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ORIGINAL ARTICLE

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A randomized controlled trial comparing myoinositol with metformin versus metformin monotherapy in polycystic ovary syndrome

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Abstract

Objective: Insulin resistance and hyperinsulinemia plays an important role in pathogenesis of polycystic ovary syndrome (PCOS). Metformin, Myoinositol and D-chiro-inositol acts as insulin sensitizers and exerts a beneficial effects in PCOS. The objective is to compare the effect of metformin monotherapy versus a combination of metformin with Myoinositol and D-chiro-inositol in PCOS.

Design: This study is a randomized controlled trial conducted over a period of 6 months. All overweight and obese women with PCOS with the age group between 18 and 35 were included and randomized into two groups, 27 in the metformin monotherapy arm and 26 in the myoinositol combination arm.

Patients and Measurements: The variables assessed were duration of menstrual cycle, anthropometric parameters, modified Ferriman Gallwey score, global acne score, Fasting insulin, HOMA-IR, fasting lipid profile, serum testosterone, sex hormone binding globulin, luteinizing hormone, follicle stimulating hormone, anti-Mullerian hormone, and pelvic ultrasound to assess ovarian volume, PCOS Questionnaire score. Changes in the parameters from baseline at the end of 6 months of treatment were assessed and compared between the groups.

Results: Menstrual cycle regularity improved in both groups with significantly greater improvement in the group receiving myoinositol-based therapy ($p < .001$). Pregnancy rate was equal in both the arms. There was a significant improvement in PCOSQ score in myoinositol-based therapy group ($p < .001$). However, there was no statistically significant difference in other hormonal, metabolic parameters between two groups in spite of symptomatic benefits.

Conclusions: The addition of myoinositol to metformin exerts additional benefits in improving menstrual cycle regularity, and quality of life in women with PCOS.

KEYWORDS

anti-Mullerian hormone (AMH), infertility, metformin, myoinositol, polycystic ovary syndrome, SHBG, testosterone

1 | INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in reproductive age group of women.[1,2] It is characterized by menstrual irregularities with oligo-anovulation, clinical and/or biochemical evidence of hyperandrogenism and polycystic ovarian morphology on imaging. Insulin resistance and hyperinsulinemia plays an important role in pathogenesis of PCOS[3–5] and insulin sensitizers may improve the long-term outcome.[1] Metformin is an insulin sensitizer ameliorates the chronic inflammatory state of PCOS; improve ovulation, metabolic parameters and infertility.[1]

Myoinositol (MI) and D-chiro-inositol (DCI) act as second messengers for insulin signalling and exerts a beneficial effect in PCOS as an insulin sensitizers.[3] Ovarian MI:DCI ratio drops to 0.2:1 in women with PCOS and restoring the levels into 40:1 may improve the ovarian function,[6] which can be achieved by a combination of oral MI- and DCI-based therapy.[6] Inositol is currently considered as experimental therapy in PCOS.[1] Due to the different mechanisms of action in addition to the ovary-specific effects of MI, metformin and MI-based therapy may have a synergistic effect. Moreover, the dose of metformin requirement for the beneficial effect can be reduced when used in combination with MI.

There are very limited studies globally comparing MI and metformin-based therapies with equivocal results.[7–10] In addition there are no clear consensuses and guidelines regarding the use of MI in PCOS, however in off-label, MI-based therapies are being increasingly used in clinical practice in women with PCOS.[1] The drug is quite expensive as compared with metformin and whether it provides an additional benefit is not clearly known. There are only two randomized controlled trials in literature which studied the benefit of adding MI to metformin of which, only one studied anti-Mullerian hormone (AMH).[7–10] The present well-designed randomized controlled trial is the first such study from the South Indian population which compare the effect of metformin monotherapy versus a combination of metformin with MI + DCI, in clinical, hormonal and metabolic parameters of reproductive age obese/overweight women with PCOS.

