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REVIEW ARTICLE

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Pharmacological and surgical treatment of nonreproductive outcomes in polycystic ovary syndrome: An overview of systematic reviews

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Summary

Background: Polycystic ovary syndrome (PCOS) affects up to 13% women and is associated with significant complications. The quality of evidence supporting the recommendations on treatment of nonreproductive outcomes in PCOS is unknown.

Objective: To summarize and appraise the methodological quality of systematic reviews and meta-analyses evaluating pharmacological and surgical treatments for nonreproductive outcomes in PCOS.

Methods: A literature search from MEDLINE, EMBASE, CINAHL PLUS and PROSPERO was performed from inception until 15th of September 2017. Article selection, data extraction and quality appraisal of included reviews were performed in duplicate. A narrative synthesis of the findings was conducted.

Results: This overview included 31 reviews. The quality was low for 7 (23%), moderate for sixteen (52%) and high for 8 reviews (26%). Two reviews assessed psychological outcomes. Metformin improved anthropometric (7 of 10 reviews), metabolic (4 of 14 reviews) and endocrine outcomes (3 of twelve reviews). Thiazolidinediones improved metabolic (2 of 5 reviews) and endocrine outcomes (one of 5 reviews) but worsened weight gain (5 of 5 reviews). Combined oral contraceptive pill (COCP) improved clinical hyperandrogenism (2 of 2 reviews). Statins improved lipid profile (3 of 3 reviews) and testosterone level (2 of 3 reviews). There was no conclusive evidence from included systematic reviews regarding the use of other interventions.

Conclusions: There is reliable evidence regarding the use of metformin for anthropometric outcomes and COCPs for hyperandrogenism in women with PCOS but not for other interventions. There is significant gap in knowledge regarding the management of psychological outcomes in women with PCOS which needs further evaluation.

KEYWORDS
meta-analysis, overview, polycystic ovary syndrome, systematic review, treatment

1 | INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrinopathy affecting up to 13% of reproductive-aged women.[1] PCOS is diagnosed based on the presence of 2 of the following 3 reproductive features: menstrual or ovulatory dysfunction, clinical or biochemical hyperandrogenism and/or polycystic ovarian morphology on ultrasonography with exclusion of other causes of hyperandrogenism.[2-5] Whilst

the aetiology is not fully understood, insulin resistance and hyperandrogenism are the 2 key hormonal disturbances that underpin the condition.[2,6,7]

Polycystic ovary syndrome has a broad range of clinical manifestations that vary across phenotypes, ethnicities and life stages. Young women typically present with dermatological complaints (hirsutism or acne) or reproductive problems (oligo-/amenorrhoea or infertility).[4,8] Metabolic features of PCOS include a predisposition to develop obesity, metabolic syndrome, type 2 diabetes, hypertension and nonalcoholic fatty liver disease.[9-12] Psychologically, PCOS increases the risk of anxiety, depression and low quality of life.[13-15] There are increased pregnancy complications including gestational diabetes mellitus, gestational hypertension, preterm labour and preeclampsia and also increased risk of endometrial neoplasia.[16,17] These nonreproductive features in PCOS contribute to a significant health and economic burden.[18]

The management of PCOS should encompass treating fertility and nonreproductive outcomes such as reducing clinical symptoms of hyperandrogenism, improving metabolic health, improving psychological well-being and preventing long-term health risks.[6] Evidence-based guidelines published by the Australian PCOS Alliance and other professional specialty society position statements recommend lifestyle interventions as first-line treatment for women with PCOS. A 5%-10% reduction in body weight is effective in improving anthropometric, reproductive, metabolic and psychological aspects of PCOS.[2-5,7,19,20] Most guidelines discussed 3 main pharmacological therapy categories, namely insulin sensitizers (eg, metformin and thiazolidinediones), anti-androgens (eg, spironolactone, flutamide and cyproterone acetate) and combined oral contraceptive pills (COCP).[2-5,7,21,22] Bariatric surgery is also recommended for consideration in obese women with PCOS given that it is an effective means of weight reduction which may improve the clinical features of PCOS.[2-5,7,23]

However, the quality of evidence supporting these recommendations for PCOS-related nonreproductive outcomes is not known. While there has been an increasing number of systematic reviews published summarizing the evidence of different pharmacological or surgical therapies on the nonreproductive outcomes in PCOS, conclusions are difficult to interpret due to diverse methodologies and quality of both the systematic reviews and their included studies.

The aim of this study was to conduct an overview of systematic reviews evaluating pharmacological or surgical therapy for nonreproductive outcomes in women with PCOS to summarize and appraise the results and methodological quality.

2 | METHODS

2.1 | Protocol and registration

This review was designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[24] An a priori study protocol was registered with PROSPERO (CRD42016052649). Ethics application was not required.

2.2 | Literature search

The electronic databases MEDLINE in-process and other nonindexed citations (Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present), Ovid EMBASE (EBM Reviews—Cochrane Database of Systematic Reviews 2005 to 15 September 2017, EBM Reviews—ACP Journal Club 1991 to September 2017, EBM Reviews—Database of Abstracts of Reviews of Effects 1st Quarter 2016, EBM reviews—Cochrane Central Register of Controlled Trials September 2017, EBM Reviews—Cochrane Methodology Register 3rd quarter 2012, EBM Reviews—Health Technology Assessment 4th Quarter 2016, EBM Reviews—NHS Economic Evaluation Database 1st Quarter 2016) and CINAHL PLUS were searched to identify relevant published articles. Additional ongoing reviews were identified from searching the international prospective register of systematic reviews PROSPERO (http://www.crd.york.ac.uk/PROSPERO/). The literature search was last updated on the 15th of September 2017. The search terms used included "PCOS," "polycystic ovary syndrome," "Stein-Leventhal," "systematic," "review," and "meta-analysis" with the complete search strategy for each database provided in Appendix S1 (found in the Supporting Information). The search strategy was limited to human studies only.

2.3 | Eligibility criteria and study collection

Articles were included if they met the following inclusion criteria: original systematic review or meta-analysis; PCOS was the primary focus of the review with articles in which PCOS was a secondary condition assessed as part of a broader topic excluded; clear search strategy with at least keywords or terms included, documentation of search returns and performed quality appraisal of the included studies; published in English; and published from year 2009 onwards given this was when the PRISMA statement was published to guide reporting of systematic reviews and meta-analyses.[24]

The outcomes of interest were anthropometric (weight, body mass index (BMI), waist-hip ratio, waist circumference or body composition), endocrine (total or free testosterone, sex hormone binding globulin (SHBG), free androgen index (FAI), dehydroepiandrosterone sulphate (DHEAS), dehydroepiandrosterone (DHEA), androstenedione or clinical hyperandrogenism), metabolic (glucose intolerance, surrogate markers of insulin resistance, lipid profile or blood pressure) and psychological (quality of life, anxiety or depression).

2.4 | Study selection and data extraction

Identified articles from the literature search were screened in a two-step process. First, the titles and abstracts were screened for suitability. Second, all articles that meet the inclusion criteria from the first step were retrieved for detailed full-text assessment to determine eligibility. Study selection was performed independently in duplicate by 3 investigators (C.T.T, D.S.H and L.J.M) with any discrepancies resolved by consensus.

