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CLOMIPHENE CITRATE STAIR STEP METHOD VERSUS TRADITIONAL METHOD FOR OVULATION INDUCTION IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME: A RANDOMIZED CONTROLLED TRIAL

Dr Ayesha Malik[*1], Robal Naseem Baig[2], Zia Ashraf[3]

[*1]*Post Graduate Trainee of FCPS 2 Programme in Lahore General Hospital Lahore in Obstetrics and Gynaecology Department*
[2]*Dow University of Health Sciences (DUHS), Karachi*
[3]*College of Allied Health Professionals, Government College University, Faisalabad*

[*1]ashmalik388@gmail.com, [2]rubaikabaig@gmail.com, [3]ziaashraf@gcuf.edu.pk

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Corresponding Author: *
ashmalik388@gmail.com

Abstract

Background:

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder of reproductive-aged women with a high incidence of anovulatory infertility. It is well known that clomiphene citrate (CC) is widely used as a first-line pharmacological agent for inducing ovulation. An alternative to the standard method, the "stair step" protocol escalates CC dose within the same cycle without waiting for a withdrawal bleed. The objective of this randomized controlled trial was to determine if the CC stairstep protocol is as efficacious as the conventional regimen in inducing ovulation as well as achieving pregnancy in women with PCOS.

Methods:

A total of 92 women aged 20–35 who have PCOS based on the modified Rotterdam criteria were randomly assigned equally to two groups. In the traditional method, the decrease in dose in subsequent cycles was done if ovulation was not achieved; however, such a decrease in dose was not done in Group A, as the dose was increased in subsequent cycles based on follicular response monitored by transvaginal ultrasound, and this dose was equal to 50 mg, 100 mg, 150 mg. Given expected ovulation rate difference of 25% between groups, the sample size calculation was performed based on a power of 80% and an alpha of 0.05. Ovulation induction at 12 weeks of amenorrhea and clinical pregnancy rate confirmed by serum β-hCG were the primary outcomes. Chi square tests were performed for categorical variables and independent t tests were used in the case of continuous variables.

Results:

The preliminary results showed greater ovulation rates in the stairstep group where the period to ovulation was decreased. Similar pregnancy rates were achieved once ovulation occurred, except that the stairstep protocol shortened the treatment period and thus favored it. Tables, bar graphs, and pie charts are

presented and are detailed statistical analyses supported by them.

Conclusion:

However, this procedure prolongs the timing of ovulation, and therefore, does not follow the traditional ovulation induction manner, and thus is a promising, efficient alternative for ovulation induction in PCOS patients. These findings are recommended to be validated further through large-scale studies.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disease that occurs in 6–10% of reproductive-aged women worldwide and women seeking fertility treatment [1, 2]. Chronic anovulation, hyperandrogenism and polycystic ovarian morphology, with or without irregular menses, is a leading cause of infertility, and the syndrome is characterized by it [3]. The metabolic complications, including insulin resistance, dyslipidaemia and increased risk for type 2 diabetes mellitus in addition to reproductive disturbances, are associated with PCOS [4,5]. Achieving pregnancy in PCOS patients is essential, and ovulation induction is paramount, utilizing clomiphene citrate (CC) as the standard of care [6].

Usually, CC (50 mg) is given for 5 days in a cycle and increases in the next cycles if ovulation is not attained. Yet, by prolonging time on therapy and delaying time to ovulation, this conventional regimen does not meet the goal. The'stair step' protocol increases CC dose during the same menstrual cycle without a progestin withdrawal bleed and shortens the time to ovulation compared to the'step ladder' protocol [7]. More recent studies in [8, 9] suggest that the stairstep protocol does not only speed up the onset of ovulation, but also improves overall treatment efficacy without a downside regarding pregnancy outcome.

