Novel follicular-phase gonadotropin-releasing hormone antagonist stimulation protocol for in vitro fertilization in the poor responder

Poor responders continue to be vexing in infertility therapy. By using GnRH antagonists before ovarian stimulation, we demonstrate an improvement in oocyte, embryo, and zygote yield in patients with a prior poor response. (Fertil Steril® 2007;88:1442–5. ©2007 by American Society for Reproductive Medicine.)

Progress in pharmacology, sonography, and embryology continues to fuel advances in the assisted reproductive technologies (ART) (1–3). This, combined with growing acceptance of ART, enhances the utilization of such therapy (4). Yet the poor responder largely has been left behind and remains a vexing problem (5).

Because ovarian reserve is closely tied to maternal age, the prevalence of oocyte-factor infertility grows with the deferment of child bearing into the 3rd and 4th decades (6, 7). Poor responders possess guarded prognoses and continue to challenge current treatments. Current stimulation regimens afford little benefit for those exhibiting either an age-appropriate or age-inappropriate poor response (8, 9). Although not entirely understood, this poor response may be partly a result of either a shortened follicular phase with limited ability to recruit a sizable cohort or a potential increased sensitivity to the lingering suppressive effects of the recent corpus luteum (5, 7, 10, 11).

Ovarian stimulation protocols aim to enhance follicular recruitment and avoid spontaneous ovulation. Oral contraceptive pills and GnRH agonists (GnRH-a) can also prevent corpus luteum formation and provide sufficient time for luteolysis (12). However, while inducing pituitary suppression, these adjuvants may throttle the ovarian response (9, 13, 14). Similarly, so-called flare protocols can undermine the cycle by leading to premature luteinization (15).

Luteal suppression with GnRH-a can prove dire for the poor responder (9, 13, 14). We propose that rapidly acting GnRH antagonists afford an opportunity to extend the follicular phase and prevent corpus luteum formation without adversely impacting ovarian responsiveness (16, 17). As such, we present a case series to assess the impact of a follicular-phase GnRH-antagonist protocol on zygote yield in patients who previously had exhibited a poor response to traditional stimulation protocols.

Received July 5, 2006; revised and accepted January 2, 2007.
Presented at the 2004 Annual Meeting of the American Society for Reproductive Medicine, October 16–20, 2004.
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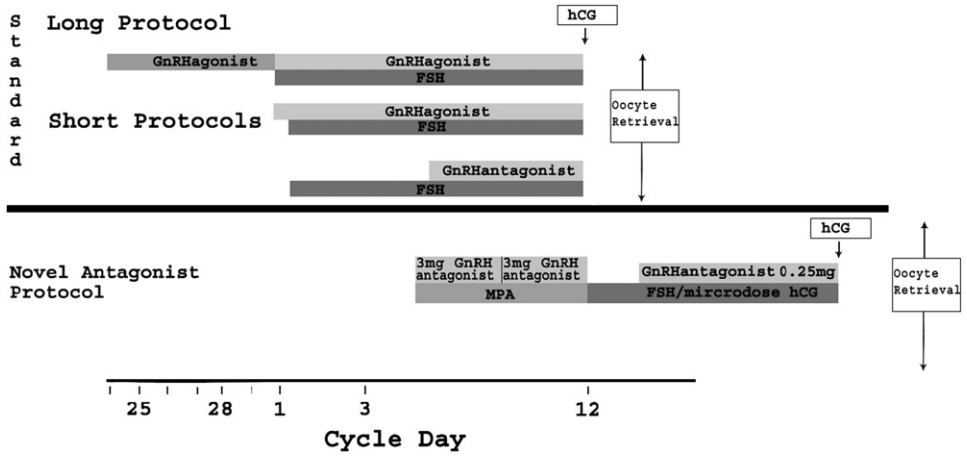
This case series involves patients who underwent two IVF cycles between May 15, 2003 and August 30, 2004. In the first cycle, subjects exhibited a peak E_2 level of <1,000 pg/mL or had fewer than five oocytes retrieved in response to a conventional long or short protocol (cycle A) and were stimulated in the next IVF attempt by a novel follicular antagonist protocol (cycle B). Cycle A was performed by using standard long and short protocols (Fig. 1). Briefly, for long protocols, pituitary desensitization was achieved with SC leuprolide acetate (LA; Lupron; TAP Pharmaceuticals, North Chicago, IL) during the luteal phase of the preceding. Ovarian stimulation was then achieved with SC administration of recombinant FSH (either follitropin alpha [Serono, Randolph, MA] or follitropin beta [Organon, West Orange, NJ]). For conventional GnRH-antagonist cycles, daily GnRH-antagonist (ganirelix, Organon) injections were initiated when a lead follicle measured 13 mm or when E_2 level reached 600 pg/mL and were continued until hCG injection. For short protocols, LA was started within the first 3 days of menses, and FSH injections were initiated 1–3 days after that.

