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Meta-Analysis

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Efficacy of Treatments for Polycystic Ovarian Syndrome Management in Adolescents

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Abbreviations: CI, confidence interval; CrI, credible interval; BMI, body mass index; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MD, mean difference; NMA, network meta-analysis; OCP, oral contraceptive pill; OR, odds ratio; PCOS, polycystic ovarian syndrome; RCT, randomized controlled trials; ROB, risk of bias; SUCRA, surface under the cumulative ranking curve.

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Abstract

Limited evidence on treatment options for polycystic ovarian syndrome (PCOS) has led to considerable variation in health care practices. We aimed to compare the effects of metformin and/or oral contraceptive pills (OCP) in combination with pioglitazone, spironolactone, flutamide, and lifestyle interventions among adolescents aged 11 to 19 years with PCOS. Literature searches were performed in Medline, Embase, and the Cochrane Central Register of Controlled Trials from database inception through December 2018, with no language restriction. Two reviewers screened titles and abstracts, assessed full text eligibility, and extracted information from eligible trials. Evidence was synthesized through network meta-analyses (NMA) using a Bayesian random-effects approach. We identified 37 randomized controlled trials, in which 2400 patients were randomized. NMA showed no statistically important difference among all interventions to improve menstrual regulation or body mass index. Moderate-quality evidence showed hirsutism scores were reduced by multiple interventions that included single and combination medications namely; lifestyle intervention, metformin, OCP, spironolactone, pioglitazone, metformin-OCP, metformin-spironolactone, and metformin-flutamide against placebo.

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Moderate-quality evidence showed OCP results in more dysglycemia compared to metformin (odds ratio, 2.98; 95% credible interval, 1.02-8.96), no intervention resulted in dysglycemia reduction. In conclusion, metformin and OCP as monotherapy or in combination with other interventions compared with placebo can reduce hirsutism scores, but none of these medications lead to effective menstrual cycle regulation or weight reduction. However, the use of OCP leads to worse cardiometabolic risk factors. Further research into new treatment options is urgently needed.
PROSPERO registration number: CRD42015016148.

Key Words: adolescents, polycystic ovarian syndrome, hirsutism, menstrual irregularity, cardiometabolic, network meta-analysis

Polycystic ovarian syndrome (PCOS) is a common endocrine reproductive disease affecting 1.8% to 15% of women [1-3]. The estimates are variable according to the diagnostic criteria used and the ethnic background of the women. PCOS is diagnosed based on a presentation with 2 of the following: clinical or biochemical hyperandrogenism, ovulatory dysfunction, or polycystic ovaries on ultrasound [4, 5]. However, diagnosing PCOS among adolescents remains difficult specially in the first 2 years after menarche. PCOS increases risk of dysglycemia, hyperlipidemia, and obesity [6-18]. PCOS is associated with increased risk for the development of endometrial hyperplasia and consequent development of endometrial cancer, infertility, pregnancy loss, and premature delivery. Moreover, patients with PCOS report low perceived health quality, often citing issues with weight control, hirsutism, acne, menstrual irregularity, and infertility as the primary drivers [19-21].

Treatment strategies, although variable and controversial because of lack of evidence, focus primarily on controlling symptomatology rather than treating the underlying etiology with the implementation of lifestyle intervention, and the use of either oral contraceptive pills (OCP), or metformin [4, 5, 22, 23]. However, this approach typically fails to achieve a good response and does not mitigate the risk of developing long-term complication [24].

Research to date has failed to define the ideal treatment approach. For example, studies in adolescents treated with various standards of care have been underpowered to draw conclusions with respect to important patient outcomes such as menstrual regulation, hirsutism, and dysglycemia [24]. We recently described the evidence for randomized controlled trials (RCTs) of metformin monotherapy compared with OCP for the treatment of adolescents with PCOS [24]. Although very few trials met the review criteria, which were categorized as very low-quality evidence, we did identify a potential reduction in the incidence of dysglycemia with the use of metformin. In addition, we identified a large number of trials that compared other treatment approaches such as placebo, spironolactone, flutamide, lifestyle modification, and pioglitazone to either metformin or OCP [24]. Given that many of the treatment combinations available to treat PCOS have not been compared in head-to-head randomized trials, we conducted a systematic literature review and network meta-analysis to assess the following objectives: (1) the efficacy and safety of treatments, including metformin monotherapy, OCP monotherapy, and various combination therapies, for adolescent women with PCOS; and (2) assess the efficacy of different OCPs formulations used to treat hirsutism.

