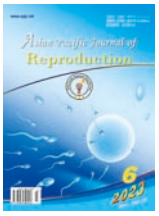

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Myo-inositol *versus* metformin effects on clinical features, endocrine and metabolic profiles in infertile women with polycystic ovary syndrome: A randomized controlled trial

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ABSTRACT

Objective: To compare the effectiveness of inositol and metformin on the clinical characteristics, and endocrine and metabolic profiles of infertile polycystic ovarian syndrome (PCOS) women from Vietnam.

Methods: From June 2018 to August 2022, a randomized trial was undertaken at the Hue Center for Endocrinology and Reproduction on infertile women aged 18 to 40 years with polycystic ovarian syndrome. The clinical, endocrine, and metabolic features of these individuals were assessed before and after 3 months of treatment with 2 g of inositol or 1700 mg of metformin per day. Natural pregnancy rates, adverse effects, and tolerance of inositol were recorded.

Results: The study included 171 infertile PCOS women who were eligible to participate and took part in the baseline assessment, of whom 132 women participated in data analysis after 3 months. After metformin treatment, 42.1% of women with oligomenorrhea experienced regular menstruation. Metformin significantly lowered body mass index (BMI), waist circumference and testosterone levels, but had no effect on other clinical characteristics, endocrine profiles, or metabolic profiles. 29.2% Of women reported experiencing side effects. 21% Of them attained pregnancy, which resulted in 17.1% of live births. In the inositol group, the rate of regular cycle increased by 18.2% and the total testosterone concentration significantly decreased. In overweight/obese women with PCOS, inositol significantly decreased weight, BMI, waist and hip circumferences (P<0.05). 100% Of women tolerated inositol and continued treatment. 18.9% Of them became pregnant, leading to 17% of live births.

Conclusions: Metformin and inositol can improve weight and waist circumference in overweight/obese infertile women with PCOS. Metformin is associated with a higher rate of regular menstruation, whereas inositol is associated with a lower rate of adverse effects. The spontaneous conception, clinical pregnancy, and live birth rates between two groups are comparable.

KEYWORDS: Polycystic ovarian syndrome; Inositol; Metformin; Endocrine; Metabolic; Menstrual cycle; Pregnancy

1. Introduction

Polycystic ovarian syndrome (PCOS) is the most prevalent endocrine condition among reproductive-aged women. Depending on the diagnostic criteria and research group, the prevalence of PCOS can range from 4% to 21%[1]. Women with PCOS are more likely to experience infertility, metabolic, physical, and psychological issues.

Significance

Metformin has been shown to be safe and effective in ameliorating the hormonal, metabolic and reproductive issues in women with polycystic ovarian syndrome (PCOS). It remains unclear whether inositol is as efficacious as metformin for PCOS women. In obese/overweight infertile women with PCOS, metformin and inositol may enhance menstrual regularity, weight, and waist circumference. Inositol is associated with a decreased rate of adverse events. This study demonstrated that inositol can be considered as an alternative to metformin for infertile PCOS women.

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Due to the association between the etiology of insulin resistance and PCOS, insulin sensitizers, such as metformin and inositols, have been utilized to alleviate clinical symptoms and metabolic indicators in women with PCOS[2,3]. Metformin is an insulin sensitizer, which works by improving the sensitivity of peripheral tissues to insulin. Consequently, it reduces circulating insulin levels, making it a therapeutic option for reducing insulin resistance in women with PCOS[4]. Several prospective randomized studies and meta-analyses have confirmed the beneficial effects of metformin on metabolic disorders, hyperinsulinemia, hyperandrogenism, blood pressure and clinical pregnancy rates[5,6]. Metformin improves menstrual cycles in controlled studies, but these benefits vary due to differences in treatment duration (ranging from 3 months to a year), and the fact that previous studies were limited to obese and/or weight-gained women rather than a full range of women diagnosed according to the Rotterdam criteria[6,7].

Myo-inositol is involved in cellular glucose absorption. It induces GLUT4 translocation to the cell membrane, inhibits adenylate cyclase, and reduces the release of free fatty acids from adipose tissue. Inositol is beneficial for women with PCOS, according to available evidence[8,9]. In several meta-analyses, inositol improved ovulation, menstrual cycle regulation, and clinical pregnancy rates. Serum androgen, total testosterone, free testosterone, and dehydroepiandrosterone decreased significantly. However, existing meta-analyses feature limited sample sizes, diverse participants, and short follow-up durations[8,9].

Although inositols were shown to be a promising new treatment in women with PCOS, there are few randomized controlled trials with inositol, especially in comparison with metformin. Hence, this study aimed to compare the effects of inositol *versus* metformin on the clinical characteristics, and endocrine and metabolic profiles of infertile PCOS women from Vietnam.

2. Subjects and methods

2.1. Study design

This was a two-arm parallel randomized clinical trial conducted at Hue Center for Endocrinology and Reproduction at Hue University of Medicine and Pharmacy (HueCREI) from June 2018 to August 2022. The study comprised 171 infertile PCOS women who met the inclusion and exclusion criteria. Participants were then assigned into two groups based on computer generated randomization sheets after taking written informed consent.

2.2. Inclusion criteria

The study included all women aged 18 to 40 years with PCOS who visited HueCrei during the afore-specified period. PCOS is diagnosed when at least two of the following three criteria are present according to the Rotterdam criteria: (1) amenorrhea and oligomenorrhea; (2) the clinical or subclinical presence of hyperandrogenism; (3) ultrasound evidence of polycystic ovaries (with 12 small follicles 2-9 mm in at least one ovary and/or ovarian volume ≥10 cm^3). PCOS is diagnosed after ruling out all other hyperandrogenic disorders[10].

2.3. Exclusion criteria

Exclusion criteria included congenital adrenal hyperplasia and androgen production-producing tumors, Cushing's disease, women with a history of ovarian surgery, ovarian tumours, ovarian endometriosis, or ovarian failure, obstruction of both fallopian tubes, and severe oligoasthenoteratozoospermia.

2.4. Study size and power calculation

The sample size was calculated following the formula:

$$n \geq \frac{\left[Z_{1-\alpha/2}\sqrt{2p(1-p)} + Z_{1-\beta}\sqrt{p_1(1-p_1)+p_2(1-p_2)}\right]^2}{(p_2-p_1)^2}$$

Previously, Thakur *et al* showed that 42.9% of PCOS women had regular cycles after using inositol and 66.7% of PCOS women had regular cycles after using metformin[10]. Based on this published data, power analysis were performed assuming a significance level of 0.05 and power of 80%. With the allocation ration 2:1, it was found that 50 women in the inositol group and 101 women in the metformin group were needed to detect this difference. Considering an expected loss to follow-up rate of 10%, the inositol group necessitated a minimum sample size of 55 women, whereas the metformin group at least 112 women. This study enrolled 171 infertile PCOS women, including 113 women in metformin-arm and 58 women in inositol-arm.

