

Clomiphene Citrate Stair Step Protocol with Phytoestrogen Vs. Traditional Protocol in Patient with Polycystic Ovary Syndrome

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Abstract: Objective: The objective of this study was to evaluate the efficacy of clomiphene citrate (CC) combined with phytoestrogens in stair step versus traditional protocol to induce ovulation in women with polycystic ovarian syndrome (PCOS). **Patients and methods:** This comparative study was conducted on 100 patients with PCOS who were divided into two groups; **Group I** (traditional protocol) included 50 patients who received CC 50 mg daily for 5 days from the second day of the cycle with folliculometry started at day 8, and **Group II** (Stair step protocol) included 50 patients who received CC 50 mg daily for 5 days from the second day of the cycle with folliculometry started at day 8, when the mean diameter of the follicle is below 11mm on cycle day 14, the dosage was increased to 100 mg/day for another 5 days with re-evaluation on cycle day 19 by ultrasound. In addition, **Group III:** including 50 patients with traditional protocol without taken phytoestrogen (control group). Both groups I and II received phytoestrogen 1500 mg daily from the third day of cycle for 10 days to alleviate the side effects of CC on the endometrium. Ovulation and pregnancy rates were the main outcome measures. Data was collected and tabulated. **Results:** Patients in the stair step protocol (group 1) exhibited a higher number of mature follicles, higher ovulation rate (72% vs 40%) and higher pregnancy rate (60% vs 22%) when compared to traditional protocol and control groups ($p < 0.05$). No significant differences between the studied groups regarding endometrial thickness, multiple pregnancy rate and ovarian hyperstimulation syndrome rate ($p > 0.05$). **Conclusion:** under the conditions of the present study, CC in the stair step protocol is safe and more effective than the traditional protocol in terms of ovulation and pregnancy rates.

[Asem A. Mousa, Mohamed A. Mohamed, Waleed A. Saad. **Clomiphene Citrate Stair Step Protocol with Phytoestrogen Vs. Traditional Protocol in Patient with Polycystic Ovary Syndrome.** *N Y Sci J* 2017;10(8):206-212]. ISSN 1554-0200 (print); ISSN 2375-723X (online). <http://www.sciencepub.net/newyork>. 24. doi:[10.7537/marsnys100817.24](https://doi.org/10.7537/marsnys100817.24).

Key words: Polycystic ovarian syndrome, stair step, clomiphene citrate.

1. Introduction

Infertility is generally defined as the inability of a couple to conceive within a certain period that is usually one year, time is the enemy and often the couple feels a sense of personal loss and frustration. Polycystic ovary disorder (PCOS) is a standout amongst the most widely recognized endocrine disorders among women of reproductive age (1). It is a condition in which a woman's levels of the sex hormones estrogen and progesterone are out of balance. This leads to the growth of ovarian cysts (benign masses on the ovaries). Ladies with PCOS have broader ovaries that contain liquid called follicles situated in both or any one ovary. The "cysts" in polycystic ovaries are not true cysts, yet rather antral follicles which have captured being developed and this is brought on because of hormonal imbalance (2).

PCOS produces symptoms in approximately 5% to 10% of women of reproductive age (12–45 years old). It is thought to be one of the leading causes of female subfertility and the most frequent endocrine problem in women of reproductive age (3).

The ovaries at the time of production have, tiny fluid-filled sacs called cysts. As the egg grows, the follicle builds up fluid and once the egg matures, the follicle breaks open, and the egg is released, and this egg travels through the fallopian tube to the uterus (womb) for fertilization this is called ovulation but in case of women with PCOS, the ovary is unable to produce all the essential hormones which are needed for an egg to fully mature. The follicles may start to grow and build up fluid however ovulation does not develop. Rather, a few follicles may remain as cysts (4). Thus, ovulation does not happen and the hormone progesterone is not made. Without progesterone, a lady's menstrual cycle is sporadic or missing. Furthermore, the ovaries make male hormones, which additionally counteract ovulation (5).

The main features of PCOS are anovulation, hyperandrogenism and insulin resistance. Anovulation results in irregular menstruation, amenorrhea, ovulation-related infertility and polycystic ovaries. Hyperandrogenism results in acne and hirsutism. Insulin resistance is often associated with obesity, Type 2 diabetes, and high cholesterol levels. The

symptoms and severity of the syndrome vary greatly among the affected women. Moreover, it may affect daily physical activities (6).

