Review | ADOLESCENT AND YOUNG ADULT HEALTH

Treatment Considerations for the Cardiometabolic Signs of Polycystic Ovary Syndrome

A Review of the Literature Since the 2013 Endocrine Society Clinical Practice Guidelines

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IMPORTANCE Polycystic ovary syndrome is characterized by an excess in androgen levels, ovarian dysfunction, and polycystic ovarian morphology but is also associated with metabolic dysfunction and risk factors for cardiovascular disease. To our knowledge, there are few therapeutic recommendations for these cardiometabolic risk factors and little evidence of their long-term clinical relevance to cardiovascular health.

OBJECTIVE To determine metabolic and/or cardiovascular outcomes in polycystic ovary syndrome treatment literature since the publication of the most recent Endocrine Society clinical practice guidelines in 2013.

EVIDENCE REVIEW We searched PubMed using a string of variations of polycystic ovary syndrome, therapy/treatment, and adolescence, and we included English-language original research articles published while the 2013 clinical practice guidelines were disseminated (ie, articles published from January 1, 2011, to June 1, 2015). Articles that appeared relevant based on a review of titles and abstracts were read in full to determine relevancy. References from relevant articles were reviewed for additional studies.

FINDINGS Four topic areas emerged: (1) lifestyle modification, (2) metformin vs placebo or estrogen-progestin oral contraceptives, (3) insulin-sensitizing agents, and (4) estrogen-progestin formulations. Most studies assessed the role of metformin as a monotherapy or dual therapy supplement and found significant benefit when including metformin in polycystic ovary syndrome treatment regimens. Studies showed improvements in cardiometabolic risk factors and, in several, androgen excess and cutaneous and menstrual symptoms. Studies were limited by sample size (range, 22-171), few adolescent participants, and short-term outcomes.

CONCLUSIONS AND RELEVANCE Findings show potential for metformin and estrogen-progestin dual therapy but warrant longitudinal studies examining outcomes from adolescence through middle age to determine the effect on long-term cardiovascular health.

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Polycystic ovary syndrome (PCOS) is the most common endocrine disorder among women of reproductive age, affecting 6% to 8% of all women.[1-3] It is a heterogeneous condition characterized by an excess of androgen levels, ovarian dysfunction, and polycystic ovarian morphology. The 3 sets of diagnostic criteria—National Institutes of Health, Rotterdam, and Androgen Excess Society criteria—are each based on combinations of these characteristics. Clinical manifestations of hormonal and reproductive disturbances include hirsutism, acne, and irregular menstrual cycles. First-line medical therapy targets these disturbances.

While not included in diagnostic criteria for PCOS, this syndrome is also characterized by metabolic dysfunction, most notably derangements in glucose metabolism (ie, insulin resistance and compensatory hyperinsulinemia). Compared with women without PCOS, adolescents and young adults with PCOS are more likely to be obese and are at increased risk for impaired glucose tolerance (IGT), type 2 diabetes (T2D), dyslipidemia, hypertension, metabolic syndrome, and other risk factors for cardiovascular disease.[4] Longitudinal PCOS data suggest that a higher prevalence of cardiovascular risk factors is not necessarily associated with higher cardiovascular mortality.[5,6] A retrospective cohort study[5] of UK women reported a higher prevalence of cardiovascular risk factors among women with PCOS but a similar history of coronary heart disease and cardiovascular mortality compared with women in the general population.[6] Long-term follow-up showed higher prevalence of T2D and nonfatal cerebrovascular disease, suggesting greater disease-related morbidity, if not mortality, compared with the general population.[5,6]

While current treatment guidelines[7] discuss management of obesity, IGT, and T2D, the primary goals of treatment in adolescent populations are menstrual regularity, improved androgen excess, and cutaneous symptoms. With the added importance of preventing unwanted teenage pregnancy, combined estrogen-progestin oral contraceptive (COC) pills have been prioritized as first-line agents for adolescents with PCOS.[7,8] However, metabolic disturbances associated with PCOS are not adequately addressed by COC regimens. Instead, there is evidence that COC regimens increase metabolic dysfunction (eg, dyslipidemia, decreased insulin sensitivity, and glucose intolerance) and risk for cardiovascular disease (eg, myocardial infarction, atherosclerosis, and hypertension).[9-12] This review focuses on therapeutic approaches for PCOS targeting or otherwise affecting metabolic dysfunction and cardiovascular risk associated with PCOS. To our knowledge, there is little guidance on these therapeutic targets for adolescents with PCOS; therefore, we focused our review on adolescent literature when possible.

