Microdose gonadotropin-releasing hormone agonist flare-up protocol versus multiple dose gonadotropin-releasing hormone antagonist protocol in poor responders undergoing intracytoplasmic sperm injection–embryo transfer cycle

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Objective: To compare the efficacy of microdose GnRH agonist (GnRH-a) flare-up and multiple dose GnRH antagonist protocols in patients who have a poor response to a long luteal GnRH-a protocol.
Design: Prospective, randomized, clinical study.
Setting: University hospital.
Patient(s): Forty-two poor responder patients undergoing intracytoplasmic sperm injection (ICSI)–embryo transfer cycle.
Intervention(s): Twenty-one patients received microdose leuprolide acetate (LA) (50 μg twice daily) starting on the second day of withdrawal bleeding. The other 21 patients received 0.25 mg of cetrorelix daily when the leading follicle reached 14 mm in diameter.
Main Outcome Measure(s): Serum E_2 levels, number of growing follicles and mature oocytes, embryo quality, dose of gonadotropin used, cancellation, fertilization, implantation rate and pregnancy rate (PR).
Result(s): The mean serum E_2 concentration on the day of hCG administration was significantly higher in the microdose GnRH-a group than in the GnRH antagonist group (1,904 vs. 1,362 pg/mL). The clinical PRs per started cycle of microdose GnRH-a and GnRH antagonist groups were 14.2% and 9.5%, respectively. There were no statistically significant differences in the other ovulation induction characteristics, fertilization and implantation rates.
Conclusion(s): Microdose GnRH-a flare-up protocol and multiple dose GnRH antagonist protocol seem to have similar efficacy in improving treatment outcomes of poor responder patients. (Fertil Steril® 2009;91:2437–44. ©2009 by American Society for Reproductive Medicine.)

Key Words: Controlled ovarian hyperstimulation, flare-up protocol, GnRH agonist, GnRH antagonist, poor responder, recombinant FSH

Despite considerable advances in assisted reproductive techniques (ART), management of poor responder patients is still a challenge. Although there is lack of uniform definitions, poor response to controlled ovarian hyperstimulation (COH) can be generally defined as unsatisfactory ovarian response in terms of low number of follicles developed, low serum E_2 levels, and low number of oocytes retrived despite adequate ovarian stimulation. However, the cutoff points for these parameters that define poor response vary between studies (1, 2). The lack of a uniform definition of poor response causes difficulty in comparing treatment outcomes.

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Multiple criteria have been suggested to assess ovarian reserve and response to ovarian stimulation including biological age, static hormonal tests for FSH, E_2, inhibin B, and anti-Müllerian hormone or dynamic hormonal tests such as the clomiphene citrate (CC) challenge test and gonadotropin agonist stimulating test, or ultrasonographic evaluations such as antral follicle count, measurement of ovarian volume, and ovarian stromal blood flow (3, 4). However, the poor responder is revealed definitively only during ovarian stimulation because there is no definitive evidence for their predictive value (1, 3).

Many treatment modalities have been suggested to improve ART outcomes in poor responders. These modalities include: [1] variations in the type, dose, and timing of gonadotropins, or GnRH analogues (agonists and antagonists), [2] the use of oral contraceptive (OC) pills, CC, aromatase inhibitors, growth hormone/growth hormone releasing hormone (GHRH), corticosteroids, E_2, testosterone, nitric oxide donors, or aspirin as adjuvant therapies. Apart from these regimens, an alternative

approach suggested for these patients is natural cycle ART (1, 5, 6). Despite all of these modalities, when poor responders are compared with normal responders, the number of oocytes and embryos is low and of poor quality. Consequently, rates of implantation and pregnancy (PR) are significantly worse. Oocyte donation offers an option for patients who have failed these treatments. However, this option may not always be feasible for couples from different religions and cultures. In addition, this option is illegal in some countries.

In the past years, several studies performed on poor responder patients have supported the use of a microdose GnRH agonist (GnRH-a) flare-up protocol (7–9). Two main advantages of this protocol are: [1] the ovarian suppression is not excessive and [2] the initial stimulation of GnRH receptors and consequent secretion of endogenous gonadotropins reinforce the effects of exogenously administered gonadotropins.

More recently the use of GnRH antagonists has been suggested as the preferred ovarian stimulation protocol in poor responders. Clinical advantage of GnRH antagonists over GnRH-a is the absence of the initial pituitary gonadotropin down-regulation phase and, as a consequence, they promptly suppress pituitary gonadotropin secretion, which allows their use without the need for a desensitization period. In addition, with the aim of preventing a premature LH surge while not causing any ovarian suppression in the early follicular phase, which is a critical period for follicular recruitment, GnRH antagonists can be administered during the late follicular phase. This is particularly important in those patients who have decreased ovarian reserve (10).

