Comparison of Various Therapeutic Approaches to Manage Infertility in Polycystic Ovarian Syndrome

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ABSTRACT

Objective: To compare the efficacies of common therapeutic regimens and their combinations, used in polycystic ovarian syndrome (PCOS) to improve fertility in reproductive-age women.

Study Design: A descriptive study.

Place and Duration of the Study: Department of Obstetric Gynaecologist, Medicare Cardiac and General Hospital, Karachi, Pakistan, from November 2022 to July 2023.

Methodology: Out of 300 patients with the symptoms of menstrual irregularities and infertility, 152 were diagnosed as PCOS patients based on the ultrasound and hormonal assays and selected for study purpose. They were divided according to their therapeutic regimen into four treatment groups, treated by different therapeutic agents. Group A received metformin 500 mg/day (n = 38); Group B received metformin + myo-inositol 1g (n = 49); Group C received metformin + letrozole 2.5 mg (n = 36), and Group D received metformin + letrozole + myo-inositol (n = 29), orally for three months. All continuous variables, such as body mass index (BMI), FSH, LH, FT4, and FSI were analysed by applying t-test to all therapeutic groups, keeping p ≤0.05 as the level of significance.

Results: HCG-positive was found as 86% (n = 33) in Group A, 63% (n = 31) in Group B, 52% (n = 19) in Group C, and 27% (n = 08) in Group D. There were statistically significant (p <0.001) changes in BMI, FSH, LH, FT4, and FSI as well. Metformin alone and metformin plus myo-inositol came out to be more effective than other regimens.

Conclusion: Metformin alone and myo-inositol plus metformin are effective therapeutic options in PCOS-induced infertility problems.

Key Words: Polycystic ovarian syndrome, Infertility, Metformin, Myo-inositol, Letrozole, Menstrual irregularities.

INTRODUCTION

Polycystic ovary syndrome (PCOS) not only affects the ovaries and ovulation, but recent studies are showing it actually as a metabolic syndrome that is closely related to insulin resistance. PCOS, a multi-system disease, is a major reason for female infertility around the world. It is no longer considered simply as a disease of ovary. It is an endocrine abnormality and typical metabolic syndrome that is associated with increased body mass index (BMI) and insulin resistance (IR). The global prevalence of PCOS is estimated between 4% and 20%. The World Health Organisation (WHO) data suggests that approximately 116 million women (3.4%) are affected by the syndrome globally.[1] Unfortunately, the frequency of the syndrome affecting women is much higher in Pakistan, at about 52%.[2]

The diagnosis of PCOS, which is a common cause of infertility, is based on chronic anovulation, hyperandrogenaemia, oligo / amenorrhea, and polycystic ovaries on ultrasound.[3] The ovulatory cycle in women in their reproductive years are the main reason for infertility. Menstrual irregularity, hirsutism, coarse hair growth, increased BMI, and infertility associated with irregularity in hormones levels are key features related to this syndrome that vary within each individual having POCS. The treatment is based on just to regulate the levels of hormones to maintain menstrual regularity which will be helpful in improving the fertility index of such patients. Stein–Leventhal syndrome, popularly known as polycystic ovary syndrome is one of the foremost causes of female infertility.[4] In previous studies,[5,6] researchers primarily attributed ovarian anovulation to apoptosis.[5] It was noticed that the increased number of neutrophils and lymphocytes was significantly responsible for the secretion of inflammatory cytokines and induction of apoptosis in ovaries. The researchers pointed out that elevated lymphocytes may induce apoptosis and that could be a reason for degeneration of follicles and macrophages may phagocytise these apoptotic follicular cells.[5] Furthermore, another study[6] has shown that along with the increase in leukocytes, other pro-inflammatory

markers may be involved, such as serum C-reactive protein,[6] IL-8 and IL-18[7], IL-23[8] adipokines including chemerin were significantly elevated in the peripheral blood.[9]

The purpose of this study was to clarify the effect of the most commonly used medicines for infertility due to PCOS, and to ease the selection by knowing the effectiveness of these commonly used medicines as a proper regimen to overcome this problem. This study aimed to compare the efficacies of different therapeutic regimens and their combinations, used in PCOS to improve fertility in reproductive-aged women.

