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THE THERAPEUTIC ROLE OF MYO-INOSITOL AND D-CHIROINOSITOL TO PREVENT MENSTRUAL DYSFUNCTION IN PCOS WOMEN

Gynaecology

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ABSTRACT

Background-Polycystic ovary syndrome (PCOS) is the commonest endocrine-disorder in the women of the reproductive age. Pathogenesis has not been fully solved. PCOS is related with the insulin resistance (IR), the menstrual irregularities, cardiovascular disease (CVD), endometrial cancer, obesity, hirsutism, and infertility. Using myo-inositol (MI) and D-chiro-inositol (DCI) for treatment of menstrual irregularities in PCOS women has been disputable with incompatible data being published.

Aim & Objective- To compare the combined effect of D-Chiroinositol (DCI) and myo-inositol (MI), in PCOS women to check menstrual irregularities

Material and Method-This randomized clinical trial was performed on 450 north Indian women attending Gynae OPD in Hind Institute of Medical Sciences diagnosed with PCOS according to Rotterdams criteria and treated with MI and DCI (Myo inositol and D Chiroinositol) combination or Myoinositol plus folic acid . Patients aged 15 to 40 years were selected randomly and a questionnaire covering the personaldetails, status of health, medications, anthropometrics and physical activity was completed beforehand and divided them into 2 groups: 225 were treated with Myo inositol and D Chiroinositol, 225 with Myo inositol plus placebo (folic acid only). We analyzed both the groups pre-treatment & post-treatment.

Result-The prevalence of obesity in the present population was 29.3%. The menstrual dysfunction was prevalent among the obese women with the polycystic ovary syndrome; the non-obese patients were also having the significant incidence of Insulin Resistance menstrual dysfunction. After three months course of treatment with MI and DCI the significant decrease in the fasting glucose, Low-Density Lipoprotein (LDL), HOMA-IR, Triglycerides (TG), Body mass index (BMI), Glycated Hemoglobin (HbA1c), weight and levels were noted.

Conclusion-In present study, we concluded that the combination of MI & DCI can improve the menstrual dysfunction and metabolic profile in PCOS women.

KEYWORDS

Myo inositol, D-Chiroinositol, and PCOS, menstrual irregularities

Introduction

Polycystic ovary syndrome is the most common endocrine abnormality in the women of reproductive age; it occurs in about 6.0% to 18.0% of this age group. It is distinguished by hyperandrogenism, menstrual abnormalities, chronic anovulation, endometrial cancer, polycystic ovaries, hirsutism, insulin resistance (IR) and the metabolic syndrome.

Overweight females with PCOS seem to acknowledge positively to the treatment with the insulin-sensitizing drugs, like metformin or troglitazone (TZDs) that reduce serum androgens level and restore the ovulation. However, various limitations been linked to their use. Indeed, the metformin influences predominantly gastrointestinal dysfunction consisting of bloating, nausea & diarrhoea.

Myoinositol supplementation is inadequate to improve oocyte or the embryo quality & pregnancy rates in women having polycystic ovary syndrome undergoing the intracytoplasmic sperm injection. The role of D-chiroinositol supplementation also remains unclear or unknown, and further research with various combinations of both inositol and isoforms should properly mention these concerns. Remarkably few studies have been performed to compare the therapeutic role of Myo inositol and D-Chiroinositol in menstrual dysfunction in PCOS Women

It was hypothesized that various insulin-sensitizing compounds been proposed as a possibly safe and efficacious long-term treatment of PCOS and in order to take advantage of the unique feature of both inositols stereoisomers, the present study was planned to evaluate the effects of Myoinositol with D-Chiroinositol administration on menstrual irregularities in cases of PCOS women.

Materials and Methods

A randomized controlled clinical trial (superiority clinical trial) was performed by enrolling 448 women who were diagnosed with polycystic ovarian syndrome as per Rotterdam criterion 3 months duration at the outpatient clinic of Department of Obstetrics and Gynaecology, , in a teaching hospital in north India in a period of 12 months between April2017- Mar2018. Patients in the study group were questioned about age, length of the marriage, level of education, number of births, and status of menstruation and the results were recorded on prescribed proforma. Body mass index (BMI) was calculated by measuring the patients' height and weight.

Total 9000 OPD patients were screened for this study out of which 546 patients were having PCOS were enrolled. Twenty-nine patients refused to participate in the study and 17 were not fit for our inclusion criteria. Finally, 500 patients were included in the study. Patients were randomized in two study groups (group 1 **Myo inositol + Placebo (folic acid) and group 2 D-Chiroinositol + Myo inositol**) using computer-generated randomization sequence (250 in each group) with about 10 percentages of patients expected to dropouts.