Materials and Methods

The design of this systematic review has been described previously (CRD42015016148) [25]. Briefly, we searched MEDLINE (via Ovid), Embase (via Ovid), and the Cochrane Central Register of Controlled Trials for RCTs of adolescents aged 11 to 19 years old with PCOS treated with metformin monotherapy, OCP monotherapy, or combination therapies with lifestyle interventions, pioglitazone, spironolactone, and flutamide from database inception until January 2019. We supplemented the searches of the medical literature databases with hand searches of identified RCTs, guidelines, trials registries (Clinicaltrials.gov, World Health Organization International Clinical Trials Registry Platform Search Portal, controlled-trials.com, and the National Institutes of Health database of funded studies for ongoing or unpublished trials), and conference proceedings and abstracts of the North American and European Endocrine Society and The Society of Adolescent Medicine and Health (supplementary file page 6) [25, 26].

The primary outcomes of interest included menstrual cycle regulation and hirsutism scores. Secondary outcomes of interest included acne scores, prevalence of dysglycemia, body mass index (BMI), total testosterone level, lipid profile (triglyceride, total cholesterol, low-density lipoprotein [LDL], high-density lipoprotein [HDL]), and adverse events.

Study selection, data extraction, and risk of bias (ROB) assessment followed standardized methodology described

in our published protocol [25]. We followed the Grading of Recommendations Assessment, Development, and Evaluation Working Group (GRADE Working Group) methodology in rating the quality of the evidence to facilitate interpretation of the evidence by end users. Briefly, GRADE categorizes the evidence into 4 levels: high quality, moderate quality, low quality, and very low quality. Evidence for pairwise comparisons that start at high can be rated down for risk of bias, imprecision, inconsistency, indirectness, and publication bias. Additionally, for network meta-analysis (NMA) the evidence can be rated down for intransitivity, and incoherence [27, 28]. We presented the evidence for every comparison in summary of the findings table recommended for reporting NMA, and added the effect estimate, evidence equality for direct, and indirect evidence [29].

Statistical analysis

For each outcome of interest, we performed a Bayesian NMA to estimate the relative treatment effects between the interventions for which evidence was available. Fixed and random effects models were fitted to the data and compared according to the deviance information criteria, where a lower deviance information criterion is indicative of better fit [30]. Consistency between direct and indirect estimates was evaluated by edge-splitting, where pairwise estimates between 2 interventions are compared with estimates derived only using indirect evidence [31]. Model runs consisted of an adaptation phase of 50 000 iterations followed by 500 000 models run with a thinning ratio of 10. Models were programmed in R (www.r-project.org) using the gemtc package [32]. We evaluated relative treatment rankings for each outcome according to the surface under the cumulative ranking curve (SUCRA) method [33].

We performed meta-regression to explain the heterogeneity in the results using study level covariates: participant' s average age, BMI status (obese and/or overweight BMI ≥ 25 kg/m^2 vs normal <25 kg/m^2), and we performed a subgroup analysis to evaluate the effectiveness of different progestins used in the OCPs on changes of hirsutism scores.

Results

Study identification and selection

Searches of the medical literature databases returned 693 records, of which 172 full texts were reviewed. Forty-two RCTs satisfied all eligibility criteria (Fig. 1). Because of heterogeneity in outcome reporting, the evidence from 4 RCTs is described in a narrative summary. A list of excluded records, with exclusion reasons, is presented in the supplementary file [26].

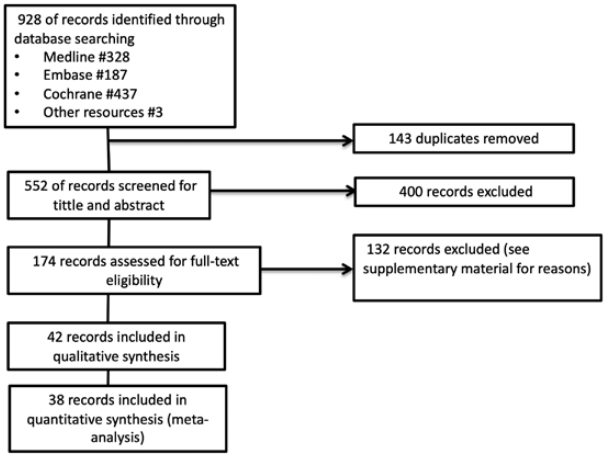

Figure 1. PRISMA flow of information.

Trial and population characteristics

The interventions represented in the complete evidence network include metformin, OCP, spironolactone, flutamide, pioglitazone, metformin-OCP, metformin-spironolactone, metformin-flutamide, lifestyle intervention, metformin-lifestyle, metformin-OCP, metformin-OCP-flutamide, and metformin-flutamide-pioglitazone. Several types of progestins were used in OCP formulations, including drospirenone, cyproterone acetate, gestodene, desogestrel, progestin, and norethindrone. Lifestyle interventions were implemented in 10 RCTs, in which 6 trials provided lifestyle modification advice at enrollment of the patients and 4 trials implemented an active lifestyle intervention, which included either a dietitian and/or exercise therapy. The overall network of evidence is presented in Fig. 2, with outcome-specific evidence networks presented in Figures S1 through S10 in the supplementary material [26].

