ORIGINAL ARTICLE

Comparison of Efficacy between Myo-Inositol versus Metformin in Women with Polycystic Ovary Syndrome

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ABSTRACT

Objective: To compare the effectiveness of myo-inositol versus metformin in treating women with polycystic ovary syndrome.

Study Design: Cross-sectional study.

Place and Duration of Study: The study was carried out at the Department of Gynae Unit II, Dr. Ruth. K.M. Pfau Civil Hospital Karachi, Pakistan from 7th February 2019 to 6th August 2019.

Methods: All eligible patients who visited the hospital were enrolled. The group-Aincluded females who received myo-inositol (n=35), whereas the group-B included females who received metformin (n=35). Females in the myo-inositol group were administered 1 gram of myo-inositol twice daily, while those in the metformin group were administered 500 mg of metformin twice daily. Regular follow-up visits were scheduled every two months, and the efficacy of the treatment was assessed after six months. Efficacy was evaluated in terms of the normalization of menstrual cycles and the achievement of ovulation.

Results: The mean age in the myo-inositol and metformin groups was 23.92±3.70 and 23.68±4.23, respectively. The mean weight in the myoinositol and metformin groups was 59.23±2.07 and 61.79±5.92, respectively. Notably, the efficacy rates for the myo-inositol and metformin groups were 68.57% and 20%, respectively with *p*-value=0.001.

Conclusion: Myo-inositol was found to demonstrate significant superiority over metformin in the treatment of polycystic ovary syndrome.

Keywords: *Hyperandrogenism, Metformin, Menstrual Cycle, Polycystic Ovary Syndrome.*

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Introduction

Polycystic Ovary Syndrome (PCOS) stands as one of the prevailing endocrinological disorders among women in their reproductive years, with an estimated prevalence of 2-26%.[1,2] This syndrome manifests as a multifaceted and diverse complex, encompassing hyperandrogenism (either clinically observable or biochemically detectable), ovarian irregularities such as oligo/anovulation or the presence of polycystic ovaries, while simultaneously ruling out related disorders. It is important to note that PCOS can manifest without overt signs of hyperandrogenism.[3,4]

PCOS was firstly identified by Stein et al. in 1931, which is characterized by oligomenorrhea, anovulation or oligoanovulation, excessive ovarian androgen secretion, and insulin resistance.[5] Clinical

manifestations include hirsutism, acne, irregular menstrual cycles, and alopecia.[1,4] PCOS not only rises the infertility risk but also increases concerns about dysfunctional uterine bleeding, endometrial carcinoma, and risk factors for cardiovascular disease, including hypertension, dyslipidemia and insulin resistance.[1,6,7] This increased risk of cardiovascular disease (CVD) could be associated with increased incidence of metabolic syndrome in this population. The complex pathogenesis of PCOS remains incompletely understood, attributed to a mix of genetic and environmental factors. Notably, insulin resistance arises from defects in both the insulin receptor and the post-receptor components of the insulin signaling pathway.[8,9]

Metformin, an insulin-sensitizing drug with hepatic selectivity, is known for its multiple benefits, including cholesterol reduction, weight loss, and regulation of endothelial function. In addition, it helps ovarian function in insulin-resistant women while avoiding the risks of hypoglycemia or hyperinsulinemia.[10,11] On the other hand, myo-inositol, a naturally occurring component of the vitamin B complex, is crucial for insulin sensitivity. In cases of myo-inositol deficiency, insulin sensitivity is compromised, which is especially relevant given the known insulin signaling pathway defects present in PCOS. The structural support that myo-inositol provides for a number of secondary messengers, such as phosphatidyl inositol 3-kinase (PI 3-kinase), which is essential for increased insulin sensitivity and decreased insulin resistance, adds to its significance. Consequently, myo-inositol has shown efficacy in achieving ovulation in 79% of women with PCOS.[12]

Building upon this, a randomized comparative study by Riju Angik et al. reported an ovulation rate of 36.84% for myoinositol versus 33.33% for the metformin group in women with PCOS.[13] A systematic review indicated 69.5% efficacy for the myoinositol group versus 21% for the metformin group ($p = 0.001$).[14] The direct influence of insulin on ovarian steroidogenesis and its inhibitory effect on insulin-like growth factor binding protein 1 (IGFBP-1) and sex hormone binding globulin (SHBG) further underscores the interconnectedness of insulin and androgen levels.[14]

While international studies have compared myoinositol and metformin efficacy in PCOS, limited local studies within our unique context are available. Differences in race, socioeconomic status, education, and environmental factors make it imperative to investigate these treatments in our population. So, the aim of current study is to compare the effectiveness of myo-inositol versus metformin in treating women with polycystic ovary syndrome presenting at tertiary care hospital. This study not only contributes new insights for gynecologists but also addresses the specific needs of our demographic. It aids in discerning the superior treatment option and management for improved care of women with PCOS.

