Comparing gonadotrophin-releasing hormone agonists or gonadotrophin-releasing hormone antagonists in poor responder in IVF

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ABSTRACT

Objective: The use of GnRH antagonist versus GnRH agonist in poor responder for patient undergoing ovarian hyperstimulation and in vitro-fertilization was compared.

Materials and Methods: In this study, 23 patients underwent ovarian hyperstimulation with recombinant FSH followed by the use of GnRH antagonist (Cetrorelix) 0.25mg during the late Follicular Phase. These patients were compared to 20 patients who underwent controlled ovarian hyperstimulation with recombinant FSH proceeded by GnRH agonist (short protocol).

Results: There was no significant difference between the two groups for mean age, duration of infertility or base line FSH, number of ampoules of gonadotrophin used, number of mature oocyte retrieved, estradiol concentration on the day of injection of human chronic gonadotrophin HCG, fertilization rate and number of embryo transferred. The clinical pregnancy rate in the antagonist group appear to be high but not significantly different (12% compared to 10%).

Conclusion: The addition of GnRH antagonist to ovarian stimulation protocol may be used for poor responder. Further randomized clinical studies with large sample size required to elicit significant differences.

Keywords: GnRH agonist, GnRH antagonist, IVF, poor responders

Gonadotrophin-releasing hormone agonists (GnRHa) and antagonists (GnRH-antag) have played an important role in reducing the incidence of premature LH surges by blocking pituitary gonadotrophin secretion. As a result, the rate of cancellation of assisted conception cycles has decreased, and pregnancy rates increased (1,2). However, each year many cycles are still cancelled due to poor ovarian response to ovarian hyperstimulation.

‘Poor responders’ are categorized as having a failure to respond to increasing doses of gonadotrophins, sometimes administered to very high levels, when used in conjunction with the analogue given. Traditionally it was considered to be related to advanced maternal age, but it also common today for some younger women, with normal day 3 follicle-stimulating hormone (FSH) values, to be difficult to stimulate. Overall, nine to twenty-four percent of infertile women undergoing assisted reproduction will have a poor response to ovarian stimulation (3).

In this select category of patients, various strategies have been investigated in an attempt to improve ovarian response, including the use of high doses of gonadotrophins (4-6), the change to a ‘flare-up’ protocol (7), and the use of growth hormone or growth hormone-releasing factor (8,9), or aspirin (10) as adjunct therapies. However, most of these interventions have met with only limited success and the optimum stimulation protocol for poor responders is still unclear.
Recently, concern about the use of GnRH agonists in ovarian stimulation of poor responders has arisen from the claim that GnRH agonists might have a direct deleterious effect through their receptors on the ovary. Since gonadotropin-releasing hormone agonists and antagonists work in using different mechanisms, we wished to determine the beneficial effect of using a GnRH antagonist compared with the ‘flare-up’ or ‘short’ GnRH agonist protocol in patients that were considered to be poor responders to the standard ‘long’ GnRH agonist protocol.

MATERIALS AND METHODS

A total of 43 poor-responder patients who underwent IVF-ET cycles were included. The primary outcome measure was the clinical pregnancy rate. The secondary outcome measures were gonadotropin needs for stimulation and ovarian response to stimulation. This study was approved by the local ethical committee, and before the treatment, informed consents were obtained from all patients.

Women were eligible for inclusion if they had a baseline FSH levels of <15 mIU/mL at previous IVF attempts. The definition of poor response was an unsuccessful stimulation (no ovarian response when ≥300 IU of FSH are administered for ≥15 days) or low number of oocytes retrieved (<5).

The sample size of (144 participants) provides 80% power and a two-sided significance level of 0.05 to test whether antagonist will be able to achieve adequate number of oocytes (more than 3). This sample size has adequate power to detect a difference of 5% between both protocols.

The poor responders were randomly assigned into two groups according to the analogue used. The first group consisted of 23 patients who underwent ovarian hyperstimulation with recombinant FSH followed by the use of GnRH antagonist (Cetrorelix) 0.25mg during the late Follicular Phase when follicle reach 15 mm. The second group consisted of 20 patients who underwent controlled ovarian hyper-stimulation with recombinant FSH proceeded by GnRH agonist (short protocol).

