Original Article

Flexible, Multi-dose GnRH Antagonist versus Long GnRH Agonist Protocol in Poor Responders: A Randomized Controlled Trial

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Abstract

Background: To compare a flexible, multi-dose GnRH antagonist protocol with a long GnRH agonist protocol in poor responders.
Materials and Methods: A randomized clinical trial of 70 poor responder patients (35 patients in GnRH antagonist protocol and 35 patients in long GnRH agonist protocol) was performed at Royan Institute, Tehran, Iran. Both groups were given a fixed dose of human menopausal gonadotropin (HMG) for stimulation and oral contraceptive pre-treatment. Data analyzed by student's group t-test or Chi square test.
Results: Stimulation duration, total gonadotrophins consumption, mean numbers of oocytes retrieved, formed embryos, cycle cancellation rate, and clinical pregnancy rate were similar between both groups. Although the miscarriage rate was higher in the agonist protocol group, the rate of miscarriage was not statistically significant between both groups.
Conclusion: A flexible, multi-dose GnRH antagonist protocol appears as effective as the long GnRH agonist protocol in poor responders. More (larger) randomized controlled trials for better statistical analysis are recommended.

Keywords: GnRH Agonist , GnRH Antagonist, IVF , Poor Ovarian Function

Introduction

Women, who respond poorly to ovulation stimulation protocols, include about 9-24% of assisted reproductive techniques (ARTs) (1). In comparison to normal responders, these patients have more problems such as impaired fertilization rates, lower embryo quality and decreased pregnancy rates (2).
The management of the poor-responder patient preparing for ART remains controversial. Failure to respond adequately may result in suboptimal oocyte maturation and production, as well as high cycle cancellation and poor pregnancy rates (3). Different protocols, such as pituitary down regulation by GnRH agonist or antagonists, modifying COH and the use of adjuvant therapy are proposed for poor response patients (1).
The use of antagonists allows initiation of gonadotropin stimulation in the absence of prior pituitary gonadotropin down-regulation. These agents cause immediate and rapid gonadotropin suppression, by occupancy of the GnRH receptor and are therefore a more logical choice for the prevention of premature LH surge in IVF cycles (4).
Although GnRH antagonists provide the advantage of a shorter duration of stimulation with reduced gonadotropin requirements, a trend towards lower pregnancy rates remains concerning (2).
The aim of this randomized clinical trial is to compare a flexible, multi-dose GnRH antagonist stimulation protocol with the long GnRH agonist protocol in poor responder patients undergoing IVF.

Materials and Methods

The study was a randomized clinical trial which included a total of 70 patients who were classified as poor responders that attended Royan Institute during a period between 2005 and 2006.
Criteria for classification as a poor responder included at least one of the following: day 3 serum FSH level > 15 MIU/ ML, less than 3 total antral follicles, prior cycle cancellation, prior poor response to COH

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(peak E2 < 500 Pg/ml on the day of ovulation triggering and/ or fewer than 3 mature oocytes retrieved).
The institutional review board of Royan Institute Research Center approved the treatment procedure. Each patient signed a written fully informed consent statement prior to inclusion in the study.
Poor responder patients were randomly allocated to receive either the flexible, multi-dose GnRH antagonist (study group) or long GnRH agonist protocol (control group). Randomization was performed by using computer-generated random numbers. Both the embryologist and statistician involved the study, were blinded to the treatment allocation.
A total of 35 patients were assigned to the long GnRH agonist protocol (control group). These patients received 14-21 days of an oral contraceptive pill (Ovocept-LD ®; Aburaihan Co., Tehran, Iran) from the second or third day of their menstrual cycle which was continued by Busereline 500 µg (Superfact; Aventis Pharma Deutshlan, Frankfurt, Germany) via subcutaneous injection starting on the 21st day of their menstrual cycle. After down regulation, gonadotrophin stimulation was commenced and continued until at least two follicles ≥18 mm were detected. Human menopausal gonadotropin (hMG; Menopur, Ferring, Germany) 150 IU daily was used for follicular stimulation during all cycles. Busereline dose was reduced to 0.2 µg daily and continued until the day of human chorionic gonadotropin (hCG, 10000 IU; Choragon, Ferring, Germany) administration.
In the study group, 35 patients received the flexible, multi-dose GnRH antagonist, Cetrorelix (Cetrotide; Serono Laboratories, Istanbul, Turkey) 0.25 mg subcutaneous daily. Cetrorelix was initiated once the leader follicle reached 14 mm in mean diameter and continued until HCG administration.
Serial transvaginal ultrasound examinations (Aloka-Alpha 10, Japan) and evaluation of serum E2 levels were used to assess follicular maturation. Endometrial thickness was also assessed on the day of hCG administration.
In both the study and control groups hCG was injected intramuscularly followed 34-36 hours later by oocyte retrieval.
Cycles in which the ovaries failed to respond after 10 days of stimulation, were cancelled. In vitro fertilization (IVF) with or without ICSI was performed, and embryos were transferred 48-72 hours after oocyte retrieval with a Wallace catheter (Marlow, Willoughby, UK).
Luteal-phase support was provided with vaginal progesterone (Aburaihan Co., Tehran, Iran), 400 mg twice a day until the day of β-hCG assay and, in the presence of pregnancy, was continued until 10 weeks gestation.
Stimulation and cycle outcomes were compared between two groups. βhCG levels were measured 14 days after oocyte retrieval. Clinical pregnancy was determined by identifying a gestational sac at 6-7 weeks gestation by means of transvaginal ultrasonography.
For sample size, 35 patients in each group were required to provide 80% power at the 5% significance level, assuming a drop-out rate of 10%.
Statistical analysis was performed using the SPSS Version 13.0 (SPSS Inc., IL). Data were analyzed by student's group t-test, χ^2 or Fischer exact test. A p-value <0.05 was considered statistically significant. Results were expressed as mean ± SD unless otherwise specified.

