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A RANDOMIZED CONTROLLED TRIAL COMPARING MYO-INOSITOL WITH METFORMIN IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME

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ABSTRACT:

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder of women of reproductive age group affecting approximately, 4 – 15 % of female population. PCOD is no longer disorder confined to ovary, but involves a complex pathophysiology of multiple organs like hypothalamus, pituitary, adrenals and adipose tissue. Environmental factors like stress, life style changes including increased fat, carbohydrate diet and reduced physical activity are important contributing factors. Genetic factors include mutations in genes coding for CYP450 enzymes like CYP 11A1, CYP 21A1 and defects in enzymes involved in cholesterol metabolism and androgen synthesis. Diagnosis is based on consensus oligo / anovulation, hyperandrogenism, polycystic ovaries, with exclusion of other endocrine disorders. Anovulation in PCOS is due to inappropriate gonadotropin secretion. This leads to preferential production of luteinizing hormone (LH) compared to follicle stimulating hormone (FSH) and LH:FSH ratio becomes 2:1 or even 3:14. **Insulin resistance** is common in approximately 60 – 70% of women with PCOS. IR is reduced response of peripheral tissues to insulin. It is due to phosphorylation of serine residues of insulin receptor leading to post binding abnormality in receptor mediated signal transduction. IR is sensed by pancreas as insulin deficiency and leads to compensatory hyperinsulinemia. This excess insulin stimulates luteinizing hormone (LH) to produce more androgens from theca cells of ovary leading to features of hyperandrogenism. Increased androgens, prevent maturation of one dominant follicle as Graafian follicle and also prevent apoptosis of small follicles, which are normally destined to disappear. This gives the appearance of polycystic ovaries in ultrasound as necklace like pattern in the peripheral rim of ovary. In addition, life style modifications like regular exercise and balanced diet are the first

line management. Insulin sensitizers like metformin are used to avoid and treat metabolic disorders associated with IR such as diabetes, dyslipidemia and cardiovascular events. But this is associated with gastrointestinal adverse effects like nausea, diarrhea, dyspepsia, flatulence and abdomen pain. This leads to poor patient compliance. Inositol is a polyalcohol, a physiological compound of sugar family of which two stereoisomers are found in our body, Myo-inositol (MI) and D-chiro inositol (DCI). MI is very scarce in diet and synthesized endogenously from Myo inositol by insulin dependent epimerase enzyme. D-chiro-inositol is an important second messenger in insulin signal transduction. It acts as a precursor for inositol triphosphate (IP3) and phosphatidyl inositol 3 kinase (PI3K), needed for actions of insulin like increased glucose uptake, thus improving insulin sensitivity. Thus, MI can be used as an alternative to metformin to improve insulin sensitivity. Certain studies have demonstrated the efficacy of MI in reducing metabolic and endocrinological abnormalities in PCOS patient. This study was undertaken to demonstrate the efficacy and safety of Myo-inositol, since limited studies are available in India regarding supplementation of Myo-inositol in PCOS.

KEYWORDS: PCOS, Myo-inositol, Metformin, Insulin Resistance

OBJECTIVES:

PRIMARY OBJECTIVE:

1) To assess the reduction in LH level. [1]

2) To assess the regulation of menstrual cycle.

SECONDARY OBJECTIVE:

1) To assess the reduction in body weight, blood glucose and serum insulin levels. [2]

2) To monitor any adverse effects with these drugs.

METHODOLOGY:

STUDY TYPE:

Interventional study.

STUDY DESIGN:

Randomized, open label, prospective and a comparative study. [3]

STUDY CENTRE:

Deepam Hospital – Perungalathur – Chennai.

STUDY DURATION:

12 weeks treatment period and 8 weeks follow up per patients. [4]

STUDY POPULATION:

Women with Polycystic ovary disease attending Gynecology OPD, Institute of obstetrics and gynecology, (IOG), Chennai.

SAMPLE SIZE:

Totally 60 patients.

20 Patients – Standard treatment (Metformin)

20 Patients – Study drug (Myo-inositol)

20 Patients – Standard drug – study treatment (Metformin and MI)

STUDY MEDICATION:

Tab. Metformin 500mg TDS, Tab. D-Chiro inositol-600mg BD.

INCLUSION CRITERIA

1. Women diagnosed with polycystic ovary syndrome, with menstrual irregularity. [5]

2. Age 18 to 40 years.

3. Oligomenorrhoea (≤ 8menstrual cycles annually).

4. Hyperandrogenism (clinically and/or biochemically). [15]

5. Patients willing to participate and give written informed consent.

6. Ability to comply with study procedure.

EXCLUSION CRITERIA

1. Patients with diabetes mellitus. [6]

2. Patients with clinically significant cardiac, pulmonary, renal, hepatic, neurological, psychiatric illness and malignant disease. [7]

3. Thyroid disorder or any other endocrine disorders. Ex. Hyperprolactinemia, adrenal disorders (CAH).

4. Ingestion of any investigational drug within 2 months prior to study enrolment. Pregnancy and lactation. [8]

TREATMENT PLAN:

Group A: (n=20) Tablet Metformin-500mg thrice daily for 12 weeks. [9]

Group B: (n=20) Tablet Myo-inositol - 600mg once daily (wt.< 60kg) and 600mg twice daily (wt.> 60kg).

