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ORIGINAL ARTICLE

Effect of Oral Contraceptive Pills Pretreatment on Ovarian Response in Patient with Clomiphene Resistant

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ABSTRACT

Background: Clomiphene citrate (CC) is the first drug and the most available treatment for ovulation induction due to it is low cost, easy to administrate and with low side effect. It can induce ovulation in 75% of women. 27% of anovulatory female with normal FSH level who do not respond to CC considered to be CC resistant. Combined Oral contraceptive pills are used for anovulatory infertile women to improve reproductive outcome.

Aim of the study: To evaluate the effectiveness of pretreatment with combined oral contraceptive pills in clomiphene resistant cases regarding ovulation & pregnancy rate.

Subjects and methods: A randomized clinical trial was conducted on 32 subfertile women proved to be resistant to clomiphene citrate. They were divided in to two groups: Group A (Study group) included 16 females received continuous OCPs for 42 days and after withdrawal bleeding received clomiphene citrate 150 mg tablet orally started on day 2 to day 6 of menstrual cycle. Group B (control group) included 16 females not received treatment for two spontaneous cycles and then received clomiphene citrate 150 mg tablet orally started on day 2 to day 6 of menstrual cycle.

Results: There was significant difference between the both groups regarding dominant follicle production in favor of the OCPs group. There was highly statistically significant difference between both groups regarding endometrial thickness in the first stimulation cycle while there was no significant difference in the second and third stimulation cycle. The level of mid-luteal progesterone in study group was higher when compared to control group with no significant difference. There was highly significant difference between the both groups in all three cycles regarding ovulation rate and pregnancy rate with higher rate in study group than control group.

Conclusion: Pretreatment with OPCs pills results in excellent rates of ovulation and pregnancy in patients who were previously clomiphene resistant.

Keywords: Oral Contraceptive Pills, Ovarian Response, Clomiphene Resistant

INTRODUCTION

Infertility is the source of social and psychological distress for the couple and put pressure on the relationship [1]. Disorder of anovulation represent around 30% of infertility in the form of amenorrhea or oligoamenorrhoea, ovulation induction not treat all causes of anovulation and the cause of anovulation determinate whether induction of ovulation possible or not [2]. Clomiphene citrate (CC) is the first drug and the most available treatment for ovulation induction due to it is low cost, easy to administrated and with low side effect.it can induce ovulation in 75% of women [3]. Results after treatment with CC reveals an ovulation rate of 73% and pregnancy rate of 36%. 27% of anovulatory female with normal FSH level who do not respond to CC considered to be CC resistant [4]. The main factors involved in CC resistant are hyperandrogenemia, insulin resistant and obesity that makes the ovaries don't respond

to endogenous FSH after CC treatment [5]. Moreover, the genetic predisposition was suggested to have a rule in cc resistant [6]. Clomiphene can give beneficial effect when it was preceded by oral contraceptive pill [7]. Combined Oral contraceptive pills (COCPs) used for anovulatory infertile women to improve reproductive outcome; moreover, it can be used with GnRH antagonist to prevent a premature LH surge [8]. Hhypothalamic-pituitary- ovarian axis shutdown for to two-month with (cocp) then retreatment with cc seem like show to improve ovulation and pregnancy rate [9].

PATIENTS AND METHODS

Study design and settings: A randomized clinical trial was conducted at outpatient infertility clinic of obstetrics& gynecology of Zagazig university hospital and cytogenetic & endoscopy unit during the period from May to September 2018.

Sample size: Calculated through Open-EPI, according to the following collected data: the proportion of cumulative pregnancy in oral contraceptive and clomiphene citrate was 54% and in control group was 4% [٧], so the sample was 32 (16 in each group), the confidence interval is 95% and the power of test is 80%.

Inclusion criteria: Subfertile female aged between 18-35y, duration of infertility between 1 to 3 years, previous received c.c by dose 150 mg and ovulation didn't occur by follicular monitoring and serum progesterone, primary or secondary infertility, absence of tubal factor which detected by hysterosalpingiography or laproscopy, normal semen analysis, and BMI not more than 30.

