Impact of GnRH Antagonists in Comparison with GnRH Agonist on Embryo Transfer in Vitro Fertilization: A Prospective Comparative Study

Disha Bansal[1], Shabina Khan[2]

ABSTRACT

Introduction: Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are produced when the pituitary is stimulated with pulsatile gonadotropin-releasing hormone (GnRH) analogs. Pituitary gonadotropin secretions are stopped when a constant GnRH stimulation is delivered by an agonist or when the pituitary receptors are dominated with a competitive antagonist. The GnRH agonist and the GnRH antagonist protocols are well-established methods for controlling ovarian hyperstimulation among patients who are going through assisted reproductive technology (ART) for infertility. Our study intended to compare the effect of GnRH agonist and antagonist protocols, their influence on IVF outcomes.

Material and methods: This was a prospective study was conducted in the department of Obstetrics and Gynaecology at Rohilkhand Medical College and Hospital, Bareilly from June 2019 to June 2021 among 80 patients matching the inclusion and exclusion norms. Recombinant FSH and GnRH analogues were administered continuously until three follicles reached a size of more than or equal to 17 mm. hCG was administered and serum levels of E2, LH, and progesterone were tested. Oocytes were retrieved after hCG administration and were fertilized. Embryo transferred and patients were put on progesterone support. The number of cycles for the long agonist protocol was 100 and that for the GnRH antagonist was 90. The rFSH interval in the GnRH agonist group was slightly more (9.07+ 1.36 days) than that of the GnRH antagonist group (8.76 + 1.22 days), but there was no statistical significance. There wasn't any statistical difference for the demographic variables, basic clinical values, or embryo retrieval amongst the two study groups.

Results: Intrauterine pregnancy when compared was significantly higher with the antagonist group. Implantation was better in the GnRH antagonist group (13.90%)when related to the agonist group (6.48%) and was statistically significant. Also, clinical pregnancy was more in the GnRH antagonist group (28.57%) than the agonist group (14.77%) resulting in statistical significance.

Cocnlusion: Our study concludes a comparable with better efficiency and safety of GnRH-antagonist protocol up to the age of 40 years. Further research may be needed to enlighten the role of GnRH-antagonist more effectively and competently.

Keywords: GnRH agonist, GnRH Antagonist, IVF, ICSI, Reproductive Outcomes

INTRODUCTION

Gonadotropin-releasing hormone (GnRH) analogs are peptides having 10 aminoacids[1]. The peptide combines to specific GnRH receptors on the pituitary gonadotrophic receptor. Their activation leads to the synthesis and discharge of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the gland. In females, gonadotroph secretion from the pituitary gland is regulated by oestradiol and progesterone[2]. Infusions of GnRH agonists cause a transitory boost in sex hormones, but continuous non-pulsatile stimulation inhibits LH and FSH production, lowering oestrogen and testosterone levels. GnRH analogues have been employed extensively in the control of sex hormone production because they are substantially more effective and long-acting than the original decapeptide. The cumulative effects and effectiveness of GnRH agonists and antagonists are comparable, with the exception of the pure antagonists' being faster in onset and lack of an early surge in sex hormone release in them[3].

For successful embryo transfer and in vitro fertilization, ovarian stimulus is a key factor. Luteinizing hormone is essential for development of follicles and oocyte maturation. It can be accomplished by pituitary desensitization by the use of GnRH agonists or GnRH antagonists.[4] Intrinsic GnRH stimulates anterior pituitary gonadotrophs and has been used to induce ovulation.

GnRH agonists are more powerful than native GnRH and have a longer half-life. They provide an initial stimulation of pituitary gonadotrophs, resulting in FSH and LH release as well as the predicted gonadal response. The pituitary-gonadal axis is therefore down-regulated and inhibited as a result of this action[5]. This GnRH agonist protocol is underuse since the early 1980s[6]. Later, GnRH antagonists too were found effective for ovarian stimulation by directly combining to GnRH receptors and blocking their activity in a competitive manner[7].