Data collected from the eligible articles included authorship, publication year, country of authors' origin, types of study eligible for the systematic review, date of literature search, language restriction, adherence to a systematic review guideline, presence of meta-analysis, the authors' interpretation of quality assessment of the included studies, number of included studies and participants involved and the Participant, Intervention, Comparison, Outcomes and Studies (PICOS) framework of the study. If the authors did not interpret the quality of the included studies nor summarize the overall quality of the entire study, the section on quality assessment was be documented as "unclear." Data extraction was conducted independently in duplicate (C.T.T, L.J.M and M.A.G) with any discrepancies resolved by consensus and discussion with a third investigator (D.S.H).

2.5 | Quality assessment (AMSTAR)

The Assessing the Methodological Quality of Systematic Reviews (AMSTAR) tool was employed to appraise the quality of the included systematic reviews.[25,26] AMSTAR evaluates the methodological aspects of systematic reviews using 11 items: (i) the provision of an a priori design, (ii) duplication of study selection and data extraction, (iii) conduction of a comprehensive literature search, (iv) inclusion of grey literature in the review, (v) availability of a list of the included and excluded studies, (vi) description of the characteristics of the included studies, (vii) clear documentation of the scientific quality of the included studies, (viii) consideration of the scientific quality of the included studies in formulating conclusions, (ix) appropriate analysis of results depending on heterogeneity, (x) assessment of publication bias and (xi) consideration of conflict of interest of both the systematic review and the included studies.[26] Each item was given 1 point if it was determined as "yes" and 0 point if it was determined as "no" or "not applicable." The reviews were categorized as low quality if the total AMSTAR score was ≤3, moderate quality if the total AMSTAR score was between 4 to 7, and high quality if the total AMSTAR score was ≥8.

Quality assessment of all eligible systematic reviews was conducted independently in duplicate (C.T.T, L.J.M and M.A.G) with any disagreements resolved by consensus and discussion with a third investigator (D.S.H).

2.6 | Data synthesis

A narrative synthesis of findings from the included reviews was performed. Results were presented according to the different types of intervention. Statistically significant outcomes of interest were presented if a meta-analysis was performed by the review.

3 | RESULTS

3.1 | Literature search

The electronic database search retrieved 978 articles, and an additional 60 were identified from PROSPERO. After removing the duplicates, 831 articles remained for screening. A total of 564 articles were excluded after reviewing the title and abstract leaving 267 articles available for full-text evaluation. A total of 140 articles were eligible for analysis of which 33 were related to treatment of nonreproductive outcomes. Of these, 2 articles were a prior version of a systematic review, and therefore, we only included the most recent publications.[27,28] Finally, 31 systematic reviews were included in this study. The PRISMA flow diagram is illustrated in Figure 1. The list of excluded articles is available in Appendix S2 (found in the Supporting Information).

3.2 | Study characteristics

The study characteristics and PICO framework of the included systematic reviews are summarized in Table 1. The country of origin of the authors included China (n = 11),[29-39] Australia (n = 6),[40-45] United Kingdom (n = 5),[43,45-48] the United States of America (n = 4),[49-52] India (n = 3),[44,52,53] Canada (n = 3),[50,54,55] Brazil (n = 2),[41,56] Iran (n = 2),[40,54] Columbia (n = 1),[46] Greece (n = 1),[57] Italy (n = 1),[57] Spain (n = 1),[58] Scotland (n = 1),[59] Luton (n = 1),[48] Netherlands (n = 1)[41] and Saudi Arabia (n = 1).[46] Thirteen reviews explicitly included randomized control trials (RCTs) only[29-32,34,36,38,42,43,46,53,57,59]; 5 reviews included RCTs and phase-1 data of cross-over trials[39,41,44,45,52]; 2 reviews included RCTs and prospective trials[50,56]; 2 reviews included RCTs and observational studies[49,58]; 1 review included RCTs, comparative studies and case series with >5 patients[55]; 2 reviews included all clinical trials[40,54]; 3 reviews included all study types[35,48,51]; and 3 reviews did not state an inclusion criteria for the study type.[33,37,47] Fifteen reviews did not set a language restriction in their literature search[30,31,39-41,43-46,49,50,52,56-58]; 11 reviews restricted their search to English publications only[32,34-38,42,51,53,55,59]; 1 review restricted its language to English and Persian[54]; 1 review restricted its language to English and Chinese[33]; and 3 reviews did not state if any language restriction was applied.[29,47,48] Twelve reviews reported following a guideline on good practice in conducting systematic reviews[30,31,35,39,41,44-47,53,57,58]; 25 reviews included meta-analyses[29-38,41-47,49-53,55-57]; and 18 reviews did not provide a clear statement as to the overall quality assessment of the included articles.[31,33,34,36,37,41-44,47,51-58] The number of studies included in each systematic review ranged from 1 to 35, and the total participants ranged from 16 to 3992. Eighteen (58%) of the systematic reviews had less than 10 studies included in total.[29-32,36,38-42,44,46-48,52,56,57,59]

3.3 | Methodological quality of systematic reviews

The AMSTAR scores of the included systematic reviews are provided in Appendix S3 (found in the Supporting Information). Majority of the included systematic reviews were of low (n = 7; 23%)[42,47,48,54,55,58,59] to moderate quality (n = 16; 52%)[29-34,36,37,39,40,43,49-51,53,56] with only 8 graded high quality (n = 8; 26%).[35,39,41,44-46,52,57] Commonly unreported items were consideration of conflict of interest of the included studies (n = 28; 90%), presence of an a priori study design (n = 23; 74%), a list of the excluded articles (n = 23; 74%), inclusion of grey literature (n = 22; 71%), duplication of study selection or data extraction (n = 21; 68%), formulation of study conclusion