Sample size calculation: The sample was calculated on the basis of prevalence using the formula:-

$$n = \frac{Z^2 P(1-P)}{d^2}$$

Z (Confidence Level) is 1.96, d (error) is 0.06, **n = 224 for each group.**

The new combination was considered as superior if the percentage of relived patients receiving **D-Chiroinositol + Myo inositol** is 10 percentages higher than the percentage of relived patient who received **Myo inositol + Placebo (folic acid)**

We randomly recruited 250 patients in each group (10 percent drop-out rate).

Inclusion Criteria:

1. Women of Reproductive age group (15-40) year.
2. PCOS Diagnosing criteria are based on the Rotterdam criteria.
3. Menstrual Dysfunction,

4. Polycystic ovary morphology on pelvic ultrasound

Exclusion Criteria:
1. Women>40 years, women<15 years,
2. Women diagnosed with hypothyroidism and hyperthyroidism
3. Women who are pregnant
4. Women diagnosed with Cushing's syndrome, hypoglycemia, androgen-secreting tumor's, or, congenital adrenal hyperplasia hyperprolactinemia, hypertension excluded from the study.

Study Protocol:
All the relevant clinical details of history, clinical examination findings and provisional clinical diagnosis will be followed.

1. Socio-demographics:
2. Anthropometric Measures:
2 (a) Body Mass Index:
2 (b) Waist Circumference:
3. Clinical History:
4. Menstrual History (Yes/No)
5. Blood pressure:
6. Polycystic Ovary Assessment:
7. Biochemical Assessment:
8. Diagnosis of metabolic syndrome:
9. Questionnaire Interview

An interview was used for filling in the questionnaire which designated for matching the study need. All interviews were conducted face to face by physicians.. Most questions were the yes/no questions, which offer a choice on the following variables: age, current medications, age of menarche, menstrual history; presence or absence of hirsutism and acanthosisnigricans (which was addressed by the existence of the characteristic pigmentary changes on posterior neck or the axillary region), acne, seborrhea, male- pattern hair loss (androgenic alopecia), heart disease, DM2, hypertension and PCOS in first-degree relatives; in order to give us more information about the characteristics of PCOS, in addition to get the agreement of population for sharing in our study.

Ethical clearance
The research procedure followed was in accordance with the approved institutional ethical committee.

Statistical Analysis:
The association between the drugs used in both the groups and menstrual abnormality at baseline and 3 months follow up was obtained by chi-square test to show the significance of the drugs on menstrual irregularity.

The association between PCOS and metabolic parameters (BMI, BP, blood sugar, peptides, liver function test) was examined while adjusting for confounding using multivariable logistic regression and the satisfying results were presented when the p-value for the interaction term was least modest ($p \leq 0.1$).

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 23 for Windows, $p<0.05$ rule was applied to detect significant differences.

Observation and results
The incidence of PCOS was found to be 6.05% in the present study. The mean age of the studied patients was found as 26.91±4.5 years ranging from 15years to 40 years [Table No.1], the patients suffering from bilateral Polycystic Ovaries were in the majority (77.9%) followed by unilateral (22.1%) [Figure No. 2]. The association of various parameters using different drugs shows the significant association with BMI (kg/m^2), Waist to hip ratio, diastolic blood pressure, fasting blood sugar, HDL-C, Androstenedione, free testosteron and FSH ($p<0.05$) while triglycerides, LDL, SBP were insignificant during follow-ups ($p>0.05$). [Table No.2] Correlation of the drugs with the menstrual regularity during follow-ups shows that a combined therapy of MI plus DCI may be the first line approach treatment in PCOS and proved to be more efficacious than Myo inositol + Placebo (folic acid) only in reducing individual components of metabolic syndrome.[Table No. 3]

Discussion
Polycystic ovary syndrome (PCOS) is one of the most frequent endocrine disorders faced by women of reproductive age. It is characterized by the menstrual abnormalities, clinical or the biochemical hyperandrogenism, multiple abnormal cysts & enlarge ovaries. Furthermore, due to its feature, PCOS is the cause of infertility because of the menstrual dysfunction.2 Inositol is the six-carbon polyol that has been characterized as the insulin sensitizer; indeed, inositolphosphoglycan (IPG) mediators play the key role in the multiple cellular processes which control glucose metabolism. Epimerization of a six hydroxyl-groups of the inositol leads to a formation of up to 9 stereoisomers, including the myo-inositol (MI) & D-chiro-inositol (DCI). Both the IPGs were insulin mimetic when administered *in vivo* magnifying the physiological insulin receptor activity & reducing the glucose levels in serum. More recently, the administration of MI & DCI has been related to the improvement of the ovulation in most PCOS women.

