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Comparison of Combination Therapy of Myoinositol and Metformin with Myoinositol Monotherapy and Metformin Monotherapy in the Treatment of Polycystic Ovary Syndrome: A Prospective Randomized Controlled Trial

Ghazala Niaz¹, Riffat Ehsan², Farah Batool³, Ammara Niaz⁴, Ayesha Khalid⁵, Adnan Murtaza⁶

		Authors' Contribution
1	Assistant Professor, Department of Gynecology & Obstetrics, Faisalabad Medical University, Faisalabad Pakistan	Manuscript writing, Collection of data
2	Assistant Professor, Department of Gynecology & Obstetrics, Faisalabad Medical University, Faisalabad Pakistan	Literature search
3	Assistant Professor, Department of Gynecology & Obstetrics, Faisalabad Medical University, Faisalabad Pakistan	Manuscript writing, References
4	Assistant Professor, Department of Gynecology & Obstetrics, Faisalabad Medical University, Faisalabad Pakistan	Data analysis
5	Women Medical Officer, Department of Gynecology & Obstetrics, Allied Hospital-II, Faisalabad Pakistan	Data analysis
6	Senior Registrar, Department of Gynecology & Obstetrics, Allied Hospital-I, Faisalabad Pakistan	Proof reading
Dr. Ghazala Niaz Correspondence: Assistant Professor, Department of Gynecology & Obstetrics, Faisalabad Medical University, Faisalabad Pakistan Email: dr.ghazala.niaz@gmail.com		Submitted for Publication: 25-02-2026 Revision Received: 12-08-2026 Accepted for Publication: 19-08-2026

ABSTRACT

Background: Polycystic ovarian syndrome (PCOS) is a prevalent endocrine and metabolic disorder in women of reproductive age, characterized by reproductive, metabolic and hormonal disturbances. Metformin (MET) and myo-inositol (MI) are two frequently used drugs. **Objective:** To evaluate the effectiveness of combination therapy with MI and MET compared to monotherapy with either MI or MET in enhancing metabolic and reproductive outcomes in women with PCOS. **Study Design:** Prospective randomized controlled. **Settings:** Department of Gynecology & Obstetrics, FTH, Faisalabad Pakistan. **Duration:** Six months from 01-08-2025 to 31-01-2026. **Methods:** Study was performed with 122 women diagnosed with PCOS allocated in three groups: Group A (MI + MET, n=41), Group B (MI alone, n=41), and Group C (MET alone, n=40). Participants monitored for six months, including evaluations of menstrual regularity, body mass index (BMI), and pregnancy rates. **Results:** Combination therapy exhibited enhanced results across all endpoints. Menstrual regularity was most pronounced in Group A (80.5%), followed by Group B (73.2%) and Group C (70%). The greatest substantial drop in BMI occurred in Group A (25.0 ± 4.6 kg/m²), followed by Group B (23.9 ± 5.83 kg/m²) and Group C (25.12 ± 4.63 kg/m²). Group A exhibited the greatest pregnancy rates at 43.9%, compared to Group B at 34.1% and Group C at 27.5%. All intergroup disparities were statistically significant ($p < 0.001$). **Conclusion:** Combination therapy of MI and MET is significantly effective than either monotherapy in enhancing menstrual regularity, decreasing BMI and improving fertility in women with PCOS.

Keywords: PCOS, Myo-inositol, Metformin.

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INTRODUCTION

Polycystic ovarian syndrome is one of the most common endocrine disorders affecting women of reproductive age, with an estimated prevalence of 8-18% worldwide.¹ From 1990 to 2019 global burden of PCOS has increased approximately 32 million cases, contributing to a substantial healthcare burden, with annual economic costs of about 8 billion US dollars by 2020.^{2,3} Consistent with this global trend, Pakistan also faces a high burden of PCOS with an estimated overall prevalence of 26.7%, highlighting it as an important health care problem.⁴

