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ORIGINAL ARTICLE

Combined pioglitazone–metformin and clomiphene citrate versus metformin and clomiphene citrate in induction of ovulation in women with clomiphene citrate-resistant polycystic ovary syndrome

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KEYWORDS

Pioglitazone;
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Abstract *Objective:* To compare the efficacy of pioglitazone + metformin and clomiphene citrate (CC) with metformin and CC in women with CC-resistant polycystic ovary syndrome (PCOS).
Design: Randomized clinical trial (RCT).
Setting: A university teaching hospital in Cairo, Egypt.
Patients: One hundred women with CC-resistant PCOS.
Methods: Fifty women received pioglitazone 15 mg + metformin 850 mg once daily from the first day of the cycle for 10 days, and 50 women received metformin (500 mg three times daily). Clomiphene citrate 100 mg from the third day of the cycle for 5 days was added to each group. Treatment was continued for three cycles.
Main outcome measure(s): Ovulation rate and pregnancy rate.
Results: Ovulation rate was significantly higher in the pioglitazone + metformin and CC group than the metformin and CC group (69.8% versus 48.8%) (*p*: 0.002). Significantly higher serum E_2 on day 12 and thicker endometrium were found in the pioglitazone + metformin and CC group in the three follow up cycles. Also, cummulative pregnancy rate was significantly higher in the pioglitazone + metformin and CC group than the metformin and CC group (58% versus 34%) (*P*: 0.027).

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Conclusion: The use of pioglitazone/metformin and CC is more effective than metformin and CC as regards ovulation and pregnancy rates in anovulatory women with CC-resistant PCOS.

1. Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrinopathy characterized by ovarian dysfunction, androgen excess and polycystic ovaries (1). It is a condition that occurs in approximately 5–10% of women of childbearing age (2).

The prevalence of insulin resistance in women with PCOS, as measured by impaired glucose tolerance, is substantially higher than expected compared with age- and weight-matched populations of women without PCOS (3).

The hyperinsulinemia reportedly contributes significantly to the development of ovarian hyperandrogenism and chronic anovulation commonly encountered in women with PCOS. In obese women with PCOS, weight loss usually leads to a decrease in insulin and androgen levels with a marked improved fertility outcome (4).

The first choice therapy used to induce ovulation is the use of anti-estrogens, among which the most frequently used is clomiphene citrate (CC) (5,6). The therapy results in the induction of dominant follicle growth and the appearance of ovulation in about 75–80% of patients (7), but 33–45% achieve pregnancy (8).

If CC does not result in ovulation, the American College of Obstetricians and Gynecologists recommends the use of the insulin sensitizer metformin and CC regardless of whether there is insulin resistance or not (9).

Insulin sensitizing agents including metformin (10,11), rosiglitazone (11–13) and pioglitazone (14) have been effective in improving fertility and ovulation in women with PCOS.

Metformin treatment has been persistently documented to improve menses cyclicity, anovulation and infertility in PCOS patients (15–17).

The most common complaint with metformin is the presence of gastrointestinal symptoms including diarrhea, nausea, vomiting and abdominal bloating. Lactic acidosis is a rare risk among patients taking this medication. This most commonly occurs in poorly controlled diabetes and impaired renal functions (18).

After troglitazone's removal from the market due to hepatotoxicity, two thiazolidinediones; rosiglitazone and pioglitazone are currently available (19).

Pioglitazone exerts multiple beneficial effects in PCOS women: metabolic, that is improved insulin sensitivity, increased HDL-C and reduced triglyceride levels, hormonal, that is, decreased insulin and free testosterone levels and increased SHBG concentrations, gynecological, that is, induced ovulation rate, improved fertility and hirsutism scores, and anti-inflammatory, that is, decreased hs-CRP and increased adiponectin levels (16,17,20,21).

The mechanism of action of pioglitazone and metformin is clearly different. Metformin lowers blood glucose levels independent of insulin secretion from pancreatic beta cells (22). Metformin promotes sugar use in the peripheral tissue, inhibits gluconeogenesis in the liver, and abrogates glucose absorption from the alimentary canal. In contrast, pioglitazone acts after insulin binding by insulin receptors to improve the action of insulin, reduces its resistance to hormones, and inhibits glucose production in the liver (23). Pioglitazone also improves the LH-to-FSH ratio and lowers androgen levels (24).

