Effects of L-carnitine supplementation for women with polycystic ovary syndrome: A systematic review and meta-analysis

Mohd Falihin Mohd Shukri [1], **Norhayati Mohd Noor** [1], **Salziyan Badrin** [Corresp., 1], **Azidah Abdul Kadir** [1]

[1] Department of Family Medicine, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia

Corresponding Author: Salziyan Badrin
Email address: salziyan@usm.my

Background Polycystic ovary syndrome (PCOS) is a disorder in reproductive age women and is characterized by hyperandrogenic anovulation and oligo-amenorrhea, which leads to infertility. Anovulation in PCOS is associated with low follicle-stimulating hormone levels and the arrest of antral follicle development in the final stages of maturation. L-carnitine (LC) plays a role in fatty acid metabolism, which is found to be lacking in PCOS patients. This systematic review and meta-analysis aimed to determine the effectiveness of LC supplementation for patients with PCOS.

Methods We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Psychological Information Database (PsycINFO), and the World Health Organization International Clinical Trials Registry Platform for all randomized control trials, comparing LC alone or in combination with other standard treatments for the treatment of PCOS from inception till June 2021. We independently screened titles and abstracts to identify available trials, and complete texts of the trials were checked for eligibility. Data on the methods, interventions, outcomes, and risk of bias from the included trials were independently extracted by the authors. The estimation of risk ratios and mean differences with a 95 percent confidence interval (CI) was performed using a random-effects model.

Results Nine studies with 995 participants were included in this review. Five comparison groups were involved. In one comparison group, LC reduced the fasting plasma glucose (FPG) (mean differences (MD) -5.10, 95% CI -6.25 to -3.95; P = 0.00001), serum low-density lipoprotein (LDL) (MD -25.00, 95% CI -27.93 to -22.07; P = 0.00001), serum total cholesterol (MD -21.00, 95% CI -24.14 to -17.86; P = 0.00001), and serum TG (MD -9.00, 95% CI -11.46 to -6.54; P = 0.00001) with moderate certainty of evidence. Another comparison group demonstrated that LC lowers the LDL (MD -12.00, 95% CI -15.80 to -8.20; P = 0.00001), serum total cholesterol (MD -24.00, 95% CI -27.61 to -20.39; P = 0.00001), and serum TG (MD -19.00, 95% CI -22.79 to -15.21; P = 0.00001) with moderate certainty of evidence.

Conclusion There was low to moderate certainty of evidence that LC improves Body Mass Index (BMI) and serum LDL, triglyceride (TG), and total cholesterol levels in women with PCOS.

PROSPERO registration number: CRD42021232433

Title: Effects of L-carnitine supplementation for women with polycystic ovary syndrome: A systematic review and meta-analysis

M Falihin M Shukri[1], Norhayati Mohd Noor[1], Salziyan Badrin[1], Azidah Abdul Kadir[1]

[1]Department of Family Medicine, Universiti Sains Malaysia, School of Medical Sciences, Kubang Kerian, Malaysia.

Author's name and affiliations:

1. Mohd Falihin Mohd Shukri
   Department of Family Medicine
   School of Medical Sciences
   Universiti Sains Malaysia
   16150 Kubang Kerian
   Kelantan, Malaysia.

2. Norhayati Mohd Noor
   Department of Family Medicine
   School of Medical Sciences
   Universiti Sains Malaysia
   16150 Kubang Kerian
   Kelantan, Malaysia

3. Salziyan Badrin (Corresponding author)
   Department of Family Medicine
   School of Medical Sciences
   Universiti Sains Malaysia
   16150 Kubang Kerian
   Kelantan, Malaysia
   Email: salziyan@usm.my
   Phone number: +609-7676608

4. Azidah Abdul Kadir
   Department of Family Medicine
   School of Medical Sciences
   Universiti Sains Malaysia
   16150 Kubang Kerian
   Kelantan, Malaysia.

Corresponding author: Salziyan Badrin, Department of Family Medicine, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia

Email: salziyan@usm.my, Contact number: +609-7676608

Title: Effects of L-carnitine supplementation for women with polycystic ovary syndrome: A systematic review and meta-analysis

Abstract

Background

Polycystic ovary syndrome (PCOS) is a disorder in reproductive age women and is characterized by hyperandrogenic anovulation and oligo-amenorrhea, which leads to infertility. Anovulation in PCOS is associated with low follicle-stimulating hormone levels and the arrest of antral follicle development in the final stages of maturation. L-carnitine (LC) plays a role in fatty acid metabolism, which is found to be lacking in PCOS patients. This systematic review and meta-analysis aimed to determine the effectiveness of LC supplementation for patients with PCOS.

Methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Psychological Information Database (PsycINFO), and the World Health Organization International Clinical Trials Registry Platform for all randomized control trials, comparing LC alone or in combination with other standard treatments for the treatment of PCOS from inception till June 2021. We independently screened titles and abstracts to identify available trials, and complete texts of the trials were checked for eligibility. Data on the methods, interventions, outcomes, and risk of bias from the included trials were independently extracted by the authors. The estimation of risk ratios and mean differences with a 95 percent confidence interval (CI) was performed using a random-effects model.

Results

Nine studies with 995 participants were included in this review. Five comparison groups were involved. In one comparison group, LC reduced the fasting plasma glucose (FPG) (mean differences (MD) -5.10, 95% CI -6.25 to -3.95; P = 0.00001), serum low-density lipoprotein (LDL) (MD -25.00, 95% CI -27.93 to -22.07; P = 0.00001), serum total cholesterol (MD -21.00, 95% CI -24.14 to -17.86; P = 0.00001), and serum TG (MD -9.00, 95% CI -11.46 to -6.54; P = 0.00001) with moderate certainty of evidence. Another comparison group demonstrated that LC lowers the LDL (MD -12.00, 95% CI -15.80 to -8.20; P = 0.00001), serum total cholesterol (MD -24.00, 95% CI -27.61 to -20.39; P = 0.00001), and serum TG (MD -19.00, 95% CI -22.79 to -15.21; P = 0.00001) with moderate certainty of evidence.

Conclusion

There was low to moderate certainty of evidence that LC improves Body Mass Index (BMI) and serum LDL, triglyceride (TG), and total cholesterol levels in women with PCOS.

PROSPERO registration number: CRD42021232433

Keywords: Carnitine; Polycystic Ovary Syndrome; Meta-analysis

Introduction

Polycystic ovary syndrome (PCOS) is a common disease that affects women of reproductive age with a prevalence ranging between 6.5 and 8 percent (Norman et al. 2007). It is an endocrine disorder that presents with irregular menses, hyperandrogenism, and polycystic ovaries. The clinical presentation includes oligomenorrhea or amenorrhea, hirsutism, and infertility (Sirmans & Pate 2013). Anovulatory PCOS is associated with low follicle-stimulating hormone levels and the arrest of antral follicle development in the final stages of maturation (Badawy & Elnashar 2011). The diagnosis of PCOS is based on the criteria defined by the Rotterdam European Society for Human Reproduction (ESHRE) and American Society of Reproductive Medicine (ASRM), which is currently known as the Rotterdam Criteria. The criteria comprise three features, including oligo or amenorrhea, clinical and biochemical signs of hyperandrogenism, and evidence of polycystic ovaries on ultrasound findings. Two out of three features confirm the diagnosis of PCOS (Badawy & Elnashar 2011). Polycystic features of the ovary on ultrasound suggest PCOS when 12 or more follicles in each ovary measure 2–9 mm in diameter and/or increased ovarian volume (Badawy & Elnashar 2011). Obesity is highly prevalent in PCOS women, and it is an independent risk factor for coronary artery disease, as obesity is associated with insulin resistance, dyslipidemia, and ovulatory dysfunction in adolescents (Traub 2011). The evaluation of risk factors for coronary arterial diseases (CADs) is essential in PCOS, as CADs entail the greatest long-term risk for PCOS (Traub 2011).

Medications such as clomiphene citrate, tamoxifen, aromatase inhibitors, metformin, glucocorticoids, gonadotropins, or laparoscopic ovarian drilling can be used to alleviate the anovulation problem faced by PCOS patients (Badawy & Elnashar 2011). L-carnitine (LC) is an endogenous compound synthesized by the human body, and it plays a key role in fatty acid metabolism (Johri et al. 2014). Carnitine is synthesized from lysine and methionine and is available from dietary sources such as meat, poultry, and dairy products (Johri et al. 2014). Carnitine acts as an obligatory cofactor for the oxidation of fatty acids by facilitating the transportation of long-chain fatty acids across the mitochondrial membrane. LC level is low in patients with PCOS; therefore, the use of LC as an adjunctive therapy in the management of insulin resistance or obesity in women may be beneficial (Celik et al. 2017). LC can boost ovarian function and decrease oxidative stress and inflammation. Furthermore, LC can normalize androgen levels, contributing to a significant decrease in testosterone levels (Della Corte et al. 2020). LC may enhance insulin sensitivity, thereby affecting the levels of androgens and ovarian hormones (Maleki et al. 2019).

This systematic review and meta-analysis aimed to determine the effectiveness of LC supplementation for patients with PCOS. The primary outcomes were clinical pregnancy and ovulation rate, Body Mass Index (BMI), fasting plasma glucose (FPG), and serum lipid levels, including low-density lipoprotein (LDL), triglycerides (TGs), total cholesterol, and high-density lipoprotein (HDL) levels. Mental health status, serum follicular stimulating hormone (FSH), and luteinizing hormone (LH) levels comprised the secondary outcomes. This review could reveal evidence of alternate therapy for improving clinical pregnancy outcomes and metabolic indicators in PCOS patients.

The effects of LC supplementation information may aid physicians in selecting and deciding on an alternate supplement to enhance PCOS metabolic indicators and increase clinical pregnancy rates.

Materials and Methods

The methodology and reporting conducted in this review are based on the guidelines recommended by the Cochrane Collaboration in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins JPT 2021). The quality of evidence was evaluated according to the Grading of Recommendation Assessment, Development and Evaluation (GRADE) guidelines (Guyatt et al. 2008).

Identification and eligibility of study

All randomized control trials (RCTs) comparing LC alone or in combination with other standard medications or other dietary supplements for the treatment and supplementation of PCOS women were considered in the review. The comparators were selected according to the availability of comparative studies versus LC. The participants included women who had been diagnosed with PCOS based on the revised ESHRE and the ASRM diagnosis of PCOS, according to the Rotterdam criteria of 2003. We excluded cross-over trials and studies other than RCTs. Werestricted the publications to the English language only.

We used the search strategy in **Appendix 1** and searched through Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Psychological Information Database (PsycINFO), and the World Health Organization International Clinical Trials Registry Platform for all available studies comparing LC alone or in combination with other standard treatments to treat PCOS. For additional datasets, we modified the search strategy. Using the Boolean operators AND as well as OR, we combined the terms “polycystic ovarian syndrome” and “L carnitine” (refer to Appendix 1). To locate unpublished trials or trials that could not be found using electronic searches, we looked through the reference lists of recognized RCTs and read the relevant articles. We also reached out to experts in the field and used the World Health Organization International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/) and www.clinicaltrials.gov to find active trials.

