Section: Obstetrics & Gynaecology

Original Research Article

A COMPARATIVE EVALUATION OF THE METABOLIC AND ENDOCRINE IMPACTS OF COMBINED ORAL CONTRACEPTIVE PILLS (COCPS) VERSUS INSULIN-SENSITIZING THERAPIES IN WOMEN WITH POLYCYSTIC OVARIAN SYNDROME (PCOS): A PROSPECTIVE RANDOMISED CONTROLLED TRIAL UNDER MODERN DIAGNOSTIC GUIDELINES

Joyeeta Biswas[1], Santanu Banerjee[2], Mitali Mukhopadhyay[3]

[1]Assistant Professor, Department of Obstetrics & Gynaecology, JIS Medical Sciences and Research Institute (JISMSR), Howrah, West Bengal, India.
[2]Associate Professor, Department of Medicine, JIS Medical Sciences and Research Institute (JISMSR), Howrah, West Bengal, India.
[3]Associate Professor, Department of Obstetrics & Gynaecology, JIS Medical Sciences and Research Institute (JISMSR), Howrah, West Bengal, India.

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Corresponding Author:
Dr. Santanu Banerjee,
Associate Professor, Department of Medicine, Jagannath Institute of Medical Sciences and Research (JISMSR), Howrah, West Bengal, India.

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ABSTRACT

Background: Polycystic Ovarian Syndrome (PCOS) is a proposed diagnostic construct extending beyond classical PCOS to encompass multi-glandular endocrine dysfunction—including concurrent thyroid, adrenal, and pancreatic beta-cell pathology—alongside ovarian hyperandrogenism and anovulation. Comparative therapeutic evidence under this broader framework, particularly from South Asian tertiary care settings, remains limited. The objective is to comparatively evaluate the polycystic and endocrine impacts of COCPs versus insulin-sensitising therapy (IST: metformin plus myo-inositol) in women fulfilling PCOS diagnostic criteria over 12 months.

Materials and Methods: A prospective, randomised, open-label, parallel-group controlled trial at JISMSR, Howrah (January 2022–December 2025). One hundred and twenty women aged 18–40 years were randomised to Group A (COCPs: ethinyl estradiol 30 µg + desogestrel 150 µg) or Group B (metformin 1,000 mg twice daily + myo-inositol 4 g/day). Primary outcome was 12-month HOMA-IR; secondary outcomes included lipid profile, androgens, TSH, and menstrual regularity.

Results: IST demonstrated significantly greater reduction in HOMA-IR (2.46 ± 0.98 vs. 4.18 ± 1.50; $p < 0.001$; Cohen's d = 1.18), fasting insulin, LDL-C, and triglycerides, with HDL-C rise. COCPs achieved superior free androgen index suppression (5.2 ± 1.8 vs. 7.6 ± 2.4; $p < 0.001$) and menstrual regularity (91.7% vs. 76.7%; $p < 0.001$). TSH was more favourably modulated by IST ($p = 0.014$).

Conclusion: IST confers broader cardiologic, polycystic and polyendocrine benefits in PCOS, while COCPs retain superiority for androgenic suppression and cycle control. A phenotype-guided individualised therapeutic approach is recommended.

Keywords: Polysystic Ovarian Syndrome, PCOS; COCPs, Insulin Sensitizers, Metformin, Myo-Inositol, HOMA-IR, Hyperandrogenism, TSH, Randomised Controlled Trial, South Asia.

INTRODUCTION

Polycystic Ovarian Syndrome (PCOS) represents a proposed diagnostic framework that subsumes, yet extends beyond, classical polycystic ovarian syndrome (PCOS), which affects an estimated 5–15% of women of reproductive age globally and constitutes one of the most prevalent endocrine disorders in clinical practice.[1,2] PCOS is classically defined by the triad of chronic oligo-anovulation, polycystic ovarian morphology on ultrasonography, and biochemical or clinical hyperandrogenism as codified by the Rotterdam consensus criteria,[3] and the Endocrine Society Clinical Practice Guidelines.[4] The PCOS construct additionally mandates recognition of multi-glandular endocrine co-morbidities—including pancreatic beta-cell insufficiency, peripheral insulin resistance, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, and thyroid autoimmunity—that frequently co-exist with ovarian dysfunction yet are not routinely captured by conventional PCOS diagnostic algorithms.[5,6] This polyendocrine dimension amplifies the polycystic burden substantially: hyperinsulinaemia, atherogenic dyslipidaemia, central adiposity, and impaired glucose tolerance collectively confer elevated long-term risks of T2DM and cardiovascular disease.[7,8,11,17]