Exclusion criteria: Uterine or adnexal pathology, medical diseases as D.M, hypertension, cardiovascular disease, endocrine disorder as hyperprolactinemia, hyperthyroidism, and PCOS patient (according to Rotterdam criteria 2003).

Sample technique: Simple random sampling was used. Patient were randomized into two groups using a computer-generated sequence and the randomization list was held in a secure box and the participant were assigned to their group using sequentially numbered opaque sealed envelopes that were opened at the start of the study; study group(A) and control group(B).

Data collection: **Complete history taking** included personal, menstruation, obstetric, medical, and surgical history to exclude systemic disorder and contraindication to use COCP. **General, abdominal and local examination**. **Basal Transvaginalsonography** on cycle D2-D3. **Laboratory Investigation** included basal FSH, LH, TSH, prolactin, Estradiol on day of triggering, mid luteal serum progesterone level on day 21 of the cycle, and Pregnancy test 2week after trigger.

Medication:

Group A (Study group): included 16 females received continous COCP (Ethinylestradiol 0.03mg/ Gestodene 0.075mg) Gynera* (BAYER scherin) for 42 days and received clomiphene citrate tecnovula* (technopharma) 150 mg tablet orally started on day 2 to day 6 of menstrual cycle.

Group B (control group): included 16 females not received treatment for two spontaneous cycles and then received clomiphene citrate tecnovula* (technopharma) 150 mg tablet orally started on day 2 to day 6 of menstrual cycle.

Monitoring of ovarian response: Folliculometry by transvaginal ultrasound (TVS) middison (x4), korea starting from day 8 of the menstrual cycle then every other day according to size of follicle, single injection of hCG (choriomon-IBSA) 10,000 IU/ IM) was given for triggering ovulation when at least one follicle $\geq$ 18 mm, measurement of endometrial thickness and estradiol level on the day of hCG administration, asking the patient for timed coitus within 36hrs from hCG injection for 4 days every other day, mid luteal serum progesterone level measured on day 21 of the cycle, ultrasound follow up for confirmation of ovulation by one of this 4 criteria : presence of corpus Luteum , echogenic cyst , absence or decreased size of preovulatoy follicle or presence of fluid in douglas pouch or pelvis, serum β-hCG was measured 2weeks later to diagnose clinical pregnancy then (TVS) will done 2weeks later to confirm fetal heart beats. Those women

who ovulate and get pregnant in 1st cycle followed up to 8weeks and those who ovulate but not get pregnant and not ovulated entered the 2nd cycle with same dose of CC 150mg starting on day2 to day6 of menstrual cycle with folliculometry by transvaginal ultrasound starting on day 8 then every other day till at least one follicle ≥ 18 mm then contines the same management. Those women who ovulate and get pregnant in 2nd cycle followed up to 8 weeks and the remaining ovulate not get pregnant and not ovulate entered the 3rd cycle with same dose of CC 150mg starting on day2 to day6 of menstrual cycle then contines the same management. Finally observe the women who get pregnant in the first, second, third cycle to estimate the ovulation and clinical pregnancy rate for getting any significant difference between the groups.

Data management: Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 22.0) **(**Statistical Package for the Social Sciences) software for analysis [10]. According to the type of data qualitative represent as number and percentage, quantitative continues group represent by mean ± SD , the following tests were used to test differences for significance; difference and association of qualitative variable by Chi square test (X^2) . Differences between quantitative independent groups by t test, paired by paired t. P value were set at < 0.05 for significant results & < 0.001 for high significant result.

Ethical Considerations:

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 [11]. Institutional Review Board (IRB) of the Faculty of Medicine, Zagazig University approved the study protocol (No.). An informed consent was obtained from all participants of this study and they were told about the aim of the study, and were informed that the data would be used for scientific purposes only.

RESULTS

Results of this study showed that the mean age of studied patients in study group was 32.25±3.0 and in control group was 33.18±3.44, without statistically significant difference between both groups **(Figure 1)**. More than 60% percent of patients in both groups had 1ry infertility **(Figure 2)**.