Group C: (n=20) Tablet Metformin 500mg taken twice daily with Tablet Myo-inositol 600mg, taken once/twice daily according to their weight. [10]

The study medication was issued for 2 weeks. After assessing the compliance of the patient at the end of 2 weeks, study medication was issued for the subsequent 2 weeks. The same procedure was followed, till the completion of the studies (12 weeks). [11,12]

STATISTICAL ANALYSIS:

The obtained data were analyzed statistically using SPSS software version 21. The biochemical parameters were analyzed statistically in all three groups. The differences within the groups before and after treatment were analyzed using student's paired t-test whereas the difference between three groups were analyzed using ANOVA. P value of < 0.05 is considered as a statistically significant [13,14].

RESULT:

This study was conducted to evaluate the effect of Myo-inositol in comparison with metformin in polycystic ovary syndrome.

• Totally 90 patients were screened off, in which 60 patients were enrolled and completed the study.

• There were no drop outs in the studies.

TABLE 1 – AGE DISTRIBUTION:

AGE IN YEARS	GROUP A		GROUP B		GROUP C	
	NUMBER	%	NUMBER	%	NUMBER	%
< 20	4	20%	7	25%	4	20%
21 – 30	10	50%	10	55%	10	55%
31 – 40	6	30%	4	20%	5	25%
TOTAL	20	100%	17	100%	15	100%

Table 1 shows the age distribution of all three groups.

Age group 21 - 30 years had more number of patients followed by age group 31 - 40 and < 20 years.

TABLE 2 – BODY MASS INDEX (kg/m2):

GROUP MEAN	0 – WEEKS		12 - WEEKS		P -VALUE
	SD	MEAN	SD	MEAN	
GROUP A	27.84	2.33	26.63	3.51	0.032
GROUP B	28.31	2.65	27.31	3.50	0.049
GROUP C	28.81	2.73	24.62	3.25	< 0.001
P-VALUE	0.453		0.042		

Table 2 shows mean body mass index in all three groups.

Statistical analysis within the groups showed significant difference in the body mass index at the end of 12 weeks.

TABLE 3 – DIASYSTOLIC BLOOD PRESSURE (mm/Hg):

GROUP MEAN	SD	MEAN	SD	MEAN	P VALUE
GROUP A	71.70	5.88	71.20	6.06	0.234
GROUP B	70.60	6.19	70.20	6.35	0.408
GROUP C	72.10	6.50	71.50	6.41	0.209
P-VALUE	0.732		0.791		

Table 3 shows mean diastolic blood pressure in all three groups.

No statistically significant difference was observed within the groups and between the groups in the diastolic blood pressure at the end of 12 weeks

TABLE 4 – SYSTOLIC BLOOD PRESSURE (mm/Hg):

GROUP MEAN	0 – WEEKS		12 - WEEKS		P -VALUE
	SD	MEAN	SD	MEAN	
GROUP A	114.80	12.57	114.00	13.10	0.163
GROUP B	112.90	13.41	112.20	13.05	0.149
GROUP C	115.60	12.44	114.90	12.28	0.149
P-VALUE	0.791		0.745		

Table 4: shows mean systolic blood pressure in all three groups.

Statistical analysis within the groups and between the groups didn't show any significant difference in the systolic blood pressure at the end of 12 week.

TABLE 5 – MENSTRUAL CYCLE REGULARITY:

GROUP	PATIENTS WITH REGULAR CYCLES 0 – WEEKS	%	PATIENTS WITH REGULAR CYCLES 12 – WEEKS	%
GROUP A	0	0	8	40
GROUP B	0	0	11	55
GROUP C	0	0	15	75

Table 5 shows number of patients who had regular menstrual cycles.

Menstrual cycle regularity was seen maximum in group C, followed by group B and group A.

TABLE 6 – FOLLICLE STIMULATING HORMONE (mIU/ml):

GROUP MEAN	0 – WEEKS		12 - WEEKS		P -VALUE
	SD	MEAN	SD	MEAN	
GROUP A	6.38	1.10	6.35	1.08	0.201
GROUP B	6.42	1.29	6.38	1.23	0.185
GROUP C	6.35	1.14	6.32	1.14	0.163
P-VALUE	0.984		0.981		

Table 6 shows mean FSH levels in all three groups at Baseline and at the end of 12 weeks.

There was no statistically, no significant difference within the groups and between the groups at the end of 12 weeks.

