Effects of L-carnitine supplementation for patient with polycystic ovarian 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 ovarian 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) has 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 polycystic ovarian syndrome.

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 randomised control trials comparing LC alone or in combination with other standard treatments for the treatment of polycystic ovarian syndrome from inception till June 2021. We independently screened titles and abstracts to identify available trials, and full texts of the trials were checked for eligibility. Data on the methods, interventions, outcomes, and risk of bias from included trials were extracted independently by the authors. Estimation of risk ratios and mean differences with a 95% confidence interval was done using a random-effects model.

Results A total of nine studies with 995 participants were included in this review. There were five groups of comparison. In one comparison group, LC reduces the fasting plasma glucose (MD -5.10, 95% CI -6.25 to -3.95; P = 0.00001), serum 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 showed 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 BMI and serum LDL, triglyceride, and total cholesterol levels in women with PCOS.

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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

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Abstract

Background

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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 randomised control trials comparing LC alone or in combination with other standard treatments for the treatment of polycystic ovarian syndrome from inception till June 2021. We independently screened titles and abstracts to identify available trials, and full texts of the trials were checked for eligibility. Data on the methods, interventions, outcomes, and risk of bias from included trials were extracted independently by the authors. Estimation of risk ratios and mean differences with a 95% confidence interval was done using a random-effects model.

Results

A total of nine studies with 995 participants were included in this review. There were five groups of comparison. In one comparison group, LC reduces the fasting plasma glucose (MD -5.10, 95% CI -6.25 to -3.95; P = 0.00001), serum 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 showed 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 BMI and serum LDL, triglyceride, and total cholesterol levels in women with PCOS.

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Keywords: Carnitine; Polycystic Ovarian Syndrome; Meta-analysis

Introduction

Polycystic ovarian syndrome (PCOS) is a common disease that affects women of reproductive age, with a prevalence of 6.5 and 8% (Norman et al. 2007b). 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). Menstrual problems commonly related to PCOS include oligomenorrhea, amenorrhea, and prolonged menstrual bleeding. 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 Rotterdam European Society for Human Reproduction and American Society of Reproductive Medicine (ASRM) criteria, currently known as the Rotterdam Criteria. The criteria comprise three features, including oligo/amenorrhea, clinical and biochemical signs of hyperandrogenism, and evidence of polycystic ovaries on ultrasound findings. Two of the three features confirm the PCOS diagnosis (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 is an independent risk factor for coronary artery disease as obesity is associated with insulin resistance, dyslipidemia, and ovulatory dysfunction in adolescents (Traub 2011). Evaluating risk factors for coronary arterial diseases (CAD) is essential in PCOS because CAD is 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 for this anovulation problem in PCOS (Badawy & Elnashar 2011). L-carnitine (LC) is an endogenous compound synthesis by human body and has a role in fatty acid metabolism (Johri et al. 2014). It is synthesized from lysine and methionine and is available from dietary sources such as meat, poultry, and dairy products (Johri et al. 2014). It acts as an obligatory cofactor for the oxidation of fatty acids by facilitating the transport of long-chain fatty acids across the mitochondrial membrane. LC levels are low in patients with PCOS, thus 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. LC could normalize androgen levels, contributing to a significant drop in testosterone levels (Della Corte et al. 2020). LC may enhance insulin sensitivity, which in turn affects 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 polycystic ovarian syndrome. The primary outcomes were clinical pregnancy and ovulation rate, BMI, fasting plasma glucose (FPG), and serum lipid levels, including LDL, triglycerides, total cholesterol, and HDL levels. Mental health status, serum FSH, and LH levels were 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 raise clinical pregnancy rates.

Materials & Methods

The methodology and reporting conducted in this review is according to 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 were women who were diagnosed with polycystic ovarian syndrome based on the revised European Society for Human Reproduction (ESHRE) and the American Society of Reproductive Medicine (ASRM) diagnosis of PCOS, Rotterdam criteria 2003. We excluded cross-over trials and studies other than RCTs. We restricted the publications to the English language only.

