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Comparative Study between Stair-step Protocol of Clomiphene Citrate and Combined Clomiphene and Gonadotropins for Induction of Ovulation in Women with Polycystic Ovary Syndrome

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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 ovary syndrome affects 7 to 8% of women and may be the most common cause of female infertility. Anovulation, early pregnancy loss has all been implicated in the low fecundity. The aim of this study was to compare between the use of clomiphene citrate by stair-step protocol and use of combined clomiphene citrate and gonadotropins in patients with polycystic ovary syndrome.
Methods: This randomized non blinded controlled clinical study was carried out on 60 Patients who was selected from outpatient clinic of Tanta university hospitals from September 2019 to September 2020. Selected patients were allocated into two groups with 1:1 ratio. Group (A): was subjected to clomiphene citrate stair-step stimulation protocol. Group (B): was subjected to combined clomiphene and gonadotropins stimulation protocol.

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Results: Mann-Whitney U test was used to compare quantitative data because it is not normally distributed (Age, BMI and duration of infertility). Significance defined by $p < 0.05$. Chi-square analysis was used for the categorical variable (number of MGF). Mann-Whitney U test was used to compare quantitative data because it is not normally distributed (Size of larger follicle and Endometrial thickness), Chi-square analysis was used for the categorical variables (Ovulation rate and Pregnancy rate). Mann-Whitney U test was used to compare quantitative data which are not normally distributed (FSH and LH). Student t test was used for the quantitative data which are normally distributed (Prolactin and TSH).

Conclusions: In conclusion, the CC stair-step protocol is a safe, simple option for the management of PCOS patients, having a larger number of mature Grafian follicle, lower endometrial thickness and higher ovulation rate compared to combined clomophine and gonadotrophin protocol.

Keywords: Clomiphene citrate; gonadotropins; ovulation; polycystic ovary syndrome.

1. INTRODUCTION

Polycystic ovary syndrome affects 7 to 8% of women and may be the most common cause of female infertility. Anovulation, early pregnancy loss has all been implicated in the low fecundity of women with this disorder. Obesity is also common in such women and this condition alone appears to have an adverse effect on reproduction. The cause of the polycystic ovary syndrome is poorly understood, and both the diagnosis and treatment of the disorder are controversial [1].

According to the Rotterdam criteria, polycystic ovary syndrome (PCOS) is diagnosed if two of 3 criteria present: oligo-anovulation, ultrasonographically defined polycystic ovaries and clinical or biochemical signs of hyperandrogenism with the exclusion of other androgen excess disorders. Chronic anovulation is one of the most common causes of infertility in women with PCOS. Oocyte quality or endometrial and implantation abnormalities also may contribute to the pathogenesis of infertility in PCO [2].

Infertile anovulatory women who want to conceive are candidates for ovulation induction. 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. In cases of anovulation, CC dose is increased by 50 mg in the subsequent cycle. With this protocol, it has been reported that 52% of patients ovulate with a CC dose of 50 mg/day, 22% with 100 mg/day and 12% with 150 mg/day. Approximately 20% of the patients is refractory to CC regimen. 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 [3].

A new protocol is the stair-step protocol in which the increasing daily CC dose is administered without intervening menses between the dosages. The important point is that ultrasonographic monitoring is required during the stimulation. 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 [4].

Gonadotropins have been widely used worldwide for many years to induce ovulation. Three main exogenous gonadotropins are used for ovulation induction—follicle stimulating hormone (FSH), luteinizing hormone (LH) and human chorionic gonadotropin (HCG). Currently, these gonadotropins are available in the urinary (with the exception of LH) and recombinant forms. FSH (± LH) is used to stimulate follicular development and HCG is used to trigger ovulation of the mature follicle(s). The choice of gonadotropin preparation and treatment regimen depends on the underlying ovarian dysfunction. Strict monitoring of gonadotropin treatment with implementation of strict cancellation criteria are recommended to minimize the risks of ovarian hyperstimulation and multiple pregnancy [5]. The aim of this study was to compare between the use of clomiphene citrate by stair-step protocol and use of combined clomiphene citrate and

gonadotropins in patients with polycystic ovary syndrome.

2. METHODOLOGY

2.1 Patients and Methods

This randomized non blinded controlled clinical study was carried out on 60 Patients who was selected from outpatient clinic of Tanta university hospitals from September 2019 to September 2020. The patients were selected according to the following inclusion and exclusion criteria.