The pathogenesis of PCOS is multifaceted, involving a complex interaction of genetic, environmental, and hormonal elements. Patients frequently demonstrate diminished insulin sensitivity,

resulting in compensatory hyperinsulinemia, which aggravates androgen production, ovulatory dysfunction, and metabolic problems.^{5,6} PCOS is diagnosed when a minimum of two of the following criteria are observed; irregular menstruation, clinically or biochemical hyperandrogenism, or the presence of polycystic ovaries as evidenced by ultrasonography. Not all patients display these characteristics, which may complicate diagnosis.^{7,8} PCOS term has recently been replaced by poly endocrine metabolic ovarian syndrome (PMOS). The revised terminology highlights that Polycystic Ovary Syndrome (PCOS) is a multisystem disorder rather than a condition limited to the ovaries.⁹

Due to complex nature of PCOS yet no single treatment is recommended, most of the patients are treated symptomatically. Metformin and myoinositol are among the most widely used treatment strategies. Metformin (MET), an insulin-sensitizing drug, is extensively utilized to raise insulin sensitivity, control menstrual cycles, and improve fertility in women with PCOS.¹⁰ By reducing hepatic glucose production and increasing insulin sensitivity, MET has been effective in boosting ovulation rates, decreasing androgen levels, and improved pregnancy outcomes in women with PCOS. Nonetheless, the efficacy of metformin may be limited, necessitating the exploration of combination therapies to improve treatment outcomes.^{11,12} Myo-inositol (MI), A naturally occurring isomer of inositol has demonstrated efficacy in enhancing insulin sensitivity, ovarian function, and fertility in women diagnosed with PCOS.¹³ MI has been suggested to function synergistically with metformin, augmenting its insulin-sensitizing properties and increasing reproductive outcomes.¹⁴ The significance of inositol-phosphoglycan mediators in insulin action has generated heightened interest throughout the past decade. MI enhances insulin signaling, lowers blood insulin levels, and diminishes serum testosterone, therefore reinstating normal ovulatory function.^{15,16}

Although growing evidence supports the efficacy of both MI and MET in the management of PCOS, further comparative research is needed to establish the optimal therapeutic approach. Therefore, this prospective randomized controlled trial aims to evaluate the effectiveness of MI plus MET combination therapy versus MI or MET monotherapy on BMI, menstrual cycle regularity and pregnancy rates in women with PCOS. The findings may help to guide clinical decision making and optimise the management.

METHODS

The study was a prospective randomized controlled trial conducted at the Department of Gynecology and Obstetrics, Faisalabad Teaching Hospital. Ethical approval was granted by the institutional Ethical Review Committee (Approval No. 48.ERC/FMU/2024-25/92) dated: 23-06-2025. A total of 122 female subjects were included in this study. The sample size for this study was calculated with the Open Epi calculator, based on the study by Karadag.⁷ A two-sided confidence interval of 95% and a study power of 80% were selected. The sample size formula used was $n = (Z_{\alpha/2} + Z_{\beta})^2 \times [(\sigma_1^2 + \sigma_2^2)] / \Delta^2$, where $Z_{\alpha/2}$ and Z_{β} represent the Z-values for the chosen confidence level and power, σ_1^2 and σ_2^2 are the variances in the two groups, and Δ is the clinically meaningful difference between group means to be detected. Inclusion criteria involved age 18-40 years, diagnosis with PCOS by Rotterdam criteria - including oligomenorrhea or anovulation, clinical or biochemical hyperandrogenism, or polycystic ovaries on ultrasound were enrolled. All participants were married and consented to a six-month follow-up. The exclusion criteria comprised recent administration of PCOS medicines, substances influencing insulin sensitivity, or refusal to participate. Upon acquiring written informed consent, comprehensive demographic, gynecological and menstruation histories were documented, followed by physical examinations including BMI assessment and laboratory evaluations,

including complete blood count, HbA1c, renal and liver function tests, and urinalysis. Participants were randomized into three treatment groups via a computer-generated software; Group A received a combined therapy of MI (2g) and MET (500mg) once a day; Group B received MI monotherapy (2g daily); and Group C received MET monotherapy (500mg daily). All groups were monitored on a monthly basis for a duration of six months. During each visit, menstrual cycle regularity was evaluated, BMI was recalibrated, and urine pregnancy tests were conducted. Positive pregnancy tests were validated with pelvic ultrasound. Patients recorded supplementary symptoms or problems utilizing a predefined proforma. Data were gathered, processed, and analyzed utilizing SPSS version 25.

