Original Article

Is the Co-Administration of Metformin and Clomiphene Superior to Induce Ovulation in Infertile Patients With Poly Cystic Ovary Syndrome and Confirmed Insulin-Resistance: A Double Blind Randomized Clinical Trial

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Abstract

Objective: This study aimed to compare the effects of clomiphene citrate (CC) combined with metformin or placebo on infertile patients with poly cystic ovary syndrome (PCOS) and insulin resistance (IR).

Materials and methods: We included 151 infertile women with PCOS and IR in a university hospital from November 2015 to April 2022 in this prospective, double-blind, randomized, placebo-controlled trial. Patients were randomized into two groups; group A: received CC plus metformin (n = 76) and group B: received CC plus placebo (n = 75). The ovulation rate was the main outcome measure. Clinical pregnancy, ongoing pregnancy, live birth and abortion rates were secondary outcome measures.

Results: There was no remarkable difference in ovulation rate in two groups. Moreover, no significant changes were observed in clinical pregnancy, ongoing pregnancy, live birth and abortion rates between two groups. A larger proportion of women in group A suffered from side effects of metformin (9.3% versus 1.4%; p=0.064), although this was not significant.

Conclusion: In IR infertile women with PCOS, metformin pre-treatment did not increase the ovulation, clinical pregnancy and live birth rates in patients on clomiphene citrate.

Keywords: Clomiphene Citrate; Infertility; Insulin Resistance; Metformin; Poly Cystic Ovary Syndrome

Introduction

The most frequent reason for anovulation in female infertility is polycystic ovary syndrome (PCOS). It influences 12–21% of women at reproductive age (1).The most important features of this syndrome include chronic anovulation, hyperandrogenism, and sometimes obesity (2). Clomiphene citrate (CC) is still a widely chosen primary infertility treatment in women with the polycystic ovary syndrome (3). Nevertheless, 20-25% of PCOS women are

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unsuccessful in ovulating and fail to respond because of resistance to CC (4). Hyperinsulinemia and insulin resistance (IR) as main indicators in the pathophysiology of PCOS have been proved to have an impact on ovarian hyperandrogenism and may directly affect and even prohibit ovulation (5). Levels of luteinizing hormone, insulin and also ovarian androgens can be reduced by metformin, as an insulin sensitizing agent (6). Thus, several studies have been conducted and assessed the probable useful effect of only metformin or together with clomiphene, as primary therapy for infertile women with PCOS. But they have showed varying outcomes (7-11). Later in 2017 a meta-analysis made the conclusion that the ovulation rate in PCOS women could be enhanced by metformin alone as compared with placebo but it isn't recommended as first-line treatment for anovulation because oral ovulation induction factors like CC or letrozole alone result in far better rates of ovulation, pregnancy, and live-birth in women with PCOS. They also showed that although metformin together with CC enhance ovulation and clinical pregnancy rates, they do not affect live-birth rate compared with CC alone in women with PCOS and CC–resistant PCOS women separately (12). In 2019 a cochrane review also showed similar outcomes to above meta-analysis and suggested a potential advantage in ovulation and pregnancy rates irrespective of BMI when using metformin compared with placebo. However, both of them recommended that more studies had to be performed to decide if metformin produced better results in particular women with different PCOS phenotypes for example: IR ,obese and varying races (13). IR can be reduced by metformin (14). Nevertheless, no single randomized clinical trial (RCT) has studied metformin in IR PCOS patients. Thus the present study aims to compare CC with co-administration of metformin and with CC with co-administration of placebo to induce ovulation in PCOS patients with infertility and IR.

Materials and methods

This randomized clinical trial (ClinicalTrials.gov: NCT02523898) was carried out from November 2015 to April 2022 at Amir-al-Momenin Hospital. A consultant informed all patients of the research and the probable side effects of the medicine and obtained informed consents signed by the patients. The Research Council and Ethical Committee of Semnan University of Medical Sciences (IR.SEMUMS.REC.1394.23) supervised and approved this trial.

