Comparative Study between Combined Metformin - Clomiphene Citrate and Bilateral Laparoscopic Ovarian Drilling in Clomiphene Citrate Resistant Infertile Women with Polycystic Ovarian Syndrome. A randomized controlled trial

Mohammed Abd El-Razik Ramadan, Ahmed Walid Anwar Morad, Mohammed Ibrahim Mohammed and Aziza Negm

Department of Obstetrics & Gynecology, Benha Faculty of Medicine, Benha University, Egypt
Aziza.negm@fmed.bu.edu.eg azizanegm25@yahoo.com

Abstract: Aim: To compare the hormonal-metabolic profiles LH, FSH, Fasting Glucose, Fasting Insulin, Serum testosterone level and reproductive outcomes between women receiving metformin and clomiphene and those undergoing bilateral ovarian drilling in clomiphene citrate resistant women. **Methods:** The study included 160 infertile women diagnosed were randomized into two groups; group 1 (80 women) were subjected to Metformin850 mg twice daily and Clomiphene Citrate 100 mg daily for 5 days starting from the third day of spontaneous or induced menses. Group 2 included (80women) were subjected to bilateral laparoscopic ovarian drilling. **Results:** There were no significant differences between the 2 groups in the rates of ovulation (57.8 vs. 60.3% in groups 1 and 2, respectively with p value = 0.495) and pregnancy (13.7% 12.1% respectively; P =0.55). There was no significant difference in the first trimester miscarriage rate between both groups. This study showed that, PCOS patients benefit from metformin treatment with regard to hyperandrogenism. The current study showed a significant decrease in the levels of LH in drilling group. **Conclusions:** The current study showed that LOD and CC plus metformin seem to be two effective approaches to the treatment of patients with CC-resistant PCOS. In view of the invasiveness and cost of surgery, Metformin plus CC should be considered as the best second-line treatment to induce ovulation in patient with CC-resistant PCOS, LOD may still be considered a further valid strategy, specifically in the case of anovulatory patients.

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1. Introduction:

Polycystic ovary syndrome (PCOS) is a common disorder in women in their reproductive years and is characterized by androgen excess, ovulatory dysfunction, and polycystic ovarian morphology. It is also associated with several metabolic abnormalities, particularly insulin resistance and obesity, which play an important role in the pathophysiology of PCOS and, in particular, negatively influence ovarian function and fertility **(Pasquali. 2018).** Insulin sensitizers are a useful tool for the long-term management of reproductive outcomes of PCOS **(Conway et al., 2014).** Metformin use in PCOS women is also supported by its favorable effects on insulin resistance **(Moghetti et al., 2015).** Metformin plus CCco-administration improves fertility outcomes in infertile CC-resistant patients with PCOS with no other infertility factors **(Palomba et al., 2018).** CC has been the first line medical treatment for ovulation in PCOS patients for over 60 years **(Samara and Casper., 2018).** Laparoscopic ovarian drilling (LOD) is still a controversial decision; **(Seyam and Hefzy., 2018).** As a reflection, various oral ovulation induction agents have also evolved over time competing with LOD for treatment of CC resistant PCOS. As the pendulum swings for ovulatory agents prescribing for women with CC-resistant PCOS, we must ensure that LOD will not harm the patient by any iatrogenic complication such as pelvic adhesions or premature ovarian failure **(Hashim, 2018).**

2. Patients and Methods:

This randomized controlled study was conducted at Benha University Hospital and included 160 young infertile women with clomiphene citrate resistant polycystic ovary syndrome during the period from April 2014 to July 2017 to compare the hormonal-metabolic profiles LH, FSH, FG, FI, Serum testosterone level and reproductive outcomes between women receiving metformin and CC (Group 1) and those undergoing LOD (Group 2). Clomiphene Citrate- resistance is defined as failure to achieve adequate follicular maturation after 3 consecutive induction cycles with clomiphene citrate at 150

mg/day for 5 days **(Shapiro et al., 2017)**. PCOS was defined based on Rotterdam criteria. Patients were collected among those attending the infertility clinic. Women with other causes of infertility as male factor or tubal factor and other endocrine disorders as thyroid dysfunction and hyperprolactinemia were excluded.

The sample size was determined using the following equation:-**M= (Z^2*P*Q)/ (E^2).** Informed consent was obtained from each participant after explaining the study purpose and procedures to all enrolled women. Basal hormone assays had been be performed with Transvaginal ultrasound. After 6 months, all the previous investigations were repeated.

The participant women were randomized according to computer generated random numeric table. The random allocation sequence were concealed in sealed dark envelope

During the 6 months of treatment, the ovulation, pregnancy and abortion rates were evaluated in each woman.. Ovulation rate, Pregnancy rate and abortion rate were calculated.