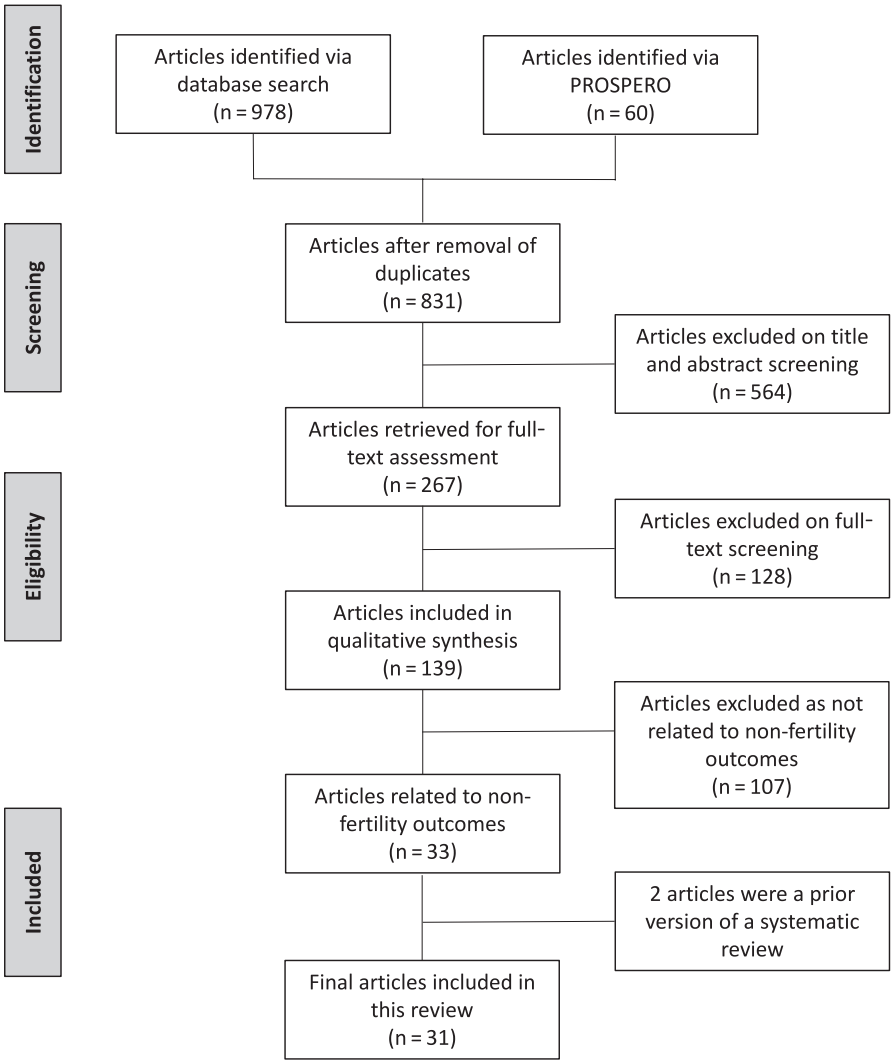

FIGURE 1 Study selection process

based on the scientific quality of the included studies (n = 18; 58%) and conduction of a comprehensive literature search (n = 18; 58%). Assessment of publication bias was not appropriately performed in 9 reviews (29%), documentation of the scientific quality of the included studies was unsatisfactory in 6 reviews (19%), and heterogeneity was not taken into account by 2 reviews (6%). All reviews reported the study characteristics of the included studies.

3.4 | Types of intervention

The types of treatments assessed were metformin, thiazolidinedione, oral contraceptive pills (OCP), anti-androgens, statins, orlistat, bariatric surgery and antidepressants. Nonconventional therapies such as vitamin D, inositol, N-acetyl-cysteine and antioxidants were also included in this review.

3.4.1 | Insulin sensitizer: metformin

Sixteen reviews evaluated the efficacy of metformin (Table 2).[29,30,32,34-36,38,41,43,45,46,49,53,56,57,59] Five were rated high quality, 10 were rated moderate quality, and 1 was rated low quality. A total of 174 trials and 10 525 adolescent and adult participants were involved.

Anthropometric outcomes were assessed by 10 reviews. Seven reviews (n = 3 comparing metformin vs thiazolidinediones,[29,30,34] n = 2 comparing metformin vs placebo,[45,53] n = 1 comparing metformin vs COCPs[46] and n = 1 comparing combination therapy with metformin and clomiphene citrate vs clomiphene citrate alone)[59] reported results favouring metformin in terms of BMI and/or waist-hip ratio. There was no significant difference in anthropometric outcomes when metformin was compared to acarbose[38] or orlistat,[56] or when combination therapy with metformin and statin was compared to metformin alone.[36] Endocrine outcomes were assessed by 12 reviews. Three reviews (n = 2 comparing metformin vs placebo[45,53] and n = 1 comparing metformin and clomiphene citrate vs clomiphene citrate alone[59]) reported reductions in testosterone when using metformin. There was no significant difference in endocrine outcomes when metformin was compared to acarbose,[38] OCP,[46] vitamin D,[32,57] thiazolidinediones,[29,30,34] orlistat,[56] inositol[43] or combination therapy with statin.[36] Metabolic outcomes were assessed by 14 reviews with 4 reviews reporting beneficial outcomes favouring metformin for the prevalence of type 2 diabetes

mellitus or prediabetes (n = 1 comparing metformin vs OCP),[46] total cholesterol and low-density lipoprotein (LDL) (n = 1 comparing metformin vs OCP),[46] blood pressure (n = 2 comparing metformin vs placebo),[45,53] triglycerides (n = 1 comparing metformin vs placebo,[53] n = 1 comparing metformin vs thiazolidinediones),[34] glucose (n = 1 comparing metformin vs placebo),[45] insulin (n = 1 comparing metformin vs placebo)[45] and glucose/insulin ratio (n = 1 comparing metformin vs placebo).[53] No significant metabolic outcomes were detected when comparing metformin to vitamin D,[32,57] orlistat,[56] inositol,[43] acarbose[38] or with the addition of metformin to follicle stimulating hormone (FSH)-containing gonadotrophin ovulation induction or clomiphene citrate.[59] Psychological outcomes were not assessed by any of the above reviews.

3.4.2 | Insulin sensitizer: thiazolidinediones

Five reviews[29-31,34,45] evaluated the efficacy of thiazolidinediones in which one was high quality and 4 were moderate quality (Table 2). A total of 74 trials and 5282 participants with PCOS were involved. All 5 reviews assessed the anthropometric, endocrine and metabolic outcomes of thiazolidinediones (n = 3 compared with metformin,[29,30,34] n = 2 compared with placebo).[31,45] BMI was significantly increased with thiazolidinediones in all 5 reviews while endocrine benefits (reduced free testosterone) were reported in one review when compared to metformin.[34] For metabolic outcomes, one review showed improved fasting glucose and insulin in comparison with placebo,[31] one review showed improved fasting insulin and homoeostatic model assessment of insulin resistance (HOMA-IR) when compared to metformin,[30] and one review showed worsened triglycerides when compared to metformin.[34] Psychological outcomes were not assessed by any of the above reviews.

3.4.3 | Insulin sensitizer: inositol

Three reviews[43,45,48] evaluated the efficacy of inositol (Table 2). The reviews were of low (n = 1), moderate (n = 1) and high (n = 1) quality. A total of 62 trials with 5072 women with PCOS were involved. In all 3 reviews, inositol was compared against placebo. Anthropometric outcomes were reported by 2 reviews with one review reporting reduced BMI and waist-hip ratio.[48] Endocrine outcomes were assessed by all 3 reviews with 2 of these reporting benefits (testosterone, DHEAS or androstenedione).[43,48] Metabolic outcomes were also assessed by all 3 reviews with 2 reviews reporting reduced insulin,[43,48] one review reporting reduced glucose and HOMA-IR,[43] and one review reporting improved blood pressure, triglycerides and high-density lipoprotein (HDL).[48] Psychological outcomes were not assessed by any of the above reviews.

3.4.4 | Hormonal therapy: combined oral contraceptive pill

The efficacy of COCPs was assessed by 4 reviews[46,49,50,58] (Table 3) of low to high quality (n = 1 high, n = 2 moderate, and n = 1 low). Results from 88 trials involving 3722 adolescent and adult women with PCOS were analysed. Anthropometric outcomes were reported by one review with COCP being associated with a lesser reduction of BMI compared with metformin.[46] Endocrine outcomes were assessed by 2 reviews with one reporting greater acne reduction when compared to metformin[46] and one review reporting general improvement in clinical hyperandrogenism when using COCP as monotherapy or in combination with metformin.[58] Two reviews assessed metabolic outcomes of which one review reported that COCP use was less effective than metformin in reducing the prevalence of dysglycaemia, total cholesterol and LDL,[46] and one review reported that COCP use was associated with increased HDL and triglycerides compared with baseline.[50] Psychological outcomes were not assessed by any of the above reviews.

