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Evaluation of GnRH Antagonists in Ovarian Stimulation Protocols for IVF Cycles Compared to GnRH Agonists

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S u m m a r y. In the present study, 82 treatment cycles (40 patients) of ovulation induction for IVF/ICSI were analyzed. The pituitary-gonadal axis suppression treatment GnRH antagonists were used in 41 of these cycles and GnRH agonists in the other 41 cycles. The data showed that GnRH antagonists are associated with shorter duration of treatment (9.84±1.8d vs 12.38±2.1d; p<0.05), lower total amount of FSH needed (2240±972.3 iu vs 2830±1075.8 iu; p<0.05), significantly lower level of serum E_2 (1695.6 pg/ml vs 2382.5 pg/ml; p<0.05) and reduced thickness of the endometrium (9.1±1.8 mm vs 10.4±1.2mm; p<0.05). Regarding the ovarian response to the two regimes, the use of antagonists was found to be followed by reduced number of follicles developed (12.1±3.1 vs 13.45±2.8; p=NS) and oocytes retrieved (10.9±1.8 vs 11.8±2.9; p=NS), though the differences were not statistically significant. Finally, the fertilization rate in both the regimes did not differ (68.7%, vs 70.9%; p=NS).

INTRODUCTION

The prevention of premature LH surges during ovarian stimulation for assisted reproduction techniques (ART) is essential to avoid premature luteinization, which disrupts oocyte maturation and leads to treatment cycle cancellation. The main care to prevent premature LH surges has been the administration of gonadotrophin releasing hormone (GnRH) agonists together with gonadotrophins (1,2).

Although GnRH agonists have been proved to be safe and effective, they are associated with certain disadvantages including initial release of gonadotrophins before suppression (flare-ups), long duration of pre-treatment (2-3 weeks), higher therapeutic dose of FSH required and follicle cyst formation.

Recently, the 3rd generation GnRH antagonists were introduced to clinical practice. They proved to be safe and effective and presented with the advantage of rapid, profound and reversible suppression of the pituitary-gonadal axis (3).

These compounds are far more complex than the agonists, with modifications in the molecular structure not only at positions 6 and 10, but also at positions 1, 2, 3 and 8. In comparison to GnRH agonists, the pharmacological mechanism by which the antagonists suppress the release of gonadotropins is completely different. The chronic administration of agonists, down-regulates of receptors and desensitization of the gonadotrophic cells, the antagonists bind competitively to the receptors, thereby preventing the endogenous GnRH from exerting its stimulatory effect on the pituitary cells avoiding the flare-up effect (2,4).

The available clinical studies have shown that the administration of antagonists in ovarian stimulation treatment cycles seems to be at least equally effective to the agonists (5-8).

In the current study, our aim was to evaluate the follicular and oocyte development in a population of patients treated with GnRH agonists and antagonists for *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI).

MATERIALS AND METHODS

We retrospectively analyzed 40 patients with average age of 30.55±2.9 years (patients aged >37 years were excluded) that during the years

2002 and 2003 underwent ovarian stimulation treatment using both GnRH antagonists and agonists combined with FSH for IVF/ICSI.

In total we studied 82 treatment cycles of which 41 with the use of GnRH antagonists (Group I) and 41 with the use of GnRH agonists (Group II). Between the two groups we compared the total dose of FSH needed for the ovarian stimulation, the duration of the treatment, serum estradiol levels on the day of hCG administration, the thickness of the endometrium on that day, the number of follicles formed during the cycle, the number of oocytes collected and their fertilization were compared.

RESULTS

We found that the total amount of gonadotrophins was significantly lower in the Group I compared to Group II (2240±972.3 iu vs 2830±1075.8 iu; $p<0.05$) and the duration of the treatment was also shorter (9.84±1.8d vs 12.38±2.1d; $p<0.05$).

Serum estradiol levels on the day of hCG administration were found to be significantly lower in Group I than in Group II (1695.6±1120.3 pg/ml vs 2382.5±940.1 pg/ml; $p<0.05$) as was also the thickness of the endometrium (9.1±1.8 mm vs 10.4±1.2; $p<0.05$).

The number of follicles developed was smaller in the antagonist group (I: 12.1±3.1 vs II: 13.45±2.8; p=NS) as well as the number of oocytes retrieved (I: 10.9±1.8 vs II: 11.8±2.4; p=NS), though the above differences were not statistically significant. Finally, the fertilization rate after ICSI did not differ between the two groups (I: 68.7% vs II: 70.9%; p=NS).

Table

Effects of GnRH antagonists (Group I, 41 cycles) and GnRHAgonists (Group II, 41 cycles) in the same population of patients (40 patients) in ovulation induction protocols with FSH for IVF/ICSI. *p<0.05

	Group I (Antagonists)	*Group II (Agonists)*
Treatment duration (days)	9.84±1.8*	12.38±2.1*
Total FSH dose (IU)	2240±972.3*	2830±1075.8*
Estradiol (pg/ml)	1695.6±1120.3*	2382.5±940.1*
Endometrial thickness (mm)	9.1±1.8	10.4±1.2
Follicles (N)	12.1±3.1	13.45±2.8
Oocytes (N)	10.9±1.8	11.8±2.4
Fertilization rate (%)	68.7	70.9

CONCLUSIONS

Our study evaluated the ovarian response of the same population of women treated with GnRH antagonists and agonists with FSH for IVF/ICSI. Our results are in accordance with published prospective studies (5,8), comparing the agonist with the antagonists in different women.

Thus our data confirm that the use of GnRH antagonists is related with shorter period of treatment followed by lower total amount of FSH required. This finding is very important as it indicates that treatment with GnRH antagonists has a significantly lower cost taking into considerations also that there is no pretreatment period as with the GnRH-agonist regimes.

Regarding the ovarian response, i.e. the number of follicles developed and oocytes retrieved, in most of the studies, appears to be smaller in women using antagonists compared with those using agonists. Our results agree with these findings when comparing the two regimes in the same population of patients, though the differences are not statistically significant. This also comes to accordance with the lower serum E_2 found in the antagonists group and possibly correlates with the significant lower incidence of ovarian hyperstimulation syndrome that was noted in the antagonist regimes, in other studies. Finally the fertilization rate in both groups after ICSI was found to be similar in both groups as in most other studies (7-9).

In conclusion these new compounds present with certain advantages such as more adequate suppression of the pituitary-gonadal axis, shorter and lower cost stimulation cycles with comparable to the GnRH agonists ovarian response.

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