We used the search strategy in **Appendix** 1 and searched through 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 available studies comparing LC alone or in combination with other standard treatments for the treatment of polycystic ovarian syndrome. For additional datasets, we modified the search strategy. Using the Boolean operators AND, OR, we combined the terms "polycystic ovarian syndrome" and "L carnitine" (Refer to Appendix 1). To locate unpublished trials or trials not found using electronic searches, we looked through the reference lists of recognised RCTs and read 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 look for active trials.

Three authors (MFMS, SB, and AAK) scanned for trial selection through the titles and abstracts from the searches. From there, 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 for exclusion after the authors independently reviewed the studies' eligibility. Any differences were settled by discussion among the authors. If more information is required, we will contact the authors. We utilised the Cochrane Handbook for Systematic Reviews of Interventions' recommended procedure 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 a total of 33 records after

duplicates were removed. We reviewed the full texts of 28 records: nine studies met the inclusion criteria, and 19 studies did not fulfill the inclusion criteria and were 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 extracted the data independently. We extracted data on the study setting, participant characteristics (age), methodology (inclusion and exclusion criteria, number of participants randomized and analyzed, duration of follow-up), interventions described (dose, frequency, preparation, and duration used) and the outcomes measured. We extracted data on 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 low-density lipoprotein (LDL), serum high-density lipoprotein (HDL), triglyceride (TG), total cholesterol in mmol/l or mg/dl, and fasting blood glucose (FPG) in mg/dl serum follicular stimulating hormone (FSH) and luteinizing hormone (LH) in IU/L, mental health status assessment using any questionnaires, and adverse side effects such as gastrointestinal disturbances (abdominal pain, nausea, vomiting), which occurred at any time during the study period after randomization using a data extraction form. Disagreements between the review authors (MFMS, SB, and 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 each of the included studies (Higgins JPT 2021). Three authors (MFMS, SB, AAK) assessed selection bias (randomization, allocation concealment), performance bias (blinding of participants and health personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other bias (recall bias, transfer bias and etc.) independently. We classified the risk of bias as very low, low, moderate, or high. We resolved disagreements through discussion with the fourth author (NMN). 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). 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 analysed the data using Review Manager 5.4 software (Manager 2020) for the statistical analyses. We used a random-effects model to pool the data. We measured the treatment effect using risk ratios (RR) for dichotomous outcomes and mean differences (MD) with 95% confidence intervals (CI) for continuous outcomes. We assessed the presence of heterogeneity in two steps

and first, at face value by comparing populations, settings, interventions, and outcomes(Higgins JPT 2021). Then, 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% to 100% would be considerable heterogeneity (Higgins JPT 2021). We checked the included trials for unit of analysis errors. 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 intracluster correlation coefficient, we adjusted the results from trials with unit of analysis errors (Higgins JPT 2021). We contacted the trial's original authors to request data that was 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 high risk of bias for sequence generation and allocation concealment of included studies. If there were sufficient studies, 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), 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), and 2 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 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 were diagnosed with PCOS based on the Rotterdam criteria. Six trials involved participants aged 18-40 years old (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). Two trials

included BMI > 25kg/m^2 as one of the inclusion criteria(Jamilian et al. 2019b; Samimi et al. 2016) and three trials used clomiphene citrate resistant PCOS as an inclusion criteria (El Sharkwy & Sharaf El-Din 2019; El Sharkwy & Abd El Aziz 2019; Ismail et al. 2014). All nine trials reported hyperprolactinemia as an exclusion criteria. Eight trials excluded participants with endocrine disorder, and the duration of the study was 12 weeks, except one trial(Kortam et al. 2020) which did not mention the duration of the study. 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 addressing various comparisons and outcomes, resulting in several comparisons contributing to each of the predefined outcomes. All the 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 ovulation rate (El Sharkwy & Sharaf El-Din 2019; El Sharkwy & Abd El Aziz 2019; Ismail et al. 2014; Kortam et al. 2020), seven out of nine included trials reported body mass index (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). Lipid profile including serum LDL, HDL, total cholesterol and triglyceride levels 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), and fasting plasma glucose 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 are reported for the secondary outcomes, which are hormonal level, including the serum FSH level, and LH level, 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 mental health status was reported in two trials (Jamilian et al. 2017; Jamilian et al. 2019a).

