Original Article

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Comparison of Metformin and Myoinositol on Clinical, Hormonal and Metabolic Profile of Patients with Polycystic Ovarian Syndrome: An Open-label Randomised Clinical Trial

Obstetrics and Gynaecology Section

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ABSTRACT

Introduction: The prevalence of Polycystic Ovarian Syndrome (PCOS), one of the common endocrine disorders among women of reproductive age, varies from 2.2% to 26% globally. The treatment for PCOS aims to reduce Body Mass Index (BMI), improve underlying hormonal disturbances, prevent future reproductive and metabolic complications, and enhance the quality of life.

Aim: To evaluate the efficacy of metformin and Myoinositol (MI) on the metabolic, hormonal, and clinical profiles in PCOS.

Materials and Methods: An open-label randomised clinical trial was conducted at the Department of Obstetrics and Gynaecology, SRM Medical College Hospital and Research Centre, Kattankulathur, Chengelpet, Tamil Nadu, India, from January 2019 to May 2020. The study included 80 women with PCOS who were randomly assigned to two groups. One group received metformin 1500 mg/day (in three divided doses), while the other group received MI 1 gram/day for three months. At the end of the 12-week therapy, the participants were evaluated for changes in clinical, metabolic, and hormonal profiles. The data were analysed using Statistical Package for Social Sciences (SPSS) version 20.0. Descriptive statistics such as frequency, proportion, mean, and standard deviation were used for quantitative data.

Results: Both the metformin and MI-treated groups showed a significant reduction in BMI, fasting blood glucose, and fasting insulin. Both drugs were equally effective in changing the hormonal profile. There was a significant improvement in lipid parameters in both groups, with High-density Lipoprotein (HDL) levels being more significantly raised in the metformin group. The post-treatment HDL values in the metformin group were 75.69±19.16 mg/dL compared to 41.43±6.18 mg/dL in the MI group ($p<0.0001$). Both groups demonstrated similar efficacy in improving menstrual regularity, with 60% of the patients in the metformin group and 65% in the MI group having regular cycles at the end of treatment. Among infertility patients, the conception rate was 40% in the metformin group and 25% in the MI group ($p=0.70$).

Conclusion: Both drugs were equally efficient in improving the clinical, metabolic, and hormonal profiles in PCOS. Metformin was found to be superior to MI in improving fertility and increasing HDL levels.

Keywords: Fertility, Menstrual cycle, Myoinositol

INTRODUCTION

Polycystic Ovarian Syndrome (PCOS), a diverse multisystemic condition affecting women of reproductive age, is characterised by anovulation (oligomenorrhoea/amenorrhoea), hyperandrogenism (hirsutism, acne, alopecia), and Insulin Resistance (IR) [1]. PCOS is diagnosed using the Rotterdam criteria, which require the presence of any 2 of the following: 1) Oligoovulation and/or anovulation; 2) hyperandrogenism; 3) Polycystic ovarian morphology observed through ultrasound, after excluding other related disorders [2]. The prevalence of PCOS ranges between 2.2% and 26% globally and 3.7% to 22.5% among women of childbearing age in India [3]. IR and resulting hyperinsulinemia play a key role in the pathogenesis of anovulation and hyperandrogenism, contributing to a range of metabolic disorders like obesity, type 2 diabetes mellitus, hypertension, dyslipidemia, and gonadal dysfunction. Additionally, it significantly increases metabolic and cardiovascular morbidity in women [3].

The management of PCOS is multidisciplinary and should be individualised to address the presenting clinical symptoms while considering long-term consequences through a customised approach. The treatment aims to reduce BMI, improve underlying hormonal disturbances, prevent future reproductive and metabolic complications, and enhance the quality of life [4].

