Efficacy of Myo-inositol in Improving Pregnancy Rate and Regulation of Menstrual Cycle for Patients With Polycystic Ovarian Syndrome: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Polycystic ovarian syndrome (PCOS) is a common, reproductive endocrinopathy associated with ovarian dysfunction, cardiovascular disorders, obesity, and infertility. Myo-inositol is a novel treatment for women with PCOS that claimed to have improved fertility rate in this population. This systematic review and meta-analysis examined the effect of myo-inositol on pregnancy rate, menstrual cycle, and adverse effects from randomized controlled trials (RCTs).

Methods: RCTs that evaluated the efficacy of myo-inositol in improving pregnancy rate and regulation of menstrual cycle in women with PCOS. Electronic databases were searched and studies published up to October 24, 2021 were included in the systematic review and meta-analysis. Study selection and assessment of quality were conducted independently by two review authors.

Results: Seven studies with 729 patients treated with myo-inositol and 677 patients treated with placebo and/or metformin were included in the analysis. The research groups did not diverge significantly in terms of basic characteristics, such as age, adnexal or uterine pathology, body mass index, and duration of infertility. In the myo-inositol group, regulation of the normal menstrual cycle is at 20%, significantly higher than the metformin group at 12%, ($p<0.001$). However, there is no significant difference in the pregnancy rate between myoinositol and placebo ($p=0.42$) and/or metformin ($p=0.17$).

Conclusion: This systematic review and meta-analysis showed that myo-inositol can be an alternative treatment for PCOS in terms of regulation of menses and may improve the success of spontaneous pregnancies. However, additional randomized, double-blind controlled trials with larger sample sizes, low heterogeneity, and uniform inclusion criteria are recommended to establish the effects of myo-inositol on PCOS treatment and pregnancy rate.

Key words: Polycystic ovarian syndrome, PCOS, pregnancy rate, myo-inositol, menstrual regulation, menstrual cycle, randomized control trial, RCT

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is the state of hormonal dysregulation and unbalanced ovarian/follicle dynamics affecting 5–15% of women in the reproductive age and accounts for approximately 75% of anovulatory infertility cases.[1,2] It is the

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most common cause of serious short- and long-term health risks namely ovarian dysfunction, obesity, metabolic disorders, and infertility in women. The etiopathology of PCOS is not clear, but most probably a strong genetic cause that is influenced by gestational environment and lifestyle seems to be the key factor.[3]

The heterogeneity of clinical signs and symptoms of PCOS makes its severity grading challenging. PCOS can be characterized by some or all of these features: 1) hyperandrogenism 2) menstrual irregularity 3) insulin resistance 4) presence of 2–9 mm ovarian cysts and 5) ovarian volume greater than 10 ml. [1] Several studies have supported the role of insulin resistance and compensatory hyperinsulinemia, which are both observed in obese and lean patients. In patients with PCOS, insulin resistance and compensatory hyperinsulinemia stimulates both ovarian and adrenal androgen secretion and suppresses the hepatic synthesis of the sex hormone-binding globulin (SHBG), leading to hyperandrogenism and anovulation. Insulin resistance also determines the risk for obesity, impaired glucose tolerance, type 2 diabetes, dyslipidemia, hypertension, metabolic syndrome, and cardiovascular disease.[4] The role of insulin resistance and hyperinsulinemia in the pathogenesis of PCOS is confirmed by improved ovulatory function and reduced circulating androgens in PCOS patients to insulin-sensitizing drugs. Given the central role of insulin resistance in the onset of PCOS, insulin-sensitizing agents, such as metformin, have been proposed as the first-line approaches. [5] However, metformin use has been associated with some adverse effects namely gastrointestinal disturbance, lactic acidosis, hepatotoxicity, acute pancreatitis, vitamin B12 deficiency, coagulation disorders, and hypoglycemia.[6]

Metformin

The most commonly used insulin sensitizer that has been frequently used in the management of PCOS is metformin. It inhibits mitochondrial respiratory chain in the liver, enhances insulin sensitivity, fat metabolism, and reduces gluconeogenesis. Increased insulin sensitivity is brought about by improved peripheral glucose uptake with no significant effect on pancreatic insulin production. [7] It has long been studied alone or in combination with other agents to restore ovulation and reduce the risk of ovarian hyperstimulation during in vitro fertilization. However, aside from its limitation of use due to gastrointestinal effects, metformin alone is not recommended as a first-line agent for patients with infertility and PCOS.[7]

Several studies have shown a 40% improvement in menstrual cyclicity. A meta-analysis by Haas, et al. (2003) established the beneficial effects of using metformin, namely improved metabolism and 30-40% increase in spontaneous ovulation.[8]

Myo-inositol

Inositol is a novel treatment for PCOS that is gaining more recognition due to its lack of adverse effects. Studies have supported that insulin resistance is related to altered insulin signaling, probably due to a defect in the inositol-phosphoglycan (IPG) second messenger pathway.[4] The decline in insulin resistance is positively correlated with increasing fasting insulin plasma levels, which supports the role of inositol as a modulator of insulin-mediated metabolic pathway, glucose metabolism, insulin sensitivity, and oxidative stress.[2,5] This discovery opened the opportunity for this drug to be used as a safe and effective alternative treatment in patients with PCOS, through the restoration of their metabolic profile and consequent ovulation induction in infertile PCOS patients with only mild gastrointestinal side effects noted.[3]

Due to the role of insulin resistance in the physiology of PCOS, several insulin sensitizer drugs have been used to improve signs and symptoms present in PCOS. Although metformin has represented the landmark of PCOS therapy, myo-inositol is an insulin sensitizer drug that addresses hyperinsulinemia and hyperandrogenism in metabolic disorders, ie, PCOS.[9,10]

Myo-inositol is a cyclic carbohydrate with six hydroxyl groups that is converted into various derivatives by epimerase, an enzyme regulated well by insulin action.[10] In the form of inositol-phosphoglycans, these facilitate the signaling cascade of G-protein-coupled insulin receptor to activate phospholipase, thereby allowing the release of second messengers stimulating pyruvate dehydrogenase and glycogen synthase activities - the enzymes involved in oxidative and non-oxidative glucose metabolism. The administration

of myo-inositol showed that this supplement could play a crucial role in insulin sensitivity by mediating inositol phosphoglycan, modulating glucose uptake.[10] Due to these mechanistic functionalities, myo-inositol can stimulate the use of insulin and support hormonal balance, ovarian function, oocyte quality, and menstrual cycle regularity.[9] Aside from insulin resistance, Zacché, et al. showed that myo-inositol leads to a decrease in LH and androgen levels with the re-establishment of ovulatory menstrual cycles.[11,12] The decrease in LH levels also decreases testosterone and androstenedione levels, corrects LH/FSH ratio and restores menstrual cycles, induces ovulation, and helps facilitate spontaneous pregnancies with adequate progesterone production in the luteal phase.[12] Myo-inositol plays a critical role in oocyte development specifically, in meiotic resumption - responsible for final oocyte development by acting as a second messenger in calcium signaling and facilitating the release of calcium through receptors in oocytes.[13] This supports that myo-inositol may improve pregnancy rate by supporting oocyte development and modulating hormonal balance.

