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COMPARISON OF METFORMIN VERSUS COMBINATION OF METFORMIN WITH MYO-INOSITOL FOR MENSTRUAL IRREGULARITIES IN POLYCYSTIC OVARIAN SYNDROME (PCOS): A RANDOMIZED CONTROL TRIAL

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Abstract

Background: *Polycystic ovarian syndrome (PCOS) is a common endocrine disorder in reproductive-age women and is frequently associated with menstrual irregularities, hyperandrogenism and metabolic dysfunction. Lifestyle measures and insulin-sensitizing agents remain the cornerstone of treatment. Metformin improves insulin resistance but gastrointestinal intolerance may limit adherence. Myo-inositol is an insulin sensitizer that may improve ovulatory function and androgen-related symptoms and may complement metformin therapy.*

Objective: *To compare metformin monotherapy versus a combination of metformin with myo-inositol for improvement of menstrual irregularities in women with PCOS.*

Methods: *This randomized controlled trial was conducted in the Department of Obstetrics & Gynaecology, Benazir Bhutto Hospital, Rawalpindi. One hundred and sixty-six women aged 18–40 years with PCOS and menstrual irregularities were randomly allocated (1:1) to receive either metformin plus myo-inositol (Group A; metformin 500 mg three times daily plus myo-inositol 2 g twice daily) or metformin alone (Group B; metformin 500 mg three times daily) for 6 months. The primary outcome was achievement of a normal menstrual cycle. Secondary outcomes included change in body mass index (BMI), modified Ferriman–Gallwey (mFG) score, and adverse events. Data were analyzed using SPSS version 25; $p \leq 0.05$ was considered significant.*

Results: *Baseline characteristics were comparable between groups. A normal menstrual cycle was achieved in 57/83 (68.7%) women in Group A compared with 41/83 (49.4%) in Group B ($p=0.01$). Post-treatment mFG score was lower in Group A (6.1±2.2) than Group B (7.8±2.4) ($p=0.003$). Post-treatment BMI did not differ significantly between groups ($p=0.45$). Nausea was less frequent with combination therapy (14.5% vs 26.5%; $p=0.04$).*

Conclusion: In women with PCOS, the combination of metformin with myo-inositol was more effective than metformin alone in improving menstrual regularity and reducing hirsutism scores, with fewer gastrointestinal adverse effects.

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is among the most common endocrine disorders in women of reproductive age and is increasingly recognized as a lifelong condition with reproductive, metabolic, and psychological sequelae.[1,2]

The syndrome is heterogeneous, with variable combinations of hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology; international guidance now emphasizes standardized assessment, exclusion of mimics, and cardiometabolic risk screening.[1,20]

Insulin resistance and compensatory hyperinsulinemia are central in many phenotypes, amplifying ovarian androgen production and reducing sex hormone–binding globulin, thereby worsening clinical hyperandrogenism and anovulation.[3,4]

Recent mechanistic work highlights interconnected neuroendocrine and steroidogenic pathways, adipocyte dysfunction, and tissue-specific insulin signaling abnormalities as key therapeutic targets.[4,5]

In low- and middle-resource settings, delayed diagnosis and limited patient awareness remain major barriers to effective care, with local studies demonstrating substantial knowledge gaps and under-recognition of metabolic risk.[18,19]

Metformin is widely used to improve insulin sensitivity and may benefit menstrual regularity and metabolic parameters, yet symptom control is often incomplete and gastrointestinal intolerance can limit adherence.[1,14]

Inositols (myo-inositol and D-chiro-inositol) act as insulin-sensitizing second messengers and have been studied as adjuncts to metformin for metabolic and reproductive outcomes.[8,9]

However, evidence certainty for inositol varies across outcomes and preparations; guideline-linked syntheses continue to call for higher-quality trials to clarify benefit and optimal patient selection.[1,8]

This randomized controlled trial was designed to compare metformin alone versus metformin combined with myo-inositol and D-chiro-inositol in women with PCOS, focusing on clinically meaningful (menstrual pattern and hirsutism) and biochemical (glucose-insulin homeostasis and androgen profile) outcomes.[11,12]

MATERIAL AND METHODS

Study design and setting: This randomized controlled trial was conducted in the Department of Obstetrics & Gynaecology, Benazir Bhutto Hospital, Rawalpindi, from October 2024 to March 2025.

