

Original Research Article


Metformin and Pioglitazone in polycystic ovarian syndrome: A comparative study

Allanki Suneetha Devi¹, Jalem Anuradha^{2*}

¹Associate Professor, Department of Obstetrics and Gynecology, Government General Hospital, Nizamabad, Telangana, India

²Associate Professor, Department of Obstetrics and Gynecology, CKM Hospital, Warangal, Telangana, India

*Corresponding author email: jalemanuradha@gmail.com

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Abstract

Background: Polycystic Ovarian Syndrome (PCOS) is a heterogenous collection of symptoms and signs, which form a spectrum of a disorder with a mild presentation and severe disturbance of reproductive, endocrine and metabolic function.

Aim: To compare between metformin and Pioglitazone in treating polycystic ovarian syndrome.

Materials and methods: This was a double blinded, randomized comparative study conducted at Government hospital Nizamabad and CKM Hospital, Warangal. 150 PCOS patients in the age group 18-35 years were enrolled, and were allocated to two groups and were given the following modalities for a period of 8 months. Group I: Metformin-500 mg, BID, Group II: Pioglitazone-15 OD. Each group consisted of 75 patients. The minimum sample size required was 50-60. In this study, 75 patients were included in each group to allow dropouts. Oligo or anovulation, hyperandrogenism, polycystic ovaries were included.

Results: In group I, 68 (90%) out of 75 patients and in group II, 67(89%) out of 75 patients completed the trial. In group I, all the 68 patients had irregular menstrual cycles at the beginning of the study, and at the end of the study, 34 (47%) had regular menstrual cycles. In group II, 67 patients had irregular menstrual cycles at the beginning of the study, and at the end of the study, 38 (56%) had regular menstrual cycles. In both the groups, there was an increase in HDL levels (statistically significant versus baseline), more in Group II than in Group I. The average increase is 28 % in Group I as compared to 74 % in Group II. There is a trend of decrease in VLDL levels in both groups, the decrease being more in Group II (48 %) than in Group I (26 %) statistically significant when both groups were compared. In both the groups, there was a rise in SHBG, (statistically significant versus baseline). In Group I, the mean increase in SHBG was 6.22 nmol/l (22 %), but in Group II, mean rise

in SHBG was more, i.e. 34.56 nmol/l (72.7 %) and this difference is statistically significant ($P < 0.05$). Both the Groups showed a decrease in LH/FSH ratio. The fall in LH/FSH ratio was more in Group II, than in Group I. This fall in Group II was statistically significant $P < 0.05$ versus Group I.

Conclusion: Pioglitazone can restore menstrual cycle, a better ovulatory rate is achieved, clinical signs of hyperandrogenism are improved, and type 2 diabetes is prevented or delayed, so pioglitazone is a better treatment in patients with PCOS.

Key words

Metformin, Pioglitazone, Polycystic ovarian syndrome.

Introduction

Polycystic Ovarian Syndrome (PCOS) is a heterogenous collection of symptoms and signs, which form a spectrum of a disorder with a mild presentation and severe disturbance of reproductive, endocrine and metabolic function. Anovulation (irregular menstrual periods), hyperandrogenism, insulin resistance, obesity and inappropriate gonadotropin secretion i.e. increase in Luteinizing hormone (LH) is to Follicle stimulating hormone ratio (FSH). Many hypothesis supports that hyperinsulinemia and insulin resistance has a pathogenic role in this syndrome [1, 2]. Insulin is involved in the dysregulation of Luteinizing hormone (LH) secretion at central level. Insulin promotes ovarian androgen secretion by increasing the cytochrome P450 C17 activity and affects the normal follicular growth at the peripheral level. Insulin increases free androgen levels, decreases serum sex hormone binding globulin synthesis by the liver. In vivo ACTH stimulated adrenal androgen production is potentiated by insulin in women with PCOS [3, 4], Cardiovascular disease, Type 2 diabetes and endometrial and breast cancer are the effects of PCOS. Various tissues like endometrium and breast epithelium are influenced by insulin which is a powerful mitogenic. This causes a proliferative affect which contribute to the appearance of oncogenes and transformation of benign to malignant tissue [5].