Myo-inositol may improve fertility outcomes by modulating hyperandrogenism and may positively affect pregnancy rate and regulation of menstrual cycle, a critical outcome of concern for women with PCOS. A number of meta-analyses and systematic reviews could not establish any differences between metformin and myo-inositol concerning the hormonal profile and ovarian function due to limited related research and high heterogeneity of published randomized controlled trials (RCT). This study aimed to synthesize and update the evidence of efficacy and safety of myo-inositol in women with PCOS.

Clinical Guide Question, Research Objectives, and Significance of the Study

Using the PICO framework, this study will be guided by the clinical question: "Among PCOS patients, is myo-inositol effective in improving pregnancy rate and regulation of menstrual cycle?"

The main objective of the study is to determine the efficacy and safety of myo-inositol in improving pregnancy rate and regulation of menstruation in patients with PCOS. This study would also aim to compare the clinical pregnancy rate and proportion with regular menstrual cycle, which are efficacy measures used between the myo-inositol and control groups and to identify adverse events with myo-inositol treatment.

This meta-analysis regarding the use of myo-inositol in improving pregnancy rates in PCOS patients can widen the armamentarium of clinicians in the management of PCOS. Furthermore, this can help clinicians improve clinical outcomes of menstrual cycle regulation in patients with PCOS.

METHODS

Research Design and Eligibility Criteria

The researcher conducted a systematic review and meta-analysis for qualitative and quantitative synthesis of relevant studies using the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Appendix A). The study was conducted from August 28, 2021 to October 27, 2021.

This study included randomized controlled trials (RCTs) which assessed the efficacy of myo-inositol in improving pregnancy rate and regulation of menstrual cycle; population of interest involved patients diagnosed with PCOS; studies which measured and reported any of the following outcomes: pregnancy rate, regulation of menstrual cycle, adverse effects; published primary research articles regardless of year and country, in English language or has an English translation available; and can be assessed as a full article.

However, research papers were excluded from the analysis if they did not report complete information or the data cannot be estimated or derived from reported results; observational studies including case studies or series; editorials or letters to the editor; secondary research (eg, review articles, systematic reviews, meta-analysis); with incomplete reported data; and conference abstracts only.

Information Sources and Search Strategy

Two independent researchers conducted a literature search of relevant studies from electronic databases. The following databases were searched for pertinent research articles: Cochrane Library, PubMed, ScienceDirect, Google Scholar, and Wiley Online. Likewise, reference lists were searched to identify additional studies. Studies published up to October 24, 2021 were included.

Different search techniques were employed including keyword search and Boolean logic search. Using keyword search and Boolean logic, the following terms were used: *"myo-inositol", "myoinositol", "polycystic ovarian syndrome", "PCOS", "pregnancy", "menstrual cycle regulation, "menstruation", "menstrual cycle", "adverse effects"*

Study Selection

Selected titles and abstracts were screened for eligibility by two independent researchers. The research title, keywords, and abstracts of research articles were initially screened. Then, these two team members independently scrutinized the full text research for final inclusion. Excluded articles and reasons for exclusion were recorded and tabulated. In case of disagreements, the researchers handled this through a discussion between the two reviewers and a third assessor assisted to arrive at a consensus.

Assessment of Risk of Bias

The two independent researchers adopted the Cochrane risk of bias tool embedded in the Review Manager (RevMan 5.4) software (Appendix B) to independently appraise the risk of bias of each eligible RCT. The following domains were graded as having low, unclear, or high risk of bias: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other bias. The overall bias of each study was rated as low if all key domains were rated as low, high if at least one of the key domains is rated as high, and unclear if the study did not satisfy any of the criteria mentioned.

Data Collection Process

The primary author extracted data from the included studies and these were recorded in a standardized Excel file. The extracted data was verified by another second member of the research team. The standardized Excel file was utilized to record pertinent study information which includes the following: authors, publication year, country, sample size, study population, myo-inositol dose, control group, treatment duration, pregnancy rate, proportion of regular menstruation, and adverse effects. Patient demographics and clinical profile including age, infertility duration, cycle length, fertility treatment, and BMI were also collected (Appendix C).

Outcome Variables and Definitions

The primary outcome of this study was pregnancy rate, which was defined as percentage of successful pregnancies after treatment with myo-inositol or control. The secondary outcomes would include regular menstruation defined as percentage of patients who had regular menstruation after treatment with myo-inositol or control, cycle length, and bleeding days; and adverse effects after treatment with myo-inositol or control.

SUMMARY MEASURES

Data Analysis

Stata MP version 16 software was used to perform the meta-analysis. Heterogeneity was assessed based on I2 statistics wherein a I2>50% indicates substantial heterogeneity.[4] P value <0.10 for the Cochrane's Q statistic also indicates significant heterogeneity.[4] A random-effect model was used across all analyses performed. The risk ratio or risk difference (in case of 0 event/non-event)[14] was presented for pregnancy rate, and the weighted mean difference for menstruation cycle length.

Ethical Considerations

No ethics approval and patient consent are needed since the study will involve the use of data from results of previously published studies.

Study Selection

A total of 10,893 records were identified through electronic and manual searches. Following initial screening, 67 articles were retrieved for detailed evaluation (Figure 1). Twenty four full text articles were excluded since inclusion criteria were not met, and some reported incomplete data. Following detailed evaluation of 43 studies, a further 16 studies were excluded due to unavailability of full text studies. Twenty-seven RCTs were assessed for eligibility and 20 studies were excluded due to wrong study design and different outcomes of interest. From this, seven

