Received: 28 March 2021 | Revised: 4 September 2021 | Accepted: 6 October 2021 | First published online: 10 November 2021

DOI: 10.1002/ijgo.13971

CLINICAL ARTICLE

Gynecology

Efficacy of myo-inositol and D-chiro-inositol combination on menstrual cycle regulation and improving insulin resistance in young women with polycystic ovary syndrome: A randomized open-label study

Garima Kachhawa[1] | Krithika V. Senthil Kumar[1] | Vidushi Kulshrestha[1] | Rajesh Khadgawat[2] | Reeta Mahey[1] | Neerja Bhatla[1]

[1]Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, New Delhi, India

[2]Department of Endocrinology & Metabolism, All India Institute of Medical Sciences, New Delhi, India

***Correspondence**
Garima Kachhawa, Room no: 3086, 3rd floor Teaching Block, RAK OPD, All India Institute of Medical Sciences, New Delhi, 110029, India.
Email: garimakachhawa2012@gmail.com

Abstract

Objective: To compare the effect of myo-inositol and D-chiro-inositol in combination (MI + DCI) with combined hormonal contraceptive (CHC) on menstrual cycle regulation in young Indian women with polycystic ovary syndrome (PCOS).

Methods: Seventy young women with PCOS aged 15–24 years with delayed cycles were randomized into two groups and were treated for 6 months with MI + DCI (550 + 150 mg, 3.6:1 ratio) twice a day and CHC (ethinyl estradiol 20 µg + drospirenone 3 mg) once a day.

Results: Spontaneous menses resumed in 28 (84.85%) young women on MI + DCI, compared with withdrawal bleeding in 34 (100%) on CHC. The mean cycle length reduced with both MI + DCI (124.54 ± 8.08 to 57.75 ± 3.00 days, $P < 0.001$) and CHC (105.88 ± 7.96 to 30.53 ± 2.95 days, $P < 0.001$). Regular menstrual cycles were established in 9 (27.27%) young women with MI + DCI ($P = 0.001$) and 30 (88.23%) with CHC ($P < 0.001$). Three months after stopping the treatment, 24 young women (85.71%) on MI + DCI and 25 (73.53%) on CHC continued to have spontaneous cycles. Anti-Müllerian hormone decreased with both the drugs ($P = 0.001$), whereas luteinizing hormone ($P = 0.001$) and testosterone ($P = 0.04$) decreased with CHC and homeostatic model assessment of insulin resistance ($P < 0.001$) with MI + DCI.

Conclusion: Myo-inositol and D-chiro-inositol in combination (3.6:1 ratio) are effective in regularizing menstrual cycles and improving insulin resistance.

Trial registration: Clinical Trials Registry of India (CTRI/2018/03/012643). http://ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=20969&EncHid=&userName=myo-inositol

KEYWORDS
menstrual cycle regulation, myo-inositol and D-chiro-inositol combination, polycystic ovary syndrome, young women

1 | INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine cause of menstrual irregularity and ovarian dysfunction in women of reproductive age, with a global prevalence of about 5.5%–16%.[1] Menstrual complaints such as delayed menarche, oligo-amenorrhea, or polymenorrhea are the most common presenting complaints in adolescents and young women with PCOS. Delayed menses particularly in young women creates a lot of anxiety among their parents, warranting prompt symptomatic relief. Also, prolonged oligo-amenorrheic cycles at the age of 14–19 years are a predictive factor for persistent ovulatory dysfunction in adulthood.[2] In addition, the associated features of hyperandrogenism and weight issues increase the stress in young women, leading to negative body image and low self-esteem.

As the name suggests, PCOS is not a disease confined to the ovaries. Instead, it has complex clinical manifestations predisposing to an increased risk of type 2 diabetes mellitus, metabolic syndrome, dyslipidemia, and coronary heart disease.[3] Also, prolonged periods of oligoamenorrhea increase the risk of endometrial hyperplasia and cancer due to unopposed estrogen. Recent evidence suggests insulin resistance to be the primary pathogenic factor for the development of PCOS,[4] which further explains the cardio-metabolic manifestations of PCOS. Hence, prompt treatment of PCOS in young women is not only essential for regularizing menstrual cycles but is also significant to address the long-term consequences.

