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Original Research Article

Addition of gonadotropin releasing hormone antagonist for women undergoing intrauterine insemination: a randomized controlled trial

Lakshmi Gopal[1]*, Pradeepa Sudhakar[2], Dhanabagyam Kandaswami[3], Saranya Manivannan[4]

[1]Department of Obstetrics and Gynecology, Sudha Hospitals, Salem, Tamil Nadu, India
[2]Department of Reproductive Medicine, [4]Department of Obstetrics and Gynecology, Sudha Hospitals, Erode, Tamil Nadu, India
[3]Department of Reproductive Medicine, Sudha Hospital, Coimbatore, Tamil Nadu, India

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***Correspondence:**
Dr. Lakshmi Gopal,
E-mail: sudharesearch2021@gmail.com

ABSTRACT

Background: Intrauterine insemination (IUI) is a widely acceptable fertility treatment modality. GnRH antagonists have been proven effective in restricting the LH surge. The aim of the study was to assess whether the addition of gonadotropin releasing hormone antagonist (Cetrorelix) would improve clinical pregnancy rate in women undergoing IUI.
Methods: This prospective randomized controlled trial was conducted at a Sudha fertility center where 730 women with primary or secondary infertility were subjected to controlled ovarian stimulation with tablet letrozole 5mg once daily for 5 days and then human menopausal gonadotrophins 75 IU/150 IU administered intramuscularly for both the groups and for study group alone Cetrorelix (0.25 mg/day, started when the leading follicle was ≥16 mm; GnRH antagonist) was given additionally. A double insemination was performed at 36 hours and 60 hours after hCG was given (5,000 IU, intramuscularly) in both groups. Chi-square and independent t test was done.
Results: Baseline characteristics in both the groups were almost equal without any statistically significant difference. Significant difference (p=0.017) was found on calculating with statistics among both groups on analyzing LH on hCG day. Clinical pregnancy rates (29.3%) were higher among the study group compared with the control group (21.7%).
Conclusions: From the present study results it shows that addition of GnRH antagonists to controlled ovarian stimulation IUI significantly decreases the incidence of premature luteinization and increases the clinical pregnancy rates and live birth rate.

Keywords: Cetrorelix, antagonist, Ovarian stimulation, Clinical pregnancy, Stimulation

INTRODUCTION

Intrauterine insemination (IUI) is the most widely acceptable infertility treatment modality. IUI usage came into limelight as one of the utmost used first line treatment procedures in cases of infertility treatments and assisted reproductive technologies.[1] Depending on the diagnostic criteria, unexplained infertility accounts for about 15-28% of subfertility. The principle behind the controlled ovarian stimulation (COS) and IUI is to escalate the number of obtainable female and male gametes at the fertilization site which is obtained using two or three dominant follicles at the place and time of fertilization which is followed by magnificently timed insemination.[2,3] The success rate of this procedure was calculated to be somewhere between 10% to 17.5%. Several causes such as the patient's age, sperm quality and treatment indication can be responsible and might influence the pregnancy rate after IUI.[4]

Though multifollicular employment due to controlled ovarian stimulation immediately shoots up the estradiol (E2) serum levels which leads to a Luteinizing hormone (LH) release whereas growth of follicle is still in growth phase. Premature LH surge happens in 25% -30% of IUI cycles which is accountable for luteinization and poor quality oocyte formation which ultimately lead the way for cycle cancellation.[4] Normally, physicians should start the ovulation triggers as soon as the leading follicle attains 18mm in diameter without considering the number of other recruited follicles. This should be done for stimulated cycles to be mono follicular and to avoid the risk of accidental premature follicular luteinization.[5,6] GnRH agonist usage is not suggested in IUI patients due to multiple administration of injections from premenstrual cycle and during stimulation phase, more requirement of injections, prolonged duration of stimulation and no improvement in fecundity cycle.[7,8] On the other side, GnRH antagonists occlude the GnRH receptors which inturn reduces follicle stimulating hormone secretion and luteinizing hormone secretion within 2-4 hours. Premature LH surge can be avoided, as is widely known. The GnRH antagonist's intermediate impact is dose-dependent, reversible, and associated with an equilibrium between the concentrations of endogenous GnRH and GnRH antagonist.[9,10] The two most popular GnRH antagonists that are widely utilized in clinical settings are cetrorelix and ganirelix.

Aims and objectives

Aim and objectives of current study were; the study's objective was to determine whether giving women undergoing IUI gonadotropin-releasing hormone antagonist (Cetrorelix) would increase the clinical pregnancy rate, to further assess the miscarriage rate among both the groups and to compare the rates of pregnancy and live births for the two groups.

