

## Comparing therapeutic effects of Metformin and Pioglitazone in Polycystic ovary syndrome (PCOS)

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### ABSTRACT

**Objective:** To compare therapeutic effects of Metformin and Pioglitazone in Polycystic ovary syndrome (PCOS).

**Methodology:** In a randomized clinical trial, 100 women with PCOS were recruited during a one year period in Al-Zahra Hospital of Tabriz. These patients were randomized into two groups of 50 patients receiving either Metformin 500 mg(TDS), or Pioglitazone 15 mg(BID), for six months. Clinical and laboratory findings were compared between the two groups at the baseline and end of the study.

**Results:** Pregnancy frequency was higher in Metformin group. Amelioration of menstrual cycles, hirsutism, and laboratory tests, including FBS, Hyperinsulinemia, oral glucose tolerance test, 2hpps and insulin, free testosterone and prolactin was significant in both groups. The change of serum total cholesterol and HDL was not significant in the Pioglitazone group.

**Conclusion:** According to our results, Metformin is superior to Pioglitazone due to better influence on pregnancy and lipid profile.

**KEY WORDS:** Polycystic Ovary Syndrome, Metformin, Pioglitazone.

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### INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in reproductive ages, the most common cause of infertility due to ovulatory disorder and makes up 73% of the causes of hirsutism in this age group.<sup>1,2</sup>

Impaired *folliculogenesis*, hyperandrogenism (acne, hirsutism and alopecia) and abnormal menstrual cycles are seen in 38.4%, 70.3% and 66.2% of patients, respectively. The diagnosis of the disease is made according to the Netherland criteria when at least two of the three criteria including polycystic ovaries detected by ultrasonography, irregular menstrual bleeding, hyperandrogenism, exist. PCOS's etiology is complicated and still unknown, but there is a kind of insulin resistance due to changes of two types of cytochrome p450 producing genes. Various treatments have been proposed for the management of this syndrome.

Weight loss, inhibition of ovarian androgen with progestin, oral contraceptive pills (OCPs), GnRH agonists, anti-androgens, ovulation stimulators and drugs used in type 2 diabetes such as Metformin and Glitazone are the most commonly used medical treatments.<sup>1,3,4</sup>

It seems patient response rates are different based on the clinical and constitutional differences, and the kind of the drug chosen. So far, few studies have been conducted comparing therapeutic results of Metformin and Glitazone, two different types of antidiabetic drugs. In addition, due to the probable genetic basis of the disease, the effect of these two drugs with different structure and mechanism of action may vary in our area. So, comparison of the effectiveness of these two drugs in PCOS patients seems necessary which may help us choosing the more effective and convenient drug in controlling clinical and vitro signs of PCO.

### METHODOLOGY

In a randomized clinical trial in Al-Zahra Educational and Health Hospital Center and Sheikh Alra' is Clinic of Tabriz University of Medical Sciences, during 12 months period between 2008-2009, 100 women with PCO were randomly divided into two groups of 50 patients and treated with Metformin or Pioglitazone. Clinical, hormonal and endocrinal changes in the two groups were compared. In Pioglitazone group, 6 people withdrew the study due to weight gain during the few weeks beginning the study, which were replaced with six other patients.

All PCOS patients were verified by Netherland criteria<sup>1</sup> consisting of polycystic ovaries and/or hyperandrogenism and/or and irregular menstrual bleedings and found suitable for treatments.

Metformin with dose of 1500 mg per day in three divided doses or Pioglitazone 15mg (BID) were administered for six months. Clinical and laboratory parameters, including pattern of menstrual cycles, hirsutism, and FBS, Hyperinsulinemia, oral glucose tolerance test(GTT), 2hpps and insulin, free testosterone and prolactin were determined and measured at the baseline and at the end of the six months period. Fertility rate was also studied in patients who had this tendency.

**Ethical considerations:** Due to the use of proven safe drugs on these patients, there was no specific moral problem. Meanwhile this study had been approved by the Ethical Committee of Tabriz University of Medical Sciences.

It should be noted that Glucose 2hhp of less than 140 mg/dl is considered as normal, 140-199 mg/dl as disturbed, and 200 mg/dl or higher as non-insulin dependent diabetes mellitus; and insulin levels 2 hours after a meal of 100-150 mu/ml is considered as likely insulin resistance, 151-300 mu/ml as insulin resistance and more than 300 mu/ml as severe insulin resistance.

After data being collected by the researchers, all data were entered in SPSS software and analyzed. In this research, statistical and descriptive analysis, and statistical indices like mean, median and Chi-Square and independent t-test were used to compare the means. It should be mentioned that P less than 0.05 was considered to be meaningful.