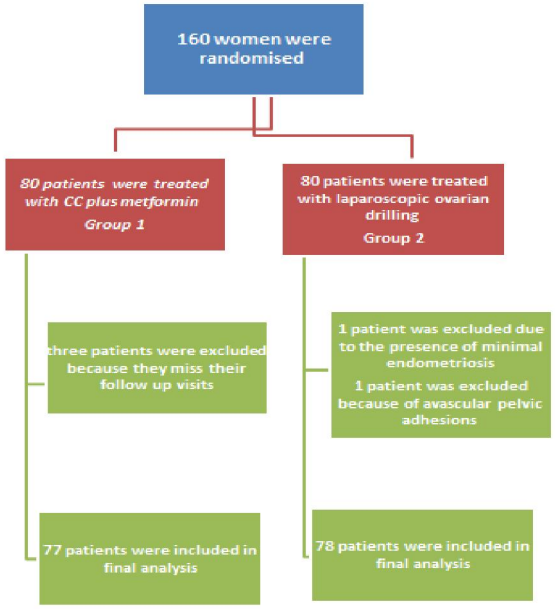

Fig. (1): shows the flow chart of the study.

3. Results:

The Statistics Package for Social Science (version 22; SPSS Inc) was used for all statistical analyses.

The analyzed data were collected and tabulated and the following results were obtained.

I. Baseline characteristics:

Table (1): Clinical, hormonal, and metabolic data of women in **group 1** and **group 2** at studyentry.

Groups / Variables	Group 1 Mean±SD	Group 2 Mean±SD	Test of significance	P-value
Age	25.9±2.5	26±2.3	Mann-Whitney U test U = 3.091	0.753
BMI	28.9±2.4	29.6±2.7	independent-samples t test t (153) = 1.86	0.061
Infertility Period	3.1±0.6	3.3±0.6	Mann-Whitney U test U= 3.27	0.338
Menstrual irregularity	62(80.5%)	65 (83.3%)	Chi square (χ^2) test χ2(1, N= 155) = 0.207	0.649
FSH	6.1±1	6.2±1.3	independent-samples t test t (153) = 0.552	0.634
LH	8.6±0.94	8.9±1.8	Mann-Whitney U test U = 3.55	0.199
Testosterone	1.6±0.5	1.7±0.5	independent-samples t test t (153) = 1.59	0.87
Fasting blood Glucose	84.9±3.9	83.7±4.5	Mann-Whitney U test U = 2.47	0.056
Fasting Insulin	13.4±1.3	13.2±3.3	independent-samples t test t (153) = 1.86	0.339

These data shows that there was no statistical significant difference between the 2 groups regarding baseline characteristics

II. Clinical outcome:

Table (2): Comparison between group 1 and group 2 according to the menstrual regularity before and after treatment.

	Before	After	test	P value
Group 1 (CC plus metformin)	**15/77(19.5%)**	**23/33 (69.7%)**	Chi square (χ^2) test χ2(1, N= 110) = 1.98	p ≤ 0.001*
Group 2 (LOD)	**13/78 (16.7%)**	**23/34(67.6%)**	Chi square (χ^2) test χ2(1, N= 112) = 2.8	p ≤ 0.001)*

Six months after treatment CC plus metformin group (Group 1) showed significant improvement of cycle regularity (p ≤ 0.001).

On the other side ovarian drilling group (Group 2) showed significant improvement of cycle regularity (p ≤0.001).

The proportion of women who achieved a regular menstrual cycle was higher in the CC plus metformin group when compared with the LOD group, but the difference using Chi square (χ^2) test was not statistically significant χ2(1, N= 67) = 0.033, (p = 0.86).

III. Reproductive outcome data:

Table (3): Reproductive outcomes in PCOS women treated with CC plus metformin (group 1) or LOD (group 2)

Reproductive outcomes	Group 1	Group 2	TEST	P value
Ovulation rate (no. ovulating cycles / no. cycles).	186/322 (57.8 %)	219/363 (60.3%)	Chi square (χ^2) test $\chi2(1, N= 685) = 0.465$	0.495
Pregnancy rate (no. pregnancies / no. cycles)	44/322 (13.7 %)	44/363 (12.1 %)	Chi square (χ^2) test $\chi2(1, N= 685) = 0.363$	0.55
Abortion rate (no. abortion / no. pregnancies)	6/44 (13.6 %)	8/44 (18.2%)	Chi square (χ^2) test $\chi2(1, N= 88) = 0.34$	0.56

There was no significant difference in ovulation, pregnancy and abortion rates between both groups (p = 0.49, 0.55 and 0.56 respectively).

Multiple pregnancies: None of the women had multiple pregnancies.

1- Biochemical outcomes:

Table (4): Hormonal and metabolic data of women with polycystic ovary Syndrome treatedwith group 1.

Hormonal and metabolic profile [mean ± (SD)]	Before	After	TEST	P value
FSH	6.6±1.8	6.6±1.9	ANOVA with repeated measure F (1,65) = 0.24	0.97
LH	8.8±1	7.6±1.3	ANOVA with repeated measure F (1,65) = 47.13	≤0.001*
Testosterone	1.9±0.3	1.6±0.3	ANOVA with repeated measure F (1,65) = 32.67	≤0.001*
FG	85±4	84.2±8.6	ANOVA with repeated measure F (1,65) = 0.24	0.59
FI	13.7±1.2	12.3±1.5	ANOVA with repeated measure F (1,65) = 1.144	≤0.001*

There was significant decrease in LH level ($p \leq 0.001$), testosterone level ($p \leq 0.001$) and FI ($p \leq 0.001$), while other hormonal and metabolic levels showed no significant changes by using Mixed ANOVA followed by Bonferroni's test for multiple comparison.

