

# Investigation of pregnancy outcome and ovarian hyper stimulation syndrome prevention in agonist and antagonist gonadotropin-releasing hormone protocol

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**Background:** Given the controversies regarding the effectiveness of gonadotropin-releasing hormone (GnRH) antagonists in prevention of ovarian hyper stimulation syndrome stimulation, this study was designed to compare GnRH agonist protocol with GnRH antagonist protocol in patients who were candidate for assisted reproductive techniques (ARTs). **Materials and Methods:** This investigation was performed on 136 patients who were randomly allocated to two groups of GnRH agonist and GnRH antagonist. In the first group stimulation was performed by administration of Buserelin, and in the second group, it was performed by giving Cetorelix. Then patients were compared regarding results of ovarian stimulation, pregnancy outcomes and rate of ovarian hyper stimulation syndrome (OHSS). **Results:** There were not significant differences between 2 groups regarding the ovarian stimulation, pregnancy outcomes and rate of OHSS ( $P$  value  $>0.05$ ). **Conclusion:** Administration of GnRH antagonists in ovarian stimulation will be a reasonable option to GnRH agonists in assessment reproduction treatment; however, further studies are suggested.

**Key words:** Assisted reproductive techniques, gonadotropin-releasing hormone antagonist, gonadotropin-releasing hormone agonist, ovarian hyper stimulation syndrome, ovarian stimulation, pregnancy rate

## INTRODUCTION

*In vitro* fertilization (IVF) has been widely used to treat most causes of subfertility; however, pregnancy rate following IVF remains around 20-30% per started cycle. Therefore, some adjuvant therapies are used to achieve better outcomes.<sup>[1]</sup> Administration of high doses of exogenous gonadotropins stimulates ovaries, and improves IVF success rate.<sup>[1,2]</sup> In order to prevent the premature surge of luteinizing hormone (LH), Gonadotropin-releasing hormone (GnRH) agonists were introduced in ovarian stimulation for IVF.<sup>[3]</sup> Despite several benefits, use of GnRH agonists is associated with some adverse effects including initial flare up with possible ovarian cyst formation and gonadotrophin release down-regulation which may cause spotting,

hot flushes tiredness, sleep disturbance, headaches and dizziness. In addition, along with the increased rate of pregnancy, long GnRH agonist protocols are associated with increased incidence of ovarian hyperstimulation syndrome (OHSS).<sup>[3,4]</sup>

Given the potentially fatal outcomes related to OHSS, many studies are performed to find out safer methods of ovarian stimulation therapy to minimize this risk. Treatment with GnRH antagonists is considered as an alternative for prevention of premature LH surge during ovarian stimulation. In contrast with GnRH agonists which downregulate pituitary GnRH receptors, and desensitize gonadotropic cells, GnRH antagonists bind pituitary GnRH receptors competitively, and inhibit gonadotropin release directly.<sup>[3,5]</sup> Lower incidence of OHSS has been reported in recent studies after using GnRH antagonists;<sup>[6]</sup> however, some other studies doubted these results.<sup>[7]</sup>

Given the controversies regarding the effectiveness of gonadotropin-releasing hormone (GnRH) antagonists in ovarian stimulation, this study was designed to compare GnRH agonist protocol with GnRH antagonist protocol in ovarian stimulation of patients who were candidate for assisted reproductive techniques (ARTs).

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## MATERIALS AND METHODS

### Study design and patients

This randomized clinical trial (RCT) was performed on women who were referred to the infertility center of Beheshti hospital, Isfahan, Iran, for IVF or intra cytoplasmic sperm injection (ICSI) and was approved by chancellor of reach in Isfahan medical University. According to the study criteria, 136 patients were randomly allocated to 2 groups: 67 patients were treated with GnRH agonist, and 69 patients were treated with GnRH antagonist. Patients were selected by simple randomization. Inclusion criteria were undergoing assisted reproduction techniques (ARTs) for the first time, age  $\leq 35$  years and serum FSH level  $\leq 10$  IU/literin 3<sup>th</sup> days of menstrual cycle and male or female factor In addition to women with the previous history of IVF or ICSI, patients who had hyperprolactinemia, thyroid dysfunction, uterine abnormality, severe endometriosis (diagnose d by laparoscopy) and secondary infertility were excluded from the study.<sup>[8]</sup>

### Intervention

According to the previous studies, treatment protocols were defined for patients in each group.<sup>[8-11]</sup>

In the first group, a daily dose of Buserelin 500  $\mu\text{g}$  (Suprefact, Aventis, Germany) was given to the patients subcutaneously. Treatment was commenced on the 21<sup>st</sup> day of pervious menstrual cycle, and vaginal ultrasonography was done and Buserelin continued onward until the baseline evaluation of serum level of estradiol (E2) on the second day of the menstruation.

