The Scientific Journal of Medical Scholar

SJMS

Volume 1, Issue 6 , November 2022

https://realpub.org/index.php/sjms

Online ISSN: 2833-3772

The Scientific Journal of Medical Scholar

Available online at Journal Website
https://realpublishers.us/index.php/sjms/index
Subject (Obstetrics and Gynecology)

Original Article

Metformin plus Clomiphene Citrate versus Gonadotropins in Clomiphene Citrate- Resistant Polycystic Ovary Syndrome

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Article information

Received: August, 3rd, 2022

Accepted: November, 26th, 2022

DOI: 10.55675/sjms.v1i6.42

Citation: Midan MF, El Bassione WM, Hassan SM. Metformin plus Clomiphene Citrate versus Gonadotropins in Clomiphene Citrate- Resistant Polycystic Ovary Syndrome. SJMS **2022**; 1 (6): 159-164. DOI: 10.55675/sjms.v1i6.42

ABSTRACT

Background and Aim: Clomiphene citrate (CC) is the first-line pharmacological therapy for ovulation induction in polycystic ovary syndrome (PCOS). However, 15%-40% of patients show CC-resistance. Different drugs and drug combinations were in trial to overcome resistance. The Current work aimed to compare between the metformin plus CC and low dose exogenous follicle stimulating hormone (FSH) in CC-resistant PCOS.

Patients and Methods: A prospective comparative trial was carried out for a period of 36 months (between June 2019 to June 2022) with ovulation induction period of 3 months. It included 40 patients with CC- resistance. They were divided into 2 groups. The first received metformin plus CC and the second received low dose exogenous FSH for 3 months. The cycles were monitored by transvaginal sonography (TVS), starting on the 11th day of the cycle. The primary outcome was the successful ovulation, and the secondary outcome was the detection of pregnancy sac (clinical pregnancy).

Results: Metformin plus CC succeeded to produce a higher rate of ovulation. However, gonadotrophins are more effective as it produced a significantly higher rate in the first cycle (45.0% vs. 15%). However, there were no significant differences at the second and third cycles. The overall ovulation rate was 60% and 80.0% in metformin-CC group compared to gonadotrophin group. The clinical pregnancy rate was 25% and 15% in groups I and II, respectively (p value >0.05). Complications were confined to gonadotrophin group (multiple pregnancy and ovarian hyperstimulation syndrome (each in one patient).

Conclusion: Gonadotrophins are more effective than metformin plus CC in the management of CC-resistant PCOS. However, it was associated with lower clinical pregnancy rate and higher complications rate. But the difference was statistically non-significant.

Keywords: Gonadotrophins; Metformin; Clomiphene citrate; Polycystic ovary syndrome; Resistance.

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrinal disorder of reproductive aged women and the most common cause of anovulatory infertility [1]. It is a heterogeneous disorder that affects several body systems and leads to reproductive and metabolic complications [2,3]. It is the most common cause of anovulation and hyperandrogenism in young women [4]. PCOS is defined by two out of three criteria: 1) Menstrual irregularity (oligo-ovulation or anovulation), 2) Hyper-androgenism (clinical or biochemical) and 3) Polycystic ovarian morphology [5].

It is often accompanied by infertility, obesity, insulin resistance, and dyslipidemia [3]. Clomiphene citrate (CC) still the first-line pharmacological therapy for ovulation induction in PCOS patients. Clomiphene citrate is anti-estrogen that competes for estrogen receptors centrally, thereby releasing the hypo-thalamus and pituitary from the estrogenic negative feedback and increasing the discharge of follicle stimulating hormone, leading to follicular growth and maturation [6]. However, 15%-40% of PCOS patients show persistent anovulation following treatment with 150 mg of clomiphene/day for three successive attempts, and they are considered to have CC-resistance [7].

Insulin resistance not only underpins the PCOS etiology but also contributes to the occurrence of CC-resistance (CCR) [8].

