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Evaluating Hormonal Modulation in PCOS-Related Infertility: Metformin Alone Versus Metformin Plus Myoinositol in a Randomized Controlled trial

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ABSTRACT

Objective: To compare the benefits of metformin with myo-inositol to metformin alone on hormonal profile in women with polycystic ovarian syndrome (PCOS) who are unable to conceive.

Methodology:

A double-blinded, randomize d controlled experiment was carried out from September 2022 to February 2023. 114 PCOS females who were infertile were randomly assigned to Group A (n=57) took Metformin orally in a dose of 500 mg 3 times per day plus oral Myo-inositol 4 g once daily; Group B (n=57) received oral Metformin 500 mg three times a day only. It was suggested to the subjects to try for spontaneous conception. All the parameters of the hormonal and metabolic profile were measured at baseline after initiating therapy and then at one month, three months, and six months. The main aim of this study was establishment of clinical pregnancy and improvement of hormonal profile in terms of mean changes in serum LH/FSH ratio, mean serum Progesterone and serum Anti Müllerian Hormone over a period of 1 month, 3 months and 6 months. Both groups baseline demographic, hormonal, bio-chemical and clinical traits were the same.

Results:

Significant progress was made in mean serum LH/FSH ratio (p=0.00), serum Progesterone (p=0.00) and serum Anti Müllerian Hormone (p=0.00) in Group A as compared to Group B. Number of clinical pregnancies were higher in Group A as compared to Group B [27.3 % (15/55); 14.8% (8/54); p=0.113] although not statistically significant.

Conclusion:

Metformin and myo-inositol together considerably ameliorated the hormonal profile and raised fertility in contrast to metformin alone.

Keywords:

Polycystic ovarian syndrome, infertility, metformin, myo-inositol

Introduction:

Endocrine-gynecological disorder i.e. PCOS affects 5–10% of women of reproductive age(1). Although a portion of

the mechanism involved in the development of PCOS has been identified, the precise etiology and pathophysiology are still not fully known(2). Oligo/anovulation, hyperandrogenemia, and the appearance of a polycystic ovary on ultrasonography are characteristics of PCOS(3)(4).

Dietary and lifestyle changes, insulin sensitizers, oral ovulation induction drugs, gonadotrophins, and laparoscopic ovarian drilling are the main therapy methods for oligo/anovulatory infertile PCOS women (5). In addition, insulin resistance is the most prevalent symptom in PCOS women; as a result, using an insulin sensitizer like metformin causes weight loss, which in turn reduces insulin resistance and restores ovulation(6). However, metformin has adverse effects on the digestive system(7)(8) the most frequent ones being diarrhoea and nausea, along with flatulence, indigestion, vomiting, and abdominal pain. Myo-inositol, one type of inositol, has just been made available for the treatment of PCOS patients as a novel insulin sensitizer. It enhances ovarian function, lowers insulin resistance, reduces serum androgens lowers, sex hormone binding globulin, and levels of total and free testosterone, and the ratio of Luteinizing hormone to Follicle Stimulating Hormone (LH/FSH) in the blood (9).

As both of the two insulin sensitizers have a unique mode of action, thus by combining them, they might work together effectively to improve PCOS women reproductive and hormonal outcomes who are infertile (10)(11). Few studies have been reported that contrast myo-inositol plus metformin with metformin alone in terms of improving hormonal and reproductive indicators in PCOS women and enhancing their ability to reproduce who are having trouble getting pregnant. Our literature review did not find any such study in our KPK region. Our study will be a beneficial resource and will educate clinicians in treating their PCOS patient who are trying to get pregnant. Also novelty of the study is secondary outcomes and to assess the efficacy broadly.

Materials and Methods

Sample was collected from Khyber Teaching Hospital Peshawar's outpatient department of obstetrics and gynecology, a double-blinded, randomized controlled experiment was carried out from September 2022 to February 2023. After receiving approval from the institute's Clinical Research Ethics Committee, the study was launched. According to Rotterdam criteria, 114 women with PCOS who were infertile with PCOS were assessed for the study.

Inclusion Criteria: Married female patient age (20–38) years with infertility lasting for more than a year, and bilaterally patent fallopian tubes confirmed by laparoscopy/hysterosalpingography

Exclusion Criteria: Semen analysis-based male infertility, congenital adrenal hyperplasia (ambiguous genitalia), androgen-secreting tumors, uncontrolled hyperthyroidism or hypothyroidism, and patients with Cushing's syndrome were among the exclusion criteria.