If the serum level of E2 is less than 50 pg/ml, the dose of Buserline would be reduced to 250  $\mu\text{g}$  per day, and ovarian stimulation would be commenced with subcutaneous injection of recombinant FSH (Gonal F, Serono, Switzerland), 75 IU daily.

In the second group, GnRH antagonist (Cetrorelix, Serono, Switzerland) was administered. Ovarian stimulation was started on the second day of the cycle by subcutaneous injection of 75 IU of recombinant FSH daily.

On the sixth day of stimulation, 0.25 mg Cetrorelix was initiated when the follicle reaches to 14 mm diameter. Based on the ovarian response detected by ultrasonography every 2-3 days, gonadotropin dose was adjusted in both groups.

Administration of Buserelin and Cetrorelix was continued until the time of human chorionic gonadotropin (HCG) injection. When at least 3 follicles with a mean diameter of 18 mm were developed, HCG 10,000 IU (Profasi, Serono, Switzerland) was

injected intramuscularly. At this stage, endometrial thickness was studied Trans vaginal ultrasonographically, and after 36 h, oocyte retrieval was performed.

After IVF or ICSI, Cyclogest suppository 800 mg (Abureihan, Iran) was prescribed daily to provide luteal phase support. Cyclogest was continued till the activity of fetal heart was confirmed by trans vaginal ultra sono graphy (TVS).

Sixteen days after the oocyte retrieval, serum HCG level was checked to determine chemical pregnancy.<sup>[8]</sup> TVS was carried out for clinical determination of pregnancy. Patients with ovarian enlargement up to 12 by 12 cm, accompanied by abdominal discomfort and gastrointestinal symptoms, or a sudden weight increase more than 3 kg were considered as moderate OHSS.<sup>[8-11]</sup>

Severe OHSS was described as presence of enlarged ovarian cysts more than 12 by 12 cm, ascites, pleural and/or pericardial effusion, electrolyte imbalance (hyponatremia, hyperkalemia), hypovolemia, and hypovolemic shock.<sup>[12-14]</sup>

### Statistical analysis

Data were analyzed by SPSS 16 software Chicago, IL, USA). Chi-square and independent *t*-test were used for the analysis. *P* values less than 0.05 were considered statistically significant.

### Ethical issues

This study was approved by the ethic committee of Isfahan University of Medical Sciences (IRCT201205309910N1). The study was completely explained to the patients, and informed consent was obtained before starting the intervention.

## RESULTS

There was no statistically significant difference in the baseline characteristics between 2 groups [Table 1].

No significant difference was found between 2 groups regarding the duration of the treatment, the number of retrieved oocytes, number of transferred embryo and serum E2 level on the day of HCG administration; however, in the antagonist group, the total number of gonadotropin ampoules was significantly lower than the agonist group [Table 2].

Despite higher relative frequency of chemical pregnancy and ongoing pregnancy and lower rate of OHSS (moderate and severe) in the antagonist group, no significant difference was observed between 2 groups [Table 3].

## DISCUSSION

According to our findings: Several important parameters including the rate of ongoing pregnancy, rate of OHSS, and the number of needed gonadotropin ampoules, GnRH antagonist treated patients have better condition than GnRH agonist treated women. However, only the number of ampoules is statistically different between 2 groups. In the previous studies performed by the North American Ganirelix Study Group and European and Middle East Study Group, shorter duration of stimulation and fewer number of used gonadotropin ampoules were reported in the antagonist group.<sup>[15,16]</sup> Although this study does not support the former finding, it confirms the latter one. The