Key Points

Question What is the evidence in the literature for treatment recommendations for cardiometabolic risk factors associated with polycystic ovary syndrome in adolescents?

Findings In this review, most studies assessed metformin as a monotherapy or dual therapy supplement and found significant improvements to cardiometabolic parameters when including metformin in polycystic ovary syndrome treatment regimens. Studies were limited by sample size, few adolescent participants, and short-term outcomes.

Meaning Findings show potential for metformin and estrogen-progestin dual therapy but warrant longitudinal studies examining outcomes from adolescence through middle age to determine the effect on long-term cardiovascular health.

Methods

We searched PubMed using the following string: *(Polycystic Ovary Syndrome OR polycystic ovary syndrome OR PCOS OR polycystic ovarian syndrome) AND (Therapeutics OR therapeutics OR therapy OR treatment OR treatments OR treat) AND (Adolescent OR adolescent OR adolescents OR pediatric patient OR pediatric patients OR adolescence OR youth OR youths OR juvenile OR teenager OR teenagers OR teen OR teens OR pediatric OR pediatrics OR pediatric OR pediatrics)*. Evidence-based clinical practice guidelines (CPGs) on PCOS were published by the Endocrine Society in 2013.[7] We reviewed literature published while these guidelines were developed and since their dissemination (ie, articles published from January 1, 2011, to June 1, 2015). We limited the search to original research, including randomized clinical trials (RCTs) and observational designs; case studies, scientific meeting abstracts, and articles not specifically focused on PCOS were excluded. Only English-language articles were reviewed. One author obtained articles that appeared relevant based on a review of titles and abstracts. Final relevance was determined after reading the full texts. References from relevant articles were reviewed for additional studies. We limited our review to articles that included cardiometabolic outcomes and excluded articles only focused on hormonal or reproductive outcomes. Authors coded articles based on the evaluated therapeutic regimen, age of patient population, study design, and inclusion of cardiometabolic outcomes in the study, then abstracted and synthesized all relevant findings. Disagreements were resolved by consensus-based discussion between the coauthors.

Results

Our PubMed search returned 272 articles; 18 met inclusion criteria and were relevant to treatment for cardiometabolic disturbances in PCOS. Two articles on thiazolinediones were not included in this review because this class of drugs is no longer used or available in the United States. Four topic areas emerged from this review: (1) lifestyle changes, including diet and exercise; (2) metformin vs placebo or estrogen-progestin contraceptives; (3) insulin-sensitizing agents; and (4) estrogen-progestin formulations and metabolic outcomes. A summary review and synthesis of the literature by topic area is described below. We prioritized adolescent-specific studies (n = 4) where possible but included both adult and adolescent articles. In each topic area, we reference relevant recommendations from the Endocrine Society CPGs.

Lifestyle Changes Including Diet and Exercise

The Endocrine Society CPGs include exercise and lifestyle therapy focused on weight loss as suggested strategies for managing overweight/obesity in adolescents and adults with PCOS. Guidelines are based on general population studies demonstrating risk reduction

for T2D and cardiovascular disease. In our review, 3 articles[13-15] reported positive associations between diet and/or exercise and cardiometabolic parameters in women with PCOS.

A single-arm study[13] assessed the effect of 1 year of the Obeldicks lifestyle intervention[16] in obese adolescents (N = 59; age range, 12-18 years; mean [SD], 15.0 [0.7] years) on intima media thickness. Intima media thickness is a marker of early atherosclerotic changes and is associated with cardiovascular disease. Among adolescents to achieve successful weight loss (ie, >0.20 body mass index [BMI, calculated as weight in kilograms divided by height in meters squared] SD score), the study reports a significant decrease in intima media thickness and improvements in waist circumference, lipid profile, blood pressure, 2-hour glucose level in an oral glucose tolerance test, and Homeostasis Model Assessment (HOMA) for insulin resistance. Significant decreases in testosterone levels, increases in sex hormone–binding globulin (SHBG) levels, and decreased prevalence of oligomenorrhea and amenorrhea were also seen in adolescents who achieved weight loss. Notably, testosterone and SHBG level changes were significantly associated with changes in insulin level and insulin resistance rather than BMI changes. While not evidence of causation, this association supports the hypothesis that insulin resistance/hyperinsulinism is a mediating factor between obesity and androgen excess/ovarian dysfunction in PCOS and may be a therapeutic target for improving metabolic and androgen/ovarian symptoms.