Women with PCOS, in addition to anovulation and infertility, have an increased risk of developing hypertension and cardiovascular disease in association with metabolic syndrome. The diagnosis of PCOS is fundamentally clinical. Treatment of PCOS is limited to management of signs and symptoms since the etiology of the disorder is unknown. There is a need for further studies to understand the pathophysiology of PCOS and the development of high blood pressure in women suffering from the disorder (7).

Clomiphene citrate is the drug most commonly used for ovulation induction starting with a daily dose of (50 mg) for 5 days beginning on day 3-5 of the menstrual cycle if ovulation achieved this is usually continued for 6 cycles or until pregnancy occurs. However, if the patient fails to ovulate on this dose a further increase by (50mg) per day to a maximum of (200-250mg) is used next cycle (8). A disadvantage with the mentioned traditional protocol that several months may pass to ultimately determine that patient is non-responsive to clomiphene.

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 ultra-sonographic 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 (9).

The aim of this study was to evaluate the efficacy of clomiphene citrate (CC) combined with phytoestrogens in stair step versus traditional protocol to induce ovulation in women with polycystic ovarian syndrome (PCOS).

2. Patients and Methods

This study was conducted on 100 patients with polycystic ovarian syndrome were divided into two groups, Group I: including 50 patients with traditional protocol and Group II: including 50 patients with stair step protocol. In addition, Group III: including 50 patients with traditional protocol without taken phytoestrogen (control group) who were clinically free and volunteered to participate in the study. All subjects were selected from Outpatient Clinic of Obstetrics and Gynecology in El-Shohadaa Central Hospital, Menoufia governorate, Egypt from the period of January 2016 till January 2017.

Ethical consideration:

All subjects participating in the study signed an informed written consent after explaining the purpose

of this study to each participant before the study initiation. The consent form was take according to the standard in Quality Improvement System in Ministry of Health and Population in Egypt, which was modified according to international ethical guidelines for Biochemical Research involving human subjects as prepared by the Council for Faculty of Medicine, Al Azhar University.

Inclusion criteria:

Female patient age 25-30 years, primary infertility diagnosed as PCOS according to rotterdam criteria 2003, free of medical disorders as renal, hepatic and cardiac, body mass index (BMI) >25<30 and no other factors of infertility as tubal pathology, male factor.

Exclusion criteria:

We're confounding factors such as: other causes of infertility such as: tubal pathology, endocrinal disorder, previous gynecological operation, women's aged >35y, as well as, older or male infertility.

The study group divided into two groups as follow:

Group I: Traditional protocol group (n=50):

In this group clomiphene citrate was administered at 100 mg daily for 5 days after the onset of a progestin-induced menses, follicular response was monitored with transvaginal ultrasonography starting with day 8. When the mean diameter of leading follicle reached 17 mm, HCG was administrated. When no follicular response observed on cycle day 20 the cycle was cancelled. Patient was taken phytoestrogen from the third day of cycle for 10 days 1500 mg daily to avoid the side effects of clomiphene citrate on the endometrium.

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

Group II: Stair step protocol group (n=50):

In this group 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 transvaginal ultrasonography (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 5 days. Then on cycle day 19 re-evaluations by TVS was restarted. When the mean diameter of leading follicle reached 17 mm, human chorionic gonadotropin (HCG) was administrated. When no follicular response is observed on cycle day 23, the cycle was cancelled. The daily dosage of clomiphene citrate wasn't increased for 150 mg daily because of potentially adverse effect of the cumulative doses. Patient was taken phytoestrogen from the third day of cycle for 10 days 1500 mg daily to avoid the side effects of clomiphene citrate on the endometrium. The

method as the same mentioned is group 1 (traditional protocol).

Group III: Control group (n = 50):

In this group clomiphene citrate was administered at 100 mg daily for 5 days after the onset of a progestin-induced menses, follicular response was monitored with transvaginal ultrasonography starting with day 8. When the mean diameter of leading follicle reached 17 mm, HCG was administered. When no follicular response observed on cycle day 20 the cycle was cancelled. This method as the same mentioned is group I (traditional protocol) without take any phytoestrogen.

