Gonadotropin-releasing hormone agonist to induce final oocyte maturation prevents the development of ovarian hyperstimulation syndrome in high-risk patients and leads to improved clinical outcomes compared with coasting

Ninety-four women undergoing IVF with peak E_2 level >4000 pg/mL received leuprolide acetate (LA) trigger (LA trigger group) or had gonadotropins withheld for one or more days (coasting group) followed by hCG trigger, unless cycle cancellation occurred. There were no cases of ovarian hyperstimulation syndrome in either group, and the LA trigger group had significantly more oocytes retrieved (26.9 ± 9.5 vs. 17.7 ± 9.3) $P<0.001$, more normally fertilized oocytes (15.0 ± 7.8 vs. 10.3 ± 6.3) $P=0.01$, and higher clinical and ongoing pregnancy rates than the coasting group (52.5% vs. 27.2%; 49.2% vs. 24.2%, $P=0.02$ for both comparisons, respectively). (Fertil Steril® 2010;94:1111–4. ©2010 by American Society for Reproductive Medicine.)

Key Words: GnRH agonist, GnRH antagonist, OHSS, high responder

Ovarian hyperstimulation syndrome (OHSS) is a potentially severe and dangerous complication resulting from controlled ovarian hyperstimulation (1). When a high response is noted during controlled ovarian hyperstimulation, steps should be taken to minimize the risk of OHSS. Although withholding hCG and cycle cancellation may be the safest option in some cases, this may have adverse emotional and financial implications for the patient. Coasting is the withholding of gonadotropin medication for one or more days to allow an elevated E_2 level to drop to a safer threshold at which to trigger oocyte maturation (2). Although coasting may decrease the risk of OHSS (3–28), it may have adverse effects on clinical outcomes such as a lower oocyte yield and decreased implantation and pregnancy rates, especially in cases of prolonged coasting (26–28).

Human chorionic gonadotropin is believed to be a key etiologic factor in the development of OHSS because of its luteotropic effects (29). Gonadotropin-releasing hormone agonists have decreased luteotropic effects when compared with hCG (29) and have been shown to be effective in preventing OHSS in high-risk patients (29, 30–33). Some studies have reported lower ongoing pregnancy rates and higher miscarriage rates with GnRH agonist trigger compared with hCG (34–36), whereas others have shown similar pregnancy rates (33, 37, 38).

To our knowledge, there are no studies to date that have compared outcomes of coasting and hCG trigger with GnRH agonist trigger in high responders undergoing IVF. The aim of the present study was to compare the incidence of OHSS and clinical outcomes after leuprolide acetate (LA) trigger following an antagonist protocol versus coasting and hCG trigger after a pituitary down-regulation protocol for IVF in patients at very high risk for the development of OHSS.

Institutional Review Board approval was obtained for this study. Data were reviewed from fresh IVF-ET cycles occurring between January 2004 and December 2008 in which patients had a serum E_2 level >4000 pg/mL on the day of LA trigger for final oocyte maturation or during coasting. This E_2 level was selected because patients with such levels generally are considered to be at high risk for the development of OHSS at our center. All patients underwent ovarian stimulation with recombinant FSH (Follistim; Organon USA Inc., Roseland, NJ, or Gonal-F; Serono Inc., Randolph, MA) with or without hMG (Menopur or Repronex; Ferring Pharmaceuticals, Parsippany, NJ) starting on the second day of menses. Medication and protocol choice were based on physician

Andrea J. DiLuigi, M.D.
Lawrence Engmann, M.D.
David W. Schmidt, M.D.
Donald B. Maier, M.D.
John C. Nulsen, M.D.
Claudio A. Benadiva, M.D.
The Center for Advanced Reproductive Services, Division of Reproductive Endocrinology and Infertility, University of Connecticut Health Center, Farmington, Connecticut

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Reprint requests: Andrea J. DiLuigi, M.D., The Center for Advanced Reproductive Services, University of Connecticut Health Center, 263 Farmington Ave., Dowling South Building, Farmington, CT 06030-6224 (FAX: 860-679-3639; E-mail: diluigi@uchc.edu).

TABLE 1

Clinical characteristics and outcomes.

