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Original Research Article

Comparative Efficacy of Zinc and Folic Acid Supplementation as Adjuncts to Metformin in Women with Polycystic Ovary Syndrome: A Randomized Controlled, Open-Label Study

Sukanya M.[1], C.K. Devipriya[2], V.C. Sangeetha[3], Rida Zoya Logashree Irshad[4]

[1]Assistant Professor, Department of Pharmacology, KMCH Institute of Health Sciences and Research, Coimbatore, Tamil Nadu, India

[2]Assistant Professor, Department of Pharmacology, Chengalpattu Medical College, Chengalpattu, Tamil Nadu, India

[3]Assistant Professor, Department of Pharmacology, Karpaga Vinayaga Institute of Medical Sciences and Research Centre, Karpaga Vinayaga Educational Lore for Learning - Deemed to be University, Tamil Nadu, India

[4]Assistant Professor, Department of Biochemistry, Madha Medical College and Research Institute, Kovur, Chennai, Tamil Nadu, India

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Corresponding author: Dr. Sukanya M

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Abstract

Background: Polycystic ovary syndrome (PCOS) is a common endocrine disorder of reproductive-age women characterised by menstrual irregularity, hyperandrogenism, insulin resistance and dyslipidaemia. Zinc and folic acid have been proposed as adjuncts to metformin, but Indian data are scarce. This study compared the effect of zinc and folic acid supplementation, added to metformin, with metformin alone on menstrual pattern, hirsutism, glycaemic indices and lipid profile in PCOS.

Methods: A prospective, randomized, controlled, open-label comparative study was conducted in the Gynaecology Outpatient Department of Chengalpattu Medical College and Hospital from March 2019 to May 2020. Of 180 women screened, 150 treatment-naive women aged 18–40 years with PCOS (Rotterdam criteria) were randomized equally (n=50 each) to Group A (metformin 500 mg thrice daily), Group B (metformin plus zinc sulfate monohydrate, 12.5 mg elemental zinc thrice daily) or Group C (metformin plus folic acid 5 mg once daily) for 24 weeks. Menstrual pattern, modified Ferriman–Gallwey (mFG) score, body mass index (BMI), fasting blood sugar (FBS), fasting insulin, HOMA-IR and lipid profile were assessed at baseline and 24 weeks. Data were analysed using SPSS 23.0 with chi-square, paired t and one-way ANOVA tests ($p<0.05$ significant).

Results: One hundred and forty-five women completed the study (Group A 48, B 49, C 48); the groups were comparable at baseline (mean age 26.9±6.3, 27.1±5.9 and 26.8±5.5 years; $p=0.974$). Within each group, weight, BMI, FBS, fasting insulin, HOMA-IR, total cholesterol, triglycerides and VLDL fell significantly and menstrual regularity improved significantly (eumenorrhoea 10.4% to 35.4% in A, 12.2% to 40.8% in B and 12.5% to 29.2% in C; all $p<0.01$), whereas mFG score, LDL-C and HDL-C did not change significantly. Between groups, no parameter differed significantly after treatment (menstrual pattern $p=0.568$; HOMA-IR $p=0.257$; triglycerides $p=0.145$). Adverse effects, all mild gastrointestinal events, occurred in 10 of 145 women (6.9%), and none required discontinuation.

Conclusion: Metformin 1500 mg/day for 24 weeks improved menstrual regularity, glycaemic indices and selected lipid parameters in PCOS, but adding zinc or folic acid conferred no additional clinical or biochemical benefit. Larger, multicentre, placebo-controlled trials are warranted.

Keywords: Polycystic ovary syndrome; Zinc; Folic acid; Metformin; Insulin resistance; Hirsutism; Lipid profile.

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Introduction

Polycystic ovary syndrome (PCOS) is among the commonest endocrine disorders of women of reproductive age, with a worldwide prevalence usually quoted at 5–10% and substantially higher estimates reported from some Indian cohorts [1,2]. Diagnosis rests on the Rotterdam criteria, which require any two of three features: oligo-ovulation or anovulation, clinical or biochemical

hyperandrogenism, and polycystic ovaries on ultrasonography [3]. Beyond infertility, menstrual disturbance and hirsutism, the syndrome carries a heavy metabolic burden, including insulin resistance, glucose intolerance, dyslipidaemia, type 2 diabetes mellitus, hypertension and cardiovascular disease, together with a higher prevalence of anxiety and depression [1,4]. Hyperinsulinaemia is considered central to the pathogenesis, since insulin acts with luteinising hormone to stimulate ovarian androgen production, suppresses hepatic sex hormone binding globulin and contributes to arrested follicular growth and anovulation [5–7].

