GnRH agonists stop antagonist protocol versus GnRH antagonist protocol in poor ovarian responders undergoing IVF

Protocolo de antagonista de parada de agonista de GnRH versus protocolo de antagonista de GnRH en pacientes con respuesta de ovario deficiente sometidos a FIV

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Abstract

Introduction and objective: This study aims to clarify if the GnRH agonist STOP-antagonist protocol versus the GnRH antagonist protocol can be useful in improving IVF (In vitro fertilization) outcomes in patients with poor ovarian response candidates for IVF.

Methods: The present study was conducted as a single-blind clinical trial in the infertility ward of Arash Hospital of Tehran University of Medical Sciences. In this study, 133 patients with a poor ovarian response (POR) according to Bologna criteria were randomly assigned to two groups GnRH agonist stop-antagonist protocol and GnRH antagonist protocol. The number of dominant follicles and number of oocytes retrieved, the number of embryos and their grade, level of antagonist used, level of gonadotropin used, length of days of stimulation and endometrial thickness, level of estrogen, level of progesterone, trigger day, and fertilization rate were measured.

Results: In the present study, the frequency of dominant follicles in the GnRH agonist stop-antagonist group was significantly higher than that in the GnRH antagonist group (p-value = 0.01). The number of embryos in the GnRH agonist stop antagonist group was significantly higher than that in the GnRH antagonist group (p-value = 0.02). The percentage of AB embryo agonists in the GnRH agonist stop _anta group was significantly higher than that in the GnRH antagonist group (p-value = 0.003). The number of mature oocytes in the GnRH agonist stop _antagonist group was more than that in the GnRH antagonist group, but the difference between the two groups was not statistically significant. The number of used gonadotropin doses in the GnRH agonist stop _antagonist group was significantly higher than that in the GnRH antagonist group (p-value = 0.01). The number of used antagonists in the GnRH antagonist group was significantly higher than that in the GnRH agonist stop _antagonist group (p-value = 0.02).

Conclusion: The GnRH agonist stop-Anta protocol is a valuable tool for the treatment of poor ovarian responders. However, controlled prospective randomized studies with larger sample sizes are needed.

Keywords: Gonadotropin, Gonadotropin Releasing Hormone (GnRH) agonist; GnRH antagonist; Intracytoplasmic Sperm Injection (ICSI) cycles; Poor Ovarian Response (POR).

Resumen

Introducción y objetivo: Este estudio tiene como objetivo aclarar si el protocolo STOP-antagonista del agonista de GnRH versus el protocolo del antagonista de GnRH puede ser útil para mejorar los resultados de FIV (fertilización in vitro) en pacientes con respuesta ovárica deficiente candidatas para FIV.

Métodos: El presente estudio se realizó como un ensayo clínico ciego simple en la sala de infertilidad del Hospital Arash de la Universidad de Ciencias Médicas de Teherán. En este estudio, 133 pacientes con mala respuesta ovárica (POR) según los criterios de Bolonia fueron asignados aleatoriamente a dos grupos de protocolo de antagonista de parada de agonista de GnRH y protocolo de antagonista de GnRH. El número de folículos dominantes y el número de ovocitos recuperados, el número de embriones y su grado, nivel de antagonista utilizado, nivel de gonadotropina utilizado, duración de los días de estimulación y grosor del endometrio, nivel de estrógeno, nivel de progesterona, día de activación y se midió la tasa de fertilización.

Resultados: En el presente estudio, la frecuencia de folículos dominantes en el grupo de antagonistas de parada del agonista de GnRH fue significativamente mayor que en el grupo de antagonistas de GnRH (valor de p = 0,01). El número de embriones en el grupo de antagonistas de parada del agonista de GnRH fue significativamente mayor que el del grupo de antagonistas de GnRH (valor de p = 0,02). El porcentaje de agonistas de embriones AB en el grupo de agonistas de GnRH stop _anta fue significativamente mayor que en el grupo de antagonistas de GnRH (valor de p = 0,003). El número de ovocitos maduros en el grupo antagonista de parada agonista de GnRH fue mayor que en el grupo antagonista de GnRH / bhn lk, pero la diferencia entre los dos grupos no fue estadísticamente significativa. El número de dosis de gonadotropina utilizadas en el grupo de antagonistas de parada del agonista de GnRH fue significativamente mayor que en el grupo de antagonistas de GnRH (valor de p = 0,01). El número de antagonistas usados en el grupo de antagonistas de GnRH fue significativamente mayor que en el grupo de antagonistas de parada de agonistas de GnRH (valor de p = 0,02).

