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A randomized, single-blind, prospective trial comparing three different gonadotropin doses with or without addition of letrozole during ovulation stimulation in patients with poor ovarian response

Ercan Bastu [a,*], Faruk Buyru [a], Mehmet Ozsurmeli [a], Irem Demiral [a], Murat Dogan [a], John Yeh [b]

[a] Department of Obstetrics and Gynecology, Istanbul University School of Medicine, Istanbul, Turkey
[b] Department of Obstetrics and Gynecology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

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ABSTRACT

Objective: The aim of this randomized controlled trial (RCT) was to investigate whether IVF outcomes would differ between patients with POR who received three different gonadotropin doses with or without the addition of letrozole during ovulation stimulation.
Study design: Only those who fulfilled two of the three Bologna criteria were included to the study. 95 patients met the inclusion criteria and agreed to participate in the study. In the first group, 31 patients were treated with 450 IU gonadotropins. In the second group, 31 patients were treated with 300 IU gonadotropins. The third group comprised 33 patients and was treated with 150 IU gonadotropins in combination with letrozole.
Results: The results indicate that differences in doses of hMG and rFSH in patients with POR result in a similar number of retrieved MII and fertilized oocytes, similar fertilization rates, number of transferred embryos, implantation, cancelation, chemical, clinical, and ongoing pregnancy rates.
Conclusions: Increasing the dose of gonadotropins during ovulation stimulation is an intuitively appealing approach when the patient is a poor responder. However, increasing the dose does not necessarily improve the reproductive outcome. Using a mild stimulation with addition of letrozole was as effective as stimulation with higher doses of gonadotropins alone in this patient population.

Introduction

During assisted reproduction technology (ART) treatments like in vitro fertilization (IVF), some patients give a poor ovarian response (POR) to controlled ovarian hyperstimulation (COH). Until 2011, there was no consensus on the definition of poor responders. The diagnostic criteria of patients with POR led to the European Society of Human Reproduction and Embryology (ESHRE) consensus on the definition of poor response to ovarian stimulation during IVF (the Bologna criteria) [1].

Additionally, there is still no consensus in the literature on the ideal COH protocol for patients with POR. Many strategies have been studied, increasing the gonadotropin dosages; administration of adjuvant therapies, such as use of letrozole; or the modified natural IVF cycle [2–7]. However, no compelling advantage for one stimulation protocol over another has been identified. Increasing the doses of gonadotropins has been shown to lower cycle cancelation rates [8]. On the other hand, potential adverse implications of aggressive COH on pregnancy rates after IVF are emerging [8,9], which have led to suggestions that a more conservative approach to COH may be recommended [10–12]. Furthermore, aromatase inhibitors (AI) have been utilized as adjuvant agents in some COH protocols as they can suppress serum estradiol level and subsequently cause an increase in serum LH and FSH levels [13].

Letrozole is an adjuvant agent that is efficient and a very specific non-steroidal AI, which was at first given to postmenopausal women with breast cancer to suppress estrogen production [14]. It inhibits aromatase, and as a result, conversion of androgens into estrogen is blocked, which leads to an increase in androgens [15]. Letrozole can inhibit aromatase activity by around 97–99% between doses of 1–5 mg/day [16]. There are studies in the

* Corresponding author at: Istanbul University School of Medicine, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, Capa 34093, Istanbul, Turkey. Tel.: +90 532 413 4195.
E-mail address: ercan.bastu@istanbul.edu.tr (E. Bastu).

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literature that documented androgens also have a major role in the development of ovarian follicles [17,18]. Preliminary studies in poor ovarian responders noted decreased gonadotropin consumption [19] and increased numbers of oocytes retrieved [17] with the use of letrozole [20].

The aim of this randomized controlled trial (RCT) was to investigate whether IVF outcomes would differ between patients with POR who received three different gonadotropin doses with or without the addition of letrozole during ovulation stimulation.

Materials and methods

Study design and population

We recruited women who attended the infertility clinic of Istanbul University School of Medicine (Istanbul, Turkey) to undergo IVF/ICSI treatment between November 2014 and August 2015.

Poor responder patients during conventional IVF/ICSI cycles as defined in the Bologna criteria were included [1]. The elimination of bias was achieved by including strictly "genuine" patients with POR; only those who fulfilled two of the three Bologna criteria were included to the study. The Bologna criteria states that for a patient to be considered as POR, at least two of the following three criteria have to be met: (1) advanced maternal age (≥40 years) and/or any other risk factor for POR; (2) previous history of POR (retrieval of ≤3 oocytes during conventional COH protocol); and (3) an abnormal ovarian reserve test.

Further inclusion criteria were as follows: (1) aged between 18 and 42 years, (2) regular menstrual cycles (menstrual cycles of 25–34 days), (3) normal BMI of 19.3–28.9 kg/m^2 (4) no metabolic or endocrine disorders (5) normal hormone panel, (6) couples undergoing the ICSI cycle with ejaculated sperm, (7) normal uterine documented by hysterosalpingography or hysteroscopy.

