Ovarian response and pregnancy outcome in poor-responder women: a randomized controlled trial on the effect of luteinizing hormone supplementation on in vitro fertilization cycles

Gorka Barrenetxea, Ph.D.,[a,b] *Jon Ander Agirregoikoa, M.D.,*[a] *María Rosario Jiménez, M.D.,*[a] *Arantza Lopez de Larruzea, M.D.,*[a] *Teresa Ganzabal, M.D.,*[a] *and Koldo Carbonero, M.D.*[a]

[a] Center for Reproductive Medicine and Infertility Quirón Bilbao; and [b] Department of Obstetrics and Gynecology, Universidad del País Vasco/Euskal Herriko Unibertsitatea, Bilbao, Spain

Objective: To prospectively assess the effect of using a combination of recombinant follicle-stimulating hormone (rFSH) and recombinant luteinizing hormone (rLH) on ovarian stimulation parameters and treatment outcome among poor-responder patients.
Design: Prospective randomized trial.
Setting: University-associated private medical center.
Patient(s): Eighty-four patients who had a basal FSH level of $\geq$10 mIU/mL, who were $\geq$40 years of age, and who were undergoing their first IVF cycle participated in this controlled trial.
Intervention(s): Patients were randomly allocated into two study groups: group A, in which ovarian stimulation included GnRH analogue and rFSH and rLH, and group B, in which patients received GnRH analogue and rFSH without further LH addition.
Main Outcome Measure(s): Primary outcome measures included the ongoing pregnancy rate per retrieval and implantation rate per embryo transferred. The number of days of gonadotropin treatment, E_2 level on rHCG administration day, number of developed follicles, number of retrieved oocytes, number of normally fertilized zygotes (at the two-pronuclear [2PN] stage), cumulative embryo score, and number of transferred embryos were also evaluated.
Result(s): The overall pregnancy rate was 22.61% (19 pregnancies among 84 couples). The pregnancy wastage rate was 30.00% in group A and 22.22% in group B. There were no differences in either primary or secondary end points.
Conclusion(s): The results of this prospective and randomized trial show that the addition of rLH at a given time of follicular development produces no further benefit in the patient population of our study. A reduced ovarian response cannot be overcome by changes in the stimulation protocol. (Fertil Steril® 2008;89:546–53. ©2008 by American Society for Reproductive Medicine.)

Key Words: Controlled trial, prospective study, IVF ovarian stimulation, gonadotropin stimulation, poor responder, ovarian ageing, implantation rate, pregnancy rate, LH supplementation

The inability to conceive has become more commonplace as women delay childbearing for various reasons. As technology progresses in reproductive medicine, success rates, particularly those for assisted reproductive technologies (ART), have soared, increasing hope to childless couples and society as a whole (1). This has given many women in contemporary society the impression that it is safe to delay starting a family, because they believe that reproductive technology can come to the rescue when the time is right (2).

Since the first IVF baby born in 1978, IVF has become an established and highly effective therapy for treating infertility, and thousands of childless couples with a variety of etiologic causes have benefited from the increasing numbers of successes achieved by ART (3). However, the treatment of infertility related to reproductive aging remains a challenge. The prognosis for older patients is, as in the past, of limited success (3, 4).

The central issue in ovarian aging is the decline in the number of follicles (5). It is assumed that the ovarian follicle cohort available for recruitment by gonadotropin

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Reprint requests: Gorka Barrenetxea, Ph.D., Department of Obstetrics and Gynecology, Universidad del Paìs Vasco/Euskal Herriko Unibertsitatea, Quirón Bilbao, C/Perez Galdos, 19-4° 48010 Bilbao, Spain (FAX: 00-34-94-4395424; E-mail: gorkabz@euskalnet.net).

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stimulation for IVF is essentially constant until a certain age (5, 6).

During assisted ovarian stimulation for IVF, some women respond poorly to stimulation and are defined as poor responders. Although different criteria have been proposed to describe the poor responders, they are traditionally identified as women who are at the end of their reproductive years with both, a quantitative and qualitative reduction in the oocyte pool. However, age alone is not the sole predictor (7).