The importance of insulin levels in PCOS pathology was demonstrated in a second study[14] comparing the influence of dietary management and/or exercise on ovarian function, endocrine factors, metabolic status, and body composition in overweight/obese women with PCOS (N = 57; age range, 18-40 years). Through a randomized 4-month, 3-arm trial with 1-year follow-up, the study demonstrated an overall decrease ($P < .001$) in BMI without significant differences between groups. Body mass index decrease was greatest in the dietary (−1.74) and combined (−1.90) groups and lowest in the exercise group (−0.85). There was also equivalent improvement in menstrual and ovarian function through diet and exercise separately and in combination. No significant changes in glucose or insulin levels or HOMA index were detected in any group; however, high postintervention insulinlike growth factor-binding protein 1, a marker of insulin sensitivity, was the strongest predictor of ovulation across treatment groups.

A third study[15] examined the effect of the Dietary Approaches to Stop Hypertension diet on lipid profiles and biomarkers of oxidative stress (eg, total antioxidant capacity and plasma glutathione levels). Through a 2-arm RCT in adult women with PCOS (N = 48; age range, 18-40 years) comparing an 8-week Dietary Approaches to Stop Hypertension diet with a control diet, the study showed significant decreases in weight (mean [SD], 4.4 [2.7] kg vs 1.5 [2.6] kg; $P < .001$), BMI (1.7 [1.1] vs 0.6 [0.9]; $P < .001$), serum triglyceride levels, and very low-density lipoprotein cholesterol levels and improvement in biomarkers of oxidative stress in the treatment group relative to the control. Similar to previously mentioned studies,[13,14] insulin parameters were improved in the intervention group.

Metformin vs Placebo and/or Estrogen-Progestin Contraceptives and Metabolic Outcomes

Metformin is a well-established medical regimen for treating insulin resistance. In the context of PCOS, a reduction in insulin levels by metformin is associated with an increase in SBHG levels and a decrease in circulating androgens, thereby improving ovarian function and menstrual regularity.[8]

For adolescents with PCOS, the Endocrine Society CPGs suggest using metformin to treat IGT or metabolic syndrome, citing limited data on metformin treatment in adolescents with PCOS. Similarly in adults, the CPGs strongly recommend metformin for those with IGT or T2D in whom lifestyle modification has failed and suggest metformin as second-line treatment for women with menstrual irregularities who are unable to take or tolerate COCs. These guidelines suggest against using metformin as first-line therapy for treatment of obesity or cutaneous PCOS symptoms. Since these guidelines were published, several studies[17-24] have demonstrated significant improvements in metabolic disturbances among adolescents and adults with PCOS in head-to-head comparisons of metformin monotherapy or dual therapy (metformin and COCs) vs placebo and/or oral COC monotherapy.

Metformin vs Placebo

We identified 1 study[17] investigating metformin vs placebo. This RCT was designed to determine the effect of metformin monotherapy on sleep disorders in adolescents with PCOS (N = 60) and demonstrated significant decreases in the sleep disturbances scale and Epworth sleepiness scale in the treatment group vs untreated control group after a 3-month trial. There were also significant decreases in weight, BMI, Ferriman-Gallwey score, fasting and postprandial glucose levels, fasting serum insulin levels, and HOMA index.

Metformin Monotherapy vs COC Monotherapy

Two studies[18,19] comparing the effects of metformin and COC monotherapy on cardiometabolic outcomes were reviewed. Both studies were RCTs with relatively short treatment duration and small study samples. As expected, COC monotherapy was superior at improving androgen excess, but significant differences in cardiometabolic outcomes were minimal.

In the first study,[18] 22 adolescents with PCOS were randomized to a 6-month trial of COC monotherapy vs metformin monotherapy to evaluate improvements in BMI, free testosterone levels, SHBG levels, number of menstrual cycles, insulin resistance, and quality of life. There were few differences between treatment groups. As expected, free testosterone levels decreased and SHBG levels and menstrual cycles increased significantly in the COC group. However, BMI decreased significantly in both groups. Trends in data suggested an improved effect on metabolic parameters in the metformin treatment group, but improvements did not reach statistical significance.

