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## Comparative study on the use of myoinositol and metformin in the improvement of clinical symptoms and biochemical parameters in women with polycystic ovarian syndrome

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### Abstract

**Introduction:** Polycystic ovaries is one of the most common endocrinological disorder of the ovaries, commonly seen among the women belonging to the reproductive age group with prevalence about 5 - 10 %<sup>[1]</sup>. Insulin sensitising drugs are used in the treatment of PCOS and Metformin was the first insulin sensitising drug and it showed a reduction in circulating androgen level, significant reduction in the body weight and improvement in menstrual regularity<sup>[7]</sup>. Inositol phosphoglycan molecule is known to have a role in activating enzymes that control glucose metabolism<sup>[8-10]</sup>. Eventhough D-Chiro-inositol was the primary form studied initially in PCOS, the main focus of many recent studies has turned on myo-inositol<sup>[11]</sup>. The aim of our study was to compare the clinical outcome of long- term treatment of women with polycystic ovarian syndrome with myoinositol and metformin and to monitor the changes in bio-chemical parameters following treatment.

**Methodology:** This ethical committee approved study was done in the Department of Obstetrics and Gynaecology, Rajah Muthiah Medical College and Hospital, Chidambaram for the duration of two years from June 2018 to October 2020. A random hundred women (Married/un married) between the age of 18 to 40 years with signs and symptoms of PCOS (According to Rotterdam Criteria) attending the OPD were included in the study after obtaining consent from them. A detailed history regarding the menstrual cycle, gynaecological complaints, hirsutism, acne, acanthosis nigricans were dealt in detail followed by anthropometric measurements, general and systemic examination. All the patients were subjected to pelvis ultrasonography. They were divided into two groups (group 1 and group 2) each group consisting of fifty members each. A fasting venous blood sample was taken on day two of menstruation and sent for biochemical investigations. Group 1 patients were treated with Metformin 500mg daily for 6 months. Group 2 patients were treated with Myoinositol 1gm with folic acid daily for 6 months. These patients were called after 6 months and again subjected to anthropometric measurements followed by general and systemic examination. Blood sample was taken for investigations and subjected for ultrasonography. The side effects of each group was noted. The efficacy of Metformin Vs Myoinositol, in the PCOS patients, were compared and statistically analysed.

**Results:** Both the treatment groups i.e. Myoinositol and metformin were found to be almost equally effective in improving biochemical profile. In our study glucose-insulin ratio improved significantly in both groups but more in Group 1 as compared with Group 2. Both the groups showed improvement in the menstrual pattern with group 1 showing comparatively better results. There was no significant decrease in body weight and BMI. Acanthosis nigricans was very much reduced after treatment with metformin (Group 1), whereas there was no significant improvement in Group 2. Metformin therapy lead to a reduction in ovarian volume. Though both groups reported improvement in biochemical parameters, metformin group showed significant decrease in free testosterone level as compared with myoinositol group. Group 1 showed significant decrease in insulin resistance as compared with Group 2. In our study the reduction in the mean modified Ferriman Gallwey score (mFG) of hirsutism was statistically significant in both the groups, but on comparing the two groups, group 1 had a significant reduction than group 2.

**Conclusion:** Metformin and myo-inositol substantially enhanced insulin sensitivity in PCOS women. Both the treatment groups i.e. Myoinositol and metformin were found to be almost equally effective in improving biochemical profile. However metformin performed better than myoinositol in improving menstrual irregularities, BMI, insulin resistance, biochemical profile and clinical features. Hence, Metformin as an insulin sensitizer is effective in the treatment of PCOS as first line therapy in PCOS. Myo-inositol can be a new addition in the armamentarium for the treatment of PCOS with comparable efficacy.

**Keywords:** Polycystic ovarian syndrome, metformin, myoinositol, insulin sensitising drug

### Introduction

Polycystic ovaries is one of the most common endocrinological disorder of the ovaries.

The prevalence of PCOS in reproductive age was reported as 5 - 10 % [1]. PCOS has multifactorial origin. It may be due to intrauterine androgen exposure, post natal insulin resistance and hyperinsulinemia [2]. The diagnostic criteria for polycystic ovary syndrome (PCOS), as suggested in the Rotterdam conference sponsored by the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine in 2003, include (1) oligo- and/or anovulation, (2) hyperandrogenemia and/or hyperandrogenism and (3) polycystic ovaries.<sup>3</sup> Diagnosis is done if at least two features out of three are present and only after excluding other causes of androgen excess disorder [3].

