

Comparison of Clomiphene Citrate vs Clomiphene Citrate in Combination with Pioglitazone in Terms of Ovarian Stimulation and Pregnancy Rates among Infertile Women Suffering from Polycystic Ovarian Syndrome

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ABSTRACT

Objective: To compare the ovarian stimulation rate and pregnancy rate among patients of PCOS treated with Clomiphene alone vs those treated with Clomiphene and Pioglitazone.

Methodology: This randomized control trial enrolled 62 patients that were randomly divided into two groups with group A patient receiving Pioglitazone and Clomiphene treatment while group B only receiving Clomiphene.

Results: The addition of pioglitazone to clomiphene resulted in significantly greater endometrial thickness (8.83 ± 0.90 mm vs 7.31 ± 0.54 mm, $p < 0.001$), a higher number of large follicles [2 (IQR 2) vs 1 (IQR 2), $p < 0.001$], larger dominant follicle size [20 (IQR 4) mm vs 18 (IQR 4) mm, $p = 0.009$], higher β -hCG positivity (93.8% vs 75.0%, $p = 0.039$), and a significantly higher confirmed pregnancy rate (46.9% vs 18.8%, $p = 0.017$).

Conclusion:

Addition of Pioglitazone to Clomiphene significantly improves ovarian stimulation rate, endometrial thickness and pregnancy rates among patients suffering from PCOS.

Keywords: Pioglitazone, Polycystic Ovarian syndrome, Sub-fertility..

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1. INTRODUCTION

Polycystic ovarian syndrome (PCOS) is the most common endocrine pathology affecting females of reproductive age group. It has a worldwide prevalence of 5 to 15%. For diagnosis at least two of the following three criteria must be met which include chronic anovulation, hyperandrogenism (clinical or biological), and polycystic ovaries. It is a diagnosis of exclusion(1). This is an endocrinal pathology associated with derangements in a number of hormones and it ultimately results in infertility. There are a number of changes observed in body hormones such as increased insulin, reduced growth hormone, increased ghrelin, increased leptin resistance which results in obesity and diabetes. On the other hand a reduction in growth hormone, increased LEAP-2 levels, high Leuitizing hormone(LH) basal levels, increased LH/FSH ratio, high androgens, and low estrogen results in infertility(2). Treatment of PCOS involves a number of modalities to manage the associated endocrinal problems so that quality of life can be improved and fertility rates can be enhanced. The treatment starts from lifestyle modifications such as smoking cessation, physical exercise and weight loss and includes management of diabetes and use of ovarian stimulation drugs to improve fertility. The first line drug for ovarian stimulation remains Clomiphene citrate. Clomiphene citrate is used to stimulate ovaries in patients suffering from PCOS. Metformin can be added to treatment based on clinical and biochemical judgement(1),(3). Other treatment options include different surgical techniques which aim to enhance ovulation and pregnancy rate and are utilized when medical treatment has failed. These include ovarian drilling by laparoscopy or by transvaginal hydrolaparoscopy(3). However, new medical treatment options are emerging for management of infertility associated with PCOS. Pioglitazone has recently been tried to improve fertility rates among female patients suffering from PCOS. Pioglitazone is an oral anti-diabetic medication which belongs to thiazolidinedione drug class. It acts by activating a nuclear receptor known as gamma isoform of peroxisome proliferator-activated receptor (PPAR-gamma) which in turn, alters the gene transcription of several genes involved in glucose and lipid metabolism, increasing peripheral glucose utilization and decreasing hepatic glucose production(4). By affecting gene transcription, the drug may help to manage endocrinal abnormalities thus improving fertility rates in PCOS patients.

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Pioglitazone has been used alone and in combination with a number of other drugs to manage infertility associated with PCOS. In a comparative study when pioglitazone was compared to alpha lipoic acid i.e. naturally occurring antioxidant, it was found that Pioglitazone alone as well as with alpha lipoic acid were better in improving oxidative stress levels, BMI, and menstrual cyclicity as compared to monotherapy with alpha lipoic acid (5). In another study involving normal-weight patients suffering from PCOS, Pioglitazone was given along with Metformin and the treatment had better effects in improving Serum Hormone Binding Globulin, Anti Mullerian hormone, and postprandial glucose levels than monotherapy (6). However larger sample size studies were recommended. Similarly, Diane-35 and pioglitazone were found to improve symptoms of sex hormone secretion, blood glucose, and lipid disorder in PCOS patients(7). Furthermore pioglitazone was found to be superior to metformin in In-vitro fertilization cycles leading to a higher pregnancy rate among PCOS patients(8). Therefore, Pioglitazone is found to be superior to be non-first line therapies such as Metformin and alpha lipoic acid in improving fertility rates among PCOS patients.