METHODOLOGY

This was a descriptive study, started from November 2022 to July 2023 followed by data collection and then follow-up of three months in Medicare Hospital Karachi, Pakistan. The sample size calculation was carried out by statistical software (WHO sample size calculation), by the reference of Ayaz et al.[10] This sample size was calculated to reject the null hypothesis by employing population means of PCOS with level of significance of 5%, 90% power of test, the minimum calculated sample size was 174 participants.

All females with menstrual irregularities and infertility, aged between 18 and 45 years were included in the study. Exclusion criteria were, age less than 18 years, more than 45 years old women, with cardiovascular diseases, and diabetes mellitus or any other endocrine abnormalities. Patients included in the control group had symptoms of menstrual irregularities and infertility, but no ultrasound findings of PCOS.

Data were collected after informed written consent, menstrual history / family history, height, weight (BMI), blood sugar levels, abdominal / pelvis, and transvaginal ultrasound were done, blood samples were taken for LH levels, follicle-stimulating hormone (FSH), free thyroxine in the blood (FT4) levels and fasting serum insulin (FSI). Treatment continued till pregnancy was achieved.

The study was conducted after taking informed consent from the patients and ERC approval from the University Ethical Review Committee referred to U/S Department of Hospital. All these patients were recommended ultrasound (pelvis / transvaginal) on the basis of irregular menstrual cycles (oligo / amenorrhea), weight gain (obesity), and infertility. Ultrasound pelvis (per abdominal / transvaginal) was done to get the best results, in which the location, size, and position of uterus were noted with the ovarian measurements and volumes of both the ovaries (right / left), number of follicles, follicular arrangement, central stromal texture, and endometrial thickness. In females with irregular menstrual cycles, the ultrasound diagnosis of PCOS was made on the basis of ESHRE/ASRM criteria i.e., 10 or more cystic follicles per ovary, varying in size from 2-9 mm or ovarian volume of 10 cm[3].[11] Although the modified Rotterdam criteria have been updated recently,[12] blood tests were taken to detect hormone levels to achieve the required objectives. Questionnaires were also used for the data collection.

In patients with PCOS, the ovaries were enlarged i.e. ≥10ml (one or both), endometrium of uterus, was thickened and there was an increased number of follicles (more than 10-12) with peripheral immature follicular arrangement along and central echogenic stroma as pearl-beaded appearance. Once the U/S was done, the patients returned to the gynaecological OPD and blood samples were taken from all patients to assess their hormonal levels (FSH, LH, FT4, and FSI) and confirm the diagnosis.

All suspected PCOS were prescribed therapy with respect to their laboratory and ultrasonography analysis and divided into groups according to therapeutic regimens. Metformin (M) 500mg was used alone in Group A (n = 38), metformin along with myo-inositol (MI) 1g in Group B (n = 49), metformin with letrozole (LTZ) 2.5mg in Group C (n = 36), and all of three (M + MI + LTZ) in combination were used in Group D (n = 29) for three months duration.

Four therapeutic groups of PCOS female patients on the basis of convenient sampling selected for the period of three months of therapy and continuous follow-up for betterment in menstrual irregularities, ultrasound was done to get ovulation induction, and BMI recordings along with hormonal assessment in each follow-up.

Continuous variables were expressed as mean and standard deviation (SD). This study compared the baseline values of PCOS with non-PCOS by applying paired t-test, and final outcome of the four therapeutic groups statistically by applying t-test, to evaluate all the four therapeutic groups, as the level of significance $p \leq 0.05$, in SPSS version 25, to all therapeutic groups.

RESULTS

Baseline investigations of all the patients were done, then based on diagnosis, as the PCOS and non-PCOS groups. Table I shows basal values of right and left ovarian volumes, BMI, FSH, LH, FSI, and FT4 at the time of diagnosis. The authors continued the study by taking PCOS patients (152), as four therapeutic groups depending on the treatment regimens given to the patients. The values of all parameters are aligned in Table II to show the comparisons before and after the treatment given.

