

Treatment Outcome of Ovulation-inducing Agents in Patients with Anovulatory Infertility: A Prospective, Observational Study

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Abstract

Objective: To compare different treatment regimens on pregnancy rate and outcome in patients with anovulatory infertility. **Patients and Methods:** A prospective observational study was conducted on patients with infertility due to anovulation. Patients treated with clomiphene citrate (CC) 50/100 mg/day from 2nd to 6th day of menstrual cycle (MC) ($n = 38$), short gonadotropin-releasing hormone (GnRH) agonist regimen (leuprolide [0.5 mg subcutaneous] + recombinant follicle-stimulating hormone [rFSH] [225 IU intramuscular [IM]] from 2nd to 10th day of MC [$n = 32$]), long GnRH agonist regimen (leuprolide from 21st day followed by leuprolide + rFSH from 2nd to 10th day of MC [$n = 19$]), and antagonist regimen (human menopausal gonadotropin [hMG] [150 IU IM] from 2nd day followed by hMG + cetorelix from 7th to 10th day of MC) ($n = 6$) were recruited and followed up for follicular size, endometrial thickness, and pregnancy test. Data were analyzed using appropriate statistical test and $P < 0.05$ was considered statistically significant. **Results:** A significant increase in follicular diameter and endometrial thickness was observed in patients treated with gonadotropin regimens as compared to CC alone ($P < 0.0001$). The highest number of positive pregnancy test with ultrasonographic evidence of gestational sac was observed with leuprolide + rFSH (long regimen) (10/19, 52.6%) followed by leuprolide + rFSH (short regimen) (13/32, 40.6%) while least in antagonist regimen (2/6, 33.3%) and CC (1/38, 2.63%). All regimens were well tolerated. **Conclusion:** Treatment outcome was better with long agonist regimen.

Keywords: Anovulatory infertility, clomiphene citrate, gonadotropins, pregnancy outcome

INTRODUCTION

Infertility is defined as the “failure to achieve a clinical pregnancy after 12 months or more of regular, unprotected sexual intercourse.”^[1] Female infertility is a complex problem and requires effective interventions and solutions.^[2] Ovulatory disorders account for 30%–40% of female infertility.^[3]

Polycystic ovarian disease (PCOD) is one of the common causes for anovulation. It is a common reproductive and endocrinologic disorder found in 6%–10% of the female population, characterized by hyperandrogenism, polycystic ovaries, and anovulation.^[4] Medicines commonly used to treat infertility and induce ovulation include antiestrogens, gonadotropins, gonadotropin-releasing hormone (GnRH) agonists, GnRH antagonists, and dopamine agonists. The second-line ovulation-inducing agents include gonadotropins such as follicle-stimulating hormone (FSH) and luteinizing hormone (LH), available as recombinant gonadotropins (recombinant FSH [rFSH], rLH). These are

used along with GnRH agonists/antagonist in different doses, duration, and combination are prescribed as short, long, or antagonist protocol. In recent years, rFSH has increasingly been used in ovulation induction and *in vitro* fertilization (IVF) treatments although meta-analysis of compromising true randomized-controlled trials showed an equivalent clinical efficacy of rFSH and human menopausal gonadotropin (hMG).^[5] However, a systematic review of randomized trials showed a significant difference in the pregnancy outcome in different gonadotropin preparation.^[6] In context with, which regimen is best in terms of pregnancy rate and outcome in anovulatory infertility needs to be investigated. The present study was

