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Overview of systematic reviews of non-pharmacological interventions in women with polycystic ovary syndrome

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BACKGROUND: Polycystic ovary syndrome (PCOS) is a major contributor to subfertility, diabetes and cardiovascular disease in women. The role of non-pharmacological interventions to prevent these outcomes has been reported in many systematic reviews, but robust conclusions have not been made due to variations in the scope, quality and findings of these reviews.

OBJECTIVE AND RATIONALE: Our aim was to provide an overview of existing evidence on the effects of non-pharmacological interventions in women with PCOS on fertility and non-fertility outcomes by a review of existing systematic reviews.

SEARCH METHODS: We reviewed systematic reviews of randomized trials that have evaluated the effects of non-pharmacological interventions, such as lifestyle interventions, nutritional supplements or alternative medicine therapies in women with PCOS on fertility, endocrine, glycaemic and weight-related outcomes. We assessed the quality of systematic reviews with the AMSTAR tool, and reported the outcomes with regard to: fertility (live birth, clinical pregnancy, ovulation and menstrual cycle regularization); endocrine outcomes (Ferriman–Gallwey score, free androgen index, free testosterone and total testosterone levels); and glycaemic (fasting blood insulin, fasting blood glucose, homoeostatic model assessment) and weight-related (BMI) outcomes. We assessed the strength of evidence for significant outcomes as per the grading of recommendations assessment, development and evaluation (GRADE) system.

OUTCOMES: We found twelve eligible systematic reviews which included between three (143 women) and 27 randomized trials (2093 women). Four reviews assessed the effects of lifestyle interventions (diet, physical activity and/or behavioural interventions); four evaluated nutritional supplements (one each on n-acetylcysteine, omega-3 fatty acids, inositol and vitamin D); and four studied alternative medical therapies (Chinese herbal medicine and acupuncture). All of the included reviews were of high quality and scored between 8 and 11 with the AMSTAR tool (with a maximum score of 11).

Randomized evidence is lacking for live birth rate. *N*-acetylcysteine, inositol and the addition of alternative medicine to ovulation induction agents show preliminary potential to improve fertility (odds ratios (OR) for clinical pregnancy rate range from 1.99 to 4.83). Lifestyle interventions show benefits in improving hirsutism (mean difference (MD): −1.01 to −1.19). Lifestyle interventions (MD: −1.10 to −2.02), inositol (MD: −2.1) and acupuncture (MD: −1.90 to −3.43) all show some evidence of improvement in glycaemic outcomes and there is some evidence of reduced BMI with lifestyle interventions (MD: −0.15 to −1.12). All of these outcomes scored either low or very low quality of evidence on the GRADE score.

WIDER IMPLICATIONS: Lifestyle interventions in women with PCOS appear to improve glycaemic results, androgenic symptoms and anthropometric outcomes. The role of inositol and *N*-acetylcysteine in women with PCOS needs further evaluation. Large primary trials on all interventions are needed for an agreed set of core outcomes.

Key words: PCOS / lifestyle intervention / inositol / *n*-acetylcysteine / Chinese herbal medicine / acupuncture / non-pharmacological interventions

Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous condition characterized by irregular anovulatory periods, hyperandrogenism and/or polycystic appearance of ovaries (March *et al.*, 2010; Bozdag *et al.*, 2016). It affects up to one in six women of reproductive age, and is a major contributor to subfertility (Hart *et al.*, 2004). It also increases the long-term risks of diabetes, cardiovascular disease and endometrial cancer (Azziz *et al.*, 2005; Toulis *et al.*, 2009; Qin *et al.*, 2013), and has an adverse impact on the psychological wellbeing of women (Teede *et al.*, 2010; Cooney *et al.*, 2017).

Numerous interventions (pharmacological, non-pharmacological and surgical) have been evaluated in women with PCOS to target the reproductive, androgenic, metabolic, weight-related and psychological outcomes associated with the condition. The interventions target the various life-stages of a woman from adolescence, pre-pregnancy and pregnancy to pre-menopause. Currently, lifestyle interventions to optimize the weight of the women is the first-line of therapy in guidelines (Teede *et al.*, 2011). There is also an increasing interest in the effect of nutritional supplements and alternative therapies such as Chinese herbal medicine and acupuncture. However, primary studies on these interventions show varied and heterogeneous effects, making it difficult to draw conclusions as to overall treatment efficacy. Furthermore, systematic reviews that summarize the evidence vary in their scope, quality, size and reporting of outcomes, making interpretation of the evidence difficult for consumers, clinicians and policy makers.

We undertook an overview of systematic reviews to evaluate the quality of the systematic reviews of non-pharmacological interventions and summarize the evidence on their effects on fertility, endocrine, glycaemic and weight-related outcomes in women with PCOS.

Methods

Protocol and registration

We undertook an overview of systematic reviews in line with existing recommendations (Smith *et al.*, 2011) and in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher *et al.*, 2009) along with a prospective protocol registered in PROSPERO (CRD42016052649). Ethics application was not required.

Literature search

We searched MEDLINE (1950 to August 2017), EMBASE (1980 to August 2017), Cochrane Library and PROSPERO for any published or ongoing systematic reviews. We combined the Medical Subject Headings (MeSH) and text words for PCOS (PCOS; Polycystic ovary syndrome; polycystic ovar*; PCO) and 'systematic review'. The reference lists of all known primary and review articles were examined for relevant citations that were not captured by the electronic searches. There were no language restrictions.

Study selection

Two independent researchers (J.P. and D.C.) selected the relevant reviews in a two-step process. In the first step, we reviewed the abstracts of the identified reviews for potential eligibility. The full texts of these were then retrieved for detailed evaluation. Any disagreements about inclusion were resolved by consensus, or by consultation with a third reviewer (S.T.). We included systematic reviews if the target population was women with PCOS (as defined by the authors) who were undergoing treatment for fertility or non-fertility problems, if the interventions included non-pharmacological approaches such as lifestyle interventions, nutritional supplements or alternative medicine therapies, if they reported fertility or non-fertility outcomes, and if some degree of quality assessment of the included trials was undertaken. We only included reviews of randomized trials, and excluded narrative reviews and reviews on non-randomized controlled trials and observational cohort studies. If there were duplicate publications, we selected the most recent or complete version.

Assessment of quality of included reviews

Two independent reviewers (J.P. and D.C.) assessed the quality of the included reviews using the AMSTAR tool (Shea *et al.*, 2007) within eleven domains: the extent of literature search undertaken; description of study selection and inclusion criteria; comparability of included studies; assessment of publication bias and assessment of heterogeneity. Each domain was given a score of 1 if it clearly addressed the question, 0 if not addressed, and 'not applicable' if we were unable to robustly assess it due to inadequate reporting, with a total possible score of 11. The reviews were categorized as low quality if the total AMSTAR score was ≤3, moderate quality if the total AMSTAR score was between 4 and 7, and high quality if the total AMSTAR score was ≥8 (Silva *et al.*, 2015).

