**Clomiphene citrate ‘stair-step’ protocol vs. traditional protocol in patients with polycystic ovary syndrome: a randomized controlled trial**

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**Abstract:** Purpose The aim of this work is to evaluate the efficacy of the stair-step protocol using clomiphene citrate (CC) in ovulation induction in patients with PCOS and to assess the uterine and systemic side effects of this protocol. **Methods** A total of 60 PCOS patients who failed to respond to 50 mg/day for 5 days of CC treatment within the cycle were randomly allocated to the control (traditional protocol) and study (stair-step protocol) groups. In the stair-step protocol, patients were treated with CC 50 mg/day for 5 days and then in nonresponsive patients, the dosage was increased to 100 mg/day for 5 days in the same cycle. Patients who failed the 50 mg/day CC treatment in the previous cycle were stimulated with 100 mg/ day CC and were accepted as the control group. Ovulation and pregnancy rates, duration of treatment and uterine and systemic side effects were evaluated. **Results** Ovulation and pregnancy rates were similar between the stair-step and the control group (46.7 vs. 30 %, respectively) (20% vs. 6.7 %, respectively). The duration of treatment was significantly shorter in stair-step compared to traditional protocol (19.2±3.0 vs. 47.4±1.7 days, respectively). There were no significant differences in the systemic side effects between the groups. Uterine side effects were evaluated with endometrial thickness and uterine artery Doppler ultrasound; no significant differences were observed in stair-step compared to traditional protocol. Conclusions The present study demonstrated that ovarian stimulation using the stair-step protocol revealed shorter time period to reach to ovulation and/or decision resistance to CC without any detrimental effect on the ovulation and maternal and systemic side effects.

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**Keywords:** Clomiphene citrate - Stair-step protocol - Traditional protocol - Polycystic ovary syndrome

**1. Introduction**

Infertility is defined as failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse ***(WHO-ICMAR Tglossary, 2009).***

Anovulatory dysfunction is a common problem and is responsible for 40% of all female infertilities. Polycystic ovary syndrome (PCOS)is the most common endocrine disorder of reproductive-aged women and the most common cause of anovulatory infertility ***(Sirmans and Pate, 2013).*** It is a heterogeneous endocrine condition that affects approximately 5% to 10% of women in the reproductive age group ***(Tannys and Anthony, 2010).*** An increased awareness of this disorder in the general population and medical communities has taken place in recent years with the knowledge that women with polycystic ovary syndrome are susceptible to metabolic syndrome and its associated co-morbidities ***(Saha et al., 2012).***

According to Rotterdam criteria PCOS is characterized by two of the following three criteria: Oligo-anovulation, ultrasonographically defined polycystic ovaries (12 or more follicles measuring 2-9 mm in diameter or increased ovarian volume more than 10cm3) and clinical or biochemical signs of hyperandrogenism with the exclusion of other androgen excess disorders ***(Rotterdam, 2004).***

Clomiphene citrate is the first drug of choice in management of infertility in PCOS because it is readily available, inexpensive, well tolerated, safe, and efficacious ***(Thessaloniki, 2008).*** As a selective estrogen receptor modulator, CC acts by binding to estrogen receptors and inhibiting the negative feedback of estrogen on the hypothalamus ***(The American Society for Reproductive Medicine, 2013)***. This causes a compensatory increase in follicle-stimulating hormone levels, thereby stimulating follicular development and subsequent ovulation. Although CC is known to have a relatively long half-life, approximately 85% of the drug is excreted from the body after 7 days ***(Mikkelson et al., 1986).*** A commonly used CC protocol for ovulation induction involves a starting dose of 50 mg per day for 5 days during the follicular phase. If ovulation does not occur, the dose is often increased by 50 mg in the next cycle after a progesterone-induced withdrawal period ***(Sirmans and Pate, 2013).*** With this protocol it has been reported that 46% of patients ovulate with a CC dose of 50 mg/day, 21% with 100mg/day, 8% with 150mg/day ***(Rostami et al., 2004).*** Approximately 20% of patients are refractory to CC regimen ***(Imani et al., 2002).*** Although the maximum dose of CC is 250 mg/day, clinicians prefer not to use doses above 150 mg/day to avoid potentially adverse effects of the cumulative doses in the same cycle on the endometrium and on systemic side effects ***(ACOG Practice Bulletin 2002).*** A new protocol is the stair-step protocol in which the increasing daily CC dose is administered without intervening menses between the dosages ***(Hurst et al., 2009).*** The potential advantage of stair-step protocol is the lack of a waiting period until the next menstruation. Potentially adverse effects of the cumulative doses in the same cycle on the endometrium and on systemic side effects may be disadvantages of stair-step protocol ***(Cannon et al., 2014).***

