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REVIEW ARTICLE

Short-term effects of metformin and myo-inositol in women with polycystic ovarian syndrome (PCOS): a meta-analysis of randomized clinical trials

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ABSTRACT

Metformin (MET), the most commonly used insulin sensitizer, is the reference off-label drug for the treatment of polycystic ovary syndrome (PCOS), worldwide. However, its use may be limited mainly by gastrointestinal adverse effects. Myo-inositol (MI), a well-recognized food supplement, also represents an evidence-based treatment for PCOS women, popular in many countries. Our aim is to provide a systematic review of the literature and a meta-analysis which compares these two treatments, for their short-term efficacy and safety in PCOS patients. Systematic review and meta-analysis of randomized clinical trials (RCTs). RCTs were identified from 1994 through 2017 using MEDLINE, Cochrane Library, PubMed, and ResearchGate. Included studies were limited to those one directly comparing MET to MI on several hormones changes. Standardized mean difference (SMD) or risk ratios (RRs) with 95% CIs were calculated. Changes in fasting insulin was the main outcome of measure. Six trials with a total of 355 patients were included. At the end of treatment, no difference between MET and MI was found on fasting insulin (SMD = 0.08 μU/ml, 95% CI: −0.31–0.46, $p = .697$), HOMA index (SMD = 0.17, 95% CI: −0.53–0.88, $p = .635$), testosterone (SMD = −0.01, 95% CI: −0.24–0.21, $p = .922$), SHBG levels (SMD = −0.50 nmol/l, 95% CI: −1.39–0.38, $p = .263$) and body mass index (BMI) (SMD = −0.22, 95% CI: −0.60–0.16, $p = .265$). There was strong evidence of an increased risk of adverse events among women receiving MET compared to those receiving MI (RR = 5.17, 95% CI: 2.91–9.17, $p < .001$). No differences were found in the effect of MET and MI on short-term hormone changes. The better tolerability of MI makes it more acceptable for the recovery of androgenic and metabolic profile in PCOS women.

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PCOS; metformin; myo-inositol; fasting insulin; HOMA index; testosterone; androstenedione; SHBG; BMI; side effects

Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous disorder presenting with several complaints including ovarian dysfunction, hyperandrogenism, menstrual irregularity, insulin resistance (IR), and obesity [1]. Hyperinsulinemia is one of the main factors in PCOS causing hyperandrogenism [2], as it directly induces both ovarian and adrenal androgen release and, increasing glucose concentrations, restrains liver sex hormone binding globulin (SHBG) synthesis, as well as production of insulin-like growth factor binding protein 1 (IGFBP-1). The increased androgen signaling causes premature follicular atresia and anovulation [1, 3]. IR and reactive hyperinsulinemia are further stimulated by adipose tissue, being enhanced in obese patients [4].

Due to the pathophysiological link between IR and PCOS aberrations, insulin sensitizers have been used to counteract the above described clinical and metabolic signs. Metformin (MET) is the most common insulin sensitizer, used over the past 50 years for type 2 diabetes in many countries [5], as well as an off-label drug in nondiabetic women with PCOS. Existing evidence shows that MET may have metabolic and reproductive benefits, including weight reduction, decreasing IR, and androgen levels, besides restoration of normal menstrual cyclicity and ovulation [6, 7]. However, its use may be limited by significant side effects such as nausea, vomiting, and gastrointestinal discomfort [8]. The poor compliance observed with MET motivated clinicians worldwide to find novel approaches for PCOS.

Myo-inositol (MI), a naturally-occurring compound, has been investigated in the last decade because of its insulin-sensitizing effects [9]. Accordingly, several clinical trials have been carried out for the evaluation of the efficacy of MI in the treatment of metabolic and reproductive complaints of PCOS women [10, 11], also in view of its safety profile [12].

More recently, different authors performed head to head comparisons of MET and MI. For this reason, we have decided to systematically review those randomized studies and to perform a meta-analysis in order to compare these two treatments, MET and MI, for their short-term efficacy and safety in PCOS patients.