Prior to the treatment, the mean values of BMI, FSH, LH, FSI, and FT4 for Group A were 31 ± 6.6 kg/m^2, 6.3 ± 1.4 mIU/ml, 9.8 ± 3.8 mIU/ml, 17.3 ± 6.9 u/U/ml, and 2.9 ± 1.2 nmol/L, respectively, showing difference statistically significant ($p = <0.001$) in all the variables after the treatment i.e. 28 ± 6.2 kg/m^2, 5.7 ± 1.3 mIU/ml, 11 ± 3.7 mIU/ml, 12.3 ± 5.6 u/U/ml, and 1.1 ± 0.3 nmol/L. In Group B before treatment, the values were 29.5 ± 5.9 kg/m^2, 6.5 ± 1.5 mIU/ml, 10.5 ± 3.6 mIU/ml, 18.9 ± 8.2 u/U/ml, and 3 ± 1.3 nmol/L, respectively, showing difference statistically significant ($p = <0.001$) in all the variables after the treatment i.e. 28.4 ± 5.7 kg/m^2, 5.8 ± 1.7 mIU/ml, 9.5 ± 3 mIU/ml, 15 ± 5.1 u/U/ml, and 2.2 ± 1.3 nmol/L. In Group C and D, the results were less significant statistically. SPSS version 25 with confidence interval (CI) 95%, showing the results of Group A and B were more significant, it proves statistically that the drugs and their combinations used in Group A and B were more effective than the drugs and their combinations used in Group C and D.

Table I: Baseline general characteristics of all patients with symptoms of PCOS (n = 300).

Characteristics of patients (n = 300)	PCOS group (n = 152) M ± SD	Non-PCOS group (n = 148) M ± SD	p-value
Age (years)	26 ± 5.4	30 ± 7	0.20
BMI (kg/m^2)	30 ± 9	22 ± 2.3	<0.001
Right ovarian volume (ml)	10.6 ± 4.6	6.8 ± 3.6	<0.001
Left ovarian volume (ml)	9.7 ± 6.9	6.1 ± 3.4	<0.001
FSH (mIU/ml)	6.4 ± 1.6	4.9 ± 1.7	<0.001
LH (mIU/ml)	10 ± 3.8	4.6 ± 2	<0.001
FT4 (nmol/L)	3.8 ± 8.9	1.1 ± 0.3	<0.001
FSI (u/U/ml)	18 ± 7.7	13.6 ± 4	<0.001

*Mean ± SD Standard deviation, BMI = Body mass index, FSH = Follicle stimulating hormone, LH = Luteinising hormone, FT4 = Free thyroxine, FSI = Fasting serum insulin, and HCG = Human chorionic gonadotropic hormone. Paired t-test *p-value (≤0.5 is statistically significant).*

Table II: Comparison of the outcome of all therapeutic groups (n = 300).

