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Weight Management in Adolescents with Polycystic Ovary Syndrome

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Abstract

Purpose of Review.—Polycystic ovary syndrome (PCOS) is a common condition that clinically presents during adolescence. PCOS is associated with increased rates of overweight and obesity, as well as higher rates of metabolic disease, especially type 2 diabetes. Weight loss decreases PCOS symptoms and risk for metabolic disease. The goal of this review is to evaluate recent studies describing the hormonal, metabolic and weight effects of different weight loss strategies: dietary, physical activity, pharmacotherapy, bariatric surgery, mood modification and sleep.

Recent Findings: Calorie restriction continues to be supported as the primary nutrition intervention to achieve weight loss in individuals with PCOS, and a dietary macronutrient composition with lower-compared to higher-glycemic carbohydrates may be more effective. There is limited data that vitamins, nutraceuticals and probiotics may improve hormonal and metabolic outcomes. Most types of physical activity are effective in improving outcomes in PCOS and lowering weight. Whereas there are promising data on anti-obesity medications such as glucagon like peptide-1 receptor agonists in adults with PCOS and adolescents with obesity, further work is needed to know if these therapies are effective in youth with PCOS. Research is lacking on the effectiveness of other anti-obesity medications in PCOS. Bariatric surgery is especially promising for decreasing weight in adults and youth, and reversing type 2 diabetes in youth, though PCOS data are lacking. Treatment of depression in adolescents with insulin resistance and women with PCOS is associated with improved weight loss. Adolescents with PCOS and obesity may have greater sleep-related risks including circadian misalignment and obstructive sleep apnea, interventions for which have not yet been conducted.

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Summary: Clinical trials on weight-loss strategies in adolescents with PCOS remain limited, with most information inferred from studies in women with PCOS or adolescents with obesity. However, there are multiple options to optimize weight loss in dietary, activity, pharmacotherapy, bariatric surgery, mood modification and sleep domains.

Keywords

polycystic ovary syndrome; obesity; adolescence; weight loss

Introduction

Polycystic ovary syndrome (**PCOS**) in adolescents includes excess testosterone, irregular menses and an increased risk for development of obesity and metabolic disease.(1) There is a complex relationship between excess body weight and the development and severity of PCOS, which has not been fully elucidated. PCOS may include a pathologic cycle with excess insulin secondary to insulin resistance (**IR**), increasing testosterone release from the ovary, and then excess testosterone feeding back to cause further IR.(2) Thus, anything that increases insulin concentrations is thought to worsen PCOS, including obesity, high glycemic diets or lack of activity.(3) Conversely, lifestyle changes and pharmaceutical therapies that decrease IR such as metformin or thiazolidinediones (**TZD**) not only mitigate metabolic disease but cause mild improvements in hormonal parameters.(4–6)

Excess weight also increases the risk of metabolic disease development in PCOS, similar to other conditions.(7) For example, in an Australian cohort, women with a normal body mass index (**BMI**) had a 2-fold increased risk of developing type 2 diabetes (**T2D**), compared to an 8-fold increased risk in women with obesity.(8) In addition to baseline weight status, weight gain in early adulthood has been demonstrated to be one of the most important risk factors for development of metabolic disease later in life.(9) In youth who develop T2D or non-alcoholic fatty liver disease (**NAFLD**), serious co-morbidities and even early mortality have been noted.(10) Per the 2018 international guidelines, PCOS can now be diagnosed starting one year after menarche.(11) Early diagnosis and individualized treatment of both PCOS and concurrent overweight/obesity represent key opportunities for secondary and tertiary prevention with high public health impact across metabolic, reproductive and psychological outcomes.

First line therapy for adolescents with PCOS and excess weight include lifestyle modifications encompassing diet, exercise, and behavior change.(12) In those who have excess weight, weight loss is paramount for not only treating hormonal aspects of PCOS but mitigating metabolic risk.(1) The goal of this review is to highlight recent advances in lifestyle, psychologic, pharmacologic, and surgical management of obesity in adolescents with PCOS, which have evolved since the release of the 2018 international guidelines.(1) This review will not include animal studies, and for the most part does not include trials with a focus on lean adolescents with PCOS. Unfortunately, data from adolescents with PCOS and obesity is extremely limited, and thus studies from adult women with PCOS, or adolescents with obesity are also referenced.