Since IR and hyperinsulinemia play a major role in the pathophysiology of PCOS, the use of insulin sensitizers such as Metformin, thiazolidinediones, and inositols may be vital in its management [5]. Metformin, the standard treatment for PCOS worldwide, reduces glucose absorption from the gastrointestinal tract, suppresses gluconeogenesis, and promotes peripheral insulin sensitivity. It decreases IR by activating Glucose Transporters (GLUT), facilitating the entry of glucose into hepatic and skeletal muscle cells, reducing hepatic gluconeogenesis, and promoting the oxidation of free fatty acids [6]. Metformin affects ovarian function by improving insulin sensitivity and inhibiting androgen synthesis by theca cells, directly impacting ovarian steroid hormone synthesis [7]. However, its use is restricted mainly by gastrointestinal side-effects [8].

In recent research, the role of Myoinositol (MI) in the pathophysiology of PCOS has gained attention. MI, previously classified as part of the vitamin B complex group and a well known dietary supplement, is now being used as evidence-based medicine for PCOS treatment. Among the numerous inositol isomers, MI and D-Chiro Inositol (DCI) are known to have insulin-simulating properties and are considered beneficial in managing PCOS. The enzyme epimerase converts MI to DCI and maintains a physiological ratio, which varies across different tissues. A ratio of 40:1 is considered physiological for most tissues. In PCOS, hyperinsulinemia attenuates the function of epimerase, leading to an imbalance in the DCI-to-MI ratio.

This diminishes the efficiency of MI-mediated FSH signaling and promotes hyperandrogenism [9].

They exhibit their action by promoting insulin transmembrane signaling, and recent studies have revealed that they remarkably activate the enzymes that control glucose metabolism [10].

As insulin sensitisers, both metformin and MI correct the metabolic and hormonal parameters, eventually leading to improvements in menstrual irregularities and hyperandrogenism, and aiding in conception. However, studies have shown variable responses to these treatments [11-14].

Metformin has been found to significantly decrease fasting glucose and insulin levels in PCOS patients but is associated with gastrointestinal side-effects [7,8]. Literature has also shown that inositol has a beneficial effect in PCOS patients due to its action on insulin sensitivity. However, the main drawback is its expense, and the usual dosage studied is 2-4 grams per day [9,10]. Furthermore, the correlations between hormonal levels (Luteinising Hormone [LH] and Follicle Stimulating Hormone [FSH]) with metformin and MI have not been extensively studied in women with PCOS. Hence, the objective of the study was to compare the efficacy of insulin sensitizers metformin and MI at a lower dose of 1 gram per day in improving the hormonal (Day 2 serum LH levels, FSH levels, and LH/FSH ratio), metabolic (lipid profile, fasting blood glucose, and fasting insulin), and clinical (menstrual pattern and BMI) outcomes in PCOS patients. The study also compared the pregnancy rates of both metformin and MI-treated PCOS women who were anxious to conceive.

MATERIALS AND METHODS

This open-label randomised clinical trial was conducted in the Department of Obstetrics and Gynaecology, SRM Medical College Hospital and Research Centre, Kattankulathur, Chengelpet, Tamil Nadu, India , during the period of January 2019 to May 2020, after obtaining institutional ethical committee clearance (1516/IEC/2018).

Inclusion and Exclusion criteria: Women diagnosed with PCOS according to the Rotterdam criteria [2], aged between 18 and 40 years, and willing to participate in the trial were registered. Women suffering from any neoplastic disease, acute liver disease, or endocrine disorders like hyperprolactinemia, Cushing's disease, and thyroid disorders were excluded. Pregnant, lactating women, and women with a recent history of hormone or antidiabetic drug use were also excluded.

Sample size calculation: The sample size was calculated using the formula:

$N=\{Z(1-\alpha)+Z(1-\beta)\}^2(\sigma1^2-\sigma2^2)/(M1-M2)^2$

where,

M1-Mean fasting glucose/insulin (MI group)

M2-Mean fasting glucose/insulin (Metformin group)

Z (1-α)-Type 1 error=2.58

Z (1-β)-Type 2 error=2.33 (99% confidence interval)

σ-standard deviation

$N=\{Z(1-\alpha)+Z(1-\beta)\}^2(\sigma1^2-2^2)/(M1-M2)^2$

$=(2.58+2.33)^2((1.032+0.472)/1)/(7.87-6.90)^2$ [12]

=33 in each group

Thus, the minimal sample size required was 33 per group.