**2. Materials and methods**

This randomized controlled prospective study was carried on 60 patients with PCOS attending the infertility clinic at Al- Maadi Military Hospital from January 2016 till September 2016. The study was approved by the Ethical Committee of the hospital. Informed consent was obtained from all the cases enrolled in the study.

**The inclusion criteria were as follows:**

1. Women aged 20-35 years.
2. Tubal patency confirmed by either hysterosalpingogram or during diagnostic laparoscopy.
3. Normal semen analysis according to WHO criteria (2010).
4. Diagnosis of PCOS, by two of the following three criteria according to Rotterdam criteria(2004): Oligo-anovulation, ultrasonographically defined polycystic ovaries (12 or more follicles measuring 2-9 mm in diameter or increased ovarian volume more than 10cm3) and clinical or biochemical signs of hyperandrogenism with the exclusion of other androgen excess disorders, were enrolled in this study.

**The exclusion criteria were as follows:**

1. Womens aged >35 years old.
2. Female with bilateral tubal blockage diagnosed either by hysterosalpingogram or during diagnostic laparoscopy.
3. Endocrinolgical disorders.
4. Previous gynecological operations.

**All patients participated were subjected to the following:**

1. Written informed consent.
2. Thorough History taking; including menstrual history, obstetric history, medical history, surgical history, history of drug intake and family history.
3. Physical examination especially measurement of body mass index.
4. General examination especially for acne and hair distribution.
5. Thyroid, breast and Abdominal examination.
6. Investigation;
7. Hormonal profile (Day2 FSH, LH, Prolactin and TSH),
8. Tubal patency evaluated by HSG or diagnostic laparoscopy.
9. Husband semen analysis.

Folliculometry by (transvaginal ultrasound) starting from day 9 of the menstrual cycle and then every other day.

HCG (10000 IU) was given when at least one follicle ≥18mm in the ovary.

1. Measurement of endometrial thickness and RI.&PI of the uterine artery on the day of HCG administrated.

Atotal of 60 patients who failed to respond to 50 mg/day for 5 days of CC treatment within the cycle (if follicle size < 11 mm on cycle day 14) were randomly allocated to the control (traditional protocol) and study (stair-step protocol) groups.

In the stair-step protocol (n = 30), the dosage was increased to 100 mg daily for 5 days in the same cycle. On cycle day 19, evaluation by transvaginal ultrasonography was restarted. When the mean diameter of the leading follicle reached 18 mm, HCG 10000 IU was administered. When no follicular response was observed on cycle day 23, the cycle was cancelled.

The daily dosage of CC was not increased to 150 mg daily because of the potentially adverse effects of the cumulative doses.

**In the control group** (n = 30), CC was administered 100 mg daily for 5 days after the onset of a progestin-induced menstruation. Follicular response was monitored with transvaginal ultrasonography starting with day 8. When the mean diameter of leading follicle reached 18 mm, hCG was administered. When no follicular response was observed on cycle day 20, the cycle was cancelled.

**The Primary outcomes were**

1. The time to ovulate (measured from the start of therapy till maturation of follicle).
2. Uterine side effects of the CC. evaluated by the measurement of the endometrial thickness and uterine artery Doppler.
3. Systemic side effects evaluated with a questionnaire. It was composed of six scale including hot flushes, mood disturbance, pelvic pressure, nausea, pelvic pain, and breast tenderness.