The efficacy of metformin plus CC compared with other options such as gonadotrophins, as well as other insulin sensitizers+ clomiphene for treatment of CCR-PCOS patients have been tested in randomized controlled trials (RCTs). The trials have shown superiority of gonadotropin's [9,10].

Fixed dose, step up, step down and sequential use of CC and gonadotropins were the conventionally used gonadotropin regimens for induction of ovulation in PCOS. In all these regimens, a high gonadotropin starting doses (150 IU/day) have been associated with increased risk of multiple pregnancies and ovarian hyperstimulation syndrome [11]. Subsequent efforts have resulted in the development of low dose protocol, where a starting daily dose of 37.5 IU/day is incrementally increased. The low dose protocol has essentially replaced the original conventional protocols [12]. In a recent randomized trial, low dose, exogenous FSH has been suggested as the first line of treatment in PCOS [13].

The current study designed to compare between the metformin plus CC and low dose exogenous follicle stimulating hormone (FSH) in treatment of CC-resistant PCOS

PATIENTS AND METHODS

It was a prospective comparative randomized trial. It had been held at the Gynecology and Obstetrics Department, Al-Azhar University Hospital (New-Damietta) for a period of 36 months starting from June 2019 to June 2021 with ovulation induction period of 3 months. The study included 40 patients with CC-resistant PCOS. They were divided into two equal groups. The first (Group 1) received metformin plus CC for 3 months. The second (Group 2), received highly purified (HP) FSH for 3 months.

The inclusion criteria: to be included, the patient must have PCOS according to Rotterdam Criteria; there was a failure of ovulation with 150 mg of CC for 5 days in the early follicular phase for three consecutive cycles; the age ranged between 19 and 32 years; the body mass index (BMI) is lower than or equal to 35 kg/m^2; no other causes of infertility or previous gynecological operations.

The exclusion criteria: patient was excluded if she was on a hormonal medication or systemic drugs, had systemic disease, or she had history of previous gynecological surgery.

Methods:

All patients are eligible for participation according to inclusion criteria. For each patient, medical history and clinical examinations were performed in a systematic pattern and the results were document. Then the laboratory testing of fasting blood glucose, insulin, fasting triglycerides, high density lipoprotein (HDL), free testosterone, and basal FSH and luteinizing hormone (LH) levels were assayed. All patients were subjected to ovulation induction protocols as described afterwards. The stimulation protocols were metformin plus CC induction protocol versus gonadotropin induction protocol for 3 months. The doses were modified according to ovarian response. During that period, folliculometry was evaluated by regular visits in the 11th, 13th and 15th day of the cycle. When follicles reached a diameter of 18 mm and the endometrial thickness was > 9 mm visible in transvaginal ultrasound, ovulation triggering was performed by the injection of human chorionic gonadotrophins (hCG) (5000 or 10000 IU) [14]. The follow up were also for any side effects related to the medication. Cases who developed any complications were excluded. Primary outcome measure was ovulation rate. Secondary outcome measures were clinical pregnancy rate per woman randomized (CPR), and complications of treatment.

Folliculometry was done with regular visits in 11, 13 and day 15 of the cycle to detect ovulation, which considered positive when follicles reached a diameter of 18 mm. Also, endometrial thickness was > 9mm visible in transvaginal ultrasound. Clinical pregnancy was defined by intrauterine gestational sac observed by an ultrasound scan 2 weeks after a positive pregnancy test in urine or blood [15].