Traditionally, cyclical progesterone therapy or Combined Hormonal Contraceptives (CHC) formed the mainstay of treatment for menstrual dysfunction in PCOS patients. Later, considering insulin resistance in mind, metformin was added to the treatment options.[5] Recently, inositols (myo-inositol [MI] and D-chiro-inositol [DCI]), group B vitamins with insulin-sensitizing action, have been shown to improve insulin signaling, decrease serum androgens, improve follicular maturity, and restore spontaneous ovarian activity in women with PCOS.[6] Evidence from assisted reproductive therapy cycles has shown that a combination of MI and DCI improves hormonal and metabolic parameters, ovulation rates, and pregnancy rates.[7] Extrapolating these findings that improved ovulation rates should also regularize the menstrual cycles (frequency between 24 and 38 days), we aimed to study the effect of MI (550 mg) plus DCI (150 mg) in combination on normalizing the menstrual cycle pattern in young Indian women with PCOS.

2 | MATERIALS AND METHODS

The present study was a randomized clinical trial, an open-labeled study conducted in the tertiary care center from March 2018 to November 2019, according to the Declaration of Helsinki. Permission was obtained from the Institutional Ethics Committee before the start of the study (IECPG-536/20.12.2017, RT-7/31.01.2018) and the trial was registered with the Clinical Trials Registry of India (CTRI/2018/03/012643).

For sample size calculation, considering 100% improvement in the menstrual cycle with combined hormonal contraceptives and 65% with inositols,[8] an a priori sample of 30 young women in each arm would have achieved statistical significance with 80% power at a 5% level of one-sided significance. Taking into account the 10% dropout rate, a sample size of 70 was proposed and the study participants were randomized into two groups of 35 each to maintain a 1:1 ratio. Finally, based on the results obtained from repeated measures analyses of variance, we estimated post-hoc power for average cycle length duration.

Seventy young women aged 15–24 years who were diagnosed with PCOS based on 2003 Rotterdam criteria were recruited. The informed consent form, including the assent form for participants younger than 18 years, was signed at the start of the course. Young women who were pregnant or wanting to become pregnant during the study period, with a body mass index (BMI calculated as weight in kilograms divided by the square of height in meters) more than 30, with diabetes mellitus, or with a history of any hormonal treatment including contraceptives, glucocorticoids, lipid-lowering drugs, glucose-lowering drugs, or anti-obesity drugs within 3 months of the study were excluded from the study.

Detailed menstrual histories recording duration of cycle and bleeding days, abnormal body hair growth, and weight gain were taken for all study participants. Anthropometric measurements, modified Ferriman-Gallwey score and Global Acne Grading System were made. All the participants were shown and encouraged to maintain a menstrual diary. Ultrasound was performed to evaluate ovarian morphology and to rule out pelvic pathology. Hormone profile including follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone, thyroid-stimulating hormone (TSH), prolactin, and anti-Müllerian hormone (AMH) was recorded on days 2–4 of a spontaneous or withdrawal cycle. Only in patients presenting with hyperandrogenism was 17-hydroxyprogesterone measured. Also, baseline fasting serum samples were taken for lipid profile, glucose, insulin, liver and kidney functions, and homeostatic model assessment of insulin resistance (HOMA-IR) was calculated.

The study participants were randomized into two groups based on a computer-generated randomization table and the opaque envelope method was followed. The MI + DCI group ($n = 35$) received the intervention drug, Mychiro (myo-inositol 550 mg and D-chiro-inositol 150 mg, USV Private Ltd.) twice a day for 6 months and the CHC group ($n = 35$) received the control drug, a monophasic combined hormonal contraceptive pill, Dronis-20 (ethinyl estradiol 20 μg and drospirenone 3 mg, Sun Pharmaceutical Industries Ltd., Goregaon, Mumbai, India) to induce cyclical withdrawal bleeding for 6 months.

The primary outcome was the improvement in menstrual cycle length and resumption of spontaneous cycles. Secondary outcome measures included metabolic (BMI, waist-hip ratio, fasting blood glucose, fasting insulin, HOMA-IR, lipid profile) and hormonal (FSH, LH, testosterone, AMH) parameters and ovarian volume.

The normal or regular cycle was defined as the frequency of the menstrual cycle between 24 and 38 days.[9] The spontaneous cycle was defined as the menstrual bleeding occurring without hormone therapy, whereas withdrawal bleeding referred to menstrual

bleeding secondary to cyclical progesterone or combined hormonal pills. Non-responder was defined as no spontaneous menstrual cycle for 3 months, thereby requiring withdrawal bleeding.

The participants were followed up at 3 and 6 months of treatment and 3 months after stopping treatment. Compliance with the treatment drug was ensured over the phone and further verified by counting empty packets during each follow-up visit. If the participant did not resume her menstrual cycles during the 3-month period, progesterone withdrawal was given, while she continued to take the study drug.