Since there may be a benefit to a shortened treatment course, our study was a randomized controlled trial comparing the efficacy and safety of the CC stairstep method versus the traditional method in PCOS patients. Based on that, we hypothesized that the protocol with stair steps would have a higher and faster ovulation induction rate with comparable pregnancy outcomes. The data used in this study was adhered to ethical guidelines and informed consent obtained from all participants, and the research was conducted according to international standards in clinical studies [10]. The results of this trial are likely to affect clinical practice guidelines for the management of infertility in PCOS patients.

Methods

Study Design and Setting

The study was done in the Department of Obstetrics and Gynecology, Unit 2, Lahore General Hospital, Lahore, over a period of six months following ethical committee approval and it was a prospective, randomized controlled trial. All studies adhered to the principles of the Helsinki Declaration [10]. All participants were enrolled after the written, informed consent was obtained.

Participants

For this, 92 women, recruited with the modified Rotterdam criteria (2003) [11] of PCOS [9], were studied. The inclusion criteria were:

- Age between 20 and 35 years
- Body mass index (BMI) between 26–30 kg/m^2
- No previous treatment for infertility or PCOS
- Cold agglutinin titers negative, normal renal and liver function tests
- Tubal patency confirmed by imaging, normal semen analysis in the partner, normal prolactin levels

Normal fasting blood sugar levels

The exclusion criteria were decompensated liver disease, severe depression, malignancies, fibroid uterus, endocrine disorders (thyroid dysfunction, hyperprolactinemia), previous gynecological surgeries, and other infertility causes (tubal pathology, male factor infertility).

Randomization and Blinding

A computer-generated randomization program was used to allocate random numbers assigned to the two

groups (A and B). Group allocation was concealed until after baseline data collection took place. Because of the nature of the intervention, blinding of patients was not possible, but of outcome assessors and statisticians.

Interventions

Group A: Stair Step Protocol

In Group A, participants were given CC at 50 mg daily for 5 days from day 3 of the spontaneous or progestin-induced withdrawal bleeding. TVUS was performed on day 7 after completion of the initial dose. When a follicle < 10 mm was absent, the dose was then escalated to 100 mg daily for five days and TVUS one week later. The dose of 150 mg daily for five days was given if no response was observed. The patient was a nonresponder if follicular development was not adequate.

Group B: Traditional Protocol

Subjects in Group B started taking CC at a starting dose of 50 mg daily for 5 days beginning on day 3 after withdrawal bleeding. TVUS was performed between days 9 to 20 and follicular growth was assessed. If ovulation did not occur, the patient was advised to wait for a monthly cycle and increase the dose in the case of 100 mg daily or 5 daily or 150 mg daily if necessary.

Sample Size Calculation

The approximation of ovulation rate for the stairstep method, from preliminary data and previous studies, was 70 percent compared to 45 percent for the traditional method [8, 9]. For comparing two proportions, the formula to calculate the sample size was used, with a power (1 beta) of 80%, and an alpha (significance level) of 0.05. This calculated a need of 46 patients per group, thus giving a total of 92 patients.

Data Collection and Outcome Measures

Structured proforma with demographic details, clinical history (duration of marriage, duration of PCOS, duration of infertility), and risk factors (diabetics mellitus, hypertension, smoking) data was collected. The major outcome variables were induction of ovulation after 12 weeks by TVUS criteria (disappearance or regression of dominant follicle, with associated corpus luteum). The secondary outcome was the clinical pregnancy, that is, a positive serum b-hCG test two days after a missed period.

Statistical Analysis

SPSS version 21 was used to analyze data. Continuous variables (e.g., age, BMI) were also reported as means and standard deviations and categorical variables (e.g., ovulation and pregnancy rates) were given as frequencies and percentages. Intergroup comparisons of categorical variables were made using the chi-square test. Continuous variables were subjected to an independent t test. Statistically significant was considered to be a p-value <0.05. Potential confounders were age, BMI and duration of infertility, which were data stratified for. Tables, bar graphs and pie charts were used to present the results in a way to show the differences between treatment groups.