The procedure:

In group (1), the CCR protocol was adapted from Hurst

et al. [16]. Starting from the 2nd day of the cycle, and for 5 days, patients received CC oral tablets (Clomid, 50 mg tablets Global Napy Pharmaceuticals, Egypt) at a dose of 50 mg on days 2–6, plus metformin tablets (Cidophage, Amon, Egypt) at the dose of 500 mg three times daily continuously for three cycles. The transvaginal sonography (TVS) and follicular tracking were done to document follicular growth and ovulation on days 10, 13, and 15 of the cycle, and if no dominant follicle was seen, the dose was increased to 100mg/day (50 mg incremental dose per cycle) after a spontaneous withdrawal bleeds to a maximum of 150 mg, and if still no dominant follicle was seen, the treatment was labeled a failure. In group (2), starting from the 3rd day of the cycle (spontaneous cycle), women received highly purified (HP) urinary FSH (uFSH) intramuscular (IM) injection of 37.5 IU/day HP uFSH (Fostimone, IBSA CH 6903 Lugano, Switzerland) to the 13th day of the cycle.

According to the classic low-dose FSH regimen described by Polson *et al.* [17], which uses a low starting dose of gonadotrophin. At the first follow-up; if the follicle diameter was medium sized (12–15 mm), the starting dose was maintained. The lowest dose that achieved significant follicular increase was maintained until hCG ovulation trigger. Subsequent visits were scheduled according to ovarian response until the leading follicle mean diameter reached ≥18 mm. At this time ovulation was triggered by injection of hCG 10000 IU (Choriomon, IBSA, Switzerland) and regular every other day sexual relations were advised. If 4 or more follicles were found to be getting >16 mm diameter, hCG injection was canceled [18]. Ovulation was documented by TVS, 7 days after ovulation triggering. The end points of the treatment cycle were either menstruation or clinical pregnancy. If there was absence of ovulation, the same dosage was continued for a maximum of three cycles.

Outcomes:

The primary outcome of this study was the ovulation rate after 3 cycles of treatment. Secondary outcomes included pregnancy rate and complications of the treatment as multiple pregnancy and ovarian hyperstimulation syndrome (OHSS).

Follow –up:

All study participants were followed up for a period of 3 cycles from the start of treatment. During each visit, the patients were evaluated clinically. Folliculo-metry was done with regular visits in 10, 13 and day 15 of the cycle. During folliculometry, ovarian size and endometrial sickness were measured. The clinical pregnancy was defined by intrauterine gestational sac detected on ultrasound scan 2 weeks after a positive pregnancy test in urine or blood [19].

Statistical analysis:

Statistical analysis was performed by the statistical package for social sciences (SPSS) computer software (version 16) (SPSS Inc., Chicago, USA). The quantitative data were presented by arithmetic mean and standard deviation, while categorical variables were represented by frequency and percentages. Independent samples "t" test and Chi Square were used to inspect association between groups and p value < 0.05 was considered significant.

RESULTS

A total of 40 patients were recruited and were divided equally into the two groups as described above. Both groups were followed up for three months regarding the ovulation outcome. The study flow chart describes the study stages from inclusion to outcome (figure 1). The women age ranged between 19 and 32 years and there was no significant difference between groups I and II respectively. In addition, there was no significant difference between groups I and II regarding women weight, height and body mass index (Table 1).

The oval size did not differ significantly between groups I and II at the first, second and third cycles. In addition, the largest diameter through the three cycles did not differ between both groups (Table 2).

In the first cycle, successful ovulation was significantly higher among group II than group I (45.0% vs 15.0%). However, in the second and third cycles, the successful ovulation did not significantly different between groups. In addition, the overall successful ovulation after the three cycles was did not significant between groups I and II (60.0% vs 80.0%, respectively) (Table 3).

The clinical pregnancy rate was reported among 25% and 15.0% in groups I and II, respectively, with no significant difference (Table 3).

Complications were reported among 2 cases in the group II (10.0%). One had multiple pregnancy and the second had ovarian hyperstimulation syndrome with no significant difference between groups (Table 3).