METHODS

This study was conducted at a Sudha fertility center from January 2021 to March 2022 in the South part of Tamil Nadu. Study design was designed as a prospective randomized controlled trial. Seven hundred and thirty participants with unexplained infertility, mild male factor infertility and minimal to mild endometriosis were included in the study to assess the GnRH antagonist. Informed written informed consent was obtained from the participants after the counseling session. Ethical approval was obtained from the Ethical review board. The patients were divided into two groups such as the GnRH antagonist group (study group) and control group with each 375 patients. Computer generated randomization was done to prevent bias. Before the start of the study all patients underwent hormonal profile tests such as FSH, LH, Estradiol (E2) and anti mullerian hormone. Tubal patency test was also performed. Semen was collected to test male factor infertility according to WHO criteria. Patients with unexplained infertility, unilateral or bilateral tubes patent and normal uterine cavity, menstrual cycle in regular pattern with follicle stimulating hormone less than or equal to 10 IU/L and patients with age less than 35 years were included for the study. Patients with severe male factor, severe endometriosis, age more than 35 years, polycystic ovary syndrome were excluded from the study. No patients were canceled after recruitment to the study. On the second day of the menstrual cycle before the start of treatment, transvaginal ultrasound was done to assess uterine cavity and to ensure the absence of cysts in both ovaries. Controlled ovarian stimulation was initiated for all the participants on the second or third day of the menstrual cycle using tablet letrozole 5mg once daily for 5 days and treated with human menopausal gonadotrophins 75 IU administered intramuscularly daily for only 3 days depending upon the body mass index (BMI). If the follicular growth suboptimal means HMG dose increased to 150 IU for 2 to 3 days. Follicular monitoring was also started at day 7 of the cycle after ovulation induction using transvaginal ultrasonography (TVS) to evaluate the ovarian response and to initiate the hMG dose. This was done every 2 days once until the leading follicle attained the maximum size of 18-20 mm. Whereas in the study group when the leading follicle attains 15-16mm, 0.25 mg Cetrorelix was administered subcutaneously daily up to the day of hCG administration (follicle size reaches 18-20 mm). Once it reaches its size, 5000 IU hCG was given intramuscularly and IUI was done after 36 hours and 60 hours for both the groups with an insemination volume of 0.5ml. Double density gradient technique was mostly used for semen preparation. Vaginal micronized progesterone (200mg 12 hourly) was given as luteal support for all patients irrespective of groups. Pregnancy was detected using a urinary detection kit after 18 days of IUI. Transvaginal sonography was done after 1 week to confirm pregnancy. Positive hCG together with the presence of gestational sac in TVS accounts as clinical pregnancy. Statistical analysis was performed using statistical packages of social sciences (SPSS) version 26.0. Shapiro wilks test was done to test the normality of the data. Data were computed and summarized as mean and standard deviation. Differences in variables between two groups were compared using Chi-square association test. Independent t test was used to test the statistical differences between the means of two groups, $p<0.05$ was considered as statistically significant.

RESULTS

A total of 730 participants agreed to participate in the trial with 365 women in the study group and 365 women in the control group. No loss of participants were noted. Baseline Characteristics of patients such as age, Body mass index (BMI), duration of infertility, basal FSH, LH and E2 in study and control group before initiation of treatment was evaluated and compared (Table 1). No statistically significant difference was found between the two groups among the variables. Almost all the baseline characteristics in both the groups were almost equal without any significant difference. Mean age in the study

group was 27.2±3.9 whereas in the control group 26.8±3.6. Mean basal follicle stimulating hormone in the study group was 8.2±8.3 whereas in the control group 7.9±8.1. Mean LH was 4.2±5.1 whereas 4.9±3.8 in the control group.

Table 1: Baseline characteristics of patients in study and control group before initiation of treatment (n=365).

Variables	Study group	Control group	P value
Age	27.2±3.9	26.8±3.6	0.543
BMI	24.9±4.6	23.7±3.8	0.417
Duration of infertility			
Primary infertility	268 (73.4)	257 (70.4)	0.083
Secondary infertility	97 (26.6)	108 (29.6)	
Basal FSH	8.2±8.3	7.9±8.1	0.177
Basal LH	4.2±5.1	4.9±3.8	0.232
Basal E2	76.1±140.3	69.5±129.3	0.529

Table 2: Characteristics of GnRH Antagonist protocol during stimulation cycles (n=365).

Variables	Study group	Control group	P value
Endometrial thickness	0.91±0.2	0.82±1.3	0.083
Follicles >16 mm	1.3±70.1	1.7±38.4	0.138
HMG dose (IU)	827.3±183.4	834.9±259.7	0.519
E2 on hCG day	618.3±89.7	584.5±104.2	0.672
P on hCG day	17.5±13.5	19.2±24.6	0.003*
LH on hCG day	6.47±3.6	6.83±4.1	0.017**
Sperm motility	52.5±10.2	55.7±7.5	0.074

*Significant at the 0.01 level (2-tailed), ** Significant at the 0.05 level (2-tailed).