Lifestyle modification is the first line of management, and insulin sensitisers, particularly metformin, are widely used because they reduce hyperinsulinaemia and androgen levels and can restore menstrual cyclicity and ovulation [8–10]. Attention has also turned to micronutrients that influence insulin signalling and oxidative stress. Zinc is a cofactor in more than 300 enzymatic reactions, including superoxide dismutase, and lower circulating zinc has been reported in women with PCOS [11]. In randomized trials, zinc supplementation improved markers of insulin resistance and lipid profile in PCOS [12], and combined zinc and magnesium supplementation favourably altered inflammatory and oxidative stress biomarkers [13]. Folate deficiency and raised homocysteine are likewise reported in PCOS, and folic acid has been shown to lower homocysteine, serum insulin and HOMA-IR in some studies, as well as to enhance the effect of metformin on vascular endothelium [14–17].

However, the evidence for zinc and folic acid as add-on therapy to metformin is limited and inconsistent, most trials are of short duration (about 8 weeks) and were done in non-Indian populations, and the two supplements have not been compared head to head. Studies in Indian women with PCOS are very limited. The present study was therefore designed to compare the effects of zinc and folic acid supplementation, each added to standard metformin therapy, on clinical and biochemical outcomes over 24 weeks. The primary objective was to compare the efficacy of zinc and folic acid supplementation among women with PCOS, given along with metformin, in improving menstrual symptoms and hirsutism. The secondary objectives were to assess their effects on fasting blood glucose, fasting serum insulin, HOMA-IR and lipid profile, and to document the adverse effects of therapy.

Materials and Methods

This was a prospective, randomized, and controlled, open-label, three-arm comparative study conducted by Department of pharmacology in the Outpatient Department of Gynaecology, Chengalpattu Medical College and Hospital, Tamil Nadu, over 15 months. The study was approved by the Institutional Ethics Committee, and written informed consent was obtained in the regional language from every participant, with a left thumb impression in the presence of an impartial witness for illiterate participants. Newly diagnosed, treatment-naive women aged 18–40 years who fulfilled the Rotterdam criteria [3] (any two of oligomenorrhoea/anovulation, hyperandrogenism and polycystic ovaries on ultrasonography) were eligible. Women who were pregnant or lactating, had known diabetes mellitus, hypertension or chronic kidney disease, had a major systemic illness, or had used oral contraceptives, steroid hormones, or zinc or folic acid supplements in the preceding three months were excluded. Of 180 women screened, 30 were excluded (18 declined consent, 7 were unwilling to stop other medications and 5 were lactating), and 150 were enrolled. Participants were allocated by simple randomization to Group A (n=50), Group B (n=50) or Group C (n=50).

All participants received metformin 500 mg orally three times daily (1500 mg/day) for 24 weeks. Group B additionally received zinc sulfate monohydrate tablets providing 12.5 mg elemental zinc, one tablet three times daily, and Group C received folic acid 5 mg once daily. A detailed history and gynaecological examination were done at baseline. Menstrual pattern was classified as amenorrhoea, oligomenorrhoea or eumenorrhoea, and hirsutism was scored with the modified Ferriman–Gallwey (mFG) system. Weight, height, BMI and blood pressure were recorded. Fasting blood sugar, fasting serum insulin and lipid profile (total cholesterol, LDL-C, HDL-C, triglycerides and VLDL-C) were measured, and insulin resistance was calculated as HOMA-IR. Participants were asked to return empty blister packs at follow-up to check adherence and to report adverse effects immediately. After 24 weeks, treatment was stopped and all clinical and biochemical assessments were repeated. Five women (three lost to follow-up and two who migrated) dropped out, and 145 women (Group A 48, Group B 49, Group C 48) were analysed. Participants were also reviewed after a six-month treatment-free interval for delayed adverse events.

Data were analysed with SPSS version 23.0. Categorical variables are presented as frequencies and percentages and continuous variables as mean±standard deviation. The chi-square test was used for categorical data, the paired t test for before–after comparisons within groups, and one-way ANOVA for comparison among the three groups. A p value below 0.05 was considered statistically significant.

Results

Of the 150 women randomized, 145 (96.7%) completed 24 weeks of treatment and were analysed.

