

Research Article

Comparison of Efficacy of Metformin versus Pioglitazone in Patients with Polycystic Ovarian Syndrome

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Abstract:

Objective: To compare the efficacy of metformin and pioglitazone in women with polycystic ovary syndrome

Material and methods: This comparative study was conducted at Department of Obstetrics & Gynecology, Nishter Hospital, Multan from February 2018 to August 2018. Total 104 married woman having age from 20-40 years suffering from polycystic ovarian syndrome recruited for this randomize controlled trial. Efficacy of metformin and pioglitazone were assessed.

Results: Mean age of patients was 31.33 ± 6.89 years, mean age of patients in group A was 28.53 ± 6.45 years and in group B was 29.85 ± 5.77 years. Mean duration of disease was 3.23 ± 1.45 years. The mean duration of disease in group A was 3.34 ± 1.65 years and in group B was 3.79 ± 1.69 years. Mean BMI was 29.22 ± 3.33 kg/m². The mean BMI in group A was 29.53 ± 3.47 kg/m² and in group B was 29.73 ± 3.32 kg/m². Treatment was found effective in 30 (57.69%) patients of study group A in 45 (86.54%) patients of study group B. Significantly higher efficacy rate was noted in study group B as compared to study group A with p value 0.001.

Conclusion: This study concludes that Pioglitazone is more effective than metformin for ovulation induction in women with PCOS. So, we recommend that Pioglitazone should be used as a first line therapy for ovulation induction in women with PCOS.

Key words: PCOS, BMI, syndrome, ovulation

INTRODUCTION:

Polycystic ovary syndrome (PCOS) is a complex condition characterized by elevated androgen levels, menstrual irregularities, and/or small cysts on one or both ovaries.¹ The disorder can be morphological (polycystic ovaries) or predominantly biochemical (hyperandrogenemia). Hyperandrogenism, a clinical hallmark of PCOS, can cause inhibition of follicular development, microcysts in the ovaries, anovulation, and menstrual changes.² Research suggests that 5% to 10% of females 18 to 44 years of age are affected

by PCOS, making it the most common endocrine abnormality among women of reproductive age in the U.S.³ Women seeking help from health care professionals to resolve issues of obesity, acne, amenorrhea, excessive hair growth, and infertility often receive a diagnosis of PCOS. Women with PCOS have higher rates of endometrial cancer, cardiovascular disease, dyslipidemia, and type-2 diabetes mellitus.⁴

Multiple treatments have been recommended for infertility in patients with polycystic ovary

syndrome, including weight reduction, clomiphene citrate, metformin, thiazolidinedione, letrozole, and assisted reproductive technology, such as in vitro fertilization.⁵Metformin appears to restore menstrual cycles and also improve fertility in initially anovulatory and oligo-ovulatory women with polycystic ovary syndrome. Studies have demonstrated that metformin affects the endometrium so as to create an environment more suitable for pregnancy.⁶The use of metformin is associated with increased menstrual cyclicality, improved ovulation, and a reduction in circulating androgen levels.⁷Thiazolidinediones (TZDs), including pioglitazone, are peroxisome proliferator-activated receptor (PPAR)- α agonists that induce adipogenesis and have insulin-sensitizing and anti diabetic properties.⁸

The rationale of this study was to compare the efficacy of metformin and pioglitazone in restoring ovulation induction in patients with polycystic ovarian syndrome in local population. Although previously their efficacy had been studied but that was very little work done on this. So our study would not only provide the local stats on this but also provide clinicians with a more efficacious drug for ovulation induction in polycystic ovarian syndrome patients which ultimately restores their fertility. Then on the basis of the clinical evidence, some practical recommendations could be made in our routine guidelines for recommending the better drug in these particular patients for ovulation induction.

MATERIAL AND METHODS:

This comparative study was conducted at Department of Obstetrics & Gynecology, Nishtar Hospital, Multan from February 2018 to August 2018. Total 104 married woman having age from 20-40 years suffering from polycystic ovarian syndrome recruited for this randomize controlled trial. Pregnant and nursing women, cases with any systemic

disease were excluded from the study.

