Does the addition of growth hormone to the in vitro fertilization/intracytoplasmic sperm injection antagonist protocol improve outcomes in poor responders? A randomized, controlled trial

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Objective: To evaluate the effectiveness of the addition of growth hormone (GH) to the antagonist protocol in IVF/intracytoplasmic sperm injection cycles in poor responders.
Design: Parallel randomized, controlled, open-label trial.
Setting: University hospital.
Patient(s): A total of 141 patients (GH, n = 68; gonadotropins only, n = 73) were enrolled. Twenty-five patients had their cycles cancelled. Analysis was performed per cycle start as well as per ET.
Intervention(s): Patients received the antagonist protocol with or without GH supplementation.
Main Outcome Measure(s): Mean number of cumulus complexes, metaphase II oocytes retrieved and fertilized, chemical and clinical pregnancy rates, early miscarriage rate, ongoing pregnancy and live birth rates.
Result(s): The addition of GH significantly lowered duration of hMG treatment, duration of GnRH antagonist treatment, and dose of gonadotropin. It significantly increased mean E_2 levels on the day of hCG administration, number of collected oocytes (7.58 ± 1.40 vs. 4.90 ± 1.78 [mean ± SD]), number of metaphase II oocytes (4.53 ± 1.29 vs. 2.53 ± 1.18), number of fertilized oocytes (4.04 ± 0.96 vs. 2.42 ± 1.03), and number of transferred embryos (2.89 ± 0.45 vs. 2.03 ± 0.81). There was no significant difference in the clinical pregnancy rate per cycle (22.1% vs. 15.1%) or live birth rate per cycle (14.7% vs. 10.9%).
Conclusion(s): Growth hormone as an adjuvant treatment in IVF/intracytoplasmic sperm injection cycles for poor responders should be cautiously used with the antagonist protocol, because there is still no identified impact on pregnancy outcomes. However, evaluation of the clinical pregnancy and live birth rates in our data was limited by low statistical power.
Clinical Trial Registration Number: ClinicalTrials.gov Identifier: NCT02195947. (Fertil Steril® 2016;105:697–702. ©2016 by American Society for Reproductive Medicine.)
Key Words: Antagonist protocol, IVF/ICSI, poor ovarian response, poor responders

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The incidence of poor ovarian response (POR) ranges from 9% to 24%, according to different studies (1). The definition of POR was debated in the literature, with no uniform agreement for many years. The European Society of Human Reproduction and Embryology resolved this problem through a consensus study conducted in 2011, and a definition for POR was determined to include at least two of the following three features: increased maternal age (≥40 years) or any other risk factor for POR, history of POR (three or fewer oocytes with ovulation induction), and low scores on tests of ovarian reserve (i.e., antral follicular count [AFC] <5–7 follicles or antimüllerian hormone [AMH] <0.5–1.1 ng/mL) (2).

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Despite the use of different stimulation protocols, clinical pregnancy rates remain low in couples with POR. Thus, many options have been suggested to improve the results, such as adding growth hormone (GH) as an adjuvant treatment to the stimulation protocols (3).

The impact of GH on the process of ovulation has long been studied (4). The addition of GH enhances the response of granulosa cells to gonadotropins in both animal and human studies (5). It acts by increasing the local production of insulin-like growth factor I, which plays a critical role in ovarian steroidogenesis (3).

Despite GH's proven effect, there is still controversy regarding its efficacy in improving IVF/intracytoplasmic sperm injection (ICSI) cycle outcomes in poor responders, owing to either the limited number of participants or the insignificant results of those studies.

Gonadotropin–releasing hormone agonists, once used to treat poor responder patients, have been shown to have many limitations: they cause excessive suppression of ovarian function and response, which leads to increased hMG dose and duration, and they also cause LH to surge prematurely, which increases cancellation rates (6). Thus, there was a need for a different stimulation protocol without the drawbacks of the agonist protocol in poor responders, which led to the use of the antagonist protocol (7, 8). Unlike the agonist protocol, the antagonist protocol prevents premature LH surge without affecting the follicular recruitment process (9).