The three groups were well matched at baseline (Table 1). Mean age was 26.9±6.3 years in Group A, 27.1±5.9 years in Group B and 26.8±5.5 years in Group C (p=0.974), and the 21–25-year band was the most frequent in Groups A and C (29% each), while 26–30 years was the most frequent in Group B (28%). Baseline weight (p=0.414) and BMI (p=0.347) did not differ among groups, and systolic and diastolic blood pressure were similar at baseline and unchanged after treatment. Weight and BMI fell significantly within every group (p<0.01), for example from 63.56±5.47 to 62.04±5.02 kg in Group A, 62.53±5.35 to 60.94±4.45 kg in Group B and 62.08±5.92 to 60.58±5.22 kg in Group C, but the post-treatment values did not differ between groups (weight p=0.318; BMI p=0.302).

Table 1: Baseline characteristics and anthropometric response (mean±SD)

Parameter	Group A Metformin (n=48)	Group B Met + Zinc (n=49)	Group C Met + Folic acid (n=48)	p value (between groups)
Age (years)	26.9±6.3	27.1±5.9	26.8±5.5	0.974
Weight, baseline (kg)	63.56±5.47	62.53±5.35	62.08±5.92	0.414
Weight, 24 weeks (kg)*	62.04±5.02	60.94±4.45	60.58±5.22	0.318
BMI, baseline (kg/m²)	25.13±1.36	24.76±1.16	24.91±1.15	0.347
BMI, 24 weeks (kg/m²)*	24.53±1.31	24.16±1.10	24.34±1.17	0.302
SBP, baseline / 24 weeks (mmHg)	118.83±7.84 / 118.71±8.24	116.04±7.33 / 115.88±7.60	118.79±6.99 / 118.75±7.33	NS
DBP, baseline / 24 weeks (mmHg)	76.45±7.29 / 76.04±7.92	76.12±6.71 / 75.71±7.36	76.87±7.48 / 76.66±7.81	NS

***Significant reduction from baseline within each group (paired t test, p<0.01). BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; NS, not significant (p>0.05).**

Menstrual pattern improved significantly in all three groups (Table 2). In Group A, eumenorrhoea rose from 10.4% (5/48) to 35.4% (17/48) and amenorrhoea fell from 47.9% to 35.4% and oligomenorrhoea from 41.7% to 29.2%. In Group B, eumenorrhoea rose from 12.2% (6/49) to 40.8% (20/49), amenorrhoea fell from 44.9% to 34.7% and oligomenorrhoea from 42.9% to 24.5%. In Group C, eumenorrhoea rose from 12.5% (6/48) to 29.2% (14/48), amenorrhoea fell from 39.6% to 31.3% and oligomenorrhoea from 47.9% to 39.6%. The within-group change was highly significant in each arm (chi-square, p<0.01). Although the numerical gain in eumenorrhoea was greatest with zinc, followed by metformin alone and then folic acid, the distribution of cycle patterns did not differ significantly among groups either at baseline (p=0.947) or at 24 weeks (p=0.568).

Table 2: Menstrual cycle pattern before and after 24 weeks of treatment, n (%)

Menstrual pattern	Time point	Group A (n=48)	Group B (n=49)	Group C (n=48)	p value (between groups)
Amenorrhoea	Baseline	23 (47.9)	22 (44.9)	19 (39.6)	0.989
Amenorrhoea	24 weeks	17 (35.4)	17 (34.7)	15 (31.3)	
Oligomenorrhoea	Baseline	20 (41.7)	21 (42.9)	23 (47.9)	0.740
Oligomenorrhoea	24 weeks	14 (29.2)	12 (24.5)	19 (39.6)	
Eumenorrhoea	Baseline	5 (10.4)	6 (12.2)	6 (12.5)	0.827
Eumenorrhoea	24 weeks	17 (35.4)	20 (40.8)	14 (29.2)	

Within-group improvement from baseline to 24 weeks: p<0.01 in Groups A, B and C (chi-square test).

Hirsutism scores were low at baseline (mean mFG 3.02–3.42) and did not change significantly in any group (Table 3), and there was no difference between groups at baseline (p=0.374) or after treatment (p=0.343). Glycaemic indices, by contrast, improved significantly within all three groups (p<0.01 for each). Fasting blood sugar fell by about 2.3–2.8 mg/dl (for example from 102.35±5.48 to 99.55±3.51 mg/dl in Group B), fasting insulin fell from 8.45±1.48 to 7.84±1.12 µIU/ml in Group A, from 9.11±1.47 to 8.22±1.03 µIU/ml in Group B and from 8.50±1.60 to 7.99±1.19 µIU/ml in Group C, and HOMA-IR fell from 2.14±0.47 to 1.93±0.32, from 2.32±0.46 to 2.04±0.30 and from 2.16±0.49 to 1.97±0.34 respectively in each group. After treatment, FBS (p=0.999), fasting insulin (p=0.252) and HOMA-IR (p=0.257) were statistically indistinguishable among groups, indicating no additional effect of zinc or folic acid over metformin.