2.5. Treatment protocol

All participants were assessed according to the following study procedure: Evaluation of clinical characteristics, including height, weight, body mass index (BMI), waist circumference, and evaluation of hirsutism, acne, baldness, acanthosis nigricans symptoms.

On days 2-4 of the menstrual cycle, the women underwent an ultrasound utilizing an Aloka SSD3500SX system with a 7 MHz frequency vaginal probe. Ovary volumes were measured in all three planes, and the antral follicle number in each ovary was counted. The volume of the ovary was computed using the formula: length × width × height × 0.523[11].

On the same day, serum blood tests quantified anti-Mullerian hormone (AMH), follicle stimulation hormone (FSH), estradiol (E_2), luteinizing hormone (LH), testosterone, prolactin, blood lipid

balance including triglycerid (TG), total cholesterol, high-density lipoprotein cholesterol (HDL-cholesterol), low-density cholesterol (LDL-cholesterol), fasting blood glucose levels, blood glucose levels 2 hours after the glucose tolerance test, and hemoglobin A1C (HbA1C). By radioimmunoassay, the levels of FSH, LH, E_2, progesterone, prolactin, and testosterone were determined. Electrochemiluminescence immunoassay (ECLIA) was used to quantify serum AMH on an Elecsys Roche System equipment. Blood lipids were measured using a Roche/Hitachi Cobas C system.

In this open-label study, subjects were randomly assigned to two groups: the metformin intervention group and the inositol intervention group with a ratio of 2:1 based on computer-generated randomization sheets. The metformin group was given metformin 850 mg×2 tablets per day (glucophage tablets containing 850 mg of metformin hydrochloride, Merck Sante S.A.S, France) within three months. The inositol group was given inositol 500 mg×4 tablets per day (inositol tablets containing 500 mg of the active component Inositol-Baxco Pharmaceutical, Inc. Irwindale, CA 91010, USA) within three months. Intervention results were monitored after three months, including adverse effects (if any); menstrual cycle characteristics; re-examination of clinical features; re-testing of blood tests and spontaneous pregnancy.

2.6. Assessment of variables

2.6.1. Primary outcomes

Primary outcomes included changes in regular menstrual rate; clinical hyperandrogenism; and metabolic endocrinology after treatment.

Amenorrhea or oligomenorrhea was characterized as a menstrual cycle lasting longer than 35 days or having less than eight cycles per year[12]. Clinical hyperandrogenism was defined as the presence of acne, male pattern baldness, acanthosis nigrican, or hirsutism [enhanced modified Ferriman and Gallwey (mFG) scores 3 for Asian women][13]. BMI was computed using the square formula of weight/height. Women were classified as obese if their BMI was equal or greater than 25 kg/m^2 and as overweight if their BMI was greater than or equal to 23 kg/m^2[14]. Hyperandrogenemia was described when the total concentration of testosterone was greater than 0.70 ng/mL[15,16]. Diagnosis of metabolic syndrome in Asian populations is based on the 2005 NCEP ATP Ⅲ clinical practice guidelines[17]. Diagnosis of insulin resistance syndrome is based on the ACE IRS 2003 criteria[18]. Diagnosis of dyslipidemia is based on the Chinese guidelines for the management of dyslipidemia in adults[19].

2.6.2. Secondary outcomes

Secondary outcomes included spontaneous pregnancy (achieved until 3 months after treatment) rate; clinical pregnancy and live birth rates; incidence of adverse effects.

Subgroup-analysis included overweight/obese group and non overweight/obese group.

2.7. Statistical analysis

The statistical program SPSS 20.0 was used for data entry and processing (SPSS Inc, Chicago Ⅲ). Categorical variables are expressed as the number of cases and percentages, while continuously distributed variables are expressed as the mean and standard deviation (mean±SD). Before and after therapy, differences in metabolic endocrine parameters were assessed using the paired *t*-test if the data were normally distributed and the Wilcoxon test if the data were not normally distributed. Using Mc Nemar's test, the difference in rates before and after treatment was determined. Changes (before and after treatment) between two treated groups were compared using the Mann Whitney *U* test. $P<0.05$ is considered statistically significant.

2.8. Ethics statement

This study was approved by the Ethics Committee in Biomedical Research, University of Medicine and Pharmacy, Hue University (approval number: H2018/432). Before enrolling in the trial, the participants were provided with a thorough explanation and written confirmation about the research.

3. Results

3.1. Demographic characteristics of study population

Our study included 171 infertile PCOS women who were eligible to participate and took part in the baseline assessment, of whom 132 women participated in data analysis after 3 months (after excluding women who were lost to follow-up or achieved pregnancy during treatment) (Figure 1). 89.5% Of the women had irregular menstruation. In general, women with PCOS were thin with a mean BMI of (21.10±2.43) kg/m^2; they exhibited few symptoms of hyperandrogenism and hirsutism, as measured by a median mFG score of (0) and a low percentage of acne, alopecia and acanthosis nigricans (Table 1). Regarding reproductive endocrine characteristics, they had relatively high AMH levels and low testosterone levels, with median AMH and testosterone concentrations of (6.82) ng/mL and (0.268) ng/mL, respectively (Table 1). The metabolic parameters had mean values within the normal range. However, 12.3% of the women had metabolic syndrome and 18.1% had insulin resistance (Table 2). The median volume of the right and left ovaries were only (8.67) mL and (7.73) mL, respectively (Table 2).

Except for menstrual irregularities, systolic blood pressure and HbA1c, the majority of clinical, laboratory, and ultrasound parameter differences between the metformin and inositol-treated groups were not statistically significant (Table 1 and 2).