Table S1 in the supplementary material [26] shows the baseline characteristics of all included studies. Across the included studies, 2400 patients were randomized. Patient age range varied from 12 to 35 years. Some of the included RCTs had included adolescents and adults, and therefore we tried to contact the authors to provide data for adolescents alone, but we received no response. The mean BMI was 27.6 kg/m^2, and 19 studies (43%) included overweight or obese patients; 8 of these studies enrolled patients with insulin resistance as an inclusion criterion. The diagnostic criteria for PCOS varied by study. In 19 (43.2%) studies, an ultrasound documenting polycystic ovaries was required for enrollment. Dysglycemia was diagnosed based on glucose results at 2-hour post-oral glucose load based on the

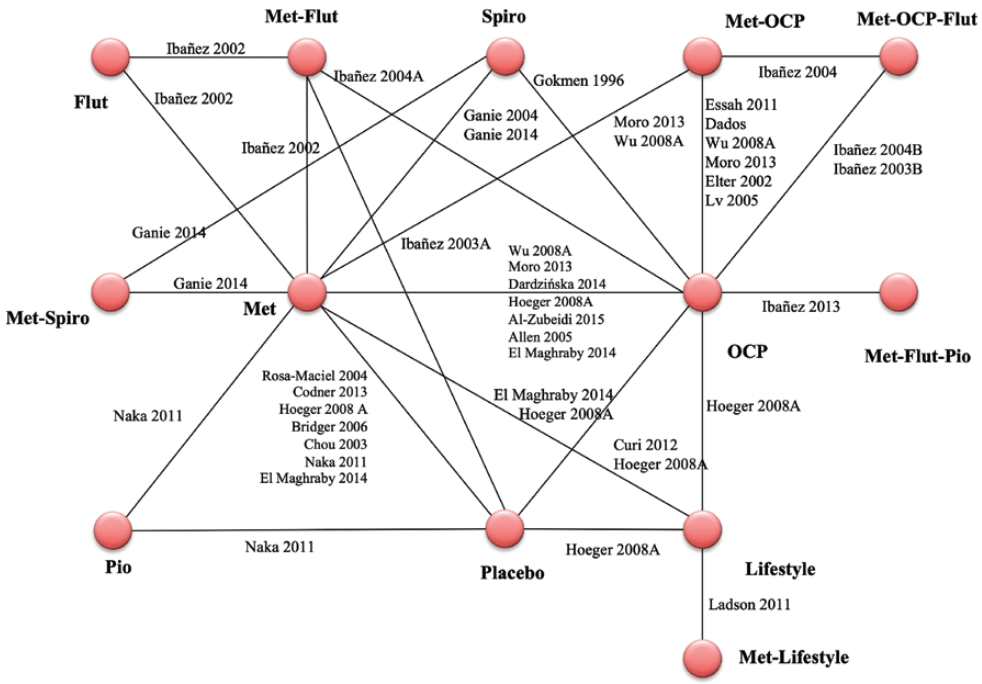

Figure 2. Overall network evidence. Circles represent interventions. Lines represent treatments compared in head-to-head trials. flut, flutamide; Met, metformin; OCP, oral contraceptive pill; pio, pioglitazone; spiro, spironolactone.

American Diabetes Association definition. The median duration of the treatment was 6 months, varying from a minimum of 3 to 24 months.

Risk of bias in individual studies

Overall, ROB was considered high for most trials because the majority did not report methods of concealment of allocation or blinding. Several trials also reported incomplete follow-up data. Details of the risk of bias assessments using the Cochrane Risk of Bias tool are presented in Figures S11 and S12 in the supplementary material [26].

Network meta-analyses

Results of the quality of evidence as well as complete analyses are presented in the supplementary file, including separate estimates of direct, indirect, and NMA evidence as well as SUCRA ranking estimates [26]. Summary of the evidence is provided in the infographics Fig. 3.

Menstrual regulation

This evidence was identified from 10 trials where 607 patients were randomized to 8 interventions. The menstrual cycle regulation was defined as number of cycles per month. NMA evidence showed no statistically important change in menstrual regulation across all interventions. Moderate-quality evidence from direct evidence coming from 1 RCT with 18 patients showed increased menstrual regulation by metformin-lifestyle versus lifestyle (mean difference [MD], 0.33 cycle/month; 95% confidence interval [CI], 0.02-0.64), and low-quality evidence showed increased menstrual regulation by metformin versus lifestyle (MD, 0.14; 95% CI, 0.04-0.25), OCP versus placebo (MD, 0.58; 95% CI, 0.49-0.67), OCP versus lifestyle intervention (MD, 0.62; 95% CI, 0.71-0.53).

