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ARTICLE

Randomized, controlled, open-label, non-inferiority study of the CONSORT algorithm for individualized dosing of follitropin alfa

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Abstract In this randomized, controlled, open-label, phase IV study, ovarian response after a follitropin alfa starting dose determined by the CONSORT calculator was compared with a standard dose (150 IU). Normo-ovulatory women (aged 18–34 years) eligible for assisted reproductive techniques were recruited (23 centres: nine European countries and Chile); 200 women were randomized (CONSORT [$n = 96$]; standard dosing [$n = 104$]). Significantly lower mean daily (121.5 versus 167.4 IU; $P < 0.001$) and total (1288.5 versus 1810.0 IU; $P < 0.001$) doses of follitropin alfa were administered in the CONSORT group. Clinical pregnancy rates were CONSORT (36.0%) and standard dosing (35.5%); estimated difference (confidence interval 0.6%; −13.5 to 14.6). Ovarian hyperstimulation syndrome occurred in 6.3% and 12.5% of patients in the CONSORT and standard-dosing groups, respectively. The primary efficacy analysis found a significantly lower mean [SD] number of oocytes retrieved in the CONSORT (10.0 [5.6]; $P = 0.037$) versus standard-dosing group (11.8 [5.3]). Although the CONSORT calculator was statistically inferior to standard dosing in the number of oocytes retrieved, clinical pregnancy rates (fresh embryo transfers) were similar in both groups, and incidence of ovarian hyperstimulation syndrome was lower in the CONSORT group.

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Introduction

All ovarian stimulation protocols aim to produce a high-quality oocyte cohort while avoiding the development of an excessive number of follicles (Fauser et al., 2008; van der Gaast et al., 2006; Verberg et al., 2009). The quantity of exogenous gonadotrophin required to induce follicle development, however, may vary among women (Devroey et al., 2009). Women with a poor ovarian response develop fewer oocytes (Ferraretti et al., 2011) and have lower pregnancy rates (Oudendijk et al., 2012) compared with normal responders. An excessive response carries a risk of ovarian hyperstimulation syndrome (OHSS) (Delvigne and Rozenberg, 2002) and may have detrimental effects on endometrial receptivity (Bourgain and Devroey, 2003; Simon et al., 1995; van der Gaast et al., 2006).

Selection of the optimal starting dose of FSH to retrieve an appropriate number of oocytes and avoid OHSS is complex (Howles et al., 2006) and is largely empirical (Nardo et al., 2011). Accurate prediction of an individual's ovarian response could reduce the risk of OHSS and avoid poor ovarian response. To this end, numerous biomarkers predictive of a woman's ovarian response to ovarian stimulation have been proposed, but few algorithms have been evaluated for their ability to determine the optimal starting dose of gonadotrophin (Popovic-Todorovic et al., 2003a).

The CONSORT (CONsistency in r-FSH Starting dOses for individualized tReatmenT) algorithm (the CONSORT calculator) was developed to define the optimal starting dose of recombinant human (r) FSH (follitropin alfa [GONAL-f®]; Merck Serono SA, Geneva, Switzerland) for women undergoing ovarian stimulation in a long gonadotrophin-releasing hormone (GnRH) agonist protocol (Howles et al., 2006). The CONSORT algorithm was developed through the analysis of data from women (n = 1378) who were aged less than 35 years were normo-ovulatory and who had received rFSH in a GnRH agonist long protocol. This analysis identified four predictive factors of ovarian response for this specific population of women undergoing ovarian stimulation for assisted reproductive techniques. These four baseline factors were included in the algorithm (Howles et al., 2006): age, body mass index (BMI), early follicular phase FSH level and antral follicle count (AFC). Subsequently, the algorithm was prospectively evaluated in a pilot study of normo-ovulatory women aged 18–34 years, which analysed data from five starting-dose groups (75 IU–225 IU) (Olivennes et al., 2009).

The objective of the present study was to compare ovarian response in women undergoing assisted reproductive techniques who were administered follitropin alfa determined by the CONSORT calculator compared with a standard starting daily dose of follitropin alfa (150 IU) that could be adjusted. It was anticipated that, although women in the CONSORT calculator group would require less total rFSH than those in the standard-dosing group, there would be no difference between the two treatment groups in the total number of oocytes retrieved per patient; therefore, a non-inferiority study was conducted.

Materials and methods

Study design

This was a prospective, randomized, controlled, multiregional, open-label, phase IV study (NCT00829244).

Ethical approval

This study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization guideline for Good Clinical Practice and local regulations. Written, informed consent was obtained.

Patients

Normo-ovulatory women aged 18–34 years who were eligible for assisted reproduction techniques and embryo transfer were recruited from 22 centres across nine European countries and one centre in Chile. Patients (about 10 patients per centre) were enrolled by study centre staff.

Key inclusion criteria were as follows: a regular, spontaneous menstrual cycle of 21–35 days; BMI less than 30 kg/m^2; an early follicular phase (cycle day 2–4) serum FSH level 12 IU/L or less; and a male partner with semen analysis (within the past 6 months) considered adequate for regular in-vitro insemination or intracytoplasmic sperm injection (ICSI) according to the centre's standard practice. Donor sperm was required if the partner's semen analysis was considered inadequate.

Key exclusion criteria included the following: a previous poor response to ovarian stimulation (defined as five or fewer mature follicles or three or fewer oocytes collected) in two or more assisted reproductive technique cycles; previous hyper-response to ovarian stimulation (defined as 25 or more oocytes retrieved) in two or more assisted reproduction technique cycles; previous severe OHSS; three or more spontaneous abortions; polycystic ovary syndrome (according to the Rotterdam criteria [Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004]), endometriosis or uterine fibroids that require treatment; or any other medical condition that may have affected the absorption, distribution, metabolism or excretion of follitropin alfa.

Patients underwent a single assisted reproduction technique treatment cycle.

Assessments and interventions

Early follicular phase (cycle day 2–4) FSH (evaluated at a local laboratory), progesterone and anti-Müllerian hormone (AMH) levels (analysed retrospectively at a central laboratory), and AFC at screening were recorded. AFC was measured using the combined number of follicles measuring 2 mm or more in

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