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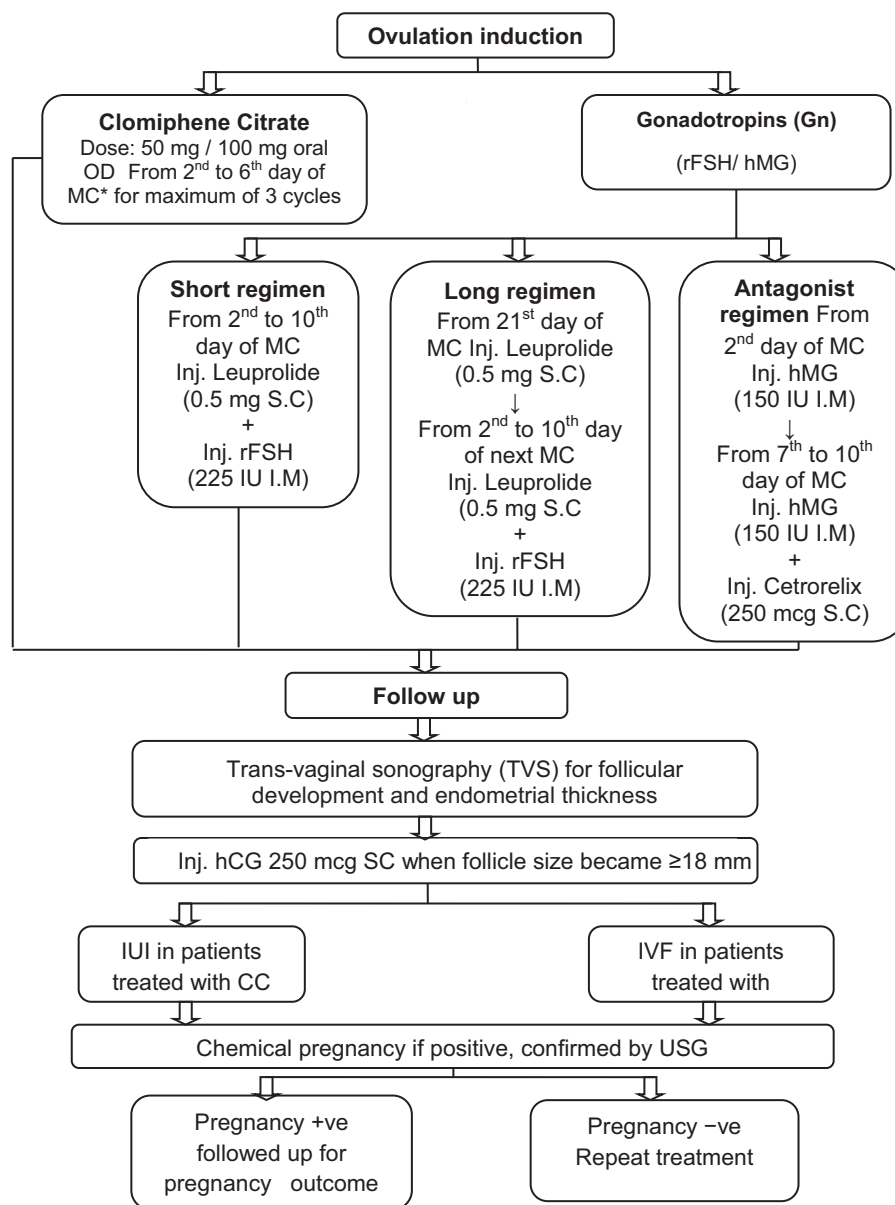
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[*MC= Menstrual cycle]

Figure 1: Treatment details of the patients with anovulatory infertility

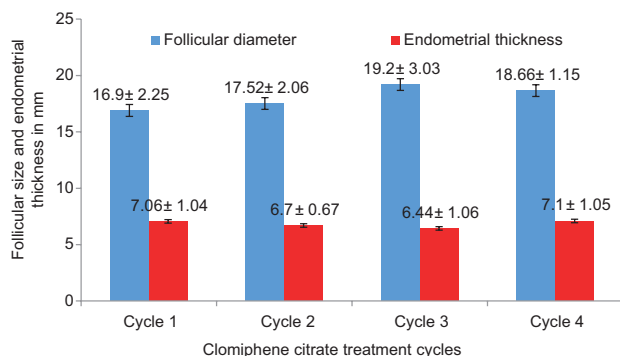


Figure 2: Effect of clomiphene citrate on follicular size and endometrial thickness in patients with anovulatory infertility (n=38) (values are mean ± SEM)

undertaken to investigate pregnancy rate and outcome as well as safety of these drugs in patients with anovulatory infertility.

