

Comparison of Outcome of Metformin And Inositol on Hormonal Aspects in Women with Polycystic Ovaries: A Quasi-Experimental Study

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ABSTRACT

Objective: To individually assess the role of Metformin and Inositol in dealing with hormonal problems in terms of serum Luteinizing Hormone/ Follicular stimulating hormone ratio, serum prolactin and serum progesterone in females with polycystic ovarian disease over a period of one year.

Study Design: Quasi-experimental study.

Place and Duration of Study: Department of Gynaecology and Obstetrics, PAF Hospital Islamabad Pakistan, from Jul 2020 to Jul 2021.

Methodology: Patients (n=80) presenting with OPD were divided into two equal groups and followed over a period of six months. Group-A was given Tab Inositol 4g once daily, and Group-B was given Tab Metformin 500 mg three times daily. Over a period of three to six months, Metformin and Inositol were used to compare biochemical parameters such as serum Luteinizing Hormone/ Follicular stimulating hormone ratio, serum prolactin, and serum progesterone.

Results The results showed that Inositol has better results in terms of hormonal aspects, with a mean Luteinizing Hormone/ Follicular stimulating hormone ratio of 2.55 ± 0.02 at 6 months. At three and six months, the mean serum prolactin and mean serum progesterone were comparable in both groups.

Conclusion: Inositol has a better impact on hormonal aspects in women with polycystic ovarian disease by improving patients' biochemical profiles.

Keywords: Inositol, Metformin, polycystic ovarian disease.

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INTRODUCTION

Polycystic ovarian syndrome, characterised by anovulation, hyperandrogenism, infertility, or subfertility, and the typical ultrasound morphology of polycystic ovarian disease (PCOS).¹ affects almost 10% of women in their reproductive years.² It is associated with metabolic disturbances such as insulin resistance, dyslipidemia,³ and vascular and endothelial dysfunction. Infertility is noted in 72% of polycystic ovarian disease patients.⁴ 15-fold higher as compared to women without polycystic ovarian disease. Metabolic syndrome is found in almost 33% of women with PCOS.⁵ Metabolic changes in polycystic ovarian syndrome are associated with increased glucose intolerance, Type II Diabetes mellitus, and increased cardiovascular events in later stages of life. Resistance to insulin plays an important role in the development of clinical and metabolic disorders

related to PCOs. After binding, there is a problem with insulin signalling because the insulin receptor and insulin receptor substrate-1 have more serine phosphorylation than tyrosine phosphorylation. This alters the metabolic pathways in the ovaries and other common insulin targets. Insulin resistance leads to higher insulin production and stimulates ovarian androgen secretion, causing anovulation, amenorrhoea, and infertility.⁶ These androgens alter insulin action in target tissues, increasing visceral adipose tissue deposition in such patients. Besides lifestyle modifications,⁷ insulin-sensitizers have been proposed for treating PCOS.

A large number of studies show that Metformin has metabolic as well as reproductive benefits, which include a decrease in insulin and lipid levels, a reduction in weight, a control in blood pressure, a decrease in plasma androgen levels, the restoration of normal menstrual cyclical activity, and the restoration of ovulation.⁸ In addition to Metformin, other new insulin-sensitising agents containing Inositol have been suggested for treating patients with polycystic

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ovarian disease. Inositol is a compound with nine stereoisomers, two of which are myo-Inositol and D-chiroInositol. Myo and d-chiro-Inositol (DCI) balance metabolic deregulations associated with insulin resistance in different ways.⁹ Giving the Inositol isomers has been shown to improve the activity of insulin receptors, lower the amount of androgen in the blood, and help with metabolic disorders and glucose intolerance that are linked to insulin resistance.¹⁰ Various studies have shown that, in contrast to Metformin, which is associated with gastrointestinal side effects, no adverse effects were observed during treatment with Inositol.

Our study particularly aimed at a comparison of the effects of Metformin and Inositol in Asian women, with PCOs placing special emphasis on their hormonal profiles. The target population of our study, i.e., Asian women, has a high incidence of polycystic ovarian disease-related gynaecological issues, with subfertility being one of the most important social concerns. Such studies will enable future management improvisation in light of evidence-based statistics, particularly in the Asian population.

METHODOLOGY

The quasi-experimental study was conducted at the Department of Gynaecology, PAF Hospital Islamabad, from July 2020 to July 2021. The sample size was calculated using the WHO sample size calculator.¹¹ Approval was obtained from the Ethical Review Committee (via letter no. ERC/03).

Inclusion Criteria: Female patients of reproductive age group (age 18–40 years) reporting to Gynaecology OPD and diagnosed with PCOS based on their biochemical profiles and ultrasound scans, were included.