Assessment risk of bias

The assessment of the risk of bias is 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) except one trial (Jamilian et al. 2019b) in which the randomization sequence done manually at the clinic. Therefore, we judged a- high risk of random sequence generation bias for this trial (Jamilian et al. 2019b), whereas the other eight trials were low risk of bias. Allocation concealment was reported in all the trials. All trials conducted their studies using placebo capsules, which are designed identically as

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. Blinding of participants and personnel was mentioned in eight trials (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), which made the risk of bias unclear. One trial (Kortam et al. 2020), did not mention blinding of participants and personnel. 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) which mentioned that patients and physicians were blinded to the treatment allocation. Only one trial (Talari et al. 2019) mentioned that researchers and participants were not blinded to the allocation concealment, thus causing a high risk of bias.

Eight trials reported the number of participants who completed the study, including the number of patients who dropped out of the study for various 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% (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)One trial (Talari et al. 2019) did not have any missing participants from both 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. It also did not summarize the patients' flow diagram, thus making it unclear the 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: three trials (Jamilian et al. 2017; Jamilian et al. 2019a; Samimi et al. 2016) registered in the Iranian Registry of Clinical Trials and one trial (El Sharkwy & Abd El Aziz 2019) registered in National Clinical Trials.

L-carnitine supplementation for women with PCOS

There are five comparisons in this review, and we performed meta-analysis for each comparison group. For the first comparison, the combination of clomiphene citrate and LC was compared with clomiphene citrate and placebo (Ismail et al. 2014; Kortam et al. 2020). In one study, an amount of 250 milligrams (mg) of oral clomiphene citrate was given together with 3 grams (g) of LC in one study compared with the same 250 mg clomiphene citrate combined with placebo (Ismail et al. 2014), while in another study, they used 100 mg clomiphene citrate daily in combination with 3 g of LC daily and compared it with 100 mg clomiphene citrate plus the placebo(Kortam et al. 2020). The second comparison was the study which used 150 mg clomiphene citrate, 850 mg metformin and 1 g of LC versus 150 mg clomiphene citrate, 850 mg metformin and placebo (El Sharkwy & Sharaf El-Din 2019) whereas the third comparison was the studies which used a

combination of 150 g clomiphene citrate and 600 mg of oral N-Acetylcysteine versus 150 mg clomiphene citrate plus 3 g of LC (El Sharkwy & Abd El Aziz 2019). The fourth comparison was the studies using 250 mg of LC versus placebo (Jamilian et al. 2017; Samimi et al. 2016; Talari et al. 2019), and the fifth comparison was the studies using 200 mg of chromium picolinate and 1 g of LC daily versus 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. There was no difference in clinical pregnancy rate between the two groups (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). There was a difference for the primary outcome, ovulation rate between the two groups which favors 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** shows the Forest plot comparing clomiphene citrate and LC versus clomiphene citrate plus placebo for primary outcomes, clinical pregnancy rate and ovulation rate. There is a difference for the primary outcome, BMI within one group which favors 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). There is no difference 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 -0.20, 95% CI -0.91 to 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 pregnancy rate, FSH, and LH levels; however, there was a significant difference favoring the placebo in ovulation rate and BMI. **Table 2** shows the summary of findings and GRADE quality assessment for primary and secondary outcomes of comparison 1.

Comparison 2: clomiphene citrate, metformin plus LC versus clomiphene citrate, metformin plus placebo

We performed meta-analysis in this comparison. There is a significant difference for 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 was a significant difference for 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**). 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 favors 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 favors 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 was 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 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** shows the summary of findings 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 was no difference for the primary outcome, clinical pregnancy rate, in one group (RR 1.16, 95% CI 0.72 to 1.89; P = 0.54; one trial, n = 162; moderate quality evidence) (El Sharkwy & Abd El Aziz 2019). There was no difference for the primary outcome, ovulation rate, in one group (RR 1.11, -95% CI 0.79 to 1.56; P = 0.54; one trial, n = 162; moderate quality evidence) (El Sharkwy & Abd El Aziz 2019). There was 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 was a significant difference for the primary outcome, FPG in one group which favors 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 favors 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 favors 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 favors 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 favors 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 favors 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 pregnancy rate, ovulation rate, BMI or LH level. There was a significant difference that favored the combination of LC in LDL, TC, TG, and FSH levels, whereas there was a significant difference that favored the combination with NAC in 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 of the LC versus 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 triglyceride 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 the 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 versus placebo for the primary outcome, body mass index (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 as measured by assessment score, BDI score in one group that favors 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 that favors 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 that favors 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 FPG, LDL, TC, HDL, and TG levels, whereas there were significant differences that favored LC in 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 significant difference for the primary outcome, TG level in one group which favors 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, 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, whereas there was a significant difference which favored combination with LC in TG level. The summary of secondary outcomes findings and GRADE quality assessment are shown in **Table 6**.