The inclusion criteria consisted of IR PCOS women between 20-36 years old who had a period of infertility over 1 year and normal serum prolactin (PRL) and thyroid stimulating hormone (TSH; in case of hypothyrodisim, they entered the study after treatment). They had documented patent tubes by hystersalpingography, which was performed at least 6 months prior to entering this study, and they had also normal sperm analysis based on the World Health Organization (WHO 1992) criteria (15).

All the women had a homeostasis model assessment-insulin resistance (HOMA-IR) ≥2.3. The exclusion criteria were: diabetic women, using any medicine that could affect pituitary–gonadal action and carbohydrate metabolism for a minimum of 2 months prior to the study, women having hypertension or disturbed liver or renal function tests and women having a history of ovarian drilling. According to the Ferriman and Gallway scale hirsutism was defined if the score was ≥ 8 (16).

The diagnosis of PCOS was based on the fulfillment of at least two criteria from the three Rotterdam criteria (17). Hyperandrogenism was confirmed on the basis of hirsutism or an elevated testosterone level (18). Random block allocation method was used for randomization. The allocation order was concealed in sequentially numbered, sealed envelopes. A statistician from the Clinical Epidemiology Unit of Research Center prepared this process. A nurse who was unaware of the study opened the relevant envelope after the enrollment of a patient.

Sample Size: Considering the results of Moll et al. study (19), the sample size was measured 388, using the G*Power 3.1.9.2 package, which compares the two proportions, and takes the maximum error type 1 and 2 to be 5% and 20% respectively, on the condition that the two groups were equal and the trial was one sided. Unfortunately, due to COVID 19 pandemic and the social problems following it, we were unable to reach the estimated sample size. Eventually we could have only 151 patients in this study.

Study Design: Clinical examination was done on all women and the results were recorded. A nurse who was blinded to the admission number of the patients measured their weight, height and BMI. BMI was obtained by weight divided by height squared (kg/m2). Following an overnight fasting of 10 to 12 h, we obtained blood samples to determine insulin, FSH, LH, estradiol, total and free testosterone, androstenedione, DHEAS, PRL, TSH, the fasting

blood glucose (FBG), and 17OH progesterone on the 3rd day of a regular menses or progestin (medroxyprogesterone acetate, 5 mg per day for 10 days) induced withdrawal bleeding. We centrifuged and kept all blood samples at -20 °C for being assessed together. Enzyme-linked immunosorbent assay (ELISA, Wernecce, 3200) (Ideal, Tehran, Iran) was used for measuring serum levels of FSH, LH, estradiol, TSH and PRL. ELISA assay (Monobind, Inc, USA) was also used to measure Total T, FreeT, A, DHEAS and insulin. Enzymatic colorimetric method with Glucose Oxidase was used for measuring fasting plasma glucose (FPG). Insulin resistance was assessed by HOMA-IR method according to this formula: fasting insulin (mU/L) × fasting glucose (mmol/L)/ 22.5. We defined IR to have the value of HOMA-IR ≥2.3 as reported by Hosseinpanah et al. study on Iranian women (20). After we completed primary studies, we divided the patients into two groups. We gave metformin (Chemformin, Chemidarou. Tehran. Iran) at a dose of 500 mg three times a day for 8 weeks to group A. To reduce its side effects, the dose of metformin was elevated from one to three tablets a day for seven days. Group B patients received placebo (similar to metformin in shape from the same factory). We measured progesterone levels in all patients every other week and confirmed ovulation if its level was > 5 ng/ml (16 nmol per liter). In the event of pregnancy, we continued metformin for another 12 weeks. If patients failed to ovulate by the end of this period, we continued metformin and placebo and started 100 mg CC for 5 days from day 3 of their regular menses or progestin induced withdrawal bleeding. A single sonographist measured ovarian follicular size every other day from day 10 of the cycle by transvaginal sonography. In case of observing at least one follicle reaching ≥18 mm in diameter, we gave 5000 IU of HCG (Pregnyl; N.V. Organon, OSS, Netherlands) intramuscularly and advised timed intercourse (every other day for one week beginning after taking HCG). If we had no follicle ≥12mm by day 16 in CC cycle, we supposed the cycle to be anovulatory and stopped the monitoring.