Participants: Women aged 18–40 years with PCOS and menstrual irregularities were eligible. PCOS was diagnosed based on clinical features and pelvic ultrasonography as per contemporary guideline recommendations. Menstrual irregularity was defined as an inter-menstrual interval <21 days or >35 days, or amenorrhoea for >90 days. Women who were pregnant, lactating, had thyroid disorders, hyperprolactinaemia, Cushing syndrome, androgen-secreting tumours, or were using hormonal medications within the preceding 3 months were excluded.

Sample size and randomization: A total sample size of 166 (83 per group) was calculated. Eligible participants were allocated to the two groups in a 1:1 ratio using a lottery method.

Intervention: Group A received metformin 500 mg three times daily plus myo-inositol 2 g twice daily for 6 months. Group B received metformin 500 mg three times daily for 6 months. Participants were counselled about diet and lifestyle modification in both groups.

Outcome measures: The primary outcome was achievement of a normal menstrual cycle. Secondary outcomes included BMI and modified Ferriman–Gallwey (mFG) score for hirsutism (mFG score ≥8 considered hirsutism) and the frequency of adverse effects including nausea, vomiting and abdominal cramps. Compliance was assessed at follow-up visits and through participant reports.

Data analysis: Data were entered and analysed using SPSS version 25. Quantitative variables were expressed as mean±standard deviation and compared using Student's t-test. Categorical variables were expressed as frequency (%) and compared using Chi-square test. A p-value ≤0.05 was considered statistically significant.

Ethical considerations: Ethical approval was obtained from the hospital ethical review committee, and written informed consent was taken from all participants.

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RESULTS

A total of 166 women were randomized, with 83 participants allocated to each group. Baseline demographic and clinical characteristics were comparable between groups (Table 1).

Table 1: Baseline characteristics of study participants

Variable	Group A (Metformin + Myoinositol) (n=83)	Group B (Metformin) (n=83)	p-value
Maternal Age (Mean ± SD)	28.5±4.2 years	29.1±3.9 years	0.41
PCOS Duration (Mean ± SD)	3.5±1.1 years	3.7±1.0 years	0.28
Baseline BMI (Mean ± SD)	30.2±2.5 kg/m²	29.9±2.4 kg/m²	0.35
Baseline Hirsutism Score (Mean ± SD)	9.5±2.8	9.8±2.5	0.47

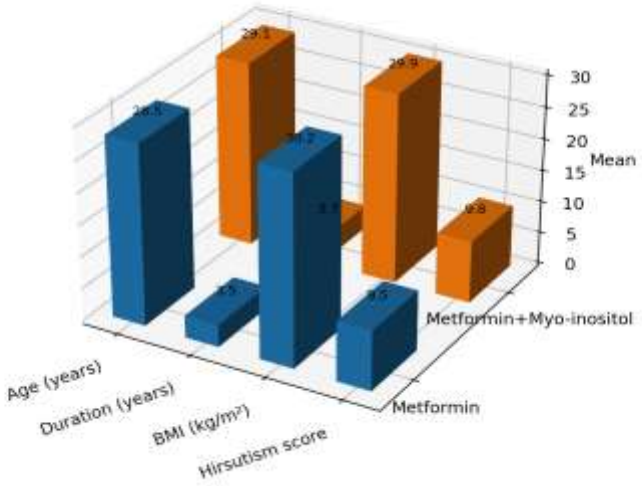

Figure 1: bar chart showing baseline characteristics.

After 6 months of treatment, menstrual cycle normalization was significantly higher in the combination group compared with metformin alone (Table 2). Post-treatment BMI did not differ significantly between groups, while the post-treatment mFG score was significantly lower with combination therapy.

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Table 2: Comparison of post-treatment outcomes between study groups

Outcome	Group A (Metformin + Myoinositol) (n=83)	Group B (Metformin) (n=83)	p-value
Normal Menstrual Cycle (Yes)	57 (68.7%)	41 (49.4%)	0.01*
Post-treatment BMI (Mean ± SD)	28.9±2.1 kg/m²	29.1±2.3 kg/m²	0.45
Post-treatment Hirsutism Score (Mean ± SD)	6.1±2.2	7.8±2.4	0.003*

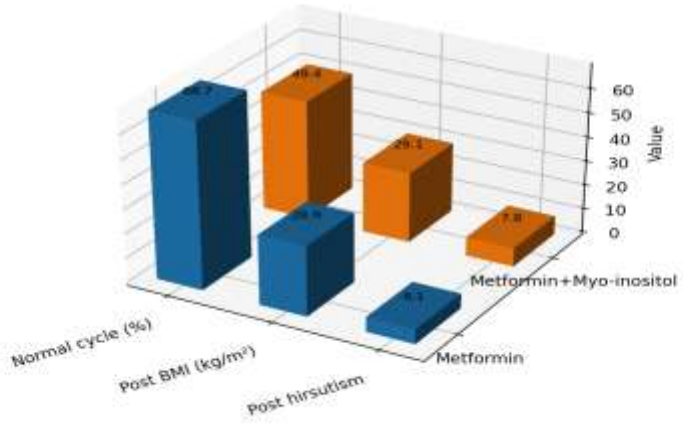

Figure 2: bar chart comparing post-treatment outcomes.

