CLINICAL STUDY

Comparison of Myoinositol and Metformin in Women with Polycystic Ovarian Syndrome

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ABSTRACT

Objective: The aim of the study was to compare the effects of 16-week treatment with two insulin-lowering therapies on the clinical, endocrine-metabolic and ovulatory parameters in women affected by polycystic ovarian syndrome (PCOS). **Material and methods:** A total of 70 patients attending the Gynecology OPD of Holy Family Hospital, Okhla, New Delhi, with clinical features of PCOS in the age group of 17-35 years, between June 2015 and May 2016, were selected. Patients were randomly distributed into two groups with 35 patients each. Group 1 received myoinositol (MYO) 2 g/day, while Group 2 received metformin 500 mg/day twice-daily. Baseline anthropometry, biochemical investigations and pelvic ultrasonography were done and repeated after 16 weeks. **Results:** Modified Ferriman-Gallwey (mFG) score was reduced from 4.66 ± 4.06 SD to 3.56 ± 3.29 SD in Group 1 and 4.94 ± 4.05 SD to 3.87 ± 3.24 SD in Group 2; the fall in Group 1 was more significant than Group 2. Fasting insulin decreased from 13.90 ± 6.88 SD to 11.66 ± 6.05 SD in Group 1 and from 12.85 ± 4.46 SD to 11.78 ± 4.39 SD in Group 2; reduction was highly significant in Group 1 than Group 2. Results for luteinizing hormone (LH) were not significant. Free testosterone decreased from mean of 1.47 ± 0.37 SD to 1.37 ± 0.37 SD in Group 1 and from 1.43 ± 0.37 SD to 1.36 ± 0.36 SD in Group 2; the fall in Group 1 was more significant than Group 2. **Conclusion:** Metformin is effective in reducing the metabolic and hormonal parameters and improves fertility. MYO not only improves all the above parameters but also decreases insulin resistance significantly. Thus, MYO supplementation is essential in the management of PCOS to improve insulin sensitivity.

Keywords: Polycystic ovarian syndrome, myoinositol, metformin, fasting insulin

Polycystic ovarian syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age, affecting 5-10% of women worldwide. It is defined as a heterogeneous syndrome complex characterized by hyperandrogenism (clinical and/or bio-clinical), ovarian dysfunction (oligo- and/or anovulation) and polycystic ovaries, with exclusion of related disorders. This is with the recognition that forms of PCOS may occur without overt incidence of hyperandrogenism.[1]

Initially defined by Stein and Leventhal in 1953, this syndrome has changed in definition over the years and is briefly defined in Table 1. In 2003, Rotterdam proposed a revised criterion for PCOS that included ultrasound morphology of ovaries as potential criteria to define PCOS:[2]

- Menstrual irregularity (due to oligo- and/or anovulation)
- Clinical and/or biochemical signs of hyperandrogenism
- Polycystic ovaries (by ultrasound).

Table 1. Definition of PCOS

National Institute of Health (NIH) - 1990	Androgen Excess Society (AES)
Evidence of clinical or biochemical hyperandrogenism	Androgen excess (clinical and/or biochemical hyperandrogenism)
Chronic anovulation	Ovarian dysfunction (oligo-anovulation and/or polycystic ovarian morphology on ultrasonography)

All criteria require exclusion of other causes of hyperandrogenism such as adult onset congenital adrenal hyperplasia, hyperprolactinemia and androgen secreting tumors.

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In addition, other etiology must be excluded (congenital adrenal hyperplasia, androgen secreting tumors, thyroid dysfunction, Cushing's syndrome).

In young women with PCOS, insulin resistance may occur with higher frequency of about 30-40%. Additionally, a defect in insulin signalling pathway seems to be implicated in the pathogenesis of insulin resistance. The exact cause of insulin resistance observed in PCOS women is not known; however, a post-receptor defect that could affect glucose transport has been proposed.[3] The importance of insulin resistance in PCOS is suggested by the fact that insulin-sensitizing drugs such as metformin, pioglitazone, troglitazone and myoinositol (MYO) have been proposed as treatment to resolve hyperinsulinemia-induced dysfunction of ovarian response to endogenous gonadotropins, metformin being the oldest drug in use whilst MYO being the recent development in insulin-sensitizing drugs. The focus of this study is primarily based on these two insulin-sensitizing drugs, i.e, MYO and metformin.