2 | MATERIALS AND METHODS

All overweight and obese PCOS women with the age group between 18 and 35, overweight and obesity is defined as body mass index (BMI) ≥ 23,[11] attending the outpatient clinics of the Endocrinology and Obstetrics and Gynecology Department of Government Rajaji Hospital between October 2020 and February 2022 were included in the study. The diagnosis of PCOS was made according to the Rotterdam criteria by presence of any two of the following: oligo/anovulation, clinical and/or biochemical evidence of hyperandrogenism, polycystic ovarian morphology by ultrasound.[12] The secondary PCOS like hyperprolactinemia, hypothyroidism, Cushing's syndrome, adrenal and ovarian androgen-secreting tumours, patients on drugs causing PCOS like valproate therapy, liver disease or renal impairment, Type 2 Diabetes mellitus, any drugs for PCOS treatment in recent 3 months, previous history of ovarian surgical procedures, and patients not willing to participate or follow up were excluded. As per the Declaration of Helsinki, medical research involving the human subjects, the well-being of individual research subjects are taken precedence than all other interests. The written informed consent was obtained from all the participants after full explanation of the disease and the intervention procedures, need for regular follow-up and venous sampling.

All eligible patients were randomized by block randomization in blocks of eight with each block containing four participants allocated to metformin monotherapy and four patients receiving metformin monotherapy in combination with MI in 1:1 ratio. Group A received Metformin 500 mg twice daily and Group B, metformin 500 mg and MI 1.1 g with DCI 27.6 mg twice daily. The trial was approved by the Institutional Ethical Committee, Madurai Medical College and Government Rajaji Hospital, Madurai, CDSCO: Reg No ECR/1365/Inst/TN/2020 and also registered in the Clinical Trial Registry—India (CTRI) with CTRI number: CTRI/2021/03/032468. The clinical parameters evaluated are frequency and duration of menstrual cycle, modified Ferriman Gallwey score (mFG), global acne score (GAS), weight, height, BMI, waist circumference (WC). Irregular menstrual cycles are defined as in 1–3 years post menarche <21 or >45 days and after 3 years post menarche to perimenopause: <21 or >35 days or <8 cycles per year.[1] The various hormonal and biochemical parameters included are fasting insulin, fasting blood glucose, HOMA-IR, fasting lipid profile, serum testosterone, sex hormone binding globulin (SHBG), luteinizing hormone (LH), follicle stimulating hormone (FSH), AMH, pelvic ultrasound by two radiologists to assess ovarian volume of right and left ovaries separately and polycystic ovary syndrome questionnaire (PCOSQ) score. All hormonal tests were done by electrochemiluminescence immunoassay (ECLIA) method by Roche Cobas e411, and HOMA-IR, free androgen index (FAI) and LH:FSH ratio was calculated by mathematical formula. Changes in the parameters from baseline and at the end of 3 and 6 months of treatment were assessed and compared between the two groups.

2.1 | STATISTICS

Sample size and power was calculated as per apriori power calculation. Data were analysed using SPSS22 including descriptive and inferential statistical analyses. χ^2 test was used to compare categorical variables between the two groups, Student's *t* test for parametric and Mann–Whitney *U* test for nonparametric data for between group analysis. The baseline and postintervention data at 6 months within each group was assessed using Student's paired *t* test for parametric and Wilcoxon signed rank test for nonparametric variables. $p < .05$ was taken as significant.

3 | RESULTS

We screened 151 clinically suspected reproductive age group PCOS women. Eighty-six were excluded due to various reasons summarized in algorithm (Supporting Information: Figure 1). Finally, 65 cases were enrolled in the study and randomized into two groups: 33 to

metformin monotherapy group (Group A) and 32 into group receiving metformin in combination with MI-based therapy (Group B). In each group, six patients were excluded due to poor adherence to medications and minor adverse effects. Hence, finally, 53 cases were included for statistical analysis, 27 in the metformin monotherapy arm and 26 in the MI with metformin combination therapy arm.

