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A comparative study of GnRH antagonist and GnRH agonist in PCO patients undergoing IVF/ICSI cycles

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Abstract

Background: Polycystic ovarian syndrome (PCOS) patients are prone to premature LH surge and ovarian hyperstimulation syndrome (OHSS). Long GnRH analogue protocol and GnRH antagonist protocol are two methods utilized for induction ovulation in patients undergoing IVF/ICSI.

Objective: The aim of this study was to compare the effects of GnRH agonists and antagonists in PCOS patients.

Materials and Methods: A total of 60 PCOS patients under 35 years old were enrolled in this study. The patients have no history of thyroid disorder and hyperprolactinemia. All patients received OCP (LD) before starting the treatment. Then patients randomly divided into two groups. The agonist group underwent standard long GnRH analogue protocol. In antagonist group, HMG (150 IU/day) was started from third day of cycle. Then GnRH antagonist (0.25mg) was administered from 6th day after HMG initiation (LH≤5 IU/ml) to the day of HCG injection. Follicular development monitored by vaginal ultra sonography and serum estradiol measurement.

Results: There were no significant differences in age, duration of infertility, BMI, number of HMG ampules, number of follicles≥18mm, serum estradiol level on 6th day of HMG initiation and HCG injection time, fertilization and pregnancy rate between two groups. However there were significant differences regarding duration of treatment, duration of HMG usage, LH level at the initiation of HMG, OHSS rate and number of Metaphase II oocytes between two groups ($p<0.05$).

Conclusion: Usage of the GnRH antagonist may have more advantages such as the shorter duration of treatment and less gonadotrophin requirement. Furthermore, the incidence of OHSS can be reduced in GnRH antagonist comparing to agonist. For decreasing the risk of OHSS and abortion rate, we recommend long term use of OCP before starting the treatment.

Key words: *PCOS , GnRH agonist, GnRH antagonist , OHSS, IVF, ICSI.*

Introduction

Regarding advanced technological methods in ART, ovarian stimulation protocols developed rapidly. The objective of controlled ovarian hyperstimulation (COH) is to achieve enough number of mature oocytes which are able to produce well qualified embryos to transfer or freeze (1, 2). The main cause of failure in primary classic ART protocols was premature LH surge in follicular phase which ended up in immature oocyte that was unable to be fertilized or in case of fertilization was prone to abortion (3, 4), furthermore premature LH surge causes premature luteinization of granulosa cells and progesterone production which causes adverse effects on endometrium and implantation rate (2, 4). For prevention of premature LH surge, long time and continuously usage of gonadotrophin releasing

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hormone (GnRH) agonists which leads to pituitary suppression, is recommended (1, 2). GnRH antagonists investigation coincides with GnRH agonists. First generation of antagonists is not used anymore because of histamine release and allergic reaction. But in new generation of GnRH antagonists (Ganirelix acetate, Organon, Netherlands) this effect is not seen (5). GnRH antagonists prevent premature LH surge with a different mechanism in comparison of agonists (5). The GnRH antagonist binds competitively to the GnRH receptors and prevents production of endogenous gonadotrophin without primary flare-up phase (1, 2). Also the side effects due to estrogen reduction such as hot flush or headache are not seen in antagonist administration (5). In order to find the effective dose of antagonist capable of suppressing premature LH surge several studies have been performed .The dosage of 250µg daily has been suggested to suppress premature LH surge and achieve 40% pregnancy rate (5). In addition, several studies have been done to compare GnRH agonist and antagonist in ART cycles (1, 2, 6, 7). Most of these studies evaluate the effects of this protocol in non PCOS patients (5, 6) whereas our objective was to compare these two protocols in PCOS patients. Similarly, Hwang *et al.* (2004) compared these two protocols in PCOS patients (8). In standard long GnRH agonist protocol, flare up stage and then pituitary suppression have been achieved. Then ovarian hyperstimulation has been conducted after LH suppression by gonadotrophins. But in GnRH antagonist protocol, without change in hormonal status and primary pituitary suppression, ovulation induction has been conducted and then antagonist has been utilized for LH suppression. Therefore there is a possibility of adverse effect of high LH in primary stage of ovulation induction in PCOS patients underwent GnRH antagonist protocol. Considering this difference in LH level at the beginning of stimulation by gonadotrophins in PCO patients, we aimed this research to compare GnRH agonist and antagonist in PCOS patients who were referred to Royan institute between 2001 and 2002.

