Cetrorelix protocol versus gonadotropin-releasing hormone analog suppression long protocol for superovulation in intracytoplasmic sperm injection patients older than 40

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Objective: To determine which protocols work better between cetrorelix and long protocols in older patients in a randomized controlled study.
Design: A controlled randomized study in a single private IVF center.
Setting: Infertile women referred to a private IVF center.
Patient(s): Five hundred sixty-four women 40 years or older undergoing IVF.
Intervention(s): At their first IVF cycle, the women were randomized into two study groups using a computer-generated number sequence: 281 cases were treated with the cetrorelix protocol, and 283 patients were treated with a long protocol for controlled ovarian hyperstimulation.
Main Outcome Measure(s): Days of stimulation, E_2 on the day of hCG administration, amount of FSH administered, number of oocytes yielded, number of embryos obtained, pregnancy rate, and implantation rate.
Result(s): Patients treated with the long protocol showed a significantly higher number of oocytes retrieved and a higher pregnancy rate for both the cycle and transfer with respect to the cetrorelix protocol patients. The other parameter evaluated did not show any statistically significant differences.
Conclusion(s): Our study showed that the long protocol performed better in older women than the cetrorelix protocol and that the GnRH antagonist may be detrimental in older women. (Fertil Steril® 2009;91:1842–7. ©2009 by American Society for Reproductive Medicine.)

Key Words: GnRH antagonist, cetrorelix, long protocol, GnRH analog, IVF outcome, controlled ovarian hyperstimulation

The introduction of pituitary suppression with GnRH analog during ovarian stimulation with hMG or FSH resulted in improved clinical pregnancy rates (1–5). Follicular recruitment is enhanced, and premature LH surges and follicular luteinization are avoided (6). It has been shown that without GnRH analog desensitization, about 20% of patients experienced premature LH surge during controlled ovarian hyperstimulation (COH) and that daily administration of 15 μg triptorelin is sufficient to prevent the LH surge (7).

The antagonists of GnRH, cetrorelix and ganerelix, have recently been introduced on the market for COH in IVF cycles (8–10). The GnRH antagonists have been proven to be effective and reliable in preventing the LH surge in cycles stimulated with gonadotropins for IVF; these substances do not show the so-called flare-up phenomenon. Instead, they induce the inhibition of pituitary secretion of FSH and LH immediately after injection (11).

Various stimulation protocols that incorporate the use of cetrorelix have been suggested. The multiple-dose regimen requires daily injections of the antagonist starting on day 5 or 6 of the stimulation period until the administration of hCG (12, 13): the dose of 0.25 mg per day, starting from day 7 of gonadotropin administration, is the minimal effective dose for a multiple-dose protocol to prevent the onset of premature rises of LH (10). On the other hand, the use of a single-dose protocol in the late follicular phase to prevent the LH surge has been proposed (14). Both protocols have shown good performance, even though the multiple dose gains more consensus from physicians because it also prevents LH rises during the entire stimulation, including the premature surge, with a lower LH tone for the entire follicular phase (12–14).

Several investigators have shown that the use of the antagonist reduces the dose of FSH needed to stimulate the ovary, especially when compared with the classical long protocol with GnRH analogs (16–20). Furthermore, it has been shown that the use of GnRH antagonists associated with

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gonadotropin COH for IVF is at least as effective as the GnRH analog long protocol in patients with normal ovarian response, like women at the younger reproductive age (<35 years old). Furthermore, from the data published in the literature, it seems that cetrorelix decreases the risk of ovarian hyperstimulation syndrome (OHSS) with respect to the long protocol with GnRH analog (15–21).

However, with respect to poor responder patients or older women, the data in the literature are more conflicting. Early reports showed that the use of cetrorelix in these patients may improve the ovarian response and the number of oocytes that are yielded (22–25, 27). On the other hand, other data published did not confirm these findings (26, 28–30). In our previous report, we showed that the GnRH analog long protocol worked better than the short protocol in women 40 years or older, who in turn have a lower chance of pregnancy even for their reduced ovarian reserve (31). The aim of our study was to evaluate which protocol between cetrorelix and the GnRH analog long protocol is more effective in ovarian stimulation for IVF in women 40 years or older.