Three authors (MFMS, SB, AAK) scanned the repository of articles for trial selection from the titles and abstracts derived from the searches. Therein, we obtained full-text articles when they appeared to meet the eligibility criteria or when there was insufficient information to assess the eligibility. We documented the reasons behind exclusion after the authors independently reviewed the eligibility of the studies. Any differences were settled by discussion among the authors. If more information is required, then we will contact the authors. We utilized the procedure recommended by the Cochrane Handbook for Systematic Reviews of Interventions for searching and selecting studies (Higgins JPT 2021).

We retrieved 56 records from the search of the electronic databases, 22 records from Cochrane, 30 from MEDLINE, and four records from other databases. We screened 33 records after removing duplicates. Furthermore, we reviewed the complete text of 28 records—nine studies met the inclusion criteria, whereas 19 studies did not fulfill the inclusion criteria and were, therefore, excluded (refer to **Figure 1**). The number of records retrieved, screened, included, and excluded was presented in the PRISMA study flow diagram (**Figure 1)**.

Data collection and analysis

Three authors independently extracted data. We extracted data on the study setting, participant characteristics (age), methodology (inclusion and exclusion criteria, number of participants randomized and analyzed, and duration of follow-up), description of interventions used (dose, frequency, preparation, and duration used), and the measured outcomes. We also extracted data pertaining to the number of intrauterine gestational sacs and fetal heart rate visible by transvaginal ultrasound within 12 weeks of intervention (clinical pregnancy rate), the number of visible leading follicles of more than or equal to 18 mm by transvaginal ultrasound within 12 weeks of intervention (ovulation rate), BMI in kg/m2, serum LDL, serum HDL, TG, total cholesterol in mmol/l or mg/dl, and fasting blood glucose (FPG) in mg/dl, serum FSH and LH in IU/L, mental health status assessment using any questionnaires, and adverse side effects such as gastrointestinal disturbances (abdominal pain, nausea, and vomiting Disagreements between the review authors (MFMS, SB, AAK) were resolved by discussion with the fourth author (NMN).

Assessment risk of bias

We used the Cochrane Collaboration's risk-of-bias tools to assess the risk of bias in the included studies (Higgins JPT 2021). Three authors (MFMS, SB, AAK) assessed the selection bias (randomization and allocation concealment), performance bias (blinding of participant and health personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other biases (recall bias, transfer bias and etc.) independently. We classified the risk of bias as very low, low, moderate, or high. We also resolved disagreements by conducting discussions with the fourth author (NMN). In addition, we assessed the quality of evidence for primary and secondary outcomes, according to the GRADE methodology for risk of bias, inconsistency, indirectness, imprecision, and publication bias and classified it as very low, low, moderate, or high (Guyatt et al. 2008). Furthermore, we assessed the presence of the risk of bias, inconsistency or unexplained heterogeneity, indirectness of evidence, imprecision, and publication bias. We classified them as very low, low, moderate, and high.

Statistical analysis

We analyzed data using Review Manager 5.4 software (Manager 2020) for the statistical analyses. Moreover, we used a random-effects model to pool data. We measured the treatment effect using risk ratios (RR) for dichotomous outcomes and mean differences (MD) with 95 percent confidence intervals (CI) for continuous outcomes. We assessed the presence of heterogeneity in two steps.

First, the assessment was performed at face value by comparing populations, settings, interventions, and outcomes (Higgins JPT 2021). Second, the statistical heterogeneity was assessed by using the I^2 statistic (Higgins JPT 2021). We used the interpretation of heterogeneity as follows: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75 percent to 100 percent would indicate considerable heterogeneity (Higgins JPT 2021). We checked the included trials for the unit of analysis errors. The unit of analysis errors can occur when trials randomize participants to intervention or control groups in clusters but analyze the results using the total number of individual participants. Based on the mean cluster size and intra-cluster correlation coefficient, we adjusted the results from trials with the unit of analysis errors (Higgins JPT 2021). Thereafter, we contacted the trial's original authors to request data that had been missing or incorrectly reported. If missing data was not accessible, we conducted analyses using the available data. We performed a sensitivity analysis to investigate the impact of the high risk of bias on sequence generation and allocation concealment of included studies. If there were sufficient studies, then we used funnel plots to assess the possibility of reporting biases or small study biases, or both.

GRADEPro software was used to analyze the quality of evidence or certainty in the body of evidence for each outcome, and we classified the quality of evidence as high, moderate, low, and very low.

Results

Trial selection

We retrieved 56 records from the electronic searches that were available from inception until June 2021. We screened a total of 33 records after duplicates were removed, and we excluded five studies that did not meet the eligibility criteria. Out of these 28 studies, another 19 studies were excluded. Five out of 19 studies were not RCT studies (Celik et al. 2017; Eyupoglu et al. 2019; Fenkci et al. 2008; Maleki et al. 2019; Salehpour et al. 2019), and 12 studies were excluded because they did not report outcomes of interest for this review (Chen et al. 2020; Chen et al. 2016; Cree-Green et al. 2019; Dong et al. 2015; Hamed 2016; Jia et al. 2019; Karakas et al. 2016; Selen Alpergin et al. 2017; Sheida et al. 2021; Sun et al. 2019; Vonica et al. 2019; Zhao et al. 2015). Two other studies reported the effects of other supplementations other than LC and did not fulfil the eligibility criteria (Nct 2019; Vigerust et al. 2012). We have summarized the results of the search strategy in **Figure 1**.

Characteristics of included trials

We included nine trials with a total of 987 participants (El Sharkwy & Sharaf El-Din 2019; El Sharkwy & Abd El Aziz 2019; Ismail et al. 2014; Jamilian et al. 2017; Jamilian et al. 2019a; Jamilian et al. 2019b; Kortam et al. 2020; Samimi et al. 2016; Talari et al. 2019). All nine trials recruited women who had been diagnosed with PCOS based on the Rotterdam criteria. Six trials involved the participants aged between 18 and 40 years (El Sharkwy & Abd El Aziz 2019; Jamilian et al. 2017; Jamilian et al. 2019a; Jamilian et al. 2019b; Samimi et al. 2016; Talari et al. 2019). On

the other hand, two trials include BMI > 25kg/m2 as one of the inclusion criteria (Jamilian et al. 2019b; Samimi et al. 2016), and three trials used clomiphene citrate resistant PCOS as the inclusion criteria (El Sharkwy & Sharaf El-Din 2019; El Sharkwy & Abd El Aziz 2019; Ismail et al. 2014). All nine trials reported hyperprolactinemia as the exclusion criteria. Eight trials excluded participants with endocrine disorder, and the duration of the study was 12 weeks, with the exception of one trial (Kortam et al. 2020) that did not mention the study duration. Four out of nine included trials excluded women who were pregnant in the trial (Jamilian et al. 2017; Jamilian et al. 2019a; Jamilian et al. 2019b; Talari et al. 2019). Three studies excluded diabetic patients as participants in the trial (Jamilian et al. 2019a; Jamilian et al. 2019b; Samimi et al. 2016).

Outcomes

The nine included trials had diverse groups, which addressed various comparisons and outcomes, resulting in several comparisons that contributed to each of predefined outcomes. All studies had methodological limitations, and there were too few studies to allow pooling of all primary and secondary outcomes.

Four included trials reported on the clinical pregnancy rate and the ovulation rate (El Sharkwy & Sharaf El-Din 2019; El Sharkwy & Abd El Aziz 2019; Ismail et al. 2014; Kortam et al. 2020), whereas seven out of nine included trials reported BMI (El Sharkwy & Sharaf El-Din 2019; El Sharkwy & Abd El Aziz 2019; Jamilian et al. 2017; Jamilian et al. 2019b; Kortam et al. 2020; Samimi et al. 2016; Talari et al. 2019). The lipid profile, including serum LDL, HDL, total cholesterol, and TG levels, were reported in four trials (El Sharkwy & Sharaf El-Din 2019; El Sharkwy & Abd El Aziz 2019; Jamilian et al. 2019b; Samimi et al. 2016), and FPG was reported in four trials (El Sharkwy & Sharaf El-Din 2019; El Sharkwy & Abd El Aziz 2019; Jamilian et al. 2019b; Samimi et al. 2016).

Five trials reported secondary outcomes, which are hormonal levels, including the serum FSH levels, and LH levels, and mental health status. The serum FSH and LH levels were reported in three trials (El Sharkwy & Sharaf El-Din 2019; El Sharkwy & Abd El Aziz 2019; Kortam et al. 2020), and the mental health status was reported in two trials (Jamilian et al. 2017; Jamilian et al. 2019a).

Assessment risk of bias

The assessment of risk of bias has been presented in **Figure 2** and **Figure 3**. The details of these trials are summarized in **Table 1**. All nine trials described the method of randomization used. Eight trials randomized the participants using computer-generated randomization (El Sharkwy & Sharaf El-Din 2019; El Sharkwy & Abd El Aziz 2019; Ismail et al. 2014; Jamilian et al. 2017; Jamilian et al. 2019a; Jamilian et al. 2019b; Samimi et al. 2016; Talari et al. 2019), with the exception of one trial (Jamilian et al. 2019b) in which the randomization sequence was manually executed at the clinic. Therefore, we judged a high risk of random sequence generation bias for this trial (Jamilian et al. 2019b), whereas a low risk of bias was assigned to the other eight trials. Allocation concealment was reported in all trials. All trials conducting the study using placebo capsules,

which were designed to be identical to LC capsules. Three trials (El Sharkwy & Sharaf El-Din 2019; El Sharkwy & Abd El Aziz 2019; Ismail et al. 2014) distributed the capsules using opaque and sealed envelopes. Therefore, for allocation concealment, all trials had a low risk of bias. Eight trials mentioned blinding of participants and personnel (El Sharkwy & Sharaf El-Din 2019; El Sharkwy & Abd El Aziz 2019; Ismail et al. 2014; Jamilian et al. 2017; Jamilian et al. 2019a; Jamilian et al. 2019b; Samimi et al. 2016; Talari et al. 2019), with the exception of one trial (Kortam et al. 2020), which resulted in an unclear risk of bias. Seven trials had a low risk of bias (El Sharkwy & Sharaf El-Din 2019; El Sharkwy & Abd El Aziz 2019; Ismail et al. 2014; Jamilian et al. 2017; Jamilian et al. 2019a; Jamilian et al. 2019b; Samimi et al. 2016), highlighting that the patients and physicians were blinded to the treatment allocation. Only one trial (Talari et al. 2019) mentioned that the researchers and participants were not blinded to the allocation concealment, thereby resulting in a high risk of bias.

Eight trials reported the number of participants who completed the study, including the number of patients who dropped out from the study with justified reasons (El Sharkwy & Sharaf El-Din 2019; El Sharkwy & Abd El Aziz 2019; Ismail et al. 2014; Jamilian et al. 2017; Jamilian et al. 2019a; Jamilian et al. 2019b; Samimi et al. 2016; Talari et al. 2019). The missing participants for these trials were less than 15 percent (El Sharkwy & Sharaf El-Din 2019; El Sharkwy & Abd El Aziz 2019; Ismail et al. 2014; Jamilian et al. 2017; Jamilian et al. 2019a; Jamilian et al. 2019b; Samimi et al. 2016; Talari et al. 2019), and one trial (Talari et al. 2019) did not have any missing participants from both the control and intervention groups. Only one trial (Kortam et al. 2020) did not mention the number of participants who completed or withdrew from the study. Neither did it summarize the patients' flow diagram, resulting in an unclear risk of bias.