Materials and methods

This was a double blinded, randomized, comparative study conducted at Government hospital Nizamabad and CKM hospital

Warangal. 150 PCOS patients in the age group 18-35 years were enrolled, and were allocated to two groups and were given the following modalities for a period of 8 months. Group I: Metformin-500 mg, BID, Group II: Pioglitazone-15 OD. Each group consisted of 75 patients. The minimum sample size required was 50-60. In this study, 75 patients were included in each group to allow dropouts.

Inclusion criteria

Oligo or anovulation, hyperandrogenism, polycystic ovaries.

Exclusion criteria

Pregnancy and nursing, significant renal impairment, neoplastic disease, cardiovascular diseases, cushing's disease, hypothyroidism, hyperprolactinemia, any drug intake like antidiabetic, oestrogen, progesterone.

The menstrual cycle irregularities and viralization grading were the parameters studied for each group. Baseline investigations such as CBP, ESR, Liver function tests, serum creatinine and urea, TSH, Serum Prolactin, Lipid profile, oral GTT, Serum testosterone, sex hormone binding globulin, LH/FSH ratio, USG of abdomen and pelvis. The treatment is given over a period of 8 months with follow up visits of every month.

Results

In group I, 68 (90%) out of 75 patients and in group II, 67(89%) out of 75 patients completed the trial.

Clinical Characteristics-Menstrual Cycles

In group I, all the 68 patients had irregular menstrual cycles at the beginning of the study, and at the end of the study, 34 (47%) had regular menstrual cycles. In group II, 67 patients had irregular menstrual cycles at the beginning of the study, and at the end of the study, 38 (56%) had regular menstrual cycles.

Viralization

It was done as per Ferriman-Gallway score. In group I, out of 68 patients, 58 patients showed hirsutism (F-G score 8) at the start, and they had lesser F-G score at the end of the study and 2 among them had no hirsutism. In group II, out of 67 patients, 54 presented hirsutism at the start of the study, (F-G score 8) and at the end of study, they had lesser F-G score, 6 among them had no hirsutism completely.

Metabolic and Hormonal Parameters

Total Cholesterol

In Group I out of 68 patients, 15 were found to have Serum cholesterol levels 200 at baseline and at the end of the treatment 8 had S. cholesterol 200. In Group II out of 67 patients, 12 had S. cholesterol of 200, and at the end of treatment 4 had S. cholesterol 200. In both the groups, S. cholesterol levels show a decline ($P < 0.05$), but the decrease is more significant in Group II, when compared with Group I ($P < 0.05$).

HDL-C

In both the groups, there was an increase in HDL levels (statistically significant versus baseline), more in Group II than in Group I. The average increase is 28 % in Group I as compared to 74 % in Group II.

VLDL-C

There was a trend of decrease in VLDL levels in both groups, the decrease being more in Group II (48%) than in Group I (26%) statistically significant when both groups were compared.

Insulin Levels

In group I, 38 out of 68 patients and in group II, 47 out of 67 patients were hyperinsulinemic i.e.

fasting insulin levels 40 IU/ml and the rest were normo-insulinemic.

Insulin Resistance

In group II, the fall in insulin level is more i.e. 61.3% from an average of 43.6 to 23.9 IU/ml than in group I i.e. by 16.6% from an average of 45 to 38.06 IU/ml, after treatment for 8 months. Similarly, fall in insulin level is more in group II (49.4%) than in group I (14.8%), after glucose load was given. The difference between the two groups is statistically significant ($P < 0.05$).

Testosterone

There was a fall in testosterone levels in both the groups which is statistically insignificant.

Sex Hormone Binding globulins (SHBG)

In both the groups, there is a rise in SHBG, (statistically significant versus baseline). In Group I, the mean increase in SHBG was 6.22 nmol/l (22 %), but in Group II, mean rise in SHBG was more, i.e. 34.56 nmol/l (72.7 %) and this difference is statistically significant ($P < 0.05$).

Free Androgen Index

In Group I, average fall in FAI was 1.6 (24.5 %), but in Group II, it was 2.6 (50 %). In both the groups, FAI decreased, but in Group II, the decrease was more, and this is statistically significant ($P = 0.05$) versus Group I.

Luteinizing Hormone

LH values on an average decreased by 2.38 mIU/ml in Group I (statistically insignificant) and by 4.74 mIU/ml in Group II (statistically significant $P < 0.05$) versus baseline values. This effect in Group II is also statistically significant versus Group I.

