

The Role of GnRH-Analogues used in Elderly (>38 yrs) Patients Undergoing Controlled Ovarian Hyperstimulation for IVF

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Abstract

Objectives: To examine the influence of type of GnRH-analogue used, on reproductive outcome of elderly patients (≥ 38 years old) undergoing controlled ovarian hyperstimulation (COH) for IVF.

Patients and Methods: We studied 2436 consecutive cycles, 1369 in the agonist group and 1067 in the antagonist group. Infertility-treatment-related variables and pregnancy rates were compared between young (<38 years) and elderly patients and between those undergoing the GnRH-agonist or antagonist COH protocols.

Results: While a significantly higher pregnancy rate was observed in young patients undergoing the GnRH-agonist as compared to the GnRH-antagonist COH protocols (30.1% vs 21.1%, respectively; $p < 0.001$), no difference was demonstrated in elderly patients.

Conclusions: The long GnRH agonist suppressive protocol has a clear advantage over the GnRH antagonist in young patients with favorable outcome- *a priori*, but not in elderly patient undergoing COH for IVF.

Keywords: GnRH antagonist; GnRH-antagonist; IVF outcome; Pregnancy; Elderly

Introduction

Controlled Ovarian Hyperstimulation (COH) is considered a key factor in the success of *In Vitro* Fertilization-Embryo Transfer (IVF-ET) because it enables the recruitment of multiple healthy fertilizable oocytes [1]. Usually, COH includes the co-administration of gonadotropins and GnRH-analogues, aiming to prevent the premature increase in luteinizing.

Studies comparing GnRH agonist long protocols with GnRH antagonist protocols have yielded conflicting results for pregnancy rate, and have related the lower pregnancy rate observed during GnRH antagonist cycles, to their use in cycles with an unfavorable prognosis *a priori*, i.e., repeated failures and elderly low responders [2-3]. Moreover, an increasing number of publications have appeared in literature reinforcing the advantages in using GnRH-antagonists over the agonists, including the lack of hypoestrogenism, the shorter treatment duration, the lower gonadotropin requirement, and a reduction in the incidence of severe ovarian hyperstimulation syndrome (OHSS) [4-5].

Recently, while examining the influence of type of GnRH-analog used during COH on IVF outcome, in patients with an unfavourable outcome- *a priori*, i.e. patients with repeated IVF failure, patients undergoing COH using the GnRH agonist long protocol showed significantly higher clinical pregnancy rate, as compared to the antagonist group [6].

Prompted by these observations, and in an attempt to further clarify the effect of the type of GnRH-analogues on reproductive outcome of patients with an unfavorable prognosis *a priori*, we decided to compare the IVF cycle outcome of elderly patients (≥ 38 years old) undergoing COH using GnRH-agonists versus GnRH-antagonists younger patients (<38 years old).

Patients and Methods

We reviewed the computerized files of all consecutive women admitted to our IVF unit during a 8 year period, who reached the Ovum Pick-up (OPU) stage. Exclusion criteria included use of donor

oocytes or transfer of frozen-thawed embryos, and use of other than a midluteal long GnRH-agonist suppressive protocol (agonist group) or the flexible multidose GnRH-antagonist protocol (antagonist group). The selection of type of analogue used was the decision of the treating physician and largely dependent on the fashion at that time. 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.

Data on patients' age 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. Clinical pregnancy was defined as visualization of a gestational sac and fetal cardiac activity on transvaginal ultrasound.

Results are presented as mean \pm standard deviation. Differences in variables between the two COH protocol groups were statistically analysed with Student t test and chi-squared test as appropriate. A p value of < 0.05 was considered to be significant.

Results

Two thousands and four hundreds and thirty six consecutive cycles were evaluated, 1369 in the agonist group and 1067 in the antagonist group. Causes of infertility in the agonist and antagonist groups were: anovulatory - 4% and 7%, male factor - 55% and 61%, mechanical-23%

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	Patients <38 years old			Patients ≥ 38 years old		
	Agonist Group	Antagonist Group	p value	Agonist Group	Antagonist Group	p value
Number of cycles	1001	858		368	209	
Patient age(yrs)	30.3 ± 3.9	29.8 ± 4	p<0.003	40.6 ± 2.0	40.8 ± 2.2	ns
FSH levels (IU/L)	6.7 ± 2.6	6.4 ± 2.3	p<0.02	7.3 ± 3.4	7.3 ± 5.2	ns
Length of stimulation (days)	10.7 ± 2.2	9.6 ± 2.0	p<0.001	10.9 ± 2.5	9.6 ± 2.4	p<0.001
Number of gonadotropin ampoules used	38 ± 29	33 ± 39	p<0.02	59 ± 27	52 ± 26	p<0.01
Peak E2 levels on day of hCG administration (pg/ml)	2088 ± 1479	1740 ± 939	p<0.001	1812 ± 1145	1565 ± 935	p<0.02
Progesterone levels on day of hCG administration (ng/ml)	0.8 ± 0.4	0.8 ± 0.7	ns	0.7 ± 0.5	0.9 ± 1.0	ns
Endometrial thickness (mm)	11.3 ± 2.3	10.7 ± 2.1	p<0.001	10.6 ± 2.5	10.2 ± 2.4	p<0.04
Number of oocytes retrieved	10.6 ± 6.9	9.8 ± 6.3	p<0.03	8.8 ± 6.5	7.4 ± 6.0	p<0.02
Fertilization rate (%)	52 ± 24	54 ± 24	ns	55 ± 28	53 ± 29	ns
Number of embryos transferred	2.7 ± 0.9	2.7 ± 1.1	ns	2.6 ± 1.2	2.5 ± 1.2	ns
Pregnancy rate (%)	30.1% (301/1001)	21.1% (181/858)	p<0.001	12.2% (45/368)	10.5% (22/209)	ns