Materials and methods

Search strategy and data extraction

A systematic review of studies that compared MET to MI treatment in patients with PCOS was carried out. The database of MEDLINE, the Cochrane Library, PubMed, ResearchGate, and bibliographies were searched with the following medical subject headings (MeSH): 'Myo-inositol,' 'Metformin,' 'PCOS,' 'randomized clinical trials (RCTs).' No language restriction was imposed. The search

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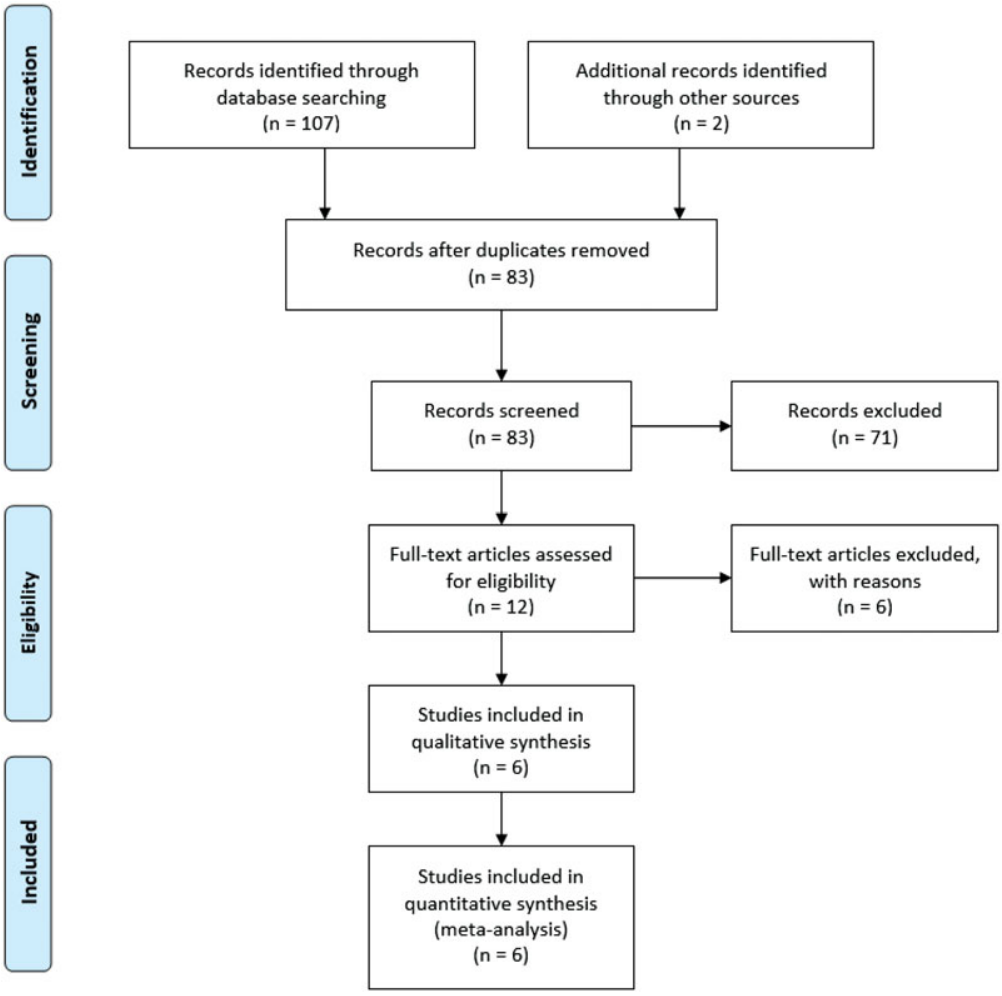


Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of study selection and inclusion [14].

included literature published until December 2017. Article titles and abstracts were first reviewed and then the full-texts were obtained to assess study eligibility. Two review authors (F.F. and V.U.) independently evaluated and classified studies for inclusion and trial quality and extracted data. Any disagreement among reviewers was resolved by discussion.

The meta-analysis was performed according to the Cochrane Collaboration recommendations [13]. The analysis of results was reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [14]. The characteristics of each study were extracted from the article full-text including: study's first author and year of publication, Country where the study was performed, study design, number (N°) of subjects, inclusion and exclusion criteria, lifestyle change, intervention, and duration of treatment expressed in weeks. Data [means ± standard deviation (SD) or ± standard error of the mean (SEM)] for each outcome pre- and post-treatment were extracted and, if required, converted accordingly for homogeneity. Missing outcome data in the original article were asked directly to the authors.

Including and excluding criteria

Studies were included in the analysis if they met the following conditions: (a) designed as RCT; (b) use of MET versus MI; (c) population is represented by patients with PCOS diagnosed according Rotterdam Criteria [15] or Androgen Excess Society (AES) Guidelines [16]; (d) outcomes include at least one among the following, fasting insulin, homeostasis model assessment (HOMA) index, testosterone, androstenedione, SHBG, body mass index (BMI); and (f) side effects related to treatments are described. Studies were excluded if: (a) selected treatments were combined with other drugs or supplements (excluding folic acid), (b) duplicate publications, and duplicates on different database, (c) review papers, and (d) animal or cell culture studies.