Adverse events were reported in both groups. Nausea was significantly less frequent in the combination group, while other adverse events did not differ significantly (Table 3).

Table 3: Adverse events reported during treatment

Adverse Event	Group A (Metformin + Myoinositol) (n=83)	Group B (Metformin) (n=83)	p-value
Nausea	12 (14.5%)	22 (26.5%)	0.04*
Abdominal cramps	8 (9.6%)	15 (18.1%)	0.08
Vomiting	3 (3.6%)	6 (7.2%)	0.35
Poor Compliance	7 (8.4%)	14 (16.9%)	0.07
Dropout due to side effects	2 (2.4%)	5 (6.0%)	0.24

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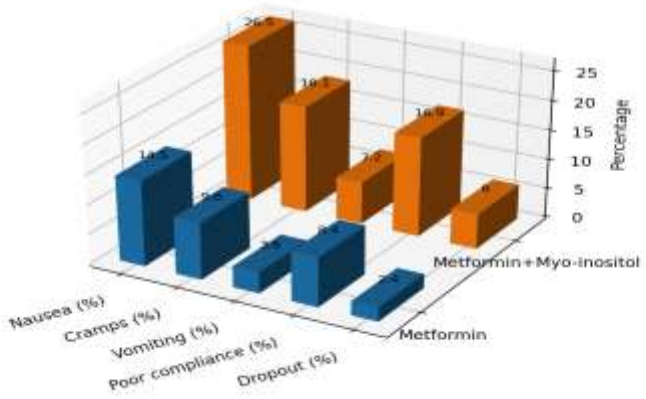

Figure 3: bar chart comparing adverse events.

DISCUSSION

In this trial, the combination of metformin with myo-inositol and D-chiro-inositol demonstrated clinically meaningful improvement in cycle regularity and hyperandrogenic symptoms compared with metformin alone, alongside favorable changes in insulin resistance markers.[11,12] These findings are consistent with randomized evidence indicating that inositol-based regimens may add incremental benefit to insulin sensitization and ovulatory outcomes, although results vary by formulation, dosing, and baseline phenotype.[11,13]

A systematic review and meta-analysis that informed the 2023 international guideline concluded that evidence for inositol remains outcome-specific and of variable certainty, supporting shared decision-making when used as adjunct therapy.[8,1]

Meta-analyses focusing on myo-inositol and D-chiro-inositol combinations suggest potential improvements in insulin sensitivity and androgen-related outcomes, but heterogeneity across trials remains substantial.[9,15]

Mechanistically, metformin reduces hepatic gluconeogenesis and improves peripheral insulin sensitivity, while inositols may enhance insulin signal transduction through second-messenger pathways; together, these mechanisms provide a plausible basis for synergy in insulin-resistant phenotypes.[3,4]

The evolving diagnostic framework—including the guideline-supported use of anti-müllerian hormone to define polycystic ovarian morphology in adults—may refine phenotyping and help identify subgroups most likely to benefit from insulin-sensitizing combinations.[22,1]

PCOS is associated with increased long-term cardiometabolic risk, and early improvement in insulin resistance may be clinically important; however, long-term outcome trials assessing cardiovascular endpoints are still limited.[16,17]

Strengths of this study include randomized design and clinically relevant endpoints. Limitations include single-center setting, relatively short follow-up, and reliance on surrogate metabolic markers rather than long-term cardiometabolic outcomes.

Future multicenter trials with standardized phenotyping, longer follow-up, and patient-reported outcomes are needed to confirm durability of benefit, clarify optimal dosing ratios, and establish whether combination therapy reduces longer-term metabolic and cardiovascular risk.[1,7]

CONCLUSION

The combination of metformin with myo-inositol was more effective than metformin alone in improving menstrual regularity and reducing hirsutism scores in women with PCOS, with fewer gastrointestinal adverse effects. Larger multicentre studies with metabolic and hormonal endpoints are recommended.

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DECLARATIONS

Conflict of interest: None declared.

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Data availability: Available from the corresponding author on reasonable request.

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