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Clomiphene Citrate and Metformin" Stair Step" Protocol Vs. Traditional Protocol in Patients with Polycystic Ovary Syndrome "PCOS"

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ABSTRACT

Background: Clomiphene citrate is the most popular drug for ovulation induction mainly in cases of PCOS, used alone or with combination of other drugs e.g. metformin.

Aim: To evaluate the efficacy of stair step protocol versus traditional protocol using clomiphene citrate alone or combined with metformin and to assess the uterine and systemic side effects of cumulative doses in single cycle.

Patient and Methods: Sixty (60) patients in two groups diagnosed as PCOS, based on the revised Rotterdam criteria (2003), *Group 1: In the stair-step protocol (n = 30), Clomiphene Citrate was administered at 50 mg daily for 5 days following the onset of a spontaneous or progestin- induced menses. The follicular response monitored by TVS starting on day 8. When the mean diameter of the follicle size is below 11mm on cycle day 14, the dosage increases to 100 mg/day for 5days.Then on cycle day 19 re-evaluation by TVS was restarted. Metformin with initial dose 500mg/day (and gradually increased to 1,500 mg /day during 6 weeks).**Group 2: In the traditional protocol (n = 30), Clomiphene citrate was administered 100 mg daily for 5 days after the onset of spontaneous or progestin-induced menstruation. The following variables were measured: ovulation rate (The number of follicles that mature and ovulate during given menstrual cycle), Side effects on uterine artery & systemic side effects e.g. Hot flushes.

Results: The findings of this study indicated no significant difference between the 2 groups in using clomiphene citrate by stair step protocol or traditional protocol (P>0.05).

Conclusion: Clomiphene citrate in the stair step protocol combined with metformin has a higher efficacy compared to CC in the traditional protocol in patients with PCOS in terms of ovulation and clinical pregnancy rates without any detrimental side effects on endometrial thickness or Doppler of uterine arteries, stair step protocol suitable for use in clinical practice.

Keywords: Clomiphene citrate- Stair step- Metformin- Ovulation induction.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrine system disorder among women of reproductive age. Women with PCOS may have enlarged ovaries that contain small collections of fluid called follicles located in each ovary as seen during an ultrasound exam. Infrequent or prolonged menstrual periods, excess hair growth, acne, and obesity can all occur in women with polycystic ovary syndrome. In adolescents, infrequent or absent menstruation may raise suspicion for the condition [(1)].

Polycystic ovary syndrome (PCOS) is the most common cause of female infertility and affects 5-10% of women of reproductive age [(2)].

Infertility affects 40% of women with PCOS. PCOS is the most common cause of anovulatory infertility. Approximately 90%–95% of anovulatory women presenting to infertility clinics have PCOS. Women with PCOS have a normal number of primordial follicles and primary and secondary follicles are significantly increased [(3)].

Clomiphene citrate (CC) is the first drug of choice for ovulation induction 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 in the subsequent cycle [(4)].

A new protocol is the stair-step protocol in which the increasing daily clomiphene citrate dose is administered without intervening menses between the dosages. The important point is that U\S 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 [(5)].

Metformin is an oral biguanides and firstly used to treat type 2 diabetes mellitus. It acts primarily in the liver by inhibiting gluconeogenesis and also by increasing peripheral insulin sensitivity [(6)].

Obesity may reduce the beneficial effects of Metformin as the response to Metformin in PCOS

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patients is related to BMI and the dosage of Metformin. It seems that the dose of Metformin might be critical for response to treatment in obese patients [7].

AIM OF THE STUDY

To evaluate the efficacy of stair step protocol versus traditional protocol using clomiphene citrate alone or combined with metformin and to assess the uterine and systemic side effects of cumulative doses in single cycle.

PATIENTS AND METHODS

This is Prospective observational Study that conducted at the department of Obstetrics & Gynecology and its out-patient clinic, El-Hussein University Hospital in the period from the beginnings of June 2017 to the end of March 2018.

The Medical Ethics Committee for Human Research at Al-Azhar Faculty of Medicine approved the study protocol and an informed consent was obtained from all participants prior to commencing the study.

Inclusion Criteria: (1) Women diagnosed as PCOS according to modified Rotterdam 2003 criteria [8]. (2) All patients have normal renal, kidney function and blood sugar. (3) Ages between 20 years and 35y.