Inclusion criteria

1. Patients diagnosed as polycystic ovary syndrome according to Rotterdam criteria 2016 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 10 cm3), and clinical or biochemical signs of hyperandrogenism with exclusion of other androgen excess disorders.
2. BMI less than 30kg/m^2
3. Patients who failed induction of ovulation at low dose clomiphene citrate 100mg.

Exclusion criteria

1. Any other associated reasons for infertility such as tubal pathology or male factor.
2. Previous gynecological operation.
3. Woman's age more than 35 years old.
4. Any other endocrinological diseases such as Cushing syndrome, hyperthyroidism and diabetes mellitus.
5. Women with any contraindication to get pregnant

Privacy of all patients' data is granted by a special code number for every patient file that includes all investigations.

Randomization &Allocation:

Randomization:

It was done by computer-generated program.

Allocation:

Selected patients were allocated into two groups with 1:1 ratio.

Group (A): was subjected to clomiphene citrate stair-step stimulation protocol.

Group (B): was subjected to combined clomiphene and gonadotropins stimulation protocol

Methods:

Full history taking:

A full history was taken from all patients:

1) Full personal 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) Obstetric history: e.g. pregnancy complications such as miscarriage, retained placenta and previous ectopic pregnancy.
4) Past Medical history: e.g. liver and renal diseases.
5) Past Surgical history: with special attention to pelvic and abdominal surgeries e.g. myomectomy
6) History of drugs: hormonal, hepatic or renal drugs.
7) History of previous operation and investigation e.g. hystrosalpingography, serum FSH, LH and Testosterone level.

Complete 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) Thyroid examination.
3) Breast examination with special attention to galactorrhea.
4) 4) Abdominal and pelvic examination: to detect any pelviabdominal mass such as myoma, ovarian masses or cysts and vaginal masses.

Laboratory investigations

- Day 3 serum follicle stimulating hormone (FSH) &Luteinizing hormone (LH).
- Prolactin.
- Thyroid stimulating hormone (TSH) levels.

- Semen analysis of husband
- 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.

Blood Collection and Laboratory Assay:

Laboratory assays were performed on blood obtained from polycystic ovary syndrome patients at day 3 of menstrual cycle. Serum blood samples were collected by standard venipuncture in VACUETTE® Blood Collection Tubes (Greiner Bio-One, Austria) containing clot activator/Sep. Serum samples were left to clot 5 to 10 minutes at room temperature. Serum samples were used for routine laboratory investigations. serum samples were stored at -20°C till the time of laboratory assay. Day3 serum FSH and LH, prolactin and TSH levels were measured by ELISA kit (ready-to-use Sandwich ELISA).

These women were randomly divided in to two groups

The two groups are group A they were subjected to clomiphene citrate by stair-step stimulation protocol and group B were subjected to combined clomiphene citrate &gonadotropins stimulation protocol.

- In group A (n = 30) (stair-step protocol)
- The cycle start time was defined as cycle day 1 of the first treatment cycle.
- 50 mg CC was given daily for 5 days following the onset of a spontaneous or progestin-induced menses.
- Follicular response was monitored with transvaginal ultrasonography starting on day 8.
- When the follicle failed to reach size above 10mm on cycle day 14, the dosage was increased to 100 mg daily for 5 days.
- On cycle day 19, the evaluation by transvaginal ultrasonography was done.
- When follicle failed to reach size above 10mm on cycle day 21 150mg clomiphene was given daily for 5 days
- When the mean diameter of the leading follicle reached 18 mm, HCG (human chorionic gonadotropins) 10000 IU was administered.
- Cycle cancellation was done when there was a failure of follicular response on cycle day 28.
- The cycle was cancelled in patients who failed to ovulate even after 72h of HCG injection
- Pregnancy was diagnosed by serum pregnancy test and a gestational sac with fetal heart beat was detected on transvaginal ultrasound examination 4 weeks following HCG administration.
- The daily dosage of CC was not increased above 150 mg daily because of the potentially adverse effects of the cumulative doses.
- In group (B) (n = 30) (combined clomiphene and gonadotropins stimulation protocol)

1. The cycle start time was defined as cycle day 1 of the first treatment cycle.
2. Clomiphene citrate was adminstered at 100mg daily for five days from the second day of the cycle.
3. Gonadotropins was given subcutaneously at third, fifth and seventh day of cycle in dose 75 international units rFSH (e.g gonal f).
4. Evaluation by transvaginal ultrasonography was done on cycle day 8 and 12.
5. When the mean diameter of leading follicle reached 18 mm, 10000 IU hCG was administered subcutaneously as a single dose.
6. When there was no follicular response on cycle day 20, the cycle was cancelled.
7. The cycle was cancelled in patients who failed to ovulate even after 72h of HCG injection.