Quality assessment

For the risk of bias the Cochrane recommendations were followed, considering random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting [13]. Categories were assessed as low, unclear or high risk of bias and summarized in a table with a plus, question mark or minus, respectively. A debate over the risk of bias was undertaken for the studies in order to find unanimity between the review authors.

Statistical analysis

The effect size was measured as the standardized mean difference (SMD) obtained as Hedges' adjusted *g*, for continuous outcomes and the risk ratios (RR_s) with 95% confidence intervals (CIs) for the dichotomous outcome. The heterogeneity among the

Table 1. Characteristics of the included studies.

Study's first author	Country	Study design	N° of subjects (Mean BMI)	Inclusion criteria	Exclusion criteria	Life style change	Intervention	Duration (weeks)
[26]	India	RCT	(N° = 71) MI: 35 MET: 36	Age: 15–45 years PCOS according to AES/2006 criteria, hyperandrogenism, oligo or anovulation, PCOM	Pregnancy/nursing, neoplastic disease, Cushing's disease, Hypo- hyperthyroidism, Hyperprolactinemia. Active liver disease, renal impairment, type 1/2 diabetes mellitus, antidiabetic/estrogen/ progesterone, any treatment taken in last 3 months, Smokers/ alcoholic subjects	*N*	MI 2 g/d vs. MET 1.5 g/d	12
[25]	India	RCT	(N° = 100) MI: 50 (24.1) MET: 50 (23.2)	Age: 15–40 years PCOS according to Rotterdam's criteria	Undergoing other drug treatment for PCOS (like oral contraceptive pills); Deranged kidney or liver function tests; Thyroid disorders; Known hypersensitivity to MI	*N*	MI 2 g/d vs. MET 2g/d	24
[27]	Iran	RCT	(N° = 60) MI: 30 (25.8) MET: 30 (27.1)	Age: 18–40 years PCOS according to Rotterdam's criteria	Pregnancy during intervention, adrenal hyperplasia, androgen-secreting tumors, hyperprolactinemia, thyroid dysfunction, diabetes impaired glucose tolerance	*N*	MI 4 g/d vs. MET 1.5 g/d	12
[30]	Italy	RCT	(N° = 34) MI: 17 (31.5) MET: 17 (29.7)	PCOS according to Rotterdam's criteria	Adrenal enzyme defect, neoplasm, pregnancy/ nursing, Liver/renal impairment, cardiovascular disease, and other hormonal dysfunctions	*N*	MI 2 g/d vs. MET 1.7 g/d	24
[28]	Italy	RCT	(N° = 50) MI: 25 (27.3) MET: 25 (28.4)	Age: 18–28 years PCOS according to Rotterdam's criteria, oligomenorrhea hyperandrogenism	Hyperprolactinemia, Cushing's syndrome, androgen-secreting tumors, hypo-hyperthyroidism, congenital adrenal hyperplasia	*N*	MI 4 g/d vs. MET 1.5 g/d	24
[29]	Italy	RCT	(N° = 40) MI: 20 (28.2) MET: 20 (28.8)	Age: 24–32 years, PCOS according to Rotterdam's criteria, IR	Other endocrinopathies	*N*	MI 3 g/d vs. MET 1.7 g/d	24

RCT: randomized controlled trial; BMI: body mass index; MI: myo-inositol; MET: metformin; Y: yes; N: no; AES: androgen excess society; PCOM: polycystic ovarian morphology; IR: insulin resistance

included studies was tested using the Cochran's Q test and the I^2 statistic, with a p value=.10. A fixed-effect model (Mantel–Haenszel method) [17] and a random-effects model (Der Simonian–Laird method) [18] were used to obtain the pooled estimates as appropriate. No differences of baseline values between the two groups were found. Comparison among studies was carried out on parameter values post-treatments. Forest plots showed the results of the analyses performed. Meta-analysis was evaluated by use of Stata Statistical Software: Release 12 (College Station, TX: StataCorp LP). Results were considered statistically significant when the two-sided p value $< .05$.

Results

Description of the studies

Literature search yielded a total of 109 studies. After removing of duplicates, 83 articles remained and were reviewed by the titles and abstracts. A total of 12 full-texts had been carefully evaluated for eligibility and 6 left for the quality assessment (Figure 1). One study was excluded because it has a retrospective design [19] and another one was an observational non-RCT [20]. In one study, differences of baseline values between the two groups were found, particularly reporting mistaken results in the insulin parameter. The corresponding author was required twice to explain, but a reply was never received and study was then excluded [21]. Three further studies were excluded because they reported outcomes not considered in this meta-analysis [22–24]. The characteristics of the included studies are summarized in Table 1. The six RCTs were published between 2013 and 2017 and originated from three countries, i.e. India [25, 26], Iran [27], and Italy [28–30] (Table 1). A total of 355 patients had been randomized into treatment with MET ($n = 178$) or MI ($n = 177$). The specific doses for MET (ranging between 1.5 and 2 g/d and MI (ranging between 2 and 4 g/d used are reported in Table 1. Their mean age was 25.4 ± 4.1 years in MET group and 25.7 ± 4.2 years in MI group. Treatments duration ranged between 12 and 24 weeks. All studies but one [26] reported BMI.

