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Original article

Effect of Short Period Administration of Inositol and Metformin on Hormonal and Lipid Profile in Women with Polycystic Ovary Syndrome

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ABSTRACT

Background: It has been difficult to diagnose and treat polycystic ovarian syndrome (PCOS). Because it functions as an insulin sensitizer, metformin plays a significant role in the treatment of PCOS. It has been found that inositol, a new natural chemical, affects PCOS hormones. Therefore, our goal was to compare the efficacy of metformin, inositol, or both on the lipid and hormonal profiles of women with PCOS.

Methods: This study was carried out in department of obstetrics & gynecology in Zagazig university hospitals on patients with PCOS. Patients were divided into: **Group 1:** received inositol. **Group 2:** received metformin. **Group 3:** received inositol and metformin.

Results: Regarding oligomenorrhea, amenorrhea and acne, there was no significant difference before and after treatment in the three studied groups while there was significant improvement after treatment in each group, regarding hirsutism score there was significant decreased in group3 than group 1 and group 2. There was a significant difference regarding cholesterol that was lower in group 1 than group 2 and group 3 and HDL that was higher in group 3 than group 1 and group 3. There was a significant decrease in FSH and LH after treatment in group 1, group 2 and group 3 .

Conclusions: Both metformine and inositol have a positive impact on PCOS symptoms and test findings. However, combining the two produced superior outcomes.

Keywords: Polycystic ovary syndrome; inositol; metformin.

INTRODUCTION

An estimated 5–15% of women in their reproductive years worldwide suffer from PCOS, an endocrine reproductive metabolic condition [1].

Although PCOS symptoms can vary greatly, hyperandrogenism, ovarian cysts, and irregular menstrual periods are some of the more frequent ones. This can lead to infertility, insulin resistance, hirsutism, and acne [2].

Research has indicated that dyslipidemia, namely raised triglycerides (TG) and decreased high-density lipoprotein cholesterol (HDL-C), is more common in obese women with polycystic ovarian syndrome (PCOS). In PCOS patients who are overweight or obese, anthropometric traits like body mass index (BMI) and hip circumference are significant metrics associated with lipid profiles [3]. In PCOS patients, lean mass percentages have been demonstrated to predict a better metabolic profile [4].

It has been discovered that women with PCOS, whether they are fat or lean, have higher visceral adiposity and worse metabolic health when compared to the control group [5]. In PCOS patients, lipid ratios and obesity indices have been found to be reliable indicators of metabolic syndrome [6].

Because of its wide range of symptoms, PCOS is difficult to diagnose. The Rotterdam criteria can be used to diagnose PCOS, even

though there isn't a test for it [7]. These requirements state that a person must exhibit two of the three symptoms listed below: aberrant ovarian morphology, irregular menstruation, or hyperandrogenism [8]. Notably, when diagnosing PCOS, lifestyle factors, age, race, and ethnicity must also be taken into account [9].

A variety of tactics and therapies are used in PCOS control. One of the primary lines of treatment for PCOS is lifestyle modifications, such as diet and exercise, which have been demonstrated to control its symptoms. Losing weight as a result of these modifications has been demonstrated to lessen insulin sensitivity and irregular menstruation, two symptoms of PCOS. According to recent studies, women with PCOS can benefit from a diet that is high in fiber and protein sources and moderate in fats and carbs [9].

PCOS symptoms are often treated with insulin sensitizers and hormone-acting medications [10]. In particular, insulin sensitizers lessen the body's resistance to insulin. This is important because insulin resistance in PCOS has several pathophysiological effects, such as hyperinsulinemia, ovulation disruption, and increased androgen production. Numerous studies have shown that insulin sensitizers have demonstrated encouraging results in the treatment of infertility because of their pathophysiological effects [9].

The spectrum of therapy choices is expanded by the discovery that some progestins, in addition to insulin sensitizers, contain antiandrogen qualities. Hyperandrogenism-induced hirsutism is frequently treated with cosmetic procedures such laser hair removal or hair growth therapies [11]. All things considered, a variety of therapeutic approaches are available to treat the different PCOS symptoms, and by customizing them to meet the needs of each patient, their efficacy can be maximized [12].