The second study[19] was a crossover trial with adults (N = 42; age range, 18-36 years) comparing effects of a 4-month trial of metformin vs COCs containing cyproterone acetate (COC/CA), a formulation not available in the United States. During COC/CA treatment, there were significant increases in high-density lipoprotein and triglyceride levels, a known adverse effect of COCs, as well as a significant increase in C-reactive protein level due to first-past liver effect of estrogen rather than activation of an inflammatory pathway.[20] There were no significant changes in weight, but the percentage of participants who gained weight was significantly greater after treatment with COC/CA vs metformin.

COCs vs Metformin: Comparisons Between Monotherapy and Dual Therapy

Two 3-arm RCTs evaluated the effects of metformin monotherapy vs COC monotherapy vs dual therapy on cardiometabolic risks associated with PCOS in adult women. The first study[21] assessed the effect of COCs formulated with desogestrel (COC/De) on body composition, metabolic syndrome, and cardiovascular disease. The second study[22] used a COC formulated with drospirenone (COC/Dr) and assessed effects on $CD4^+CD28^{null}$ T-lymphocyte frequency, a marker of cardiovascular disease risk. Both studies demonstrated significant improvement in cardiometabolic outcomes in both metformin-containing treatment arms compared with COC monotherapy.

In the first trial,[21] 90 women (including normal-weight and overweight/obese women) were randomized to 1 of 3 twelve-month treatment arms: COC/De, metformin, or COC/De and metformin. The primary outcome, body composition, was measured by weight, BMI, waist and hip measures, and peripheral vs central fat mass assessed by dual-energy x-ray absorptiometry. Independent of baseline BMI, metformin-containing regimens (dual therapy or monotherapy) were superior to COC/De monotherapy in improving body composition. Compared with COC/De monotherapy, metformin-containing regimens also significantly decreased insulin and C-peptide levels. Combined estrogen-progestin oral contraceptives formulated with desogestrel monotherapy was associated with increased SHBG levels and decreased free testosterone levels but was also associated with increased C-peptide levels and worsened body composition. Dual therapy had comparable improvements in testosterone and SHBG levels and an improved Ferriman-Gallwey score compared with COC/De monotherapy without the negative effects on metabolic parameters (eg, body composition or C-peptide levels). Based on improvements in both metabolic parameters and androgen excess and improvements in body composition independent of baseline BMI, study authors suggested that dual therapy may be an effective treatment approach, even among normal-weight women with PCOS.

In the second trial,[22] 93 women with PCOS and hyperinsulinemia were matched by age and BMI and were randomized to 1 of 3 six-month treatment arms—COC/Dr, metformin, or COC/Dr and metformin—to evaluate the treatment effect on $CD4^+CD28^{null}$ T-lymphocyte frequencies and other metabolic parameters. Dual therapy was the only treatment group to show a significant decrease in $CD4^+CD28^{null}$ T-lymphocyte frequency. There were no significant changes in BMI within or between treatment groups, yet metabolic parameters (eg, post–oral glucose tolerance test insulinemia and high-density lipoprotein levels) improved significantly in metformin-containing regimens, suggesting a medication effect independent of weight loss. Total cholesterol and triglyceride levels increased significantly after treatment with COC/Dr-containing regimens. Low-density lipoprotein levels increased with dual therapy, but there was no increase with metformin monotherapy. Consistent with other studies, significant improvements in serum androgen levels and ovarian volume were seen in COC/Dr-containing therapy groups.

Two additional studies comparing monotherapy and dual therapy were reviewed. One study[23] compared dual therapy with metformin monotherapy, and a second study[24] compared dual therapy with COC monotherapy. The first study[23] was a retrospective medical record review of adolescent girls with PCOS (mean [SD] age = 15.3 [0.48] years) and compared the effect of metformin monotherapy with metformin and COC dual therapy (formulation unspecified) on lipid profiles, BMI, and hemoglobin A_{1c} level. Similar to the above study,[22] treatment with metformin monotherapy was associated with greater improvement in lipid panels (decreased total cholesterol and triglyceride levels) compared with COC-containing regimens (ie, dual therapy in this study). The changes between groups were significant after controlling for baseline BMI and changes in BMI, suggesting a medication effect independent of weight loss.