Exclusion Criteria: (1) other causes of infertility e.g. tubal pathology & male infertility. (2) Presence of any diagnosed endocrinopathy e.g. hypo/ hyperthyroidism and hyperprolactinemia. (3) A woman's age less than 20 years or more than 35 years.

All patients were subjected to: 1. Full history taking: e.g. obstetric history & (LMP). 2. Clinical examination (clinical criteria): e.g. complete general examination & Complete local examination. 3. Laboratory investigation e.g. LFT, RFT, RBS, FSH, LH & TSH. 4. U/S (TVS) of female reproductive system (Radiological findings): Peripheral location of 12 follicles or more, ovarian volume>10CC. Ovarian cysts. Endometrial thickness. -Uterine abnormalities.

Sample size calculation and groups: Based on the rate of ovulation with CC treatment of 60-80% from the literature [9], we calculated the sample size at alpha = 0.05 and a study power of 90%, a total sample size of 60 patients.

Sixty (60) patients in two groups diagnosed as PCOS, based on the revised Rotterdam criteria (2003), as follows when two of the three following criteria are present: oligo/anovulation, clinical and/or biochemical signs of hyperandrogenemia, and polycystic ovaries (≥12 follicles measuring 2-9 mm in each ovary). All included patients have LH: FSH > 2.

Group 1: In the stair-step protocol (n = 30), Clomiphene Citrate was administered at 50 mg daily for 5 days following the onset of a spontaneous or progestin- induced menses. The follicular response monitored by TVS starting on day 8. When the mean diameter of the follicle size is below 11mm on cycle day 14, the dosage increases to 100 mg/day for 5days.Then on cycle day 19 re-evaluation by TVS was restarted. Metformin with initial dose 500mg/day (and gradually increased to 1,500 mg /day during 6 weeks).

Group 2: In the traditional protocol (n = 30), Clomiphene citrate was administered 100 mg daily for 5 days after the onset of spontaneous or progestin-induced menstruation.

Follicular response was monitored with TVS starting with day 8 every other day till the mean follicular diameter reached 18mm or more, HCG (5000 IU, im) injection was given; sexual intercourse was advised after this injection by about 36 hours.

Outcome measures: 1. Ovulation rate: The number of follicles that mature and ovulate during given menstrual cycle. 2. Side effects on uterine artery after use of CC are evaluated by measuring endometrial thickness uterine Doppler U/S between 8 and 12 am to exclude effect of circadian rhythm on blood flow. The amounts of change on pulsatility index and resistivity index were calculated in each group then compared. The endometrial thickness changes were calculated in each group then compared. The systemic side effects composed of (hot flushes, mood disturbance, blurred vision, pelvic pressure, nausea, pelvic pain and breast tenderness) were evaluated with a questionnaire and evaluated.

RESULTS

Table (1): Comparison between the two studied groups according to demography:

	Stair-step protocol (n=30	Traditional protocol (n=30)	t	p
Age(years) Min. – Max. Mean ± SD. Median	 20.0 – 35.0 28.33 ± 4.57 29.0	 20.0 – 35.0 28.73 ± 4.51 29.0	 0.341	 0.734
Body mass index(kg/m) Min. – Max. Mean ± SD. Median	 22.90 – 31.0 26.50 ± 2.01 26.55	 22.80 – 31.30 26.26 ± 2.02 26.10	 0.467	 0.642
Duration of infertility(years) Min. – Max. Mean ± SD. Median	 8.0 – 52.0 25.87 ± 11.17 24.0	 8.0 – 48.0 22.43 ± 10.04 20.50	 1.140	 0.254
Type of Infertility Primary Type Secondary TYPE	 16 (53.3%) 14(46.7%)	 18(60%) 12(40%)	X2 1.33	 0.096

There was no significant difference between the two groups (P>0.05).

