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The effects of myo-inositol *vs.* metformin on the ovarian function in the polycystic ovary syndrome: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: Recent studies have revealed that myo-inositol could be more influential in patients with polycystic ovary syndrome (PCOS). This study was aimed to determine and compare the effects of myo-inositol and metformin on hormonal and metabolic profiles and fertility outcomes.

MATERIALS AND METHODS: A comprehensive search was carried out among the English-language databases, including PubMed, Scopus, Cochrane Library, Google Scholar, and Web of Science, and the articles published from April 2010 to February 2019 were tracked down. The fixed and random-effects meta-analysis was used to estimate the pooled effect size. The meta-analysis was performed in Stata Version 14.0.

RESULTS: Nine studies with 331 patients treated with metformin and 307 patients treated with myo-inositol groups were included in the analysis. The research groups did not diverge significantly in terms of the basic characteristics, such as age and Body Mass Index (BMI). In the myo-inositol group, the levels of Luteinizing Hormone (LH) [12.55% (95% I: 11.41-13.68%)], S. testosterone [44.38% (95% CI: 38.09-50.67%)] and prolactin [7.97% (95% CI: 6.58- 9.37%)] were significantly higher than those recorded, i.e., LH [7.97% (95% CI: 6.58- 9.37%)], S. testosterone [8.48% (95% CI: 3.14-13.83%)] and prolactin [7.14% (95% CI: 1.50-14.79%)] for the metformin group ($p<0.001$).

CONCLUSIONS: Due to the dearth of related research and the high heterogeneity of the Randomized Clinical Trials (RCTs) included in other studies, the present systematic review could not establish any differences between metformin and myo-inositol concerning the hormonal profile and the ovarian function. However, the findings indicated that myo-inositol could improve fertility outcomes by modulating hyperandrogenism. Randomized trials are required to understand the mechanistic actions of myo-inositol in comparison with those of metformin regarding oocyte and embryo quality, fertilization, pregnancy, and live birth rates.

Key Words:
Metformin, Myo-inositol, Meta-analysis, Polycystic ovary syndrome (PCOS).

Introduction

Polycystic ovary syndrome (PCOS) is a common heterogeneous disorder with genetic, endocrine, metabolic, and reproductive manifestations that affects health care quality during a patient's lifespan[1]. PCOS patients exhibit many reproductive and metabolic abnormalities, which are manifested through insulin resistance, hyperandrogenism, and metabolic abnormalities[2]. Insulin resistance has proved to promote metabolic disturbances and it provides us with some information about the pathogenesis in PCOS patients[3]. High insulin concentration (hyperinsulinemia) can induce androgens production and reduce Sex hormone-binding globulin (SHBG) synthesis. These endocrine dysfunctions result in hyperandrogenism[4]. A high level of androgens disturbs communication between the oocyte and its companion granulosa cells and results in increased atretic and arrested follicles during the growing phase of PCOS ovaries[2]. Therefore, many pathological features of PCOS patients, including anovulatory infertility, menstrual irregularities, and hirsutism, arise from a high level of insulin and, subsequently, hyperandrogenism.

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Many scholars[5] have tried to ameliorate the reproductive dysfunction by triggering metabolic disorders in PCOS patients. Two insulin-sensitizers, i.e., metformin and myo-inositol, in different forms, combinations, and doses were used to improve reproductive dysfunctions in PCOS patients who had undergone either Assisted Reproduction Techniques (ART) or spontaneous ovulation[6-8]. Although metformin uptake is accompanied by improvement in the metabolic and reproductive systems, its positive effects are somehow limited by its gastrointestinal adverse effects[9]. Therefore, another alternative treatment, myo-inositol, which is a precursor in the phosphatidyl-inositol secondary messenger pathway, has been used to treat PCOS patients[10]. Myo-inositol produces inositol triphosphate, which regulates some hormones, such as Thyroid-Stimulating Hormone (TSH) and Follicle-Stimulating Hormone (FSH). Moreover, myo-inositol is responsible for glucose uptake, which, in turn, increases insulin sensitivity[11]. Thus, it can be concluded that myo-inositol reduces insulin and androgens concentrations and ameliorates glucose metabolism[12]. On the other hand, mechanistically, myo-inositol improves the oxidative status of the cell membrane and saves cytosolic glutathione levels[13]. Thus, it can be argued that some alterations in myo-inositol metabolism are involved in PCOS-related hormonal impairment. This would suggest that myo-inositol deficiency plays a crucial role in the metabolic dysfunctions in PCOS patients[14]. Several systematic reviews and meta-analyses[10-14] have shown that myo-inositol outperforms placebo in terms of ovulation and pregnancy rates. Hence, it can be suggested that myo-inositol is applicable to PCOS[10].

Clinically, the effectiveness of metformin and myo-inositol, along with the role of both drugs in treating infertility in women with PCOS, is important to be addressed in comparative review studies. Accordingly, in the present study, an attempt was aimed to conduct a methodically demanding systematic review and meta-analysis of RCTs to compare the effects of metformin and myo-inositol in PCOS in terms of menstrual regularity, hormonal and metabolic profile, and pregnancy outcomes.

Materials and Methods

This systematic review and meta-analysis followed the recommendations of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (http://www.prisma-statement.org/). The protocol was prospectively registered with PROSPERO (registration: IR.HUMS.REC.1397.190). The statement of informed consent was not applicable to this study.