Study Procedure

A detailed history and clinical examination were performed after getting informed consent from the participants, and the following parameters were noted: age, parity, marital status, menstrual abnormalities, and BMI. At the time of enrollment, the following laboratory investigations were performed: fasting blood glucose, fasting insulin, day 2 FSH, LH, LH/FSH ratio, and fasting lipid profile.

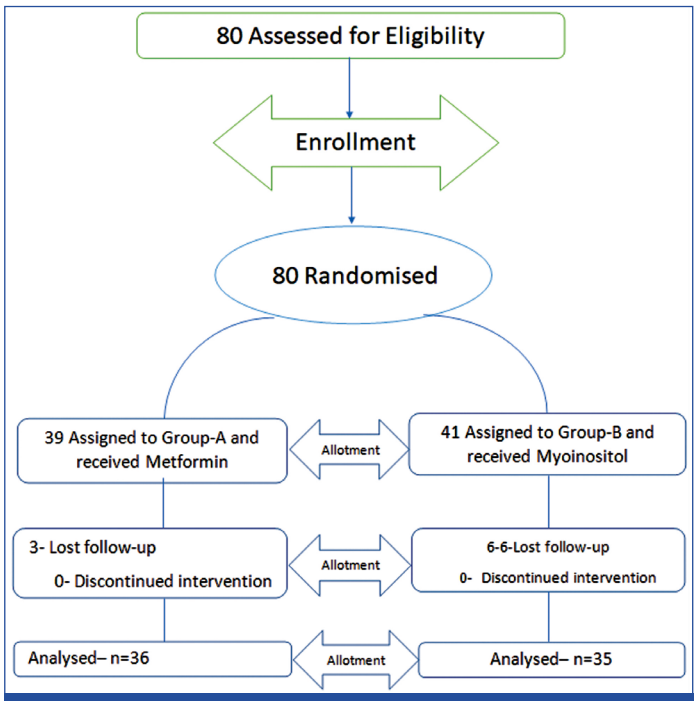
Using a computer-generated random number table, patients were assigned to both groups. Group A received tablet Metformin 500 mg three times a day [12], and Group B received tablet MI one gram per day for 12 weeks. After 12 weeks, the improvement in clinical parameters was noted, and the laboratory investigations were repeated. The metabolic parameters (fasting blood glucose, fasting lipid profile), clinical parameters (BMI, menstrual regularity, fertility), and hormonal parameters (FSH, LH, fasting insulin) were compared between the two groups.

STATISTICAL ANALYSIS

The data were analysed using SPSS version 20.0. Descriptive statistics such as frequency, proportion, mean, and standard deviation were used for quantitative data. The Chi-square test was used to compare the proportions between the groups, unpaired t-test to compare means between the groups, and paired t-test to compare the means before and after intervention.

RESULTS

Out of the 80 PCOS patients recruited in the trial, 39 were assigned to Group A and 41 were assigned to Group B through randomisation with a computer-generated number table. Three participants in Group A and six in Group B were lost to follow-up and dropped out of the study. The remaining 36 in Group A and 35 in Group B successfully completed the treatment [Table/Fig-1].



[Table/Fig-1]: Consolidated Standards of Reporting Trial (CONSORT) flowchart.

Age, baseline BMI, hormonal, and biochemical parameters were comparable between the metformin and MI-treated groups. The mean age was 25.11±3.21 years in the metformin group and 24.94±3.88 years in the MI group. Among the study population in the metformin group, 27.77% were anxious to conceive, while in the MI group, it was 11.4%. All PCOS patients in the study had menstrual irregularity [Table/Fig-2].

There was a significant reduction in BMI in both groups following treatment (p=0.0001). Both fasting blood glucose levels and fasting insulin significantly reduced in both the metformin and MI groups (Fasting Blood Glucose levels p=0.0001 in Group A, p=0.005 in Group B). Total cholesterol, triglycerides, LDL cholesterol decreased, and HDL cholesterol increased significantly post-treatment in both groups [Table/Fig-3].