Both the GnRH agonist and antagonist protocols can suppress the incidence of premature LH surges by reversibly blocking pituitary gonadotropin secretion although the precise impact of these two distinct protocols on the clinical setting of

[1]3rd year resident, Department of Obstetrics and Gynaecology, Rohilkhand Medical College and Hospital, Bareilly, Uttar Pradesh, [2]Professor, Department of Obstetrics and Gynaecology, Rohilkhand Medical College and Hospital, Bareilly, Uttar Pradesh, India

Corresponding author: Dr. Disha Bansal, Rohilkhand Medical College and Hospital, Bareilly, Uttar Pradesh, India

How to cite this article: Bansal D, Khan S. Impact of GnRH antagonists in comparison with GnRH agonist on embryo transfer in vitro fertilization: a prospective comparative study. International Journal of Contemporary Medical Research 2022;9(2):B1-B4.

patients enduring in vitro fertilization and embryo transfer (IVF-ET) treatment is still unknown.[8]

As gonadotroph desensitization is preceded by initial activation of GnRH receptors, inhibiting a premature LH increase with GnRH agonists takes at least 7 days. GnRH antagonists, on the other hand, compete directly with intrinsic GnRH for receptor binding and so reduce gonadotropin and steroid hormone production quickly[9]. However, because of the ongoing demand to inhibit endogenous GnRH, significantly higher antagonist dosages (mg per day vs. 0.1 mg per day for GnRH agonists) are needed[10].

GnRH antagonists have the advantage over GnRH agonists as treatment is of shorter duration, short duration of FSH stimulation is required, and has a very low risk of ovarian hyperstimulation syndrome (OHSS).[11] There have been various discussions regarding the efficiency of GnRH agonists and GnRH antagonists for embryo transfer during in vitro fertilization.

Our study was designed to compare the impact of GnRH agonist and antagonist protocols, their influence on IVF outcomes and to discuss the individualized best method for an infertile patient for embryo transfer and its best possible results.

MATETRIAL AND METHODS

A prospective study was carried out in the department of Obstetrics and Gynaecology at Rohilkhand Medical College and Hospital, Bareilly from June 2019 to June 2021 among 80 patients fulfilling the inclusion and exclusion criteria. The study was approved by the ethical committee of the college. Written and informed consent was taken in from all patients undergoing the study.

40 patients endured GnRH agonist protocol while 40 patients endured GnRH antagonist protocol. Patients selected for the study were <40 years of age, had regular menstrual cycles, and were undergoing treatment for infertility either primary or secondary. None of the patients selected for the study had undergone any ovulation induction for the past 3 months nor took any form of hormonal contraceptives 3 months before this study. The cause for infertility was either primary or secondary.

Selected patients underwent basic investigations like an ultrasound for endometrial thickness and antral follicle count; blood tests for FSH, progesterone, and AMH levels before initiation of the study.

Patients posted for GnRH agonist protocol had their pituitaries downregulated for 14 days before undergoing basic investigations. Recombinant FSH started on the day of examination in which patients aged less than 35 years were given 150 IU while patients aged more than 35 years were administered 225 IU daily for 5 days. After 5 days of continuous rFSH, transvaginal ultrasound was performed to assess the development of follicles and rFSH dose optimization.

For the GnRH antagonist protocol, basic investigations were done on day 3 of the menstrual cycle and then recombinant FSH was started similar to the GnRH agonist protocol. After 5 days repeat ultrasound was done to assess the number and growth of follicles and dose optimization. GnRH antagonist was then administered by subcutaneous injection from the 6th day of the stimulation cycle to the day of HCG administration. Ultrasound examination was then repeated on days 8th, 10th, and 12th of the medication.

Recombinant FSH and GnRH antagonists were administered continuously until three follicles reached a size of more than or equal to 17 mm. HCG (10000 IU) was administered and serum levels of E2, LH, and progesterone were tested on the day of HCG administration. Oocytes were retrieved after 34-40 hours of HCG administration and were fertilized.

