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Clomiphene Stair-Step Protocol versus Traditional Protocol for Ovulation Induction in Polycystic Ovarian Syndrome Patients

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder among women in the reproductive period. It is one of the leading causes of infertility. The manifestations of PCOS include irregular or no menstrual periods, excess body weight and facial hair, acne, heavy periods and pelvic pain. The aim of this study is to determine the efficacy of stair step protocol compared to traditional protocol in ovulation induction of polycystic ovarian syndrome (PCOS) patients in terms of increasing rate of ovulation and pregnancy.
Methods: This study is non-blinded, multicenter, randomized controlled study and was carried out on infertile women attending the Fertility Clinic of Tanta University Hospital and Hurghada General Hospital. Two Hundred infertile patients with PCOS criteria and no other causes of infertility were enrolled according to inclusion and exclusion criteria.
Results: Student t test was used for the continuous variables (FSH, LH, Prolactin, AMH, TSH, Free testosterone). Student t test was used for the continuous variables (Endometrial thickness, Time to ovulate (d)). Chi-square analysis was used for the categorical variables (Ovulation rate, Pregnancy rate). Chi-square analysis was used for the categorical variables (Ovulation rate per

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cycle). There was no significant difference between two groups as regards mild and severe side effects.

Conclusions: This study concluded that stair step regimen improves the ovulation rate and pregnancy rate without any detrimental side effects compared to traditional regimen. It helps to know the sensitivity and resistance of an individual to **clomiphene citrate** much earlier and helps to plan ahead with alternative treatment for desired outcome. The advantage of shorter treatment period with similar side effects makes the stair step protocol suitable for use in routine clinical practice.

Keywords: Clomiphene; stair-step protocol; ovulation; polycystic ovarian syndrome.

1. INTRODUCTION

Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder among women in the reproductive period [1]. It is one of the leading causes of infertility. The manifestations of PCOS include irregular or no menstrual periods, excess body weight and facial hair, acne, heavy periods and pelvic pain. Classically clomiphene citrate (CC) is the first approach to induce ovulation in patients with PCOS. Although 70-80% of PCOS women can ovulate by the treatment with CC, only 40% of the PCOS women become pregnant. Women who do not ovulate with increasing doses of CC are described as being CC-resistant and remain a major challenge in gynecologic endocrinology [2].

Over the last years, there have been different regimens to treat patients who fail to ovulate with the initial dose of clomiphene citrate. Each one of these regimens have advantages and disadvantages, these include: A simple dose increase of clomiphene citrate in the next cycle after progestin withdrawal [3] A recent, large, prospective, randomized, multi-center trial does not support the hypothesis that metformin, either alone or in combination with CC, improves the rate of live birth in women with PCOS [4].

Other modalities of treatment include the use of aromatase inhibitors, gonadotropin therapy, which is very expensive and require intensive monitoring with serum estradiol and ultrasound assessments to minimize the risks of multiple pregnancy, and ovarian hyper stimulation [5].

Hurst et al described a novel clomiphene stair-step protocol that is designed to reduce time to ovulation in women with polycystic ovary syndrome [6].

Stair-step protocol is new protocol for ovulation induction and not well studied by large randomized controlled study, so we designed this study to evaluate its efficacy in patients with PCO [7]. The aim of this study was to compare among the use of clomiphene citrate by stair-step protocol and use of combined clomiphene citrate and gonadotropins in patients with polycystic ovary syndrome. The aim of this study is to determine the efficacy of stair step protocol compared to traditional protocol in ovulation induction of polycystic ovarian syndrome (PCOS) patients in terms of increasing rate of ovulation and pregnancy.

2. PATIENTS AND METHODS

This study is non-blinded, multicenter, randomized controlled study and was carried out on infertile women attending the Fertility Clinic of Tanta University Hospital and Hurghada General Hospital. The study started from November 2018 till September 2019. Two Hundred infertile patients with PCOS criteria and no other causes of infertility were enrolled according to inclusion and exclusion criteria.

2.1 Inclusion Criteria

The selected females fulfilled the following criteria:

1) Age: 20-35 years old. 2) BMI: 22- 25.
3) Tubal patency confirmed by either hysterosalpingogram or during diagnostic laproscope.
4)Normal semen analysis according to WHO criteria (2010).
5)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 10 cm3), and clinical or biochemical signs of hyperandrogenism with exclusion of other androgen excess disorders.