Discussion

Polycystic ovarian syndrome (PCOS) is affecting women of reproductive age (Norman et al. 2007a). Menstrual problems, hyperandrogenism, and infertility are the most common symptoms in the early reproductive years (Peigné & Dewailly 2014). Pregnancy complication, obesity, glucose intolerance, type 2 diabetes, cardiovascular disease, and gynecological malignancies can all develop as women get older. For these "at-risk" women, lifelong monitoring is required, and preventative actions must 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 and are likely to last beyond the reproductive age until menopause(Cooney & Dokras 2018). There has been little research into the risk of cardiovascular morbidity and mortality in women with PCOS after 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, resulting in several comparisons contributing to each of our predefined outcomes. We were unable to do subgroup analyses as there were inadequate trials that used the similar comparisons.

We conducted a comprehensive literature study to evaluate the effect of LC on PCOS patients. From nine trials, only five trials can be sub grouped into similar combinations of comparisons in

which two trials (Ismail et al. 2014; Kortam et al. 2020) in Comparison 1 for the outcome 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 for BMI outcome. Thus, as a result, the application of the findings in this review is limited. On the outcome basis, three primary outcomes: clinical pregnancy rate, ovulation rate, and FPG have similar trials with similar combination of comparisons, in which two trials in clinical pregnancy rates, two trials in ovulation rate, and three trials in FPG. From the reported incidence of adverse events, we detected side effects in one trial (Kortam et al. 2020), i.e. abdominal pain, dizziness and nausea. However, none of the trial investigators reported serious side effects from 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.

Except for one trial (Jamilian et al. 2019b), most trials had a low risk of bias for allocation bias because randomization was done manually at the clinic. One trial (Kortam et al. 2020) had unclear risk of bias for blinding of participants and personnel, while another (Talari et al. 2019) had a high risk of bias because the researchers and participants were not blinded in their trial. All trials had reported outcomes as stated in their method section, while four trials published their protocols. The risk of attrition bias was present in only one trial (Kortam et al. 2020) as the number of participants who withdrew or completed the study was not stated. In eight trials, the percentage of participants who were lost to follow-up was less than 15%, and two trials (Jamilian et al. 2017; Talari et al. 2019) declared that they received financing from a 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 publication bias by searching multiple databases without regard to language restrictions and looking through the reference lists of all linked articles for additional references. We cannot, however, guarantee that we have discovered all the trials in this area. We could not create a funnel plot to detect bias or heterogeneity because there were only nine trials included, and not all included trials reported similar outcomes.

In one systematic review, the effect of LC on patients with polycystic ovary syndrome was investigated (Maleki et al. 2019). They investigated the potential roles of LC in PCOS patients. It included two observational studies (Celik et al. 2017; Fenkci et al. 2008) and four randomized controlled studies, three of which were included in this meta-analysis (Ismail et al. 2014; Jamilian et al. 2019b; Samimi et al. 2016) and one study (Slomaz Latifian 2015) not related to our primary and secondary outcomes. Similar to our meta-analysis, BMI had a significant effect on LC

supplementation based on three trials (Ismail et al. 2014; Jamilian et al. 2019b; Samimi et al. 2016), but for lipid profile, one study had a significant effect (Ismail et al. 2014) and two studies had no effect (Fenkci et al. 2008; Samimi et al. 2016).