Obesity, muscle mass and body fat location also alters the insulin sensitivity. In PCOS alteration in these parameters are seen which results in elevated insulin resistance when compared to normal women [4]. Even lean women with PCOS have insulin resistance independent of the parameters above mentioned [5]. Under the action of insulin the theca cells of ovary produce androgen in excess amount which is evident from the cells from controls [6]. Insulin sensitising drugs are therefore used in the treatment of PCOS.

Metformin was the first insulin sensitising drug and it showed a reduction in circulating androgen levels, significant reduction in the body weight and improvement in menstrual regularity [7]. Inositol phosphoglycan molecule is known to have a role in activating enzymes that control glucose metabolism [8-10]. Eventhough D-Chiro-inositol was the primary form studied initially in PCOS, the main focus of many recent studies has turned on myo-inositol [11].

## Methods

This prospective study was done in the Department of Obstetrics and Gynaecology, Rajah Muthiah Medical College and Hospital for the duration of two years from June 2018 to October 2020. All women (Married/un married) between the age of 18 to 40 years with signs and symptoms of PCOS (According to Rotterdam Criteria) attending the outpatient department were included in the study after obtaining their consent.

## Inclusion Criteria

- Patient between the age group of 18 to 40 years with PCOS full filling the Rotterdam criteria.

## Rotterdam criteria

1. Oligo-and/or anovulation.
2. Clinical and/or biochemical signs of hyperandrogenism.
3. Polycystic ovaries. (Two of three criteria needed)

## Exclusion Criteria

- Patient with other metabolic syndromes
- Patient with congenital disorders
- Any contraindications for myoinositol/Metformin use or any allergic reactions to the same were excluded.

In the OPD detailed history regarding the menstrual cycles, gynaecological complaints, hirsutism, acne, acanthosis nigricans were dealt in detail followed by anthropometric measurements, general and systemic examination was done and noted in the proforma. All the patient were subjected to pelvis

ultrasonography and the size, number of follicles and volume of both ovaries noted. Randomly hundred patients were taken as the study population. They were divided into two groups (group 1 and group 2) each group consisting of fifty members each. Then fasting and venous blood was taken on day two of menstruation and sent for the following investigations.

## Biochemical Markers

- Serum progesterone
- Fasting glucose/insulin ratio.
- Free Testosterone
- Thyroid function test

Group 1 patients were treated with Metformin 500mg daily for 6 months. Group 2 patients were treated with Myoinositol 1gm with folic acid daily for 6 months. These patients were called after 6 months and again subjected to anthropometric measurements followed by general and systemic examination. Fasting and postprandial venous blood samples were taken for investigations and subjected for ultrasonography to see the above said features. The side effects of each group were noted. The efficacy of Metformin Vs Myoinositol, in the PCOS patients, were compared and statistically analysed.

## Results

The results of our study were as follows

1. Mean age of the study group, is 23.85±4.04 of Std. Deviation. In the present study maximum number of patients were between 21 to 25 yrs.
2. In the study group, total 38% patients had regular menstrual cycle and 62% had irregular cycle. After treatment in the study group, total 77% patients had regular menstrual cycle and 23% had irregular cycle. Both the groups showed good improvement in regularization of the menstrual cycle.
3. In our study, majority of the patients were between 18.5 – 29.9 BMI. Predominantly women belonged to the normal weight category. The mean was around 24.9 ± 3.6 Std. Deviation. After treatment majority of patients in both groups had a slight decrease in BMI and both the groups had similar results.
4. Hirsutism is a sign of hyperandrogenism and it was found to be more in both the groups of patients. After treatment, it was found to be decreased (80%) more in patients treated with metformin than the myoinositol group.
5. Acne is one of the common complaints in patient with PCOS. Here acne was present in higher incidence in both the groups. There is a marked decrease in acne in the group of females treated by metformin than in myoinositol. Group 2 also showed decrease in the sign of acne but it is very less when compared to group 1.
6. Acanthosis nigricans is an important feature which shows the presence of insulin resistance in PCOS patients. It was seen in both groups with higher percentage before treatment. After treatment it was found to be decreased in both groups but it is drastically decreased in Group 1 than Group 2.

