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Comparison of the Effect of Metformin and Rosiglitazone Alone and in Combination on Ovarian and Endometrium of Polycystic Ovarian Syndrome Patients

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Abstract

This study investigated the influence of metformin and rosiglitazone on ovarian and endometrium of polycystic ovarian syndrome patients. Forty-four women were chosen by simple random sampling from referred women to obstetrics and gynecology clinic of Al-Zahra and Shahid Beheshiti Hospitals, Isfahan, Iran. The study consisted of a 6-week baseline observation period, a 12-weeks treatment period of single-agent therapy (rosiglitazone or metformin), and then a 12-weeks period of combined therapy. Repeated measure analysis showed that there was significant difference between measurements of waist, TG, hirsutism, FBS and testosterone in both treatment groups over thirty weeks (all p-values < 0.05). Ovary size was statistically different in metformin group in three measured time (p-value < 0.001). Also number of follicles (p-value= 1 and 0.564) and follicle size (p-value= 1 and 1) were not different in three phases of study in metformin and rosiglitazone groups according to Wilcoxon signed ranks test. It was concluded that there was significant change in waist, TG, hirsutism, FBS, testosterone and insulin resistance over thirty weeks in each of metformine and rosiglitazon groups but there was not statistical difference in HDL and BMI. Testosterone level after single therapy and combination therapy in rosiglitazone reduced more significantly than metformin group. On the other hand, ovary size decreased more in metformin group after single therapy and combination therapy than rosiglitazone.

Key words: metformine, rosiglitazone, endometrium, polycystic ovarian syndrome patients, insulin resistance.

Introduction

Polycystic ovarian syndrome (PCOS) is one of the important endocrine disorders with a prevalence of 6-10% among females in reproductive ages. (Allahbadia and Merchant, 2011; Baillargeon et al., 2004; Tso, 2010) PCSO results in various side effects including hirsutism, metabolic syndrome, insulin resistance, hypertension, dyslipidemia, type 2 diabetes, cardiovascular disease, and endometrial hyperplasia. (Allahbadia and Merchant, 2011; Tang et al., 2012; Lord et al., 2003) Although pathophysiological causes of PCOS have not been distinguished well yet, (Legro et al., 2007) hyperinsulinemia is seen among 30% of patients with normal weight and 80% of patients with obesity. (Tso, 2010) The etiologic mechanism of this syndrome is not explained distinctly and as a result, various treatments have been proposed based on symptoms. However, there are a few numbers of comprehensive treatments considering all aspects of endocrine disorders of PCOS. (Legro et al., 2007)

It seems insulin-sensitizing drugs are effective in the treatment of PCOS. Two groups of insulin-sensitizing drugs are available now: Biguanides such as metformin, thiazolidinediones such as troglitazone. Several studies showed that troglitazone improves ovulation, decreases glycemic parameters such as fasting blood sugar and also testosterone and increases SHBG. (Azziz et al., 2001; Ehrmann et al., 1997) But, it was forbidden because of hepatotoxicity signs. However, the same achievements have been seen for rosiglitazone. (Baillargeon et al., 2004; Legro et al., 2007) Metformin is an edible biguanide that is used extensively for controlling glycemic in type 2

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diabetes. Also, it is recently applied for restoring ovulation along with other fertility drugs in the treatment of PCOS as adjuvant therapy. The main effects of PCOS include a decrease in glucose, an increase in insulin sensitivity, and reduction of androstenedione and testosterone levels. In recent years, lots of studies have shown the application of ends in the decrease of insulin resistance, improvement of PCOS symptoms, restoration of ovulation cycle and improvement of fertility rate. (Baillargeon et al., 2004; Tso, L. O. (2010; Tang et al., 2012; Legro et al., 2007; Azziz et al., 2001; Ehrmann et al., 1997; Kilicdag et al., 2005; Mitkov et al., 2006; Yilmaz et al., 2005; Kim et al., 2000; Kocak et al., 2002; Kashyap et al., 2004; Moghetti et al., 2000; Brettenthaler et al., 2004)