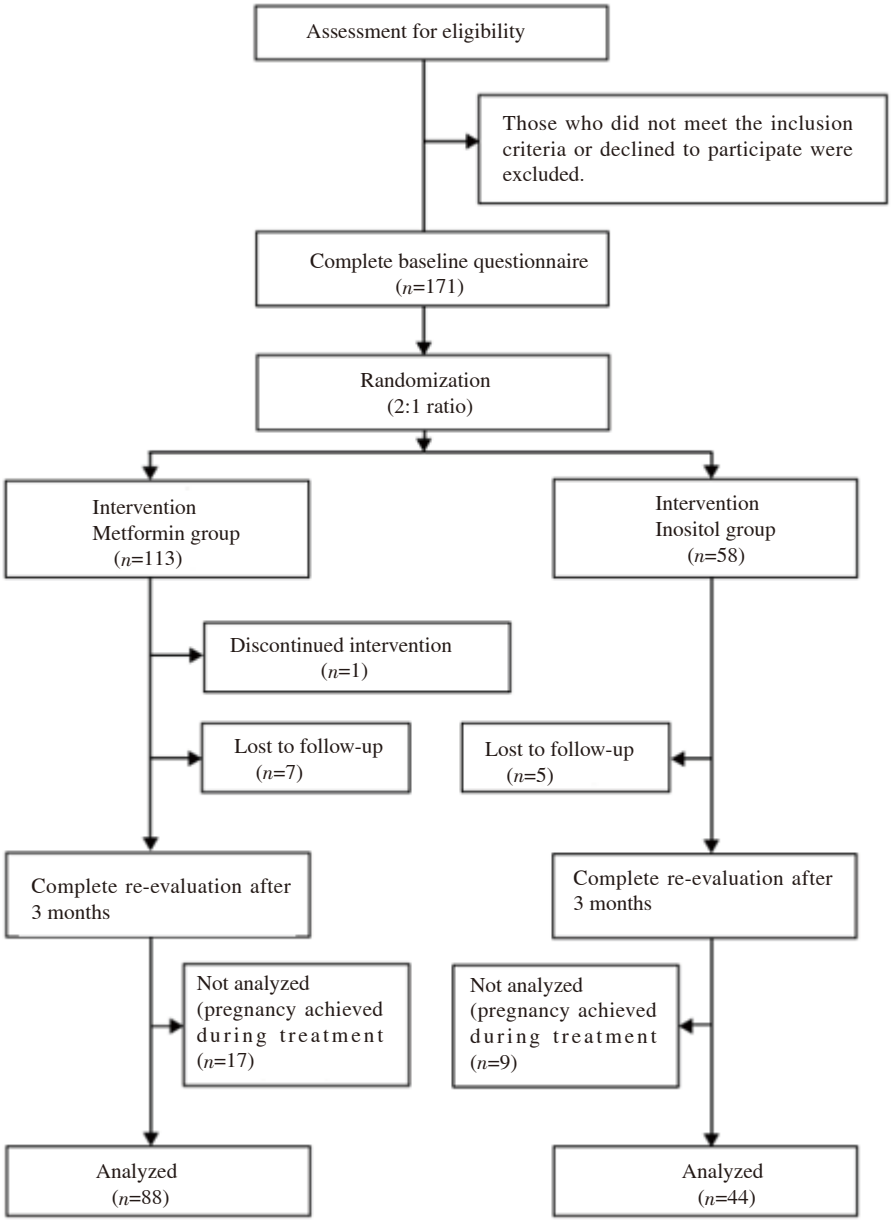

Figure 1. Participant flow diagram.

3.2. Effects of metformin/inositol on clinical features

Total 27 women who spontaneously became pregnant within three months of starting treatment and 12 women who were lost to follow-up were excluded from the analysis.

In the metformin group, compared to previous treatment, the rate of regular menstruation increased significantly (+42.1%, $P<0.001$). Both weight and BMI decreased significantly (both $P=0.002$). Except for the statistically significant decrease in mFG score ($P<0.05$), the remaining characteristics of hyperandrogenism did not change, or changed very marginally without statistical significance ($P>0.05$). In both the overweight/obese and non-overweight groups, subgroup analysis revealed an increased rate of regular menstruation (both $P<0.05$). Weight, BMI, and waist circumference decreased significantly in the overweight/obese group [(-2.00) kg, $P=0.001$; (-0.78) kg/m^2, and (-1.00) cm, $P=0.041$, respectively]. In the group of women who were not overweight or obese, metformin increased the rate of regular menstruation (+42.2%, $P<0.001$) (Table 3).

In the inositol group, the rate of regular cycle increased (+18.2%, $P=0.008$). Weight, BMI, and waist circumference all decreased without statistical significance ($P>0.05$), whereas hip circumference decreased significantly ($P=0.016$). A subgroup analysis showed that in overweight/obese women with PCOS, inositol significantly decreased weight, BMI, waist and hip circumference ($P<0.05$), while the rate of menstrual cycle increased significantly in women with PCOS who were not overweight/obese (+18.4%, $P=0.031$). The characteristics of hyperandrogenism did not change significantly ($P>0.05$) (Table 3).

Table 1. Clinical and reproductive hormonal characteristics of infertile women with polycystic ovarian syndrome (PCOS).

Characteristic	Total (n=171)	Metformin (n=113)	Inositol (n=58)	P
Age, years (Min-max)	28.4±3.4 (20–39)	28.3±3.5 (20–38)	28.5±3.2 (22–39)	0.858
Weight, kg (Min-max)	51.55±6.88 (39.00–73.00)	52.04±6.44 (40.00–72.00)	50.59±7.63 (39.00–73.00)	0.085
BMI, kg/m^2 (Min-max)	21.10±2.43 (16.44–29.52)	21.30±2.32 (17.04–29.52)	20.69 ± 2.60 (16.44–28.40)	0.058
Irregular cycle#, n(%)	153 (89.5)	105 (92.9)	48 (82.8)	0.040
SPB, mmHg (Min-max)	106.40±8.89 (80.00–145.00)	107.38±7.04 (90.00–125.00)	104.48±11.54 (80.00–145.00)	0.041
DPB, mmHg (Min-max)	67.40±6.88 (50.00–90.00)	67.74 ± 6.51 (60.00–85.00)	66.72 ± 7.58 (50.00–90.00)	0.275
Waist circumference*, cm	75 (60.00–102.00)	76 (60.00–100.00)	74 (60.00–102.00)	0.377
Hips circumference*, cm	90 (68.00–110.00)	91 (68.00–110.00)	90 (80.00–108.00)	0.647
WHR (Min-max)	0.83±0.06 (0.68–1.09)	0.83±0.06 (0.68–1.09)	0.83 ± 0.06 (0.72–0.95)	0.547
mFG*	0 (0.00–15.00)	0 (0.00–9.00)	0 (0.00–15.00)	0.068
Acne#, n(%)	19 (11.1)	10 (8.8)	9 (15.5)	0.189
Alopecia#, n(%)	8 (4.7)	5 (4.4)	3 (5.2)	1.000
Acanthosis nigricans#, n(%)	1 (0.6)	1 (0.9)	0 (0.0)	1.000
Reproductive endocrinology				
Basal FSH, IU/L (Min-max)	6.05±1.32 (0.88–12.02)	6.00±1.41 (0.88–12.02)	6.16±1.13 (3.83–8.32)	0.448
Basal LH*, IU/L	8.26 (1.42–30.63)	8.25 (1.42–27.67)	8.39 (2.55–30.63)	0.352
LH/FSH ratio*	1.40 (0.31–5.22)	1.40 (0.31–5.22)	1.39 (0.55–4.81)	0.765
Basal E_2*, pg/mL	36.54 (5.00–167.30)	35.41 (5.00-167.30)	39.77 (5.00-120.90)	0.299
Basal testosterone*, ng/mL	0.268 (0.025–0.829)	0.274 (0.025–0.829)	0.248 (0.029–0.624)	0.324
Basal prolactin*, IU/L	380.90 (36.10–1332.00)	350.80 (36.10–1243.00)	391.05(124.90–1332.00)	0.532
AMH*, ng/mL	6.82 (2.00–27.40)	6.57 (2.00–22.27)	7.13 (2.04–27.40)	0.921