Results

Figure 1 shows the study flow chart and patient outcomes. A total of 70 patients were recruited to the study, with 35 randomized to each treatment arm.
There were no significant differences between two groups in any of baseline characteristics including the mean female age (study versus control: 39.57 years vs. 40.69 years), and the mean duration of infertility (13.09 years vs. 10.2 years).
The stimulation and cycle outcomes are compared in Table 1.

Table 1: Stimulation and cycle outcomes between antagonist and agonist groups

	Antagonist n=35	Agonist n =35	P-Value
Duration of stimulation (days)	0.392	9.69±2.77	10.13±2.08
Total gonadotropin consumption	0.513	40.06±14.21	42.57±17.62
Number of oocytes retrieved	0.10	5.31±3.80	4.06±2.31
Number of metaphase II oocytes	0.169	4.17±3.12	3.26±2.32
Number of embryos transferred	0.472	3.03±2.19	2.69±1.55
Number of PN	0.677	2.34±1.86	2.18±.403
Number of grade A, B embryos	0.505	2.19±2.08	1.91±1.12
Number of grade C, D embryos	0.824	0.84±1.22	0.78±1.008
Clinical pregnancy rate per cycle	1.00	9 (25.7%)	9 (25.7%)
Abortion rate	0.576	3 (33.3%)	1 (11.1%)
Ongoing pregnancy rate	0.55	6 (17.14%)	8 (22.86%)

In the long GnRH agonist group no cycle was cancelled. However one cycle was cancelled due to no oocyte recovery in the flexible, multi-dose GnRH antagonist group.

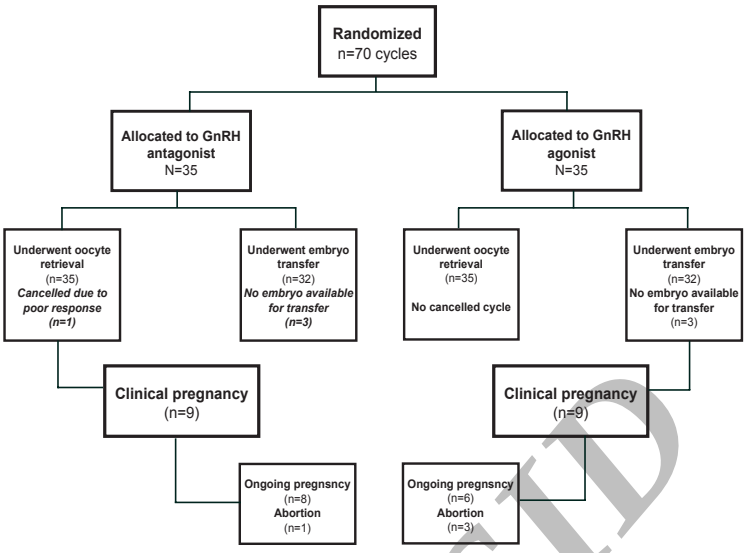

Fig 1: Study flow chart and patients outcomes.