Table (1): Showed that the number of dominant follicles was 8 (80%), while in control group there were 5 dominant follicles (33.3%), there was a significant difference between the two groups regarding dominant follicle production (p = 0.00) in favor of the OCPs group. The endometrial thickness in the first stimulation cycle was about 9.43±0. 31 mm in study group and7.48±0.89 mm in control group. There was highly statistically significant difference between the study and control group regarding endometrial thickness, while there was no significant difference in the second and third stimulation cycle regarding endometrial thickness (p > 0.05).

Table (2): Showed that the level of **mid-luteal progesterone** level in study group was higher with a mean of 22.93±5.24 when compared to control group with a mean of 19.81±6.2, with no significant difference between both groups.

There were differences in three cycles regarding ovulation and pregnancy rate as well as abortion rate between both groups. However, the difference was statistically significant regarding pregnancy rate in 2nd cycle and abortion rate in 1st cycle **(Table 3)**.

The result of this study noticed that**,** there was a highly significant difference between the study and control groups in all three cycles regarding ovulation rate with higher rate in study group than control group to be 15/39 (38.4%), 7/46 (15.2%) respectively and there was a significant difference between the two groups regarding pregnancy (p = 0.0004) in all three cycles. in the study group there were 7 (43.8%) pregnant patients, while in the control group, there were 1(6.2%) pregnant patient in all three cycles **(Table 4)**.

Table (1): Comparison between Stimulating characters among three cycles:

		Study group	Control group	X2/T	P
1st cycle	No. of DF ≥18mm	6(37.5%)	2(12.5%)	2.28	0.24
	IMF(12-14mm)	3(18.8%)	2(12.5%)	0.23	0.62
	Endometrial thickness(mm)	9.43±0.31	7.48±0.89	8.247	0.00*
2ndcycle	No. of DF ≥18mm	5(38.5%)	3(20%)	1.19	0.54
	IMF(12-14mm)	2(15.4%)	0(0.0%)	0.72	0.41
	Endometrial thickness(m)	9.37±0.37	9.14±0.86	0.917	0.367
3rd cycle	No. of DF ≥18mm	8(80%)	5(33.3%)	10.24	0.00*
	IMF(12-14mm)	4(40%)	5(33.3%)	0.11	0.73
	Endometrial thickness(mm)	9.57±0.34	9.18±0.72	1.584	0.127

Table (2): Comparison between Biochemical markers in all three cycle:

		Study group	Control group	T	P
1st cycle	Estradiol on day of trigger(pg/ml)	45.28±18.2	57.15±9.34	-1.977	0.057
	Mid-luteal Progesterone(ng/ml)	22.93±5.24	19.81±6.2	1.538	0.135
2nd cycle	Estradiol on day of trigger(pg/ml)	50.82±18.5	55.9±8.15	-0.883	0.386
	Mid-luteal Progesterone (ng/ml)	21.07±4.21	19.6±4.9	0.844	0.406
3rd cycle	Estradiol on day of trigger (pg/ml)	59.6±15.45	56.2±7.83	0.728	0.474
	Mid-luteal Progesterone(ng/ml)	22.5±2.5	22.07±2.57	0.416	0.681

Table (3): Outcome measures / patient in both groups in all three cycle:

		Study	Control	P
Ovulation rate	1st cycle	6/16 37.5%	2/16 12.5%	0.12
	2nd cycle	5/13 38.5%	3/15 20.0%	0.28
	3rd cycle	4/10 40.0%	2/15 13.3%	0.12
Pregnancy rate	1st cycle	3/16 18.8%	1/16 6.2%	0.28
	2nd cycle	3/13 23.1%	0/15 0.0%	0.049*
	3rd cycle	1/10 10.0%	0/15 0.0%	0.21
Abortion rate	1st cycle	0/3 0.0%	1/1 100%	0.00**
	2nd cycle	1/13 7.7%	0/15 0.0%	0.27
	3rd cycle	0/10 0.0%	0/15 0.0%	1.0

Table (4):Outcome measures /cycle in both groups in all three cycle:

	Study	Control	P
Ovulation per /cycle	15/39 38.4%	7/46 15.2%	0.001**
Pregnancy per /cycle	7/39 17.9%	1/46 2.1%	0.0004**
Abortion per /cycle	1/39(2.5%)	1/46(2.1%)	0.49

Table (5):Accumulation pregnancy distribution between groups:

		Group		Total	X^2	P
		study group	Control group			
Accumulation pregnancy	-VE	9(56.2%)	15(93.8%)	24(75.0%)	6.0	0.014*
	+VE	7(43.8%)	1(6.2%)	8(25.0%)		
Total		16(100%)	16(100%)	32(100%)		

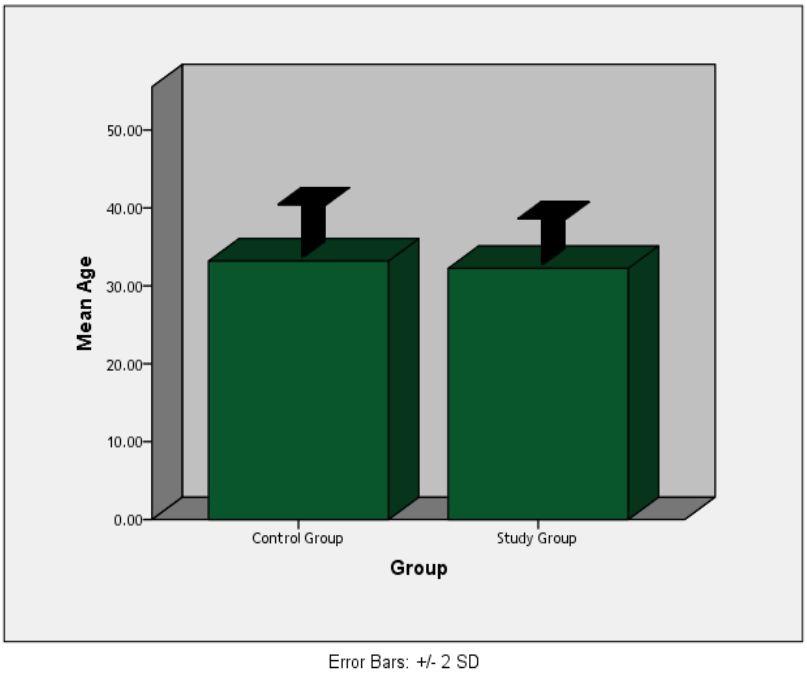

Figure (١): Mean age of study and control groups.

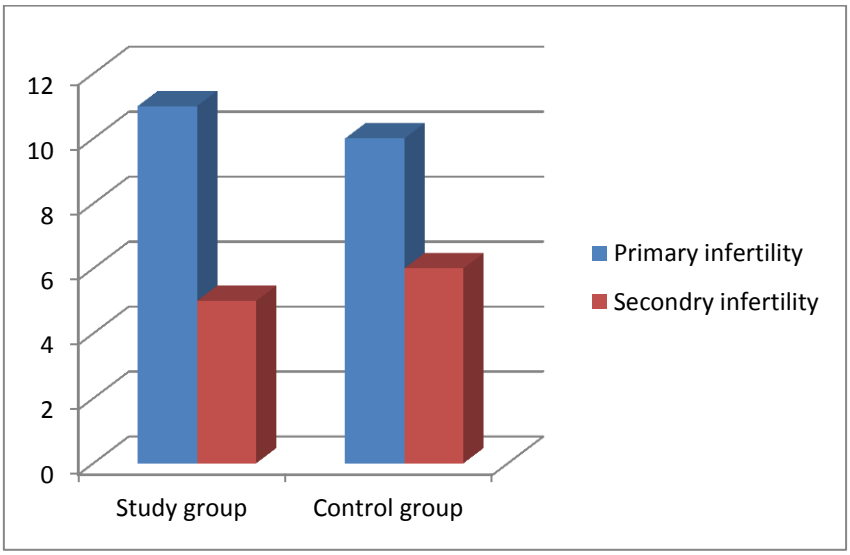

Figure (٢):Types of infertility in bot study and control groups.