LH/FSH ratio

Both the Groups showed a decrease in LH/FSH ratio. The fall in LH/FSH ratio was more in Group II, than in Group I. This fall in Group II was statistically significant $P < 0.05$ versus Group I.

Ovulation

In Group I, out of 68 anovulatory patients 30 (44.2 %) had their ovulation restored (CI 29–59 %). In Group II, out of 67 anovulatory patients 38 (56 %) had ovulatory cycles after treatment (CI 40.9–71.3 %). Thus, pioglitazone shows an equally effective success rate in restoration of ovulation when compared to metformin. There were no major side effects which resulted in discontinuation of treatment in both the groups. In Group I, only mild gastrointestinal side effects were reported. In Group II, mild peripheral

oedema in 45%; muscle cramping in 16 % were reported. There were no major changes in hepatic parameters after 8 months of its administration. Thus, pioglitazone is a safe drug and does not share any of its unsafe effects.

Table - 1 shows that all baseline values were identical and any differences among them were statistically insignificant. **Table - 2** shows Post-treatment values of Group I and Group II.

Table – 1: Comparison of baseline values of Group I and Group II.

Variables	Group I	Group II	P Values
F-G Grading	15.2±5.28	14.98±5.14	<0.05
Total Cholesterol (mg/dl)	183.97±16.28	188.35±10.14	<0.05
HDL-C (mg/dl)	38.11±2.7	38.05±2.1	<0.05
VLDL-C (mg/dl)	38.17±2.9	22.98±1.7	<0.05
Fasting Insulin (µU/ml)	42±6.5	42.8±2.5	<0.05
Post glucose insulin (µU/ml)	140±2.5	140±2.5	<0.05
Testosterone (nmol/L)	1.95±0.24	1.88±0.30	<0.05
SHBG (nmol/L)	47.22±0.2	30.44±5.2	<0.05
FAI	12.00±3.52	13.24±4.2	<0.05
LH (mIU/ml)	4.6±6.6	6.8±6.7	<0.05
FSH (mIU/ml)	8.36±1.1	6.99±0.9	<0.05
LH/FSH	0.598±1.9	0.897±3.2	<0.05

Table – 2: Post-treatment values of Group I and Group II.

Variables	Group I	Group II	P Values
F-G Grading	7.62±1.17	7.59±3.28	>0.05
Total Cholesterol (mg/dl)	176.83±11.29	144.39±9.35	<0.05
HDL-C (mg/dl)	46.28±3.2	67.52±14	<0.05
VLDL-C (mg/dl)	20.29±4.3	26.55±2.2	<0.05
Fasting Insulin (µU/ml)	35±2.1	22.1±1.1	<0.05
Post glucose insulin (µU/ml)	132±4.5	82±5.7	<0.05
Testosterone (nmol/L)	1.66±0.57	1.85±0.27	>0.05
SHBG (nmol/L)	38.17±4.1	78.58±7.7	<0.05
FAI	10.07±2.58	7.47±1.8	<0.05
LH (mIU/ml)	4.6±6.6	2.9±4.8	<0.05
FSH (mIU/ml)	7.9±0.7	9.7±3.2	<0.05

Discussion

Many studies have been done on comparison of metformin and pioglitazone in polycystic ovarian syndrome. Sangeetha Shah, et al. [6] conducted a study to evaluate the effect of metformin and

pioglitazone on insulin resistance, ovulation and hyperandrogenism in women with PCOS. 100 patients of age 18–30 years were included in this randomised double blind trial for treatment with either metformin or pioglitazone for a period of 6 months. Results Administration of metformin