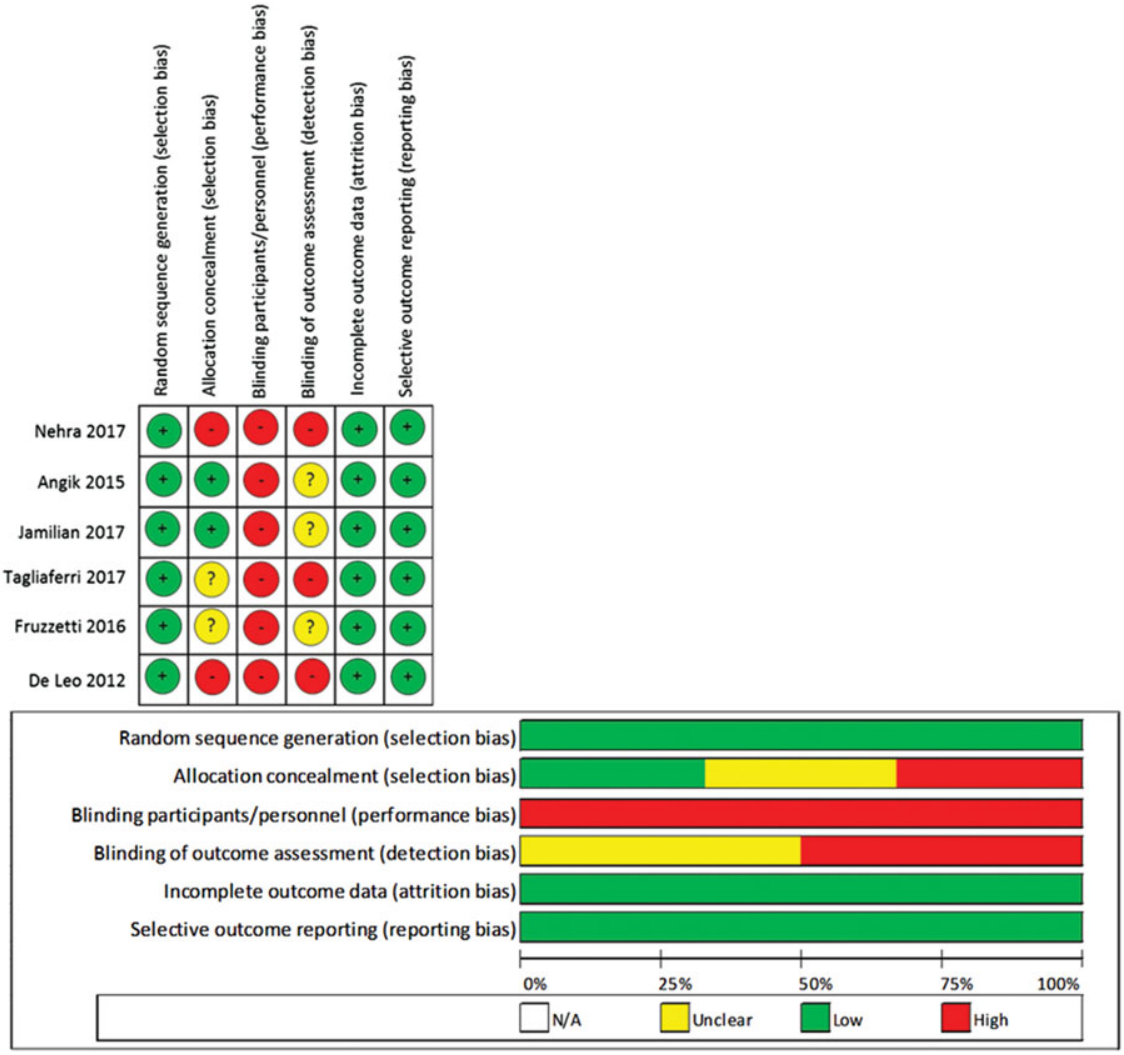


Figure 2. Assessment of risk of bias for included studies. Upper part: Risk of bias summary for each RCT assessed according to the methods recommended by the Cochrane Collaboration. In green: positive sign, low risk of bias; in red: negative sign, high risk of bias; in yellow: question mark, unclear risk of bias; Risk of bias graph about each risk of bias item illustrated as percentage across all selected RCTs.

