

Efficacy of Stair Step Protocol of Clomiphene Citrate in PCOS

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Abstract

Objective: To evaluate the effectiveness of extended clomiphene citrate therapy in the women who failed to ovulate despite of traditional regimen of clomiphene citrate.

Study Design : It is a prospective study done on 25 women who failed to ovulate despite of standard dose of clomiphene citrate. The stair step protocol is performed as follows – 50mg of clomiphene citrate is given for 5 days. USG done on day 11 to day 14 . If result is unresponsive, immediate begins 100mg of clomiphene citrate for 5 days . Repeat USG in 1 week. If result is unresponsive start 150mg of clomiphene citrate for 5 days and repeat USG after 1 week.

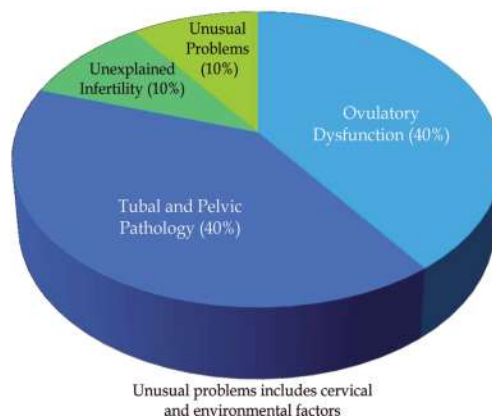
Result : Total time required to ovulate in extended clomiphene citrate is less as compared to traditional regimen in women with ovulatory disorders.

Keywords: Extended Clomiphene Citrate; Stair Step Protocol; Ovulation.

Introduction

Ovulatory dysfunction accounts for about 40% of infertility [1]. It is one of the most common cause of reproductive failure in subfertile and infertile couples. Anovulatory infertility secondary to PCOS is most common endocrine disorder in

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reproductive age, with an incidence of 5-10%[2,3]. All women of anovulation, are classified according to criteria adopted by the World Health Organization (WHO)[4].

WHO Group I: Hypogonadotropic Hypogonadal Anovulation. Approx. 5-10% of anovulatory women accounts under this group. These have low or low normal serum FSH concentrations, and low serum estradiol levels, due to absent or abnormal hypothalamic gonadotropin-releasing hormone(GnRH) secretion or pituitary insensitivity to GnRH. Eg: weight loss, physical, nutritional or emotional stress, anorexia nervosa, kallmann syndrome.

WHO Group II: Eugonadotropic Euestrogenic Anovulation. It includes about 75-85% of anovulatory women and is characterized by normal serum FSH and estradiol levels and normal or elevated LH concentrations. Eg: PCOS.

WHO Group III: Hypergonadotropic Anovulation. It includes about 10-20% of anovulatory women. It has elevated serum FSH and most but not all have amenorrhoea. Eg : Premature ovarian failure.

WHO Group IV: Hyperprolactinemic

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Anovulation. Approximately 5-10% of anovulatory women have hyperprolactinemia, which inhibits gonadotropin secretion. Serum FSH level is low or low normal and serum estradiol levels is also low. In patients with PCOS, Clomiphene citrate is first choice of drug for ovulation induction [5]. Over the last few years, there have been different regimens to treat patients who fail to ovulate with initial dose of Clomiphene Citrate. Traditional alternatives for CC-resistant patients include gonadotropin therapy and laproscopic ovarian dithermy[6]. Clomiphene citrate was first synthesized in 1956 and approved for clinical use in 1967 [7,8].

Clomiphene have two different stereoisomers, (a) Enclomiphene (62%; originally known as cis-clomiphene) and it is more potent, responsible for its ovulation inducing action (b) Zuclomiphene (38%; originally known as trans-clomiphene)[9,10]. Clomiphene is a non-steroidal triphenylethylene derivatives, acts as selective estrogen receptor modulator (SERM). It has estrogen agonist and antagonist properties[9]. However, almost always clomiphene citrate acts purely as an antagonists or antiestrogen. Its weak estrogenic actions are clinically apparent only when endogenous estrogen levels are very low.

Mode of Action

Unlike estrogen, clomiphene binds to nuclear estrogen receptors for an extended interval of time and it depletes receptor concentrations by interfering with receptor recycling. At the hypothalamic level, estrogen receptor depletion prevents accurate interpretation of circulating estrogen levels; circulating estrogen levels are perceived as lower than they truly are. *Reduced negative estrogen feedback triggers normal compensatory mechanisms that alter the pattern of GnRH secretion and stimulate increased pituitary gonadotropin release which, in turn, drives ovarian follicular development.* At pituitary level, clomiphene

Case Selection

Inclusion Criteria	Exclusion Criteria
Reproductive age group	Male factor infertility
Diagnosed as PCOS (a/c to ESHRE/ASRM)	Bilateral tubal blockage
1. Oligomenorrhea or Anovulation	
2. Hyperandrogenism	
3. Polycystic Ovaries - 12 or more follicle	
with diameter 2-9 mm and ovarian volume >10cm ³	
Serum FSH ≤10mIU/ml	Endometriosis
Bleeding - Spontaneous or withdrawal	Systemic disorder - Diabetes, thyroid.

