Original Article

Comparison of Two Regimens of Gonadotropin-releasing Hormone Antagonists in Clomiphene-gonadotropin Induced Controlled Ovulation and Intrauterine Insemination Cycles: Randomized Controlled Study

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Abstract

Context: Gonadotropin-releasing hormone (GnRH) antagonists in fixed or flexible regimens are used for prevention of premature luteinizing hormone (LH) surge, however, data comparing these regimens in stimulated intrauterine insemination (IUI) cycles are lacking. **Aims:** The aim of this study is to evaluate the effectiveness of GnRH antagonists in fixed and flexible regimens on the rate of premature luteinization (PL) and ovulation rate in sequential clomiphene-gonadotropin controlled ovulation–IUI cycles. **Settings and Design:** This study was conducted at tertiary care center; this was randomized controlled study. **Materials and Methods:** A total of 45 infertile women randomized into three groups of 15 each received clomiphene citrate + human menopausal gonadotrophin. GnRH antagonist was added according to fixed (n = 15) and flexible (n = 15) protocol. No antagonist in control group (n = 15). PL was defined as LH level ≥10 mIU/ml and progesterone level ≥1.0 ng/ml. **Statistical Analysis:** Mean values compared using the Student's t-test or one-way analysis of variance. Categorical variables distribution tested using either Pearson's Chi-square or Fisher's exact test as appropriate. **Results:** Of a total of 45 women, 58% (n = 26) presented with primary and 42% (n = 19) secondary infertility with mean age of 30.8 ± 3.43 years and BMI 26.57 ± 3.22 kg/m^2. Fixed regimen (3.7%) showed most reduction in PL compared to flexible (15.38%, P = 0.33) or control (36.67%, P = 0.004). On human chorionic gonadotropin day, mean LH (P = 0.002) and progesterone (P = 0.079) levels in fixed, flexible, and control groups were as follows: 5.04 ± 5.47 mIU/ml, 3.95 ± 4.16 mIU/ml, 9.57 ± 7.91 mIU/ml, and 0.409 ± 0.320 ng/ml, 0.579 ± 0.727 ng/ml, and 1.033 ± 1.022 ng/ml, respectively. Ovulation (P = 0.813) and pregnancy rates (P = 0.99) were 88.9%, 84.6%, and 90% and 22.2%, 19.23%, and 10% in fixed, flexible, and control groups, respectively. **Conclusions:** Addition of antagonist in any regimen appears to lower PL rates and improve pregnancy rates in controlled ovarian stimulation and IUI cycles.

Keywords: *Clomiphene-gonadotropin, fixed regimen, flexible regimen, gonadotropin-releasing hormone antagonist, intrauterine insemination, premature luteinization*

Introduction

Controlled ovarian stimulation (COS) with intrauterine insemination (IUI) is widely used in the treatment of infertility. It is a less invasive and inexpensive treatment option compared to advanced assisted reproductive techniques (ART).[1-3] One

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problem frequently encountered in gonadotropin ovulation induction–IUI (OI-IUI) cycles is premature luteinisation (PL) caused by endogenous luteinizing hormone (LH) surge before the leading follicle reaches optimum diameter for triggering ovulation by human chorionic gonadotropin (hCG). The incidence of premature luteinization is around 25%–30%.[4-6] PL is detrimental to oocyte quality, fertilization, and embryo implantation as LH surge may lead to premature secretory transformation of the endometrium,[7] which causes asynchrony between the embryo and the endometrium; therefore, it is a negative predictive factor for implantation causing a significant degree of cycle cancellation and subsequent psychological stress and financial burden.[8,9]