Subjects were submitted to the following:

1. Careful history:

Personal history: Including name, age, education, occupation, residence, marital state and special habits.

Present history: Including symptoms which are usually associated with PCOS such as: infertility either primary or secondary and menstrual irregularities such as oligomenorrhea menorrhagia or amenorrhea.

Contraceptive history: history of any medical disease or previous surgical operations.

Physical examination: including Weight, height, BMI, BP, pulse, temperature, Examination for pallor, jaundice or cyanosis, thyroid examination, chest and heart examination and measurement of endometrial thickness

2. Investigations: including trans-vaginal U/S showing 12 or more peripheral small cysts 2- 9 mm in

diameter or total ovarian volume of > 10 mm³), day 3 serum FSH, day 3 serum LH, the ratio of LH (Luteinizing hormone) to FSH (Follicle stimulating hormone) is greater than 1:1 (sometimes more than 3:1), as tested on day 3 of the menstrual cycle, duration of fertility and Hystrosalpingiography to exclude tubal factor of infertility.

Statistical Analysis:

Results were tabulated and statistically analyzed by using personal computer using MICROSOFT EXCEL 2016 and SPSS v. 20 (SPSS Inc., Chicago, IL, USA. Statistical analysis was done through: Descriptive: e.g. percentage (%), mean and standard deviation. Analytical: that includes: Chi-Squared (χ^2), paired student t test. A value of P less than 0.05 was considered statistically significant.

3. Results

Results in table 1 showed that there were no significant differences between the studied groups as regard their age (p=0.956), body mass index (p=0.765), duration of infertility (p-value 0.622), Day 3 FSH level, Day 3 LH level, LH/FSH ratio and Endometrial thickness. On the other hand, there was a statically significant difference (P=0.047) between the studied groups regarding number of follicles (**Fig 1**). The highest number of follicles (2) was recorded by stair-step protocol (group II) versus, traditional protocol (group I) and control which scored the lowest number of follicles, (**Table 1**).

Table (1): Comparison between the two studied groups according to their demographic characteristics (N = 100).

Characteristics	Traditional Group I (No= 50)	Stair-step Group II (No= 50)	Control Group III (N=50)	T- test	
	Mean + SD	Mean + SD	Mean + SD	t	P
Age	27.50 + 1.79	27.52 + 1.81	27.50 + 1.79	0.056	0.956 ^{NS}
BMI	27.14 + 1.29	27.06 + 1.38	27.14 + 1.29	0.299	0.765 ^{NS}
Duration of infertility	3.84 + 1.18	3.96 + 1.24	3.11 + 1.02	0.494	0.622 ^{NS}
Day 3 FSH	3.72 + 0.76	3.88 + 0.87	3.5 + 0.60	0.980	0.330 ^{NS}
Day 3 LH	5.33 + 1.16	5.39 + 1.27	4.98 + 1.02	0.263	0.793 ^{NS}
LH / FSH Ratio	1.51 + 0.51	1.48 + 0.56	1.42 + 0.51	0.259	0.796 ^{NS}
Number of follicles	1 ± 0.03	2 ± 0.06	1 ± 0.03	3.5	0.047*
Endometrial thickness	8.3 ± 2.33	8.1 ± 3.7	8.4 ± 2.04	0.216	0.67 ^{NS}

According to results represented in table (2) indicated that Ovulation rate was higher in stair-step protocol (group II) as 72% (n=36) of patients in this group had increase in Ovulation rate, as compared with traditional protocol (group I) and control (group III) which was 40% (n=20) and 30% (n=15) of their patient had Ovulation rate, respectively. As well as statistically significant differences (p=0.029) were

observed between the studied groups as regards ovulation rate (**Fig 2**), (**Table 2**).

Regarding chemical pregnancy, results of the current study revealed that it was significantly higher in stair-step protocol (group II) (n=30) 60% more than traditional protocol (group I) and control (group II) which recorded the lowest value (n=11) 22% and (n=7) 14% for that pregnancy rate, and the differences

between them reached to the significant level of p-value 0.046 (Fig 3). (Table, 2).