Metformin and rosiglitazone are both effective treatments for PCOS, but it is not clear which one is more effective, and neither is their combination in comparison with a single therapy. In the treatment of type 2 diabetes, the combination of these two drugs has more benefits than single therapy and has an additional effect on the decrease of glucose level and insulin. The same effect can be seen in PCOS women because of the same insulin resistance. (Legro et al., 2007) Clinical trials have demonstrated the endometrial influence of insulin sensitizers. It is suggested that PCOS women suffer from pregnancy loss and are at high risk of endometrial cancer. (Legro et al., 2007)

Few investigations have been done on the effect of metformin and rosiglitazone alone and in combination. (Baillargeon et al., 2004; Legro et al., 2007) So, the aim of this study was to assess the effect of metformin and rosiglitazone (alone and in combination) on ovarian and endometrium of polycystic ovarian syndrome patients of Al-Zahra and Shahid Beheshti hospitals in Isfahan during 2013-2014.

Method and Material

Patients

This randomized clinical trial was conducted in 2013 for thirty weeks. Forty-four women were chosen by simple random sampling method from women referred to the Obstetrics and Gynecology Clinic of Al-Zahra and Shahid Beheshti Hospitals, Isfahan, Iran. Registration code of this investigation in the Iranian Registry of Clinical Trials and the Ethical Committee of the Isfahan University of Medical Sciences verified the study protocol. All patients filled an informed consent form. Inclusion criteria were age between 18-40 years old, Euthyroid, non-smoking, healthy physical condition, no use of drugs with an effect on the metabolism of sex hormones or glucose within the last month before the examination, and no use of contraceptive steroids for at least 3 months. Exclusion criteria were a nonclassical 21-Hydroxylase deficiency, hyperprolactinemia, androgen-secreting tumors, pregnancy, an increase in liver function tests at baseline or kidney dysfunction, type 2 diabetes, anemia, thrombocytopenia, and hypertension. The flow chart of the research is depicted in Figure 1.