Gr. A	Before Rx A (38 pts.) M ± SD	After Rx A (38 pts.) M ± SD	p-value
BMI	31 ± 6.6	28 ± 6.2	<0.001 ***
FSH	6.3 ±1.4	5.7 ± 1.3	<0.001 ***
LH	9.8 ± 3.8	11 ± 3.7	<0.001 ***
FSI	17.3 ± 6.9	12.3 ± 5.6	<0.001 ***
FT4	2.9 ± 1.2	1.1 ± 0.3	<0.001 ***
Gr. B	**Before Rx B (49 pts.) M± SD**	**After Rx B (49 pts.) M± SD**	
BMI	29.5 ± 5.9	28.4 ± 5.7	<0.001 ***
FSH	6.5 ± 1.5	5.8 ± 1.7	<0.001 ***
LH	10.5 ± 3.6	9.5 ± 3	<0.001 ***
FSI	18.9 ± 8.2	15 ± 5.1	<0.001 ***
FT4	3 ± 1.3	2.2 ± 1.3	<0.001 ***
Gr. C	**Before Rx C (36 pts.) M± SD**	**After Rx C (36 pts.) M± SD**	
BMI	29.9 ± 5	29.5 ± 5	0.003 **
FSH	6.2 ± 1.7	5.1 ± 1.7	0.001 **
LH	10.9 ± 3.8	8.8 ± 3.2	<0.001 ***
FSI	18 ± 7.1	15 ± 5	0.008 **
FT4	5.9 ± 18	2.3 ± 2.6	0.240
Gr. D	**Before Rx D (29 pts.) M± SD**	**After Rx D (29 pts.) M± SD**	
BMI	29.6 ±5	29.5 ± 5	0.023 *
FSH	6.5 ± 1.5	5.6 ± 1.3	<0.001 ***
LH	9.9 ± 4.3	9.3 ± 3.3	0.067 *
FSI	19 ± 9.1	15 ± 6	0.001 **
FT4	3.1 ± 2.1	2.0 ± 1.0	0.008 **

Comparison of basal characteristics found before treatment with the secondary outcomes of hormonal levels in PCO patients (after 3 months of treatment), showing statistic p-values in (***), the most significant, (*)less significant outcome values.
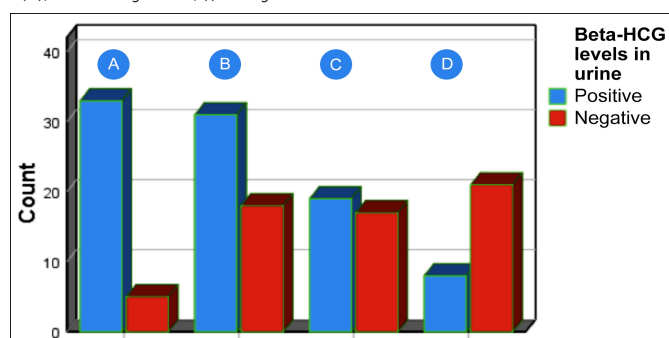
Figure 1: Bar-chart for the treatment options in PCO patients showing positive and negative results.

As mentioned before, PCOS patients were divided into four groups; A-metformin 500mg/d alone (n = 38), B-metformin + myo-inositol (n = 49), C-metformin + letrozole 2.5mg (n = 36), D-metformin + letrozole + myo-inositol (n = 29) for three months. B-HCG tests were obtained positive at different levels of treatment in Group A = 33(86%), in Group B = 31 (63%), in Group C = 19 (52%), and in Group D = 8 (27%) that represented the most effective outcome in Group A and B.

An outcome of PCOS patients in each group was, A = 86%, B = 63%, C = 52%, and D = 27% in which it is more obvious to find out comparative outcomes in all four therapeutic groups and medicine's effectiveness, also shown in the form of bar graph in Figure 1.

DISCUSSION

PCOS, a multisystem disease, is a major reason for female infertility around the world. It is no longer considered simply as a disease of ovary. It is an endocrine abnormality and typical metabolic syndrome that is associated with increased BMI and IR.

The objective of the study was to measure the outcome of efficacies of multiple drug therapy options to help PCOS patients in reproductive age that help in minimising menstrual irregularities, hormonal imbalance, and improving their life quality. The current study help understand this disease which is more likely a metabolic disorder associated with multiple follicles in the ovaries, that can be related to the cause of infertility. These findings may help to reconstruct the regimen for PCOS in terms of metabolic disorder syndrome associated with ovarian features along with their symptoms.

Patients diagnosed with PCOS in this study were found to have most significant outcome of fertility. The mean age of the participants was 26 ± 5 years as compared to controls, BMI mean was increased as mean 29.9 ± 5, FSI was also high as mean 18.2 ± 7.7, and FT4 was above as mean 3.8 ± 8.9 as shown in Table I.