All nine trials reported the outcomes as specified in their methods section (El Sharkwy & Sharaf El-Din 2019; El Sharkwy & Abd El Aziz 2019; Ismail et al. 2014; Jamilian et al. 2017; Jamilian et al. 2019a; Jamilian et al. 2019b; Kortam et al. 2020; Samimi et al. 2016; Talari et al. 2019). Four trials registered their protocols, and three trials (Jamilian et al. 2017; Jamilian et al. 2019a; Samimi et al. 2016) were registered in the Iranian Registry of Clinical Trials. Only one trial (El Sharkwy & Abd El Aziz 2019) was registered in the National Clinical Trials.

LC supplementation for women with PCOS

We performed meta-analysis for each of the five comparison groups in this review. For the first comparison, the combination of clomiphene citrate and LC was compared with the combination of clomiphene citrate and placebo (Ismail et al. 2014; Kortam et al. 2020). In total, 250 milligrams (mg) of oral clomiphene citrate was administered along with 3 grams (g) of LC in one study in comparison with the same 250 mg clomiphene citrate combined with placebo (Ismail et al. 2014). In another study, the researchers used 100 mg clomiphene citrate daily in combination with 3 g of LC when compared with the use of 100 mg clomiphene citrate and the placebo (Kortam et al. 2020). The second comparison comprised the study that used 150 mg clomiphene citrate, 850 mg metformin and 1 g LC versus 150 mg clomiphene citrate, 850 mg metformin, and placebo (El Sharkwy & Sharaf El-Din 2019). The third comparison included the studies that used a

combination of 150 g clomiphene citrate and 600 mg oral N-Acetylcysteine in comparison with 150 mg clomiphene citrate and 3 g LC (El Sharkwy & Abd El Aziz 2019). The fourth comparison included the studies that used 250 mg of LC in comparison with placebo (Jamilian et al. 2017; Samimi et al. 2016; Talari et al. 2019). Finally, the fifth comparison comprised the studies that used 200 mg chromium picolinate and 1g LC daily in comparison with the placebo (Jamilian et al. 2019a; Jamilian et al. 2019b).

Comparison 1: Clomiphene citrate and LC versus clomiphene citrate and placebo

We performed meta-analysis in this comparison. No difference was observed in terms of the clinical pregnancy rate between the two groups (Risk ratio (RR) 7.12, 95% CI 0.14 to 350.06; I^2 = 90%, P = 0.32; two trials, n = 264; low quality evidence) (Ismail et al. 2014; Kortam et al. 2020). However, a difference was observed in terms of the primary outcome, ovulation rate between the two groups, which favored combination with placebo (RR 2.37, 95% CI 0.99 to 5.66; I^2 = 88%, P = 0.05; two trials, n = 264; low quality evidence) (Ismail et al. 2014; Kortam et al. 2020). **Figure 4** showed the Forest plot, comparing the use of clomiphene citrate and LC in comparison with the use of clomiphene citrate and placebo for primary outcomes, clinical pregnancy rate, and ovulation rate. There is a difference in terms of the primary outcome, BMI within one group, which favored combination with placebo (MD 1.10, 95% CI 0.32 to1.88; P = 0.006; one trial, n = 94; moderate quality evidence) (Kortam et al. 2020). No difference is observed for the secondary outcome, FSH within one group (MD -0.10, 95% CI, -0.50 to 0.70; P = 0.75; one trial, n = 94; moderate quality evidence) (Kortam et al. 2020). There is no difference for the secondary outcome, LH within one group (MD (95% CI) -0.20 (-0.91, 0.51); P = 0.58; one trial, n = 94; moderate quality evidence) (Kortam et al. 2020). Therefore, in this comparison group, there was no significant difference in the pregnancy rate, FSH, and LH levels. However, there was a significant difference, favoring the placebo in terms of the ovulation rate and BMI. **Table 2** showed the summary of findings and GRADE quality assessment for primary and secondary outcomes of Comparison 1.

Comparison 2: Clomiphene citrate, metformin and LC versus clomiphene citrate, metformin, and placebo

We performed meta-analysis in this comparison. There is a significant difference in the primary outcome, clinical pregnancy rate in one group, which favored combination with placebo (RR 4.27, 95% CI 2.15 to 8.47; P = 0.0001; one trial, n = 274; moderate quality evidence) (El Sharkwy & Sharaf El-Din 2019). There is a significant difference in the ovulation rate in one group, which favored combination with placebo (RR 3.15 95% CI 1.86 to 5.35; P = 0.0001; one trial, n = 274; moderate quality evidence) (El Sharkwy & Sharaf El-Din 2019). There is a significant difference for BMI in one group, which favored combination with placebo (MD 1.10, 95% CI 0.32 to 1.88; P = 0.006; one trial, n = 274; moderate quality evidence) (El Sharkwy & Sharaf El-Din 2019). There is a significant difference for the primary outcome, FPG in one group, which favored combination with LC (MD -5.10, 95% CI -6.25 to -3.95; P = 0.00001; one trial, n = 274; moderate quality evidence) (El Sharkwy & Sharaf El-Din 2019) (Table 3). In addition, there is a significant

difference for the primary outcomes, LDL level in one group, which favored combination with LC (MD -25.00, 95% CI -27.93 to -22.07; P = 0.00001; one trial, n = 274; moderate quality evidence) (El Sharkwy & Sharaf El-Din 2019), TC level in one group, which favored combination with LC (MD -21.00, 95% CI -24.14 to -17.86; P = 0.00001; one trial, n = 274; moderate quality evidence) (El Sharkwy & Sharaf El-Din 2019) and TG level in one group, which favored combination with LC (MD -9.00, 95% CI -11.46 to -6.54; P = 0.00001; one trial, n = 274; moderate quality evidence) (El Sharkwy & Sharaf El-Din 2019). There is a significant difference for the primary outcome, HDL level in one group, which favored combination with placebo (MD 15.50, 95% CI 12.42 to 18.58; P = 0.00001; one trial, n = 274; moderate quality evidence) (El Sharkwy & Sharaf El-Din 2019) (Table 3). There is a significant difference for the secondary outcomes, FSH level in one group, which favored combination with LC (MD -0.63, 95% CI -0.92 to -0.34; P = 0.00001; one trial, n = 274; moderate quality evidence) (El Sharkwy & Sharaf El-Din 2019). There is a significant difference for LH level in one group, which favored combination with LC (MD-2.36, 95% CI -3.04 to -1.68; P = 0.00001; one trial, n = 274; moderate quality evidence) (El Sharkwy & Sharaf El-Din 2019). In this comparison, there was a significant difference that favored combination with LC in terms of the FPG, LDL, TC, TG, HDL, FSH, and LH levels. There was a significant difference favoring the combination with placebo in pregnancy rate, ovulation rate, HDL level, and BMI. **Table 3** showed the summary of finding and GRADE quality assessment for primary and secondary outcomes of Comparison 1.

Comparison 3: Clomiphene citrate plus LC versus clomiphene citrate plus n-acetylcysteine

We performed meta-analysis in this comparison. There is no difference for the primary outcome, clinical pregnancy rate in one group (RR (95% CI) 1.16 (0.72, 1.89); P = 0.54; one trials, n = 162; moderate quality evidence) (El Sharkwy & Abd El Aziz 2019). There is no difference for the primary outcome, ovulation rate in one group (RR (95% CI) 1.11 (0.79, 1.56); P = 0.54; one trials, n = 162; moderate quality evidence) (El Sharkwy & Abd El Aziz 2019). There is no difference for the primary outcome, BMI in one group (MD 0.10, 95% CI -0.78 to 0.98; P = 0.82; one trial, n = 162; moderate quality evidence) (El Sharkwy & Abd El Aziz 2019). There is a significant difference for the primary outcome, FPG in one group, which favored combination with NAC (MD 2.30, 95% CI 1.02 to3.58; P = 0.0004; one trial, n = 162; moderate quality evidence) (El Sharkwy & Abd El Aziz 2019). There is a significant difference for the primary outcome, LDL level in one group, which favored combination with LC (MD -12.00, 95% CI -15.80 to -8.20; P = 0.00001; one trial, n = 162; moderate quality evidence) (El Sharkwy & Abd El Aziz 2019). There is a significant difference for the primary outcome, TC level in one group, which favored combination with LC (MD -24.00, 95% CI -27.61 to -20.39; P = 0.00001; one trial, n = 162; moderate quality evidence) (El Sharkwy & Abd El Aziz 2019). There is a significant difference for the primary outcome, HDL level in one group, which favored combination with NAC (MD 9.60, 95% CI 5.30 to 13.90; P = 0.0001; one trial, n = 162; moderate quality evidence) (El Sharkwy & Abd El Aziz 2019). There is a significant difference for the primary outcome, TG level in one group, which favored combination with LC (MD -19.00, 95% CI -22.79 to -15.21; P = 0.00001; one trial, n = 162;

moderate quality evidence) (El Sharkwy & Abd El Aziz 2019). The summary of all findings and GRADE quality assessment for primary outcomes of Comparison 3 is shown in **Table 4**.
There is a significant difference for the secondary outcome, FSH level in one group, which favored combination with LC (MD-0.50, 95% CI -0.84 to -0.16; P = 0.004; one trial, n = 162; moderate quality evidence) (El Sharkwy & Abd El Aziz 2019). There is no difference for the secondary outcome, LH level in one group (MD -0.40, 95% CI -1.51 to 0.71; P = 0.48; one trial, n = 162; moderate quality evidence) (El Sharkwy & Abd El Aziz 2019). In this comparison, there was no significant difference in the pregnancy rate, ovulation rate, BMI, and LH level. There was a significant difference that favored the combination of LC in LDL, TC, TG, and FSH levels, and there was a significant difference that favored the combination with NAC in terms of the FPG and HDL levels. The summary of all findings and GRADE quality assessment for secondary outcomes of Comparison 3 is shown in **Table 4**.

