ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Assessing the adequacy of gonadotropin-releasing hormone agonist leuprolide to trigger oocyte maturation and management of inadequate response

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Objective: To compare outcomes of in vitro fertilization (IVF) cycles with adequate versus inadequate response to the gonadotropin-releasing hormone (GnRH) agonist trigger rescued with the use of human chorionic gonadotropin (hCG) retrigger, and to identify risk factors associated with an inadequate trigger.
Design: Retrospective cohort study.
Setting: Private practice.
Patient(s): Women at high risk for ovarian hyperstimulation syndrome who underwent an autologous IVF cycle and used GnRH agonist to trigger oocyte maturation before oocyte retrieval.
Intervention(s): Patients were triggered with GnRH agonist for final oocyte maturation before retrieval. Patients with an inadequate response, defined by low post-trigger serum LH and P concentrations or failure to recover oocytes after aspiration of several follicles, were retriggered with hCG.
Main Outcome Measure(s): Number of oocytes retrieved, fertilization rate, clinical pregnancy, and live birth.
Result(s): Two percent of patients triggered with GnRH agonist had an inadequate response and were retriggered with hCG. There was no statistically significant difference in clinical outcomes between the cycles that were retriggered with hCG and successful GnRH agonist triggers. Low body mass index, low baseline LH, and higher total dosage of gonadotropins required for stimulation were associated with an increased risk of having an inadequate response to the GnRH agonist trigger.
Conclusion(s): A small minority of patients triggered with GnRH agonist had an inadequate response. Rescheduling of oocyte retrieval after hCG retrigger yielded similar IVF outcomes. Evaluation of trigger response based on serum LH and P concentrations is time dependent. Patient characteristics suggestive of hypothalamic hypofunction were predictive of an inadequate response to the GnRH agonist trigger. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Gonadotropin-releasing hormone (GnRH) agonist, leuprolide acetate, human chorionic gonadotropin (hCG), retrigger, in vitro fertilization (IVF)

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The use of a gonadotropin-releasing hormone (GnRH) agonist to trigger final oocyte maturation after controlled ovarian hyperstimulation for in vitro fertilization (IVF) has gained popularity in recent years as a safer alternative to the use of human chorionic gonadotropin (hCG), particularly among higher responders, because its use greatly reduces the frequency and severity of ovarian hyperstimulation syndrome (OHSS) (1). However, one factor that has prevented more widespread adoption of this treatment protocol is that some patients fail to respond adequately to the GnRH agonist. Several groups have reported the

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occurrence of failed GnRH agonist triggers in which no oocytes were recovered from patients despite the aspiration of many available follicles (2–7).

In the present study, we report on our experience using the GnRH agonist trigger protocol in more than 1,800 autologous IVF patients at a large private metropolitan infertility practice, with a focus on risk factors for and management of inadequate trigger response. An inadequate, i.e., failed, response to the GnRH agonist trigger was defined as a cycle requiring retrigger with the use of hCG, based either on post-trigger assays of serum LH and P concentrations indicating that the expected LH surge did not occur or on failure to recover oocytes from the first several aspirated follicles, prompting termination of the initial oocyte retrieval attempt. We investigated various potential risk factors for failed trigger, in particular hypothesizing that both low body mass index (BMI) and low baseline (menstrual cycle day 3) LH concentration might be associated with higher risk for GnRH agonist trigger failure. These factors may be indicative of an increased probability of hypothalamic dysfunction and suboptimal LH surge. The efficacy of managing failed GnRH agonist triggers by retriggering with the use of hCG was evaluated by comparing treatment outcomes of these cycles with outcomes of successful GnRH agonist trigger cycles.

