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ORIGINAL ARTICLE

Comparing GnRH agonist long protocol and gnrh antagonist protocol in outcome the first cycle of ART

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Abstract
Purpose This prospective study evaluated the efficacy of gonadotropin-releasing hormone (GnRH) antagonist protocol incomparison with the GnRH agonist protocol in the first cycle of assisted reproductive technique (ART).
Methods We randomized 235 patients undergoing ART for the first time. The first group wasstimulated with a standard long protocol and the second group stimulated with GnRH antagonis.
Results There was no statistically significant difference in the age, infertility cause, basal FSH,BMI, the number of oocytes retrieved, number of M2 oocytes, embryo obtained and endometrialthickness between the two groups. But Serum estradiol, consumption of gonadotropins and ovarianhyperstimulation syndrome were significantly lower in the antagonist protocol. Cancellation rateof embryo transfer due to poor-quality embryo in the antagonist protocol was higher, but itwas not significant. There was no significant difference in the clinical pregnancy and ongoingpregnancy between the two groups.
Conclusion GnRH-antagonist is an effective, safe, and well-tolerated alternative to agonist inthe first cycle of ART.

Keywords GnRH antagonist · GnRH agonist · Pregnancy rate · Assisted reproductive technology · Ovarian stimulation

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Introduction

In the early days of in vitro fertilization (IVF), natural cycles were commonly restored by using clomiphene citrate and gonadotropins as classic stimulation protocols [1]. However, in these cycles, premature LH surge is considered as a challenge on termination of the treatment phase [2]. Later, using gonadotropin-releasing hormone (GnRH) analogs has become routine [3]; these medications prevent spontaneous ovulation during the cycles by inducing a state of hypophyseal desensitization and subsequently reducing premature luteinization. Despite GnRH agonist advantages, long duration of treatment (2–3 weeks required to obtain desensitization), daily administration (in the case of luperolide acetate) and the large quantity of gonadotropin used [4], have all inspired pharmaceutical industries to develop more patient-friendly analogs that immediately initiate action. Using of GnRH antagonists on the other hand, competitively binds to pituitary GnRH receptors and blocks the ability of GnRH to initiate dimer formation, signal transduction and FSH, LH secretion from the pituitary gonadotroph, remains controversial [6]. Five large randomized controlled trials, which compared GnRH antagonist with a long GnRH agonist protocol have shown that GnRH antagonists are effective in preventing the onset of a premature LH surge during ovarian over simulation [7–9], and