The variety of PCOS treatment options available offers encouraging results in controlling the disorder's many symptoms. Inositol and metformin are two possible PCOS-management therapies. A well-known prescription insulin sensitizer, metformin is used to treat PCOS symptoms such infertility, irregular menstruation, and hirsutism [13]. It works by decreasing hepatic glucose synthesis, increasing insulin sensitivity, and decreasing intestinal glucose absorption, all of which lower high insulin levels [14]. This is especially pertinent to the pathophysiology of PCOS because insulin resistance is a common feature that contributes to its different forms. Metformin is a useful treatment choice for women with PCOS who are trying to conceive because it has been shown to improve insulin sensitivity, decrease androgen levels, and boost ovulation rates [11]. Higher clinical pregnancy rates result from metformin's regulation of menstrual periods and promotion of ovulation [15].

Natural substances called myo-inositol and d-chiro-inositol are involved in numerous cellular processes. Numerous gynecological and endocrinological disorders have been treated with inositol-based supplements since their role in endocrine signal transduction was discovered. An increasingly popular treatment for polycystic ovarian syndrome (PCOS) is the use of inositols, a well-tolerated and efficient substitute for traditional insulin sensitizers. Insulin resistance, metabolic syndrome, and gestational diabetes mellitus are among the metabolic disorders for which inositols have been shown to have positive benefits. They also increase insulin activity. [16].

Therefore, our goal was to compare the efficacy of metformin, inositol, or both on the lipid and hormonal profiles of women with PCOS.

METHODS

This prospective, randomized, controlled, comparative clinical study was carried out in department of obstetrics & gynecology in Zagazig university hospitals, Egypt on patients with PCOS during the period from January 2024 to January 2025.. Patients were divided into three groups: Group 1: received inositol (1g two times daily) for 6 months. Group 2: received metformin (500 mg three times daily) for 6 months. Group 3: received inositol (1g two times daily) and metformin (500 mg three times daily) for 6 months; 52 cases in each group **[17].** After approval of the ethical committee (IRB number 64/31-Jan-2024), all participants in the study were given a written and informed consent, after explaining the details of the study to them.

Inclusion criteria:

• Age: 18 to 40 years.
• The modified Rotterdam criteria were used to diagnose PCOS in these patients. possessing, after ruling out alternative causes, at least two of the following three requirements.
• Anovulation and/or oligo.
• Hyperandrogenism, either biochemical or clinical.
• A polycystic ovary ultrasound image.
• ≥20 cysts in one or two ovaries with a diameter of 2–9 mm or an ovarian volume of at least 10 ml.

Exclusion criteria

• Women with Cushing's illness, hyperprolactinemia, hypothyroidism/hyperthyroidism, or any neoplastic condition.
• Nursing and pregnancy.
• Renal impairment and/or active liver disease.
• Diabetes mellitus, either type 1 or type 2.
• Hormonal therapy history throughout the previous three months.
• People who smoke and drink alcohol.
• Unable to attend routine follow-up appointments.
• An allergy to metformin or inositol.

Every woman who participated in the study underwent a general and local checkup as well as a history taking. The Ferryman Gallways scoring system classified hirsutism as having a score of eight or higher out of nine body areas **[18].**

Investigations:

1-Transabdominal and trans vaginal ultrasound: were completed either spontaneously or through withdrawal on days two through five of the cycle.

Ultrasound criteria to diagnosis PCOS .

According to transvaginal ultrasonography, there should be at least 20 follicles per ovary in each ovary with a transducer frequency of at least 8 MHz OR at least 12 follicles per ovary in either ovary with a transducer frequency of at least 8 MHz.
• At least one ovary has an ovarian volume of ≥10 cm3 [19].
• TVS examination for adenexal masses or anomalies in the uterus and cervix.

Laboratory investigations:

These were completed in accordance with the procedures used in the laboratories and clinical pathology departments of Zagazig University hospitals. All research participants had their venous blood samples taken under aseptic conditions by skilled nurses or doctors using minimally intrusive techniques, such as placing tourniquets to the patient's arm to highlight the veins.