Search Strategy

The search for the existing literature on the topic was done among the English-language databases, including PubMed, Scopus, Cochrane Library, Google Scholar, and Web of Science. The keywords searched were metformin, myo-inositol, PCOS, ovarian function, pregnancy rate, hormonal profile. The focus was on articles published between April 2010 and February 2019.

Inclusion and Exclusion Criteria

The following criteria were used to include studies: 1) comparison of the effects of myo-inositol and metformin on patients affected by polycystic ovarian disease; 2) a report of all the required statistical index of the outcomes; 3) at least reporting on one of the characteristics, such as free fasting blood sugar (FBS), homeostatic model assessment (HOMA) index, insulin, prolactin, LH, FSH, dehydroepiandrosterone (DHEA), androgens, testosterone, progesterone, estradiol, SHBG, and conception rate, which were of interest to the present study. The exclusion criteria were review studies, non-English articles, and animal studies.

Patient Characteristics

The overall patients across the studies were women in the reproductive age (15-45 years), diagnosed with PCOS according to Androgen Excess Society (AES), 2006 criteria, and Rotterdam 2003 criteria. In all studies included, the patients were randomly assigned to metformin or myo-inositol groups. These studies examined FSH, LH, F. insulin, FBS, LH/FSH, HOMA, insulin, S. testosterone, ovarian volume, progesterone, prolactin, DHEA, 17-hydroxyprogesterone (17-OH-P), SHBG, estradiol, and androgens.

Data Extraction and Quality Evaluation

Two reviewers (MA and FE) initially read the full text of the studies independently using a standardized data recording form to extract the basic characteristics and outcomes of interest to the studies included. Any disagreement between the two reviewers was then resolved through discussion, and the corresponding authors of the studies

were contacted if the information was incomplete. The following pieces of information were extracted from each study for both the metformin and myo-inositol groups: the first author, publication year, sample size, and the mean and standard deviation (SD) of variables. The variables included menstrual period time, age, BMI, FSH, LH, F. insulin, FBS, LH/FSH, HOMA, insulin, S. testosterone, ovarian volume, progesterone, prolactin, DHEA, 17-OH-P, SHBG, estradiol, and androgens.

The quality of each study was evaluated by two independent authors (FE, SHT). The Newcastle-Ottawa Scale (NOS) (0-9) was used to evaluate the studies included concerning three domains: selection, comparability, and outcomes. Higher scores for any given study represented a higher quality of that study. The scores given by the two independent authors for each of the studies examined ranged from 7 to 9, which reflected the high quality of the studies included (Table I).

Statistical Analysis

Following the extraction of the mean and standard deviation for each study, the effect size of each study was determined through SE (SD divided by the square root of sample size). Q-test ($p<0.01$ as heterogeneity) and the I^2 statistics (25%, 50%, and 75% representing low, moderate, and high levels of heterogeneity, respectively) were applied to examine the heterogeneity of the data. Moreover, a sensitivity analysis was performed to determine to what extent the findings of the present study were reliable. The result of a fixed-effect (Mantle-Haenszel) or random-effects (Der Simonian-Laird method) meta-analysis showed a pooled estimate with 95% CI for both groups, i.e., the metformin and myo-inositol group.

To test publication bias, the Begg's test was applied as a statistical test. All analyses were carried out in Stata (version 14.0, Stata Corp, College Station, TX, USA). The significance level was set at $p<0.05$.

Results

The number of relevant articles found in the preliminary search was 796. Following the removal of the duplicate studies, 258 studies were left. Through a pilot screening, 308 records were excluded since they did not meet the inclusion/exclusion criteria. The full texts of the remaining 230 articles were evaluated for eligibility. Finally, 9 articles which met the criteria were included in the meta-analysis. Both the search of the existing literature and the selection process are summarized in Figure 1.

Baseline Characteristics

All studies belonged to a four-year span, starting in 2012 and ending in 2016, and most of them were prospective or retrospective in type. The total number of participants in these studies was 353 patients treated with metformin and 331 patients treated with myo-inositol. The treatment period ranged from 12 weeks to 6 months. The mean age of the patients in the metformin group and the myo-inositol group was 23.96 and 26.6, respectively ($p=0.77$). The mean BMI was 25.71 for the metformin group and 25.14 for the myo-inositol group ($p=0.97$) (Table I).

LH

As the results showed, the outcome of the LH in the metformin group [10.15 (95% CI: 8.24-12.05)] was significantly more effective than that of the myo-inositol group [9.87 (95% CI: 7.62-12.12)] ($p<0.001$) (Table II).

LH/FSH

According to the results of a random-effect model test based on four studies, the LH/FSH ratio in the myo-inositol group [1.97 (95% CI: 1.75-2.18)] was significantly higher than that of the metformin group [1.76, (95% CI: 1.59-1.93)] ($p=0.03$) (Table II).

S. Testosterone

Substantial heterogeneity was detected among the studies. The results of the pooled estimate of testosterone based on a random-effect model showed that the level of testosterone in the metformin group [62.6 (95% CI: 43.31-82.00)] was significantly higher than that observed in the myo-inositol group [59.98 (95% CI: 53.09-66.96)] ($p<0.001$). In other words, myo-inositol was more effective than metformin (Table II).

Prolactin

Four studies, with 160 patients in the myo-inositol group and 180 patients in the metformin, were used to compare the level of prolactin in the two study groups. There was evidence of a high heterogeneity among the studies. The results of

Table I. Characteristics of the studies included in the present meta-analysis.