Data extraction and analysis

Two independent researchers (J.P. and D.C.) extracted information on the objectives of the reviews, their inclusion and exclusion criteria, year of publication, type of intervention and comparator, numbers of included trials and participants, and outcomes reported. We extracted summary estimates of intervention effects on fertility, endocrine, glycaemic and weight-related outcomes, and reported these as relative risk (RR), odds ratio (OR) or Peto odds ratio (pOR) for dichotomous outcomes and weighted mean difference (WMD), mean difference (MD) or standardized mean difference (SMD) for continuous outcomes, alongside the 95% CI, for each outcome. Out of all reported outcomes, we analysed in detail the most commonly reported outcomes in each subgroup: fertility (live birth, clinical pregnancy, ovulation and menstrual cycle regularization); endocrine outcomes (Ferriman–Gallwey score, free androgen index, free testosterone and total testosterone levels); and glycaemic (fasting blood insulin, fasting blood glucose, homoeostatic model assessment (HOMA-IR)) and weight-related (BMI) outcomes.

GRADE scoring

We assessed the strength of evidence for significant outcomes as per the GRADE recommendations (Guyatt *et al.*, 2008). For each significant outcome, we awarded 4 points to begin with as these were based on randomized trials and assessed the limitations that can reduce the quality of this evidence. We deducted points if the there were: study limitations (lack of allocation concealment, lack of blinding, large losses to follow-up, failure to adhere to an intention to treat analysis, stopping early for benefit or failure to report outcomes); sparse data on an outcome of interest (deduction of a quality point); inconsistent results (statistical heterogeneity between RCTs and conflicting results or evidence of dose response across or within studies); indirectness of evidence (differences between the population, intervention, comparator and outcomes of interest); or imprecision (in sample size, events and resulting confidence intervals or statistical significance). Based on these, we use four categories of evidence quality based on the overall GRADE scores for each comparison: high (at least 4 points overall), moderate (3 points), low (2 points) and very low (one or less). (http://www.us.bestpractice.bmj.com/best-practice/marketing/what-is-grade.html)

Results

Literature search

From 273 potential citations, we included 12 reviews (Fig. 1). The list of excluded studies is provided in Supplementary Table SI.

Characteristics of the included reviews

We included 12 reviews that reported three (143 women) (Sadeghi *et al.*, 2017) to 27 randomized trials (2093 women) (Jo *et al.*, 2017). Most of the trials from the included reviews were of small sample size and had moderate risk of bias. Six reviews defined PCOS using the Rotterdam criteria only (ESHRE/ASRM Consensus, 2004; Thakker *et al.*, 2015; Lim *et al.*, 2016; Qu *et al.*, 2016; Jo *et al.*, 2017; Pundir *et al.*, 2017; Sadeghi *et al.*, 2017); one used both Rotterdam and National Institute of Child Health and Human Development (NICHD) criteria, (Zawadski and Dunaif, 1992; Sadeghi *et al.*, 2017); one accepted any definition that was used (Moran *et al.*, 2011); and four did not specify the criteria (Domecq *et al.*, 2013; Haqq *et al.*, 2014, 2015; Fang *et al.*, 2017).

Four reviews assessed the effects of lifestyle interventions (diet, physical activity and/or behavioural interventions) (Moran *et al.*, 2011; Domecq *et al.*, 2013; Haqq *et al.*, 2014, 2015), four assessed nutritional supplements with one each on *n*-acetylcysteine, omega-3 fatty acids, inositol and vitamin D (Thakker *et al.*, 2015; Fang *et al.*, 2017; Pundir *et al.*, 2017; Sadeghi *et al.*, 2017), and four evaluated alternative medical therapies (Chinese herbal medicine and

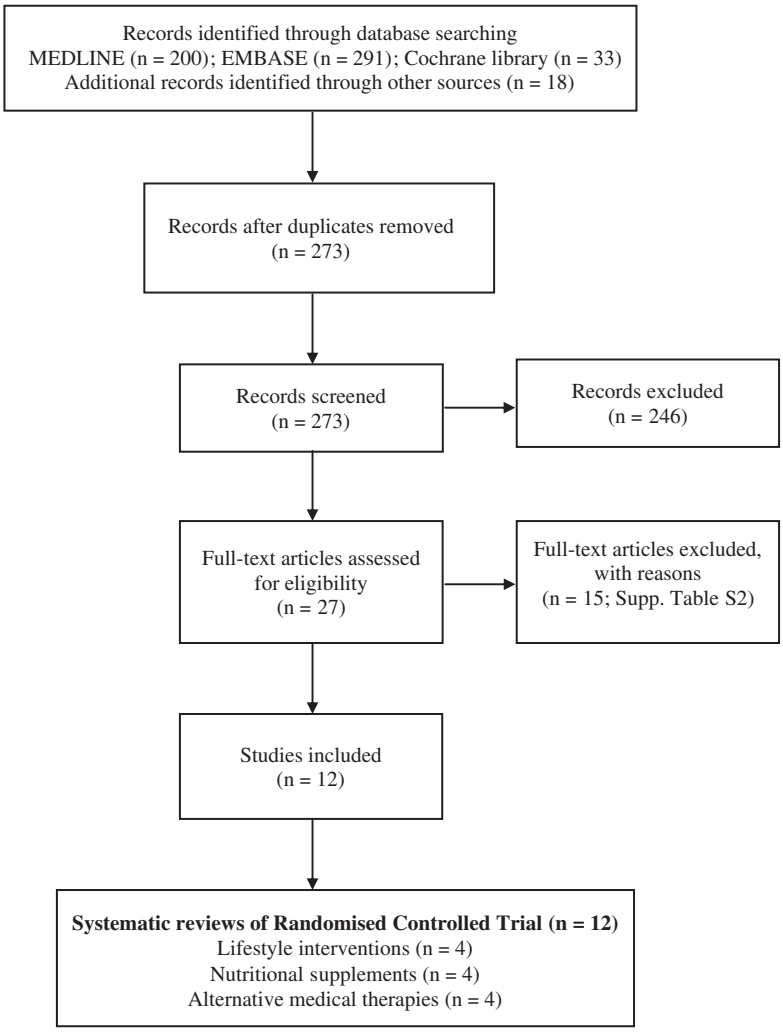

Figure 1 Study selection process for the overview of systematic reviews of non-pharmacological interventions in women with polycystic ovary syndrome.

acupuncture) (Lim *et al.*, 2016; Qu *et al.*, 2016; Zhou *et al.*, 2016; Jo *et al.*, 2017).