In comparing the post-treatment BMI, mean fasting blood glucose, fasting insulin, and FSH between the metformin and MI-treated

Parameters	Group A (n=36)	Group B (n=35)	p-value
Mean age (years)	25.11±3.21	24.94±3.88	0.73
Married	22 (61%)	15 (43%)	0.18
Unmarried	14 (39%)	20 (57%)	
BMI (kg/m²) n (%)			0.55
<18.5	0	0	
18.5-24.9	13 (36%)	17 (48%)	
25-29.9	18 (50%)	13 (37%)	
>30	5 (13%)	5 (15%)	
Menstrual irregularity n (%)	36 (100)	35 (100)	-
Infertility n (%)	10 (27.77%)	4 (11.4%)	0.06
Mean fasting blood glucose (mg/dL)	92.17±12.63	96.06±13.13	0.17
Mean fasting insulin (µu/mL)	24.06±5.36	23.5±4.61	0.87
Mean LH (IU/mL)	7.48±2.67	6.37±2.33	0.02*
Mean FSH (IU/mL)	13.26±4.54	11.83±3.03	0.07
Mean LH/FSH ratio	0.62±0.29	0.54±0.16	0.3
Mean total cholesterol (mg/dL)	185.36±28.12	187.29±26.25	0.70
Mean triglycerides (mg/dL)	143.1±18.53	144.43±15.72	0.86
Mean high density cholesterol (mg/dL)	39.44±10.29	39.51±6.31	0.72
Mean low density cholesterol (mg/dL)	125±19.81	129.34±14.91	0.32

[Table/Fig-2]: Baseline profile of the studied population.
*p<0.05- statistically significant Values presented as mean±SD

groups, no significant difference was noted. The post-treatment BMI was comparable in both the metformin and MI groups (p=0.36). The reduction in fasting blood glucose was also not found to be statistically significant in both groups (p=0.24). The fall in mean LH level was significantly greater in the MI group compared to the metformin group (7.80±2.78 vs. 5.77±2.27 IU/mL, p=0.001). There was a statistically significant reduction in post-treatment total cholesterol, LDL, and triglyceride (TGL) values in both groups, but the levels of reduction were not statistically different between the two groups. There was a statistically significant elevation in HDL levels post-treatment in the metformin group (p=0.0001) [Table/Fig-4].

At the end of treatment, 22 (60%) patients resumed their cycle regularity in the metformin-treated group, and 20 (65%) patients in the MI-treated group. There was no significant difference in the resumption of cycle regularity between metformin and MI (p=0.86) [Table/Fig-5].

Among the 36 patients in the metformin group, 22 were married, and at the end of 12 weeks, 50% conceived spontaneously. Out of the 11 patients who conceived, four were being evaluated for infertility. Similarly, in the MI group, among 35 patients, 15 were married, and at the end of 12 weeks, 4 (26.66%) had conceived spontaneously. Out of the four patients, one was undergoing infertility evaluation. The conception rate among infertility patients was 40% for the metformin group and 25% for the MI group [Table/Fig-6]. No significant difference was noted between the two groups (p=0.70).

Parameters	Group A (Metformin)			Group B (Myoinositol)		
	Pretreatment	Post-treatment	p-value	Pretreatment	Post-treatment	p-value
BMI (kg/m²)	25.64±3.46	23.49±3.34	0.0001*	25.69±3.79	24.28±3.89	0.0001*
Fasting blood glucose (mg/dL)	92.17±12.63	89.89±12.86	0.0001*	96.06±13.13	93.60±13.76	0.005*
Mean fasting insulin (µu/mL)	24.06±5.36	22.75±5.25	0.0001*	23.50±4.61	20.18± 4.31	0.0001*
Mean LH (IU/mL)	7.48±2.67	7.80±2.78	0.002*	6.37±2.33	5.77±2.27	0.0001*
Mean FSH (IU/mL)	13.26±4.54	14.41±4.18	0.018	11.83±3.03	12.68±3.44	0.0001*
Mean LH/FSH ratio	0.62±0.29	0.56±0.18	0.116	0.54±0.16	0.45±0.14	0.0001*
Mean total cholesterol (mg/dL)	185.36±28.12	178.19±26.76	0.0001*	187.29±26.25	174.06±29.40	0.003*
Mean triglycerides (mg/dL)	143.11±18.53	135.72±18.30	0.0001*	144.43±15.72	136.37±15.13	0.0001*
Mean high density cholesterol (mg/dL)	39.44±10.29	75.69±19.16	0.0001*	39.51±6.31	41.43±6.18	0.003*
Mean low density cholesterol (mg/dL)	125.00±19.81	119.81±19.75	0.0001*	129.34±14.91	122.77±14.86	0.0001*