MYO is one of the nine stereoisomeric forms of a C6 sugar alcohol that belongs to vitamin B-complex group.[4] Studies have suggested that impairment in insulin pathway could be due to a defect in inositol phosphoglycans (IPGs) second messenger. In PCOS, defect in tissue availability or altered metabolism of inositol or IPGs mediators may contribute to insulin resistance.[5] Therefore, supplying MYO can accelerate glucose disposal and decrease circulating insulin, serum testosterone and enhance ovulation. The commonly used dose is 200-4,000 mg once-daily before breakfast in PCOS. Very high doses of MYO can cause gastrointestinal side effects like nausea, diarrhea, dizziness, insomnia and possible worsening of bipolar disorder. No toxicity has been reported. There is no evidence for MYO drug interaction till date.

Metformin is an oral biguanide antihyperglycemic drug. It lowers blood glucose by inhibiting hepatic glucose production (by decreasing gluconeogenesis), enhancing peripheral glucose uptake by skeletal muscles and adipose tissue and reduces intestinal glucose absorption. It enhances insulin sensitivity at the post-receptor level and stimulates insulin mediated glucose disposal without producing hypoglycemia in PCOS women. It has been used to treat anovulatory infertility, insulin resistance and hyperandrogenism in PCOS patients. The action of metformin is limited due to low levels of inositol in PCOS. Dose of metformin can vary from 500 to 2,500 mg/day. Metformin causes a significant increase in nausea, vomiting and gastrointestinal distress in women with PCOS. There are; however, no published reports of lactic acidosis with metformin therapy in women with PCOS.

MATERIAL AND METHODS

This study was carried out at Holy Family Hospital, New Delhi, from June 2015 to May 2016. The patients attending Gynecological OPD, with clinical features suggestive of PCOS (menstrual abnormalities, infertility, obesity, acne, hirsuitism), were selected. It was a randomized comparative study with sample size of 70. Patients were defined as having PCOS according to Rotterdam criteria (2003). The patients would have to satisfy a minimum of two criteria listed below in order to be diagnosed as PCOS:

- Oligo- and/or anovulation: Oligomenorrhea would be defined if menses occurred less than 9 times a year or if 3 cycles more than 36 days long occurred during the last year.
- Clinical and/or biochemical signs of hyperandrogenism: Clinical hyperandrogenism would be diagnosed if the modified Ferriman-Gallwey (mFG) score is 8 or greater or the patient has moderate-to-severe acne, defined by the presence of inflammatory lesions and their extension.
- Polycystic ovaries (by ultrasound): Presence of 12 or more follicles in each ovary measuring 2-9 mm in diameter and/or increased ovarian volume (>10 mL, calculated using the formula 0.5 × length × width × thickness). Single ovary fitting this definition is enough to define PCOS.

The inclusion and exclusion criteria are mentioned in Table 2.

Table 2. Inclusion and Exclusion Criteria

Inclusion criteria	Exclusion criteria
Women with PCOS, diagnosed in accordance with Rotterdam consensus conference criteria 2003 in the age group of 17-35 years.	• Pregnancy • Thyroid disorders • Significant liver or renal impairment • Unstable mental illness • Diagnosis of diabetes mellitus or impaired glucose tolerance • Use of drugs able to interfere with glucoinsulinemic metabolism for at least 3 months prior to entering the study • Hypersensitivity to MYO

Patients were randomly allocated to two groups; Group 1 (MYO) and Group 2 (metformin). At the beginning of the study, baseline levels of various study variables were recorded. Patients were subjected to anthropometry - body weight, body mass index (BMI), waist-hip ratio (WHR) - and biochemical investigations which included fasting blood sugar (FBS), post-meal blood sugar (PMBS), fasting insulin, luteinizing hormone (LH), LH/follicle-stimulating hormone (FSH) ratio, free testosterone, prolactin (PL). Hirsutism was scored by mFG using 9 body sights - lip, chin, chest, upper abdomen, lower abdomen, upper arm, upper back, lower back and thigh. Each body area was visually scored on a scale of 0 to 4, where "0" indicated no terminal hair growth and "4" indicated full male pattern terminal hair growth. Cut-off was taken as score of "8" or more. Ovulatory activity was monitored with serum progesterone. It was recorded at the baseline and repeated every month in the mid-luteal phase. The peak value during the study was taken as final value. Cut-off was taken as 8 ng/mL. In addition, a baseline ultrasonography was done for noting down the number of follicles and/or ovarian volume.