Nutrition

Current knowledge and recommendations for dietary intake in PCOS

The 2018 international PCOS guidelines suggest low calorie diets as the mainstay of nutrition therapy for women with excess weight and PCOS.(1) A consistently observed finding is that PCOS outcomes are improved by caloric restriction targeting weight loss among those with excess weight, and weight maintenance in those who are lean.(13) The 2018 guidelines suggest there is insufficient evidence to recommend any specific dietary macronutrient composition in improving the health outcomes of women with PCOS.(1) However, we will review aspects of the diet that have been recently studied including macronutrient and micronutrient composition, glycemic index and load, fiber intake, anti-inflammatory dietary patterns, and the impact of nutraceuticals.

Dietary weight management and evaluation of metabolic/reproductive outcomes

Hypocaloric diets with a goal of weight loss or weight maintenance are an effective primary treatment strategy for women with PCOS and excess weight.(14) Calorically restricted diets ranging from 1000–1500 kilocalories (kcal) per day have proven useful for weight loss in the general population, and can result in 5–15% weight loss, which is known to improve cardiometabolic parameters.(14) Such weight loss has been associated with improved hirsutism, IR and menstrual regularity in women with PCOS.(14) Caloric targets in adolescents should take into account individual energy needs and energy expenditure. Care must be taken to balance these recommendations with increasing the risk for eating disorders, which is already high in women with PCOS and obesity.(15) However, from the general pediatric weight management experience, the prevalence of eating disorders is reduced in youth engaged in professionally structured weight management programs. (16)

Low glycemic dietary patterns have also shown benefits in the setting of IR and PCOS. Shishehgar et al. showed that over 24 weeks, an energy restricted, low glycemic index diet produces comparable decreases in weight, BMI, and insulin levels in women with overweight status with and without PCOS.(6) It also improved total testosterone (**TT**), free androgen index (**FAI**), sex hormone binding globulin (**SHBG**), menstrual regularity, and acne.(6) A randomized controlled trial (**RCT**) comparing the low-glycemic index high legume diet to a standard low cholesterol and sodium diet in women with PCOS, showed that despite the diets being isocaloric, the legume based diet decreased total insulin response to an oral glucose tolerance test (**OGTT**) and reduced low density lipoprotein cholesterol (**LDL-C**), triglycerides (**TG**), total cholesterol to high density lipoprotein (**HDL-C**) ratio and diastolic blood pressure.(13) In addition, Panjeshahin et al., using principal component analysis to define dietary patterns, revealed that a high glycemic index, high fat diet increased the odds of PCOS, increased BMI, waist circumference, fasting blood sugar and visceral fat.(3) Moderate adherence to an anti-inflammatory diet (rich in dried fruits, nuts, low-fat dairy, low in sweets) decreased the odds of developing PCOS.(3) Increased dietary protein and reduced carbohydrate also improves IR measured by homeostatic model assessment for IR (**HOMA-IR**) (17,18) and increased dietary fiber promotes a less android body fat distribution and improves measures of IR.(19)

Effects of specific nutrients and nutraceuticals

Recent studies of specific micronutrients and nutraceuticals address varied aspects of PCOS pathophysiology including inflammation, oxidative stress, IR, hormonal dysfunction, and gut microbial composition. Some studies suggest that PCOS and its long-term metabolic complications are the consequence of low-grade systemic inflammation.(20–22) Inflammation in PCOS is associated with increased oxidative stress and damage due to hyperandrogenism, hyperinsulinemia, altered estrogen levels as well as increased lipid catabolism in association with obesity, which increases free radical production.(21,23–25) Women with PCOS have been found to have lower plasma levels of B vitamins potentially placing them at higher risk of oxidative stress. (24) Shahrokhi et al. found significantly higher levels of malondialdehyde, lower total antioxidant capacity, and lower levels of dietary antioxidants (e.g. vitamin E, zinc, beta-carotene, selenium) in individuals with PCOS compared to controls.(21) Data on endogenous vitamin C are mixed, with both lower (21) and higher (24) concentrations reported in PCOS. Higher plasma vitamin C may reflect an increased physiologic demand to counteract high systemic oxidative stress, but warrants further study.

