



Efficacy of Myo-inositol on Anthropometric, Metabolic, and Endocrine Outcomes in PCOS Patients: a Meta-analysis of Randomized Controlled Trial

Hardik Jethaliya¹ · Nirva Gajjar¹ · Vrushank Patel¹ · Shrikalp Deshpande¹ · Roshni Patel¹

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Abstract

Polycystic ovary syndrome (PCOS) is a common cause of female infertility, affecting 5–10% of women of reproductive age. Many studies have reported improvement in insulin resistance and thereby intracellular glucose uptake after myo-inositol treatment in PCOS patients, but these studies have a small sample size, varying methodology, and outcome analysis. Therefore, we designed a present meta-analysis of randomized controlled trials to explore the effect of myo-inositol supplementation on anthropometric, metabolic, and endocrine outcomes in PCOS patients. Randomized controlled trials assessing the effectiveness of myo-inositol were identified in electronic databases like PubMed, Cochrane, Embase, MEDLINE, CINAHL, and AMED. Listed references and citations of related articles were also screened manually to identify additional studies. Research papers for which full-text copies were not available on scientific databases were procured from respective authors. Thereafter, data were extracted from included studies and analyzed using RevMan 5.3 of the Cochrane Collaboration. A total of 17 randomized controlled trials with 1083 PCOS patients were included in this meta-analysis. Among the 17 trials, 7 trials compared myo-inositol with folic acid, 8 trials compared myo-inositol with metformin, and 2 trials compared myo-inositol with oral contraceptives. No significant improvement in body mass index, waist-to-hip ratio, fasting insulin, fasting glucose, HOMA, LH, FSH, estradiol, sex hormone-binding globulin, dehydroepiandrosterone, and total testosterone levels were observed after myo-inositol treatment in PCOS patients except androstenedione and prolactin levels. Clinically significant improvement was not observed in anthropometric, metabolic, and endocrine outcomes after myo-inositol treatment in PCOS patients. However, heterogeneity between studies was high.

Keywords Meta-analysis · Myo-inositol · Endocrine · Anthropometric · Metabolic · PCOS

Abbreviations

A	Androstenedione
BMI	Body mass index
DCI	D-Chiro-inositol
DHEAS	Dehydroepiandrosterone sulfate
FG	Fasting glucose
FI	Fasting insulin
FSH	Follicle-stimulating hormone
HOMA	Homeostatic model assessment
IR	Insulin resistance
LH	Luteinizing hormone

MI	Myo-inositol
P	Prolactin
PCOS	Polycystic ovary syndrome
SHBG	Sex hormone-binding globulin
T	Total testosterone
WHR	Waist-to-hip ratio

Introduction

Polycystic ovary syndrome (PCOS) is the most common cause of female infertility, characterized by the presence of clinical and/or biochemical hyperandrogenism, irregular menstrual cycle, chronic anovulation, and polycystic ovaries [1]. Along with this, long-term health consequences of PCOS are type 2 diabetes mellitus [2, 3], dyslipidemia [4], low-grade inflammation [5], endothelial dysfunction [6], and psychological distress [7, 8]. The worldwide prevalence of

✉ Roshni Patel
roshni.patel@kbiper.ac.in

¹ Department of Pharmacology and Pharmacy Practice, K. B. Institute of Pharmaceutical Education and Research, Near Gh-6 circle, Sector-23, Gandhinagar 382023, Gujarat, India

this heterogeneous disease is around 5–10% in reproductive-aged women [9]. Though the prevalence of PCOS is higher, the exact pathogenesis is still unclear. It was observed that androgen, gonadotropin, and insulin play a pivotal role in the development of this syndrome [1]. Approximately 80% of obese PCOS patients and 30–40% of lean PCOS patients have insulin resistance (IR) [10, 11]. Pieces of evidence suggest that IR and resulting hyperinsulinemia are correlated with abnormal steroidogenesis of the ovary [12] and also contribute to the pathogenesis of anovulation and hyperandrogenism [11, 13]. Moreover, hyperinsulinemia decreases sex hormone-binding globulin level in the body, which results in a rise in free testosterone level and altered gonadotropin level [14–17]. Hence, insulin sensitizers have been used to counteract the clinical as well as metabolic signs of PCOS [18].

Inositol is a carboxylic sugar, belonging to the vitamin B complex family. Two stereoisomers of inositol, found in the human body, are myo-inositol (MI) and D-chiro-inositol (DCI). DCI mediates insulin-dependent androgen synthesis, whereas uptake of glucose and follicle-stimulating hormone (FSH) signaling is mediated by MI [19, 20]. Human ovaries consist of MI and DCI in a ratio of 99:1. The disproportion of ovarian MI and DCI concentrations might be responsible for impaired FSH signaling in PCOS patients. Along with this, the conversion of MI to DCI is facilitated by the epimerase enzyme. Increased epimerase enzyme activity, triggered by hyperinsulinemia, leads to MI deficiency [21], which plays a critical role in the pathogenesis of PCOS. Hence, MI supplementation can effectively improve insulin sensitivity and subsequent intracellular uptake of glucose in PCOS patients [22].

Since the last two decades, a number of studies have investigated the efficacy of MI in PCOS patients. Results of such studies suggest the improvement in IR, menstrual irregularities, acne score, and various endocrine as well as metabolic parameters [23]. Moreover, MI is also recommended as a pretreatment for PCOS patients undergoing in vitro fertilization or intra cytoplasmic sperm injection, with the aim to improve oocyte quality and clinical pregnancy rate [24]. However, all these studies have a small sample size, varying methodology, and outcome analysis. Numerous systematic reviews and meta-analysis have also been published, comparing MI with metformin [25, 26], oral contraceptives, DCI [27], and placebo [28, 29]. Arentz et al. reported improvement in reproduction, hyperandrogenism, ovulation, and pregnancy rate after inositol supplementation [30]. Contrary to this, Liuthing Zeng et al. reported improvement only in IR but not in body mass index (BMI) and hyperandrogenism, with inositol [28]. A meta-analysis by Fachinetti et al. demonstrates that MI and metformin are equally effective on various metabolic and hormonal changes in PCOS patients [26]. Unfer et al.

highlighted the beneficial effect of MI on metabolic profile with reduced hyperandrogenism in PCOS patients [27]. Myo-inositol supplementation can reduce the incidence of gestational diabetes and preterm delivery in pregnant women. All these meta-analyses have reinforced the efficacy of MI on various metabolic, endocrine, and hormonal parameters in PCOS patients.

In the present meta-analysis, we included the recently published RCTs and tried to update the information about MI treatment, to better outline the effectiveness of MI on clinical, metabolic, and endocrine outcomes in PCOS patients. Moreover, the present meta-analysis included studies comparing MI with folic acid, metformin, and oral contraceptives.

Materials and Methods

Methods

The present protocol design followed the PRISMA guidelines for reporting meta-analysis [31]. No institutional review board approval was required since the study analyzed only published data.