Exclusion Criteria: Females with multiple comorbidities, congenital adrenal hyperplasia, androgen-secreting tumours, and Cushing syndrome, were excluded.

The purpose of study was explained to participants, and written informed consent was obtained. The contact numbers of all patients were recorded for follow-up visits. Patients, were divided into two groups of 40 each via the computer generated table (Figure).

Patients were assigned to receive one of the two treatments: Group-A was advised 4g Inositol per day, and Group-B was given tablet Metformin 500 mg thrice daily, each for a period of six months. We

assessed the serum LH/FSH ratio, serum prolactin, and serum progesterone (hormonal parameters) at baseline, three-month intervals, and six-month intervals using laboratory investigations. These timings included measuring the serum LH/FSH ratio on day 2 of the menstrual cycle, measuring the serum Prolactin on any day of the menstrual cycle, and measuring the serum Progesterone on day 21 of the cycle to check ovulatory status via blood test.

Investigations were carried out at the PAF hospital laboratory. 2.5 ml of venous blood was collected in a plain tube (yellow top) containing a clot activator. Specialised chemistry Cobas e 411 analyzers were used to test all of the samples. These are fully automated analyzers that use patented Electromchemiluminescence-ECL technology for immunoassay analysis. The doctor wrote down the results of the above lab tests on Proforma.

Data was analysed on Statistical Package for the Social Sciences (SPSS) version 23.00. We looked at variables such as age, body mass index (BMI), and comorbid conditions and calculated their mean, standard deviation (SD), and frequencies. The independent sample t-test was applied to find out the mean difference in outcome variables between the two groups. The *p*-value of 0.05 or less was taken as significant.

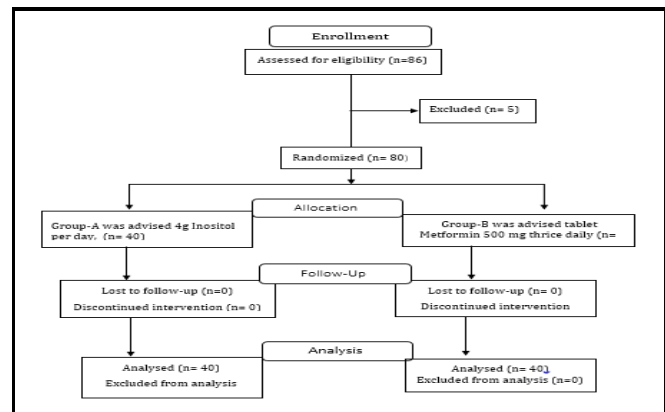


Figure: Patient Flow Diagram (n=80)

RESULTS

The study included a total of 80 patients. The mean age was 27.32±3.56 years, and the mean BMI of Group-A and Group-B was 25.85±1.88 and 27.42±0.47, respectively. 14(35%) patients in Group-A and 13(32.5%) patients in Group-B had positive family histories (Table-I).Table-II shows a comparison of

chemical biomarkers in the form of serum LH/FSH, serum prolactin, and serum progesterone. Patients taking tablet Inositol saw statistically significant improvements in serum LH/FSH ratio at 3 months (1.42±0.10) and 6 months (1.85±0.14), respectively. However, the Inositol and Metformin Groups had similar results when it came to serum Prolactin and Progesterone levels at 3 months and 6 months. The levels were 298.33±10.74 [mIU/L] and 45.28±1.05 [nmol/L], respectively.

Table-I: Characteristics of The Patients (n= 80)

Patient Variables	Mean±SD
Age (years)	27.32±3.56
Body Mass Index	
Group-A	28.4±3.1
Group-B	29.7±3.9
Positive family History of Polycystic Ovarian Syndrome n(%)	
Group-A	14(35%)
Group-B	13(32.5%)

with PCOS. This suggests that a problem with the precursors of IPG, such as Myo Inositol and D-chiro-Inositol, may cause compensatory hyperinsulinemia in most PCOS patients.^{14,15} which is seen in 30–40% of PCOS patients with normal BMI.¹⁶

Previous studies have shown that D-chiro Inositol accelerates glucose clearance and activates glycogen synthase in muscles beyond the maximal stimulation of insulin.¹⁷ Vyas *et al.* did a study on polycystic patients and found that using a combination of Inositol and chiro-Inositol made insulin resistance better and LH:FSH levels drop significantly (mean difference: 0.25; *p*=0.021).¹⁸ Similarly, a recent meta-analysis by Yuanyuan *et al.* has highlighted significant improvements in endocrine and metabolic indicators such as LH, FSH, serum LDL, and serum testosterone levels after the use of Metformin, along with significant improvements in BMI and waist circumference.¹⁸ The study by Nabi *et*