Conclusión: El protocolo stop-Anta del agonista de GnRH es una herramienta valiosa para el tratamiento de pacientes con respuesta ovárica deficiente. Sin embargo, se necesitan estudios aleatorizados prospectivos controlados con tamaños de muestra más grandes.

Palabras clave: Gonadotropina, agonista de la hormona liberadora de gonadotropina (GnRH); Antagonista de GnRH; Ciclos de inyección intracitoplasmática de espermatozoides (ICSI); Mala respuesta ovárica (POR).

Introduction

Poor response in IVF (in vitro Fertilization) can be defined as an insufficient number of mature follicles following stimulation with gonadotropin leading to the retrieval of several oocytes or cycle stop[1]. The goal of ovarian stimulation in IVF is multifollicular, but poor responders fail to achieve this goal[2]. Nine to twenty-four percent of infertile women receiving assisted reproduction have a poor response to ovarian stimulation[3]. Various strategies have been examined to improve the ovarian response, but most of these interventions have shown limited success, and the optimal stimulation protocol for poor responders is still unknown[3,4]. The European Society of Human Reproduction and Embryology (ESHRE) published the Bologna criteria in 2011 to standardize the definition of poor ovarian response (POR) in a simple and reproducible manner[4]. The main purpose of the uniform criteria was to develop evidence-based efficient and appropriate protocols or modalities of treatment for such women undergoing IVF-ET treatment. An agreement was reached on the minimal criteria needed to define POR. At least two of the following three criteria had to be present to establish the definition: Advanced maternal age (>40 years) or any other risk factor for POR. A previous POR (≤3 oocytes with a conventional stimulation protocol). An abnormal ovarian reserve test [i.e. antral follicle count (AFC) less than 5–7 follicles or anti-Müllerian hormone (AMH) below 0.5–1.1 ng/mL][5-7].

When evaluating the appropriate protocol in patients with poor ovarian response, we recently found that the combination of GnRH agonist Stop- ant protocol with GnRH-ant protocol shows the number of oocytes retrieved and top-quality embryos acceptable clinical pregnancy rate is significantly higher[5]. The rationale for the pre-treatment advantage of the mid-luteal GnRH-agonist in the GnRH agonist stops - ant protocol, was modulation of GnRH receptors (internalization) and thus suppressing pituitary LH secretion up to 10 days after the last agonist dose. This effect, combined with immediate suppression of LH by GnRH-Ant (competitive inhibitor), eliminates premature LH surge/progesterone elevation and may improve the produced embryos' quality. At present, we aim to study further the role of the GnRH agonist stop-antagonist protocol versus the GnRH antagonist protocol in improving IVF outcomes in patients with poor ovarian responses candidates for IVF.

Materials and methods

The study was a single-blind clinical trial study (the patient is not blind, but the physician completes the blind results). The necessary information was collected for the design based on the prepared checklist, patient file, and embryologist's opinion. The code of ethics was IR.TUMS.MEDICINE.REC.1399.694 and the code of clinical trial was IRCT20110731007165N10.

Study participants: Infertile poor ovarian responder (POR) women referred to the infertility clinic of Arash Hospital and had IVF indications.

Inclusion criteria include patients with POR in IVF / ICSI cycles based on Bologna criteria, who met at least two of the following three criteria:

1- Advanced maternal age (40 years and above)

2- Previous POR (≤3 oocytes with normal stimulation protocol)

3-Abnormal ovarian reserve test, for example AFC <5-7 or AMH <0.5-1.1 ng / mL

In addition to these two cases, POR after maximum stimulation is sufficient to introduce a person as POR without the need for other criteria.

Exclusion criteria:

Polycystic ovary syndrome, hypothalamic amenorrhea, congenital anomalies of the uterus and problems of anomalies of the uterine cavity (unicornuate uterus, Asherman's syndrome, myoma, polyps, etc.) and endocrine disorders (diabetes, thyroid disease, antiphospholipid syndrome, cardiovascular and hepatic diseases, repeated IVF failure (more than three consecutive failures), and severe male factor. After examining the patients for inclusion criteria, the patient's informed consent was first obtained, and they completed a questionnaire containing demographic, fertility, medical and pharmacological characteristics. Then, they were divided into two groups based on randomization blind

Group 1 (GnRH Agonist stop-Ant. Group):

