# Clomiphene Citrate Alone or Followed by Human Chorionic Gonadotropin In Induction of Ovulation.

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**Abstract: Objective:** To evaluate the incidence of ovulation and pregnancy rates in anovulatory females who received clomiphene citrate (CC) alone and those who received clomiphene citrate then Human Chorionic Gonadotropin (HCG) to trigger ovulation. **Patients and Methods:** This randomized controlled study was conducted at the infertility clinic of Ain Shams maternity hospital during the period from December 2011 to December 2012.One hundred and fifty ladies, complaining of anovular infertility, were divided into two groups. Group A: 75 ladies received CC only. Group B: 75 ladies received CC plus HCG (choriomon® 10000 IU IM) to trigger ovulation when one or more follicles reached 18-22 mm in diameter using transvaginal ultrasound folliculometry. Midluteal serum progesterone was evaluated. Pregnancy was detected with serum β-hCG in blood after missed period then transvaginal ultrasound. **Results:** There was no significant difference between women of both groups regarding the number of mature follicles (≥ 18 mm in average dimension). Although midluteal serum progesterone ≥ 3 ng/ml (as an evidence of ovulation) was slightly higher in women of group B [CC plus HCG Group] when compared to women of group A [CC Only Group] [63/75 (84%) vs. 55/75 (73.3%), respectively]; the difference was not statistically significant. There was no statistical significant difference between women of both groups regarding pregnancy rates. **Conclusion:** There is no significant difference between infertile women due to anovulation who received CC alone and those who received CC then HCG in terms of ovulation and pregnancy rates.
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**Key words:** Induction of ovulation**,** human chorionic gonadotropin.

## 1. Introduction

Anovulation is a common cause of infertility and constitutes about 21% of the fertility problems in women [1]. Clomiphene citrate remains the most commonly and extensively used anti-estrogen [2].

In a spontaneous menstrual cycle the rising level of estrogen produced from the developing follicle, initiates an LH surge. This surge triggers the process of oocyte maturation and eventually results in its expulsion from the ovarian follicle. In ovulation induction cycles monitored by ultrasound, once follicular size has reached 18 to 22 mm in size, an ovulation trigger is advocated as a surrogate for the endogenous LH surge [3]. Administration of an ovulation trigger allows better timing of either intercourse or intra-uterine insemination [4].

Yet being expensive, administration of an ovulation trigger and timing sexual intercourse to occur 36 hours later adds to the psychological stress of the couple. Ovarian hyperstimulation syndrome is also more common when HCG is used to trigger ovulation [5].

## 2-Patients and Methods

This prospective randomized controlled trial was conducted in Ain Shams University maternity hospital, Infertility Clinic.

**Inclusion criteria:** Age between 18-35 years, Duration of infertility ≥ 1 year, Normogonadotropic (WHO class II ovarian dysfunction) and Infertility with oligomenorrhea (bleeding intervals between 35 days and 6 months) or amenorrhea (bleeding interval > 6 months).

**Exclusion criteria:** History of ovulation induction, Thyroid diseases, Male factor for infertility (abnormal semen analysis) or Clomiphene citrate resistant patients by history.

**Patients included in our study were subjected to the following:**

Infertility evaluation including: Semen analysis of the male partner which exhibited WHO normal semen parameters [6], Normal Hysterosalpingogram of the patients and FSH<10 m IU /ml.

All patients were randomly allocated on either arms of the study using closed envelope technique.

**Group A:** received CC alone (50 mg tablet).

**Group B:** received the same regimen of CC followed by HCG (choriomon® 10.000 IU intramuscular) to trigger ovulation when one or more follicles reached 18-22 mm in diameter, as determined by ultrasound folliculometry.