All PCOS were symptomatic at diagnosis and most common presenting symptom was menstrual irregularity in 92.3%. 61% ($n = 28$) of study subjects had infertility. 26% ($n = 14$) had hirsutism. There were moderate acne in three and mild acne in rest of the patients. 47.8% ($n = 23$) of the patients were prediabetic, as defined by fasting plasma glucose ≥100 but <126 and 2 h plasma glucose ≥140 but <200 and HbA1C < 6.5%. There was no significant difference in between the two groups for any baseline clinical, metabolic and hormonal characteristics. The mean ovarian volumes of the right and left ovaries of the groups also were similar. The baseline characteristics are summarized in Table 1.

Menstrual cycle regularity have improved in both groups after 6 months of treatment, 62.56% ($n = 15$) in the metformin monotherapy group and 79.16% ($n = 19$) in MI based therapy group. Even though the cycle regularity is seen in both groups, significantly greater and early menstrual cycle improvement noted in the group in receiving a combination of MI with metformin (Figure 1) at the end of 6 months (χ^2 statistic 39.85, $p < .001$). Three cases in each arm became pregnant following the treatment; therefore the fecundity rate is equal in both the arms.

Mean BMI, weight, WC, mFG score and GAS score significantly decreased in both metformin monotherapy group (Supporting Information: Table 1) and MI-based therapy group at 6 months from baseline (Supporting Information: Table 2). Similarly significant improvement in markers of hyperandrogenism, total testosterone, FAI, AMH levels, and SHBG levels in the metformin monotherapy group as well as in MI based therapy group at the end of 6 months with no statistically significant difference between both the groups

TABLE 1 Baseline characteristics.

Variables	Metformin monotherapy group (Mean ± SD)	Metformin + Myoinositol with D-chiro-inositol group (Mean ± SD)	*p* Value
Clinical variables			
Age (years)	24.35 ± 5.1	24.61 ± 5.5	.406
Weight (kg)	77 ± 13.8	79.67 ± 12.9	.345
BMI (kg/m^2)	31.52 ± 4.4	33.6 ± 4.0	.744
Waist circumference (cm)	102.48 ± 9.5	109.1 ± 9.9	.703
Modified Ferriman Gallwey score (mFG)	4.24 ± 1.8	3.57 ± 1.1	.86
Global acne score (GAS)	8.9 ± 4.8	7.24 ± 4.2	.19
Metabolic variables			
Fasting plasma glucose (mmol/L)	5.54 ± 0.98	5.53 ± 0.98	.371
2 h postprandial glucose(mmol/L)	7.68 ± 1.58	8.44 ± 2.15	.26
Fasting insulin (pmol/L)	149.10 ± 112.5	132.64 ± 80.56	.36
HOMA-IR	5.2 ± 2.68	5.2 ± 4.73	.78
Hormonal variables			
LH (mIU/mL)	15.24 ± 11.33	12.48 ± 8.29	.055
FSH (mIU/mL)	6.83 ± 3.24	9.92 ± 15.14	.145
LH:FSH ratio	2.21 ± 1.17	2.57 ± 3.61	.315
Total testosterone (nmol/L)	2.15 ± 2.23	2.05 ± 1.28	.668
SHBG (nmol/L)	22.19 ± 12.57	22.89 ± 9.14	.869
FAI	13.40 ± 13.15	15.45 ± 23.82	.801
AMH (pmo/L)	41.21 ± 31.29	37.57 ± 24.21	.339
Ovarian volumes by ultrasound			
Right ovary (mL)	15.67 ± 6.26	13.79 ± 5.64	.665
Left ovary (mL)	15.37 ± 5.23	13.62 ± 5.55	.64

Abbreviations: AMH, anti-Mullerian hormone; BMI, body mass index; FAI, free androgen index; FSH, follicle stimulating hormone; LH, luteinizing hormone; SHBG, sex hormone binding globulin.