Methods

The observational study was conducted at the Department of Gynae Unit II, Dr. Ruth. K.M. Pfau Civil Hospital Karachi, Pakistan from 7th February 2019 to 6th August 2019 after taking ethical permission from the hospital vide letter no: GYN-139-19, dated 05th February 2019. The determination of the sample size was facilitated through the WHO sample size calculator. By utilizing the observed efficacy rates of 69.5% for the myoinositol group[14] and 21% for the metformin group,[14] significance level of 5%, and a test power of 80%, the initial calculated sample size was set at n=16 for each group. Considering potential attrition, a sample size of n=35 was included in each group. Eligible participants were infertile females within the reproductive age bracket of 16-40 years, diagnosed with PCOS. PCOS was diagnosed using criteria such the existence of 12 or more follicles in each ovary that were 2 to 9 mm in diameter and/or an elevated ovarian volume (>10 mL; estimated using the formula 0.5 x length, breadth, and thickness) as assessed by ultrasonography.

Exclusions from the study encompassed females already receiving alternative drug treatments for PCOS (e.g., oral contraceptive pills), those with abnormal kidney function (serum creatinine greater than 1.4 mg/dL) or liver function tests (SGPT greater than 35), individuals undergoing medical or surgical interventions for thyroid disorders, and those with a history of hypersensitivity to myoinositol or prior surgery or irradiation therapy. The selection of participants was accomplished through the Non-probability, Consecutive Sampling method.

Data collection commenced following ethical committee approval. Participants were divided into two groups i.e. group-A (n=35) or group-B (n=35). Written informed consent was obtained before enrollment. Females in exposed group were administered 1 gm of myoinositol two times per day, while females in group-B administered 500 mg metformin tablets two times per day.

Throughout the study, participants were scheduled for follow-up visits every two months, with the outcome variable being efficacy assessed after six months of drug therapy. Effectiveness of the drug was gauged by the normalization of menstrual cycles (cycles lasting < 35 days) and the achievement of ovulation (mid-luteal phase progesterone levels exceeding 3.0 ng/mL) within the six-month timeframe.

Data compilation was overseen by a researcher under the supervision of a consultant with more than five years of experience. Collected information was then entered into a pre-designed form. Statistical analysis took place using the SPSS Version 23. For quantitative variables like age, height, weight, and BMI, mean and SD were computed. Efficacy was expressed in frequencies and percentages. The comparison of efficacy between the two groups utilized the Chi-square test/Fisher exact test. A two-sided *p*-value of less than 0.05 was considered indicative of statistical significance. Additionally, age and BMI stratification were performed to control confounding factors or effect modifiers, evaluated through Chi-square test/Fisher exact test to ascertain their impact on the outcome variable, with a two-sided *p*-value less than 0.05 deemed as significant.

Results

Mean age of females in myo-inositol group was 23.92 years and in metformin group was 23.68 years. Similarly, the mean weight, height and BMI values were also calculated for both groups and displayed in Table 1.

The efficacy of myo-inositol and metformin treatments was compared in terms of achieving the desired outcomes. In the myo-inositol group, 68.57% of participants experienced efficacy (achieved outcomes), while in the metformin group, only 20.0% achieved the desired outcomes. The difference in efficacy between the two groups was found to be highly significant (p = 0.001) using the Chi-square test.

Table 1: Descriptive statistics of baseline characteristics in both groups

Groups	Parameter	MEAN	±SD
Group-A Myoinositol (n=35)	Age (years)	23.92	3.70
	Weight [kgs]	59.23	2.07
	Height [cm]	157.03	6.06
	BMI [kg/m^2]	24.63	3.32
Group-B Metformin (n=35)	Age (years)	23.68	4.23
	Weight [kgs]	61.79	5.92
	Height [cm]	162.73	7.32
	BMI [kg/m2]	25.44	2.68

In the 16-25 age group, 24.5% of participants in the myo-inositol group achieved the desired outcomes compared to 43.1% in the metformin group. In the >25 age group, 23.2% in the myo-inositol group achieved the desired outcomes compared to 35.7% in the metformin group. These differences were found to be statistically significant (p = 0.002 and p = 0.022, respectively) using Fisher's Exact test. Moreover, in the 18-25 BMI group, 24.5% of participants in the myo-inositol group achieved the desired outcomes compared to 43.1% in the metformin group. In the >25 BMI group, 23.2% in the myo-inositol group achieved the desired outcomes compared to 35.7% in the metformin group. These

differences were statistically significant (p<0.001 and p = 0.055, respectively) using Fisher's Exact test.