Participants of Group 1 received 2 g MYO daily and those of Group 2 received 500 mg metformin twice-daily. Patients were called for follow-up after 16 weeks of drug therapy and tests for all the study variables were repeated and compared with the baseline findings. Patients who conceived after treatment were noted. The side effects experienced in each study group were noted down. Outcome was studied in terms of regularization of cycle, reduction in mFG score, improvement in anthropometric, biochemical and ultrasonographic parameters before and after the treatment in the two groups. The summary of the findings has been described in tables below.

RESULTS

In all, 70 patients were enrolled for the study within the age group of 17-35 years. Patients were randomly distributed into two groups with 35 patients each. Two patients were lost during follow-up from Group 2 and 5 patients conceived during early stages of the study (3 from Group 1 and 2 from Group 2). The final study was based on 63 patients - 32 patients in Group 1 and 31 in Group 2. Since the age distribution of patients was from 17 to 35 years, the study covers the mean population age of 26.62 ± 5.38 in Group 1 and 26.23 ± 4.58 in Group 2. It is noteworthy that race, ethnicity, socioeconomic factors were almost similar in both the groups.

The most common complaint was irregular cycles (53.1% in Group 1 and 64.5% in Group 2) followed by scanty flow, secondary amenorrhea, weight gain, hirsutism and infertility. After treatment, in Group 1 53.1% of patients achieved regular cycles whilst in Group 2, 41.9% of patients achieved regular cycles (Table 3).

The fall in body weight and WHR was significant in both groups, but on comparing the two, it was more significant in Group 1 than Group 2. The fall in BMI was more significant in Group 2 than Group 1 (Table 4).

The fall in mFG score was more significant in Group 1 as compared to Group 2. While LH results were not significant, the fall in LH/FSH ratio was more significant in Group 2 than Group 1. The reduction in fasting insulin was highly significant in Group 1 than Group 2. Free testosterone decrease was more significant in Group 1 than Group 2. FBS was normal in all patients; the fall in Group 2 was more significant than Group 1. For postprandial blood sugar (PPBS), fall was more significant in Group 1 (Table 5).

In Group 1 serum, progesterone changed from mean of 3.73 ± 1.44 SD to 6.73 ± 1.90 SD and in Group 2 from mean of 3.76 ± 1.57 SD to 5.82 ± 2.03 SD. Change in serum progesterone value was more significant in Group 1 than Group 2. In Group 1, 36.1% of patients ovulated, 8.6% conceived and in Group 2, 27.6% ovulated and 5.7% conceived. The reduction in number of follicles was more significant in Group 1 than Group 2 whilst decrease in ovarian volume (mean ovarian volume of >10 mL) was almost same in both groups (Table 6).

Table 3. Regularization of Cycles

	Group 1		Group 2		P value
	Frequency	%	Frequency	%	
Improved (I)	17	53.1	13	41.9	
Not improved (N)	15	46.9	18	58.1	0.374
Total	**32**	**100**	**31**	**100**	

Table 4. Anthropometry Findings

Item description	Body weight			BMI			WHR		
	Group 1	Group 2	P value	Group 1	Group 2	P value	Group 1	Group 2	P value
Before	65.99 ± 10.12	66.37 ± 7.84	0.869	22.26 ± 2.71	23.04 ± 2.94	0.272	0.80 ± 0.06	0.80 ± 0.07	0.907
After	63.25 ± 9.06	64.47 ± 7.05	0.556	20.82 ± 2.37	21.35 ± 2.70	0.410	0.77 ± 0.05	0.78 ± 0.06	0.557
Mean difference ± SD	-2.74 ± 2.24	-1.91 ± 1.91	0.116	-1.44 ± 0.80	-1.69 ± 1.27	0.338	-0.03 ± 0.04	-0.02 ± 0.03	0.443
P value	<0.001	<0.001		<0.001	<0.001		<0.001	<0.001	