This table shows that no ovarian hyperstimulation was observed in all studied groups (Fig 4). Regarding incidence of twins, results showed that 86% (n=43) of stair-step protocol patients

(groupII) had singleton pregnancy and 7% (n=17%) of them had multiple pregnant. While, in traditional protocol patients (group I) 90% (n=45) of patients had singleton pregnancy and 10% (n=5) of them had multiple pregnant. (Fig 5). (Table, 2).

Table (2): Comparison between the two studied groups according to ovulation rate and clinical pregnancy rate, number of follicles and (N = 100).

Items	Traditional Group I (No= 50)		Stair-step Group II (No= 50)		Control Group III (No= 50)		Chi square	
	No	%	No	%	No	%	X ²	P value
Ovulation rate								
No	30.0	60.0	14.0	28.0	35	70.0	4.778	0.029*
Yes	20.0	40.0	36.0	72.0	15	30.0		
Chemical pregnancy								
No	39.0	78.0	20.0	40.0	43	86.0	0.175	0.046*
Yes	11.0	22.0	30.0	60.0	7	14.0		
Ovarian hyperstimulation								
Yes	0	0%	0	0%	0	0%	-	-
No	50	100%	50	100%	50	100%		
Incidence of twins								
Singleton pregnancy	45	90%	43	86%	45	90%	-	-
Multiple pregnancy	5	10%	7	14%	5	10%		

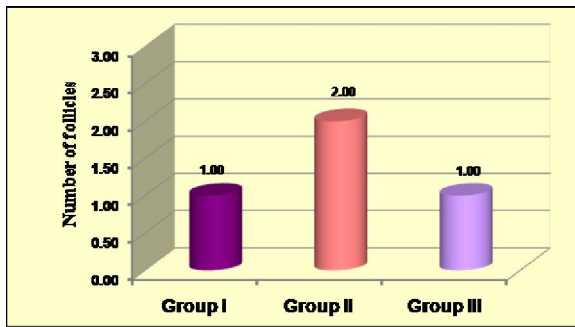


Figure 1. Distribution of the two studied groups according to number of follicles

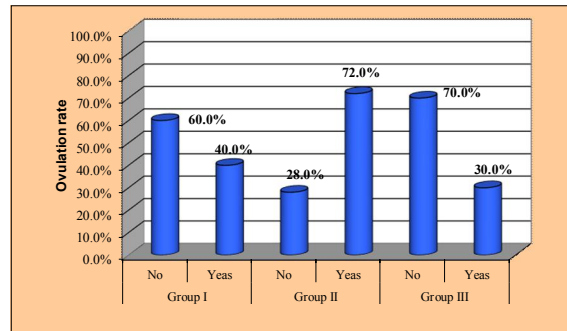


Figure 2. Distribution of the two studied groups regarding ovulation rate.

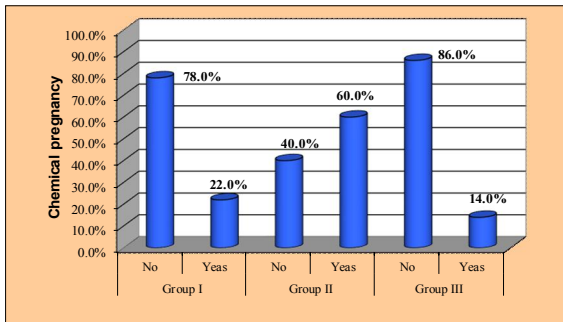


Figure 3. Distribution of the two studied groups regarding clinical pregnancy rate.

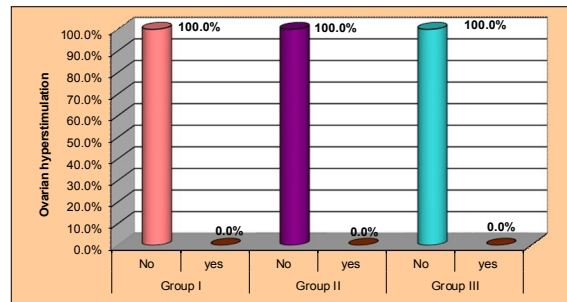


Figure 4. Distribution of the two studied groups regarding Ovarian hyperstimulation.