Patients selected using the inclusion & exclusion criteria were randomized using the computer-generated randomization sequence into the two groups. A similar study was opted by **Pande M et al.**, **Nordio M & Proietti E**2, and **Benelli E et al.** as it was the ideal study for observing the effect of the drugs in two groups. We haven't gone for case-control study because we have to compare the two drugs and in both the groups, we required the patients, not the healthy individual.
PCOS Diagnosing criteria are based on the Rotterdam criteria, and Anthropometric evaluation was performed by measuring tape, weighing scale, & standard height rod. Rotterdam criteria was used in several other studies by **Ranwa M et al., Benelli E et al**9, and **Pande M et al**8 and it is used as a gold standard for diagnosing PCOS.

In our study, the mean age of the patients was found as 26.91±4.5 years which was similar to the mean age reported by **Ranwa M et al**[10] that is 22.65±4.30 years. Also **Benelli E et al**9 and **Nordio M**2 24 and 28 years respectively this is in accordance with our study. This implies that the women of 3rd decade were mostly affected by PCOS.

Raffone et al. reported that insulin sensitizer agents, in both metformin and Myoinositol, may be considered first-line treatment in most patients with PCOS, for establishing regular menstrual cycles contrasting to the present study.

According to the Rotterdam, criteria to diagnose PCOS hyperandrogenism is one of the criteria to diagnose PCOS which may be defined by the presence of acne, hirsutism, oily skin etc. Hyperandrogenism is a key feature of PCOS, primarily resulting from the excess androgen production in ovaries and, to the lesser extent, in adrenals.

In our study with Myoinositol + placebo 71 out of 224 (31.6%) cases achieved regular menstrual cycles during therapy. While that with Myoinositol + D-chiro-inositol out of 224 cases, 161 cases (71.9%) cases were achieved regular menstrual cycles during the therapy. Similar results were observed by **Rawna M et al**[10] who reported that in their study with 2 gm Myoinositol supplementation 53 out of 71 (74.65%) cases achieved regular menstrual cycles during therapy. Our results are similar as observed by **Papaleo et al.** after a mean of 34.6+5.5 days of Myoinositol + D-chiro-inositol administration, 22 out of the 25 (88.0%) patients restored at-least one spontaneous menstrual-cycle, of whom eighteen (72.0%) maintained the monthly menstruations during follow-ups period. Similarly, **Ventuerella et al.** and **Le Donne et al.** had shown significant improvement in menstrual abnormality in their studies in 2012. Present results are much better than observed by **Lin L et al.**, in 55 cases of PCOS after 24 weeks therapy with 1.5gm Metformin out of these 55, only 60.7% of cases had spontaneous regular menses.

Importantly, no related side effect was recorded during combined therapy with the MI & DCI. Overall, these results depicted the clinical importance of the combined therapy of MI & DCI to rectify the PCOS metabolic & reproductive aspects, and they are in agreement with the problems discussed on the 2 international consensus conferences on MI, DCI, and their link with PCOS

In our study, the association of various parameters with the two drugs was found statistically significant ($p<0.05$) except systolic blood pressure, LDL and Triglycerides ($p>0.05$). The same findings were reported by **Pande M et al**8 in their study. **Benelli E et al**9 in their study depicts the significant association among Androstenedione and Free testosterone with the two groups.

A trial was performed by **Nordio M and Proietti E**2 on 50 patients

where the metabolic effect & predetermined parameters were evaluated between 2 groups; one group with combined (Myo-inositol and D-chiroinositol) and the second group was placebo (folic acid) only. The study showed that combined therapy is effective in reducing diastolic blood pressure and serum sex hormones significantly.

A study conducted by **Mnozzi M et al.** on Cardio-vascular risk factor of PCOS patients by giving [Myo-inositol (550 mg) + D-chiro-inositol (13.8 mg)] (MI+DCI) twice daily for three months. Statistical analysis shows a statistically significant reduction in serum fasting insulin, fasting blood sugar, Androstenedione, Free testosterone, LDL and a statistically significant increase in HDL level.

Limitations:

There were few limitations in the present study as the follow up was only for 3 months and the exogenous sources of the inositol which can affect the results like the interaction b/w MI or DCI and coffee which can affect the absorption in the gastrointestinal tract.

Strengths:

The study was performed on the basis of concerned proforma and the adequate sample size was used regarding the randomized clinical trial and the assignment of patients to treatments has provided the strongest possible basis for inference about treatment effects.