Comparison 4: Comparing LC with the placebo

We performed meta-analysis in this comparison. There was no difference for FPG in one group (MD -1.26, 95% CI -7.50 to 4.98); P = 0.69; one trial, n = 60; moderate quality evidence) (Samimi et al. 2016), LDL level in one group (MD 0.33, 95% CI -0.05 to 0.71; P = 0.09; one trial, n = 60; moderate quality evidence) (Samimi et al. 2016), total cholesterol level in one group (MD 6.84, 95% CI -0.45 to 14.13; P = 0.07; one trial, n = 60; moderate quality evidence) (Samimi et al. 2016), HDL level in one group (MD 0.00, 95% CI -3.60 to 3.60; P = 1.00; one trial, n = 60; moderate quality evidence) (Samimi et al. 2016), and TG level in one group (MD 0.15, 95% CI -0.14 to 0.44; P = 1.00; one trial, n = 60; moderate quality evidence) (Samimi et al. 2016). There was significant difference for BMI level in three groups, which favored LC group (MD -1.33, 95% CI -1.52 to -1.44; $I^{2=}$ 0%, P = 0.00001; three trials, n = 180; moderate quality evidence) (Jamilian et al. 2017; Samimi et al. 2016; Talari et al. 2019). **Figure 5** showed the Forest plot of Comparison 4, comparing LC with placebo for the primary outcome, BMI. The summary of findings of primary outcomes and GRADE quality assessment for Comparison 4 is shown in **Table 5**.
There is a significant difference for the secondary outcome, mental health status, by using assessment score, BDI score in one group, which favored placebo (MD 2.50, 95% CI 2.35 to 2.65; P = 0.00001; one trial, n = 60 ; moderate quality evidence) (Jamilian et al. 2017), general health questionnaire (GHQ) score in one group, which favored LC (MD -5.80, 95% CI -6.10 to -5.50; P = 0.00001; one trial, n = 60 ; moderate quality evidence) (Jamilian et al. 2017), and depression anxiety stress score (DASS) in one group, which favored LC (MD -6.80, 95% CI -7.20 to -6.40; P = 0.00001; one trials, n = 60 ; moderate quality evidence) (Jamilian et al. 2017). Therefore, in this comparison, there was no significant difference in terms of the FPG, LDL, TC, HDL, and TG levels, whereas there were significant differences that favored LC with respect to BMI, GHQ, and DASS scores, and significant differences that favored placebo in the BDI score. The summary of findings of secondary outcomes and GRADE quality assessment for Comparison 4 is shown in **Table 5**.

Comparisons 5: LC plus chromium and placebo

We performed meta-analysis in this comparison. There is no difference for the primary outcome, FPG in one group (MD -3.40, 95% CI -7.60 to 0.80; P = 0.11; one trial, n = 54; moderate quality evidence) (Jamilian et al. 2019b). There is no difference for the primary outcome, LDL level in one group (MD -0.60, 95% CI -19.95 to 18.75; P = 0.95; one trial, n = 54; moderate quality evidence) (Jamilian et al. 2019b). There is no difference for the primary outcome, TC in one group (MD -9.70, 95% CI -28.53 to 9.13; P = 0.31; one trial, n = 54; moderate quality evidence) (Jamilian et al. 2019b). There is no difference for the primary outcome, HDL level in one group (MD -3.40, 95% CI -8.20 to 1.40; P = 0.17; one trial, n = 54 moderate quality evidence) (Jamilian et al. 2019b). There is significance difference for the primary outcome, TG level in one group, which favored combination with LC (MD -28.10, 95% CI -47.25 to -8.95; P = 0.004; one trial, n = 54; moderate quality evidence) (Jamilian et al. 2019b). The summary of primary outcomes' findings and GRADE quality assessment is shown in **Table 6**.

There is no difference for the secondary outcome, mental health status, by using BDI scoring in one group (MD -1.50, 95% CI -4.17 to 1.17; P = 0.27; one trial, n = 53; moderate quality evidence) (Jamilian et al. 2019a), GHQ scoring in one group (MD -1.80, 95% CI -7.10 to 3.50; P = 0.51; one trial, n = 53; moderate quality evidence) (Jamilian et al. 2019a), and DASS scoring in one group (MD -3.50, 95% CI -11.42 to 4.42; P = 0.39; one trial, n = 53; moderate quality evidence) (Jamilian et al. 2019a). Therefore, in this comparison, there was no difference in FPG, LDL, TC, HDL, BDI score, GHQ score, and DASS score. On the other hand, there was a significant difference that favored combination with LC in terms of the TG level. The summary of secondary outcomes' findings and GRADE quality assessment is shown in **Table 6**.

Discussion

Menstrual problems, hyperandrogenism, and infertility are the most common symptoms observed during the early reproductive years in PCOS (Peigné & Dewailly 2014). Pregnancy-specific complications, obesity, glucose intolerance, type 2 diabetes, cardiovascular diseases, and gynecological malignancies can all develop as women get older. For these "at-risk" women, lifelong monitoring is required, and preventative actions need to be implemented early (Peigné & Dewailly 2014). The health risks associated with PCOS may extend far beyond the management of the common presenting symptoms or fertility treatment, as this disease and its symptoms are likely to last beyond the reproductive age until menopause (Cooney & Dokras 2018). The scope of studies has been limited in terms of evaluating the risk for cardiovascular morbidity and mortality in women with PCOS after they undergo menopause.

This review was designed to include all RCTs addressing the effect of LC supplementation in women with PCOS. The nine selected trials had created a diverse group, addressing various comparisons and outcomes, thereby resulting in several comparisons that contributed to each of our predefined outcomes. We were unable to perform subgroup analyses, as there were inadequate trials that used similar comparisons.

To evaluate the impact of LC on PCOS patients, we conducted a comprehensive literature study. From nine trials, only five trials can be sub-grouped into similar combination of comparisons, wherein two trials (Ismail et al. 2014; Kortam et al. 2020) in Comparison 1 were associated with the outcomes of clinical pregnancy rate and ovulation rate, and three trials (Jamilian et al. 2017; Samimi et al. 2016; Talari et al. 2019) in Comparison 4 were related to BMI outcomes. Thus, as a result, the application of the findings in this review is limited. On the outcome basis, three primary outcomes, namely clinical pregnancy rate, ovulation rate, and FPG, have similar trials with similar combination of comparisons, in which two trials were related to clinical pregnancy rates, two trials were associated with ovulation rate, and three trials were focused on FPG. From the reported incidence of adverse events, we detected side effects in one trial (Kortam et al. 2020), that is, abdominal pain, dizziness, and nausea. However, none of the trial investigators reported serious side effects due to the use of LC. Most of PCOS women have issues with infertility. Given the scarcity of trials comparing similar comparisons, future clinical trials comparing LC alone with other comparators in similar comparisons are needed to determine the effect of LC on improving pregnancy rate and ovulation rate in PCOS patients. The overall quality of the evidence used in this review ranges from moderate to low. The trials differed in terms of comparison type and supplementation dosage. We also recommend that future trials consider using standardized LC dosages, regimes, and consumption durations, either alone or in combination, to produce homogeneous results across trials to demonstrate the safety and effectiveness of the LC.

The overall quality of the evidence contributing to this review ranges from moderate to low. The type of comparison and supplementation dosage varied among the trials. Most trials had low risk of bias for allocation bias with the exception of one trial (Jamilian et al. 2019b), as randomization was manually performed at the clinic. In terms of the blinding of participants and personnel, one trial (Kortam et al. 2020) had unclear risk of bias, and one trial (Talari et al. 2019) had high risk of bias, as the researchers and participants were not blinded in their trial. All trials had reported outcomes in their method section, whereas four trials published their protocols. The risk of attrition bias was only observed in one trial (Kortam et al. 2020), as it did not state the number of participants who withdrew from the study or completed the study. The percentage of participants who failed to follow-up was less than 15 percent in eight trials, and two trials (Jamilian et al. 2017; Talari et al. 2019) declared that financing had been received from the university grant. We encountered high heterogeneity in the meta-analysis, and we were unable to segment any further because there were insufficient trials in each group comparison. Even though all of the included studies showed the same direction of effect, we found significant heterogeneity in our primary outcomes. Due to the small number of trials, we were unable to conduct subgroup analysis.

We aimed to reduce the publication bias by searching different databases without language restrictions and examining the reference lists of all linked articles for additional references. Unfortunately, we cannot guarantee that we have discovered all the trials in this area. As only nine trials were included, we could not create a funnel plot to detect bias or heterogeneity, and not all included trials reported similar outcomes. Although all the included studies showed the same

direction of effect, we encountered high heterogeneity in our primary outcomes. We could not perform sub-group analysis due to limited number of trials.

One systematic review has examined the impact of LC on patients with PCOS (Maleki et al. 2019). The researchers in this review evaluated the potential roles played by LC in PCOS patients. It included two observational studies (Celik et al. 2017; Fenkci et al. 2008) and four randomized controlled studies, wherein three studies (Ismail et al. 2014; Jamilian et al. 2019b; Samimi et al. 2016) were included in this meta-analysis, and one study (Slomaz Latifian 2015) was unrelated to our primary and secondary outcomes. Similar to our meta-analysis, the BMI had a significant impact on LC supplementation based on three trials (Ismail et al. 2014; Jamilian et al. 2019b; Samimi et al. 2016). However, for the lipid profile, one study had a significant impact (Ismail et al. 2014), whereas two studies had an insignificant impact (Fenkci et al. 2008; Samimi et al. 2016).

Conclusions

Based on this meta-analysis, it has been observed that LC is beneficial for improving BMI as well as LDL, TC, and TG levels, in women with PCOS. However, in terms of the clinical pregnancy rate and ovulation rate, the meta-analysis showed insignificant effect. Therefore, the justification of LC usage for these outcomes requires further evaluations and clinical trials. The findings of this review would need to be considered in the context of LC, as supplementation with other medications in the treatment of PCOS. In this study, the scope of evaluation of the side effects of LC use is limited, and more safety data is needed to assess the risks of using it. If further studies are conducted to examine the use of LC in women with PCOS, they should include pregnancy rate and ovulation rate as part of their outcomes. This is because PCOS women mostly seek treatment to alleviate fertility problems. Data on physical findings such as hirsutism, acne, and weight reduction can also be considered in the subsequent research studies.

OTHER INFORMATIONS

Registration and Protocol

Our systematic review and meta-analysis protocol has been registered and published in PROSPERO (Registration number: CRD42021232433).

Funding

The authors received no funding for this work.

Conflict of Interests

NMN is serving as an academic editor for PeerJ.

Author Contributions

Designing the review: SB, MFMS, AAK

Search Strategy: MFMS, SB, AAK
Quality assessment: MFMS, NMN, SB, AAK
Entering data into RevMan: MFMS
Data analysis and interpretation: MFMS, AAK, SB
Writing the review: MFMS

Raw Data information

All raw data and materials used in this review are available in the supplementary files.

REFERENCES

Badawy A, and Elnashar A. 2011. Treatment options for polycystic ovary syndrome. *International journal of women's health* 3:25-35. 10.2147/IJWH.S11304

Celik F, Kose M, Yilmazer M, Köken GN, Arioz DT, and Kanat Pektas M. 2017. Plasma L-carnitine levels of obese and non-obese polycystic ovary syndrome patients. *J Obstet Gynaecol* 37:476-479. 10.1080/01443615.2016.1264375

Chen X, Lu T, Wang X, Sun X, Zhang J, Zhou K, Ji X, Sun R, Wang X, Chen M, and Ling X. 2020. Metabolic alterations associated with polycystic ovary syndrome: A UPLC Q-Exactive based metabolomic study. *Clin Chim Acta* 502:280-286. 10.1016/j.cca.2019.11.016

Chen YX, Zhang XJ, Huang J, Zhou SJ, Liu F, Jiang LL, Chen M, Wan JB, and Yang DZ. 2016. UHPLC/Q-TOFMS-based plasma metabolomics of polycystic ovary syndrome patients with and without insulin resistance. *J Pharm Biomed Anal* 121:141-150. 10.1016/j.jpba.2016.01.025

Cooney LG, and Dokras A. 2018. Beyond fertility: polycystic ovary syndrome and long-term health. *Fertility and sterility* 110:794-809. https://doi.org/10.1016/j.fertnstert.2018.08.021

Cree-Green M, Carreau AM, Rahat H, Garcia-Reyes Y, Bergman BC, Pyle L, and Nadeau KJ. 2019. Amino acid and fatty acid metabolomic profile during fasting and hyperinsulinemia in girls with polycystic ovarian syndrome. *Am J Physiol Endocrinol Metab* 316:E707-e718. 10.1152/ajpendo.00532.2018

Della Corte L, Foreste V, Barra F, Gustavino C, Alessandri F, Centurioni MG, Ferrero S, Bifulco G, and Giampaolino P. 2020. Current and experimental drug therapy for the treatment of polycystic ovarian syndrome. *Expert Opinion on Investigational Drugs* 29:819-830.