MATERIALS AND METHODS

We conducted a retrospective analysis of IVF cycles performed over a 2-year time period from January 1, 2010, to December 31, 2011, in a large metropolitan infertility practice including Washington, D.C., and Baltimore, Maryland. This retrospective cohort study was Institutional Review Board approved. A protocol of controlled ovarian hyperstimulation with the use of gonadotropins, coupled with GnRH antagonist suppression of spontaneous ovulation and GnRH agonist (leuprolide acetate) trigger of final oocyte maturation, was selectively used among women expected to be relatively high responders and therefore at higher risk of developing OHSS. Women were identified as high responders by a high number of follicles and/or a high serum E_2 level on the day of trigger. Women with a diagnosis of hypothalamic amenorrhea were excluded from this treatment protocol because they were expected to have a high failure rate due to inadequate pituitary priming.

Patients underwent controlled ovarian hyperstimulation following 2–4 weeks of oral contraception (norethindrone/ethinyl estradiol) if not otherwise contraindicated. Stimulation of follicular growth was achieved with the use of a combination of FSH (follitropin beta [Follistim], follitropin alpha [Gonal-F], or urofollitropin [Bravelle]) and menotropin (Menopur). The GnRH antagonist ganirelix acetate (Ganirelix) at a daily dose of 0.25 mg subcutaneously was started when the lead follicle measured $\geq$12 mm. Initially, 1 mg leuprolide acetate (Lupron) was used for triggering, and then 2 mg was used as the triggering dose. Trigger injections were administered subcutaneously and were given 36 hours before the scheduled oocyte retrieval. Most oocyte retrievals were scheduled for 7:00 AM through noon, so most triggers were administered at 7:00 PM to midnight, although some retrievals were scheduled for after noon. The morning following the trigger (generally between 7:00 AM and 10:00 AM), patients returned to have blood drawn for assay of serum LH and P concentrations. Our goal was to assay serum LH and P at ~8–13 hours after the trigger injection, but because of variation in the timings of both the trigger injections and the subsequent blood draws, the duration between the trigger injection and the hormone assay was sometimes shorter or longer.

Values of 15 mIU/mL for LH and 3 ng/mL for serum P were used as thresholds between what was considered to be an adequate versus inadequate response to the GnRH agonist trigger based on post-trigger hormone assays. If both LH level was >15 mIU/mL and serum P level was >3 ng/mL, we proceeded with oocyte retrieval as originally scheduled; otherwise the patient was retriggered with hCG and oocytes retrieved 36 hours after retrigger. These guidelines were used with some flexibility and modification depending on the duration between trigger administration and blood draw, the number of follicles, and the judgment of the treating physician. Specifically, patients having a longer interval between trigger injection and hormone assay were expected to have a lower LH value and higher progesterone value. Similarly, patients having a shorter interval between trigger and hormone assay were expected to have a higher LH value and lower P value. Early research on GnRH agonist triggers indicated that the mean serum P concentration reaches ~3 ng/mL by 6 hours after GnRH agonist trigger (8). However, patients with fewer follicles were expected to have lower P values than patients with higher number of follicles owing to less luteinization. Therefore, patients with fewer follicles were still taken to retrieval as originally scheduled if their LH levels were sufficiently high even if their P values were <3 ng/mL. In addition, we were more likely to proceed with retrieval as scheduled despite low post-trigger LH and P concentrations in our earliest days of using this protocol, when we were less sure about how to interpret these measures. Because these "thresholds" were not always strictly followed, there were several cases in which we proceeded with retrieval as scheduled despite falling below the thresholds, and a few cases in which patients fell slightly outside of these thresholds yet were still retriggered with hCG without attempting retrieval as originally scheduled (Supplemental Fig. 1, available online at fertstert.org). These cases were included in the analysis because they shaped our understanding of the clinical physiology of the GnRH agonist trigger and how to manage these patients.

If an oocyte retrieval was attempted as originally scheduled after the GnRH agonist trigger but no oocytes were recovered from the first several follicles aspirated, the retrieval was aborted based on the assumption that the trigger injection had failed. The number of follicles aspirated before abandoning the retrieval attempt in these cases varied, mostly from four to seven, depending on the post-trigger hormone assays, the size of aspirated follicles, and the judgment of the retrieval physician. Physicians would be more cognizant of the potential for failed trigger when post-trigger LH or P concentrations were relatively low, and so would be more