1 – Routine investigations:

- **Complete blood count:** white blood cell (WBC) count, platelet count, hemoglobin level, hematocrit value, and red blood cell count (RBC). Hematological grading was used to interpret the CBC results.
- **Coagulation profile (prothrombin time, concentration and INR).**
- **Liver function tests:** The kinetic approach was used to quantify serum albumin, serum alanine transferase, serum aspartate transferase, and serum bilirubin (total and direct).
- **Renal function tests:** serum creatinine **,** serum urea by colorimetric method **.**

2 – Lipid profiles: Triglyceride, total cholesterol, HDL-C, LDL-C:

Following a 12-hour overnight fast, blood samples were drawn and placed in EDTA-containing dry tubes. The plasma was separated right away using chilled centrifugation for ten minutes at 2,500–3,000 rpm.Adults should aim for LDL cholesterol levels below 100 mg/dL, HDL cholesterol levels at or above 50 mg/dL, undesirable triglyceride levels below 150 mg/dL, and a desired cholesterol level below 200 mg/dL.

3- Hormonal profile for FSH, LH, TSH , T3, T4 , Prolactin and serum total testosterone,DHEA-S.

• Blood samples, either spontaneous or withdrawn, collected during minimally invasive procedures under aseptic conditions on days 2–5 of the cycle were analyzed by Cobas c 702 using (EIA) enzyme immune assay kits for hormone testing.

Before and after drug use, the lipid and hormone profiles of every patient in each group were measured.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) version 20.0 software was then used to import and analyze the data. The Shapiro-Wilk test was used to determine whether the data distribution was normal. The chi-square test,

post hoc least significant difference (LSD) test, and one-way ANOVA were employed.

RESULTS

Regarding demographic information, no discernible variations were found between the groups under study (Table 1). Before therapy, there was no significant difference in the three groups under study with regard to oligomenorrhea, amenorrhea, and acne; however, following treatment, each group showed a significant improvement in these conditions (Table 2). Prior to therapy, there was no discernible difference in the three groups under investigation's hirsutism scores; however, following treatment, groups 1 and 3 showed a considerable improvement. But in group 3, the improvement was more noticeable. (Table 2).

Regarding HDL, LDL, triglycerides, and cholesterol, no discernible differences were found between the groups under study (Table 3). Following treatment, each group's lipid profile significantly improved. Comparison of the results revealed that group (1) had significantly lower cholesterol than group (2), whereas group (3) had significantly higher HDL than group (1,2) (Table 4). While there was a significant drop in FSH, LH, total testosterone, and DHEAs following therapy in each group, there was no significant difference in FSH, LH, or DHEAs before and after drug intake (Table 5).

Table 1: Comparison between different studied groups regarding demographic data.

		Inositol group (N=52)	Metformin group (N=52)	Inositol and metformin group (N=52)	P value
Age (Years)	**Mean ± SD**	26±5.3	26.4±5.4	26.6±5.7	0.85
	Range	19-37	19-37	19-37	
Weight (Kg)	**Mean ± SD**	61.6 ± 4.3	60.9 ± 4.7	61.3 ± 4.1	0.72
	Range	55 - 72	54-71	54-70	
BMI (kg/m2)	**Mean ± SD**	27.3 ± 2.9	26.7 ± 3.1	27.1 ± 2.7	0.69
	Range	24 - 31	23-31	24-31	
Waist circumference (cm)	**Mean ± SD**	76.6 ± 1.6	77.1 ± 1.8	76.8 ± 1.7	0.34
	Range	74- 79	75 -80	74-80	

Table 2: Comparison between different studied groups regarding symptoms before and after treatment.

		Inositol group (N=52)	Metformin group (N=52)	Inositol and metformin group (N=52)	P value
Oligomenorrhea (Before treatment)	**Number (%)**	23 (44.20%)	20 (38.5%)	21 (40.4%)	0.89
Oligomenorrhea (After treatment)		14 (26.9%)	12 (23.1%)	9 (17.3%)	0.49
P value		**0.001**	**0.001**	**0.001**	
Amenorrhea (Before treatment)	**Number (%)**	16 (30.80%)	15 (28.8%)	17 (32.7%)	0.97
Amenorrhea (After treatment)		10 (19.2%)	9 (17.3%)	6 (11.5%)	0.53
P value		**0.001**	**0.001**	**0.001**	
Hirsutism score (Before treatment)		**18.9±4**	**18.9±4**	**18.8±3**	0.9
Hirsutism score					