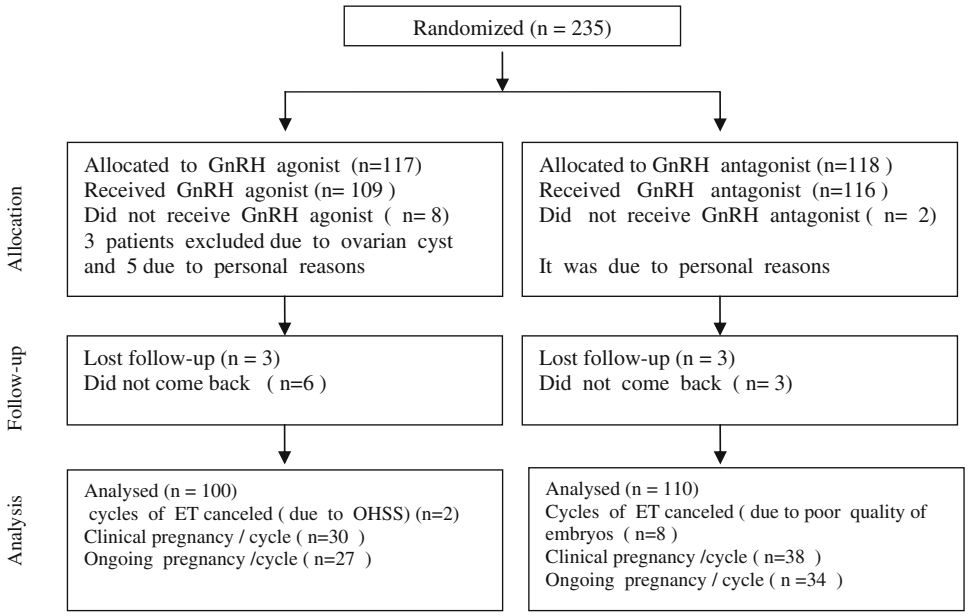

Fig. 1 Recruitment follow-up and drop outs over the course of the study

compared to the long agonist protocol, GnRH antagonists have more rapid reversibility [10, 11], shortened duration of stimulation, lowered dosage of gonadotropin ampoules [5] and decreased severity of the ovarian hyper-stimulation syndrome (OHSS) [12]. Furthermore, some women in an agonist protocol may suffer from common problems of hypoestrogenism in the form of hot flush and headache during treatment [13]. Therefore, based on this evidence, an antagonist protocol is more appropriate for infertile patients. Cetrorelix and Ganirelix are two available GnRH antagonists that are used based on follicular size on a fixed day. GnRH antagonist initiated on day 6 of stimulation (fixed day) appears to be superior to flexible initiation by a follicle of size between 14–16-millimeters (mm) [14].

The data from the German registry suggest that GnRH antagonists are comparatively more often used in cycles, which have an unfavorable poor prognosis [15] and this protocol is reserved to unresponsive patients [16–18]. But up to now, not enough prospective studies have been published to prove the beneficial effect of antagonists on the first cycle-assisted reproductive technique (ART).

The purpose of our prospective study is to compare hormonal and clinical effects of GnRH antagonist (fixed dose) with GnRH agonist (long protocol) on the first cycle of ART.

Materials and methods

We studied a total of 235 patients who underwent in vitro fertilization (IVF) or intra cytoplasmic sperm injection (ICSI) in Yazd research and clinical center for infertility, from December 2007 to January 2009. The flowchart for the study is shown in Fig. 1. Inclusion criteria were the first cycle of the ART, age <35 years, and basal FSH <10 IU/L. The patients were excluded from the study if they had previous IVF or ICSI, hyperprolactinemia, hyperthyroidism, hypothyroidism, uterine abnormality, severe endometriosis, or solitary ovary. The ethical committee approved the study protocol and a written informed consent was obtained from all patients. Patients were randomized to two treatment groups using computer-generated randomized schedules that were sealed in envelopes and handed to patients. In the first group, the patients were desensitized with 500 μg Buserelin per day (Suprefact, Aventis, Germany) subcutaneously (SC), during menstrual cycle 21 and onwards, until the baseline evaluation, which takes place in the first few days of menstruation. If the baseline levels of estradiol (E2) (<50 pg/mL) are achieved, then the dose of Buserelin would be reduced to 250 μg and ovarian stimulation would commence with 150–225 IU r-hFSH, (Gonal F, Serono, Switzerland) subcutaneous (SC) once a day to enhance stimulation.

The patients in the second group were treated with GnRH antagonist (Ganirelix, Organon, Netherland). The ovarian stimulation in these patients was started with 150–225 IU Gonal F on the second day of menstrual cycle with an S·C injection once a day. Initiation of 0.25 mg Ganirelix took place on the sixth day of the stimulation (fixed protocol). HMG (Menogon, ferring, pharmaceuticals, Germany) was also added to the initial gonadotropin dose. This protocol has been developed in previous studies (18, 19).

The dose of gonadotropin in the two groups was adjusted based on the ovarian response, which was monitored by ultrasonography. Buserelin and Ganirelix were continued till the day of hCG administration.