DISCUSSION

Clomiphene resistance defined as failure to ovulate after receiving 150 mg of CC daily for 5 days per cycle, for at least three cycles, is common and occurs in approximately 15 to 40% in women with anovulation. Other options for assistance are OCPs [12], the goal of treatment is the rebound effect after the pills were stoped, the OCPs prevent ovulation by decreasing hypothalamic GnRH secretion, reducing pituitary responsiveness to GnRH and thereby decreasing LH and FSH. It is known that the poor FSH: LH ratio is improved due to LH suppression with OCP [13]. There is also improvement in the adverse androgeneic microenvironment in the ovary the combination of these changes after OCP therapy allows CC to work more

effectively [7]. In this study, the number of dominant follicles was 8 (80%), while in control group there were 5 dominant follicles (33.3%), there was a significant difference between the two groups regarding dominant follicle production (p = 0.00) in favor of the OCPs group. Prospective randomized study of [13], on 46 anovulatory Indian patients noticed 67.3% (31/46) dominant follicle, with 100 mg CC per day for 5 days following two cycles of OPCs. In agreement with this study [14] a study in Alexandria on 50 PCO patients, which found that the number of patients with mature follicles was 16 (64%) in control group, while in OCPs group there were 22 patients (88%). In this study, the endometrial thickness in the first stimulation cycle was about 9.43±0. 31 mm in study group and 7.48±0.8 mm in control group. There was highly statistically significant difference between the study and control group regarding endometrial thickness, while there was no significant difference in the second and third stimulation cycle regarding endometrial thickness (p > 0.05). Different results were obtained by [7], which was conducted on 48 patients from a private tertiary infertility clinic in Bellingham; WA; USA, and divided randomly to group 1 who received 0.03 mg ethinyl estradiol and 0.15 mg desogestrel (Desogen) continuously for 42 to 50 days followed by 1 cycle of 100 mg CC (Days 5 to 9); group 2 (control) who received 38 to 56 days no treatment followed by 1 cycle of 100 mg CC (Days5 to 9). Their results revealed that the suppression of the hypothalamic–pituitary–ovarian axis with OCPs followed by CC treatment had developed adequate endometrial thickness .The OCPs treatment group had better developed endometrium (9.4 mm vs 7.1 mm) but did not reach statistical significance. Furthermore [14], in in Alexandria revealed that in control group, the endometrial thickness ranged from 5 to 9 mm with a mean of 7.44 ± 1.35 mm, while in the OCPs group it ranged from 6 to 9 mm with a mean of 8.08 ± 0.996 mm but with no significant difference between the two groups, and this can be explained by different sample size in different studies. In this study, the level of mid-luteal progesterone level in study group was higher with a mean of 22.93±5.24 when compared to control group with a mean of 19.81±6.2, with no significant difference between both groups. In a study done by [7], they stated that the OCPs pretreatment followed by CC treatment results in higher levels of progesterone when measured in the mid-luteal phase to confirm ovulation, which showed statistical significance. Also, [14] reported that the progesterone level 7 days after the expected day of ovulation in control group ranged from 0.70 to 40.0 (ng/dl) with a mean of 18.30 ± 14.582 (ng/dl), while in the OCP group it ranged from 10.00 to 40.00 (ng/dl) with a mean of 28.04 ± 10.17 (ng/dl). The result of this study noticed that, there was a highly significant difference between the study and control groups in all three cycles regarding ovulation rate with higher rate in study group than control group to be 15/39(38.4%), 7/46 (15.2%) respectively. In agreement to this study, a study of [7], which was conducted on 84 patients in USA, reported that there were significantly higher percentages of patients who initially achieved ovulation (17/24 [71%] vs 2/24 [8%]) which resulted in a significantly higher number of total ovulatory treatment cycles (40/62 [64.5%] vs 3/27 [11%]). A prospective randomized study of [13], showed high ovulation rate following two cycls of OCP twenty five patient with single follicle and six showed two follicles development. Moreover, a study of [9] in India where, 30 patients received the low dose OCPs (EE .03mg & desogestrol 150 mg) continuously for 2 months, 7 days pill free interval was used to allow menstrual bleeding to occur, after withdrawal bleeding they were given 100mg cc from day3 to day 7, Day 3 s, then follicular growth was monitored by sonography from day 12 till max size (>20mm) reached, and 10,000 IU Hcg given to those patients who failed to show spontaneous rupture, their results showed that total number of 30 patients completed 75 treatment cycles, and 23 of them achieved ovulation with ovulation rate around 73.2%. In this study, there was a significant difference between the two groups regarding

