ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Cost-effectiveness comparison between pituitary down-regulation with a gonadotropin-releasing hormone agonist short regimen on alternate days and an antagonist protocol for assisted fertilization treatments

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Objective: To compare cost-effectiveness between pituitary down-regulation with a GnRH agonist (GnRHa) short regimen on alternate days and GnRH antagonist (GnRHant) multidose protocol on in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) outcome.
Design: Prospective, randomized.
Setting: A private center.
Patient(s): Patients were randomized into GnRHa (n = 48) and GnRHant (n = 48) groups.
Intervention(s): GnRHa stimulation protocol: administration of triptorelin on alternate days starting on the first day of the cycle, recombinant FSH (rFSH), and recombinant hCG (rhCG) microdose. GnRHant protocol: administration of a daily dose of rFSH, cetrorelix, and rhCG microdose.
Main Outcome Measure(s): ICSI outcomes and treatment costs.
Result(s): A significantly lower number of patients underwent embryo transfer in the GnRHa group. Clinical pregnancy rate was significantly lower and miscarriage rate was significantly higher in the GnRHa group. It was observed a significant lower cost per cycle in the GnRHa group compared with the GnRHant group ($5,327.80 ± 387.30 vs. $5,900.40 ± 472.50). However, mean cost per pregnancy in the GnRHa was higher than in the GnRHant group ($19,671.80 ± 1,430.00 vs. $11,328.70 ± 907.20).
Conclusion(s): Although the short controlled ovarian stimulation protocol with GnRHa on alternate days, rFSH, and rhCG microdose may lower the cost of an individual IVF cycle, it requires more cycles to achieve pregnancy.
Clinical Trial Registration Number: NCT01468441. (Fertil Steril® 2013;■:■–■. ©2013 by American Society for Reproductive Medicine.)
Key Words: Controlled ovarian stimulation, GnRHa, GnRHant ICSI, pituitary down-regulation

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Pituitary suppression is a well established strategy in the protocols of controlled ovarian stimulation (COS) for in vitro fertilization (IVF). For the past 20 years GnRH agonists (GnRHa's) were used for this purpose (1). By inducing hypophyseal desensitization, GnRHa protocols

prevent premature ovulation and luteinization, and significantly reduce the cycle cancellation rate compared with cycles where gonadotropins are administered alone (2). However, the mechanism of action of GnRHa requires a long period of treatment and has a long-lasting, potentially detrimental, effect in the luteal phase (2, 3). In contrast to GnRHa, GnRH antagonists (GnRHant's) competitively block pituitary GnRH receptors, inducing a fast and reversible suppression of gonadotropin secretion (4). The use of antagonist protocols is more convenient for the patient because treatment time is shortened and fewer injections and lower amounts of gonadotropins are required (5). However, it has been suggested that GnRHant is an inhibitor of the cell cycle by decreasing the synthesis of growth factors and therefore compromises the mitotic program of follicles, embryo blastomere, and endometrium (6).

GnRHant-treated patients showed lower clinical pregnancy rates compared with GnRHa-treated patients (7). Hernandez et al. (6) reported that the embryo, as well as granulosa and endometrial cells, harbors GnRH receptors, and therefore, a direct effect from the GnRHant on these cells may be a possible cause for implantation failure. Nevertheless, this difference disappeared in frozen-thawed embryo transfers. Possibly, an endometrial impact could be attributed to this result (8). On the other hand, Bodri et al. (5), in a systematic review and meta-analysis, demonstrated that there are no statistically significant differences in ovarian response or recipient ongoing pregnancy rates with the use of either GnRHa or GnRHant protocols. Similarly, Al-Inany and Aboulghar (7) and Kolibianakis et al. (9) showed that no clear benefit regarding live birth rate was attributed to one type of GnRH analogue.