Table (1): Demographic data and base line characteristics:

Variable	Group I	Group II	Test	P
Age	24.60 ± 1.96	24.75± 2.80	0.19	0.84
Weight (kg)	70.10±4.61	67.85±4.48	1.56	0.13
Height (m)	1.6180±0.03458	1.6025±0.02693	1.58	0.12
BMI (kg/m^2)	26.74±0.92	26.39±1.05	1.13	0.26

Table (2): Comparison between study groups in the three cycles regarding ovum size

Ova size	Group I	Group II	Test	P
First cycle	13.95±2.50	15.45±3.57	1.53	0.13
Second cycle	15.23±2.75	16.09±2.54	0.82	0.42
Third cycle	16.08±2.64	16.71±3.45	0.45	0.65
The largest diameter	17.30±2.49	18.35±2.20	1.41	0.16

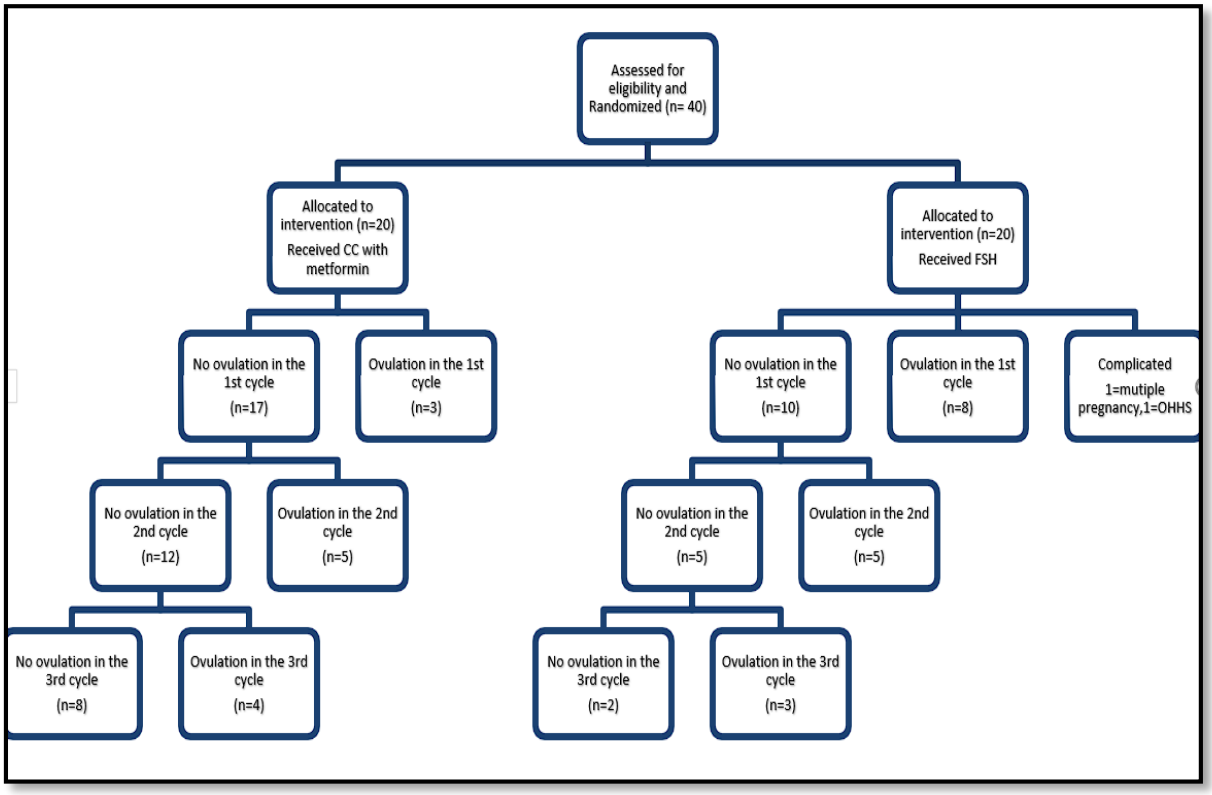

Figure (1): Flow chart

Table (3): Incidence of successful ovulation among study groups

		Group I	Group II	Total	Test	P
Successful ovulation	First cycle	3 (15.0%)	9(45.0%)	12(30.0%)	***4.28***	***0.038****
	Second cycle	5/17 (29.4%)	4/11 (36.4%)	9/28 (32.1%)	0.14	0.70
	Third cycle	4/12 (33.3%)	3/7(42.9%)	7/19(36.8%)	0.17	0.76
	Overall rate	12 (60.0%)	16 (80.0%)	28(70.0%)	1.90	0.17
Clinical pregnancy rate		5 (25.0%)	3 (15.0%)	8 (20.0%)	0.62	0.42
Complications	Multiple pregnancy	0 (0.0%)	1 (5.0%)	1 (2.5%)	1.02	0.31
	OHSS	0 (0.0%)	1 (5.0%)	1 (2.5%)	1.02	0.31
	Overall	0 (0.0%)	2 (10.0%)	2 (5.0%)	2.10	0.14

DISCUSSION

This study was designed to find out the efficacy of metformin plus CC for ovulation achievement versus low dose exogenous uFSH in woman with CC- resistant polycystic ovary syndrome.

Results showed that, the ovulation rate at the first cycle is significantly higher among the second group (uFSH) (45.0%) than the first group (CC plus metformin (15.0%). After the third cycle it reached 60% and 80.0% in the first and second groups, respectively. However, the clinical pregnancy rate was higher in the first than the second group (25.0% vs 15.0%, respectively). However, the difference was statistically non-significant.

The rationale for the use of metformin (insulin-sensitizing drug) in management of polycystic ovary syndrome is based on the insulin resistance associated with compensatory hyper-insulinemia with an increase in the production of androgens. It seems to lower circulating insulin levels and reduce hyperandrogenism, attempting to restore normal evaluation [20].