Continuous data are expressed as mean±SD and unpaired sample t-test is used; non-normally distributed data (*) is expressed as median (IQR) and Mann-Whitney U test is used; categorical data (#) are expressed as n (%) and Fisher's Exact test is used. BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FSH: follicle stimulation hormone; LH: luteinizing hormone; E_2: estradiol; AMH: anti-Mullerian hormone; mFG: modified Ferriman and Gallwey score; WHR: waist-to-hip ratio.

Table 2. Metabolic and ultrasound characteristics of infertile women with PCOS.

Characteristic	Total (n=171)	Metformin (n=113)	Inositol (n=58)	P
Lipid profile, mmol/L				
Cholesterol (Min-max)	4.48±0.80 (2.8–7.39)	4.46±0.85 (2.80–7.39)	4.50±0.71 (3.16–6.52)	0.778
Triglycerid*	1.02 (0.39–11.18)	1.05 (0.39–11.18)	0.97 (0.44–5.99)	0.682
LDL-Cholesterol (Min-max)	3.03±0.72 (1.29–5.38)	3.00±0.75 (1.29–5.01)	3.08±0.67 (1.67–5.38)	0.486
HDL-Cholesterol (Min-max)	1.31±0.31 (0.48–2.61)	1.30±0.31 (0.48–2.61)	1.34±0.31 (0.75-2.36)	0.479
Glucose, mmol/L				
Fasting glucose (G0)*	5.19 (3.97–6.75)	5.21 (3.99–6.75)	5.04 (3.97–6.67)	0.094
2 h plasma glucose (G2) (Min-max)	6.54±1.45 (3.31–11.04)	6.58±1.44 (3.31–11.04)	6.46±1.48 (3.51–10.77)	0.610
HbA1c*, %	5.10 (4.10–6.99)	5.10 (4.30–6.99)	5.00 (4.10–6.01)	0.001
Insulin resistance#, n (%)	10 (5.8)	7 (6.2)	3 (5.2)	1.000
Metabolic syndrome#, n (%)	21 (12.3)	13 (11.5)	8 (13.8)	0.666
Dyslipidemia#, n (%)	75 (43.9)	51 (45.1)	24 (41.4)	0.640
Ultrasound findings				
Left ovarian volume*, mL	7.73 (2.67–23.30)	7.72 (2.67–23.30)	8.21 (3.72–20.56)	0.146
Right ovarian volume*, mL	8.67 (2.02–23.72)	8.59 (2.02–17.54)	8.81 (3.16–23.72)	0.788

Continuous data are expressed as mean±SD and unpaired sample t-test is used; non-normally distributed data (*) is expressed as median (IQR) and Mann-Whitney U test is used; categorical data (#) are expressed as n (%) and Fisher's Exact test is used. LDL-Cholesterol: low-density lipoprotein cholesterol; HDL-Cholesterol: high-density lipoprotein cholesterol; HbA1C: hemoglobin A1C.

3.3. Effects of metformin/inositol on metabolic endocrinology

Metformin treatment significantly decreased basal LH (P=0.031) and caused a slight decrease in total testosterone (P=0.011). The mean TG concentration increased marginally significantly (P=0.040). There was no statistically significant (P>0.05) change in the concentrations of total cholesterol, LDL-cholesterol, and HDL-cholesterol. The endocrine and metabolic parameters of overweight/

Table 3. Changes in clinical features after 3 months of metformin and inositol treatment in the infertile women with PCOS and in the overweight/obese and non-overweight/obese subgroups.

Parameters	Metformin group (n=88)						Inositol group (n=44)					
	Total (n=88)		Overweight/Obese (n=17)		Non Overweight/Obese (n=71)		Total (n=44)		Overweight/Obese (n=11)		Non overweight/obese (n=33)	
	(T3-T0)	P	(T3-T0)	P	(T3-T0)	P	(T3-T0)	P	(T3-T0)	P	(T3-T0)	P
Regular cycle	42.1%	<0.001**	41.2%	0.016**	42.2%	<0.001**	18.2%	0.008**	16.7%	0.500**	18.4%	0.031**
SBP, mmHg	0	0.195*	0	0.157*	0	0.361*	0	0.119*	0.00	>0.999*	0	0.119*
DBP, mmHg	0	0.297*	0	0.564*	0	0.371*	0	0.366*	0.00±0.00	>0.999	0	0.366*
Weight, kg	-1.00	0.002*	-2.00	0.001*	0	0.228*	-0.50±1.63	0.089	-2.09±0.83	<0.001	0	0.761*
BMI, kg/m^2	-0.21	0.002*	-0.78	0.001*	0	0.250*	-0.39	0.102*	-0.85±0.30	<0.001	0.02±0.60	0.885
WC, cm	-1.00	0.066*	-1.00	0.041*	-1.0	0.457*	-1.00	0.367*	-1.82±1.47	0.002	-1.00	0.580*
HC, cm	0	0.095*	-1.00	0.075*	0	0.384*	-0.82±2.85	0.016	-1.82±2.63	0.045	-0.48±2.87	0.340
mFG	0	0.038*	0	0.317*	0	0.063*	0	0.157*	0.00	>0.999*	0	0.157*
Hirsutism	-1.1%	>0.999**	0%	>0.999**	-1.4%	>0.999**	0%	>0.999**	0%	>0.999**	0%	>0.999**
Acne	-2.3%	0.625**	5.9%	>0.999**	-4.2%	0.250**	0%	>0.999**	0%	>0.999**	0%	>0.999**
Alopecia	1.1%	>0.999**	0%	NA	1.4%	>0.999**	-2.3%	>0.999**	0%	NA**	-2.6%	>0.999**
Acanthosis nigricans	0%	>0.999**	0%	NA	0%	>0.999**	2.3%	>0.999**	0%	NA**	2.6%	>0.999**

Continuous data are expressed as mean±SD and paired t-test is used; non-normally distributed data (*) is expressed as median (IQR) and Wilcoxon Signed Ranks test is used; categorical data (**) are expressed as n (%) and McNemar test is used. BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; WC: waist circumference; HC: hip circumference; mFG: modified Ferriman-Galway scores. Pre-treatment (T0), Post-treatment (T3).