3.4.5 | Hormonal therapy: anti-androgens

One high-quality review evaluated the side effects of anti-androgens and their efficacy on metabolic outcomes (Table 3).[49] No significant effects on metabolic outcomes were reported.

3.4.6 | Weight loss therapy: orlistat

Orlistat was evaluated by one moderate quality review in comparison with placebo, metformin or other anti-obesity drugs[56] (Table 4) where 9 trials and 602 adolescent and adult women with PCOS were involved. Meta-analysis of the studies comparing orlistat to placebo was not possible but the systematic review reported improvements in anthropometric (BMI, weight, waist circumference or waist-hip ratio), endocrine (testosterone) and metabolic outcomes (triglycerides, HDL, LDL, HOMA-IR and insulin). Meta-analysis of the studies comparing orlistat to metformin showed no significant differences.[56] Psychological outcomes were not assessed by the above review.

3.4.7 | Weight loss therapy: bariatric surgery

The effect of bariatric surgery in women with PCOS was evaluated in 2 low-quality reviews[47,55] (Table 4). They involved 19 trials and 2394 participants with and without PCOS. Both reviews compared the same group of women before and after bariatric surgery. Both reviews assessed anthropometric and endocrine outcomes and reported reductions in BMI, percentage of excess weight loss and hirsutism.[47,55] Metabolic outcomes were assessed by one review and showed reductions in blood pressure, improvement in dyslipidaemia, normalization of glucose levels, improvement of glycaemic control and resolution of type 2 diabetes mellitus.[47] Psychological outcomes were assessed by one review and reported benefits in depression.[47]

3.4.8 | Other therapy: statins

Three reviews evaluated the efficacy of statins[36,42,44] (Appendix S3, found in the Supporting Information) with rating of one low,

TABLE 1 Study characteristics

Author (y)	Country	Included study type	Date of last literature search	Language	Systematic review guideline followed	Meta-analysis performed	Number of included papers	Total number of included participants	Population and PCOS diagnostic criteria
Al Khalifah et al (2016)[46]	Canada, Saudi Arabia, Columbia, United Kingdom	RCTs	15-Jan	All	Yes	Yes	4	170	Adolescents (11-19 y) ESHRE/ASRM
Amini et al (2015)[54]	Iran	Experimental or quasiexperimental trials	13-Nov	English, Persian	No	No	11	834	Iranian ESHRE/ASRM
Azadi-Yazdi et al (2017)[40]	Iran, Australia	Clinical trials	17-Jan	All	No	No	6	183	Diagnostic criteria not stated
Bordewijk et al (2017)[41]	Netherlands, Australia, Brazil	RCTs and phase 1 of cross-over trials	16-Sep	All	Yes	Yes	5	264	Anovulatory women undergoing ovulation induction with FSH ESHRE/ASRM
Butterworth et al (2016)[47]	United Kingdom	Not stated	15-Mar	Not stated	Yes	Yes	6	264	ESHRE/ASRM
Domecq et al (2013)[49]	United States	RCTs and comparative observational studies	11-Apr	All	No	Yes	22	1335	Diagnostic criteria not stated
Du et al (2012)[31]	China	RCTs	12-Jun	All	Yes	Yes	8	286	ESHRE/ASRM
Du et al (2012)[29]	China	RCTs	12-Feb	Not stated	No	Yes	6	267	ESHRE/ASRM
Du et al (2012)[30]	China	RCTs	11-Nov	All	Yes	Yes	6	278	ESHRE/ASRM
Fang et al (2017)[32]	China	RCTs	15-Dec	English	No	Yes	9	502	ESHRE/ASRM
Galazis et al (2011)[48]	United Kingdom, Luton	All study types	10-Jul	Not stated	No	No	8	479	Diagnostic criteria not stated
Gao et al (2012)[42]	Australia	RCTs	11-Sep	English	No	Yes	4	254	Diagnostic criteria not stated
Gill et al (2014)[59]	Scotland	RCTs	13-May	English	No	No	4	129	Clomiphene resistant women Diagnostic criteria not stated
Graff et al (2016)[56]	Brazil	RCTs and prospective studies	15-May	All	No	Yes	9	602	Without pre-existing diabetes, 13-44 y ESHRE/ASRM
Halperin et al (2011)[50]	Canada, United States	RCTs and prospective cohorts	10-Apr	All	No	Yes	35	798	Without pre-existing diabetes, 13-44 y ESHRE/ASRM
He et al (2015)[51]	United States	All study types	15-Jan	English	No	Yes	30 (7 regarding intervention)	3182 (283 included for intervention)	ESHRE/ASRM
Jia et al (2015)[33]	China	Not stated	14-Sep	English, Chinese	No	Yes	17	2397	ESHRE/ASRM

Author (y)	Country	Included study type	Date of last literature search	Language	Systematic review guideline followed	Meta-analysis performed	Number of included papers	Total number of included participants	Population and PCOS diagnostic criteria
Li et al (2011)[34]	China	Parallel-group designed RCTs	10-May	English	No	Yes	10	459	Diagnostic criteria not stated
Mendoza et al (2014)[58]	Spain, Italy	RCTs, nonrandomized studies and noncontrolled studies	13-Oct	All	Yes	No	27	1589	Diagnostic criteria not stated
Meng et al (2016)[35]	China	All study types	15-Dec	English	Yes	Yes	34 (7 regarding interven-tion)	3117 (141 included for intervention)	ESHRE/ASRM
Patel et al (2017)[53]	India	RCTs	16-May-	English	Yes	Yes	14	593	16-45 y (exclude pregnancy or clomiphene resistant) Diagnostic criteria not stated
Pergialiotis et al (2017)[57]	Greece	RCTs	16-Sep	All	Yes	Yes	9	647	Diagnostic criteria not stated
Pundir et al (2017)[43]	United Kingdom, Australia	RCTs	16-Aug-	All	No	Yes	10	601	Diagnostic criteria not stated
Raval et al (2011)[44]	India, Australia	RCTs and phase 1 of cross-over trials	11-Jul	All	Yes	Yes	4	244	ESHRE/ASRM
Skubleny et al (2016)[55]	Canada	RCTs, comparison studies, and case series > 5 patients	Not stated	English	No	Yes	13	2130	Women with or without PCOS Diagnostic criteria not stated
Sun et al (2015)[36]	China	RCTs (excluding trails comparing statins with OCP or other statins)	14-Oct	English	No	Yes	9	282	Diagnostic criteria not stated
Tang et al (2012)[45]	United Kingdom, Australia	RCTs and phase 1 of cross-over trials	11-Oct	All	Yes	Yes	44	3992	Oligo- or anovulatory ESHRE/ASRM
Thakker et al (2015)[52]	India, United States	RCTs and phase 1 of cross-over trials	13-Sep	All	No	Yes	8	910	ESHRE/ASRM
Xue et al (2017)[37]	China	Not stated	16-Apr	English	No	Yes	16	855	ESHRE/ASRM
Zhang et al (2014)[38]	China	RCTs	13-Sep	English	No	Yes	6	263	ESHRE/ASRM
Zhuang et al (2013)[39]	China	RCTs and phase 1 of cross-over trials	12-Jun	All	Yes	No	1	16	ESHRE/ASRM

RCT, randomized control trials; ESHRE, European Society of Human Reproduction and Embryology; ASRM, American Society for Reproductive Medicine; OCP, oral contraceptive pill.