Vitamin supplementation may have a role in PCOS management through antioxidant and anti-inflammatory effects.(24) Magnesium and vitamin E co-supplementation in women with PCOS reduced inflammation and improved antioxidant status as evidenced by a decline in high sensitivity C-reactive protein (**hs-CRP**) and increased plasma antioxidant capacity and nitric oxide levels.(21) In women with overweight, PCOS and vitamin D deficiency, repletion doses (50,000 IU vitamin D3/week for 12 weeks) significantly reduced hirsutism, TT, and FAI.(23) Further, SHBG increased significantly, and favorable changes in ovarian morphology and menstrual regularity were also noted.(23)

The role of dietary intake of omega 3 polyunsaturated fatty acids (**PUFA**s) in mitigating PCOS complications has not been fully assessed.(25) The effect of omega 3 PUFAs is postulated to stem from their effects on anti-inflammatory eicosanoid gene expression and production, which may decrease IR, inflammation, and promote favorable lipid, hormonal, and anthropometric profiles.(25) A systematic review found that supplementation with omega 3 PUFAs (i.e. 1000–2000 mg of omega 3 PUFAs or DHA/EPA ranging from 180–360mg and 120–240 mg, respectively) for at least 6 months resulted in significantly lower waist circumference and decreased BMI. (25) In addition, significant decreases in HOMA-IR and insulin levels occurred with supplementation as did favorable changes in markers of inflammation (e.g. hs-CRP, adiponectin levels). Finally, significant decreases in luteinizing hormone and TT were found.(25)

Contemporary literature reflects increased interest in the use of phytochemicals, botanicals, and herbal traditional medicines in the treatment of PCOS. Data from systematic reviews and meta-analyses report cinnamon supplementation (i.e. 1/3 teaspoon, daily for 6 to 52 weeks) to be effective in significantly reducing markers of IR as well as promoting significant decreases in LDL-C, TC and TG, though no effect was noted on body weight or BMI.(26,27) Curcumin, a component of turmeric, is another phytochemical that has been hypothesized to improve IR through improved glucose uptake, decreased hepatic glucose

production, increased glucagon like protein -1 (**GLP**-1) secretion and increased fatty acid oxidation.(28) Heshmati et al. showed that 1500mg (1/3 tsp) of curcumin daily for 12 weeks improved fasting plasma glucose levels and reduced DHEA levels in the supplemented group.(28)

Limited studies have evaluated the impact of prebiotics in the form of fiber supplements, probiotics, and synbiotics (prebiotic+probiotic) to alter metabolic, hormonal and anthropometric indices in women with PCOS. Twenty grams of soluble fiber (resistant dextrin) given daily for 3 months to women with PCOS produced significant decreases in LDL-C, TG, TC and an increase in HDL-C.(29) Decreases were also seen in glucose, hs-CRP and free testosterone. Hirsutism scores and menstrual regularity also improved.(29) Co-supplementation with therapeutic doses of vitamin D and a probiotic (Lactobacillus acidophilus, Bifidobacterium bifidum, Lactobacillus reuteri and Lactobacillus fermentum) supplying 8×10^9 colony-forming units/day in women with PCOS over 12 weeks improved TT, hirsutism, hs-CRP, and measures of antioxidant capacity.(30)