In this study, we aimed to compare the efficacy of pioglitazone + metformin and CC with metformin and CC in the induction of ovulation in women with CC-resistant PCOS.

2. Patients and methods

2.1. Subjects

This randomized clinical trial (RCT) included 100 women who were recruited from the Gynecologic outpatient's clinic of Kasr El Aini, Cairo University, Egypt.

The inclusion criteria for the study included women 20–40 years of age, with primary or secondary infertility and PCOS, with desire of becoming pregnant, with exclusion of other factors of infertility (documented normal semen analysis and patent tubes by hysterosalpingography), who failed to ovulate with a dose of CC of 150 mg/day for 5 days starting from day 3 of the menstrual cycle for three cycles.

The diagnosis of PCOS was made based on the revised Rotterdam criteria (25), according to which at least two of the following three features must be present: oligo-ovulation and/or anovulation, clinical and/or biochemical signs of hyperandrogenism including hirsutism, acne and/or increased testosterone levels, and polycystic ovaries at vaginal ultrasound; defined as those containing at least 12 follicles measuring 2–9 mm in diameter arranged peripherally around an echo-dense stroma and/or with increased ovarian volume of at least 10 ml.

Exclusion criteria were patients with type I or II diabetes mellitus, patients with abnormal liver or kidney functions, patients with hypertension, those with known heart disease and those with any urinary symptom (frequency, urgency or bloody micturition). Patients with persistent hyperprolactinemia or thyroid dysfunction, women who had gonadotropin induction or who had ovarian drilling before were also excluded. No diet restriction was recommended.

A written informed consent was obtained from each woman participating in the study. The study was a self-funded one. The study was approved by the research ethics committee of the Faculty of Medicine-Cairo University No.: 30-2012.

2.2. Study protocol

A detailed history was taken from all the study population with special concern about menstrual history.

Clinical examination was done for all women. Weight, height, body mass index (BMI), waist/hip ratio and systolic and diastolic blood pressure (SBP and DBP) were recorded.

On day 3 of the menstrual cycle [either spontaneous or induced by the intake of a 10 day course of norethisterone ace-

Table 1 Baseline criteria of the study population before treatment.

Variable	Pioglitazone + metformin and CC group	Metformin and CC group	*P* value
Age (years)	25.76 ± 361	26.88 ± 3.39	0.113
Duration of infertility	2.87 ± 1.64	3.38 ± 0.96	0.353
BMI (kg/m^2)	27.21 ± 2.83	27.44 ± 2.33	0.091
Waist/hip ratio	0.84 ± 0.023	0.85 ± 0.016	0.130
Menstrual pattern:			
Oigomenorrhea	41/50 (82%)	46/50 (92%)	0.234
Amenorrhea	9/50 (18%)	4/50 (8%)	0.234
Type of infertility:			
Primary	35/50 (70%)	33/50 (66%)	0.668
Secondary	15/50 (30%)	17/50 (34%)	0.668
SBP (mmHg)	104 ± 8.43	106 ± 8.37	0.167
DBP (mmHg)	69.6 ± 5.3	71.9 ± 5.6	0.087
Hirsutism	11/50 (22%)	7/50 (14%)	0.435
Acne	7/50 (14%)	2/50 (4%)	0.162
Ovarian volume (cm^3)	14.58 ± 1.42	14.17 ± 0.76	0.083
FSH (mIU/L)	5.71 ± 1.37	5.98 ± 1.01	0.269
LH (mIU/L)	9.26 ± 3.42	9.39 ± 1.2	0.807
E_2 (Pmol/dL)	47.76 ± 10.02	49.84 ± 7.31	0.239
Prolactin (ng/ml)	15.12 ± 5.42	14 ± 3.98	0.241
Total testosterone (nmol/L)	1.17 ± 0.27	1.24 ± 0.3	0.193
Free testosterone (pmol/dL)	3.93 ± 0.67	4.19 ± 0.52	0.121
TSH (mIU/L)	3.42 ± 0.61	3.3 ± 0.46	0.269
FT_4 (nmol/L)	13.78 ± 0.84	14.11 ± 1.37	0.152
Fasting plasma glucose	84.1 ± 12.2	83.76 ± 9.9	0.879

Table 2 Rate of ovulation in the two groups in three follow up cycles.

