Original Articles

Reproductive Biology Section

GnRH agonist versus GnRH antagonist in ovarian stimulation: Is the emperor naked?

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Summary

Objective: The aim of the study was to evaluate the influence of type of GnRH-analog used during controlled ovarian hyperstimulation (COH) on the outcome of in vitro fertilization (IVF) cycles.

Patients and Methods: All consecutive women aged ≤ 35 years admitted to our IVF unit from January 2001 to December 2004 were enrolled in the study. Only patients undergoing up to their third IVF cycle attempt were included. Ovarian stimulation characteristics, number of oocytes retrieved, number of embryos transferred, and clinical pregnancy rate were compared between women given GnRH-agonist or GnRH-antagonist during COH.

Results: Four hundred and eighty-seven consecutive IVF cycles were evaluated, 226 in the agonist group and 261 in the antagonist group. A clinical pregnancy was achieved in 93 patients in the agonist group (pregnancy rate 41.2% per cycle) and 66 patients in the antagonist grup (pregnancy rate 25.3%); this difference was statistically significant ($p < 0.01$). The agonist group also used significantly more gonadotropin ampoules, required longer stimulation, and had higher estradiol levels on the day of human chorionic gonadotropin administration.

Conclusion: The midluteal long GhRH-agonist suppressive protocol should be the protocol of choice in young patients in their first three IVF cycle attempts.

Key words: GnRH agonist; GnRH antagonist; IVF outcome; Pregnancy.

Introduction

Controlled ovarian hyperstimulation (COH) is apparently a key factor in the success of in vitro fertilization-embryo transfer (IVF-ET). The ability of GhRH-analog co-treatment to prevent a premature increase in luteinizing hormone during COH has made it the standard of care worldwide. More recently, researchers have noted numerous advantages to the use of GnRH-antagonists and have added them to the COH armamentarium. These include lack of hypoestrogenism, short treatment duration, lower gonadotropin requirement, and consequently, a probable reduction in the incidence of severe ovarian hyperstimulation syndrome (OHSS). However, meta-analyses of studies comparing GnRH agonist long protocols with GnRH antagonist protocols have yielded conflicting results for pregnancy rate [1-3], with a tendency toward a better outcome for GnRH agonists [1, 2]. This has prompted an ongoing debate on the place of GnRH antagonists in infertility treatment and a search for factors to explain their low utilization by physicians [4, 5].

The aim of the present study was to evaluate the influence of GnRH-agonists versus GnRH-antagonists on IVF cycle outcome in a single tertiary center. These findings should help to clarify the proper approach to GnRH analogs in COH and to aid fertility specialists and their patients in the decision-making process.

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Patients and Methods

We reviewed the computerized files of all consecutive women aged ≤ 35 years admitted to our IVF unit from January 2001 through December 2004 who reached the ovum pick-up stage. To eliminate the deleterious effect of repeated failure, we included only women undergoing up to their third IVF cycle attempt. Other exclusion criteria were use of donor oocytes or transfer of frozen-thawed embryos, and use of other than a midluteal long GnRH-agonist (Triptorelin, Ferring, Lapidot, Netanya, Israel; daily s.c. 0.1 mg) suppressive protocol (agonist group) or the flexible multidose GnRH-antagonist (Cetrorelix, Serono Laboratories, Aubonne, Switzerland; daily s.c. 0.25 mg) protocol (antagonist group). In both protocols, gonadotropins were administered in variable doses, depending on patient age and/or ovarian responsiveness in previous cycles, and further adjusted according to serum estradiol levels and vaginal ultrasound measurements of follicular diameter, obtained every two or three days. Human chorionic gonadotropin (hCG) was administered for final maturation of oocytes when at least three mature (> 17 mm) follicles were identified by transvaginal scan, combined with appropriate peripheral serum estradiol levels. Routine IVF/intracytoplasmic sperm injection (ICSI) was then performed as appropriate. Transvaginal ET was performed 48-72 hours after oocyte retrieval. For luteal phase support, patients received either 50 mg progesterone IM (Gestone, Ferring Lapidot) daily or 600 mg micronized progesterone soft gel vaginal capsules (Utrogestan, Besins, Iscovesco, C.T.S., Petach Tikva, Israel) in three divided doses daily. Clinical pregnancy was defined as visualization of a gestational sac and fetal cardiac activity on transvaginal ultrasound. Data on patient age, cause of infertility and infertility-treatment-related variables

were collected from the files. Ovarian stimulation characteristics, number of oocytes retrieved, and number of embryos transferred per cycle were recorded. Outcome was defined as the proportion of cycles with oocyte retrieval that led to clinical pregnancy.

Results are presented as means ± standard deviations. Differences in variables between the two COH-protocol groups were statistically analysed with the Student's t-test and chi-square test, as appropriate. A p value of less than 0.05 was considered significant.

Results

Four hundred and eighty-seven consecutive IVF cycles were evaluated, 226 in the agonist group and 261 in the antagonist group. Causes of infertility in the agonist and antagonist groups, respectively, were as follows: unexplained - 15.5% and 9.6%, anovulatory - 2.7% and 3.2%; male factor - 62.7% and 66.9%; mechanical - 16.4% and 18.5%; none of these differences was statistically significant. The clinical characteristics of the IVF cycles in the two study groups are shown in Table 1.

