polycystic ovary syndrome. Hormones (Athens) 2015;14:81–90.
[134] Jensterle M, Goricar K, Janez A. Metformin as an initial adjunct to low-dose liraglutide enhances the weight-decreasing potential of liraglutide in obese polycystic ovary syndrome: randomized control study. Exp Ther Med 2016;11:1194–200.
[135] Jensterle M, Kravos NA, Goricar K, Janez A. Short-term effectiveness of low dose liraglutide in combination with metformin versus high dose liraglutide alone in treatment of obese PCOS: randomized trial. BMC Endocr Disord 2017;17:5.

[136] Salamun V, Jensterle M, Janez A, Vrtacnik Bokal E. Liraglutide increases IVF pregnancy rates in obese PCOS women with poor response to first-line reproductive treatments: a pilot randomized study. Eur J Endocrinol 2018;179(1):1–11.
[137] Elkind-Hirsch K, Marrioneaux O, Bhushan M, Vernor D, Bhushan R. Comparison of single and combined treatment with exenatide and metformin on menstrual cyclicity in overweight women with polycystic ovary syndrome. J Clin Endocrinol Metab 2008;93:2670–8.
[138] Tzotzas T, Karras SN, Katsiki N. Glucagon-like peptide-1 (GLP-1) receptor agonists in the treatment of obese women with polycystic ovary syndrome. Curr Vasc Pharmacol 2017;15:218–29.
[139] Baillargeon JP, Jakubowicz DJ, Iuorno MJ, Jakubowicz S, Nestler JE. Effects of metformin and rosiglitazone, alone and in combination, in nonobese women with polycystic ovary syndrome and normal indices of insulin sensitivity. Fertil Steril 2004; 82:893–902.
[140] Du Q, Wang YJ, Yang S, Wu B, Han P, Zhao YY. A systematic review and meta-analysis of randomized controlled trials comparing pioglitazone versus metformin in the treatment of polycystic ovary syndrome. Curr Med Res Opin 2012;28: 723–30.
[141] Xu Y, Wu Y, Huang Q. Comparison of the effect between pioglitazone and metformin in treating patients with PCOS: a meta-analysis. Arch Gynecol Obstet 2017; 296:661–77.
[142] Bucher KG, Wiltz SA. Alternatives to metformin for patients with PCOS. Am Fam Physician 2016;94:378–9.
[143] Du Q, Yang S, Wang YJ, Wu B, Zhao YY, Fan B. Effects of thiazolidinediones on polycystic ovary syndrome: a meta-analysis of randomized placebo-controlled trials. Adv Ther 2012;29:763–74.
[144] Glueck CJ, Moreira A, Goldenberg N, Sieve L, Wang P. Pioglitazone and metformin in obese women with polycystic ovary syndrome not optimally responsive to metformin. Hum Reprod 2003;18:1618–25.
[145] Graff SK, Mario FM, Ziegelmann P, Spritzer PM. Effects of orlistat vs. metformin on weight loss-related clinical variables in women with PCOS: systematic review and meta-analysis. Int J Clin Pract 2016;70:450–61.
[146] Cho LW, Kilpatrick ES, Keevil BG, Coady AM, Atkin SL. Effect of metformin, orlistat and pioglitazone treatment on mean insulin resistance and its biological variability in polycystic ovary syndrome. Clin Endocrinol (Oxf) 2009;70:233–7.
[147] Kumar P, Arora S. Orlistat in polycystic ovarian syndrome reduces weight with improvement in lipid profile and pregnancy rates. J Hum Reprod Sci 2014;7:255–61.
[148] Panidis D, Farmakiotis D, Rousso D, Kourtis A, Katsikis I, Krassas G. Obesity, weight loss, and the polycystic ovary syndrome: effect of treatment with diet and orlistat for 24 weeks on insulin resistance and androgen levels. Fertil Steril 2008;89:899–906.
[149] Panidis D, Tziomalos K, Papadakis E, Chatzis P, Kandaraki EA, Tsourdi EA, et al. The role of orlistat combined with lifestyle changes in the management of overweight and obese patients with polycystic ovary syndrome. Clin Endocrinol (Oxf) 2014;80:432–8.
[150] Diamanti-Kandarakis E, Katsikis I, Piperi C, Alexandraki K, Panidis D. Effect of long-term orlistat treatment on serum levels of advanced glycation end-products in women with polycystic ovary syndrome. Clin Endocrinol (Oxf) 2007;66:103–9.
[151] Zhang YY, Hou LQ, Zhao TY. Effects of acarbose on polycystic ovary syndrome: a meta-analysis. Exp Clin Endocrinol Diabetes 2014;122:373–8.
[152] Kircher C, Smith KP. Acarbose for polycystic ovary syndrome. Ann Pharmacother 2008;42:847–51.
[153] Hanjalic-Beck A, Gabriel B, Schaefer W, Zahradnik HP, Schories M, Tempfer C, et al. Metformin versus acarbose therapy in patients with polycystic ovary syndrome (PCOS): a prospective randomised double-blind study. Gynecol Endocrinol 2010; 26:690–7.
[154] Penna IA, Canella PR, Reis RM, Silva de Sa MF, Ferriani RA. Acarbose in obese patients with polycystic ovarian syndrome: a double-blind, randomized, placebo-controlled study. Hum Reprod 2005;20:2396–401.
[155] Robinson MK. Surgical treatment of obesity—weighing the facts. N Engl J Med 2009;361:520–1.
[156] Eid GM, Cottam DR, Velcu LM, Mattar SG, Korytkowski MT, Gosman G, et al. Effective treatment of polycystic ovarian syndrome with Roux-en-Y gastric bypass. Surg Obes Relat Dis 2005;1:77–80.