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| Women who were diagnosed as PCOS according to the Rotterdam 2003 criteria who failed to respond to 50 mg/day for 5 days of CC treatment were enrolled to study (n=68) |

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| **Patients who have any reasons for infertility except as oligo-anovulation like*** Tubal pathology,
* Endocrinological disorders,
* Previous gynecological operation,
* Women’s age ≥35 years’ old,
* Male infertility, were excluded the study (n=8).
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| A total of 60 patients who failed to respond to 50 mg/day for 5 days of CC treatment within the cycle (If follicle size was below 11 mm on cycle day 14) were randomly allocated to the control (traditional protocol) and study (stair-step protocol) groups. |

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| --- | --- |
| **Stair-step protocol** (n=30) the dosage was increased to 100 mgdaily for 5 days. | **Traditional protocol** (n=30) CC was administered 100 mg daily for 5 days after the onset of a progestin-induced menstruation |

|  |  |
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| Ultrasonographic monitorization was started with day 8. | On cycle day 19, the evaluation bytransvaginal ultrasonography was restarted |

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| Mean diameter of the leading follicle was reached 17 mm, hCG was administered. Intrauterine insemination was performed at 36 hours after the hCG administration |

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| No follicular response was observed on cycle day 20, the cycle was cancelled | No follicular response was observed on cycle day 23, the cycle was cancelled |

***The secondary outcome was:*** *occurrence of clinical pregnancy****.***

***Sample size*** If the primary outcome was accepted as the time to ovulate with 10% difference and 80 % power 401 patients were required as sample size. A multicenter based study would be required for the collection of such large sample size. Therefore, the sample size of this prospective study failed the required power.

**3. Results**

With this protocol, we have found that 46.7% of patients have ovulated in the study group while 30% in the control group (Table 1).

Regarding Pregnancy rate, it was non-significantly more frequent among study group than among control group. It was 6 cases (20%) among the study group while it was 2 cases (6.7 %)in the control group.(Table 2)

Regarding Endometrial thickness (mm), It was 7.9(mm) in the study group while it was 8.9(mm) in the control group and there was no significant difference between the 2 groups. (Table 3)

Regarding duration of treatment (days), it was about 19 days in the study group while in the control groups it was 47 days which was significantly lower among Stair-step group than among control group (Table 4).

No significant adverse effects were observed on the endometrial thickness or the maternal systemic side effects in the stair-step protocol compared with the traditional protocol.

**Table (1):** Ovulation among the studied groups.

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| --- | --- | --- | --- |
| **Measures** | **Study****(N=30)** | **Control****N=30)** | **#P** |
| Ovulation | 14 (46.7%) | 9 (30.0%) | 0.184 |
| Efficacy of Stair-step in increasing Ovulation |
| Items | Value | 95% CI |
| Rate in study group | 46.7% | 32.8–59.1% |
| Rate in control group | 30.0% | 17.6%–43.9% |
| Rate elevation | 16.7% | -11.1%–41.5% |
| Relative Rate | 1.555 | 0.748–3.365 |
| Number needed to treat | 6.0 | 2.4–>100.0 |

#Chi square test, \*Significant, **CI:** Confidence interval

**Table (2):** Pregnancy among the studied groups.

|  |  |  |  |
| --- | --- | --- | --- |
| **Measures** | **Study****(N=50)** | **Control****(N=50)** | **#P** |
| **Present** | 6 (20.0%) | 2 (6.7%) | 0.129 |
| **Efficacy of Stair-step in increasing pregnancy** |
| **Items** | **Value** | **95% CI** |
| **Rate in study group** | 20.0% | 14.6%–32.4% |
| **Rate in control group** | 6.7% | 1.2%–%19.1% |
| **Rate elevation** | 13.3% | -6.7%–24.3% |
| **Relative Rate** | 3.000 | 0.598–21.073 |
| **Number needed to treat** | 7.5 | 4.1–>100.0 |