Conclusion

Considering the wide range of presenting signs and symptoms of PCOS, early diagnosis and treatment, not only to control gynaecological problems but also to prevent and treat metabolic complications, is necessary. Combined therapy of MI & DCI may be the first-line approach treatment in PCOS and proved to be more efficacious than Myo-inositol only in reducing individual components of the metabolic syndrome.

Tables and Figures

Table No. 1 Demographic Parameters of the studied patients

Parameters	mean±SD
Age	26.91±4.5 years
Waist-Hip Ratio	0.872±0.024
BMI	29.74±3.16 kg/m2

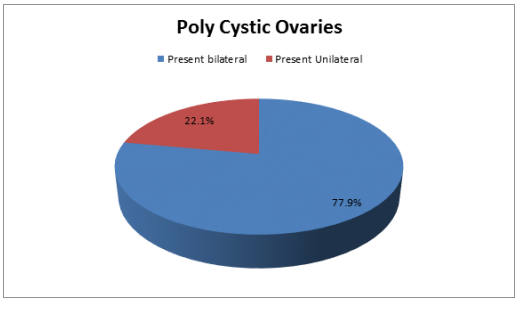
Table No. 2 The association of various parameters using different drugs

Metabolic Parameters		At starting	After 3 months	P value
BMI (kg/m^2)	Myo inositol + Placebo (folic acid)	29.74±3.16	30.01±2.98	0.232
	D-Chiroinositol + Myo inositol	29.48±3.23	28.37±2. 67	0.015
Waist/Hip Ratio	Myo inositol + Placebo (folic acid)	0.872±0.024	0.873±0.013	0.481
	D-Chiroinositol + Myo inositol	0.853±0.022	0.832±0.011	0.001
SBP (mmHg)	Myo inositol + Placebo (folic acid)	121.34±16.41	123.54±13.94	0.054
	D-Chiroinositol + Myo inositol	123.2±15.92	123.54±8.79	0.751
DBP (mmHg)	Myo inositol + Placebo (folic acid)	78.21±6.51	79.11±5.95	0.051
	D-Chiroinositol + Myo inositol	78.43±6.69	77.19±5.12	0.005
FBS (mg/dl)	Myo inositol + Placebo (folic acid)	96.51±8.13	97.60±9.15	0.087
	D-Chiroinositol + Myo inositol	96.78±8.33	93.41±8.67	<0.001
OGTT (mg/dl)	Myo inositol + Placebo (folic acid)	144.64±23.41	147.37±22.16	0.104
	D-Chiroinositol + Myo inositol	138.72±26.43	135.94±35.62	0.229
Triglycerides (mg/dl)	Myo inositol + Placebo (folic acid)	165.16±20.68	167.07±20.59	0.209
	D-Chiroinositol + Myo inositol	168.47±21.04	171.14±20.65	0.082
HDL-C (mg/dl)	Myo inositol + Placebo (folic acid)	49.21±7.04	49.59±6.74	0.454
	D-Chiroinositol + Myo inositol	50.46±7.39	53.04±6.52	<0.001
LDL (mg/dl)	Myo inositol + Placebo (folic acid)	125.26±15.49	127.16±15.54	0.096
	D-Chiroinositol + Myo inositol	125.57±15.74	126.78±15.11	0.287
Androstenedione (ng/ML)	Myo inositol + Placebo (folic acid)	3.47±1.23	3.32±1.21	0.095
	D-Chiroinositol + Myo inositol	4.22±1.42	3.93±1.60	0.009
Free testosterone (ng/dl)	Myo inositol + Placebo (folic acid)	0.87±0.12	0.86±0.13	0.278
	D-Chiroinositol + Myo inositol	0.74±0.18	0.61±0.16	<0.05
FSH (mIU/mL)	Myo inositol + Placebo (folic acid)	5.01±3.68	5.36±4.19	0.501
	D-Chiroinositol + Myo inositol	5.47±0.66	4.96±1.74	0.256

Table No. 3 Correlation of the drugs with the menstrual regularity during follow ups

Group	Menstruation abnormality	At starting	Number of cases improved	p-value
Myo inositol + Placebo (folic acid)	Oligomenorrhoea	97 (43.3)	36 (37.1)	0.441
	Amenorrhoea	44 (19.6)	13 (29.5)	
	Hypomenorrhoea+ Oligomenorrhoea	34 (15.2)	10 (29.4)	
	Oligomenorrhoea +menorrhagia	49 (21.8)	12 (24.5)	
	Total	224(100.0)	71 (31.6)	
D-Chiroinositol + Myo inositol	Oligomenorrhoea	97 (43.3)	74 (76.3)	0.331
	Amenorrhoea	44 (19.6)	23 (52.3)	
	Hypomenorrhoea+ Oligomenorrhoea	34 (15.2)	28 (82.3)	
	Oligomenorrhoea+ menorrhagia	49 (21.8)	36 (73.5)	
	Total	224(100.0)	161 (71.9)	