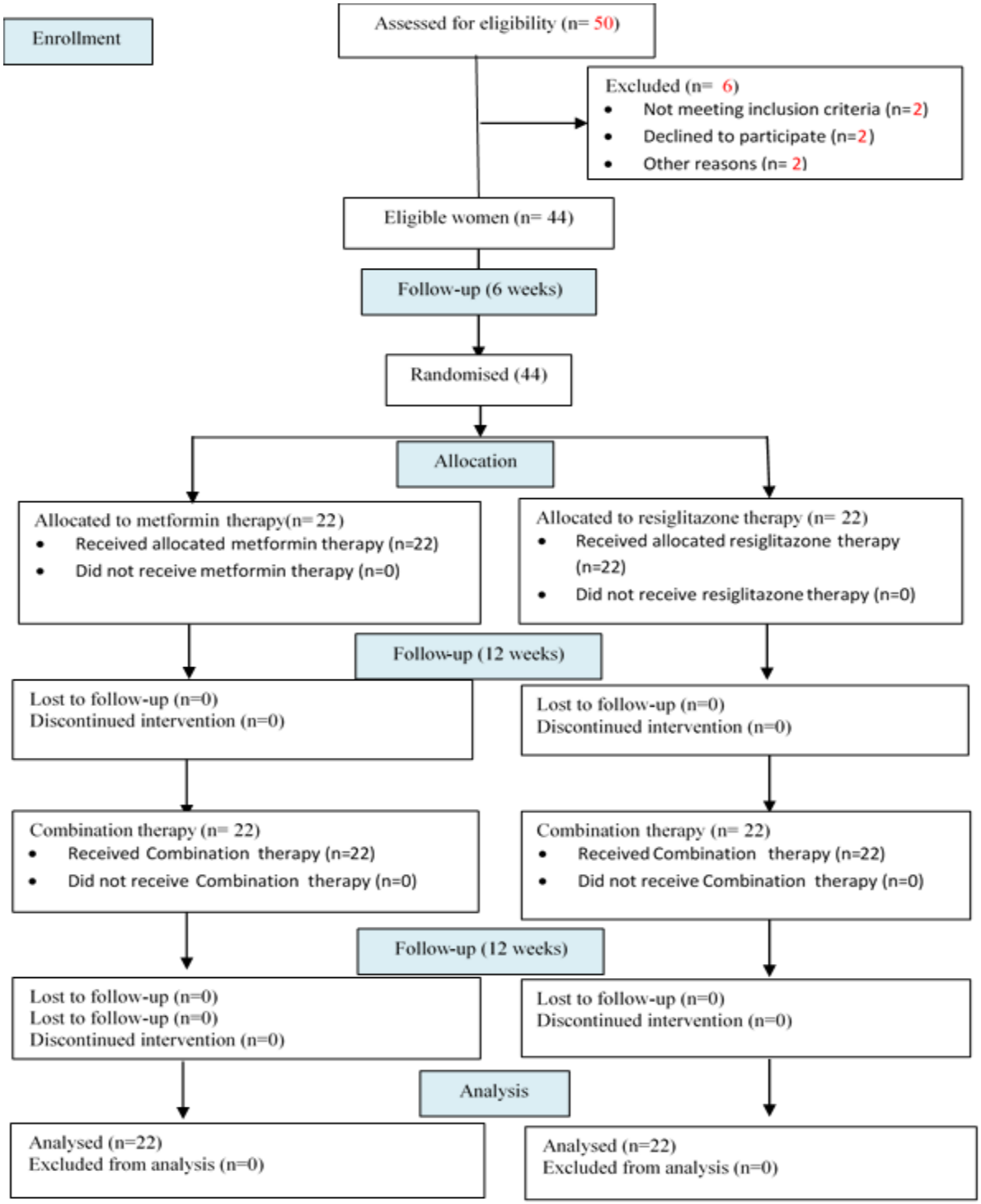

Figure 1. CONSORT flow chart for two treatments of the study.

Treatment

At first, patients were followed up for 6 weeks without any medication. Then, they were randomly allocated to one of two groups: the first group was treated by metformin for 12 weeks and the second group took rosiglitazone in the same period of time. Then, both groups were treated by a combination of metformin and rosiglitazone for 12 weeks. The first group took metformin 1000 mg twice a day and the second group took rosiglitazone 4 mg twice a day. Metformin dosage started by 500 mg per day and increased to the desired dosage of 2000 mg per day.

Measurements and Evaluations

At baseline before randomization, weight, height, blood pressure, hirsutism by Ferriman-Gallwey score, glucose level, and sex hormones (total testosterone) were measured. Also, complete blood count, as well as kidney and urine tests were done to reject the pregnancy.

At first visit and before the start of medication, transvaginal sonography (TVS), 3-hour oral glucose tolerance test (OGTT) with 100 mg glucose and endometrial biopsy with Pipelle catheter were done. The patient had to eat nothing ten to twelve hours before the OGTT test. Pipelle catheter has a sensitivity of 97.5% in endometrial biopsy in diagnosing endometrial cancer. In comparison with D&C, it has histology coordination in 83.3% of cases. (Stovall et al., 1991) The following variables were measured In TVS: endometrial thickness, size of ovaries, size of the biggest ovarian follicles, and ovarian morphology based on Adams criteria. At the end of twelve weeks, TVS, OGTT, and biopsy were repeated again. Then, patients were medicated by a combination therapy for the second twelve-weeks and then tests repeated for the third time.

Clinical examination, hormone test, Gravindex test, and hirsutism evaluation were repeated after a single therapy and combination therapy course. Also, patients were asked to complete a timetable about their menstrual cycles. They were recommended to not change their diets and physical activity and use one of the contraception methods of birth control.

Hirsutism is defined as the growth of coarse hair in females with male-like patterns. Its prevalence is about 5-15%. (Azziz, 2003) It results from an increase in androgens. (Hatch et al., 1981) Ferriman- Gallwey score was used to evaluate hirsutism in this study. It is a visual scoring for hair growth in females. In this scoring, nine parts of the body were considered (upper lip, chin, chest, upper back, lower back, upper abdomen, lower abdomen, arm, and thigh) and scored between 0 (absence of coarse hair) to 4 (extensive growth of coarse hair). Then scores of each area were summed for a total score. The score between six to eight or more was considered hirsutism. (Azziz, 2003)

Insulin resistance (IR) was calculated according to the homeostasis model assessment of IR (HOMA-IR) by using the following formula (Kelishadi et al., 2004):

$$\mathrm{HOMA-IR} = \frac{\text{fasting insulin (mU/L)} \times \text{fasting glucose(mmol/L)}}{22.5}$$

HOMA-IR more than 3.5 was considered as severe IR. (Mehrabian et al., 2011)

High blood pressure or hypertension was defined as systolic blood pressure equal or more than 140 mm Hg and diastolic blood pressure equal or more than 90 mm Hg.

