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

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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. Anovulatory 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 l-carnitine (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 l-carnitine 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 demonstrated 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 l-carnitine improves BMI and serum LDL, triglyceride, and total cholesterol levels in women with PCOS.

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Abstract

Background

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Methods

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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 demonstrated 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 l-carnitine 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 affecting women of reproductive age with a prevalence ranging between 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 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 is an independent risk factor for coronary artery disease as obesity is associated with insulin resistance, dyslipidemia, and ovulatory dysfunction in adolescents (Traub 2011). valuating risk factors for coronary arterial diseases (CAD) is essential in PCOS as coronary arterial diseases are 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). 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 transport of long-chain fatty acids across the mitochondrial membrane. LC level is 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. L-carnitine could normalize androgen levels, contributing to a significant drop in testosterone levels (Della Corte et al. 2020). L-carnitine 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 l-carnitine (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 level. 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 l-carnitine 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 l-carnitine. 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 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 L-carnitine 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, AAK) scanned for trial selection through the titles and abstracts from the searches. From there, we obtained full-text articles when they appear 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 full text 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 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 description used (dose, frequency, preparation and duration used) and the outcomes measured. We extracted data 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 data extraction form. 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 of the included studies (Higgins JPT 2021). Three authors (MFMS, SB, AAK) assessed selection bias (randomization, 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 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 data using Review Manager 5.4 software (Manager 2020) for the statistical analyses. We used random-effects model to pool 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 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 analyse 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 l-carnitine 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 Rotterdam Criteria. Six trials involved the 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

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 inclusion criteria (El Sharkwy & Sharaf El-Din 2019; El Sharkwy & Abd El Aziz 2019; Ismail et al. 2014). All nine trials reported hyperprolactinemia as 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 pregnant in the trial (Jamilian et al. 2017; Jamilian et al. 2019a; Jamilian et al. 2019b; Talari et al. 2019). Three studies exclude 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 group addressing various comparisons and outcomes, resulting in several comparisons contributing to each of 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 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 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 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 risk of bias presented in **Figure 2** and **Figure 3.** The details of these trials 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 as high risk of random sequence generation bias for this trial (Jamilian et al. 2019b), whereas the other eight rials with low risk of bias. Allocation concealment was reported in all the trials. All trials conducted their study using placebo capsules which designed identical as LC

capsules. Three trials (El Sharkwy & Sharaf El-Din 2019; El Sharkwy & Abd El Aziz 2019; Ismail et al. 2014) distribute 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) except for one trial (Kortam et al. 2020), which cause it to be 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) which mentioned that patient 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 from the study with 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), and 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 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, combination of clomiphene citrate and LC was compared with clomiphene citrate and placebo (Ismail et al. 2014; Kortam et al. 2020). An amount of 250 milligrams (mg) of oral clomiphene citrate was given together with 3 grams(g) of LC in one study compared with 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 with 100mg 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 1g 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 600mg oral N-Acetylcysteine versus 150 mg clomiphene citrate plus 3 g

LC (El Sharkwy & Abd El Aziz 2019). The fourth comparison was the studies used 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 used 200 mg chromium picolinate and 1g LC daily versus the placebo (Jamilian et al. 2019a; Jamilian et al. 2019b).

Comparison 1: clomiphene citrate and l-carnitine versus clomiphene citrate and placebo

We performed meta-analysis in this comparison. There was no difference for 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** showed 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 (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 pregnancy rate, FSH, and LH levels; however, there was a significant difference favoring the placebo in 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 plus l-carnitine 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 is 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) and 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 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 l-carnitine 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 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 showed 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, and 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 showed in **Table 4**.

Comparison 4: comparing of the l-carnitine 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 favors 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 primary outcome, body mass index (BMI). The summary of findings of primary outcomes and GRADE quality assessment for comparison 4 showed 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 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 which 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 which 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 showed in **Table 5**.

Comparisons 5: l-carnitine 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 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 showed 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, whereas there was a significant difference which favored combination with LC in TG level. The summary of secondary outcomes findings and GRADE quality assessment showed in **Table 6**.