TABLE 2 Results of systematic reviews regarding insulin sensitizers

Reviews	AMSTAR	Quality of included studies	Outcomes assessed		Comparison	Significant results	
Metformin							
Al Khalifah et al (2016)[46]	High	Very low to low	Anthropometric	BMI	Metformin vs OCP	Anthropometric	BMI (WMD −4.02, 95%CI −5.23 to −2.81)
			Reproductive	Hirsutism, acne, testosterone		Reproductive	Acne scores (WMD 0.3, 95% 0.05 to 0.55)[a]
			Metabolic	Dysglycaemia, cholesterol, TG, HDL, LDL		Metabolic	Dysglycaemia (risk ratio 0.41, 95%CI 0.19 to 0.86) Cholesterol (WMD −43.23, 95%CI −64.15 to −22.32) LDL (WMD −35.5, 95%CI −57.45 to −13.33)
			Psychologic	–			NA
Bordewijk et al (2017)[41]	High	Unclear	Anthropometric	–	Metformin + ovulation induction vs ovulation induction		
			Reproductive	–			
			Metabolic	Insulin, glucose			
			Psychologic	–			
Meng et al (2016)[35]	High	RCTs: low to moderate risk of bias; observational studies: high risk of bias	Anthropometric	–	Metformin vs no treatment		NA
			Reproductive	–			
			Metabolic	–			
			Psychologic	–			
Pergialiotis et al (2017)[57]	High	Unclear	Anthropometric	–	Metformin ± vit D vs vitamin D		NA
			Reproductive	DHEAS, SHBG			
			Metabolic	Glucose, insulin			
			Psychologic	–			
Tang et al (2012)[45]	High	Very low to low	Anthropometric	BMI, waist-hip ratio	Metformin vs placebo	Anthropometric	Waist-hip ratio (MD −0.01, 95%CI −0.01 to 0.00)
			Reproductive	Testosterone, SHBG		Reproductive	Total testosterone (MD −0.60, 95%CI −0.73 to −0.48)
			Metabolic	BP, glucose, insulin, cholesterol, TG		Metabolic	Systolic BP (MD −3.59, 95%CI −5.13 to −2.04) Glucose (MD −0.15, 95%CI 0.25 to −0.06) Insulin (MD −3.51, 95%CI −6.50 to 0.53)
			Psychologic	–			
Domecq et al (2013)[49]	Moderate	RCTs: low to moderate risk of bias; observational studies: high risk of bias	Anthropometric	–	Metformin (no comparators)		NA
			Reproductive	–			
			Metabolic	–			
			Psychologic	–			

(Continues)

TABLE 2 (Continued)

Reviews	AMSTAR	Quality of included studies	Outcomes assessed		Comparison	Significant results	
Du et al (2012)[29]	Moderate	High	Anthropometric	BMI	Metformin vs thiazolidinediones	Anthropometric	BMI (SMD −0.4, 95%CI 0.16 to 0.65)
			Reproductive	Testosterone			
			Metabolic	Glucose, HOMA-IR			
			Psychologic	–			
Du et al (2012)[30]	Moderate	Very low to low	Anthropometric	BMI	Metformin vs pioglitazone	Anthropometric	BMI (SMD −0.25, 95%CI 0.01 to 0.49)
			Reproductive	Testosterone, hirsutism		Metabolic	Insulin (SMD 0.37, 95%CI −0.61 to −0.13)[a] HOMA-IR (SMD 0.32, 95%CI −0.57 to −0.06)[a]
			Metabolic	Glucose, insulin, HOMA-IR			
			Psychologic	–			
Fang et al (2017)[32]	Moderate	Low to moderate risk of bias	Anthropometric	–	Metformin vs vitamin D		NA
			Reproductive	–			
			Metabolic	Cholesterol, TG, HDL, LDL, insulin, glucose, QUICKI, HOMA-IR			
			Psychologic	–			
Graff et al (2016)[56]	Moderate	Unclear	Anthropometric	BMI, weight, waist circumference	Metformin vs orlistat		NA
			Reproductive	Testosterone			
			Metabolic	Insulin, HOMA-IR, cholesterol, TG, HDL, LDL			
			Psychologic	–			
Li et al (2011)[34]	Moderate	Unclear	Anthropometric	BMI	Metformin vs thiazolidinediones	Anthropometric	BMI at 3-mo (SMD −2.47, 95%CI −3.33 to −1.62) BMI at 6-mo (SMD −0.70, 95%CI −0.76 to −0.65)
			Reproductive	Hirsutism, androsten-edione, testosterone, DHEA		Reproductive	Free testosterone (SMD 0.36, 95%CI −0.03 to −0.69)[a]
			Metabolic	Glucose, insulin, HOMA-IR, HDL, LDL, TG		Metabolic	TG at 6-mo (SMD −1.13, 95%CI −1.68 to −0.57)
			Psychologic	–			

(Continues)

TABLE 2 (Continued)

Reviews	AMSTAR	Quality of included studies	Outcomes assessed		Comparison	Significant results	
Patel et al (2017)[53]	Moderate	Unclear	Anthropometric	BMI, waist-hip ratio	Metformin vs placebo	Anthropometric	BMI (MD −1.18, 95%CI −2.0 to −0.36) WHR (MD −0.02, 95%CI −0.03 to 0.00)
			Reproductive	Hirsutism, testosterone, free testosterone, FAI, SHBG, DHEAS		Reproductive	Testosterone (MD −14.32, 95%CI −26.80 to −1.85)
			Metabolic	Blood pressure, cholesterol, TG, HDL, LDL, glucose, insulin, glucose/insulin ratio, HOMA-IR, QUICKI		Metabolic	Systolic BP (MD −4.92, 95%CI −7.51 to −2.33) Diastolic BP (MD −1.51, 95%CI −2.23 to −0.79) TG (MD −10.74, 95%CI −17.93 to −3.56) Glucose/insulin ratio (MD 2.28, 95%CI 1.16 to 3.41)
			Psychologic	–			
Pundir et al (2017)[43]	Moderate	Unclear	Anthropometric	–	Metformin vs inositol		NA
			Reproductive	Androstenedione, testosterone, DHEAS, SHBG			
			Metabolic	Insulin, glucose, glucose/insulin ratio, HOMA-IR			
			Psychologic	–			
Sun et al (2015)[36]	Moderate	Unclear	Anthropometric	BMI	Metformin + statin vs metformin	Metabolic	Total cholesterol (SMD −1.28, 95%CI −1.59 to −0.97) LDL (SMD −0.74, 95%CI −1.03 to −0.44) TG (SMD −1.37, 95%CI −2.46 to −0.28)
			Reproductive	Testosterone, androstenedione, DHEAS, SHBG, FAI			
			Metabolic	Cholesterol, LDL, HDL, TG, glucose, insulin, HOMA-IR			
			Psychologic	–			
Zhang et al (2014)[38]	Moderate	Poor	Anthropometric	BMI	Metformin vs acarbose		NA
			Reproductive	Hirsutism, testosterone			
			Metabolic	TG, HDL			
			Psychologic	–			

(Continues)

TABLE 2 (Continued)