Gonadotropin-releasing hormone (GnRH) analogs are widely used in ovarian stimulation protocols for their ability to prevent a premature LH surge.[10] While GnRH agonists have played an important role in reducing premature LH surge, especially in *in vitro* fertilization (IVF) cycles, GnRH antagonists have recently emerged as an alternative.[9] Unlike agonist, GnRH antagonists are easy to incorporate in an IUI cycle due to immediate mode of action, no initial flare up and shorter treatment duration. GnRH antagonists can be administered either on a fixed day of stimulation[11] or as flexible regimen (after follicle size ≥14 mm).[12] All the previous studies have compared between the two regimens in IVF/intra-cytoplasmic sperm injection (ICSI) cycles.[13-17] Data from stimulated IUI cycles comparing between these two regimens is lacking, and hence, we planned a trial to compare the fixed and flexible regimens of GnRH antagonist in controlled ovarian hyperstimulation-IUI cycles. The aim of this study was to evaluate the effectiveness of GnRH antagonists in fixed and flexible regimens on the rate of premature luteinization and ovulation rate in sequential clomiphene- gonadotropin controlled ovulation – IUI cycles.

Materials and Methods

This study was a prospective open-label, randomized controlled clinical trial conducted from May 2012 to May 2013 in outpatient Department of Obstetrics and Gynecology in a Tertiary Center. Ethical approval was obtained from the Institute's Ethics Committee before start of the study.

A total of 45 infertile women attending the outpatient department were recruited for the study. Women aged 21–38 years of age with unexplained infertility or mild male factor infertility and at least one patent fallopian tube; ovulation dysfunction infertility; euthyroid state and no associated medical problems or drug allergies were included in the study. Women with Stage III or IV endometriosis; severe male factor or tubal factor infertility; baseline follicle-stimulating hormone (FSH) >12 IU/l or antral follicle count <4 per ovary were excluded for this study.

After detailed history and examination, baseline hormone profile was done. Husband semen analysis after abstinence of 3–5 days was done. Tubal patency confirmed either by hysterosalpingography or diagnostic laparoscopy. After obtaining written consent of the couple, the women were randomized into one of the three groups and each patient was allowed a maximum of three cycles.

Each woman received clomiphene citrate (tablet Siphene– Serum Institute of India Ltd.) 50 mg/d orally on day 2–6 of menstrual cycle followed by human menopausal gonadotrophin (hMG) 75 IU IM (injection GMH– Sun Inca Pharmaceuticals), given daily from day 6 to day 8 of cycle and dose increased according to response. In group I (fixed), cetrorelix 0.25 mg SC (injection Ciscure– Emcure Pharmaceuticals) was given from day 8 of the cycle, and in group II (flexible) it is given on the day of follicle size ≥14 mm, but group III (control) did not receive cetrorelix. The strict timing of cetrorelix administration was maintained. Transvaginal ultrasound was done from day 8 of cycle onward and repeated every 2 days or early (determined by follicle size) to look for the follicle size, number, and endometrial thickness. If four or more mature follicles reach >16 mm in diameter, the cycle was cancelled, and the patient was advised to avoid intercourse until her next menstrual period. Cycles were also canceled when poor follicle response is noted until day 18 of the cycle, i.e., no follicle size >10 mm.

LH, progesterone, and estradiol levels were measured on day 8, day 10, day 12, etc., (i.e., every 2 days) until the day of hCG. hCG 5000 IU (injection HUMOG– Bharat serum and vaccines Ltd.) was given to all patients once the dominant follicle is ≥18 mm in size and IUI was done after 36–38 h. Before doing IUI, ultrasound was done only to document ovulation. Semen washing was done by double density gradient technique. IUI was done within a maximum time of 80 min with a flexible IUI catheter. Luteal phase was supported by oral micronized progesterone 200 mg BD for 15 days and periconceptional folic acid supplementation 5 mg OD was given. Patients were followed up by doing urine pregnancy test after 15 days.