Conclusions

Based on this meta-analysis, LC is beneficial for improving BMI, as well as the lipid profile, which includes LDL, TC, and TG levels in women with PCOS. However, the meta-analysis found no significant effect in clinical pregnancy rate and ovulation rate; thus, justification of LC use for these outcomes requires further research and clinical trials. The findings of this review should be interpreted in the context of LC supplementation in conjunction with other medications in the treatment of PCOS. The evaluation of the side effects of LC use in the studies are limited, and more safety data is needed to assess the risks of using it. If more research is done on the use of LC in PCOS women, the pregnancy rate and ovulation rate should be included as outcomes. It is because PCOS women seek treatment for infertility issues. Physical findings such as hirsutism, acne, and weight reduction can also be considered as other important outcome in future research.

OTHER INFORMATIONS

Registration and protocol

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

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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 were available in the supplementary files.

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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

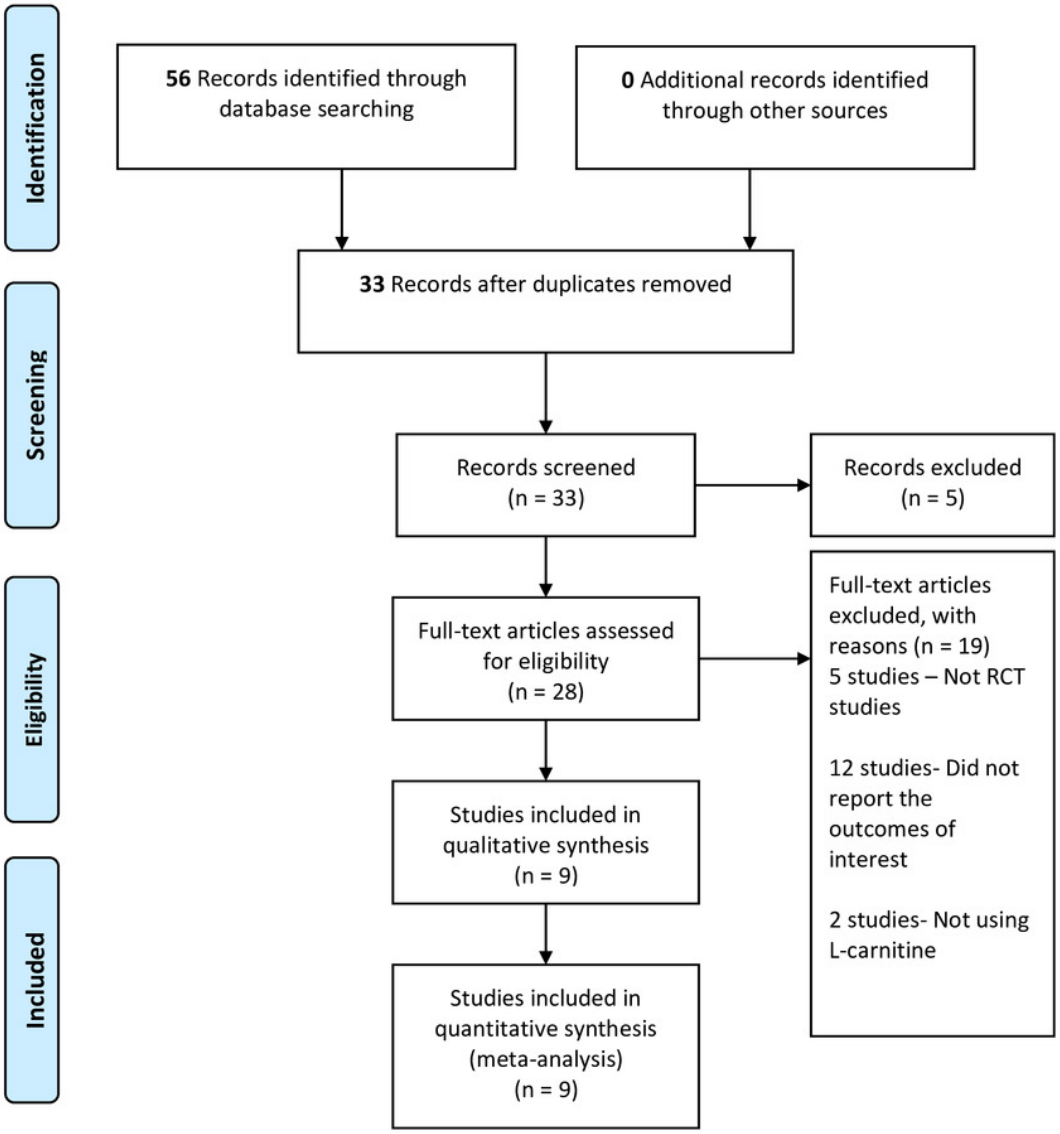

Identification
Screening
Eligibility
Included
56 Records identified through database searching
0 Additional records identified through other sources
33 Records after duplicates removed
Records screened (n = 33)
Records excluded (n = 5)
Full-text articles assessed for eligibility (n = 28)
Full-text articles 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 summary

