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.

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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.[1] 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.[2-4] The first use of gonadotropin-releasing hormone (GnRH) agonists in ovulation induction[5] 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

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especially important for poor responders.[6] 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. In GnRH + HMG group, GnRH-a was used to suppress hypothalamus-pituitary axis and HMG was used for ovarian stimulation. For complete suppression, GnRH agonist was used at the dose of 800µg/day by nasal spray or 500µg/day subcutaneously in the mid-luteal phase. Stimulation with HMG was initiated after confirmation of complete suppression (E2 <50pg/ml, LH <5mIU/ml and progesterone <2pg/ml) by administration of 3 ampoules (225IU) per day. The daily dose 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.

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 1 - The effect of 3 ovarian stimulation protocols on response in poor responder patients.

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

FSH - follicle-stimulating hormone, HMG -human menopausal gonadotropin, GnRH - gonadotropin-releasing hormone, CC - Clomiphene Citrate, LH - luteinizing hormone

36.74±5.60 and day 3 serum FSH (p=0.317) which averaged 11.60±5.79. Results for the 3 treatment protocols are shown in **Table 1**. There were no differences between the three treatment protocols in number of mature oocytes recovered (p=0.216), incidence of canceled cycles (p=0.537), number of patients with fewer than 3 recovered oocytes (p=0.17) or the number of patients with FSH higher than 12mIU/ml (p=0.36). Cycle cancellations were mainly due to lack of ovarian response to the gonadotropins and premature LH surge. There were highly significant differences between treatment protocols (p=0.0001) in the number of HMG ampoules used and in the incidence of premature LH surge. The patients on the GnRH +HMG protocol required more ampoules of HMG than the other patients and none had a premature LH surge. By using logistic regression test it became clear that there was a significant relationship between premature LH surge and GnRH+HMG group (p=0.0001).

Discussion. Stimulation protocols for poor responders should have an acceptable rate of cancellation, yield an acceptable number of healthy mature oocytes at a reasonable cost and duration of therapy, and result in maximal pregnancy and delivery rates. Although there are reports of a significantly higher number of retrieved oocytes, fertilization and pregnancy rates and lower number of cycle cancellations[7-11] with the use of GnRH-a, other studies did not record these advantages.[12] There are also reports that support the use of special regimens such as microdose,[13-15] flare-up,[16-18] and stop dose,[19] but the best regimen for using GnRH agonist still is not clear.[3] We suppressed the hypothalamus-pituitary axis with almost high dose GnRH that has been shown that by procedure, suppression begins in 6 days and total effect can be seen after 3 weeks.[20] In this study, there were no significant differences in responses to the 3 protocols tested. Gonadotropin-releasing hormone-a protocol was not superior to the older protocols using clomiphene citrate and HMG alone.

It has been reported that premature LH surges are associated with an adverse cycle outcome[21-23] and it is clear that LH surge is associated with premature ovulation and/or follicular luteinization resulting in treatment cancellation in approximately 30% of cycles. It has been reported previously that the GnRH regimen prevents premature LH surge.[7,13-15] The results in this study confirmed these observations, but the cancellation rate in the GnRH-a group was not significantly different from that in the other treatment protocol groups. It was suggested that the reduction in incidence of LH surge with the GnRH-a protocol is not of practical significance. The result reported in this study confirms previous reports,[24,25] that gonadotropin 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.

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