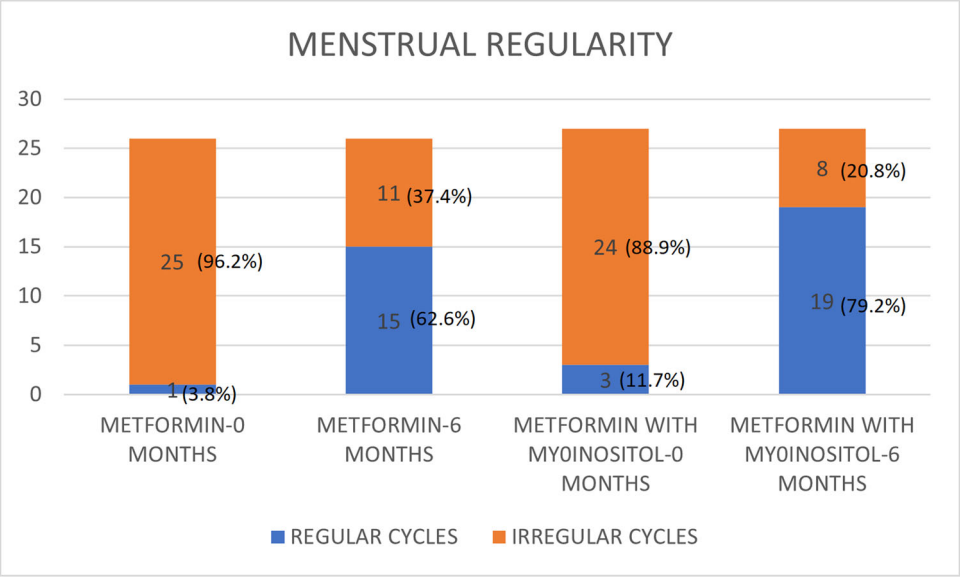

FIGURE 1 Comparison of change in menstrual cycle regularity before and after 6 months treatment in metformin with myoinositol group versus metformin monotherapy group. χ^2 statistic 39.8575. $p < .00$.

TABLE 2 Comparison of clinical, metabolic and biochemical outcome measures between the two groups at 6 months.

Variables	Metformin monotherapy	Metformin + Myoinositol with D-chiro-inositol	*p* Value
Weight (kg)	73.14 ± 13.57	77.90 ± 13.46	.16
BMI	29.70 ± 4.52	32.66 ± 3.96	.237
Waist circumference (cm)	97.38 ± 10.37	103.67 ± 10.15	.87
mFG score	3.5 ± 1.12	2.62 ± 1.20	.945
Global acne score (GAS)	4.90 ± 2.14	4.81 ± 1.94	.068
PCOSQ score	88.1 ± 15.9	108.1 ± 12.2	<.001
Fasting insulin (pmol/L)	93.68 ± 55.35	90.97 ± 44.51	.33
HOMA-IR	3.19 ± 1.46	2.95 ± 1.91	.163
LH	8.40	12.07 ± 8	.13
LH:FSH ratio	0.48	1.78 ± 0.66	.067
Total testosterone (nmol/L)	0.71	1.52 ± 0.87	.85
SHBG (nmol/L)	26.14 ± 12.44	31.03 ± 22.86	.87
FAI	6.95	6.09 ± 4.17	.606
AMH (pmol/L)	14.5	36.86 (18.57–47.92)	.39
Right ovarian volume	11.45 ± 4.68	10.71 ± 3.42	.504
Left ovarian volume	10.91 ± 4.39	9.73 ± 3.59	.99

Abbreviations: AMH, anti-Mullerian hormone; BMI, body mass index; FAI, free androgen index; FSH, follicle stimulating hormone; LH, luteinizing hormone; SHBG, sex hormone binding globulin.

(Table 2). In spite of significant reduction in HOMA-IR, fasting plasma glucose levels, fasting insulin levels in both groups at the end of 6 months, there was no statistically significant difference between both the groups (Figure 2).

There was a significant improvement in quality of life at the end of 6 months as assessed by PCOSQ in MI based therapy group as compared with metformin monotherapy group ($p < .001$) (Table 3). Adverse effects were reported by seven women in entire study population. Most of them had minor gastrointestinal adverse effects—five in metformin monotherapy and two in MI based therapy group. No major adverse effects were noted. In summary, menstrual cycle regularity and quality of life improvement was greater and

statistically significant in MI with metformin group when compared with metformin monotherapy group. There was no significant difference between the two groups at the end of 6 months for any of the other continuous variables.