RESULTS

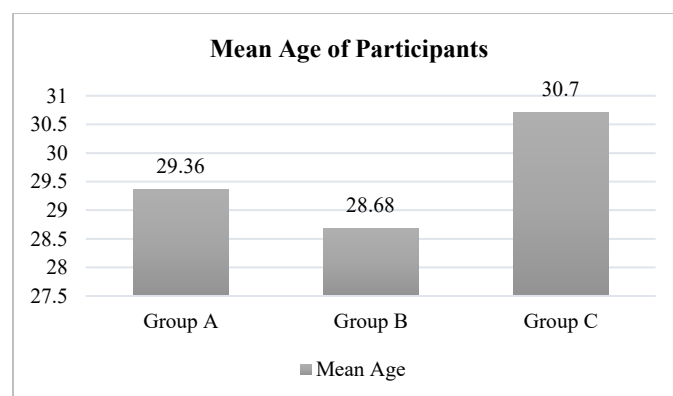
The research study was performed in the Department of Gynecology and Obstetrics at Faisalabad Teaching Hospital, involving 122 patients allocated to three independent groups. The study groups were nearly equal, consisting of 41 patients in Group A, 41 in Group B, and 40 in Group C.

The age was comparable among the groups, with all groups consisting of young female of reproductive age. In Group A, the mean age of patients was 29.36 ± 6.41 years; in Group B, it was 28.68 ± 5.79 years; and in Group C, the mean age was 30.70 ± 6.68 years. A slight but statistically significant difference in mean age was observed between the groups, shown by a p-value of 0.001. The age range differences confirm that all the groups were appropriately matched and representative of the PCOS population seeking therapy.

Table 1: Age based division of participants

Data	Group-A	Group-B	Group-C	P-value
Age (mean $\pm$ SD) years	29.36 $\pm$ 6.41	28.68 $\pm$ 5.79	30.70 $\pm$ 6.68	0.001
Numbers	41	41	40	

Figure 1: Mean age of participants by group



At the initial presentation, the distribution of patients by BMI categories was comparable among all three study groups Table 3. The mean baseline BMI values were similar throughout the groups, measured at 25.85 ± 4.92 kg/m² for Group A, 24.5 ± 5.06 kg/m² for Group B, and 25.77 ± 4.81 kg/m² for Group C. After six months of therapy, a decrease in mean BMI was noted

across all treatment groups, signifying a favorable metabolic response to the various treatments Table 2.

Table 2: BMI of participants at initial visit and at 6th month of treatment

Mean BMI	Group-A	Group-B	Group-C	p-value
At initial visit	25.85 ± 4.92	24.5 ± 5.06	25.77 ± 4.81	0.001
At 6 th month	25.0 ± 4.6	23.9 ± 5.83	25.12 ± 4.63	0.001

Figure 2: BMI of participants at initial visit and at 6th month of treatment

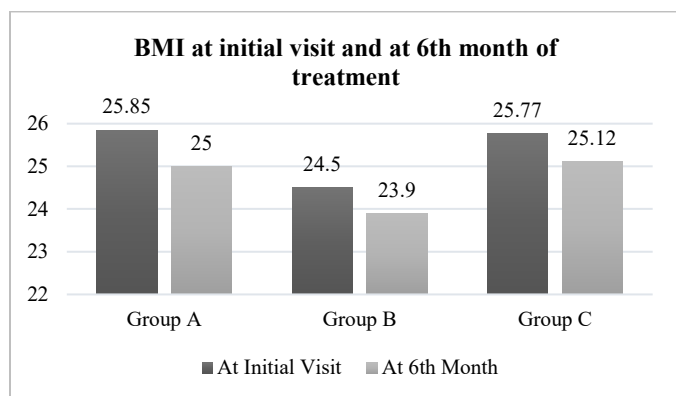


Table 3: BMI class-based division of participants

BMI class	Group A	Group B	Group C
Normal weight	13	13	12
Overweight	17	18	17
Obese	8	7	7
Underweight	3	3	4