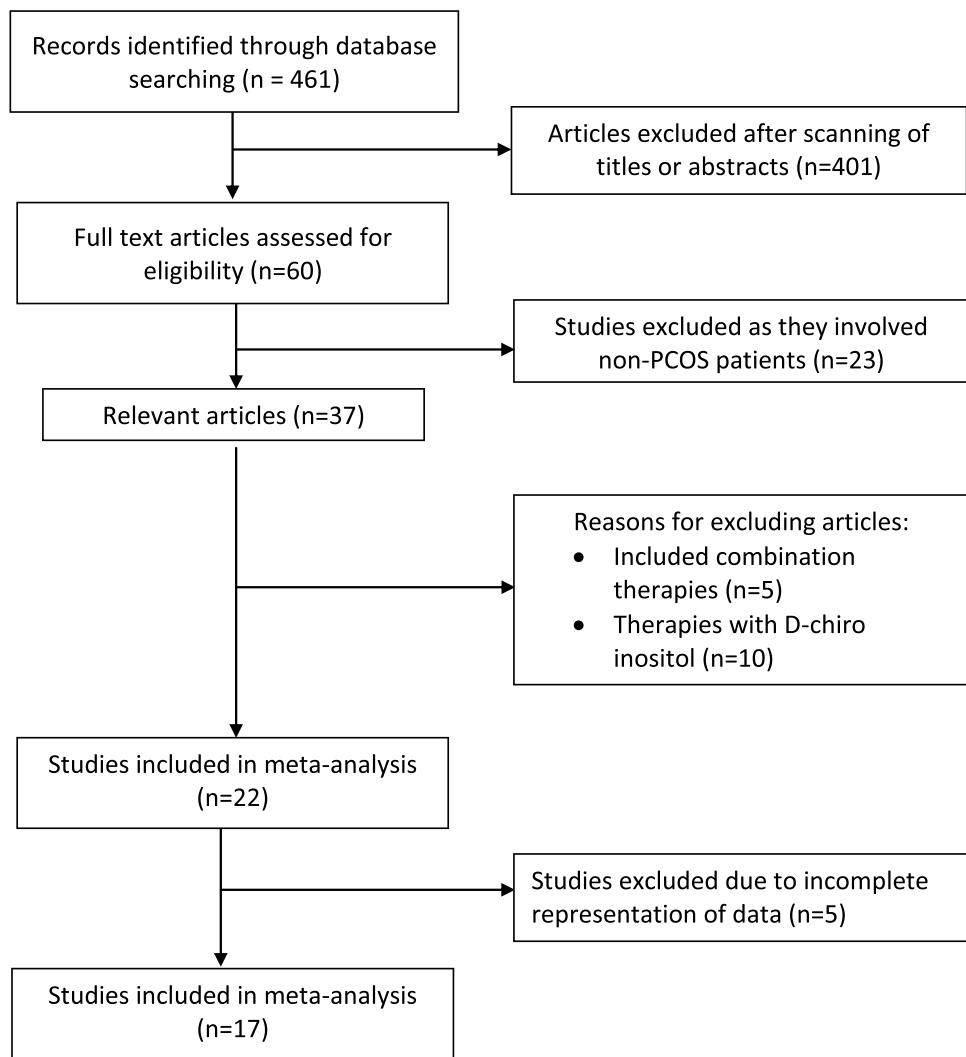
Selection of Studies

The literature search was conducted in electronic databases like PubMed, Cochrane, Embase, MEDLINE, CINAHL, and AMED. The search comprised of literature published till January 2020. Keywords that were used for searching databases were “Inositol,” “Myo-inositol,” “MI,” “RCT,” “Randomized Controlled Trial,” “Polycystic Ovary Syndrome,” “PCOS,” “PCOD,” “PCO,” “Polycystic Ovary,” “Metformin,” “Oral Contraceptives,” “OC pills,” “COC,” “Folic acid,” “Ethinyl estradiol,” “Drospirenone.”

The inclusion and exclusion criteria for the selection of studies are given in Table 1. After the initial database search, titles and abstracts of identified studies were screened by reviewers independently. If a study was deemed eligible on the basis of abstract review, a full-text version of the article was accessed. Reference lists and citations of related articles were also screened manually to identify additional studies. Research articles for which full-text copies were not available on scientific databases were procured from respective authors. Data from gray literature were not included in the present meta-analysis. Any discrepancies between the reviewers on selected articles were settled by consensus. Figure 1 shows the PRISMA flow diagram for the selection of studies.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	<ul style="list-style-type: none"> • Women diagnosed with PCOS • Study design should be a randomized controlled trial where the control group received a placebo, folic acid, metformin or oral contraceptives • Studies where treatment of myo-inositol, with or without folic acid was given to PCOS patients • Studies were reported in the English language only
Exclusion criteria	<ul style="list-style-type: none"> • If the type of article was review articles, letter to the editor, commentary, or meta-analysis • Data from gray literature • Preclinical studies and cell culture studies • RCTs measured pregnancy outcomes related parameters (pregnancy rate, oocyte quality, live birth rate) or RCTs with a graphical representation of data • Articles describing myo-inositol treatment in combination with other drugs/supplements (except folic acid) • Treatment with D-chiro inositol

Fig. 1 The PRISMA flow diagram for the selection of studies

Data Extraction Process

Data were extracted from each included study. The information extracted from studies were study features (type of study, methods of recruitment, study period, allocation

concealment, masking, and diagnostic criteria), participant characteristics (number of participants and age), and interventions (dose and duration of MI treatment). Data for anthropometric outcomes (body mass index (BMI), waist-to-hip ratio (WHR)), endocrine outcomes (sex

Table 2 Characteristics of included studies

Sr. no	References	Method of allocation	Allocation concealed?	Masking	Study sight	Study period	PCOS diagnostic criteria	Inclusion criteria	Age	Interventions	No. of patients	Duration of treatment	Outcome measures
1	Constantino et al. 2009 [34]	-	Yes	Yes	Women's Health Center, USL company, Ferrara, Italy	--	Oligomenorrhea, high-serum-free testosterone, and/or hirsutism	18–40 years	MI 4000 mg + FA 400 mcg vs. FA 400 mcg	23 vs. 19	12–16 weeks	WHR, BMI, free and total testosterone, androstenedione, DHEAS, 17-β estradiol, SHBG, CH, glucose AUC, BP, FG, FI	
2	Artini et al. 2012 [33]	Computer-generated randomization	Yes	Yes	Division of Obstetrics and Gynecology, University Of Pisa, Italy	2008–2009 Rotterdam criteria	Micropoly cystic ovaries, hirsutism and/or acne, oligomenorrhea or amenorrhea, absence of enzymatic adrenal deficiency and/or other endocrine disease, normal prolactin level, no hormonal treatment	-	MI 2000 mg + FA 200 mcg vs. FA 200 mcg	25 vs. 25	12 months	LH, FSH, prolactin, estradiol, 17-hydroxy-progesterone, androstenedione, testosterone, FG, FI, C-peptide, BMI, HOMA, GI ratio	
3	Genazzani et al. 2008 [35]	-	-	-	University of Modena and Reggio, Emilia, Italy	- Rotterdam criteria	Micropoly cystic ovaries, hirsutism and/or acne, oligomenorrhea or amenorrhea, absence of enzymatic adrenal deficiency and/or other endocrine diseases, normal prolactin level, no hormonal treatment	-	MI 2000 mg + FA 200 mcg vs. FA 200 mcg	10 vs. 10	12 weeks	LH, FSH, prolactin, estradiol, testosterone, 17-hydroxy-progesterone, androstenedione, C-peptide, FG, FI, LH/FSH ratio, BMI, GI ratio, HOMA	
4	Pourghasem et al. 2018 [42]	Table of random numbers	Yes	Yes	University of Medical Sciences, Hormozgan, Iran	2015–2016 Rotterdam criteria	Oligomenorrhea and/or anovulation, hyperandrogenism, polycystic ovaries	15–38 years	MI 2000 mg + FA 200 mcg vs. FA 200 mcg	50 vs. 50	12 weeks	FG, TG, CH, LH/FSH ratio, menstrual pattern	