All statistical analyses were done by the Statistical Package of Social Sciences (SPSS) version 20. Independent t-test, Mann-Whitney test, Kruskal Wallis test, Friedman test, repeated measure analysis, and Chi-square test were used. All analyses were performed at the 0.05 significance level.

Results

The mean age among the metformin group was 29.91±1.89 years and among the rosiglitazone group was 29.91±1.88. Nearly 82% of women in the metformin group had PCOS and this percentage was 86.4% in the rosiglitazone group. High blood pressure was seen in 22.7% of women in both groups. Means of hirsutism scores at baseline were 11.82±0.54 and 11.77±0.61 in metformin and rosiglitazone groups, respectively. Other characteristics of patients at baseline are shown in Table 1.

Table 1: Characteristics of patients at baseline in the two treatment groups (Mean±Standard deviation/frequency (%))

Variables	Metformin (n=22)	Rosiglitazone (n=22)
Age	29.91±1.89	29.91±1.88
BMI	29.87±0.91	29.82±0.93
waist	96.23±1.38	96.73±1.28
HDL	43.68±1.41	43.82±1.45
TG	199.86± 12.06	199.82±12.06
Blood pressure		
- Yes	5 (22.7%)	5 (22.7%)
- NO	17 (77.3%)	17 (77.3%)

PCO		
- Yes	18 (81.8%)	19 (86.4%)
- NO	4 (18.2%)	3 (13.6%)
FBS	91±3.10	91.31±3.03
Testosterone	66.95±4.46	67.14±4.54
Ovary size	25.36±1.59	25.54±1.67
Hirsutism	11.82±0.54	11.77±0.61
Histology		
- secretory	3 (13.6%)	4 (18.2%)
- Proliferative	17 (77.3%)	15 (68.2%)
- hyperplasia	2 (9.1%)	3 (13.6%)
Insulin Resistance		
- Yes	19 (86.4%)	22 (100%)
- No	3 (13.6%)	0 (0%)

There was no statistically significant difference between the two groups (p-value>0.05) among baseline variables based on the results of the independent t-test and Mann-Whitney test. Also, univariate analysis of measured variables after single therapy and combination therapy showed no significant difference between the two groups (p-value>0.05) (Table 2).

Table 2: Univaraite analysis of measured variables in two treatment groups

Variables	**Metformin (n=22)**	**Rosiglitazone (n=22)**	**p-value**
	Mean± SD / Median		
Waist at baseline	96.23±6.49	96.73±6	0.792*
Waist after the single therapy	95.32±6.01	95.09±5.47	0.896*
Waist after combination therapy	94.59±6.52	94.18±5.36	0.821*
HDL at baseline	43.68±6.64	43.82±6.81	0.947*
HDL after the single therapy	42.91±6.93	43.27±7.26	0.866*
HDL after combination therapy	42.54±6.90	42.64±7.56	0.967*
TG at baseline	199.86±56.59	199.81±56.56	0.998*
TG after the single therapy	187.91±57.36	187.45±56.97	0.979*
TG after combination therapy	192±58.42	186.91±56.93	0.771*
Hirsutism at baseline	11.82±2.54	11.77±2.86	0.956*
Hirsutism after monotherapy	10.36±1.89	9.63±2.06	0.229*
Hirsutism after combination therapy	10.27±1.98	9.23±1.85	0.078*
FBS at baseline	91±14.55	91.32±14.19	0.942*
FBS after the single therapy	80.5±10.94	81.5±10.86	0.762*
FBS after combination therapy	80.14±11.33	81.45±9.93	0.684*
Testosterone at baseline	61	61.5	0.991**
Testosterone after the single therapy	60.32±18.5	56.04±18.6	0.449*
Testosterone after combination therapy	60.27±18.52	55.59±18.43	0.405*
Ovary size at baseline	23.5	23	0.869**
Ovary size after the single therapy	21.5±5.53	24.73±8.37	0.139*
Ovary size combine	20	23.5	0.194**
BMI at baseline	29.87±4.28	29.82±4.36	0.968*
BMI after the single therapy	29.53±4.4	29.51±4.37	0.991*
BMI after combination therapy	29.47±4.49	29.64±4.28	0.9*