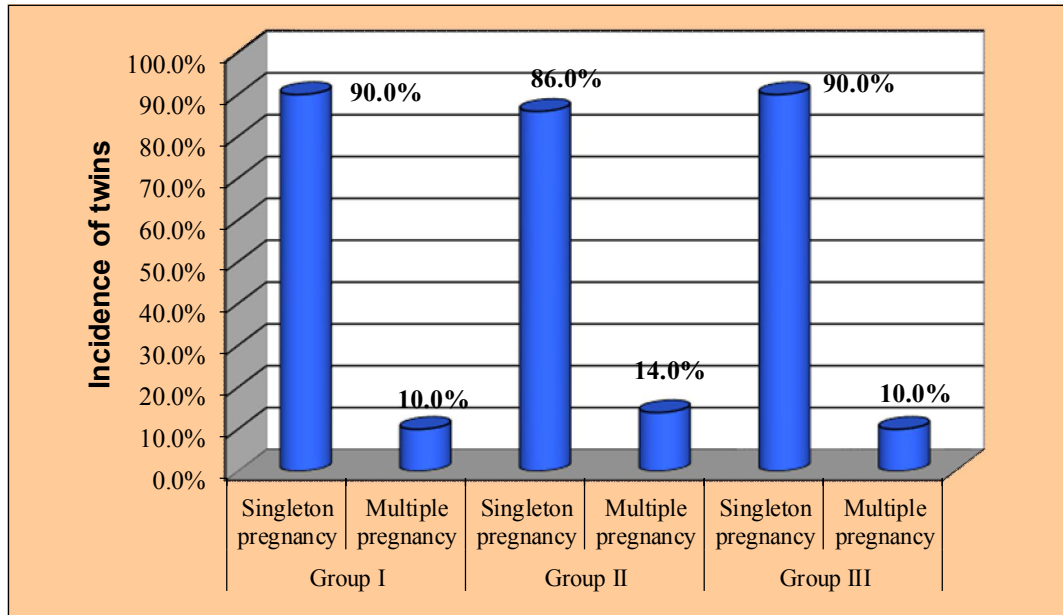


Figure 5. Distribution of the two studied groups regarding incidence of twins.

4. Discussion

In the current study, it was found that no statistically significant differences between studied groups in the clinical criteria of patients regarding their age and body mass index with mean age of (27.52, 27.50 & 27.50) and mean of BMI (27.06, 27.14 & 27.14) in traditional, stair step protocol and control groups respectively. These comes in agreement with several studies. **Moubarak, (10)** who found that no significant differences between stair step and traditional protocol patients regarding age with mean age (23.8 & 24.7) in stair step and traditional protocol respectively. In addition, **Algezawy, (11)** found that age was insignificant between two groups with p-value 0.734. mean age in Stair-step group I was 28.33 years and 28.73 years in control group II. Also, results added that, BMI was insignificant between two groups with p-value 0.642, Mean BMI in group I was 26.5 kg/m² and 26.26 kg/m² in group II. Moreover, **Abdel Hamid et al (12)** found that no difference between the two groups regarding age, BMI, race or infertility status. Also, **Dong, (13)** found that no differences were found in terms of age, BMI, duration of infertility between the two groups. While, **Deveci, et al (9)** found that insignificant differences between two groups regarding age and BMI p-value 0.86, 0.06 respectively, mean age in Stair-step group was 23.1 years and BMI was 25.2 kg/m², in control group mean age was 24.9 years and BMI was 27.1 kg/m².

Our finding results revealed that duration of

infertility increased in stair step protocol with mean (3.96) but not reached to significantly level (0.05) then traditional protocols and control groups. These comes in agreement with **Algezawy (11)** who found that mean duration of infertility in group I was 25.87 months and 22.43 months in group II, duration of infertility was insignificant between two groups with p-value 0.254. In addition, **Deveci et al (9)** found that insignificant differences between two groups regarding duration of infertility p-value 0.17. Duration of infertility in stair-step was 22.4 months and in control group it was 28.2 months. Moreover, **Begum et al (14)** found that insignificant differences between three groups regarding duration of infertility p-value 0.603. duration of infertility in group I was 6.13 years, 5.06 years in group II.