#Chi square test, \*Significant, **CI:** Confidence interval

**Table (3):** Endometrial thickness (mm) among the studied groups.

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| --- | --- | --- | --- |
| **Measures** | **Stair-step****(N=30)** | **Control****(N=30)** | ^**P** |
| **Mean±SD** | 7.9±2.0 | 8.9±2.7 | 0.124 |
| **Range** | 5.0–13.0 | 3.0–14.0 |
| **95% CI** | 7.2–8.6 | 7.9–9.8 |
| **Efficacy of Stair-step in reducing ET** |
| **ET** | **Mean±SE** | **95% CI** |
| **ET reduction** | 0.9±0.6 | 2.2–0.3 |

^Independent t-test, \*Significant, **CI:** Confidence interval

**Table (4):** Durationm of treatment (days) among the studied groups.

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| --- | --- | --- | --- |
| **Measures** | **Stair-step****(N=30)** | **Control****(N=30)** | ^**P** |
| **Mean±SD** | 19.2±3.0 | 47.4±1.7 | **<0.001\*** |
| **Range** | 13.0–24.0 | 44.0–51.0 |
| **95% CI** | 18.1–20.3 | 46.7–48.0 |
| **Efficacy of Stair-step in reducing duration** |
| **Items** | **Mean±SE** | **95% CI** |
| **Duration reduction** | 28.2±0.6 | 26.9–29.4 |

^Independent t-test, \*Significant, **CI:** Confidence interval

**4. Discussion**

Clomiphene citrate (CC) is the first drug of choice in the management of infertility in PCOS ***(Thessaloniki*** ***ESHRE/ASRM 2008).*** Although CC treatment is usually initiated in days 2–5 of menstruation, it may be initiated at any time in patients with oligo-amenorrhea. Generally 50 mg CC for 5 days is used in the first cycle. In cases of anovulation, CC dose is increased by 50 mg in the subsequent cycle. A meta-analysis has suggested that only 46 % will respond to 50 mg/day, a further 21 % will respond to 100 mg and another 8 % will ovulate with 150 mg/day ***(Rostami-Hodjegan et al., 2004).*** Approximately 20 %of the patients are refractory to CC regimen ***(Imani et al., 2002).*** Although the maximum dose of CC is 250 mg/day, clinicians prefer not to use doses above 150 mg/day for the fear adverse effect of this large dose and these patients are regarded as CC resistant ***(ACOG, 2002).***

A new protocol is the stair-step protocol in which the increasing daily CC dose is administered without intervening menses between the dosages. The potential advantage of stair-step protocol is the lack of a waiting period until the next menstruation. Potentially adverse effects of the cumulative doses in the same cycle on the endometrium and on systemic side effects may be disadvantages of stair-step protocol ***(Canan et al., 2014).***

This randomized controlled prospective study that includes 60 patients with PCOS attending the infertility clinic in Al Maadi Military Hospital, who failed to respond to 50 mg per day for 5 days were randomly allocated to the control group (n:30) and the study group(n:30).

The results of this study indicated that the duration of treatment was significantly lower among Stair-step group than among control group (19 days versus 47days) while ovulation was non-significantly more frequent among Stair-step group than among control group (46.7% versus 30%). This was in agreement with ***Hurst et al. (2009)***, who studied anovulatory or oligoovulatory women with PCOS who failed to respond to 50 mg clomiphene for 5 days and were subsequently treated with the stair-step protocol from 2000 to 2007, that found that the time to ovulation was shorter with the stair-step protocol (21-28 days) as compared with a traditional progestin withdrawal regimen (55-88 days). While they found a significantly higher ovulation rate of 64% with the stair-step protocol at a clomiphene dose of 100 mg compared with the expected ovulation rate of 22% with this dose in a traditional regimen which disagree with our results. This may be explained by the large sample size and the long duration of their study. In addition, they depended on historical result from published data and not from a controlled study group to compare the result of both protocols as compared to our study. Also, ***Farhi et al. (2010)*** concluded that time can be saved and the process made more efficient, without affecting the outcome of treatment, by starting CC at a time unrelated to the onset of bleeding, on condition that no dominant follicle is present. This allows time saving in the initiation of treatment for newly diagnosed patients and justifies a stair-step protocol allowing a step-up in dose after a lack of response to CC, without having to induce a menstrual period.