According to a study conducted on the Karachi population myo inositol was found efficacious in the treatment of PCOS. The efficacy of myo-inositol in regulating menstrual flow severity increased with decreasing age. In treating infertility caused by polycystic ovarian syndrome. Letrozole (an aromatase inhibitor) appears to be more successful than clomiphene citrate (an antioestrogen and a reference infertility drug). Compound oral contraceptives are the most common kind of androgen inhibitor and are the preferred therapy for menstrual disruption in patients who do not want to get pregnant.[13] This study presents the efficacy of myo-inositol along with metformin in PCOS-induced infertility and helps in reducing hormonal imbalances.

It is obvious that PCOS is more of a metabolic syndrome rather than simply a female reproductive disorder of ovaries. Excess ovarian activity, chronic anovulation, and androgen excess are the common traits of polycystic ovary syndrome. Androgen excess in these patients was found to correlate with markedly elevated luteinising hormone. Impaired insulin response is also attributed to this syndrome. Combination of myo-inositol and D-chiro-inositol restores ovulation in women with clomiphene citrate-resistant PCOS.[4,14] Lifestyle intervention is still the first line treatment option for overweight females seeking pregnancy.[15] Recent studies have shown that this syndrome is associated with 80% of anovulatory infertility; however, the precise mechanism of PCOS-induced anovulation is still undetermined. Research article published,[16] concluded that the use of specific therapeutic agents and patient's adherence to lifestyle interventions could help patients recover their reproductive and metabolic health.[16]

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PCOS is a combination of menstrual irregularities and metabolic disorders leading to hyperandrogenism insulin resistance and infertility as we have seen in this study, that affect the psychological status and quality of life, of an individual. In the last decade, concluded that metabolic syndrome was high in females that have the syndrome as compared to the age-related controls. Females with PCOS are at a higher frequency of metabolic syndrome (MS) and its related symptoms, especially lower high-density lipoprotein (HDL-C) levels.[17]

Metformin, an oral hypoglycaemic agent of the biguanide class, reduces the circulating insulin levels. It has positive effects on adipose tissues, especially in obese people with raised BMI. Metformin possibly improves induction of ovulation in women with PCOS[18] by reducing gluconeogenesis, improving insulin sensitivity, and reducing ovarian androgen production. In this study, metformin alone (86%) and metformin with myo-inositol (63%) in total, got significant results to bring β-HCG test positive in PCO patients in a duration of 3 months study.[19]

Myo inositol, related to the inositol family, which acts as a second messenger for insulin, PCOS are about 30-40% related to insulin resistance and raised testosterone levels.[20,21] Myo inositol therapy may help in improving metabolic, menstrual / ovulation and hyper-androgenic cutaneous features in PCOS by regulating hormones such as FSH, TSH, and insulin.[22-24]

Letrozole, an aromatase inhibitor is an ovulation induction agent, for this purpose, exclusively quite successful in PCOS disease-induced chronic infertility.[25] It works by releasing pituitary-hypothalamus axis centrally from oestrogen-negative feedback as well as local effects by inhibiting oestrogen synthesis by blocking the alteration of testosterone to oestradiol. A number of studies done previously on the combinational effectiveness of letrozole drug with other therapeutic agents were used in PCOS as done by Davar *et al*.[26] In the current study, the combination of metformin and letrozole gave 52% positive β-HCG results, whereas together with metformin and myo-inositol combination 63% in total in PCOS patients for three months duration.

It is more obvious to find out comparative outcome in all four therapeutic groups and medicines' effectiveness. Hence, met-formin alone and metformin along with myo-inositol is more effective as compared to metformin with letrozole or in combination of all three medicines used in PCOS patients with high BMI induced infertility. It requires prompt attention to designate raised IR as a diagnostic parameter related to PCOS diagnosis.

CONCLUSION

The current study concluded that metformin alone and myo-inositol plus metformin are the effective therapeutic options in PCOS-induced infertility problems by improving endocrine imbalances. Moreover, PCOS involve the body's endocrine system and the authors found remarkable imbalances not only in reproductive as well as other hormones like FT4 and FSI levels. It could be the most common endocrinal disorder in females in future and require proper assessment with comprehensive therapeutic consideration.

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