Materials and Methods

This study was conducted as a prospective and RCT (randomized clinical trial) study in Royan institute on 60 PCOS patients with oligomenorrhea, hyperandrogenism, LH/FSH>2.5 and ultrasonographic features of PCOS (Adams criteria) (9).

In all patients thyroid tests and prolactin were normal and written informed consent was obtained from each participant .This study was approved by the Royan research center ethics committee. All patients received OCP-LD from the 5th day of their previous menstrual cycle. Then they were randomly divided into two groups. Agonist group was treated from the 21st day of cycle with the GnRH agonist (Suprefact, Hoechst, Germany) 500µg/day, S.C. When pituitary suppression was achieved (on second day of menstrual cycle FSH≤5IU/ml, LH≤5IU/ml, progesterone≤1ng/ml, and Estradiol≤50pg/ml), Buserline was reduced to 200µg/day and gonadotrophin (Pregonal, Organon, Netherland) 150IU/day was started. The dose of gonadotropin was changed according to follicule growth. Follicular development was monitored by transvaginal sonography. When more than 3 follicles≥18mm were seen, HCG (Pregnyle, Organon, Germany) 10000 IU were injected to induce final oocyte maturation and 36-40 hour later, ovum pick up was done. After 2-3 days if fertilization occurred, embryo transfer was performed. If more than 20 follicles were visited in each ovary or E_2>3000pg/ml, the patient was considered as prone to ovarian hyperstimulation syndrome (OHSS) and necessary management has been taken.

In antagonist group, on second day of menstrual cycle, FSH, LH and estradiol were measured. From the third day of cycle, gonadotrophins (Pregonal, Organon, Netherland) 150 IU IM was started. When there were follicles>12mm (around 6th day of ovulation induction or 8th of cycle) after FSH, LH, E_2 tests, the GnRH antagonist (Cetrotide, Orgalutron, Netherland) 0.25mg/day S.C was initiated and continued up to HCG injection. Daily sonographic monitoring was performed to evaluate follicular development. When at least 3 follicles≥18mm were visited, HCG 10000 IU were injected for final oocyte maturation and 36-40 hours later, ovum pick up was done. In this group, if the patient was prone to OHSS, GnRH agonist 500µg S.C was prescribed instead of HCG. 10 to 12 days after embryonic transfer, βHCG was tested. Duration of treatment was defined as days between initiation of GnRH agonist and injection of HCG in agonist group while in antagonist group, duration of HMG usage was considered as it.

Data were analyzed using the commercially available software package SPSS version 11. Student's t-test and χ^2 were used for analysis and results were informed with Mean±SD. $p<0.05$ was considered as significant level.

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Table I. Demographic characteristics and pretreatment hormonal profiles of patients

	GnRH agonist n=24	GnRH antagonist n=23	p value
Age (yr)	28.3±4	29.2±4.6	0.449
Duration of infertility (yr)	9.2±4.1	8.8±4.7	0.72
Body mass index (kg/m^2)	30.45±6.09	27.97±6.71	0.213
FSH on day 2 (mIU/ml)	5.24±2.42	5.53±2.77	0.7
LH on day 2 (mIU/ml)	7.72±4.47	8.31±4.32	0.58
Estradiol on day 2 (pg/ml)	57.62±43.48	89.41±64.74	0.69

Table II: Results in the two groups

	GnRH agonist n=24	GnRH antagonist n=23	p value
Duration of treatment (day)	25.8±4	10.1±2.6	0.000
Number of HMG ampoules	30±11.3	24.5±9.6	0.057
Duration of HMG stimulation (day)	12.8±3.2	10.1±2.6	0.002
Number of follicules≥18mm	8.3±6.1	9±7.8	0.761
Serum LH level at the onset of hMG (mIU/ml)	2.5±2.5	6.7±4.7	0.000
Serum LH level on the day HCG injection (mIU/ml)	3±6.1	6.3±11.3	0.214
Number of patients at risk of developing OHSS (E_2>3000pg/ml)	0(0%)	7(30.4%)	0.004
Level of E_2 on 6th day of HMG injection (onset of antagonist) (pg/ml)	182.9±192	257.8±276	0.284
Serum level of E_2 on the day of hCG injection (pg/ml)	961.1±756.9	1624.6±1618.6	0.085
Number of retrieved oocytes	6.17±4.44	10.96±8.54	0.022
Number of Metaphase II oocytes	1.8±3.3	4.8±5.6	0.035
Number of embryos	4±3.49	5.47±4.17	0.21
Rate of fertilization (%)	95.5%	100%	1
Rate of pregnancy per embryo transfer	27.3%	40.9%	0.34

Results

From all the 60 patients in both groups, 5 cases from agonist group and 3 patients in antagonist group were excluded from the study because of discontinuation of the cycle. In addition, one patient from agonist group and 3 patients in antagonist group were excluded because of failure in follicular development. Demographic characteristics and pretreatment hormonal profiles of two groups are shown in table I. There were no statistically significant differences in mean age, mean duration of infertility, BMI, FSH, LH, and E2 between the two groups.