Table 2 (continued)

Sr. no	References	Method of allocation	Allocation concealed?	Masking	Study sight	Study period	PCOS diagnostic criteria	Inclusion criteria	Age	Interventions	No. of patients	Duration of treatment	Outcome measures
5	Gerisi S. et al. 2007 [63]	Computer-generated randomization	Yes	Yes	-	- Adam's criteria	Age < 35 years, oligomenorrhea, or amenorrhea	< 35 years	MI 400 mg + FA 400 mcg vs. FA 400 mcg	45 vs. 47	16 weeks	Estradiol, androstenedione, LH, FSH, TG, TC, LDL, HDL, OGTT, insulin AUC	
6	Dona et al. 2012 [36]	Computer-generated randomization	Yes	-	Department of Medical and Surgical Sciences, University of Padua, Italy	- Rotterdam criteria	Oligo- or anovulation (< 8 menstrual cycles/year), signs of hyperandrogenism, polycystic ovaries	22–30 years	MI 1200 mg vs. placebo	18 vs. 8	12 weeks	Weight, BMI, BP, testosterone, androstenedione, FI, FG, HOMA, glucose AUC, insulin AUC	
7	Papaleo et al. 2009 [37]	Randomization through table for randomization	Yes	Yes	Gynecology Department, San Raffaele Hospital, Italy	- Rotterdam criteria	Oligomenorrhea, sign of hyperandrogenism	< 40 years	MI 4000 mg + FA 400 mcg Vs. FA 400 mcg	30 vs. 30	12 months	BMI, prolactin, TSH, 17-beta estradiol, duration of infertility, number of retrieved oocytes	
8	Fruzzetti et al. 2016 [38]	Randomization through table	Yes	-	Clinic of Reproductive Endocrinology of University of Pisa, Italy	2014–2015 Rotterdam criteria	Oligomenorrhea, hyperinsulinemia, hirsutism, acne	18–28 years	MI 4000 mg + FA 400 mcg vs. MET 1500 mg	24 vs. 22	12 months	BMI, prolactin, TSH, HOMA, insulin AUC, LH, FSH, mat-suda index, estradiol, testosterone, androstenedione, DHEAS, 17-hydroxy-progesterone, cortisol	
9	Jamilian M. et al. 2017 [43]	Computer-generated randomization	-	No	Kosar Clinic in Arak, Iran	Nov 2016 – Rotterdam criteria	-	18–40 years	MI 2000 mg + FA 200 mcg vs. MET 1500 mg	30 vs. 30	4 months	Testosterone, FG score, SHBG, DHEAS, CRP, BMI, FAI, nitric oxide	

Table 2 (continued)

Sr. no	References	Method of allocation	Allocation concealed?	Masking	Study sight	Study period	PCOS diagnostic criteria	Inclusion criteria	Age	Interventions	No. of patients	Duration of treatment	Outcome measures
10	Raffone et al. 2010 [39]	-	Yes	-	Obstetrics and Gynecology Department, G. Martino Hospital, Messina, Italy	June 2006 – Rotterdam criteria June 2008	Age <35 years with PCOS	<35 years	MI 400 mg plus 400 mg FA vs. MET 1500 mg	60 vs. 60	24 months	BMI, WHR, duration of infertility, FSH, LH, TSH, prolactin, estradiol, 17-hydroxy-progesterone, progesterone, DHEAS, testosterone, androgen, SHBG, FG, FI	
11	Angik et al. 2014 [45]	Computer-generated randomization	Yes	Yes	Jawaharlal Nehru Medical College and Acharya Vinoba Bhau Rural Hospital, Maharashtra, India	Sep 2012 – Rotterdam criteria Aug 2014	Age 15–40 years with PCOS	15–40 years	MI 2000 mg vs. MET 500 mg	50 vs. 50	6 months	BMI, WHR, FG, PPBS, FI, post-meal insulin, testosterone, LH, LH/FSH ratio, mean ovarian volume, antral follicle count, HOMA, FG score	
12	Nehra et al. 2017 [46]	Computer-generated randomization	-	No	Department of Pharmacology and Obstetrics and Gynecology, Pt. B. D. Sharma PGIMS, Rohtak, Haryana, India	Nov 2016 – Androgen excess society criteria 2006	Reproductive age group 15–45 years with PCOS	15–45 years	MI 2000 mg vs. MET 1500 mg	30 vs. 30	6 months	BMI, WHR	
13	De Leo et al. 2013 [41]	-	-	-	-	-	- ESHRE/ ASRM criteria	Insulin resistance, age 24–32 years, PCOS	24–32 years	MI 3000 mg vs. MET 1700 mg	20 vs. 20	6 months	BMI, LH, FSH, testosterone, SHBG, FG, FI, CH, TG, HOMA, HDL, LDL, FG score

Table 2 (continued)

Sr. no	References	Method of allocation	Allocation concealed?	Masking	Study sight	Study period	PCOS diagnostic criteria	Inclusion criteria	Age	Interventions	No. of patients	Duration of treatment	Outcome measures
14	Tagliaferri et al. 2016 [40]	Computer-generated randomization	-	No	Department of Obstetrics and Gynecology, Catholic University of Sacred Heart, Italy	- Rotterdam criteria	-	-	MI 2000 mg vs. MET 1700 mg	34 vs. 34	6 months	BMI, WHR, FG score, FSH, LH, estradiol, prolactin, androstenedione, testosterone, FAI, 17-hydroxyprogesterone, DHEAS, SHBG, AMH, ovarian volume	
15	Shokrpour et al. 2019 [44]	-	Yes	-	Kosar Clinic in Arak, Iran	Sep 2017 – Rotterdam criteria Dec 2017	-	18–40 years	MI 2000 mg+FA 200 mcg vs. MET 1500 mg	26 vs. 27	12 weeks	BMI, body weight, FG, FI, HOMA, TG, CH, VLDL, HDL, LDL, QUICKI	
16	Ali Ozay et al. 2016 [47]	Manually Odd/Even ratio	Yes	-	Department of Obstetrics & Gynecology, Medical School, Dokuz Eytul University, Izmir, Turkey	May 2013–Rotterdam criteria June 2014	-	MI 1000 mg+ 100 mcg FA vs. cyproterone acetate 2 mg+ethynodiol 0.035 mg	52 vs. 54	12–16 weeks	BMI, FG, FI, HOMA, HDL, LDL, TG, CH, CRP, apolipoprotein-B, DHEAS, C-peptide, total and free testosterone, androstenedione, progesterone, 17-hydroxyprogesterone, SHBG, estradiol, FG score, WHR, antral follicle count, total ovarian volume, AMH		