	LA trigger group (n = 61)	Coasting group (n = 33)	*P* value
Age (y)	32.6 ± 5.9	34.2 ± 4.4	NS (.18)
Basal FSH (mIU/mL)	6.4 ± 1.7	6.7 ± 1.7	NS (.38)
Peak E_2 (pg/mL)	5926 ± 1366	6108 ± 1105	NS (.56)
Peak E_2 range (pg/mL)	4049–9905	4665–10,530	—
E_2 at start of coasting (pg/mL)	—	4306 ± 897	—
Days coasted	—	2.6 ± 1.2	—
E_2 on day of trigger (pg/mL)	4824 ± 844	3744 ± 1224	.001
Days of stimulation	10.1 ± 1.2	11.6 ± 1.8	.001
Total IU FSH	1930 ± 1131	1939 ± 580	NS (.96)
Cancellation rate (%)	0	30.3	< .001
No. embryos transferred	2.3 ± 0.9	2.3 ± 1.0	NS (.97)
No. good-quality embryos transferred	2.0 ± 1.0	1.5 ± 0.8	NS (.06)
No. oocytes per oocyte retrieval	26.9 ± 9.5	17.7 ± 9.3	< .001
No. normally fertilized oocytes (2PN)	15.0 ± 7.8	10.3 ± 6.3	.01
Fertilization rate (%)	669/921 (72.6)	186/281 (66.2)	.04
Implantation rate (%)	44/140 (31.4)	12/53 (22.6)	NS (.23)
Clinical pregnancy rate (%)	32/61 (52.5)	9/33 (27.2)	.02
Ongoing pregnancy rate (%)	30/61 (49.2)	8/33 (24.2)	.02
Patients with surplus cryopreserved embryos (%)	40/60 (66.7)	9/23 (39.1)	.02
No. of cryopreserved embryos	4.4 ± 4.5	2.0 ± 3.5	.02
OHSS (%)	0	0	NS

Note: PN = pronuclei; NS = not significant.

DiLuigi. Correspondence. Fertil Steril 2010.

preference. Starting doses of FSH ranged from 100 to 225 IU daily. Medication dose was adjusted on the basis of response. Patients in the LA group received ganirelix acetate (Organon) (0.25 mg SC daily when the lead follicle was ≥14 mm or serum E_2 was ≥300 pg/mL) followed by LA (1 mg SC) when at least three follicles were ≥18 mm in mean diameter. Patients in the coasting group underwent pituitary down-regulation with LA. Coasting generally was initiated when the serum E_2 level was >3000 pg/mL, and hCG was administered (3300–5000 IU SC) if at least three follicles were ≥18 mm in mean diameter and the E_2 declined to an acceptable level, usually below 3000 pg/mL. Transvaginal ultrasound–guided oocyte retrieval was performed 35 hours after trigger. All patients received 50 mg of IM P daily for luteal phase support starting the day after the oocyte retrieval, and patients in the LA group also received three 0.1-mg transdermal E_2 patches every other day. Embryo transfer was performed on day 3 or 5 of development. Supernumerary embryos of good quality were cryopreserved after the ET. Embryos were graded according to the criteria described by Cummins et al. (39). In patients having the LA trigger, serum levels of E_2 and P were assessed on the day of the ET and 7 days after retrieval. Estradiol and P doses were adjusted if the serum E_2 level was ≤200 pg/mL or P level was ≤20 ng/mL. Samples for serum β-hCG and P levels were drawn 14 days after oocyte retrieval in all patients. If pregnancy was achieved in coasted patients, P was continued until 7 weeks gestation. In patients having the LA trigger, an E_2 level also was taken 14 days after oocyte retrieval; E_2 and P levels were monitored on a weekly basis, and E_2 and P supplementation was continued until 10 weeks gestation. Charts were reviewed for recorded signs and symptoms of OHSS throughout the IVF cycle and during early pregnancy. The main outcome variables were the incidence of OHSS, clinical pregnancy rate, and ongoing pregnancy rate. Secondary outcomes were number of oocytes retrieved, number of normally fertilized oocytes, implantation rates, and number of cryopreserved embryos. Clinical pregnancy was defined by the presence of a gestational sac on transvaginal ultrasound examination. The implantation rate was defined as the number of gestational sacs at 6.5 to 7 weeks gestation, divided by the number of embryos transferred. Ovarian hyperstimulation syndrome was defined with use of the criteria of Golan et al. (40). Statistical analyses were performed with use of Student's *t*-test for continuous variables and Fisher's exact or χ^2 tests for categorical variables where appropriate. All *P* values are two-tailed, and values < .05 were considered to be statistically significant.

Ninety-four patients were included in this study: 61 in the LA trigger group and 33 in the coasting group. Clinical characteristics and outcomes are presented in Table 1. Diagnoses were similarly distributed between the two groups. Intracytoplasmic sperm injection was used in a similar proportion of cases in both groups (83.6% vs. 82.6 % in the LA trigger group vs. the coasting group; *P*=.96). Ten of the patients in the coasting group underwent cycle cancellation before oocyte retrieval. Eight of these patients had considerably elevated E_2 levels despite 4 days of coasting and did not receive hCG because of the inherent risk of development of OHSS. Treatment in one of the coasting patients was cancelled because of a very precipitous drop in E_2 level after 4 days of coasting, and in another was cancelled because of a considerable E_2 drop the day after hCG administration (54% decline in E_2 level). None of the patients in the LA trigger group underwent cycle cancellation. Five patients in the LA trigger group underwent day 5 transfer of a single blastocyst, and two patients in the coasting group did so (8.2 vs. 8.7%). Ovarian hyperstimulation syndrome did not develop in any of the patients