Table 4. Changes in paraclinical features after 3 months of metformin and inositol treatment in the infertile women with PCOS and in the overweight/obese and non-overweight/obese subgroups.

Parameters	Metformin group (n=88)						Inositol Group (n = 44)					
	Total (n=88)		Overweight/Obese (n=17)		Non Overweight/ Obese (n=71)		Total (n=44)		Overweight/Obese (n=11)		Non overweight/obese (n=33)	
	(T3-T0)	P	(T3-T0)	P	(T3-T0)	P	(T3-T0)	P	(T3-T0)	P	(T3-T0)	P
FSH, IU/L	-0.01	0.453*	-0.01±1.06	0.982	-0.12±1.48	0.494	-0.18±0.82	0.148	-0.25	0.859*	-0.30±0.59	0.005
LH, IU/L	-0.36	0.031*	-0.89±4.60	0.436	-0.32	0.019*	-0.36	0.104*	0.79±4.89	0.604	-0.38	0.047*
E_2, pg/mL	-1.01	0.861*	-3.30	0.432	-0.86	0.947*	-0.86	0.852*	6.23	0.091*	-1.51±12.52	0.492
Testosterone, ng/mL	-0.024	0.011*	-0.008	0.266*	-0.024	0.017*	-0.032±0.098	0.033	-0.015±0.100	0.618	-0.038±0.098	0.033
Prolactin, IU/L	-3.10	0.758*	-18.90	0.906*	9.70	0.651*	-19.40±170.55	0.455	-96.90	0.075*	24.75±82.32	0.094
Cholesterol, mmol/L	-0.06±0.64	0.345	-0.09±0.75	0.638	-0.06±0.62	0.432	0.05±0.90	0.735	0.18	0.286*	-0.08±0.71	0.534
TG, mmol/L	0.125	0.040*	0.31	0.332*	0.01	0.097*	0.03	0.674*	-0.03	0.859*	0.034	0.681*
LDL-Cho, mmol/L	-0.09±0.56	0.159	-0.08±0.54	0.544	-0.09±0.57	0.208	0.01±0.90	0.918	0.31±1.27	0.437	-0.08±0.74	0.516
HDL-Cho, mmol/L	0.01	0.493*	0.06	0.381*	0.01	0.740*	-0.02±0.25	0.647	0.03±0.29	0.713	-0.03±0.24	0.420
G0, mmol/L	0.01	0.878*	-0.21	0.191*	0.01	0.501*	-0.07±0.35	0.194	-0.19±0.34	0.095	-0.03±0.34	0.633
G2, mmol/L	0.27	0.059*	0.78±1.05	0.008	0.15±1.34	0.344	-0.27±1.30	0.171	-0.26±1.44	0.560	-0.27±1.27	0.221
HbA1c, %	-0.01	0.451*	-0.09±0.38	0.346	0	0.756*	0.03±0.41	0.579	0.07±0.50	0.667	0.02±0.38	0.726

Continuous data are expressed as mean±SD and paired t–test is used; non-normally distributed data (*) is expressed as median (IQR) and Wilcoxon Signed Ranks test is used; FSH: follicle stimulation hormone; LH: luteinizing hormone; E_2: estradiol; TG: triglyceride; LDL-Cho: low-density lipoprotein cholesterol; HDL-Cho: high-density lipoprotein cholesterol; G0: Fasting glucose; G2: 2h plasma glucose. Pre-treatment (T0), Post-treatment (T3).