Table 2 (continued)

Sr. no	References	Method of allocation	Allocation concealed?	Masking	Study sight	Study period	PCOS diagnostic criteria	Inclusion criteria	Age	Interventions	No. of patients	Duration of treatment	Outcome measures
17	Pkhaladze et.al. 2016 [48]	-	Yes	No	Achil Kho-masuridze Institute of Repro-ductology, Georgia	June-Aug 2016	Age: 13–19 years with PCOS	13–19 years	MI 2000 mg+400 mg FA vs. drospirenone 3 mg/ethinyl estradiol 30 mcg	20 vs. 20	3 months	BMI, weight, prolactin, LH, DHEAS, total and free testosterone, FAI, SHBG, FG, FI, AMH, C-peptide, HOMA, AMH	

WHR, waist-to-hip ratio; BMI, body mass index; DHEAS, dehydroepiandrosterone; SHBG, sex hormone-binding globulin; CH, cholesterol; BP, blood pressure; FG, fasting glucose; FI, fasting insulin; LH, luteinizing hormone; FSH, follicle-stimulating hormone; BM, body mass index; HOMA, homeostatic model assessment; GI ratio, glucose-insulin ratio; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; OGTT, oral glucose tolerance test; AUC, area under the curve; TSH, thyroid-stimulating hormone; CRP, C reactive protein; FAI, free androgen index; PPBS, post-prandial blood glucose; FG score, Ferriman-Gallwey score; AMH, anti-Mullerian hormone; QUILCKI, quantitative insulin sensitivity check index; MI, myo-inositol; FA, folic acid; MET, metformin

hormone-binding globulin (SHBG), total testosterone (T) levels, dehydroepiandrosterone sulfate (DHEAS) levels, luteinizing hormone (LH) levels, follicle-stimulating hormone (FSH) levels, androstenedione (A) levels, prolactin (P) levels), and metabolic outcomes (fasting glucose (FG) levels, fasting insulin (FI) levels, homeostatic model assessment (HOMA)) were also extracted from included studies.

Statistical Analysis

Results from each study were extracted as mean \pm SD for each group to estimate the effect of MI treatment in PCOS patients. The statistical analysis was performed using RevMan 5.3 from Cochrane Collaboration [32]. Continuous data were expressed as mean difference and 95% confidence intervals. Heterogeneity was assessed using I^2 statistics. The degree of heterogeneity was low when I^2 was $< 30\%$, moderate when 30–50%, and high when $> 50\%$. For moderate and high heterogeneity, a random effect model was used. The fixed-effect model was used when heterogeneity was low.

Results

A literature search was conducted in different databases and 461 studies were identified. After the screening of titles and abstracts, 60 RCTs were selected. After reading the full texts of these articles, 23 RCTs which involved non-PCOS patients, and 15 RCTs which used combination therapy with MI, were further excluded. During the data extraction process, 5 more RCTs were excluded due to measurement of pregnancy outcome-related parameters (pregnancy rate, oocyte quality, live birth rate) or lack of numerical data. Ultimately, 17 RCTs were included for quantitative synthesis. Among these 17 RCTs, seven RCTs compared MI with folic acid, eight RCTs compared MI with metformin, and two RCTs compared MI with combined oral contraceptives.

Studies were conducted at the women's health center, department of reproductive medicine and child development, department of medical and surgical sciences, clinic of reproductive endocrinology, and obstetrics and gynecology department. The RCTs included in the meta-analysis were conducted in various countries, viz. Italy [33–41], Iran [42–44], India [45, 46], Turkey [47], and USA [48]. The characteristics of included studies are summarized in Table 2.

Anthropometric Data

The effect of MI on anthropometric data like BMI and WHR was evaluated in 16 RCTs (1023 participants) and 6 RCTs (482 participants), respectively. As compared to control group, no significant effects of MI treatment on BMI

