Are gonadotropin-releasing hormone agonists losing popularity? Current trends at a large fertility center

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Objective: To explore the long- and short-term trends in LH-suppression protocol use and patient profile characteristics.
Design: Descriptive study, retrospective cohort.
Setting: Large, university-based IVF center.
Patient(s): Four thousand five hundred one fresh IVF cycles categorized by use of GnRH antagonist, luteal GnRH agonist, and follicular microdose GnRH agonist.
Intervention(s): None.
Main Outcome Measure(s): Frequency of use of LH-suppression protocol, patient and cycle characteristics, and outcomes at 10-year (1996–2005), 5-year (2001–5), and 3-year intervals (2004–6).
Result(s): In both the <40 and ≥ 40 age groups, GnRH antagonist use increased from 2001 to 2005, while luteal GnRH agonist and microdose use decreased. The most recent luteal agonist patients were better responders and had higher implantation, clinical pregnancy, and delivery rates. Antagonist patients in the <40 and ≥ 40 age groups had a better response in 2005 than in 2001 with higher clinical pregnancy rates. Microdose patients responded worse in 2005 than in 2001, although pregnancy rates did not change significantly. Such trends were echoed from 2004 to 2006.
Conclusion(s): The target population for GnRH antagonist has broadened to include younger, normal responders in addition to the traditional poor responder. Luteal agonist and microdose protocols are chosen less frequently and remain targeted toward good and poor responders, respectively. (Fertil Steril® 2010;93:101–8. ©2010 by American Society for Reproductive Medicine.)

Key Words: GnRH antagonist, GnRH agonist, poor responder, in vitro fertilization, LH suppression

Luteinizing hormone suppression allows for maximum follicular recruitment and development in an IVF cycle, and as newer agents are introduced, today's physicians are provided with additional protocol options. The first agents successfully developed were the GnRH agonists, which reduced the incidence of premature LH surge by reversibly blocking the secretion of pituitary gonadotropins. When compared with cycles with no LH suppression, the use of GnRH agonists led to higher pregnancy rates per started cycle (1) and a higher cumulative conception and live-birth rate in IVF, especially with the so-called long protocol (2). Such a protocol involves beginning a GnRH agonist in the midluteal phase of the preceding cycle and beginning gonadotropin stimulation once pituitary suppression is achieved.

While the long GnRH agonist regimen is one of the oldest and most commonly used protocols by many IVF programs to suppress ovulation and luteinization, such a protocol requires a longer course of ovarian stimulation, usually with higher exogenous gonadotropin requirements (3). GnRH agonists have been reported to inhibit ovarian responsiveness to gonadotropins (4). However, if a lower dose of GnRH agonists is used, the gonadotropin requirements can be decreased while also increasing oocyte yield, as was shown in a population of poor responders (5, 6). Some investigators feel that the luteal suppression achieved with GnRH agonists may be too profound for some patients and thus consider their use potentially detrimental in a known poor responder (7, 8).

The microdose GnRH agonist protocol begins with one cycle of oral contraceptives followed by an attenuated dose of GnRH agonist in the early follicular phase, followed by the initiation of gonadotropin stimulation 1–2 days later. Such a protocol has been touted as advantageous for poor responders, with some studies showing improved ovarian response (9) and ongoing pregnancy rates (10, 11). Other prospective randomized trials have not shown such an effect when comparing the microdose protocol with either the more traditional long luteal GnRH agonist protocol (12) or with the use of GnRH antagonists to suppress LH (13). Nonetheless, such initial research on the long GnRH agonist regimen and microdose GnRH agonist protocols were the basis for our center's incorporation of such protocols into clinical use.

With certain poor responders, it has been hypothesized that failure to respond to gonadotropin hyperstimulation may be

Received June 17, 2008; revised September 9, 2008; accepted September 11, 2008; published online October 29, 2008.
A.R. has nothing to disclose. L.K. has nothing to disclose. N.N. has nothing to disclose.
Presented at the 63rd Annual Meeting of the American Society of Reproductive Medicine, which was held in Washington, D.C., on October 13–17, 2007.
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due to a direct suppressive effect of the GnRH analogue on the ovary (14). Earlier primate research demonstrated that GnRH antagonists produce a "medical hypophysectomy" without the initial enhancement of gonadotropin secretion that occurs during the initiation of GnRH agonist therapy (15).

Through an application of this work, GnRH antagonists were initially added to human superovulation cycles (16) and later to IVF treatment regimens (17, 18). The benefits of GnRH antagonists included shorter stimulation time, lower gonadotropin dosage requirements (19), reduced patient costs, and shorter downtimes between consecutive cycles, as well as the ability to assess ovarian reserve immediately before stimulation (20). As the GnRH antagonists allowed maximal stimulation of a normal, nonsuppressed pituitary-ovarian axis, they were suggested to be of value in the treatment of poor responders (21–23). Due to these aforementioned reasons, the GnRH antagonists were initially incorporated into the clinical practice at our center. However, in the only randomized trial that compares GnRH antagonists with long GnRH agonist protocols in poor responders, the GnRH antagonists showed an improved ovarian response, yet no difference in the cancellation or clinical pregnancy rate (24).