### RESULTS

Mean age of Metformin group patients was 26.8±4.5 year and in Pioglitazone group patients was 28.8±5.2 year (P=0.051). Mean BMI of Metformin group patients was 27.9±0.9 and in Pioglitazone group patients was 27.8±0.7 (P=0.449). Mean gravidity of Metformin group patients was 0.3±0.7 year and in Pioglitazone group patients was 0.2±0.4 year (P=0.394).

Forty four percent of Metformin group patients and 34% of Pioglitazone group patients had primary infertility, 30% of Metformin group patients and 38% of Pioglitazone group patients had secondary infertility, 10% of Metformin group patients and 12% of Pioglitazone group patients were single and 16% of patients in both groups were fertile.

Skin rash was observed in 4% of Metformin group patients, Galactorrhea in 12% of Metformin group patients and Alopecia was found in 4% of patients in both groups. Ten and three patients of Metformin and Pioglitazone groups were pregnant at the end of study respectively, so the frequency of pregnancy was significantly more prevalent in Metformin group patients than in Pioglitazone group (P=0.037).

Frequency (%) of Irregular menstrual cycles, hirsutism, Abnormal GTT and Hyperinsulinemia at baseline and at the end of study is showed in Table-I.

### DISCUSSION

In our study, we evaluated and compared the results of treatment with Metformin (500 mg (TDS)) and Pioglitazone (15 mg (BID)) in treating PCOS for six months. At the end of the study, normalized cycles, improved hirsutism, normalized glucose tolerance test, improved *Hyperinsulinemia*

Table-I: Frequency (%) of Irregular menstrual cycle, hirsutism, Abnormal GTT and Hyperinsulinemia at baseline and at the end of study.

	Groups	Baseline		End of study		P_value Baseline-end
		Frequency (%)	P_Value	Frequency (%)	P_Value	
Irregular menstrual cycle	Metformin	31(62%)	0.836	18(36%)	0.414	0.001
	Pioglitazone	32(64%)		22(44%)		0.007
hirsutism	Metformin	31(62%)	0.836	18(36%)	0.836	<0.001
	Pioglitazone	32(64%)		19(38%)		0.005
Abnormal GTT*	Metformin	15(30%)	0.668	6(12%)	0.564	<0.001
	Pioglitazone	17(34%)		8(16%)		<0.001
Hyperinsulinemia	Metformin	33(66%)	0.668	3(6%)	1	<0.001
	Pioglitazone	35(70%)		3(6%)		<0.001

\*\_GTT: Glucose Tolerance Test

were observed and improved results of vitro tests of serum including FBS, 2hppps and insulin, free testosterone and prolactin, was seen in both groups.

In Pioglitazone receiving group, HDL and total cholesterol changes were not significant and a triglyceride level of serum was significantly increased at the end of the study. Frequency of pregnancy in Metformin group was significantly higher. For the first time, Velazquez used Metformin for PCOS and showed that treatment with Metformin improves metabolic and hormonal status, including hyperandrogenism, reproductive status and lipid profile in patients with PCOS.<sup>5</sup>

The improvement of menstrual cycle in women with PCOS is obvious after taking Metformin.<sup>6</sup> Today, Metformin is used as the first or second line drug in infertile PCOS cases with no ovulation and in cases where the patient is undergoing treatment with gonadotropins.<sup>7,8</sup> In another study, Lord et al (2003) emphasized the effectiveness of Metformin modification of lipid profile in women with PCOS.<sup>9</sup> As observed, the results of our study on the effect of Metformin on hormonal and endocrinal parameters in women with PCOS are in line with the findings of other studies in this field. Today, Pioglitazone and rosiglitazone, are used in the treatment of PCOS patients.<sup>9,10</sup>

Brettenthaler et al (2004) showed that Pioglitazone can remedy insulin resistance, hyperandrogenism, ovulation and menstrual cycle disorders in women with PCOS<sup>10</sup>; and Rautio et al (2006) reported similar results in heavy weight women with PCOS.<sup>11</sup> As noted, also with this drug, results by the present study are in line with results of other studies. Although the role of the two drugs in clinical, endocrinal and fertility improvement in PCOS women is proven in various studies, but

direct comparison of these two categories in this field have been less performed.