2.2 Exclusion Criteria

1) Women aged > 35 years old. 2) BMI > 25.
3) Female with bilateral tubal blockage diagnosed either by hystrosalpingogram or during diagnostic laproscope.
4) Endocrine disorders.
5) Pelvic endometriosis.
6) Previous gynecological operations.
7) Hormonal drugs 6 months before inclusion in the study.
8) Medical disorders like renal or hepatic diseases.

2.3 Randomization and Allocation:

Randomization: It was done by computer-generated program. Allocation: Selected patients were allocated into two groups with 1:1
ratio.

Group (1): was subjected to stair-step stimulation protocol.
Group (2) was subjected to traditional stimulation protocol.

2.4 Methods

All cases were subjected to the following:

2.5 I. History Taking:

A full detailed history was taken from all patients:

1) Full history with special attention to age, type and duration of infertility.
2) Full menstrual history as regards rhythm of cycle, duration, amount of bleeding, presence of dysmenorrhea and last menstrual period.
3) Male history: as regards medical history e.g. DM and surgical history
e.g. varicocele.
4) Obstetric history: e.g. pregnancy complications such as miscarriage, retained placenta and previous ectopic pregnancy.
5) Past history which include:
a) Medical history: e.g. liver and renal diseases.
b) Surgical history: focusing on pelvic and abdominal surgeries
e.g. myomectomy
c) Drug history: hormonal, hepatic or renal drugs.
6) History of previous operation and investigation e.g. hystrosalpingography, serum FSH, LH, Testosterone and Anti- Mullerian hormone level.

III. Physical examination:

All patients subjected to general, abdominal and pelvic examination as follow:

1) General examination with special attention to measurement of BMI, acne, hair distribution, exophthalmos and skin pigmentation.
2) Abdominal and pelvic examination: to detect any pelvi-abdominal mass such as myoma, ovarian masses or cysts and vaginal masses.
3) Thyroid examination.
4) Breast examination with special attention to galactorrhea.

IV. Investigation:

1) Serum FSH and LH on the third day of menstrual flow.
2) Serum Testosterone and Prolactin level.
3) Serum AMH level.
4) Husband semen analysis.
5) Baseline ultrasound using a 7.5 MHz vaginal probe of ultrasound at day 3 of cycle before starting the initial dose of CC to identify pretreatment ovarian cysts and confirm ovarian morphology for PCOS.

V. Follow up:

Ovulation was confirmed by folliculometry (follicle tracing) by TVUS. When leading follicle (10 mm) was seen, HCG (10000IU) was administered intramuscularly and the patient was advised to have intercourse after 36 hours and on two subsequent days.

For both protocols, follow up of the follicular growth was made every other day. TVUS monitoring, which has the advantage of providing direct information about the size and number of follicle and measurement of endometrial thickness during CC medication.

2.6 Intervention:

First group (Stair-step protocol):

Stair-step protocol: 50mg CC was given for 5 days beginning on day 3 after spontaneous or progestin-induced withdrawal bleeding. TV US was done at the seventh day after the last pill. When there was no response (no follicle >10 mm), 100 mg CC was initiated immediately for 5 days, and U/S was repeated 1 week after the first Ultrasound and when there was no response , another 150 mg CC was initiated immediately for 5 days and Ultrasound was performed 1week after the second Ultrasound. If there is no response, another 200mg CC (maximum dose) was initiated immediately for 5 days and U/S was performed 1 week after the last Ultrasound.

Patients who failed to respond to this dose were considered a treatment failure.

If we detect endometrial suppression, women were given estradiol tablets 2 tabs/day till the time of ovulation.

2.7 Technique of Folliculometry:

1) A baseline transvaginal ultrasound was done at the start of the cycle (day 1 of the cycle) before the initiation of ovulation inducing agent to provide baseline information on the ovarian morphology and to delineate pelvic structures and then before the start of drug therapy in the next cycle. Any residual follicle more than 15mm in diameter was excluded from the study.