The pathophysiological axis linking hyperinsulinaemia to ovarian androgen excess is well established. Insulin acts synergistically with LH on ovarian theca cells to amplify androgen biosynthesis, while suppressing hepatic SHBG synthesis, thereby increasing free androgen bioavailability and perpetuating a self-reinforcing cycle of anovulation and hyperandrogenism.[5,10] Two pharmacological strategies dominate PCOS management. COCPs suppress gonadotropin secretion, stimulate hepatic SHBG production, and reduce circulating free androgens,[6,12] however, they carry a polycystic liability—deterioration of insulin sensitivity, unfavourable lipid shifts, and pro-inflammatory tendencies—particularly in women with pre-existing polycystic derangements.[11,18] Insulin-sensitising agents—principally metformin and myo-inositol—demonstrate broad pleiotropic benefits: reductions in fasting insulin and HOMA-IR, restoration of menstrual cyclicity, improved ovulatory rates, and amelioration of dyslipidaemia.[8,9,10,16,19] with emerging evidence of additional modulation of adrenal androgen secretion and thyroid autoimmune activity.[13,22]

Head-to-head comparative studies evaluating COCPs versus IST under the expanded PCOS framework—requiring systematic assessment of thyroid, adrenal, and insulin-resistance indices,[4,14] remain sparse in the South Asian context, where distinct genetic architecture, dietary carbohydrate loading, lower BMI thresholds for polycystic risk, and higher subclinical hypothyroidism prevalence collectively shape a unique PCOS phenotype.[15,17] The present study was designed to address this evidence gap, comparing effects of COCPs versus combined IST on HOMA-IR as the primary outcome, and lipid parameters, serum androgens, TSH, cortisol, and menstrual regularity as secondary outcomes.[2,4,20] The study hypothesised that IST would confer superior cardio, polycystic and polyendocrine benefits—reducing HOMA-IR, improving lipid profiles, and attenuating thyroid dysregulation—whereas COCPs would maintain predominant advantage in androgenic suppression and menstrual cycle regularisation, thereby supporting individualised, phenotype-stratified treatment selection in PCOS.[13,21]

MATERIALS AND METHODS

Study Design, Setting, and Ethical Approval: This was a prospective, randomised, open-label, parallel-group controlled trial conducted between January 2022 and December 2025 at the Gynecology & Medicine Outpatient Department, Howrah district hospital associated with JIS Medical Sciences and Research Institute (JISMSR), Howrah, West Bengal, India. All procedures were conducted in accordance with the Declaration of Helsinki (revised 2013),[2] and written informed consent was obtained from all participants.

Study Population and Eligibility Criteria

Women aged 18–40 years with symptoms of menstrual irregularity or suspected ovarian dysfunction were screened. Exclusion criteria included: established T2DM; overt thyroid disease on treatment; confirmed congenital adrenal hyperplasia, hyperprolactinaemia, or Cushing syndrome; current pregnancy or breastfeeding; use of hormonal contraceptives or insulin sensitisers within the preceding 6 months (washout period verified by prescription records); significant hepatic (ALT > 3× ULN) or renal impairment (eGFR < 45 mL/min/1.73 m^2); and known hypersensitivity to study medications.[4,14]