Embryo transfer was done about 72 hours after oocyte retrieval. Progesterone 80 mg was administered daily intramuscularly to support pregnancy from day 1 of oocyte retrieval to maintain corpus luteal function. HCG

Urine pregnancy tests, β-hCG levels, and transvaginal sonography was done for confirmation of pregnancy.

SPSS-23 was used for statistical analysis and interpretation. Results were formulated and compared to provide the conclusion of the study. Statistical significance was taken when $p<0.05$.

RESULTS

On studying the demographic and clinical details of GnRH -Antagonists the mean age in years was 35.12 ± 4.20, body mass index (BMI) was 26.16 ± 2.55, duration of infertility was 5.9 + 3.4 years, FSH basal was 8.33±2.33 IU/l, E2 48.12 ±18.60 pg/ml and progesterone were 0.45±0.27 ng/ml. This was similar to the GnRH agonist group where mean age in years was 32.66±3.87, body mass index (BMI) was 24.35 ±2.83, duration of infertility was 5.5 + 2.8 years, FSH basal was 6.20±1.78 IU/l, E2 44.10 ±18.33 pg/ml, and progesterone was 00.43±0.11 ng/ml. There was no statistically significant difference in both groups' demographic and clinical profiles. (Table 1)

The number of cycles for the long agonist protocol was 100 and that for the GnRH antagonist was 90. The rFSH duration in the GnRH agonist group was slightly more (9.07+ 1.36 days) than that of the GnRH antagonist group (8.76 + 1.22 days), but there was no statistical significance. There was no statistical difference for the endometrial thickness, progesterone level, the number of follicles with size ≥ 17 mm, the number of oocytes retrieved, fertilization rate, cleavage rate, and the number of embryos transferred between the two study groups. Of note, the cancellation rate for the antagonist protocol was slightly higher, in which 13 out of 90 cycles (14.44%) were canceled in the GnRH antagonist group, but only 12 out of 100 cycles (12.0%) were canceled in the GnRH agonist group. The cancellation was due to the poor quality of embryos and uterine bleeding after medication. Semen abnormality was excluded from this study. (Table 2)

On Comparing the pregnancy outcomes of both the groups; the GnRH antagonist group had higher clinical pregnancies as confirmed by urine and blood β-hCG level estimation

Variable	GnRH agonists	GnRH antagonists
AGE (years)	32.66±3.87	35.12 ±4.20
BMI (kg/mt^2)	24.35±2.83	26.16±2.55
Duration of infertility (years)	5.5 ± 2.8	5.9 ± 3.4
FSH (IU/l)	6.20±1.78	8.33±2.33
E2 (pg/ml)	44.10±18.33	48.12±18.60
PROGESTERONE (ng/ml)	0.43±0.11	0.45±0.27
AMH	2.12 ±0.81	2.32 ± 1.1
AFC	13.24 ± 1.01	12.97 ± 0.96

Table-1: Baseline variables of GnRH agonist and antagonists study group

Parameters	GnRH agonist	GnRH antagonist
Cycles	100	90
rFSH (days)	9.07± 1.36	8.76 ± 1.22
Endometrial thickness	9.06 ± 2.42	10.17 ± 2.26
Progesterone	0.94 ± 0.45	0.97 ± 0.36
Oocytes retrieved	7.58 ± 5.11	7.71 ± 5.06
Fertilization rate	53.7%	54.1%
No. of embryo transferred	2.31 ± 0.63	2.43 ± 0.81
Transfer cycles canceled	12.0 (12/100)	14.44 (13/90)

Table-2: Comparison of clinical and laboratory parameter for best IVF outcome among GnRH agonist and antagonists study group