		Inositol group (N=52)	Metformin group (N=52)	Inositol and metformin group (N=52)	P value
(After treatment)		**14.6±3**	**17.4±3**	**12.3±2**	**0.001**
P value		**0.001**	0.06	**0.001**	
Acne (Before treatment)	**Number (%)**	**13 (25%)**	**14 (26.9%)**	**13 (25%)**	0.96
Acne (after treatment)	**Number (%)**	**8 (15.4%)**	**9 (17.3%)**	**6 (11.5%)**	0.69
P value		**0.001**	**0.001**	**0.001**	

Table 3: Comparison between different studied groups regarding lipid profile before drug intake.

		Inositol group (N=52)	Metformin group (N=52)	Inositol and metformin group (N=52)	P value
Cholesterol (mg/dl)	**Mean ± SD**	187.1±36.3	185.6±36.1	179.8±38.5	0.573
	Range	100.2-264	100.2-264	100.2-264	
Triglycerides (mg/dl)	**Mean ± SD**	169.6±33.6	168.9±34.4	169.5±34.2	0.994
	Range	109-246	109-246	109-246	
HDL (mg/dl)	**Mean ± SD**	34.1±3.2	33.5±3.4	34.5±3.9	0.543
	Range	30-38	29-40	30-44	
LDL (mg/dl)	**Mean ± SD**	161.8±31.6	163.1±29.2	164.1±29.1	0.929
	Range	102-223	102-223	102-223	

HDL = High-density lipoprotein, LDL = low-density lipoprotein.

Table 4: Comparison between different studied groups regarding lipid profile after drug intake.

		Inositol group (N=52)	Metformin group (N=52)	Inositol and metformin group (N=52)	P value	P value
Cholesterol (mg/dl)	**Before**	187.1±36.3	185.6±36.1	179.8±38.5	0.573	
	After	153.3±29.8	168.4±28.7	162±28.9	0.032	P1=0.009 P2=0.132 P3=0.26
P value		**0.001**	**0.001**	**0.001**		
Triglycerides (mg/dl)	**Before**	169.6±33.6	168.9±34.4	169.5±34.2	0.994	
	After	121.1±25.3	122.1±28.3	120.4±26.5	0.948	
P value						

		Inositol group (N=52)	Metformin group (N=52)	Inositol and metformin group (N=52)	P value	P value
		0.001	**0.001**	**0.001**		
HDL (mg/dl)	**Before**	34.1±3.2	33.5±3.4	34.5±3.9	0.543	
	After	43.5±6.4	44.1 ±6.2	49.2±7.2	0.003	P1=0.431 P2=0.001 P3=0.001
P value		**0.001**	**0.001**	**0.001**		
LDL (mg/dl)	**Before**	161.8±31.6	163.1±29.2	164.1±29.1	0.929	
	After	125.1±23.9	125.5±23.6	128.1±25.4	0.795	
P value		**0.001**	**0.001**	**0.001**		

HDL = High-density lipoprotein, LDL = low-density lipoprotein. P1= Inositol group and metformin group, P2= Inositol group and inositol and metformin group, P3= metformin group and inositol and metformin group.

Table 5: Comparison between different studied groups regarding hormonal profile after drug intake**.**

		Inositol group (N=52)	**Metformin group (N=52)**	**Inositol and metformin group (N=52)**	**P value**
FSH (miu/ml)	**Before**	6.1±1.9	6.09±1.8	6.09±1.9	0.999
	After	5.2±0.7	5.2±1.3	5.1±0.7	0.94
P value		**0.001**	**0.001**	**0.002**	
LH (miu/ml)	**Before**	8.6±4.1	8.6±4.1	8.7±4.2	0.982
	After	7.5±1.9	7.6±3.4	7.2±2.5	0.785
P value		**0.025**	**0.035**	**0.021**	
Total testosterone (ng/ml)	**Before**	2.6±1.1	2.7±1.1	2.7±1.2	0.948
	After	2.5±0.4	2.4±0.5	2.5±0.4	0.634
P value		0.355	0.106	0.283	
DHEAs (ug/dl)	Before	274.7±36.1	272.9±37.9	271.2±38.2	0.724
	After	195±25.6	204±24.3	199.7±24.9	0.642
P value		**0.001**	**0.001**	**0.001**	

FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, DHEAs: dehydroepiandrosterone sulfate.