Reviews	AMSTAR	Quality of included studies	Outcomes assessed		Comparison	Significant results	
Gill et al (2014)[59]	Low	3 high, 1 low	Anthropometric	BMI	Metformin + clomiphene vs clomiphene	Anthropometric	2 trials: BMI was decreased
			Reproductive	SHBG, testosterone		Reproductive	2 trials: testosterone was decreased
			Metabolic	Insulin			
			Psychologic	–			
Thiazolidinediones							
Tang et al (2012)[45]	High	Very low to low	Anthropometric	BMI, waist, hip ratio	Rosiglitazone vs placebo	Anthropometric	BMI (MD +0.68, 95%CI 0.40 to 0.96)
			Reproductive	Testosterone, SHBG	Pioglitazone vs placebo		NA
			Metabolic	BP, glucose, insulin, cholesterol, TG			
			Psychologic	–			
Du et al (2012)[31]	Moderate	Unclear	Anthropometric	BMI	Thiazolidinediones vs placebo	Anthropometric	BMI (SMD +0.39, 95%CI 0.13 to 0.66)
			Reproductive	Hirsutism, testosterone		Metabolic	Insulin (SMD −0.81, 95%CI −1.5 to −0.12) Glucose (SMD −0.55, 95%CI −1.06 to −0.05)
			Metabolic	Glucose, insulin			
			Psychologic	–			
Du et al (2012)[30]	Moderate	Very low to low	Anthropometric	BMI	Pioglitazone vs metformin	Anthropometric	BMI (SMD 0.25, 95%CI 0.01 to 0.49)[a]
			Reproductive	Hirsutism, testosterone		Metabolic	Insulin (SMD −0.37, 95%CI −0.61 to −0.13) HOMA-IR (SMD −0.32, 95%CI −0.57 to −0.06)
			Metabolic	Glucose, insulin, HOMA-IR			
			Psychologic	–			
Du et al (2012)[29]	Moderate	High	Anthropometric	BMI	Thiazolidinediones vs metformin	Anthropometric	BMI (SMD 0.4, 95%CI 0.16 to 0.65)[a]
			Reproductive	Testosterone			
			Metabolic	Glucose, HOMA-IR			
			Psychologic	–			

(Continues)

TABLE 2 (Continued)

Reviews	AMSTAR	Quality of included studies	Outcomes assessed		Comparison	Significant results	
Li et al (2011)[34]	Moderate	Unclear	Anthropometric	BMI	Thiazolidinediones vs metformin	Anthropometric	BMI at 3-mo (SMD 2.47, 95%CI −3.33 to −1.62)[a] BMI at 6-mo (SMD 0.70, 95%CI −0.76 to −0.65)[a]
			Reproductive	Hirsutism, androsten-edione, testosterone, DHEA		Reproductive	Free testosterone (SMD −0.36, 95%CI −0.03 to −0.69)
			Metabolic	Glucose, insulin, HOMA-IR, cholesterol, TG, HDL, LDL		Reproductive	TG at 6-mo (SMD 1.13, 95%CI −1.68 to −0.57)[a]
			Psychologic	–			
Inositol							
Tang et al (2012)[45]	High	Very low to low	Anthropometric	BMI, waist, hip ratio	D-chiro-inositol vs placebo		NA
			Reproductive	Testosterone, SHBG			
			Metabolic	BP, glucose, insulin, cholesterol, TG			
			Psychologic	–			
Pundir et al (2017)[43]	Moderate	Unclear	Anthropometric	–	Inositol (myo- or di-chiro isomers) vs placebo	Reproductive	Androstenedione (SMD −1.6, 95%CI −2.3 to −0.6) Total testosterone (SMD −3.3, 95%CI −5.1 to −1.5) DHEAS (SMD −3.2, 95%CI −5.7 to −0.6)
			Reproductive	Androstenedione, testosterone, DHEAS, SHBG		Metabolic	Insulin (SMD −2.1, 95%CI −3.2 to −0.9) Glucose (SMD −1.0, 95%CI −1.7 to −0.2) HOMA-IR (SMD −1.8, 95%CI −2.6 to −1.0) Insulin AUC (SMD −1.6, 95%CI −2.8 to −0.4) Glucose/insulin ratio (SMD 2.9, 95%CI 2.2 to 3.6)
			Metabolic	Insulin, glucose, glucose/insulin ratio, HOMA-IR			
			Psychologic	–			
Galazis et al (2011)[48]	Low	4 low, 4 high	Anthropometric	Not specified	D-chiro-inositol vs placebo	Anthropometric	2 trials: improved BMI, waist-hip ratio
			Reproductive	Reproductive steroids		Reproductive	3 trials: reduced testosterone
			Metabolic	BP, cholesterol, insulin sensitivity		Metabolic	3 trials: reduced insulin, BP, TG
			Psychologic	–			1 trial: increased HDL

NA, not available; MD, mean difference; WMD, weighted mean difference; SMD, standardized mean difference; CI, confidence interval; BMI, body mass index; SHBG, sex hormone binding globulin; FAI, free androgen index; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulphate; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides; HOMA-IR, homoeostatic model assessment of insulin resistance; QUIKI, quantitative insulin sensitivity check index; AUC, area under the curve; OCP, oral contraceptive pill.

[a]Results less beneficial than comparator.

TABLE 3 Results of systematic reviews regarding hormonal therapies

Reviews	AMSTAR	Quality of included studies	Outcomes assessed		Comparison	Significant results	
Oral contraceptive pills							
Al Khalifah et al (2016)[46]	High	Very low to low	Anthropometric	BMI	OCP vs metformin	Anthropometric	BMI (WMD 4.02, 95%CI −5.23 to −2.81)[a]
			Reproductive	Hirsutism, acne, testosterone		Reproductive	Acne scores (WMD −0.3, 95% 0.05 to 0.55)
			Metabolic	Dysglycaemia, cholesterol, TG, HDL, LDL		Metabolic	Dysglycaemia (risk ratio 0.41, 95%CI 0.19 to 0.86)[a] Cholesterol (WMD 43.23, 95%CI −64.15 to −22.32)[a] LDL (WMD 35.5, 95%CI −57.45 to −13.33)[a]
			Psychologic	–			
Domecq et al (2013)[49]	Moderate	RCTs: low to moderate risk of bias; observational studies: high risk of bias	Anthropometric	Weight, BMI	OCP (no comparator)		NA
			Reproductive	–			
			Metabolic	Fasting glucose, postprandial glucose, glucose tolerance test, random glucose, area under the curve of glucose, glucose/insulin ratio, HOMA-IR, QUICKI			
			Psychologic	–			
Halperin et al (2011)[50]	Moderate	17 high, 9 moderate, 16 low	Anthropometric	–	Pre- vs post-OCP	Metabolic	HDL (SMD 0.46, 95%CI 0.14 to 0.78) TG (SMD 0.55, 95%CI 0.17 to 0.93)
			Reproductive	–			
			Metabolic	Insulin, glucose, cholesterol, TG, HDL, LDL, hyperinsulinemic euglycaemic clamp (m-value), glucose/insulin ratio, HOMA-IR			
			Psychologic	–			
Mendoza et al (2014)[58]	Low	Unclear	Anthropometric	BMI, weight	OCP ± metformin/ anti-androgen (no clear comparator)	Reproductive	Relieved hyperandrogenism after 6 mo
			Reproductive	Hirsutism, acne, seborrhoea, testosterone, DHEAS, SHBG, FAI, androstenedione		Metabolic	Combination with metformin more effective in reducing IR
			Metabolic	BP, cholesterol, TG, HDL, LDL, glucose, insulin, HOMA-IR			
			Psychologic	–			

