Evaluating the role of exogenous luteinizing hormone in poor responders undergoing in vitro fertilization with gonadotropin-releasing hormone antagonists

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Objective: To evaluate the importance of exogenous LH in poor responders undergoing IVF with GnRH antagonists.
Design: Retrospective cohort study.
Setting: University-based IVF center.
Patient(s): All patients with a history of poor response to ovarian stimulation undergoing IVF with GnRH antagonists between September 2000 and August 2001.
Intervention(s): None.
Main Outcome Measure(s): Clinical pregnancy rates.
Result(s): Two hundred forty GnRH-antagonist cycles were initiated in poor responders. One hundred fifty-three progressed to oocyte retrieval. Seventy-five patients received recombinant FSH (Rec) for ovarian stimulation, and 66 received hMG in combination with Rec. In patients aged <40 years, there were no significant differences in amount and duration of treatment, number of oocytes retrieved, and number of embryos between treatment groups. In patients aged ≥40 years, significantly fewer oocytes were retrieved in groups who received exogenous LH in their stimulation, resulting in significantly fewer fertilized embryos. Implantation and clinical pregnancy rates did not differ by treatment group.
Conclusion(s): In poor responders undergoing IVF with GnRH antagonists, outcomes are comparable whether stimulation is achieved in the presence or absence of supplemental LH. Exogenous LH does not appear to be necessary to achieve pregnancy in these challenging patients and may be detrimental to older patients with a history of poor response. (Fertil Steril® 2005;84:313–8. ©2005 by American Society for Reproductive Medicine.)

Key Words: Gonadotropin-releasing hormone antagonist, luteinizing hormone, poor responders, IVF

Controlled ovarian hyperstimulation in patients undergoing IVF traditionally has been accomplished using recombinant or highly purified urinary gonadotropins in combination with GnRH agonists (GnRH-a) to prevent the premature LH surge. Patients with diminished ovarian reserve often demonstrate minimal response to this treatment, and alternative strategies are needed. The introduction of GnRH antagonists has provided an opportunity to offer patients with a history of poor response a different approach to treatment. Promising results have been reported (1–5). The immediate competitive blockade accomplished by the antagonists allows for their initiation in the mid- to late-follicular phase, thereby avoiding prolonged suppression and potential interference with early follicular development that may be critical in patients with diminished ovarian reserve. With the use of GnRH antagonists, the relative contribution of endogenous gonadotropins is optimized, and the amount of exogenous medication required is reduced (6).

Because of the dramatic inhibition of LH secretion associated with the GnRH antagonists, there has been concern about the need for supplementation with exogenous LH. In a natural cycle, LH is essential in maintaining adequate steroidogenesis and follicular development (7), but in the setting of controlled ovarian hyperstimulation, its role has been debated. Profound suppression of LH in cycles using GnRH-a and recombinant FSH that is devoid of LH reportedly has led to fewer oocytes retrieved and lower fertilization rates (8). On the contrary, it also has been reported that in cycles down-regulated with GnRH-a, there is sufficient residual endogenous LH to achieve adequate follicular development, steroid production, and pregnancy (9).

Gonadotropin-releasing hormone antagonists demonstrate a more powerful dose-dependent suppression that can result in nearly undetectable levels of LH (10). Additionally, they result in LH deprivation just as the granulosa cells of the

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ovarian follicles become receptive to LH (11). Such effects may be detrimental to follicular development, thereby necessitating supplementation with exogenous LH. The purpose of our study is to evaluate the role of exogenous LH specifically in poor responders undergoing IVF with GnRH antagonists.

MATERIALS AND METHODS

A total of 240 IVF cycles using GnRH antagonists between September 2000 and August 2001 were retrospectively reviewed. All patients had demonstrated suboptimal response to stimulation in prior cycles; that is, they had less than four total follicles and/or a history of elevated FSH (range, 10.1–18). Primary outcome measures included the pregnancy rate per retrieval and implantation rate per embryo transferred. Pregnancy rate is defined as fetal heartbeat visualized on ultrasound per retrieval. Implantation rate reflects the number of gestational sacs seen per embryo replaced. Secondary outcomes evaluated were the amount of gonadotropin used, the number of days of gonadotropin treatment, number of oocytes retrieved, and number of normally fertilized zygotes (2PN).

In all patients, basal serum E_2 and FSH levels were obtained on day 2 or 3 of the treatment cycle. If the E_2 level was <70 pg/mL and the FSH level was <12 mIU/ml, stimulation was initiated. At the time of this study, oral contraceptives were generally not used before antagonist cycles.

Stimulation regimens were selected on the basis of physician preference. There were no specific criteria used to determine the stimulation protocol. In the management of patients who had previously demonstrated poor response to conventional protocols of GnRH agonist and recombinant FSH, some of the treating physicians believed that supplementing LH, particularly in the face of GnRH antagonists, would be beneficial, whereas others believed it was unnecessary. A daily dose of recombinant FSH (Gonal F, Serono Laboratories, Inc., Norwell, MA; Follistim, Organon, Annapolis, MD; Rec, n = 75) or a combination of Rec and hMGs (Pergonal, Serono Laboratories; Repronex, Ferring Pharmaceuticals, Tarrytown, NY) in a 1:1 or 1:2 ratio (Rec+hMG, n = 66) was administered with dosing adjusted in a step-down fashion. A third group of 12 patients who received hMG alone was excluded from the analysis because the sample was believed to be too small to provide meaningful results. For the analysis, stimulation protocols were classified as either *LH absent* if patients received recombinant FSH only (n = 75) or as *LH present* if some amount of hMG was used during the cycle (n = 66).

In all patients, GnRH-antagonist treatment (0.25 mg Ganirelix daily; Antagon, Organon) was initiated when the lead follicle reached 12–14 mm in diameter on transvaginal ultrasound and was continued until the day of hCG. When at least two follicles developed to ≥16mm in diameter, hCG injection was administered (10,000 IU; IM). Ultrasound-guided oocyte retrieval was performed approximately 36 hours later, and embryos were transferred on the 3rd day after retrieval. Intramuscular P supplementation was initiated on the day after oocyte retrieval.

For our analysis, data were stratified by patient age into two groups, age <40 years and age ≥40 years. Descriptive statistics were performed to examine whether baseline characteristics were similar between the stimulation groups. Comparisons of continuous variables were made by using Student's *t* test. Fisher's exact analyses were used for dichotomous outcomes.

Because of the retrospective nature of the study, and because all data were collected as part of routine medical care, institutional review board approval was not obtained.

RESULTS

Of the 240 GnRH-antagonist cycles initiated in poor responders, 153 (60%) progressed to oocyte retrieval, and 141 were included in the analysis. As described in Materials and Methods, 12 patients received hMG only and were excluded.

TABLE 1

Baseline characteristics by treatment group in each age stratum.

Characteristic	LH absent	LH present	*P* value
Age <40 y			
Age in y	35.7 ± 2.6 (n=35)	35.6 ± 2.6 (n=25)	.87
Day 3 FSH (mIU/ml)	6.4 ± 2.2	6.3 ± 2.3	.84
Age ≥40 y			
Age in y	42.6 ± 1.7 (n=40)	42.6 ± 1.6 (n=41)	.98
Day 3 FSH (mIU/ml)	6.1 ± 2.2	6.6 ± 2.1	.29

Note: Data are expressed as mean ± SD. The LH-absent group received recombinant FSH. The LH-present group received hMGs in combination with recombinant FSH.

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