The mean BMI of the subjects treated falls into the overweight range (> 25) (Table 1) for all trials considered with the exception of a study including normal-weight subjects [25]. No study reported the contemporary prescription of lifestyle changes. Data of the selected outcomes were provided in most of the studies. Insulin was reported in 4/6 articles, HOMA index in 4/6, testosterone in 5/6, androstenedione in 2/6, SHBG in 3/6, BMI in 5/6, and side effects in 4/6 articles.

Quality assessment

Overall, the risk of all types of bias in the RCTs was mainly low to unclear (Figure 2). All the studies clearly reported the random sequence generation. Only two reported the allocation concealment, while in two other studies it was not specified, leaving risk of bias unclear. The most evident risk of bias was the lack of blinding procedures. All RCTs had no adequate description of blinding of outcome assessment thus having an unclear risk of bias. The doses of the two treatments groups (MET and MI) are variables between different trials. Outcomes were well reported in most of the studies.

Meta-analysis

In the six selected studies, a total of 178 women received MET and 177 women received MI alone or combined with folic acid. The random model showed no difference in fasting insulin between women receiving MET and those receiving MI (SMD=0.08 μU/ml, 95% CI: −0.31–0.46, p=.697) (Figure 3(A)). A moderate heterogeneity among studies was found (Q = 6.99, df= 3, I^2 =57.1%, p=.072).

No evidence of a difference in the effect on HOMA was found between the MET and MI group (SMD =0.17, 95% CI: −0.53–0.88, p=.635). For this outcome, considerable heterogeneity across studies was found (Q = 22.62, df =3, I^2 =86.7%, p < .001) (Figure 3(B)). On the contrary, five trials reporting the effect of MET and MI on serum testosterone revealed no heterogeneity across studies (Q = 5.69, df =4, I^2 =29.8%, p=.223). There were no differences in the changes of testosterone concentrations between MET and MI treatments (SMD= −0.01, 95% CI: −0.24–0.21, p=.922) (Figure 3(C)). As well, for the androstenedione outcome, heterogeneity across studies was not found (Q = 0.15, df =1, I^2 =0.0%, p=.701). No differences were observed between treatments on androstenedione concentrations