2.2 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 in treatment group 90% compared to 60% for control groups.

Analysis of data was 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

Mann-Whitney U test was used to compare quantitative data because it is not normally distributed (Age, BMI and duration of infertility). Significance defined by p < 0.05.

Table 1 showed that, there was no significant difference between both studied groups as regard to patients characteristics as age, BMI and duration of infertility (P = 0.348, 0.165, and 0 .942).

Mann-Whitney U test was used to compare quantitative data which are not normally distributed (FSH and LH). Student t test was used for the quantitative data which are normally distributed (Prolactin and TSH), Significance defined by p < 0.05.

Table 2 showed that, there was no significant difference between both studied groups as regard to serum FSH, LH, Prolactin and TSH level (P = 0.147, 0.311, 0.651 and 0.505).

Table 1. Patients characteristics of the studied groups

Variable name		Stair-Step (n = 30)	Clomiphene and Gonadotropin (n = 30)	P value
Age (y)	Mean ± SD	26.00 ± 3.26	26.70 ± 3.18	0.348
	Median (range)	25 (22 – 33)	26 (22 – 33)	
BMI (kg/m^2)	Mean ± SD	25.51 ± 1.37	26.08 ± 1.27	0.165
	Median (range)	25.6 (23.4 – 27.8)	25.8 (24.2 – 29.1)	
Duration of infertility (y)	Mean ± SD	2.60 ± 0.80	2.58 ± 0.72	0.942
	Median (range)	2 (1.5 – 4)	2 (2 – 4)	

BMI, body mass index. Data are presented as mean ± SD and median (range).

Table 2. Hormonal profile of the studied cases

Variable name		Stair-Step (n = 30)	Clomiphene and Gonadotropin (n = 30)	P value
FSH	Mean ± SD	5.55 ± 1.96	6.33 ± 1.53	0.147
	Median (range)	6.3 (2.4–8.5)	6.6 (3.2–9.2)	
LH	Mean ± SD	12.70 ± 4.67	13.11 ± 3.26	0.311
	Median (range)	11.1 (5.6–23.1)	12.5 (9.2–20.1)	
Prolactin	Mean ± SD	19.59 ± 6.51	20.28 ± 5.09	0.651
	Median (range)	19.5 (8.6–35.6)	20.6 (9.8–28.5)	
TSH	Mean ± SD	2.02 ± 0.74	1.91 ± 0.57	0.505
	Median (range)	2.2 (0.8–3.5)	2.1 (0.7–3.1)	

FSH, follicular stimulating hormone; LH, luteinizing hormone; TSH, thyroid stimulating hormone. Data are presented as mean ± SD and median (range).

Table 3. Number of MGF & its Diameter and endometrial thickness of the studied groups

Variable name		Stair-Step (n = 30)	Clomiphene and Gonadotropin (n = 30)	P value
Number of MGF	0 N (%)	4 (13.3)	16 (53.3)	
	1 N (%)	15 (50.0)	11 (36.7)	**0.002***
	2 N (%)	11 (36.7)	3 (10.0)	
Diameter of larger follicle (mm)	Mean ± SD	21.69 ± 1.49	21.07 ± 2.19	0.517
	Median (range)	22 (18–23)	22 (18–24)	
Endometrial thickness	Mean ± SD	9.67 ± 1.29	11.47 ± 0.83	**<**
	Median (range)	10 (8.0–11.5)	11.5 (10.0–12.5)	**0.001***

MGF, Mature graffian follicle.
Data are presented as mean ± SD and median (range) or number (%).

Chi-square analysis was used for the categorical variable (number of MGF). Mann-Whitney U test was used to compare quantitative data because it is not normally distributed (Size of larger follicle and Endometrial thickness), *Significance defined by $p < 0.05$.

Table 3 showed that, there was significant relation as regard to number of MGF between both studied groups ($P = 0.002$) as follow; for stair step group there was 4 (13%) versus 16 (53%) in combined group showed no ovulation, 15 (50%) in stair step group versus 11 (37%) in combined group showed one MGF and 11 (37%) in stair step group versus 3 (10%) showed two MGF.

There was no significant relation as regard to the mean size of larger follicle (mm) between both studied groups ($P = 0.517$) for stair step group was 21.69 ± 1.49 and ranged from 18 to 23 mm while in combined group it was 21.07 ± 2.19 and ranged from 18 to 24 mm.