The statistical analysis was carried out using Statistical Package STATA version 12.0 (StataCorp LLC, College Station, TX, USA). Continuous variables were tested for normality assumptions using the Kolmogorov-Smirnov test. Mean values were compared using Student's *t* independent test and non-normal/skewed data using the Mann-Whitney *U* test. Categorical variables were compared using the χ^2 test or Fisher exact test as appropriate. Post-treatment improvement from baseline was tested based on Student's *t* paired test within each group. Repeated measures analysis of variance was applied to see the trend in cycle regularization over time. For all statistical tests, a two-sided probability of $P < 0.05$ was considered as statistical significance.

3 | RESULTS

Of the 70 young women, two in the MI + DCI group and one in the CHC group were lost to follow up 3 months after starting treatment. The patient flow is shown in the consort diagram (Figure 1).

The baseline and demographic profiles of participants in both groups were comparable (Table 1). Hirsutism was complained of by 24 (34.28%) study participants, and 22 (31.42%) had a history of excessive weight gain. PCOS phenotypes are currently classified based on three parameters—menstrual dysfunction (MD), hyperandrogenism (HA), and polycystic ovarian morphology (PCOM). The majority of the study participants (44; 62.85%) belonged to phenotype D (MD + PCOM). Phenotype A (MD + HA + PCOM), which is the most severe type, constituted a third of the study participants (23; 32.86%). The remaining three (4.29%) young women belonged to phenotype B (MD + HA). As menstrual cycle regulation was the primary outcome, phenotype C (HA + PCOM), which comprises patients with regular cycles, was not included in the study.

Spontaneous menses resumed in 28 (84.85%) young women in the MI + DCI group after 6 months of treatment, compared with withdrawal bleeding in 34 (100%) young women on CHC. The mean cycle length significantly ($P < 0.001$) decreased in both the groups, although more in the CHC group (Table 2). The reduction in mean cycle length was 54% in the MI + DCI group compared with 70% in the CHC group. At 3 months of treatment with MI + DCI, spontaneous menses occurred in 26 (78.79%) young women with a mean cycle length of 62.81 ± 3.21 days. Regular menstrual cycles (24–38 days) occurred in nine (27.27%) young women ($P = 0.001$) after 6 months of treatment compared with none at presentation (Figure 2). Furthermore, 3 months after stopping treatment, 24 (85.71%) in the MI+DCI group and 25 (73.53%) in the CHC group continued to have spontaneous cycles. At the end of treatment,

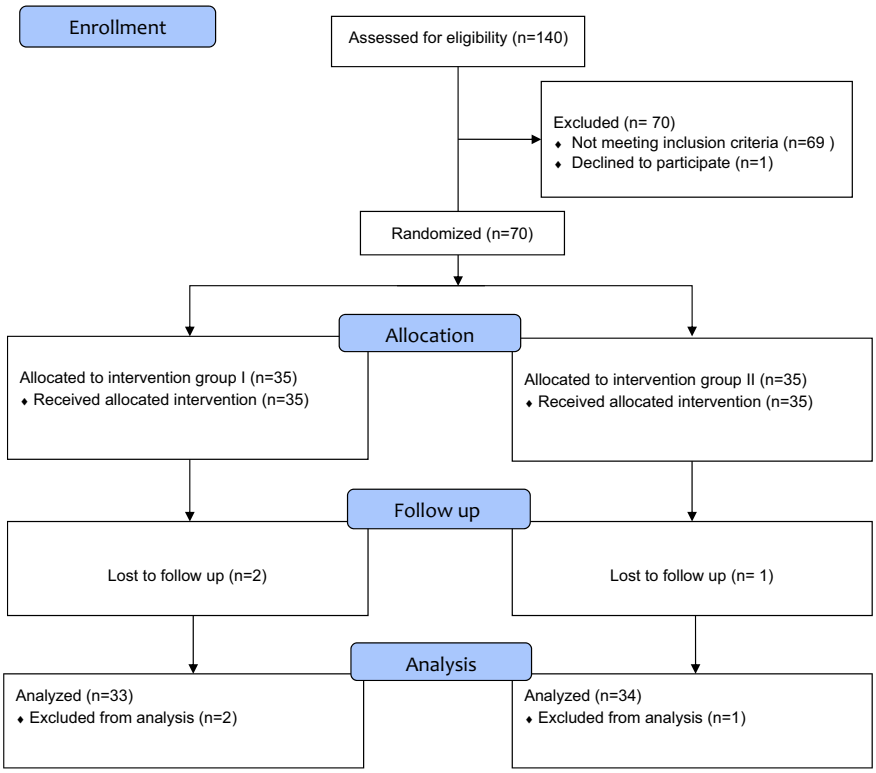

FIGURE 1 CONSORT flow diagram

TABLE 1 Comparison of demographic and baseline characteristics between the groups[a]