Cycle B stimulation involved an initial injection of cetrorelix acetate (3.0 mg SC; Serono, Randolph, MA) on cycle day 5–8, followed by a second injection of cetrorelix acetate (3.0 mg SC) 4 days later. With cetrorelix start, medroxyprogesterone acetate (10 mg, 1 time per day) was given and was continued until ovarian suppression was confirmed. Patients were assessed for ovarian suppression (serum E_2 of <50 pg/mL and basal ultrasonography [General Electric L4; General Electric, Fairfield, CT]) 3 days after the second cetrorelix injection. With ovarian suppression demonstrated, a combination of recombinant FSH (225 IU SC, 2 times per day) and recombinant hCG (2.5 μg, SC, 4 times per day) was initiated, and medroxyprogesterone acetate was discontinued to allow for vaginal bleeding. Dilute recombinant hCG was given to provide LH activity and compensate for the decline in LH activity that has been seen by some investigators with the use of GnRH antagonists (18). Patients were followed by serial ultrasonography and E_2 monitoring, starting on recombinant FSH day 5. When a lead follicle size of 13 mm was observed, cetrorelix (0.25 mg SC, 4 times per day) was started and continued until the triggering hCG injection.

0015-0282/07/$32.00
doi:10.1016/j.fertnstert.2007.01.022

FIGURE 1

Schematic representation of protocols employed in study.



Frankfurter. Follicular phase GnRH-antagonist protocol for poor responder. Fertil Steril 2007.

We administered hCG (10,000 IU SC) when the lead follicle was ≥18 mm and the majority of the cohort was >15 mm (Fig. 1). Transvaginal oocyte retrieval was performed 36 hours later. Standard IVF, ICSI, or assisted hatching were performed on the basis of infertility diagnosis and agreement between patient and physician, as indicated. Embryos were transferred on postretrieval day 2 or 3 under transabdominal ultrasound guidance with a full bladder with an Echotip (Cook, Bloomington, IN) catheter (19).

Comparisons between groups were made with paired Wilcoxon, Fisher's, and McNemar tests. *P* values of $<.05$ were considered statistically significant.

This study was approved by the institutional review board at The George Washington University.

A total of 12 patients, with a median age of 39.5 years (range, 31–41 y), were included. Median duration of infertility and day 3 FSH were 2.0 years (95% CI, 1.3–4.6 y) and 6.25 IU/L (95% CI, 3.2–11.7 IU/L), respectively. Table 1 summarizes the characteristics and outcome measures of cycles A and B. Of the traditional protocols used for cycle A, one was luteal GnRH-a suppression and three were antagonist and eight were flare protocols. The median peak E_2 was 1,262 pg/mL (95% CI: 750–2,244 pg/mL) in cycle B and was 658 pg/mL (95% CI: 35–1,331 pg/mL) in cycle A ($P<.05$). The median number of recruited follicles sized >10 mm at the time of hCG was 6.5 (95% CI: 2.54 to 8.4) in cycle B, compared with 3.5 (95% CI: 1.0–8.0) in cycle A ($P<.05$). This is consistent with the higher oocyte, zygote, and cleavage-stage embryo yield seen in cycle B compared with in cycle A (4.5 vs. 1.5, $P<.01$; 2.5 vs. 0.5, $P<.05$; 2.5 vs. 0.5, $P<.05$, respectively). The implantation rate, number of pregnancies, and number of ongoing pregnancies were higher in cycle B compared with in cycle A (21.4% vs. 6.23%; relative risk, 4.3; 95% CI: 0.58–31.16; 5 vs. 1, $P=.22$; and 3 vs. 0, $P=.20$, respectively).

The development of a rapidly acting GnRH antagonist enabled us to design a stimulation protocol that does not compromise the ovarian stimulatory response of poor responders. By using a GnRH antagonist in the follicular phase before ovarian stimulation, we demonstrated a significant improvement in oocyte, zygote, and embryo yield. A trend toward improved implantation, clinical-pregnancy, and ongoing-pregnancy rates in the follicular GnRH-antagonist cycle was noted. However, although we believed that it was important to provide pregnancy outcome data for completeness sake, comparisons between cycles regarding these rates are not appropriate because entry criteria required an initial nonpregnancy cycle.

Improved ART pregnancy rates continue at the exclusion of the poor responder (8). Prior efforts have failed to show that flare regimens, agonist, and traditional antagonist protocols significantly benefit the poor responder (8, 9). In this series, cases were defined on the basis of a poor response to any traditional protocol. A subanalysis of the data on the basis of type of initial stimulation protocol used (flare, luteal suppression, or conventional antagonist) did not affect our findings (data not shown).

Local and systemic factors play a role in the follicular response. These culminate with the pituitary gland triggering ovulation and subsequent corpus luteum formation (7). Luteinizing hormone may serve to support corpus luteum activity, and corpus luteum factors such as inhibin A, prostaglandin $F_{2\alpha}$, and endothelin-1 may negatively affect ovarian steroidogenesis and oocyte maturation (10, 11, 20, 21). Individuals with diminished ovarian reserve exhibit early ovulation and corpus luteum formation (7). They have