Enrolled patients were divided into two groups by Randomization : Group A (n = 25) and Group B

citrate also increase the sensitivity of gonadotrophs to GnRH stimulations[11]. As explained, its mechanism of action, it is not surprising that clomiphene typically is ineffective in women with hypogonadotropic hypogonadism (WHO group I).

Clomiphene induce ovulation successfully in 70-80% of properly selected women. Women who do not ovulate with increasing dose of clomiphene citrate are described as being CC resistant and remains a major challenge in gynecologic endocrinology [4]. However, gonadotropin therapy is associated with increased costs and risks of ovarian hyperstimulation syndrome(OHSS) as well as multiple pregnancy compared to ovulation induction with CC[12]. Hurst et al in 2009[13], described a novel Clomiphene Citrate stair step protocol that is hoped to reduce time of ovulation in women with PCOS and increasing rate of ovulation from 35.5% to 74% .

OLD DRUG, NEW TRICK

Aim

To determine the efficacy of stair step clomiphene citrate in women with PCOS compared to traditional protocol.

Material & Methods

This is a prospective study conducted in department of Obstetrics and Gynecology at Mahatma Gandhi Hospital, Jaipur after approval from institutional ethical committee. Total number of 50 patients fulfilling the selection criteria were selected after taking written consent. They were explained about the pros and cons of ovulation induction and each women enrolled in the study subjected to have serum assays of FSH, LH, Prolactin, Estradiol at Day 2 of cycle before initiation of clomiphene citrate therapy.

(n =25). Induction of ovulation for both protocols were performed as following -

Stair-Step Protocol

In stair step protocol 50mg of clomiphene citrate given for 5 days beginning on day 2 of spontaneous or progesteron induced withdrawal bleeding. Trans vaginal sonography is advised to be done at days 11-14. when there is no response (no follicle >10mm), 100mg of clomiphene is initiated immediately for 5 days, and TVS is repeated after 1 week i.e. on day 21. if there is no response another 150mg of clomiphene is initiated immediately for 5 days and TVS is performed 1 week after the second USG i.e. on day 28. Ovulation for stair step cycles was confirmed by TVS. Follicles measured between 18-24mm considered to be mature. HCG was given intramuscularly when follicle size reaches ≥ 18 mm in diameter and patient was advised to have intercourse after 36 hours and on two subsequent days.

Traditional Protocol

Clomiphene was initiated by day 2 on spontaneous or progesteron withdrawal bleeding. The starting dose

was 50mg of CC for 5 consecutive days. Then TVS was advised on day 11-14. in case of no response patient was treated with medroxyprogesterone acetate (MPA) for 10 days. Daily doses of CC was increased by 50mg in the next 3 treatment cycles. In each cycles monitoring of follicular growth was by TVS at day 11-14. first ovulation was used as endpoint. Ovulation was assessed by TVS. Between 18-24mm of follicular size considered as mature follicles. HCG 10,000IU was given intramuscularly when follicles becomes mature. Patient was advised to have intercourse after 36 hours and on two subsequent days.

TVS monitoring helps us in increasing the dose of clomiphene in the same cycle of PCOS patient who do not ovulate or respond to CC initially in stair - step protocol. Responders are the patients who ovulate during CC therapy independent of the dose administration. Total number of the treatment cycles and the CC dose at which first ovulation occurs were recorded. Non responders are those who do not ovulate even after receiving the maximum dose of CC i.e. 150mg/ day.

Table 1:

Screening Parameters	Stair Step Protocol (N 25)	Traditional (N25)
Age (years)	27.65 \pm 5.634	28.58 \pm 5.979
Duration of Infertility (years)	5.67 \pm 2.277	6.15 \pm 3.595
Primary Infertility	17 (69%)	20 (79%)
Secondary Infertility	7 (31%)	5 (21%)
BMI (gm/m ²)	27.85 \pm 5.229	29.17 \pm 5.462

Clinical baseline patient of the two treatment group.

Table 2:

Screening Parameters	Stair Step Protocol (N 25)	Traditional (N 25)
LH (mIU/ml)	8.67 \pm 5.471	7.59 \pm 4.251
FSH(mIU/ml)	5.39 \pm 1.547	5.43 \pm 2.29
PROLACTIN (ng/ml)	11.19 \pm 6.664	11.90 \pm 6.204
E2 (pg/ml)	24.72 \pm 17.949	24.11 \pm 3.251

The hormonal baseline patient characteristics of the two treatment groups

Table 3:

Clomiphene Citrate Dose	Stair Step Protocol (N 25)	Traditional (N25)	P Value
50 mg	4 (16%)	5 (20%)	Not Significant
100mg	11 (43%)	7 (28%)	Significant
150mg	5 (21%)	3 (12%)	Significant
Non responder	5 (20%)	10(40%)	Significant

Rate of ovulation between the stair step and the traditional protocol.