At the initial phase of the trial, the majority of participants in all groups presented with menstrual irregularity, reflecting high prevalence of this hallmark feature of PCOS Table 4. After six months of treatment, a statistically significant improvement in menstrual regularity was observed across all three study groups. Regular menstruation was achieved in 33 patients (80.5%) in Group A, 30 patients (73.2%) in Group B, and 28 patients (70.0%) in Group C, while menstrual irregularity persisted in 8 (19.5%), 11 (26.8%), and 12 (30.0%) patients in Groups A, B, and C respectively.

Table 4: Menstruation status of participants at initial stage and at 6 month of therapy

Menstruation		Group-A N (%)	Group-B N (%)	Group-C N (%)	p-value
At initial visit	Irregular	36 (87.8%)	37 (90.2%)	36 (90.0%)	0.001
	Regular	5 (12.2%)	4 (9.8%)	4 (10.0%)	0.001
At 6 th month	Irregular	8 (19.5%)	11 (26.8%)	12 (30.0%)	0.001
	Regular	33 (80.5%)	30 (73.2%)	28 (70.0%)	0.001

Pregnancy rates differed significantly across the three study groups (Table 5). Within six months of treatment, pregnancy

was achieved by 18 of 41 patients (43.9%) in Group A, 14 of 41 patients (34.1%) in Group B, and 11 of 40 patients (27.5%) in Group C. Group A had the highest conception rate, with 18 out of 41 patients (43.9%) successfully achieving pregnancy within a 6-month period. Group B exhibited an intermediate outcome, with 14 out of 41 patients (34.1%) achieving pregnancy. Group C exhibited the lowest pregnancy rate, with 11 out of 40 patients (27.5%) successfully conceiving Table 5.

Table 5: Pregnancy status of participants at 6 month of therapy

Pregnancy status	Group-A N (%)	Group-B N (%)	Group-C N (%)	p-value
At 6 th month	18 (43.9%)	14 (34.1%)	11 (27.5%)	0.001

The research findings suggest that combination therapy (Group A) was associated with greater improvements in reproductive function, menstrual regularity, and BMI reduction than either monotherapy.

DISCUSSION

Polycystic ovary syndrome (PCOS) is one of the most common metabolic and endocrine disorder affecting women of reproductive age.¹⁷ Given the central role of insulin resistance in PCOS pathophysiology, insulin-sensitizing agents such as metformin and myo-inositol (MI), have gained considerable clinical importance in its management.⁹ Although numerous international studies have demonstrated the beneficial effects of metformin and MI individually, evidence regarding the efficacy of their combined use remains limited and have controversial results. Therefore, present study was conducted to evaluate the effectiveness of combined use of MI and metformin on BMI, menstrual cycle regularization and pregnancy rate in women with PCOS.

Life style modifications with weight reduction and physical activity remains the first-line management for overweight and obese women with PCOS, but in resistant cases metformin is frequently prescribed as an adjuvant treatment. In the present study significant reduction in BMI was observed in all 3 treatment groups, with pronounced decrease in the combined group. This finding is consistent with another study conducted in India comparing combined use of MI and MET versus monotherapy.¹⁸ In contrast Nehra *et al.* found no statistically significant difference in BMI when compared myoinositol with metformin.¹⁹ Similarly Chirania K *et al.*, reported significant reduction in BMI in groups treated with myoinositol (p=0.001) and metformin (p=0.001) but not in group treated with combination of metformin and myoinositol (p=0.687).²⁰ This discrepancy could be due to different study design, patient characteristics, treatment duration, and follow-up period. Nevertheless, our study findings suggest a possible synergistic effect of myo-inositol (MI) and metformin (MET) on weight-related metabolic outcomes in women with PCOS.