Table (5): Hormonal, and metabolic data of women with polycystic ovary Syndrome treated with group 2

Hormonal and metabolic profile [mean ± (SD)]	Before	After	TEST	P value
FSH xc	6.5±1.17	6.4±1.5	ANOVA with repeated measure F (1,65) = 0.24	0.46
LH	8.5±1.4	8.4±1.25	ANOVA with repeated measure F (1,65) = 47.13	≤0.001*
Testosterone	1.8±0.45	1.5±0.6	ANOVA with repeated measure F (1,65) = 32.67	0.002
FG	83.8±4.1	82.3±6.3	ANOVA with repeated measure F (1,65) = 1.144	0.34
FI	12.1±2.9	11.9±2.2	ANOVA with repeated measure F (1,65) = 0.24	0.58

There was significant decrease in LH level ($p \leq 0.001$) and testosterone level (p 0.002), while other hormonal and metabolic levels showed no significant changes.

There was no statistical difference between the two groups before and after receiving the treatment both are equally effective regarding the hormonal and metabolic parameters measured by using Mixed ANOVA followed by Bonferroni's test for multiple comparisons.

4. Discussion:

There were no significant differences between the 2 groups in the rates of ovulation (57.8 vs. 60.3% in groups 1 and 2, respectively with p value = 0.495) and pregnancy (13.7% 12.1% respectively; P =0.55)

These results are consistent with**) Malkawi et al., 2003 (**who found no significant difference in the ovulation or pregnancy rates between patients who received metformin or LOD and disagree with **Palomba, 2004** who reported a higher pregnancy rate in the metformin group also disagree with**) Hamed et al., 2010, El Sharkwy., 2013 (**that reported Ovulation and pregnancy rates were better in the unilateral drilling group compared with metformin.

When ranked according to efficacy of ovulation induction, the systemic review found out that the clomiphene citrate in combination with metformin was the most efficacious followed by follicle-stimulating hormone, letrozole, metformin, clomiphene, tamoxifen, laparoscopic ovarian drilling, and placebo or no treatment in that order. This when ranked in percentage efficacy of effectiveness showed 90, 82, 80, 50, 46, 27, 22 and 3%, respectively **(Wang et al., 2017).**

In the present study there was no significant difference in the first trimester miscarriage rate between both groups. These results are consistent with those of **(Hamed et al. 2010)** in contrast to those of **) Palomba et al. 2004)** who reported significantly lower miscarriage rates with metformin compared with LOD also consistent with the results of a systematic review of 17 randomized controlled trials published up to June 2008 and subsequent meta-analysis evaluating the effect of pre-gestational metformin administration on the abortion risk in PCOS patients. Overall, metformin was found to have no effect on the abortion risk in PCOS patients when administered before pregnancy **(Palomba et al., 2009)**.

This study showed that, PCOS patients benefit from metformin treatment with regard to hyperandrogenism. Metformin possibly exerts this effect through increasing sex hormone binding globulins (SHBG), modulation of adrenal androgen production, or decreasing intra ovarian androgen production **(Pirwany and Tulandi, 2003)** Also a significant reduction in FI that could be explained by the metabolic actions of metformin were seen. It inhibits hepatic glucose output and improves the peripheral insulin sensitivity with an increase in glucose utilization by skeletal muscles **(Norman, 2004),** the decrease in testosterone and FI in addition to improved FG/FI ratio are consistent with those reported by **(Palombaet al., 2010)**. Also **(Trolle et al., 2007)** who studied the effect of metformin treatment on obese and non-obese women in a randomized, double-blind, placebo controlled cross-over trial concluded that metformin therapy significantly reduced testosterone and improved insulin resistance in obese women. Our findings are in contrast to **(Aruna et al., 2004)**. Who found no changes were noticed in the total testosterone and FI these different results can be attributed to criteria of their patient selection.

The current study showed a significant decrease in the levels of LH in drilling group that could be explained by the reduction of ovarian theca cell mass and consequently androgen production. Converting this androgen to an estrogen corrects disturbances of the ovarian–pituitary feedback, resulting in a decrease of luteinizing hormone pulse amplitude **(Farquhar, 2004)**.

5. Conclusion:

The current RCT showed that LOD and CC plus metformin seem to be two effective approaches to the treatment of patients with CC-resistant PCOS. Even if, wider trials to detect statistically significant differences between the 2 different strategies are recommended. In view of the invasiveness and cost of surgery, Metformin plus CC should be considered as the best second-line treatment to induce ovulation in patient with CC-resistant PCOS, LOD may still be considered a further valid strategy, specifically in the case of anovulatory patients.

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