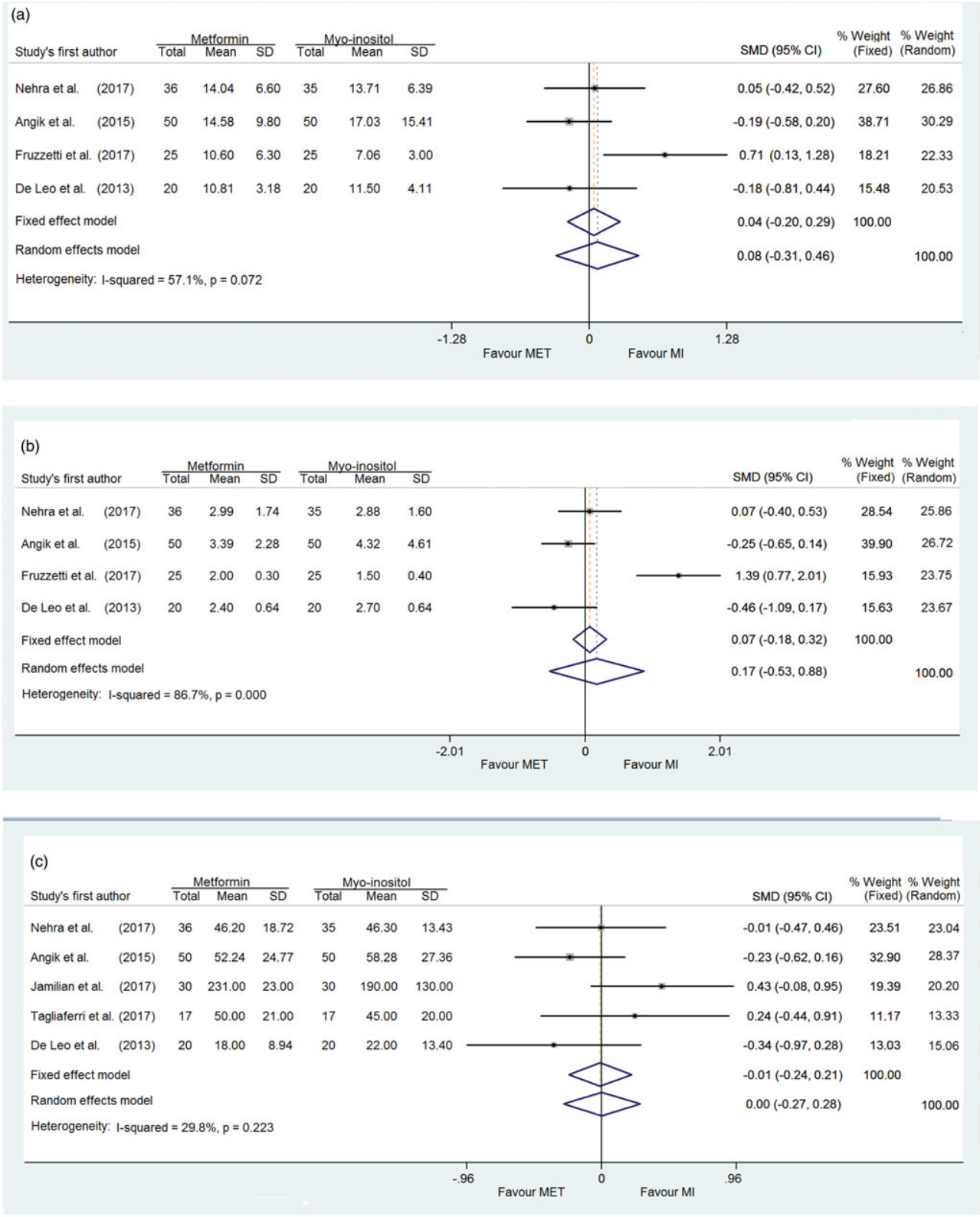
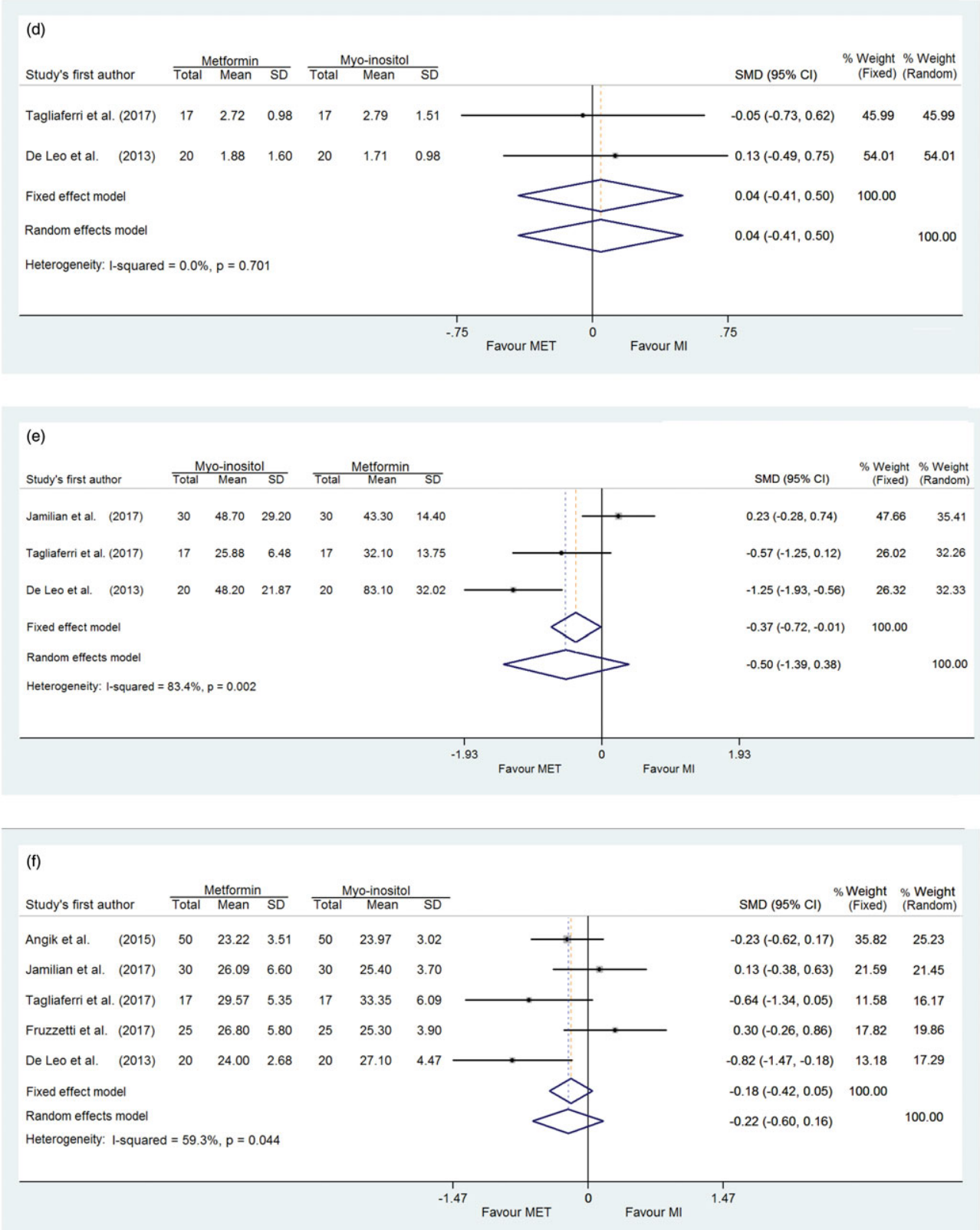