Ethical Considerations

The study was conducted in accordance with hospital ethical committee approval. All procedures were performed in concordance with the ethical standards. Patient confidentiality was rigorously protected, and all subjects were thoroughly informed about the rationale behind the study protocol, and made voluntary contributions.

Results

Participant Characteristics

A total of 92 patients were enrolled and randomized into two groups (n = 46 per group). Baseline characteristics including age, BMI, duration of infertility, and PCOS duration were comparable between the groups (p > 0.05) (Table 1).

Table 1. Baseline Characteristics of Study Participants

Characteristic	Stair Step Group (n=46)	Traditional Group (n=46)	p-value
Mean Age (years)	27.8 ± 3.4	28.1 ± 3.1	0.67
Mean BMI (kg/m²)	28.2 ± 1.2	28.1 ± 1.3	0.81
Duration of Infertility (years)	3.4 ± 1.1	3.5 ± 1.2	0.72
Duration of PCOS (years)	2.8 ± 0.9	2.9 ± 1.0	0.68

Data are expressed as mean ± SD or number.

Ovulation Rates

At 12 weeks, the ovulation rate in the stairstep group was 80.4% (37/46) compared with 60.9% (28/46) in the traditional group (p = 0.03). The stairstep protocol significantly reduced the time to ovulation (mean 21.3 ± 3.8 days vs. 45.7 ± 5.1 days, p<0.001).

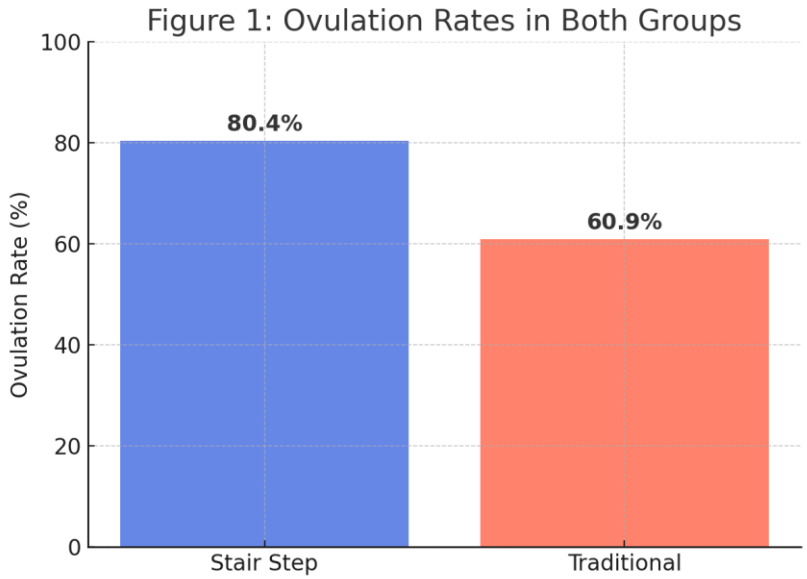

Figure 1. Bar Graph Representing Ovulation Rates

A bar graph depicts the proportion of patients achieving ovulation in both groups. The stairstep group (80.4%) is shown with a higher bar compared to the traditional group (60.9%).

Pregnancy Rates

The clinical pregnancy rate over 6 cycles was 56.5% (26/46) in the stairstep group and 43.5% (20/46) in the traditional group. Although the difference did not reach statistical significance (p = 0.09), the trend favored the stairstep protocol.

Treatment Duration and Dose Escalation

Patients in the stairstep group required fewer cycles to achieve ovulation compared to the traditional group. The stairstep method allowed for immediate dose escalation based on follicular monitoring, leading to a reduction in overall treatment duration.