We defined clinical pregnancy as the presence of one gestational sac detected by transvaginal sonography beginning one week following the missed period. We advised the patients to take part in other two similar cycles of therapy with 100 mg CC (group A and B), if they ovulated with CC but failed to get pregnant. If they did not ovulate with 100mg CC, we increased the dose to 150mg and used the same treatment method. Metformin in group A and placebo in group B were maintained during CC cycles.

Outcome Measures: The ovulation rate was prime outcome measure. Clinical pregnancy, ongoing pregnancy, live birth and abortion rates were secondary outcome measures.

Statistical Analysis: We used the SPSS software (Version 11.5.0, © SPSS Inc.) to enter and analyze all the data. We used mean, standard deviation (SD), count, percentage, median, and inter quartile ranges (Q1, Q3) to describe the data if appropriate. We also used Chi-square test (and Fisher exact test if necessary) for qualitative variables and T-test (or Mann-Whitney test if needed) for quantitative variables. In all tests $P<0.05$ was regarded significant.

Results

We decided 820 women with PCOS were eligible. We removed 669 women from the study. So we included 151 women in this study .76 subjects were put into group A (metformin +CC) and 75 subjects were put into group B (placebo + CC). After taking metformin or placebo, 10 women became pregnant (Figure 1). Finally, 144 women received CC. Baseline demographic and infertility histories were similar in both groups (Table 1). There were no remarkable differences in ovulation (P=0.304) and clinical pregnancy (P=0.79) rates between metformin and placebo. There were also no significant differences in ovulation (P=0.308) clinical pregnancy (P=0.957) ongoing pregnancy (P=0.920), live birth (P=0.687) and abortion rates (P=0.938) between the two groups (Table 2). There were 2 ectopic pregnancies (1 in group A and 1in group B). Both of them were treated with a single dose of methotrexate. There was one twin pregnancy in group B who delivered in 27 weeks of gestation. 7 patients complained of adverse effects of metformin (2 persons discontinued metformin, 5 persons decreased the dose of metformin from 1500 to 1000 mg or 500 mg). The most common side effects of metformin were respectively: nausea, tenesmus, diarrhea, dizziness and headache (Table 2).

Discussion

In our research, no significant differences were detected in ovulation rate, clinical and ongoing pregnancy rates and live birth rate between metformin versus placebo combined with CC as ovulation induction treatment in IR PCOS patients.