The primary outcomes were as follows: premature luteinization rate defined as LH level of ≥10 mIU/ml

and a progesterone level of ≥1.0 ng/ml. Ovulation is assumed to have happened when after a dominant follicle of ≥18 mm is triggered with hCG injection and after 36 h, if there is the absence of follicle or crumpled follicle or free fluid in the pouch of Douglas is noted on ultrasound. The secondary outcomes were clinical pregnancy rate, the effect on endometrial thickness and hormonal levels, cycle cancellation rate, and adverse effects.

Statistical analysis

Data were computerized in Microsoft Excel worksheet. Descriptive statistics, namely mean, median, standard deviation (SD), and minimum and maximum values were computed for all the study variables. Comparison of two group means was carried out using "T" independent sample test after ensuring that both mean and median were almost equal and SD was about 40% of the mean. With the same assumption of normality, more than two group means were compared using one-way analysis of variance. When the assumption of normality was not fulfilled, nonparametric median comparison test was carried out. The frequency of categorical variables was represented in percentages and their distribution tested within the groups using either Pearson's Chi-square test or Fisher's exact test wherever appropriate. All these analyses were carried out using IBM SPSS version 21 (IBM corporation, Armonk, New York, U.S). For all statistical tests, level of significance $P < 0.05$ was considered.

Results

Forty-five women with a mean age of 30.89 ± 3.43 years were recruited for this study. Primary infertility was seen in 58% (n = 26) and 42% (n = 19) had secondary infertility. In each group of 15 women, there were a total of 27 cycles in fixed group, 26 cycles in the flexible group, and 30 cycles in control group. All the three groups were comparable with respect to baseline characteristics and day two hormonal profile as shown in Table 1.

The PL rate was 19.2% (16 of 83 cycles) with a group wise incidence of 3.7% in fixed, 15.4% in flexible and 36.7% in control group (P = 0.006) as shown in Table 2. The reduction in PL rate was significant between fixed and control groups (P = 0.004) but not between fixed and flexible groups (P = 0.33) or flexible and control groups (P = 0.13).

Ovulation rates per stimulated cycle were similar among three groups [Table 2]. A number of 16 mm size follicles were 1.48 ± 0.893, 1.85 ± 1.347, and 1.63 ± 0.850 in fixed, flexible, and control groups, respectively, and not significantly different between the groups (P = 0.446).

Table 1: Baseline characteristics between the three groups (n=15)

Characteristics	Mean±SD			*P**
	Fixed group	Flexible group	Control group	
Age (years)	31.73±3.01	30.33±2.74	30.60±4.39	0.505
BMI (kg/m^2)	27.59±2.77	26.49±3.11	25.62±3.63	0.247
WC/HC	0.92±0.04	0.89±0.04	0.89±0.05	0.176
Infertility duration (years)	3.93±1.83	5.20±3.46	6.27±2.37	0.065
Serum FSH (mIU/ml)	6.19±1.93	5.62±0.93	6.13±2.01	0.601
Serum LH (mIU/ml)	5.20±1.80	5.41±1.43	4.36±1.22	0.144
Serum estradiol (pg/ml)	50.14±24.31	39.80±20.01	62.00±31.53	0.072
Serum testosterone (ng/ml)	0.36±0.18	0.44±0.17	0.41±0.21	0.466
Serum progesterone (ng/ml)	0.40±0.11	0.36±0.09	0.34±0.15	0.373
Serum prolactin (ng/ml)	12.2±6.05	16.45±6.81	14.82±5.89	0.186
Serum TSH (μIU/ml)	2.67±0.91	2.09±1.18	2.41±0.97	0.315

*One-way ANOVA test. BMI=Body mass index, FSH=Follicle-stimulating hormone, LH=Luteinizing hormone, TSH=Thyroid-stimulating hormone, WC=Waist circumference, HC=Hip circumference, SD=Standard deviation, ANOVA=Analysis of variance

