Does Centre's Experience Influence IVF Success in Patients Undergoing Controlled Ovarian Stimulation with GnRH-Antagonists?

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Abstract: In an attempt to examine whether centre's experience may influence IVF outcome in patients undergoing GnRH-antagonists COH protocols, we studied patients, with a *favorable* prognosis *a priori*, undergoing 557 consecutive IVF cycles during a 9 years period. Throughout the study period patients consumed a significantly lower number of gonadotropin ampoules, achieved significantly lower peak estrogen level on the day of hCG administration and number of oocytes retrieved with no significant difference in pregnancy rates.

Keywords: GnRH antagonist, centre's experience, IVF outcome, pregnancy.

INTRODUCTION

Controlled ovarian hyperstimulation (COH) is considered as a key factor in the success of *in vitro* fertilization-embryo transfer (IVF-ET). Usually, COH includes the co-administration of gonadotropins and GnRH-analogues, aiming to prevent the pre-mature increase in luteinizing hormone.

Studies comparing GnRH agonist long protocols with GnRH antagonist protocols have yielded conflicting results for pregnancy rate, with a tendency toward a better outcome for GnRH agonists [1, 2]. Most studies related the lower pregnancy rate observed during the GnRH- antagonist cycles to "centres' inexperience" or their use in cycles with an unfavourable prognosis *a priori*, that is, repeated failures and elderly low responders [3, 4].

Prompted by these observations, and in an attempt to further clarify the effect of the "centre's inexperience" on reproductive outcome, we decided to compare the IVF cycle outcome of patients undergoing GnRH-antagonists COH protocols during a 9 years period in a single center.

MATERIAL AND METHODOLOGY

We reviewed the computerized files of all consecutive women admitted to our IVF unit during a 9 year period, who reached the ovum pick-up (OPU) stage. In order to study a more homogenous population, for the purpose of this study, we included only patients with *favorable* prognosis (*a priori)*, that is women $\leq$35 years old, undergoing up to their third IVF cycle attempt. Other exclusion criterias were, use of donor oocytes or transfer of frozen-thawed embryos, and use of other than the flexible multidose GnRH-antagonist protocol. This protocol was performed by the administration of gonadotropins, starting at the 2nd or 3rd day of menses. Once the leading follicle had reached a size of 14 mm, or E2 levels exceeded 400 pg/mL, co-treatment with the GnRH antagonist-cetrorelix (Serono Laboratories, Aubonne, Switzerland) 0.25 mg/day, was initiated and continued up to and including the day of HCG administration.

Patients were divided into four groups according to the timing of their OPU. Group A: patients who underwent OPU between the years 2000-2002; Group B: between 2003-2004; Group C: between 2005-2006; and Group D: between 2007-2008. Data on patient 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 means $\pm$ standard deviations. Differences in variables between the four study periods were statistically analyzed with nonparametric Wilcoxon signed rank test, student's t-test and chi-square test, as appropriate. A p value of less than 0.05 was considered significant. The study was approved by our institutional ethics review board.

RESULTS

Five hundred and fifty seven consecutive IVF cycles were retrospectively evaluated. The clinical characteristics of the IVF cycles in the four different study periods are shown in Table **1**. While no significant difference in pregnancy rates was observed between the different study periods, throughout study period patients consumed a significantly lower number of gonadotropin ampoules, achieved significantly lower peak estrogen level on day of hCG administration and number of oocytes retrieved and had a significantly lower number of embryos transferred (Fig. **1**).

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Table 1. Comparison Between IVF Cycles in the Different Study Periods

	Groups				*P* values					
	A	**B**	**C**	**D**	**A vs. B**	**A vs. C**	**A vs. D**	**B vs. C**	**B vs. D**	**C vs. D**
Number of cycles	142	138	134	143						
Patient age	28.6±3.2	29.5±3.4	28.5±3.8	28.5±3.8	0.02	ns	ns	0.02	0.02	ns
Day 3 FSH (IU/L)	6.1±1.5	6.0±2.4	6.5±2.3	6.2±2.6	ns	ns	ns	ns	ns	ns
Number of gonadotropin ampoules used	29.6±9.5	31.3±14.4	25.9±13.9	22.9±10.2	ns	0.01	0.001	0.002	0.001	0.04
Length of stimulation (days)	9.5±1.6	9.7±1.8	9.5±2.0	9.9±2.3	ns	ns	ns	ns	ns	ns
Peak E2 levels on day of hCG administration (pg/ml)	1909±930	1836±1072	1664±955	1352±710	ns	0.04	0.001	ns	0.001	0.002
Progesterone levels on Day of hCG administration (ng/ml)	0.8±0.6	0.8±0.9	0.7±0.6	0.7±0.6	ns	ns	ns	ns	ns	ns
Number of oocytes retrieved	14.9±8.7	12.6±7.5	12.1±6.1	10.0±6.7	0.02	0.002	0.001	ns	0.002	0.007
Fertilization rate (%)	53±23	55±24	55±23	54±27	ns	ns	ns	ns	ns	ns
Number of embryos transferred	2.4±0.6	2.0±0.6	1.9±0.4	1.9±0.4	0.001	0.001	0.001	ns	ns	ns
Pregnancy rate (%) (n)	28.9 (41)	24.6 (34)	26.9 (36)	30.8 (44)	ns	ns	ns	ns	ns	ns

The different study periods:
A. Between years 2000-2002.
B. Between years 2003-2004.
C. Between years 2005-2006.
D. Between years 2007-2008.

There were no differences between the groups in basal day 3 FSH levels, length of stimulation, peak progesterone levels or fertilization rate (Table **1**).