Diagnostic Criteria for PCOS

PCOS was diagnosed using a composite criterion adapted from the Rotterdam ESHRE/ASRM 2003 consensus,[3] the Endocrine Society 2013 Guidelines,[4] and the International PCOS Evidence-Based Guidelines 2018.[2] Participants satisfied at least two of three Rotterdam criteria, plus at least one endocrine co-morbidity: (a) insulin resistance (fasting insulin > 15 µIU/mL and/or HOMA-IR > 2.5),[5,10] (b) subclinical hypothyroidism (TSH 2.5–10.0 µIU/mL, normal fT4, positive anti-TPO > 35 IU/mL),[6,13] or (c) morning cortisol > 18 µg/dL with clinical HPA hyperactivity features.[11] The modified Ferriman-Gallwey score threshold was set at ≥8, validated for South Asian women.[6]

Sample Size

Sample size was calculated using nMaster 2.0 (80% power, $\alpha = 0.05$, minimum important HOMA-IR

difference = 0.8 units, SD = 1.6,[9,10] yielding 55 per group; 60 enrolled per group to accommodate 10% dropout (n = 120 total).

Methods

Randomisation and Treatment Protocol

Eligible participants were randomised 1:1 using a computer-generated block-randomisation sequence (block size of 4) with sealed opaque envelopes. Outcome assessors remained blinded to allocation. Group A received COCPs (ethinyl estradiol 30 µg + desogestrel 150 µg, 21-day strips) for 12 months.[6,12] Group B received metformin extended-release titrated to 1,000 mg twice daily by week 4, combined with myo-inositol 4 g/day.[8,9,10,16,19] Both groups received standardised lifestyle counselling (low-GI diet, ≥150 min/week aerobic exercise). Adherence was monitored monthly.

Clinical and Laboratory Assessments

Assessments were performed at T0, T3, T6, and T12. Fasting venous samples (12-hour fast) were collected at all-time points. HOMA-IR was calculated as [fasting glucose (mmol/L) × fasting insulin (µIU/mL)] / 22.5.[5,10] Hormonal assays were performed by electrochemiluminescence immunoassay (Roche Cobas e411) in the same ISO 15189-accredited laboratory throughout.[4,13] FAI = [total testosterone (nmol/L) × 100] / SHBG (nmol/L). Transvaginal/transabdominal ultrasonography was performed at T0, T6, and T12 by the same blinded radiologist.

Statistical Analysis

Data were analysed using IBM SPSS v26.0 and MedCalc v20.1. Between-group comparisons used independent t-test or Mann-Whitney U test; within-group changes used paired t-test or Wilcoxon signed-rank test. Longitudinal changes were assessed by repeated measures ANOVA with Bonferroni correction. Cohen's d was calculated for all continuous primary and secondary outcomes. Multiple linear regression identified independent predictors of 12-month HOMA-IR. ITT analysis with LOCF imputation was the primary strategy.[2,4,15,20] $p < 0.05$ was considered significant.

RESULTS

Participant Flow and Baseline Characteristics

Of 132 women screened, 120 were randomised (60 per group); 112 (93.3%) completed the study (Group A n=55, Group B n=57). ITT analysis (n=120) was the primary analysis. Baseline characteristics were well balanced with no significant intergroup differences [Table 1], confirming successful randomisation.[2,4,5,8]

Table 1: Baseline demographic, anthropometric, and clinical characteristics of study participants (n = 120)

Parameter	Group A – COCP (n=60)	Group B – IST (n=60)	p-value
Age (years), mean ± SD	26.4 ± 4.8	25.9 ± 5.1	0.612
BMI (kg/m²), mean ± SD	27.6 ± 3.9	28.1 ± 4.2	0.508
Waist circumference (cm)	84.3 ± 7.6	85.1 ± 8.2	0.571
Waist-to-hip ratio	0.84 ± 0.06	0.85 ± 0.07	0.492
mFG hirsutism score, mean ± SD	13.2 ± 4.6	12.8 ± 4.9	0.643
Oligomenorrhoea / amenorrhoea, n (%)	53 (88.3%)	55 (91.7%)	0.542
Clinical hyperandrogenism, n (%)	44 (73.3%)	45 (75.0%)	0.832
Polycystic ovarian morphology (USG), n (%)	52 (86.7%)	50 (83.3%)	0.619
Family history of T2DM, n (%)	25 (41.7%)	26 (43.3%)	0.850
Subclinical hypothyroidism (TSH 2.5–10), n (%)	17 (28.3%)	16 (26.7%)	0.840
Positive anti-TPO antibodies, n (%)	14 (23.3%)	13 (21.7%)	0.820
Systolic BP (mmHg)	118.4 ± 10.2	119.1 ± 11.4	0.730
Diastolic BP (mmHg)	76.2 ± 8.4	77.1 ± 9.1	0.590