Physical Activity

Current knowledge and recommendations on exercise and PCOS

The benefits of physical activity for women with PCOS have been well-delineated with respect to cardiometabolic risk factors, anthropometric parameters, menstrual cycle regularity, cardiorespiratory fitness and psychological well-being.(31) Compared to no treatment, exercise interventions improve cardiometabolic, reproductive and functional ability (i.e. strength and fitness) and can lead to weight loss. Longer sustained exercise interventions are more efficacious in altering metabolic markers and anthropometric parameters. The 2018 international guidelines recommend that adolescents with PCOS engage in 60 minutes of moderate to vigorous activity three times a week and suggest that musculoskeletal strengthening be included, although this is less than the seven days a week recommended for youth in the Physical Activity Guidelines for Americans.(1,32) While unable to prescribe a specific exercise type, the guidelines acknowledge that vigorous types of training may hold promise in promoting more favorable health outcomes for women with PCOS.(31)

Effects of general and specific types of exercise on PCOS clinical parameters

There is increased interest in understanding the specific effects of distinct types of exercise on PCOS and its co-morbidities.(33) In an RCT of women with healthy weight or obesity with PCOS, continuous aerobic training (30–50 minutes at 65–80% maximum heart rate) or intermittent aerobic training (eight, 2-minute intervals at 70–90% maximum heart rate) over 16 weeks were compared to no training.(5) Neither training protocol had an effect on body weight, body composition, fasting glucose, insulin or HOMA-IR.(5) Continuous training improved total TC, LDL-C and TT, while the intermittent regimen decreased waist circumference, TT and the FAI.(5) This study suggests that exercise routines of varying intensity may differentially effect health outcomes in PCOS.(5)

It has been suggested that high-intensity interval training (**HIIT**), an aerobic exercise model characterized by cycles of alternating high and low intensity and tempo, may be more effective for women with PCOS.(34,35) HIIT has been noted to favorably alter blood lipid and adiponectin levels in adolescent females with obesity and decrease IR compared to moderate-intensity exercise.(34) Twelve weeks of HIIT increased serum adiponectin in women compared to those who completed moderate continuous training.(34) HIIT also significantly decreased insulin levels, TG, TC, and LDL-C, and significantly increased HDL-C.(34) Aquatic HIIT in women with obesity and PCOS taking metformin decreased BMI, fat mass, hirsutism, IR, free testosterone and follicle stimulating hormone and increased SHBG compared to the control group on metformin alone.(35)

Limitations of exercise as a therapeutic strategy in PCOS

Despite strong evidence supporting the importance and effectiveness of exercise as a therapeutic modality for women with PCOS, the feasibility and sustainability of such interventions may be challenging.(36) Factors to be considered include increased resource utilization of allied health professionals and/or certified exercise professionals, increased cost to patients, and the need for strategies that ensure access to exercise regardless of socioeconomic status.(31) Exercise alone may improve but not eliminate complications of PCOS (31,37) and thus may be most effective when paired with other lifestyle interventions. Psychological barriers (e.g. body image concerns, fear of injury, low self-esteem, anxiety, depression) associated with PCOS could decrease engagement with physical activity interventions, and should be proactively addressed.(38) For weight loss intervention programs more broadly, Moran et al. found that high depressive symptoms in women with PCOS increased attrition and greater attendance was needed to achieve clinically significant weight loss.(39)

Pharmacotherapy

The approach to pharmacotherapy in PCOS is multi-pronged and includes treating signs of hyperandrogenism (combined oral contraceptives +/- anti-androgens), IR (e.g. metformin, TZD, GLP1 receptor agonists (**GLP1Ra**)), overweight/obesity (anti-obesity medications), and comorbidities (e.g. diabetes medications). For all adolescents with PCOS, weight-promoting medications should be avoided whenever possible (e.g. intramuscular medroxyprogesterone, insulin, atypical antipsychotics), and pharmacotherapy should be individualized to the adolescent's PCOS phenotype and personal health risks.

Combined oral contraceptives (COCP)

As part of the 2018 guidelines, a systematic review and meta-analysis was conducted to assess the effects of COCP and/or metformin or anti-androgens on several outcomes including BMI.(40) Adolescent-specific data was low-quality, but showed that metformin was superior to COCP for BMI (mean difference $-4.02 kg/m^2$ [−5.23, −2.81], $p < 0.001$). In women, COCP alone was superior to COCP plus an anti-androgen for BMI (mean difference $-3.04 kg/m^2$ [−5.45, −0.64], $p = 0.01$).