Author	Year of publication	Type of study	Group	Sample (n)	Period time	Age	BMI	FSH	LH	NOS	Group	F. insulin	FBS	LH /FSH	HOMA	S. testosterone	Ovarian volume	prolactin	DHEA	17-OH-P	Androgens
Chirania et al[18]	2015-2016	RCT	Me	28	NR	23.7	25.4	5.14	12.6	8	Me	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
			My	26	NR	23.9	24.6	5.63	13.4		My	13.55	90.69	2.17	NR	NR	NR	NR	NR	NR	NR
Nas and Tuu[19]	2013-2016	Retrospective	Me	81	6 m	35.0	NR	5.14	12.6	8	Me	18.7	86.51	2.43	NR	NR	NR	3.823	NR	NR	NR
			My	62	6 m	35	NR	NR	NR		My	NR	NR	NR	NR	NR	NR	0.2548	NR	NR	NR
Angik et al[14]	2012-2014	RCT	Me	50	6 m	25	23.2	NR	8.3	9	Me	14.58	92.34	1.61	3.39	52.24	12.24	NR	NR	NR	NR
			My	50	6 m	25	23.9	NR	10		My	17.03	98.16	1.94	4.32	58.28	12.35	NR	NR	NR	NR
Nehra et al[17]	NR	RCT	Me	30	24 w	23.26	NR	7.5	11.9	8	Me	14.04	82.76	1.64	2.99	46.2	NR	NR	NR	NR	NR
			My	30	24 w	23.8	NR	7.4	11.3		My	13.71	82	1.75	2.88	46.2	NR	NR	NR	NR	NR
Jamilian et al[44]	2016	RCT	Me	30	12 w	25.9	26.9	NR	NR	8	Me	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
			My	30	12 w	27.2	25.4	NR	NR		My	NR	NR	NR	2.1	80	NR	16.4	2.3	0.9	2.8
Fruzzetti et al[51]	2014-2015	RCT	Me	22	6 m	22.3	28.4	NR	NR	7	Me	NR	NR	NR	NR	NR	NR	16.3	2.5	1.1	3
			My	24	6 m	21.6	27.3	NR	NR		My	NR	NR	1.7	15.21	NR	NR	NR	NR	NR	NR
Awalekar et al[20]	2013-2015	NN-RCT	Me	35	3 m	NR	27.1	NR	NR	8	Me	NR	NR	2.1	23.8	NR	NR	NR	NR	NR	NR
			My	32	3 m	NR	24.4	NR	NR		My	20.3	77.5	NR	NR	90	NR	NR	2.71	1.8	NR
Raffone et al[16]	NR	RCT	Me	60	NR	29.7	24.9	7.5	9.1	7	Me	21.2	80.1	NR	NR	110	NR	NR	2.45	2	1.4
			My	60	NR	29.1	25	7.2	9.6		My	NR	NR	NR	NR	55.19	10.02	11.52	2.5	0.72	1.8
Tagliaferri et al[21]	2013-2015	RCT	Me	17	6 m	25.6	32.5	5.5	6.2	8	Me	NR	NR	NR	NR	41.14	10.52	NR	NR	0.75	2.58
			My	17	6 m	25.6	31.2	5.25	7		My	NR	NR	NR	NR	NR	NR	NR	NR	NR	2.368

RCT = Randomized Clinical Trial; NN-RCT = Non-Randomized Clinical Trial; M = Month; W = Week; NR = Not reported; Me= Metformin; My = Myo-inositol; NOS = Newcastle-Ottawa Scale.

Table II. A comparison of the characteristic parameters in metformin vs. myo-inositol groups.

Study characteristics	Metformin			Myo-inositol				Egger's test	
	N	I^2 (%)	ES (95% CI)	N	I^2 (%)	ES (95% CI)	*p*	Z score	*p*
Age	6	93.4	23.73 (23.39-24.07)	6	92.7	24.00 (23.77-24.24)	0.18	.19	0.09
BMI	7	93.5	26.79 (25.00-28.50)	7	88.8	25.85 (24.54-27.16)	0.135	2.52	0.03
LH	6	98.0	9.87 (7.62- 12.12)	7	97.8	10.15 (8.24-12.05)	< 0.001	-0.3	0.77
FBS	4	93.7	84.58 (79.45-89.71)	4	95.2	87.23 (81.72-92.73)	0.58	-0.12	0.91
FSH	6	98.0	5.93 (4.81-7.04)	6	98.2	5.98 (4.78-7.18)	0.60	-3.30	0.01
LH/FSH	4	83.3	1.76 (1.59-1.93)	4	82.6	1.97 (1.75-2.18)	0.03	1.44	0.15
HOMA	4	96.4	3.09 (2.48-3.70)	4	95.0	2.89 (2.14-3.64)	0.70	0.00	1.00
S. testosterone	5	93.9	62.60 (43.31-82.00)	5	98.0	59.98 (53.09-66.96)	< 0.001	1.04	0.30
Prolactin	4	99.5	9.86 (5.49-14.21)	4	99.7	9.14 (2.60-15.67)	< 0.001	0.48	0.63
DHEA	3	0.3	2.69 (2.57-2.79)	3	0.0	2.44 (2.33-2.55)	0.01	-1.48	0.14
17-OH-P	3	99.2	1.21 (0.393-2.02)	3	98.4	1.32 (0.51-1.91)	0.001	1.49	0.21
Androgen	3	95.8	2.30 (0.88- 2.41)	3	86.1	2.27 (1.21-2.64)	0.56	3.65	0.02
Estradiol	2	0.0	34.89 (32.84-32.93)	2	22.0	38.01 (35.66-40.35)	0.06	0.93	0.32
SHBG	2	7.1	30.00 (23.24-36.54)	2	5.9	26.46 (17.63-35.29)	0.97	0.63	0.24
Ovarian volume	2	62.0	12.04 (11.30-12.79)	2	44.3	12.19 (11.44-12.94)	0.79	-8.98	0.01
Insulin	2	96.0	20.30 (7.87-32.20)	2	96.1	22.88 (3.29-44.20)	0.19	7.48	0.02

FE = Fixed-effect; RE = Random-effects; n = The number of study; ES = Effect size, I^2 = I-square statistics. *p* = *p*-value.