[157] Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Brethauer SA, Navaneethan SD, et al. Bariatric surgery versus intensive medical therapy for diabetes—3-year outcomes. N Engl J Med 2014;370:2002–13.
[158] Hutch CR, Sandoval D. The role of GLP-1 in the metabolic success of bariatric surgery. Endocrinology 2017;158:4139–51.
[159] Pareek M, Schauer PR, Kaplan LM, Leiter LA, Rubino F, Bhatt DL. Metabolic surgery: weight loss, diabetes, and beyond. J Am Coll Cardiol 2018;71:670–87.
[160] Johansson K, Cnattingius S, Naslund I, Roos N, Trolle Lagerros Y, Granath F, et al. Outcomes of pregnancy after bariatric surgery. N Engl J Med 2015;372:814–24.
[161] Mechanick JI, Youdim A, Jones DB, Garvey WT, Hurley DL, McMahon MM, et al. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient—2013 update: cosponsored by American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery. Obesity (Silver Spring) 2013; 21(Suppl. 1):S1–27.
[162] Bhandari S, Ganguly I, Bhandari M, Agarwal P, Singh A, Gupta N, et al. Effect of sleeve gastrectomy bariatric surgery-induced weight loss on serum AMH levels in reproductive aged women. Gynecol Endocrinol 2016;32:799–802.
[163] Wang K, Jiang Q, Zhi Y, Zhu Z, Zhou Z, Xie Y, et al. Contrasting sleeve gastrectomy with lifestyle modification therapy in the treatment of polycystic ovary syndrome. J Laparoendosc Adv Surg Tech A 2015;25:493–8.
[164] Jakobsen GS, Smastuen MC, Sandbu R, Nordstrand N, Hofso D, Lindberg M, et al. Association of bariatric surgery vs medical obesity treatment with long-term medical complications and obesity-related comorbidities. JAMA 2018;319:291–301.
[165] Cook FJ, Khanna I, Giordano J, Matarese L, Hudson S. Long-term bone health after Roux-en-Y gastric bypass: a pilot study. Endocr Pract 2017;23:1077–84.
[166] Switzer NJ, Marcil G, Prasad S, Debru E, Church N, Mitchell P, et al. Long-term hypovitaminosis D and secondary hyperparathyroidism outcomes of the Roux-en-Y gastric bypass: a systematic review. Obes Rev 2017;18:560–6.
[167] Daigle CR, Brethauer SA, Tu C, Petrick AT, Morton JM, Schauer PR, et al. Which postoperative complications matter most after bariatric surgery? Prioritizing quality improvement efforts to improve national outcomes. Surg Obes Relat Dis 2018;14 (5):652–7.
[168] Axelsson KF, Werling M, Eliasson B, Szabo E, Naslund I, Wedel H, et al. Fracture risk after gastric bypass surgery: a retrospective cohort study. J Bone Miner Res 2018. https://doi.org/10.02/jbmr.3553.
[169] Wang FG, Yan WM, Yan M, Song MM. Outcomes of Mini vs Roux-en-Y gastric bypass: a meta-analysis and systematic review. Int J Surg 2018;56:7–14.
[170] Sudan R, Jain-Spangler K. Tailoring bariatric surgery: sleeve gastrectomy, Roux-en-Y gastric bypass and biliopancreatic diversion with duodenal switch. J Laparoendosc Adv Surg Tech A 2018;28:956–61.
[171] Kolotkin RL, Kim J, Davidson LE, Crosby RD, Hunt SC, Adams TD. 12-year trajectory of health-related quality of life in gastric bypass patients versus comparison groups. Surg Obes Relat Dis 2018;14(9):1359–65.
[172] Janik MR, Mustafa RR, Rogula TG, Alhaj Saleh A, Abbas M, Khaitan L. Safety of laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass in elderly patients - analysis of the MBSAQIP. Surg Obes Relat Dis 2018;14(9):1276–82.
[173] Coleman KJ, Huang YC, Hendee F, Watson HL, Casillas RA, Brookey J. Three-year weight outcomes from a bariatric surgery registry in a large integrated healthcare system. Surg Obes Relat Dis 2014;10:396–403.
[174] Garb J, Welch G, Zagarins S, Kuhn J, Romanelli J. Bariatric surgery for the treatment of morbid obesity: a meta-analysis of weight loss outcomes for laparoscopic adjustable gastric banding and laparoscopic gastric bypass. Obes Surg 2009;19:1447–55.
[175] Kjaer MM, Madsbad S, Hougaard DM, Cohen AS, Nilas L. The impact of gastric bypass surgery on sex hormones and menstrual cycles in premenopausal women. Gynecol Endocrinol 2017;33:160–3.
[176] Zhou JQ, Zhou LM, Chen LJ, Han JD, Wang Q, Fang ZY, et al. Polycystic ovary syndrome in patients with epilepsy: a study in 102 Chinese women. Seizure 2012; 21:729–33.
[177] Zhang L, Li H, Li S, Zou X. Reproductive and metabolic abnormalities in women taking valproate for bipolar disorder: a meta-analysis. Eur J Obstet Gynecol Reprod Biol 2016;202:26–31.
[178] Yazici D, Sezer H. Insulin resistance, obesity and lipotoxicity. Adv Exp Med Biol 2017;960:277–304.
[179] Khera R, Murad MH, Chandar AK, Dulai PS, Wang Z, Prokop LJ, et al. Association of pharmacological treatments for obesity with weight loss and adverse events: a systematic review and meta-analysis. JAMA 2016;315:2424–34.