Baseline characteristics	MI + DCI group ($n = 35$)	CHC group ($n = 35$)	p value
Age, years	20.80 ± 2.24	20.62 ± 2.34	0.756
Age at menarche, years	13.24 ± 1.61	13.8 ± 1.41	0.129
Weight, kg	60.23 ± 10.78	60.92 ± 11.48	0.794
Body mass index[b]	24.97 ± 4.03	24.93 ± 4.09	0.965
Waist-hip ratio	0.93 ± 0.04	0.91 ± 0.05	0.078
Mean cycle length, days	124.54 ± 8.08	105.88 ± 7.96	0.050
Clinical and/or biochemical hyperandrogenism	15 (42.85%)	10 (28.57%)	0.371
Fasting blood glucose, mg/dl	88.28 ± 9.62	88.22 ± 9.21	0.980
Fasting insulin, μU/ml	11.28 ± 5.62	10.27 ± 4.52	0.411
HOMA-IR	2.50 ± 1.39	2.25 ± 1.07	0.408
Follicle-stimulating hormone, mIU/ml	5.38 ± 1.33	5.70 ± 2.02	0.426
Luteinizing hormone, mIU/ml	8.84 ± 4.57	9.99 ± 6.04	0.372
Prolactin, ng/ml	16.67 ± 8.77	15.63 ± 7.29	0.592
Thyroid-stimulating hormone, μIU/ml	2.64 ± 1.19	2.22 ± 1.10	0.135
Testosterone, ng/ml	0.476 ± 0.18	0.413 ± 0.11	0.116
Anti-Müllerian hormone, ng/ml	10.35 ± 4.66	11.26 ± 4.71	0.419
Total cholesterol, mg/dl	164.78 ± 30.76	157.94 ± 23.47	0.299
Low-density lipoprotein cholesterol, mg/dl	108.34 ± 22.61	101.77 ± 19.56	0.198
High-density lipoprotein cholesterol, mg/dl	39.97 ± 9.88	43.65 ± 6.71	0.073
Triglyceride, mg/dl	115.48 ± 43.24	107.31 ± 43.73	0.435
Right ovarian volume, cm^3	11.78 ± 2.78	12.92 ± 3.6	0.145
Left ovarian volume, cm^3	12.53 ± 2.66	11.92 ± 2.6	0.424

Note: Abbreviations: CHC, combined hormonal contraceptive; HOMA-IR, homeostatic model assessment of insulin resistance; MI + DCI, myo-inositol and D-chiro-inositol combination.

[a]Values are presented as means ± standard deviation or as number (percentage).

[b]Body mass index (calculated as weight in kilograms divided by the square of height in meters).

amenorrhea persisted in five (15.15%) young women receiving MI + DCI.

The secondary outcome measures in terms of anthropometry, insulin resistance, and hormonal parameters (Table 2) showed a significant reduction in markers of insulin resistance with the MI + DCI group compared with CHC. Further, the improvement in fasting insulin and HOMA-IR continued even 3 months after stopping the treatment.

Serum LH ($P = 0.026$), testosterone ($P = 0.042$), and AMH ($P < 0.001$) showed a significant reduction in the CHC-treated groups, but only AMH ($P < 0.001$) showed a significant reduction in the MI + DCI group.

No significant adverse effects were noted in either of the groups.

4 | DISCUSSION

Menstrual cycle irregularity during adolescence may be caused by various factors such as thyroid disorders, eating disorders, adrenal disorders, pituitary causes, or more commonly PCOS.[10] Despite its varying etiology, irregular menses requires immediate attention and correction.

Menstrual dysfunction is the hallmark of hormonal and metabolic imbalance, and its management also requires a multipronged approach. Lifestyle management significantly improves metabolic parameters long term but has not been prescribed as a stand-alone treatment for cycle regulation.[11] Also, long-term commitment is a challenge in young women. Initially, cyclical progesterone and CHC were primarily used for cycle regularization in PCOS. However, there are several constraints in prescribing CHC for a long duration in young women. CHC induce withdrawal bleeding by direct action on the endometrium and causing ovarian suppression. The association of CHC with an increased incidence of thrombosis, adverse metabolic changes, and increased risk of breast cancer, precludes their use over a prolonged period in young women.[12,13] There remains parental anxiety for cultural reasons for CHC use in young women. As non-hyperandrogenic PCOS is the predominant phenotype in the Indian population,[14] CHC use in such young women may be an overprescription. Our study also revealed non-hyperandrogenic PCOS to be the dominant phenotype (62.8%). Hence, there is a need for a suitable alternative in these young women for cycle regulation.