The start of the menses spontaneously was accepted as the 1st day of the treatment cycle. CC (50 mg tablet) was administered twice daily from the second day for five days to both groups. Ultrasound

examination was resumed to both groups at day 3 to detect any ovarian cysts, and at day 12 to evaluate the dominant follicle size. When the follicle reached 18-22mm, ovulation was triggered in group B by 10000 IU HCG, intramuscular. Midluteal serum progesterone was evaluated in both groups at Ain Shams university maternity hospital Laboratories 9 days after the last ultrasound in Group A and one week after HCG Administration in Group B.

Both groups were allowed to have regular or timed intercourse every other day for one week. Luteal phase support to both groups in the form of Uterogestan capsules 100mg oral twice daily was taken. Clinical pregnancy was defined as all the pregnancies detected with β-HCG in blood and intrauterine sac at 5 weeks gestation on transvaginal ultrasound.

All results were tabulated and analyzed statistically. Statistical analysis was performed using Microsoft® Excel® Version 2007 and statistical package for social sciences (SPSS®) for Windows® version 15.0. Demographic data of included women were presented as descriptive statistics (using range, mean and standard deviation for metric data, and primary and secondary outcomes of both groups will be compared using student t-test (for parametric measures), Mann-Whitney U-test (for non-parametric measures) and chi-squared and Fischer exact tests (for categorical measures). Association between two variables was assessed using Pearson correlation coefficient (for parametric variables) and Spearman correlation coefficient (for non-parametric variables). Significance level was set at 0.05.

**Sample size calculation**

EPI INFO program was used for sample size calculation guided by:

- Power of test=80%
- Confidence level=95%
- Alpha error=5%
- Ovulation rate in Group A =80% ***(American Society For Reproductive Medicine; 2006)*** [2].
- Ovulation rate in Group B =96 %***( American Society For Reproductive Medicine; 2006)*** [2].
- Required sample size:
- Total=150 cycles
- N1=75 cycles
- N2=75 cycles

**3-Results**

There were no significant differences between women of both groups regarding age, weight, BMI and parity (Table 1).

**Table (1): Difference between Groups regarding Demographic Data:**

| | **Group I [CC Only Group] (n=75)** | **Group II [CC plus hCG Group] (n=75)** | ***P*** |
|---|---|---|---|
| **Age (Years)** | | | |
| **Range** | 18 – 35 | 17 – 35 | 0.888* |
| **Mean ± SD** | 25.55 ± 5.19 | 25.67 ± 5.23 | NS |
| **Weight (Kg)** | | | |
| **Range** | 51 – 89 | 51 – 89 | 0.299* |
| **Mean ± SD** | 68.77 ± 9.99 | 70.49 ± 10.21 | NS |
| **BMI (Kg/m$^2$)** | | | |
| **Range** | 20.2 – 40.8 | 19.4 – 42.3 | 0.232* |
| **Mean ± SD** | 28.69 ± 4.52 | 29.63 ± 5.07 | NS |
| **Parity** | | | |
| **Range** | 0 – 3 | 0 – 2 | 0.336** |
| **Median (IQR)** | 0 (0 – 1) | 0 (0 – 1) | NS |

SD standard deviation IQR interquartile range Data presented as range, mean ± SD or range, median (IQR)
* Analysis using Independent Student's t-Test ** Analysis using Mann-Whitney's U-Test NS non-significant

There were no significant differences between women of both groups regarding age of menarche, regularity of menstrual cycles, frequency of hirsutism, duration and type of infertility (Table 2, 3). There were no significant differences between women of both groups regarding basal hormonal profile (Table 4).

There was no significant difference between women of both groups regarding no. of mature follicles (≥ 18 mm in average dimension).

The proportion of women who had reached at least one mature follicle was slightly higher in women of group B [CC plus HCG Group] when compared to women of group A [CC Only Group] [60/75 (80%) vs. 53/75 (70.7%), respectively]. However, this difference was not significant.