Hirsutism

Twenty-five trials (n = 1401) of 13 interventions reported hirsutism using the Ferriman-Gallwey scoring system. Monotherapy with lifestyle intervention, metformin, OCP, spironolactone, flutamide, pioglitazone, or combination therapy with metformin-OCP, metformin-spironolactone, metformin-flutamide were associated with statistically important reductions in hirsutism against placebo. All combination therapy led to more reduction in hirsutism scores compared with monotherapy. Table 1, S2, and S9 summarize evidence form direct, indirect, NMA, SUCRA, and evidence quality [26].

NMA stratified by progestins used in OCP showed statistically important reduction of hirsutism scores compared with placebo, progesterone (MD, -5.66; 95% credible interval [CrI], -8.97 to -2.46), cyproterone acetate (MD, -3.06; 95% CrI, -5.05 to -1.02), desogestrel (MD, -3.16; 95% CrI, -5.29 to -0.9), and drospirenone (MD, -3.00; 95% CrI, -5.52 to -0.48). No statistically important improvements were observed with gestodene or norgestimate compared with any comparator (Table S9).

Dysglycemia

Dysglycemia outcomes were available for 7 interventions across 10 RCTs (n = 639). Moderate-quality evidence suggests that treatment with OCP monotherapy results in statistically important increases in dysglycemia compared to metformin monotherapy OR 2.98 (95% CrI, 1.02-8.96) (Table S2) [26]. This means that the absolute risk of dysglycemia is 57 per 100 patients among OCP users (95% CI, 1-100 more patients), given baseline risk of 24% among controls. There was no statistically important difference among other interventions in the network.

The estimated odds ratio (OR) through meta-regression, which controlled for age and baseline BMI, showed no important differences compared with the base case model.

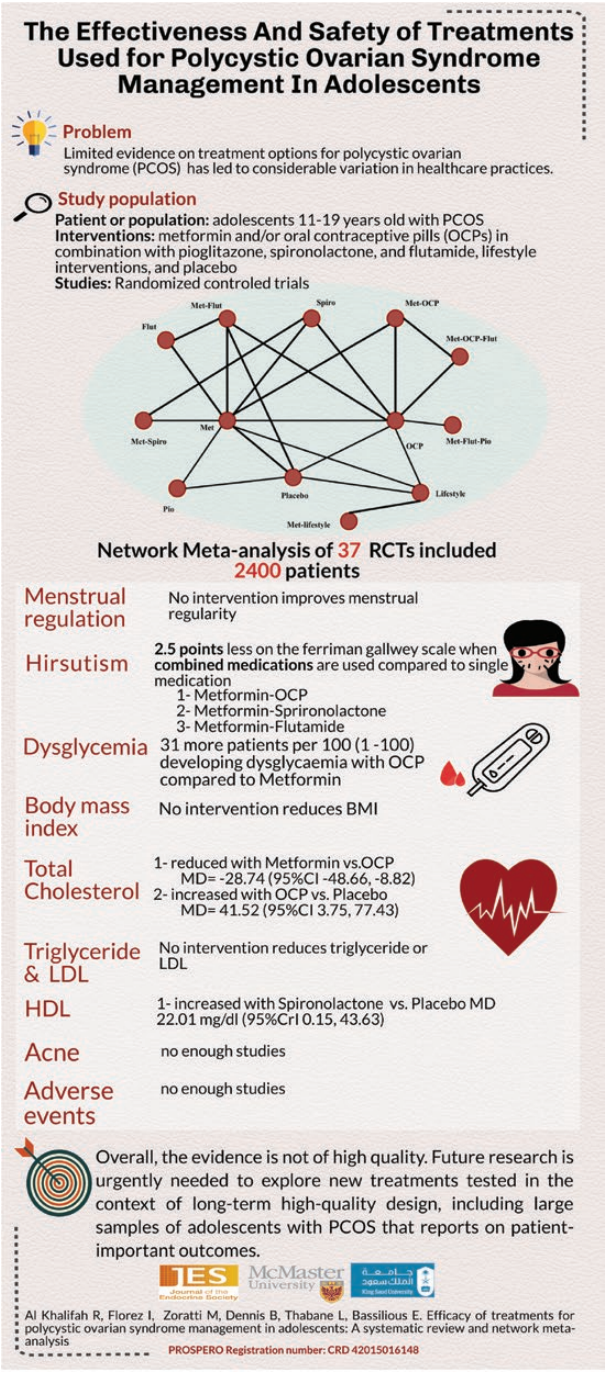

Figure 3. Infographics of the evidence summary.

