COMPARISON BETWEEN THE EFFICACY OF SHORT-TERM AND FIXED PROTOCOLS OF GNRH ANTAGONIST IN IVF CYCLES

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ABSTRACT

Background: Aim of this study is to compare the short-term effect of GnRH antagonist in follicular phase with fixed protocol of GnRH antagonist in IVF cycles in infertile women.

Materials and methods: The present study was conducted on 60 patients. Patients were divided into two groups of 30, based on random table of Excel. The target group received 0.25 mg per day subcutaneous Cetrorelix on days 1, 2 and 3, which was injected on the fourth day of menstruation and for the control group, fixed Cetrorelix, was started on the 6th day of cycle and continued until HCG injection. Both groups received 300 IU gonadotropin for four days that was adjusted based on the ultrasound results. Then gonadotropin consumption, number of oocytes and pregnancy rates were clinically compared.

Results: In the present study, there was no difference between the case and control group regarding pregnancy rate (P value = 0.54). Cetrorelix dose used and the total number of days of treatment were significantly different between the two groups (P value = 0.0001) and the target group used higher dose of Cetrorelix but had a lower duration of therapy. The two groups were not significantly different in the primary outcome, including chemical and clinical pregnancy (P value = 0.58) (P value = 0.68).

Conclusion: It was demonstrated in the present study that short-term and fixed use of GnRH antagonist in the follicular phase was not different and the short-term protocol decreases the length of treatment and increases the costs.

Keywords: infertility, IVF, gonadotropins, follicular phase.

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Introduction

GnRH antagonists in clinical medicine, another option has been provided for ovarian stimulation in assisted reproductive techniques (ART). Access to GnRH antagonists to inhibit ovulation is a relatively new, simple, and safe method of ovulation induction(1).

Antagonists competitively bind to pituitary GnRH receptor and inhibit the ability of GnRH to secrete LH, and FSH from gonadotropes.

In sufficient amounts of antagonists, LH, and FSH will be completely suppressed(2). Clinical studies have demonstrated that antagonists are effective in preventing LH surge in ovarian stimulation cycles. In ovulation stimulation cycles, antagonists are prescribed when the blood levels of estradiol increases. The patient will have no symptoms of estrogen deficiency(3). As antagonists will not completely deplete pituitary gland, the preventive effects appear when proper dose is administered.

Another advantage of antagonists is shorter duration of using antagonists and gonadotropins(3).

It is yet not clear, whether antagonists will ultimately be able to completely replace agonists and change into the standard stimulation regimens in assisted reproductive techniques. Some studies have suggested that endometrial development is closer to natural cycle in cycles receiving antagonists, compared to the group receiving agonist(4).
Antagonists are considered a hopeful method in women with polycystic ovarian syndrome and in weak response to agonist treatment\(^5,6\). Some extensive controlled trials show that using GnRH antagonists have the same results than women treated with GnRH agonists; along with this advantage that it reduces the use of gonadotropin stimulation periods\(^7,8\).

So, there are a few strategies that GnRH antagonist protocol can give better results in assisted reproductive techniques. Using this protocol in short term gives better results than fixed protocol of GnRH antagonist\(^9\) and GnRH antagonists can be started from the first ovulation day and continued to the day of administering HCG\(^10\).

Given the benefits of antagonists in treatment of in vitro fertilization (IVF), this study aimed to change the antagonist protocol to increase the pregnancy chance. Administration of short-term antagonist in the follicular phase inhibits the internal FSH and causes symmetrical growth. In addition, it inhibits progesterone and LH levels in follicular phase that makes the endometrial receptivity more appropriate for implantation. Therefore, this study aimed to achieve higher pregnancy rate by short-term administration of GnRH on days 1, 2, and 3 of menstruation than the usual treatment with GnRH antagonists.

Materials and methods

In this RCT, after approval by the Ethics Committee of Bushehr University of Medical Sciences, patients undergoing IVF at Persian Gulf Omid Infertility Center of Bushehr from April 2014 until March 2015 were included into the study. The study was conducted on 60 patients after obtaining written informed consent. The patients were divided into two groups of 30 by random tables of Excel. The inclusion criteria consisted of FSH level less than 10 IU/L, age of patients from 20 to 39 years old, entering IVF cycle for the first time, and patients undergoing IVF because of male infertility or tubal factor. The exclusion criteria were patients with ovulatory disorders, liver, kidney, and heart diseases, diabetes and endometriosis.