TABLE 7 – LUTEINIZING HORMONE (mIU/ml):

GROUP MEAN	0 – WEEKS		12 - WEEKS		P -VALUE
	SD	MEAN	SD	MEAN	
GROUP A	14.79	2.14	14.47	2.04	0.023
GROUP B	15.60	3.28	13.82	3.03	0.001
GROUP C	16.26	2.96	11.88	3.11	< 0.001
P-VALUE	0.268		0.021		

Table 7 shows mean LH levels in all three groups at Baseline and at the end of 12 weeks. Statistical analysis within the groups showed a significant decrease in the LH level at the end of 12 weeks ($p<0.05$). Statistical analysis in between the groups showed a significant decrease in the LH level at the end of 12 weeks ($p=0.02$).

TABLE 8 – FASTING BLOOD GLUCOSE (mg/dl):

GROUP MEAN	0 – WEEKS		12 - WEEKS		P -VALUE
	SD	MEAN	SD	MEAN	
GROUP A	112.20	10.38	107.60	7.22	<0.001
GROUP B	109.60	10.72	108.45	9.68	0.009
GROUP C	106.80	11.96	102.15	8.17	<0.001
P-VALUE	0.310		0.044		

Table 8 shows fasting blood glucose levels in all three groups at Baseline and at the end of 12 weeks. Statistical analysis within the groups showed a significant decrease in the fasting blood glucose levels at the end of 12 weeks ($p<0.05$).

TABLE 9 – FASTING SERUM INSULIN (µIU /ml):

GROUP MEAN	0 – WEEKS		12 - WEEKS		P -VALUE
	SD	MEAN	SD	MEAN	
GROUP A	14.40	5.94	11.79	3.64	0.001
GROUP B	15.90	6.03	14.05	4.71	0.001
GROUP C	17.16	6.52	10.07	2.90	< 0.0001
P-VALUE	0.345		0.005		

Table 9 shows fasting serum insulin levels in all three groups at Baseline and at the end of 12 weeks. Statistical analysis within the groups showed a significant decrease in the fasting serum insulin levels at the end of 12 weeks ($p<0.05$).

DISCUSSION:

Insulin resistance (IR). It is due to abnormality in insulin receptor mediated signal transduction. Some actions of insulin are mediated by inositol phosphoglycan mediators. Deficient release of a putative D-chiro-inositol containing inositol phosphoglycan (DCI-IPG) mediator may contribute to insulin resistance in women with polycystic ovary syndrome (PCOS). IR leads to compensatory hyperinsulinemia. This excess insulin stimulates luteinizing hormone (LH) to produce more androgens from ovary leading to hyperandrogenism. Also, inappropriate gonadotropin secretion leads to preferential production of luteinizing hormone (LH) compared to follicle stimulating hormone (FSH) 1,7 and LH:FSH ratio becomes 2:1 or even 3:1. This vicious cycle leads to increased insulin, LH and androgen levels. These lead to anovulation, menstrual irregularity and infertility. **Inositol** is a physiological compound of sugar family of which two stereoisomers are found in our body, Myo-inositol (MI) and D-chiro inositol (DCI). DCI is synthesized endogenously from MI by insulin dependent epimerase enzyme. DCI is an important second messenger in insulin signal transduction. It acts as a precursor for inositol triphosphate (IP3) and phosphatidyl inositol 3 kinase (PI3K), needed for actions of insulin like increased glucose uptake, thus improving insulin sensitivity. Thus, DCI can be used as an alternative to metformin to improve insulin sensitivity.60 patients who fulfilled the eligibility criteria were enrolled and randomized into three groups, 20 patients in each group. Group A received Tab Metformin 500mg TDS and the Group B received Myo inositol 600mg OD (wt. < 60kg) or 600mg BD (wt.> 60kg) and Group C received Tab Metformin plus Tab Myo inositol for 12 weeks duration and all three groups were followed up for 8 weeks. There were no drop outs in the study. Body mass index,
systolic and diastolic blood pressure, serum FSH and LH levels, fasting glucose and insulin levels and regularity of menstrual cycle were assessed.

- Metformin combination with MI helps in greater weight reduction then given alone.
- The mean **FSH** levels didn`t show any significant difference between the groups at the end of 12 weeks. This shows Myo-inositol has no effect on FSH.

- The **mean LH levels** shows that combining metformin with MI helps in greater reduction of LH levels especially in Group A.

- There was significant reduction in mean fasting blood glucose levels between the three groups at the end of 12 weeks. This shows that combining metformin with MI helps in greater reduction of **mean fasting blood glucose levels.**

- At 0 weeks, all 60 patients in three groups had irregular menstrual cycle. At the end of 12 weeks, 40% of patients in group A, 55% of patients in group B and 75% of patients in group C resumed regular menstrual cycles.

CONCULSION:

Statistical significance was seen in between the groups using ANOVA at the end of 12 weeks treatment. The limitations of our study are that it was done for a shorter period and also in small group of patients. Effect of MI in various hormone levels like androgen levels and other metabolic parameters like lipid levels were not monitored. Further studies are needed to be done in larger group of patients for longer duration to prove its effect in polycystic ovary syndrome.

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