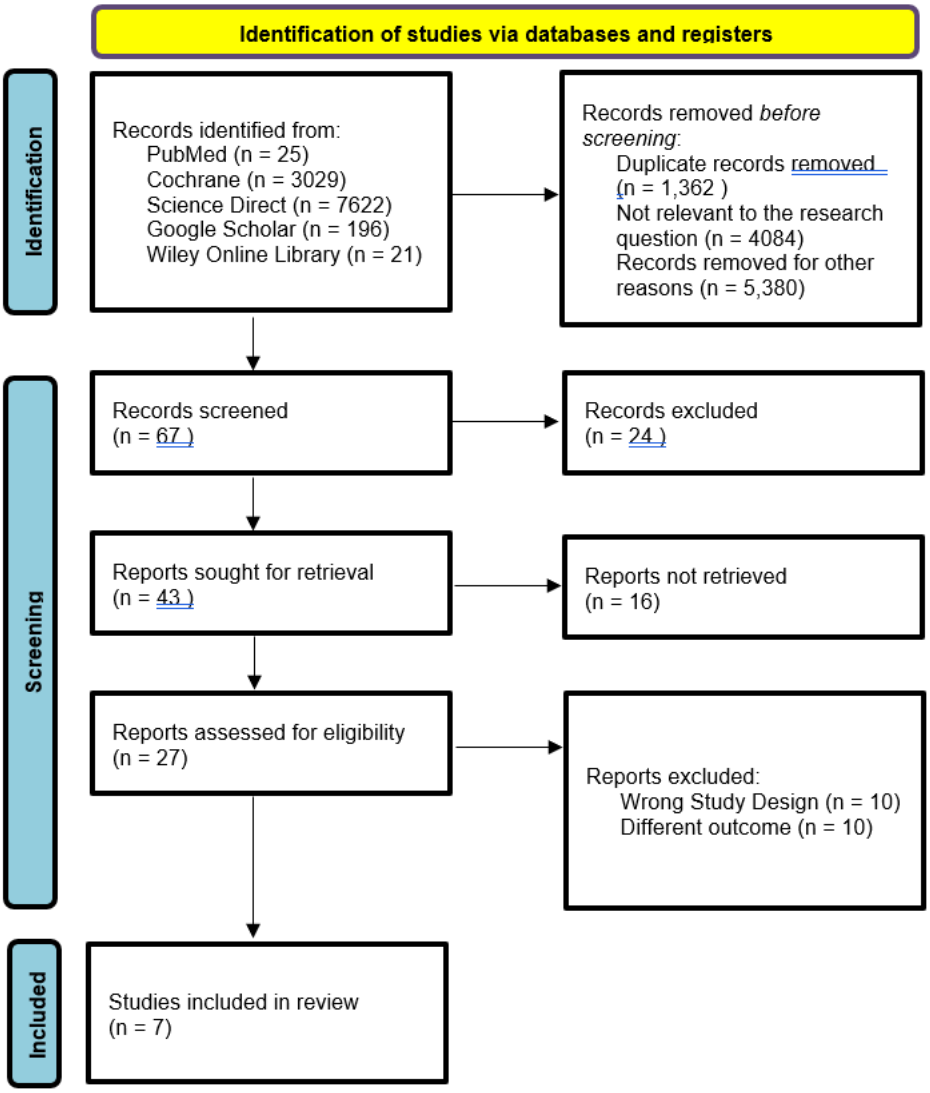

Figure 1. Study selection flow process
From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71

full text RCTs met the inclusion criteria including 1406 women.

Table 1 presents the characteristics of the included study. Studies were done in India (n=3), Iran (n=2), Turkey (n=1), and Italy (n=1). The total sample size was 1407 and ranged from 60 to 569 patients. The dose of myo-inositol varied per study ranging from 1200 mg per day to 8000 mg per day in divided doses. One study used only myo-inositol[14], the other four combined myo-inositol with folic acid[15-18]; and three studies included treatment arms that combined myo-inositol with metformin[2,14]. One study also used myo-inositol with its other form, which is d-chiro-inositol[19], and another one with melatonin.[17] Treatment duration lasted from two months[15] up to six months[2,19]. Three studies[16-18] had three months duration and one study lasted for four months.[14]

The study population (Table 2) included patients in their reproductive age (ranges 15-45 years old) diagnosed with PCOS based on the Rotterdam criteria. Among the studies, five RCTs included patients who failed to conceive for more than one year.[2,15-18] The mean BMI of the sample population ranged from 22 to 29.9 kg/m^2. Three studies reported baseline cycle length ranging from 32 days to 2.04 months[2,17], and the study of Chirania, et al, (2017) reported that -14% of their sample population had irregular menses.

Table 1. Characteristics of the included in the present meta-analytic PCOS study

Author, year	Country	Sample size	Study population	Treatment group	Control group	Treatment duration	Outcomes
Pourghasem, et al, 2019	Iran	186	Infertile PCOS resistant to letrozole	2 g myo-inositol + 200 ug folic acid, twice daily	Placebo (200 ug folic acid) 1500 mg metformin daily + 200 ug folic acid	3 months	Pregnancy rate
Agrawal, et al, 2019	India	120	Infertile PCOS	Metformin 500 mg + myo-inositol 600 mg three times a day for 6 months	Metformin 500 mg three times a day for 6 months	6 months	Pregnancy rate
Thalamati 2019	India	200	PCOS	Myo-inositol 550 mg + D-chiro-inositol 13.8 mg twice daily	Metformin 500 mg thrice daily	6 months	Regularity of menstrual cycle, cycle length
Sene, et al, 2019	Iran	60	Infertile PCOS	4 g Myo-inositol + 400 mg folic acid once daily	400 mg folic acid once daily	2 months	Pregnancy rate
Chirania, et al, 2017	India	76	PCOS with or without obesity and hyperandrogenism	Group A: myo-inositol 1 g/day Group C: myo-inositol 1 g/day + Metformin 1000 mg/day	Metformin 1000 mg/day	4 months	Pregnancy rate
Ozay, et al, 2017	Turkey	196	Infertile PCOS	4 g myo-inositol + 400 ug folic acid twice a day	Recombinant FSH on day 3 of cycle + 400 ug folic acid	3 months	Pregnancy Rate
Pacchiarotti, et al, 2015	Italy	569	PCOS	Group A: myo-inositol 4000 mg + folic acid 400 ug + Melatonin 3 mg twice daily Group B: myo-inositol 4000 mg + folic acid 400 ug twice daily	Folic acid 400 ug once daily	3 months	Pregnancy rate

Table 2. Demographics of patients in included in the meta-analytic PCOS study

Author, year	Mean age (years old)	Infertility duration (years)	Cycle Length	Mean BMI (kg/m²)
Pourghasem, et al, 2019	15 - 38	2-5	None mentioned	25 – 29.9
Agrawal, et al, 2019	20 - 38	>1	2.04 months	<30, no specific range mentioned
Thalamati 2019	15 - 45	None mentioned	None mentioned	None mentioned, weight was the data provided
Sene, et al, 2019	20 - 35	6 - 7	None mentioned	25 - 26
Chirania, et al, 2017	21 - 24	None mentioned	9 – 14% of sample population has irregular menses	24 - 25
Ozay, et al, 2017	18 - 35	1 - 2	None mentioned	24 - 25
Pacchiarotti, et al, 2015	27 - 38	1.5 - 2.5	32 – 37 days	22 - 23

