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ARTICLE

Follicular and endocrine profiles associated with different GnRH-antagonist regimens: a randomized controlled trial

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Abstract This trial assessed the impact of early initiation of gonadotrophin-releasing hormone (GnRH) antagonist on follicular and endocrine profiles compared with the fixed GnRH-antagonist protocol. Eighty-five oocyte donors were randomized to GnRH antagonist starting in the mid-luteal phase of the prestimulation cycle (degarelix-ML group), on stimulation day 1 (early follicular phase, degarelix-EF group) or day 6 (fixed protocol) (mid-follicular phase, ganirelix-MF group). Subjects in the degarelix-EF and ganirelix-MF groups received placebo in the prestimulation cycle. At start of stimulation, serum concentrations of FSH (4.6 ± 2.3 versus 6.0 ± 1.8 IU/l), LH (2.7 ± 1.4 versus 4.7 ± 1.9 IU/l) and oestradiol (87 ± 35 versus 129 ± 50 pmol/l) were markedly lower ($P < 0.001$) in the degarelix-ML group than in the placebo group. The coefficients of variation of follicle size (36.7 ± 5.5% versus 39.2 ± 9.4%) were not significantly different. No differences in endometrial histology, embryo quality and pregnancy rates in recipient cycles were observed between the regimens. In conclusion, early administration of GnRH antagonist altered the endocrine profile without modifying the follicular synchrony for the majority of subjects. Whether patients with a more heterogeneous follicle size at start of stimulation may benefit from an earlier intervention remains to be proven.

KEYWORDS: degarelix, endocrinology, follicular development, GnRH antagonist, ovarian stimulation

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Introduction

The introduction of gonadotrophin-releasing hormone (GnRH) antagonist protocols in patients undergoing IVF/intracytoplasmic sperm injection has been associated with a lower number of retrieved oocytes compared with the long GnRH-agonist protocol (Albano et al., 2000; Al-Inany et al., 2007; Borm and Mannaerts, 2000; Fluker et al., 2001; Olivennes et al., 2000; Roulier et al., 2003; The European Middle East Orgalutran study group, 2001). GnRH agonists suppress endogenous LH and FSH and the co-ordinated follicle recruitment is a direct response to exogenous gonadotrophin stimulation alone (Fauser and van Heusden, 1997). The standard fixed GnRH-antagonist protocol, on the other hand, in which the antagonist is administered from stimulation day 5 or 6 is associated with a two-stage follicular recruitment, since growth of a few leading follicles will be initiated by endogenous FSH before exogenous gonadotrophin is administered. As a result, a more heterogeneous follicle cohort in terms of size (asynchrony) will be achieved with the standard GnRH-antagonist protocol compared with the long GnRH-agonist protocol, potentially leading to reduced number of oocytes retrieved (Fleming, 2002; Huirne et al., 2007).

To improve ovarian-stimulation outcome in GnRH-antagonist cycles, it has been suggested to induce pituitary suppression of endogenous FSH and LH during the transitional luteal—follicular phase to allow optimal synchronization of the follicular cohort before exogenous gonadotrophin stimulation. This suppression can be achieved by administration of oestrogen in high doses or combined oestrogen/progestogen preparations in the transitional phase. Thus, pretreatment with oestradiol (Fanchin et al., 2003) or the oral contraceptive pill (Cedrin-Durnerin et al., 2007; Huirne et al., 2006; Rombauts et al., 2006) has been suggested to improve synchronization in GnRH-antagonist cycles through its FSH-suppressive effects. However, oestrogen preparations and oral contraceptives may have an impact on follicle/oocyte development parameters and the endometrial profile. Actually, oral-contraceptive pretreatment in GnRH-antagonist cycles may lower implantation rates (Rombauts et al., 2006) and increase pregnancy-loss rates (Griesinger et al., 2010; Kolibianakis et al., 2006).

A different approach to achieve a more synchronized follicular growth and lower exposures to FSH, LH, oestradiol and progesterone (endocrine synchrony) in the follicular phase of the stimulation cycle in GnRH-antagonist regimens is to initiate the GnRH-antagonist treatment earlier than in the mid-follicular phase. In particular, a mid-luteal start of GnRH-antagonist treatment may mimic more closely the follicular growth and endocrine profile of the standard long GnRH-agonist protocol than the fixed GnRH-antagonist protocol. Furthermore, due to the immediate onset of action of GnRH antagonists on pituitary suppression and subsequent decrease of ovarian steroid concentrations and menstrual shedding, gonadotrophin stimulation could start just a few days after administration of the GnRH antagonist. In line with this approach, a study performed in healthy female volunteers suggested that GnRH-antagonist administration during the last days of the luteal phase reduces the serum concentration of FSH and the mean follicular size as well as attenuates follicular-size discrepancies during the subsequent early follicular phase (Fanchin et al., 2004).

The purpose of the present phase-II prospective randomized trial was to assess if earlier initiation of GnRH antagonist than in the standard fixed GnRH-antagonist protocol could improve endocrine and follicular synchrony at the start of stimulation. Two GnRH-antagonist compounds with different profiles were used for this investigation: (i) the investigational degarelix depot formulation (2.5 mg); and (ii) the commercially available ganirelix daily formulation (0.25 mg). Clinical data from healthy female volunteers have shown that degarelix administration at a dose of 2.5 mg causes an immediately profound suppression of LH and FSH and that it takes approximately 7 days for LH to return to the baseline concentration. In contrast, dosing with ganirelix 0.25 mg causes only temporary drops in LH and FSH concentrations before returning to baseline within 24 h (Oberyé et al., 1999). Given that regimens with early administration of GnRH antagonist would require dosing for more than 15 days, a 7-day administration of degarelix 2.5 mg (i.e. one injection/week) would be more convenient as it minimizes the number of injections for the study subjects. The reference arm was chosen to be ganirelix 0.25 mg daily starting on day 6 of stimulation as the efficacy and safety of this regimen have been established in comparative clinical trials (Borm and Mannaerts, 2000; The European and Middle East Orgalutran study group, 2001). Since degarelix 2.5 mg starting on day 6 of stimulation would be expected to be associated with a different endocrine response compared with daily administration of ganirelix 0.25 mg, given the stronger suppression of LH and FSH with the depot regimen, it would not represent the most appropriate reference arm for this investigation on early initiation of GnRH antagonist.

Materials and methods

Study population

Subjects eligible for this trial were oocyte donors undergoing ovarian stimulation for assisted reproduction technology and recipient couples receiving oocytes from these donors.

Oocyte donors

Main inclusion criteria were: age 18—35 years; body mass index (BMI) 18—29 kg/m^2; regular menstrual cycle of 26—35 days, presumed to be ovulatory; early follicular-phase serum concentration of FSH within normal limits (1—12 IU/l). Main exclusion criteria were: abnormal karyotype; polycystic ovarian syndrome, endometriosis stage III/IV; history of being a 'poor responder', defined as >20 days of gonadotrophin in a previous stimulation cycle, or any previous cancellation of a stimulation cycle due to limited follicular response, or development of less than 4 follicles ≥15 mm in a previous stimulation cycle; history of recurrent miscarriage; severe OHSS in a previous stimulation cycle or any contraindication for the use of gonadotrophins.