Poor responders represent a major challenge in assisted reproduction. Despite the implementation of strategies devised to optimize stimulation in this subset of patients, there is a high rate of cycle cancellation and implantation failure (8–11). The high variety of protocols that are proposed for ovarian hyperstimulation of low-responder women reflects both a high within-group variability and an overall compromised outcome (3).

In a natural cycle, FSH and LH play complementary roles in stimulating follicle growth and ovulation. Ovarian follicle growth and development is not solely dependent on FSH (12, 13).

The actual importance of LH during controlled ovarian hyperstimulation (COH) is a matter of debate (14). Some studies have indicated that a group of normogonadotropic women undergoing ovarian stimulation with GnRH agonist (GnRH-a) and recombinant FSH (rFSH) may experience such a profound suppression of LH levels that a negative effect on treatment outcome becomes manifest (15–17). Others studies suggest that the so-called resting levels, as seen in women undergoing ovarian down-regulation with the use of GnRH-a and stimulation with rFSH, are sufficient to support development and maturation of follicles and oocytes in normogonadotropic women, showing no significant differences in either performance or clinical outcome among groups of patients with varying degrees of LH suppression (18).

Controversies still exist in considering ovarian hyperstimulation in poor-responder women. The debate continues regarding the addition of LH to cycles stimulated with a combination of GnRH-a and rFSH. Addition of LH may be considered in poor responders and in patients pretreated with oral contraceptives or who have had a more severe pituitary GnRH-a suppression. Addition of LH appears not to be needed in high-responder patients for a successful outcome. Conversely, a LH addition may be considered in poor responders (3, 6, 13).

The aim of this study was to prospectively assess the effect of using a combination of rFSH and rLH on ovarian stimulation parameters and treatment outcome among poor-responder patients.

MATERIALS AND METHODS

Study Design

The present study was a prospective, randomized, open, single-center clinical trial to assess the efficacy of two different stimulation protocols in poor-responder patients. The patients reported infertility for ≥ 1 year in a university-associated, private, medical reproductive center. Patient recruitment was performed between January and June of 2005.

Patients

Poor responders were defined when both factors, age ≥ 40 years and elevated 3-day FSH level (≥ 10 mIU/mL) were present. Patients with only one ovary were excluded from the study.

To reduce the bias inherent in including multiple cycles per patient, only first cycles were included in the trial. Because no patients with previous cycles were enrolled in the study, poor responders <40 years of age and with normal basal FSH levels were not included.

All patients underwent an infertility evaluation that was described elsewhere (19).

Patients were randomly allocated into two study groups, as shown in Table 1: group A, in which ovarian stimulation included GnRH analogue and rFSH and rLH; and group B, in which patients received the GnRH analogue and rFSH (with no addition of rLH).

A method of computer-generated block randomization using sealed envelopes was employed. Sealed envelopes with treatment allocation instructions were opened on the day of stimulation start by a nurse who assigned participants to their groups and was responsible for coding protection. The doctor and the biological team performing the ART were blinded to group assignment. Patients were free to start ovarian stimulation within the next three spontaneous menstrual cycles after randomization.

The study was reviewed and approved by the institutional review board of the Universidad del Paìs Vasco/Euskal Herriko Unibertsitatea. A written informed consent form was obtained from all patients before their inclusion in the study.

Treatment

A flare-up protocol was used for ovarian stimulation. Ovarian stimulation started on day 2 of a natural cycle with GnRH-a (Procrin, leuprolide acetate, 0.10 mL [0.5 mg]; Abbot Laboratories S.A., Madrid, Spain) and rFSH (Gonal F, 375 IU; Serono Europe Ltd., London, United Kingdom) in both groups.

On day 7 of ovarian stimulation, 150 IU of rLH (Luveris; Serono Europe Ltd.) was added in group A. No rLH addition was performed in group B. From this stage, the dose of gonadotropins was adjusted as scheduled (Table 1).

From day 7 of stimulation in both groups, monitoring of follicle size by ultrasound was performed, and plasma levels of E_2 were measured every 2 days as described elsewhere (19). The average follicle size on the 1st day of LH supplementation was 14 mm.