The injection of GnRH agonist (Sinagen Company) at the dose of 0.5 mg/day continues from the mid-luteal menstrual cycle to the patient's period. On the second day of menstruation and after the measurement of antral follicular count, Human menopausal gonadotropin (HMG) along with FSH recombinant (Cinnal-f and HMG_ PD of Karma or Pooyesh Daroo Company) started with a dose of 300-450 IU / day. The dose starts at 0.25 mg/day until the final maturation of the oocyte and continues until the day of the HCG trigger (Karma or Pooyesh Drug Company), and the patient is monitored for vaginal sonography in terms of follicle size. When the follicle size reaches 12 mm, the GnRH antagonist started at a dose of 0.25 mg/day until the final maturation of oocytes and HCG trigger day (Karma or Pooyesh Daroo Company). When two or more follicles size reaches above 17 mm, HCG is injected at a dose of 10,000 units, and an ovarian puncture is performed 36 hours later.

Group 2: Antagonist GnRH

Ovarian stimulation starts from the second day of menstruation after measurement of AFC (antral follicular count) with HMG gonadotropin along with Recombinant FSH (Menotropin of Karma or Pooyesh Daroo Company) at a dose of 300-450 IU / day, and the patient was monitored through vaginal sonography for follicle size. When the follicle size reaches 12 mm, the GnRH antagonist started at a dose of 0.25 mg/day until the final maturation of oocytes and HCG trigger day (Karma or Pooyesh Daroo Company). When two or more follicles size reaches above 17 mm, HCG is injected at a dose of 10000 units, and an ovarian puncture is performed 36 hours later. Then, primary and secondary outcomes (number of dominant follicles and number of oocytes retrieved, number of embryos and their grade, level of antagonist used, level of gonadotropin used, days of stimulation and endometrial thickness, level of estrogen, level of progesterone trigger day and fertilization rate were recorded and compared.

The random allocation concealment and blinding were performed so that the randomization list was prepared by a randomized statistician, and the treatments were placed in a special order in pockets with a 10-digit code and were kept by a nurse out of the study ward. Once the patient's eligibility was determined, the procedure was explained, and their satisfaction was obtained. Then, the nurse provided the pockets containing the type of treatment to the physician, and the type of treatment was determined based on the treatment in the pocket. Completing the final information is the person's responsibility who knows the type of treatment and the statistician was unaware of the type of treatment. The collected data was analyzed using SPSS IBM software under Windows version 20 through descriptive statistics such as tables, central index, dispersion, and statistical analytical tests with a 95% confidence interval and $p < 0.05$.

A total of 133 patients were selected for this study, of which 65 patients were randomly assigned to the Agonist stop - Ant group, and 68 patients were assigned to the antagonist group. Also, 12 patients (5 in the GnRH Agonist stop – Anta group and 7 in the antagonist group) were excluded from the study after participating in the study. The exclusion reason in the GnRH Agonist stop – Anta group: Three people withdrew, and two people did not respond to treatment. The exclusion reason in the group: Two people withdrew, and five people did not respond to treatment.

According to Table 1, patients did not differ in terms of demographic characteristics.

Table 1. Patient characteristics

Variables (121)	GnRH Agonist stop – Antagonist group (60)	Antagonist group (61)	P-value
Age in year (mean ± SD)	38.75±4.48	38.26±4.26	0.54
BMI (mean ± SD)	26.76±3.83	26.39±3.30	0.56
Underlying disease (N, %)	9 (15%)	6 (9.8%)	0.38
Type of infertility (N, %) First Second	 43 (71.7%) 17 (28.3%)	 40 (65.6%) 21 (34.4%)	0.47
Causes of infertility Tubal Ovarian Uterine Multifactorial	 1 (1.7%) 46 (76.7%) 1 (1.7%) 12 (20%)	 2 (3.3%) 36 (59%) 1 (1.6%) 22 (36.1%)	0.14
Infertility Duration (year) (Median ± IQR)	4±5.5	2.5±3.5	0.054
Number of previous IVF (N, %) 0 1 time >2 time	 36 (60%) 17 (28.3%) 7 (11.7%)	 42 (68.9%) 12 (19.7%) 7 (11.5%)	0.51
Result of previous IVF (N=43) Successful Unsuccessful	 1 (4.2%) 23 (95.8%)	 1 (5.3%) 18 (94.7%)	0.99
AMH ng/ml (mean ± SD)	0.96±0.85	0.84±0.63	0.40
Left AFC (mean ± SD)	2.76±1.43	3±1.26	0.34
Right AFC (mean ± SD)	2.78 ± 1.22	2.90 ± 1.36	0.61