4 | DISCUSSION

PCOS is one of the most common endocrine disorders of reproductive age group women with rising prevalence of obesity, gestational and type 2 diabetes mellitus globally. Due to its progressive nature, untreated PCOS results in long-term metabolic and fertility consequences as well as distressing symptoms to affected women, lead to an important public health issues. In the present well-designed randomized controlled trial, we studied the efficacy of metformin monotherapy versus combination of metformin and MI-based therapy in various clinical, hormonal and metabolic parameters in obese reproductive age group women from South Indian population of 2900 bedded multispecialty tertiary care state government

TABLE 3 Comparison of change in PCOSQ before and after 6 months treatment in the two groups.

	MF	MI + MF
Before treatment	34.8 ± 7.9	36.3 ± 8.3
After 6 months of treatment	88.1 ± 15.9	108.1 ± 12.2
Mean difference	−15.45	−63.13
Wilcoxon signed-rank test	$p < .001$	$p < .001$
Mann–Whitney (6 m b/w groups)	$p < .001$	

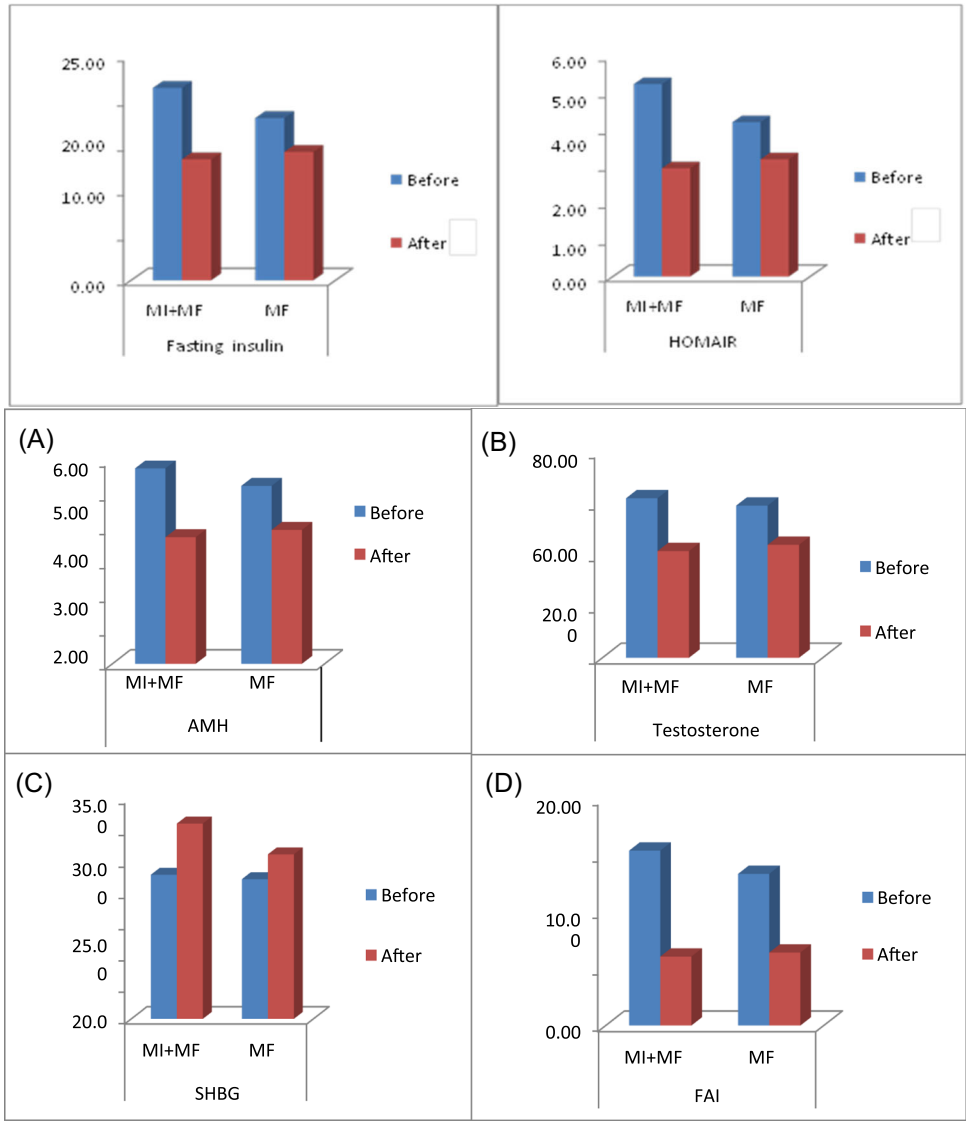

FIGURE 2 Comparison of fasting insulin, HOMA-IR, hormonal parameters—(A) AMH (B) Testosterone (C) SHBG (D) FAI before and after 6 months treatment in metformin with myoinositol group versus metformin monotherapy group. AMH, anti-Mullerian hormone; FAI, free androgen index; SHBG, sex hormone binding globulin.

hospital. Studies in the past regarding the benefits of MI in PCOS as compared with metformin and placebo are very limited with equivocal and conflicting results.[13–15] Couple of studies showed that both were equally effective,[16,17] few showed MI was superior to metformin in significantly improving different outcome measures[7,10] and one study reported that metformin was superior to MI.[18] Two recent research articles studied only the effects of MI without any controlled population.[19,20] To the best of our knowledge, the present study is the only randomized trial exclusively studying obese and overweight PCOS women of reproductive age group, comparing metformin monotherapy versus metformin in combination with MI-based therapy.

A greater proportion of patients had regular menstrual cycles at the end of 6 months in the group receiving MI with DCI along with metformin as compared with metformin monotherapy. This statistically significantly greater improvement in cycle regularity by using a combination of MI and metformin than metformin alone is in agreement with the findings of Aggarwal et al.[7] and Chabbra et al.[8] In contradictory few studies, reported that menstrual cycle regularity improved in both groups treated with metformin as well as MI monotherapy and no significant difference between them.[9,16] Hence, the present study revealed that both metformin and MI exert independent beneficial effects in improving menstrual cycle regularity and have an additive effect when used together, probably because they act synergistically through different mechanisms to improve the pathogenic mechanisms underlying PCOS.[6,16] The local action in the ovarian follicle by MI with DCI, may account for the greater improvement in cycle regularity with normalization of menstrual cycle length seen with MI in the present study. Even though conception rate is similar in both arms, significantly earlier pregnancy rate noted in the group receiving MI with DCI in addition to metformin (51.67 ± 7.09 vs. 77 ± 11.3 days, $p < .001$).