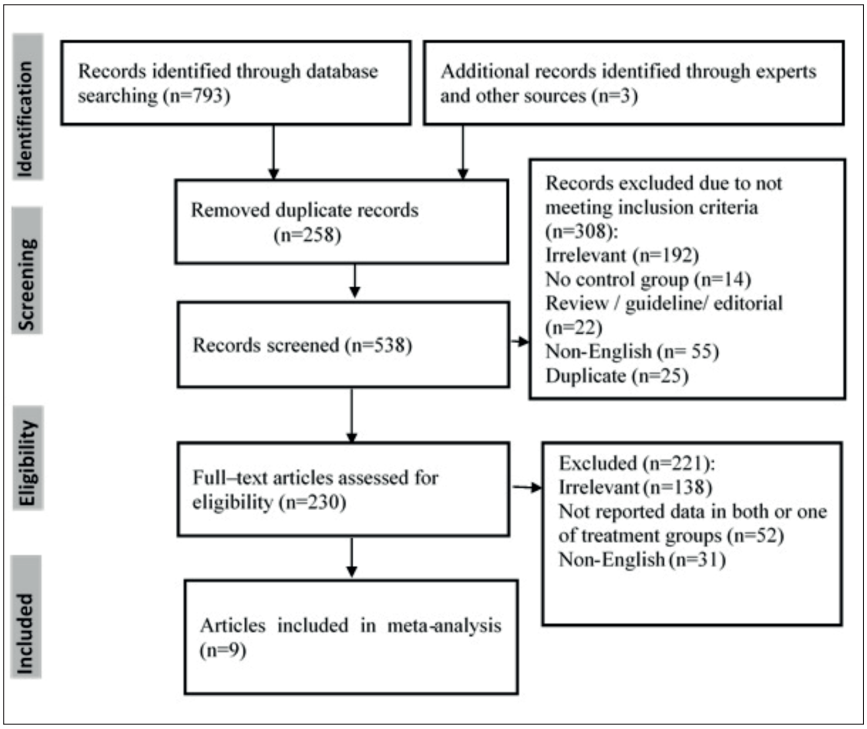

Figure 1. PRISMA flow diagram describing the study design process.

the pooled estimate showed that the level of prolactin in the myo-inositol group [8.48 (95% CI: 3.14-13.83)] was significantly higher than that of the metformin group [7.14 (95% CI: 1.50-14.79)] (p<0.001) (Table II).

DHEA

The results of a fixed-effect model for three studies (101 patients in the myo-inositol group and 99 in the metformin group) showed that DHEA in the metformin group [2.69 (2.57-2.79)] was significantly higher than that of the myo-inositol group [2.44 (2.33-2.55)] (p=0.001). Therefore, it could be stated that myo-inositol was more effective than metformin in modulating hyperandrogenism (Table II).

17-OH-P

According to the results of a random-effect meta-analysis, metformin [1.21 (0.393-2.02)] was more effective than myo-inositol [1.32 (0.51-1.91)] in reducing the 17-OH-P (p=0.001) (Table II).

Other Characteristics

Other indices, such as FBS, FSH, estradiol, ovarian volume, and insulin, were estimated to be lower in the metformin group compared to those of the myo-inositol group. However, there was no statistically significant difference between the effectiveness of the two treatments. Nor was there any statistically significant difference between the two treatments with regard to other indices (p>0.05) (Table II).

Discussion

The present systematic review and meta-analysis included nine studies, 7 RCTs, 1 non-RCT, and 1 retrospective study, on 838 women with PCOS, according to the strict criteria for PCOS diagnosis. Recently, one systematic review and meta-analysis has been published addressing the effects of metformin therapy in comparison to the myo-inositol therapy on hormonal profile in women with PCOS[15]. In the present research, the myo-inositol and metformin supplementations were investigated, and the results of the meta-analysis conducted were reported for the metabolic and reproductive profiles of PCOS patients. Based on the results, menstrual irregularity, the most common feature in PCOS, was examined in four studies, and no significant difference was observed in them with regard to the therapeutic effects of myo-inositol *vs.* metformin supplementations in treating patients[14,16,17].

Regarding the hormonal profile and insulin resistance, similarly, both supplements managed

to improve FBS, fasting insulin, HOMA index, estradiol, and SHBG. Also, the ovarian volume was not significantly different in PCOS patients treated with either myo-inositol or metformin. However, the LH level, LH/FSH ratio, and prolactin levels were improved only by the metformin treatment. A significant decrease in the DHEA and testosterone levels, as circulating androgens, was observed in the PCOS patients who received myo-inositol supplementation compared to those who received the metformin supplementation. In this review, only three studies reported the pregnancy rate. These studies[16,18-20] indicated that the pregnancy rate was higher in women with PCOS who had taken myo-inositol compared to those who had taken metformin. Other studies did not address the pregnancy rate. Due to the limited clinical findings and inadequate evidence regarding the comparative effects of myo-inositol and metformin on the pregnancy rate, no definite conclusion can be drawn as to which of these two drugs have more beneficial effects on pregnancy outcomes in PCOS patients.