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

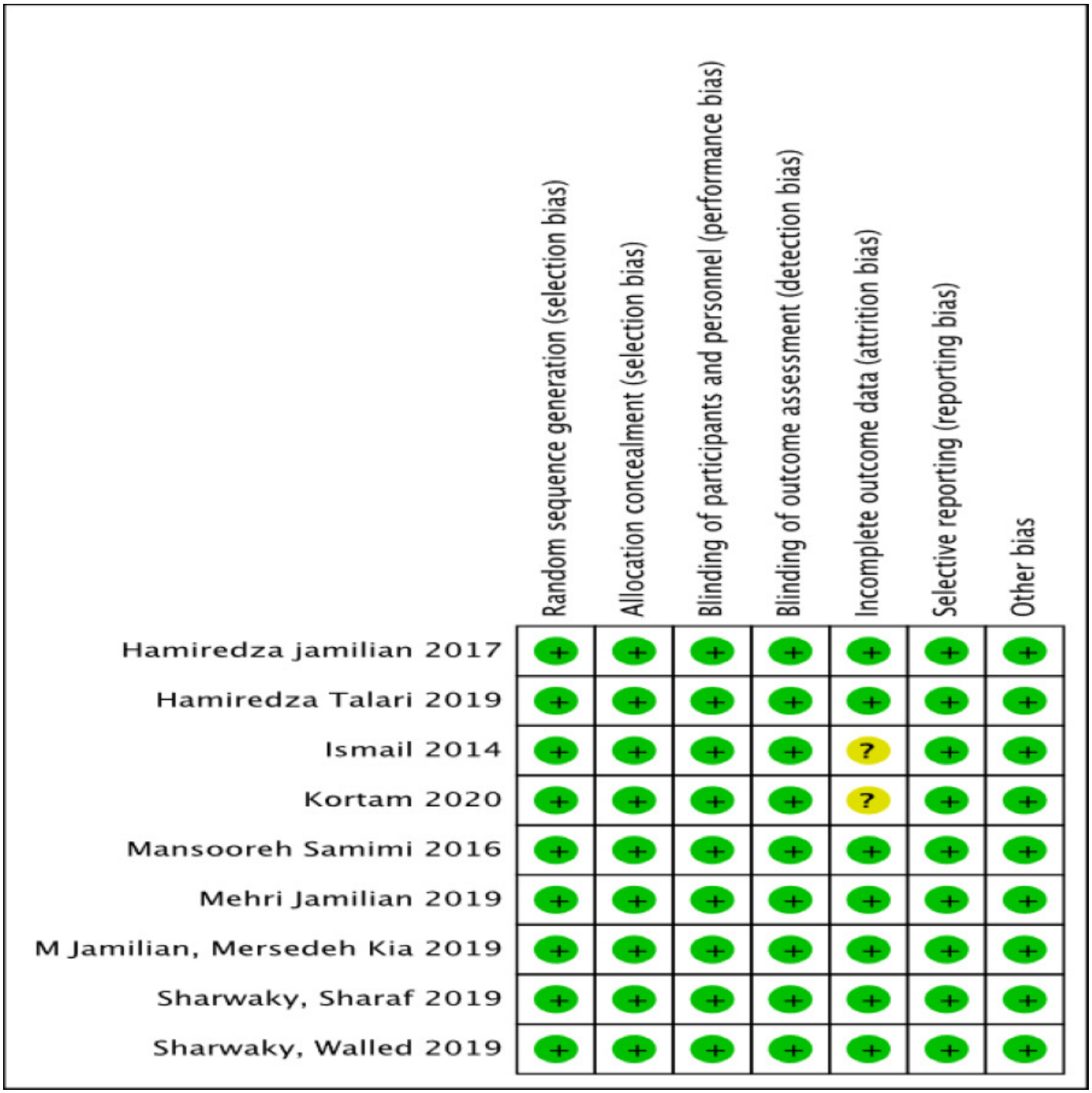

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Hamiredza jamilian 2017
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 3

Risk of bias