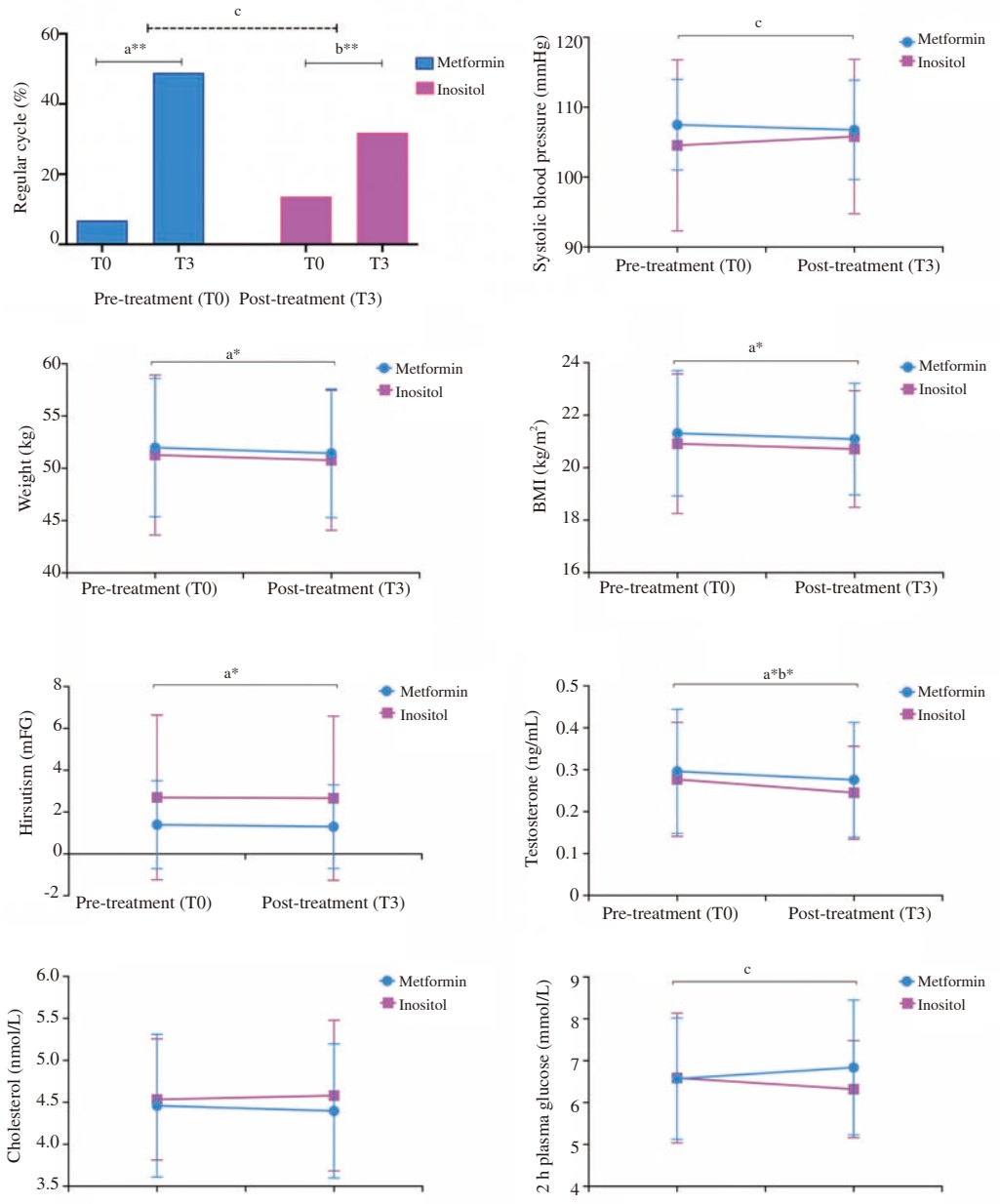

Figure 2. Comparison of clinical, endocrine, and metabolic changes after 3 months of treatment with metformin and inositol. *Wilcoxon signed ranks test/ Paird samples *t* test, $P<0.05$; ** McNemar test, $P<0.05$. a: $P<0.05$, in metformin group; b: $P<0.05$, in the Inositol group, c: $P<0.05$, between two treated groups (Mann Whitney *U* test).

Table 5. Adverse effect and tolerability rate.

Parameters	Metformin (*n*=106)	Inoitol (*n*=53)	*P*
Side effects	31 (29.2%)	5 (9.4%)	0.005
Digestive disorders	23	1	-
Tiredness	5	3	
Others	0	1	
Many side effects	3	0	
Tolerabilities	105 (99.1%)	53 (100%)	>0.999*

Categorical data are expressed as *n* (%) and *Chi*-square test is used or Fisher's Exact test is used (*)

Table 6. Spontaneous pregnancy rates [*n* (%)].

Parameters	Metformin (*n*=105)	Inoitol (*n*=53)	*P*
Pregnancy	22 (21.0)	10 (18.9)	0.758
Clinical pregnancy	20 (19.0)	9 (17.0)	0.751
Ongoing pregnancy	19 (17.9)	9 (17.0)	0.883
Miscarriage	4 (3.8)	1 (1.9)	0.665*
Live birth	18 (17.1)	9 (17.0)	0.980

Categorical data are expressed as *n* (%) and *Chi*-square test is used or Fisher's Exact test is used (*)

obese women with PCOS did not improve significantly (P>0.05) based on subgroup analysis. In contrast, LH and testosterone levels decreased significantly (P<0.05) among women with a normal BMI. In the inositol group, we observed a statistically significant reduction in total testosterone concentrations [(-0.032±0.098) ng/mL; P=0.033]. There was no significant change in the other parameters of the lipid profile and related parameters of glucose metabolism (P>0.05). In the subgroup analysis of non-overweight/obese women, basal FSH levels, basal LH levels, and total testosterone levels decreased significantly (P<0.05) (Table 4).

3.4. Comparison of the effectiveness of metformin and inositol on infertile PCOS women

There was a statistically significant (P<0.05) increase in the rate of regular menstruation in the metformin group compared to the inositol group. The change in systolic blood pressure (SBP) and in 2 hours plasma glucose were significantly (P<0.05) different between the two treatment groups; however, the change before and after treatment in each group was not statistically significant (P>0.05). (Figure 2). On other hand, the other changes in the two distinct drug groups were not statistically significant (P>0.05) (Figure 2). The incidence of adverse events (after excluding cases lost to follow-up) was significantly higher in the metformin group than in the inositol group (29.2% *versus* 9.4%, P=0.005). The rates of spontaneous pregnancy, clinical pregnancy, miscarriage, and live birth (calculated per number of women completing treatment) did not differ significantly (P>0.05) between the two groups (Table 5, Table 6).

4. Discussion

In our study, infertile women with PCOS had low BMIs, irregular menstruation, few symptoms of hyperandrogenism and less hirsutism, low total testosterone levels, and small mean ovarian volumes. These characteristics are comparable to those found in previous studies on infertile women with PCOS in Vietnam[20] and a few other studies in Asia, but distinct from those found in Caucasian studies[21,22]. The low incidence of hirsutism in East Asian women of Chinese, Korean, Thai, and Japanese origins may be attributable to weak alpha reductase activities in the hair follicles[15]. The 2018 International evidence-based guidelines for the assessment and management of PCOS recommend that medical professionals take into account ethnic differences in the presentation of PCOS: Caucasian women have higher BMIs, particularly in North America and Australia, whereas East Asian women have lower BMIs and less hirsutism[23]. In this study, the median volume of the left ovary was (7.73) mL; the median volume of the right ovary was (8.67 mL). 83.0% Of the women had polycystic ovaries on both sides. PCOS ovarian volumes have been documented to be smaller in the Asian population, and it is believed that this volume varies among ethnic groups. Multiple studies based on the Rotterdam consensus criteria suggested a lower cutoff of ovarian volumes spanning from 6.40 to 7.50 mL in order to increase the diagnostic sensitivity of PCOS[24].

The prevalence of MetS in our study was 12.3%. The findings were comparable to those of other studies conducted in Vietnam, as well as in Korea and Taiwan, China[20,25,26]. We know that the incidence of MetS in women with PCOS varies considerably across countries and races, most likely as a result of differences in diet, lifestyles, and genetics. Despite a low prevalence of obesity, the dyslipidemia status of women with PCOS in Vietnam is alarming, according to the findings of this study.

Our research revealed that metformin treatment enhanced menstrual cycle regularity, statistically significant weight loss and BMI, and a slight reduction in mFG scores. Metformin's use in PCOS is based on the significant role insulin resistance plays in the pathogenesis of the syndrome. Metformin has been shown to be beneficial for weight loss, lowering androgen levels, restoring menstrual cycles, and inducing ovulation in PCOS women. Patel *et al* revealed that metformin reduced BMI, waist-to-hip ratio, systolic blood pressure, and diastolic blood pressure relative to placebo, but did not affect mFG scores[27]. Another meta-analysis comparing metformin to placebo or no treatment found that metformin increased the rate of menstrual regularity based on seven studies[5]. Metformin could theoretically ameliorate hyperandrogenism and its clinical manifestations, such as acne and hirsutism, because it reduces ovarian androgen production, ovarian P450c17 activity, and free testosterone levels, resulting in a reduction of mFG scores within a few months[28].