Cycle	Pioglitazone + metformin and CC group		Metformin and CC group		*P* value
	Number	%	Number	%	
Cycle (1)	31/50	62	19/50	38	0.001
Cycle (2)	24/33	72	22/42	52	0.006
Cycle (3)	19/23	82	22/37	59.4	0.002

tate (Stero nor, 5 mg tablets, Hi Pharm for manufactured pharmaceuticals, Cairo, Egypt) at 10 mg/day], a venous sample was collected in the morning after an over-night fast to measure: follicle stimulating hormone (FSH), luteinizing hormone (LH), thyroid stimulating hormone (TSH), free thyroxine (FT_4), total testosterone (T), free testosterone, fasting plasma glucose, liver enzymes (AST and ALT) and kidney functions (blood urea and serum creatinine). All hormones were measured by methods based on electrochemiluminescence immunoassay (ECLIA) in the hormones unit of the chemical pathology department (principal laboratory) of the Kasr El Aini Hospital.

Before initiation of the study, computer randomization was performed. One hundred sealed opaque envelopes were numbered from 1 to 100 with a code inside (A or B), where A indicated pioglitazone + metformin and CC treatment and B indicated metformin and CC treatment. The sealed envelopes were available to the clinic nurse who is not involved in the study. The sealed envelope in turn was then opened. Hence the study population was divided into two equal groups:

Group (A) {50 patients}: were given CC (Clomid, 50 mg tablets, Global Napi Pharmaceutical, under license of Sanofi Aventis, France) (100 mg daily from the third day of the cycle for 5 days) and pioglitazone + metformin (Bioglita plus, 15/850 mg coated tablets, The Arab Company of Gelatin and Pharmaceutical Products CAPS, Al Andalos medical company, Egypt) (containing pioglitazone 15 mg + metformin 850 mg to be taken once daily starting on the first day of the cycle for 10 days).

Group (B) {50 patients}: were given CC (Clomid, 50 mg tablets, Global Napi Pharmaceutical, under license of Sanofi Aventis, France) (100 mg daily from the third day of the cycle for 5 days) and metformin (Cidophage, 500 mg tablets, Chemical Industries Development CID, Giza, Egypt) (500 mg three times daily with meals starting from the first day of the cycle and continuous for three cycles, stopped when pregnancy is achieved).

Trans-vaginal ultrasound was done for all women starting from day 10 of the menstrual cycle and every 48 h until a dominant follicle (18–23 mm in diameter) is seen or till day 20 of the cycle. Serum E_2 was measured on day 12 of the cycle and serum progesterone was measured on day 21 of the cycle.

When ovulation was achieved (by serum progesterone $\geqslant$10 ng/ml or visualizing corpus luteum on vaginal ultra-

Table 3 Outcome of ovulation induction in both groups.

Variable	Cycle 1			Cycle 2			Cycle 3		
	Pioglitazone + metformin group	Metformin group	*P*	Pioglitazone + metformin group	Metformin group	*P*	Pioglitazone + metformin group	Metformin group	*P*
Number of follicles ⩾18 mm	1.18 ± 1.22	0.42 ± 0.57	0.000	0.9 ± 0.88	0.48 ± 0.54	0.008	1.47 ± 0.60	0.59 ± 0.62	0.000
Endometrial thickness (mm)	9.3 ± 2.53	7.56 ± 1.93	0.000	10.18 ± 1.86	8.06 ± 2.31	0.000	9.78 ± 1.8	8.45 ± 2.73	0.04
Serum E_2 (pmol/dL)	265.88 ± 237.96	130.26 ± 9.36	0.000	289.5 ± 137.31	140.34 ± 82.56	0.000	292.08 ± 147.04	155.75 ± 95.99	0.000
Serum P (ng/ml)	12.44 ± 10.3	5.69 ± 6.13	0.000	14.33 ± 7.38	6.61 ± 5.96	0.000	14.58 ± 7.54	7.17 ± 6.14	0.000

sound), pregnancy test in blood was done and metformin was stopped if pregnancy test showed positive.