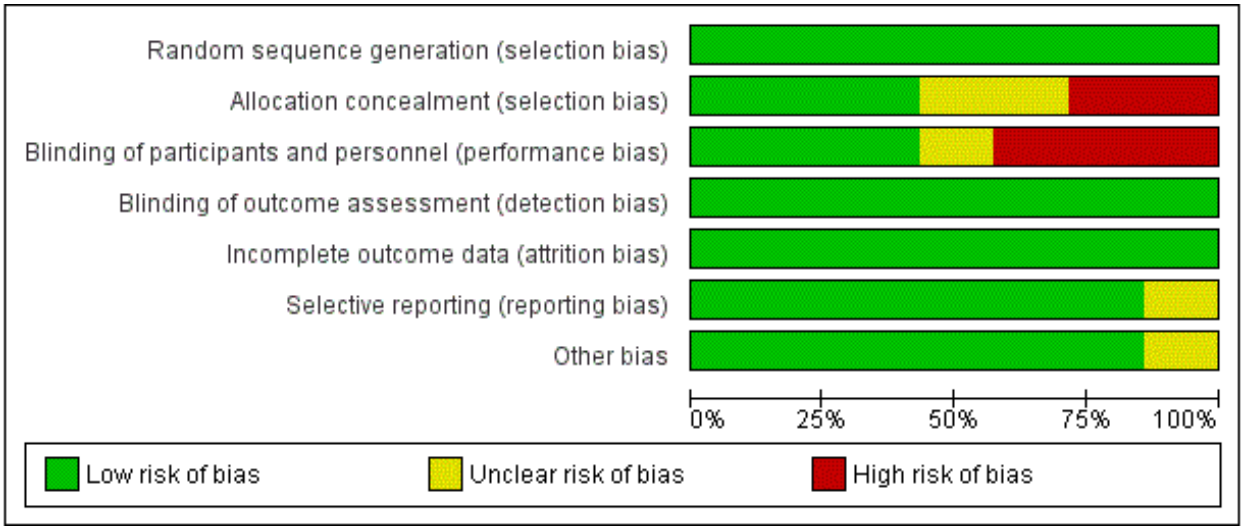

Figure 7. Risk of Bias Graph in the present meta-analytic PCOS study

BIAS ASSESSMENT

All seven studies were assessed as having some risk of bias (Figure 7). Incomplete or poor reporting of allocation concealment and blinding of authors impacted the assessment, and consequently an unclear risk of bias was determined in three studies[2,15,18]. Four studies were found to have high risks of bias in two domains including concealment[14,19], and blinding.[14,16,18] Six studies reported no conflicts of interest and one study reported potential conflict of interest due to authors' affiliations.[17] Two studies were funded by university or research institute grants[15,18] and the remaining studies did not have any financial relationship with any organization. [2,14,16,17,19]

RESULTS

PREGNANCY RATE

Myo-inositol + Folic acid vs. Folic acid

Pregnancy rate comparing myo-inositol + folic acid and folic acid alone (Figure 2) was reported by four studies[15-18], having a total sample size of 687 patients. Three studies consistently showed that pregnancy rate was higher when using myo-inositol (range: 19-40%) compared to folic acid alone (range: 12-36%)[15-17], except for the study of Pourghasem, et al. (2019) wherein the use of folic acid alone obtained a slightly higher pregnancy rate at 32% compared to the myo-inositol group at 28%. However, none of the studies showed a significant difference in pregnancy rate between the two groups. Also of importance is to note that the

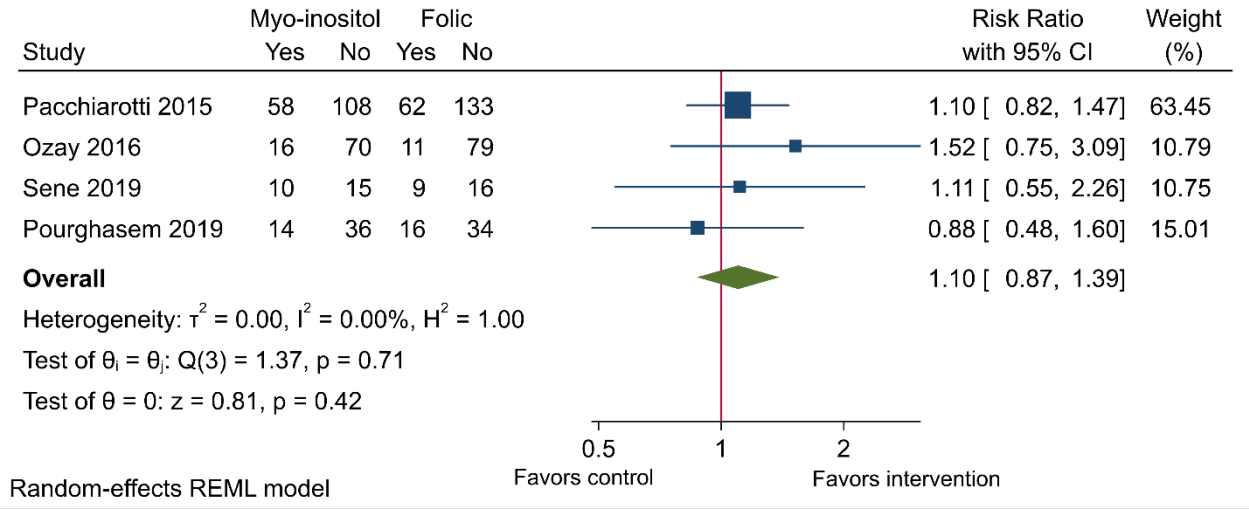

Figure 2. Forest plot: Pregnancy rate of Myo-inositol + Folic acid vs. Folic acid among PCOS patients

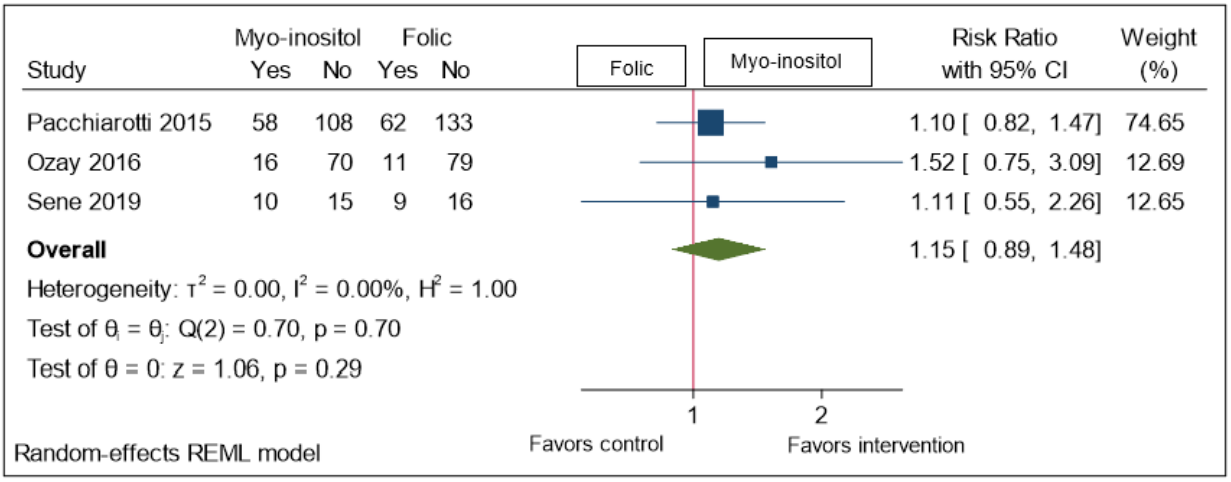

Figure 3. Forest plot: Pregnancy rate of Myo-inositol + Folic acid vs. Folic acid among PCOS patients undergoing fertility treatment

studies of Pacchiarotti, et al. (2015) and Ozay, et al. (2016) used a much higher dose of myo-inositol per day at 4000 mg twice a day while Sene, et al. (2019) and Pourghasem (2019) used the dosage of 4000 mg per day.