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

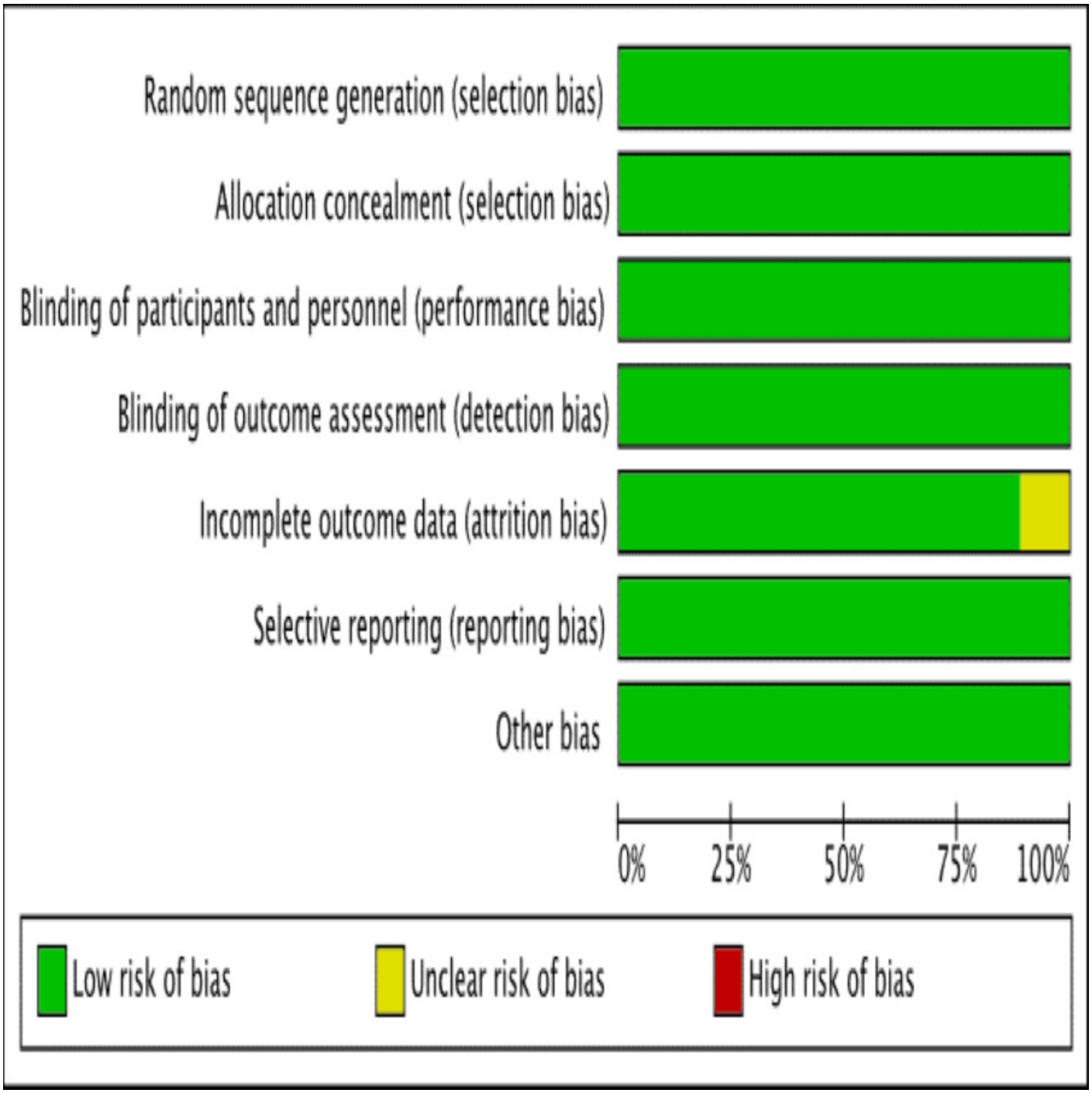

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
0%
25%
50%
75%
100%
Low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

Figure 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.