Next, HCG 10,000 IU (Profasi, Serono, Switzerland) was administrated intramuscularly (IM) when at least two

follicles reached a mean diameter of 18 mm. At this stage, endometrial thickness was measured by ultrasonography and venous blood samples were obtained to determine the serum levels of E2. Oocyte retrieval was performed 36 h later, followed by IVF or ICSI. All the embryos were scored by the number of blastomeres, size, shape, symmetry cytoplasmic appearance of blastomeres and the presence of nucleate cytoplasmic fragments on the third day after oocyte collection, as previously described [20, 21]. Embryo transfer (ET) was determined based on the American Society for Reproductive Medicine (ASRM) guidelines [22], and it was performed using Labotect Catheter (Labotect Gmbh. babor-Technik, Gottingen, Germany). 800 mg daily cyclogest suppository (Aburaihan, Iran) was started on the day of oocyte collection to provide luteal phase support, and it continued until the fetal heart activity was documented by ultrasonography. The serum hCG level on day 16 after the oocyte recovery was tested to determine chemical pregnancy, if any; a vaginal ultrasonography would be carried out on day 35 following the oocyte recovery for documentation of fetal heart activity and confirmation of a clinical pregnancy. Primary outcome measures included clinical pregnancy rate per cycle and ongoing pregnancy, which later were defined as pregnancy proceeding beyond the 12th gestational week. Secondary outcome included OHSS, defined by ≥15 follicles with a mean diameter ≥14 mm per each ovary at the end of the follicular phase of stimulation and/or E2 levels on the day of hCG administration >3,000 pg/mL and/or presence of ascites after hCG administration in ultrasonography.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Science version 15.0 for windows (SPSS Inc., Chicago, IL, USA). The data were analyzed by student's *t* test and Chi square test. A *P* value of <0.05 was considered statistically significant.

Results

Demographic and infertility characteristics for both groups are presented in Table 1. The two groups were matched for age, basal FSH, body mass index and cause of infertility.

The results of the ovarian stimulation are given in Table 2. No statistically significant difference was noted in the mean number of follicle ≥14 mm, recovered oocytes, metaphase 2 oocytes and endometrial thickness between the two groups. E2 peak level on the day of hCG administration, total Ampoule gonadotropin consumption and OHSS were higher in first group. In first group embryo transfer was cancelled in two cycles due to OHSS before and in second group embryo transfer cancelled in eight cycles due to bad quality of embryos.

Table 1 Demographic and infertility characteristics of patients

Variable	Agonist group	Antagonist group	*P* value
Age (years)	28.71 ± 2.8	28.36 ± 3.1	0.06
BMI (KG/m^2)	28.1 ± 3.4	27.54 ± 4.3	0.07
Basal FSH (IU/L)	5.77 ± 1.2	5.54 ± 1.1	0.23
Cause of infertility			
Tubal	9 (9%)	14 (12.7%)	0.26
Ovary	21 (21%)	21 (19.1%)	0.49
Male	52 (52%)	66 (60%)	0.33
Unexplain	15(15%)	6 (5.5%)	0.08
Other	3 (3%)	3 (2.7%)	0.63

Data presented as mean ± SD

BMI body mass index, *FSH* follicle-stimulating hormone

$P < 0.05$ statistically significant

Table 2 Results of the ovarian stimulation of two groups

	Agonist group	Antagonist group	*P* value
No. of follicle ≥14 mm	9.52 ± 4.2	9.06 ± 2.6	0.33
No. of oocyte retrieved	7.86 ± 3.4	7.15 ± 3.2	0.13
No. of M2 oocyte	5.79 ± 3.5	5.22 ± 2.3	0.07
Endometrial thickness (mm)	9.6 ± 0.8	9.6 ± 0.8 0.91	
E2 level on day of HCG (pg/mL)	1,294.7 ± 517	981.5 ± 362	0.00
Total amp. of gonadotropin used	31.2 ± 3.0	22.1 ± 4.8	0.00
OHSS (CI)	12 (12%) (18.36–5.6%)	3 (2.7%) (5.7 to −0.3%)	0.00

M2 Metaphase 2, *E2* Estradiol, *HCG* Human chorionic gonadotropin, *AMP* ampoule, *OHSS* ovarian hyper stimulation syndrome, *CI* confidence interval 95%

$P < 0.05$ statistically significant

The results of insemination of oocytes, embryological characteristics and embryo transfers are given in Table 3. Conventional IVF, ICSI and combined insemination were used in the same percentage of cycles in both groups. The total number of embryos obtained, good quality embryos, clinical pregnancy and ongoing pregnancy were similar in the two groups.