Similarly, the meta-analysis of the four studies revealed that there was no sufficient evidence to say that the probability of pregnancy significantly differed between the two groups (RR=1.10, 95%CI: 0.87-1.39, p=0.42). No significant heterogeneity was observed (I2=0%, Q=1.37, p=0.71).

Myo-inositol + Folic acid vs. Folic acid Among PCOS Patients Undergoing Fertility Treatment

The pregnancy rate comparing myo-inositol + folic acid and folic acid undergoing fertility treatment (Figure 3) was reported by three studies[15-17] having a total sample size of 587 patients. Sene, at al., (2019) did pre-treatment with 4 g myo-inositol + 400 mg folic acid daily for the study group and the control group with 400 mg folic acid alone. Prior to the onset of menstruation, both groups underwent ovarian stimulation with the use of estradiol valerate 4 mg once daily for 10 days followed by gonadotropins, with a starting dose of 150/IU on day 3 of the cycle, then once the largest follicle, as screened by ultrasonography, reached 13-14 mm diameter, GnRH antagonist at 0.25 mg was given daily. Ovulation was triggered with a GnRH agonist and oocytes were retrieved after 36 hours, followed by in vitro fertilization (IVF). In the study of Ozay, et al. (2016), the treatment group was given 4 g myo-inositol plus 400 mg folic acid

twice daily for 12 weeks until during the cycle of controlled ovarian hyperstimulation (COH). COH was done with recombinant FSH on day 3 of the cycle followed by intrauterine insemination (IUI) once the dominant follicle was formed. Myo-inositol was discontinued on day 10 post-IUI. On the other hand, the control group received recombinant FSH (rFSH) on day 3 of the cycle plus 400 mg folic acid daily. COH was initiated with 37.5–150 IU rFSH on day 3 of the cycle and follicular development and endometrial thickness were assessed on days 10–12 of the cycle via transvaginal ultrasonography. Once a >/= 18 mm follicle was identified, they proceeded with ovulation trigger using 250 mg/0.5 mL choriogonadotropin alpha, followed by a single IUI 36 hours later. If more than five follicles of >/= 18 mm in size developed and/or the endometrial thickness was 57 mm, the cycle was canceled. Patients of Pourghasem, et al. (2019) were given letrozole at a dose of 2.5 mg per day from day 3 of the cycle for five days. The follicular and endometrial evaluations were done on days 12–16 of the menstrual cycle via vaginal ultrasonography. In the presence of at least one mature follicle (≥17 mm), 10,000 units of HCG were injected. In the last cycle of pretreatment, 7.5 mg letrozole was prescribed daily from day 3 of the cycle for five days. The ovarian function was evaluated by the presence or absence of a mature follicle during 12–16 menstrual cycles. The clinical pregnancies were identified by the presence of a gestational sac on ultrasonography five weeks after HCG injection.

Studies consistently showed that pregnancy rate was higher when using myo-inositol (range: 19-40%) compared to folic acid alone (range: 12-36%).[15-17] However, none of the studies showed a significant difference in pregnancy rate between the two groups. Meta-analysis of the three studies revealed that there was no sufficient evidence to say that the probability of pregnancy significantly differed between the two groups (RR=1.15, 95%CI: 0.89-1.48, p=0.29). There was no significant heterogeneity observed (I2=0%, Q=0.70, p=0.71).

Myo-inositol Combined With Other Drugs vs. Folic acid

Only one study[17] compared the pregnancy rate between myo-inositol combined with other drugs vs. folic acid; thus, a meta-analysis could not be performed. Results showed that myo-inositol + melatonin showed a significantly higher pregnancy rate at 39.39% compared to the group without melatonin at 31.79%. The dose of myo-inositol used in this study was at 4000 mg/day with melatonin 3 mg twice daily.

Myo-inositol vs. Metformin

Pregnancy rate comparing myo-inositol and metformin (Figure 4) was reported by two studies[14,18] having a total sample size of 123 patients. Both studies consistently showed that pregnancy rate was higher when using metformin (range: 38-100%) compared with the myo-inositol group (range: 28-42.8%).[14,18] The meta-analysis of the two studies revealed that there was no sufficient evidence to say that the probability of pregnancy significantly differed between the two groups (RD=0.33, 95%CI: -0.79-0.14, p=0.17). There was a significant and

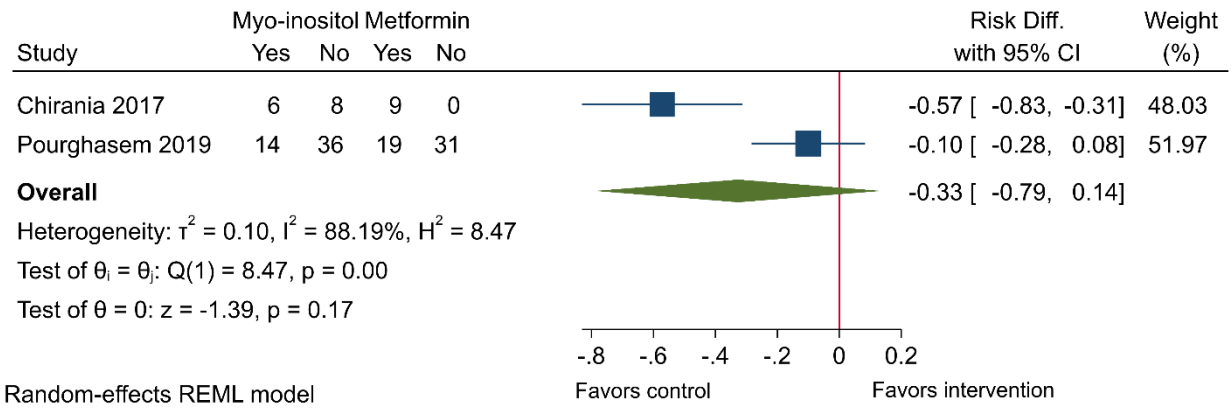

Figure 4. Forest plot: Pregnancy rate of myo-inositol vs. metformin among PCOS patients

substantial heterogeneity observed (I2=88.19%, Q=8.47, p<0.001).