Table 5. Biochemical Parameters

Item description	mFG score			LH			LH/FSH ratio			Fasting insulin		
	Group 1	Group 2	P value	Group 1	Group 2	P value	Group 1	Group 2	P value	Group 1	Group 2	P value
Before	4.66 ± 4.06	4.94 ± 4.05	0.786	3.21 ± 3.01	5.13 ± 2.14	0.254	1.97 ± 1.03	2.04 ± 0.96	0.768	13.90 ± 6.88	12.85 ± 4.46	0.479
After	3.56 ± 3.29	3.87 ± 3.24	0.709	5.13 ± 2.14	5.95 ± 3.24	0.241	1.79 ± 0.96	1.84 ± 0.86	0.829	11.66 ± 6.05	11.78 ± 4.39	0.928
Mean difference ± SD	-1.09 ± 1.03	-1.06 ± 0.10	0.909	-1.08 ± 3.31	-1.19 ± 3.53	0.899	-0.17 ± 0.18	-0.20 ± 0.26	0.664	-2.24 ± 2.09	-1.07 ± 1.51	0.013
P value	<0.001	<0.001		0.060	0.070		<0.001	<0.001		<0.001	<0.001	

Item description	Free testosterone			Prolactin			FBS			PPBS		
	Group 1	Group 2	P value	Group 1	Group 2	P value	Group 1	Group 2	P value	Group 1	Group 2	P value
Before	1.47 ± 0.37	1.43 ± 0.37	0.717	14.31 ± 4.39	13.85 ± 3.53	0.653	89.81 ± 8.32	89.23 ± 11.04	0.812	115.97 ± 12.03	111.13 ± 13.25	0.134
After	1.37 ± 0.37	1.36 ± 0.36	0.895	14.09 ± 4.17	13.35 ± 2.94	0.421	88.50 ± 7.79	87.81 ± 10.32	0.764	113.03 ± 12.00	109.84 ± 11.76	0.291
Mean difference ± SD	-0.10 ± 0.10	-0.08 ± 0.08	0.339	-0.22 ± 1.73	-0.50 ± 2.23	0.574	-1.31 ± 1.66	-1.42 ± 2.01	0.818	-2.94 ± 4.01	-1.29 ± 3.24	0.078
P value	<0.001	<0.001		0.484	0.221		<0.001	<0.001		<0.001	0.034	

Table 6. Ultrasonographic Parameters

Item description	Reduction in no. of follicles			Mean ovarian volume		
	Group 1	Group 2	P value	Group 1	Group 2	P value
Before	14.59 ± 2.69	14.08 ± 1.84	0.382	13.51 ± 2.02	12.81 ± 2.35	0.213
After	12.19 ± 1.69	12.05 ± 1.75	0.749	11.93 ± 1.91	11.65 ± 1.96	0.575
Mean difference ± SD	-2.41 ± 1.49	-2.03 ± 1.66	0.350	-1.58 ± 0.98	-1.58 ± 0.98	0.057
P value	<0.001	<0.001		<0.001	<0.001	

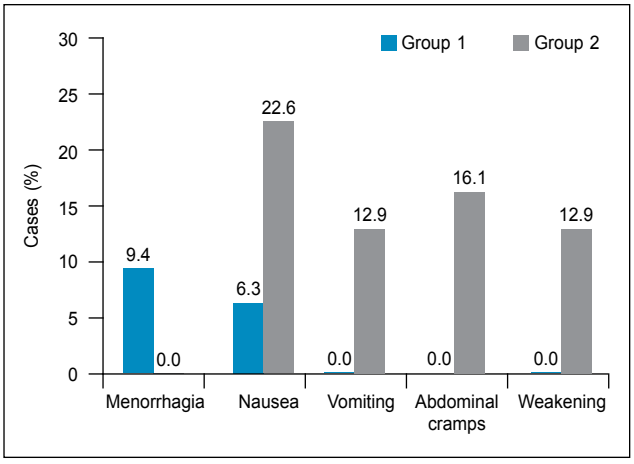

Figure 1. Side effects.

In the study, only 15.6% of patients experienced side effects in Group 1. Menorrhagia was a complaint seen only in Group 1. In Group 2, 64.5% experienced side effects. P value was significant only for abdominal cramps. Details of the side effects have been described in Figure 1.

DISCUSSION

PCOS is one of the most common endocrine disorders in women of reproductive age. Its etiology remains unclear. In young women with PCOS, insulin resistance is intrinsic to the syndrome and affects 30-40% of patients with PCOS. Studies have shown that insulin resistance in PCOS may be linked to abnormal ovarian steroidogenesis by means of altered insulin signal transduction.