The second study[24] was an RCT of women with PCOS (N = 42; age range, 17-37 years) comparing the effect of COC/Dr monotherapy with COC/Dr and metformin dual therapy on ovarian ultrasound markers, leptin-ghrelin levels (ie, hormones involved in regulation of body fat and appetite), and body fat distribution after 6 months of treatment. Study participants were randomized to each treatment group and divided by BMI (ie, overweight and normal weight). Investigators found significant reductions in abdominal fat among overweight woman treated with dual therapy and among normal-weight woman treated with COC/Dr monotherapy. There were no significant differences in BMI in the dual therapy group, which suggests a medication effect on abdominal fat independent of weight loss; however, the sample size may be too small to detect differences, and study authors did not report BMI changes in overweight and normal-weight woman separately.

Insulin Sensitizers

The Endocrine Society CPGs strongly recommend against other insulin sensitizers, notably thiazolinediones, citing an unfavorable risk-benefit ratio, and inositols, citing lack of benefit. We reviewed 1 study[2] comparing *myo*-inositol (MYO) vs D-chiro-inositol (DCI) for treating PCOS and 2 studies[25,26] investigating the effectiveness of other supplements (ie, folate and ω-3) with insulin-sensitizing properties published since or shortly before these guidelines. Each of these studies demonstrated moderate improvements in metabolic parameters.

Inositol is a polyalcohol belonging to the vitamin B complex with 9 stereoisomers; 2 of these, MYO and DCI, have insulin-mediating properties.[27] A Cochrane review by Tang et al[28] of insulin sensitizers in PCOS found that DCI had little effect on cardiometabolic risk factors or androgen excess. However, a systematic review[29] of effects of MYO in PCOS reported 1a evidence of effectiveness with a mechanism of action based on improving insulin sensitivity. We reviewed a 6-month RCT[26] comparing the effectiveness of MYO with the effectiveness of DCI on ovarian function, androgen excess, and metabolic factors in 50 women with PCOS. Both treatment arms were associated with improved menstrual regularity, decreased androgen levels, increased SHBG levels, improved insulin parameters, and improved systolic or diastolic blood pressure. The MYO arm had significantly greater improvements in insulin resistance, androgen excess, and luteinizing hormone/follicle-stimulating hormone ratio compared with the DCI treatment arm.

A second study,[30] an RCT, evaluated the effect of folate supplementation in overweight women with PCOS. An increased prevalence of folate deficiency in PCOS has been reported.[31] Folate in overweight adults has been associated with improved insulin sensitivity and glucose metabolism.[32] Elevated homocysteine levels, a risk factor for cardiovascular disease, dyslipidemia, and insulin resistance, are also prevalent in women with PCOS and have responded well to folate supplementation in previous studies.[33] Based on the potential benefit of folate supplementation in women with PCOS, the present study[30] randomized 81 obese women with PCOS to 1 of 3 eight-week treatment arms—folate (1 mg/d or 5 mg/d) or placebo—

and compared effects on plasma homocysteine levels, insulin and glucose metabolism, and lipid levels. Findings suggest a beneficial effect on metabolic profiles in women with PCOS. Compared with other treatment arms, participants supplemented with 5 mg of folate per day had significantly reduced homocysteine levels, HOMA index, and total, low-density lipoprotein and nonhigh-density lipoprotein cholesterol levels.

A smaller prospective study[25] evaluated the efficacy of ω-3 for PCOS treatment. ω-3 has antiobesity and anti-inflammatory actions and reduces insulin resistance,[34] so this study focused on proinflammatory markers (eg, tumor necrosis), metabolic outcomes, and androgen excess in adult women with PCOS (age range, 17-38 years; mean [SD] factor-α = 22.6 [4.75]). Comparing measures at baseline and after 6 months of treatment with 1500 mg of ω-3, there were significant decreases in BMI, insulin levels, HOMA index, Ferriman-Gallwey score, and luteinizing hormone and testosterone levels and an increase in SHBG levels. The expected improvement in inflammatory markers was not seen; instead, there was a significant increase in tumor necrosis.