Seven reviews reported on both fertility and non-fertility outcomes (Moran *et al.*, 2011; Domecq *et al.*, 2013; Thakker *et al.*, 2015; Qu *et al.*, 2016; Fang *et al.*, 2017; Jo *et al.*, 2017; Pundir *et al.*, 2017), one reported only on endocrine outcomes (Haqq *et al.*, 2015), two reported only on glycaemic outcomes (Haqq *et al.*, 2014; Sadeghi *et al.*, 2017) and two reported only on fertility outcomes (Lim *et al.*, 2016; Zhou *et al.*, 2016) (Table I).

Quality of the included reviews

The quality of all included reviews was high (Table II). Three reviews had minimal bias in all 11 domains of the AMSTAR tool (Zhou *et al.*, 2016; Jo *et al.*, 2017; Pundir *et al.*, 2017), four had low bias in 10 of the 11 domains (Moran *et al.*, 2011; Haqq *et al.*, 2014; Qu *et al.*, 2016; Sadeghi *et al.*, 2017), three had low bias in 9 out of 11 domains (Domecq *et al.*, 2013; Haqq *et al.*, 2015; Lim *et al.*, 2016) and two had low risk of bias in 8 out of 11 domains (Thakker *et al.*, 2015; Fang *et al.*, 2017). All the reviews clearly pre-specified the question, undertook a comprehensive literature search with study selection and data extraction in duplicate, clearly pre-specified the inclusion and exclusion criteria, provided details on the characteristics of the included studies, assessed the quality of the included studies, and reported any conflicts of interest. All except one review (Fang *et al.*, 2017) used appropriate methods to combine the findings of studies and used the data appropriately in formulating conclusions. While half of all reviews (6/12) had no language barrier in their search, two restricted their search to publications in English, and the details were unclear in four reviews. Ten reviews (83%, 10/12) planned to assess for publication bias, but 60% of these (6/10) could not perform the analysis due to the small number of included studies. All included reviews were of high quality on the AMSTAR tool with score range of 8–11 (max score 11) (Table II).

Table I Characteristics of included systematic reviews in the overview of systematic reviews of non-pharmacological interventions in women with polycystic ovary syndrome.

Study	Databases searched	*N*/*n*	Inclusion criteria	Exclusion criteria	Intervention	Control	Outcomes	Risk of bias of included RCTs
Lifestyle interventions								
Moran *et al.* (2011)	Cochrane MDSG Trials Register; The Cochrane Library, Medline, Embase, PsycINFO, AMED; mRCTs, National Institute of Health Clinical Trials register	*N* = 6 *n* = 164	PCOS women of reproductive age. Studies using any definition of PCOS or overweight; study duration lengths over two weeks	Conditions with symptoms similar to PCOS; CAH, Cushing's syndrome, hyperprolactinaemia, thyroid disease, androgen-secreting tumours	Lifestyle intervention—structured dietary, exercise and/or behavioural intervention	Minimal treatment—either no treatment or standard unstructured minimal dietary, exercise or behavioural advice	CPR, LBR, miscarriage, MC, ovulation Total testosterone, free testosterone; FG score; SHBG. BMI, WC, WHR,weight, OGTT, glucose, lipid profile, FBG, FBI, OGTT insulin; QOL, satisfaction.	Cochrane risk of bias summary Overall the quality of the evidence was considered low to moderate with overall risk of bias moderate to high.
Domecq *et al.* (2013)	Medline, Embase, Cochrane Library, Web of Science, Scopus, PsycINFO, CINAHL	*N* = 10 *n* = 610	Woman with PCOS	–	Lifestyle intervention—hypocaloric diet; physical exercise; combined	Metformin or minimal intervention	CPR modified FGS; FBG, FBI.	The overall risk of bias was moderate to high.
Haqq *et al.* (2014)	PubMed; CINAHL Cochrane Registry	*N* = 7 *n* = 206	Women with PCOS	Animal studies, review papers and non-RCTs; studies that did not have desired outcomes	Exercise alone or lifestyle (exercise plus diet)	Usual care—sedentary control, placebo, diet only or medication	LH, FSH, SHBG, total testosterone, free testosterone, FAI, LH/FSH; E2; FGS androstenedione.	Modified PEDro scale (out of 9)—median score was 7, three studies scoring 7, two studies scoring 8 and one study scoring 9.
Haqq *et al.* (2015)	PubMed; CINAHL Cochrane Registry	*N* = 12 *n* = 668	Women with PCOS	Animal studies, review papers and non-RCTs; studies that did not have desired outcomes	Exercise alone or lifestyle (exercise plus diet) groups	Usual care— sedentary control, placebo, diet only or metformin	BMI, body weight, WC, % body fat, WHR; insulin, glucose, HOMA-IR; lipids, cardio -respiratory fitness.	Modified PEDro scale (out of 9)—median score was 7, with four studies scoring 6, four studies scoring 7, three studies scoring 8 and one study scoring 9.
Nutritional supplements								
Thakker *et al.* (2015)	Medline, Embase, Cochrane; ISI Proceedings Register and Meta-Register for RCTs	*N* = 8 *n* = 910	PCOS based on Rotterdam criteria	–	NAC	Placebo or metformin	CPR, LBR, miscarriage, MC, ovulation BMI, testosterone level, FBG, FBI, G/I ratio, and HOMA-IR	Cochrane risk of bias summary The overall risk of bias was moderate to high.
Sadeghi *et al.* (2017)	Medline, Embase, Web of science	*N* = 3 *n* = 143	PCOS based on Rotterdam + NICHD	Other diseases— DM, Cushing's syndrome, hyperthyroidism, metabolic syndrome, diagnosis of PCOS was not strict; articles not in English	Omega-3	Placebo— olive oil, soybean oil or other placebo	Insulin Resistance—HOMA IR	The quality of studies were assessed using Jadad Scale, and one out of three studies scored <3. The overall risk of bias was low to moderate.
Fang *et al.* (2017)	Medline; EMBASE and PubMed Central	*N* = 9 *n* = 502	PCOS adults (aged > 18 years)	Cross-sectional, review articles, and animal studies	Vitamin D	Placebo or metformin	Number of dominant follicles, MC Serum vitamin D, PTH, serum TC, TG, LDL, VLDL, HDL, FBI, FBG, QUICK and HOMA-IR.	Cochrane risk of bias summary The overall risk of bias was considered low to moderate.
Pundir *et al.* (2017)	Cochrane Library Medline; Embase; ISI-Web of Science	*N* = 10 *n* = 601	Rotterdam criteria	Non—RCTs	Inositols—MI, DCI	Placebo, clomiphene and/or metformin	Ovulation, CPR, LBR FBI, FBG, GI ratio, HOMA- IR, SHBG total androgens, total testosterone, free testosterone, DHEA.	Cochrane risk of bias summary The overall risk of bias was considered low to moderate.