TABLE 2 Effect of treatments on clinical, hormonal and metabolic parameters.[a]

Parameter	MI + DCI group ($n = 33$)			CHC group ($n = 34$)		
	Baseline	6 months after treatment	3 months after stopping treatment	Baseline	6 months after treatment	3 months after stopping treatment
Anthropometry						
Weight (kg)	61.12 ± 10.41	60.52 ± 9.94	60.53 ± 9.80	61.39 ± 11.31	60.41 ± 10.60	60.26 ± 10.57
BMI	25.31 ± 3.90	25.11 ± 3.64	24.70 ± 3.91	25.08 ± 4.06	24.70 ± 3.91	24.65 ± 3.95
Waist-hip ratio	0.94 ± 0.03	0.94 ± 0.02	0.91 ± 0.05	0.91 ± 0.05	0.91 ± 0.06	0.91 ± 0.05
Menstrual cycle length						
Mean cycle length, days	124.54 ± 8.08	57.75 ± 3.00*	67.66 ± 4.55*	105.88 ± 7.96	30.53 ± 2.95*,†	69.47 ± 4.49*
Regular cycle	0	9 (27.27%)*	4 (12.12%)	0	34 (100%)*,†	8 (23.53%)
Oligomennorrhea	13 (39.39%)	19 (57.58%)	20 (60.61%)	21(61.76%)	0*,†	17 (50.00%)
Amenorrhea	20 (60.61%)	5 (15.15%)*	9 (27.27%)*	13 (38.24%)	0*	9 (26.47%)*
Insulin resistance						
FBG, mg/dl	88.88 ± 9.52	88.48 ± 6.29	86.30 ± 5.51	88.24 ± 9.35	88.03 ± 7.15	88.41 ± 6.16
Fasting insulin, μU/ml	11.58 ± 5.64	7.76 ± 4.51*	5.08 ± 3.84*	10.20 ± 4.45	9.64 ± 4.07	8.55 ± 3.82*,†
HOMA-IR	2.61 ± 1.39	1.79 ± 1.08*	1.09 ± 0.91*	2.29 ± 1.15	2.12 ± 0.97	1.88 ± 0.91*,†
Hormonal parameters						
FSH, mIU/ml	5.44 ± 1.34	5.35 ±1.22	5.07 ± 1.51	5.63 ± 2.00	5.78 ± 1.90	5.33 ± 1.95
LH, mIU/mL	8.34 ± 4.13	8.14 ± 3.85	7.60 ± 4.85	9.62 ± 5.71	8.45 ± 4.15*	7.58 ± 4.90*
Testosterone, ng/ml	0.46 ± 0.18	0.44 ± 0.12	0.43 ± 0.11	0.42 ± 0.11	0.38 ± 0.10*	0.38 ± 0.11*
AMH, ng/ml	10.11 ± 4.69	8.39 ± 3.67*	6.97 ± 4.27*	11.10 ± 4.67	8.89 ± 4.01*	8.72 ± 3.66*
Ovarian volume, cm^3						
Right ovary	11.78 ± 2.78	11.37 ± 2.73	11.10 ± 2.60	12.92 ± 3.6	12.15 ± 2.24	11.79 ± 2.37
Left ovary	12.53 ± 2.66	11.68 ± 2.79	11.21 ± 2.44	11.92 ± 2.6	11.14 ± 2.44	10.83 ± 2.36

Abbreviations: AMH, anti-mullerian hormone; FSH, follicle stimulating hormone; FBG, fasting blood glucose; HOMA-IR, homeostatic model assessment of insulin resistance; LH, leuteinizing hormone.

[a]Values are presented as means ± standard deviation or as number (percentage).

*$P < 0.05$, compared with the level at the baseline.

†$P < 0.05$, between MI + DCI and CHC groups.

Since the early twentieth century, inositols, which are group B vitamin supplements with insulin-sensitizing properties, have been shown to improve ovarian follicular maturity and decrease serum androgens in PCOS.[15] The two most abundant stereoisomers of inositol, MI and DCI, play integrative roles in the body. The inositols are used as an adjunct in ART cycles and improvement in menstrual cycle regularity has been observed as a result of improved ovulation and insulin sensitivity.[16,17]

Evidence shows that MI improves ovarian function, menstrual cycle regularity and insulin sensitivity. Besides, MI also improves metabolic parameters as opposed to CHC.[18] Several authors have suggested the utility of DCI in improving BMI, hormonal parameters, and insulin resistance. DCI has shown menstrual regularization in 62.5% of cases, and the effect was evident within 4 months of treatment.[19] Our study showed that spontaneous menstrual cycles occurred in around 79% of young women at 3 months of treatment with MI + DCI with a mean cycle length of 62.81 ± 3.21 days.