The aim of this prospective, randomized study was to compare the effects of microdose GnRH-a flare-up and multiple dose GnRH antagonist protocols on cycle parameters and clinical outcomes in poor responder patients. The investigators of the present study believe that, at present, these two protocols are popular in terms of treatment of poor responders and efforts to define their efficiency and safety will contribute to the improvement of therapeutic management of poor responder patients.

MATERIALS AND METHODS

Forty-two (42) consecutive poor responder infertile women admitted to Ankara University School of Medicine, Department of Obstetrics and Gynecology from November 2003 to April 2007 were recruited to this study. Poor responders were defined when one or more of the following criteria was present in at least one previous failed ART cycle (using a standard GnRH-a long protocol): [1] number of mature oocytes retrieved less than four; [2] level of E_2 <500 pg/mL on the day of hCG administration; or [3] a prior cancelled stimulation cycle due to poor ovarian response. In general, the starting dose of gonadotropin in the previous failed cycles varied between 150 and 225 IU/day, depending on the age, body mass index (BMI), and ovarian response to previous cycle (if present) and increased to a maximum of 600 IU/day depending on the ovarian response. Features of previous cycles in terms of poor ovarian response are summarized as follows: 14 of 42 cycles were cancelled because of poor ovarian response; in 25 cycles, the number of mature oocytes was <4 and in 8 of these 25 cycles, E_2 levels on the day of hCG were <500 pg/mL on the day of hCG; and in 3 cycles, the number of mature oocytes was ≥4 despite that E_2 levels on the day of hCG administration was <500 pg/mL. Forty-two women were prospectively, randomly assigned to either microdose GnRH-a flare-up group (group 1; microdose flare-up group) or multiple dose GnRH antagonist group (group 2; antagonist group). Randomization was based on the consecutive number method. Exclusion criteria were polycystic ovarian syndrome (PCOS), severe endometriosis (according to the revised American Fertility Society stage III and IV), or the presence of only one ovary.

Microdose flare-up group (group 1) consisted of 21 patients in 21 cycles. In this group, OC pill (Desolette; Organon, Istanbul, Turkey: 0.03 mg of ethinyl E_2 and 0.15 mg of desogestrel) was started on cycle day 1 of the previous cycle for 21 days. On the second day of withdrawal bleeding, leuprolide acetate (LA; Lucrin; Abbot, Istanbul, Turkey) 50 μg SC twice daily (100 μg/day) was initiated. Recombinant FSH (Gonal-F; Serono, Istanbul, Turkey) 300–450 IU/day was begun on cycle day 3. Both LA and recombinant FSH continued until the day of hCG administration.

Multiple dose GnRH antagonist group (group 2) consisted of 21 patients in 21 cycles. Oral contraceptive pills were not used in this protocol. Recombinant FSH was started on cycle day 2 and later 0.25 mg of cetrorelix was administered daily when the leading follicle reached 14 mm in diameter until the hCG injection. In both stimulations regimens all cycles received an initial gonadotropin dose of 300–450 IU/day of recombinant FSH for the first 5 days, followed by individual adjustments in gonadotropin dose according to ovarian response. When the average diameter of the leading follicles reached ≥18 mm and serum E_2 levels were ≥500 pg/mL, 10,000 IU of hCG (Profasi; Serono) was administered, followed 35–36 hours later by an ultrasound-guided transvaginal oocyte aspiration. The intracytoplasmic sperm injection (ICSI) procedure was performed 4–6 hours after oocyte aspiration for all of the mature oocytes. Oocytes were examined 16–18 hours after ICSI for pronuclei (PN). Normal fertilization was defined as existence of two pronuclei (2PN). The embryos obtained were categorized on day 2 or 3 into four categories depending on their morphologic appearance, zonal thickness, cytoplasmic fragmentation, and blastomere size (grade I [high quality]: embryos with equal blastomeres and no observed cytoplasmic fragmentation; grade II [good quality]: embryos with equal blastomeres and <20% fragmentation of the cytoplasm; grade III [fair quality]: embryos with unequal blastomers and 20%–50% fragmentation of the cytoplasm; grade IV [poor quality]: embryos with unequal blastomers and >50% fragmentation of the cytoplasm). Depending on patient's age, embryo quality, and the number of embryos available, one to five embryos were transferred 2–3 days after oocyte collection under transabdominal