*p<0.05, IQR: Interquartile range

In the present study, 133 patients were selected for this study, of which 65 patients were randomly assigned to the LONG group, and 68 patients were assigned to the antagonist group. Twelve patients (5 in the LONG group and 7 in the antagonist group) were excluded after participating in the study. The exclusion reason in the LONG group: Three people withdrew, and two people did not respond to treatment. The exclusion reason in the group: Two people withdrew, and five people did not respond to treatment. As expected, IVF / ICSI (In Vitro Fertilization / Intracytoplasmic Sperm Injection) cycles in GnRH agonist stop – ant versus GNRH ANT cycles with higher gonadotropin doses were 4204.16 ± 1088.79 vs. 3698.36 ± 1221.79, respectively, p-value = 0.01. Higher frequency of dominant follicles (4.71 ± 1.86 vs. 3.95 ± 1.60, respectively, p-value = 0.01) and more embryos (2.82 ± 2.23 vs. 1.97 ± 1.76, respectively, P-value = 0.02), percentage of embryo grade AB (75% versus 49.2%, respectively, and p-value = 0.003) were significantly higher. Also, the number of used antagonists (3.68 ± 1.17 vs. 4.18 ± 1.22, respectively, and P-value = 0.02) and trigger day progesterone (0.504 ± 0.53 vs. 0.940 ± 0.99, respectively, and p-value = 0.003) were significantly lower. The percentage of Grade A embryos (20%) in the GnRH agonist stop-ant group and GnRH ant group was 20% and 19.7%, respectively. The difference was not statistically significant. There was no statistically significant difference between the two groups regarding endometrial thickness and cycle diversion and the total number of retrieved oocytes on puncture day and fertilization rate (Table 2).

Table 2. Ovarian stimulation outcome

Variables (121)	GnRH Agonist stop – Antagonist group (60)	GnRH Antagonist group (61)	P-value
Endometrial thickness in mm (mean ± SD)	8.24 ± 1.42	8.03 ± 1.59	0.45
Trigger day estradiol (HCG) (mean ± SD)	467.43±641.05	372.21±765.83	0.46
Trigger day progesterone (HCG) (mean ± SD)	0.504±0.53	0.940±0.99	0.003*
Dose of gonadotropin (IU) (mean ± SD)	4204.16±1088.79	3698.36±1221.79	0.01*
Antagonist (mean ± SD)	3.68±1.17	4.18±1.22	0.02 *
Duration (mean ± SD)	11.2 ± 1.98	10.47 ± 2.15	0.057
Number of dominant follicles (mean ± SD)	4.71 ± 1.86	3.95 ± 1.60	0.01*
Number of oocytes retrieved (mean ± SD)	4.46 ± 2.67	4.01 ± 2.60	0.35
Oocyte maturity (M2) (mean ± SD)	3.51 ± 2.51	2.90 ± 2.15	0.15
Mean GV (median ± IQR)	0.001 ± 1	0.001 ± 1	0.07
Oocyte (M1) (mean ± SD)	0.48 ± 0.77	0.36 ± 0.60	0.33
No. of embryos (mean ± SD)	2.82 ± 2.23	1.97 ± 1.76	0.02 *
No. of embryos transferred (mean ± SD)	0.87 ± 1.2	0.62 ± 1.09	0.24
Fertilization %	69.52%	57.82%	0.07
Embryo grades (%) A B AB BC	 15 (20%) 22 (36.7%) 45 (75%) 4 (6.7%)	 12 (19.7%) 15 (24.6%) 30 (49.2%) 0	 0.49 0.14 0.003* 0.057

*p<0.05, IQR: Interquartile range

Grade A embryos had symmetrical or slightly asymmetric blastomeres without fragmentation or occasional small fragments (<5%). Grade B embryos had all the blastomeres intact but had some cytoplasmic fragmentation (5-10%) or cells of unequal size. Grade C embryos had wider asymmetry and fragmentation (10-25%), although all blastomeres remained intact. Moreover, grade D embryos had one or more fragmented blastomeres (more than 25% fragmentation)[6].

Discussion

Reproductive assistance techniques have helped millions of infertile people around the world become fathers or mothers. Poor ovarian response is a major challenge in infertility centers around the world. The present study compared GnRH agonist stop - ant and the GnRH ant group as a pituitary suppression protocol in ICSI cycle management[7,8]. Based on research conducted by Abd El Naser and Abd El Gaber Ali et al., the reason for using the GnRH Agonist protocol was to reduce base LH and suppress residual ovarian cysts and increase the quality of oocytes retrieved. However, it has the disadvantages of many gonadotropin injections and increasing the duration of gonadotropin stimulation.