The results of this study indicated that clinical pregnancy rate was non-significantly more frequent among study group than among control group(20% versus 6%). This was in agreement with ***Hurst et al. (2009)*** who found that the clinical pregnancy rate for the stair step protocol of(13%) was similar to the traditional protocol (15%). while this was disagree with ***Dickey et al. in (1997)*** who found that 14.7% of patients conceived at clomiphene citrate dose of more than 100mg. A previous study done by ***Dickey et al. in (1992)*** found that the dose of clomiphene was positively related to pregnancy rates with doses mmore than 100 mg/day which were responsible for the higher pregnancy rates (16%).

The major anti-estrogenic effect of CC treatment is on the endometrium and CC may interfere with the estrogen stimulated proliferation of endometrium. The anti-estrogenic effect of CC inhibits normal cyclical growth of the uterus and endometrium and endometrial thickness is altered in CC cycles ***(Randall et al., 1991; Haritha et al., 2003).*** The risk of negative effects on the endometrium may increase when the dose of CC is increased ***Kurosawa et al. (2010)*** reported that CC acted as an antagonist at such a high concentration via ERa and ERb, hence the antagonistic activity of CC was stronger in ERb than ERa. CC related antagonistic activity on the endometrium was dose dependent and was affected by the presence of estrogen. One possible explanation for the low pregnancy rate compared to the high ovulation rate resulting from the use of CC is that CC inhibits progesterone action in the endometrium by an antagonistic effect via ERb ***(Kurosawa et al., 2010).***

However, Homburg ***Homburg (2005)*** reported that suppression of endometrial proliferation using CC was unrelated to dose or duration of treatment but apparently idiosyncratic ***(Nakai et al., 2002).*** Suggested that uterine artery blood flow increased from the follicular phase to ovulation in spontaneous cycles but this increase in blood flow in the uterine artery in the peri-ovulational period could not be detected in CC induced cycles. This may be a result of the depletion of endometrial receptors that are responsible for the endometrial changes due to CC treatment ***(Nakai et al., 2002).*** Endometrial receptivity is difficult to evaluate by noninvasive methods.

Endometrial thickness measured by ultrasonography is an indirect marker of endometrial receptivity. It has been reported that endometrial thickness should be at least 5–6 mm for implantation ***(Dickey et al.,*** ***1993; Piver, 2005). Shahin (2008)*** suggested that endometrial thickness in the range 7.9-8.9 mm and triple line pattern is highly predictive for pregnancy. Therefore, the potential side effects on the endometrium related to the cumulative doses of CC in the stair-step protocol were evaluated on ultrasound. No significant adverse effects were observed on the endometrial thickness in the stair-step protocol. In The results of our study there was no significant difference between study groups regarding endometrial thickness.

In the results of the current study Flushes, Mood disturbance, Pelvic pressure, Abdominal pain and Breast tendernesswas significantly more frequent among study group than amoug control. Since CC causes a central misperception of low estrogen levels, natural vasomotor symptoms may be observed ***(Fritz et al., 2011).*** Mood disturbances are the most commonly observed side effect related to CC (64–78 %) ***(Blenner, 1991; Choi et al., 2005).*** Transient hot flushes occur in 10 % of women ***(Fritz et al., 2011; Blenner, 1991)***. Visual disturbances are rare (1–2 %) and, breast tenderness, pelvic discomfort and nausea have been reported at on overall rate of 2–5 % inCC treated patients ***(Purvin, 1995;*** ***ASRM, 2013).***

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