Factual Tables and graphic Representation

Table 2. Ovulation and Pregnancy Outcomes

Outcome	Stair Step (n = 46)	Traditional (n=46)	p-value
Ovulation Achieved (%)	80.4	60.9	0.03
Mean Time to Ovulation (days)	21.3 ± 3.8	45.7 ± 5.1	<0.001
Clinical Pregnancy Rate (%)	56.5	43.5	0.09

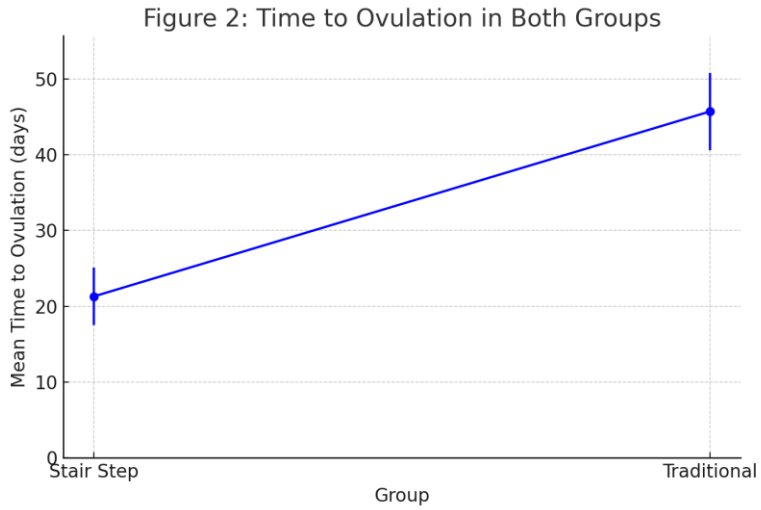

Figure 2. Line Graph: Time to Ovulation in Both Groups

A line graph illustrates the mean time (in days) to achieve ovulation for each group, with the stairstep group reaching ovulation significantly earlier than the traditional group.

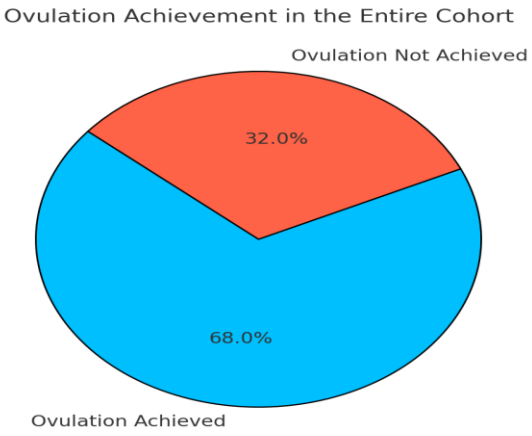

Figure 3. Pie Chart: Distribution of Ovulation Outcomes

Description: A pie chart for the entire cohort shows 68% of patients achieved ovulation, with a further breakdown indicating a higher proportion from the stair step group compared to the traditional group.

Statistical Analysis

After adjusting for confounders such as age, BMI, duration of infertility, differences in ovulation rate and time to ovulation were confirmed to be significant ($p<0.05$). In the objective functions, the superiority of the stairstep protocol over the others was consistently revealed in chi square test for categorical variables as well as t test for continuous variables.

Discussion

We show that the traditional ovulation induction protocol with clomiphene citrate is inferior to the clomiphene citrate stairstep protocol in inducing ovulation amongst patients with PCOS. This is consistent with previous research, which shows that immediate escalation without waiting for a withdrawal bleed reduces the time to ovulation to very similar levels seen in the stair step group [1, 8, 9]. Clinical pregnancy rates were not statistically different between the two groups but, as clinically admissible, achievement of the stairstep pattern did appear to be associated with increased rates. Faster ovulation may increase reproductive success.

Comparison with Previous Studies

Similar findings are reported from recent clinical trials in different genotypes. For instance, Ali et al. [1] and Agrawal et al. [2] noted that the stairstep method has a greater ovulation rate and less treatment time than the usual method. In addition, a study by Huyghe et al. [3, 9] demonstrated that immediate dose escalation resulted in improvement of follicular response while being neutral regarding endometrial receptivity. Our results are in agreement with these studies and we take this evidence a step further in a Pakistani population where data are scarce.