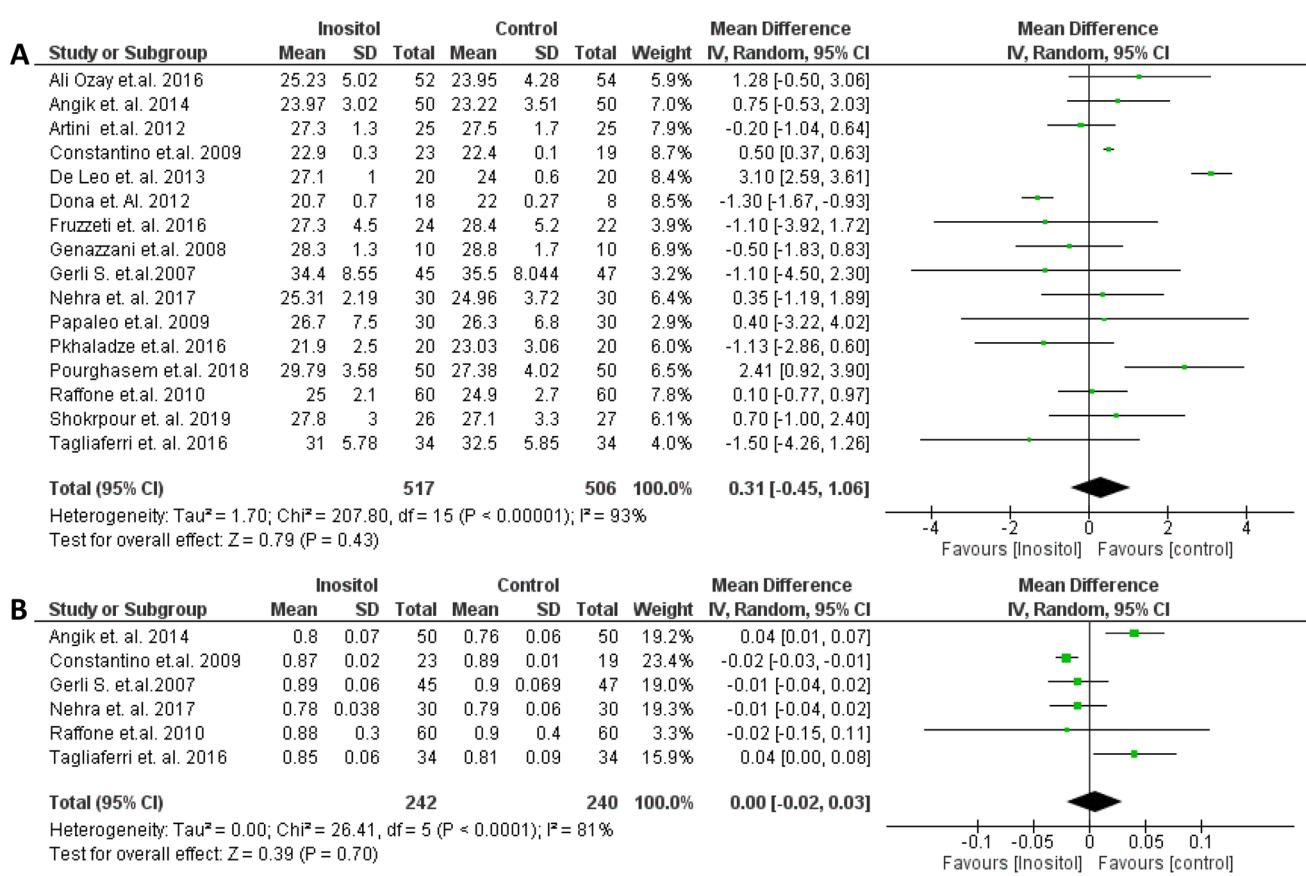


Fig. 2 Forest plot of comparison for anthropometric outcomes. **A** Body mass index (kg/m^2). **B** Waist-to-hip ratio

(mean difference (MD) 0.31; 95% CI –0.45, 1.06; $p = 0.43$) and WHR (MD 0.00; 95% CI –0.02, 0.03; $p = 0.70$.) were observed. There were considerable heterogeneities across the studies for BMI ($I^2 = 93\%$) and WHR ($I^2 = 81\%$) (Fig. 2).

Metabolic Data

The meta-analysis of FG levels included 10 RCTs (719 participants), FI levels included 9 RCTs (619 participants), and HOMA included 9 RCTs (481 participants). Myo-inositol treatment did not significantly affect FG levels (MD –0.21; 95% CI –3.11, 2.70; $p = 0.89$), FI levels (MD –1.52; 95% CI –3.04, 0.01; $p = 0.05$), and HOMA (MD –0.39; 95% CI –0.83, 0.04; $p = 0.08$) compared to control group. High heterogeneity was observed across the studies with I^2 value of 80% for FG, 84% for FI, and 92% for HOMA (Fig. 3).

Endocrine Data

Various endocrine parameters were studied in the selected 17 trials. These parameters included LH levels in 9 studies (590 participants), FSH levels in 7 studies (450 participants), estradiol levels in 7 studies (502

participants), SHBG levels in 7 studies (472 participants), DHEAS levels in 7 studies (482 participants), androstenedione levels in 8 studies (398 participants), total testosterone levels in 11 studies (684 participants), and prolactin levels in 8 studies (512 participants). There was no significant effect of MI treatment on some of the endocrine parameters like LH levels (MD 0.06; 95% CI –1.03, 1.14; $p = 0.92$), FSH levels (MD –0.33; 95% CI –0.95, 0.2; $p = 0.29$), estradiol levels (MD 6.54; 95% CI –0.98, 14.06; $p = 0.09$), SHBG levels (MD –5.09; 95% CI –18.71, 8.63; $p = 0.47$), DHEAS levels (MD –0.36; 95% CI –0.83, 0.11; $p = 0.14$), and total testosterone levels (MD –9.62; 95% CI –21.04, 1.81; $p = 0.1$). However, androstenedione levels (MD –35.98; 95% –68.29, –3.67; $p = 0.03$) and prolactin levels (MD –1.71, 95% –3.37, –0.04; $p = 0.04$) were significantly affected by MI treatment. Significantly high heterogeneities were observed with I^2 values 87% for LH levels, 96% for FSH levels, 81% for estradiol levels, 99% for SHBG levels, 94% for DHEAS levels, 93% for androstenedione levels, 99% for total testosterone levels, and 89% for prolactin levels (Fig. 4).