2) Transvaginal ultrasound folliculometry was started on the 10th day of the cycle and then according to each case till the dominant follicle reached 18 mm. Endometrial thickness and number of follicles of 17mm or more were measured when at least one follicle reaches a diameter of 18 mm. The woman was placed in the supine position with flexed legs and an empty bladder. The transvaginal probe was covered with coupling gel and introduce into one of the digits of a sterile surgical glove that was lubricated with coupling gel. Using the B-mode transvaginal sonography, morphology of the uterus (endometrial thickness) and ovaries was explored (folliculometry). The dominant follicle was measured in three planes as follows: after obtaining the roundest possible image using B-mode grayscale transvaginal ultrasound in two perpendicular dimensions, all section was obtained to gain information about the position of the uterus. Then the head of the transducer was directed into the lateral fornix of the vaginal vault and rotated 90 degrees. Therefore, a coronal section could be obtained and we were able to scan the ovaries. Lateral to and below the ovaries, a shape of a longitudinal vessel could be identified, the internal iliac artery.

2.8 Second Group (Traditional Protocol):

Traditional protocol: CC medication was initiated at day 3 after spontaneous or progestin-induced withdrawal bleeding. The starting dose was 50 mg/day for 5 consecutive days. Transvaginal ultrasound from 9th – 20th according to each case till the dominant follicle reached 18 mm diameter if ovulation occurred; the patient was excluded if no ovulation. We were waiting for next menses and were increasing dose to (100mg).

Transvaginal ultrasound from 9th_ 20th according to each case till if no ovulation occurred increase the dose to (150 mg) next cycle. Transvaginal ultrasound from 9th_20th according to each case till the dominant follicle reached 18 mm diameter if no ovulation we were wait for the next cycle and increase the dose to (200 mg) maximum dose. Transvaginal ultrasound from 9th_20th according to each case, Ovulation was used as the endpoint. If there is no ovulation for three treatment cycles, we considered it treatment failure.

The technique was the same as earlier mentioned in group 1 (stair-step protocol).
For both protocols, the cycle start time was defined as cycle day 1 of the first treatment cycle. Treatment failure was defined for the study as failure to ovulate following 200 mg clomiphene.

Side effects were obtained by reviewing all follow-up visits during the treatment cycles in which all patients were assessed for disorders associated with taking clomiphene. Vasomotor flushing, mood irritability, breast tenderness and gastrointestinal side effects (nausea and abdominal distension) were classified as mild side effects. Visual disturbances or severe headaches resulting in self-discontinuation of the medication were classified as severe side effects.

To assess comparative costs, the total expenses relating to the procedures and agents were computed and then compared. This analysis included costs of ultrasound and drug for both stair step and traditional protocol.

2.9 Outcomes of the Study:

2.9.1 Primary outcomes:

- Time to ovulate: the number of days in both protocols until ovulation occurs from the first day of the cycle.
- Ovulation rate: occurrence of ovulation by transvaginal ultrasound according to criteria of ovulation by US:
- Follicle suddenly disappears or regresses in size.
- Irregular margins.
- Intra follicular echoes, Follicle suddenly become more echogenic.

- Free fluid in pouch of Douglas.
- Increased perifollicular blood flow velocities in Doppler.
- Pregnancy rate: by serum pregnancy test two days after missed period for both protocols.

2.9.2 Secondary outcomes:

- Cost: the amount of money spent (in Egyptian pound) till ovulation including drug cost and medical services cost.
- The systemic side effects: vasomotor flushing, mood irritability, breast tenderness, gastrointestinal effects (nausea, abdominal distension) and visual disturbances were evaluated using questionnaires.
- Occurrence of complications: like ovarian hyperstimulation syndrome.

2.10 Statistical Analysis:

The sample size was calculated using Epi-Info software statistical package created by World Health organization and center for Disease Control and Prevention, Atlanta, Georgia, USA version 2002. The criteria used for sample size calculation (n>33) were 95% confidence limit, 80% power of the study, expected outcome in treatment group 90% compared to 60% for control groups.

Analysis of data were performed by SPSS v25 (SPSS Inc., Chicago, IL, USA). Quantitative parametric variables (e.g. age) were presented as mean and standard deviation (SD). They were compared between the two groups by unpaired student's t- test and within the same group by paired T test. Quantitative non-parametric variables (e.g. VAS) were presented as median and range and compared between the two groups by Mann Whitney (U) test and within the same group by Wilcoxon test. P value < 0.05 was considered significant.

3. RESULTS

Patients were randomly allocated into two groups with 1:1 ratio.

Group (1): was subjected to stair-step stimulation protocol

Group (2): was subjected to traditional stimulation protocol.

Table 1. showed that there was no significant difference between both groups as regard to patients characteristics as age, BMI, type and duration of infertility (P = 0.150, 0.303, 0.296, 0 .208 and 0.247).