Figure No. 1: Distribution of studied patients on the basis of PCO group



REFERENCES

1. Hanna R, Wehbe T, Jaoude EA. Metabolic Effects of D-Chiro-Inositol and Myo-Inositol in Polycystic Ovary Syndrome. Int J Clin Endocrinol Metab 2017;3(1):029-033.
2. Nordio M, Proietti E. The Combined therapy with myo-inositol and D-Chiro-inositol reduces the risk of metabolic disease in PCOS overweight patients compared to myo-inositol supplementation alone. European Review for Medical and Pharmacological Sciences. 2012;16: 575-581
3. Rotterdam ES, ASRM-Sponsored PC. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Human Reproduction (Oxford, England). 2004 Jan;19(1):41.
4. Chobanian AV et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and treatment of High Blood Pressure. JAMA: August 2004:1216. Diabetes Care 37 (Suppl 1). American Diabetes Association:2014:S14
5. Legro RS. Polycystic ovary syndrome and cardiovascular disease: a premature association?. Endocrine reviews. 2003;24(3):302-12.
6. Nestler JE, Jakubowicz DJ, Reamer P, Gunn RD, Allan G. Ovulatory and metabolic effects of D-chiroinositol in the polycystic ovary syndrome. N Engl J Med 1999; 340: 1314-1320.
7. Costantino D, Minozzi G, Minozzi E, Guaraldi C. Metabolic and hormonal effects of myo-inositol in women with polycystic ovary syndrome: a doubleblind trial. Eur Rev Med Pharmacol Sci. 2009;13:105-110.
8. Pande M, Seal A, Mishra S, Dasgupta A, Sengupta M, Dastider R. The effects of combined therapy of myo-inositol and D-chiro inositol in reduction of the individual components of metabolic syndrome in overweight PCOS patients compared to myo-inositol supplementation alone: a prospective randomised controlled trial. Int J Reprod Contracept Obstet Gynecol. 2017 Jul;6(7):2939-2943

9. Benelli E, Del Ghianda S, Di Cosmo C, and Tonacchera M. A Combined Therapy with Myo-Inositol and D-Chiro-Inositol Improves Endocrine Parameters and Insulin Resistance in PCOS Young Overweight Women. International Journal of Endocrinology Volume 2016, Article ID 3204083, 5 pages
10. Ranwa M, Nagaria T, Jaiswal J, Arya A. Study of effect of myoinositol on menstrual irregularities and skin problems in polycystic ovarian syndrome cases. Int J Reprod Contracept Obstet Gynecol. 2017 Jun;6(6):2310-2317
11. Raffone E, Rizzo P, Benedetto V. Insulin sensitiser agents alone and in cotreatment with r-FSH for ovulation induction in PCOS women. Gynecol Endocrinol. 2010;26(4):275-80.
12. Papaleo E, Unfer V, Baillargeon JP, De Santis L, Fusi F, Brigante C et al. Myo-inositol in patients with polycystic ovary syndrome: a novel method for ovulation induction. Gynecol Endocrinol. 2007;23:700-3.
13. Venturella R, Mocciaro R, De Trana E, D'Alessandro P, Morelli M, Zullo F. Assessment of the modification of the clinical, endocrinal and metabolic profile of patients with PCOS syndrome treated with myo-inositol. Minerva Ginecol. 2012;64(3):239-43.
14. Le Donne M, Alibrandi A, Giarrusso R, Lo Monaco I, Muraca U. Diet, metformin and inositol in overweight and obese women with polycystic ovary syndrome: effects on body composition. Minerva Ginecol. 2012;64(1):23-9.
15. Liao L, Tian YJ, Zhao JJ, Xin Y, Xing HY, Dong JJ. Metformin versus metformin plus rosiglitazone in women with polycystic ovary syndrome. Chin Med J. 2011;124(5):714-8.
16. Minozzi M, Nordio M, Pajalich R.. The combined therapy myo-inositol plus d-chiro-inositol, in a physiological ratio, reduces the cardio-vascular risk by improving the lipid profile in PCOS patients. Eur Rev Med Pharmacol Sci. 2013;17:537-40.