DISCUSSION

In the present study of patients with a *favorable* prognosis *a priori*, undergoing the GnRH-antagonists COH protocols, throughout the 9 year period, patients achieved a significantly lower number of gonadotropin ampoule, with the consequent significantly lower peak estrogen level on day of hCG administration and number of oocytes retrieved, but with apparently no significant difference in pregnancy rates.

The observed changes throughout the study periods reflect centre's adaptation to the use of GnRH-antagonist, which demands less profound stimulation (less gonadotropins), compared to the use of GnRH-agonist, and the consequent decrease in peak E2 levels and the number of oocytes retrieved.

These observations are in accordance with previously published meta-analysis showing that the number of days of analogue treatment, as well as, the number of days of gonadotropin treatment were shorter with the antagonist. Also, E2 levels measured on the day of HCG administration and the number of oocytes retrieved were lower in the antagonist arm [5, 6].

Recently, while studying IVF outcome in young patients (<35 years old) in one of their first three IVF attempts (thus excluding cycles/patients with an unfavorable prognosis), we observed a significantly higher clinical pregnancy rate in patients undergoing the midluteal long GnRH agonist suppressive protocol compared with the flexible GnRH antagonist protocol [7]. Moreover, when studying patients undergoing IVF cycles with the transfer of at least one top-quality embryo, COH using the GnRH agonist was again superior [8].

The aforementioned observations show GnRH-agonist superiority, unrelated to "centers' inexperience" or their use in cycles with an unfavorable prognosis *a priori*, and therefore add further confusion to the ongoing debate in the medi-

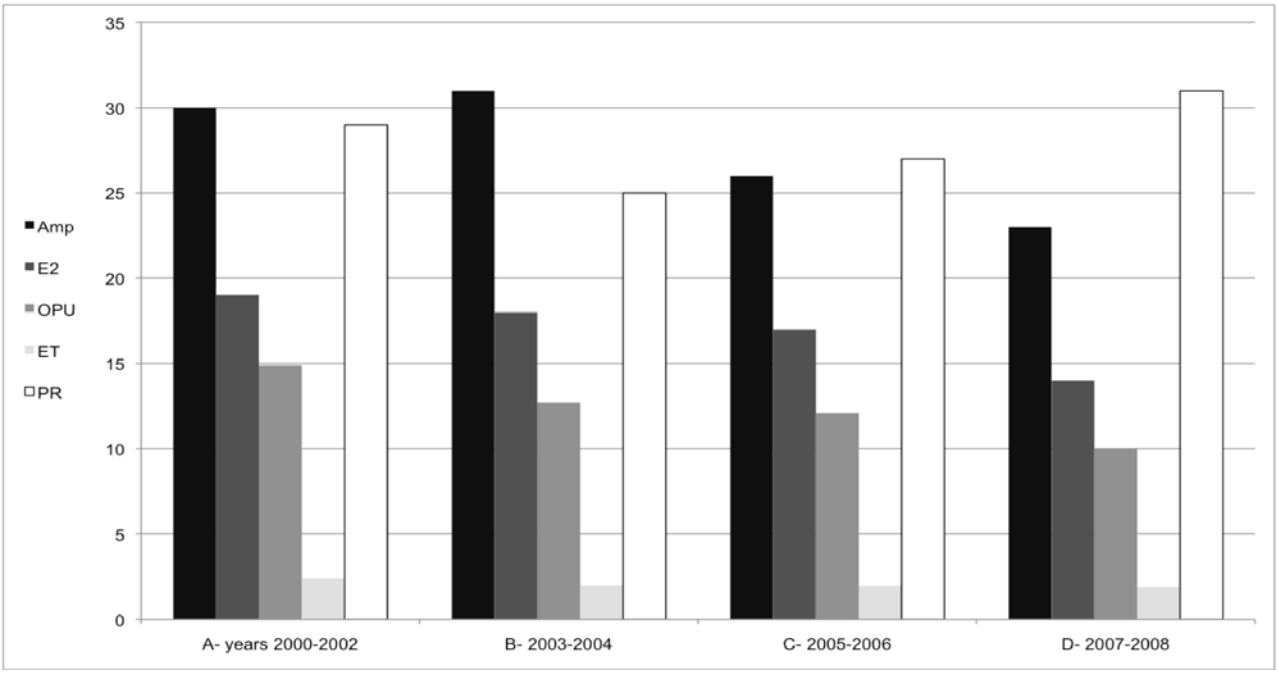

Fig. (1). Infertility-treatment-related variables throughout the different study periods.

A. Years 2000-2002: patients who underwent OPU between the years 2000-2002.

B. 2003-2004: patients who underwent OPU between the years 2003-2004.

C. 2005-2006: patients who underwent OPU between the years 2005-2006.

D. 2007-2008: patients who underwent OPU between the years 2007-2008.

Amp: Number of gonadotropin ampoules, used.

E2: Peak estradiol level on day of hCG administration (10 femptogram/mL).

OPU: Number of oocytes retrieved.

ET: Number of embryos transferred.

PR: Pregnancy rate (%).

cal community by challenging the excuses of the GnRH-antagonist's proponents [3, 4].

Further large prospective studies comparing GnRH agonist long protocols with GnRH antagonist protocols are needed to resolve the aforementioned debate. Until completed, we believe that the midluteal long GnRH agonist suppressive protocol should be offered as the protocol of choice in patients with favorable prognosis a priori, with the exception of those at high risk of severe OHSS, in whom combined GnRH antagonist/GnRH agonist is preferred [9].

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