PATIENTS AND METHODS

This prospective, observational study was conducted at the Department of Obstetrics and Gynaecology, Institute of Kidney Diseases and Research Center, Civil Hospital, Ahmedabad, to evaluate the effects of drugs on ovulation and pregnancy outcome in patients with anovulatory infertility. The study was carried out over a period of 18 months from March 2015 to September 2016 after Ethics Committee approval (Reference number-EC/Approval/42/15). Patients of 21–37 years of age with PCOD with other causes of ovulatory dysfunction, i.e.,

Table 1: Baseline characteristics of patients with anovulatory infertility (n=65)

Parameters	Treatment given to patients			
	Clomiphene citrate (n=38)	Short regimen (n=32)	Long regimen (n=19)	Antagonist regimen (n=6)
Age (years) (mean±SD) (95% CI)	28.28±4.47 (26.82-29.75)	29.12±4.03 (27.67-30.57)	30.42±4.69 (28.16-32.68)	33.33±1.05* (30.62-36.04)
BMI (Kg/m ²) (mean±SD) (95% CI)	23.64±3.72 (22.41-24.86)	24.4±4.32 (22.84-25.95)	24.79±3.91 (22.90-26.67)	25.23±3.77 (21.27-29.19)
Duration of infertility (years) (mean±SD) (95% CI)	6.78±3.29 (5.7-7.87)	7.68±3.81 (6.31-9.06)	6.89±3.39 (5.25-8.53)	7.83±2.85 (4.83-10.83)
Associated complaints and co-morbidities n (%)				
Obesity	7 (18.4)	12 (37.5)	6 (31.6)	1 (16.7)
Irregular menses	14 (36.8)	12 (37.5)	7 (36.8)	1 (16.7)
Amenorrhoea	0 (0)	1 (3.1)	3 (15.7)	0 (0)
Hirsutism	9 (23.7)	8 (25)	4 (21.0)	1 (16.7)
Hyperprolactinemia	5 (13.1)	2 (6.2)	0 (0)	1 (16.7)
Hypothyroidism	2 (5.3)	4 (12.5)	0 (0)	0 (0)

P<0.05 as compared to clomiphene citrate regimen

Table 2: Comparison of gonadotropin regimens on follicular size and endometrial thickness (mean±SEM) in patients with anovulatory infertility

Gonadotropin regimen	Short regimen (n=32)	Long regimen (n=19)	Antagonist regimen (n=6)
Follicular size in mm (mean±SEM)	20.65±0.39	21.05±0.25	20.66±0.71
Endometrial thickness in mm (mean±SEM)	8.04±0.11*	7.48±0.11	7.11±0.13

**P*<0.05 as compared to antagonist regimen administered group

Table 3: Effect of clomiphene citrate and gonadotropin regimens on follicular size and endometrial thickness (mean±SEM)

Treatment group	Follicular diameter (mm)	Endometrial thickness (mm)
Clomiphene citrate (n=38)	17.39±0.44	6.38±0.22
Short regimen (n=32)	20.65±0.39*	8.04±0.11*#
Long regimen (n=19)	21.05±0.25*	7.48±0.11
Antagonist regimen (n=6)	20.66±0.71**	7.11±0.13

P*<0.001 as compared to clomiphene citrate, *P*<0.01 as compared to clomiphene citrate, #*P*<0.05 as compared to antagonist regimen by ANOVA

Table 4: Comparison of effect of clomiphene citrate and various gonadotropin regimens on pregnancy outcome (n=65)