Table 2. showed that there was no significant difference between both groups as regard to serum FSH, LH, Prolactin, TSH, AMH and free testosterone (P = 0.912, 0.141, 0.943, 0.781, 0.350 and 0.098).

Table 3. showed that there was a significance difference between both study groups as regards time to ovulate (d) (p = 0.000) and there was a significant
difference between both study groups as regard total cost per case (p = 0.000) where stair step protocol showed lower cost, but there was no significance difference between both study groups as regards endometrial thickness (p = 0.323).

Table 4 showed there was significant difference between two study groups as regards ovulation rate and pregnancy rate. (P = .032, .049).

Table 5 and figure 1 showed there was significant difference between two study groups as regards ovulation rate at different doses of CC except 2250 mg (P = 0.038, 0.032, 0.402 0.032).

Table 6 showed there was no significant difference between two groups as regards mild and severe side effects (P= .0173, 0.203).

Table 1. Patients characteristics of the studied groups:

Range	20 - 35	23 - 35	
Mean ±SD	28.05 ±4.21	28.83 ±3.38	
Median	28	28	0.150
Range	22 – 24.9	22 – 24.9	
Mean ±SD	24.02 ±0.79	23.88 ±1.03	
Median	23.85	23.85	0.303
0	68 (47.22)	76 (52.78)	
1	16 (51.61)	15 (48.39)	

2	16 (64.00)	9 (36.00)	0.296
1ry	68 (47.22)	76 (52.78)	
2ry	32 (57.14)	24 (42.86)	0.208
Range	1 – 7	1 - 7	
Mean ±SD	3.58 ± 2.14	3.91 ± 1.87	
Median	3	4	0.247

BMI, body mass index.

Table 2. Hormonal profile of the studied cases:

Range	1.40 –11.20	1.40 – 10.00	
Mean ± SD	6.33 ± 2.22	6.29 ± 2.26	0.912
Range	2.20 –18.00	2.40 – 18.00	
Mean ± SD	10.09 ±4.54	11.05 ± 4.64	0.141
Range	9.52 –33.40	9.52 – 25.60	
Mean ± SD	15.95 ± 5.53	16.00 ± 5.19	0.943
Range	5.20 –14.70	5.20 – 14.90	0.781
Mean ± SD	9.92 ± 2.05	10.02 ± 2.65	
Range	0.50 – 4.00	0.50 – 4.00	0.350
Mean ± SD	2.30 ± 1.05	2.16 ± 1.03	
Range	1 – 4.1	1.1 – 4.2	0.098
Mean ± SD	2.40 ± 0.86	2.61 ± 0.84	

Table 3. Preovulatory Endometrial thickness, time toovulate and total cost of the studied groups:

Range	5.20 – 13.00	5.20 – 13.00	0.323
Mean ± SD	8.92 ± 2.10	9.25 ± 2.26	
Median	8.70	9.25	
Range	12 - 28	14 - 105	0.000*
Mean ± SD	18.83 ± 5.43	54.37 ± 29.73	
Median	21.00	48.00	
Range	272.50-543.5	247.50-822.50	0.000*
Mean ± SD	373.28±98.06	492.01±176.13	
Median	400.50	460.50	

Table 4. Ovulation and pregnancy rates by ClomipheneCitrate dose of the studied groups:

60 (71.43)	49 (55.68)	**0.032***
38 (45.24)	27 (30.68)	**0.049***

Table 5. Ovulation rate by total CC dose of the studiedgroups:

Total dose of CC (mg) per ovulatory cycle			**P value**
250 mg	NA	13 (14.77)	NA
750 mg	29 (34.52)	18 (20.45)	0.038*
1250 mg	20 (23.81)	10 (11.36)	0.032*
2250 mg	11 (13.10)	8 (9.09)	0.402
Total ovulation rate	60 (71.43)	49 (55.68)	0.032*

NA not applicable.