Metformin

There has been extensive prior research on the metabolic and weight effects of metformin in PCOS, with conflicting results secondary to varied inclusion criteria and dosing, although as above, meta-analysis is favorable for weight loss in adolescents.(40) Newer data are from studies that included a metformin arm compared to another medication, which show minimal weight loss when added to a COCP (41), or increased weight loss in women with PCOS and obesity who received 1500 mg/day metformin for 6 months (average weight loss of −6.81 (−7.51 to −6.10) kg).(4) A retrospective study that included ten adolescents with PCOS <18 years, found that among the entire cohort, those treated with metformin (850mg/day) had a 12% prevalence of obesity, compared to 50% of non-treated PCOS and 27% of individuals treated with COCP, although due to the nature of the study design, these should be interpreted with caution.(42)

TZDs

TZDs, including pioglitazone and rosiglitazone, have been consistently associated with weight gain, with some data suggesting increased risk of heart failure.(43,44) However, when paired with benefits including reduction of major adverse cardiovascular events in adults with insulin resistance, and NAFLD, its use in PCOS remains unclear.(44–46) In a recent RCT, 204 Chinese women with obesity and PCOS received 6 months of lifestyle plus: metformin, rosiglitazone, or metformin+rosiglitazone.(4) All three groups showed weight and BMI reduction (including rosiglitazone alone), though the metformin-only group showed significantly greater reductions. Notably, this study suggests that simultaneous lifestyle interventions may mitigate weight gain with rosiglitazone.

Anti-obesity medications

In the 2018 PCOS guidelines, only sibutramine and orlistat were included in the evidence review. Through extrapolation from the broader weight management literature, the guidelines recommend that anti-obesity medications could be considered as an adjunct to lifestyle interventions in adults with PCOS.(11) There are four FDA-approved medications for chronic weight management in adults – orlistat, phentermine/extended-release topiramate, liraglutide, and extended release bupropion/naltrexone. Of these, orlistat (since 2003) and liraglutide (in 2020) are FDA-approved for use in adolescents≥12 years.(47,48) Phentermine as a monotherapy is FDA-approved for short-term treatment of obesity in adolescents older than 16 years. A 2019 expert opinion statement suggests that pediatric weight management specialists should consider these agents in adolescents with BMI ≥95th%ile or >30kg/m^2 with a weight-related complication or severe obesity with BMI ≥120% of 95th%ile or ≥35kg/m^2.(49) A major barrier to widespread use of anti-obesity medications is the lack of state-based insurance coverage (out-of-pocket costs range from ~$22/month for phentermine to ~$1,000+/month for liraglutide). Ongoing advocacy is needed to ensure equitable access to these adjunctive therapies.

Since the 2018 PCOS guidelines, several studies have evaluated GLP1Ra in women with PCOS, but there have been scant data for all other classes. Our review yielded 2 studies on orlistat, a single case study of bupropion/naltrexone in a 23-year-old with PCOS(50) and no

studies on phentermine, topiramate, or the combination specifically in women or adolescents with PCOS.

Previous data on orlistat suggest a variable, but significant BMI reduction in women with PCOS (-0.7 to -8.1%), and head-to-head comparisons of orlistat versus metformin on weight/BMI are mixed.(51,52) In one of the largest RCTs of orlistat in PCOS to date, Ruan et al., randomized 240 women in China with overweight/obesity and PCOS open label to 12 weeks of ethinyl estradiol/cyproterone acetate alone or combined with orlistat, metformin, or orlistat+metformin.(41) Both groups receiving orlistat demonstrated significant reductions in weight, BMI, and systolic blood pressure. Reductions in LH, TT, fasting insulin, and HOMA-IR were seen in all groups with no between group differences.