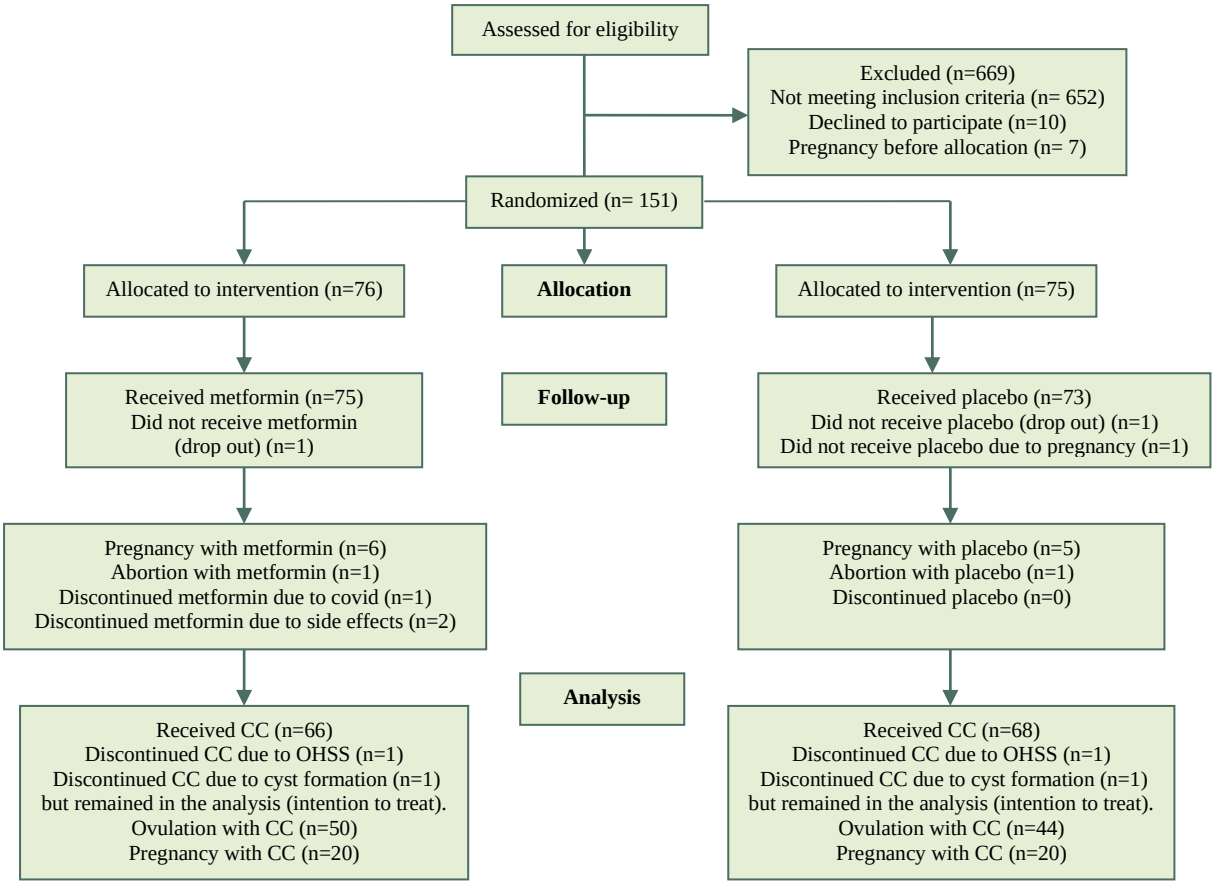

Figure 1: Flow diagram of randomization

More women in the metformin group showed adverse effects of metformin compared with placebo. Although this was not significant. Several studies are performed to decide whether to use only metformin or together with CC as primary therapy to induce ovulation in women with PCOS and a history of infertility. However, they all have shown contradictory outcomes. Some of them had a preference for metformin together with CC (10,11) and the others suggested metformin and CC were not a useful combination as the first treatment to induce ovulation in these women (7,9) and that CC should still be prescribed to this end (8,19).

Moll et al. in 2006 in a RCT on women with PCOS demonstrated no remarkable differences in either rate of ovulation (64% v 72%) or rate of ongoing pregnancy (40% v 46%) between CC combined with metformin and CC combined with placebo. In their study, a significantly bigger number of patients in the metformin group (16%v5%) stopped taking metformin due to its adverse effects (7). Later the same group in 2007 in a meta-analysis (19) concluded that CC alone and not CC combined with metformin should be recommended for these women because the side effects of metformin were more than placebo. Legro et al. in 2007 also in a RCT on infertile women with the PCOS showed that CC is more beneficial than metformin in leading to live birth (8). There are also several studies comparing the effectiveness of metformin with CC as ovulation induction agents according to body mass index (BMI) in women with anovulatory PCOS. However, their results were also contradictory (21-22). Nestler et al. in 1998 and Morin-Papunen et al. in 2012 in two separate studies showed that the ovulatory response to clomiphene can be improved with metformin in obese women with the PCOS (6, 22). In contrast, a meta-analysis by Johnson et al. in 2011 on women with PCOS and a BMI≤ 30–32 kg ⁄m2 did not demonstrate a significant change in pregnancy and live birth rates between metformin and clomiphene citrate (21). IR has a high rate of occurrence in CC-resistant and obese women. Metformin treatment may prove to be more beneficial for this subgroup (13). However, there were also some inconsistencies in using metformin in CC-resistant women (23, 24).