Dong F, Deng D, Chen H, Cheng W, Li Q, Luo R, and Ding S. 2015. Serum metabolomics study of polycystic ovary syndrome based on UPLC-QTOF-MS coupled with a pattern recognition approach. *Anal Bioanal Chem* 407:4683-4695. 10.1007/s00216-015-8670-x

El Sharkwy I, and Sharaf El-Din M. 2019. l-Carnitine plus metformin in clomiphene-resistant obese PCOS women, reproductive and metabolic effects: a randomized clinical trial. *Gynecol Endocrinol* 35:701-705. 10.1080/09513590.2019.1576622

El Sharkwy IA, and Abd El Aziz WM. 2019. Randomized controlled trial of N-acetylcysteine versus l-carnitine among women with clomiphene-citrate-resistant polycystic ovary syndrome. *Int J Gynaecol Obstet* 147:59-64. 10.1002/ijgo.12902

Eyupoglu ND, Caliskan Guzelce E, Acikgoz A, Uyanik E, Bjørndal B, Berge RK, Svardal A, and Yildiz BO. 2019. Circulating gut microbiota metabolite trimethylamine N-oxide and oral contraceptive use in polycystic ovary syndrome. *Clin Endocrinol (Oxf)* 91:810-815. 10.1111/cen.14101

Fenkci SM, Fenkci V, Oztekin O, Rota S, and Karagenc N. 2008. Serum total L-carnitine levels in non-obese women with polycystic ovary syndrome. *Hum Reprod* 23:1602-1606. 10.1093/humrep/den109

Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ, and Group GW. 2008. What is "quality of evidence" and why is it important to clinicians? *Bmj* 336:995-998. 10.1136/bmj.39490.551019.BE

Hamed SA. 2016. The effect of epilepsy and antiepileptic drugs on sexual, reproductive and gonadal health of adults with epilepsy. *Expert Rev Clin Pharmacol* 9:807-819. 10.1586/17512433.2016.1160777

Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA. 2021. Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021.

Ismail AM, Hamed AH, Saso S, and Thabet HH. 2014. Adding L-carnitine to clomiphene resistant PCOS women improves the quality of ovulation and the pregnancy rate. A randomized clinical trial. *Eur J Obstet Gynecol Reprod Biol* 180:148-152. 10.1016/j.ejogrb.2014.06.008

Jamilian H, Jamilian M, Samimi M, Afshar Ebrahimi F, Rahimi M, Bahmani F, Aghababayan S, Kouhi M, Shahabbaspour S, and Asemi Z. 2017. Oral carnitine supplementation influences mental health parameters and biomarkers of oxidative stress in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. *Gynecol Endocrinol* 33:442-447. 10.1080/09513590.2017.1290071

Jamilian M, Foroozanfard F, Kavossian E, Aghadavod E, Amirani E, Mahdavinia M, Mafi A, and Asemi Z. 2019a. Carnitine and chromium co-supplementation affects mental health, hormonal, inflammatory, genetic, and oxidative stress parameters in women with polycystic ovary syndrome. *Journal of psychosomatic obstetrics and gynaecology*.

Jamilian M, Foroozanfard F, Kavossian E, Kia M, Aghadavod E, Amirani E, and Asemi Z. 2019b. Effects of Chromium and Carnitine Co-supplementation on Body Weight and Metabolic Profiles in Overweight and Obese Women with Polycystic Ovary Syndrome: a Randomized, Double-Blind, Placebo-Controlled Trial. *Biological trace element research*. 10.1007/s12011-019-01720-8

Jia C, Xu H, Xu Y, Xu Y, and Shi Q. 2019. Serum metabolomics analysis of patients with polycystic ovary syndrome by mass spectrometry. *Mol Reprod Dev* 86:292-297. 10.1002/mrd.23104

Johri A, Heyland DK, Hetu M-F, Crawford B, and Spence JD. 2014. Carnitine therapy for the treatment of metabolic syndrome and cardiovascular disease: Evidence and controversies. *Nutrition, metabolism, and cardiovascular diseases : NMCD* 24. 10.1016/j.numecd.2014.03.007

Karakas SE, Perroud B, Kind T, Palazoglu M, and Fiehn O. 2016. Changes in plasma metabolites and glucose homeostasis during omega-3 polyunsaturated fatty acid supplementation in women with polycystic ovary syndrome. *BBA Clin* 5:179-185. 10.1016/j.bbacli.2016.04.003

Kortam M, Abdelrahman R, and Fateen H. 2020. L-Carnitine and Clomiphene Citrate for induction of ovulation in women with Polycystic Ovary Syndrome: Randomized controlled trial. *Evidence Based Women's Health Journal* 10:1-7.

Maleki V, Jafari-Vayghan H, Kashani A, Moradi F, Vajdi M, Kheirouri S, and Alizadeh M. 2019. Potential roles of carnitine in patients with polycystic ovary syndrome: a systematic review. *Gynecol Endocrinol* 35:463-469. 10.1080/09513590.2019.1576616

Manager R. 2020. Revman Manager. Version 5.4 ed: The Cochrane Collaboration

Nct. 2019. Effects of Triple Drug Cocktail Therapy on Metabolic, Endocrine Alterations and Perceived Stress in Patients With PCOS. *https://clinicaltrialsgov/show/NCT04113889*.

Norman RJ, Dewailly D, Legro RS, and Hickey TE. 2007. Polycystic ovary syndrome. *Lancet* 370:685-697. 10.1016/s0140-6736(07)61345-2

Peigné M, and Dewailly D. 2014. Long term complications of polycystic ovary syndrome (PCOS). *Annales d'Endocrinologie* 75:194-199. https://doi.org/10.1016/j.ando.2014.07.111

Salehpour S, Nazari L, Hoseini S, Moghaddam PB, and Gachkar L. 2019. Effects of L-carnitine on Polycystic Ovary Syndrome. *JBRA Assist Reprod* 23:392-395. 10.5935/1518-0557.20190033

Samimi M, Jamilian M, Ebrahimi FA, Rahimi M, Tajbakhsh B, and Asemi Z. 2016. Oral carnitine supplementation reduces body weight and insulin resistance in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. *Clin Endocrinol (Oxf)* 84:851-857. 10.1111/cen.13003

Selen Alpergin ES, Bolandnazar Z, Sabatini M, Rogowski M, Chiellini G, Zucchi R, and Assadi-Porter FM. 2017. Metabolic profiling reveals reprogramming of lipid metabolic pathways in treatment of polycystic ovary syndrome with 3-iodothyronamine. *Physiol Rep* 5. 10.14814/phy2.13097

Sheida A, Davar R, Tabibnejad N, and Eftekhar M. 2021. The effect of adding L-Carnitine to the GnRH-antagonist protocol on assisted reproductive technology outcome in women with polycystic ovarian syndrome: a randomized clinical trial. *Gynecol Endocrinol*:1-5. 10.1080/09513590.2021.1878135

679 Sirmans SM, and Pate KA. 2013. Epidemiology, diagnosis, and management of polycystic ovary
680 syndrome. *Clinical epidemiology* 6:1-13. 10.2147/CLEP.S37559
681 Slomaz Latifian KH, Ramin Totakhneh. 2015. Effect of Addition of L-Carnitine in Polycystic Ovary
682 Syndrome (PCOS) Patients with Clomiphene Citrate and Gonodotropin Resistant. *International*
683 *Journal of Current Research and Academic Review* Volume 3 Number 8 (August-2015) 469-476.
684 Sun Z, Chang HM, Wang A, Song J, Zhang X, Guo J, Leung PCK, and Lian F. 2019. Identification of
685 potential metabolic biomarkers of polycystic ovary syndrome in follicular fluid by SWATH mass
686 spectrometry. *Reprod Biol Endocrinol* 17:45. 10.1186/s12958-019-0490-y
687 Talari HR, Azad ZJ, Hamidian Y, Samimi M, Gilasi HR, Afshar FE, Ostadmohammadi V, and Asemi Z. 2019.
688 Effects of carnitine administration on carotid intima-media thickness and inflammatory factors
689 in patients with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled
690 trial. *International journal of preventive medicine* 10:1-6. 10.4103/ijpvm.IJPVM_2_18
691 Traub ML. 2011. Assessing and treating insulin resistance in women with polycystic ovarian syndrome.
692 *World journal of diabetes* 2:33-40. 10.4239/wjd.v2.i3.33
693 Vigerust NF, Bohov P, Bjørndal B, Seifert R, Nygård O, Svardal A, Glintborg D, Berge RK, and Gaster M.
694 2012. Free carnitine and acylcarnitines in obese patients with polycystic ovary syndrome and
695 effects of pioglitazone treatment. *Fertil Steril* 98:1620-1626.e1621.
696 10.1016/j.fertnstert.2012.08.024
697 Vonica CL, Ilie IR, Socaciu C, Moraru C, Georgescu B, Farcaş A, Roman G, Mureşan AA, and Georgescu CE.
698 2019. Lipidomics biomarkers in women with polycystic ovary syndrome (PCOS) using ultra-high
699 performance liquid chromatography-quadrupole time of flight electrospray in a positive
700 ionization mode mass spectrometry. *Scand J Clin Lab Invest* 79:437-442.
701 10.1080/00365513.2019.1658215
702 Zhao H, Zhao Y, Li T, Li M, Li J, Li R, Liu P, Yu Y, and Qiao J. 2015. Metabolism alteration in follicular niche:
703 The nexus among intermediary metabolism, mitochondrial function, and classic polycystic ovary
704 syndrome. *Free Radic Biol Med* 86:295-307. 10.1016/j.freeradbiomed.2015.05.013

705

Table 1(on next page)

Characteristic of the included studies

Table 1: Characteristic of the included studies

Studies	Participants	L carnitine dosage	Intervention	Comparison	Duration of intervention
(El Sharkwy & Sharaf El-Din 2019)	Intervention,n=140 Control,n=140	3 g LC daily	150 mg/day CC plus oral LC 3g and metformin 850 mg (1 tablet daily)	150 mg/d CC plus metformin and placebo capsules	12 weeks
(El Sharkwy & Abd El Aziz 2019)	Intervention,n=82 Control,n=82	3 g LC daily	150 mg/day of CC plus 3 g of oral LC daily, and placebo sachets	150 mg/day of CC from day 3 until day 7 of the menstrual cycle plus 600 mg of oral *N*-acetylcysteine three times daily, and a placebo capsule	12 weeks
(Ismail et al. 2014)	Intervention,n=85 Control,n=85	3 g LC daily	250 mg CC from day three until day seven of the cycle plus LC 3 g daily	250 mg CC with placebo	12 weeks
(Jamilian et al. 2017)	Intervention,n=30 Control,n=30	250 mg LC	250 mg carnitine supplements	Placebos (cellulose)	12 weeks
(Jamilian et al. 2019a)	Intervention,n=26 Control,n=27	1000 mg LC daily	LC 1000 mg/d plus 200 mg/d chromium as chromium picolinate	Placebo	12 weeks
(Jamilian et al. 2019b)	Intervention,n=27 Control,n=27	1000 mg LC daily	200 μg/day chromium picolinate plus 1000 mg/day LC	Placebo (starch)	12 weeks
(Samimi et al. 2016)	Intervention,n=30 Control,n=30	250 mg LC	250mg LC (capsule range 237-275mg)	Placebo (cellulose)	12 weeks
(Talari et al. 2019)	Intervention,n=30 Control,n=30	250mg LC daily	250 mg/day of LC	Placebo	12 weeks
(Kortam et al. 2020)	Intervention,n=47 Control,n=47	3g LC daily	Oral CC (50 mg tablet, two times per day) plus oral LC supplementation (1g tablet, three times per day)	Oral CC only (50 mg tablet, two times per day).	Not stated