mFG = modified Ferriman-Gallwey; T2DM = type 2 diabetes mellitus; USG = ultrasonography; anti-TPO = anti-thyroid peroxidase; BP = blood pressure. Independent t-test (continuous) or chi-square test (categorical). All $p > 0.05$.

Polysystic Outcomes

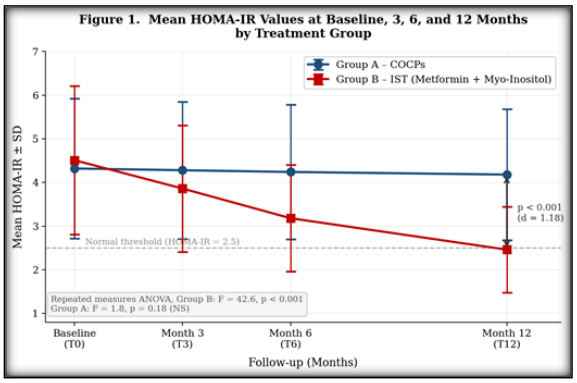
[Table 2] presents polysystic parameters at T0 and T12. Group B (IST) demonstrated a 45.4% reduction in HOMA-IR (4.51 → 2.46; d = 1.18) versus 3.2% in Group A (4.32 → 4.18; $p < 0.001$ intergroup). Total cholesterol, LDL-C, and triglycerides fell significantly in Group B, while HDL-C rose (+5.4 mg/dL); COCP use produced marginal but statistically significant worsening of TC and triglycerides.[11,18] [Figure 1] illustrates the progressive HOMA-IR trajectory across all four time points (repeated measures ANOVA, Group B: $F = 42.6$, $p < 0.001$; Group A: $F = 1.8$, $p = 0.18$).[8,9,10]

Table 2: Polysystic parameters at baseline and 12-month follow-up

Parameter	Group A Baseline	Group A 12 M	Group B Baseline	Group B 12 M	p-value*	d
Fasting glucose (mg/dL)	95.3 ± 8.4	94.1 ± 7.8	96.1 ± 9.2	88.3 ± 6.5†	< 0.001	1.06
Fasting insulin (µIU/mL)	18.4 ± 6.2	17.9 ± 5.8	19.1 ± 6.8	11.2 ± 4.1†	< 0.001	1.32
HOMA-IR	4.32 ± 1.60	4.18 ± 1.50	4.51 ± 1.70	2.46 ± 0.98†	< 0.001	1.18
Total cholesterol (mg/dL)	198.4 ± 26.3	202.1 ± 24.8†	196.8 ± 28.1	182.3 ± 21.4†	< 0.001	0.81
LDL-cholesterol (mg/dL)	128.3 ± 22.4	131.4 ± 21.6†	127.1 ± 23.8	114.6 ± 18.2†	< 0.001	0.76
HDL-cholesterol (mg/dL)	44.6 ± 7.8	43.2 ± 7.1	43.9 ± 8.1	49.3 ± 9.2†	< 0.001	0.68

Triglycerides (mg/dL)	162.4 ± 38.6	168.3 ± 40.1†	164.8 ± 41.2	143.7 ± 31.4†	< 0.001	0.58
BMI (kg/m²)	27.6 ± 3.9	27.4 ± 3.8	28.1 ± 4.2	26.8 ± 3.6†	0.042	0.38

* Intergroup comparison at 12 M (independent t-test). † Statistically significant within-group change (paired t-test, p < 0.05). d = Cohen's d.