Polycystic ovary syndrome: According to Rotterdam criteria,¹¹⁹ It was diagnosed if any two of following conditions present: Oligoovulation (cycles of ≥ 36 days or < 8 cycles a year) and anovulation (irregularity of menstrual periods), Excess androgen levels i.e. testosterone levels > 200 ng/dL, Polycystic ovaries on ultrasonography i.e. increased ovarian size (> 10 cc), > 12 follicles measuring 2-9 mm, peripheral location of follicles: which can give a string of pearl appearance and hyperechoic central stroma.

Prior permission from ethical review committee was taken and written informed consent was taken from every patient. Selected patients were divided into two equal groups i.e. group A & B. In group A patients, Metformin (Glucophage, Merck) with dose of 1500 mg per day in three divided doses were given for three months. In group B patients, Pioglitazone (Poze, AGP) 15mg (BID) was administered for three months. After three months all patients were evaluated for efficacy of the drugs in term of yes/no.

Efficacy was deemed as yes if there was ovulation induction (presence of all these; biphasic basal temperature curve, a follicle with a diameter ≥ 16 mm on transvaginal ultrasonography and progesterone ≥ 14 nmol/l in the second half of a menstrual cycle), otherwise considered as no.

All the data was entered and analyzed by using SPSS version 14.0. Age, duration of disease, duration of marriage and BMI were presented by mean \pm SD. Qualitative variables like efficacy of both groups were presented by frequency and percentage. Comparison between the groups with respect to efficacy was analyzed by chi square test. P value ≤ 0.05 was considered as statistically significant. Effect modifiers were controlled by stratification of data in terms of age, duration of disease, duration of marriage and BMI. Post-stratification chi square test was applied to see the effect of these on efficacy and p-

value ≤ 0.05 was taken as significant.

RESULTS:

Total 104 patients of PCOS were selected for this study and two groups were made A and B. Mean age of 31.33 ± 6.89 years, mean age of patients in group A was 28.53 ± 6.45 years and in group B was 29.85 ± 5.77 years. Mean duration since marriage was 4.37 ± 2.85 years. The mean duration since marriage in group A was 4.35 ± 2.52 years and in group B was 4.35 ± 2.89 years. Mean duration of disease was 3.23 ± 1.45 years. The mean duration of disease in group A was 3.34 ± 1.65 years and in group B was 3.79 ± 1.69 years. Mean BMI was 29.22 ± 3.33 kg/m². The mean BMI in group A was 29.53 ± 3.47 kg/m² and in group B was 29.73 ± 3.32 kg/m².

Patients of study group A were treated with metformin and patients of study group B were treated with pioglitazone. Treatment was found effective in 30 (57.69%) patients of study group A in 45 (86.54%) patients of study group B. Significantly higher efficacy rate was noted in study group B as compared to study group A with p value 0.001. (Table 1)

Patients were divided into two age groups i.e age group 20-30 years and age group 31-40 years. Treatment was found effective in 15 (53.57%) patients of group A and 23 (85.19%) patients of group B but the difference was statistically insignificant with p value 0.018. In age group 31-40 years, treatment was successful in 12 (50%) patients of group A and 21 (84%) patients of group B. Significantly higher rate of efficacy was found in group B as compared to group A with p value 0.015. (Table 2)

Table 1: Comparison of efficacy between the both groups

Study Group	Efficacy (P = 0.001)		Total
	Yes (%)	No (%)	
A	30 (57.69)	22 (42.31)	52
B	45 (86.54)	7 (13.46)	52

Patient of both study groups were divided in two group according to duration since marriage i.e. ≤ 5 years and >5 years. In ≤ 5 years duration since marriage group, treatment was found effective in 17 (53.13%) patients and 25 (71.43%) patients respectively in study group A and B but the difference was statistically insignificant with p value 0.137. In >5 years since marriage group, efficacy was noted in 11 (55%) patients of group A and 15 (88.23%) patients of group B and the difference of efficacy was statistically significant (P = 0.036). (Table 3)

Patients were divided into two groups according to duration of disease i.e. ≤ 3 years duration and >3 years of disease. In ≤ 3 years of duration of disease group, treatment was found effective in 12 (40%) patients of group A and 22 (78.57%) patients of group B. significant difference of efficacy between the both groups was noted with p value 0.003. In >3 years of duration of disease group, treatment of PCOS was found effective in 15 (68.18%) patients and 19 (79.17%) patients of group A and B respectively but the difference was insignificant with p value 0.507. (Table 4)

In 16 (57.4%) nonobese patients of group A and 28 (87.5%) nonobese patients of group B, treatment was successful and statistically significant (P = 0.010) difference was observed.