Myo-inositol Combined With Metformin vs. Metformin Alone

The pregnancy rate comparing myo-inositol and metformin (Figure 5) was reported by two studies[2,14] having a total sample size of 137 patients. Agrawal, et al. (2019) showed higher pregnancy rate when using myo-inositol with metformin at 63.33%, with a dose of 600 mg myo-inositol + 500 mg metformin thrice daily for 6 months, compared to metformin alone, 500 mg/day thrice daily for 6 months at 33.33%.The study of Chirania, et al. (2017) on the other hand showed 100% pregnancy rate on both groups. Meta-analysis of the two studies revealed that there was no sufficient evidence to say that the probability of pregnancy significantly differed between the two groups (RD=0.14, 95%CI: -0.16 – 0.43, p=0.36) and there was no significant heterogeneity observed (Q=0, p=1.00).

Menstruation Regularity

Only Thalamati, et al. compared the proportion of patients with regular menstruation between myo-inositol + D-chiro-inositol and metformin. Results showed statistically significant improvement with a 20% increase in women with regular cycle in the myo-inositol + D-chiro-inositol group, over a period of 24 weeks, when compared to the metformin group with only 12% increase in women with regular cycle.

Menstruation Cycle Length

The mean cycle length at month 3 comparing myo-inositol and metformin (Figure 6) was reported by two studies[2,19] having a total sample size of 320 patients. Thalamati (2019) used the two forms of inositol, myo-inositol at 550 mg and D-chiro-inositol at 13.8 mg twice daily as the study group and metformin at 500 mg thrice daily as the control group. There was no significant heterogeneity observed (I2%=0.02, Q=0.11, p=0.75). The mean cycle length showed a significant difference between the two groups. Mean cycle length was significantly lower in the myo-inositol group compared to the metformin group (MD=-0.10, 95%CI: -0.14 – -0.07, p<0.001).

Menstruation Bleeding Days

Only Agrawal, et al. compared the proportion of mean bleeding duration between myo-inositol and metformin. There was significant improvement in menstrual bleeding per cycle in myo-inositol (mean 4.34 days) as compared to metformin (mean 4.57 days) after 3 months of treatment.

Adverse Events

Three studies[14,18,19] reported adverse events associated with the treatment and control groups. None of the patients given myo-inositol experienced an adverse event in all the studies. On the other hand, Pourghasem, et al. (2019) reported 42% adverse events associated with the metformin group, however, they did not specify what kind of adverse effect was noted during the period of study.

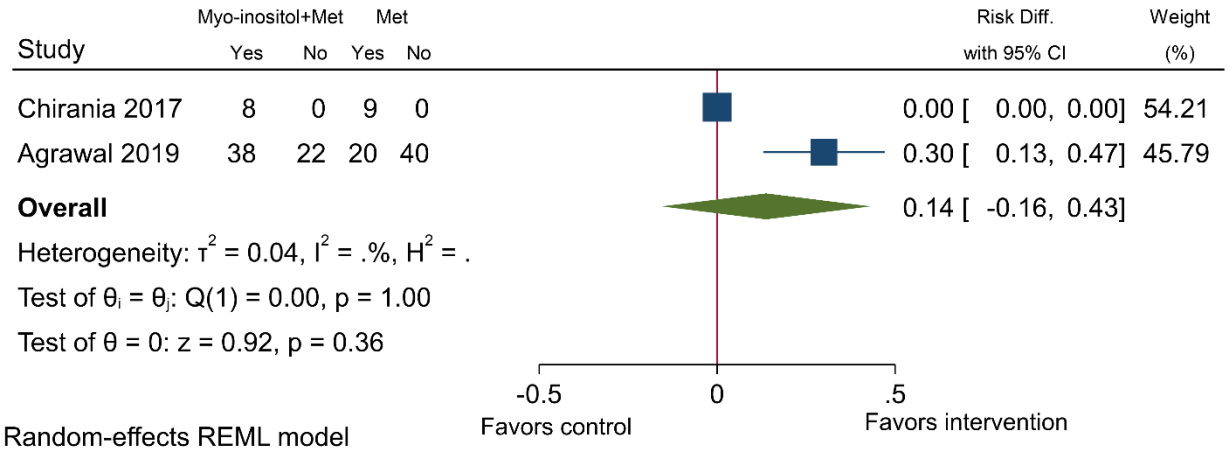

Figure 5. Forest plot: Pregnancy rate of myo-inositol + metformin vs. metformin among PCOS patients

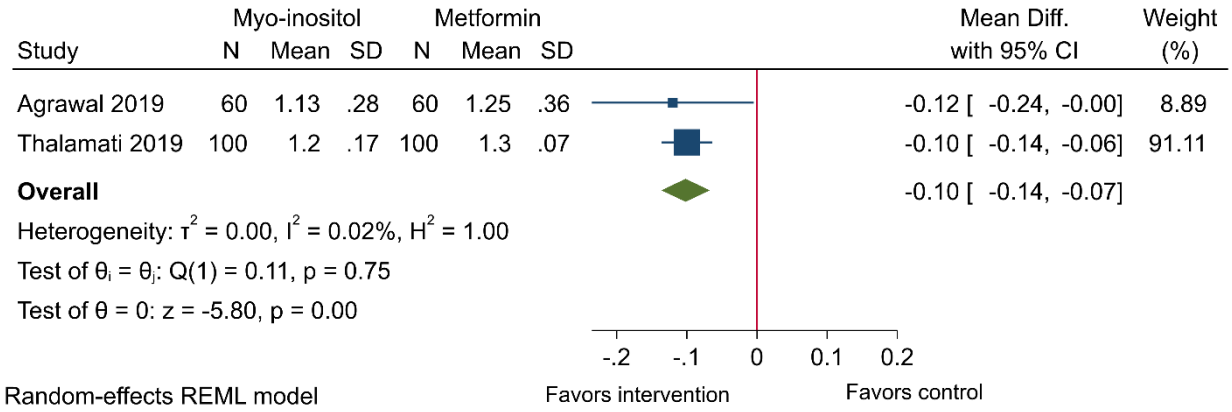

Figure 6. Forest plot: Cycle length (in months) of myo-inositol vs. metformin among PCOS patients