In a meta-analysis study, Pillai et al (2007) investigated all the studies conducted in this field and finally concluded that the information in this field is not sufficient for a definite decision. Low number of samples and inconvenient methods of studies in this field, in addition to the low number of these studies have been mentioned as the main constraints.<sup>12</sup>

Ortega-Gonzalez et al (2005) studied and compared the results of treatment with Metformin and Pioglitazone for 6 months in women with PCOS. In this study, no significant difference was observed between the two groups regarding the changes of insulin sensitivity, hyperandrogenism, menstrual cycles and successful pregnancy frequency. However, it was shown that weight changes, as increased body mass index and waist-hip ratio, was higher in Pioglitazone recipients than Metformin recipients.<sup>13</sup>

In our study, we showed that Pioglitazone has no desirable effect on lipid profile and especially the level of serum glyceride. On the other hand, at baseline, 6 cases of Pioglitazone group withdrew from the study complaining of weight gain. This is one of the major constraints of using Pioglitazone in this group of patients.

Moreover, in our study, frequency of pregnancies in Metformin recipients group was significantly higher unlike the results reported in aforementioned study. This may be due to used dose of Pioglitazone which had begun with low doses due to the lack of similar study in our patients. Since ovulation and pregnancy probability is greater with higher dose of Pioglitazone, low rate of pregnancy in Pioglitazone group can be explained.

In another study, Baillargeon et al (2004) evaluated obese PCOS women in three groups: receiving Metformin, rosiglitazone and both drugs, and reported no significant difference of ovulation and decreased androgen levels among the three groups. However, improved insulin sensitivity was reported significant only in the Metformin and two-drug groups.<sup>14</sup>

The difference between the results by the current study with those of ours on the changes of insulin sensitivity may be due to limiting the mentioned study to non-obese women. In another study by Legro et al(2007), 16 women with PCOS were divided into two groups and received Metformin or rosiglitazone (for 3 months) and then combined treatment (another 3 months). Although decreased levels of free testosterone, serum insulin and 2hpp were not significantly different in the two groups, but better conditions was reported in rosiglitazone group.<sup>15</sup>

Accordingly, it may be concluded that in the impaired range of serum glucose levels (190-140 mg/dl), the results by the two drugs are similar. In a study by Cho et al(2009), 30 PCOS patients were divided into three groups and treated with Metformin, Pioglitazone or Orlistat. In this study, no significant difference in terms of hormonal and metabolic improvement was observed among the three groups.<sup>16</sup> Wild (2007) in their study showed that the effect of both drugs on lipid profile is the same.<sup>17</sup>

As observed, the results of studies conducted in this field were similar in most cases and have shown no significant difference between Metformin and Thiazolidinediones groups and the same result is observed in the current study. As previously mentioned, the low number of patients and impaired method of study and selection of patients are the major constraints of most existing studies which were not there in the current study.

In our study, we showed that there is no significant difference between the groups in terms of the complications of drug therapy (except for adverse effects of Pioglitazone on lipid profile and weight gain). In other words, except for some temporary and minor gastrointestinal disorders, no complication was observed in treatment with either of the two groups. Also in other studies, the safety of the two drug groups in women with PCOS has been emphasized.<sup>18</sup>

We found the frequency of Hyperinsulinemia in all patient groups approximately 68%. Meanwhile, there was no instance of insulin resistance

(insulin<300) in any patient and the intensity of insulin disorder was lesser. In other studies, the frequency of this condition has been reported varying from 57 to 100 percent.<sup>19</sup>

## CONCLUSION

Rates of menstrual cycle Normalization, hirsutism improvement, and normalized glucose tolerance test after taking Metformin and Pioglitazone showed no statistically significant difference in study groups. Complications of using Metformin and Pioglitazone in study groups showed no statistically significant difference. At the time of referring, 32% and 68% of patients in total had glucose tolerance test disorder and Hyperinsulinemia respectively. Pregnancy rate in Metformin recipient group was significantly higher. At the end of the study, normalization of cycles, hirsutism improvement, normalisation of glucose tolerance test, improvement of Hyperinsulinemia and results of vitro serum tests including FBS, insulin 2hpp, free testosterone and prolactin was observed in both groups. However, in Pioglitazone recipients group, changes of HDL and total cholesterol were not significant, and the level of serum triglyceride was significantly increased at the end of the study, but in Metfomin group these tests were ameliorated. It seems that after observing these differences, it is better to compare these two drugs in non-obese women with PCO.

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**Authors contribution:** Dr. Nazli Navali conceived and designed the study protocol besides interpretation of data and its analysis, drafting and revised the final manuscript. Dr. Leila Azhary shokoufe prepared the drugs to be always at hand, guided about the dosage and prevention of the complications, was also involved in the acquisition and analysis of data, drafting and revising the article critically. Dr. Fatemeh Mallah and Dr. Parvin Bastani contributed in conception of the study and data collection and interpretation of data analysis. Dr. Omid Mashrabi was involved in data analysis, drafting and critical revision of the final manuscript.

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