Number of follicles after the single therapy	22	22	0.544**
Number of follicles after combination therapy	22	22	0.76**
Follicle size after the single therapy	8	10	0.371**
Follicle size after combination therapy	8	10	1**

*Independent t-test (Mean± SD), **Mann-Whitney test (Median)

Repeated measure analysis showed that there was a significant difference between measurements of waist, TG, hirsutism, FBS, and testosterone in both treatment groups over thirty weeks (all p-values<0.05). However, the statistical difference was not seen in HDL and BMI neither in the metformin group (p-value=0.146 and 0.296 respectively) nor in the rosiglitazone group (p-value=0.333 and 0.184 respectively). Ovary size was statistically different in the metformin group in three measured times (p-value<0.001), however, it was not different in rosiglitazone (p-value=0.843)(Table 3). Also, the number of follicles (p-value= 1 and 0.564) and follicle size (p-value= 1 and 1) were not different in three phases of study in metformin and rosiglitazone groups according to Wilcoxon signed ranks test.

Table 3: Multivariate analysis of measured variables in two treatment groups.

Variables	**Metformin**	**Rosiglitazone**
	p-value	
Waist*	0.006	0.006
HDL*	0.146	0.333
TG*	0.002	<0.001
Hirsutism*	0.001	0.001
FBS*	<0.001	<0.001
Testosterone*	<0.001	<0.001
BMI*	0.296	0.184
Ovary size**	<0.001	0.843

*Repeated measure analysis, ** Friedman Test

Considering difference means of variables between baseline and single therapy and also between baseline and combination therapy, reduction of testosterone level after single therapy and combination therapy is significantly more (p-value=0.02 and 0.011) in rosiglitazone than metformin group. On the other hand, ovary size decreased more in the metformin group (p-value<0.001 and p-valu=0.001) after single therapy and combination therapy than rosiglitazone.(table 4)

Table 4: The difference means of variables between baseline and single therapy and between baseline and combination therapy.

	Difference 1*			**Difference 2****		
	Metformin	**Rosiglitazone**	**p-value**	**Metformin**	**Rosiglitazone**	**p-value**
Waist	-0.91±2.11	-1.64±1.99	0.247	-1.64±2.46	-2.54±3.95	0.366
HDL	-0.77±2.83	-0.54±4.36	0.839	-1.14±3.10	-1.18±4.49	0.969
TG	-11.95±8.34	-12.36±9.78	0.882	-7.86±16.22	-12.91±9.37	0.213
FBS	-10.50±6.15	-9.82±6.88	0.731	-10.86±5.82	-9.86±7.05	0.611
Testosteron	-6.63±3.92	-11.09±7.66	0.02	-6.68±4.54	-11.54±7.29	0.011
Ovary size	-3.86±2.31	-0.82±2.72	<0.001	-4±2.74	-1±3.05	0.001
Hirsutism	-1.45±2.02	-2.14±2.76	0.355	-1.54±1.94	-2.54±2.75	0.172

*Difference between baseline and single therapy

**Difference between baseline and combination therapy

Chi-square test showed no relationship between following variables and treatment groups at baseline, after single therapy and combination therapy: blood pressure (p-value=1), existence of PCOS (p-value=1), endometrial histology at baseline (p-value=o.791), endometrial histology after single therapy (p-value=0.807), endometrial histology after combination therapy (p-vaue=0.546), IR at baseleine (p-

value=0.116), IR after single therapy (p-value=0.122), and IR after combination therapy (p-value=0.757) (Table 5). Cochran test indicated that blood pressure did not change over thirty weeks in the metformin (p-value=0.368) and rosiglitazone (p-value= 0.368) treatment groups. However, insulin resistance changed during this time in the metformin (p-value=0.006) and rosiglitazone (p-value= 0.003) groups.