Continued

Table I *Continued*

Study	Databases searched	*N*/*n*	Inclusion criteria	Exclusion criteria	Intervention	Control	Outcomes	Risk of bias of included RCTs
Alternative medical therapies								
Qu *et al.* (2016)	Medline; EMBASE; CENTRAL; AMED; CNKI; Wanfang DATA; Chongqing VIP; Korea Med; OASIS; KMBASE; KISS; Society Database of KISTI; NDSL; J-STAGE; Igaku Chuo Zasshi	*N* = 9 *n* = 531	PCOS Rotterdam criteria	–	Acupuncture alone or therapies with acupuncture added in to the treatment	No/sham or therapies without acupuncture	Recovery of MC BMI, FBI, FBG, LH, FSH, LH/FSH ratio, testosterone	The overall risk of bias was moderate to high.
Zhou *et al.* (2016)	Medline; EMBASE, Cochrane MDSG trials register, China Academic Journal Electronic full text Database in China National Knowledge Infrastructure, Wanfang Database, Index to Chinese Periodical Literature; ISRCTN; mRCT	*N* = 5 *n* = 414	PCOS Rotterdam criteria	–	Chinese herbal medicine alone, or combined with another treatment	Placebo, no treatment, Western medicine, exercise plus diet control, laparoscopic surgery, another type of CHM, with or without co-medications	LBR, CPR, ovulation Adverse events	The quality of the evidence for most comparisons was very low; and overall risk of bias was moderate to high.
Lim *et al.* (2016)	The CGF Specialized Register, Medline; AMED EMBASE; PsycINFO; CNKI, including CJFD, CDMD; VIP; Chinese important conference dissertations full-text database, Wanfang database	*N* = 5 *n* = 413	PCOS Rotterdam criteria and subfertility wishing to conceive (18–44 years)	–	Acupuncture, including body needling and electro-acupuncture	Placebo, no intervention, lifestyle intervention and conventional treatment of PCOS (clomiphene citrate, LOD), Sham acupuncture	LBR, CPR, ovulation Adverse events	Small sample sizes; 4 of the studies were at high risk of bias in at least one domain. The evidence was low or very low quality, the main limitations being failure to report important clinical outcomes, and very serious imprecision.
Jo *et al.* (2017)	The Cochrane MDSG Specialized Register; Medline; EMBASE PsycINFO, AMED CNKI including the CJFD, CBM, VIP database for Chinese Technical Periodicals, China's important Conference Papers Database, China dissertation database; Trial registers.	*N* = 27 *n* = 2093	Women of reproductive age (18–44 years) with PCOS (Rotterdam) and oligo/anovulation	Other causes of hyperandrogenism (androgen-secreting tumour, hyperprolactinaemia, thyroid disease, Cushing's syndrome and CAH).	Acupuncture	Sham acupuncture, medication, or no treatment	Ovulation, MC, CPR LH, LH/FSH ratio, testosterone, FBI, adverse events	The levels of evidence were found to be very low to low. Most of the studies were classified as having either an unclear or a high risk of selection, performance, and attrition bias.(Risk of bias assessed using the Cochrane 'Risk of bias' tool)

N = no. of RCTs; *n* = No. of Participants.

AMH = Anti-müllerian hormone; BBT = Basal body temperature; CHM = Chinese herbal medicine; CAH = Congenital adrenal hyperplasia; CPR = Clinical pregnancy rate; CRP = C-reactive protein; DCI = D-chiro inositol; DHEA = dehydroepiandrosterone; EA = electro-acupuncture; FBG = fasting blood glucose; FBI = fasting blood insulin; FGS = Ferriman–Gallwey score; fT = free testosterone; G/I ratio = glucose/insulin ratio; GT = gonadotropin; HCL-C = high density lipoprotein cholesterol; HOMA-IR = homoeostasis model assessment for insulin resistance; LDL-C = low-density lipoprotein cholesterol; MI = myo-inositol; NAC = *N*-acetylcysteine; LBR = live birth rate; LOD = laparoscopic ovarian drilling; LSI = lifestyle intervention; LSM = lifestyle modification; MC = menstrual cycles; E2 = oestradiol; OGTT = oral glucose tolerance test; OR = ovulation rate; P = progesterone; PRL = prolactin; QOL = quality of life; RCTs = randomized controlled trials; SHBG = sex hormone-binding globulin; TA = total androgens; TC = total cholesterol; TT = total testosterone; USS = ultrasound scan; VLDL-C = very low-density lipoprotein cholesterol; TG = triglycerides; WC = waist circumference; WHR= waist-to-hip ratio.

Table II AMSTAR tool of quality assessment of the included systematic reviews in the overview of systematic reviews of non-pharmacological interventions in women with polycystic ovary syndrome.

Study	Was an 'a priori' design provided?	Was there duplicate study selection and data extraction?	Was a comprehensive literature search performed?	Was the status of publication used as an inclusion criterion?	Was a list of studies (included and excluded) provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies assessed and documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	Was the likelihood of publication bias assessed?	Was the conflict of interest included?	Overall Score	Quality
Moran *et al.* (2011)	+	+	+	+	+	+	+	+	+	NA	+	10	High
Domecq *et al.* (2013)	+	+	+	?	+	+	+	+	+	NA	+	9	High
Haqq *et al.* (2014)	+	+	+	?	+	+	+	+	+	+	+	10	High
Haqq *et al.* (2015)	+	+	+	?	+	+	+	+	+	+	+	10	High
Zhou *et al.* (2016)	+	+	+	+	+	+	+	+	+	+	+	11	High
Lim *et al.* (2016)	+	+	+	–	+	+	+	+	+	NA	+	9	High
Qu *et al.* (2016)	+	+	+	+	+	+	+	+	+	–	+	10	High
Jo *et al.* (2017)	+	+	+	+	+	+	+	+	+	+	+	11	High
Thakker *et al.* (2015)	+	+	+	?	+	+	+	–	+	NA	+	8	High
Sadeghi *et al.* (2017)	+	+	+	+	+	+	+	+	+	?	+	10	High
Fang *et al.* (2017)	+	+	+	–	+	+	+	–	–	+	+	8	High
Pundir *et al.* (2017)	+	+	+	+	+	+	+	+	+	+	+	11	High

KEY: Yes +; No, –; Can't answer, ?; not applicable, NA.