Moreover, Anti-Mullerian Hormone (AMH) and Antral Follicle Count (AFC) were investigated in only one study, and the data provided was not sufficient to judge the effectiveness of metformin *vs.* myo-inositol[21]. Finally, no difference was observed among the pharmacologic approaches analyzed in the present study regarding the menstrual regularity and metabolic profiles. According to the studies included, it became evident that myo-inositol therapy provided additional benefits regarding hyperandrogenism and pregnancy outcomes. What limits the present findings are the type of studies included, dissimilarities in the inclusion criteria, heterogeneous definitions of PCOS, and patients' age, as well as the specifics of the interventions, such as the dose and duration of treatments. Therefore, heterogeneity was statistically high, and the effects were diverse because of the above-mentioned factors.

Metformin and myo-inositol are two insulin sensitizer drugs affecting hyperinsulinemia and hyperandrogenism in metabolic disorders[22,23]. From a clinical point of view, the relative effectiveness of metformin and myo-inositol is undeniable. Since metformin could have beneficial effects on hyperinsulinemia and physiological disorders, it improves the systemic metabolism in PCOS patients[24,25]. However, leaving aside the specific adverse effects that metformin has on the gastrointestinal tract, the efficacy of metformin on oocyte quality and subsequent pregnancy rate in PCOS remains controversial[26]. Several trials concluded that metformin helped to regulate the menstrual cycle and improved fertility[12,27]. However, other investigators showed that metformin could not have a beneficial effect on ovulation and conception rates[28].

Recently, myo-inositol has been used as the first line of medical therapy to prevent or cure certain diseases, especially the PCOS[12,29,30]. Myo-inositol is defined as a cyclic carbohydrate with six hydroxyl groups, which can convert into various derivatives within the body[31]. The epimerization of myo-inositol converts it into D-chiro-inositol. This conversion is mediated by epimerase, which is an insulin-dependent enzyme[32]. The myo-inositol/D-chiro-inositol ratio differs across various kinds of tissues and pathological conditions. For instance, myo-inositol/D-chiro-inositol ratio is 100/1 in the ovaries but diminishes in the PCOS condition due to the insulin resistance and hyperinsulinemia[33]. However, ovaries never become insulin resistant. Therefore, the overproduction of D-chiro-inositol and myo-inositol deficiency occur in PCOS patients with hyperinsulinemia[34]. Clinical evidence[35,36] also revealed that the supplementation of myo-inositol and D-chiro-inositol at a ratio of 40/1 could benefit the treatment of PCOS women. The administration of myo-inositol showed that this supplement could play a crucial role in insulin sensitivity by mediating inositol phosphoglycan, and this, in turn, modulates glucose uptake. Due to these mechanistic functionalities, myo-inositol is able to stimulate the consumption of insulin and support hormonal balance, ovarian function, oocyte quality, and menstrual cycle regularity[12,37].

Moreover, research[38] has shown that the administration of myo-inositol can result in calcium release through the interaction of myo-inositol and its receptors in oocytes. Calcium oscillation has a pivotal role in meiotic resumption and is responsible for the final oocyte development. Carlomagno et al[39] claim that myo-inositol, as a second messenger of calcium signaling, plays a critical role in oocyte development. Thus, it can be concluded that myo-inositol can improve the pregnancy rate by supporting oocyte development and modulating hormonal balance.

Murri et al[40] have shown a relationship between insulin resistance and the impairment of women's fertility. Insulin resistance occurs through the alteration in some mediators of insulin action, the mutation of insulin receptors, or inherited insulin resistance. The evidence available shows that

insulin resistance and compensatory hyperinsulinemia have a fundamental role in the pathogenesis of PCOS, as a metabolic disorder. Moreover, hyperinsulinemia is associated with hyperandrogenism, which causes endocrine-reproductive disorders in PCOS. Therefore, it must be noted that metabolic disorders and the subsequent endocrine-reproductive disorders affect women's fertility by disrupting the menstrual regularity and ovulation function.

In addition to many other metabolic disorders, hyperandrogenism also affects oocyte quality and fertility in PCOS patients[2]. Biochemical and/or chemical hyperandrogenism, the major characteristic in PCOS (60-80%), is responsible for poor oocyte quality and impaired developmental competence[41]. Also, a high level of plasma androgens has been reported to have unfavorable effects on assisted reproductive techniques. It may disturb the synchronization between the cytoplasmic and nuclear maturation of oocytes, causing poor oocyte quality. Moreover, hyperandrogenism causes oxidative stress in PCOS ovaries by disturbing antioxidant and pro-oxidant capacities[42]. Other studies[43,44] have shown that the elevation of DHAE could disturb oocyte metabolism through the induction of oxidative stress and lead to poor pregnancy outcomes. Therefore, a better understanding of the role of hyperinsulinemia and hyperandrogenism is essential in evaluating oocyte development, pregnancy rate, and the selection of appropriate treatment protocol.

A high level of D-chiro-inositol has been reported to affect oocyte and blastocyst quality, as well as ovarian functionality[45]. It has been previously indicated that a high concentration of D-chiro-inositol could inhibit aromatase, an enzyme that converts androgens into estrogens and is involved actively in the biosynthesis of estrogens. Therefore, the altered functioning of the aromatase enzyme accounts for the impairment of androgen conversion into estrogens[46]. This adverse condition may be improved via myo-inositol supplementation, which can enhance the reproductive activities in PCOS patients.