In each group, all patients initially received 450 IU of recombinant human FSH, and the dose was adjusted individually according to the response of the ovaries. After 6 days of treatment with 450 IU/d, if no response was observed, the dose was increased to 600 IU/d for 9 days. When response was obtained, the dose was maintained until hCG administration. When at least one of the follicles reached 16–18 mm in diameter, 10,000 U of hCG were administered IM.

Oocyte retrieval was performed 36 hours after the hCG injection, and the embryos were transferred on day 3 after oocyte collections. The cumulus-oocyte complex was assessed according to the oocyte maturation score criteria. The oocytes were then inseminated in vitro by conventional intracytoplasmic sperm injection, and the resultant embryos were scored. After the transfer, all patients received a Progesterone vaginal supplementation (micronized P, 400 mg/d) for two weeks. Clinical pregnancy was defined as a positive BHCG at four weeks, and a visible by ultrasound at 7 weeks gestation.

Statistical Analysis

Statistical analysis was performed according to the intention to treat principle. The results of the two groups were compared using the t-test or Mann-Whitney U test for parametric and nonparametric data, respectively. Qualitative variables were compared with the use of chi-square test with Yates correction or Fisher’s exact test, when necessary, and Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated to examine the odds of improving clinical outcomes. Statistical analysis was performed using Arcus Quickstat

RESULTS

There was no significant difference between the two groups with regards the maternal age, duration of infertility or baseline FSH (Table 1). In addition, there were no significant differences with regards the number of ampoules of gonadotrophin used, number of mature oocyte retrieved, estradiol concentration on the day of injection of human
Table 1. Patient and cycle characteristics with pregnancy outcome

<table>
<thead>
<tr>
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<th>Group I</th>
<th>Group II</th>
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<tbody>
<tr>
<td>No. of patients</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>Mean (±SD) age (years)</td>
<td>39.15 ± 1.2</td>
<td>38.3 ± 1.3</td>
</tr>
<tr>
<td>Mean (±SD) duration of infertility (years)</td>
<td>13.55 ± 1.6</td>
<td>11.9 ± 1.2</td>
</tr>
<tr>
<td>No. of cycles</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>Mean (±SD) FSH concentration on cycle day 3 (mIU/ml)</td>
<td>11.49 ± 1.3</td>
<td>11.42 ± 1.2</td>
</tr>
<tr>
<td>Mean (±SD) LH concentration on cycle day 3</td>
<td>6.32 ± 0.82</td>
<td>6.44 ± 0.76</td>
</tr>
<tr>
<td>No. of retrievals</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>No. of transfers</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Mean (±SD) no. of rFSH ampoules (100IU)</td>
<td>60.8 ± 4.01</td>
<td>60.6 ± 4.02</td>
</tr>
<tr>
<td>Mean (±SD) concentration of estradiol on the day of HCG administration</td>
<td>850.46 ± 92.36</td>
<td>806.3 ± 85.51</td>
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<tr>
<td>Mean (±SD) concentration of progesterone on the day of HCG administration</td>
<td>0.7 ± 0.5</td>
<td>0.6 ± 0.4</td>
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<tr>
<td>Mean (±SD) concentration of LH on the day of HCG administration</td>
<td>7.72 ± 0.67</td>
<td>6.66 ± 0.65</td>
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<tr>
<td>Mean (±SD) no. of mature oocyte retrieved</td>
<td>3.54 ± 0.52</td>
<td>3.25 ± 0.25</td>
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<tr>
<td>Rate of metaphase II/total oocytes (%)</td>
<td>75.9</td>
<td>77.5</td>
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<tr>
<td>Fertilization rates (%)</td>
<td>73.1</td>
<td>69.1</td>
</tr>
<tr>
<td>Mean (±SD) no. of embryos transferred</td>
<td>2.42 ± 0.32</td>
<td>2.29 ± 0.67</td>
</tr>
<tr>
<td>Clinical pregnancy/cycle (%)</td>
<td>13</td>
<td>10</td>
</tr>
</tbody>
</table>

chorionic gonadotrophin (HCG), fertilization rate and number of embryo transferred (Table 1). Even though there was a higher clinical pregnancy rate in the antagonist group, but this did reach statistical significance (13% compared to 10%).