Clinical pregnancy rate in this study was 16.8% per stimulated cycle (14/83 cycles). Pregnancy rates per cycle in three groups are shown in Table 2. Even though the pregnancy rates were higher in antagonist group than control group, there was no statistically significant difference between either the antagonist and control groups or between fixed antagonist and flexible antagonist group. Subanalyses had shown ovulation in 81% (13/16) of the cycles with premature luteinization and the rest (3/16) were classified as luteinized and unruptured follicles. Ovulation rates of premature luteinized cycles were higher in antagonist group (100%) than the control group (72.7%), but it was not statistically significant (P = 0.833). In premature luteinized cycles, no pregnancy was documented in any cycle even though ovulation had happened in 81% of premature luteinized cycles showing the detrimental effect of PL on pregnancy rates.

As shown in Table 2, the mean embryo transfer (ET) on the day of hCG per cycle observed in fixed group was 8.63 ± 1.61 mm (6.5–14 mm); inflexible group was 9.84 ± 2.17 mm (7.0–14.0 mm); in control group was 8.29 ± 1.51 mm (5.5–11.5 mm) with statistically significant difference between flexible and control groups (P = 0.004) only. On subanalyses,

Table 2: Cycle characteristics and outcomes

Parameter	Fixed group (*n*=27 cycles)	Flexible group (*n*=26 cycles)	Control group (*n*=30 cycles)	*P* value between all groups	*P* value between fixed and flexible groups
Premature luteinization (%)	1 (3.7)	4 (15.4)	11 (36.7)	0.006§	0.33†
Ovulation (%)	24 (88.9)	22 (84.6)	27 (90)	0.813§	0.95†
Clinical pregnancy rate (%)	6 (22.22)	5 (19.23)	3 (10)	0.435§	0.99†
ET on day of hCG* (mm)	8.63±1.61	9.8±2.17	8.2±1.51	0.005‡	0.065‖
Estradiol on day of hCG* (pg/ml)	400.45±240.03 (363.00)	388.11±287.6 (319)	412.82±233.90 (405.00)	0.525¶	NS
LH on day of hCG* (mIU/ml)	5.04±5.47 (3.64)	3.95±4.16 (2.20)	9.57±7.91 (7.92)	0.002¶	0.248¶
Progesterone on day of hCG* (ng/ml)	0.409±0.320 (0.300)	0.579±0.727 (0.300)	1.033±1.022 (0.470)	0.079¶	NS
>16 mm size follicles	1.48±0.893	1.85±1.347	1.63±0.850	0.446‡	
Cetrorelix ampoules	3.88±2.48	2.42±1.20	-	-	0.009**
Gonadotropin (hMG) requirement (IU)	538.89±356.08 (375)	937.50±536.34 (675)	392.50±154.69 (337.5)	0.000¶	0.009¶

*Cancelled cycles are excluded, †Fisher's exact test, ‡One-way ANOVA test, §Pearson's Chi-square test, ‖Pair-wise comparison test, ¶Nonparametric median test, ***t* independent samples`. ET=Embryo transfer, hCG=Human chorionic gonadotropin, LH=Luteinizing hormone, ANOVA=Analysis of variance, NS=Not significant

ET on the day of hCG was compared between the conceived and failed cycles, which had shown nonsignificantly (P = 0.373) higher mean ET observed in conceived cycles group (9.21 ± 2.2 mm) than failed cycles group (8.72 ± 1.78 mm). Premature luteinized cycles have slightly higher mean ET (9.77 ± 2.31 mm) than the conceived cycles (9.21 ± 2.2 mm) but neither the difference was statistically significant (P = 0.504) nor this difference translated into better pregnancy rates. LH levels on hCG day have shown the statistically significant difference between fixed and control groups (P = 0.010) and between flexible and control groups (P = 0.008) but no difference between the two antagonist groups (P = 0.248).