Women with negative pregnancy test and those who failed to ovulate were asked to continue the treatment protocol. The treatment protocol was repeated for three cycles for both groups. No hCG injection was given and no Intrauterine Insemination (IUI) was performed.

Liver and kidney functions were measured pretreatment and repeated every month for the (pioglitazone + metformin) group. This group was planned to discontinue treatment if creatinine is elevated or AST or ALT is elevated even one fold over the upper limit of the normal at any time of the study.

The primary outcome of this study was the ovulation rate (percentage of ovulatory cycles in the whole follow up period). Secondary outcomes included the number of follicles ⩾18 mm, serum E_2 on day 12, endometrial thickness at the time of ovulation, pregnancy rate (clinical pregnancy was considered when an intrauterine gestational sac is seen) and the safety of pioglitazone as regards liver and kidney functions.

2.3. Statistical analysis

Statistic Package for Social Sciences (SPSS v 17.0 for Windows, Chicago, IL) software was used for data analysis. Statistical significance was assessed using the Student *t*-test and χ^2 test as appropriate data were log-transformed to correct for skewness prior to statistical analysis and values in the two groups were compared using the Mann–Whitney U test. Significance was interpreted as $p < 0.05$. All data were presented as mean ± SD.

3. Results

100 women were enrolled in the study, 50 of them were assigned to the pioglitazone + metformin and CC group, and 50 women were assigned to the metformin and CC group. All women were available for follow up and so were all included in the analysis.

No statistically significant differences were found in the base line clinical criteria between both groups of the study population (Table 1).

In the pioglitazone + metformin and CC group, the cumulative ovulation rate was 69.8% (74 out of 106 cycles) compared with 48.8% (63 out of 129 cycles) in the metformin and CC group, and this difference is statistically significant (*p*: 0.002).

Also, the pioglitazone + metformin and CC group showed significantly higher number of ovulatory women compared with the metformin and CC group cycle by cycle (Table 2).

The pioglitazone + metformin and CC group showed higher number of follicles ⩾18 mm, thicker endometrium, higher serum E_2 and higher serum progesterone in the three follow up cycles (Table 3).

A statistically significant difference (*p*: 0.027) was found in the cumulative pregnancy rate. Twenty-nine out of 50 (58%) women in the pioglitazone + metformin and CC group got pregnant (17 of them got pregnant in the first cycle, 10 in the second cycle and 2 in the third cycle), whereas 17 out of 50 (34%) women in the metformin and CC group became pregnant (eight of them in the first cycle, 5 in the second cycle and 4 in the third cycle).

Table 4 Liver enzymes and serum creatinine before and after treatment.

	Before treatment (mean ± SD)	After treatment (mean ± SD)	*P* value
AST (mg/dL)	20.45 ± 3.54	21.56 ± 6.37	0.090
ALT (mg/dL)	20.9 ± 3.55	22.31 ± 6.1	0.088
Creatinine (mg/dL)	0.76 ± 0.11	0.78 ± 0.15	0.079

Five cases of twin pregnancy occurred in the pioglitazone + metformin and CC group and three cases got twin pregnancy in the metformin and CC group. One case of triplet pregnancy occurred in the pioglitazone + metformin and CC group; she was delivered at 35 weeks due to premature rupture of membranes and gave birth to three healthy babies. Two cases of first trimester abortion occurred in each group, and the rest either have completed their pregnancies with successful live births or were still pregnant completing their antenatal care program.

Concerning the safety of pioglitazone, liver enzymes (AST and ALT) and serum creatinine were observed before and after use of the drug in the pioglitazone + metformin and CC group. The mean level of serum AST, ALT and creatinine increased very slightly after three cycles of use and this increase was statistically non significant (Table 4).

The most common side effects reported in both groups were the gastrointestinal symptoms (nausea, abdominal bloating and diarrhea) but they were mild and tolerated without the need to discontinue the drugs.

4. Discussion

Clomiphene is an ovulation induction agent that has been used and studied in patients with and without PCOS (26–31).

Although the results of many clinical trials provide different results, the compiled analysis of them indicates that long term metformin administration is associated with at least 30% improvement in ovulation frequency in comparison with the placebo (6).