The results of both the groups before and after treatment may be tabulated and summarized as follows,

**Table 1:** Comparison of Improvement in Various Clinical, Biochemical and Ultrasonography Parameters Before and after Treatment in Group 1

Variables	Mean ± SD Before Treatment	Mean ± SD after treatment	P value
BMI	24.92 ± 3.19	24.78 ± 2.17	0.097 *
Waist	84.92±8.68	84.67±7.41	0.071*
WHR	0.82±0.10	0.82±0.07	0.078*
Hirsutism	10.24±2.08	10.67±2.82	0.001
Acne	1.74 ±0.501	1.56 ± 0.443	0.002
Ovarian Volume	12.35±3.8	14.45±2.83	0.001
AFC	11.40±3.00	11.60±2.13	0.001
FBS	98.62±20.49	92.16±18.12	0.001
Fasting Insulin	14.58±9.81	11.08±9.80	0.002
FBS and Insulin Ratio	3.50±2.34	4.39±2.28	0.036
S. Testosterone	57.21±28.80	46.28±27.36	0.001
S. Progesterone	10.03±7.86	10.00±6.25	0.001

Symbol (\*) showed that they have insignificant values. P value was found to be insignificant for waist, waist hip ratio.

**Table 2:** Comparison of Improvement in Various Clinical, Biochemical and Ultrasonography Parameters Before and After Treatment in Group 2

Variables	Mean±SD Before Treatment	Mean ± SD After Treatment	P value
BMI	23.23 ±2.65	23.22 ± 3.51	0.062*
Waist	72.1±9.18	71.36±8.86	0.077*
WHR	0.79±0.08	0.79±0.06	0.089*
Hirsutism	8.47±1.68	8.79±2.37	0.066*
Acne	1.48±0.50	1.68± 0.47	0.074*
Ovarian Volume	14.53±3.44	14.35±2.83	0.004
AFC	10.20±2.31	10.18±2.08	0.044
FBS	92.44±11.23	92.34±12.17	0.048
Fasting Insulin	16.51±13.95	14.03±15.41	0.036
FBS and Insulin Ratio	4.21±3.63	6.32±4.61	0.008
S. Testosterone	54.69±24.81	54.24±24.77	0.040
S. Progesterone	7.48±5.21	7.30 ±6.65	0.045

Symbol (\*) showed that they have insignificant values. P value was found to be insignificant for BMI, waist, waist hip ratio, acne and hirsutism.

## Discussion

### Age

The estimated prevalence of PCOS in general population have ranged from 2-20% [12]. The community prevalence of PCOS in young women (18-25 years) under the NIH criteria in our study was 3.7% (95% CI-2.6-4.4%), which is less than that reported in earlier studies. Using this NIH criteria, a prevalence of 8.7% was noted in a birth cohort study from Australia. In this study, the definition of menstrual irregularity was very widely ranged, polymenorrhea (<21 days cycle) or a gap between usual cycle lengths of 4-5 days was taken as oligo-anovulation, while in our study, cycle length of more than 35 days was the criteria [13].

Under the Rotterdam criteria where ovarian ultrasonography is essential for diagnosis, in the same cohort, prevalence increased to 11.9%. Contrary to this using the Rotterdam criteria, Kumarpeli *et al.* have reported a lesser prevalence of 6.1% in Sri Lankan population and 6.3% in Chinese population by Yanmin *et al.* both are community-based studies [14]. In contrast to this, in our study, most of the patients with PCOS were between 21 – 25yrs (young adults) according to Rotterdams criteria. This may be due to increase in weight gain due to sedentary work in most of the women and more intake of junk foods nowadays.

### Menstrual irregularities

Menstrual irregularities, such as oligomenorrhea or abnormal uterine bleeding, can be noted in a majority of patients with PCOS. In large number of PCOS patients, about 75% have clinically apparent menstrual dysfunction [15]. An inappropriate gonadotropin secretion is associated with the classic form of PCOS. Compared with the follicular phase of the normal menstrual cycle, PCOS women show a disproportionately high

LH secretion with relatively constant low FSH secretion [16] which leads to menstrual irregularities. This incidence was similar to our study where 62% of women had irregular cycle before treatment.

Metformin was the first insulin sensitizing drug (ISD) to be used in PCOS to investigate the role of insulin resistance in the pathogenesis of the syndrome. Velazquez and colleagues reported in an observational study, a significant improvement in menstrual regularity and reduction in circulating androgen levels as well as a significant reduction in body weight which confounded their findings [7]. There is, however, some conflicting evidence as to whether metformin can directly affect ovarian steroidogenesis [17].