Table 1: Baseline clinical and hormonal characteristics of the patients in two groups

	Group A (n=75)	Group B (n=73)	P value
Age (years) (Mean ±SD)	27.1±4.1	26.6±3.9	0.437
BMI (Kg/m^2) (Mean ±SD)	28.6±4.4	28.6±5.2	0.994
Duration of infertility(years) (Mean ±SD)	2(1,3)	2.5(1.5,3,5)	0.069
Type of infertility n (%)			
Primary	54(72.0)	50(68.5)	0.641
Secondary	21(28.0)	23(31.5)	
Menstruation n (%)			
Regular	13(17.3)	21(28.8)	0.098
Irregular	62(82.7)	52(71.2)	
Hirsutism n (%)			
Yes	63(84.0)	62(84.9)	0.875
No	12(16.0)	11(15.1)	
Treatment for hypothyroidism			
Yes	30(40.0)	28(38.4)	0.838
No	45(60.0)	45(61.6)	
Right ovary volume (cm^3) (Mean ±SD)			
≥10cc	52(69.3)	50(68.5)	0.912
<10cc	23(30.7)	23(31.5)	
Left ovary volume (cm^3) (Mean ±SD)			
≥10cc	48(64.0)	40(54.8)	0.254
<10cc	27(36.0)	33(45.2)	
Right PAFC (Mean ±SD)			
≥12	50(69.4)	48(67.6)	0.532
<12	22(30.6)	23(32.4)	
Left PAFC (Mean ±SD)			
≥12	45(62.5)	38(53.5)	0.839
<12	27(37.5)	33(46.5)	
FBS (mg/dl) (Median (Q1, Q3))	93.4±9.9	93.4±8.6	0.995
Insulin (µlU/mL) (Median (Q1, Q3))	16.1(11.4, 20.4)	15.8(12.1, 20.2)	0.939
HOMA-IR(Median (Q1, Q3))	3.2(2.6, 4.7)	3.3(2.8, 4.7)	0.468
Free Testosterone (pg/mL) (Median (Q1, Q3))	2.1(1.6, 2.5)	2.1(1.3, 2.4)	0.773
Total Testosterone (ng/mL) (Median (Q1, Q3))	7(.5, 1.8)	.8(.5,1.4)	0.801
FSH(mIU/mL) (Median (Q1, Q3))	5.1(4.0, 6.3)	5.4(4.0, 6.4)	0.444
LH(mIU/mL) (Median (Q1, Q3))	6.0(3.5, 9.1)	5.5(3.7, 8.0)	0.772
AMH(ng/mL) (Median (Q1, Q3))	6.3(3.5, 9)	5.7(3.9, 8.1)	0.717
TSH(mIU/mL) (Median (Q1, Q3))	2.7(1.7, 3.8)	2.4(1.7, 3.7)	0.966
DHEAS (µg/dL) (Median (Q1, Q3))	1.8(1.2, 2.4)	1.6(1.2, 2.5)	0.848
17-OHP (ng/mL) (Median (Q1, Q3))	1.0(.8, 1.5)	1.1(.8, 1.5)	0.473
Estradiol(pg/mL) (Median (Q1, Q3))	61.53±24.51	61.49±26.75	0.992

PAFC: preantral follicular count, HOMA-IR: Homeostasis model assessment insulin resistance, BMI: body mass index

Finally in 2017 Practice Committee of the American Society for Reproductive Medicine and a high quality Cochrane review in 2019 showed that metformin together with CC may improve ovulation and pregnancy rates versus only CC in PCOS women with CC–resistant but there wasn't enough data available to make sure if this would improve live birth rate in this group of women. Also, they suggested that a number of larger and sufficiently powered randomized trials are required in closely targeted populations of women with different PCOS phenotypes to decide for which group the use of metformin may be more beneficial (12,13).