Discussion

Polycystic ovarian syndrome (PCOS) is a common disease 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 is still limited study in evaluating the risk for cardiovascular morbidity and mortality in women with PCOS after they 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. There were significant differences in the primary outcomes, which favours the LC usage in reducing serum FPG, LDL, TC, TG and BMI. There were significant differences in the secondary outcomes, FSH, LH and in mental health status using GHQ and DASS scores, which

favors a combination with LC. There was a significant difference in BMI in comparison of LC versus placebo in three trials with low heterogeneity. However, there were no significant differences in primary outcome, clinical pregnancy rate and ovulation rate which favoured combination with the placebo. We were unable to do subgroup analyses as there were inadequate trials that used the similar comparisons.

To evaluate the effect 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 comparison 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 effect 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 usage of LC. In view of limited trials comparing similar comparisons, future clinical trials comparing LC alone is still needed to evaluate the effect of LC on pregnancy and ovulation rate in PCOS patients.

The overall quality of the evidence contributing to this review is moderate to low. The type of comparison and supplementation dosage varied among the trials. Most trials had low risk of bias for allocation bias except for one trial (Jamilian et al. 2019b) as randomization was done manually at the clinic. For 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 are not blinded in their trial. All trials had reported outcomes as in their method section, while four trials published their protocols. The risk of attrition bias was present in one trial only (Kortam et al. 2020) as it did not state the number of participants who withdrew or completed the study. The percentage of participants who loss to follow-up was less than 15% in eight trials and two trials(Jamilian et al. 2017; Talari et al. 2019) declared received financing from university grant. We can only do meta-analysis for comparisons in most of our meta-analyses since there are not enough trials with similar combinations of comparisons. We ran into high heterogeneity in the meta-analysis, and we could not segment any further since there were not enough trials in each group comparison.

We aimed to reduce 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 we have only nine trials included, we could not create a funnel plot to detect bias or heterogeneity, and not all included trials reported similar outcomes. Although the included studies all showed the same direction of effect, we encountered high heterogeneity in our primary outcomes. We could not do subgroup analysis due to limited number of trials.

One systematic review has examined the effect of LC in patients with polycystic ovary syndrome (Maleki et al. 2019). They evaluated 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, in which three studies (Ismail et al. 2014; Jamilian et al. 2019b; Samimi et al. 2016) included in this meta-analysis and one study (Slomaz Latifian 2015) not related to our primary and secondary outcomes. Similar to our meta-analysis, the BMI had a significant effect on L-carnitine 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) whereas two studies had insignificance effect (Fenkci et al. 2008; Samimi et al. 2016).

Conclusions

Based on this meta-analysis, l-carnitine is beneficial for improving BMI in women with polycystic ovarian syndrome (PCOS), as well as the lipid profile, which includes LDL, TC, and TG levels. However, in clinical pregnancy rate and ovulation rate, the meta-analysis showed insignificant effect; thus, 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 l-carnitine as supplementation with other medications in the treatment of PCOS. In this study, evaluation of the side effect of l-carnitine usage is limited, and more safety data is needed to assess the risks of using it. If further studies were conducted to examine the use of l-carnitine in PCOS women, they should include pregnancy rate and ovulation rate as part of their outcomes. It is because PCOS women come for treatment due to fertility problems. Data on physical findings such as hirsutism, acne, and weight reduction can also be considered in the next 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 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

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

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

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 l-carnitine 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 l-carnitine 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 L-carnitine 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 L-carnitine plus chromium with the placebo.

