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Original article

GnRH antagonist and letrozole co-treatment in diminished ovarian reserve patients: a proof-of-concept study

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ABSTRACT

The current study aimed to investigate the effects of luteal gonadotropin-releasing hormone (GnRH) antagonist pretreatment on the outcomes of diminished ovarian reserve (DOR) patients who were treated using a FSH/letrozole/GnRH antagonist (FLA) protocol. Thus, patients who had luteal GnRH antagonist pretreatment (AFLA) prior to stimulation were compared to patients who had the FLA protocol, only. An electronic database was used to identify patients and stimulation characteristics. Women who had a total antral follicle count (AFC) of <7 were included in the analysis. A total of 45 cycles using luteal GnRH antagonist pretreatment in combination with a letrozole/GnRH antagonist (AFLA) protocol were compared to 76 cycles using a FLA protocol, only. The total gonadotropin dose, duration of stimulation, and peak estradiol levels were comparable between the groups ($p > 0.05$). However, the AFLA group had significantly more metaphase-2 (MII) oocytes ($p = 0.009$), a higher oocyte maturity rate (MII/total oocytes) ($p = 0.029$), and a higher mature oocyte yield (MII/AFC) ($p = 0.020$) with more cleaved embryos ($p = 0.036$), and a significantly reduced number of canceled cycles (26.7% vs. 44.7%; $p = 0.048$). The clinical pregnancy rate per cycle was 22.2% vs. 13.2% ($p = 0.195$) in the AFLA and FLA groups, respectively. Interestingly, a subgroup analysis including ESHRE Bologna criteria poor responder patients showed that the luteal administration of GnRH antagonist resulted in better outcomes when compared with the FLA protocol alone. In conclusion, luteal GnRH antagonist pretreatment improves ovarian stimulation parameters and reproductive outcomes in poor ovarian reserve IVF patients.

1. Introduction

The incidence of poor response to ovarian hyperstimulation during in vitro fertilization (IVF) varies from 9% to 24% [1], resulting in cycle cancellation rates of up to 76% and pregnancy rates of 3% to 14% [2–4]. Although several controlled ovarian hyperstimulation (COH) regimens have been suggested to optimize the oocyte yield, there is insufficient evidence to support the routine use of any particular intervention for ovarian stimulation when handling the poor ovarian responder [5]. Aromatase inhibitors have been used as adjuvants in some COH protocols. Thus, preliminary studies in poor ovarian responders revealed that letrozole treatment decreased the gonadotropin consumption and increased the number of oocytes retrieved [6,7]. The proposed mechanisms of action include increased follicular growth secondary to the release of the hypothalamus from the negative feedback effects of estradiol as well as the accumulation of intrafollicular androgen, increasing the expression of follicular stimulating hormone (FSH) receptors on the follicle [8].

Although the standard FSH/letrozole/gonadotropin-releasing hormone (GnRH) antagonist (FLA) protocol is an option in women with diminished ovarian reserve (DOR), follicular asynchrony remains a concern. Due to differences in follicular sensitivity to exogenous and endogenous FSH, the increase in circulating endogenous FSH during the late luteal phase for some patients could lead to advanced growth of a few, sensitive follicles, suppressing the growth of less sensitive follicles, and resulting in a smaller number of preovulatory follicles after stimulation with exogenous gonadotropins [9]. In line with this, some studies proposed that synchronization of the early antral follicle growth

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during the luteal phase before COH in GnRH antagonist cycles could increase the oocyte yield [10–18]. In these studies, luteal administration of a GnRH antagonist induced luteolysis, prevented FSH rise, and increased storage and release of endogenous gonadotropins [14–18].

Given the fact that the success of IVF is highly dependent on the number of retrieved oocytes, the retrieval of an additional oocyte although not statistically significant is clearly clinically relevant for poor ovarian reserve patient [19]. The primary objective of the present study was to compare COH parameters as well as reproductive outcomes in patients with DOR, using a FLA protocol with or without luteal GnRH antagonist pretreatment.

2. Materials and methods

2.1. Patient selection

This retrospective study included patients who underwent IVF treatment at the Akdeniz University IVF Centre between May 2015 and May 2016. According to our IVF unit's policy the FLA protocol was administered to patients with DOR or previous poor ovarian response (POR). Since November 2015, treatment regimens have incorporated routinely luteal GnRH antagonists into the FLA protocol in all patients with predictable menstrual cycle duration. An electronical database was screened to identify patient characteristics including age, previous POR ($\leq$3 oocytes with a conventional stimulation protocol), antral follicle count (AFC), COH protocol type and menstrual cycle characteristics. Only women who had a total AFC of $<$7 with regular menstrual cycles and who received letrozole co-treatment were included in the analysis. The luteal GnRH antagonist pretreatment status of the patient was also noted. Finally, 45 cycles using luteal GnRH antagonist pretreatment with letrozole/GnRH antagonist (AFLA) protocol and 76 cycles using the FLA protocol alone were identified. A patient could only be included once, in her first cycle, even if she had more than one cycle during the study period. To reflect routine clinical practice, no additional exclusion criteria were imposed on this data set. The study was approved by the Institutional Review Board of Akdeniz University, Antalya, Turkey (approval number 2016/559).