Effects of interventions on fertility outcomes

Live birth rate

Only one review reported on live birth rate based on one pilot RCT (Nasr, 2010), where following unilateral laparoscopic ovarian drilling in clomiphene citrate-resistant women with PCOS, administration of *N*-acetyl-cysteine versus placebo improved live birth rate (pOR = 3.00; 95% CI: 1.05, 8.60) (Thakker *et al.*, 2015) (Supplementary Table SII and Table III). There is very low-grade evidence for use of *N*-acetyl-cysteine supplementation in women with clomiphene resistant PCOS following laparoscopic ovarian drilling to improve live birth rate.

Clinical pregnancy rate

Six reviews reported the effects of interventions on clinical pregnancy rate (Domecq *et al.*, 2013; Thakker *et al.*, 2015; Lim *et al.*, 2016; Zhou *et al.*, 2016; Jo *et al.*, 2017; Pundir *et al.*, 2017). There was a 2-fold increase with *N*-acetyl-cysteine supplementation versus placebo in any women with PCOS (pOR = 2.42; 95% CI: 1.04, 5.65), and a 5-fold increase in women with clomiphene citrate resistant PCOS (pOR = 4.83; 95% CI: 2.30, 10.13) (Thakker *et al.*, 2015). A combination of Chinese herbal medicine with clomiphene citrate versus clomiphene citrate alone (OR = 2.62; 95% CI 1.65, 4.14) (Zhou *et al.*, 2016) or addition of acupuncture to ovulation induction agents versus ovulation induction agents alone (MD: 1.99; 95% CI: 1.38, 2.87) (Jo *et al.*, 2017) significantly improved clinical pregnancy rates (Supplementary Table SII and Table III). There is: very low-grade evidence to suggest for that in women with PCOS and women with clomiphene resistant PCOS, *N*-acetyl-cysteine supplementation may improve clinical pregnancy rates compared with placebo; low-grade evidence to suggest that addition of Chinese herbal medicine to clomiphene improves clinical pregnancy rates when compared with clomiphene alone; and very low-grade evidence to suggest that addition of acupuncture to medical therapies for ovulation induction in women with PCOS improves clinical pregnancy rates when compared with ovulation induction agents alone.

Ovulation rate

Seven reviews reported on ovulation rate (Moran *et al.*, 2011; Thakker *et al.*, 2015; Lim *et al.*, 2016; Zhou *et al.*, 2016; Fang *et al.*, 2017; Jo *et al.*, 2017; Pundir *et al.*, 2017). Supplementation with *N*-acetyl-cysteine versus placebo significantly increased the odds of ovulation in women with PCOS (pOR 3.13; 95% CI: 1.54, 6.36), and in those with clomiphene citrate resistant PCOS (pOR = 8.40; 95% CI: 4.50, 15.67) (Thakker *et al.*, 2015). Ovulation rates were doubled with inositol supplementation versus placebo (RR = 2.3; 95% CI 1.1, 4.7) (Pundir *et al.*, 2017). Ovulation rates were slightly higher for acupuncture versus relaxation or no treatment (MD: 0.35; 95% CI: 0.14, 0.56) (Lim *et al.*, 2016) (Supplementary Table SII and Table III). There is low-grade evidence to suggest that supplementation of *N*-acetyl-cysteine or inositols improves ovulation rate when compared with placebo; very low-grade evidence to suggest that in PCOS women resistant to clomiphene, *N*-acetyl-cysteine supplementation may improve ovulation rate compared with placebo; and very low-grade evidence to suggest that acupuncture improves ovulation rate compared with no treatment.

Menstrual cycle frequency

Seven reviews reported on menstrual cycle frequency (Moran *et al.*, 2011; Thakker *et al.*, 2015; Lim *et al.*, 2016; Qu *et al.*, 2016; Fang *et al.*, 2017; Jo *et al.*, 2017; Pundir *et al.*, 2017). The rates of menstrual cycle frequency was 6-fold for inositol versus placebo (RR = 6.8; 95% CI: 2.8, 16.6) (Pundir *et al.*, 2017). The menstrual cycle frequencies were also improved with acupuncture methods of low-frequency electro-acupuncture versus no intervention (MD: 0.37; 95% CI: 0.21, 0.53) (Lim *et al.*, 2016) acupuncture versus no treatment (MD: 0.50; 95% CI: 0.32, 0.68), acupuncture plus medication versus sham acupuncture plus medication (MD: 0.14; 95% CI: 0.05, 0.23) (Jo *et al.*, 2017), and acupuncture versus sham acupuncture (OR = 0.20; 95% CI: 0.09, 0.41) (Qu *et al.*, 2016) (Supplementary Table SII and Table III). There is: low-grade evidence to suggest that in women with PCOS, supplementation of inositols improve menstrual cycles when compared with placebo; and very low-grade evidence to suggest that acupuncture improves menstrual cycles when compared with no treatment, exercise or metformin.

Effects of Interventions on Endocrine Outcomes

Clinical parameters

Lifestyle interventions including exercise alone significantly improved Ferriman–Gallwey scores of hirsutism (MD: −1.19; 95% CI: −2.35, −0.03) (Moran *et al.*, 2011); (MD: −1.01; 95% CI: −1.54, −0.48) (Haqq *et al.*, 2014); (MD: −1.13; 95% CI: −1.88, −0.38) (Haqq *et al.*, 2014) (Supplementary Table SIII and Table III). There is very low-grade evidence to suggest that in women with PCOS, lifestyle interventions (diet±exercise) improve Ferriman–Gallwey score of hirsutism when compared with minimal or no treatment.

Biochemical parameters

Lifestyle interventions significantly improved free androgen index compared with usual care (MD: −1.64; 95% CI: −2.94, −0.35) (Haqq *et al.*, 2014). Of the four reviews that reported on total testosterone levels (Moran *et al.*, 2011; Haqq *et al.*, 2014; Thakker *et al.*, 2015; Pundir *et al.*, 2017), significant reductions were observed with lifestyle intervention versus minimal treatment (two reviews, MD: −0.27; 95% CI: −0.46, −0.09; MD: −0.13; 95% CI: −0.22, −0.03) (Moran *et al.*, 2011; Haqq *et al.*, 2014); exercise alone versus usual care (one review, MD: −0.16; 95% CI: −0.29, −0.04) (Haqq *et al.*, 2014); and inositols versus placebo (one review, SMD: −3.3; 95% CI: −5.1, −1.5) (Pundir *et al.*, 2017) (Supplementary Table SIII and Table III). There is: very low-grade evidence that lifestyle interventions (diet with or without exercise) improve free androgen index when compared with minimal or no treatment; very low-grade evidence that lifestyle interventions (diet with or without exercise) improve total testosterone levels when compared with minimal or no treatment; and low-grade evidence that inositol supplementation improves total testosterone levels when compared with placebo.