Furthermore, the combination of CC-metformin has been reported for CC-resistant PCOS [21,22]. Kocak *et al*. [23] reported that increased response to CC when combined with metformin may be gained by an intrinsic change of follicle steroidogenesis caused by the effect of metformin pretreatment. Attia et al. [24] reported that metformin improves the ovulation by the direct inhibition of androgen production in human ovarian thecal cells. la Marca *et al*. [25] reported that metformin led to a reduction in the adrenal steroidogenesis response to adrenocortico-trophic hormone in PCOS.

Another explanation to the increased ovulation with metformin is its central action on the pituitary gland with an LH reduction in the PCOS [26].

It was reported that, traditionally, ovulation induction with gonadotropins has been used as a second line treatment option for CC-resistant PCOS, however it is expensive and associated with an increased risk for OHSS and multiple pregnancy [27, 28].

Results of the current work are in line with Abu Hashim *et al*. [29] who reported that, combined metformin–CC therapy was not expected to be more effective than gonadotrophins in CC-resistant PCOS. However, it did result in ovulation and pregnancy rates that lower but not statistically significant than uFSH. Urinary FSH had good results, regarding ovulation from the first till the end of the third cycle and for overall ovulation rate. However, the low-dose, step-up regimen requires extensive monitoring and has high costs.

In conclusion, the present study showed that gonadotrophins (uFSH) are more effective in treatment of CC-resistant PCOS rather than CC-metformin combination. Ovulation rate markedly increased with gonadotrophin after the first cycle. However, two regimens were comparable at the second and third cycles. In addition, no statistically significant difference was found as regards pregnancy rate, and size of follicles in the end of first, second or third cycles.

One limitation of this study was the small sample size. However, we adhered to strict inclusion and exclusion criteria.

Another limitation is the shorter duration that other trials, which was inevitable due to higher dropout rate after the third cycle. This adds the third limitation by addressing the ovulation rate rather than live birth rate as a primary outcome. However, these limitations, although prevent generalization of results, did not reduce the value of the current work, as it is one of few studies comparing CC plus metformin to FSH.

Financial and non-financial activities and relationships of interest:

None

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The Scientific Journal of Medical Scholar

SJMS

Volume 1, Issue 6 , November 2022

https://realpub.org/index.php/sjms

Online ISSN: 2833-3772