Table 1: Characteristic of included studies

Table 2(on next page)

GRADE quality assessment for Comparison 1: Comparing clomiphene citrate plus LC versus clomiphene citrate plus placebo

Table 2: GRADE quality assessment for Comparison 1: Comparing clomiphene citrate plus LC versus clomiphene citrate plus placebo

Certainty assessment						Number of patients		Effect		Certainty
Total study	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LC + CC	CC + placebo	Relative (95% CI)	Absolute (95% CI)	
Outcome: Clinical pregnancy rate										
2 RCTs	not serious	serious [a]	not serious	serious [b]	none	46/132 (34.8%)	4/132 (3.0%)	**RR 7.12** (0.14 to 350.06)	**185 more per 1,000** (from 26 fewer to 1,000 more)	⊕⊕◯◯ LOW
Outcome: Ovulation rate										
2 RCTs	not serious	serious [a]	not serious	serious [b]	none	88/132 (66.7%)	36/132 (27.3%)	**RR 2.37** (0.99 to 5.66)	**374 more per 1,000** (from 3 fewer to 1,000 more)	⊕⊕◯◯ LOW
Outcome: BMI										
1 RCT	not serious	not serious	not serious	serious [c]	none	47	47	-	MD **0.4 lower** (2.12 lower to 1.32 higher)	⊕⊕⊕◯ MODERATE
Outcome: Serum FSH										
1 RCT	not serious	not serious	not serious	serious [c]	none	47	47	-	MD **0.1 higher** (0.5 lower to 0.7 higher)	⊕⊕⊕◯ MODERATE
Outcome: Serum LH										
1 RCT	not serious	not serious	not serious	serious [c]	none	47	47	-	MD **0.2 lower** (0.91 lower to 0.51 higher)	⊕⊕⊕◯ MODERATE

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference, RCT: Randomized controlled trial
GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. heterogeneity >75%
b. number of events< 400
c. number of participants <400

Table 2: GRADE quality assessment for Comparison 1: Comparing clomiphene citrate plus LC versus clomiphene citrate plus placebo

Table 3(on next page)

GRADE quality assessment of Comparison 2: comparing clomiphene citrate, metformin plus LC versus clomiphene citrate, metformin plus placebo

Table 3: GRADE quality assessment of Comparison 2: comparing clomiphene citrate, metformin plus LC versus clomiphene citrate, metformin plus placebo

Certainty assessment						Number of patients		Effect		Certainty
Total study	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LC +CC + MTF	CC + MTF + placebo	Relative (95% CI)	Absolute (95% CI)	
Outcome: Clinical pregnancy rate										
1 RCT	not serious	not serious	not serious	serious [a]	none	39/138 (28.3%)	9/136 (6.6%)	**RR 4.27** (2.15 to 8.47)	**216 more per 1,000** (from 76 more to 494 more)	⊕⊕⊕◯ MODERATE
Outcome: Ovulation rate										
1 RCT	not serious	not serious	not serious	serious [a]	none	48/138 (34.8%)	15/136 (11.0%)	**RR 3.15** (1.86 to 5.35)	**237 more per 1,000** (from 95 more to 480 more)	⊕⊕⊕◯ MODERATE
Outcome: BMI										
1 RCT	not serious	not serious	not serious	serious [b]	none	138	136	-	MD **1.1 higher** (0.32 higher to 1.88 higher)	⊕⊕⊕◯ MODERATE
Outcome: Serum FPG										
1 RCT	not serious	not serious	not serious	serious [b]	none	138	136	-	MD **5.1 lower** (6.25 lower to 3.95 lower)	⊕⊕⊕◯ MODERATE
Outcome: Serum LDL										
1 RCT	not serious	not serious	not serious	serious [b]	none	138	136	-	MD **25 lower** (27.93 lower to 22.07 lower)	⊕⊕⊕◯ MODERATE
Outcome: Serum total cholesterol										
1 RCT	not serious	not serious	not serious	serious [b]	none	138	136	-	MD **21 lower** (24.14 lower to 17.86 lower)	⊕⊕⊕◯ MODERATE
Outcome: Serum HDL										
1 RCT	not serious	not serious	not serious	serious [b]	none	138	136	-	MD **15.5 higher** (12.42 higher to 18.58 higher)	⊕⊕⊕◯ MODERATE
Outcome: Serum triglyceride										
1 RCT	not serious	not serious	not serious	serious [b]	none	138	136	-	MD **9 lower** (11.46 lower to 6.54 lower)	⊕⊕⊕◯ MODERATE
Outcome: serum FSH										
1 RCT	not serious	not serious	not serious	serious [b]	none	138	136	-	MD **0.63 lower** (0.92 lower to 0.34 lower)	⊕⊕⊕◯ MODERATE

Certainty assessment						Number of patients		Effect		Certainty
Total study	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LC +CC + MTF	CC + MTF + placebo	Relative (95% CI)	Absolute (95% CI)	
Outcome: serum LH										
1 RCT	not serious	not serious	not serious	serious [b]	none	138	136	-	MD **2.36 lower** (3.04 lower to 1.68 lower)	⊕⊕⊕◯ MODERATE

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference RCT: Randomized controlled trial
GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. number of events <400
b. number of participants <400

Table 3: GRADE quality assessment of **Comparison 2**: comparing clomiphene citrate, metformin plus LC versus clomiphene citrate, metformin plus placebo

Table 4(on next page)

Summary of findings and GRADE quality assessment of primary and secondary outcomes for Comparison 3: comparing clomiphene citrate plus LC versus clomiphene citrate plus n acetylcysteine

Table 4: Summary of findings and GRADE quality assessment of primary and secondary outcomes for Comparison 3: comparing clomiphene citrate plus LC versus clomiphene citrate plus n acetylcysteine

Certainty assessment						Number of patients		Effect		Certainty
Total study	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LC+CC	CC + NAC	Relative (95% CI)	Absolute (95% CI)	
Outcome: Clinical pregnancy rate										
1 RCT	not serious	not serious	not serious	serious [a]	none	25/80 (31.3%)	22/82 (26.8%)	**RR 1.16** (0.72 to 1.89)	**43 more per 1,000** (from 75 fewer to 239 more)	⊕⊕⊕◯ MODERATE
Outcome: Ovulation rate										
1 RCT	not serious	not serious	not serious	serious [a]	none	38/80 (47.5%)	35/82 (42.7%)	**RR 1.11** (0.79 to 1.56)	**47 more per 1,000** (from 90 fewer to 239 more)	⊕⊕⊕◯ MODERATE
Outcome: BMI										
1 RCT	not serious	not serious	not serious	serious [b]	none	80	82	-	MD **0.1 higher** (0.78 lower to 0.98 higher)	⊕⊕⊕◯ MODERATE
Outcome: Serum FPG										
1 RCT	not serious	not serious	not serious	serious [b]	none	80	82	-	MD **2.3 higher** (1.02 higher to 3.58 higher)	⊕⊕⊕◯ MODERATE
Outcome: serum LDL										
1 RCT	not serious	not serious	not serious	serious [b]	none	80	82	-	MD **12 lower** (15.8 lower to 8.2 lower)	⊕⊕⊕◯ MODERATE
Outcome: serum total cholesterol										
1 RCT	not serious	not serious	not serious	serious [b]	none	80	82	-	MD **24 lower** (27.61 lower to 20.39 lower)	⊕⊕⊕◯ MODERATE
Outcome: serum HDL										
1 RCT	not serious	not serious	not serious	serious [b]	none	80	82	-	MD **9.6 higher** (5.3 higher to 13.9 higher)	⊕⊕⊕◯ MODERATE
Outcome: serum triglyceride										

Certainty assessment						Number of patients		Effect		Certainty
Total study	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LC+CC	CC + NAC	Relative (95% CI)	Absolute (95% CI)	
1 RCT	not serious	not serious	not serious	serious [b]	none	80	82	-	MD **19 lower** (22.79 lower to 15.21 lower)	⊕⊕⊕◯ MODERATE
Outcome: serum FSH										
1 RCT	not serious	not serious	not serious	serious [b]	none	80	82	-	MD **0.5 lower** (0.84 lower to 0.16 lower)	⊕⊕⊕◯ MODERATE
Outcome: serum LH										
1 RCT	not serious	not serious	not serious	serious [b]	none	80	82	-	MD **0.4 lower** (1.51 lower to 0.71 higher)	⊕⊕⊕◯ MODERATE

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference, RCT: Randomized controlled trial
GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. number of events <400
b. number of participants <400

Table 4: Summary of findings and GRADE quality assessment of primary and secondary outcomes for **Comparison 3**: comparing clomiphene citrate plus LC versus clomiphene citrate plus n acetylcysteine

Table 5(on next page)

The summary of findings of outcomes and GRADE quality assessment for comparison 4: comparing of the LC versus the placebo.

Table 5: The summary of findings of outcomes and GRADE quality assessment for comparison 4: comparing of the LC versus the placebo.

Certainty assessment						Number of patients		Effect		Certainty
Total study	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LC	Placebo	Relative (95% CI)	Absolute (95% CI)	
Outcome: Serum FPG										
1 RCT	not serious	not serious	not serious	serious [a]	none	30	30	-	MD **1.26 lower** (7.5 lower to 4.98 higher)	⊕⊕⊕◯ MODERATE
Outcome: Serum LDL										
1 RCT	not serious	not serious	not serious	serious [a]	none	30	30	-	MD **0.33 higher** (0.05 lower to 0.71 higher)	⊕⊕⊕◯ MODERATE
Outcome: Serum total cholesterol										
1 RCT	not serious	not serious	not serious	serious [a]	none	30	30	-	MD **6.84 higher** (0.45 lower to 14.13 higher)	⊕⊕⊕◯ MODERATE
Outcome: Serum HDL										
1 RCT	not serious	not serious	not serious	serious [a]	none	30	30	-	MD **0** (3.6 lower to 3.6 higher)	⊕⊕⊕◯ MODERATE
Outcome: Serum Triglyceride										
1 RCT	not serious	not serious	not serious	serious [a]	none	30	30	-	MD **0.15 higher** (0.14 lower to 0.44 higher)	⊕⊕⊕◯ MODERATE
Outcome: Serum BMI										
3 RCTs	not serious	not serious	not serious	serious [a]	none	90	90	-	MD **1.33 lower** (1.52 lower to 1.14 lower)	⊕⊕⊕◯ MODERATE
Outcome: Mental health status (using BDI)										
1 RCT	not serious	not serious	not serious	serious [a]	none	30	30	-	MD **2.5 higher** (2.35 higher to 2.65 higher)	⊕⊕⊕◯ MODERATE
Outcome: Mental health status (using GHQ)										
1 RCT	not serious	not serious	not serious	serious [a]	none	30	30	-	MD **5.8 lower** (6.1 lower to 5.5 lower)	⊕⊕⊕◯ MODERATE

Certainty assessment						Number of patients		Effect		Certainty
Total study	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LC**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**	
Outcome: Mental health status (using DASS)										
1 RCT	not serious	not serious	not serious	serious [a]	none	30	30	-	MD **6.8 lower** (7.2 lower to 6.4 lower)	⊕⊕⊕◯ MODERATE

CI: Confidence interval; **MD:** Mean difference, RCT: Randomized controlled trial, BDI: Beck Depression Index, GHQ: General Health Questionnaire, DASS: Depression Anxiety Stress Score

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

[a] number of participants <400

Table 5: The summary of findings of outcomes and GRADE quality assessment for **comparison 4**: comparing of the LC versus the placebo.