Thus, in our study, we used a GnRH agonist for a short time in the luteal phase (to overcome the disadvantages above)[9]. GnRH antagonist in weak responders is due to shorter stimulation time and less need for gonadotropin and reducing patient costs[10-12].

In a study conducted by Abd El Naser and Abd El Gaber Ali et al., results showed that the GnRH agonist stop-ant protocol versus GnRH ant was superior in terms of increasing the number of top-quality oocytes, increasing the thickness of the endometrium, and increasing E2 at the time of HCG injection, increasing embryo quality in infertile women with poor ovarian response. While Prapas et al.[13] indicated that no difference was seen in oocyte quality. Our research was consistent with the research conducted by Cheung et al.[14] in terms of the number of embryos and high embryo quality and with the research conducted by Prapas et al.[13] in terms of the number of oocytes. In a prospective randomized trial conducted by Cheung et al.[14], a long-acting GnRH agonist was compared with antagonist protocol in poor patients. It did not report any significant difference between the two groups in terms of stimulation and laboratory outcomes and pregnancy outcomes, except for the number of transferred embryos transferred that was higher in the antagonist group (2.32±0.58 versus 1.50±0.83 with p-value = 0.01). Orvieto et al.[15] observed an increase in progesterone (> 3.1 nmol / L) in the late luteal cycle compared to the conventional IVF / ICSI cycle and combined Stop GnRH-ag with GnRH-ant cycles, progesterone levels were significantly lower in the combined group Stop GnRH-ag with multiple-dose GnRH-ant cycles, which is consistent with our study (2.1±1.3 vs. 10.4± 7.1 nmol/L). Moreover, they achieved significantly higher rates in terms of endometrial thickness, number of oocytes retrieved, number of mature oocytes, and more top-quality embryos. Only the quality of the embryo in our study was consistent with the above study. The study conducted by Siristatidis et al.[16] showed that the number of oocytes retrieved (NOR) in the GnRH agonist protocol was significantly higher than in the short flare protocols, which was inconsistent with our study.

Demirdağ et al.[17] showed that on 318 patients from 2014 to 2019, IVF results in three protocols microdose flare, GnRH antagonist, and long protocols in patients with poor ovarian response, total mean number of oocytes retrieved, number of metaphase II oocytes and fertilization rate were similar among the groups. The mentioned study is in line with the present study regarding the number of oocytes retrieved and the number of metaphase II oocytes, but it was not consistent with our study in terms of fertilization rate (fertilization rate was higher in our study).

Davar et al.[18] indicated that the number of metaphase II retrieved oocytes with the GnRH antagonist protocol was superior to the microdose flare GnRH agonist protocol was inconsistent with our study. In general, NOR (number of retrieved oocytes) was reported higher in the GnRH antagonist regimen compared to the long protocol[19,20]. The study conducted by Pandian et al.[19] comparing the three protocols of stop and microdose and regular dose flare showed that the number of oocytes retrieved increased in the stop protocol, although it was not statistically significant, which is in line with our study. On the other hand, an RCT showed that the long agonist protocol improved the number of oocytes retrieved in poor responders compared to the GnRH antagonist group. In a study conducted by Lai-Ping et al.[20] to compare GnrRH antagonists with GnRH agonist protocols in IVF patients, the use of GnRH antagonists was significantly associated with significantly lower gonadotropin use and shorter treatment duration. In the present study, the mean dose of gonadotropin used in the Longstop agonist _ GnRH ant group was higher than that of the anta GnRH _ group, and this difference was also statistically significant (P-value = 0.01). The mean number of antagonists used in the anta group is higher than that in the long group, and this difference was statistically significant (P-value=0.02). However, controlled prospective randomized studies with larger sample sizes are required.

Due to the simultaneous implementation of this plan with the outbreak of COVID-19 and the limitations of embryo transfer, it was not possible to transfer embryos and assess the rate of clinical pregnancy and birth rate[21].

Conclusions

A clear advantage was seen in the dose of gonadotropin in the GnRH-ant group, but the duration of stimulation did not differ between the two groups. Although there was no significant difference between the two groups regarding the number of oocytes retrieved, the quality of oocytes in the GnRH agonist stop-ant group was higher. One result of this protocol may be useful for our clinical practice.

LIMITATION: Due to the coronavirus conditions and the unwillingness of many patients to transfer embryos, they were frozen to be transferred in better conditions.

RECOMMENDATIONS: A larger multicenter randomized trial should be conducted to confirm the real benefits of the GnRH agonist.

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