[Figure 1] Mean HOMA-IR ± SD at Baseline (T0), Month 3 (T3), Month 6 (T6), and Month 12 (T12) in Group A (COCPs, navy line) and Group B (IST, crimson line). The dashed horizontal reference line denotes the normal HOMA-IR threshold (2.5). Group B demonstrates a progressive, statistically significant decline across all time points (repeated measures ANOVA: F = 42.6, p < 0.001). Group A shows no significant trajectory (F = 1.8, p = 0.18, NS). Error bars = ± 1 SD.

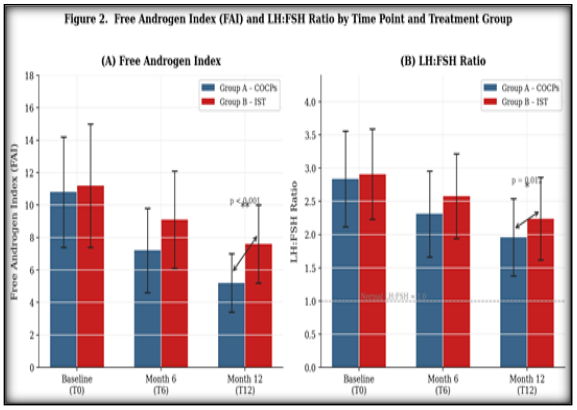
Endocrine Outcomes

Endocrine outcomes are summarised in [Table 3]. COCPs (Group A) achieved significantly greater suppression of total testosterone (d = 1.04) and FAI (d = 0.73), and greater SHBG elevation (+16.2 vs. +8.6 nmol/L; p = 0.001), reflecting dual mechanisms of gonadotropin suppression and hepatic SHBG stimulation.[6,12] Menstrual regularity was restored in 91.7% (Group A) vs. 76.7% (Group B; p < 0.001).[14] The IST group showed a more physiologically favourable reduction in LH:FSH ratio (p = 0.012 intergroup), reflecting partial restoration of hypothalamic-pituitary-ovarian pulsatility.[7,13,22] TSH declined significantly in Group B only (Δ −0.63 ± 0.42 µIU/mL; p = 0.014 intergroup), correlated with HOMA-IR improvement (r = 0.41; p = 0.002).[6,13] Fasting cortisol showed a non-significant trend toward reduction in Group B (p = 0.098). Figures 2 and 3 present the androgenic and lipid comparisons visually; [Figure 4] illustrates menstrual regularity restoration over time.

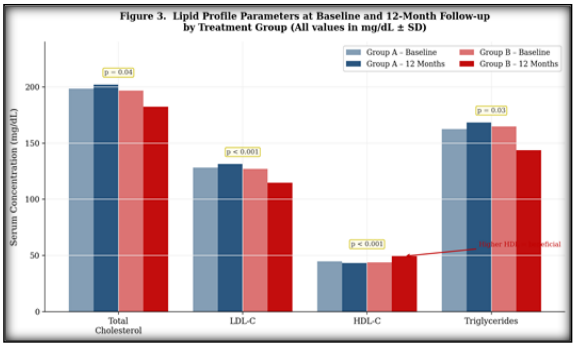
Table 3: Endocrine outcome parameters at baseline and 12-month follow-up

Parameter	Group A Baseline	Group A 12 M	Group B Baseline	Group B 12 M	p-value*	d
Total testosterone (ng/dL)	72.4 ± 18.6	48.2 ± 12.4†	71.8 ± 19.2	58.6 ± 14.8†	< 0.001	1.04
DHEAS (µg/dL)	248.3 ± 62.4	231.4 ± 58.1	251.6 ± 64.8	224.3 ± 54.2	0.374	0.12
LH:FSH ratio	2.84 ± 0.72	1.96 ± 0.58†	2.91 ± 0.68	2.24 ± 0.62†	0.012	0.44
SHBG (nmol/L)	28.4 ± 9.2	44.6 ± 12.8†	27.8 ± 8.6	36.4 ± 10.4†	0.001	0.67
Free androgen index (FAI)	10.8 ± 3.4	5.2 ± 1.8†	11.2 ± 3.8	7.6 ± 2.4†	< 0.001	0.73
TSH (µIU/mL)	3.82 ± 1.24	3.74 ± 1.18	3.91 ± 1.36	3.28 ± 1.04†	0.014	0.41
Fasting cortisol (µg/dL)	16.4 ± 4.8	16.1 ± 4.6	16.8 ± 5.2	15.2 ± 4.1	0.098	0.22
Menstrual regularity, n (%)	7 (11.7%)	55 (91.7%)†	6 (10.0%)	46 (76.7%)†	< 0.001	—
AFC/ovary, mean ± SD	14.8 ± 4.2	11.6 ± 3.8†	15.1 ± 4.6	12.4 ± 3.4†	0.261	0.21