The age distribution of patients in this study was 17-35 years. Mean age of patients was 26.62 ± 5.38 in Group 1 and 26.23 ± 4.58 in Group 2 which is similar to studies conducted by Immediata et al[6] and Costantino et al.[7]

In the study, 53.1% of patients achieved regular cycles in Group 1 (MYO) compared to 41.9% in Group 2 (metformin), which is similar to results obtained by Leo et al.[8]

Our results are supported by the study carried out by Awalekar et al.[9] They studied the effect of MYO, metformin and lifestyle modification in PCOS patients. In their study, BMI in the metformin group was reduced from a mean of 29.64 ± 3.49 to 27.13 ± 3.49 after 3 months of treatment, which is highly significant (p = 0.0000) and in MYO group, BMI changed from mean of 25.40 ± 6.53 to 24.40 ± 5.91 (p = 0.009). Similar results were seen in studies done by Le Donne et al,[10] and Cheang et al.[11] Immediata et al6 conducted a crossover study in which metformin was able to decrease body weight ($p < 0.05$), improve menstrual cycle (<0.001) and mFG score (0.05). None of these clinical changes were observed during MYO administration. These results are not in concordance with our study.

In the study by Leo et al,[8] fall in mFG score in MYO group from 11.7 ± 2.7 to 7 ± 3.9 (p = 0.001) was significant than metformin group, as in our study. Similar results were seen in a study by Zacche et al.[12] Genazzani et al[13] studied 20 overweight patients of PCOS. In MYO group, LH, PL, testosterone (T), insulin levels and LH:FSH significantly decreased along with improved insulin sensitivity. Similarly, in our study, there was highly significant decrease in fasting insulin and free testosterone in Group 1. Our results are further supported by Angik et al.[14] They studied 100 patients in a randomized controlled trial (RCT) (50 in each group). MYO decreased FBS, PPBS, fasting and post-meal insulin, homeostasis model assessment (HOMA), T levels, LH:FSH, ovarian volume significantly; whereas in metformin group, significant improvement occurred in FBS, PPBS, T, LH:FHS and ovarian volume but not in fasting insulin and HOMA index. Fasting insulin decreased from 16.51 ± 13.95 to 14.58 ± 9.79 in MYO group. This result was significant, but in metformin group, the reduction was not significant. Similar results were seen in the study by Awalekar et al.[9] In contrast, in the study by Gerli et al,[15] no change in fasting glucose concentrations, fasting insulin or insulin responses to glucose challenge was recorded after MYO therapy. In a study by Minozzi et al[16] fasting insulin changed from 12.2 to 8.3 with mean difference of -3.9 ± 1.8; results were not significant.

Raffone et al[17] studied 120 patients with PCOS and 14-16 months of infertility. The study demonstrated a statistically significant difference in restoration of spontaneous ovulation in patients receiving MYO. Though there was a higher overall rate of pregnancy in the MYO group, the effect was not significant. In our study also, there was higher ovulation (36.1%) and conception rate (8.6%) in Group 1 compared to Group 2 (27.6% and 5.7%). Our results are in contrast to the study by Papaleo et al[18] in which 88% restored at least one spontaneous menstrual cycle, of which 72% maintained normal ovulatory activity during the follow-up period and 40% pregnancies were achieved after MYO administration. Similar contrast results were seen in studies by Palomba et al[19] and Abdelhamid et al.[20]

In the study by Angik et al,[14] the number of follicles decreased from 11.40 ± 3.00 to 11.60 ± 2.13 (p = 0.001) in MYO group and in metformin group from

10.20 ± 2.31 to 10.18 ± 2.0 (p = 0.001) and ovarian volume decreased from 14.45 ± 3.8 to 12.35 ± 2.83 (p = 0.001) in MYO group and in metformin group from 14.53 ± 3.44 to 12.24 ± 2.83 (p = 0.001), which is similar to our study.

CONCLUSION

Metformin is effective in improving the metabolic and hormonal parameters and improves fertility. But MYO not only improves all the above parameters but also decreases insulin resistance significantly. MYO also has better patient compliance and is better tolerated than metformin. These beneficial effects of inositol support a future therapeutic role in women with PCOS. Inositol deficiency is the basic pathophysiology for PCOS and thus MYO supplementation is essential in the management of PCOS. MYO improves insulin sensitivity and thus, should be the first-line of therapy in PCOS.

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