There was significant relation as regard to endometrial thickness between both studied groups, ($P < 0.001$); as in stair step group it was 9.67 ± 1.29 and ranged from 8 to 12 mm while in combined group it was 11.47 ± 0.83 and ranged from 10 to 13 mm.

Chi-square analysis was used for the categorical variables (Ovulation rate and Pregnancy rate). Significance defined by $p < 0.05$ Fig. 1.

Table 4 showed that, there was a statistically significant relation as regards to the ovulation rate in both studied groups ($P = 0.001$)as it represent 26 (87%) in stair step group versus 14 (47%) in combined group with, Meanwhile there was no statistically significant difference between both studied groups ($P = 1$) as regards to the pregnancy rate.

Table 4. Ovulation and pregnancy rate of the studied cases

Variable name	Stair-Step (n = 30)	Clomiphene and Gonadotropin (n = 30)	P value
Ovulation rate	26 (86.7)	14 (46.7)	**0.001***
Pregnancy rate	6 (20.0)	6 (20.0)	1

Data are presented as n (%).

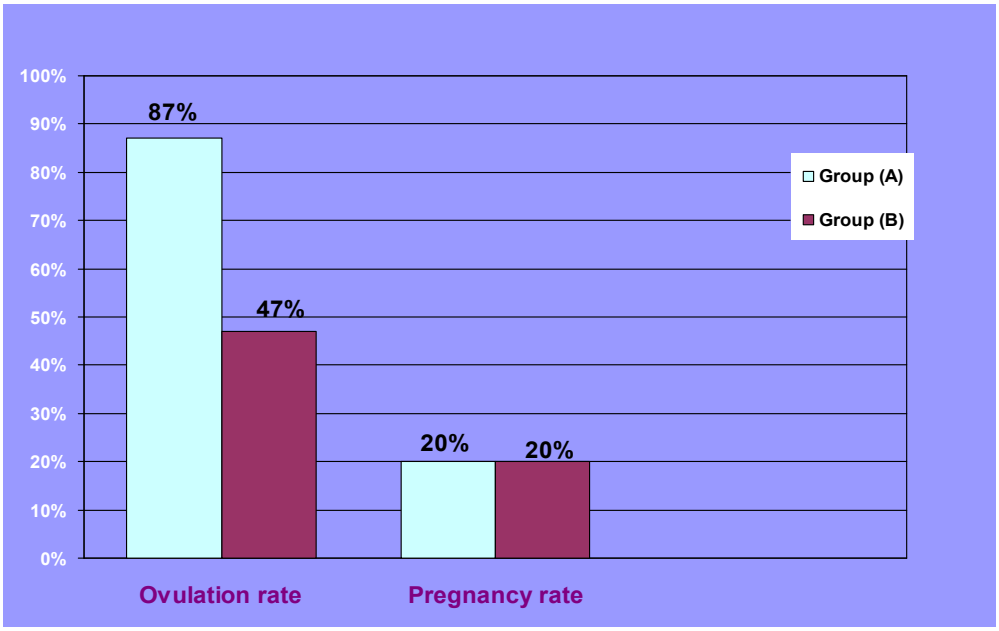

Fig. 1. Showing the difference between both studied groups as regard to the ovulation and pregnancy rate

Table 5. Correlations between the hormonal profile and the ovulation status in Stair-Step group (n=30)

Variable name		Ovulation		
		No (n = 4)	Yes (n = 26)	P value
FSH	Mean ± SD	5.64 ± 2.26	5.54 ± 1.96	0.976
	Median (range)	5.12 (3.8–8.5)	6.3 (2.4–8.1)	
LH	Mean ± SD	9.67 ± 3.47	13.17 ± 4.70	0.123
	Median (range)	8.9 (6.4–14.5)	12.0 (5.6–23.1)	
Prolactin	Mean ± SD	19.83 ± 4.65	19.55 ± 6.82	0.940
	Median (range)	18.2 (16.5–26.5)	20.1 (8.6–35.6)	
TSH	Mean ± SD	2.39 ± 0.85	1.96 ± 0.72	0.273
	Median (range)	2.4 (1.4–3.5)	2.1 (0.8–3.2)	

FSH, follicular stimulating hormone; LH, luteinizing hormone; TSH, thyroid stimulating hormone. Data are presented as mean ± SD and median (range).