Administration of HCG (10,000 IU IM injection) to trigger ovulation was associated with a 9.3% higher likelihood of finding at least one mature follicle

[number needed to treat (NNT) = 11; i.e. administration of hCG to trigger ovulation to 11 women is needed to have 1 added case of finding at least one mature follicle](Table 5).

The mean midluteal serum progesterone was significantly higher in women of group B [CC plus HCG Group] when compared to women of group A [CC Only Group] [14.04 ± 9.63 ng/ml vs. 9.44 ± 7.08 ng/ml, respectively, $p$=0.001].

The proportion of women with evidence of ovulation (a midluteal serum progesterone ≥ 3 ng/ml) was slightly higher in women of group B [CC plus HCG Group] when compared to women of group A [CC Only Group] [63/75 (84%) vs. 55/75 (73.3%), respectively]. However, the difference was not significant [$p$=0.111].

**Table (2): Difference between Groups regarding Menstrual Characteristics:**

| | Group I [CC Only Group] (n=75) | Group II [CC plus hCG Group] (n=75) | *P* |
|---|---|---|---|
| **Age of Menarche (Years)** | | | |
| **Range** | 10 – 15 | 10 – 15 | 0.698* |
| **Mean ± SD** | 12.25 ± 0.84 | 12.2 ± 0.84 | NS |
| **Menstrual Cycles** | | | |
| **Regular** | 8 (10.7%) | 7 (9.3%) | 0.785** |
| **Irregular** | 67 (89.3%) | 68 (90.7%) | NS |
| **Oligomenorrhea** | 56 (74.7%) | 50 (66.7%) | 0.282** |
| **Amenorrhea** | 11 (14.7%) | 18 (24%) | NS |
| **Hirsutism** | 14 (18.7%) | 15 (20%) | 0.836** NS |

SD standard deviation Data presented as range, mean ± SD or number (percentage) * Analysis using Independent Student's t-Test ** Analysis using Chi-Squared Test NS non-significant

**Table (3): Difference between Groups regarding Duration and Type of Infertility:**

| | Group I [CC Only Group] (n=75) | Group II [CC plus hCG Group] (n=75) | *P* |
|---|---|---|---|
| **Duration of Infertility (Years)** | | | |
| **Range** | 1 – 4 | 1 – 4 | 0.069* |
| **Mean ± SD** | 1.69 ± 0.8 | 1.97 ± 1.01 | NS |
| **Type of Infertility** | | | |
| **Primary** | 44 (58.7%) | 49 (65.3%) | 0.400** |
| **Secondary** | 31 (41.3%) | 26 (34.7%) | NS |

SD standard deviation Data presented as range, mean ± SD or number (percentage) * Analysis using Independent Student's t-Test ** Analysis using Chi-Squared Test NS non-significant

**Table (4): Difference between Groups regarding Basal Hormonal Profile:**

| | Group I [CC Only Group] (n=75) | Group II [CC plus hCG Group] (n=75) | *P** |
|---|---|---|---|
| **Basal Serum FSH (IU/ml)** | | | |
| **Range** | 1.8 – 8.3 | 1.29 – 8.2 | 0.078 |
| **Mean ± SD** | 5.42 ± 1.72 | 4.72 ± 1.59 | NS |
| **Basal Serum LH (IU/ml)** | | | |
| **Range** | 3.3 – 26.4 | 2.9 – 26.4 | 0.069 |
| **Mean ± SD** | 9.56 ± 5.17 | 8.21 ± 3.82 | NS |
| **Basal Serum LH:FSH Ratio** | | | |
| **Range** | 0.4 – 4 | 0.56 – 4 | 0.822 |
| **Mean ± SD** | 1.8 ± 0.75 | 1.83 ± 0.69 | NS |
| **Basal Serum Prolactin (ng/ml)** | | | |
| **Range** | 2.7 – 32 | 6.55 – 30 | 0.577 |
| **Mean ± SD** | 15.55 ± 6.92 | 16.15 ± 6.26 | NS |