Our study also showed improvement in the menstrual pattern after treatment with metformin in group 1 and myoinositol in group 2. Among them group 1 showed more improvement than group 2. P value was found to be significant. Myoinositol also showed improvement in the regularization of the menstrual cycle in our study and this was similar to the study done by Angik R *et al.* where eight women showed regularization of the cycle after treatment and it was statistically significant [11]. This is because myoinositol can accelerate glucose disposal and sensitize insulin action.

### BMI and PCOS

Factors that often play a role in the regularity and flow of a woman's menstrual cycle include hormonal changes, genetics, serious medical conditions and BMI. Moreover, psychological well-being is known to influence the age of menarche and common menstrual problems. Dars *et al.*, 2014, cross sectional study on Relationship of Menstrual irregularities to BMI and nutritional status in adolescent girls", found that 75.5% girls

with BMI 14-24.9 had a normal menstrual pattern. A statistically significant relationship was observed between BMI and menstrual pattern [18]. According to WHO the BMI of age group 12 to 17 years old has raised from 5.7% on 2009 to 11.1% on 2011 around the world, this had profound impact on female reproductive health [19].

According to Angioni *et al.* (2008), roughly about 40 to 50% of women with PCOS are overweight or obese, often presenting high insulin levels and reduced glucose-induced insulin metabolism [20]. In our study, there was no significant decrease in body weight and BMI in both the groups. This was similar to the study done by Angik R and Mandal SC [11]. WHR did not decrease significantly in both the groups.

### Hirsutism, ACNE and PCOS

Hirsutism is a common problem for women with PCOS and one with potentially serious psychosocial sequelae. The diagnosis of PCOS may either be asymptomatic or present with symptom such as an hirsutism, acne, alopecia, excess body weight and obesity, acanthosis nigricans, impaired glucose tolerance, hypercholesterolemia, irregular menses and infertility [21].

PCOS is a common cause of hirsutism occurring in approximately 60%. In our study the reduction in the mean modified Ferriman Gallwey score (mFG), however this varies with race and degree of obesity. Hirsutism should be assessed with a standardized scoring system i.e. modified Ferriman-Gallwey (mFG) score, which is of hirsutism was statistically significant in both the groups, but on comparing the two groups, group 1 had a significant reduction than group 2.

### Acanthosis nigricans and PCOS

Acanthosis nigricans (AN) is characterized by dark, coarse and thickened skin with a velvety texture, being symmetrically distributed on the neck, the axillae, antecubital and popliteal fossae, and groin folds, histopathologically characterized by papillomatosis and hyperkeratosis of the skin. A high prevalence of AN has been noted in the recent trend which includes benign, obesity associated, syndromic, malignant, acral, unilateral, medication-induced and mixed AN. Diagnosis is largely clinical with histopathology needed only for confirmation. Other investigations needed are fasting lipoprotein profile, fasting glucose, fasting insulin, hemoglobin and alanine aminotransferase for obesity associated AN [22].

Severity of AN in obesity correlates positively with fasting insulin concentration. Thus, insulin may promote AN through direct activation of the IGF-1 signalling pathway. The predilection of AN for areas such as neck and axillae suggests that perspiration and/or friction may be necessary cofactors. In a study done by Paula Bellot Rojas showed that the rosiglitazone group showed a significant reduction in insulin levels. Severity of AN remained same, but moderate improvements of skin texture observed in both treatment groups [23]. This was similar to our study where, after treatment with metformin (Group 1) acanthosis nigricans was very much reduced. But there was no significant improvement in Group 2.

### Insulin resistance and PCOS

Role of insulin resistance in PCOS is of great interest not only for academic purposes but also for future health and well being of women. In a study done by Afroz *et al.* (which compared two groups of PCOS patients treated with metformin and placebo) concluded that Insulin/glucose ratio was 3.45(1.04-9.21) and 3.11(1.02-15.79) while it changed after treatment to 2.52(0.79-6.86) and 2.61(0.87-10.0) in case and control group respectively.

The change was significant in case group (P-value=0.004). The treated group presented significantly lower level of fasting Insulin ((17.30(5.7-66.3) vs 10.90 (3.4-50.0)) (p=0.001) and increased insulin sensitivity (HOMA S) (38.85(10.1-11.7) vs 61.75(12.09-199.5)) (p=0.001)) after treatment with Metformin [24].