Treatment regimens	Successful pregnancy (live birth) n (%)	Intra uterine death (IUD) n (%)	Abortion n (%)	Ongoing pregnancy n (%)	Overall pregnancy rate n (%)
Clomiphene citrate (n=38)	1 (2.6)	-	-	-	1 (2.6)
Gonadotropin regimens (n=57)					
Short regimen (n=32)	3 (9.4)	2 (6.2)	2 (6.2)	6 (18.8)	13 (40.6)
Long regimen (n=19)	4 (21.1)	-	2 (10.5)	4 (21.1)	10 (52.6)
Antagonist regimen (n=6)	1 (16.7)	-	1 (16.7)	-	2 (33.3)

thyroid abnormalities and hyperprolactinemia were included while those with infertility due to other causes were excluded from the study. For induction of ovulation, patients prescribed either clomiphene citrate (CC) (50 mg or 100 mg/day from 2nd to 6th day of menstrual cycle [MC]) or gonadotropins as short or long or antagonist regimen by consultant obstetrician. The different gonadotropins regimens were as follows:

1. Short regimen = leuprolide (0.5 mg subcutaneous [SC]) + rFSH (225 IU intramuscular [IM]) from 2nd to 10th day of MC (8 days)
2. Long regimen = leuprolide from 21st day followed by leuprolide + rFSH from 2nd to 10th day of the next MC (maximum 18 days)
3. Antagonist regimen = hMG (150 IU IM) from 2nd day followed by hMG + cetrorelix (250 mcg SC) from 7th to 10th day of MC (8 days).

Treatment flowchart is depicted [Figure 1]. The patients were followed up at every MC for follicular development and endometrial thickness by transvaginal ultrasonography. If patient conceived, pregnancy was confirmed by urine pregnancy test and subsequently by ultrasonography and followed up for pregnancy outcome till end. In addition, safety monitoring was done and suspected adverse drug reactions (ADRs) were recorded and assessed for causality, severity, and preventability. Data were analyzed using ANOVA; *P* < 0.05 was considered statistically significant. Multiple regression analysis was done to find correlation of pregnancy outcome with variables such as patients' age, body mass index (BMI), type of infertility, follicular size, endometrial thickness, and regimen prescribed.

RESULTS

Of 65 patients with anovulation due to PCOD, 38 were prescribed CC, while 57 patients (including those not responded to CC) were prescribed short/long/antagonist gonadotropin regimens as per discretion of consulting obstetricians. A total seven patients were lost to follow-up [Figure 1].

Baseline characteristics of patients included in the study

Patients' characteristics such as age, BMI, duration of infertility, associated presenting complaints, and comorbidities of all four groups were comparable. However, statistically significant higher mean age was observed in antagonist group when compared to CC-treated patients [Table 1]. Oligomenorrhea, obesity, and hirsutism were the common complaints of patients with PCOD. In addition, few patients also had hypothyroidism and hyperprolactinemia [Table 1].

Primary outcome

Patients treated with clomiphene citrate

A total 38 patients were administered CC initially in a dose of 50 or 100 mg for 5 days for a maximum of 4 cycles with total 76 treatment cycles. Majority of the patients (19) received two treatment cycles with CC followed by one cycle (11 patients), three cycles (5 patients), and four cycles (3 patients). The treatment cycle was considered successful when follicular size reached ≥ 18 mm. Maximum number of cycles were cancelled in CC cycle 1 and 2.

Effect of clomiphene citrate on follicular size and endometrial thickness

The mean follicular size and endometrial thickness in CC treatment cycles are shown in Figure 2.

Patients treated with gonadotropins

A total of 57 patients were prescribed gonadotropins along with GnRH agonist/GnRH antagonist in three regimens, considering the age of the patients as well as antral follicle counts (by transvaginal sonography) on 2nd day of MC.

Effect of gonadotropin regimens on follicular size and endometrial thickness

No difference on follicular size was observed among different regimens. However, endometrial thickness was significantly increased in patients treated with short regimen as compared to antagonist regimen ($P < 0.05$) [Table 2].

Comparison of clomiphene citrate and gonadotropin regimens on follicular size and endometrial thickness

A significant increase in follicular diameter was observed in patients treated with short and long gonadotropin regimens ($P < 0.001$) and antagonist regimen ($P < 0.01$) as compared to CC alone [Table 3]. Second, a significant increase in the endometrial thickness was observed in patients treated with short regimen as compared to CC ($P < 0.001$) and antagonist regimen group ($P < 0.05$) [Table 3].