Mann-Whitney U test was used to compare quantitative data which are not normally distributed (FSH and LH). Student t test was used for the quantitative data which are normally distributed (Prolactin and TSH), Significance defined by $p < 0.05$.

Table 5 showed that, there was no statistically significant relation between the hormonal profile and the ovulation status as regard to serum FSH, LH, Prolactin and TSH level (P = 0.976, 0.123, 0.940 and 0.273).

Student t test was used to compare normally distributed quantitative data (FSH, LH, Prolactin and TSH), Significance defined by $p < 0.05$.

Figs. 2-4 showed that, in Clomiphene and Gonadotropin group (n=30), there was no significant difference in the hormonal profile according to the ovulation status as regard to serum FSH, LH, Prolactin and TSH level (P = 0.398, 0.648, 0.727 and 0.803).

Table 6 showed that, there was no statistically significant relationship as regards to the endometrial thickness between women who showed no ovulation while in women who showed ovulation (P = 0.105) in stair step group (n=30), with the mean of endometrial thickness was 8.50 ± 0.71 and ranged from 8 to 10 mm in women who showed no ovulation while in women who showed ovulation it was 9.67 ± 1.29 and ranged from 8 to 12 mm.

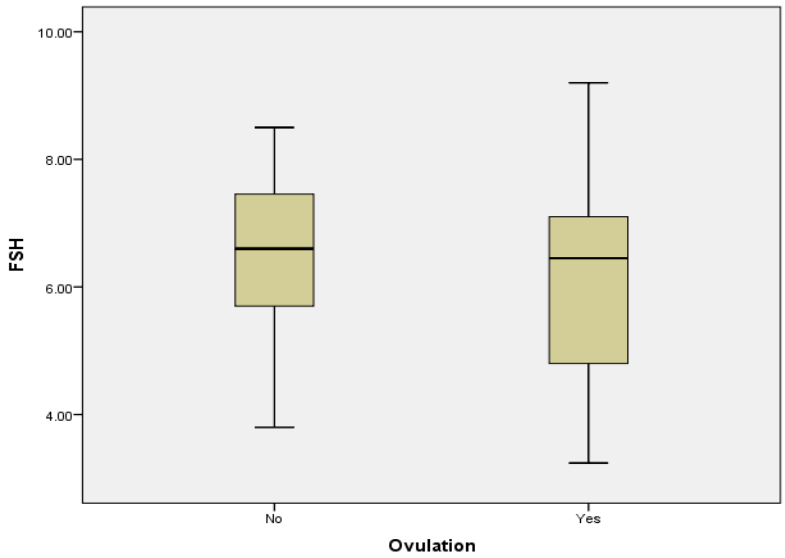

Fig. 2. Box plot graph showing the difference between women with and with-out ovulation in Clomiphene and Gonadotropin group as regard to the serum FSH

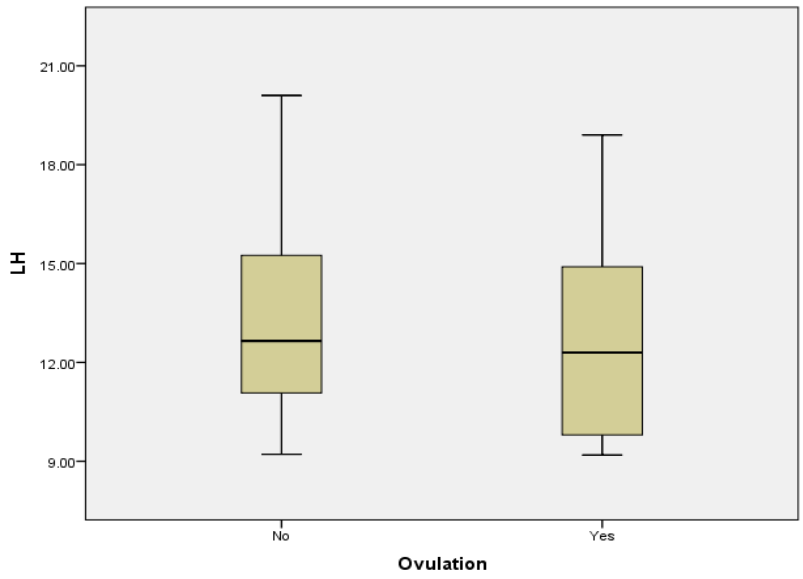

Fig. 3. Box plot graph showing the difference between women with and with-out ovulation in Clomiphene and Gonadotropin group as regard to the serum LH