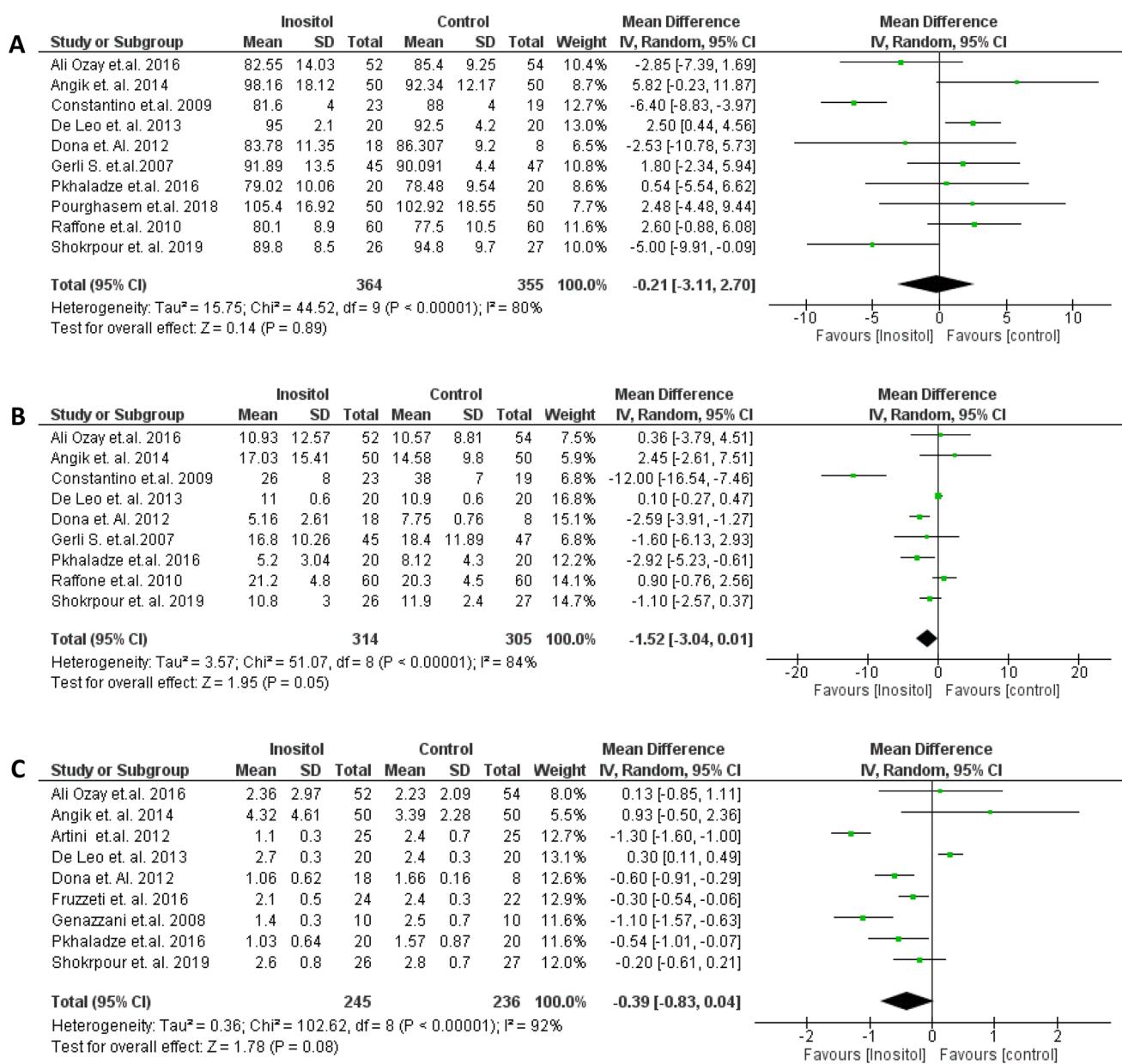


Fig. 3 Forest plot of comparison for metabolic outcomes. **A** Fasting blood glucose level (mg/dL). **B** Fasting insulin level (μIU/mL). **C** HOMA

Discussion

This meta-analysis was conducted to evaluate the effect of MI administration on anthropometric, metabolic, and endocrine parameters in PCOS patients. A total of 17 RCTs with 1083 PCOS patients were included to compare the effects of MI against placebo, metformin, folic acid or oral contraceptives, on anthropometric, metabolic, and endocrine parameters. However, the results from this meta-analysis failed to show significant improvement in any of these parameters except androstenedione and prolactin levels following MI treatment in PCOS patients. The summary of the same is provided in Table 3.

Though the present meta-analysis is more comprehensive, there are some limitations in the review process. The sample size of included studies was relatively small and high heterogeneity was found among included studies in terms of inclusion and exclusion criteria, dose (ranging from 1.2–4 gms) and duration of treatment (from 12 weeks to 24 months). Besides, it is unfair to generalize the findings of this meta-analysis to other ethnic groups, as a majority of included studies were performed in Italy. Therefore, well-designed randomized controlled trials with a larger sample size and additional parameters on lipid profile and insulin sensitivity indices are needed to confirm the benefits of MI in PCOS patients.

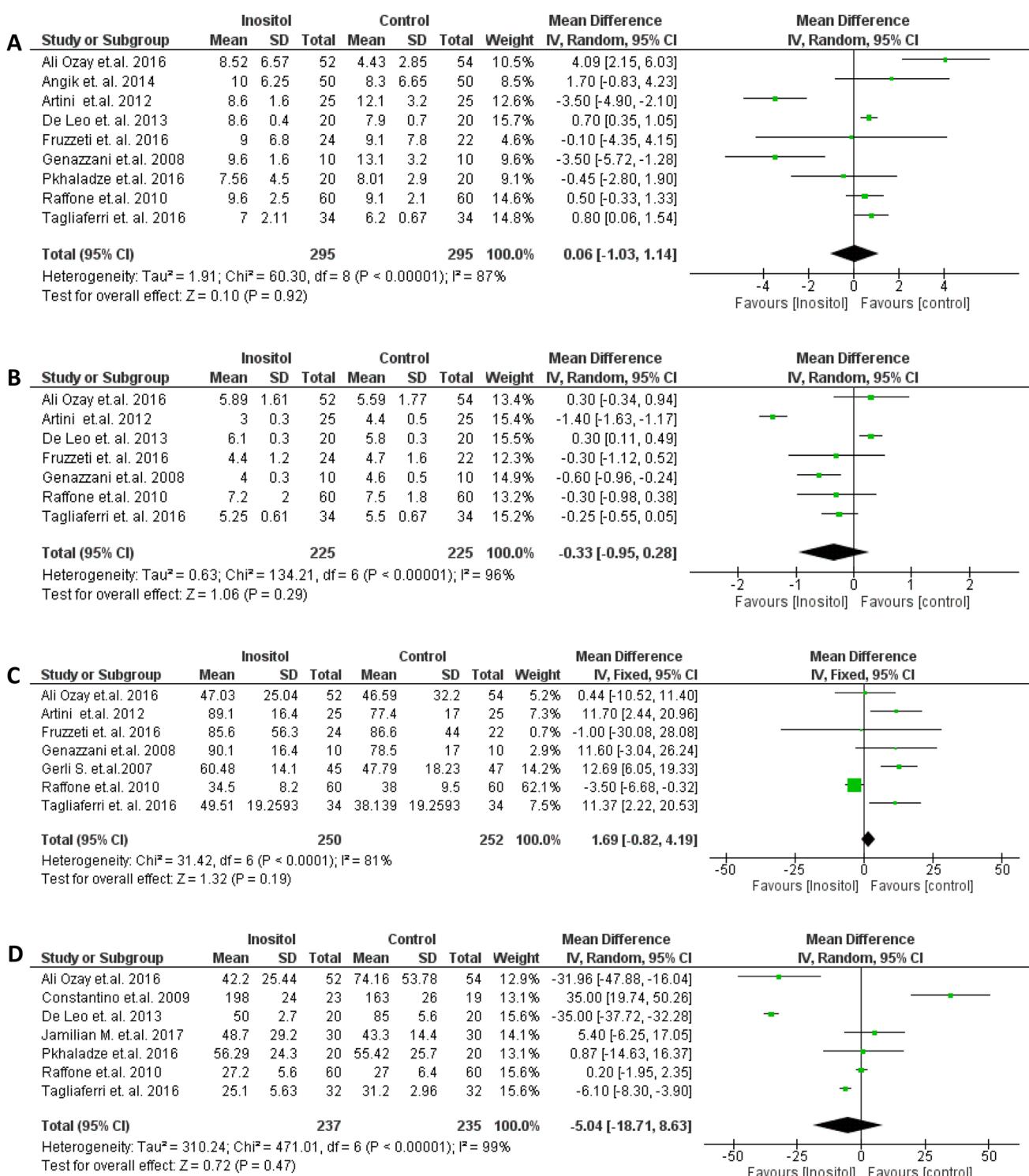


Fig. 4 Forest plot of comparison for endocrine outcomes. **A** LH level (IU/L). **B** FSH level (IU/L). **C** Estradiol level (pg/mL). **D** Sex hormone-binding globulin level (nmol/L). **E** Dehydroepiandrosterone

level (μ g/mL). **F** Androstenedione level (ng/dL). **G** Total testosterone level (ng/dL). **H** Prolactin level (ng/mL)

For assessment of the methodological quality of the included studies, a risk of bias assessment tool was applied. The descriptive component approach was used to

investigate methods of randomization, allocation of patients to study groups, blinding of patients and personnel, methods of outcome assessment, reporting, and data analysis.