The best protocol for the IVF patient is widely debated in the literature. While initial studies in a normal population did not find any difference in the pregnancy rates between GnRH agonist and antagonist cycles (7, 25), a recent meta-analysis in the Cochrane database reported that GnRH antagonists are associated with a lower pregnancy rate compared with the GnRH agonist long protocol (26). With regard to poor responders, there remains insufficient evidence to determine the optimal protocol, as reported by a different recent meta-analysis in the Cochrane database (27).

As the optimal protocol remains inconclusive, a wide variation in physician preferences remains. An increasing acceptance of GnRH antagonist protocols has led to a change in patient profiles using the different LH-suppression regimens. We present a descriptive study that explores the long- and short-term trends in stimulation protocols at a large, university-based fertility center in an effort to define the evolving role of GnRH analogues.

MATERIALS AND METHODS

A retrospective chart review was conducted on a total of 4501 fresh IVF cycles from the years 1996, 2001, and 2004–6. Cycles were excluded if they were done for purposes of oocyte cryopreservation, preimplantation genetic diagnosis, or embryo banking. Cycles were categorized by age (<40 years, ≥40 years) and the type of LH-suppressing protocol used: [1] GnRH antagonist, [2] long luteal GnRH agonist, or [3] follicular microdose GnRH agonist.

Patients on a GnRH antagonist protocol were treated with exogenous gonadotropins beginning on the evening of menstrual day 2, provided that they had serum FSH (<13.5 IU/L; DPC, Immulite, Los Angeles, CA) and E_2 (<75 pg/mL; DPC, Immulite) levels in the normal range that morning. Daily antagonists (Ganirelix 0.25 mg/0.5mL; Organon, West Orange, NJ; or Cetrotide 0.25 mg/mL, EMD Serono Inc., Rockland, MA) were initiated when the lead follicular measured ≥13 mm on transvaginal ultrasound, the serum E_2 measured ≥600 pg/mL, or the patient's stimulation reached cycle day 9. Patients on a long luteal GnRH agonist protocol began daily leuprolide acetate (0.5 or 1 mg, TAP Pharmaceuticals, Lake Forest, IL) injections in the midluteal phase and continued for at least 10 days or until pituitary suppression was evident (serum E_2 level ≤50 pg/mL). Exogenous gonadotropins were then initiated, and the daily leuprolide dose was reduced by half. Patients on the microdose GnRH agonist protocol began twice daily SC leuprolide acetate (25 μg) 4 days after a 14- to 21-day course of oral contraceptives. Exogenous gonadotropins were then initiated 2 days after beginning the low-dose GnRH agonist. The microdose GnRH agonist regimen was first used at our center in March 1997, and GnRH antagonist was first used in September 2000. Selection of an ovarian hyperstimulation protocol was determined by the same five attending physicians employed at the clinic before the beginning of the treatment cycle according to individual preference.

The starting gonadotropin dosage was determined by a combination of factors including patient age, previous stimulation response, and ovarian reserve testing and was adjusted according to individual response. IVF stimulation cycles were cancelled if less than three ovarian follicles developed and/or there was a marked (>25%) drop in serum E_2 level during hyperstimulation. In all protocols, 10,000 units of IM hCG (Novarel; Ferring Fertility, Parsippany, NJ; or Pregnyl, Organon) were administered when at least two lead follicles measured ≥17mm in diameter. Oocyte retrieval occurred 34–36 hours after hCG administration, and intracytoplasmic sperm injection (ICSI) was performed only in cases of male factor or history of failed fertilization. In 1996, only day 3 ETs were performed. Since 2001, patients have a day 5 blastocyst transfer when the following criteria are met: at least 5 two pronuclei zygotes on day 1 and at least three (age ≤40) or at least four (age 41–42) good-quality cleavage embryos on day 3. The number of embryos transferred was according to American Society for Reproductive Medicine guidelines (28). Patients received daily IM P (50 mg in sesame oil) for luteal support. Etiology of infertility was grouped into the following categories: poor responder (high FSH, history of cancelled cycles, signs of diminished ovarian reserve), high responder (polycystic ovarian syndrome, ovulatory dysfunction), male factor (ICSI, donor sperm), tubal factor (tubal, pelvic adhesions), uterine factor (fibroids, Asherman's, recurrent miscarriage), endometriosis, idiopathic, and other. Differences in demographics, total gonadotropin dosage, E_2 levels on the day of hCG administration, number of oocytes retrieved, and implantation (number of sacs