We found that both metformin alone and in combination with MI significantly improved anthropometric measures including, BMI and WC as well as clinical features of hyperandrogenism assessed by mFG and GAS scores for hirsutism and acne respectively at the end of 6 months. Fruzzetti et al.[16] showed both metformin and MI had beneficial effect in lowering BMI and WC, which are in concordance with the present study, but differed by significant improvement on hirsutism and acne in both groups. The other reported studies from India[7,9,21] showed that there were no significant difference between metformin group and MI groups. This suggests that perhaps Indians may respond faster in terms of clinical measures of hyperandrogenism as compared with the Western population to both metformin and MI.

There was a significant decrease in insulin resistance assessed by decrease in HOMA-IR, fasting insulin and fasting plasma glucose by both groups with no statistical difference between the groups. This differs from the study by Agrawal et al.[7] and Mishra et al.[20] which found a greater improvement in insulin resistance in the group receiving MI with metformin. A randomized controlled cross-over trial[18] which compared metformin with MI, reported significant decrease in insulin resistance in both MI and metformin arms without a significant difference between the two arms, similar to the present study. These reflect a need for further studies with larger sample size and better biochemical markers to assess the benefit of adding MI to metformin in improving insulin resistance as two international studies[17,18] showed improvements with both drugs though without any significant difference between the groups. Based on the present study and previously published literature, we suggest that the use of metformin and MI would be beneficial in women with PCOS with insulin resistance. As clinical improvements especially menstrual cycle regularity improvement was considerably improved by adding MI, it could be possible that the local action of MI at the level of ovarian follicles may exert a synergistic effect to the insulin sensitivity of metformin, though not reflected biochemically by greater improvement in fasting insulin and HOMA-IR.[22,23]

In both groups reduction in total testosterone and increase in SHBG at the end of 6 months. Other studies published by Fruzzetti et al.,[15] Angik et al.[9] and Agrawal et al.[7] reported similar improvement with both metformin and MI monotherapy with no significant difference between groups.