Table 6(on next page)

The summary of primary and secondary outcome findings and GRADE quality assessments for Comparison 5: comparing of LC plus chromium with the placebo.

Table 6: The summary of primary and secondary outcome findings and GRADE quality assessments for Comparison 5: comparing of LC plus chromium with the placebo.

Certainty assessment						Number of patients		Effect		Certainty
Total study	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LC + Chromium	placebo	Relative (95% CI)	Absolute (95% CI)	
Outcome: Serum FPG										
1 RCT	not serious	not serious	not serious	serious [a]	none	27	27	-	MD **3.4 lower** (7.6 lower to 0.8 higher)	⊕⊕⊕◯ MODERATE
Outcome: Serum LDL										
1 RCT	not serious	not serious	not serious	serious [a]	none	27	27	-	MD **0.6 lower** (19.95 lower to 18.75 higher)	⊕⊕⊕◯ MODERATE
Outcome: Serum Total cholesterol										
1 RCT	not serious	not serious	not serious	serious [a]	none	27	27	-	MD **9.7 lower** (28.53 lower to 9.13 higher)	⊕⊕⊕◯ MODERATE
Outcome: Serum HDL										
1 RCT	not serious	not serious	not serious	serious [a]	none	27	27	-	MD **3.4 lower** (8.2 lower to 1.4 higher)	⊕⊕⊕◯ MODERATE
Outcome: Serum Triglyceride										
1 RCT	not serious	not serious	not serious	serious [a]	none	27	27	-	MD **28.1 lower** (47.25 lower to 8.95 lower)	⊕⊕⊕◯ MODERATE
Outcome: Mental health status (using BDI)										
1 RCT	not serious	not serious	not serious	serious [a]	none	26	27	-	MD **1.5 lower** (4.17 lower to 1.17 higher)	⊕⊕⊕◯ MODERATE
Outcome: Mental health status (using GHQ)										
1 RCT	not serious	not serious	not serious	serious [a]	none	26	27	-	MD **1.8 lower** (7.1 lower to 3.5 higher)	⊕⊕⊕◯ MODERATE
Outcome: Mental health status (using DASS)										
1 RCT	not serious	not serious	not serious	serious [a]	none	26	27	-	MD **3.5 lower** (11.42 lower to 4.42 higher)	⊕⊕⊕◯ MODERATE

CI: Confidence interval; **MD:** Mean difference, RCT: Randomized controlled trial, BDI: Beck Depression Index, GHQ: General Health Questionnaire, DASS: Depression Anxiety Stress Score

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. number of participants <400

Table 6: The summary of primary and secondary outcome findings and GRADE quality assessments for **Comparison 5**: comparing of LC plus chromium with the placebo.

Figure 1

PRISMA study flow diagram

Figure 1: PRISMA study flow diagram

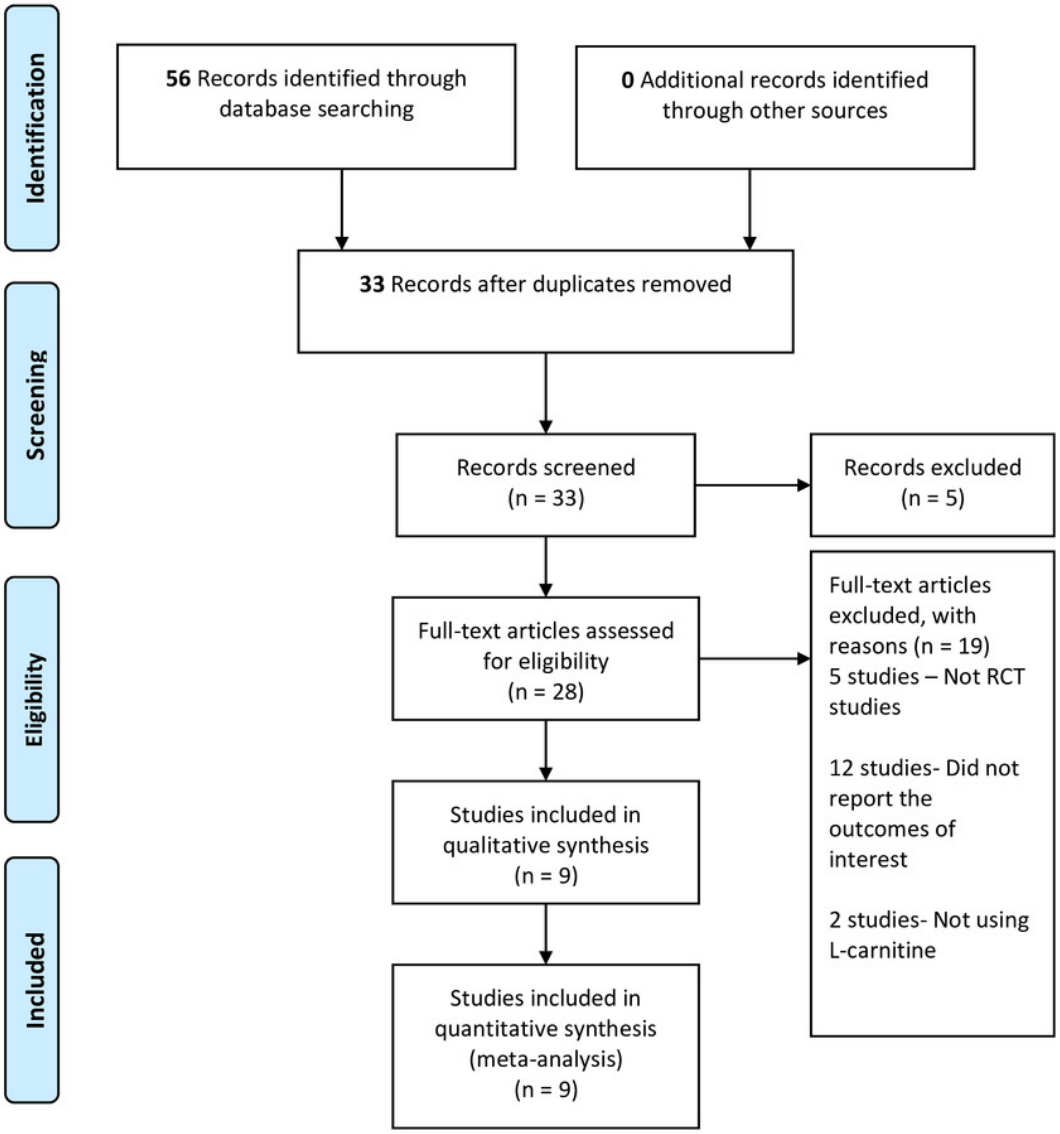

Identification
Screening
Eligibility
Included
56 Records identified through database searching
0 Additional records identified through other sources
33 Records after duplicates removed
Records screened (n = 33)
Records excluded (n = 5)
Full-text articles assessed for eligibility (n = 28)
Full-text articles excluded, with reasons (n = 19)
5 studies – Not RCT studies
12 studies- Did not report the outcomes of interest
2 studies- Not using L-carnitine
Studies included in qualitative synthesis (n = 9)
Studies included in quantitative synthesis (meta-analysis) (n = 9)

Figure 2

Risk of bias

Figure 2: Risk of bias graph: authors’ judgements about each risk of bias item presented as percentages across all included studies.

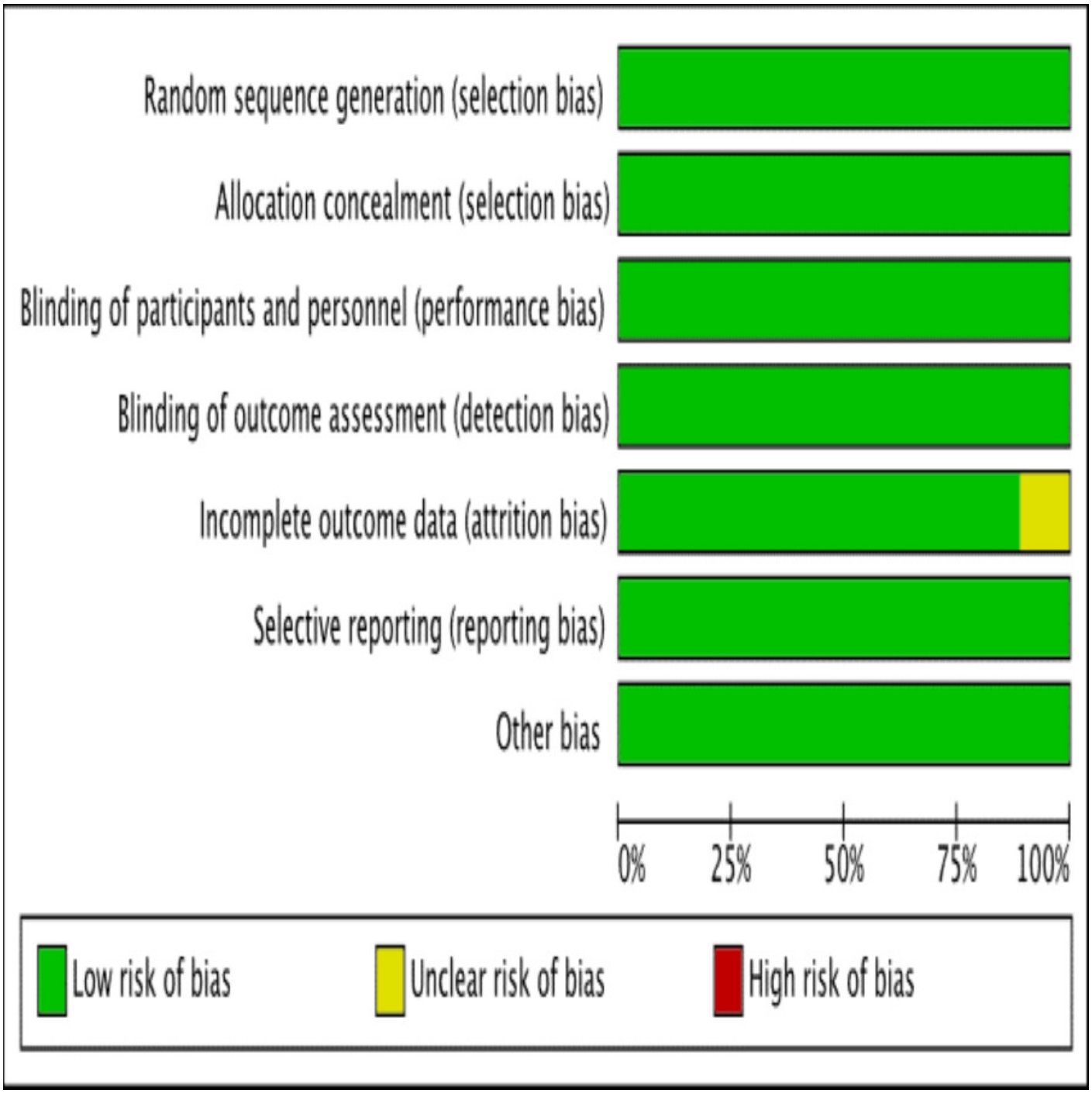

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
0%
25%
50%
75%
100%
Low risk of bias
Unclear risk of bias
High risk of bias

