Management of poor responders: can outcomes be improved with a novel gonadotropin-releasing hormone antagonist/letrozole protocol?

William B. Schoolcraft, M.D., Eric S. Surrey, M.D., Debra A. Minjarez, M.D., John M. Stevens, B.S., and David K. Gardner, D. Phil.

Colorado Center for Reproductive Medicine, Englewood, Colorado

Objective: To compare the efficacy of a microdose GnRH agonist flare (ML) with a GnRH antagonist/letrozole (AL) protocol before IVF-ET in poor responders.
Design: Prospective controlled trial.
Setting: Private assisted reproductive technology center.
Patient(s): Five hundred thirty-four infertile women classified as past or potential poor responders based on clinic-specific criteria.
Intervention(s): Poor responders were prospectively assigned to an ML or AL protocol in a 2:1 ratio, respectively.
Main Outcome Measure(s): Results of controlled ovarian hyperstimulation and implantation and ongoing pregnancy rates.
Result(s): Patient characteristics were similar between the two protocol groups. There were no significant differences in mean age, number of oocytes, fertilization rates, number of embryos transferred, or embryo score. Peak E_2 levels were significantly lower in the AL group. Ongoing pregnancy rates were significantly higher in the ML group (52% vs. 37%). Trends toward increased implantation and lower cancellation rates were also noted, but these did not reach statistical significance.
Conclusion(s): Quantitative results of stimulation between the ML and AL protocols were equivalent with the exception of peak E_2 levels. However, the higher ongoing pregnancy rates and trend toward superior implantation rates would suggest that ML represents a preferred approach for the poor responder. An increased sample size would be necessary to verify these findings. (Fertil Steril® 2008;89:151–6. ©2008 by American Society for Reproductive Medicine.)

Key Words: GnRH antagonist, letrozole, GnRH agonist, poor responder, in vitro fertilization, ovarian stimulation

The management of the poor-responder patient preparing for assisted reproductive technologies remains extremely controversial. Failure to respond adequately may result in suboptimal oocyte maturation and production as well as high cycle cancellation and poor pregnancy rates. The ideal controlled ovarian hyperstimulation (COH) protocol has not been clearly defined. A variety of regimens have been employed including the use of increased gonadotropin doses, decreased GnRH agonist (GnRH-a) doses, flare regimes, adjunctive growth hormone, GnRH antagonists, and microdose flare regimes (1).

Several studies have supported the use of a microdose GnRH-a flare protocol in this patient group, which demonstrated improved ovarian responses and clinical outcomes (2–5). This approach takes advantage of the initial release of endogenous gonadotropins that is induced by low-dose GnRH-a administration in the early follicular phase in an effort to enhance response to the subsequent administration of exogenous gonadotropins.

More recently, GnRH antagonists have been administered to poor responders during gonadotropin stimulation with mixed results (6–13). The use of antagonists allows initiation of gonadotropin stimulation in the absence of prior pituitary gonadotropin down-regulation given that these agents are not typically added to the COH protocol until follicular maturation has already been initiated.

The aromatase inhibitor letrozole has been employed as a novel approach to improving gonadotropin response. This agent acts by blocking E_2 synthesis with a resulting decrease in negative feedback at the level of the pituitary. The resulting increase in endogenous gonadotropin secretion may enhance the ovarian response to exogenous gonadotropins in COH cycles (14–16). Therefore, the combination of a GnRH

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Reprint requests: William B. Schoolcraft, 799 E. Hampden Ave., no. 300, Englewood, CO 80113 (FAX: 303-788-8310; E-mail: bschoolcraft@colocrm.com).

antagonist and letrozole in conjunction with gonadotropin COH may offer a new alternative to the microdose GnRH-a flare protocol for poor responders preparing for IVF. The objective of this investigation is to compare these two regimes in a population of poor responders.

MATERIALS AND METHODS

Patients

This investigation is a prospective controlled trial including 578 patients who were candidates for IVF and who were classified as poor responders as described below. All patients underwent precycle ovarian reserve testing, which included an assessment of cycle day 3 serum FSH and E_2 levels and a measurement of ovarian volume and number of antral follicles measuring 4–8 mm by ultrasound evaluation during the follicular phase. Criteria for classification as a poor responder included at least one of the following: day 3 serum FSH level >10 mIU/mL, <6 total antral follicles, prior cycle cancellation, prior poor response to COH (peak E_2 <500 pg/mL and/or <6 oocytes retrieved), and age >41.