DISCUSSION

Polycystic ovaries on ultrasonography, oligomenorrhea, and amenorrhea signs of hyperandrogenism are the hallmarks of PCOS [20]. Its pathophysiology is still unknown, although it is thought to be complex, involving genetics, insulin resistance, hyperinsulinemia, and other endocrinological disorders. A key element in the pathogenesis of PCOS is insulin resistance and the resulting hyperinsulinemia. Insulin acts directly in the ovary and indirectly in the pituitary gland, stimulating the ovaries to produce more androgen [21].

Resolving the symptoms of androgen excess and controlling menstrual cycles are the main objectives of treatment for PCOS patients who do not wish to become pregnant. Because of

their effectiveness in treating acne and hirsutism and their ability to shield the endometrium from the damaging effects of estrogen, oral contraceptives (OCs) are the recommended option. However, OCs may have negative effects on coagulability, vascular reactivity, insulin resistance, and glucose tolerance [22].

Insulin-sensitizing medications are frequently used to treat PCOS, particularly when hyperinsulinemia and insulin resistance are present. Metformin is a well-researched antidiabetic biguanide derivative that increases peripheral insulin sensitivity, decreases gastrointestinal glucose absorption, and inhibits gluconeogenesis. A stereoisomer of carbon-6 sugar alcohol and a member of the vitamin B group, myoinositol is an intracellular secondary messenger that affects cell morphogenesis and cytogenesis through lipid synthesis, cell membrane structure, and cell development [21, 23].

According to research, myoinositol stimulates the enzymes that control the metabolism of glucose, and in PCOS patients, a lack of it has been connected to insulin resistance. In PCOS patients with insulin resistance, myoinositol treatment has been demonstrated to improve ovulation and lower insulin and testosterone levels [24].

The obstetrics and gynecology department of Zagazig University Hospitals conducted this prospective, randomized, controlled, comparative clinical investigation on PCOS patients. Three groups of patients were formed: Group 1 was given 1g of inositol twice a day for six months. For six months, Group 2 was given 500 mg of metformin three times a day. Group 3: 52 cases per group received 500 mg of metformin three times a day and 1g of inositol twice a day for six months.

Demographic and Baseline Characteristics

The uniformity of baseline parameters strengthened the validity of our comparisons, as our study groups did not exhibit any significant disparities in demographic features.

Clinical Symptoms Improvement

Menstrual abnormalities significantly improved in all three of our study's treatment groups, but the combination therapy had the strongest impact. **Nordio and Proietti [25]** observed similar results, concluding that combination treatment was superior in managing menstrual periods.

This is consistent with the study conducted by **Ravn et al. [26]** to compare the effects of Myoinositol and Metformin (MET) monotherapy in Danish women with PCOS who were not trying to conceive. They found that the length of the menstrual cycle was positively impacted by both MET and myoinositol (MI).

Previous research by **Legro et al. [27]** showed that 88% of PCOS individuals experienced improvements in their menstrual periods after receiving myoinositol medication for six months. Similarly, **Gerli et al. [28]** discovered that following 14 weeks of myoinositol medication, 70% of PCOS patients had a normal menstrual pattern.

Ferriman-Gallwey scores significantly decreased after six months of treatment, according to studies examining hirsutism scores with myoinositol treatment in PCOS **[29].**

Gudović et al. [30] They sought to ascertain how myo-inositol (MI) affected hyperandrogenism, normal menstrual cycles, and insulin resistance (IR) in women with PCOS. They stated that both drugs demonstrated a noteworthy proportion of efficacy in controlling the cycle. Compared to 3.3% in the MET group, 6.7% of MI individuals had regular cycles at the start of the research. 90% and 93.3%, respectively, had a regular cycle at the end of the test ($p < 0.001$). They imply that the frequency of normal menstrual periods did not differ statistically significantly between patients receiving MI and MET.