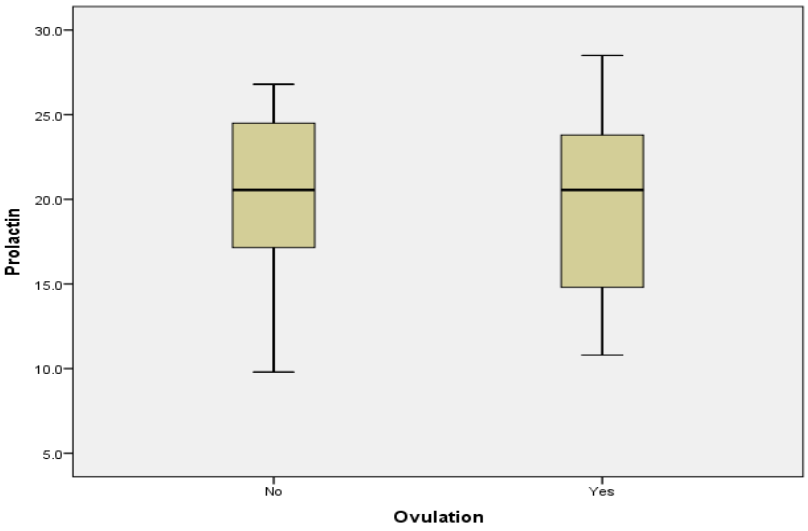

Fig. 4. Box plot graph showing the difference between women with and with-out ovulation in Clomiphene and Gonadotropin group as regard to the serum prolactin

Table 6. Relation between the ovulation status and endometrial thickness in Stair-Step group (n=30)

Variable name		Ovulation status		P value
		No (n = 4)	Yes (n = 26)	
Endometrial thickness	Mean ± SD	8.50 ± 0.71	9.67 ± 1.29	0.105
	Median (range)	8.25 (8.0–9.5)	10.0 (8.0–11.5)	

Data are presented as mean ± SD and median (range).
*Mann-Whitney U test was used to compare quantitative data because it is not normally distributed, *Significance defined by p < 0.05.*

Mann-Whitney U test was used to compare quantitative data because it is not normally distributed, *Significance defined by p < 0.05.

Fig. 5 showed that, in Clomiphene and Gonadotropin group (n=30), the mean of endometrial thickness was 11.47 ± 0.62 and ranged from 10.5 to 12.5 mm in women who showed no ovulation while in women who showed ovulation it was 11.43 ± 0.85 and ranged from 10 to 12.5 mm with no statistically significant difference between both studied groups (P = 0.949).

Table 7 showed that, there was a highly significant relation between endometrial thickness and pregnancy rate in stair step group (n=30), women with mean endometrial thickness of 9.13 ± 1.13 and ranged from 8 to 11 mm have not got pregnant while those with endometrial thickness of 11.08 ± 0.20 and ranged from 11 to 12 mm have got pregnant (P < 0.001).

Mann-Whitney U test was used to compare quantitative data because it is not normally distributed, *Significance defined by p < 0.05.

Fig. 6 showed that, in Clomiphene and Gonadotropin group (n=30), the mean of endometrial thickness was 11.25 ± 0.66 and ranged from 10 to 12.5 mm in non-pregnant women while in pregnant women it was 12.25 ± 0.27 and ranged from 12 to 12.5 mm with highly statistically significant difference (P= 0.002).