Table 1: Comparison between IVF cycles in the GnRH agonist and GnRH antagonist subgroups.

and 19% and unexplained/ endometriosis 14% and 12%, respectively. A clinical pregnancy was achieved in 346 patients in the agonist group (pregnancy rate, 25.3% per cycle) and 203 patients in the antagonist group (pregnancy rate, 19.0% per cycle); this difference was statistically significant ($p<0.001$).

Patients were further divided into 4 subgroups according to GnRH-analogues used (GnRH-agonist vs GnRH-antagonist groups) and patients' age (<38 years vs. ≥ 38 years old). The clinical characteristics of the IVF cycles in the four study groups are shown in Table 1.

In the younger age group (<38 yrs), clinical pregnancy was achieved in 301 patients in the agonist group (pregnancy rate, 30.1% per cycle) and 181 patients in the antagonist group (pregnancy rate, 21.1% per cycle); this difference was statistically significant ($p<0.001$). As expected, the agonist group required longer stimulation, used significantly more gonadotropin ampoules, achieved thicker endometrium and had higher estradiol levels on the day of hCG administration and number of oocytes retrieved, compared to the antagonist group, despite the significantly higher day 3 FSH levels and older age of the patients in the agonist group. There were no differences between the groups in peak progesterone levels, or fertilization rate (Table 1).

We conducted the same analysis in elderly patients (>38 yrs), While the same trends were observed when comparing the GnRH-agonist and antagonist subgroups regarding the ovarian stimulation variables, no in-between groups difference was observed regarding pregnancy rates (Table 1).

Discussion

In the present study of patients undergoing IVF using either, the long GnRH-agonist suppressive protocol or the GnRH-antagonist protocol, while observing a clear advantage of the GnRH-agonist over the GnRH-antagonist, on clinical pregnancy rate in young patients (<38 yrs), no significant difference was demonstrated in elderly patients (≥ 38 yrs).

These results are in accordance with Al-Inany et al. [7] previous meta-analysis, who found a significantly lower clinical pregnancy rate and ongoing pregnancy/live birth rate in the antagonist group compared with the agonist group, with a significantly lower duration of ovarian stimulation and use of significantly fewer gonadotropin ampoules in the antagonist group.

Of notice, in contrast to their previous report [7], Al-Inany et al. [8] have recently demonstrated no evidence of statistically significant differences in the rates of live-births or ongoing pregnancies when

comparing GnRH agonist long protocols with GnRH antagonist protocols. However, the results of this meta-analysis were already challenged, and a re-analysis of the data revealed significantly higher live birth and ongoing pregnancy rates in patients undergoing the long GnRH-agonist as compared to the GnRH-antagonist protocols [9].

Moreover, in the present study we also confirmed our previous observation in young patients (<35 years old) in one of their first three IVF attempts. In this study of patients with a favorable prognosis-*a priori*, we observed a significantly higher clinical pregnancy rate in those undergoing the GnRH agonist compared with the GnRH antagonist protocols [10].

Moreover, while analyzing the IVF outcome in elderly patients (≥ 38 yrs), no difference in pregnancy rate was observed between the two COH protocols. This observation is in accordance with a recent Cochrane review, showing no superiority of any suggested COH protocols over the long GnRH-agonist suppressive protocol in low/ poor responder patients undergoing IVF [11]. Of mentioned, the main limitation of the later analysis is the relatively small sample size of the elderly patients. To demonstrate a difference of 5% in the clinical pregnancy rate at a power of 80% and an alpha value of 5%, 316 study participants would be needed in each arm.

The present study has further challenged the ongoing debate in the medical community by demonstrating the no- superiority of the GnRH-analogues used in elderly patients. We therefore recommend the midluteal long GnRH-ago suppressive protocol as the first protocol of choice in patients undergoing COH for IVF, with the exception of two groups of patients: those at high risk to develop severe OHSS, where the combined GnRH-antagonist with GnRH-agonist trigger for final oocyte maturation should be offered [12,13]; or the elderly/ low-responder group who would benefit from a large armamentarium of COH protocols. Further large prospective studies are needed to clarify the effect of the GnRH-analogue used during COH of different subgroups of patients. Moreover, these studies may help fertility specialists in individualization and careful tailoring of the COH protocol for optimizing IVF success.

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