GLP1Ra

GLP1Ra therapy with exenatide was first described for women with PCOS in 2008 with at least 10 more studies since that time(53). All studies demonstrate GLP1Ra induced weight loss ranging from 3 to 6 kg, with different degrees of efficacy depending on the specific GLP1Ra, dose and duration of therapy (53). Improvements in hormonal and metabolic parameters were documented in most, but not all studies. Liraglutide was approved for use to treat obesity in adolescents in 2020, and the primary study found that nearly half of teens lowered their BMI by ≥ 5%, demonstrating similar results to that seen in adults.(48) Recent results indicate that semaglutide may be even more efficacious for weight loss than exenatide or liraglutide, as 6 months of therapy in adults resulted in an average 15% decrease in BMI and a mean loss of 15 kg.(54)

Metabolic and Bariatric Surgery (MBS)

The role of MBS for weight management in adolescents and women with PCOS is still being established, and current adult and pediatric MBS guidelines do not include PCOS as an independent qualifying medical diagnosis.(55–57) However, with the ongoing rise of severe obesity in youth,(58) and mounting data demonstrating durable efficacy and safety,(59–62) utilization of MBS is expected to steadily increase.(63) Two new systematic reviews demonstrate that MBS in women with obesity and PCOS improved menstrual regulation and hirsutism, decreased TT, increased SHBG and estradiol, and increased remission of comorbid T2D and hypertension.(64,65)

The 2018 PCOS guidelines asked a single question regarding MBS: “In women with PCOS, what is the effectiveness of lifestyle interventions compared to bariatric surgery for improving fertility and adverse outcomes?”(11) No evidence was found specifically in women with PCOS. A large retrospective study in Sweden was cited (n=670 singleton pregnancies in women who underwent MBS and matched controls), which showed lower risks of gestational diabetes and large for gestational age babies, but increased risks of small for gestational age, shorter gestational age without preterm birth, and a possible increased risk of infant mortality (p=0.06) in the MBS group.(66) The guideline development group concluded that MBS is experimental for women with PCOS as a potential fertility therapy.

In our view, the guideline's scope was too narrow on this topic and should have also assessed the cardiometabolic outcomes following MBS for women with PCOS. Implications of MBS for adolescents with PCOS should have been assessed, especially regarding T2D. Research from our group shows that adolescents with obesity/severe obesity (n=493, mean BMI 36.2kg/m^2 +/- 6.3kg/m^2) and prediabetes at the time of PCOS diagnosis have a 14.6-fold greater risk of progressing to T2D over the next 4 years compared to adolescents with a hemoglobin A1c in the normal range at the time of PCOS diagnosis.(67) Among Hispanic girls, the hazard ratio for progression to T2D increases to 18.9.(67) This excess T2D risk in adolescents with PCOS is concerning, as younger age at diagnosis of T2D is associated with higher risks of cardiovascular and overall mortality.(68) Specifically, onset of T2D in adolescence is associated with decreased survival by over a decade compared to controls.(68) In the multicenter SEARCH study, T2D in youth was associated with excess short-term mortality (185.6 deaths/100,000 person-years versus expected 70.9 deaths/100,000 person-years) over 5 years, and was highest among females and non-Hispanic black youth.(10) Further, youth onset T2D does not respond to traditional therapies.(69)

A recent comparison of medical versus surgical management of adolescents with severe obesity and T2D over two years in the Treatment Options of T2D in Adolescents and Youth (TODAY) and Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) cohorts showed superior HbA1c trajectories in the surgical versus medical group [from 6.8% (95% CI, 6.4%-7.3%) to 5.5% (95% CI, 4.7% -6.3%) in Teen-LABS and from 6.4% (95% CI, 6.1%-6.7%) to 7.8% (95% CI, 7.2%-8.3%) in TODAY]. Furthermore, in a comparison between Teen-LABS and LABS studies, adolescents with T2D who underwent Roux-en-Y gastric bypass had significantly higher remission rates than their adult counterparts (86 versus 53%, risk ratio 1.27, 95%CI 1.21–1.88) at 5 years postoperatively.(70) These data underscore the potential increased benefits of early MBS intervention among high-risk adolescents, which may include those with PCOS. As far as we are aware, the largest prospective cohorts of MBS in adolescents, have not published separate outcomes for the subset of females with PCOS.(60–62) Biochemical evaluation of hyperandrogenism may be challenging in this population given the widespread appropriate use of hormonal long acting reversible contraception perioperatively.(71) Future studies are clearly needed to evaluate the impact of MBS among adolescents with PCOS. Results should be used to inform the potential inclusion of PCOS as a therapeutic indication for MBS in the next iteration of pediatric MBS guidelines.