Recently a study was conducted where Pioglitazone was combined with first line ovarian stimulation drug that was Clomiphene in managing infertility associated PCOS (9). Ovarian stimulation rate as determined by number of large size follicles (16-24 mm in size) recruited which are likely to undergo ovulation and fertilization. The mean number of large size follicles recruited among patients being treated with Pioglitazone and Clomiphene was 2.2 ± 1.4 vs 1.3 ± 1.1 among patients only treated with Clomiphene(9). The biochemical pregnancy rates were also similar between two groups 12.9% vs 20.0% (p value= 0.508) and clinical pregnancy rates were 12.9% vs 13.3% (p value= 1)(9). However, evidence regarding addition of Pioglitazone to Clomiphene in improving the number of large size follicles recruited and pregnancy rate among patients of PCOS is limited and further studies are required to draw a definitive conclusion.

Objective

To compare the ovarian stimulation rate and pregnancy rate among patients of PCOS treated with Clomiphene alone vs those treated with Clomiphene and Pioglitazone.

2. METHODOLOGY

This Randomized Control trial was carried out at department of Gynecology and Obstetrics, Pakistan Atomic Energy Commission Hospital, Islamabad from 9-10-2025 to 15-06-2026. The trial was carried out after hospital ethical approval (PGHI-IRB (DMe)-RCD-06-098) with trial registration number being NCT07462065. The sample size was calculated using WHO calculator following sample size using Confidence interval= 95%, Power of test= 80%, Mean number of large size follicles in group A: 2.2 ± 1.4 (9), Mean number of large size follicles in group B: 1.3 ± 1.1 (9) with total sample size of 62. The patient who fulfilled the inclusion criteria that was, age 18–38 years, normal hysterosalpingography, normal spermogram, suffering from PCOS and having ovarian cysts less than 20mm were enrolled while patients with history of chronic cardiovascular disease, chronic kidney disease, diabetes, thyroid disease and pulmonary disease were excluded. Enrolled patients were divided into two groups using computer generated random numbers. The group A patients received 30 mg pioglitazone daily; from the second day of menstruation, the second group received a placebo for similar duration. 150 mg clomiphene citrate was administered to both groups between the third and seventh days of the menstrual cycle. Vaginal sonography was done on 10th day of menstrual cycle. The number of large size follicles i.e. 16-24 mm in size was noted. Human chorionic gonadotropin (HCG) was administered to the patients having at least 1 large size follicle of 16-24 mm and endometrial thickness of at least 7mm. This was followed by intrauterine insemination injection (IUI). Patients were followed till the end of menstrual cycle and in cases there is 5 days of delayed menstrual period, a blood sample was performed for evaluating the β HCG level. This will help in confirming pregnancy biochemically.

3. RESULTS

Data was entered and analyzed on SPSS version 26.0. Baseline profile was comparable across both groups. This is shown in table 1.

Table 1: Baseline profile of two groups

Variable	Group A (n=32)	Group B (n=32)	p-value
Age (years)	28.63 ± 3.99	28.78 ± 3.94	0.875
Marital Duration (years)	4.94 ± 2.23	4.91 ± 2.15	0.955
Baseline Testosterone	90.22 ± 9.58	91.03 ± 11.13	0.755
Baseline DHEA	390.00 ± 47.04	399.38 ± 52.50	0.455

Endometrial thickness on day 10 was significantly higher in Group A compared with Group B. The mean endometrial thickness was 8.83 ± 0.90 mm in Group A and 7.31 ± 0.54 mm in Group B. Independent-samples t-test demonstrated a statistically significant difference between the groups with p value being < 0.001. Rest of the quantitative variables when checked for normality Shaprio wilk test had p value less than 0.05 showing data has non-parametric distribution. Comparison of non-parametric parameters of both groups following treatment is given in table 2.

Table 2: Comparison of non-parametric variables across two groups

Variable	Group A (n=32) Median (IQR)	Group B (n=32) Median (IQR)	p-value
No. of large size follicles	2 (2)	1 (2)	<0.001
Maximum follicle size on Day 10	20 (4)	18 (4)	0.009
β-hCG level	5 (223)	5 (0)	0.033

Comparison of qualitative variables across two groups is shown in table 3.

Table 3: Comparison of Qualitative variables across two groups

Variable	Group A (n=32)	Group B (n=32)	p-value
β-hCG Given	30 (93.8%)	24 (75.0%)	0.039
Pregnancy Confirmed	15 (46.9%)	6 (18.8%)	0.017

