CORRESPONDENCE

Does physicians' experience influence in vitro fertilization success in patients undergoing controlled ovarian hyperstimulation with GnRH antagonists?

In an attempt to examine whether physicians' experience may influence IVF outcome in patients undergoing GnRH antagonist (GnRH-a) controlled ovarian hyperstimulation (COH) protocols, we studied 273 consecutive patients, with a favorable prognosis a priori, admitted to our IVF unit, of whom 88 conceived. The highest pregnancy rate (PR) (46.5%) was observed in patients achieving, on day of hCG administration, an E_2-to-follicle ratio <100 pg/mL. The timing of hCG administration is crucial in patients undergoing the GnRH-a COH for IVF to optimize success rate. (Fertil Steril® 2007;■:■-■. ©2007 by American Society for Reproductive Medicine.)

Controlled ovarian hyperstimulation (COH) is apparently a key factor in the success of IVF–embryo transfer. Studies comparing GnRH agonist long protocols with GnRH antagonist protocols have yielded conflicting results for pregnancy rate (PR), with a tendency toward a better outcome for GnRH agonists (1, 2).

Most studies related the lower PR observed during the GnRH antagonist cycles to "centers' inexperience" or their use in cycles with an unfavorable prognosis a priori, that is, repeated failures and elderly low responders (3, 4).

Recently, we studied 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 PR in patients undergoing the midluteal long GnRH agonist suppressive protocol as compared to the flexible GnRH antagonist protocol (5).

Prompted by these findings, we sought to examine whether physicians' experience, as reflected by COH and other infertility treatment-related variables, may influence IVF outcome in patients undergoing GnRH antagonists COH protocols.

We reviewed the computerized files of all consecutive women admitted to our IVF unit during an 8-year period, who reached the ovum pick-up stage. The elimination of bias in this selection, for the purposes of this study, was achieved by including only patients with a favorable prognosis a priori, that is women ≤35 years old, 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 the flexible GnRH antagonist protocol.

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. Each patient was included only once during her first IVF cycle in our Unit.

Results are presented as means ± standard deviations. Differences in variables between patients who conceived (pregnant group) and those who did not (nonpregnant group) were statistically analyzed with nonparametric Wilcoxon signed rank test, Student's *t*-test, and χ^2 test, as appropriate. A P value of less than .05 was considered significant.

Two hundred seventy-three consecutive IVF cycles were evaluated. Pregnancy was achieved in 88 patients (PR, 32.2% per cycle). Although patients who conceived used significantly fewer gonadotropin ampules (26.2 ± 9.9 vs. 29.4 ± 13.4; $P<.04$) and gained higher number of follicles of >14 mm on day of hCG administration (11.4 ± 5.3 vs. 9.9 ± 4.3; $P<.01$), there were no between-group differences in patient age and ovarian stimulation characteristics.

Patients were further divided into three groups according to their different ratios of E_2 level to number of follicles of >14 mm on day of hCG administration (E_2-to-follicle) (Table 1) or number of oocytes retrieved (E_2-to-oocyte) (A: <100 pg/mL; B: 100–200 pg/mL; C: >200 pg/mL). Although no difference in PRs was observed between groups B (27.4%) and C (32.9%), a higher PR was observed when comparing group A (E_2-to-follicle ratio <100 pg/mL) (46.5%) to groups B (E_2-to-oocyte ratio: 100–200 pg/mL) ($P<.02$) and C (E_2-to-oocyte ratio >200 pg/mL) ($P<.13$).

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TABLE 1

Comparison between IVF cycles: related variables according to patients' different E2/follicle ratio subgroups.

E2/follicle ratio (pg/mL)	<100	100–200	>200
Number of cycles	43	142	88
Age (years)	28.7 ± 3.5	28.7 ± 3.5	29.2 ± 3.7
Day 3 FSH level (IU/L)	6.6 ± 2.1	6.2 ± 1.9	6.3 ± 2.5
Number of gonadotropin ampoules used	27.1 ± 7.9	29.2 ± 13.1	27.6 ± 13.0
Length of stimulation (days)	9.8 ± 1.9	9.3 ± 1.4	9.6 ± 2.0
Day when GnRH-antagonist started	7.3 ± 1.8	7.0 ± 1.4	7.0 ± 1.5
Peak E2 levels on day of hCG administration (pg/mL)	941 ± 531[a]	1,572 ± 640[a]	2,240 ± 1,153[a]
Progesterone levels on day of hCG administration (ng/mL)	1.1 ± 1.5	0.8 ± 0.6	0.8 ± 0.7
Number of oocytes retrieved	11.9 ± 5.8	13.1 ± 7.8	14 ± 7.6
Fertilization rate (%)	55 ± 29	56 ± 23	56 ± 23
Number of embryos transferred	1.97 ± 0.7[b]	2.2 ± 0.6[b]	2.08 ± 0.6
Pregnancy rate	20/43[c] (46.5%)	39/142[c] (27.4%)	29/88 (32.9%)

[a] Significant difference between the subgroups ($P<.001$).
[b] Significant difference between the subgroups ($P<.05$).
[c] Significant difference between the subgroups ($P<.02$).

Orvieto. Estradiol to follicle ratio and IVF cycle outcome. Fertil Steril 2007.

Grouping patients according to different comparable ranges of E_2-to-oocyte ratio did not reveal any significant difference in PRs (PR: 30%, 36.4%, and 24.5% for groups A, B and C, respectively).

In the present study of patients with a favorable prognosis a priori, undergoing the GnRH antagonists COH protocols, except for a statistically (but not clinically) significant higher number of follicles of >14 mm on day of hCG administration and a consumption of fewer gonadotropin ampules, patients who conceived did not differ from those who did not.

However, although separating patients into three groups according to their different E_2-to-follicle ratios, the highest PR was observed in group A (E_2-to-follicle ratio <100 pg/mL).

This observation may resolve the ongoing debate in the medical community and relates the GnRH antagonist inferiority to "clinical inexperience" (6). It may also suggest that to gain high PR, patients undergoing the GnRH antagonist COH protocol should achieve an E_2-to-follicle ratio lower than 100 pg/mL.

Attention to timing of hCG administration in patients undergoing GnRH antagonist COH for IVF may improve PRs, but this needs to be tested in prospective randomized controlled studies.

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