Table 3. Summary of results in the present meta-analytic PCOS study

	Pooled results (95% CI)	P value
Myoinositol + Folic acid vs. Folic acid		
All PCOS patients	RR = 1.10 (0.87-1.39)	0.42
PCOS patients undergoing fertility treatment	RR = 1.15 (0.89-1.48)	0.29
Myo-inositol combined with other drugs vs. folic acid		
All PCOS patients	-	-
PCOS patients undergoing fertility treatment	-	-
Myo-inositol vs. Metformin		
All PCOS patients	RD = -0.33 (-0.79–0.14)	0.17
Myo-inositol + metformin vs. Metformin		
All PCOS patients	RD = 0.14 (-0.16–0.43)	0.36
Effects on menstruation cycle		
Menstruation regularity	-	-
Cycle length (in months)	MD = -0.10 (-0.14 – -0.07)	**<0.001***

RR: Risk ratio; RD: Risk difference; MD: Mean difference

DISCUSSION

Pregnancy Rate

The present systematic review and meta-analysis included seven RCTs, on 1406 women with PCOS, according to the Rotterdam criteria for PCOS diagnosis. Myo-inositol supplementation was investigated in terms of its role in improving pregnancy rate, which is one of the critical issues in PCOS. However, six studies have supported that there was no sufficient evidence to show a significant difference between myo-inositol and placebo or metformin in improving pregnancy rate. Hence, we may say that either of the given interventions may help improve spontaneous pregnancies in patients with PCOS.[15-18]

Since insulin resistance and hyperandrogenism plays a crucial role in the anovulation mechanism of PCOS, myo-inositol increases the action of insulin improving ovulatory function and decreases serum androgen concentrations. Insulin sensitizers, such as inositol may improve ovarian response to gonadotropins.[16] The role of myo-inositol in the process of ovulation, as discussed by Pacchiarotti,

et al. (2015), is in the FSH signaling, where evidences have shown that anti-Mullerian hormone production induced by FSH in the granulosa cells is dependent to myo-inositol.[17] During ovarian stimulation, supplementation of myo-inositol reduces the number of FSH, and therefore, increases the chance of successful pregnancy. It also plays a role in cell membrane formation, lipid synthesis, and cell growth.[20] In addition, myo-inositol regulates a number of physiological processes including those related to gamete development, oocyte maturation, fertilization, and early embryonic development.[17] Pacchiarotti, et al. (2015) also showed significantly higher pregnancy rate with combined myo-inositol and melatonin than compared to melatonin alone due to the influence of both on LH and FSH signaling.[17] These gonadotropins bind to receptors in the ovary leading to effects on follicular growth, ovulation, and luteinization, which depends on the differences in FSH and LH receptor concentrations.[17] Data suggests that PCOS patients undergoing ovulation induction benefit from myo-inositol through its insulin-lowering effect and intracellular role in oocyte maturation. Myo-inositol enhances ovarian function and usage prior to ovulation induction increases treatment success, hence, it is an effective alternative insulin sensitizer agent in PCOS with infertility.[16]

Regular Menstruation

Irregular menses is one of the three strict Rotterdam criteria to diagnose PCOS. It is a chronic problem that is the usual complaint of patients with PCOS that may progress to development of several endocrinologic and cardiovascular diseases. One study has shown 20% improvement in menstrual cycle with significant difference in mean cycle length to those patients given myo-inositol + D-chiro-inositol compared to the metformin group.[2,19]

Agrawal, et al.(2019) showed improved menstrual cyclicity with metformin alone and a combination of metformin + myo-inositol, but the improvement was noted to be significantly higher in the combination group. Improved ovulation, as previously discussed, may be the reason for spontaneous menses and higher pregnancy rate in the group who received the combination.[2] The improvement in symptom profile, weight loss, and hormonal parameters in myo-inositol and the combination group were also significantly higher. This supports the role of myo-inositol in improving ovarian function and hormonal parameters in PCOS women. They also considered the synergistic action of both drugs to have more hormonal, clinical, and reproductive benefits when compared to one drug given alone.[2]

Therefore, myo-inositol was an effective adjunct in lowering insulin levels, improved hormonal disturbances, and regulated the menstrual cycles and ovulatory functions.[16]

Adverse Effects

Agrawal, et al. (2019) reported that myo-inositol may be considered as the first line option in PCOS with insulin resistance; with similar clinical and hormonal benefits as metformin but had no gastrointestinal side effects.[2] Chirania, et al. (2017), Pourghasem, et al. (2019), and Thalamati, et al. (2020) reported that none of the patients given myo-inositol experienced an adverse event in all studies. Pourghasem, et al. (2019) reported 42% adverse events associated with the metformin group, however, they did not specify what kind of adverse effect was noted during the period of study.

Discussion on the Results

In the present study, the authors conducted a systematic review and meta-analysis of available recent studies to see the efficacy of myo-inositol in improving pregnancy rate and regulation of menstrual cycle on PCOS patients. The results revealed no significant difference between myo-inositol, folic acid, melatonin, and metformin in women with PCOS in terms of their effects on facilitating spontaneous pregnancy. Our findings also suggested that myo-inositol improved the menstrual cycle without any adverse effects compared to metformin. Several factors, such as obesity, may have an impact on the effect of myo-inositol to reproductive functionality.[18]

It is also important to consider the biases of each study that was mentioned, as they may have influenced the reliability of our findings.[2,14-16,18,19] Certain biases, such as the lack of well-designed controlled trials, concealment, and blinding, may alter the effects of myo-inositol in improving pregnancy rate in PCOS patients.

CONCLUSION

This systematic review and meta-analysis showed that myo-inositol, as supported by current evidence, can be an alternative treatment for PCOS in terms of regulation of menses and may improve the success of spontaneous pregnancies. However, we still recommend randomized, double-blind controlled trials with larger sample sizes, low heterogeneity, and uniform inclusion criteria to compare and see the effects of myo-inositol on PCOS treatment and pregnancy rate. Future studies should consider the comparison between combination of myo-inositol + metformin vs metformin alone to establish its synergistic effect in improving metabolic profile, ovulation, and menstrual cycle of patients with PCOS.

Conflict of Interest

The authors declare that they have no conflict of interests.