Thus it was concluded as per this study, treatment with Metformin reported significant decrease in insulin resistance. This is similar to results of our study i.e. Group 1 showed significant decrease in insulin resistance as compared with Group 2.

Gonzalez *et al.* showed the results of a retrospective study of women identified as having polycystic ovary morphology, aged 18-35 years, assessing them for insulin resistance (using homeostatic model assessment estimates for insulin resistance [HOMA-IR]), and comparing the results based on menstrual patterns. They noted that 78% of amenorrhoeic women with polycystic ovaries, compared with 41% of oligomenorrhoeic women, displayed insulin resistance, again suggesting that a higher degree of insulin resistance was associated with a greater prevalence of amenorrhoea [25]. According to a study by Jyoti Nehra, Metformin and myo-inositol significantly improved insulin sensitivity in PCOS women. It was associated with improvement in insulin sensitivity in HOMA-IR defined insulin resistant patients. Metformin did very well in all aspects we studied, so it can be used as first line therapy in PCOS. Both the treatment groups i.e. Myoinositol and metformin were found to be almost equally effective in improving biochemical profile.

### Ovarian volume and PCOS

The characteristics of PCOS include doubling surface area, an average volume increase of 2.8 times, presence of the same number of primordial follicles, doubling the number of growing and atretic follicles, 50% increase in the thickness of tunica (outermost layer), one-third increase in the cortical stromal thickness due to hyperplasia of theca cells, excessive follicular maturation and atresia, and quadruple increase in ovarian hilus cell nest. It is well-known that there is an intimate relationship between the increase in plasma androgen levels and the ultrasound findings of stromal hypertrophy [26]. Metformin therapy may lead to a reduction in ovarian volume. It is likely that the reduction of ovarian volume reflect a decrease in the mass of androgen producing tissues [27]. This was confirmed by other studies and this was similar to our study and found to be statistically significant in both groups [7, 11].

### Hormones and PCOS

Metabolic disorders including increased serum levels of Luteinizing hormone (LH) and Follicle-stimulating hormone (FSH) is common in these patients and health of women with PCOS is deeply affected in the long term [28]. Almost in 40% of women who have polycystic ovaries, an excess amount of LH is secreted. Attention is paid to the hypersecretion of LH and insulin resistance as well as hyperinsulinemia. The oldest theory emphasized the relation between thecal cells stimulation with LH and the consequent androgen overproduction [29].

In women with PCOS, metformin treatment had beneficial effects on hormonal profile and therefore it could be useful in the correction of menstrual irregularity, anovulation and infertility in these women. Artini *et al.* [30] found that myo-inositol treatment showed significantly lower Testosterone (2.3 nmol/liter vs. 3.4 nmol/liter; 95% CI = 0.07 and 2.1, respectively; P > 0.04), similarly to our study.

According to study by Tagliaferri V *et al.* (which compared



treatment of PCOS with metformin and myoinositol) both metformin and myoinositol significantly reduced the insulin response to OGTT and improved insulin sensitivity. Metformin significantly decreased body weight and improved menstrual pattern and Ferriman-Gallwey score. Metformin treatment was also associated with a significant decrease in LH and oestradiol levels, androgens and anti-müllerian hormone levels. None of these clinical and hormonal changes were observed during myoinositol administration. The results reported improvement in the glyco-insulinaemic features of obese PCOS patients in both groups, but only metformin seems to exert a beneficial effect on the endocrine and clinical features of the syndrome<sup>[31]</sup>. This was similar to our study wherein though both groups reported improvement in biochemical parameters metformin group showed significant decrease in free testosterone level as compared with myoinositol group.

### Conclusion

1. Myoinositol acts at the level of insulin receptors and is effective in treatment of hyperinsulinemia and insulin resistance, which is the underlying factor leading to the development of polycystic ovary syndrome.
2. Metformin and myo-inositol significantly improved insulin sensitivity in PCOS women. Both the treatment groups i.e. Myoinositol and metformin were found to be almost equally effective in improving biochemical profile. However metformin performed better than myoinositol in improving menstrual irregularities, BMI, insulin resistance, biochemical profile and clinical features. Hence, Metformin as an insulin sensitizer is effective in the treatment of PCOS as first line therapy in PCOS.

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