Table III GRADE quality of evidence score for significant outcomes reported in the systematic reviews included in the Overview of systematic reviews of non-pharmacological interventions in women with polycystic ovary syndrome.

Outcome	Systematic review	Intervention	*N*/*n*	Effect (95% CI)	GRADE SR of RCTS = +4					GRADE quality of evidence
					Quality	Consistency	Directness	Effect size	Total score	
Fertility outcomes										
Live birth rate	Thakker *et al.* (2015)	*N*-acetylcysteine vs. placebo in CC resistant PCOS	1 (60)	pOR 3.00(1.05, 8.60)*	−1	−1	−2	+1	1	⊕OOO Very low quality
Clinical pregnancy rate	Thakker *et al.* (2015)	*N*-acetylcysteine vs. placebo	1 (167)	pOR 2.42 (1.04, 5.65)*	−3	−1	0	+1	1	⊕OOO Very low quality
		N-acetylcysteine vs. placebo in CC resistant PCOS	2 (210)	pOR 4.83 (2.30, 10.13)*	−3	0	−1	+1	1	⊕OOO Very low quality
	Zhou *et al.* (2016)	Chinese herbal medicine + clomiphene vs. clomiphene	3 (300)	pOR 2.62 (1.65, 4.14)*	−2	0	−1	+1	2	⊕⊕OO Low quality
	Jo *et al.* (2017)	Acupuncture with medication vs. medication alone	6 (376)	MD 1.99 (1.38, 2.87)*	−2	0	−1	0	1	⊕OOO Very low quality
Ovulation rate	Thakker *et al.* (2015)	*N*-acetylcysteine vs. placebo	2 (200)	pOR 3.13 (1.54, 6.36)*	−3	0	0	+1	2	⊕⊕OO Low quality
		N-acetylcysteine vs. placebo in CC resistant PCOS	2 (210)	pOR 8.40 (4.50, 15.67)*	−1	−1	−2	+1	1	⊕OOO Very low quality
	Fang *et al.* (2017)	Vitamin D vs. placebo	4 (251)	OR 2.34 (1.39, 3.92)*	–	–	–	–	–	Analysis flawed—difficult to interpret
	Pundir *et al.* (2017)	Inositol vs. placebo	4 (128)	RR 2.3 (1.1, 4.7)*	−2	0	−1	+1	2	⊕⊕OO Low quality
	Lim *et al.* (2016)	Acupuncture vs. lifestyle/no treatment	1 (28)	MD 0.35 (0.14, 0.56)*	−3	−1	0	+1	1	⊕OOO Very low quality
	Jo *et al.* (2017)	Acupuncture vs. no treatment	1 (28)	MD 0.35 (0.14, 0.56)*	−3	−1	0	+1	1	⊕OOO Very low quality
Menstrual cycle	Fang *et al.* (2017)	Vitamin D + metformin vs. metformin	3 (180)	OR 1.85 (1.01, 3.39)*	–	–	–	–	–	Analysis flawed—difficult to interpret
	Pundir *et al.* (2017)	Inositol vs. placebo	2 (109)	RR 6.8 (2.8, 16.6)*	−3	0	0	+1	2	⊕⊕OO Low quality
	Lim *et al.* (2016)	Low-frequency electro-acupuncture vs. no intervention	1 (31)	MD 0.37 (0.21, 0.53)*	−3	−1	0	+1	1	⊕OOO Very low quality
	Qu *et al.* (2016)	Acupuncture vs. no/sham acupuncture or therapies with acupuncture added in to the treatment	5 (247)	OR 0.20 (0.09, 0.41)*	−2	0	−1	+1	1	⊕OOO Very low quality Too many co-interventions combined together
	Jo *et al.* (2017)	Acupuncture vs. exercise	1 (59)	MD 0.50 (0.32, 0.68)*	−3	−1	0	+1	1	⊕OOO Very low quality
		Acupuncture vs. metformin	1 (86)	MD 0.14 (0.05, 0.23)*	−2	−1	0	0	1	⊕OOO Very low quality
Androgenic outcomes										
Ferriman–Gallwey score	Moran *et al.* (2011)	Lifestyle vs. minimal treatment	4 (132)	MD −1.19 (−2.35, −0.03)*	−3	0	0	0	1	⊕OOO Very low quality
	Haqq *et al.* (2014)	Lifestyle vs. usual care	4 (154)	MD −1.01 (−1.54, −0.48)*	−3	0	0	0	1	⊕OOO Very low quality
		Exercise-alone vs. usual care	3 (136)	MD −1.13 (−1.88, −0.38)*	−3	0	0	0	1	⊕OOO Very low quality

Continued

Table III *Continued*

Outcome	Systematic review	Intervention	*N*/*n*	Effect (95% CI)	GRADE SR of RCTS = +4					GRADE quality of evidence
					Quality	Consistency	Directness	Effect size	Total score	
Free androgen index	Haqq *et al.* (2014)	Lifestyle vs. usual care	4 (132)	MD −1.64 (−2.94,−0.35)*	−3	0	0	0	1	⊕OOO Very low quality
Total testosterone	Moran *et al.* (2011)	Lifestyle vs. minimal treatment	5 (144)	MD −0.27 (−0.46, −0.09)*	−3	0	0	0	1	⊕OOO Very low quality
	Haqq *et al.* (2014)	Lifestyle vs. usual care	6 (195)	MD −0.13 (−0.22, −0.03)*	−3	−1	0	+1	1	⊕OOO Very low quality
		Exercise-alone vs. usual care	2 (125)	MD −0.16 (−0.29, −0.04)*	−3	0	0	+1	2	⊕⊕OO Low quality
	Pundir *et al.* (2017)	Inositol vs. placebo	6 (202)	SMD −3.3 (−5.1, −1.5)*	−2	−1	0	+1	2	⊕⊕OO Low quality
Glycaemic and anthropometric outcomes										
Fasting blood insulin	Moran *et al.* (2011)	Lifestyle vs. minimal treatment	5 (144)	MD −2.02 (−3.28, −0.77)*	−3	0	0	+1	2	⊕⊕OO Low quality
	Domecq *et al.* (2013)	Lifestyle vs. minimal treatment	5 (195)	WMD −2.1 (−3.3, −1.0)*	−3	0	0	+1	2	⊕⊕OO Low quality
	Haqq *et al.* (2015)	Lifestyle vs. minimal treatment	7 (199)	MD −1.10 (−2.05, −0.16)*	−2	−1	0	0	1	⊕OOO Very low quality
	Pundir *et al.* (2017)	Inositol vs. placebo	6 (202)	SMD −2.1 (−3.2, −0.9)*	−1	−1	−1	+1	2	⊕⊕OO Low quality
	Jo *et al.* (2017)	Acupuncture vs. sham acupuncture	1 (40)	MD −3.43 (−6.25, −0.61)*	−3	−1	0	+1	1	⊕OOO Very low quality
		Acupuncture + medication vs. sham acupuncture + medication	1 (104)	MD −1.90 (−2.46, −1.34)*	−3	−1	0	0	0	⊕OOO Very low quality
		Acupuncture + medication vs. medication alone	5 (531)	MD −2.50 (−2.77, −2.24)*	−2	−1	−1	+1	1	⊕OOO Very low quality
Fasting blood glucose	Domecq *et al.* (2013)	Lifestyle vs. minimal treatment	6 (208)	WMD-2.3 (−4.5, −0.1)*	−3	0	0	+1	2	⊕⊕OO Low quality
	Pundir *et al.* (2017)	Inositol vs. placebo	4 (132)	SMD −1.0 (−1.7, −0.2)*	−2	−1	0	0	1	⊕OOO Very low quality
HOMA-IR	Pundir *et al.* (2017)	Inositol vs. placebo	3 (96)	SMD −1.8 (−2.6, −1.0)*	−2	−1	0	0	1	⊕OOO Very low quality
Body mass index	Haqq *et al.* (2015)	Lifestyle vs. minimal treatment	8 (232)	MD −1.12 (−0.22, −0.03)*	−2	−1	0	0	1	⊕OOO Very low quality
		Exercise only vs. minimal treatment	3 (136)	MD −0.15 (−0.24,−0.05)*	−3	−1	0	0	0	⊕OOO Very low quality