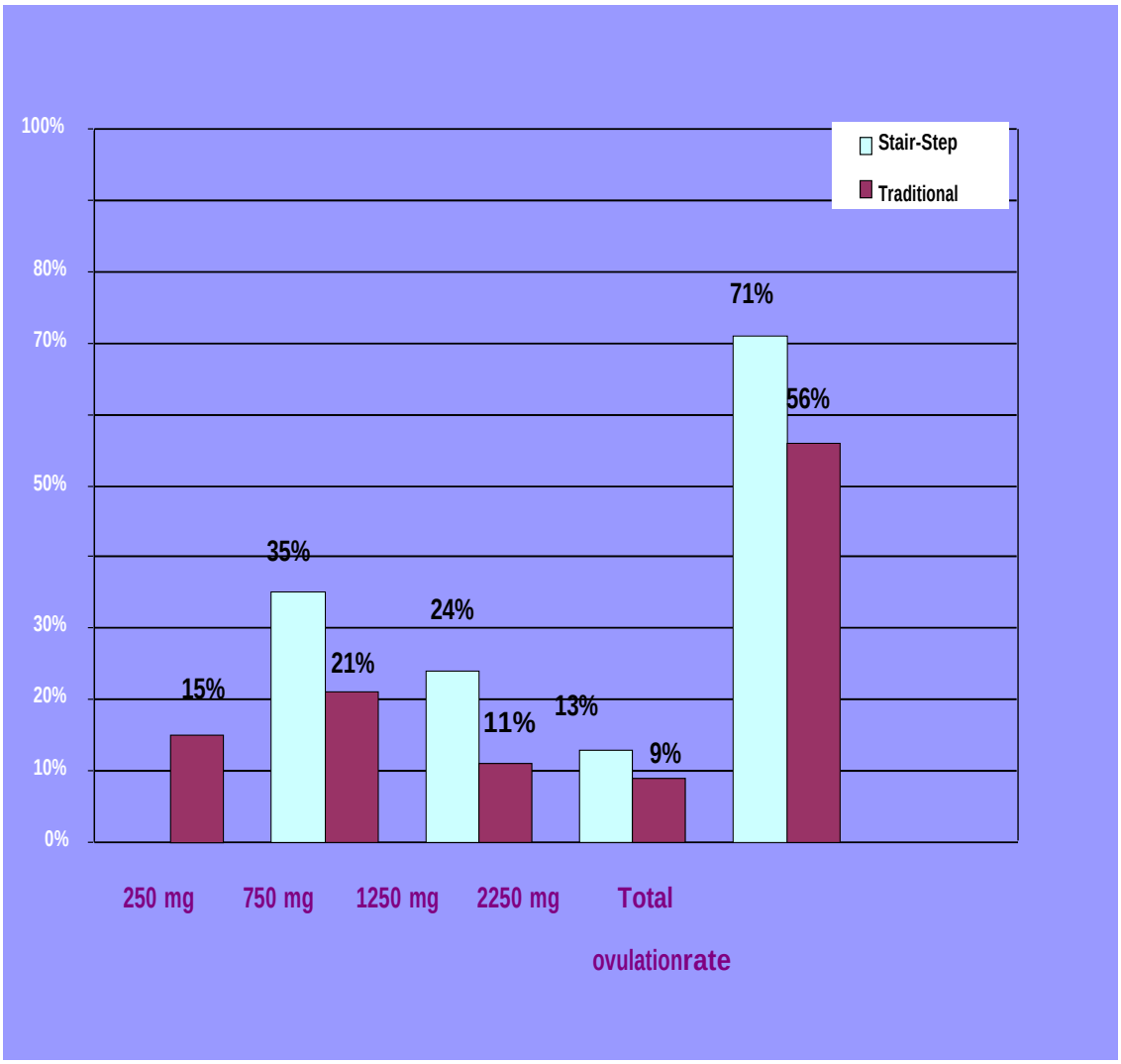

Fig. 1. shows the ovulation rate by different clomiphene citrate doses and total ovulation rate.

Table 6. The systemic side effects of the studied groups:

Mild side effects					
Not documented	60	(71.43)	75	(85.23)	
GIT symptoms	6	(7.14)	3	(3.41)	
Headache	5	(5.95)	5	(5.68)	0.173
Mastalgia	2	(2.38)	2	(2.27)	
Mood swing	2	(2.38)	0	(0.00)	
Vasomotor Symptoms	9	(10.71)	3	(3.41)	
Severe side effects					
Not documented	80	(95.24)	87	(98.86)	
Visual symptoms	4	(4.76)	1	(1.14)	0.203

4. DISCUSSION

Polycystic Ovary Syndrome (PCOS) is one of the most common causes of anovulatory infertility, affecting 8-13% of reproductive-aged women [8]. It is by far the most common cause of hyper androgenic anovulatory infertility and was described more than half a century ago, the underlying cause of this disorder is still uncertain [9]. The classic symptoms of the disease are due to increased ovarian androgen production and chronic anovulation. There are several clinical and laboratory criteria such as obesity, acanthosis nigricans, oligomenorrhea, hirsutism and acne, as well as decreased ovulatory rate [10].