Figure 1

PRISMA study flow diagram

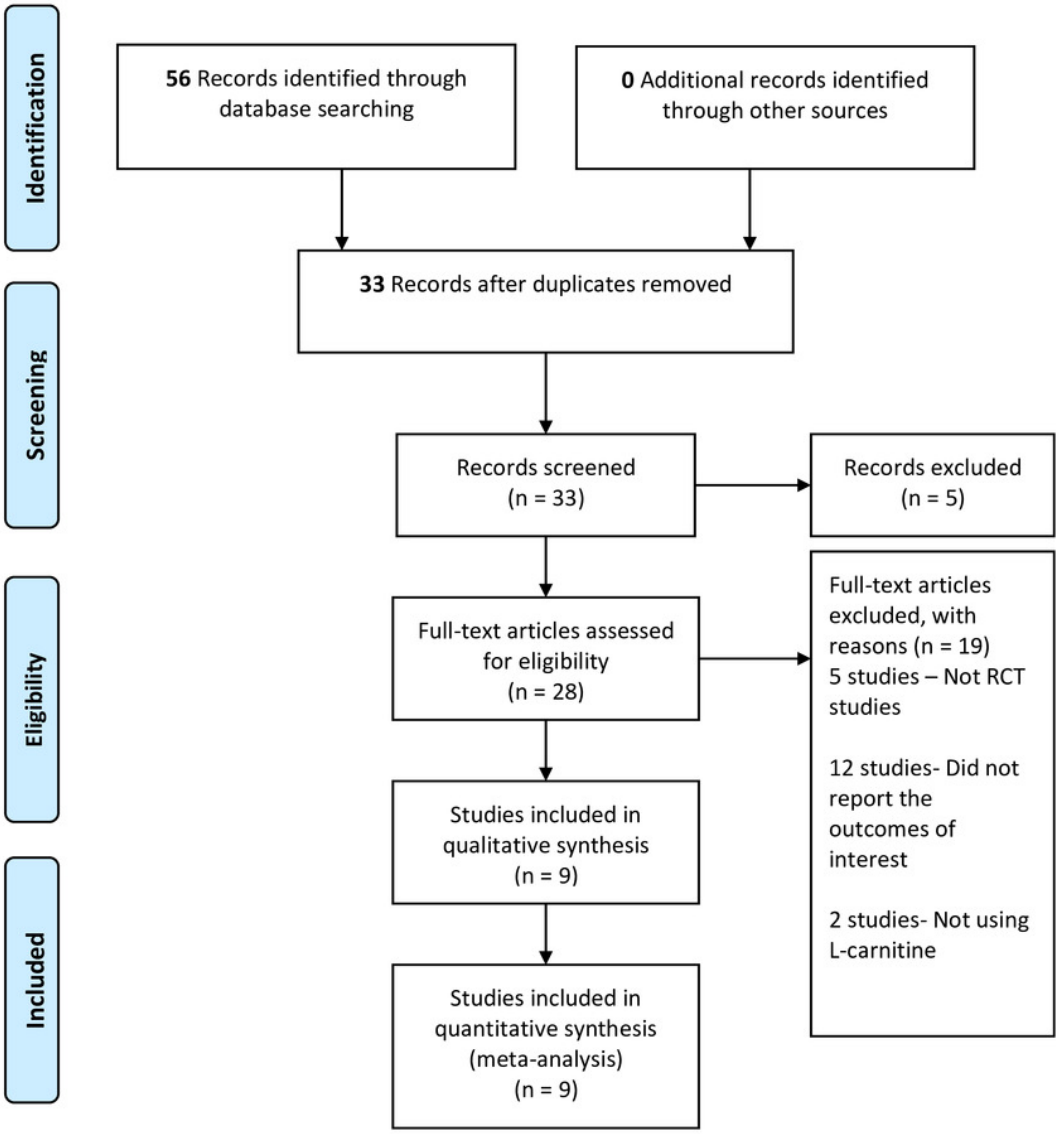

Identification
Screening
Eligibility
Included
56 Records identified through database searching
0 Additional records identified through other sources
33 Records after duplicates removed
Records screened (n = 33)
Records excluded (n = 5)
Full-text articles assessed for eligibility (n = 28)
Full-text articles 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 graph: authors' judgements about each risk of bias item presented as percentages across all included studies.