PCOS is associated with inappropriate hormonal signalling leading to higher-than-normal androgen levels and other hormonal imbalances. As a result, women with PCOS often experience irregular or infrequent menstrual periods. This irregular pattern is also observed in our study where majority of

participant in all three groups had menstrual irregularity before initiation of treatment (Table 4). Results of our study demonstrated improvement in regularization of menstrual cycle in all 3 groups with combined group achieving the most remarkable results (80.5%). Similar findings have been reported by Javanmanesh *et al.* and in another study where menstrual cycle regularization achieved in all groups 26%, 50%, and 80% with metformin, myoinositol and combined group respectively.^{21,22} Another study reported menstrual cycle regularization in 63.2% of women receiving metformin, 33.3% receiving myoinositol and 63.2% receiving combination therapy after 24 weeks of treatment. Although the effect of myoinositol therapy appeared to be less on regularization of cycle, but the difference was not statistically significant among groups (p value > 0.05).²³ Overall, these findings are consistent with the present study, supporting the beneficial effect of both metformin and myo-inositol on menstrual regularity. The superior results observed with combination therapy may be attributed to the complementary mechanisms of metformin and myo-inositol. Metformin acts by reducing hyperinsulinemia and ovarian androgen production, while myo-inositol enhances intracellular insulin signalling and ovarian function. This results in additive effects on restoring ovulation and menstrual regularity

PCOS is among the most frequently reported causative factor in the subfertility due to anovulation. In the present study pregnancy rates, a key indicator of reproductive outcome, differed across the study groups, indicating variations in effectiveness of therapeutic interventions. Group A achieved the highest conception rate (43.9%) within the six-month period, followed by Group B (34.1%) and Group C (27.5%). These findings are consistent with those of study conducted in Bangladesh which reported pregnancy rate of 43.75% in metformin plus MI and 25.00% in metformin only group.²⁴ The superior pregnancy rate observed with combination therapy may be attributed to its greater effect on improving insulin resistance compared with either monotherapy. Reduced hyperinsulinemia lowers level of free androgen, thereby promoting the normal follicular development and restoration of ovulation. In contrast, another study also reported a higher pregnancy rate with combination therapy (26.92% vs. 11.54%), but the difference was not statistically significant when compared between the two groups. This discrepancy may be explained by smaller sample size of that study population.²⁵

These results highlight the potential benefits of targeting complementary pathways involved in the pathophysiology of PCOS and improving the reproductive and metabolic outcomes.

CONCLUSION

The outcomes of this research suggest that combination therapy with metformin and myo-inositol is more effective than monotherapy in improving BMI, restoring menstrual regularity, and achieving higher pregnancy rates in women with PCOS. These findings support a paradigm shift in first-line therapy strategies, highlighting the importance of dual-pathway targeting to thoroughly tackle the complex pathophysiology of PCOS. Further large scale studies with longer follow up are warranted to confirm these findings.

LIMITATIONS

The limitation of our study is that it is a single-center investigation with a restricted patient population. Due to inadequate data on this topic, no standard exists for comparison with our research.

SUGGESTIONS / RECOMMENDATIONS

Based on the pronounced synergistic effects observed, it is recommended that a combination therapeutic approach, which simultaneously targets systemic insulin resistance and enhances ovarian insulin signaling, be considered a superior first-line strategy for managing PCOS in women of reproductive age. This regimen demonstrated the most favorable outcomes across key clinical endpoints, including significant BMI reduction, restoration of menstrual regularity, and improved pregnancy rates. Furthermore, developing clinical guidelines that integrate this combination therapy could significantly optimize metabolic and reproductive outcomes for the PCOS population.

FUNDING

Patients at Faisalabad Teaching Hospital in Ghulam Muhammadabad had access to all drugs and diagnostic tests. The entity is sponsored by the government; the patients didn't have to pay anything. The main investigator and her team paid for this task themselves and did it on their own.

CONFLICT OF INTEREST / DISCLOSURE

All authors declare that they have no conflict of interest to disclose.

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ETHICAL CONSIDERATIONS

This research complied with established ethical norms. All participants provided informed consent prior to registration, including assurance of private information and the ability to withdraw. Patient data were anonymized and securely archived. The values of beneficence and equitable recruitment were always maintained. All findings will be published transparently, and the study was subject to ongoing ethical and safety oversight to safeguard participant welfare.

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