Formuso et al. compared MI with DCI and showed that both isomers significantly improve menstrual cycle regularity and hormono-metabolic parameters in PCOS patients.[20] Considering the systemic and ovarian hallmarks of PCOS, it is prudent to use both the isomers to have a synergistic effect. This fact was highlighted in a systematic review that MI improves FSH signaling and ovulatory function, whereas DCI improves peripheral insulin sensitivity, thereby explaining the enhanced outcomes with combination therapy.[21] However, even after two decades of use in PCOS, the effective dose and the proportion of inositol isomers are not well established because of the heterogeneity of study designs. Taking into consideration the physiological blood ratio and ovarian epimerase activity resulting in the conversion of MI to DCI in the ovary, the majority of studies have used MI and DCI in the ratio of 40:1.[22,23] However, some authors have suggested that the absolute concentration of MI and DCI is essential, not the ratio.

Recently, seven different combinations of MI and DCI were studied and it was recorded that spontaneous menstrual cycles were regained in five out of eight patients in a 40:1 ratio and in one out of eight patients in a 5:1 ratio, whereas with a 2.5:1 ratio, none regained menses.[24] The recent study in intracytoplasmic sperm injection

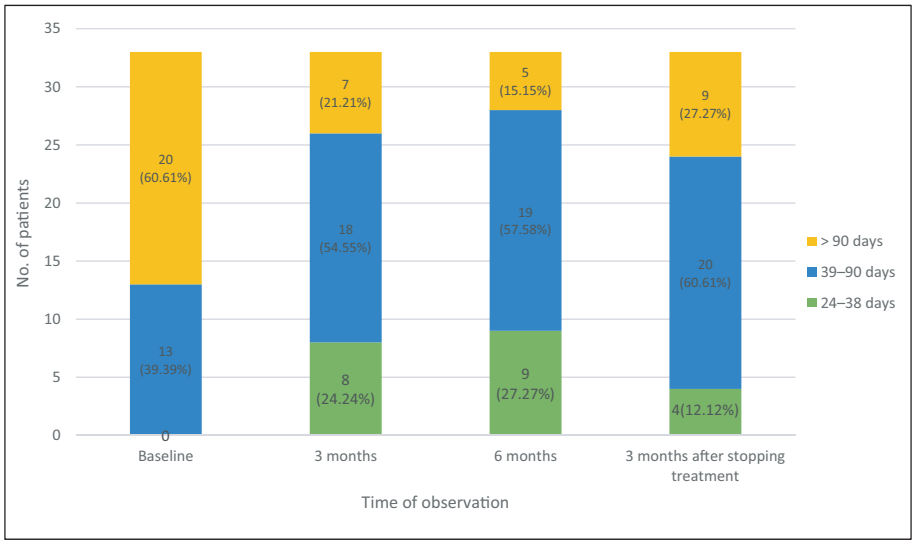

FIGURE 2 Change in menstrual pattern among young women treated with myo-inositol and D-chiro-inositol combination

TABLE 3 Comparison of parameters among the responders and non-responders in the MI + DCI group[a]

Parameters	Non-responders ($n = 5$)	Responders ($n = 28$)	p value
Cycle length, days	150.00 ± 36.74	120.00 ± 45.29	0.173
BMI	24.63 ± 3.80	25.43 ± 3.97	0.678
Waist circumference, cm	89.40 ± 8.39	89.04 ± 9.39	0.936
Waist-hip ratio	0.92 ± 0.04	0.95 ± 0.03	0.111
Testosterone, ng/ml	1.00 ± 0.00	0.32 ± 0.47	0.004
Fasting insulin, μU/ml	14.80 ± 4.43	10.89 ± 5.59	0.150
HOMA-IR	3.40 ± 1.51	2.46 ± 1.34	0.169
AMH, ng/ml	15.40 ± 3.36	9.00 ± 4.28	0.004
Phenotype A	4 (80.00%)	6 (21.43%)	0.021

Abbreviations: AMH, anti-Müllerian hormone; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CHC, combined hormonal contraceptive; HOMA-IR, homeostatic model assessment of insulin resistance; MI + DCI, myo-inositol and D-chiro-inositol combination.

[a]Values are presented as means ± standard deviation or as number (percentage).

cycles established that the pregnancy rate was significantly higher with an MI and DCI combination with higher DCI doses (3.6:1) than with lower DCI doses (40:1) group.[25] Our study has shown that MI and DCI in the 3.6:1 ratio are effective in restoring menstrual regularity in 85% of adolescents and young women with PCOS.