The IVF protocol prescribed in the two study groups

All patients entered treatment cycles without prescribing oral contraceptive pills or other hormonal drugs. The target group received 0.25 mg per day Cetrorelix (Merck-Serono Germany) on days 1, 2 and 3th menstruation, by subcutaneous injection and restarted in a short time when the size of the follicle reaches 14-15 mm and continued until the day of HCG injection. In the control group, fixed Cetrorelix was started on the 6th day of cycle and continued until the day of HCG injection. For both groups, 300 IU HMG Ampule (Merional; IBSA, Lugano, Switzerland) was administered from the 2nd day of cycle. The patients received merional for 4 days, and it was then adjusted based on the vaginal ultrasound. When ≥2 follicles reached ≥18 mm, 10,000 units HCG (Pregnyl; Organon, oss, the Netherlands) was injected. Oocyte retrieval was performed 34-36 hours after hCG administration. Conventional IVF or intracytoplasmic sperm injection was performed as appropriate. Embryos with 4-6 equal-sized and evenly shaped blastomeres on day 2 with 20% fragmentation or less and non-multinucleation were considered top quality embryos. Embryos with 2-6 even or uneven blastomeres with 20% fragmentation or less and no multinucleation were considered good quality embryos. Embryos were transferred on day 2 or 3 under ultrasound guidance with a C.C.D. embryo transfer catheter (Laboratoire C.C.D., Paris, France). Luteal support with intramuscular administration of progesterone in oil (Progesterone; Aburaihan Co., Tehran, Iran) at 100 mg daily was started on the day of oocyte retrieval. Serum \(\beta\)-hCG level was measured 14 days after embryo transfer and a Transvaginal ultrasoundography was performed 3 weeks after a positive \(\beta\)-hCG result for documentation of gestational sac and fetal heart activity. Clinical pregnancy was considered as the presence of a gestational sac with fetal heart activity.

The Statistical Analysis

SPSS software (version 18) and descriptive statistics (frequency, mean, standard deviation, and 95% confidence interval) were used, and Kolmogorov-Smirnov to investigate the normal distribution of data, independent t-test for the quantitative variables such as age, endometrial thickness, diameter of follicles, serum level of FSH, estradiol and chi-square test for qualitative variables such as chemical and clinical pregnancy rate. In case of non-normality of data distribution, non-parametric Mann-Whitney test was used. The level of significance was considered 0.05 in all tests.
Results

The two groups were matched for age, duration of infertility, serum levels of LH, FSH, TSH, prolactin and estradiol (P value > 0.05) (Table 1). Also, the reason of infertility was not different between groups, including male factor in 24 patients (80%), idiopathic in 3 patients, and tubal factor in 3 patients.

There was a significant difference between the two groups in the consumed Cetrorelix (P value = 0.0001) and the total number of treatment days (P value = 0.0001), as the intervention group higher dose of Cetrorelix was consumed but the duration of therapy was shorter (Table 2). There was also no significant difference in implantation and fertilization rate between groups (P value = 0.74, and 0.54, respectively).

Discussion

In this study, two methods of administering antagonists (fixed and short-term in the follicular phase) were compared. According to the results of this study, the variables associated with oocyte and embryo were not significantly different in terms of antral follicles, total number of oocytes, number of oocytes in metaphase I and II, number of GV oocytes, total number of embryos, number of transferred embryos, implantation and fertilization rate, chemical and clinical pregnancy rate. But the treatment duration was shorter in the target group that received short-term antagonist on days 1, 2, and 3 of menstruation, but the dose of consumed gonadotropin and stereotide was higher in the target group.

In a similar study in 2010, Younis announced that the fertilization rate in the group starting antagonist from the beginning of the cycle was better than flexible antagonist. The gonadotropin dose was not different between groups. They stated that the internal level of FSH before stimulation with gonadotropin was lower in this protocol that induced better concurrence of follicles. In addition, LH and progesterone levels are lower in patients in the follicular phase, resulting in better endometrial receptivity. These two benefits also exist in the long standard protocol. In addition, the protocol does not have the specific disadvantages of the long protocol. Starting the cycle with estrogen, contraceptive, or GnRH antagonist can cause synchronized follicular growth(1).