Figure 3. Forest plots of comparison metformin (MET) vs. myo-inositol (MI) on fasting insulin (A), HOMA index (B), testosterone (C), androstenedione (D), SHBG (E), BMI (F), and side effects (G).

(SMD =0.04, 95% CI: −0.41–0.50, p=.853) (Figure 3(E)). The random effects model showed no difference between MET and MI effect on SHBG levels (SMD= −0.50 nmol/l, 95% CI: −1.39–0.38, p=.263). Considerable heterogeneity was observed (Q = 12.03, df =2, I^2 =83.4%, p=.002) (Figure 3(D)). No evidence of a difference in the effect on BMI was found between the MET and MI group (SMD= −0.22, 95% CI: −0.60–0.16, p=.265). Substantial heterogeneity across studies was found



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($Q = 9.82$, df =4, I^2 =59.3%, p=.044) (Figure 3(E)). There was a high risk of side effects among women who received MET compared to those administered with MI (RR =5.17, 95% CI: 2.91–9.17, $p < .001$); women in MET group were almost five times more likely to have side effects than those in MI group. No heterogeneity among studies was found ($Q = 2.28$, df =3, I^2 =0.0%, p=.517) (Figure 3(F)). Most reported side effects with MET were nausea, diarrhea, in some cases also of severe entity,

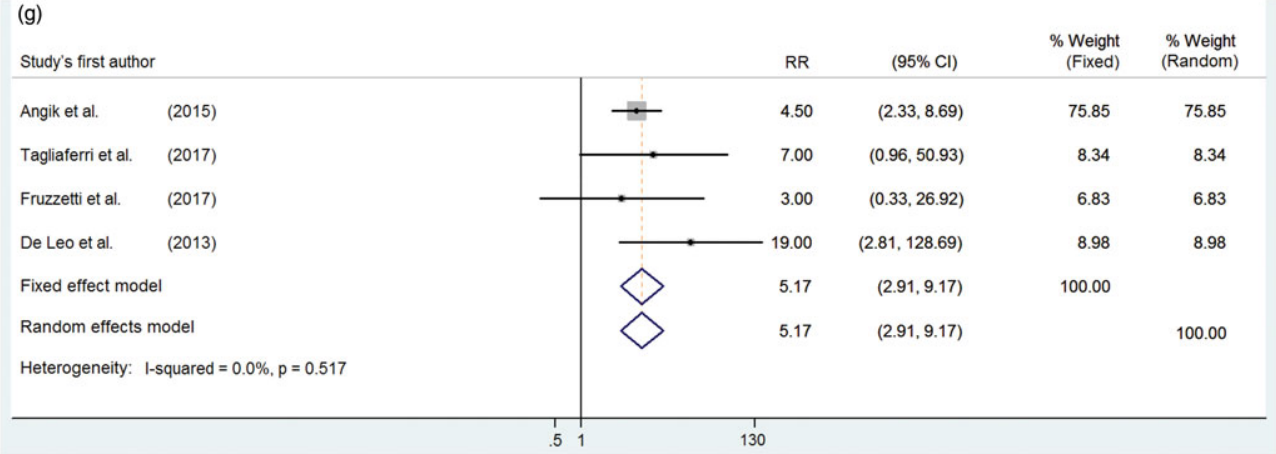

Figure 3. Continued.

abdominal pain, lactic acidosis, and generalized weakness [25, 28–30], while with MI were nausea, mild diarrhea, and menorrhagia [25, 29].