Discussion

It is debatable whether the GnRH antagonists are at least as effective as the GnRH agonist when used in IVF–ET cycles.

Table 3 Results of the insemination, embryological and embryo transfer in the two groups

	Agonist group	Antagonist group	P value
Conventional IVF	18 (18%)	17 (15.5%)	0.62
ICSI	32 (32%)	37 (33.6%)	0.80
Combined IVF–ICSI	50 (50%)	56 (50.9%)	0.89
Total embryos obtained	4.9 ± 1.9	4.41 ± 1.8	0.07
Good quality embryos%	0.85%	75%	0.07
No. ET cancelled	2 (2%)	8 (7.3%)	0.07
Clinical pregnancy/cycle (CI)	30 (30%) (21.02–38.98%)	38 (34.5%) (43.3–25.7%)	0.48
Clinical pregnancy/transfer (CI)	30 (30.6%) (35.25–25.95%)	38 (37.3%) (46.68–27.9%)	0.32
Ongoing pregnancy (CI)	27 (27.6%) (36.45–18.75%)	34 (33.3%) (42.45–24.41%)	0.37

IVF in vitro fertilization, *ICSI* intracytoplasmic injection, *ET* embryo transfer, *CI* confidence interval 95%

$P < 0.05$ statistically significant

Both the North American Ganirelix Study Group [9], the European and Middle East Study Group [8] trials showed that the duration of stimulation and the number of gonadotropin ampoules used were lower in the antagonist cycles. In these studies, fewer follicles and lower estradiol levels were observed on the day of HCG injection, with a lower number of retrieved oocytes, but no significant difference was found in the rate of M2 oocytes, fertilization, and good quality embryos. Lower pregnancy was observed with the antagonist compared with the agonists, but the finding was not statistically significant. We also demonstrate that there is no statistically significant difference in the number of oocytes, number of M2 oocytes, and the number of embryos between the two groups. Marologlu et al. also report similar results to our findings in normoresponders [6].

OHSS incidence seems to be related to the stimulation regimen used, and in particular, to the amount of gonadotropin administration and E2 level. A systemic review and meta-analysis including five randomized trials confirmed this finding [5]. Kolibianakis et al. [12] reported a low total incidence of OHSS for only the antagonist cetrorelix and not ganirelix. We observed lower OHSS in the ganirelix group, and that difference was statistically significant.

There are several controversies between antagonist protocolsand the agonist protocol. Although studies by Xavier et al. and Tazequl et al. fail to show any significant difference in clinical pregnancy [23, 24], the study by Li et al. [25] reported a high clinical pregnancy rate in the antagonist protocol. Nevertheless, Orvieto et al. [26] reported a significantly lower clinical pregnancy rate in the antagonist protocol versus the agonist protocol in the patients that were candidate for the first cycle of ART. Sirayapiwat et al. reported that in antagonist protocol, despite the same embryo quality and endometrial thickness as in the agonist protocol, there was a trend towards lower pregnancy and a decrease in endometrial receptivity [27]. However, our study did not support this difference between clinical pregnancy and ongoing pregnancy on the two protocols. We are aware of the limitation attributed to those patients in the antagonist group receiving one dose of HMG on the day that Ganirelix was administered and that might have affected the outcome of the treatment.

In summary, the safety and efficacy of GnRH antagonist and agonist in the first cycles of ARTare reported to be similar and GnRH antagonists are now part of the therapeutic routine of infertility institutes worldwide [28]. Moreover, studies with large number of patients, with enough power, are needed to compare long GnRH agonist protocols with GnRH antagonist protocol to identify difference in pregnancy rates in the first cycle of ART.

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