In 13 (54.17%) obese patients of group A and 14 (70%) obese patients of group B, treatment was successful and statistically insignificant (P = 0.358) difference was observed. (Table 5)

Table 2: Age distribution of the patients

Study Group	Efficacy		Total
	Yes (%)	No (%)	
20-30 years (P = 0.018)			
A	15 (53.57)	13 (46.43)	28 (53.85)
B	23 (85.19)	04 (14.81)	27 (51.92)
31-40 years (P = 0.015)			
A	12 (50.0)	12 (50.0)	24 (46.15)
B	21 (84)	04 (16)	25 (48.08)

Table 3: Distribution of patients according to duration since marriage

Study Group	Efficacy		Total
	Yes (%)	No (%)	
≤ 5 years (P = 0.137)			
A	17 (53.13)	15 (46.88)	32 (61.54)
B	25 (71.43)	10 (28.57)	35 (67.31)
>5 years (P = 0.036)			
A	11 (55)	9 (45)	20 (38.46)
B	15 (88.23)	2 (11.76)	17 (32.69)

Table 4: Distribution of patients according to duration of disease

Study Group	Efficacy		Total
	Yes (%)	No (%)	
≤ 3 years (P = 0.003)			
A	12 (40)	18 (60)	30 (57.69)
B	22 (78.57)	06 (21.43)	28 (53.85)
>3 years (P = 0.507)			
A	15 (68.18)	7 (31.82)	22 (42.31)
B	19 (79.17)	5 (20.83)	24 (46.15)

Table 5: Distribution of patients according to BMI

Study Group	Efficacy		Total
	Yes (%)	No (%)	
Non-obese (P = 0.010)			
A	16 (57.14)	12 (42.86)	28 (53.85)
B	28 (87.5)	4 (12.5)	32 (61.54)

Obese (P = 0.358)			
A	13 (54.17)	11 (45.83)	24 (46.15)
B	14 (70)	6 (30)	20 (38.46)

DISCUSSION:

The purpose of this RCT was to compare the efficacy of pioglitazone and metformin in women with PCOS. In our study, efficacy of metformin group was 57.69% while in pioglitazone group was 86.54%.

In one study, in cases of PCOS, metformin alone shown a significant benefit on inducing ovulation.⁹ Sangeeta S has documented the restoration of ovulation in 44.2% patients of PCOS treated with metformin.¹⁰ In one study women with PCOS were treated with pioglitazone, improvement was noted in hirsutism, menstrual frequency, and insulin sensitivity.¹¹ Ota H et al¹² has reported ovulation induction in 77.78% cases with PCOS while treated with pioglitazone. In a meta-analysis by Li XJ et al¹³ it was found that TZDs were more effective as compared to metformin in decreasing the levels of free testosterone and dehydroepiandrosterone sulfate (DHEA) (P=0.002) after 3 months of treatment. In one meta-analysis it was noted that the use of metformin in PCOS efficiently induced ovulation.¹⁴ TZDs have also improved insulin sensitivity and reduces the androgenaemia in cases of PCOS.¹⁵ Brettenthaler et al¹⁶ reported that treatment with pioglitazone, ovulation induction rate was increased from 5.6% to 41.2% as compared to placebo group. Glueck et al¹⁷ documented that pioglitazone in combination with metformin in non-responsive PCOS cases, improved the insulin sensitivity, reduced the levels of androgen and induced ovulation.

CONCLUSION:

This study concludes that Pioglitazone is more effective than metformin for ovulation

induction in women with PCOS. So, we recommend that Pioglitazone should be used as a first line therapy for ovulation induction in women with PCOS.

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