Although 27.27% of young women had regular cycles (24–38 days) and 57.58% had oligomenorrheic cycles (39–90 days), 15.15% remained amenorrheic. When compared with young women with oligomenorrhea, those with amenorrhea had significantly increased insulin resistance ($P = 0.004$) and AMH ($P = 0.029$). Univariate analysis (Table 3) showed that the PCOS patients of phenotype A, those with higher AMH and hyperandrogenism, responded poorly to treatment with inositols. However, the parameters like BMI, waist circumference, waist-hip ratio, fasting insulin, and HOMA-IR did not affect the response to treatment with inositols. This affirms that obesity, fat distribution, and insulin resistance do not preclude the use of inositol therapy in PCOS patients.

The restoration of a spontaneous menstrual cycle by inositols was associated with a significant decrease in insulin resistance ($P < 0.001$) and AMH ($P < 0.001$), thereby improving ovarian function synergistically with decreasing insulin resistance. This is reflected in the persistent positive effect on cycle regularization even after stopping treatment for 3 months. Hence, treatment with MI + DCI targets the basic pathogenesis of PCOS by improving insulin sensitivity, as opposed to CHC, which causes ovarian suppression and withdrawal bleeding. Moreover, no significant adverse effects were noted with MI+DCI in our study.

The strength of our study is that the resumption of spontaneous menstrual cycles is significant and sustained with 500 mg of MI and 150 mg of DCI twice daily, compared with CHC. Also, young women with higher BMI and insulin resistance were included in the study, thereby providing a checkpoint on an overestimation of the outcomes in young women with milder disease. The limitation of our study is the smaller sample size and lack of blinding.

The results of the present study suggest that a myo-inositol and D-chiro-inositol combination in the ratio of 3.6:1 showed promising results in regularizing menstrual cycles and improving insulin resistance with immediate effect and the effect persisted even after stopping the treatment. It is a better alternative to CHC in terms of improvement in ovarian function, favorable lipid parameters, and lack of serious adverse effects. However, further studies are required to optimize the dose and duration of use, particularly in young women.

ACKNOWLEDGMENTS

We thank Dr P Vanamail, Additional Professor of Biostatistics, All India Institute of Medical Sciences, New Delhi for his immense help in mapping out the sample size and data analysis. The authors would like to acknowledge USV Private Ltd., Bengaluru, India and Sun Pharmaceutical Industries Ltd., Mumbai, India for providing free drug samples used in this study.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

KG conceived the study. KG and KR formulated the methodology. KVS, KV, MR, and BN participated in data collection. KG and KVS performed the statistical analysis and drafted the manuscript. All authors contributed to the revision and approved the final manuscript.