A clinical pregnancy was achieved in 93 patients in the agonist group (pregnancy rate, 41.2% per cycle) and 66 patients in the antagonist group (pregnancy rate, 25.3% per cycle); this difference was statistically significant ($p < 0.01$). As expected, the agonist group used significantly more gonadotropin ampoules (36.3 ± 15.8 vs 32 ± 14.3, $p < 0.01$), required longer stimulation (10.8 ± 2 vs 9.8 ± 1.8 days, $p < 0.01$), and had higher estradiol levels on the day of hCG administration (2,120 ± 1,058 vs 1,865 ± 1,060 pg/ml, $p < 0.01$). There were no differences between the groups in patient age, gravidity, peak progesterone levels, number of oocytes retrieved, fertilization rate, or number of embryos transferred (Table 1).

Table 1. — *Comparison between IVF cycles in the GnRH agonist and GnRH antagonist groups.*

	Agonist	Antagonist	p values
Number of cycles	226	261	
Patient age	29.3 ± 3.5	29.4 ± 3.2	ns
Gravidity	1 ± 1.25	0.9 ± 1.1	ns
Number of gonadotropin ampoules used	36.3 ± 15.8	32 ± 14.3	p < 0.01
Length of stimulation (days)	10.8 ± 2	9.8 ± 1.8	p < 0.01
Peak E2 levels on day of hCG administration (pg/ml)	2,120 ± 1,058	1,865 ± 1,060	p < 0.01
Progesterone levels on day of hCG administration (ng/ml)	0.8 ± 0.45	0.9 ± 1	ns
Number of oocytes retrieved	12.8 ± 6.9	12.9 ± 7.8	ns
Fertilization rate (%)	56 ± 21	56 ± 24	ns
Number of embryos transferred	2.1 ± 0.6	2.09 ± 0.5	ns
Pregnancy rate	41.2%	25.3%	p < 0.01

Discussion

In the present study of young patients (< 35 years old) in one of their first three IVF attempts, we clearly observed a significantly higher clinical pregnancy rate in those given the midluteal long GnRH-agonist suppressive protocol than in those given the flexible multidose GnRH-antagonist protocol. This was true despite the comparable number of retrieved oocytes in the two groups and the conclusive, objective evidence of longer treatment duration, more gonadotropin ampoules used, and higher peak estradiol levels in the agonist group. Our results are in accordance with the meta-analysis of five registration trials (total 1,860 participants) reported in 2002 [2], wherein there was a statistically significant reduction in clinical pregnancy rate (odds ratio 0.79, 95% confidence interval 0.63-0.99) with GnRH antagonist compared to GnRH agonist co-treatment. The latter study also reported a significantly lower duration of ovarian stimulation and use of significantly fewer gonadotropin ampoules in the antagonist group.

There are two possible explanations for these differences between the two groups:

– A deleterious effect of GnRH-antagonists. GnRH antagonists have a known inhibitory effect on the cell cycle that decreases the synthesis of growth factors. Therefore, if mitosis is essential for folliculogenesis, blastomere formation, and endometrium development, the interaction between the GnRH antagonist and the GnRH receptor may compromise the mitotic program of these cells [6].

– A beneficial effect of GnRH-agonists [7]. Studies in monkeys have shown that GnRH-agonists are secreted by the early embryo, and that a lack of GnRH production is associated with impaired implantation [8]. Furthermore, in a randomized study, Fujii *et al.* [9] noted that GnRH-agonist administration throughout the luteal phase and early pregnancy positively influenced implantation and pregnancy outcome.

However, other studies [10-14], including a recent meta-analysis [3], failed to confirm this difference in outcome between the treatment options. These conflicting results, together with the reported higher prevalence of COH using GnRH agonists [15, 16] have led to an ongoing debate in the medical community. Several authors have reported a low utilization of GnRH antagonists and their consideration only as a second treatment option in COH [4, 5] and have encouraged investigations into the factor underlying their poor clinical acceptance by physicians.

Griesinger *et al.* [4] found that the majority of COH procedures in Germany are still performed using the long GnRH-agonist protocols. They speculated that this practice was a consequence of the general utilization of GnRH antagonists as a treatment option in cycles with an unfavorable prognosis *a priori,* that is, repeated failures and elderly low responders, and that this could explain physician reluctance to use them as the standard. Yet, althugh cycles/patients with an unfavorable prognosis were excluded from the present study, we still observed a significantly lower pregnancy rate with GnRH antagonists.

In conclusion, in our series of young patients undergoing one of their first three COH attempts, the midluteal long GnRH-agonist suppressive protocol was associated with a significantly higher clinical pregnancy rate than

the flexible multidose GnRH-antagonist protocol. We therefore recommend that the midluteal long GnRH-agonist suppressive protocol be offered as the protocol of choice in this patient group, with the exception of those at high risk of severe OHSS, in whom a combined GnRH-antagonist/GnRH-agonist is preferred [17], and low-responders/repeated failures [18], who would benefit from a large armamentarium of COH protocols.

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