There are contradictions in the literature regarding whether metformin, clomiphene or a combination of the two agents is superior for improving pregnancy rates in women with PCOS. A 2003 Cochrane review suggested that metformin should be a first line treatment for infertility in women with PCOS (32). However, a large randomized trial of more than 600 women found that clomiphene is superior to metformin in achieving live birth in infertile women with PCOS (33).

In a meta-analysis done by Tang and colleagues in 2012, where 38 trials (3495 women) using metformin were included in the analysis, there was no evidence that metformin improved live birth rates, whether it was used alone (pooled OR 1.80, 95% CI 0.52–6.16, 3 trials, 115 women) or in combination with clomiphene (pooled OR 1.16, 95% CI 0.85–1.56, 7 trials, 907 women). However, clinical pregnancy rates were improved for metformin versus placebo (pooled OR 2.31, 95% CI 1.52–3.51, 8 trials, 707 women) and for metformin and clomiphene versus clomiphene alone (pooled OR 1.51, 95% CI 1.17–1.96, 11 trials, 1208 women) (34).

Pioglitazone was much less studied in patients with PCOS than metformin. Most of the studies done on pioglitazone have studied its effects on metabolic and hormonal profiles. In one elegant trial, both pioglitazone and rosiglitazone improved insulin sensitivity, decreased free testosterone level and restored normal menses (35).

Pioglitazone administered to PCOS patients not optimally treated with metformin (2.55 g/day) plus a low caloric diet has been found to normalize menses and PCOS-induced changes in metabolic and hormonal profiles. It increased HDL and SHBG level and reduced DHEA-S, insulin and glucose concentrations (36).

A study done in 2005 showed the efficacy of pioglitazone compared with that of metformin in obese, insulin resistant PCOS women, the authors reported pioglitazone being as effective as metformin in ameliorating insulin resistance, hyperandrogenemia, anovulation and hirsutism. Weight, BMI and waist/hip ratio increased only in pioglitazone-treated patients (37).

In the present study, we intended to compare metformin and CC to pioglitazone + metformin and CC as regards the rate of ovulation and pregnancy rates and not to declare their effects on metabolic and hormonal status.

Our results showed that the pioglitazone + metformin and CC group showed a significantly higher ovulation rate than the metformin and CC group (69.8% versus 48.8%).

The statistically significant higher ovulation rate, higher number of follicles $\geqslant$ 18 mm, thicker endometrium, higher serum E_2 on day 12 and serum progesterone on day 21 in the pioglitazone + metformin and CC group compared to the metformin and CC group suggest that pioglitazone + metformin and CC may be the favorable therapeutic modality for women with CC resistant PCOS who desire fertility.

According to Brettenthaler et al. in 2004, with the use of pioglitazone, the rate of induction of ovulation was increased from 5.6% to 41.2% compared with the placebo group (14).

Glueck et al. in 2003 previously documented that, when pioglitazone was added to metformin in non-responsive PCOS patients, improved insulin sensitivity, reduced androgen levels and induced ovulation were observed (38).

In the present study, a significantly higher pregnancy rate occurred in the pioglitazone + metformin and CC group (58%) as compared to the metformin and CC group (34%).

Of the 29 women who achieved pregnancy in the pioglitazone + metformin and CC group, 17 women (58.6%) conceived in the first cycle. this is in agreement with what has been reported by Hirotaka et al. in 2008 who reported that seven out of nine patients (77.7%) succeeded in pregnancy in an average of 11.1 weeks of initiation of pioglitazone, and that four of those seven pregnant women (57%) conceived in the first cycle (39).

In the present study, assessment of the liver enzymes (AST,ALT) and serum creatinine before and after 3 months of treatment in the pioglitazone + metformin and CC group revealed non-significant changes in the liver and kidney functions which confirm safety of the use of this drug. This keeps in line with Charles et al. in 2003 who reported that none of

the women in their study developed abnormal liver function tests while taking pioglitazone + metformin (38).

In conclusion, it appears that in women with CC-resistant PCOS, treatment with insulin sensitizers' pioglitazone or metformin is promising; however, the outcome is much better with the former as indicated by the results of this study.

Conflict of interest

None.

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