Table 4:

Parameters	Stair Step Protocol (N 25)	Traditional (N 25)
Endometrial Thickness (cm)	1.01 \pm 0.169	0.832 \pm 0.153
No. of Follicle	1.62 \pm 0.634	1.28 \pm 0.544
Size of Follicle (mm)	20.69 \pm 2.112	19.78 \pm 1.504
Pregnancy Rate	4 (16%)	2(8%)

Mean ET, no. and size of follicles and pregnancy rate for both protocols after cc administration at the time of ovulation.

Table 6:

Categories	No. (%)
Endometrial Thickness	
7-9mm	2(36%)
10-13mm	4(64%)
No. of Follicles	
one follicle	1(21%)
two follicle	5(79%)
Size of Follicles	
17-19mm	1(21%)
20-23mm	5(79%)
Ovulation Dose	
100mg	4(64%)
150mg	2(36%)

ET, no. and size of follicles and ovulating dose for all pregnant women in both protocols. (Number 6)

Observations

Clinical Baseline Patient of the Two Treatment Group: From the total study group of 50 patients treated with clomiphene citrate drug, 25 women were included in stair step protocol and 25 women were included in traditional protocol. Their mean age was 27.65 ± 5.634 , 28.58 ± 5.979 , duration of infertility was 5.67 ± 2.277 , 6.15 ± 3.595 , and BMI 27.85 ± 5.229 , 29.17 ± 5.462 for both group respectively, as summarized in Table 1.

The Endocrine Screening Parameters at day 2 of Cycle for the Stair-Step and Traditional Protocols: For the stair step protocol mean FSH level were 5.39 ± 1.547 , 5.43 ± 2.29 , LH 8.67 ± 5.471 , 7.59 ± 4.251 , Prolactin 11.19 ± 6.664 , 11.90 ± 6.204 and estradiol 24.72 ± 17.949 , 24.11 ± 3.251 respectively as summerised in Table 2. For both protocol there were no statistical significant differences among two groups with respect to clinical and hormonal parameters as shown in Tables 1,2.

Ovulation Rate between both Protocols: A significantly higher rate 43% was observed with stair step protocol at a clomiphene dose 100mg compared to the ovulation rate of 28% with the same dose in the traditional regimen. At 150mg of clomiphene ovulation rate for stair step and traditional group was 21% and 12% respectively. In stair step protocols total 20% of patients were found as non responder where as 40% in traditional protocols. It shows the significant difference between these two protocols. As shown in Table 3.

Mean Endometrial Thickness, Number and Size of Follicle and Pregnancy Rate for Both Protocols after Clomiphene Citrate Administration at the Time of Ovulation: The mean endometrial thickness in stair step protocol 1.01 ± 0.169 , which was significantly higher than in traditional protocol which was 0.832 ± 0.153 . the highest number of follicle found in stair-step protocol 1.62 ± 0.634 and the largest size of follicle found in same protocol was 20.69 ± 2.112 which are statistically significant. Regarding the pregnancy

rate 16% of women get pregnant in stair-step protocol and 8% women get pregnant in traditional protocol was shows the significant difference between the both protocols. As shown in Table 4.

Endometrial Thickness, Number and Size of the Follicles and Ovulating Dose for All Pregnant Women in Both Protocols: Table - 5 shows endometrial thickness, size of follicle, number of follicles and dose of clomiphene citrate at which patients became pregnant for both protocols. About endometrial thickness 36% got pregnant at endometrial thickness measured between 7-9mm and the 64% at 10- 13mm. 79% of those pregnant women have two follicles and 79% of follicles have size between 20-23mm. 64% of women ovulate at 100mg clomiphene citrate and 36% of them at 150mg. No one of our patients had multiple pregnancies.

Adverse Effects

1. Multiple Pregnancy–Multi-follicular development is relatively common and the overall risk of multiple pregnancy is increased to approximately 7-10% [14,15,16].
2. Ovarian hyperstimulation syndrome (OHSS) – when induction of ovulation proceeds in the recommended incremental fashion to established the minimum effective dose, the risk of clinical significant OHSS (massive ovarian enlargement, progressive weight gain, severe abdominal pain, intractable nausea, vomiting, gross ascites, oliguria) is remote.

Discussion

The present study shows that in stair-step protocol at 100mg and 150mg was 43% and 21% as compared to traditional protocol i.e. 28% and 12% respectively.

The total ovulation rate for stair-step protocol was 80% which is higher than that for the traditional regimen which was 60%. Regarding time of ovulation to achieve required in traditional protocol is 50-90 days and in stair - step protocol is 21-31 days, which is much shorter as compared to traditional protocols.

In our trial, the pregnancy rate for stair-step protocol was 16% whereas in traditional protocol it is 8%. Regarding pregnancy rate and clomiphene dose it was found that from all the pregnant women in both protocols, 64% become pregnant at 100mg of dose and 36% became pregnant at 100mg of dose.

Conclusion

Clomiphene stair step protocol decreases the time of ovulation. And is shown to improve ovulation rates in clomiphene citrate resistant women. Pregnancy occurs in less time compared to traditional regimen. Thus improving quality of life for couples facing infertility.

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