Psychiatric Comorbidities

The 2018 PCOS guidelines included an expanded set of recommendations on assessing and treating mood and quality of life concerns via tailored psychological interventions to the adolescent's personal priorities, phenotype, and relevant cultural factors.(11) This can be accomplished via the integration of a pediatric clinical psychologist into the multidisciplinary weight management team treating adolescents with PCOS, as well as systematic assessments of mood.(72,73) A combination of one-on-one and group-based peer support options in-person and virtually can be considered to support mental health and emotional well-being.

Adolescents with PCOS, compared to those without, have higher rates of depression and anxiety, lower self-esteem and body image, and reduced quality of life.(74–76) They also have higher depressive symptoms compared to adolescents with T2D.(72) Higher prevalence of depression may be mediated but not fully explained by obesity.(72,75,77,78) This is in apparent contrast to qualitative data from adolescents with PCOS which highlight low confidence, sadness, shame, and stress related to obesity and signs of hyperandrogenism.(79) Proposed pathophysiologic mechanisms linking PCOS to depression include dysregulation of the hypothalamic pituitary adrenal axis (high cortisol, sympathetic activation) and complex interactions among IR, neural circuitry/transmission, and systemic inflammation.(80,81) These hypothesized mechanisms have not been rigorously tested in adolescents or women with PCOS.

Treatment of depression in adolescents with IR using cognitive behavioral therapy (CBT) has been shown to improve response to weight management interventions.(82) In women with PCOS, both weight loss and androgen reduction have been shown to improve mood disorders and quality of life.(77,83) Three recent trials of CBT + lifestyle, CBT alone, or acceptance and commitment therapy in women with PCOS demonstrated significant improvements in BMI, depression,(84) quality of life,(85) body image, and self-esteem.(86,87) In this review, there were no published results identified for behaviorally-based interventions targeting adolescents with PCOS. However, one actively recruiting protocol in Australia aims to assess the effect of 8 weeks of transcendental meditation on quality of life and coping in adolescents with PCOS.(88)

Effects of Sleep

Adolescence is characterized by a shift in sleep timing and circadian phase, governed by the hypothalamus.(89) This biological preference paired with social expectations (late bed time, early wake time) often leads to chronic insufficient sleep in this age group, which has been associated with obesity, increased energy intake and worse mood.(90–92) There is very little data on the topic of sleep and weight management among adolescents with PCOS. Our group has shown that adolescents with PCOS, obesity, and metabolic syndrome have more sleep-disordered breathing (higher apnea-hypopnea and arousal indices) compared to adolescents with PCOS and obesity without metabolic syndrome.(93) Higher apnea-hypopnea index was correlated with higher TG, and poor sleep efficiency correlated with increased NAFLD, waist circumference and TG. Additionally, in this study, poor sleep behaviors (e.g. short sleep duration, higher variability between weekday and weekend bedtimes) were found to be associated with more components of metabolic syndrome. We have also demonstrated that adolescents with obesity and PCOS versus those without PCOS display circadian misalignment with later offset of melatonin.(94) Later melatonin offset (waking up during the biological night) was associated with higher free testosterone and worse insulin sensitivity in adolescents regardless of PCOS status. Together, these studies suggest that sleep is a compelling area to better characterize and target for possible weight and metabolic management in adolescents with PCOS.