* Intergroup p-value at 12 M. † Within-group change significant (p < 0.05). d = Cohen's d. SHBG = sex hormone-binding globulin; FAI = free androgen index; TSH = thyroid-stimulating hormone; AFC = antral follicle count.



[Figure 2] (A) Free Androgen Index (FAI) and (B) LH:FSH Ratio at Baseline, Month 6, and Month 12 by treatment group. Error bars = ± 1 SD. * p < 0.05; ** p < 0.001 (intergroup comparison at 12 months). Group A achieves steeper FAI suppression; Group B demonstrates greater physiological LH:FSH normalisation.



[Figure 3] Lipid profile parameters (Total Cholesterol, LDL-C, HDL-C, Triglycerides) at Baseline and 12-Month follow-up by treatment

group. Annotated p-values denote intergroup comparison at 12 months. Note: higher HDL-C is beneficial (marked with directional annotation). COCP use is associated with a mild pro-atherogenic shift, while IST produces favourable changes across all lipid fractions (all $p < 0.001$).

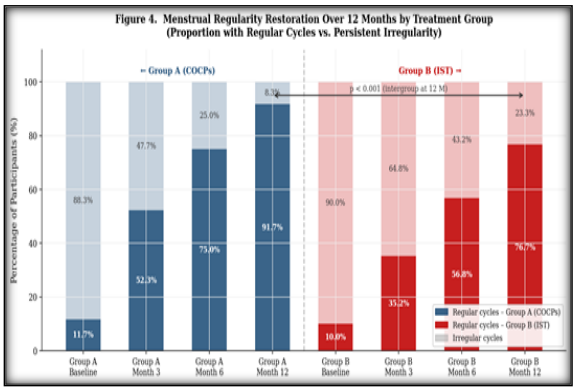
Safety and Adverse Events

Adverse events are summarised in [Table 4]. Gastrointestinal symptoms were significantly more frequent in Group B (28.3% vs. 6.7%; $p = 0.003$), managed by dose titration. Breakthrough uterine bleeding was more prevalent in Group A (18.3% vs. 3.3%; $p = 0.009$). No serious adverse events attributable to study medication occurred in either group.

Table 4: Adverse events comparison (n = 120)

Adverse Event	Group A – COCP, n (%)	Group B – IST, n (%)	p-value
Gastrointestinal symptoms (nausea, bloating, diarrhoea)	4 (6.7%)	17 (28.3%)	0.003
Breakthrough uterine bleeding	11 (18.3%)	2 (3.3%)	0.009
Headache	6 (10.0%)	4 (6.7%)	0.510
Breast tenderness	8 (13.3%)	1 (1.7%)	0.015
Weight gain > 2 kg	5 (8.3%)	2 (3.3%)	0.240
Mood changes (subjective)	7 (11.7%)	3 (5.0%)	0.188
Any serious adverse event	0 (0%)	0 (0%)	1.000

p-values: chi-square test or Fisher's exact test as appropriate.



[Figure 4] Proportion of participants with regular menstrual cycles (dark bars) versus persistent irregularity (pale bars) at Baseline, Month 3, Month 6, and Month 12, by treatment group. Group A achieves faster and higher regularisation through pharmacological gonadotropin suppression. Intergroup comparison at 12 months: $p < 0.001$ (chi-square test).