Body mass index

Evidence for change from baseline in BMI was available from 34 RCTs (n = 1798). No statistically important differences were observed between interventions (Table S2) [26].

Lipid profile

Total cholesterol. Twenty-two RCTs (n = 1017) reported total cholesterol. Moderate- to high-quality evidence suggests a statistically important decrease in total cholesterol was observed in patients managed with metformin monotherapy compared with OCP monotherapy (MD, -28.74 mg/dL; 95% CrI, -48.66 to -8.82), with a statistically important increase in total cholesterol level for the comparison of OCP monotherapy compared with placebo (MD, 41.52 mg/dL; 95% CrI, 3.75-77.43) (Table S3) [26].

Triglyceride. Evidence on triglycerides was available from 27 RCTs (n = 1056). No statistically important differences were observed across interventions.

LDL. Evidence on LDL was reported in 28 RCTs (n = 1197). A statistically important reduction, based on moderate- to high-quality evidence, was observed for patients managed with metformin-flutamide combination therapy compared with OCP monotherapy (MD, -22.43 mg/dL; 95% CrI, -42.31 to -2.75). No statistically important differences were estimated for any intervention compared with placebo.

HDL. Evidence on HDL was reported in 30 RCTs (n = 1255 patients). Moderate- to high-quality evidence suggests treatment with spironolactone was associated with an increase in HDL compared with placebo (MD, 22.01 mg/dL; 95% CrI, 0.15-43.63) and compared with flutamide (MD, -31.89 mg/dL; 95% CrI, -58.25 to -5.78).

Testosterone

Evidence on testosterone was reported in 34 trials (n = 1811). All interventions, with the exception of lifestyle, flutamide, and pioglitazone, were estimated to reduce total testosterone levels relative to placebo (Tables S3, S5, S13) [26].

Narrative synthesis

Acne. Eight trials (n = 478) reported acne outcomes. The trials did not use a validated scale to measure acne; some implemented active lesion count per patient, number of patients with acne, or severe acne. Therefore, heterogeneity in outcome definitions precluded a quantitative synthesis of the evidence. Table S4 summarizes the data qualitatively.

Table 1. Relative Treatment Effects at End of Treatment With Respect to Menstrual Cycle Regulation (9 cycles/mo) and Hirsutism (F-G scale)