Effects of Interventions on Glycaemic and Anthropometric Outcomes

Fasting blood insulin

Of the nine reviews that reported on fasting blood insulin levels (Moran *et al.*, 2011; Domecq *et al.*, 2013; Haqq *et al.*, 2015; Thakker *et al.*, 2015; Qu *et al.*, 2016; Fang *et al.*, 2017; Jo *et al.*, 2017; Pundir *et al.*, 2017; Sadeghi *et al.*, 2017), levels were significantly reduced with lifestyle interventions versus minimal treatment (three reviews; MD: −2.02; 95% CI: −3.28, −0.77; WMD: −2.1; 95% CI: −3.3, −1.0; MD: −1.10; 95% CI: −2.05, −0.16) (Moran *et al.*, 2011; Domecq *et al.*, 2013; Haqq *et al.*, 2015) and with inositols versus placebo (SMD: −2.1; 95% CI: −3.2, −0.9) (Pundir *et al.*, 2017), acupuncture versus sham acupuncture, acupuncture plus medication versus sham acupuncture plus medication, and with acupuncture plus medication versus medication alone (MD: −3.43; 95% CI: −6.25, −0.61; MD: −1.90; 95% CI: −2.46, −1.34; MD: −2.50; 95% CI: −2.77, −2.24) (Jo *et al.*, 2017) (Supplementary Table SIV and Table III). There is: low-grade evidence that lifestyle interventions (diet with or without exercise) improve fasting insulin levels when compared with minimal or no treatment; low-grade evidence that inositol supplementation improves fasting insulin levels when compared with placebo; and very low-grade evidence that acupuncture improves fasting insulin levels when compared with sham acupuncture or when acupuncture is added to medication compared with medication alone.

Fasting blood glucose

Fasting blood glucose levels were reported by seven reviews (Moran *et al.*, 2011; Domecq *et al.*, 2013; Haqq *et al.*, 2015; Thakker *et al.*, 2015; Qu *et al.*, 2016; Fang *et al.*, 2017; Pundir *et al.*, 2017) and were significantly lowered with lifestyle intervention (one review, WMD: −2.3; 95% CI: −4.5, −0.1) (Domecq *et al.*, 2013) and inositols versus placebo (one review, SMD: −1.0; 95% CI: −1.7, −0.2) (Pundir *et al.*, 2017) (Supplementary Table SIV and Table III). There is: low-grade evidence lifestyle interventions (diet with or without exercise) improve fasting glucose levels when compared with minimal treatment; and very low-grade evidence that inositol supplementation improves fasting glucose levels when compared with placebo.

Homoeostatic model assessment—insulin resistance

Of the four reviews which reported on HOMA-IR levels (Haqq *et al.*, 2015; Fang *et al.*, 2017; Pundir *et al.*, 2017; Sadeghi *et al.*, 2017), only one review which compared inositols versus placebo reported a significant improvement (SMD: −1.8; 95% CI: −2.6, −1.0) (Pundir *et al.*, 2017) (Supplementary Table SIV and Table III). There is very low-grade evidence to suggest that in women with PCOS, inositol supplementation improves HOMA-IR levels when compared with placebo.

Body mass index

Two reviews reported on BMI (Moran *et al.*, 2006; Haqq *et al.*, 2015). One review reported a significant reduction in BMI with lifestyle intervention as well as with exercise alone versus minimal treatment (MD: −1.12; 95% CI: −0.22, −0.03); (MD: −0.15; 95% CI: −0.24, −0.05) (Haqq *et al.*, 2015) (Supplementary Table SIV and Table III). There is very low-grade evidence to suggest that lifestyle interventions improve BMI when compared with minimal or no treatment.

Discussion

Main findings

Primary evidence is lacking for the most important fertility outcome of live birth rate in women with PCOS, and is reflected in published reviews. *N*-acetyl-cysteine, inositol and the addition of alternative medicine to ovulation induction agents show preliminary potential to improve fertility. Lifestyle interventions reduce hirsutism. Inositol, lifestyle interventions, and acupuncture may improve in glycaemic outcomes, and there is some evidence of reduced BMI with lifestyle interventions. The strength of evidence is low to very low for all outcomes.

Strengths and weaknesses of the review

We undertook a comprehensive overview on non-pharmacological interventions in women with PCOS undergoing treatment for fertility or non-fertility reasons, with no language restrictions. We only included systematic reviews of randomized trials and excluded narrative reviews and reviews with non-randomized controlled trials and observational cohort studies to reduce the risk of bias. We assessed the quality of the reviews against the 11 domains of AMSTAR tool of assessment of systematic reviews, which reflected that the majority of the reviews included in this review were of high quality. We assessed the significant outcomes by the GRADE score to determine the information on the strength of evidence.