In this study we aimed to assess the outcome of IVF/ICSI cycles after the addition of GH as an adjuvant treatment to the antagonist protocol in poor responders.

MATERIALS AND METHODS

This parallel randomized, open-label study was conducted in Kasr el Aini IVF Center, Cairo University, Egypt. It included 141 couples that were enrolled starting in July 2014. Before the initial recruitment of the first patient, the study was approved by the institutional review board of Cairo University.

The study population included poor-responder women who fulfilled the criteria defined by the European Society of Human Reproduction and Embryology consensus in 2011 (2). Women with FSH levels above 20 IU/L, women with previous ovarian surgery, women suffering from causes of infertility other than POR, and women refusing to be enrolled in the study were excluded.

Before the start of the study, all couples were asked to provide informed consent, with all of the details of the study written out and verbally explained.

Patients were randomly allocated into two groups (labeled A and B). Then the assignments were concealed in sealed opaque envelopes until the time of enrolment: group A (GH/hMG/GnRH antagonist) and group B (hMG/GnRH antagonist).

The GnRH antagonist protocol was given as follows: hMG IM was administered daily from the second day of the cycle, with a starting dose ranging from 300 to 450 IU according to the patient's age, AFC, and AMH level. The GnRH antagonist (Cetrotide, Serono) was given as 0.25 mg SC daily when the leading follicle was 12–14 mm. Growth hormone (Norditropin, Novo Nordisk) cotreatment was introduced on day 6 of hMG stimulation in a daily dose of 2.5 mg SC until the day of hCG triggering, which is the standard GH dose used in our center, and 2.5 mg is equivalent to 7.5 IU and approaches the daily maximum dose of 8 IU/d, although some clinicians use higher doses (3). It is also appropriate for our average community weight of approximately 70 kg, given the recommendation of a dose of 0.1 IU/kg/d. It is similar to the dose used by Tesarik et al. (10): they used a daily injection of 8 IU of GH or placebo from day 7 of stimulation until the day after hCG administration. Growth of patients' follicles was monitored from the eighth day of hMG administration. When the leading follicle reached $\geq$18 mm, ovulation was triggered with 10,000 IU hCG (Choriomon, IBSA) IM. Serum P, LH, and E_2 were analyzed on the day of hCG administration.

Oocyte retrieval was completed 35 hours after hCG administration by transvaginal ultrasound guidance. Our protocol was to transfer a maximum of three embryos on day 3 of oocyte retrieval. Any surplus embryos were cryopreserved. Cyclogest 400 mg (Alpharma) vaginal suppositories were administered twice daily for luteal phase support.

The main outcomes of the study were as follows: total hMG dose and duration of hMG and antagonist stimulation (in days); endometrial thickness; E_2, LH, and P levels on the day of hCG administration; mean number of oocytes retrieved; number of metaphase II (MII) and fertilized oocytes; fertilization rate; numbers of embryos transferred; implantation rate; chemical and clinical pregnancy rates; early miscarriage rate; and ongoing pregnancy and live birth rates per cycle start and per ET.

Chemical pregnancy was defined as serum β-hCG level $>$50 IU/L 14 days after ET. Clinical pregnancy was defined as the presence of a positive heart beat by transvaginal ultrasound evaluation in a healthy gestational sac 5 weeks after positive β-hCG. The implantation rate was calculated as the ratio of the number of gestational sacs to the number of embryos transferred. Early miscarriage was defined as pregnancy loss before 12 weeks' gestation. Ongoing pregnancy was defined as pregnancy continuing beyond 12 weeks' gestation. Live birth rate was defined as the number of achieved live births after 28 weeks' gestation.

Precoded data were entered into the Statistical Package for the Social Sciences program (SPSS), version 15, to be statistically analyzed. The data were summarized using the mean and SD of quantitative variables and the frequency and percentage of qualitative ones. The odds ratio and 95% confidence interval were calculated for clinical pregnancy rate and live birth rate. Comparisons between groups were performed using Student's t test for quantitative variables and the χ^2 test for qualitative ones. A P value of $<.05$ was considered statistically significant.

RESULTS

The flow chart for patient recruitment in this study is shown in Figure 1. Our study included 141 patients who were