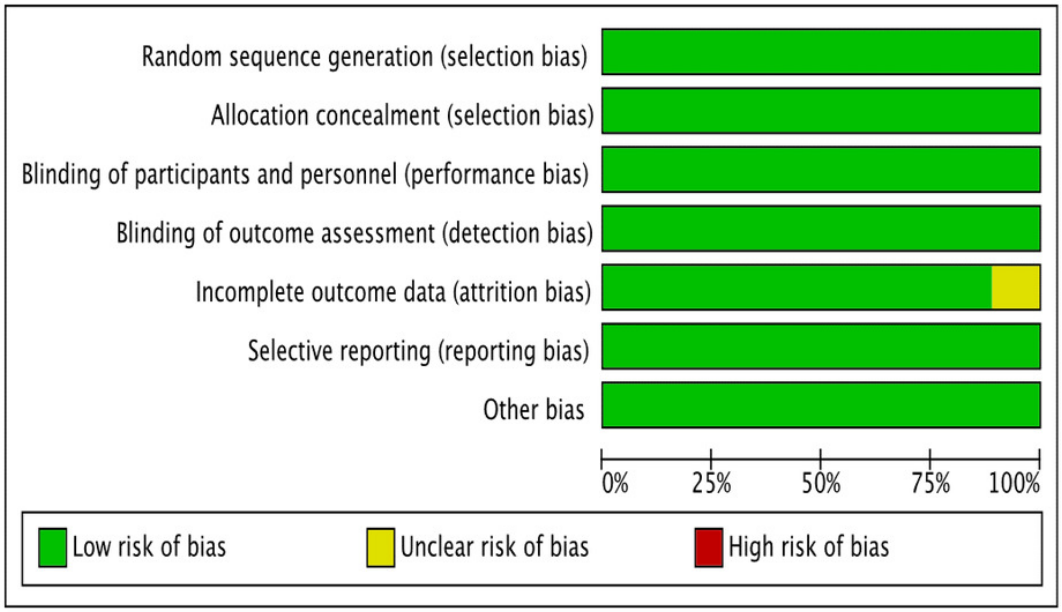

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
0%
25%
50%
75%
100%
Low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

Figure 3

Risk of bias summary: authors’ judgements on each risk of bias item for each included study.