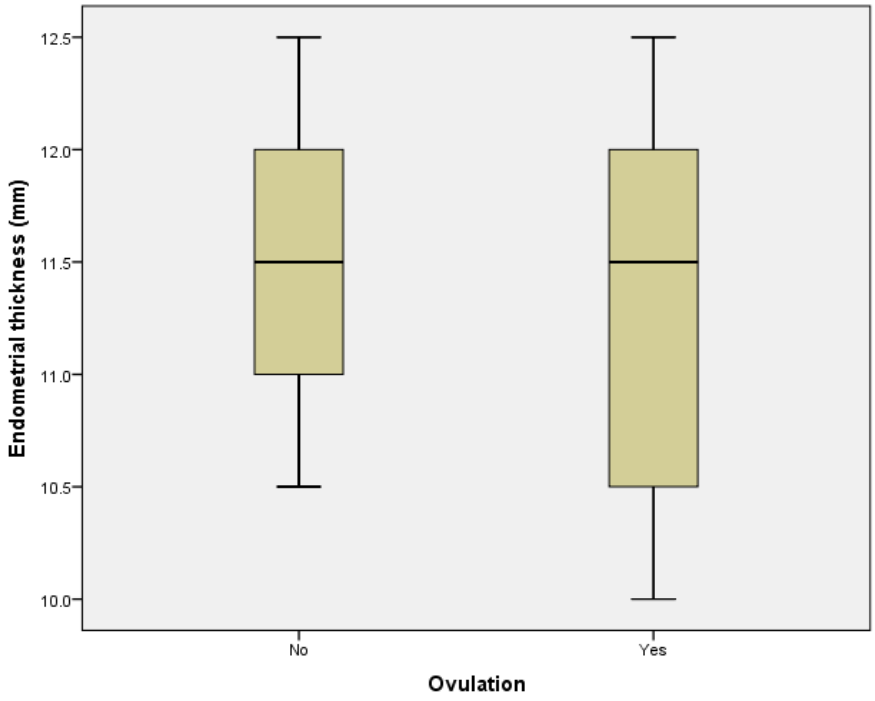

Fig. 5. Box plot graph showing the difference between women with and with-out ovulation in Clomiphene and Gonadotropin group as regard to the endometrial thickness

Table 7. Relation between the pregnancy status and endometrial thickness in Stair-Step group (n=30)

Variable name		Pregnancy status		P value
		No (n = 24)	Yes (n = 6)	
Endometrial thickness	Mean ± SD	9.13 ± 1.13	11.08 ± 0.20	**<0.001***
	Median (range)	8.75 (8.0–11.0)	11.0 (11.0–11.5)	

Data are presented as mean ± SD and median (range).
*Mann-Whitney U test was used to compare quantitative data because it is not normally distributed, *Significance defined by p < 0.05.*

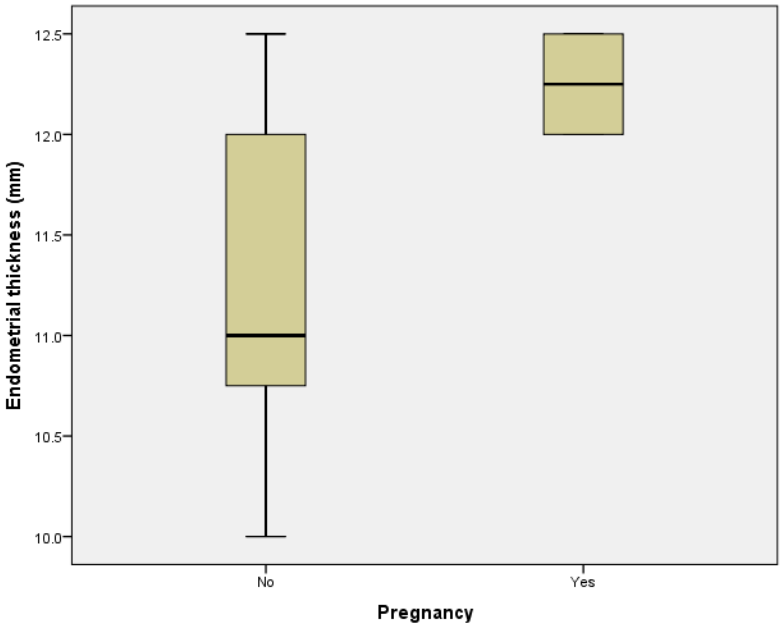

Fig. 6. Box plot graph showing the difference between pregnant and non-pregnant women in Clomiphene and Gonadotropin group as regard to the endometrial thickness

4. DISCUSSION

Polycystic ovary syndrome affects 7 to 8% of women and may be the most common cause of female infertility. Clomiphene citrate (CC) is the first drug of choice in the management of infertility in PCOS [6].

Clomiphene ovulation induction protocols for women who fail to ovulate with the initial dose of clomiphene have changed little in recent decades. Today the most commonly used approaches for clomiphene-resistant patients include either a simple dose increase in the next cycle after progestin withdrawal or co-treatment. A new protocol is the stair-step protocol in which the increasing daily CC dose is administered without intervening menses between the dosages [7].

Gonadotropins have been widely used worldwide for many years to induce ovulation. The choice of gonadotropin preparation and treatment regimen depends on the underlying ovarian dysfunction [8].

In the present study, there was no significant difference between both studied groups as regards to patients characteristics as age, BMI and duration of infertility (P = 0.348, 0.165, and 0 .942).

Also, there was no significant difference between both studied groups as regards serum FSH, LH, Prolactin and TSH level (P = 0.147, 0.311, 0.651 and 0.505).