Study Groups: According to a computer produced randomization table, each participant was randomly assigned to one of two groups. The patients' informed written consent was obtained after a thorough explanation of the study's goal, length, and comprehensive strategy in their native language.

Thotough physical examination, involving weight, height, BMI (kg/m^2), ratio of waist to hips, modified Ferriman Gallwey score, Global acne score, and secondary sexual characteristics were documented after a thorough history about PCOS and infertility.

Lipid profile (Triglycerides, HDL), fasting blood sugar, fasting serum insulin, and HOMA-IR (Homeostatic Model Assessment of Insulin Resistance), serum AMH, LH/FSH ratio were among the baseline studies performed on 2^{nd} to 5^{th} day of menstrual cycle, with serum Progesterone being tested on the 21^{st} day of the menstrual cycle instead. Additionally, lower abdomen ultrasound for ovarian cysts was also performed. The treatment was administered in accordance with the procedure. Tab. Metformin 500mg TDS and tab. Myo-inositol 4gm once a day were given to Group A (n=57) in envelopes for six months and Group B (n=57) got Tab Metformin 500 mg TDS for six months in envelopes. Patients were instructed to keep up with their menstrual cycles and encouraged to try for a spontaneous pregnancy.

Follow up: After starting their medication, every patient was followed up after the first, third, and sixth month and all biochemical and hormonal measures were redone to assess any progress.

All study participants engaged in direct dialogue with the researchers to resolve this problem over the course of the 6-month trial period. They got a phone text every month to check on how well they were taking their prescriptions and whether there were any negative side effects. During the course of the trial, they were also urged to text the researchers to provide updates on their progress and to ask any questions about PCOS or their meds. The frequent contact probably increased compliance and may have had an impact on both treatment outcomes and washout period outcomes.

Documentation was made on those who became pregnant during six months of therapy. Two patients from A Group and three from B Group dropped out of the study early, due to side effects related to GIT as well as found the therapies to be ineffective. A record of these events was kept. A clinical pregnancy or spontaneous conception was the primary outcome. Improvement in the mean blood LH/FSH ratio, serum Progesterone, and Anti-Müllerian hormone were among the secondary outcomes.

Statistical Analysis: In order to analyze the data, SPSS version 23 was used. Levene's an independent sample t-test was done to determine mean difference in outcome variables. Where $p \leq 0.05$, the significance level was accepted.

Results:

114 infertile PCOS women were chosen for the study based on inclusion and exclusion criteria, and they underwent randomization. Group A (n=57) undergone through Metformin and Myo-inositol therapy while Group B (n=57) got Metformin only. 2 patients from Group A and 3 from Group B dropped out of the study early. Table 1 lists the research participants baseline demographic, clinical, hormonal and metabolic data.

Table I. Baseline demographic, clinical characteristics, hormonal and metabolic characteristics. *p*<.05 is statistically significant

Characteristics	Group A (n=55)	Group B (n=54)	p-Value*
Clinical parameters			
Age	28.94±3.77	28.61± 3.64	(0.64)
BMI(kg/m^2)	28.58±2.52	28.65±2.35	(0.88)
Length of infertility	3.27±1.36	2.79±0.94	(0.03)
Length of Menstrual cycle	2.36±0.86	2.57±0.59	(0.14)
Days of Bleeding each cycle	13.05±4.5	14.6±4.13	(0.06)
Ferriman Gallawey score	5.31±1.30	5.24±1.32	(0.82)
Global Acne score	2.82±1.10	2.67±1.15	(0.41)
Hormonal parameters			
Sr. AMH(ng/ml)	11.06±1.24	11.24±1.23	(0.73)
Sr. LH(mIU/ml)	15.08±2.6	15.03±2.71	(0.92)
Sr. FSH(mIU/ml)	5.72±0.69	5.71±0.71	(0.94)
LH/FSH ratio	2.64±0.44	2.58±0.24	(0.38)
Sr.Progesterone(nmol/l)	1.91±0.38	1.92±0.37	(0.88)

During six months of therapy the total number of patients who conceived spontaneously was higher in Group A (27.3% 15/55) as compared to Group B (14.8% 8/54) but the difference was not statistically significant (p=0.113) (Table 2).