Parameters	GnRH agonist	GnRH antagonist	Significance
Cycles	100	90	
β-hCG + clinical pregnancy	12	24	p<0.05
Intrauterine pregnancy	8	14	p<0.05
Abortion	7	7	p>0.05
Ectopic	1	0	p>0.05
Implantation rate (%)	6.48 (14/203)	13.90 (26/187)	p<0.05
Clinical pregnancy (%)	14.77	28.57	p<0.05

Table-3: Comparison of pregnancy outcomes in GnRH agonist and antagonists study group

Parameters	GnRH agonist	GnRH antagonist	Significance
Gestational age at delivery (weeks)	37.01 ± 1.51	36.82 ± 1.76	p>0.05
Birth weight average (gms)	2856 ± 321.5	2901 ± 333.7	p>0.05
Preterm births (%)	15.38	22.72	p>0.05

Table-4: Comparison of perinatal outcomes in GnRH agonist and antagonists study group

24 in 90 cycles than GnRH agonist study group 12 out of 100 cycles, which were statistically significant. GnRH antagonist group had 14 intrauterine pregnancies from which 7 underwent an abortion, and none of them was ectopic pregnancy when confirmed on TVS whereas the GnRH agonist group had 8 intrauterine pregnancies from which 7 underwent an abortion, and 1 of them was an ectopic pregnancy. Intrauterine pregnancy when compared was significantly higher with the antagonist group. Implantation was better in the GnRH antagonist group (13.90 %)when compared to the agonist group (6.48 %) and was statistically significant. Also, clinical pregnancy was more in the GnRH antagonist group (28.57%) than the agonist group (14.77%) resulting in statistical significance. (Table 3)

On comparing the perinatal outcomes amongst the two groups; there was no statistical difference between gestational age at delivery, average birth weight of baby, and percentage of preterm births (p>0.05). (table 4)

DISCUSSION

The success of modern ART has completely revolutionized both the evaluation and treatment of infertility. IVF was initially created to treat infertility caused by irreversible tubal disease, but it is currently used to treat practically all types of infertility.

Our study compares the efficacy of two different ovarian stimulation protocols (GnRH antagonist vs. GnRH agonist) during IVF treatment in reproductive females <40 years of age. Our findings of higher implantation rate in the antagonist group were supported by studies by Lai Q et al6, Nadkarni PM et al[12]. who also found a higher implantation rate and clinical pregnancy rate. Their study also stated that GnRH antagonist protocol could be more efficient for improving the outcome of pregnancy in those patients with a history of multiple failures for the IVF-ET treatment. In our study also, the number of oocytes retrieved was

maximum in the antagonist group i.e. 10.52±3.11 followed by 7.11±3.31 in the agonist group which is in line with Lai Q et al[6], Nadkarni PM et al[12] but different from Xu Y et al[4]. intrauterine pregnancy rates were also higher in antagonist group which was different from De Souza Jordao & v et al[13] but was similar to the study of Xu Y et al[4].

Though our study contains a limited number of patients, future studies with more subjects and stimulation cycles are required to further confirm those observations. In the study by Lai Q et al[6], embryo quality was better with the antagonist protocol but in our study maximum grade, I embryos was seen in the subjects who underwent ovarian stimulation with the agonist protocol which is in line with Nadkarni PM et al[12].

GnRH agonists were commonly utilised in IVF-ET therapy for regulated ovarian hyperstimulation. GnRH antagonists, on the other hand, have a very limited clinical application period, and their influence on the result of IVF-ET therapy is still being studied. The research in our database showed that the antagonist protocol had a plausible advantage over the agonist long protocol in terms of implantation rate and pregnancy rate. However, additional studies with more subjects and stimulation cycles are required to further confirm these data.

CONCLUSION

After the compilation of results, It can be concluded that GnRH antagonists are safe to use, do not compromise the effectiveness, and significantly prevent OHSS .flare response as seen in agonist protocols can be significantly abolished by the use of antagonist. Keeping infertile couples' sentiments and pocket in mid-GnRH antagonist provide shorter IVF cycles with better cost-effectiveness of the procedure. strict compliance with the recommended treatment regimen is essential for antagonist use which limits its application. Overall our study demonstrates a comparable with better efficacy and safety of GnRH-antagonist protocol up to the age of 40 years. Further research may be needed to enlighten the role of GnRH-antagonist more effectively and competently.