Significant higher number of cetrorelix ampoules were used in fixed than flexible group (P = 0.009) 3.88 ± 2.48 vs. 2.42 ± 1.20, respectively. About 7.4% cycles in the fixed group (2/27) and 15.4% cycles (4/26) in flexible group but none in control group were canceled. Four cycles (66.7%), one in fixed and three in flexible group were cancelled due to poor follicular development (poor ovarian response); one cycle (16.7%) in flexible group was cancelled due to mild ovarian hyperstimulation syndrome (OHSS) and IVF conversion was not done due to financial constraints of the patient. In flexible group, one woman had triplet pregnancy who underwent triplet reduction at 13 weeks and delivered twins at full term.

Discussion

GnRH antagonists are used to lowering premature LH surge and consequent luteinization in IVF cycles. Limited studies are available comparing the GnRH antagonists in fixed and flexible regimens on various outcomes and all the previous studies compared the two regimens in IVF/ICSI cycles. To the best of our knowledge, our study was the first to compare the two different regimens of GnRH antagonists in clomiphene citrate HMG (CC-HMG) stimulated IUI cycles.

The incidences of PL rates in other studies are presented in Table 3.

The study had shown that the PL was higher in control group (36.67%) than combined antagonist group (9.4%) (P = 0.006). Although not statistically significant, fixed protocol (3.7%) showed better prevention of PL than flexible (15.38%). This is due to early initiation of antagonist which also resulted in usage of a higher number of cetrorelix ampoules in fixed group. Our PL rates were comparable with the previous studies.

The clinical pregnancy rate in our study was 22.22% in fixed antagonist cycles, 19.23% in flexible antagonist cycles and 10% in control cycles. The pregnancy rate in our antagonist group was comparable to other similar studies in stimulated IUI cycles in which the only one of the antagonist regimen (either fixed or flexible) was compared with control group.[19,23] The studies comparing between the two regimens of antagonists in IVF cycles had higher pregnancy rates than our study which is due to their IVF study design.[15-17] However, the significant difference between the two antagonist regimens was not shown in any of the studies. Studies done in IUI cycles using the flexible antagonist regimen have shown conflicting pregnancy rates, with some studies showing significantly

Table 3: Premature luteinization among previous studies and current study

Studies	Study year	Total study cycles	Flexible antagonist regimen (%)	Control group (%)	*P*
Lambalk *et al*.[5]	2006	203	1	17	0.015
Allegra *et al*.[18]	2007	104	1.4	10.4	0.001
Lee *et al*.[19]	2008	61	19.4	43.3	0.043
Bakas *et al*.[20]	2011	93	1.7	17.5	<0.05
Kamath *et al*.[21]	2013	141	5	13.8	0.31
Wadhwa *et al*.[22]	2016	70	2.9	13.9	<0.001
Kolibianakis *et al*.[17]	2011	146	11, (15.1*)	-	NA (0.38)†
Present study	2012-2013	83	15.38, (3.7*)	36.67	0.13 (0.33)† (0.004)‡

*PL in fixed antagonist group, †*P* value between flexible and fixed antagonist group, ‡*P* value between fixed antagonist and control group. NA=Not available, PL=Premature Luteinization

better pregnancy rates[18,20,24] and the other reporting no difference in pregnancy rates[5,19,21-27] in antagonist groups.

Addition of antagonist did not affect the ovulation rates in our study. However, sub analyses had shown that pregnancy was not documented in any premature luteinized cycle even though ovulation had happened in 81% of those cycles. This result, of our study, was similar to and supported by the results of Lambalk *et al*.,[5] Allegra *et al*.[18] and Lee *et al*.,[19] with no pregnancies documented if LH ≥10 mIU/ml + *P* ≥1 ng/ml. This gives an emphasis on the importance of premature luteinization and its detrimental effect on fertility outcome, oocyte quality, and embryo-endometrial asynchrony. The study thus supports the evidence of PL as a negative predictive factor due to increase in serum E2 levels inducing an LH surge while still, the follicles are growing which occur during multifollicular recruitment in OI.