Clomiphene citrate (CC) is the first drug of choice in the management of infertility in PCOS. Although CC treatment is usually initiated in days 2–5 of menstruation, it may be initiated at any time in patients with oligo- amenorrhea. However, clinicians usually prefer to begin CC treatment following spontaneous or progesterone-induced menstruation in these patients. Generally, 50 mg CC for 5 days is used in the first cycle [11].

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. Approximately20 % of the patients is refractory to CC regimen (12). Although the maximum dose of CC is 250 mg/day, clinicians prefer not to use doses above 150 mg/day and these patients are regarded as CC. Resistant [13]. It is reported to be effective in inducing ovulation, increased pregnancy rate, improve uterine environment, endometrial development with favorable cervical mucus [14]. This is why the study was selected to compare Clomiphene citrate 'stair-step' protocol and traditional protocol in patients with polycystic ovary syndrome.

The present study showed that there was no significant difference between groups regarding age. The mean ± SD ages of patients and controls were (28.05 ± 4.21) years and (28.83 ± 3.38) years, respectively. In addition, there was no significant difference between groups regarding BMI.

These results are in the agreement with study conducted by [15] who reported that the mean ± SD ages of patients and controls were (23.1 ± 3.7) years and (24.9 ± 3.5) years, respectively. Also in agreement with (Agrawal et al., 2017) who reported that mean ± SD ages of patients and controls were (26.17 ± 3.9) years and (26.87 ± 3.87) years.

There was no significant difference between groups regarding to parity. The present study showed that there was insignificant difference between both groups as regard to serum FSH, LH, Prolactin, TSH, AMH and free testesrone levels.

Clomiphene citrate (CC) is advised to be the first-line treatment for polycystic ovary syndrome (PCOS) and other subfertility illnesses associated with oligo ovulation since it is effective, low-cost, easily available, and the majority of women tolerate it well, it increases the ovulation rate (60-85%) but decreases the pregnancy rate (only by about 20%) due to its adverse effects on the endometrium [16].

According to the previous studies, the administration of HCG following pre-stimulation with CC inhibits detrimental effects of CC on the endometrial competence and therefore increases the development, proliferation, and thickness of endometrium [17].

In the present study, we demonstrated that ovarian hyper-stimulation using the stair step protocol revealed shorter time period to reach to ovulation and/or decision resistance to CC. The duration of treatment taken for success in stair-step protocol group was 12-28 days. In traditional group, this time duration for ovulation was 14-105 days with total mean time to ovulate (18.83 ± 5.43 days vs 54.37 ± 29.73) days, respectively (P=0.00). The difference in the period required to attain ovulation was statistically significance (P=0.000) .

Agrawal K et al. in his study concluded with similar mean duration of treatment taken for success in SSP group which was 13.65 ± 6.78 days. In traditional group, this time duration for ovulation was 32.80 ± 20.44 days [18]. The difference in the period required to attain ovulation was statistically significance (P = 0.003). Hurst et al. in his study had similar results where ovulation time was shorter with the SSP (23–25 days) compared with the traditional regimen (55–88 days). The shortened time

required to achieve ovulation or determine failure was a clear advantage over traditional group [19].

In our study, ovulation and clinical pregnancy rates were higher in the stair-step protocol which is consistent with previous studies. Cumulative ovulation rate was significantly higher in patients who underwent ovulation using the stair-step protocol compared with those undergoing the traditional protocol (60/84 [71.43%] vs 49/88 [55.68%], P ≥ .048). When comparing ovulation rates by dose, A significantly higher ovulation rates 34.52 %, 23.81% were observed at stair step protocol at a clomiphene total dose per ovulatory cycle 750 mg, 1250 mg compared with the expected ovulation rate of 20.45 % , 11.36 % with these doses respectively in a traditional regimen (p=0.003).

These results were in agreement with study conducted by Jones et al. were cumulative ovulation rate was significantly higher in patients who underwent ovulation introduction using the stair-step protocol compared with those undergoing the traditional protocol [20].

Improved ovulation rates are thought to be the result of an additive effect of multiple doses. The half-life of clomiphene is 5–7 days, but may be longer resulting from variability in metabolism. When patients take their next dose, active isomers are still circulating in the system, making the total circulating concentration higher than in traditional protocols, in which previous clomiphene has time to wash out.