Table 2: Comparative analysis of efficacy among both groups

Groups	Yes	No	Total	*P*-value
Group A (Myoinositol)	24 (68.57%)	11 (31.43%)	35	0.001
Group-B (Metformin)	7 (20%)	28 (80%)	35	

Table 3: Stratified analysis of efficacy among both groups

Age Group	Group	Efficacy		*P-Value*
		Yes	No	
16-25 years	MYOINOSITOL	18 (24.5%)	7 (17.6%)	0.002
	METFORMIN	5 (43.1%)	15 (14.7%)	
> 25 years	MYOINOSITOL	6 (23.2%)	4 (33.9%)	0.022
	Metformin	2 (35.7%)	13 (7.1%)	
BMI categories				
18-25 kg/m^2	MYOINOSITOL	16 (24.5%)	6 (17.6%)	0.001
	METFORMIN	4 (43.1%)	18 (14.7%)	
>25 kg/m^2	MYOINOSITOL	8 (23.2%)	5 (33.9%)	0.055
	METFORMIN	3 (35.7%)	10 (7.1%)	

Discussion

PCOS usually leads to metabolic disturbances, infertility, and various long-term health complications.[4,15] The management of PCOS involves a multidisciplinary approach, including pharmacological interventions, lifestyle modifications, and sometimes assisted reproductive technologies.[4,15] Among pharmacological options, two commonly used treatments are Myo-Inositol and Metformin.[16-19] This study was also conducted to compare the efficacy of these two treatments in women with PCOS.

In the current study, the mean age of the females within the myoinositol group was 23.92±3.70, while the metformin group exhibited a mean age of 23.68±4.23. This aligns closely with a similar study by Sadia et al., where the mean ages for the myo-inositol and metformin groups were documented as 24.6±3.22 and 23.12±7.40 years, respectively.[20] Nehra et al. also reported the mean age as 23.8±0.69 in myoinositol group and 23.26± 1.03 in metformin group.[21]

The efficacy of myo-inositol and metformin in PCOS management has been extensively studied, yielding variable results.[14,16-22] Some trials suggest that both treatments are comparable in terms of restoring ovulatory function, improving insulin sensitivity, and reducing androgen levels. However, other studies highlight potential differences in their mechanisms of action and effectiveness.[14,16-22]

Ravn et al. found the decrease in length of menstrual cycle in myoinositol group as compared to metformin group (9 days versus 13 days, p=0.03).[22] Sadia et al. found a significant improvement in all symptoms in both groups at 3rd and 6th month after treatment. Furthermore, they found myo-inositol was associated with lesser adverse events as compared to metformin.[20] Shivani et al. reported after six months of treatment, there was a decrease in PCOs in 50% of females who received metformin, whereas, 80% decrease in PCOs was observed in females who received myoinositol. Hence, they concluded myoinositol is useful in reducing endocrine abnormalities in PCOS patients.[17] Redigor et al. administered combination of myoinositol and folic acid for the duration of 2 to 3 months and found that this combination treatment was superior than metformin.[16] Kutenaei et al. conducted a systematic review of 9 studies and found no differences in the ovarian function and hormonal profile between metformin and myo-inositol group. However, they found myo-inositol could be beneficial for fertility outcomes by modulating hyperandrogenism.[18] Another systematic review by Bodepudi et al. also

found that myo-inositol was more efficacious than metformin for treating PCOS for hormonal, clinical, glycemic, lipid, and insulinemic benefits, as well as it has better tolerance and minimal side effects than metformin.[19] Our study's strengths lie in its carefully selected participant population, rigorous statistical methodologies, and comprehensive exploration of treatment efficacy. The robustness of our findings is bolstered by the clear superiority of myo-inositol over metformin in achieving desired outcomes, aligning with previous research. Stratifying results by age and initial BMI provides a nuanced understanding of treatment responses and offers personalized insights for clinical decision-making. However, our study has limitations. The relatively small sample size and focus solely on female participants with PCOS limit generalizability, warranting caution in applying results to broader populations. To address these limitations, future research should adopt prospective designs, and explore mechanistic underpinnings of age and BMI-dependent responses. Additionally, expanding treatment comparisons and considering emerging options will ensure more informed and tailored interventions, advancing patient care and clinical knowledge

Conclusion

Myo-inositol is significantly better than metformin in the treatment of polycystic ovary syndrome. However, further comprehensive research, encompassing larger sample sizes across multiple study centers in Pakistan, is imperative to validate and corroborate our study's outcomes. This endeavor would enhance our understanding of the therapeutic landscape for this prevalent disorder and guide future clinical practice.

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Authors Contribution

NL: Idea conception, study designing, data collection, data analysis, results and interpretation, manuscript writing and proof reading
SR: Idea conception, study designing, data collection, data analysis, results and interpretation
MY: Idea conception, study designing, data collection, data analysis, results and interpretation
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