Table 3: Hirsutism score and glucose homeostasis parameters, baseline → 24 weeks (mean±SD)

Parameter	Group A	Group B	Group C	Within-group p	Between-group p (24 wk)
mFG score	3.35±1.54 → 3.31±1.48	3.42±1.77 → 3.38±1.67	3.02±1.18 → 2.97±1.18	NS	0.343
FBS (mg/dl)	101.83±5.37 → 99.58±3.64	102.35±5.48 → 99.55±3.51	101.90±5.30 → 99.58±3.65	<0.01	0.999
Fasting insulin (μIU/ml)	8.45±1.48 → 7.84±1.12	9.11±1.47 → 8.22±1.03	8.50±1.60 → 7.99±1.19	<0.01	0.252
HOMA-IR	2.14±0.47 → 1.93±0.32	2.32±0.46 → 2.04±0.30	2.16±0.49 → 1.97±0.34	<0.01	0.257

mFG, modified Ferriman–Gallwey score; FBS, fasting blood sugar; HOMA-IR, homeostasis model assessment of insulin resistance; NS, not significant.

The lipid profile showed a consistent pattern (Table 4). Total cholesterol, triglycerides and VLDL-C decreased significantly within every group (p<0.01); for instance, triglycerides fell from 113.54±15.54 to 109.19±13.02 mg/dl in Group A, from 119.57±17.29 to 115.04±15.55 mg/dl in Group B and from 115.92±18.15 to 111.94±15.00 mg/dl in Group C. LDL-C and HDL-C showed no significant change within any group. Between-group comparison after treatment showed no significant difference for total cholesterol (p=0.329), LDL-C (p=0.387), HDL-C (p=0.541), triglycerides (p=0.145) or VLDL-C (p=0.145).

Table 4: Lipid profile, baseline → 24 weeks (mean±SD, mg/dl)

Parameter	Group A	Group B	Group C	Within-group p	Between-group p (24 wk)
Total cholesterol	185.35±19.36 → 184.52±18.41	191.29±21.76 → 190.06±20.29	187.15±18.57 → 186.13±17.53	<0.01	0.329
LDL-C	106.29±19.91 → 105.91±18.69	111.56±20.37 → 110.89±18.79	107.59±19.50 → 107.05±18.33	NS	0.387
HDL-C	50.04±3.20 → 50.21±3.04	49.92±2.54 → 50.10±2.15	50.67±2.35 → 50.63±2.03	NS	0.541
Triglycerides	113.54±15.54 → 109.19±13.02	119.57±17.29 → 115.04±15.55	115.92±18.15 → 111.94±15.00	<0.01	0.145
VLDL-C	22.71±3.11 → 21.84±2.60	23.91±3.46 → 23.01±3.11	23.18±3.63 → 22.39±3.00	<0.01	0.145

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; VLDL-C, very-low-density lipoprotein cholesterol; NS, not significant.

Of the 145 participants, 135 (93.1%) reported no adverse effects and 10 (6.9%) reported mild gastrointestinal symptoms (Table 5). Bloating (3 events), nausea (2), vomiting (2) and heartburn (2) were the commonest, with one episode of diarrhoea; seven events were in the metformin-alone group, two in the zinc group and one in the folic acid group. No event required stopping treatment, and no serious adverse event occurred during the study or during the six-month treatment-free follow-up.

Table 5: Adverse effects among the 145 participants (number of events; 10 patients, one event each)

Adverse effect	Group A	Group B	Group C	Total
Nausea	2	0	0	2
Vomiting	1	1	0	2
Diarrhoea	1	0	0	1
Bloating	2	0	1	3
Heartburn	1	1	0	2
Total events	7	2	1	10

No adverse effect in 135/145 participants (93.1%); no discontinuation of therapy and no serious adverse event.