Discussion

These meta-analyses demonstrate that in PCOS patients there is no difference in the short-term effect of MET versus MI as far as fasting insulin, HOMA index, testosterone, androstenedione, SHBG, and BMI are concerned. However, a statistically significant heterogeneity among studies was found for HOMA, SHBG, BMI changes. The main difference observed was the absence of adverse reactions in patients treated with MI compared to those reported in women treated with MET. This seems remarkable as a natural molecule such as MI can be used effectively as treatment for PCOS women, while assuring a great patients' compliance. Avoiding discontinuation of the treatment, due to any intolerable side effect, is quite recommendable as this disorder is associated with severe consequences such as infertility [31, 32].

MET is a complex drug with multiple sites of action and multiple molecular mechanisms. It acts directly or indirectly on the liver to lower glucose production and on the gut to increase glucose utilization and glucagon-like peptide 1 production and alter the microbiome. At the molecular level, MET inhibits the mitochondrial respiratory chain in the liver, enhancing insulin sensitivity with effects on fat metabolism and reducing the expression of gluconeogenic enzymes [33].

MET has proven to reduce glucose absorption and hepatic glucose synthesis and increase insulin sensitivity by increasing peripheral glucose uptake with no significant direct effect on pancreatic insulin production [7, 34, 35]. It has long been studied alone or in combination with other agents to restore ovulation [36]. MET has also been shown to reduce the risk for hyperstimulation during *in vitro* fertilization, but insufficient evidence reporting an increased live-birth rate [37, 38]. However, according to the new guidelines [39], MET alone offers little advantage and therefore, is not recommended as a first-line agent for correcting infertility in patients with PCOS. Moreover, a review of RCTs about MET treatment in PCOS could not confirm any weight-reducing effect [36].

MI is one of the nine stereoisomers of inositol, a physiological compound belonging to the sugar family, contained in foods such as legumes, nuts, fruits, whole grains. Furthermore, it is synthesized endogenously from glucose 6-phosphate [40, 41], and it is found at the level of cell membranes in the form of phosphatidylinositol, bound to membrane phospholipids. MI is the most abundant form among inositol(s) family, accounting for about 99% of the intracellular inositol in ovaries and testis [42, 43]. Its effect starts when it is incorporated into cell membranes as phosphatidyl-MI, the precursor of inositol triphosphate that acts as second messenger regulating the activities of several hormones such as thyroid-stimulating hormone, stimulating follicle hormone, and insulin, improving their signals [44, 45]. MI has been shown to improve insulin sensitivity and oocyte quality, to reduce hyperandrogenism and regulate menstrual cycles ovulation and hirsutism [10, 46].

This meta-analysis clearly shows that MI is associated with a lower risk of adverse events in comparison to MET: for this reason its use could be safer or possible also in association with lower levels of MET in subjects that do not tolerate higher MET therapeutic dose.

Much more studies are available on MET respect with MI, the former being used since a longer period of time. Indeed, in subjects at risk for developing diabetes including PCOS women, MET administration was associated with an improvement of lipid profile and IR while reducing new onset diabetes, respect with placebo or no treatment [47]. On the contrary, the long-term effects of MI on the above health-related parameters are still unknown, in particular its long-term effect on the onset of type II diabetes and cardiovascular diseases in users.

Strength and weaknesses

To our knowledge, this is the first meta-analysis providing quantitative estimates of the comparison of MET versus MI treatment in PCOS women. A comprehensive search was carried out to avoid missing any relevant information. Subjects included in the studies were from different ethnic groups allowing the findings to have a wide transferability. Only RCTs were included to remove potential bias although all the studies lack of blinding. However, a double-blind design was objectively difficult because of the diverse pharmaceutical presentation of treatments (sachet versus pill) and poor reliability due to different adverse reactions associated with treatments.

Another weakness was that every single outcome was not reported in every study. Moreover, in some case the main

outcome, we choose was not the primary outcome in the primary study.

The specific doses of treatments (MET versus MI) are variable between different trials and this issue could be a source of heterogeneity, especially for the dose of MI that has the biggest range.

The BMI of the included trials ranges between normal and over weight: the relationship between the efficacy of these treatments and the specific BMI of subjects treated has to be evaluated in future studies.

The short-term length of follow up of all the studies included (between 12 and 24 weeks) is another important limitation of this meta-analysis: RCTs with a longer follow up must be performed in order to confirm these short-term comparable effects.

Conclusion

This meta-analysis demonstrates no differences in the effect of MET and MI on short-term hormone changes in subjects with PCOS. The better tolerability of MI makes it more acceptable for the recovery of androgen and metabolic profile in PCOS women.

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Disclosure statement

F.F. and G.G. declare that they have no conflict of interest and have received no payment in preparation of their manuscript. B.O. is employee at LO.LI. Pharma, Rome, Italy. V.U. is employee at LO.LI. Pharma, Rome, Italy.

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