		Menstrual Regulation												
		Lifestyle	Flutamide	Metformin	Metformin + Lifestyle	Metformin + Flutamide	Metformin + Flutamide + Pioglitazone	Metformin + OCP	Metformin + OCP + Flutamide	Metformin + Spironolactone	OCP	Pioglitazone	Placebo	Spironolactone
Hirsutism	Lifestyle		--	-0.05 (-0.54, 0.45)	-0.33 (-0.82, 0.16)	--	--	-0.26 (-0.92, 0.4)	--	-0.14 (-0.76, 0.48)	-0.29 (-0.81, 0.24)	--	0.06 (-0.5, 0.6)	-0.11 (-0.68, 0.46)
	Flutamide	-2.73 (-5.98, 0.29)	**Flutamide**	--	--	--	--	--	--	--	--	--	--	--
	Metformin	1.27 (-1.12, 3.45)	**4 (1.74, 6.25)**	**Metformin**	-0.28 (-0.98, 0.42)	--	--	-0.21 (-0.69, 0.27)	--	-0.09 (-0.47, 0.3)	-0.24 (-0.48, 0)	--	0.11 (-0.22, 0.39)	-0.06 (-0.35, 0.23)
	Metformin + lifestyle	-5.22 (-13.28, 3.12)	-2.52 (-11.07, 6.52)	-6.51 (-14.78, 2.1)	**Metformin + lifestyle**	--	--	0.07 (-0.76, 0.9)	--	0.19 (-0.6, 0.99)	0.05 (-0.68, 0.76)	--	0.4 (-0.37, 1.12)	0.22 (-0.54, 0.97)
	Metformin + Flutamide	-1.21 (-4.24, 1.65)	1.51 (-0.43, 3.50)	**-2.49 (-4.52, -0.46)**	4.04 (-4.85, 12.5)	**Metformin + Flutamide**	--	--	--	(-0.6, 0.99)	--	--	--	--
	Metformin + flutamide + pioglitazone	-1.29 (-4.24, 1.52)	1.42 (-1.49, 4.49)	**-2.57 (-4.59, -0.38)**	3.96 (-4.92, 12.40)	-0.09 (-2.77, 2.72)	**Metformin + flutamide + pioglitazone**	--	--	--	--	--	--	--
	Metformin + OCP	-0.6 (-3.29, 1.89)	2.11 (-0.52, 4.79)	**-1.87 (-3.45, -0.32)**	4.59 (-4.1, 12.93)	0.61 (-1.8, 3.06)	0.69 (-1.73, 2.94)	**Metformin + OCP**	--	0.12 (-0.5, 0.74)	-0.03 (-0.45, 0.38)	--	0.33 (-0.23, 0.83)	0.15 (-0.41, 0.71)
	Metformin + OCP + flutamide	-1.02 (-4.32, 2.23)	1.72 (-1.56, 5.12)	-2.28 (-4.8, 0.39)	4.23 (-4.73, 12.84)	0.21 (-2.91, 3.39)	0.28 (-2.74, 3.35)	-0.41 (-3.16, 2.52)	**Metformin + OCP + flutamide**	--	--	--	--	--
	Metformin + spironolactone	0.45 (-2.49, 3.01)	**3.15 (0.35, 5.89)**	-0.83 (-2.52, 0.71)	5.64 (-3.13, 14.05)	1.64 (-0.99, 4.16)	1.75 (-1.09, 4.22)	1.04 (-1.23, 3.21)	1.45 (-1.73, 4.35)	**Metformin + spironolactone**	-0.15 (-0.61, 0.31)	--	0.21 (-0.31, 0.67)	0.03 (-0.35, 0.41)
	OCP	0 (-2.25, 2.16)	**2.73 (0.49, 5.12)**	**-1.28 (-2.14, -0.23)**	5.24 (-3.38, 13.51)	1.23 (-0.75, 3.28)	1.29 (-0.58, 3.17)	0.62 (-0.77, 2.09)	1.02 (-1.46, 3.44)	-0.45 (-2.13, 1.57)	**OCP**	--	0.35 (0, 0.67)	0.18 (-0.19, 0.56)
	Pioglitazone	1.03 (-1.75, 3.79)	**3.77 (1.01, 6.57)**	-0.23 (-1.83, 1.46)	6.29 (-2.42, 14.69)	2.26 (-0.32, 4.87)	2.34 (-0.33, 5)	1.65 (-0.54, 3.93)	2.07 (-1.01, 5.03)	0.6 (-1.59, 2.97)	1.05 (-0.84, 2.9)	**Pioglitazone**	--	--
	Placebo	**3.47 (0.79, 5.99)**	**6.18 (3.38, 9.12)**	**2.2 (0.39, 4.01)**	**8.71 (0.03, 17.06)**	**4.68 (2.05, 7.39)**	**4.75 (2.1, 7.39)**	**4.08 (1.79, 6.40)**	**4.47 (1.39, 7.56)**	**3.04 (0.72, 5.54)**	**3.47 (1.56, 5.35)**	**2.42 (0.27, 4.52)**	**Placebo**	-0.18 (-0.57, 0.28)
	Spironolactone	0.62 (-2.13, 3.02)	**3.34 (0.73, 5.84)**	-0.64 (-1.97, 0.47)	5.84 (-2.85, 14.17)	1.84 (-0.57, 4.13)	1.93 (-0.67, 4.14)	1.23 (-0.79, 3.08)	1.64 (-1.36, 4.32)	0.20 (-1.46, 1.75)	0.64 (-1.06, 1.95)	-0.42 (-2.56, 1.49)	**-2.86 (-5.11, -0.75)**	**Spironolactone**

Comparisons should be read from left to right. Menstrual regulation (top right part of the table), hirsutism (bottom left part of the table). The effectiveness estimate is located at the intersection of row vs. column. Effect estimates are presented as MD with the 95% CrI. Estimate in bold are statistically important.

Abbreviations: CrI, credible interval; F-G, Ferriman-Gallwey; MD, mean difference; OCP, oral contraceptive pill.

Overall, patients using metformin, OCP, and lifestyle intervention showed reduction in acne by MD 0.5 to 2 from baseline.

Adverse events. Fourteen trials enrolled 1133 patients. Six trials reported minor adverse events, 7 gastrointestinal adverse events, and 2 serious adverse events for patients randomized to receive metformin, OCP, metformin-spironolactone, metformin-OCP, OCP-spironolactone, or placebo. However, heterogeneity in outcome reporting precluded quantitative synthesis of the evidence. All events are summarized in Tables S6–S8 [26]. Overall, patients experienced either minor or gastrointestinal adverse events with metformin and OCP more than spironolactone. Although few patients developed serious adverse events with OCP. Bhattacharya et al. reported 1 patient in the ethinyl estradiol 30-mcg + desogestrel 150-mg group who developed hypertension, and 1 patient in the ethinyl estradiol 30-mcg + drospirenone 3-mg group who developed altered liver function test [34]. Hagag et al. reported 3 patients developed minor depressive symptoms and 1 patient developed menorrhagia who received ethinyl estradiol 35 mcg + cyproterone acetate 10 mg [35]. Kriplani et al. trial reported suspected thrombosis. The patient was randomized to receive ethinyl estradiol 30 mcg + desogestrel 150 mcg [36]. The patient had severe left lower limb pain. Doppler evaluation showed no evidence of thrombosis.