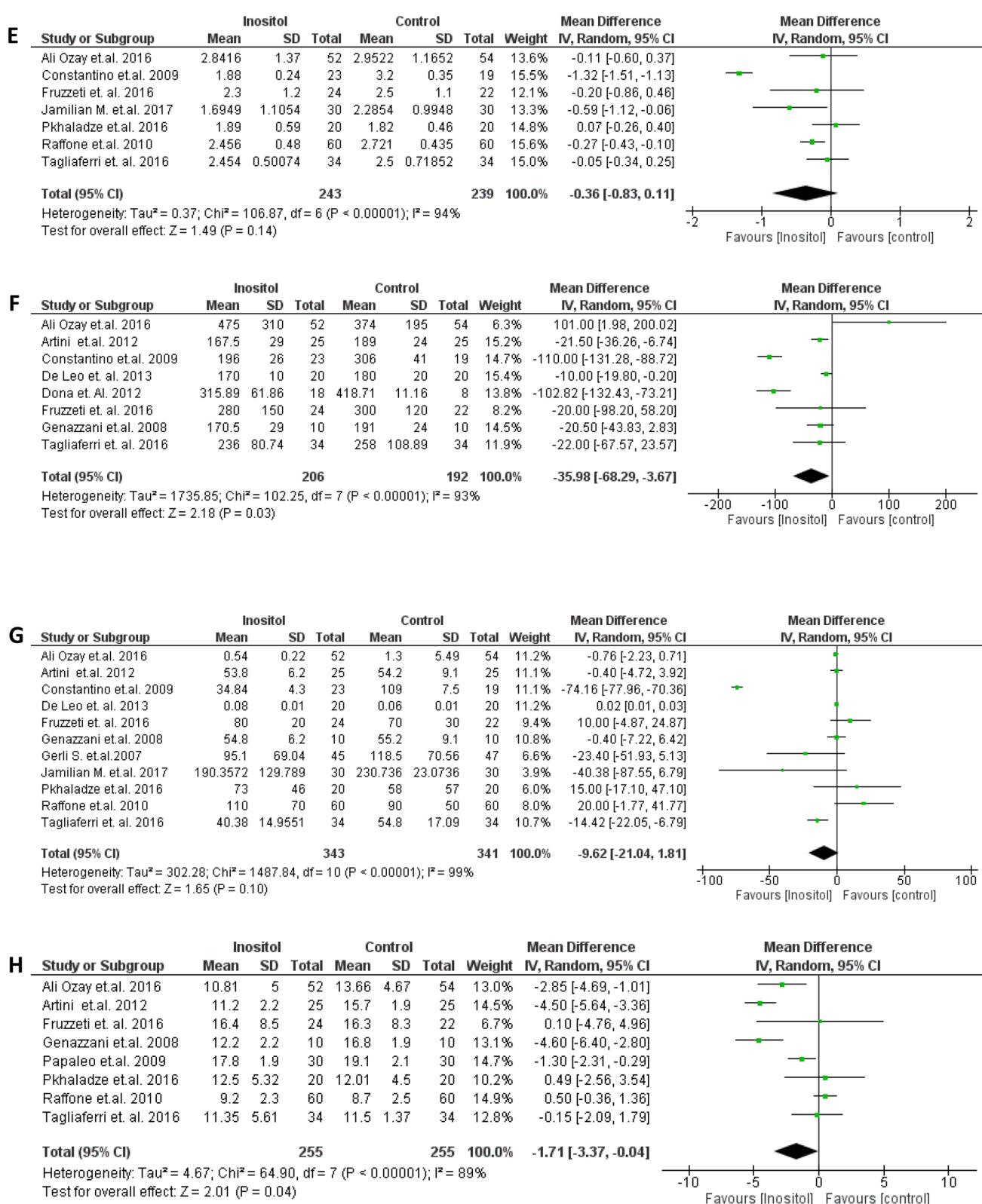


Fig. 4 (continued)

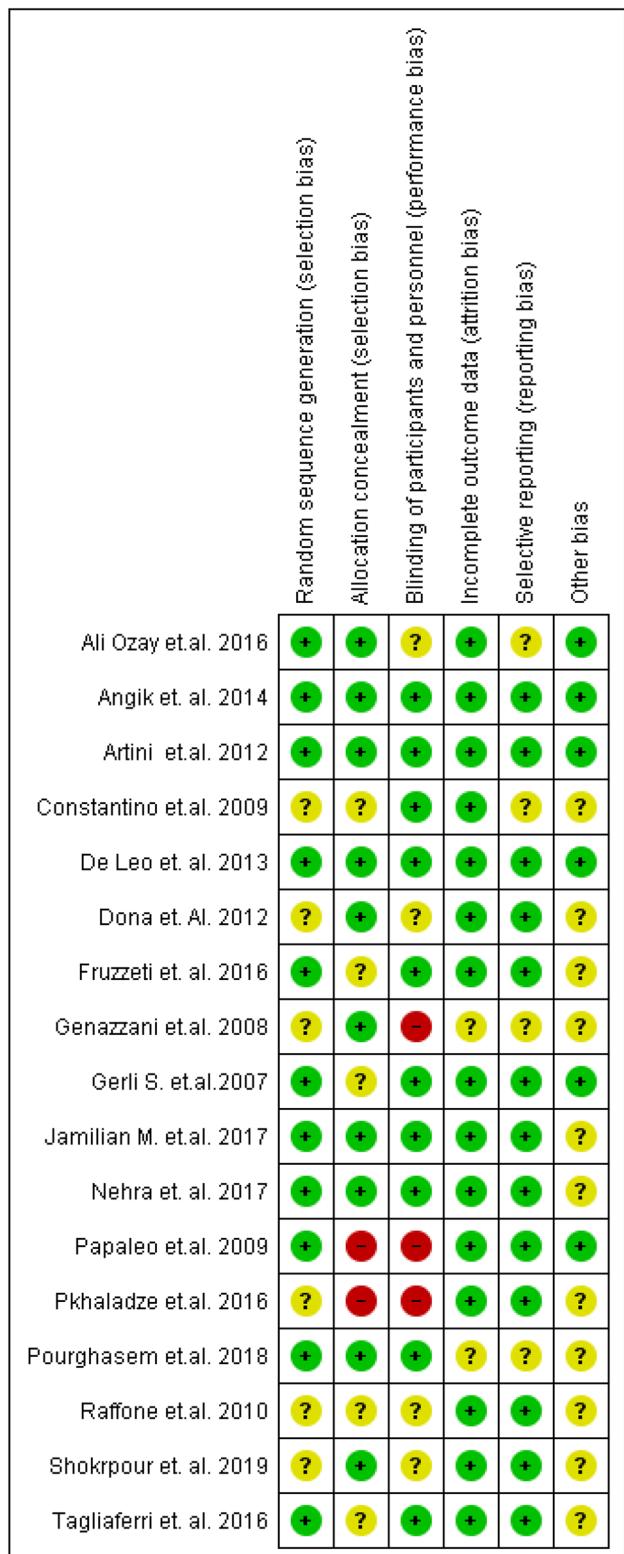
**Fig. 5** Risk of bias summary for included studies

Figure 5 describes the summary of the risk of bias among the included studies. In included studies, randomization is done by computer-generated randomization, random numbers table, and manual odd/even ratio; treatment allocation is concealed either by nurse or pharmacist using opaque sealed envelopes; and a majority of studies were double-blinded. Moreover, studies also reported all the outcomes listed in the method section of the papers including the patient dropout and poor patient compliance. However, in some of the studies, a lack of information about randomization, blinding, patient drop-outs, and non-compliance was observed. Some studies did not report the results of outcomes mentioned in the method section. The outcome of our meta-analysis also gets considerably affected due to such biases in the included studies.