We discovered that after metformin treatment, LH and testosterone levels decreased statistically. Other metabolic and endocrine parameters were not significantly altered. Oner *et al* reported that, in addition to enhancing BMI, hirsutism, and regular menstruation, decreasing free testosterone concentration, fasting blood insulin, and the HOMA index, metformin 1 500 mg/day reduced total cholesterol concentration[29]. Evidence-based guidelines for the assessment and management of PCOS have aggregated relevant clinical trials. The consensus is that metformin was effective in improving weight, BMI, waist circumference, testosterone, cholesterol, and TG in general or in specific groups in women with polycystic ovary syndrome. There is stronger evidence of metabolic benefits in obese women with PCOS[23].

We found a statistically significant improvement in the menstrual cycle after three months of treatment with inositol. Weight, BMI, waist circumference, and mFG scores tended to decline, but this trend was not statistically significant. In addition, the concentration of total testosterone decreased significantly. Other endocrine and lipid parameters' changes were not statistically significant. Genazzani *et al* reported that after 8 weeks of treatment with myo-inositol and an unrestricted diet, their participants lost weight at a statistically significant level (decrease in BMI)[30]. Zarezadeh *et al* conducted a meta-analysis of the effects of inositol on BMI and discovered that inositol supplementation substantially decreased BMI. Women with PCOS and overweight/obesity exhibited the most pronounced effect. Inositol in the form of myo-inositol has an even greater effect on reducing BMI[31]. There was a significant decrease in testosterone levels after 12 weeks of treatment with myo-inositol, as well as a decrease in mFG scores that did not reach statistical significance according to the study by Genazzani *et al*[32]. Papaleo *et al* reported that the menstrual cycle was restored and preserved

during six months of treatment with myo-inositol[33]. Unfer *et al* conducted a meta-analysis that demonstrated a significant decrease in fasting insulin concentration and HOMA index in the myo-inositol-supplemented group. In addition, there was a trend toward a decrease in testosterone levels in the myo-inositol group compared to the control group, but this difference did not reach statistical significance. These findings demonstrated the beneficial effects of myo-inositol in enhancing the metabolism and hyperandrogenism of PCOS-affected females[34]. Similarly, Hayamizu *et al* found that compared to the control group, inositol improved fasting insulin concentration, area under the curves of glucose tolerance test, free testosterone and sex hormone binding globulin, as well as ovulation rate[35].

Our research was one of the few to investigate the difference in efficacy between the two groups of insulin sensitizers. The results revealed that the metformin group had a significantly higher menstrual regularity rate than the inositol group. Changes in clinical and paraclinical parameters following treatment with two distinct drugs were not statistically significant. Comparing the two groups, pregnancy rates were comparable while adverse events were significantly higher in the metformin group. In a randomized controlled trial comparing the effects of metformin with myo-inositol and with metformin+myo-inositol on ovarian function and metabolic factors in women, Thakur *et al* found that myo-inositol appeared to be less effective than metformin and the other group in restoring the menstrual cycle, but the difference was not statistically significant. After treatment, both metformin and inositol significantly decreased BMI, and the difference between the two groups was not statistically significant. Regarding the rate of spontaneous pregnancy after six months of treatment, the metformin group significantly improved while the inositol group did not. It should be noted, however, that the sample size of this study was extremely limited[10]. The meta-analysis of Facchinetti *et al* reported that there was no difference in the effectiveness of metformin and myo-inositol on short-term endocrine changes, and because myo-inositol was more tolerable, this class of medications is more acceptable for restoring androgen expression and metabolism in women with PCOS[36].

Our study was one of the few randomized clinical trials with a sufficiently large sample size to compare the effectiveness of two commonly used insulin sensitizers. Nevertheless, the research has some limitations. As a single center study, the sample size was not representative of the Vietnamese PCOS population. Also, despite randomization, some variables differed between the two treatment groups; however, these differences had no effect on the study's primary findings.

In conclusion, metformin and inositol can improve weight and waist circumference in overweight/obese infertile women with PCOS. Metformin is associated with a higher rate of regular menstruation, whereas inositol is associated with a lower rate of adverse effects. The spontaneous conception, clinical pregnancy, and live birth rates between two groups are comparable.

Conflict of interest statement

All authors declare no conflicts of interest.

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Authors' contributions

Nguyen Sa Viet Le participated in the study design, execution, analysis, manuscript drafting and critical discussion. Minh Tam Le participated in the study design and execution. Thanh Ngoc Cao participated in the study design and critical discussion. All authors have read and approved the final manuscript.

References

[1] Lizneva D, Suturina L, Walker W, Brakta S, Gavrilova-Jordan L, Azziz R. Criteria, prevalence, and phenotypes of polycystic ovary syndrome. *Fertil Steril* 2016; **106**(1): 6-15.

[2] Sortino MA, Salomone S, Carruba MO, Drago F. Polycystic ovary syndrome: Insights into the therapeutic approach with inositols. *Frontiers Pharmacol* 2017; **8**: 341.

[3] Zhao H, Zhang J, Cheng X, Nie X, He B. Insulin resistance in polycystic ovary syndrome across various tissues: An updated review of pathogenesis, evaluation, and treatment. *J Ovarian Res* 2023; **16**(1): 9. doi: 10.1186/s13048-022-01091-0.

[4] Lashen H. Role of metformin in the management of polycystic ovary syndrome. Therapeutic advances in endocrinology metabolism. *Ther Adv Endocrinol Metab* 2010; **1**(3): 117-128. doi: 10.1177/2042018810380215.

[5] Morley L, Tang T, Balen A. On behalf of the royal college of obstetricians and gynaecologists. Metformin therapy for the management of infertility in women with polycystic ovary syndrome. *BJOG* 2017; **124**(12): e306-e313.

[6] Eisenhardt S, Schwarzmann N, Henschel V, Germeyer A, Von Wolff M, Hamann A, et al. Early effects of metformin in women with polycystic ovary syndrome: A prospective randomized, double-blind, placebo-controlled trial. *J Clin Endocrinol* 2006; **91**(3): 946-952.

[7] Hoeger KM, Kochman L, Wixom N, Craig K, Miller RK, Guzick DS. A randomized, 48-week, placebo-controlled trial of intensive lifestyle modification and/or metformin therapy in overweight women with polycystic ovary syndrome: A pilot study. *Fertil Steril* 2004; **82**(2): 421-429.

[8] Morley LC, Tang T, Yasmin E, Norman RJ, 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* 2017; **11**(11): CD003053.