(Continues)

TABLE 3 (Continued)

Reviews	AMSTAR	Quality of included studies	Outcomes assessed		Comparison	Significant results
Anti-androgens						
Domecq et al (2013)[49]	Moderate	RCTs: low to moderate risk of bias; observational studies: high risk of bias	Anthropometric	–	Anti-androgen (no comparator)	NA
			Reproductive	–		
			Metabolic	Fasting glucose, postprandial glucose, glucose tolerance test, random glucose, area under the curve of glucose, glucose/insulin ratio, HOMA-IR, QUICKI		
			Psychologic	–		

NA, not available; WMD, weighted mean difference; SMD, standardized mean difference; CI, confidence interval; BMI, body mass index; SHBG, sex hormone binding globulin; FAI, free androgen index; DHEAS, dehydroepiandrosterone sulphate; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides; IR, insulin resistance; HOMA-IR, homoeostatic model assessment of insulin resistance; QUIKI, quantitative insulin sensitivity check index; OCP, oral contraceptive pill.

[a]Results less beneficial than comparator.

one moderate and one high quality. Results were derived from 17 trials and 780 participants with PCOS. Statins were evaluated either as a standalone therapy compared to placebo or as combination therapy with metformin compared to metformin. All 3 reviews reported improvements in metabolic outcomes (n = 3 for the lipid profile[36,42,44] and n = 1 for insulin),[42] and 2 reviews reported improvement in endocrine outcomes (testosterone).[42,44] The effects of statins on anthropometric outcomes were not significant (n = 2).[36,44] Psychological outcomes were not assessed by any of the reviews.

3.4.9 | Other therapy: vitamin D

Seven reviews evaluated vitamin D[32,33,37,40,51,54,57] (Appendix S3, found in the Supporting Information) either as monotherapy vs placebo or metformin, as combination therapy with metformin vs metformin or comparing the effects of before and after vitamin D. Only one review had a high rating while the majority of the reviews (n = 5) were of moderate quality, and one review was of low quality. A total of 75 trials and 5701 participants women with PCOS were involved.

Five reviews assessed endocrine outcomes with 2 reviews reporting benefits DHEAS (n = 1 comparing vitamin D vs placebo and vitamin D with metformin vs metformin)[57] or testosterone (n = 1 comparing vitamin D vs placebo).[40] Metabolic outcomes were assessed by 6 reviews with 4 reviews reported benefits as reductions in HOMA-IR (n = 1 comparing vitamin D vs placebo or combination therapy vs metformin),[57] total cholesterol (n = 1 comparing vitamin D vs placebo)[57] or triglycerides (n = 2 comparing before and after vitamin D).[37,51] One review reported significant improvements in blood pressure for vitamin D vs placebo.[54] Anthropometric outcomes were assessed by one review which did not show any significant results.[54] Psychological outcomes were not assessed by any of the reviews.

3.4.10 | Other therapy: N-acetyl-cysteine

Two reviews[52,54] evaluated the efficacy of *N*-acetyl-cysteine of which one review was of high quality and one review was of low quality (Appendix S3, found in the Supporting Information). A total of 19 trials with 1744 participants with PCOS were involved. Both reviews assessed anthropometric, endocrine and metabolic effects of N-acetyl-cysteine in comparison with placebo or metformin. One review reported improvements in anthropometric anthropology (reduced BMI, weight and waist-hip ratio) and metabolic outcomes (improved lipid profile, reduced fasting glucose, insulin and HOMA-IR).[54] Psychological outcomes were not assessed by any of the reviews.

3.4.11 | Other therapy: antidepressants

One high-quality review[39] aimed to investigate the efficacy of antidepressants in PCOS (Appendix S3, found in the Supporting Information) and identified one study involving 16 women with PCOS comparing fluoxetine (antidepressant) and sibutramine (anti-obesity

TABLE 4 Results of systematic reviews regarding weight loss therapies

Reviews	AMSTAR	Quality of included studies	Outcomes assessed		Comparison	Significant results	
Bariatric surgery							
Butterworth et al (2016)[47]	Low	Unclear	Anthropometric	Percentage of excess weight loss	Pre- vs postbariatric surgery	Anthropometric	1 trial: improved percentage of excess weight loss
			Reproductive	Hirsutism		Reproductive	2 trials: improved hirsutism
			Metabolic	T2DM, blood pressure, cholesterol, TG, HDL, LDL, glucose		Metabolic	3 trials: improved glycaemic profile (resolution of T2DM, improvement of glycaemic control, or normalization of glucose levels) 2 trials: improved blood pressure
			Psychologic	Depression		Psychologic	1 trial: improved dyslipidaemia 1 trial: improved depression
Skubleny et al (2016)[55]	Low	Unclear	Anthropometric	BMI, weight, percentage of excess weight loss	Pre- vs postbariatric surgery	Anthropometric	Percentage of excess weight loss (weighted mean 57.2%, range 33% to 75%) Mean BMI improved from 46.3 to 34.2
			Reproductive	Hirsutism		Reproductive	Hirsutism (OR 0.12, 95%CI 0.04 to 0.36)
			Metabolic	–			
			Psychologic	–			
Orlistat							
Graff et al (2016)[56]	Moderate	Unclear	Anthropometric	BMI, weight, waist circumference	Insulin, HOMA-IR, cholesterol, TG, HDL, LDL	Anthropometric	8 trials: reduced BMI and/or weight 5 trials: reduced waist-hip ratio or waist circumference
			Reproductive	Testosterone		Reproductive	7 trials: reduced testosterone
			Metabolic	Insulin, HOMA-IR, cholesterol, TG, HDL, LDL		Metabolic	4 trials: improved lipid profile (TG, HDL, LDL) 5 trials: reduced HOMA-IR and/or insulin
			Psychologic	–			

OR, odds ratio; CI, confidence interval; T2DM, type 2 diabetes mellitus; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides; HOMA-IR, homoeostatic model assessment (of insulin resistance).

drug). No significant differences were reported between treatments for anthropometric, endocrine or metabolic outcomes. No study assessing psychological outcomes was found.

3.4.12 | Other therapy: acarbose

Acarbose was compared against placebo in one moderate quality review including 6 trials and 263 women with PCOS (Appendix S3, found in the Supporting Information).[38] Acarbose was associated with improvement in endocrine (testosterone) and metabolic (triglyceride and HDL) outcomes. No significant change in anthropometric outcomes was detected. Psychological outcomes were not assessed by the review.

3.4.13 | Other therapy: antioxidants

One low-quality systematic review assessed the efficacy of antioxidants[54] (Appendix S3, found in the Supporting Information) involving 11 trials and 834 Iranian women with PCOS. This review reported one trial for soy vs placebo which improved endocrine outcomes (DHEAS and testosterone); one trial for folic acid vs placebo without any significant outcome; 3 trials for omega-3 vs placebo which improved metabolic outcomes (increased HDL, reduced total cholesterol, total cholesterol/HDL ratio, LDL/HDL ratio, triglycerides, LDL, glucose, insulin and insulin resistance); and one trial for zinc vs placebo which improved endocrine (testosterone) and metabolic outcomes (HOMA-IR, cholesterol, triglycerides and LDL).[54] No significant improvements in anthropometric outcomes were reported.[54] Psychological outcomes were not assessed by the review.