Characteristics of the GnRH Antagonist protocol during stimulation cycles among two groups were represented as mean and standard deviation (table 2). A statistically significant difference (p=0.017) was found between two groups on analyzing LH on hCG day. A statistically significant difference (p=0.003) was found between both the groups on analyzing P on hCG day. No statistically significant difference was found on analyzing other variables such as endometrial thickness, follicles >16 mm, HMG dose (IU), E2 on hCG day and sperm motility. Clinical outcomes like clinical pregnancy rate, miscarriage rate, live birth rate and ongoing pregnancy rate were evaluated among both the groups. Clinical pregnancy rates (29.3%) were higher among the study group compared with the control group (21.7%). Miscarriage rate was also higher among the study group (2.2%) when compared with the control group (1.4%) which is a concern. Live birth rate was also higher in relation to the study group (25.5%) when compared with control groups (19.5%) (Table 3).

Table 3: Comparison of clinical outcomes among the GnRH antagonist protocol (n=365).

Variables	Study group	Control group	P value
Clinical pregnancy rate N (%)	107/365 (29.3)	79/365 (21.7)	0.038**
Miscarriage rate N (%)	8/365 (2.2)	5/365 (1.4)	0.019**
Live birth rate N (%)	93/365 (25.5)	71/365 (19.5)	0.006*
Ongoing pregnancy rate N (%)	6/365 (1.6)	3/365 (0.8)	0.029**

*Significant at the 0.01 level (2-tailed), **Significant at the 0.05 level (2-tailed).

A statistically significant difference was found among both the groups in relation to all four outcomes. Significant differences at the level of 0.05 (p=0.038; 0.019; 0.029) were found for clinical pregnancy rate, miscarriage rate and ongoing pregnancy rate respectively. Significant differences at the level of 0.01 for live birth rate between both the groups (p=0.006).

DISCUSSION

The purpose of this 730-participant study is to demonstrate the effectiveness of GnRH antagonists in raising pregnancy rates. The GnRH antagonist's function was well known.[10,11] We learned from the literature that in the majority of cases, premature LH surge does not mostly occur, if the leading follicle size is less than or equal to 14-15 mm.[12,13] Due to the aforementioned data, we decided to start the GnRH antagonist treatment for research group participants at a cutoff limit of 16 mm. Natural intercourse was not limited for both the groups from which it can exclude the bias of spontaneous conception (subfertile couples reduces). Luteal phase support was also given for both the group participants. According to a study by Monraisin et al use of GnRH antagonists had positive effects, especially in multifollicular stimulation, among the 707 participants who were enrolled for the study to determine the optimal.[1] The results of the present study such as one or two follicles greater than equal to 18mm was present on the day of hCG trigger was comparable with the study results by Gomes-Palomares (more than one follicle attaining 18mm). On the contrary, according to Lambalk et al has no effect on GnRH antagonists in which the number of mature follicles was 1.3±0.6.[14,15]

In the control group, when the GnRH antagonist was not given after the 18mm size attainment of leading mature follicle, hCG was given irrespective of other factors to avoid the risk of premature ovulation. Since the likelihood

of pregnancy depends on the quantity of mature follicles present on the day of the hCG trigger, the chances of conception were significantly reduced in the control group.[16] According to earlier research, GnRh antagonists have been successful in reducing the LH surge.[17] According to Allegra et al, the study group had a patient pregnancy rate of 53.85%, compared to 30.8% in the control group. Premature LH surge were also less frequent in the research group. The combined meta-analysis results from six randomized controlled trials revealed that the study group's pregnancy rates were considerably higher, with an odds ratio of 1.56. Studies done at earlier stages support antagonist groups than latter studies.[18] According to Cantineau AEP, no difference was found between both the groups in relation to live birth rate. There was no change in the clinical pregnancy rates between the two groups, according to Lambalk et al and other placebo-controlled experiment.[15] In our study, study groups with statistically significant differences had greater clinical pregnancy rates. Since the present study was done in a less time duration (time constraint) we could not approach it on a larger scale. Further meta-analysis was definitely needed to extricate the issue.

CONCLUSION

The findings of our investigation unequivocally demonstrate that the addition of GnRH antagonists to controlled ovarian stimulation using intrauterine insemination (IUI) considerably lowers the incidence of premature luteinization and raises the rates of clinical pregnancy and live birth. In the study group, a higher miscarriage rate was also observed. more measures must be done to lower the miscarriage rate in upcoming trials.

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