We also found significant improvement in quality of life as assessed by PCOS-Q questionnaire in both groups with statistically greater improvement in group receiving MI-based therapy as compared with the metformin monotherapy group. Ovarian MI:DCI ratio drops to 0.2:1 in women with PCOS and restoring the levels into 40:1 may improve the ovarian function as well as greater improvement in cycle regularity with normalization of cycle length is seen with MI.[24,25] This supports the use of MI-based therapy in addition to metformin young reproductive age group women with more disturbing symptoms of PCOS. None of the previous studies assessed the PCOS questionnaire and hence the quality of life questionnaire is unique in our study.

There was a statistically significant reduction in the ovarian volumes measured by ultrasound in both groups with no significant difference between the two groups at the end of 6 months.

Six women, three in each group, became pregnant during the study; In spite of significant improvement in GAS, mFG score, weight, BMI, WC, fasting plasma glucose, HOMA-IR, serum AMH, serum testosterone, SHBG and FAI in both groups, there was no statistically significant difference between the two groups in terms of improvement in metabolic parameters or clinical measures of hyperandrogenism at the end of 6 months treatment.

Three previous studies compared metformin monotherapy versus combination therapy of metformin with MI in PCOS women with the primary outcome as AMH.[7,8] Measurement of AMH reflects underlying ovarian reserve and high levels prevent follicle dominance and recruitment of multiple follicles into dominant follicle. AMH levels are higher in PCOS women as compared with normal women, with levels being five times higher in anovulatory PCOS than ovulatory PCOS.[8] Among the studies which included AMH as a parameter, one showed that MI had no significant effect[26]; another demonstrated that there was fall in AMH in all groups but no significant difference[8] and the third reported that both metformin and MI improved AMH.[7] In the present study, we noted similar

findings like previous Indian studies[7,8] that the AMH levels decreased significantly in both groups. We perform AMH in reliable ECLIA method (Roche Diagnostics) as compared with different assay methology in previous studies.

The strengths of the present study are this is the first well-defined randomized controlled trial by studying the effects of metformin and MI in PCOS and also the first trial in India that studied reproductive and noninfertility subjects. In addition, it is a prospective trial using an active comparator, a large number of clinical and relevant hormonal parameters including AMH, SHBG, total testosterone, insulin by ECLIA estimation which was assessed and followed up meticulously at 3 and 6 month interval. To the best of our knowledge, this is the first study the quality of life was also assessed by PCOSQ questionnaire, as compared with previous published study.

Limitations of our study are sample size and duration of follow-up is 6 months, longer duration of the treatment needs to be studied. A large multicenter study including women with PCOS of different ethnicities is required to support the findings of the present study.

5 | CONCLUSION

Metformin alone as well as in combination with MI significantly improved the clinical, metabolic and biochemical markers of hyperandrogenism after 6 months. The menstrual cycle regularity and quality of life are significantly greater in the group receiving MI-based therapy as compared with metformin monotherapy. Thus the addition of MI with metformin exerts more beneficial effects in improvement of menstrual cycle regularity and quality of life.

AUTHOR CONTRIBUTIONS

Roshan Nazirudeen was involved in collection of data. Raghavendran Priyanka was involved preparation of the manuscript for submission. Baskaran Sumathi was involved in workup of patients and management. Vasanthiy Natarajan was involved in workup of patients and management. Eagappan Subbiah was involved in supervision of workup. Kasthuri Santharam Raghavan was involved in statistical analysis. Subbiah Sridhar was involved in the concept, design and final approval of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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