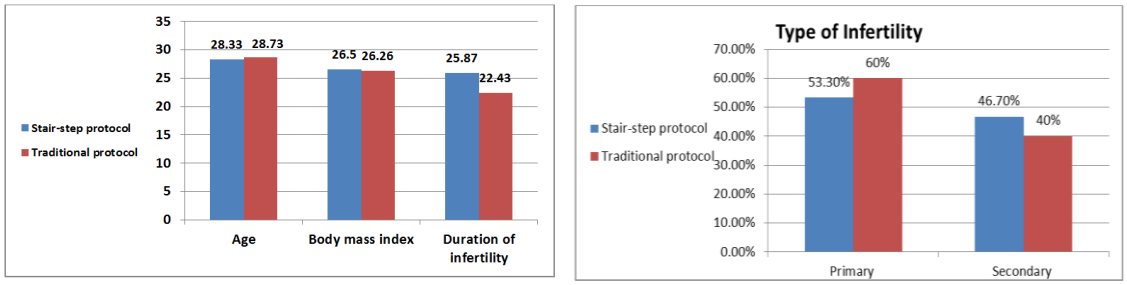

Figure (1): Comparison between the two studied groups according to age, BMI and duration of infertility.

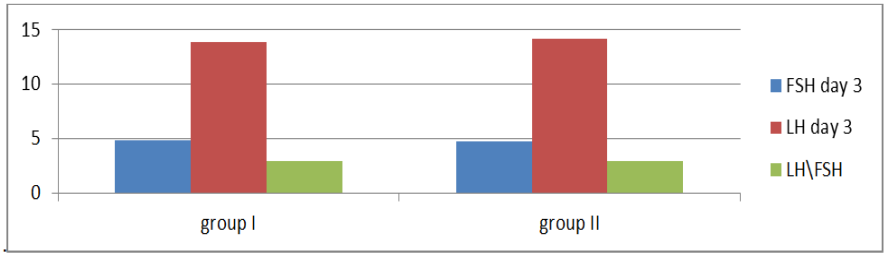

Figure (2): Comparison between the two studied groups according to FSH and LH.

Table (2): Comparison between the two studied groups according to ovulation rate, clinical pregnancy rate and cumulative pregnancy rate.

	Stair-step protocol (n=30		Traditional protocol (n=30)		t	p
	No.	%	No.	%		
Ovulation Rate No Yes	 6 24	 20.0 80.0	 11 19	 36.7 63.3	2.052	0.152
Clinical pregnancy rate No	 10	 33.3	 18	 60.0		
Yes(cumulative pregnancy rate)	20	66.7	12	40.0	4.286*	0.038*
After one cycle After two cycles After three cycles After four cycles After five cycles After six cycles	1 2 2 4 5 6	5% 10% 10% 20% 25% 30%	0 0 1 2 3 6	0 0 8.3% 16.6% 25% 50%	0.95	0.62

There was no significant difference between the two groups regarding the ovulation rate (P>0.05) with significant difference regarding the clinical pregnancy rate (p<0.05).

Table (3): Comparison between the two studied groups according to endometrial thickness and uterine artery Doppler.

	Stair-step (n=30	**Control (n=30)**	**t**	**p**
Endometrial thickness				
Min. – Max.	5.50 – 9.50	6.30 – 12.0		
Mean ± SD.	7.41 ± 1.15	8.42 ± 1.45	2.986*	0.004*
Median	7.20	8.25		
RI				
Min. – Max.	0.07 – 0.91	0.41 – 0.81		
Mean ± SD.	0.70 ± 0.15	0.61 ± 0.11	2.906*	0.005*
Median	0.71	0.61		
PI				
Min. – Max.	0.98 – 1.60	0.81 – 1.90		
Mean ± SD.	1.27 ± 0.19	1.18 ± 0.30	1.412	0.163
Median	1.30	1.10		

There was significant difference between the two groups regarding to endometrial thickness and uterine artery Doppler u/s (p<.005).

Table (4): Comparison between the two studied groups according to metformin dose.

	No.	**%**
Metformin dose		
No	10	33.3
Yes	20	66.7
Min. – Max.	500.0 – 1500.0	
Mean ± SD.	1000.0 ± 593.83	
Median	1000.0	

This table shows that mean metformin dose given in stair-step group was 1gm for about 66.7% of involved patients to this group.

Table (5): Comparison between the two studied groups according to side effect of used drugs.