A Cochrane systematic review and meta-analysis of RCTs compared the metformin treatment with or without placebo in PCOS women. It revealed that metformin could enhance ovulation and clinical pregnancy rates, but it did not influence the live birth rate. The significant adverse effects of metformin on the gastrointestinal system were confirmed in Tang's study[22]. Another Cochrane systematic review and meta-analysis showed that compared to the folic acid administered to the control group, the myo-inositol administered to the treatment group increased the ovulation and clinical pregnancy rates in infertile women undergoing ovulation induction for assisted reproductive techniques[10]. However, the data obtained from a systematic review by Mendoza et al[47] who compared myo-inositol with placebo, indicated that myo-inositol supplementation had no beneficial effects on either the oocyte and embryo quality or the pregnancy rate in PCOS patients. It should be emphasized that the results reported by Mendoza et al[47] were highly heterogeneous. Hence, the reliability of their findings was debatable[47]. In their systematic review and meta-analysis, Pundir et al[12] revealed that myo-inositol, in comparison with placebo, appeared to improve the ovulation rate, and metabolic and hormonal profiles significantly in women with PCOS[12]. Furthermore, the findings of a comprehensive review by Kamenov et al[48] and Gateva et al[49] showed that the use of myo-inositol was an important therapeutic approach to improve the metabolic and reproductive disorders in PCOS patients. In the last two studies mentioned above, remarkable clinical outcomes were obtained through myo-inositol pretreatment, followed by ART protocols[48,49].

In the present study, the authors conducted a systematic review and meta-analysis of the available studies to compare myo-inositol with metformin regarding their effects on PCOS patients. The results revealed no significant difference between the two treatments, i.e., metformin and myo-inositol, in women with PCOS in terms of their effects on FBS, HOMA index, estradiol, SHBG, ovarian volume, and insulin. Our findings also suggested that although a significant decrease was observed in the levels of LH, LH/FSH ratio, and prolactin in the group treated with metformin, compared to those of the group treated with myo-inositol, androgens, such as testosterone and DHEA, were reduced more in the myo-inositol group than in the metformin group. It seems that various factors, such as obesity, can have a significant impact on myo-inositol and, subsequently, reproductive functionality. On this basis, a recent randomized clinical study showed that inositol was more effective than metformin in improving ovarian function in PCOS patients with normal BMI[50].

Moreover, there was no clear difference between the metabolic, endocrine, and reproductive parameters, such as the hormonal profile, menstrual cycle disorders, and pregnancy rate,

in PCOS women although certain biases in some of the studies mentioned above could have obstructed the emergence of any meaningful difference[17,19,51]. It is therefore necessary to consider the biases of the mentioned studies as they may have influenced the reliability of our findings. As such, it seems that certain biases, such as the lack of well-designed controlled trials, small sample size, and the use of various criteria for describing PCOS patients, can cause some changes in the effects of myo-inositol in comparison to those of metformin.

Conclusions

Our systematic review and meta-analysis revealed that myo-inositol would probably be an alternative treatment for PCOS patients undergoing conventional drug therapies. Moreover, and based on the current evidence, myo-inositol can be recommended for the treatment of PCOS women with hyperandrogenism, as well as enhancing pregnancy outcomes. Nonetheless, the current RCTs are limited because of limited sample sizes, high heterogeneity, and different inclusion criteria. Thus, it is suggested that the effects of myo-inositol, in comparison with those of metformin, on PCOS treatment and some variables, such as oocyte quality, embryonic development potential, pregnancy rate, and oxidative stress, should be investigated in more randomized, double-blind, and large sample size trials.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Teede H, Deeks A, Moran L. Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. BMC Med 2010; 8: 41.
2) Eini F, Novin MG, Joharchi K, Hosseini A, Nazarian H, Piryaei A, Bidadkosh A. Intracytoplasmic oxidative stress reverses epigenetic modifications in polycystic ovary syndrome. Reprod Fertil Dev 2017; 29: 2313-2323.
3) González F. Inflammation in polycystic ovary syndrome: underpinning of insulin resistance and ovarian dysfunction. Steroids 2012; 77: 300-305.
4) Baptiste CG, Battista M-C, Trottier A, Baillargeon J-P. Insulin and hyperandrogenism in women with polycystic ovary syndrome. J Steroid Biochem Mol Biol 2010; 122: 42-52.
5) Sun L, Hu W, Liu Q, Hao Q, Sun B, Zhang Q, Mao S, Qiao J, Yan X. Metabonomics reveals plasma metabolic changes and inflammatory marker in polycystic ovary syndrome patients. J Proteome Res 2012; 11: 2937-2946.
6) Tso LO, Costello MF, Albuquerque LET, Andriolo RB, Marjoribanks J, MacEdo CR. Metformin treatment before and during in vitro fertilization or intracytoplasmic sperm injection in women with polycystic ovary syndrome: Summary of a Cochrane review. Fertil Steril 2015; 104: 542-544.
7) Naderpoor N, Shorakae S, de Courten B, Misso ML, Moran LJ, Teede HJ. Metformin and lifestyle modification in polycystic ovary syndrome: systematic review and meta-analysis. Hum Reprod Update 2015; 21: 560-574.
8) Genazzani AD. Inositol as putative integrative treatment for PCOS. Reprod Biomed Online 2016; 33: 770-780.
9) Palomba S, Falbo A, Zullo F, Orio Jr F. Evidence-based and potential benefits of metformin in the polycystic ovary syndrome: a comprehensive review. Endocr Rev 2008; 30: 1-50.
10) Zheng X, Lin D, Zhang Y, Lin Y, Song J, Li S, Sun Y. Inositol supplement improves clinical pregnancy rate in infertile women undergoing ovulation induction for ICSI or IVF-ET. Med 2017; 96: e8842.
11) Lagana AS, Barbaro L, Pizzo A. Evaluation of ovarian function and metabolic factors in women affected by polycystic ovary syndrome after treatment with D-Chiro-Inositol. Arch Gynecol Obstet 2015; 291: 1181-1186.
12) Pundir J, Psaroudakis D, Savnur P, Bhide P, Sabatini L, Teede H, Coomarasamy A, Thangaratinam S. Inositol treatment of anovulation in women with polycystic ovary syndrome: a meta-analysis of randomised trials. BJOG 2018; 125: 299-308.
13) Donà G, Sabbadin C, Fiore C, Bragadin M, Giorgino FL, Ragazzi E, Clari G, Bordin L, Armanini D. Inositol administration reduces oxidative stress in erythrocytes of patients with polycystic ovary syndrome. Eur J Endocrinol 2012; 166: 703-710.
14) Angik R, Jajoo SS, Hariharan C, Chimote A. A comparative study of metabolic and hormonal effects of myoinositol vs. metformin in women with polycystic ovary syndrome: A randomised controlled trial. Int J Reprod Contracept Obstet Gynecol 2017; 4: 189-194.
15) Facchinetti F, Orrù B, Grandi G, Unfer V. Short-term effects of metformin and myo-inositol in women with polycystic ovarian syndrome (PCOS): a meta-analysis of randomized clinical trials. Gynecol Endocrinol 2019; 35: 198-206.
16) Raffone E, Rizzo P, Benedetto V. Insulin sensitiser agents alone and in co-treatment with r-FSH for ovulation induction in PCOS women. Gynecol Endocrinol 2010; 26: 275-280.