Secondary outcome

Pregnancy rate

Patients treated with clomiphene citrate

Of 38 patients treated with CC, one patient conceived (with intra uterine insemination) after 3 treatment cycles.

Patients treated with gonadotropins

The overall pregnancy rate (positive pregnancy test with ultrasonographic evidence of gestational sac) observed with gonadotropin regimen was 43.5% (25/57). However, among different regimens, it was highest with leuprolide + rFSH (long regimen) (10/19, 52.6%) followed by leuprolide + rFSH (short regimen) (13/32, 40.6%) while least in antagonist regimen (2/6, 33.3%) as shown in Table 4.

Of 57 patients treated with gonadotropins, 25 patients conceived, 8 delivered successfully, 5 had abortion, 2 had intrauterine death, while 10 patients had ongoing pregnancy [Table 4].

Moreover, an attempt made to do multiple regression analysis to find correlation of pregnancy outcome with variables such as patients' age, BMI, type of infertility, follicular size, endometrial thickness, and regimen prescribed showed no statistically significant difference ($P > 0.05$).

Safety of the drug regimens

All the drugs were well tolerated. Total seven patients developed ADRs such as ovarian hyperstimulation (mild), headache, and abdominal pain. Patients treated with CC ($n = 1$) developed ovarian hyperstimulation, with short regimen ($n = 4$) developed ovarian hyperstimulation, headache, and abdominal pain while in long regimen ($n = 2$) headache developed. However, none of them required stoppage of the ongoing drug treatment or hospitalization. Majority of the ADRs were of moderate severity, not preventable and categorized as possible in nature as per the WHO-UMC and Naranjo's algorithm.

DISCUSSION

In recent years, multiple products with variety of regimens have been employed to stimulate ovaries to obtain an adequate number of good quality follicles to treat anovulatory infertility patients undergoing IVF. Several studies comparing different gonadotropin preparations in different doses have been designed to explore the quantitative response (number of oocytes retrieved).^[7] However, from patient and clinician perspective, more important is pregnancy rate and live birth following pharmacological interventions. The present study represents evaluation of ovarian response, pregnancy rate, and outcome in patients undergoing assisted reproduction with CC and three different gonadotropin regimes at a tertiary care infertility center.

Comparison of different gonadotropin regimens revealed no statistical significant difference ($P > 0.05$) on the follicular size, but endometrial thickness was significantly higher in

short regimen as compared to antagonist regimen. A significant increase in follicular size and endometrial thickness was observed with gonadotropin regimens as compared to CC. In addition, overall pregnancy rate was superior with gonadotropin regimens (43.9%) as compared to CC. Further, among all three gonadotropin regimens, it was highest with long regimen (52.6%).

It has been reported that obesity is associated with abnormal function of the hypothalamic-pituitary-ovarian (HPO) axis that contributes to development of PCOD along with altered hormonal profile, clinically represents as hirsutism (hyperandrogenism) and oligomenorrhea.^[8-10] Majority of the patients in the study presented with these features along with obesity and BMI ≥ 25 kg/m² higher than normal Asian women (18.6–22.9).^[11] A study by Dasari and Pranahita supports our observation.^[12] Interestingly, fertility problems such as anovulation and pregnancy loss are linked with obesity.^[13] This indicates that patients enrolled in our study displayed typical features of altered HPO axis.

CC being a first-line drug for ovulation induction is generally offered for maximum six ovulatory cycles. While in the present study, patients were treated with CC for a maximum of four cycles with an average of two cycles. The US Food and Drug Administration approved initial dosage is 50 mg daily for 5 days per cycle; which can be increased to 150 mg daily if patients do not respond. Surprisingly, no benefit in ovarian response and pregnancy rate was observed by increasing the CC dose and treatment cycle subsequently. Similar observation has been reported by Moy and Ekpo.^[14] In addition, the cycle cancellation rate was high (11 out of 27, 40.7%) during the second cycle. The cycle was considered as cancelled if mean follicular size in patients treated with CC could not reach the cutoff value of 18 mm.^[15] The response was much less as compared to observation by Shalom-Paz *et al.*^[16] Poor response can be attributed to clomiphene resistance. Moreover, most of these patients were treated at private clinic for infertility and it is possible that this may not be the actual number of treatment cycles with CC.