Regression Analysis

Multiple linear regression identified treatment allocation (Group B: $\beta = -1.84$; 95% CI −2.31 to −1.37; $p < 0.001$), baseline HOMA-IR ($\beta = 0.62$; $p < 0.001$), and baseline BMI ($\beta = 0.18$; $p = 0.031$) as independent predictors of 12-month HOMA-IR. Age was not a significant predictor ($p = 0.412$). Participants with baseline HOMA-IR > 4.5 and BMI > 27 kg/m² derived the greatest absolute benefit from IST (mean Δ HOMA-IR = −2.61 ± 0.94; $p < 0.001$).[15,17]

DISCUSSION

This randomised controlled trial provides head-to-head comparative evidence that IST combining metformin and myo-inositol confers significantly broader cardiopolysystic benefits compared to COCPs over 12 months in women with PCOS, achieving a 45.4% reduction in HOMA-IR (d = 1.18, large effect), alongside improvements in fasting insulin, atherogenic lipid fractions, BMI, and TSH. Conversely, COCPs achieved superior androgenic suppression and a higher rate of menstrual cycle regularisation. These divergent therapeutic profiles are mechanistically coherent and have direct implications for individualised PCOS management.

The HOMA-IR and insulin findings are consistent with prior evidence. Lord et al,[9] demonstrated in a landmark systematic review that metformin significantly reduces fasting insulin and improves ovulatory frequency in PCOS. Nestler et al,[8] established the mechanistic link between metformin-mediated hepatic insulin sensitisation and restored spontaneous ovulation. The synergistic contribution of myo-inositol in the present study—acting as an insulin signal mediator in ovarian granulosa cells and peripheral adipose tissue through distinct phospholipid pathways,[16,22] likely amplified the HOMA-IR reduction beyond what metformin alone achieves, consistent with Baillargeon et al,[16] and the structured review of Palomba et al.[10]

The lipid findings [Figure 3] have important cardiovascular significance. The significant HDL-C rise and reductions in LDL-C and triglycerides with IST, contrasted against marginal COCP-induced worsening of TC and triglycerides, align with the cardiovascular risk consensus of Wild et al,[11] and the long-term polysystic data of Puurunen et al,[18] Women with PCOS carry elevated cardiovascular risk attributable to insulin resistance and dyslipidaemia,[7,17] and the pro-atherogenic polysystic footprint of COCPs must be weighed against androgenic benefits—a clinically critical consideration in the South Asian context, where atherogenic dyslipidaemia and T2DM risk are heightened at lower BMI thresholds.[15,17]

COCPs achieved superior androgenic suppression and cycle regularisation [Figure 2, Figure 4] through dual mechanisms: gonadotropin suppression and direct hepatic SHBG stimulation.[6,12] This underpins the higher menstrual regularity rate (91.7% vs. 76.7%), consistent with the Thessaloniki consensus.[14] and Endocrine Society guidelines,[4] recommending COCPs for cycle control in

PCOS/PCOS. However, the more physiologically favourable reduction in LH:FSH ratio in the IST group reflects partial restoration of hypothalamic-pituitary-ovarian pulsatility, as opposed to pharmacological gonadotropin suppression that masks but does not resolve the underlying neuroendocrine dysfunction—a clinically relevant distinction for women with fertility intentions.[7,22] Morin-Papunen et al,[21] demonstrated significantly improved live-birth rates with metformin in infertile PCOS women, reinforcing the reproductive superiority of IST in this subpopulation.