Discussion

Treating PCOS in adolescents poses clinical challenges for the patients and physicians. Our NMA is the first to investigate the effectiveness and safety of single and combination regimens used to treat adolescent with PCOS. The results of our NMA highlight importantly the lack of highly effective intervention to treat PCOS in its entirety as a complex disease, but rather that each symptom can be treated individually by a specific intervention targeted at the symptom of concern. Unfortunately, those effective interventions resulted in improvement that is less than what clinicians consider as minimally important for patients.

The current Endocrine Society clinical practice guideline recommends implementing lifestyle intervention as primary first approach, followed by OCP as a second-line agent [4, 5, 37]. Direct evidence suggests minimal improvement in menstrual cycle regulation with metformin-lifestyle compared with lifestyle (MD, 0.33 cycle/mo), OCP compared with placebo (MD, 0.22 cycle/mo), and no statistically important difference between metformin compared with OCP. This is in line with findings from our NMA showing that the difference between metformin, and OCP as monotherapy or in combination with other interventions compared with placebo or other interventions were not statistically important in improving menstrual cycle regulation. Although in our previous pediatric meta-analysis, we showed that OCP increased menstrual cycle regulation compared with metformin (MD, 0.25 cycle/mo) [24]. This minimal improvement translates to a difference of 2.7 months per year that is uncertain if it meets what patients would perceive as clinically important difference, and if it provides long-term endometrial protection. Healthy women taking OCP over a period of 12 months had 20% absent withdrawal bleeding during the placebo week [38-41]. This pattern could be due to poor compliance with OCP intake or abnormal endometrial function [5]. Overall, the pattern amenorrhea, risk of endometrial hyperplasia, and future endometrial cancer is different among healthy women using OCP and non-OCP users. A systematic review of observational studies has shown decreased risk of endometrial cancer among healthy women taking hormonal contraception compared to nonusers. This is due to reduced periods of unopposed estrogen associated with taking hormonal contraception [42]. Such an observation of reduced prevalence of endometrial pathology among hormonal contraception users is not reported yet in PCOS population-based studies. Therefore, the withdrawal bleeding pattern for women with PCOS during the placebo week provides valuable information about endometrial health and therefore should be closely monitored and reported as well as future long-term risk of endometrial cancer.

Hirsutism scores were reduced by a large number of single and combined interventions compared with placebo. All these interventions led to a reduction in hirsutism scores by about 2.5 points. The greatest reduction of hirsutism scores was observed with combination interventions compared to single medications. Interestingly, only some of the interventions led to reduction in both hirsutism scores and testosterone level, but the magnitude of reduction was not consistent (Table S5). This highlights that surrogate biomarker changes do not necessarily lead to important patient outcome change. Among all types of OCPs, those that contain progesterone, cyproterone acetate, desogestrel, and drospirenone showed statistically important reduction of Ferriman-Gallwey score, whereas gestodene and norgestimate did not lead to statistically important reduction. This is similar to the results of a recent adult NMA evaluated treatment options for women with idiopathic hirsutism or secondary to PCOS, or presumed nonclassic congenital adrenal hyperplasia [43].

Meanwhile, OCPs were associated with an increased dysglycemia risk compared with metformin absolute risk 31 more patients per 100 (95% CI, 1-100 more patients). This is in line with our previous meta-analysis finding that showed that OCP compared with metformin increased dysglycemia risk ratio by 2.43 (absolute risk, 24 patients