In short regimen, GnRH agonist stimulates release of a large amount of FSH (and LH) that leads to flare-up of the follicles so that more mature follicles for IVF can be obtained.^[17] However, in the long regimen, GnRH agonist is started (in previous MC) to “switch off” ovarian function (desensitization) followed by ovarian stimulation with FSH from day 2 of next MC.^[17] Therefore, the total duration of treatment is more (maximum 18 days) in long regimen as compared to short regimen. Thus, the rationale of using short and long regimen is to strongly stimulate ovaries. The preference of prescribing short or long regimen depends on ovarian substance, i.e., the existing antral follicle counts in ovaries. The use of GnRH antagonist has given new hope for the management of poor responders to short and long regimens. Antagonist regimen is safer in the patients with previous experience of hyperstimulation with FSH. The administration of GnRH antagonists avoids the premature LH surge and utilize maximum ovarian oocyte

cohort by minimizing the suppressing effects of the GnRH on the ovarian receptors.

Our study showed that short regimen was commonly prescribed and administered to patients with 25–32 years age group, while antagonist regimen was prescribed to higher age group having low ovarian reserve. All three regimens had equal efficacy in terms of ovarian response except for endometrial thickness which was significantly higher in short regimen as compared to antagonist regimen. Moreover, no cycle cancellation was observed with all the three gonadotropin regimens which were seen with CC. Further, the successful pregnancy rate (live birth) was higher in long regimen (21.1%), followed by antagonist regimen (16.7%) and short regimen (9.4%) in our study. Furthermore, the ongoing pregnancy rate was higher in both agonist long regimen 21.1% and short regimen (18.8%). A study done by Al-Inany *et al.* 2007 showed significantly higher ongoing pregnancy/live birth rate in the agonist group.^[18] Thus, successful pregnancy rate was superior with long agonist regimen while ongoing pregnancy was almost similar in long and short regimen. This mixed picture clearly restricts us to identify the best regimen for successful treatment outcome. Multiple regression analysis showed no association between different variables including drug regimen, ovarian response, and successful treatment outcome. Moreover, we also observed that short regimen had a trend toward higher endometrial thickness and probably implantation. However, it failed to reflect on pregnancy rate. This suggests that good ovarian response does not predict pregnancy rate and successful treatment. It will be of great relevance to identify other factors that will enable prescriber to achieve desired outcome and minimize chance of treatment failure. The use of CC and all three gonadotropin regimens were very well tolerated. Although the use of gonadotropins often cause multiple pregnancies, our study reported a single case of twin pregnancy and two cases of mild ovarian hyperstimulation syndrome.^[19,20]

The present study too has a few limitations. The small sample size, particularly in antagonist regimen, is a concern. Being a tertiary care referral center, most of these patients were treated at private clinic for infertility and did not respond to conventional ovulation-inducing agents, i.e., CC and required gonadotropins. Further, they were not able to quantify antral follicles on day 2 and number of oocytes retrieved with different regimens. Despite these limitations, this prospective study was undertaken over a period of 18 months, wherein all the information was recorded precisely. Each patient was followed up till the end of pregnancy, observed clinically and ovarian response was measured objectively. Thus, the data collected lead to some important conclusion.

CONCLUSION

The treatment outcome of gonadotropin regimens is better than CC in terms of ovarian response and pregnancy rate. The successful pregnancy rate and ongoing pregnancy rate

were high with long agonist regimen. However, we failed to establish the drug treatment as positive predictor for successful treatment outcome. Further research to identify predictors of successful treatment in women undergoing ovulation induction with appropriate sample size will be helpful in this regard.

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Conflicts of interest

There are no conflicts of interest.

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