SD standard deviation Data presented as range, mean ± SD * Analysis using Independent Student's t-Test NS non-significant

**Table (5): Difference between Groups regarding Response to Induction of Ovulation**

| | Group I [CC Only Group] (n=75) | Group II [CC plus hCG Group] (n=75) | *P** |
|---|---|---|---|
| **No. of Mature Follicle**<br>**None**<br>**1**<br>**2**<br>**≥ 3** | <br>22 (29.3%)<br>33 (44%)<br>15 (20%)<br>5 (6.7%) | <br>15 (20%)<br>29 (38.7%)<br>17 (22.7%)<br>14 (18.6%) | 0.117<br>NS |
| **At least one Mature Follicle** | 53 (70.7%) | 60 (80%) | 0.185<br>NS |
| | ARR = 9.3%, NNT = 10.71 ≅ 11 | | |

Data presented as number (percentage) * Analysis using Chi-Squared Test NS non-significant
ARR absolute risk reduction NNT number needed to treat

Administration of HCG (10,000 IU IM injection) to trigger ovulation was associated with a 10.7% higher likelihood of successful ovulation [NNT = 9; i.e. administration of HCG to trigger ovulation to 9 women is needed to have 1 added case of successful ovulation] (Table 6).

The proportion of women with successful pregnancy was slightly higher in women of group B [CC plus HCG Group] when compared to women of group A [CC Only Group] [4/75 (5.33%) vs. 7/75 (9.33%), respectively]; the difference was, however, not significant [*p*=0531](Table 7).

**Table (6):** Difference between Groups regarding Midluteal Serum Progesterone and Successful Ovulation:

| | Group I [CC Only Group] (n=75) | Group II [CC plus hCG Group] (n=75) | *P* |
|---|---|---|---|
| **Midluteal Serum Progesterone (ng/ml)**<br>**Range**<br>**Mean ± SD** | <br>0.26 – 30<br>9.44 ± 7.08 | <br>0.26 – 36<br>14.04 ± 9.63 | 0.001*<br>S |
| **Evidence of Ovulation (Midluteal Serum Progesterone ≥ 3 ng/ml)** | 55 (73.3%) | 63 (84%) | 0.111**<br>NS |
| | ARR = 10.7%, NNT = 9.4≅9 | | |

Data presented as number (percentage) * Analysis using Independent Student's t-Test ** Analysis using Chi-Squared Test
S significant – NS non-significant ARR absolute risk reduction NNT number needed to treat

**Table (7): Difference between Groups regarding Successful Pregnancy:**

| | Group I [CC Only Group] (n=75) | Group II [CC plus hCG Group] (n=75) | *P* |
|---|---|---|---|
| **Successful Pregnancy** | 4 (5.33%) | 7 (9.33%) | 0.531<br>NS |

Data presented as number (percentage) * Analysis using Chi-Squared Test NS non-significant

**4-Discussion**

The success of ovulation in all patients after treatment with CC alone or followed by BHCG was 75.3 % (113 ovulated out of 150 women). The ovulation rate achieved in this study was lower than reported by ***Dicky et al.*** [7], ***and Kousta et al.*** [8](the ovulation rates were 80%, 88.3% respectively). The difference can be explained by differences in ages, number of patients, doses of CC between our study and their studies since they used 150 mg of clomiphene citrate and the mean age in their study was 30.5 years.

In this study there is no significant difference in ovulation rate between group A (70%) and group B (80%), this agrees with the results by ***Vlahos et al.*** [9]**,** ***George et al.*** [10].

Also in agreement with our ovulation rate ***Manizheh et al.*** [11], who compared two groups of anovulatory infertile women, one group was treated by clomiphene citrate plus oxytocin and the other group

was treated by clomiphene citrate plus HCG for two months. He found no significant difference in the ovulation rate between the oxytocin group (92%) and the HCG group (84%).