[Table/Fig-3]: Comparison of pre and post-treatment metabolic and hormonal characteristics in Group A and Group B.
*p<0.05- statistically significant

Parameters	Group A (Metformin)	Group B (Myoinositol)	p-value
BMI (kg/m²)	23.49±3.34	24.28±3.89	0.36
Fasting blood glucose (mg/dL)	89.89±12.86	93.60±13.76	0.24
Mean fasting insulin (µu/mL)	22.75±5.25	20.18± 4.31	0.06
Mean LH (IU/mL)	7.80±2.78	5.77±2.27	0.001*
Mean FSH (IU/mL)	14.41±4.18	12.68±3.44	0.06
Mean LH/FSH ratio	0.56±0.18	0.45±0.14	0.42
Mean total cholesterol (mg/dL)	178.19±26.76	174.06±29.40	0.53
Mean triglycerides (mg/dL)	135.72±18.30	136.37±15.13	0.87
Mean high density cholesterol (mg/dL)	75.69±19.16	41.43±6.18	0.0001*
Mean low density cholesterol (mg/dL)	119.81±19.75	122.77±14.86	0.478

[Table/Fig-4]: Comparison of post-treatment metabolic and hormonal characteristics between Group A and Group B. Values presented as mean±SD.
*p<0.05- statistically significant

Menstrual irregularity	Irregular Menstrual cycles (Pretreatment)	Regular cycles (Post-treatment)	Comparison between pre and post-treatment (p-value)	Comparison between Group A and B (post-treatment) (p-value)
Group A (n=36)	36	22	0.0001*	0.8631
Group B (n=35)	35	20	0.0001*	

[Table/Fig-5]: Comparison of menstrual regularity pre and post-treatment between Group A and Group B.
*p<0.05- statistically significant

Group	Conceived	Infertility		Without infertility	
Group A -Metformin (22)	11 (50%)	10		12	
		Conceived	Didn't conceive	Conceived	Didn't conceive
		4 (40%)	6 (60%)	7 (58.33%)	5 (41.67%)
Group B -Myoinositol (15)	4 (26.66%)	4		11	
		Conceived	Didn't conceive	Conceived	Didn't conceive
		1 (25%)	3 (75%)	3 (27.27%)	8 (72.73%)

[Table/Fig-6]: Comparison of conception post-treatment between Group A and Group B.

DISCUSSION

In the present study, both metformin and MI were equally effective in improving the clinical, metabolic, and hormonal profile in PCOS patients. BMI was significantly reduced in both the metformin and MI groups after 12 weeks of treatment (p=0.0001). This finding was supported by Awalekar J et al., who showed that BMI in both groups significantly reduced after three months of treatment, but the dose of MI was 2 g/day, higher than in the present study [15].

In the study by Genazzani AD et al., a combination of alpha-lipoic acid (400 mg) and MI 1g was given every day for a period of 12 weeks. BMI decreased following treatment with alpha-lipoic acid and MI by 0.50 kg/m^2 [16]. In contrast, in this study, the BMI reduced by 2.15 kg/m^2 in the metformin group and 1.41 kg/m^2 in the MI group, even without the combination with alpha-lipoic acid (400 mg). Though there was a significant decrease in BMI in both groups, the decrease was not significant when post-treatment BMI was compared between both drugs (p=0.360) [Table/Fig-4].