17) Nehra J, Kaushal J, Singhal SR, Gehlaut V. A comparative study of myo inositol versus metformin on biochemical profile in polycystic ovarian syndrome in women. Int J Pharm Sci Res 2017; 8: 1664-1670.

18) Chirania K, Misra S, Behera S. A randomised clinical trial comparing myoinositol and metformin in PCOS. Int J Reprod Contracept Obstet Gynecol 2017; 6: 1814-1820.

19) Nas K, Tuu L. A comparative study between myo-inositol and metformin in the treatment of insulin-resistant women. Eur Rev Med Pharmacol Sci 2017; 21: 77-82.

20) Awalekar J, Awalekar C, Jadhav V, Chivate C, Patwardhan M. Effect of metformin & myoinositol & life style modification in patients of polycystic ovarian disease (PCOD). Int J Biomed Res 2015; 6: 698-704.

21) Tagliaferri V, Romualdi D, Immediata V, De Cicco S, Di Florio C, Lanzone A, Guido M. Metformin vs myoinositol: which is better in obese polycystic ovary syndrome patients? A randomized controlled crossover study. Clin Endocrinol 2017; 86: 725-730.

22) Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. Cochrane Database Syst Rev 2012: Cd003053.

23) Dunaif A. Drug insight: insulin-sensitizing drugs in the treatment of polycystic ovary syndrome—a reappraisal. Nat Rev Endocrinol 2008; 4: 272.

24) Diamanti-Kandarakis E, Christakou CD, Kandaraki E, Economou FN. Metformin: an old medication of new fashion: evolving new molecular mechanisms and clinical implications in polycystic ovary syndrome. Eur J Endocrinol 2010; 162: 193-212.

25) Kolodziejczyk B, Duleba AJ, Spaczynski RZ, Pawelczyk L. Metformin therapy decreases hyperandrogenism and hyperinsulinemia in women with polycystic ovary syndrome. Fertil Steril 2000; 73: 1149-1154.

26) Legro RS, Barnhart HX, Schlaff WD, Carr BR, Diamond MP, Carson SA, Steinkampf MP, Coutifaris C, McGovern PG, Cataldo NA. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. N Engl J Med 2007; 356: 551-566.

27) Morin-Papunen L, Rantala AS, Unkila-Kallio L, Tiitinen A, Hippeläinen M, Perheentupa A, Tinkanen H, Bloigu R, Puukka K, Ruokonen A. Metformin improves pregnancy and live-birth rates in women with polycystic ovary syndrome (PCOS): a multicenter, double-blind, placebo-controlled randomized trial. J Clin Endocrinol 2012; 97: 1492-1500.

28) Johnson N, Stewart A, Falkiner J, Farquhar C, Milsom S, Singh V-P, Okonkwo Q, Buckingham K, REACT-NZ am-cftg. PCOSMIC: a multi-centre randomized trial in women with PolyCystic Ovary Syndrome evaluating Metformin for Infertility with Clomiphene. Hum Reprod 2010; 25: 1675-1683.

29) Popescu I, Ionescu C, Dimitriu M, Banacu M, Tarcomnicu I, Calin D, Socea B, Furau C, Furau G, Bacalbavea N. Myo-inositol--a possible first-line treatment for PSOS? Arch Balk Med Union 2016; 51: 221-223.

30) Showell MG, Mackenzie-Proctor R, Jordan V, Hodgson R, Farquhar C. Inositol for subfertile women with polycystic ovary syndrome. Cochrane Database Syst Rev 2018; 12: Cd012378.

31) Gurale BP, Sardessai RS, Shashidhar MS. myo-Inositol 1, 3-acetals as early intermediates during the synthesis of cyclitol derivatives. Carbohydr Res 2014; 399: 8-14.