[9] Pundir J, Psaroudakis D, Savnur P, Bhide P, Sabatini L, Teede H, et

al. Inositol treatment of anovulation in women with polycystic ovary syndrome: A meta-analysis of randomised trials. *BJOG* 2018; **125**(3): 299-308.

[10]Thakur SS, Anjum S, Siddiqui S. Randomised controlled trial: Comparing effects of metformin *versus* myoinositol *versus* metformin and myoinositol on ovarian functions and metabolic factors in polycystic ovarian syndrome. *Int J Reprod Contracep Obstet Gynecol* 2020; **9**(6): 2542-2550.

[11]Lee TT, Rausch ME. Polycystic ovarian syndrome: Role of imaging in diagnosis. *Radiographics* 2012; **32**(6): 1643-1657.

[12]ESHRE The Rotterdam, ASRM-Sponsored PCOS consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril* 2004; **81**(1): 19-25.

[13]Escobar-Morreale H, Carmina E, Dewailly D, Gambineri A, Kelestimur F, Moghetti P, et al. Epidemiology, diagnosis and management of hirsutism: A consensus statement by the Androgen Excess and Polycystic Ovary Syndrome Society. *Hum Reprod Update* 2012; **18**(2): 146-170.

[14]World Health Organization. Regional Office for the Western Pacific. *The Asia-Pacific perspective: Redefining obesity and its treatment*. Sydney: Health Communications Australia; 2020.

[15]Huang Z, Yong EL. Ethnic differences: Is there an Asian phenotype for polycystic ovarian syndrome? *Best Practice Res Clin Obstet Gynaecol* 2016; **37**: 46-55.

[16]Mansour A, Hashemi Taheri AP, Moradi B, Mohajeri-Tehrani MR, Qorbani M, Ghorbani Pashakolaee S, et al. Ovarian volume, not follicle count, is independently associated with androgens in patients with polycystic ovary syndrome. *BMC Endocrine Disorders* 2022; **22**(1): 1-9.

[17]Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: An American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Circulation* 2005; **112**(17): 2735-2752.

[18]Einhorn D. American College of Endocrinology position statement on the insulin resistance syndrome. *Endocrine Practice* 2003; **9**: 5-21.

[19]Zhu JR, Gao RL, Zhao SP, Lu GP, Zhao D, Li JJ. 2016 Chinese guidelines for the management of dyslipidemia in adults. *J Geriatr Cardiol* 2018; **15**(1): 1-29.

[20]Cao NT, Le MT, Nguyen VQH, Pilgrim J, Le VNS, Le DD, et al. Defining polycystic ovary syndrome phenotype in Vietnamese women. *J Obstet Gynaecol Res* 2019; **45**(11): 2209-2219.

[21]Agrawal A, Mahey R, Kachhawa G, Khadgawat R, Vanamail P, Kriplani A. Comparison of metformin plus myoinositol *vs* metformin alone in PCOS women undergoing ovulation induction cycles: Randomized controlled trial. *Gynecol Endocrinol* 2019; **35**(6): 511-514.

[22]Prabhakar P, Mahey R, Gupta M, Khadgawat R, Kachhawa G, Sharma JB, et al. Impact of myoinositol with metformin and myoinositol alone in infertile PCOS women undergoing ovulation induction cycles-randomized controlled trial. *Gynecol Endocrinol* 2021; **37**(4): 332-336.

[23]Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, et al. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Hum Reprod* 2018; **33**(9): 1602-1618.

[24]Le NSV, Le MT, Nguyen ND, Tran NQT, Nguyen QHV, Cao TN. A cross-sectional study on potential ovarian volume and related factors in women with polycystic ovary syndrome from infertile couples. *Int J Women's Health* 2021; **13**: 793-801.

[25]Park HR, Choi Y, Lee HJ, Oh JY, Hong YS, Sung YA. The metabolic syndrome in young Korean women with polycystic ovary syndrome. *Diabetes Res Clin Pract* 2007; **77**(3): S243-S246.

[26]Chen MJ, Yang WS, Yang JH, Hsiao CK, Yang YS, Ho HN. Low sex hormone-binding globulin is associated with low high-density lipoprotein cholesterol and metabolic syndrome in women with PCOS. *Hum Reprod* 2006; **21**(9): 2266-2271.

[27]Patel R, Shah G. Effect of metformin on clinical, metabolic and endocrine outcomes in women with polycystic ovary syndrome: A meta-analysis of randomized controlled trials. *Curr Med Res Opinion* 2017; **33**(9): 1545-1557.

[28]Genazzani AD, Ricchieri F, Lanzoni C. Use of metformin in the treatment of polycystic ovary syndrome. *Women's Health* 2010; **6**(4): 577-593.

[29]Oner G, Muderris II. Clinical, endocrine and metabolic effects of metformin *vs N*-acetyl-cysteine in women with polycystic ovary syndrome. *Eur J Obstet Gynecol Reprod Biol* 2011; **159**(1): 127-131.

[30]Genazzani AD, Prati A, Santagni S, Ricchieri F, Chierchia E, Rattighieri E, et al. Differential insulin response to myo-inositol administration in obese polycystic ovary syndrome patients. *Gynecol Endocrinol* 2012; **28**(12): 969-973.

[31]Zarezadeh M, Dehghani A, Faghfouri AH, Radkhah N, Naemi Kermanshahi M, Hamedi Kalajahi F, et al. Inositol supplementation and body mass index: A systematic review and meta-analysis of randomized clinical trials. *Obes Sci Pract* 2022; **8**(3): 387-397.

[32]Genazzani AD, Lanzoni C, Ricchieri F, Jasonni VM. Myo-inositol administration positively affects hyperinsulinemia and hormonal parameters in overweight patients with polycystic ovary syndrome. *Gynecol Endocrinol* 2008; **24**(3): 139-144.

[33]Papaleo E, Unfer V, Baillargeon JP, De Santis L, Fusi F, Brigante C, et al. Myo-inositol in patients with polycystic ovary syndrome: A novel method for ovulation induction. *Gynecol Endocrinol* 2007; **23**(12): 700-703.

[34]Unfer V, Facchinetti F, Orru B, Giordani B, Nestler J. Myo-inositol effects in women with PCOS: A meta-analysis of randomized controlled trials. *Endocr Connect* 2017; **6**(8): 647-658.

[35]Hayamizu K, Kuramochi Y, Sumoni A, Izumo N. Effects of inositol in women with polycystic ovary syndrome: A systematic review and meta-analysis of randomized controlled trials. *J Nutrit Health Food Sci* 2022; **10**(1): 1-8.

[36]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**(3): 198-206.

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