Table - II: Comparison of Biochemical Profile (n=80)

Duration	Serum Luteinizing Hormone to Follicular Stimulating Hormone Ratio (LH/FSH) (Mean±SD)			Serum Prolactin (Mean±SD) (mIU/L)			Serum Progesterone (Mean±SD) (nmol/L)		
	Group A n=40	Group B n=40	<i>p</i> -value	Group A n=40	Group B n=40	<i>p</i> -value	Group A n=40	Group B n=40	<i>p</i> -value
Baseline Investigation	2.58±0.07	2.74±0.05	0.045	366.7±24.1	402.8±4.4	0.692	38.4±0.75	40.5±0.46	0.787
3 Months interval	1.43±0.10	2.73±0.43	0.037	298.3±10.70	390.9±3.01	0.382	45.2±1.05	49.1±0.95	0.264
6 Months interval	1.85±0.13	2.53±0.09	0.025	253.4±6.10	372.1±3.70	0.192	47.8±0.89	56±0.80	0.504

DISCUSSION

PCOS is a multifaceted complex heterogeneous disorder affecting reproductive age as well as the adolescent population among females. The prevalence may vary depending on the diagnostic criteria used and the population being studied.¹² It is characterized by oligomenorrhea or amenorrhea, hyperandrogenism (clinical or biochemical), and polycystic ovarian morphology.¹³ which refers to the presence of 12 or more follicles in each ovary, ranging from 2–9 mm, or an ovarian volume greater than 10 ml, as per the Rotterdam criteria approved in 2003 by the American Society of Reproductive Medicine. At the receptor level, PCOs are linked to a derangement in insulin receptor phosphorylation, which serves as the foundation for the associated metabolic disorder. Several studies have shown that insulin sensitising drugs like Metformin and Inositol can help women

al. compared Inositol and Metformin in 102 obese women who were having trouble getting pregnant. The patients were split into three Groups: Metformin with a dose of 500 mg TDS, myo-Inositol with a dose of 2 g BD plus folic acid (5 mg OD), and a lifestyle change Group. The HOMA-IR index went down by 10.64 points in the Metformin Group, which was more than the Inositol Group.¹¹ Our study was unique in that it was the first to observe and compare the efficacy of Metformin and Inositol in this high-risk population of Pakistan. It's important to note that individuals with PCOs from the South Asian population exhibit more severe clinical manifestations of the disease and a higher level of insulin resistance compared to those from other ethnicities. Additionally, they tend to present at a younger age compared to other ethnic Groups.¹⁹ Furthermore, the proportion of women suffering from subfertility

secondary to PCOS is also higher in this population as compared to the western world. In our study, we looked at hormones over 3 months and found that serum prolactin levels were lower in the Group that took Inositol compared to the Group that didn't (298.33 ± 10.74 mIU/L versus 390.96 ± 3.01 mIU/L ($p=0.000$)). At 6 months, they were lower again, at 253.48 ± 6.16 mIU/L versus 372.18 ± 3.71 mIU/L ($p<0.001$). On the other hand, the parameter to detect ovulation showed remarkable improvement in the majority of patients, even after 3 months of starting medication. Mean serum Progesterone at baseline was 38.46 ± 0.75 nmol/L versus 40.55 ± 0.46 nmol/L ($p=0.000$), mean serum Progesterone at 3 months was 45.28 ± 1.05 nmol/L versus 49.17 ± 0.95 nmol/L ($p<0.001$), and mean serum Progesterone at 6 months was 47.80 ± 0.89 nmol/L versus 56.01 ± 0.80 nmol/L ($p<0.001$). It was further assumed that more improvement could be observed in terms of outcome by adding lifestyle modifications, particularly dietary control. Other agents, such as melatonin and lactalbumin, are also being studied in light of PCOS and can be added to future studies to further improve the efficacy of treatment for PCOD patients. Furthermore, adolescents were not included in this study, and future studies may include that age Group to further enhance its scope.

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CONCLUSION

Our study has concluded that Inositol significantly improved the hormonal profile of patients suffering from polycystic ovarian syndrome when compared to Metformin. This study shows that Inositol should be employed in the treatment of PCOS. A literature review has further demonstrated that Inositol plays a role in decreasing insulin resistance, but more research is required to clarify the mode of action.

Conflict of Interest: None.

Authors' Contributions

Following authors have made substantial contributions to the manuscript as under:

NT & GM: Conception of study, study design, drafting of manuscript and approval of final version to be published

MA: Data analysis, data interpretation, approval of final version to be published, critical review.

ST, AA & FI: Data acquisition, drafting of text, solicitation of approval of final version to be published

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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