The achievement of a simple, safe, and cost-effective treatment protocol in COS is of pivotal importance to improve the quality of care in assisted reproduction. An alternative would be the use of a short GnRHa, as suggested by Orvieto et al. (10). Furthermore, the unwanted effects of the agonists are thought to be eliminated by stopping or decreasing doses of the analogues (11). A previous study of daily or alternate day administration of long-acting GnRH analogue found similar pituitary suppression with each dose (2).

Although some authors have aimed to improve IVF cycle outcome through modifications of the COS protocol (12, 13), others have focused on lowering the cost of the cycles through a reduction of the total dose of FSH administered. Some studies have demonstrated that the administration of recombinant hCG (rhCG) microdoses in the late stages of COS resulted in adequate response to stimulation and successful pregnancies (14, 15). Moreover, the addition of rhCG shortened the interval of stimulation, significantly reduced FSH requirement, and thus minimized patient cost (16). An interesting approach would be to unite the reduced costs of both pituitary suppression with GnRHa on alternate days and the administration of rhCG microdoses in the late stages of COS. Therefore, the present prospective randomized study was undertaken to compare the effects of administering a daily dose of GnRHant versus an alternate-day dosage of short GnRHa on ovarian response and intracytoplasmic sperm injection (ICSI) outcome in patients stimulated with recombinant FSH (rFSH) and rhCG microdoses.

MATERIALS AND METHODS

A randomized clinical trial, approved by the local Institutional Review Board, was performed in a private fertility center. Inclusion criteria were as follows: women of good physical and mental health, $\leq$37 years old, with regular menstrual cycles of 25–35 days, normal basal FSH and LH levels, body mass index (BMI) $<$30 kg/m^2, presence of both ovaries and intact uterus, absence of polycystic ovaries, endometriosis, or gynecologic/medical disorders, and a negative result in a screening for sexually transmitted diseases. All patients signed a written informed consent form.

No patient had received any hormone therapy for $\geq$60 days preceding the study. Eligible patients who agreed to participate were randomized into two treatment groups: GnRHa group (n = 48), and GnRHant group (n = 48; Fig. 1). Patients were allocated by a single nurse to a GnRH analogue treatment group according to a computer-generated randomization table.

Controlled Ovarian Stimulation Protocols

All patients received oral contraceptive pills (OCPs; 20 μg etinilestradiol and 75 μg gestodeno; Ginesse; Farmoquímica) to synchronize cycles.

GnRH Agonist Short Regimen (Fig. 2A)

In the GnRHa group, a dose of tryptorelin (0.1 mg Gonapeptyl; Ferring) was administered on alternate days from day 1 of the menstrual cycle. After 3 days, ovarian stimulation was commenced with 225 IU rFSH (Gonal F; Serono) daily (day 1 of ovarian stimulation = S1), for 3 days. On S4, the recombinant FSH dose was reduced to 150 IU, until the visualization of at least one follicle $\geq$ 14 mm. The day after the recombinant FSH dose was reduced to 75 IU and concomitantly administered with the rhCG microdose (7.7 μg, equivalent to 200 IU hCG), which was obtained by the dilution of one ampule of 250 μg rhCG (Ovidrel; Serono), subcutaneously (SC) for 2 days. After that, the rhCG microdose was administered alone until the day of ovulation trigger (see next section).

GnRH Antagonist Regimen (Fig. 2B)

In the GnRHant group, ovarian stimulation was performed as follows. On day 3 of the cycle, ovarian stimulation was commenced with 225 IU rFSH on a daily basis (day 1 of ovarian stimulation = S1). On S4, the recombinant FSH dose was reduced to 150 IU until the visualization of at least one follicle $\geq$14 mm, at which time we began the administration of 0.25 mg cetrorelix acetate (Cetrotide; Serono) SC. The day after beginning the antagonist therapy, the rFSH dose was reduced to 75 IU and the concomitant SC administration of the rhCG microdose was initiated and continued for 2 days. After that, the rhCG microdose and GnRHant were administered until the day of ovulation trigger.

The following steps of the treatment were the same for both treatment regimens.