Estrogen-Progestin Formulations and Metabolic Outcomes

The Endocrine Society CPGs strongly recommend COCs for adults and suggest COCs for adolescents as first-line treatment for PCOS. It does not comment on the utility of various available formulations of COC. There is evidence that both the dose of ethinyl-estradiol and the level of androgen activity of selected progestin in combined estrogen-progestin formulations may affect the deterioration of metabolic parameters in PCOS associated with COC therapy.[20] We reviewed 3 studies[35-37] investigating the effect of varying the progestin type or ethinyl-estradiol dose on metabolic and endocrine parameters in adult women with PCOS, and each showed little difference in outcomes between interventions. The first trial[35] was a 3-arm RCT comparing the effects of COCs formulated with desogestrel, cyproterone acetate, or drospirenone on BMI, anthropomorphic measures, cutaneous signs of androgen excess and insulin resistance, serum androgens levels, and insulin and glucose measures after 6 and 12 months of treatment. Signs and symptoms of androgen excess improved at 12 months in the COC/CA arm. However, there were no significant differences in any of the metabolic measures at 6 or 12 months.

In the second trial,[36] investigators randomized 52 women to a 12-month trial of either ethinyl-estradiol and drospirenone or cyproterone acetate. Outcomes also included BMI, anthropomorphic measures, hirsutism score, androgen levels, insulin and glucose measures, lipid levels, and measures of oxidative stress. Waist-hip ratio decreased significantly in the COC/Dr treatment arm compared with the COC/CA arm. Otherwise, there were no differences in metabolic outcomes.

The third trial[37] compared COC/Dr and 20 μg vs 30 μg of ethinyl-estradiol over 12 months in an RCT of 30 normal-weight, young (age range, 18-30 years) women. Outcomes similarly included hirsutism score, androgen levels, insulin and glucose measures, and lipid levels. Notably, lipid (total, low-density lipoprotein, and high-density lipoprotein cholesterol, and triglyceride) levels significantly increased in both groups, and the increase in triglycerides was significantly higher in the 30 μg treatment arm; other endocrine outcomes were comparable across groups.

Conclusions

We reviewed literature on treatment of PCOS cardiometabolic outcomes published since the Endocrine Society CPGs on PCOS in 2013. Most studies assessed the role of metformin as monotherapy or in combination with estrogen-progestin contraceptives as dual therapy and found significant added benefit of including metformin in the treatment regimen for PCOS. Studies showed improvement in cardiometabolic risk factors and, in several studies, androgen excess and associated cutaneous and menstrual symptoms. The strength of most of these studies was their RCT study design; however, most of these studies were small, focused on adults, and reported on relatively short-term findings.

Studies on lifestyle changes, including weight loss and exercise, confirmed recommendations from the Endocrine Society CPGs by demonstrating improvements in cardiometabolic risk factors and androgen excess with weight loss, and these studies should continue to be encouraged. The study on inositols[26] was not sufficient in rigor, size, or cardiometabolic outcomes to warrant changing recommendations described in the CPGs. Studies on folate and ω-3 supplements suggest a promising new area of research, but there is not yet evidence to definitively recommend these agents. Finally, study findings on the effects of different COC formulations on cardiometabolic outcomes suggest little reason to recommend one formulation over another for PCOS treatment.

The studies reviewed on metformin-containing therapies warrant the question of whether metformin should be added to treatment regimens for adolescents with PCOS without IGT or T2D. The short-term outcomes from these studies would support a recommendation for dual metformin/COC therapy. However, there are a number of considerations not addressed by any of the studies in this review that should temper such a recommendation considerably, most notably a lack of long-term outcome data or cohort studies starting in adolescence. Without these data, we do not know the appropriate age at which to start metformin to prevent cardiovascular disease or whether short-term improvements in cardiometabolic risk factors identified in these studies lead to positive cardiometabolic outcomes later in life. Moreover, the diversity of cardiometabolic risk factors, antecedent risk markers (eg, leptin-ghrelin levels, inflammatory markers, T-lymphocyte frequency, and endothelial dysfunction), and measurement/diagnostic tools (eg, dual-energy x-ray absorptiometry for body composition and Epworth sleepiness scale) evaluated in these studies raise additional questions about the most important and relevant targets for therapeutic and prevention strategies.

Findings from these studies show potential for metformin/COC dual therapy; however, rather than a change in existing guidelines, these findings warrant longitudinal studies examining outcomes from diagnosis in adolescence through middle age to determine the effect of these treatment regimens on cardiometabolic outcomes.

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