32) Sun TH, Heimark DB, Nguygen T, Nadler JL, Larner J. Both myo-inositol to chiro-inositol epimerase activities and chiro-inositol to myo-inositol ratios are decreased in tissues of GK type 2 diabetic rats compared to Wistar controls. Biochem Biophys Res Commun 2002; 293: 1092-1098.

33) Unfer V, Carlomagno G, Papaleo E, Vailati S, Candiani M, Baillargeon J-P. Hyperinsulinemia alters myoinositol to d-chiroinositol ratio in the follicular fluid of patients with PCOS. Reprod Sci 2014; 21: 854-858.

34) Unfer V, Facchinetti F, Orrù B, Giordani B, Nestler J. Myo-inositol effects in women with PCOS: a meta-analysis of randomized controlled trials. Endocr Connect 2017; 6: 647-658.

35) Nordio M, Proietti E. The combined therapy with myo-inositol and D-chiro-inositol reduces the risk of metabolic disease in PCOS overweight patients compared to myo-inositol supplementation alone. Eur Rev Med Pharmacol Sci 2012; 16: 575-581.

36) Benelli E, Del Ghianda S, Di Cosmo C, Tonacchera M. A Combined Therapy with Myo-Inositol and D-Chiro-Inositol Improves Endocrine Parameters and Insulin Resistance in PCOS Young Overweight Women. Int J Endocrinol 2016; 2016: 3204083-3204083.

37) Papaleo E, Unfer V, Baillargeon J-P, Fusi F, Occhi F, De Santis L. Myo-inositol may improve oocyte quality in intracytoplasmic sperm injection cycles. A prospective, controlled, randomized trial. Fertil Steril 2009; 91: 1750-1754.

38) Colazingari S, Treglia M, Najjar R, Bevilacqua A. The combined therapy myo-inositol plus D-chiro-inositol, rather than D-chiro-inositol, is able to improve IVF outcomes: results from a randomized controlled trial. Arch Gynecol Obstet 2013; 288: 1405-1411.

39) Carlomagno G, Nordio M, Chiu T, Unfer V. Contribution of myo-inositol and melatonin to human reproduction. Eur J Obstet Gynecol Reprod Biol 2011; 159: 267-272.

40) Murri M, Luque-Ramírez M, Insenser M, Ojeda-Ojeda M, Escobar-Morreale HF. Circulating markers of oxidative stress and polycystic ovary

syndrome (PCOS): a systematic review and meta-analysis. Hum Reprod Update 2013; 19: 268-288.

41) Huang Y, Yu Y, Gao J, Li R, Zhang C, Zhao H, Zhao Y, Qiao J. Impaired oocyte quality induced by dehydroepiandrosterone is partially rescued by metformin treatment. PLoS One 2015; 10: e0122370.

42) Suresh S, Vijayakumar T. Correlations of Insulin Resistance and Serum Testosterone Levels with LH:FSH Ratio and Oxidative Stress in Women with Functional Ovarian Hyperandrogenism. Indian J Clin Biochem 2015; 30: 345-350.

43) Zhu JQ, Zhu L, Liang XW, Xing FQ, Schatten H, Sun QY. Demethylation of LHR in dehydroepiandrosterone-induced mouse model of polycystic ovary syndrome. Mol Hum Reprod 2010; 16: 260-266.

44) Jamilian H, Jamilian M, Foroozanfard F, Afshar Ebrahimi F, Bahmani F, Asemi Z. Comparison of myo-inositol and metformin on mental health parameters and biomarkers of oxidative stress in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. J Psychosom Obstet Gynaecol 2018; 39: 307-314.

45) Ravanos K, Monastra G, Pavlidou T, Goudakou M, Prapas N. Can high levels of D-chiro-inositol in follicular fluid exert detrimental effects on blastocyst quality. Eur Rev Med Pharmacol Sci 2017; 21: 5491-5498.

46) Sacchi S, Marinaro F, Tondelli D, Lui J, Xella S, Marsella T, Tagliasacchi D, Argento C, Tirelli A, Giulini S. Modulation of gonadotrophin induced steroidogenic enzymes in granulosa cells by d-chiroinositol. Reprod Biol Endocrinol 2016; 14: 52.

47) Mendoza N, Pérez L, Simoncini T, Genazzani A. Inositol supplementation in women with polycystic ovary syndrome undergoing intracytoplasmic sperm injection: a systematic review and meta-analysis of randomized controlled trials. Reprod Biomed Online 2017; 35: 529-535.

48) Kamenov Z, Kolarov G, Gateva A, Carlomagno G, Genazzani AD. Ovulation induction with myo-inositol alone and in combination with clomiphene citrate in polycystic ovarian syndrome patients with insulin resistance. Gynecol Endocrinol 2015; 31: 131-135.

49) Gateva A, Unfer V, Kamenov Z. The use of inositol (s) isomers in the management of polycystic ovary syndrome: a comprehensive review. Gynecol Endocrinol 2018; 34: 545-550.

50) Pourghasem S, Bazarganipour F, Taghavi SA, Kutenaee MA. The effectiveness of inositol and metformin on infertile polycystic ovary syndrome women with resistant to letrozole. Arch Gynecol Obstet 2019; 299: 1193-1199.

51) Fruzzetti F, Perini D, Russo M, Bucci F, Gadducci A. Comparison of two insulin sensitizers, metformin and myo-inositol, in women with polycystic ovary syndrome (PCOS). Gynecol Endocrinol 2017; 33: 39-42.