Cumulative pregnancy rate was (45.24% vs. 30.68%) in stair step group compared to traditional group, respectively that was significantly higher (P=0.049%).

These results disagreed with result obtained by Hurst et al. with clinical pregnancy rate for stair step protocol of 13% and for traditional protocol of 15 %.[21]. This difference in pregnancy rate between our study and his study could be explained that in Hurst et al the total number of patients enrolled in the stair step protocol was 31 patients while in our study the total number was 84 patients, and about traditional protocol Hurst et al 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 In our study, although endometrial thickness was less in the stair- step group (8.92 ± 2.10 mm) compared to traditional group (9.25 ± 2.26 mm) there was no significance difference between the stair step and control groups in endometrial thickness, which may be explained by the fact that endometrial thickness in the range 5.5–8.25 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 [22].

These results were in agreement with study conducted by Deveci et al [23] who revealed that there was no significant difference between the stair-step and control groups in endometrial thickness (8.3± 2.1 vs 9.3 ± 2.4 mm, respectively) on the day of HCG administration.

Our study reported that there were no significant differences between groups at any CC dose in the occurrence of any side effect of CC. There were no differences in symptom severity at any dose of CC between groups. While more participants in the stair-step protocol experienced severe symptoms as visual disturbances (4.76 %) more than the traditional group (1.13%), this did not reach statistical significance.

In the results of the current study, there was a tendency for a higher rate of hot flushes, pelvic pressure, pelvic pain and breast tenderness in the stair-step protocol. However, these side effects did not reach statistical significance. These results agreed with result of study conducted by Deveci et al. which revealed that the distribution of the systemic side effects according to the severity of the symptoms was similar between the groups. Although there were no statistically significant differences between the two groups in systemic adverse effects, rates of hot flushes, pelvic pressure, pelvic pain and breast tenderness were slightly higher in the stair-step group [24].

Several cases of visual disturbances have been reported and are reversible with no significant sequelae. Authors conclude that visual disturbance is likely the result of the temporary effect of clomiphene on the visual cortex and not the retina [25].

Many patients desire a more active and aggressive management and get very distressed

by having to wait for menses or have their menses induced. They are at higher risk for depressive illnesses, anxiety symptoms, and social phobias. For many patients, the stair-step protocol might be a good option, since women are more likely to drop out of therapy if they are anovulatory with treatment as their frustration increases [26].

Overall, severe adverse events with clomiphene administration are rare. The effectiveness of the stair-step protocol and benign nature of the majority of side effects make the stair-step method an acceptable and tolerable protocol for patients.

In our study to assess comparative costs, the total expenses related to the procedures and agents were computed. This analysis included cost of ultrasounds and total drug cost for both the stair-step protocol and the traditional protocol.

The stair-step technique cost 373.98 LE each ovulatory cycle, while the conventional strategy cost 492.01 176.13 LE every ovulatory cycle. There was a statistically Cost difference between two groups, with stair step procedure showing reduced cost.

(P=0.000). The result of our study agreed with results of Hurst et al. study which concluded that the estimated cost of treatment per ovulatory cycle was $589 with the stair-step protocol and $879 with the traditional approach [27].

The stair-step approach requires U/S monitoring, which may not be practical for all providers. However, the shortened time required to achieve ovulation or determine a treatment failure is a clear advantage over traditional progestin withdrawal dose increases. The stair-step protocol is simple to incorporate into a practice that utilizes U/S for clomiphene monitoring. Patient satisfaction with this approach is high because virtually all our initially nonresponsive PCOS patients choose the stair-step approach.

5. CONCLUSIONS

This study concluded that stair step regimen improves the ovulation rate and pregnancy rate without any detrimental side effects compared to traditional regimen. It helps to know the sensitivity and resistance of an individual to CC much earlier and helps to plan ahead with alternative treatment for desired outcome. The advantage of shorter treatment period with similar side effects makes the stair step protocol suitable for use in routine clinical practice.

ETHICAL APPROVAL AND CONSENT

Written confirm consent from every patient included in this study. The permission proved by the medical ethical committee of Tanta University Hospital.

DISCLAIMER

The authors claim no conflicting interests. The items utilised in this study are widely used in our research area and nation. There is no conflict of interest between the writers and manufacturers of the goods since we are not using them for litigation but for scientific progress. Also, the study was not financed by the production business but by the writers themselves.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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