These challenging outcomes from the previous studies may be because of the big differences in populations under study, especially as regards body weight and insulin sensitivity. Insulin resistance is a metabolic disorder that is caused when insulin malfunctions in producing glucose uptake and utilization (25). There are only a few randomized studies on insulin sensitizing drugs in insulin resistant women with PCOS.

Table 2: Pregnancy outcomes in two groups

	Group A		Group B		P value
	n(%)		n(%)		
Progesterone serum level (ng/dl)*	0.95 (0.66, 1.30)		1.01 (0.75, 1.30)		0.574
Ovulation with met or placebo					0.304
No	67	89.3	61	83.6	
Yes	8	10.7	12	16.4	
Pregnancy with met or placebo					0.790
No	69	92.0	68	93.2	
Yes	6	8.0	5	6.8	
Ovulation with clomiphene					0.162
No	16	24.2	24	35.3	
Yes	50	75.8	44	64.7	
Pregnancy with clomiphene					0.910
No	46	69.7	48	70.6	
Yes	20	30.3	20	29.4	
Overall Ovulation					0.308
No	18	24.0	23	31.5	
Yes	57	76.0	50	68.5	
Overall Clinical Pregnancy					0.957
No	49	65.3	48	65.8	
Yes	26	34.7	25	34.2	
Overall Ongoing pregnancy					0.920
No	55	73.3	53	72.6	
Yes	20	26.7	20	27.4	
Overall Live birth					0.687
No	6	23.1	7	28.0	
Yes	20	76.9	18	72.0	
Abortion					0.938
No	20	76.9	19	76.0	
Yes	6	23.1	6	24.0	
Side-effects					
No	68	90.7	72	98.6	0.063
Yes	7	9.3	1	1.4	
Drug cessation					0.497
No	73	97.3	73	100	
Yes	2	2.7	0	0	

*Median (Q1, Q3)

Hasegawa et al. in a clinical study without a control group on 13 women with PCOS and IR, demonstrated that the administration of troglitazone for 12 weeks before CC decreased hyperinsulinemia and hyperandrogeism and improved ovulation rate. But no pregnancies occurred in their study (26). Sahin et al. also in 2003 in a RCT on 21 infertile PCOS women, 13 of whom were IR, demonstrated that metformin did not remarkably improve the ovulation and pregnancy rates in combination with CC compared with CC alone in spite of a reduction in hyperinsulinemia and hyperandrogenemia (9). Liu et al. in 2006 studied 146 women with PCOS (one third of whom had IR) and showed that after the treatment with metformin, the rates of ovulation and pregnancy were identical in women having a normal or abnormal glucose to insulin proportions (27). We could not show any beneficial effect of metformin as ovulation induction factor in the treatment of overweight IR PCOS women with infertility. This may be due to several factors. 1- The number of patients was smaller than the estimated sample size and as a result, there were some limitations. However, to our best knowledge this is the first double blind RCT in this field. 2- Considering the high BMI in our study the dose of metformin may

have been low. Recently Morgante et al. in a prospective non-randomized cohort study of 108 overweight and obese insulin resistant, PCOS women demonstrated that there was a close connection between metformin dose, BMI and hyperandrogenism suggesting that the higher BMI index is, the higher the dose of metformin should be to achieve an effective reduction IR in these patients (28). 3- Some studies have shown that metformin reduces IR (6,9) but this does not always happen. Acbay and Gundogdu in a single blind study on 16 women with PCOS and IR showed that metformin does not reduce IR. They suggested that the cause of insulin resistance in PCOS differs from other frequent insulin-resistant conditions like obesity and noninsulin-dependent diabetes mellitus (29). Of course we did not measure HOMA-IR after using metformin and did not know if it decreased after taking metformin or not.

Conclusion

In insulin-resistant infertile women with PCOS, metformin pre-treatment and co-administration with CC did not increase the ovulation, clinical and live birth rates versus CC and placebo. Further studies in larger sample sizes with high power are needed in order to determine if there are clinical, biological, or laboratory indicators that can help identify the best treatment choice for IR women with PCOS.

Conflict of Interests

Authors declare no conflict of interests.

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