There was no significant difference between women of both groups regarding the number of mature follicles, which is similar to the results by ***Agarwal and Buyalos*** [12] that showed no significant difference between the HCG group (1.2 ±1) and the LH kit group (1±1), also the study by ***Vlahos et al.*** [9] showed no significant difference in the number of mature follicles as the HCG group was1.55 and the LH group was 1.54, also this agrees with ***Manizheh et al.*** [11] who found no significant difference in the mean number of follicles in the first month (HCG group2.57±2.47)and (oxytocin group 2.38 ± 1.39) but disagrees with him in the second month as the oxytocin group had significantly more follicles(3.25±2.41)than the HCG group (2.12±1.49).

The proportion of women with evidence of ovulation (midluteal serum progesterone ≥3 ng/mL) was insignificantly higher in group B than in group A (84% in group B vs 73.3% in group A) which is similar to the results by ***Kosmas et al.*** [13].

The mean midluteal serum progesterone was significantly higher in group B (14.04 ng/ml) compared to group A (9.44 ng/ml), in the above mentioned ***Manizheh et al.*** [11] he found mean midluteal serum progesterone in the HCG group (7.96 ng/ml) while in the oxytocin group (12.79 ng/ml).

The proportion of women with successful pregnancy as detected by positive fetal heart rate on ultrasound was insignificantly higher in group B compared to group A (9.33% vs 5.33%, respectively), the results by ***Vlahos et al.*** [9], was 14.3% in the spontaneous LH surge group versus 12.4% in the HCG group, also the rate of pregnancy was insignificantly different in both groups.

Our result also agrees with ***Awonuga and Govindbhai*** [14] who found no significant difference in pregnancy rate with the use of HCG (4.2%) versus LH monitoring (4.3%).

The results by ***Agarwal and Buyalos*** [12] who did their study on larger number of patients (233) performing 247 cycles of artificial insemination in HCG triggered clomiphene induced patients resulting in 0.35% clinical pregnancy (group 1) and 261 cycles IUI were performed in spontaneous LH surge clomiphene induced patients after detecting ovulation by LH kit and resulted in 0.54% clinical pregnancy rate which is insignificantly higher (group2).

Our study disagrees with ***Mitwally et al.*** [15] who supported the practice of administering HCG to trigger ovulation and time insemination and to time its administration according to LH surge, taking in consideration that they did retrospective analysis of 2000 cycles (637 timed-intercourse and 1363 IUI cycles), in which different stimulation protocols were used (CC alone or with FSH or letrozole alone or with FSH or FSH alone) in PCOS and unexplained infertility patients, and they divided them into 3 groups (group 1 HCG-only, group 2 both HCG was given and LH surge occurred on the same day, group 3 LH-surge only), they found that group 2 had significantly higher clinical pregnancy rate when compared to the other two groups (HCG-only group $P<0.05$ and LH-surge group $P<0.01$) in CC treatment cycles.

The discrepancy between ovulation and pregnancy rates in our study may be explained by the peripheral antiestrogenic effects of CC on the quality of cervical mucus and endometrium which may inhibit sperm penetration and affect implantation, also the use of more controlled and advanced methods in the other studies like IUI could have a better impression on pregnancy rates in their studies, eventually the compliance of the patients, their low socioeconomic and cultural levels played a big role in delaying the whole process.

## 5-Conclusion

There is no significant difference between infertile women due to anovulation who received CC alone and those who received CC then HCG in terms of ovulation and pregnancy rates. So, during induction of ovulation, HCG trigger may not be given depending on endogenous LH surge without affection of ovulation or pregnancy rate. This may be more economic; sometimes HCG may be deficient in the market and if there is a risk of ovarian hyperstimulation syndrome. If your patient asked you, is it necessary to take HCG trigger? You may answer her no.

## 6. Conflict of interest

No conflict of interest or supporting agencies**.**

## 7. Acknowledgement

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