There is no conflict of interest in this study. There was no funding for this study.

REFERENCES

1. Itskovitz-Eldor J, Kol S, Mannaerts B. Use of a single bolus of GnRH agonist triptorelin to trigger ovulation after GnRH antagonist ganirelix treatment in women undergoing ovarian stimulation for assisted reproduction, with special reference to the prevention of ovarian hyperstimulation syndrome: preliminary report: short communication. Hum Reprod. 2000;15:1965–1968.
2. Ortmann O, Weiss JM, Diedrich K. Gonadotrophin-releasing hormone (GnRH) and GnRH agonists: mechanisms of action. Reprod Biomed Online. 2002;5 Suppl 1:1-7.
3. Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Gonadotropin Releasing Hormone (GnRH) Analogues. [Updated 2018 Mar 20].
4. Xu Y, Zhang YS, Zhu DY, Zhai XH, Wu FX, Wang AC. Influence of GnRH antagonist in reproductive women on in vitro fertilization and embryo transfer in fresh cycles. Biomed Rep. 2019 Feb;10(2):113-118.
5. Kumar P, Sharma A. Gonadotropin-releasing hormone analogs: Understanding advantages and limitations. J Hum Reprod Sci. 2014;7(3):170-174.
6. Lai Q, Zhang H, Zhu G, Li Y, Jin L, He L, Zhang Z, Yang P, Yu Q, Zhang S, Xu JF, Wang CY. Comparison of the GnRH agonist and antagonist protocol on the same patients in assisted reproduction during controlled ovarian stimulation cycles. Int J Clin Exp Pathol. 2013 ;6(9):1903-10.
7. Ludwig M, Felberbaum RE, Devroey P, Albano C, Riethmu¨ller-Winzen H, Schu¨ler A, Engel W and Diedrich K. Significant reduction of the incidence of ovarian hyperstimulation syndrome (OHSS) by using the LHRH antagonists Cetrorelix (Cetrotidew) in controlled ovarian stimulation for assisted reproduction. Arch Gynecol Obstet 2000;264,29–32
8. Huirne JA, Homburg R, Lambalk CB. Are GnRH antagonists comparable to agonists for use in IVF? Hum Reprod. 2007;22:2805–2813.
9. Klingmuller D, Schepke M, Enzweiler C and Bidlingmaier F. Hormonal responses to the new potent GnRH antagonist Cetrorelix. Acta Endocrinol (Copenh) 1993;128:15–18.
10. B.C. Tarlatzis, B.C. Fauser, E.M. Kolibianakis, K. Diedrich, P. Devroey, , On Behalf of the Brussels GnRH Antagonist Consensus Workshop Group, GnRH antagonists in ovarian stimulation for IVF, Human Reproduction Update 2006;12:333–340.
11. Weiss JM, Ludwig M, Ortmann O, Diedrich K. GnRH antagonists in the treatment of infertility. Ann Med. 2003;35:512–522.
12. Nadkarni, Purnima Kishor; Nadkarni, Kishore Mohan; Kalyani, Kanika Rajendra. A comparative study between agonist and antagonist protocol for ovarian stimulation in art cycles at a rural set up in South Gujarat. International Journal of Reproduction, Contraception, Obstetrics and Gynecology, [S.l.], 2017;4,:617-621.
13. De Souza Jordao &V, Nakagawa HM, Estrela FS, de Morais RB, Gomes-Sobrinho DB, de Carvalho BR. Outcomes of GnRH agonist and GnRH antagonist regimens for IVF in women aged up to 40. Acta Med Int 2016;3:46-9

Source of Support: Nil; **Conflict of Interest:** None

Submitted: 30-11-2021; **Accepted:** 29-01-2022; **Published:** 28-02-2022