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APPENDICES

Appendix A. PRISMA 2020 Checklist

Section and Topic	Item#	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 1
INTRODUCTION			
Rationale	3	Describe the rationale for review in the context of existing knowledge.	Page 3
Objectives	4	Provide an explicit statement of objective(s) or question(s) the review addresses.	Page 5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for review and how studies were grouped for the syntheses.	Page 6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 7
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 7
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 10
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 10
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (eg, for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 9
	10b	List and define all other variables for which data were sought (eg, participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 9
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 8
Effect measures	12	Specify for each outcome the effect measure(s) (eg, risk ratio, mean difference) used in the synthesis or presentation of results.	Page 9

Section and Topic	Item#	Checklist item	Location where item is reported
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (eg, tabulating the study intervention characteristics and comparing against the planned groups for each synthesis [item #5]).	Page 10
	13b	Describe any method required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 10
	13c	Describe any method used to tabulate or visually display results of individual studies and syntheses.	Page 10
	13d	Describe any method used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 10
	13e	Describe any method used to explore possible causes of heterogeneity among study results (eg, subgroup analysis, meta-regression).	Page 10
	13f	Describe any sensitivity analyses conducted to assess robustness of synthesized results.	Page 10
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 14
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 9
RESULTS			
Study selection	16a	Describe results of the search and selection process, from the number of records identified in the search to number of studies included in review, ideally using a flow diagram.	Page 10
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 10
Study characteristics	17	Cite each included study and present its characteristics.	Page 12
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 14
Results of individual studies	19	For all outcomes present for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (eg, confidence/credible interval), ideally using structured tables or plots.	Pages 15 - 21
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	Pages 15 - 21
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (eg, confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of effect.	Pages 15 - 21
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Pages 15 - 21
	20d	Present results of all sensitivity analyses conducted to assess the robustness of synthesized results.	Pages 15 - 21
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Pages 15 - 21
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Pages 15 - 21

Section and Topic	Item#	Checklist item	Location where item is reported
DISCUSSION			
Discussion	23a	Provide general interpretation of results in the context of other evidence.	Page 22
	23b	Discuss any limitations of evidence included in the review.	Page 22
	23c	Discuss any limitations of the review processes used.	Page 22
	23d	Discuss implications of the results for practice, policy, and future research.	Page 23
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for review, including registered name and registration number, or state that the review was not registered.	N/A
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	N/A
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for review, and the role of funders or sponsors in the review.	N/A
Competing interests	26	Declare any competing interests of review authors.	Page 22
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 23

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71

APPENDIX B. Cochrane Risk of Bias tool from Revman 5.4

Ozay, et al.

⊟ Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization done according to the protocol numbers of the patients
Allocation concealment (selection bias)	Low risk	Odd-even allocation
Blinding of participants and personnel (performance bias)	High risk	no blinding of participants done
Blinding of outcome assessment (detection bias)	Low risk	outcome not likely influenced by blinding
Incomplete outcome data (attrition bias)	Low risk	no missing outcome data
Selective reporting (reporting bias)	Low risk	published reports include all expected outcomes
Other bias	Low risk	study appears to be free of other sources bias

Pourghasem, et al.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	table of random numbers used for randomization
Allocation concealment (selection bias)	Unclear risk	Insufficient information available
Blinding of participants and personnel (performance bias)	High risk	no blinding of participant
Blinding of outcome assessment (detection bias)	Low risk	outcome not likely influenced by blinding
Incomplete outcome data (attrition bias)	Low risk	no missing outcome data
Selective reporting (reporting bias)	Low risk	Studies' prespecified outcomes that are of interest in the review have been reported in the prespecified way
Other bias	Low risk	Study appears to be free of other sources of bias

Sene, et al.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	randomly designated in two groups using permuted block randomization
Allocation concealment (selection bias)	Low risk	both study and control group received intervention in a sachet form
Blinding of participants and personnel (performance bias)	Low risk	outcome not likely influenced by blinding
Blinding of outcome assessment (detection bias)	Low risk	outcome not likely influenced by blinding
Incomplete outcome data (attrition bias)	Low risk	no missing outcome data
Selective reporting (reporting bias)	Unclear risk	Insufficient information available
Other bias	Unclear risk	Insufficient information available

Thalamati, et al.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Alternating designation of into two groups
Allocation concealment (selection bias)	High risk	No allocation concealment mentioned
Blinding of participants and personnel (performance bias)	Low risk	No blinding of participant done
Blinding of outcome assessment (detection bias)	Low risk	outcome not likely influenced by blinding
Incomplete outcome data (attrition bias)	Low risk	no missing outcome data
Selective reporting (reporting bias)	Low risk	published reports include all expected oucomes
Other bias	Low risk	study appears to be free of other sources bias

Agrawal, et al.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	used computer-generated randomization table
Allocation concealment (selection bias)	Unclear risk	no concealment mentioned
Blinding of participants and personnel (performance bias)	Unclear risk	no blinding mentioned
Blinding of outcome assessment (detection bias)	Low risk	outcome not likely influenced by blinding
Incomplete outcome data (attrition bias)	Low risk	no missing outcome data
Selective reporting (reporting bias)	Low risk	published reports include all expected outcomes
Other bias	Low risk	study appears to be free of other sources bias

Chirania, et al.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	computer-generated numbers used in a 3-arm prospective randomized comparative study
Allocation concealment (selection bias)	High risk	No concealment mentioned
Blinding of participants and personnel (performance bias)	High risk	No blinding done
Blinding of outcome assessment (detection bias)	Low risk	outcome not likely influenced by blinding
Incomplete outcome data (attrition bias)	Low risk	no missing outcome data
Selective reporting (reporting bias)	Low risk	published reports include all expected outcomes
Other bias	Low risk	study appears to be free of other sources bias

Pacchiarotti, et al.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	computer-based random assignment schedule for each patient and was double-blinded
Allocation concealment (selection bias)	Low risk	both study and control group received intervention in a sachet form
Blinding of participants and personnel (performance bias)	Low risk	outcome not likely influenced by blinding
Blinding of outcome assessment (detection bias)	Low risk	outcome not likely influenced by blinding
Incomplete outcome data (attrition bias)	Low risk	no missing outcome data
Selective reporting (reporting bias)	Low risk	published reports include all expected outcomes.
Other bias	Low risk	Study appears to be free of other sources of bias

APPENDIX C. Demographics of patients in included studies

Author, year	Mean age (years old)	Infertility duration (years)	Cycle Length	Mean BMI (kg/m^2)
Pourghasem, et al., 2019	15 – 38	2-5	None mentioned	25 – 29.9
Agrawal, et al., 2019	20 - 38	>1	2.04 months	<30, no specific range mentioned
Thalamati 2019	15 – 45	None mentioned	None mentioned	None mentioned, weight was the data provided
Sene, et al., 2019	20 - 35	6 - 7	None mentioned	25 - 26
Chirania, et al., 2017	21 - 24	None mentioned	9 – 14% of sample population has irregular menses	24 - 25
Ozay, et al., 2017	18 - 35	1 - 2	None mentioned	24 - 25
Pacchiarotti, et al., 2015	27 - 38	1.5 – 2.5	32 – 37 days	22 - 23

Study Population

Author, year	No ART	IVF	IUI
Sene, et al., 2019	None	50 out of 50	None
Ozay, et al., 2017	98 out of 196	None	196 out of 196
Pacchiarotti, et al., 2015	None	None	Control (FA): Mean 1.5 patients MI+FA+M: Mean 2.5 MI+FA: Mean 2.7

**ART* = Assisted Reproductive Technology, IVF = In Vitro Fertilization, IUI = Intra-uterine Insemination
***FA* = Folic Acid, MI = Myoinositol, M = Metformin