Discussion

In this randomized comparison of 145 women with newly diagnosed PCOS, 24 weeks of metformin 1500 mg/day improved menstrual regularity, glycaemic indices and several lipid parameters, whereas the addition of zinc (37.5 mg elemental zinc/day) or folic acid (5 mg/day) produced no statistically detectable incremental benefit on any clinical or biochemical end point. The groups were comparable in age (p=0.974) and baseline anthropometry, so the similar outcomes are unlikely to reflect baseline imbalance. Menstrual cyclicity

improved significantly in all groups, with eumenorrhoea rising roughly three- to fourfold (10.4% to 35.4% with metformin, 12.2% to 40.8% with zinc and 12.5% to 29.2% with folic acid). The numerically larger gain with zinc did not translate into a significant between-group difference (p=0.568). This agrees with earlier work showing that metformin restores menstrual pattern by correcting hyperinsulinaemia and hyperandrogenism, particularly in women with both abnormalities [8,9], and with a Cochrane review that found metformin effective for menstrual pattern [18]. Hirsutism did not improve in any arm, which is consistent with reports that metformin has little effect on hirsutism over short periods [8,18,19]. A plausible reason is that terminal hair follicles respond slowly, so six months may be too short, and that the baseline mFG scores in our cohort (about 3) were low, leaving little room for change. This may also reflect the lower prevalence of overt hirsutism in Asian women with PCOS.

Weight and BMI fell modestly but significantly in every group, without differences between groups, which suggests that the reduction is attributable to metformin and lifestyle advice rather than to the micronutrients. Blood pressure was unchanged, in keeping with the normotensive status of our participants. FBS, fasting insulin and HOMA-IR declined significantly in all three arms, in line with trials of metformin in PCOS [8,17]. The absence of an additional effect of zinc contrasts with the placebo-controlled trial of Foroozanfard et al., in which zinc given for eight weeks reduced insulin resistance markers [12], and the absence of an added effect of folic acid contrasts with the findings of Asemi et al. and Bahmani et al. in overweight women [15,16]. Several differences may explain these discrepancies: those trials used zinc or folate as monotherapy against placebo, whereas in our study every arm already received a potent insulin sensitiser, so any marginal contribution of the micronutrient would be small and hard to detect. Their participants were also overweight or obese, whereas ours had a mean BMI of about 25 kg/m². The participants in our study were in addition newly diagnosed and had only mild insulin resistance (mean HOMA-IR 2.1–2.3), which narrows the room for further improvement.

Total cholesterol, triglycerides and VLDL-C decreased within each group, but LDL-C and HDL-C did not change, and between-group differences were not significant. Foroozanfard et al. reported significant falls in triglycerides and VLDL-C with zinc [12], and Kazerooni et al. suggested that lowering homocysteine with folic acid could favourably affect cholesterol biosynthesis [14], whereas high-dose folic acid did not alter lipids in familial hypercholesterolaemia [20], which is consistent with our findings. The lack of change in LDL-C and HDL-C may be due to the influence of diet, physical activity and other lifestyle factors on these fractions, and the lipid-modifying role of metformin itself remains uncertain [10,15]. The lipid improvements in our study are therefore best attributed to metformin.

All three regimens were well tolerated. Only 6.9% of participants experienced adverse effects, all mild and gastrointestinal, none needing discontinuation, and most events occurred in the metformin-alone arm, which is in keeping with the known gastrointestinal effects of metformin; zinc and folic acid at the doses used did not add to the burden of adverse effects. The strengths of this study include its randomized three-arm design, a head-to-head comparison of the two supplements, a 24-week duration longer than most previous trials, a low attrition rate (3.3%), and post-treatment safety follow-up. Its limitations include the open-label design and simple randomization without allocation concealment, the absence of a placebo or no-metformin control, a modest sample from a single centre, and the lack of measurement of serum zinc, folate, homocysteine and androgen levels, which would have clarified mechanisms. The study was not powered to detect small between-group differences, so a modest benefit of the supplements cannot be excluded.

Conclusion

Metformin 1500 mg/day for 24 weeks significantly improved menstrual regularity, fasting glucose, fasting insulin, HOMA-IR, total cholesterol, triglycerides and VLDL-C in women with PCOS, with a low incidence (6.9%) of mild adverse effects.

Supplementation with zinc (12.5 mg elemental zinc thrice daily) or folic acid (5 mg daily) in addition to metformin did not provide any further clinical or biochemical benefit in this cohort of 145 women. Routine addition of these supplements to metformin therefore cannot be recommended on the basis of the present evidence, although larger multicentre, placebo-controlled trials with micronutrient and hormonal assays and quality-of-life endpoints are needed to settle the question.

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