Impact of coasting in patients undergoing controlled ovarian stimulation with the gonadotropin-releasing hormone antagonist cetrorelix

Coasting is the most popular modality for the prevention of ovarian hyperstimulation syndrome, but this procedure has not been evaluated in patients undergoing controlled ovarian hyperstimulation (COH) with GnRH antagonists. The impact of coasting in a cycle in which GnRH antagonist is used was evaluated in 29 women, and it was found that coasting did not deleteriously affect the outcome in high-responder patients undergoing COH with GnRH antagonists. (Fertil Steril 2006;85:1523–5. ©2006 by American Society for Reproductive Medicine.)

Ovarian response to controlled ovarian hyperstimulation (COH) by gonadotropins is in many cases a prognostic factor for the ultimate success of the treatment. In certain cases, however, it may also be an early sign of impending ovarian hyperstimulation syndrome (OHSS), which is associated with increased E2 levels (1). As there is at present no completely curative therapy for OHSS, the most effective treatment is prevention. Coasting is the most popular modality for the prevention of OHSS (2). It involves withdrawing exogenous gonadotropins and postponing injection of hCG until the serum concentration of E2 decreases to a safer level.

Administration of GnRH agonists along with exogenous gonadotropins to high-responder patients made them vulnerable to uncontrolled E2 peaks. Although the appropriate use of coasting does not have a deleterious effect on the outcome of IVF in patients treated with the long GnRH agonist protocol (3, 4), this procedure has not been evaluated in patients undergoing COH with GnRH antagonists. We therefore retrospectively evaluated patients who underwent COH with GnRH antagonists in whom coasting was applied as a preventive method for severe OHSS.

Among the 1,533 women who underwent COH with GnRH antagonists for assisted conception between January 2003 and December 2004 in our center, coasting was applied to 29 (1.8%). During the course of coasting, the same dosage of GnRH antagonist was continued until the day of hCG injection. The protocol for administration of GnRH antagonist was similar to that described by Bahceci and coworkers (5).

Briefly, exogenous gonadotropins (Gonal F; Serono, Geneva, Switzerland), at dosages of 150–300 IU, were started on day 2, and, starting when the leading follicle reached 14 mm in diameter, 0.25 mg of cetrorelix (Cetrotide; Serono) was administered daily until the day of hCG injection. The starting regimen was fixed for the first 4 days, and thereafter the gonadotropin dose was adjusted according to the individual ovarian response. Recombinant LH (Luveris; Serono), at a dose of 75 IU per day, was also administered starting the same day as the antagonist. Coasting has been applied in COH cycles when the serum E2 concentration was >4,000 pg/mL or when at least 20 follicles, each measuring ≥10 mm in diameter and ≥20% measuring ≥15 mm in diameter, were present (3).

During the coasting period, cetrorelix was administered in the same dosage. When the E2 concentration dropped below 4,000 pg/mL or at least two follicles reached 18 mm in diameter, ovulation was triggered by administration of 5,000/10,000 IU hCG (Pregnyl; Organon, Oss, The Netherlands). Oocytes were retrieved 35 hours after hCG injection and subjected to intracytoplasmic sperm injection, which has been used universally for assisted conception in our practice regardless of infertility etiology. After oocyte retrieval, all patients were prophylactically administered 50 mL human albumin IV. Three days after oocyte retrieval, embryos were transferred transcervically under ultrasound control. Luteal phases were supported by 100 mg (IM) of P in oil. Clinical pregnancy was defined by a demonstrable gestational sac accompanied by fetal heart activity on ultrasound.

The mean age of the women was 32.1 ± 5.0 years (range, 24–43 years). Among these women, polycystic ovary syndrome (PCOS) was the most frequently diagnosed infertility etiology. The duration of coasting was 1 day in 22 (75.8%) women, 2 days in 4 (13.7%) women, and 3 days in 2 (6.8%) women. The mean coasting duration was 1.2 ± 0.5 days. Three (10.3%) patients did not proceed to ET after oocyte retrieval: two because of prolonged coasting (>3 days) and one for personal reasons. Embryos from 19 women (65.5%) were frozen after ET. Severe or mod-
erate OHSS was not detected in any patients, but four (13.7%) patients complained of mild OHSS (6).

The characteristics of the 29 women and COH outcome are shown in Table 1. The implantation rate was 27.9%, and the clinical pregnancy rate was 48.2% per oocyte retrieval. Relative to embryos transferred, the clinical pregnancy rate was 53.8%. Multiple pregnancies were detected in 28.5% of the women. While two (14.2%) women aborted before 20 weeks of gestation, ectopic pregnancy was detected in one patient.

The clinical use of GnRH antagonists in IVF practice occurred much later than that of GnRH agonists. In randomized studies, pregnancy rates after the administration of antagonists and agonists did not differ, but a Cochrane review that collected all the data from those trials revealed that women undergoing COH with GnRH antagonists had a significantly lower pregnancy rate than women undergoing COH with agonists (7). On the other hand, shorter duration of treatment, fewer injections, and lower peak E<sub>2</sub> levels were detected during COH cycles with antagonist compared with agonists (8). It is therefore likely that the incidence of multifollicular ovarian and severe OHSS can be lower in antagonist cycles compared with agonist cycles.

In this regard, it was shown that there was a significant reduction in the number of OHSS cases when GnRH antagonist was used in COH compared with cycles in which GnRH agonist was used (9, 10). Patients with PCOS in particular are the most vulnerable to excessive ovarian multifollicular development and OHSS during treatment with exogenous gonadotropins. In a comparison of GnRH antagonists and GnRH agonists in women with PCOS undergoing IVF, no difference was found in pregnancy rates, but in antagonist cycles, a lower amount of gonadotropins was used and lower peak E<sub>2</sub> concentrations were yielded, which suggests that GnRH antagonist cycles can provide better COH control (5, 11).

From this point of view, our retrospective analysis also showed that, during the same time period, 195 (8.3%) were coasted among the 2,345 COH cycles in which the long GnRH agonist protocol was used (P <.0001; odd ratio, 0.1; 95% confidence interval, 0.07–0.15), indicating that coasting to prevent OHSS in cases demonstrating excessive E<sub>2</sub> levels appeared to be performed less frequently in GnRH antagonist compared with agonist cycles.

One of the advantages in using GnRH antagonists for COH protocols is the ability to trigger ovulation using GnRH agonists. A prerequisite for the development of OHSS is the long life of hCG that was administered for induction of ovulation. Because of the relatively short half-life of GnRH agonists, this modality can be used in the prevention of OHSS (12). On the other hand, because of the reduced implantation and pregnancy rates after the injection of GnRH agonist to trigger ovulation in COH cycles in which antagonist was used, the results are not promising so far (13, 14).

To date, coasting in GnRH antagonist cycles without compromising outcome has been described only in case reports (15, 16). It is also important to note that a randomized study should be performed to test the effect of coasting in antagonist cycles, although there are ethical consider-
ations (3). We have shown here, however, that coasting in antagonist cycles results in acceptable pregnancy rates. In addition, duration of coasting as the most significant prognostic factor on IVF outcome in patients undergoing coasting was found to be shorter among coasted GnRH antagonist cycles (3, 4, 17).

The high percentage of embryo freezing after fresh ET among coasted patients in our study group also revealed that coasting in GnRH antagonist cycles results in good embryo quality. Finally, there were no cases of severe OHSS among the assessed individuals, which may have been also due to physician awareness and/or prophylactic albumin administration in addition to the possible advantages of GnRH antagonists (18).

In conclusion, coasting can be well tolerated in high-responder patients undergoing COH with GnRH antagonists without compromising outcome.

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