Figure 3

Risk of bias summary

Figure 3: Risk of bias summary: authors' judgements on each risk of bias item for each included study

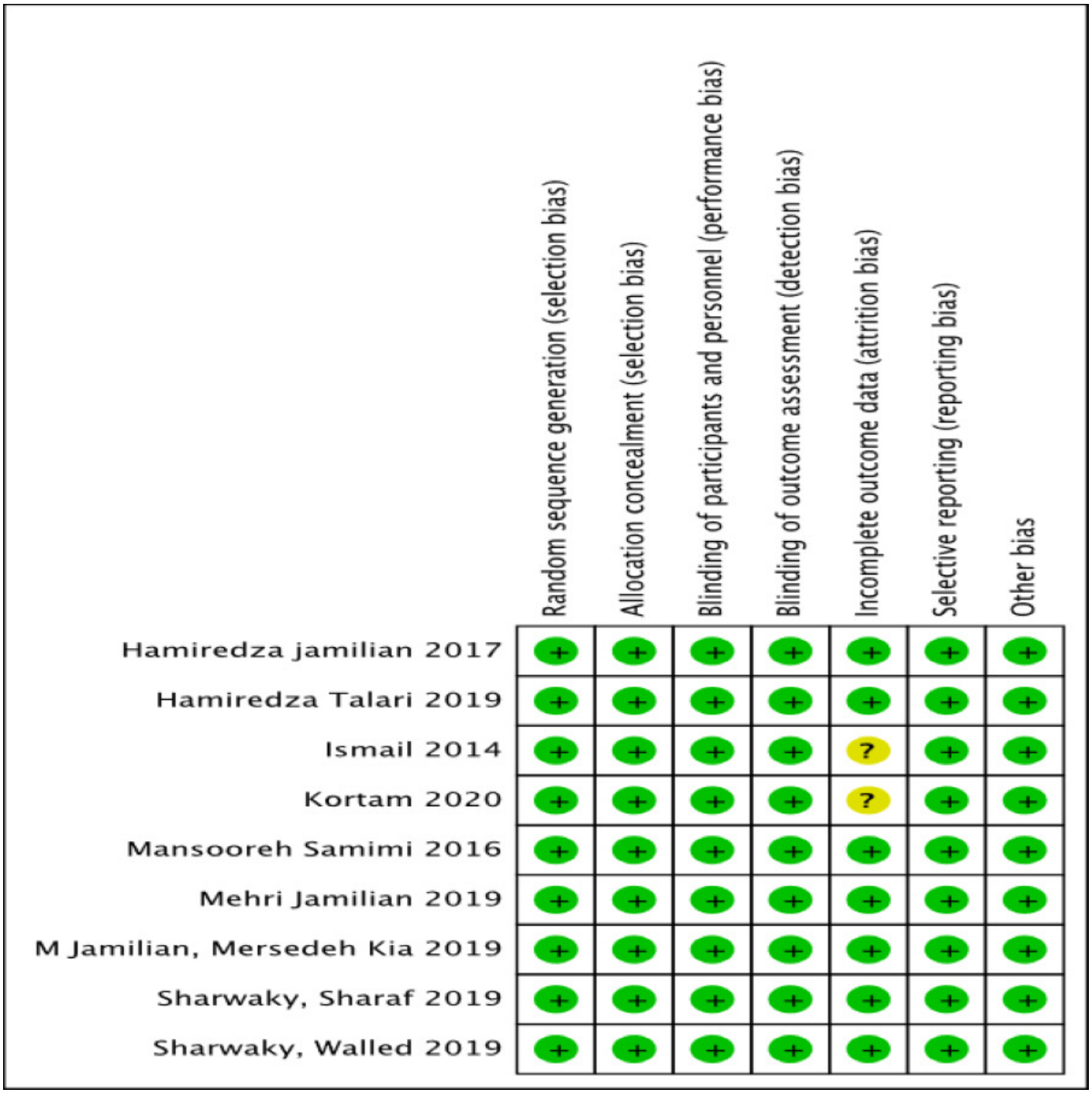

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Hamiredza jamilian 2017
Hamiredza Talari 2019
Ismail 2014
Kortam 2020
Mansooreh Samimi 2016
Mehri Jamilian 2019
M Jamilian, Mersedeh Kia 2019
Sharwaky, Sharaf 2019
Sharwaky, Walled 2019

Figure 4

Forest plot comparing clomiphene citrate and LC versus clomiphene citrate plus placebo for primary outcomes, clinical pregnancy rate and ovulation rate.

Figure 4: Forest plot comparing clomiphene citrate and LC versus clomiphene citrate plus placebo for primary outcomes, clinical pregnancy rate and ovulation rate.

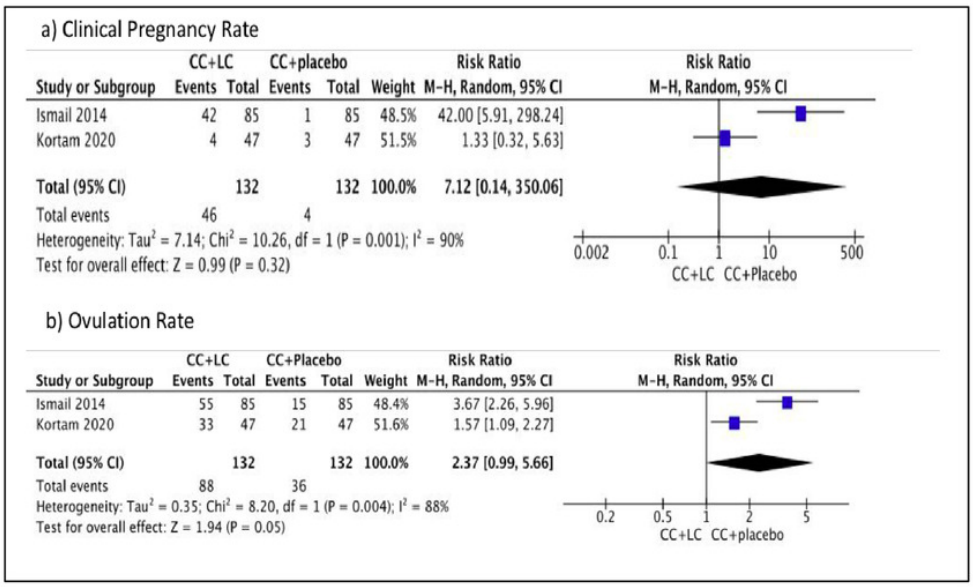
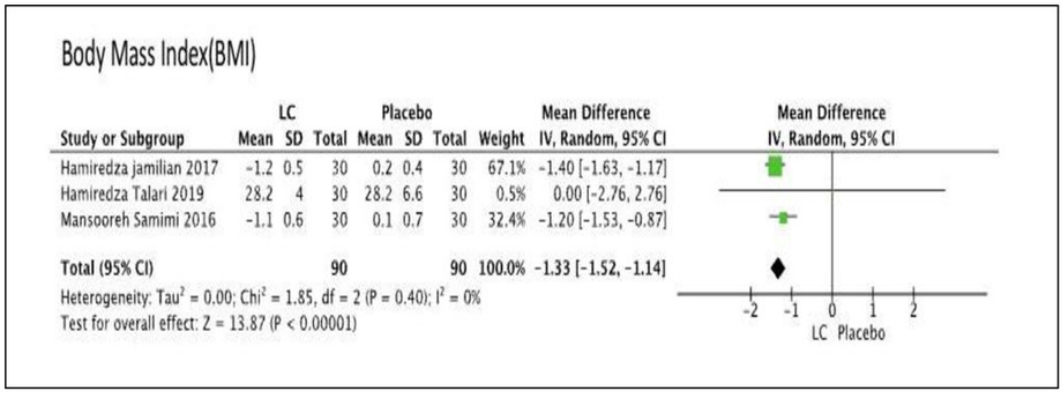

a) Clinical Pregnancy Rate
CC+LC
CC+placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Ismail 2014 42 85 1 85 48.5% 42.00 [5.91, 298.24]
Kortam 2020 4 47 3 47 51.5% 1.33 [0.32, 5.63]
Total (95% CI) 132 132 100.0% 7.12 [0.14, 350.06]
Total events 46 4
Heterogeneity: Tau² = 7.14; Chi² = 10.26, df = 1 (P = 0.001); I² = 90%
Test for overall effect: Z = 0.99 (P = 0.32)
0.002 0.1 1 10 500
CC+LC CC+Placebo
b) Ovulation Rate
CC+LC
CC+Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Ismail 2014 55 85 15 85 48.4% 3.67 [2.26, 5.96]
Kortam 2020 33 47 21 47 51.6% 1.57 [1.09, 2.27]
Total (95% CI) 132 132 100.0% 2.37 [0.99, 5.66]
Total events 88 36
Heterogeneity: Tau² = 0.35; Chi² = 8.20, df = 1 (P = 0.004); I² = 88%
Test for overall effect: Z = 1.94 (P = 0.05)
0.2 0.5 1 2 5
CC+LC CC+placebo

Figure 5

Forest plot for the primary outcome, body mass index (BMI) of comparison 4: comparing of the LC versus the placebo.

Figure 5: Forest plot for the primary outcome, body mass index (BMI) of comparison 4: comparing of the LC versus the placebo.


Body Mass Index(BMI)
LC
Placebo
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Hamiredza jamilian 2017 -1.2 0.5 30 0.2 0.4 30 67.1% -1.40 [-1.63, -1.17]
Hamiredza Talari 2019 28.2 4 30 28.2 6.6 30 0.5% 0.00 [-2.76, 2.76]
Mansooreh Samimi 2016 -1.1 0.6 30 0.1 0.7 30 32.4% -1.20 [-1.53, -0.87]
Total (95% CI) 90 90 100.0% -1.33 [-1.52, -1.14]
Heterogeneity: Tau² = 0.00; Chi² = 1.85, df = 2 (P = 0.40); I² = 0%
Test for overall effect: Z = 13.87 (P < 0.00001)
-2
-1
0
1
2
LC
Placebo