The exclusion criteria were: (1) history of cytotoxic chemotherapy and/or radiotherapy, (2) history of ovarian surgery such as oophorectomy or cystectomy, (3) history of dehydroepiandrosterone (DHEA) and/or testosterone supplement use, (4) patients undergoing natural IVF cycle.

The study was approved by the Ethics Committee of Istanbul University School of Medicine (Istanbul, Turkey) and was registered at ClinicalTrials.gov, a service of the United States National Institutes of Health, in accordance with good clinical practice guidelines. The ClinicalTrials.gov identifier is NCT02293668. All recruited patients who met the inclusion criteria were extensively briefed about the potential benefits and risks and informed consent was obtained.

Randomization

Ninety-five patients met the inclusion criteria and agreed to participate in the study. Patients were randomly assigned to one of three study groups. The randomization took place on the first day of COH. The randomization list was a computer-generated sequence. Sealed envelopes were used for the randomization list. Following randomization, the infertility nurse (N.D.) provided the appropriate instruction on the treatment protocol to the patients. The infertility specialist (E.B.) who was blinded observed follicular development using ultrasound and retrieved oocytes in all participating patients. The embryologist (S.B.) was also blinded to the assigned treatment protocol.

Intervention

The COH was started on the second or third day of the menstrual cycle. Baseline evaluation was performed on the same day. The evaluation included serum levels of estradiol (E2), follicle stimulating hormone (FSH), and ultrasound examination.

In the first group, 31 patients were treated with 450 IU gonadotropins (225 IU hMG; Menogon; Ferring Pharmaceuticals, Saint-Prex, Switzerland and 225 IU rFSH; follitropin alpha; Gonal-f; Merck KGaA, Darmstadt, Germany). In the second group, 31 patients were treated with 300 IU gonadotropins (150 IU hMG; Menogon; Ferring Pharmaceuticals, Saint-Prex, Switzerland and 150 IU rFSH; follitropin alpha; Gonal-f; Merck KGaA, Darmstadt, Germany). The third group comprised 33 patients and was treated with 150 IU gonadotropins in combination with letrozole. For the first 5 days of stimulation, 33 patients were additionally treated with letrozole 5 mg/day (75 IU hMG; Menogon; Ferring Pharmaceuticals, Saint-Prex, Switzerland and 75 IU rFSH; follitropin alpha; Gonal-f; Merck KGaA, Darmstadt, Germany and letrozole; Femara; Novartis, Basel, Switzerland). Gonadotropin preparations were administered as a subcutaneous injection.

The infertility specialist (E.B.) observed ovarian follicular development using vaginal ultrasound at a 1–3 day frequency. Patients were treated with daily 0.25 mg GnRH antagonist (Cetrotide, 0.25 mg; Merck KGaA, Darmstadt, Germany) given from stimulation day 6 onwards (fixed regimen). A 250 μg dose of hCG (Ovitrelle, Merck KGaA, Darmstadt, Germany) was injected to achieve follicular maturation when at least three follicles were ≥17 mm in size. Oocyte retrieval took place 34–36 h after hCG injection and fertilized by conventional ICSI and cultured until the day of transfer in commercially available culture medium.

Cycles were canceled when the infertility specialist found no visible follicle ≥11 mm in size on ultrasound on the day-8 of the stimulation.

Embryo transfer took place on day-3 after fertilization for all patients. All transferred embryos were good quality (grades 1 or 2) according to the morphologic classification adapted from Lens and Rijnders [21]. During the study, one embryo was transferred to patients <35 years of age in their first two IVF attempts; two embryos were transferred only after previous ≥2 failed IVF attempts. In patients who were aged ≥35 years, two embryos were transferred regardless of previous IVF attempts in accordance with the Turkish legislation of elective single embryo transfer (SET).

All patients received luteal phase support with vaginal progesterone gel (8% Crinone, Actavis, Parsippany, NJ, USA) starting on the evening of the oocyte retrieval day and continued for 10 gestational weeks until pregnancy loss or a negative pregnancy test was observed.

On the 14th day after embryo transfer, blood levels of β-hCG were measured and recorded. If the β-hCG level was >5 mIU/mL, it was considered as positive β-hCG and patients with such levels were regarded as chemically pregnant. Clinical pregnancy was confirmed by the presence of a fetal heartbeat using vaginal ultrasound at 6 weeks of amenorrhea. Ongoing pregnancy was defined as the presence of fetal cardiac activity beyond 12 weeks of amenorrhea. Implantation rate was calculated as the number of gestational sacs with fetal cardiac activity observed using ultrasound, divided by the number of embryos transferred.

The primary outcome measure was the number of oocytes retrieved. The secondary outcome measures were the total dose of gonadotropin used for ovarian stimulation, duration of stimulation, number cycles canceled before oocyte retrieval, number of mature eggs retrieved, fertilization rate, number of cycles reaching ET, chemical, clinical and ongoing pregnancy rates.

Sample size

The sample size was calculated to prevent type-II errors. Earlier data indicated that increasing the number of retrieved oocytes from 3 to 5 would constitute a minimally importance difference