Conclusions

PCOS in adolescents is associated with obesity and metabolic disease, and decreasing BMI is central to improving hormonal and metabolic health. The key evidence in each of the domains explored nutrition, physical activity, pharmacology, MBS, mood and sleep are summarized in Table 1. The majority of these recommendations are based on evidence in adult women with PCOS, or adolescents without PCOS. Comprehensive treatment of PCOS and weight management among adolescents may be best accomplished by an interdisciplinary team where during each visit the adolescent can see a medical provider, registered dietitian, exercise specialist, clinical psychologist, gynecologist, and/or dermatologist, tailored to her needs. Extensive further research to optimize therapy in youth with PCOS is needed, with specific areas highlighted in Table 2.

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Table 1.

Highlights of the evidence for weight management in adolescents with PCOS by domain

Domain			
Nutrition	*Primary intervention*: caloric restriction (reduction of ~500–1000kcal/day from baseline)	*Secondary interventions*: low glycemic index/load; high protein/fiber & low carbohydrate; anti-inflammatory pattern	*Complementary*: supplementation with cinnamon, curcumin, B vitamins, omega 3 PUFAs
Physical Activity	60 minutes ≥3x/week moderate-vigorous activity including strength training	Consider high intensity interval training (HIIT) to reduce time burden	Tailor activity plan to maximize engagement and self-efficacy
Pharmacotherapy	Individualize based on phenotype and personal health risks	Consider anti-obesity medications as an adjunct to lifestyle	Avoid weight-promoting medications
Bariatric Surgery	T2D risk is higher in PCOS and adolescents with T2D experience premature short and long-term mortality; MBS leads to greater T2D remission when performed in adolescence versus adulthood	Risks of MBS include micronutrient deficiencies; pregnancy/infant outcomes are mixed and need to be repeated prospectively	MBS requires additional study specifically among adolescents with PCOS
Mood	Screen at PCOS diagnosis for depression, low self-esteem, unhealthy body image, disordered eating, and quality of life, all of which are more common in PCOS	Include a pediatric clinical psychologist as a core member of the interdisciplinary adolescent PCOS management team	Consider cognitive behavioral therapy for weight loss and improved mood/emotional outcomes
Sleep	Sleep-disordered breathing and poor sleep behaviors are more prevalent in adolescents with versus without PCOS	Circadian misalignment with late melatonin offset in adolescents with PCOS may exacerbate weight-related and metabolic complications	Sleep represents an understudied target of PCOS research

Major domains for achieving weight loss in youth with PCOS and overweight or obesity are shown, with leading recommendations listed

Table 2.

Gaps/future directions for weight management in adolescents with PCOS

Category	Adolescent/Family	Provider	Research
Physiology	Personalized treatment (i.e. for different PCOS phenotypes, genotypes, family history)	Improved provider knowledge of PCOS pathophysiology, comorbidities, treatment strategies, holistic interdisciplinary approach	Identification of molecular mechanisms (e.g. role of hypothalamic signaling) to guide personalized treatment
Feasibility and Acceptability of Interventions	Identify and address adolescent-specific barriers (e.g. time, cost, access, psychological concerns)	Support provider engagement and training	Conduct cost benefit analyses; Use CBPR, SMART, and/or Dissemination & Implementation methodologies
Sustainability of Effects	Develop individualized treatments for weight loss maintenance and prevention of regain through combination therapies	Create and test new models of care delivery with increased dose/intensity	Conduct research with stakeholders at multiple levels (individual, medical home, community, policy) to reduce barriers and maximize success
Equity	Elicit and incorporate adolescent/family input about facilitators and barriers	Improve provider/program knowledge of community resources	Test novel intervention strategies (e.g. online exercise sessions, social media) that directly address social determinants of health
Lifespan approach	Understand and address cultural beliefs/attitudes about food/growth, activity, sleep, across the lifespan (e.g. infancy, adolescence, pregnancy)	Build adult/pediatric care collaborations	Establish stitched or continuous cohorts from adolescence through adulthood; Transition work from pediatric to adult weight management/PCOS homes

CBPR – Community Based Participatory Research | SMART – Sequential Multiple Assignment Randomized Trial

Significant gaps in the literature with suggested future directions to advance the field of weight management among adolescents with PCOS