Table 2. Clinical Pregnancy rate in both groups

Group A	Group B	*t*	*p*-Value
n=55 15 (27.3%)	n=54 08(14.8%)	1.598	0.113

With a p value of 0.00, Group A's mean blood LH/FSH ratio significantly improved after the first month of treatment as compared to Group B. (Table III), similarly significant improvement after 3 months of therapy was seen in Group A as compared to Group B p=0.00 (Table IV), after 6 months significant improvement was observed in case of mean serum LH/FSH ratio in Group A as compared to Group B=0.00 (Table V).

Similarly after 1 month of therapy, there was significant improvement in mean serum Progesterone in Group A in comparison with Group B p=0.00 (Table III), similarly there was significant improvement after 3 months in Group A in comparison with Group B p=0.00 (Table IV), after 6 months of therapy significant increased levels of mean serum progesterone was recorded in Group A in comparison with Group B p=0.00 (Table V).

In case of mean serum Anti Müllerian Hormone significant improvement was recorded in Group A in comparison to Group B after 1st month of therapy p=0.00 (Table III), after 3 months similar significant results were observed in Group A in comparison to Group B p=0.00 (Table IV), and significant reduction of mean serum AMH was observed in Group A in comparison to Group B with a p value of 0.00 after 6 months of therapy (Table V).

Table III. Improvement in hormonal parameters after 1 month.

Hormonal parameters	After 1 month		
	Group A n=55	Group B n=54	*p*-Value
LH/FSH ratio	2.294 ±0.26	2.488 ±0.25	(0.00)
Sr.Progesterone(nmol/l)	6.620 ±0.66	5.545 ±0.70	(0.00)
Sr. AMH (ng/ml)	9.548 ±1.23	10.547 ±1.24	(0.00)

p <.05 is statistically significant

Table IV. Improvement in hormonal parameters after 3 months.

Hormonal parameters	After 3 months		
	Group A n=55	Group B n=54	*p*- value
LH/FSH ratio	1.994±0.26	2.385±0.25	(0.00)
Sr. Progesterone(nmol/l)	9.666±0.67	7.48±0.72	(0.00)
Sr. AMH (ng/ml)	7.075±1.25	8.821±1.31	(0.00)

p <.05 is statistically significant.

Table V. Improvement in hormonal parameters after 6 months.

Hormonal parameters	After 6 months

	Group A n=55	Group B n=54	*p*-value
LH/FSH ratio	1.692±0.26	2.277±0.25	(0.00)
Sr.Progesterone(nmol/l)	19.125±6.20	12.522±5.03	(0.00)
Sr. AMH (ng/ml)	3.648±1.13	6.133±1.31	(0.00)

p <.05 is statistically significant**.**

Discussion

Both metformin and myo-inositol are known to increase insulin sensitivity, but their respective mechanisms of action are distinct (12)(13). Although metformin is a traditional and regularly used drug to treat PCOS(14), the attention paid to myo-inositol is relatively new(15). Myo-inositol is considered safe and studies have demonstrated better metabolic, hormonal, and reproductive outcomes(16)(17).

According to the current study, the group who took metformin and myo-inositol together had more pregnancies than those who received metformin alone.

In a studies performed by Agrawal A. et al(11), Nagaria et al(18) ,Ria et al(19) and Thakur et al(20), more number of conceptions were observed in the group using metformin plus myoinositol therapy as compared to groups using metformin or myoinositol alone. However in the surveys conducted by Lara C Morley et al(21), Ashrafi M et al(22) and Angik R et al(23) group showed improvement with metformin alone in case of live birth rates. According to a study conducted by Papaleo E et al(24) fertility had improved much further. i.e. 40% of patients conceived. Improvement was also observed by Rani et al(25) as well as Chirania K. et al(26), (p=<0.001).

However According to Pourghasem S. et al(27) there was no significant differences existed between treatments when myo-inositol and metformin are used as a monotherapies. Emekci Ozay et al(28) found that the myo-inositol group had considerably greater rates of clinical pregnancies. Raffone et al(29) compared metformin and myo-inositol, despite the fact that the myo-inositol group had higher total conception rate, but the study failed to show any statistically significant difference between the two groups. In case of present study, although there was no significant difference in both groups with regard to clinical pregnancy rates at the end of sixth month but still there was improvement in pregnancy rates in Group A (metformin+ myo-inositol) as compared to group B (p=0.113).