4. DISCUSSION

This study provided an insight by evaluating the effect of pioglitazone along with clomiphene citrate for ovulation induction in females suffering from polycystic ovary syndrome (PCOS). The addition of pioglitazone to clomiphene resulted in significantly greater endometrial thickness (8.83 ± 0.90 mm vs 7.31 ± 0.54 mm, $p < 0.001$), a higher number of large follicles [2 (IQR 2) vs 1 (IQR 2), $p < 0.001$], larger dominant follicle size [20 (IQR 4) mm vs 18 (IQR 4) mm, $p = 0.009$], higher β-hCG positivity (93.8% vs 75.0%, $p = 0.039$), and a significantly higher confirmed pregnancy rate (46.9% vs 18.8%, $p = 0.017$). These findings reveal that pioglitazone when added to clomiphene it enhances both ovarian stimulations as well it makes the endometrial thickness and profile more favorable. Previously only on randomized control trial was relevant to our study(9). This relevant randomized controlled trial carried out by Amirian et al. showed that women receiving pioglitazone with clomiphene had significantly greater number of large follicles that was 2.2 ± 1.4 when compared with 1.3 ± 1.1 in the control group(9). The findings are similar to our study which showed higher number of large follicles among patients treated with Pioglitazone that was higher number of large follicles 2 (IQR 2) while it was significantly lower in control group being 1 (IQR 2), $p < 0.001$. Amirian et al. showed that endometrial thickness remained identical between groups (7.6 ± 2.9 mm vs 7.6 ± 2.2 mm with p value > 0.05)(9). However, in our study endometrial thickness was significantly higher in Pioglitazone treated group i.e. 8.83 ± 0.90 mm vs 7.31 ± 0.54 mm, $p < 0.001$. Furthermore, reported chemical pregnancy rates by Amirian et al. were identical between two groups 12.9% and 20%, whereas clinical pregnancy rates were also identical being 12.9% and 13.3%, respectively(9). Maximum follicular size was also comparable between groups (16.6 ± 2.7 mm vs 17.5 ± 2.6 mm)(9). In contrast, our study demonstrated significantly superior follicular growth with larger dominant follicle size being 20 (IQR 4) mm in Pioglitazone group while it was 18 (IQR 4) mm in control group with p value being 0.009. Furthermore, this study revealed significantly higher pregnancy rates in Pioglitazone group that was 46.9% while it was 18.8% in control group with p value being 0.017. Although Amirian et al. did not demonstrate a statistically significant reproductive advantage, they reported a numerically greater follicular response in the pioglitazone group, supporting the biological plausibility of our findings(9). Differences in study populations characteristics such as metabolic profiles, extent of insulin resistance and duration of treatment may account for the differences observed between the two studies.

The substantial improvement in pregnancy outcomes observed in this study is supported by the randomized trial conducted by Taheripanah et al(8). They compared the effect of addition of pioglitazone to metformin on in vitro fertilization in women with PCOS. Although reported number of retrieved oocytes (11.87 ± 3.73 vs 11.76 ± 3.79) and embryos formed (7.87 ± 3.52 vs 7.43 ± 2.82) did not differ significantly between groups(8). But clinical pregnancy rate was significantly higher in women receiving pioglitazone (48.8% vs 32.6%, $p = 0.03$)(8). This is similar to 46.9% pregnancy rate observed in our intervention arm. These findings across different fertility treatment settings such as in vitro fertilization and in vivo fertilization suggests that pioglitazone may improve reproductive success rate through mechanisms which may extend beyond simple enhancement of follicular recruitment.

In a study done by Zhao et al. combining pioglitazone with metformin produced greater improvements in menstrual recovery, anti-Müllerian hormone levels, sex hormone profiles, and metabolic parameters compared with metformin alone(6). Similarly, Pei et al. reported significant improvements in insulin resistance, testosterone levels, menstrual cyclicity, and metabolic status following pioglitazone therapy(5). Although these studies did not specifically focus on pregnancy rates, but their findings of improved biochemical profile may form the basis of improved reproductive rates as observed in our study.

Furthermore, the improved reproductive outcomes observed in this study can be explained by the pharmacological effects of pioglitazone on the underlying pathophysiology of PCOS. Insulin resistance is central feature of PCOS(10). Insulin resistance results in hyperinsulinemia, ovarian androgen excess, low FSH, high LH which results in follicular arrest, and impaired endometrial receptivity(11). Pioglitazone acts as a peroxisome proliferator-activated receptor-gamma (PPAR-γ) agonist which increases peripheral insulin sensitivity which in turns reduces plasma insulin concentrations(12). Decreased

insulin levels results in diminish stimulation of ovarian theca cells, resulting in lower androgen levels having a favorable effect on folliculogenesis (12). Furthermore Pioglitazone is thought to have anti-inflammatory effect which may reduce the level of inflammation seen in PCOS resulting in favorable effect on fertility (10,12). Furthermore, addition of Pioglitazone to Clomiphene improved endometrial thickness which may be due to favorable effects of Pioglitazone on inflammatory and hormonal profile in patients suffering from PCOS.

Although the present study has several strengths as it provides effects of Pioglitazone on clinical reproductive outcomes in terms of endometrial thickness, follicular development, β -hCG positivity, and confirmed pregnancy rates but it also has certain limitations such as metabolic parameters that includes fasting insulin levels, inflammatory mediator levels, and serum androgen concentrations were not evaluated. Therefore, the precise metabolic mechanisms underlying the observed reproductive benefits could not be directly confirmed. Long-term outcomes including live birth rate, miscarriage rate, and neonatal outcomes were also not assessed. Therefore, further multi center randomized control trials should be carried out to lay foundation for formal guidelines.

5. CONCLUSION

Addition of Pioglitazone to Clomiphene significantly improves ovarian stimulation rate, endometrial thickness and pregnancy rates among patients suffering from PCOS

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