Evaluation of ovulation induction protocols for poor responders undergoing assisted reproduction techniques

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ABSTRACT

Objective: To compare 3 stimulation protocols in poor ovulation responders undergoing in-vitro fertilization (IVF).

Methods: The study was a randomized, prospective clinical trial from June 2003 to July 2004, in Royan Institute, Tehran, Iran. One hundred and fifty-four patients, who had poor responses to ovulation induction in at least one previous IVF attempt, were randomly divided into 3 groups. In the first group, human menopausal gonadotropin (HMG) was administered from day 3 of the cycle at a dose rate of 150IU/day. In the second group, gonadotropin-releasing hormone (GnRH) agonist was started at a dose rate of 800µg/day by nasal spray or 500µg/day subcutaneously in the mid-luteal phase, followed by a standard HMG dose after pituitary down regulation was confirmed. In the third group, clomiphene at a dose rate of 100 mg/day was given from day 3 and HMG from day 6. Our main outcomes were number of mature oocytes, cancellation rate, number of HMG ampoules used and incidence premature luteinizing hormone (LH) surge.

Results: There was a high incidence of premature LH surge in all groups except in the GnRH group (p=0.0001) and there were significant differences between groups in HMG requirements (p=0.004). There were no significant differences between groups in number of mature oocytes recovered and cancellation rate.

Conclusion: Results showed no advantage in the use of GnRH agonist compared to the older regimens of clomiphene plus HMG and HMG alone. The cancellation rate was similar for 3 protocols and HMG requirement was higher with the use of GnRH agonist. The treatment of poor responders in assisted reproductive technologies remains a challenge.


Obtaining multiple mature oocytes with acceptable quality for fertilization is the first aim in assisted reproduction techniques. However, some women respond poorly or not at all to controlled ovarian hyperstimulation (COH) and thus do not achieve this goal. It has been reported that poor response to stimulation occurs in approximately 10% of cycles. Since the evolution of assisted reproductive technologies (ART), the management of poor responders has been one of the most difficult challenges. Efforts to improve ovarian response in patients vary and include the application of almost all the currently known stimulation protocols. However, definite recommendations regarding the ideal approach for their treatment cannot yet be made. The first use of gonadotropin-releasing hormone (GnRH) agonists in ovulation induction the success rate in in-vitro fertilization (IVF) started to increase. The discovery of GnRH receptors in the human ovary, some investigators assumed that GnRH agonists may have a direct, deleterious effect on the ovary, which is
especially important for poor responders. In this study, 3 stimulation protocols were compared in poor responder IVF patients. The protocols were human menopausal gonadotropin (HMG) alone, GnRH plus HMG, and Clomiphene citrate (CC) plus HMG.

Methods. The study population consisted of 154 poor responder ART patients who had undergone at least one previous IVF attempt with a poor response. Responses were assessed as poor when baseline follicle-stimulating hormone concentration was >15mIU/ml, estradiol concentration on the day of human chorionic gonadotropin (HCG) injection was <500 pg/ml, or the number of preovulatory follicles >16mm in diameter was fewer than 3. Intracytoplasmic sperm injection had been used for all patients. The study was approved by the ethics committee of the institute. After each patient had given written informed consent, randomization was performed and 45 patients went into the HMG group, 52 patients into the GnRH agonist plus HMG group and 34 patients went into the CC plus HMG group. Human menopausal gonadotropin group stimulation by HMG started on the third day of menstruation at the baseline dose of 150 IU/day and was increased dependent upon the growth rate of the follicles as monitored by trans-vaginal ultrasonography. Ten thousand IU of HCG was administrated when trans-vaginal ultrasound showed an acceptable number and size of follicles. For patients CC plus HMG group, Clomiphene administration commenced on the third day at 100mg/day and was continued to the seventh day. From day 6 HMG was administrated at a baseline dose of 150 IU/day and was increased dependent upon the growth rate of the follicles. Ten thousand IU of HCG was administrated when trans-vaginal ultrasound showed an acceptable number and size of follicles. Cycle monitoring for every group consisted of ovarian ultrasonography with dose adjustments based on patient response. For every group at the beginning of induction serum FSH and LH levels were checked on the third menstrual day and LH level was checked every other day from day 8 to detect premature LH surges. Following of oocyte retrieval, luteal phase support was provided by administration of oil soluble progesterone at the dose rate of 100 mg/day intramuscular. The main outcomes evaluated and analyzed were incidence of premature LH surges, cycles canceled in the follicular phase and the number of mature oocytes retrieved.

Statistical analysis was performed by Statistical Package for Social Sciences program using analysis of variance, t-test and logistic regression. Data are expressed as means±SD and p<0.05 is considered statistically significant.

Results. There were no significant difference between groups in age (p=0.135) which averaged

<table>
<thead>
<tr>
<th>Observations</th>
<th>HMG alone</th>
<th>GnRH + HMG</th>
<th>CC + HMG</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancellation rate (%)</td>
<td>38.8</td>
<td>50.1</td>
<td>45.45</td>
<td>0.537</td>
</tr>
<tr>
<td>N of mature oocytes</td>
<td>1.52 ± 1.47</td>
<td>2.28 ± 2.20</td>
<td>1.53 ± 1.77</td>
<td>0.214</td>
</tr>
<tr>
<td>&lt;3 oocytes cases (%)</td>
<td>95.4</td>
<td>76</td>
<td>91.6</td>
<td>0.17</td>
</tr>
<tr>
<td>Day 3 FSH &gt; 12mIU/ml</td>
<td>33.3</td>
<td>43.1</td>
<td>52.3</td>
<td>0.36</td>
</tr>
<tr>
<td>N of HMG ampoules</td>
<td>26.61 ± 11.2</td>
<td>39.23 ± 14.9</td>
<td>17.24 ± 8.48</td>
<td>0.0001</td>
</tr>
<tr>
<td>Premature LH surge(%)</td>
<td>30.55</td>
<td>0</td>
<td>28</td>
<td>0.004</td>
</tr>
</tbody>
</table>

FSH - follicle-stimulating hormone, HMG - human menopausal gonadotropin, GnRH - gonadotropin-releasing hormone, CC - Clomiphene Citrate, LH - luteinizing hormone
requirement increases when GnRH protocols are used. Overall, the observations reported here support a conclusion that use of GnRHa in poor responders imposes the stress of injections and additional cost on patients without improving the outcome.

In conclusion, there is no significant difference between HMG alone, GnRH-a plus HMG and clomiphene citrate plus HMG protocols in controlled ovarian hyperstimulation for poor responders. As the gonadotropin requirement in the GnRH-a agonist regimen is higher, this regimen cannot be recommended for poor responders.

References