A recent meta-analysis of twelve studies by Luo *et al*., in 2014 have shown that addition of antagonist can significantly decrease PL rate (odds ratio [OR] = 0.22, 95% confidence interval [CI], 0.16–0.30) and increase clinical pregnancy rate (OR = 1.42; 95% CI, 1.13–1.78) in COS-IUI cycles. These results hold especially true for nonpolycystic ovary syndrome (PCOS) patients. theHowever, role in PCOS patients is still unclear.[28]

The study had shown higher endometrial thickness on the day of dominant follicle in antagonist group than control group. This is slightly lower than the ET values of other studies probably due to the use of sequential CC-HMG regimen in our study rather than rFSH stimulated cycles. However, the higher ET in flexible group in our study, did not translate into better pregnancy rates when compared to fixed group (19.23% vs. 22.22%, $P > 0.05$) probably due to smaller study sample size. In our study, the mean ET was 9.21 ± 2.2 mm in conceived cycles and 8.72 ± 1.78 mm in nonconceived cycles. In a study to predict IVF outcome considering the endometrial thickness on day of embryo transfer, Sharma had shown that pregnancy rates were higher (34.5%) in the cycles with ET between 9 and 10 mm.[29]

A study by Wadhwa *et al*. had shown that addition of antagonist in COS-IUI cycles when follicles reach 16 mm or more in diameter also significantly lower the incidence of premature LH surge. This delayed administration, with 1.85 ± 0.61 days of antagonist duration, also decreases the requirement of antagonist hence lowering the cost of COS-IUI. However, clinical pregnancy rates were similar in both groups.[22] The average day of starting antagonist in our study in the flexible group was 11.34 ± 2.88 days and mean duration of administration was 2.42 ± 1.20 days.

In 2011, the randomized controlled trial by Kolibianakis *et al*., had shown a significant difference in mean LH value between fixed antagonist (3.7 mIU/ml) and flexible antagonist (2.4 mIU/ml) groups on the day of the dominant follicle.[17] However, the same study did not show a significant difference in estradiol levels between those two groups, with slightly higher mean E2 level in flexible group (2503 pg/ml) than fixed group (2412 pg/ml). Similar to Kolibianakis *et al*., study,[17] the mean LH value in fixed antagonist group (5.04 mIU/ml) was higher than flexible antagonist group (3.95 mIU/ml) in our study, but it did not reach statistical significance.

In this study, the cycle cancellation rate was 11.3% in antagonist group (n = 6), and no cycle was canceled in control group. Despite the higher rate of PL in control group, there was no cycle canceled in control group, and paradoxically all the canceled cycles belong to antagonist group. This is similar to the randomized controlled trial by Steward *et al*.[23] Poor ovarian response contributed to 66.7% of canceled cycles (4/6) in our study. Three of the four (75%) poor ovarian response patients were in flexible group which means it may be the patient's profile which effected the cycle cancellation rather than the use of antagonist. Compared to the previous studies, the incidence of the OHSS and multiple gestations was lower in our study probably due to smaller small size and differences in stimulation protocols. The main limitation of our study was lack of sufficient power and low sample size.

Conclusions

The study findings have shown the addition of GnRH antagonist in any regimen have significantly decreased

the rate of PL with better pregnancy rates. It also shows the detrimental effect of PL on pregnancy. However, there was no difference between the two antagonist regimen in CC-HMG + IUI cycles in terms of PL, ovulation, endometrial thickness, and pregnancy rates. In developing countries, as the cost of the ART is high, for nonaffording couples who satisfy IUI criteria, COS (CC + HMG) + IUI cycles with antagonist inclusion offer relatively cost-effective method for achieving fairly good pregnancy outcomes. However, more multicenter randomized trials with larger sample size are required to answer which GnRH antagonist regimen is better in COS-IUI cycles in terms of clinical efficiency and cost effectiveness.

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Conflicts of interest

There are no conflicts of interest.

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