	Stair-step (n=30						**Control (n=30)**						**x2**	**p**
	Non		**Mild**		**Moderate**		**Non**		**Mild**		**Moderate**			
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**		
HOT flushes	21	70.0	9	30.0	0	0.0	26	86.7	3	10.0	1	3.3	4.371	Mcp= 0.106
Mood disturbance	28	93.3	0	0.0	2	6.7	29	96.7	0	0.0	1	3.3	0.351	FEp= 1.000
pelvic pressure	28	93.3	2	6.7	0	0.0	29	96.7	1	3.3	0	0.0	0.351	FEp= 1.000
Nausea	25	83.3	6	16.7	0	0.0	24	80.0	6	20.0	0	0.0	0.111	0.739
Pelvic pain	26	86.7	4	13.3	0	0.0	27	90.0	3	10.0	0	0.0	0.162	FEp= 1.000
Breast tenderness	21	70.0	6	20.0	3	10.0	22	73.3	8	26.7	0	0.0	2.937	Mcp= 0.281
O.H.S.S	3(10%)						1(3.3%)						1.07	0.61

This table shows that there was no significant difference between the two studied groups regarding side effects of the used drug (p>0.05).

DISCUSSION

In this comparative study, Clomiphene Citrate(CC) was administered in the stair-step protocol combined with metformin in comparison to CC in the traditional protocol in patients with PCOS to assess the ovulation and clinical pregnancy rates as well as uterine side effects in terms of endometrial thickness and Doppler indices of the uterine arteries and systemic side effects.

In this study, ovulation and clinical pregnancy rates were higher in the stair-step protocol which is consistent with previous studies.

In this study, ovulation rate was (80% vs. 63.3%) in stair step group compared to traditional group. cumulative pregnancy rate over 6 cycles was (66.7% vs. 40.0%) in stair step group compared to traditional group.comparable effects on uterine artery Doppler PI &RI were measured,systemic side effects were compared between the two studied groups.

These results are in agreement with a retrospective study by ***Naka et al.*** [10] 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-ovulation period couldn't 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 [10].

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 cyclic growth of the uterus and endometrium. Endometrial thickness is altered in CC cycles [11].

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 6 mm for implantation [12].

The primary clinical action of metformin is reducing the hypergluconeogenesis. Metformin also increases sensitivity to insulin. It has been reported that metformin dosage might be a critical factor for a good response and a vital point for the treatment success particularly in obese women with PCOS [13].

Bruno et al. concluded that higher dose of metformin is more effective. They compared metformin 1,500 mg/day with metformin 2,500 mg/day for reduction of BMI and waist circumference [14].

In our study, although endometrial thickness was lesser in the stair-step group (7.41 ± 1.15mm) compared to traditional group (8.42 ± 1.45mm), pregnancy rate was higher 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 [15].

Hurst et al. of 31 women with PCOS, 50 mg/day CC was given for 5 days and U/S evaluation was performed on days 11–14. In non-responsive patients, 100 mg/day CC was initiated for 5 days and ultrasonography was repeated 1 week later. If the patient was still non-responsive, 150 mg/day CC was administered for 5 days and ultrasonography was applied again 1 week after later. There was no control group in this study. Comparisons were made using the CC outcome results of published studies. The time to ovulation by the stair-step protocol was 32–53 days less compared to the traditional regimen. 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 (13 vs. 15 %, respectively) [16].

In general, metformin in doses up to 2500 mg per day was relatively safe and well tolerated [17].

More recently, ***Deveci et al.*** conducted a randomized controlled trial to evaluate the efficacy of the stair-step protocol using clomiphene citrate (CC) and to assess the uterine and systemic side effects in patients with polycystic ovary syndrome (PCOS).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. Ovulation and pregnancy rates were similar between the stair-step and the control group (43.3 vs. 33.3 %, respectively) (16.7 vs. 10 %, respectively). The duration of treatment was significantly shorter in stair-step compared to traditional protocol (20.5 ± 2.0 vs. 48.6 ± 2.4 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 [9].

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.

The main limitation of this study was the small sample size of the study. Therefore, the presented study is accepted as a pilot study. A multicentre study is needed to confirm or refute our results.

CONCLUSION

Clomiphene citrate in the stair step protocol combined with metformin has a higher efficacy compared to CC in the traditional protocol in patients with PCOS in terms of ovulation and clinical pregnancy rates without any detrimental side effects on endometrial thickness or Doppler indices of the uterine arteries. The stair step protocol suitable for use in routine clinical practice.

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