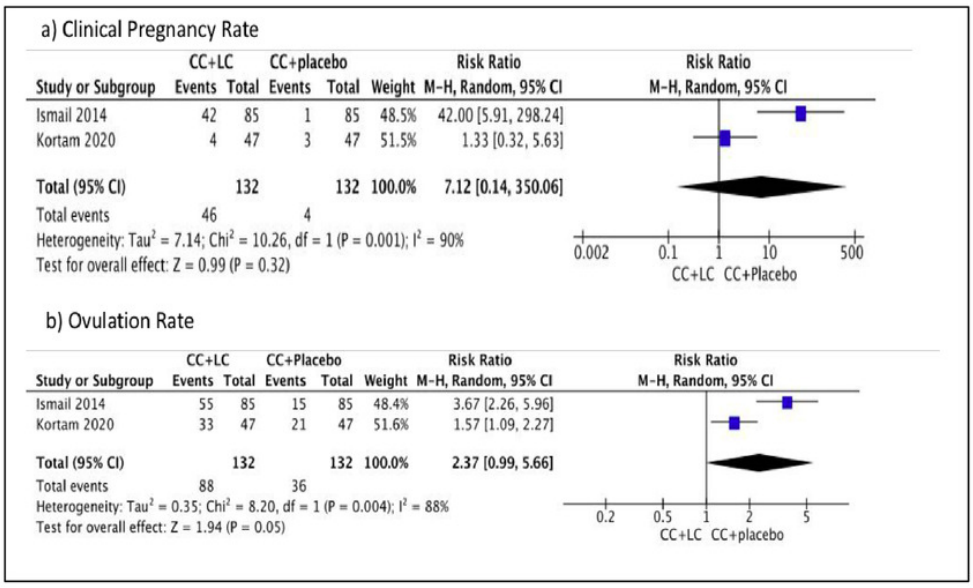
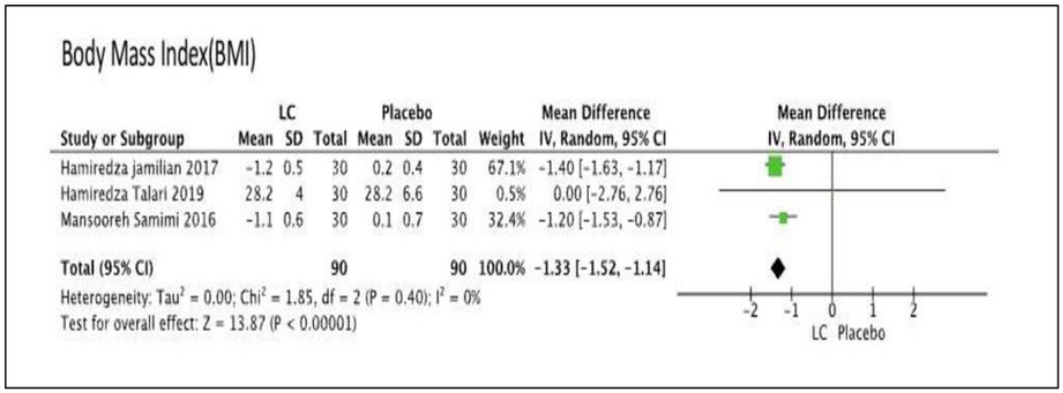

a) Clinical Pregnancy Rate
CC+LC
CC+placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Ismail 2014 42 85 1 85 48.5% 42.00 [5.91, 298.24]
Kortam 2020 4 47 3 47 51.5% 1.33 [0.32, 5.63]
Total (95% CI) 132 132 100.0% 7.12 [0.14, 350.06]
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