REFERENCES

1. Ding T, Hardiman PJ, Petersen I, Wang F-F, Qu F, Baio G. The prevalence of polycystic ovary syndrome in reproductive-aged women of different ethnicity: a systematic review and meta-analysis. *Oncotarget*. 2017;8(56):96351-96358.
2. Rosenfield RL, Ehrmann DA, Littlejohn EE. Adolescent polycystic ovary syndrome due to functional ovarian hyperandrogenism persists into adulthood. *J Endocrinol Metab*. 2015;100(4):1537-1543.
3. Ramezani Tehrani F, Amiri M, Behboudi-Gandevani S, Bidhendi-Yarandi R, Carmina E. Cardiovascular events among reproductive and menopausal age women with polycystic ovary syndrome: a systematic review and meta-analysis. *Gynecol Endocrinol*. 2020;36(1):12-23.
4. Diamanti-Kandarakis E, Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. *Endocr Rev*. 2012;33(6):981-1030.
5. Al Khalifah RA, Florez ID, Dennis B, Thabane L, Bassilious E. Metformin or oral contraceptives for adolescents with polycystic ovarian syndrome: a meta-analysis. *Pediatrics*. 2016;137(5):e20154089.
6. Sortino MA, Salomone S, Carruba MO, Drago F. Polycystic ovary syndrome: insights into the therapeutic approach with inositols. *Front Pharmacol*. 2017;8(8):341.
7. Bevilacqua A, Carlomagno G, Gerli S, et al. Results from the International Consensus Conference on myo-inositol and D-chiro-inositol in Obstetrics and Gynecology—assisted reproduction technology. *Gynecol Endocrinol*. 2015;31(6):441-446.
8. Raffone E, Rizzo P, Benedetto V. Insulin sensitiser agents alone and in co-treatment with r-FSH for ovulation induction in PCOS women. *Gynecol Endocrinol*. 2010;26(4):275-280.
9. Munro MG, Critchley HOD, Fraser IS, The FIGO Menstrual Disorders Committee. The two FIGO systems for normal and abnormal uterine bleeding symptoms and classification of causes of abnormal uterine bleeding in the reproductive years: 2018 revisions. *Int J Gynecol Obstet*. 2018;143(3):393-408.
10. Witchel SF, Burghard AC, Tao RH, Oberfield SE. Diagnosis and treatment of PCOS in adolescents: an update. *Curr Opin Pediatr*. 2019;31(4):562-569.
11. Lass N, Kleber M, Winkel K, Wunsch R, Reinehr T. Effect of lifestyle intervention on features of polycystic ovarian syndrome, metabolic syndrome, and intima-media thickness in obese adolescent girls. *J Endocrinol Metab*. 2011;96(11):3533-3540.
12. Wu C, Grandi S, Filion K, Abenhaim H, Joseph L, Eisenberg M. Drospirenone-containing oral contraceptive pills and the risk of venous and arterial thrombosis: a systematic review. *BJOG Int J Obstet Gynaecol*. 2013;120(7):801-811.
13. Manzoor S, Ganie MA, Amin S, et al. Oral contraceptive use increases risk of inflammatory and coagulatory disorders in women with Polycystic Ovarian Syndrome: an observational study. *Sci Rep*. 2019;9(1):10182.
14. Panidis D, Tziomalos K, Papadakis E, et al. Associations of menstrual cycle irregularities with age, obesity and phenotype in patients with polycystic ovary syndrome. *Hormones*. 2015;14(3):431-437.
15. Wojciechowska A, Osowski A, Jóźwik M, Górecki R, Rynkiewicz A, Wojtkiewicz J. Inositols' importance in the improvement of the endocrine-metabolic profile in PCOS. *Int J Mol Sci*. 2019;20(22):5787.
16. Wdowiak A. Myoinositol improves embryo development in PCOS patients undergoing ICSI. *Int J Endocrinol*. 2016;2016:1-8.
17. Regidor PA, Schindler AE, Lesoine B, Druckman R. Management of women with PCOS using myo-inositol and folic acid. New clinical data and review of the literature. *Horm Mol Biol Clin Investig*. 2018;34(2). 10.1515/hmbci-2017-0067
18. Zeng L, Yang K. Effectiveness of myoinositol for polycystic ovary syndrome: a systematic review and meta-analysis. *Endocrine*. 2018;59(1):30-38.
19. Laganà AS, Barbaro L, Pizzo A. Evaluation of ovarian function and metabolic factors in women affected by polycystic ovary syndrome after treatment with d-Chiro-Inositol. *Arch Gynecol Obstet*. 2015;291(5):1181-1186.
20. Formuso C, Stracquadanio M, Ciotta L. Myo-inositol vs. D-chiro inositol in PCOS treatment. *Minerva Ginecol*. 2015;67(4):321-325.
21. Wojciechowska A, Osowski A, Jóźwik M, Górecki R, Rynkiewicz A, Wojtkiewicz J. Inositols' importance in the improvement of the endocrine-metabolic profile in PCOS. *Int J Mol Sci*. 2019;20(22):5787.
22. Monastra G, Unfer V, Harrath AH, Bizzarri M. Combining treatment with myo-inositol and D -chiro-inositol (40:1) is effective in restoring ovary function and metabolic balance in PCOS patients. *Gynecol Endocrinol*. 2017;33(1):1-9.
23. Roseff S, Montenegro M. Inositol treatment for PCOS should be science-based and not arbitrary. *Int J Endocrinol*. 2020;27(2020):6461254.
24. Nordio M, Basciani S, Camajani E. The 40:1 myo-inositol/D-chiro-inositol plasma ratio is able to restore ovulation in PCOS patients: comparison with other ratios. *Eur Rev Med Pharmacol Sci*. 2019;23(12):5512-5521.
25. Mendoza N, Diaz-Ropero MP, Aragon M, et al. Comparison of the effect of two combinations of myo-inositol and D -chiro-inositol in women with polycystic ovary syndrome undergoing ICSI: a randomized controlled trial. *Gynecol Endocrinol*. 2019;35(8):695-700.

How to cite this article: Kachhawa G, Senthil Kumar KV, Kulshrestha V, Khadgawat R, Mahey R, Bhatla N. Efficacy of myo-inositol and D-chiro-inositol combination on menstrual cycle regulation and improving insulin resistance in young women with polycystic ovary syndrome: A randomized open-label study. *Int J Gynecol Obstet*. 2022;158:278–284. doi:10.1002/ijgo.13971