Obesity is a common but underestimated condition, affecting one-third of the world's adult population [51]. According to World Health Organization, if this trend continues, 38% adult population worldwide will be affected by obesity by 2030. The role of obesity in the causation of metabolic syndrome is well understood. Furthermore, the association between obesity and PCOS has been well established through epidemiological studies, which reveal that more than 50% of PCOS patients are obese or overweight [52]. Though the increase in body weight represents obesity, BMI and WHR are the surrogate markers of obesity in clinical practice. The present meta-analysis does not show significant improvement in both BMI and WHR after MI treatment in PCOS patients. The outcome of our meta-analysis is in agreement with recently published meta-analysis studies [28, 53]. However, a meta-analysis by Unfer et al. showed a decrease in BMI but not in WHR after MI treatment in PCOS patients [54].

The IR and associated hyperinsulinemia play an important role in the developing reproductive and endocrine features of PCOS. It is estimated that 80% of obese PCOS patients and 30–40% of lean PCOS patients are insulin resistant [55]. Myo-inositol, a mediator of insulin action, ameliorates IR and improves hormonal profile as well as the metabolic factors in PCOS patients. Therefore, it is recommended for the treatment of PCOS [56]. Several previously conducted meta-analysis reported improvement in glycemic parameters like fasting glucose levels, fasting insulin levels, glucose/insulin ratio, and HOMA after MI treatment in PCOS patients [25–29, 54, 57]. However, the present meta-analysis does not observe any improvement in any of these glycemic parameters in PCOS patients. The meta-analysis by Facchinet et al. also supports our results [18].

Table 3 Meta-analysis of anthropometric, metabolic, and endocrine outcomes in PCOS patients comparing myo-inositol with control

Variable	Overall effect		P	I^2	P	Heterogeneity test	Studies	Sample size
	MD	95% CI						
BMI (kg/m^2)	0.31	-0.45, 1.06	0.43	93%	<.00001	Random effect	16	1013
WHR	0.00	-0.02, 0.03	0.7	81%	<.0001	Random effect	06	482
FG (mg/dL)	-0.21	-3.11, 2.70	0.89	80%	<.00001	Random effect	10	719
FI ($\mu\text{IU}/\text{mL}$)	-1.52	-3.04, 0.01	0.05	84%	<.00001	Random effect	9	619
HOMA	-0.39	-0.83, 0.04	0.08	92%	<.00001	Random effect	9	481
LH (IU/L)	0.06	-1.03, 1.14	0.92	87%	<.00001	Random effect	9	590
FSH (IU/L)	-0.33	-0.95, 0.28	0.29	96%	<.00001	Random effect	7	450
Estradiol (pg/mL)	1.69	-0.82, 4.19	0.19	81%	<.0001	Random effect	7	502
SHBG (nmol/L)	-5.04	-18.71, 8.63	0.47	99%	<.00001	Random effect	7	472
DHEAS ($\mu\text{g}/\text{mL}$)	-0.36	-0.83, 0.11	0.14	94%	<.00001	Random effect	7	482
Androstenedione (ng/dL)	-35.98	-68.29, -3.67	0.03	93%	<.00001	Random effect	8	398
Total testosterone (ng/dL)	-9.62	-21.04, 1.81	0.1	99%	<.00001	Random effect	11	484
Prolactin (ng/mL)	-1.71	-3.37, -0.04	0.04	89%	<.00001	Random effect	8	510

BMI, body mass index; WHR, waist-to-hip ratio; FG, fasting glucose; FI, fasting insulin; HOMA, homeostatic model assessment; LH, luteinizing hormone; FSH, follicle-stimulating hormone; SHBG, sex hormone-binding globulin; DHEAS, dehydroepiandrosterone; MD, mean difference

Hyperandrogenism, clinically manifested as hirsutism, alopecia, and acne vulgaris, is the leading cause of infertility in PCOS patients. It is well understood that abnormal neuroendocrine function like increased GnRH pulse frequency is responsible for alteration in ovarian folliculogenesis, steroidogenesis, and resulting excess androgen production in PCOS patients [58]. Moreover, IR and hyperinsulinemia also trigger hyperandrogenism in PCOS patients [49], which is evident from the improvement in hyperinsulinemia as well as hyperandrogenism after insulin-sensitizing pharmacotherapy in PCOS patient [50]. Many previously conducted meta-analysis reported the effect of MI on various endocrine parameters. A meta-analysis by Unfer et al. reported a reduction in testosterone and SHBG levels in PCOS patients after MI treatment, whereas androstenedione levels remained unaffected [27]. Researchers also reported an observable effect of MI on SHBG, androstenedione, prolactin, and total testosterone levels in PCOS patients [25, 29]. On the contrary, other meta-analysis studies reported no significant improvement in endocrine parameters like testosterone level [28, 53]. In the present meta-analysis, a remarkable effect of MI was found only on androstenedione and prolactin levels but not on other endocrine parameters like LH, FSH, estradiol, SHBG, dehydroepiandrosterone, and total testosterone levels in PCOS patients. Normal physiological serum prolactin level is important for insulin sensitivity, distribution of adipose tissue, lipid storage, and lipid metabolism [59]. Moreover, a significant co-relation between serum prolactin level and metabolic risk is found in infertile PCOS patients [60]. Increased serum androstenedione level is

also associated with more severe PCOS symptoms due to increased LH, testosterone, DHEAS, and progesterone levels and ovarian volume [61]. Besides, serum androstenedione level is a more sensitive indicator of PCOS-related androgen excess than serum total testosterone concentrations [62].

We were unable to analyze parameters like free androgen index, glucose-insulin ratio, progesterone level, and also parameters for lipid profile, reproductive, and ovarian function in the present meta-analysis because these parameters were reported by only one or two RCTs, which were insufficient for conducting evaluation [37, 39, 42, 47, 63].

In conclusion, MI supplementation in PCOS patients did not affect anthropometric, metabolic, and endocrine parameters except prolactin and androstenedione levels.

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Data Availability Data used during the study appear in the submitted article.

Code Availability RevMan 5.3 from Cochrane Collaboration.

Declarations

Ethical Approval No ethics committee approval was required because the study analyzed only published data.

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Consent for Publication All authors have read and agreed to the published version of the manuscript.

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