In the current study, it was found that no significant differences in stair-step and traditional protocol and control groups regarding FSH, LH and LH/FSH levels at day 3 with mean value (3.88, 5.39 IU/L and 1.48) in stair-step group respectively, and (3.72, 5.33 IU/L and 1.51) in traditional group. This comes in agreement with **Deveci et al (9)** who found that FSH and LH levels at day 3 were insignificant differences between two groups with p-value 0.51, 0.38 respectively. FSH and LH levels at day 3 were 5.5 IU/L and 10.7 IU/L in Stair-step group while 5.7 IU/L and 9.7 IU/L in Control Group. As well as, **Al Ghazali (15)** found that for the stair step protocol mean FSH level were 5.39±1.547, LH 8.67±5.471, For the traditional protocol mean FSH level

5.43±2.29, LH 7.59±4.251. LH: FSH ratio for the stair step and the traditional protocol was 1.804±1.201 and 1.78±1.304 respectively. For both protocol, there were no statistical significant differences among the two groups with respect to hormonal parameters.

In the results of the current study, it was found that ovarian rate and chemical pregnancy were significantly increased in stair-step group that recorded 72% and 60% of patients respectively, more than traditional protocol and control groups. Our results confirmed by **Algezawy (11)** who found that clinically pregnancy rate it was significantly higher in group I 66.7% than group II 40% p-value 0.038. In addition, **Abd Elsalam, et al (16)** found that ovulation and pregnancy rates were significantly higher in the stair-step (46.7 vs. 30 %, respectively) compared the control group (20% vs. 6.7 %, respectively). Moreover, **Abdel Hamid et al (12)** found that the ovulation rate was significantly higher at a dose of 100 mg (64% vs 22%). A total of 74% of their patients ovulated on 100 or 150 mg CC, and this too was significantly higher than the expected ovulation rate of 35.5% with a traditional protocol.

On the other hand, our results are disagreement with **Algezawy (11)** who found that ovarian rate was higher in group I as 80% of patients in this group had increase in ovarian rate regarding group II were 63.3% but this difference was insignificant between two groups p value 0.152. Also, **Hurst et al (17)** who found that the clinical pregnancy rate for the stair step protocol of (13%) was similar to the traditional protocol (15%). While, **Abdel Hamid et al., (12)** found that the clinical pregnancy rate was nevertheless not different between the two groups (15, 30% vs 13, 26%). 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.

Our finding results revealed that, number of follicles was significantly increased (P=0.047) in stair-step protocol (group II) more than traditional protocol and control groups which scored the lowest number of follicles. Our results are in line with **Moubarak, (10)** who found that there were significantly increase in number of follicles in stair step protocol with mean value (2 & 1) in stair step and traditional protocols respectively. In addition, **Ghosh et al (18)** found that women with follicular diameter of 20mm and more are less likely to become pregnant as compared to women of follicular diameter of 15-19mm. He concludes that women with the largest follicular diameter of ≥ 20 mm in a cycle appeared to have a 40% less chance of conceiving as compared to women with the largest follicular diameter between 15

and 19.99 mm.

Results of the current study showed that no statistically significant difference (P=0.67) between studied groups regarding Endometrial thickness. This comes in agreement with **Deveci et al (9)** who found that 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 p-value 0.24. The changes in uterine artery pulsatility index and resistivity index were similar between the groups p-value 0.39, 0.20 respectively. Also, **Shahin (19)** suggested 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. No significant adverse effects were observed on the endometrial thickness in the stair-step protocol. While **Palomba et al (6)**, demonstrated that CC acts on human endometrium with an antiestrogenic effect, reducing endometrial thickness and impairing endometrial pattern and vascularization.

On contrast our results **Algezawy (11)** who found that mean endometrial thickness in group I was 7.41 and 8.42 in group II, endometrial thickness was significant better in group II p-value 0.004. Mean RI was 0.71, 0.61 in group I and II respectively RI was significant between two groups with p-value 0.005. Regarding PI mean level was 1.27 in group I and 1.18 in group II, there was insignificant differences between two groups regarding PI p-value 0.163.

Conclusion

Under the conditions of the present study, CC in the stair step protocol is safe and more effective than the traditional protocol in terms of ovulation and pregnancy rates. Lager studies are warranted to confirm or refute our findings.

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8/9/2017