In our study, in contrast to the above-mentioned study, the two groups were not different regarding fertilization, and the consumed dose of gonadotropin was higher in the target group. In our study, like this study, serum level of LH was not significantly different. In our study, like this study, the serum levels of LH and estradiol was not significantly different between the two groups. Blockeel noted that the antagonist administered in the follicular phase induces higher estradiol levels on the day HCG is injected, due to the simultaneous growth in oocyte. Though, higher estradiol levels

Table 1: Basal characteristics of patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(years)</td>
<td>Control (mean ± SD)</td>
<td>Target (mean ± SD)</td>
</tr>
<tr>
<td>Infertility duration</td>
<td>30.37±3.45</td>
<td>29.17±3.53</td>
</tr>
<tr>
<td>(years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSH(IU/L)</td>
<td>7.23±4.08</td>
<td>6.23±2.94</td>
</tr>
<tr>
<td>LH(IU/L)</td>
<td>5.28±1.72</td>
<td>5.85±1.66</td>
</tr>
<tr>
<td>TSH</td>
<td>31.23±9.37</td>
<td>29.77±8.93</td>
</tr>
<tr>
<td>Prolactin(IU/L)</td>
<td>3.03±0.90</td>
<td>3.09±0.92</td>
</tr>
<tr>
<td></td>
<td>15.05±5.09</td>
<td>16.1±5.45</td>
</tr>
</tbody>
</table>

Table 2: Dose of drugs in two groups for stimulation.

<table>
<thead>
<tr>
<th>Variable</th>
<th>group</th>
<th>T</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>consumption dose of HMG (IU)</td>
<td>Control (mean ± SD)</td>
<td>Target (mean ± SD)</td>
<td>1.79</td>
</tr>
<tr>
<td></td>
<td>2200 ± 699.83</td>
<td>2487 ± 527.42</td>
<td></td>
</tr>
<tr>
<td>Consumption dose of cetrotide (mg)</td>
<td>3.66±0.994</td>
<td>5.80±0.961</td>
<td>8.44</td>
</tr>
<tr>
<td>Duration of stimulation (days)</td>
<td>13.96±8.58</td>
<td>14.63±5.91</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Table 3: Cycle outcome characteristics. ET: embryo transfer

<table>
<thead>
<tr>
<th>variable</th>
<th>Group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fertilization rate (%)</td>
<td>66.03±28.84</td>
<td>0.54</td>
</tr>
<tr>
<td>Implantation rate (%)</td>
<td>16.11±25.7</td>
<td>0.74</td>
</tr>
<tr>
<td>Chemical pregnancy/ET (%)</td>
<td>30</td>
<td>0.58</td>
</tr>
<tr>
<td>Clinical pregnancy/ET (%)</td>
<td>30</td>
<td>0.58</td>
</tr>
</tbody>
</table>

Phase: embryo transfer
can negatively affect endometrial reception, oocyte’s quality, and the embryo, but the negative effects were not observed in these patients\(^{(11)}\). In our study, as well, serum level of estradiol, the quality of oocyte, and embryo were not significantly different in the two groups.

In the protocol starting antagonist late, higher serum gonadotropin concentrations occurs in the beginning of the ovarian stimulation cycle\(^{(12)}\). As a result, a number of follicles grow before adding gonadotropins, due to high levels of FSH\(^{(13)}\). But early start of antagonists suppresses FSH and there is a greater need for gonadotropins, but as the internal hormones are suppressed, higher co-operation is required between follicles, and the quality of follicles would improve\(^{(14)}\). Some factors can affect embryo implantation\(^{(15-16)}\). In our study, as well, the consumption of gonadotropin was higher in the experimental group, but the quality of the oocytes did not differ with each other.

**Conclusion**

In the present study, there was no difference in the fertilization rate between the groups using GnRH antagonist in fixed or short-term protocol, but the group using short-term GnRH antagonist had shorter time of administration, higher dose of gonadotropin, and higher costs. So, the fixed protocol is superior to short-term protocol of antagonist, although more study is required.

**References**