Most of these systematic reviews acknowledged the poor quality of the included primary trials, which is also reflected in our GRADE scores. There was high heterogeneity between the included systematic reviews in the definition of outcomes such as pregnancy, intervention type and combination, which limited the ability to interpret overall pooled estimates. For example, even though ovulation rate and improvement in menstrual cycle regularity were reported in many studies, reporting was inconsistent and they did not follow the strict criteria as suggested by the Cochrane review of Moran, Hutchison *et al.* (2011), i.e. ovulation defined as number of ovulatory menstrual cycles confirmed by ultrasound scan or blood progesterone levels and menstrual cycle regularity defined as initiation of menses or significant shortening of cycle length.

Comparison to current recommendations

From our extensive overview of systematic reviews, there is no evidence of any improvement in fertility outcomes, including live birth rates, with lifestyle interventions. Previous reviews have commented on a lack of evidence based on well-designed studies to support that weight loss prior to conception improves live birth rate in women with PCOS (Moran *et al.*, 2006). Despite the lack of such evidence, ESHRE/ASRM and other international bodies recommend weight loss as first-line therapy in obese women with PCOS seeking

pregnancy, even though they acknowledge the paucity of evidence (Balen et al., 2016). These recommendations are based on extrapolation from the benefits of weight loss on ovulation rates from observational studies in women with PCOS (Kiddy et al., 1992; Moran et al., 2006) and from reported association between the obesity and poor reproductive outcomes (Boots and Stephenson, 2011). However, we did not identify any reported increase in fertility outcomes with lifestyle interventions, and their role as primary treatment for fertility in women with PCOS is therefore not clear. Furthermore, a recent randomized trial which assessed the benefit of preconception lifestyle modification to promote weight loss followed by ovulation induction with clomiphene citrate in women with PCOS reported a significant weight loss and improvement in ovulation rates, but showed no significant difference in live birth rates (Legro et al., 2015). There is a need for further large lifestyle intervention trials in women with PCOS to assess the effects on fertility and non-fertility outcomes.

There is low or very low quality evidence to suggest that nutritional supplementation with *N*-acetyl-cysteine or alternative medical therapies of acupuncture and Chinese herbal medicine when added on to ovulation induction agents can improve clinical pregnancy rates and that *N*-acetyl-cysteine or inositol supplementation or acupuncture can improve ovulation rates in women with PCOS. However these need to be further evaluated by adequately powered and well conducted randomized controlled trials.

Our review shows there is very low quality evidence to suggest that lifestyle interventions can improve androgenic outcomes (Ferriman–Gallwey score, free androgen index and total testosterone levels) and lifestyle interventions, acupuncture or inositol supplementation can improve glycaemic outcomes (fasting blood insulin and fasting blood glucose levels). The only intervention which has shown a positive impact on BMI in women with PCOS is lifestyle interventions (diet and/or exercise). The recent international guidelines (Teede et al., 2018) recommend healthy lifestyle (diet and exercise) to achieve and maintain healthy weight, optimize hormonal outcomes, general health and quality of life and to improve insulin resistance. Results from our study support these recommendations that lifestyle interventions may be of use in improving androgenic and metabolic outcomes (Goodman et al., 2001), preventing metabolic complications and weight management (Glueck et al., 2005) in women with PCOS.

Currently, all the recommendations in the Teede 2018 guidelines on effectiveness of lifestyle interventions in women with PCOS are only categorized as clinical practice points (CPP), suggesting a lack of robust evidence based on randomized trials.

Inositol shows promising potential in improving not only reproductive outcomes, but also endocrine and glycaemic outcomes in women with PCOS. In women with PCOS, a defect in tissue availability or altered metabolism of inositol and/or inositolphosphoglycans mediators (involved in the second messenger pathway of insulin signalling) have been suggested to contribute to insulin resistance (Baillargeon et al., 2010). With inositol, a vitamin B complex nutritional supplement, epimerization of the six-hydroxyl groups of inositol leads to the formation of up to nine stereoisomers. Of these, myo-inositol and di-chiro-inositol, because of their involvement as second messengers of insulin, result in insulin senitization (Papaleo et al., 2009) and therefore have a potential role in improving endocrine and reproductive outcome in women with PCOS, including beneficial effects in reducing the risk of gestational diabetes (D'Anna et al., 2015). There are conflicting data about the potential effects of di-chiro-inositol on oocyte and embryo quality, and this needs to be evaluated in further studies. (Brusco and Mariani, 2013; Ravnos et al., 2017)

Relevance to clinical practice and research

Lifestyle interventions, used for prevention of weight gain and/or weight maintenance, are associated with a reduction in insulin resistance by reducing BMI, which can in turn lead to an improvement in the metabolic and reproductive features of PCOS. Weight management in PCOS women is important since overweight and obese women display worsened clinical reproductive (Balen et al., 1995) and metabolic features (Ehrmann et al., 2006). Even though there is some evidence on the role of lifestyle interventions in improving metabolic markers in women with PCOS, there is a lack of data on long-term prevention of type 2 diabetes mellitus or cardiovascular disease (Moran et al., 2011). Moreover, it is important to acknowledge the challenges associated with sustainability of lifestyle interventions as authors have reported high attrition in the majority of the studies, therefore the benefits of lifestyle intervention on PCOS may not be sustainable in the long-term (Moran et al., 2011). Clinicians should be aware of these limiting factors, whilst counselling these women. There needs to be further research into measures to improve the sustainability of lifestyle changes: possibly, introduction of the measures in adolescence to integrate as health education and/or simpler and enjoyable lifestyle intervention alternatives to achieve sustainability. Nutritional supplements of *N*-acetyl-cysteine or inositol or addition of acupuncture or Chinese herbal medicine to ovulation induction agents are also showing some encouraging results, which need to be further evaluated.

Conclusion

Lifestyle interventions in women with PCOS improve glycaemic results, androgenic symptoms and anthropometric outcomes, but evidence is lacking on their role in improving fertility outcomes. The role of inositol and *N*-acetyl-cysteine in women with PCOS needs further evaluation as preliminary data suggests benefits on fertility and non-fertility outcomes. Further methodologically rigorous and adequately powered primary studies are necessary for each of these non-pharmacological interventions, with reporting on consistently defined core outcomes in women with PCOS.

Supplementary data

Supplementary data are available at *Human Reproduction Update* online.

Authors' roles

J.P.: participation in study design, execution, analysis, article drafting and critical discussion; D.C.: participation in study design, execution, analysis; L.S.: participation in study design, critical discussion; D.H.: participation in study design, critical discussion; S.J.: participation in study design, critical discussion; H.T.: participation in study design,

critical discussion; A.C.: participation in study design, critical discussion; L.M.: participation in study design, article drafting and critical discussion; S.T.: participation in study design, article drafting and critical discussion.

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Conflict of interest

None declared.

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