per 100) [24]. The effect was not different after adjusting for baseline BMI and age. The increased dysglycemia risk was not seen with other interventions, including combination therapies including metformin-OCP, metformin, or OCP compared with placebo. The evidence quality for the comparison between metformin versus OCP was moderate, whereas it was low to very low for the other comparisons, this can explain the lack of difference seen with metformin and OCP compared with placebo when one should have expected a difference. This begs the question of possible metformin treatment effect that provides protective effect against the development of dysglycemia, or that OCPs are associated with increased risk of dysglycemia. Future high-quality long-term RCTs are needed to confirm these findings. Recent adult systematic review with pairwise meta-analysis showed no statistically important difference between OCP and insulin sensitizers with regard to fasting glucose level only [44]. The study did not evaluate other glycemic indexes like 2-hour oral glucose tolerance test or hemoglobin A1c. Systematic review and meta-analysis of observational studies yield controversial conclusions regarding OCPs and the impact on glucose hemostasis [45]. OCPs causes increase insulin resistance, abnormal carbohydrate metabolism among women with and without increased risk for diabetes, and increased breast cancer risk among healthy women [45-49]. The fact that PCOS is associated with an increased prevalence of metabolic syndrome (OR, 2.69; 95% CI, 1.29-5.60) compared with healthy girls and impaired glucose tolerance compared with healthy women (OR, 3.26; 95% CI, 2.17-4.90) and type 2 diabetes mellitus (OR, 2.87; 95% CI, 1.44-5.72) emphasizes the need for risk minimization [17, 18, 50]. In addition, it highlights the need for informing patients about their future disease risk in addition to risk and benefit with the use of any intervention, because dysglycemia increases health care utilization and impairs health-related quality of life of patients [19, 51, 52].

NMA evidence showed that BMI was not improved by any intervention, whereas total cholesterol levels increased with the use of OCP or pioglitazone compared with placebo and HDL levels increased with the use of spironolactone. Previous systematic reviews with meta-analysis of observational studies have shown that OCPs cause increases in total cholesterol, HDL, and triglyceride level among women with PCOS syndrome [45, 47]. The clinical implications of the increased lipids level on cardiovascular events need long-term studies.

We believe that our NMA challenges the current practice and belief that OCPs improve menstrual cycle regulation and reduces hirsutism. The included RCTs in our review used small sample sizes and, although PCOS is a common disease, the designs were at high ROB and had large numbers of patients lost to follow-up. Therefore, the observed results are either because of the methodological limitations of the included studies, which can lead to an effect estimate substantially different from the true effect, or that there is a true lack of statistical significance. PCOS pathophysiology is complex and poorly understood. Included trials did not report outcomes based on PCOS phenotypes, and most of the medications used in trials target the end pathway rather than key mechanisms leading to the pathology [53]. Therefore, this might lead to poor disease response. Moreover, the duration of the studies was possibly too short to allow observation of significant clinical changes.

Our review has many strengths. We implemented a sensitive search strategy that included unpublished work, included trials with mixed adolescents and young adults, and presented meta-regression based on mean age. We modeled both single and combination therapy. We presented effects of single and complex treatments including 3 combinations (in tables), even if not frequently used in clinical practice, to inform planning for future RCTs. Those complex regimens did not prove to be superior to simpler regimens and there is no assurance of safety by using such regimens. Additionally, we evaluated the quality of evidence using GRADE methodology for all estimates reported in our review and focused in the discussion on those commonly used in clinical practice that are of high to moderate quality of evidence.

The observation on the limitation from methodological conduct of PCOS studies is unexpected given that PCOS is a disease with high prevalence, which should allow for properly conducted clinical trials in which it is feasible to perform blinding of patient and outcome assessor and to perform complete follow-up of patients enrolled. Similar to previous systematic reviews in PCOS, most of the studies used variable definitions for PCOS, variably reported menstrual regulation, used variable scales to measure acne, and variably reported adverse events. Notably, 9 trials (n = 434) reported menses as a dichotomous outcome with respect to the number of girls who achieved menstrual regulation. The definition of menstrual regulation was not provided by the trials. NMA and meta-analyses were not possible to conduct because of inflated OR that is possibly related to differences in the outcome definition. This calls urgently for working groups to set forth guidance for unifying PCOS patient important outcome reports for clinical trials that will enable future knowledge synthesis of this valuable data. The median duration of follow up in the trials was 3 to 6 months, which is considered relatively short to properly assess some of the clinical outcomes such as hair growth and dysglycemia. Although we could not evaluate publication bias for the whole NMA because of limited available statistical approaches, it remains likely because there is a clear selective reporting bias of outcomes in the reviewed RCTs; for example, 30 trials collected lipid outcomes and only 22 reported total cholesterol

compared with 30 studies which reported HDL, incomplete evidence for acne, and adverse events.

In conclusion, metformin and OCP singly or in combination with other interventions can reduce hirsutism scores, but none of these medications led to effective menstrual cycle regulation or weight reduction. However, the use of OCP leads to worse cardiometabolic risk factors. This emphasizes the need for informed decision-making based on underlying risk and patient needs and preferences to select effective balanced treatment approaches, which are not based on need for contraception during childbearing age, in addition to providing future long-term risk monitoring. Further research is urgently needed to look into new treatments that can be evaluated in the context of long-term high-quality design that report on patient important outcomes based on PCOS phenotypes. All supplementary material and figures are located in a digital research materials repository (26).

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