2.2. Stimulation

The study protocol is depicted in Fig. 1. In the AFLA protocol, on day 2 or 3 of menstrual cycle, the patient underwent blood sampling for serum FSH, luteinizing hormone (LH), and estradiol measurements at approximately 9 am, followed by ultrasound scans of their ovaries. Subsequently, the patient received a daily dose of 0.25 mg of GnRH antagonist (Cetrotide; Merck-Serono, Istanbul, Turkey) from day 3 before the expected start of menses for a total of 5 days. Patients were instructed to come to the clinic on the day after the fifth dose, irrespective of menstrual status. Subsequently, the patient would undergo hormonal and ultrasonographic measurements similar to the preceding cycle. Letrozole (Femara; Novartis, Istanbul, Turkey) at a dose of 2.5 mg/day was initiated on the same day and continued for 5 days. Moreover, ovarian stimulation commenced with 150 IU of recombinant FSH (Gonal-F; Merck-Serono, Istanbul, Turkey) and 75 IU of human menopausal gonadotropin (Menogon; Ferring, Istanbul, Turkey) for 5 days, after which doses were individualized according to the ovarian response of the patient.

In patients without luteal GnRH antagonist pretreatment (FLA protocol), hormonal-ultrasonographic measurements were performed on day 2 or 3 of the menstrual cycle. On that same day, letrozole and ovarian stimulation commenced directly with the same dosages as described in the AFLA protocol. The infertility specialist (S.O.) monitored the ovarian response, using vaginal ultrasound at a frequency of 1–3 days. Patients were treated with daily GnRH antagonist (Cetrotide, 0.25 mg) from stimulation day 6 and onward (fixed regimen). Recombinant human chorionic gonadotropin (hCG) 250 μg (Ovitrelle; Merck-Serono, Istanbul, Turkey) was administered to all subjects for final oocyte maturation when at least two follicles reached a mean diameter of 17 mm.

2.3. Oocyte retrieval, embryo culture, grading and transfer

Oocyte retrieval took place 34–36 h after hCG injection, and fertilization was performed by conventional intracytoplasmic sperm injection (ICSI). Embryos were cultured in a commercially

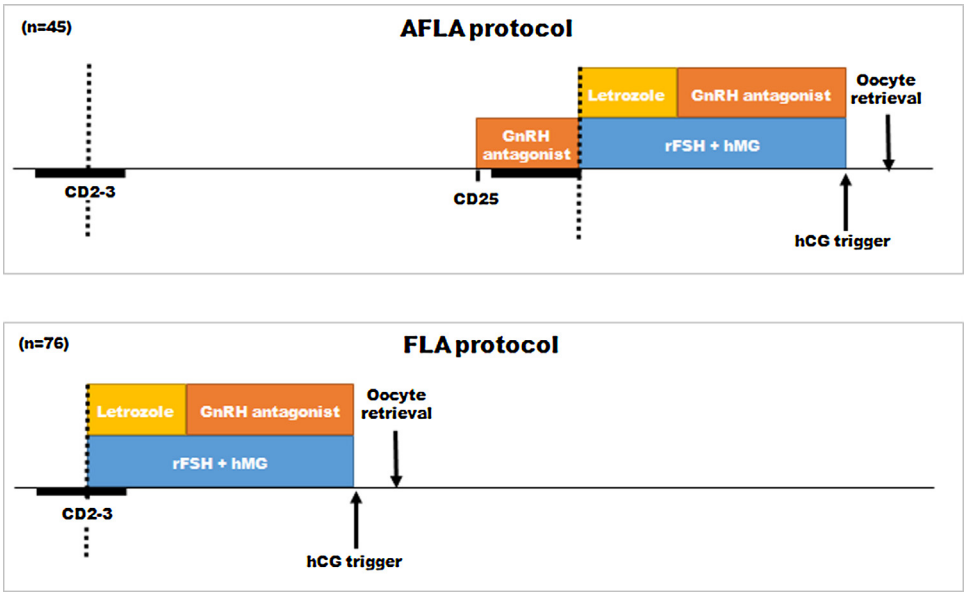

Fig. 1. Study protocol. Horizontal black bars and dotted lines represent menstrual bleeding and baseline hormonal-ultrasonographic measurements, respectively. Note that in the AFLA protocol, ovarian stimulation was started on the day after GnRH antagonist discontinuation. CD, cycle day.