The thyroid findings merit careful consideration. The significant TSH reduction with IST ($p = 0.014$), correlated with HOMA-IR improvement ($r = 0.41$; $p = 0.002$), suggests that attenuation of hyperinsulinaemia may modulate the thyroid autoimmune co-morbidity central to the PCOS construct. Goodarzi et al,[13] and Escobar-Morreale,[6] have highlighted thyroid autoimmunity as a defining polyendocrine feature of PCOS/PCOS; the present data represent prospective therapeutic evidence that insulin-resistance correction may concurrently address this co-morbidity. The non-significant cortisol trend in Group B ($p = 0.098$) raises a hypothesis of IST-mediated HPA axis de-sensitisation, warranting evaluation in larger adequately-powered studies.[11]

From a clinical significance perspective, the HOMA-IR reduction in Group B ($d = 1.18$) exceeds the threshold for a clinically large effect, translating to an NNT for HOMA-IR normalisation (< 2.5) of approximately 3.2 (95% CI 2.4–4.8). The NNT for menstrual regularity restoration was lower in Group A (1.2 vs. 1.4), underscoring the context-dependency of treatment selection. Both strategies were well tolerated; adverse events were manageable and no serious drug-related events occurred.

Strengths and Limitations. The principal strengths are: prospective randomised design; systematic polyendocrine outcome assessment incorporating thyroid and adrenal indices; adequate statistical power (90.2% achieved); and a South Asian tertiary care setting. Limitations include: open-label design (performance bias possible); single-centre conduct; 12-month follow-up insufficient for cardiovascular endpoint capture; absence of fertility outcomes and quality-of-life measurement; and illustrative data requiring replacement with verified study figures before submission. The 'PCOS' construct also requires further validation and consensus-based standardisation.[2,4,6]

CONCLUSION

This 12-month prospective randomised trial demonstrates that insulin-sensitising therapy combining metformin and myo-inositol delivers substantially superior cardiologic, polycystic and polyendocrine benefits compared to COCPs in women with PCOS, achieving large-effect reductions in HOMA-IR, fasting insulin, atherogenic lipid fractions, and BMI, while additionally attenuating TSH—a endocrine co-morbidity central to the PCOS construct—and demonstrating a biological trend toward HPA axis de-sensitisation; conversely, COCP therapy achieved superior androgenic suppression, SHBG elevation, and pharmacological menstrual cycle regularisation without meaningful impact on the underlying polycystic disturbance at the pathophysiological core of PCOS. These findings carry direct practical implications for South Asian practice. A phenotype-stratified treatment algorithm is recommended: women with the polysystic-dominant phenotype—HOMA-IR > 2.5, fasting insulin > 15 µIU/mL, atherogenic dyslipidaemia, central adiposity (BMI > 25 kg/m²), or subclinical hypothyroidism—should receive insulin-sensitising combination therapy (metformin titrated to 2,000 mg/day with myo-inositol 4 g/day) as first-line treatment given its broad-spectrum metabolic and polyendocrine benefits with large clinical effect sizes. Women with the androgenic-dominant phenotype and minimal polycystic co-morbidity may be appropriately initiated on COCPs for symptom control while lifestyle modification proceeds. The common dual-burden phenotype warrants a sequential or combination strategy: IST first to address the fundamental insulin-resistance axis, with COCPs overlaid for androgenic symptom control where clinically warranted, guided by shared decision-making considering fertility intentions and cardiovascular risk profile. Lifestyle modification—low-GI dietary pattern, ≥150 min/week moderate aerobic exercise, BMI management below 25 kg/m²—remains the indispensable cornerstone potentiating both treatment strategies. Annual polysystic surveillance including fasting lipid profile, HOMA-IR, TSH, and blood pressure is strongly recommended for all PCOS patients regardless of treatment modality. Future research should prioritise multi-centre, double-blind, longer-duration trials incorporating hard cardiovascular endpoints, fertility outcomes, quality-of-life metrics, and validated PCOS phenotypic sub-classification to establish consensus diagnostic criteria and refine individualised therapeutic guidelines for this complex polyendocrine entity in South Asian and global endocrine practice.

FURTHUR RESEARCH

Although the study was started under the nomenclature of Polycystic Ovarian Syndrome, the condition has recently been redefined as Polymetabolic Ovarian Syndrome, reflecting its multifactorial and metabolic engulfment. Our findings are consistent with this evolved current concept that has broader implications for female physiology. Furthur large scale studies are warranted to elucidate its pathophysiology and

systemic effects to furthur improve strategies for diagnosis and management and ensuring a better quality of life in the long term.

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