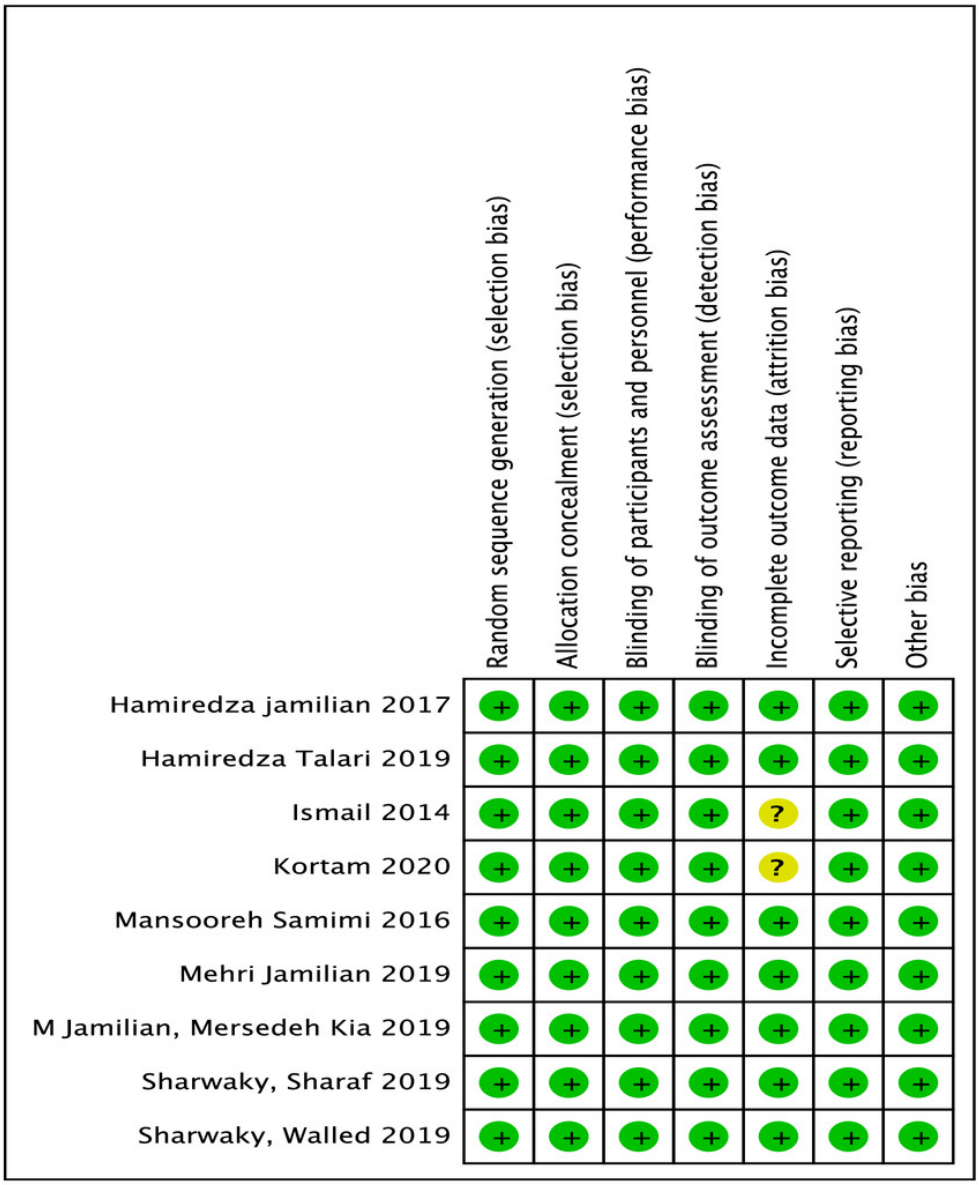

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Hamiredza jamilian 2017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

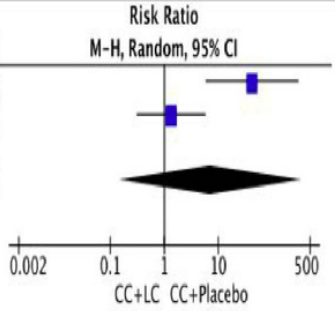
Comparison 1: Clomiphene Citrate+L Carnitine versus Clomiphene Citrate+placebo

a) Clinical Pregnancy Rate

Study or Subgroup	CC+LC Events	Total	CC+placebo Events	Total	Weight	Risk Ratio 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: $Tau^2 = 7.14$; $Chi^2 = 10.26$, df = 1 (P = 0.001); $I^2 = 90\%$

Test for overall effect: Z = 0.99 (P = 0.32)



b) Ovulation Rate

Study or Subgroup	CC+LC Events	Total	CC+Placebo Events	Total	Weight	Risk Ratio 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: $Tau^2 = 0.35$; $Chi^2 = 8.20$, df = 1 (P = 0.004); $I^2 = 88\%$

Test for overall effect: Z = 1.94 (P = 0.05)

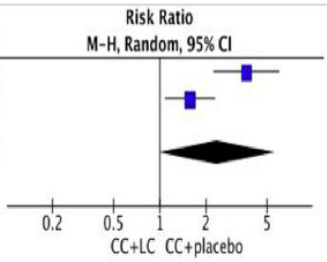
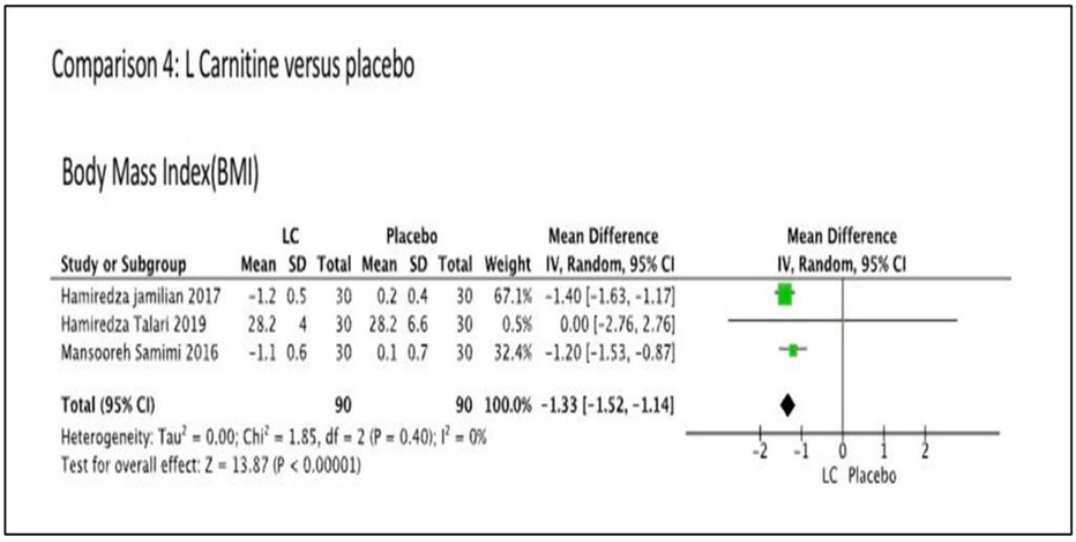


Figure 5

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


Comparison 4: L Carnitine versus 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