4 | DISCUSSION

This is the first overview of systematic reviews assessing pharmacological or surgical interventions for nonreproductive outcomes in women with PCOS, and it demonstrates a lack of high-quality systematic reviews or meta-analyses presenting data from high-quality studies.

There is diversity in the quality of identified reviews in regard to the use of metformin. Most demonstrated a reduction in BMI or waist-hip ratio, and some reported benefits in metabolic outcomes including blood pressure, triglycerides, markers of glucose tolerance and insulin resistance in comparison with placebo or COCP. Efficacy in hyperandrogenism is less convincing. Our findings support current evidence-based guidelines and speciality society position statements where metformin is recommended for women with PCOS who failed to achieve target weight loss with lifestyle management or those with impaired glucose tolerance or type 2 diabetes mellitus, and it is also not recommended as a treatment for hirsutism or acne due to a lack of efficacy.[2,3,5,7,21,22,60]

We report that thiazolidinediones were more effective than metformin or placebo in reducing markers of insulin resistance.[30,31] Only one of 5 reviews showed superiority for thiazolidinediones in reducing testosterone.[34] However, these benefits come with the price of increased weight which is contradictory for PCOS given the high prevalence of obesity and the negative impact on metabolic, endocrine and reproductive outcomes. Thiazolidinediones may also increase risks of bladder cancer and osteoporosis.[2,5,7,61,62] Considering these risks, thiazolidinediones are not recommended as routine treatment for women with PCOS.[2,3,5,7,21,22]

We report here that the COCP was the only treatment modality that improved clinical hyperandrogenism. The use of COCP was not associated with worsening insulin resistance in this review.[46,49,50,58] The effects on lipid profile were more controversial as the positive effect of increase in HDL may be offset by an unfavourable increase in triglyceride.[50] Notably, the review by Domecq et al[49] did not report any thromboembolic or cardiovascular events with COCP use. There is consensus in recommending COCPs as first-line pharmacological therapy for acne, hirsutism and oligo-/amenorrhoea with careful consideration of the potential risk of increased venous thromboembolism extrapolated from evidence from the general population.[2,3,5,21] Although previous studies have raised concerns of worsening insulin resistance and triglycerides, there is no available evidence of increased cardiovascular events with long-term use with COCP.[2,7,63-65] There is inadequate evidence to compare or recommend specific COCP preparations or hormonal components.

While anti-androgens have been used widely to treat hirsutism, especially in patients where hirsutism is not resolved by COCP or where COCP is contraindicated or poorly tolerated, our study failed to find any evidence.[2,3,21,60] The only review we retrieved focused on reporting the adverse events where flutamide was associated with hepatotoxicity in 2 case series.[49] One reason for the lack of findings in our study is likely related to our restriction publications after 2009. Two reviews by Swiglo et al and Brown et al involving 12 and 9 RCTs, respectively, concluded that anti-androgens are an effective treatment of hirsutism but the evidence is weak.[66,67] Both reviews included RCTs of small sample sizes (14 to 82 participants) and highlighted the need of more well-designed RCTs investigating the use of anti-androgens in women with PCOS.

Weight loss treatments in PCOS were explored by 3 reviews in our study. Two reviews investigating bariatric surgery were of low quality which impacts on the robustness of their results.[47,55] We report that in women with PCOS, bariatric surgery-induced weight loss, improved hirsutism, blood pressure, glycaemic and lipid profile. Orlistat improved anthropometric, endocrine and metabolic outcomes when compared to placebo but not metformin.[56] However, we acknowledge that there is encouraging evidence in the general population showing that bariatric surgery improves weight loss and metabolic outcomes such as glycaemic control, lipid profile and blood pressure.[68-70] Bariatric surgery was recommended as a second-line therapy to improve fertility outcomes in women with PCOS by the evidence-based Australian guideline and to be considered in morbidly obese women with PCOS by the European Society of Endocrinology.[2,4] Other societies concluded that better quality trials with long-term data are required before incorporating bariatric surgery into their recommendations for women with PCOS.[5,20] We found that statins, a family of

cholesterol-lowering drugs, are effective in improving the lipid profile.[36,42,44] Given the lack of definite benefits in treatment of hyperandrogenaemia or anovulation, paucity of data in reproductive-aged women and considering the disadvantage of type 2 diabetes development, statins are reserved for women with PCOS who meet the standard indications for lipid-lowering therapy.[5,7,22,71]

Our review included several nonconventional interventions that are not recommended by any guidelines or specialty society position statements. Although the evidence is not robust, there may be some benefits with the use of vitamin D and inositol. We found several moderate quality reviews assessing vitamin D demonstrated reductions in triglyceride and testosterone levels. One high-quality review by Pergialiotis et al reported beneficial effects of vitamin D in reducing DHEAS, insulin resistance and cholesterol.[57] Inositol is a nutritional supplement with proposed insulin-sensitizing characteristics.[5,43,48] As reported here in low to moderate quality reviews, they may have advantageous effects in nonreproductive-related endocrine and metabolic outcomes including improving biochemical hyperandrogenism and insulin resistance. No conclusion can be made regarding the use of acarbose, N-acetyl-cysteine, soy, folic acid, omega-3 or zinc in women with PCOS as the number of studies involved is limited.

Our study has several strengths. Being an overview of systematic reviews, we collated evidence of interventions for PCOS in a nonbiased and systematic manner. We reported our findings following the PRISMA guidelines utilizing rigorous methodology with duplication in all study tasks. However, we note study limitations including the diverse AMSTAR quality of the included reviews and the lack of clear interpretation of the quality of individual studies within the included systematic reviews. However, performing additional quality assessment of more than 350 included studies would be unfeasible. We also excluded publications before year 2009 as an attempt to filter out reviews that did not follow the PRISMA guidelines. As some interventions for PCOS have been used for decades, we may have excluded significant earlier studies, albeit potentially of lower quality. In our study, we found that only anti-androgens were affected by this limitation.[66,67]

Lastly, quality of future systematic reviews may be strengthened by addressing reporting conflict of interest of included studies, registering for an a priori protocol and provides a list of excluded studies. We also identified significant gaps in knowledge regarding the lack of data on psychological outcomes in treatment of women with PCOS. We retrieved included psychological outcomes as an outcome of interest only in 2 reviews[39,47] despite the widely known increased prevalence of depression, anxiety and lower quality of life in women with PCOS which future studies should address.[72]

5 | CONCLUSIONS

This overview of systematic reviews consolidates the evidence of treatment options for nonreproductive related outcomes in women with PCOS. We call attention to the lack of studies investigating psychological outcomes in any intervention in women with PCOS warranting further examination. Overall, we note evidence for metformin and COCP use in nonreproductive outcomes in PCOS, caution against thiazolidinediones and highlight that further research is warranted in a number of interventions such as statins, bariatric surgery, vitamin D or inositol to clarify outstanding clinical gaps.

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CONFLICT OF INTEREST

Nothing to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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