Table 5: Relationship between variables and treatment group

	Metformin	**Rosiglitazone**	**p-value**
BP at baseline			
- NO	17 (77.3%)	17 (77.3%)	1
- Yes	5 (22.7%)	5 (22.7%)	
BP after the single therapy			
- NO	17 (77.3%)	18 (81.8%)	1*
- Yes	5 (22.7%)	4 (18.2%)	
BP after the combination therapy			
- NO	18 (81.8%)	17 (77.3%)	
- Yes	4 (18.2%)	5 (22.7%)	1*
PCO at baseline			
- NO	4 (18.2%)	3 (13.6%)	
- Yes	18 (81.8%)	19 (86.4%)	1*
Histology at the baseline			
- secretory	3 (13.6%)	4 (18.2%)	0.791*
- Proliferative	17 (77.3%)	15 (68.2%)	
- hyperplasia	2 (9.1%)	3 (13.6%)	
Histology after the single therapy			
- secretory	6 (27.3%)	8 (36.4%)	0.807*
- Proliferative	15 (53.6%)	13 (59.1%)	
- hyperplasia	1 (4.5%)	1 (4.5%)	
Histology after the combination therapy			
- secretory	7 (31.8%)	8 (36.4%)	0.546
- Proliferative	15 (68.2%)	13 (59.1%)	
- hyperplasia	0 (0%)	1 (4.5%)	
IR at the baseline			0.116*
- No	3 (13.6%)	0 (0%)	
- Yes	19 (86.4%)	22 (100%)	
IR after the single therapy			0.122
- No	11 (10%)	6 (27.3%)	
- Yes	11 (50%)	16 (72.7%)	
IR after the combination therapy			0.757
- No	9 (40.9%)	8 (36.4%)	
- Yes	13 (59.1%)	14 (63.6%)	

Chi-square test, *Fisher exact test

Discussion

The results of this study showed that there was no significant difference between the metformin and rosiglitazone groups after single and combination therapy. Longitudinal analysis showed a significant change in the waist, TG, hirsutism, FBS, testosterone, and insulin resistance over thirty weeks in each of the metformin and rosiglitazone groups, but there was no statistical difference in HDL and BMI. Also, ovary size was changed significantly in the metformin group but not in the rosiglitazone group. The number and size of the follicle after single and combination therapy were not different in both treatment groups. Testosterone level after single therapy and combination

therapy in rosiglitazone reduced more significantly in comparison with the metformin group. On the other hand, ovary size decreased more in the metformin group after single therapy and combination therapy compared to rosiglitazone.

In a similar study by Baillargeon et al. (2004), the effects of metformin and rosiglitazone on ovulation and T levels were studied among nonobese women with PCOS. In this randomized controlled trial, 100 women were randomly assigned to one of these groups; metformin, rosiglitazone, the combination of two drugs and placebo and followed for 6 months. Results showed that frequencies of ovulation increased more in treatment groups than placebo. However, this increase was more in metformin and combination groups in comparison with rosiglitazone. Also, serum free-T levels were higher in the placebo group compared with treatment groups. Results of some other variables such as homeostatic model assessment of insulin sensitivity, insulin sensitivity index, fasting insulin levels, and the area under the insulin curve showed the benefit of metformin and combination groups over rosiglitazone and placebo groups.

Another study by Legero et al. (2007) compared the effects of metformin and rosiglitazone on the ovary and endometrium of PCOS women. Fifteen selected women were followed up for 6 weeks. Then, nine women were allocated to the rosiglitazone and six women to the metformin group. After three months of single therapy, they received three months of combination therapy. After three months of single therapy more improvement was seen in rosiglitazone than metformin according to the results of testosterone levels, 2-hour glucose, and 2-hour insulin. Ovulatory rates were improved on single and combined treatments in comparison with baseline measurements. So, rosiglitazone was more effective than metformin. Combination therapy did not show a significant advantage over single therapy.

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