In our investigation, the metformin group (Group 2) showed only modest improvement, with scores falling from 18.7 ± 4 to 17.4 ± 3 ($p = 0.06$), whereas the inositol group (Group 1) exhibited a considerable improvement in hirsutism ratings, going from 18.9 ± 4 to 14.6 ± 3 ($p = 0.001$). The greatest improvement was seen in Group 3, which received combination therapy; their scores dropped from 18.8 ± 4 to 12.3 ± 2 ($p = 0.001$). These results demonstrate how well combination therapy works to lower hirsutism in PCOS-afflicted women.

In their study **Matossian et al. [31]** reported similar synergistic effects. **Karadağ et al. [21]** showed that the short-term effects of myoinositol, metformin, and their combination on

hirsutism in PCOS patients did not differ significantly. After just three months of treatment, they discovered a statistically significant decrease in Ferriman-Gallwey scores in each of the three groups. This early reaction implies that the observed improvement was a result of weight reduction and lifestyle modifications brought about by the three-month treatment plan.

Metabolic Parameters

Lipid Profile

Although to differing degrees, all therapy groups in our study showed notable changes in their lipid profiles. The inositol group's total cholesterol levels dropped significantly from 187.1 ± 36.3 to 153.3 ± 29.8 mg/dL, the metformin group's from 185.6 ± 36.1 to 168.4 ± 28.7 mg/dL, and the inositol and metformin group's from 179.8 ± 38.5 to 162 ± 28.9 mg/dL. All groups experienced steady drops in triglyceride levels, which reached between 120 and 122 mg/dL after therapy. Both HDL and LDL levels showed notable improvements as well; the inositol and metformin groups achieved more balanced HDL levels (49.2±7.2 mg/dL) than the inositol and metformin groups (43.5±6.4 and 44.1±6.2 mg/dL, to be exact). These results imply that although lipid profiles were improved by all treatments, combination therapy produced the most thorough and well-rounded gains.

In the study by **Shokrpour et al. [32]** When compared to metformine, oinositol supplementation significantly improved triglyceride and VLDL-cholesterol levels in women with PCOS, according to a 12-week randomized controlled trial. **Zhang et al. [33]** demonstrated that myo-ins may be more effective than metformin at lowering TG. **Karadağ et al. [21]** showed that the short-term effects of myoinositol, metformin, and their combination on lipid profiles in PCOS patients did not differ significantly. Similar short-term metabolic effects were identified by a meta-analysis comparing metformin with myoinositol **[34].**

Hormonal Profile

All treatment groups in our study showed significant decreases in FSH, LH, and DHEA levels, with post-treatment FSH levels averaging between 5.1 and 5.2 mIU/mL for all groups. The combined therapy group (Group III) had the lowest post-treatment LH levels (7.2 ± 2.5 mIU/mL), with LH levels also declining significantly. There were not much changes in total testosterone levels.

Accordingly, it has been demonstrated that myoinositol functions as a second messenger in the FSH signaling pathway, suggesting that it directly affects ovulatory activity **[35]. Facchinetti et al. [36]** stated that there were no differences in the effects of myoinositol and metformin on short-term hormone levels. **Zacchè et al. [37]** found that following three months of myoinositol administration, both free and total testosterone levels significantly decreased.

The comparison of two treatments (MET and MI) in a major meta-analysis of RCTs revealed no statistically significant change in testosterone levels between the two drugs ($p = 0.922$). **[38]. Greff et al. [39]** found that when compared to a placebo, inositol therapy caused a larger drop in both free and total testosterone.

Gudović et al. [30] Examine how the treatment affects the endocrine system, specifically the levels of total testosterone (TT), luteinizing hormone (LH), and follicle-stimulating hormone (FSH). The LH/FSH ratio did not significantly improve, although other hyperandrogenism markers showed a statistically significant improvement.

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Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interest.

CONCLUSIONS

Our research offers proof of the superior effectiveness of inositol and metformin combination therapy in treating PCOS symptoms. This combination may be used as the main therapeutic approach for PCOS patients, especially those with more severe symptoms of the syndrome, given the synergistic effects seen in treating monthly irregularities, hirsutism, acne, and metabolic parameters.

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