There were no significant differences between two groups in the number of mature follicles, total oocytes retrieved, treatment duration and gonadotrophin consumption. The number of embryos transferred and best grade embryos (A or B) showed no significant differences between the antagonist and agonist protocols. Both groups showed similarities in the rate of chemical and clinical pregnancies, as well as ongoing pregnancy rates. The abortion rate was lower (11.1%) in the flexible, multi-dose GnRH antagonist protocol compared with long GnRH agonist group (33.3%). However, this rate did not reach a statistically significant level.

Discussion

The objective of our study was to compare the advantages of using flexible, multi-dose GnRH antagonist to long GnRH agonists in these patients. In the literature, GnRH agonist and antagonist protocols were compared utilizing different strategies. However, the clinical and methodological heterogeneity between studies makes it difficult to compare their results. Based on our knowledge, a few trials have compared the flexible, multi-dose GnRH antagonists to the long agonist protocol (5-9). Among these studies, two trials used the long agonist protocol (6, 9). Both trials showed reduced duration of stimulation and consumption of gonadotrophins in the flexible, multi-dose antagonist group. One study also showed an increased number of follicles and oocytes retrieved and fewer cancelled cycles in the antagonist group (6).

Our results showed similar pregnancy rates in both the agonist and antagonist groups (nine pregnancies in each group). Both groups also showed similar ovarian response (more than 3 mature oocytes retrieved). It seems that cycle repeating by GnRH agonist analogues or changing the gonadotrophin to HMG has an effective role for ovarian response in poor responder patients. In other words, there was no major difference between agonist or antagonist regimens.

In the present study, we found a higher abortion rate in the agonist group versus antagonist but this difference was not statistically significant. Future clinical trials with larger sample sizes may be needed for confirming this result.

In this trial, the GnRH antagonist protocol consisted of flexible, oral contraceptive pretreatment and HMG for ovarian stimulation.

Since GnRH antagonist agents are not produced by pharmacological factories in Iran and it is considered an expensive protocol for most patients, we used the flexible protocol. In the flexible protocol, the GnRH antagonist is usually administered based on the size of the leading follicle; therefore the lower dose of gonadotrophin is needed for stimulation. Stable and early suppression of endogenous gonadotropin (i.e. OC pretreated fixed GnRH antagonist protocol) may be advantageous for achieving follicular synchronization and the highest clinical pregnancy rates. In this respect, flexible regimens seem to be far from optimal (4). However, some studies have demonstrated that a flexible antagonist protocol can optimize ovarian stimulation and improve the yield of oocytes retrieved (10). In the present study, we could not find any significant differences concerning

stimulation and cycle outcomes between flexible GnRH antagonist and GnRH agonist protocols. It seems that using fixed or flexible antagonist regimens may be chosen based on individual or center needs.

Oral contraceptive pre-treatment in non-down regulation protocols helps to abolish corpus luteum rescue and synchronize follicular development during IVF (11). OC pretreatment using a GnRH antagonist can be associated with deep suppression of LH and FSH levels (12, 13). Poor responder patients have low ovarian reserve and over suppression of LH and FSH levels may compromise their treatment outcomes. Although we did not evaluate hormone profiles in our study, it seems that inclusion of OC pretreatment in our study did not have any adverse effect on over suppression of endogenous gonadotrophins. However, our sample size is small and a larger randomized trial is necessary for evaluation of OC pretreatment role in flexible GnRH antagonist patients.

Finally, our stimulation regimen included exogenous LH in the form of HMG. Administration of GnRH antagonist in the late follicular phase for prevention of LH surge could induce a sharp decrease in serum LH level, even less than a threshold. In the present trial, we used HMG in both agonist and antagonist groups. Our results showed no significant effect for adding HMG to the GnRH antagonist regimen and we found a similar number of mature oocytes between both groups. However, LH levels were not measured throughout the study and we could not assess LH suppression in our patients. LH suppression could be evaluated in future randomized trials.

Conclusion

In conclusion, a protocol including a GnRH antagonist appears at least as effective as one using a GnRH agonist in patients who are poor responders on a long agonist protocol. Since GnRH agonists are more available and less expensive than antagonist agents, repeating the GnRH agonist protocol may be a reasonable solution for achieving sufficient oocytes and pregnancy rates. However, more (larger) randomized controlled trials for statistical analysis are required to optimally compare GnRH agonists and antagonists for their use in IVF or ICSI therapy.

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