The findings were similar to the study by Nehra J et al., in which the comparison of MI and metformin was not statistically significant at the end of 12 and 24 weeks (p=0.001) [12]. Thus, both drugs are equally effective in reducing BMI.

The present study showed a significant decrease in fasting blood glucose from 92.17±12.63 to 89.89±12.86 mg/dL in the metformin-treated group and from 96.06±13.13 to 93.60 mg/dL in the MI-treated group following 12 weeks of treatment. Costantino D et al., showed that the fasting plasma insulin and glucose concentration did not change significantly with MI [17]. The results of this study were comparable to Nehra J et al., where there was a decrease in fasting blood sugar in both groups [12].

In both the metformin and MI treatment groups, fasting insulin was significantly reduced. However, in Angik R et al.,'s study, there was a significant reduction in fasting insulin in the MI group and a non-significant reduction in the metformin group [18].

There was a significant rise in LH in Group A (p=0.002) following treatment, but a significant reduction was noted following treatment in Group B (p=0.0001). Similarly, there was a rise in FSH following treatment in both groups, though the rise was significant in the MI group (p=0.0001). Despite contradictory results for both LH and FSH, there was a fall in the LH/FSH ratio in both Group A and Group B following treatment. The LH/FSH ratio was significantly reduced in Group B (p=0.0001). However, in Nehra J et al.,'s study, there was a fall in the LH/FSH ratio by 0.48 in the MI group, whereas in the metformin group, the fall was greater (0.60) after 12 weeks [12].

In the study by Costantino D et al., the triglyceride levels were decreased by 100 mg/dL (52%) and total cholesterol levels were decreased by 39 mg/dL post-treatment in the MI group, whereas there was not much change in the control group [17]. Similarly, a significant reduction in cholesterol was noted following treatment in both the metformin and MI groups in the present study (p=0.0001 and p=0.003). However, the effect was achieved with a lesser dose of MI compared to the above study. Nehra J et al., observed a rise in HDL value in both the MI and metformin-treated groups, but metformin was more effective in increasing HDL levels compared to MI (p=0.0001) [12].

In the present study, the most common clinical presentation was menstrual irregularity, and this irregularity significantly improved after 12 weeks of treatment with both modalities of treatment. This finding was supported by Nagaria T et al., where 90.09% of cases showed improvement in menstrual irregularities [19]. Ravn et al., also found that the effect on cycle length was comparable in both the metformin and MI groups [20].

The clinical pregnancy rate was 50% with metformin and 26% with MI after six months of treatment. Several studies support the fact that both MI and metformin can significantly improve fertility in women with PCOS by decreasing insulin resistance (IR). In a study by Papaleo E et al., 40% of patients conceived after treatment with MI at a dose of 2 gm/day [21]. Raffone E et al., reported a clinical pregnancy rate of 26% with metformin and 28.9% in the MI group when using a dose of 4 grams MI/day [22]. Although some studies have shown better results in fertility outcomes with MI, the present study observed a better clinical pregnancy rate with metformin compared to MI [20,23].

While the usual dose of MI used for PCOS is 2-4 gm/day, the present study used 1 gm of MI to reduce the cost of the drug. Fewer studies have examined the efficacy of lower dosages of the drug. In a study by Chirania K et al., the use of 1 gm of MI resulted in the resumption of spontaneous menstrual cycles in 66.66% of women with menstrual complaints, and 57.14% of infertile women conceived without the need for ovulation induction [24].

Thus, similar to a previously reported study [25], the results of combined therapy with metformin and MI in women with PCOS and IR seem promising.

Limitation(s)

Limitations of the study include a smaller sample size and some patients being lost to follow-up due to the Coronavirus Disease-2019 (COVID-19) pandemic. The long-term effects of the drugs were not studied.

CONCLUSION(S)

In conclusion, both metformin and MI, which are insulin sensitisers, equally improve clinical and metabolic parameters in PCOS patients. MI has a better impact on hormonal parameters, while metformin has a better role in achieving a clinical pregnancy rate. Although both treatments are effective, MI has fewer side-effects. Future randomised trials with larger sample sizes are required to study the duration of treatment and understand the long-term effects of the drug.

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