Results in the two groups are shown in table II. There were statistically significant differences with respect to duration of treatment, duration of using HMG, Serum LH level at the onset of HMG, risk of OHSS, number of retrieved oocytes and number of metaphase II oocytes between the two groups.

No patients in agonist group and 7 cases in antagonist group were prone to OHSS. In these 7 cases for prevention of OHSS, Buserelin (500µg-S.C) were injected instead of HCG. Mean number of retrieved oocytes in these 7 patients was 20 and in 2 cases, pregnancy occurred .In none of these patients, developed OHSS was seen.In agonist group, 1 case and in antagonist group, 4 cases had abortion

Discussion

The objective of present study was to compare advantages of using GnRH antagonist to GnRH agonist in PCOS patients undergoing IVF/ICSI cycles. Previous studies mostly have been shown the differences of these drugs in non PCOS patients (6, 10-13).We found significant lower duration of treatment in antagonist group which

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was similar to the result of two previous studies in non PCOS patients (5, 7).

Also in our study, the mean of used HMG ampules was lower in antagonist group comparing to the agonist group but this difference was not statistically significant although it was very near significant level (p=0.057) . This result was similar to the previous studies done on non PCOS patients (6, 11) whereas some researchers have shown significant reduction in number of used HMG in non PCOS patients (12, 13) and PCOs patients who underwent treatment with GnRH antagonist (8).

In the present study, serum LH level at the onset of HMG in the antagonist group showed significant elevation comparing to the agonist group although in both groups, it was suppressed in comparison to baseline. This result was similar to that of Hwang *et al.* study (2004) while in their study, the elevation in LH level at the onset of HMG in antagonist group was not statistically significant (8). It seems that LH elevation in antagonist group in comparison to agonist group in our study is secondary to higher LH level in antagonist group at baseline (Table I) and lower LH in the agonist group which is due to effect of GnRH agonist in suppression of LH. In our study, the suppress on LH in antagonist group was not as much as the rate in Hwang study .This can be due to lower duration of OCP administration (one cycle in our study in comparison to three cycles in Hwang study).

In our study, 7 cases of patients in the antagonist group were at risk of OHSS, whereas no case was seen in the agonist group. However this difference was significant, but incidence of developed OHSS was similar in two groups because in the antagonist group, one dose of GnRH agonist was administered instead of hCG for prevention of OHSS.

According to serum E_2 level on day of hCG injection, there was no statistically significant difference between the two groups in our study while in three other studies on non PCOS patients (6, 12, 14) and Hwang's study on PCOS patients (8), they found significant difference in serum E_2 level on day of hCG injection which has inconsistency with our study.

In present study, number of retrieved and Metaphase II oocytes in the antagonist group were significantly higher than the agonist group while Minaretzis *et al.* (1995) found no difference in the number of retrieved oocyte but higher portion of mature oocyte in antagonist group in non PCOS patients (11) and Hwang *et al.* (2004) found no significant difference in retrieved oocyte in PCOS patients (8).

Our data showed that number of fertilized oocytes and pregnancy rate were similar in both groups which was similar to the previous researches in non PCOS (12, 13) and PCOS patients (8).

In our study, abortion rate in the antagonist group was higher than agonist group (4 cases comparing to 1 case, respectively) which was statistically significant. This increase in abortion rate can be due to the higher LH level in PCOS patients in antagonist group which according to Hwang *et al.* opinion, higher LH level can cause higher abortion (8).

Conclusion

These data suggest that using GnRH antagonist in PCOS patients can shorten the duration of treatment. Furthermore, less amount of HMG, decrease in occurrence of OHSS and more number of good quality retrieved oocytes make this kind of treatment financially beneficial. Therefore, the usage of GnRH antagonist prevents waste of time and money for PCOS patients. Finally, prescribing OCP before starting the treatment is recommended to decrease the risk of developing OHSS and abortion rate.

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