**DISCUSSION**

Despite the marked advances made in ovulation stimulation in the past twenty-years, the ideal approach to poor ovarian responders is still highly debatable. The goal of a stimulation protocol in these patients would be able to achieve optimum oocyte retrieval, and at the same time, pregnancy rates.

Pituitary down-regulation with GnRH agonists is characterized by an initial release of FSH and LH during a short period (“flare-up”), followed by a subsequent reduction of gonadotrophin release. In contrast, the pharmacological mechanism by which GnRH antagonists suppress the release of gonadotrophins is completely different.

In general the agonists act on chronic administration through down-regulation of receptors and desensitization of the gonadotrophic cells, while the antagonists bind competitively to the receptors and thereby prevent the endogenous GnRH from exerting its stimulatory effects on the pituitary cells. The GnRH antagonists immediately and rapidly inhibit gonadotropin release by the anterior pituitary gland by competitive blockage of the GnRH receptor, preventing and interrupting luteinising hormone surges. The competitive blockade of the receptors leads to an immediate arrest of gonadotrophin secretion (11).

Recently, it has been postulated that there may be a direct effect of GnRH agonists on the ovary. This assumption is built on the fact that the ovary, like the pituitary, has receptors to LHRH (12). This concept also hypothesizes that that the human ovary may have its response to gonadotrophins suppressed to a variable degree by the direct effect of GnRH analogues in certain patients. These concerns about the use of GnRH agonists for poor responder patients, in which there is a diminished ovarian reserve and therefore the use of GnRH agonists might cause additional suppression, have encouraged clinicians to attempt other protocols, including the use of the flare-up agonist and the antagonist protocols.

Various studies have attempted to determine which of these protocols is more efficient and effective in patients with a history of being poor responders. Malmusi et al performed a randomized controlled trial (RCT) in fifty-five poor-responder patients in order to compare the efficacy of GnRH agonist flare-up and GnRH-antagonist treatment
protocols (13). They noticed that the number of ampoules and units of FSH administered were significantly less in the flare-up group, but the numbers of mature oocytes retrieved and of top-quality embryos transferred were significantly greater in the flare-up group. The fertilization rate (84% vs. 63%) was reported to be significantly higher in the flare-up than in the GnRH-antagonist group. However this did not affect the implantation and pregnancy rate were similar in the two groups.

Recently a systematic review comparing the efficacy of gonadotrophin antagonist (GnRH-ant) versus GnRH agonist (GnRHa) as coadjuvant therapy for ovarian stimulation in poor ovarian responders in IVF/intracytoplasmic sperm injection cycles was performed (14). The authors concluded that there was a significantly higher number of retrieved oocytes (P = 0.032; WMD: -0.51, 95% CI -0.99, -0.04) in the GnRHa protocols compared to the antagonist protocol.

In our current study, 23 poor responders underwent ovarian hyperstimulation with recombinant FSH followed by the use of GnRH antagonist (Cetrorelix) 0.25mg during the late Follicular Phase. These patients were compared to 20 patients who underwent controlled ovarian hyperstimulation with recombinant FSH proceeded by GnRH agonist (short protocol). The control group was justified to be of short protocol as most of trials in the medical literature compared antagonist to short protocol in normal responders. This is the value of such study: to compare them in poor responders.

There was no significant difference between the two groups for number of ampoules of gonadotrophin used, number of mature oocyte retrieved, estradiol concentration on the day of injection of human chronic gonadotrophin HCG, fertilization rate and number of embryo transferred. In addition, there was no significant difference with regards the clinical pregnancy rates (13% compared to 10%). The small number of participants can be explained by the usual percent of poor responders within a certain period of time in a single center like ours.

CONCLUSIONS

The use of GnRH agonist ‘flare-up’ or antagonist protocols may be used for poor responders. Further randomized clinical studies with large sample size are required to confirm no significant differences in the outcome measures.

REFERENCES


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