MATERIALS AND METHODS

Patient Selection

All patients who were at least 40 years old but younger than 45 who referred to the IVF program of Bioroma Paideia Hospital, Rome, Italy, to undergo their first IVF cycle from January 2003 to June 2007 were eligible for the study. The inclusion criteria were age 40 years or older and no previous IVF cycle, and the exclusion criteria were FSH >10 IU/mL, a previous IVF cycle, and age 45 years or older.

The trial was designed according to Consolidated Standard of Reporting Trials guidelines. The study was reviewed and approved by the Institutional Review Board. Of the 585 eligible patients undergoing IVF during the study period, 570 agreed to participate. The patients were randomized by means of a computer-generated randomization number sequence at the time that their cycle was scheduled, with 285 patients for each arm of the study. All patients undergoing IVF and participating in the study gave their informed consent. All patients were nulliparous who underwent a standard infertility evaluation, and none of the patients eligible for the study showed FSH >10 IU/mL. Women with polycystic ovaries were excluded from the study because these women often respond unpredictably, with an increased risk of hyperstimulation or a low response and bad-quality oocytes. All basal FSH assays were done in the same laboratory using the same radioimmunoassay kit (OCFF07-FSH RIAgnost, CIS Bio-International, Milan, Italy).

Patients were randomly allocated into two study groups: the cetrorelix group (group A) in which ovarian stimulation comprised GnRH antagonist and recombinant FSH (recFSH) alone starting from cycle day 2, and the long protocol group in which GnRH analog, bBuserelin (group B), was given as a pretreatment; recFSH administration took place when pituitary desensitization was established. The patients allocated to group A started recFSH (Gonal-f, Serono, Italy) at a dosage of 300 IU daily from the second day of their menstrual cycle for 5 days until the first ovarian ultrasound on the sixth cycle day and plasma E_2 test; cetrorelix (Cetrotide, Serono, Italy) at a dosage of 0.25 mg/die was administered when the dominant follicle was of 14 mm in mean diameter or the E_2 plasma levels were 600 pg/mL, until the day of hCG administration. Patients in group B were administered buserelin (Suprefact, Hoechst, Milan, Italy) SC, 0.4 mg daily, on days 22–24 of their previous cycle; ovarian suppression was assessed by daily hormonal profiles of E_2, and ultrasound scan of the ovaries every third day. Suppression was confirmed when E_2 reached the level of <30 pg/mL and follicles with a dimension <15 mm in mean diameter were visible on ultrasound scan examination. When suppression was confirmed by E_2 and ultrasound examinations, recFSH was commenced at 300 IU of recFSH on the second day of the menstrual cycle in the long protocol.

From the sixth day of stimulation in both groups, daily monitoring of follicle size by ultrasound was performed, and plasma levels of E_2 were measured. From this stage, the dose of recFSH was adjusted depending on the individual response of each patient. The criteria used for triggering ovulation with 10,000 IU of IM hCG (Gonasi HP 5000, AMSA, Rome, Italy) were plasma E_2 between 800 and 3500 pg/mL and at least three follicles >16 mm in mean diameter (two perpendicular measurements). The cycle was cancelled in case of poor ovarian response, when less than three follicles were observed on the ninth day, or in case of OHSS with E_2 >3500 pg/mL.

Oocyte retrieval was performed under ultrasound guidance by the transvaginal route on day 0, 36 hours after the injection of hCG, and all patients underwent intracytoplasmic sperm injection (ICSI) according to published procedures (32) to maximize chances of fertilization, especially considering the age of the women and to avoid confounding factors due to different procedures of oocyte fertilization. Patients were aware of ICSI risks, and they agreed to undergo the procedure. Oocytes were observed 18 hours after ICSI for their pronuclei and 44 hours after insemination for embryo development.

The embryos obtained were categorized on day 3 into three categories, depending on their morphological appearance. Grade A embryos had six to eight or more equal and regular blastomeres without the presence of cytoplasm fragments; grade B embryos had less than six to eight unequal blastomeres with or without cytoplasmatic fragments; grade C embryos were fragmented embryos (more than 50%) (33).

Embryos were transferred about 72 hours after insemination using the Sydney Embryo Transfer Catheter (Cook Ireland Ltd., Limerick, Ireland). The policy of our clinic is to transfer no more than three embryos (preferably of the best quality). All transfer procedures were performed by the same physician to avoid interoperator variability. All