Patients were assigned in a 2:1 ratio to either a GnRH-a microdose flare (ML) or GnRH antagonist/letrozole (AL) protocol. Protocol assignment was made by the nursing staff based on the order in which the patient accessed the IVF program, without input by any of the investigators.

Treatment Protocols

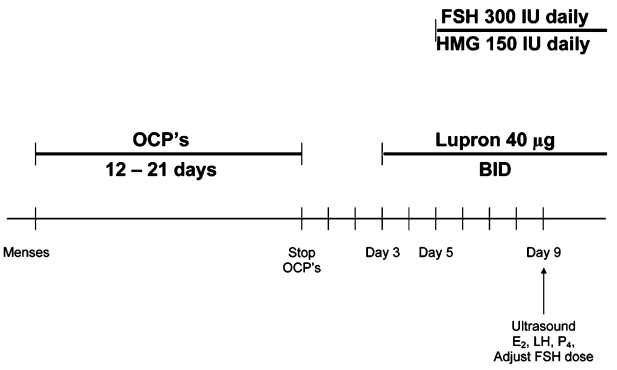
A total of 355 patients were assigned to the ML protocol. All patients received 14–21 days of an oral contraceptive. Three days after the last oral contraceptive pill was taken, leuprolide acetate (Lupron, TAP Pharmaceuticals, Waukegan, IL) 40 μg SC twice daily was self-administered until the day of hCG administration. Two days after initiation of GnRH-a, gonadotropin stimulation consisting of recombinant FSH (Gonal-F, Serono, Rockland, MA) 300 IU and hMG (Pergonal, Serono) 150 IU daily was initiated. A schematic for this protocol is provided in Figure 1.

A total of 179 patients were assigned to the GnRH AL protocol. Oral contraceptives were not used in this regimen. On day 3 of a spontaneous cycle, gonadotropin stimulation was initiated with recombinant FSH and hMG in the doses described above. Letrozole (Femara, Novartis, East Hanover, NJ) 2.5 mg per os daily was also initiated on day 3 and continued for 5 days. A GnRH antagonist, ganirelex acetate (Antagon, Organon, West Orange, NJ) or cetrorelix (Cetrotide, Serono) 0.25 mg SC daily was initiated once the lead follicle reached 14 mm in mean diameter. A schematic for this protocol is provided in Figure 2.

Serial ultrasound examinations and evaluation of serum E_2, LH, and P levels were used to assess follicular maturation. Gonadotropin doses were adjusted but not increased after 4 days of stimulation. Human chorionic gonadotropin (hCG) 10,000 IU IM was administered when at least two follicles achieved a mean diameter of 18 mm and serum E_2 levels were ≥500 pg/mL. Oocyte aspiration was performed 35 hours after hCG administration. Cycle cancellation was recommended when fewer than four developing follicles of an appropriate growth pattern were noted.

FIGURE 1

Schematic representation of the ML protocol.



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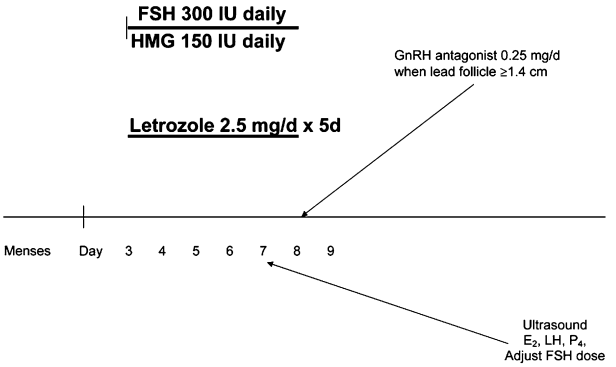
Embryo Culture and Transfer

Standard insemination or intracytoplasmic sperm injection (ICSI) was performed as clinically appropriate. Gametes and embryos were cultured in sequential G medium (Vitrolife, Englewood, CO) and incubated in 6% CO_2, 5% O_2, and 89% N_2. Indications for day 5 ET have been described elsewhere (17). If embryos were transferred on day 3, assisted hatching was routinely used in this patient population. Embryo transfers were performed under ultrasound guidance using a Wallace catheter (Marlow, Willoughby, OK) as described elsewhere (18).

Luteal support consisted of P in oil 50 mg IM initiated 2 days after oocyte retrieval and continued until the day of pregnancy testing. Transdermal E_2 (Vivelle-Dot, Novartis,

FIGURE 2

Schematic representation of the AL protocol.



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