**Table 1: Baseline characteristics of patients**

	Agonist group (N=67)	Antagonist group (N=69)	P value
Age (year)	28.65±3.94	28.36±3.40	0.64
BMI (kg/m <sup>2</sup> )	24.94±2.53	24.91±2.57	0.95
Basal FSH (IU/L)	5.98±1.73	5.94±1.62	0.90

Data are presented as mean±SD, BMI=Body mass index, FSH=Follicle-stimulating hormone

**Table 2: Comparison of results of the ovarian stimulation between 2 groups**

	Agonist group (N=67)	Antagonist group (N=69)	P value
Treatment duration (day)	12.11±2.63	12.25±2.82	0.78
Retrieved oocytes (number)	9.76±5.22	9.29±4.80	0.59
Serum E2 level (pg/ml) in day of HCG administration	1,144.04±490.10	1,227.48±435.71	0.29
Gonadotropin ampoules (number)	20.14±9.51	17.04±6.04	0.02
Transferred embryo (number)	2.71±0.86	2.66±0.90	0.74

Data are presented as mean±SD, Serum E2 level=Serum estradiol level on day of administration of HCG

**Table 3: Comparison of outcomes between 2 groups**

	Agonist group (N=67) (%)	Antagonist group (N=69) (%)	P value
Chemical pregnancy			0.55
Positive	23 (34)	24 (35)	
Negative	44 (66)	45 (65)	
Clinical pregnancy			0.45
Positive	21 (31)	20 (29)	
Negative	46 (69)	49 (71)	
Ongoing pregnancy			0.38
Positive	15 (22)	18 (26)	
Negative	52 (78)	51 (74)	
OHSS			
Moderate	15 (22)	9 (13)	0.11
Severe	10 (15)	6 (8)	0.19

Data are presented as number (%), OHSS=Ovarian hyperstimulation syndrome

less need for gonadotropin results in fewer probable adverse effects and makes ovarian stimulation less costly.<sup>[17,18]</sup>

They reported lower estradiol levels on the HCG injection day and lower number of retrieved oocytes as well. In the present study, we did not find significant difference regarding these parameters.

Another study by Firouzabadi *et al.*,<sup>[8]</sup> also found lower amount of gonadotropin consumption in the antagonist group. They observed significantly lower rate of OHSS in the antagonist group. Similarly, we found lower rate of OHSS in the antagonist group, but it was not statistically significant. This difference may be related to the stimulation regimen. Using different medication or different treatment regimens may lead to different results.<sup>[7]</sup> Aforementioned studies administered Ganirelix, while we used Cetrorelix.

It is believed that GnRH antagonists usually do not induce cyst formation or stimulate gonadotropins and steroid hormones acutely which is more prevalent in the initial stimulation by GnRH agonists. Thus, lower rates of OHSS are expected.<sup>[17,19]</sup>

Another controversy between agonist and antagonist protocols is regarding their effects on pregnancy. It is supposed that GnRH antagonists improve LH instability, and this may be the reason for their better performance. LH instability means any fluctuation in the LH level such as LH surge or rise in the LH concentration. Therefore, GnRH antagonists improve LH instability, and this may be the reason for their better performance. LH instability means any fluctuation in the LH level such as LH surge or rise in the LH concentration. Therefore, decreased relative incidence of LH instability may result in better pregnancy outcomes.<sup>[3]</sup>

We found more chemical and ongoing pregnancy in the antagonist group, while clinical pregnancy was more in agonist group; however, none of these findings were statistically significant. Our findings are similar to what Tazequ *et al.*,<sup>[20]</sup> Xavier *et al.*,<sup>[21]</sup> and Firouzabadi *et al.*<sup>[8]</sup> have found. They reported no significant difference between agonist and antagonist groups in clinical pregnancy.

Unlike to the present study, Sirayapiwat *et al.*<sup>[22]</sup> and Orvieto *et al.*<sup>[23]</sup> reported significantly lower rate of clinical pregnancy. These controversies are mostly due to difference in the study design. Given the above evidence, we may conclude that administration of GnRH antagonists in ovarian stimulation will be a reasonable option which is at least as effective and safe as GnRH agonists. Moreover, less need for gonadotropin consumption decreases the

procedure cost and adverse effects. However, in order to overcome the controversies, further studies with larger sample size are needed to investigate and compare different treatment protocols.

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