pregnancy (p = 0.0004) in all three cycles. In the study group there were 7 (43.8%) pregnant patients, while in the control group; there were 1(6.2%) pregnant patient in all three cycles. These results are in accordance with a study of [7] , in private tertiary infertility clinic of Washington, as it showed that the cumulative pregnancy rate was 13/24 (54%) in the OC-CC group, compared to 1/24 (4%) in the CC group (p = 0.0001). Studies of [9] [13] [14] found similar higher pregnancy rate in OPCs group rather than in control group.

Conclusion: Pretreatment with OPCs pills results in excellent rates of ovulation and pregnancy in patients who were previously clomiphene resistant.

Declaration of interest
The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.
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REFERENCES

[1] Ghavi F, Jamale S, Mosalanejad L and Mosallanezhad Z. A Study of Couple Burnout in Infertile Couples. *Glob J Health Sci*, 2015; 68(4):158-65.

[2] Hamilton- Fairley D and Taylor A. ABC of subfertility, Anovulation. BMJ, 2006 ; 327: 546-49.

[3] Homburg R, Hendriks M.L and Konig T.E. clomiphene citrate or low dose FSH for the first – line treatment of infertile women with anovulation associated with polycystic ovary syndrome :a prospective randomized multinational study. *Hum Reprod*, 2012; 27: 468-73.

[4] Homburg R. clomiphene citrate- end of an era? A mini-review. *Hum Reprod*, 2005; 20: 2043-51.

[5] Abu Hashim H and Mukherjee S. Management of women with clomifene citrate resistant polycystic ovary syndrome: An evidence based approach. Polycystic Ovary Syndrome, 2012 :1–20.

[6] Overbeek A, Kuijper EA, Hendriks ML, Blankenstein M.A, Ketel I.J, Twisk J.W, et al.. Clomiphene citrate resistance in relation to follicle-stimulating hormone receptor Ser680Ser-polymorphism in polycystic ovary syndrome. *Human Reproduction*, 2009; 24(8): 2007–13.

[7] Branigan E F and Estes M A (2003). A randomized clinical trial of treatment of clomiphene citrate-resistant anovulation with the use of oral contraceptive pill suppression and repeat clomiphene citrate treatment. *American journal of obstetrics and gynecology*, 2003 ;188(6):1424-30.

[8] Palomba S, Falbo A, Orio F Jr, Tolino A and Zullo F. Efficacy predictors for metformin and clomiphene citrate treatment in anovulatory infertile patients with polycystic ovary syndrome. *Fertil Steril*, 2009 ; 91(6):2557-67.

[9] Sangam K and Mitra N. Oral contraceptive pills in the management of clomiphene resistant anovulation. *Int J Med Res Rev*, 2015; 3(10):1182-7.

[10] IBM Corp. IBM SPSS Statistic for windows, version 22.0.Armonk, NY 2013; IBM Corp.

[11] World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects: Bull. World Health Organ. *Epub*, 2001; 74: 373–374. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11357217

[12] Gibson B A and Wilkerson J. Basic Management of Infertility. *Handbook of Gynecology*, 2017; 467-83.

[13] Goenka Deepak . Oral contraceptive pill pretreatment for clomiphene citrate resistant cases followed by repeat clomiphene citrate treatment . *J Obstet Gynecol India*, 2006; 56(2):159-61.

[14] Orief Y I, Darwish E A E, Elsamra M A, and Ragab D H A. Gestagen versus oral contraceptive pills to induce withdrawal bleeding before induction of ovulation by clomiphene citrate in polycystic ovary syndrome. *Middle East Fertility Society Journal*, 2014; 19(2): 115-23.

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