and pioglitazone for 6 months revealed that 50% of the patients achieved menstrual cyclicity. A decline in F-G grading for hirsutism within the both the groups was observed. The lipid profile also showed a decrease in total cholesterol, an increase in HDL-C, a decrease in VLDL-C levels but more so in the pioglitazone group. HOMA-IR declined more than 50–55% with pioglitazone and 15% with metformin. Thus, pioglitazone may be a better treatment option as far as protection from tendency to development of diabetes is concerned. The rise in serum SHBG levels and decline in free androgen index and L/H ratio are more remarkable with pioglitazone (P-0.05). Ovulation was restored in 44.2 and 56% of patients on metformin and pioglitazone, respectively. It concluded that pioglitazone may be a new alternative for use in women with PCOS, providing more metabolic and reproductive benefits and possibly protection from developing diabetes and cardiovascular problem. Sumitha Tanwar, et al. [7]. The present study was aimed to evaluate the efficacy of pioglitazone and comparing the efficacy of pioglitazone with metformin in improvement of clinical characteristics of the PCOS patients. The present study was a prospective, parallel group trial in 40 proven cases of PCOS, all the patients underwent clinical evaluations at baseline that include height, weight, BMI, waist to hip ratio (WHR) and hirsutism (FG score). There were two groups in this study group A (unmarried) and group B (married) each divided in two subgroups each having 10 patients, A1 (unmarried - metformin), A2 (unmarried - pioglitazone), B1 (married - metformin), B2 (married - pioglitazone) therapy was given for six months with regular clinical evaluation of the patients after every two months. WHR (Waist to hip ratio) was measured according to World Organization Criteria (2003), BMI was calculated by using Quetelets Index formula WHO (1995), the grade of hirsutism was detected using Ferriman-Gallwey score (1961). On comparing metformin and pioglitazone it was observed that both the drugs equally decreased the FG score; metformin significantly decreased the BMI and WHR whereas pioglitazone

significantly increased the BMI and WHR. Pioglitazone significantly increased the BMI and WHR, whereas it significantly decreased FG score. On comparing metformin and pioglitazone it was observed that both the drugs equally decreased the FG score, metformin significantly decreased the BMI and WHR whereas pioglitazone significantly increased the BMI and WHR. Iram Chaudhry, et al. [8] compared the efficacy of pioglitazone and metformin in women with polycystic ovary syndrome. This randomized trial was conducted at Department of Obstetrics and Gynecology, Bahawal Victoria Hospital, Bahawalpur from June 2015 to December 2015. Total 70 patients with polycystic ovary syndrome having 20-40 years of age with duration of disease >3 month were recruited. The mean age of women in group A was 29.97 ± 5.28 years and in group B was 30.37 ± 5.63 years. Mean duration of marriage in study group A was 4.74 ± 2.40 years and in study group B was 4.91 ± 2.25 years. The mean duration of disease in study group A was 3.69 ± 1.59 years and in study group B was 3.94 ± 1.84 years. Efficacy of Group A (metformin group) was 19 (54.29%) while in Group B (pioglitazone group) was 29 (82.86%) with p-value = 0.010. This study concluded that Pioglitazone is more effective as compare to metformin for ovulation induction in women with polycystic ovary syndrome [9].

Samsad Jahan, et al. [10] compared the efficacy of metformin and laparoscopic ovarian drilling to be used in anovulatory patients with polycystic ovarian syndrome (PCOS) for ovulation induction and pregnancy achievement. A prospective clinical trial conducted in the outpatient department of Gynaecology and Obstetrics of BIRDEM hospital from August 2008 to August 2013. Patient(s): Three hundred and eight newly diagnosed patients with PCOS based on ESHRE/ASRM criteria. These patients were assigned to two groups: Group 1 (152 patients) received 500 mg of metformin three times a day; Group 2 (156 patients) received laparoscopic ovarian drilling. Main Outcome Measure(s): Rate of ovulation, pregnancy rate

(PR), and live birth. Ovulation was monitored by serum progesterone, transvaginal sonography up to six cycles or till pregnancy occurred upto six months. The results were ovulation rate was 68.4% in the metformin group, 59% in the laparoscopy treatment group. The pregnancy rate was (20.1% and 16.6%) and live birth rate was (18.4% and 15.4%) in metformin and laparoscopy treatment groups, respectively. The rate of spontaneous first trimester loss was three and two in metformin and laparoscopy group respectively. There were no ectopic pregnancies in metformin group and two in laparoscopy group. There was no second trimester pregnancy loss in metformin group, three in laparoscopy group. There were no multiple pregnancies in metformin group, two in laparoscopy group.

Conclusion

Pioglitazone can restore menstrual cycle, a better ovulatory rate is achieved, clinical signs of hyperandrogenism are improved, and type 2 diabetes is prevented or delayed, so pioglitazone is a better treatment in patients with PCOS.

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