In a study performed by Bahadur et al(30) there was considerable improvement in Group II LH/FSH ratio after 6 months of treatment with metformin+myo-inositol (p=0.007) versus to Group I LH/FSH ratio using metformin alone. In another study conducted by Ibrahim et al. 2023 (31) significant improvement was observed in group 3 LH/FSH ratio after using 1g of metformin along with 4g of myo-inositol for about three months (p<0.004). Similarly In a study conducted by Nagaria et al(18) significant improvement was seen in LH/FSH ratio (p=0.01) with a combination therapy of metformin + myo-inositol. Abou-Seido et al. 2023 (32) also concluded a drop in LH:FSH ratio by 30 to 40%. In the present study improvement in mean LH/FSH after 1 month was significantly higher in Group A as compared to Group B (p=0.000), Similarly improvement in mean LH/FSH at 3rd month was significantly higher in Group A versus Group B (p=0.000), Improvement in mean LH/FSH at 6th month was significant higher in Group A versus Group B (p=0.000). Similarly, in a study performed by Agrawal A et al(11) there was improvement in LH/FSH ratio in Group I using metformin+myo-inositol therapy as compared to Group II using metformin alone (p=0.38), although not statistically significant but due to the fact that the results were recorded just after three months of trial. Thakur et al(20) also found out that combination therapy resulted in significant improvement in serum LH/FSH ratio (p<0.05). However in a study conducted by Seyam et al(33) metformin seemed to have promising results in reducing

LH/FSH ratio in case of using metformin alone.

A study conducted by Nagaria et al(18) showed an improvement in progesterone levels after treatments with combination therapy of myo-inositol plus metformin (p=0.627) as compared to pretreatment, although not statistically significant. In contrast to this study, the present study resulted in statistically considerable improvement with a mean of serum Progesterone after 1st, 3rd and 6th month in Group A versus Group B (p=0.000).According to Rani et al (25), in the metformin plus myo-inositol group, mid-luteal serum progesterone levels were considerably higher (60.9% against 28.0% and 73.9% compared 44.0%). In another study conducted by K. Nass and L. Tuu(34), compared Myo-inositol and Metformin and found out significant improvement in both groups after 6 months of treatment (p=<0.05), however, no significant differences among the groups were retrieved in case of progesterone. A study performed by Regidor et al(35) found out increase in progesterone levels from 2.1 ng/mL to a value of 12.3 ng/mL in infertile PCOS women using Myo-inositol therapy.

In a study conducted by Agrawal et al(11) the mean serum AMH (ng/ml) significantly improved in both groups i.e. in Group I (myo-inositol + metformin) and Group II (metformin) but there was no discernable distinction between the two groups (p=0.10). In another study conducted by Prabhakar p. et al(36) found after three months of study i.e. combination therapy of myo-inositol plus metformin (Group I) vs. myo-inositol alone therapy (Group II), showed more improvement in serum AMH profile in Group II as compared to Group I but there was no statistical significant difference between the two groups. In another study conducted by V. Tagliaferri et al(37) it was concluded that in comparison to myo-inositol, metformin treatment was associated with a significant decrease in serum AMH levels while no changes were observed in case of myo-inositol therapy but in the present study, mean serum AMH after 1st, 3rd and 6th month was significantly improved in Group A versus Group B (p=0.000).

Whereas in a study conducted by Chhabra et al(38) the group using metformin monotherapy (Group A) showed significant improvement in serum AMH concentration as compared to Group B (p=0.01) using metformin plus myo-inositol therapy.

Limitations:

Although the study's findings are positive, the authors are conscious of its shortcomings, namely its short duration and small sample size. To support these findings, it is necessary to use a larger sample size and longer follow-up period.

Conclusion

As a result, the current study draws the conclusion that myo-inositol plus metformin, as opposed to the more commonly used metformin alone, can be a successful treatment for cases of infertile PCOS patients. To confirm or refute the advantages of combinations, additional randomized controlled trials contrasting the two molecules alone and with different combination are required.

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Disclosure statement

There is no financial connection to any organization. All primary data are entirely under the authors' control. The patients provided written informed consent before to publications. The authors state that they have no competing interests.

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