In the same way, a previous retrospective cohort study on 61 anovulatory patients <40 years of age with polycystic ovary syndrome who underwent ovulation induction with a CC-SS protocol and a subsequent CC cycle. The total number of follicles ≥15 mm (2.8 ± 1.2 vs. 1.6 ± 0.7) was statistically significantly higher in the CC-SS cycle compared with the subsequent CC cycle, respectively [9].

The differences between this results and ours can be explained as follow; they selected patients resistant to traditional CC protocol while we selected patients who failed to respond to 100 mg CC dose, another reason they compared stair step CC versus gonadotrophin while we compared stair step CC versus combined CC and gonadotrophin.In concordance to the current study, a previous retrospective cohort study by Budinetz and his colleagues found that the endometrial lining was statistically significantly thinner in the CC-SS than the CC cycle (7.8 ± 1.8 vs. 9.2 ± 2.7, respectively) [10].

In a previous pilot randomized trial by Jones and his colleagues in which women with infertility and

oligomenorrhea or amenorrhea were randomly assigned to take either CC after a withdrawal bleed induced by medroxyprogesterone acetate (MPA) 10 mg daily for 10 days or to take CC without such a bleed. Study participants underwent cycle monitoring with ultrasound assessment of endometrial thickness at the time of LH surge or a human chorionic gonadotropin trigger [11]. They reported that there was no significant difference in endometrial thickness on the day of LH surge or HCG trigger between women in the MPA group and in the control group (P=0.65) [12].

Furthermore, similar findings were recently reported in an RCT by Agrawal and colleagues where they randomized into the study (SSP – 30 patients) and control group (traditional protocol – 30 patients). In the SSP, patients were treated with CC 50 mg/day for 5 days and in nonresponsive patients, the dosage was increased to 100 mg/day for 5 days in the same cycle. Maximum dose of 150 mg was given until the dominant follicle was generated. In control group, the dose increment in nonovulatory cases was done in subsequent cycle. Ultrasonography follow-up was done to detect ovulation [13].

Agrawal and colleagues found that there was no statistically 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. The uterine anti-estrogenic effect of CC was evaluated by endometrial thickness and uterine artery Doppler ultrasound testing; no significant differences were observed in CC-SS compared with the traditional protocol [14].

The present study showed that, the ovulation rate represent 26 (87%) in stair step group versus 14 (47%) in combined group with statistically significant difference between both studied groups (P = 0.001), Meanwhile the pregnancy rate was the same in both studied groups (P = 1).

Similarly, in a retrospective study by Hurst et al. of 31 women with PCOS, applied the same methodology of our current study, There was no control group in his study. Comparisons were made using the CC outcome results of published studies [15].

The dose-dependent ovulation rate was significantly higher in the stair-step protocol with 100 mg CC compared to the traditional protocol (64 vs. 22 %, respectively). The clinical pregnancy rates were similar between the stair-step and traditional protocol groups (13vs. 15 %, respectively) [16].

Meanwhile, In another study by Agrawal and his colleagues, there was a trend for a higher ovulation rate and pregnancy rate in the SSP group compared to the traditional protocol group. Although these outcomes could not achieve statistical significance (he ovulation rate in Group SSP was 20 (66.7%) women out of 30 while in Group traditional, it was 15 (50%), successful outcome for ovulation did not attain significance when compared) (94). Discussing the pregnancy rate, 8 (26.66%) women became pregnant in the SSP group whereas in the traditional protocol group, 5 (16.66%) women had positive pregnancy test. Pregnancy rate in both the groups was comparable though this result was not statistically significant with a P = 0.546 [17].

The enhanced ovulation rates achieved using the CC-SS protocol are considered 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 additional SS dose, active isomers are still present in the circulation, making the total circulating (concentration higher than in traditional protocols, where CC has ample time to wash out [18].

Endometrial thickness has been implicated in the success of ART including IUI but reports of its significance have been conflicting. Several studies have shown significant correlations between endometrial thickness and pregnancy rates (122), while others have failed to uncover such relationships [19].

5. CONCLUSIONS

In conclusion, the CC stair-step protocol is a safe, simple option for the management of PCOS patients, having a larger number of mature Grafian follicle, lower endometrial thickness and higher ovulation rate compared to combined clomiphene and gonadotrophin protocol.

CONSENT

All cases included in the study were subjected to the following after obtaining an informed consent. Informed written consent was taken from all

women after full explanation of benefits and risks of the study.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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