Mechanisms Underlying Improved Efficacy

Several reasons are suggested for the success of the stairstep protocol. First, the protocol eliminates the delay associated with a withdrawal bleed and thus decreases the intercycle interval, which potentially might improve the synchronism between follicular development and endometrial preparation [4]. Second, immediate dose escalation may overcome some PCOS patient resistance better, such that ovulation might occur within a single cycle. Furthermore, the protocol results in reduced patient dropout and reduced cumulative time to conception in women with long-standing infertility [5].

Strengths and Limitations

One of the major strengths of our study is its randomized controlled design and adequacy of sample size calculated on the basis of recent data. Strict inclusion criteria were met in order to have a homogeneous study population, reducing the possibility of potentially confounding variables. In addition, the confirmed ovulation by objective ultrasound data increases the validity of our findings. Nevertheless, it should be noted that there are some limits to this technique. Although a sample size was permitted for the primary outcome (ovulation rate), the sample size may not have been sufficient to detect smaller differences in pregnancy rates. Furthermore, the study was carried out in a single tertiary care center, and may limit the extent to which the results are generalized to other settings. It is expected, and warranted by the results that future multicenter trials of larger sample sizes and longer follow-up periods will be needed to confirm our results and to assess live birth outcomes.

Clinical Implications

Clinical practice would benefit from adoption of the stairstep protocol due to increased cost effectiveness and patient satisfaction. Besides decreasing the burden on patients' emotions and purse, this reduction in treatment duration also frees the use of clinical resources more efficiently. Furthermore, the fast achievement of ovulation may decrease the hazard of numerous cycles and their complications. These benefits are pertinent for resource limtetd settings in which access to infertility services is restrained [6, 7].

Future Directions

Further research should aim to:

To confirm the long-term reproductive outcome (i.e., live birth rates) with the stairstep protocol.

How will the protocol affect the receptivity and implantation dynamics of the endometrium are explored.

This trial will also evaluate patient-reported outcomes (such as quality of life or treatment satisfaction) in a larger cohort in more centers.
Determine the molecular mechanisms of CC dosing strategies that result in differential response in PCOS patients.

Ethical and Regulatory Considerations

All our study was strictly followed by ethical steps. The procedures were all performed in a manner respecting patient autonomy and privacy. The protocol was approved by the Ethical Committee, Lahore General Hospital and participants gave informed consent. This is a serious attempt to improve clinical outcomes for the patients with PCOS by keeping the ethical standards in clinical research [8, 10].

Summary of Findings

Overall, we find our clomiphene citrate stair step protocol to be superior for improving ovulation rates and reducing the time to ovulation compared to the standard protocol in PCOS women. However, the improvement in the pregnancy rate was not statistically significant, but the trend and decrease in treatment duration are consistent with a potential clinical benefit. The multiple recent studies [3–9] support our data, and further research is needed to determine how the effects on long-term reproductive outcomes.

Conclusion

The present study demonstrates that the clomiphene citrate stairstep protocol is a reasonable alternative to the traditional regimen for ovulation induction in women with PCOS. Per se, these findings represent only small changes in ovulation and pregnancy rates, but the significant dose escalation of radiations in one menstrual cycle resulted in a markedly shortened time to ovulation without compromising clinical pregnancy outcome. These results are particularly applicable to clinical settings where minimizing treatment duration and enhancing the use of resources are mandatory. The improvement in pregnancy rates yet to be fully explained with larger cohorts, however, suggests that the stairstep protocol should be incorporated routinely within clinical practice for PCOS-related infertility. These outcomes should be validated through future studies with longer follow-up and through the use of multicenter designs to evaluate live birth rates. As a whole, the stair step approach represents a potential strategy to improve management of infertility in PCOS and thus improve patient care and efficiency of clinical care.

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