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.
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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.

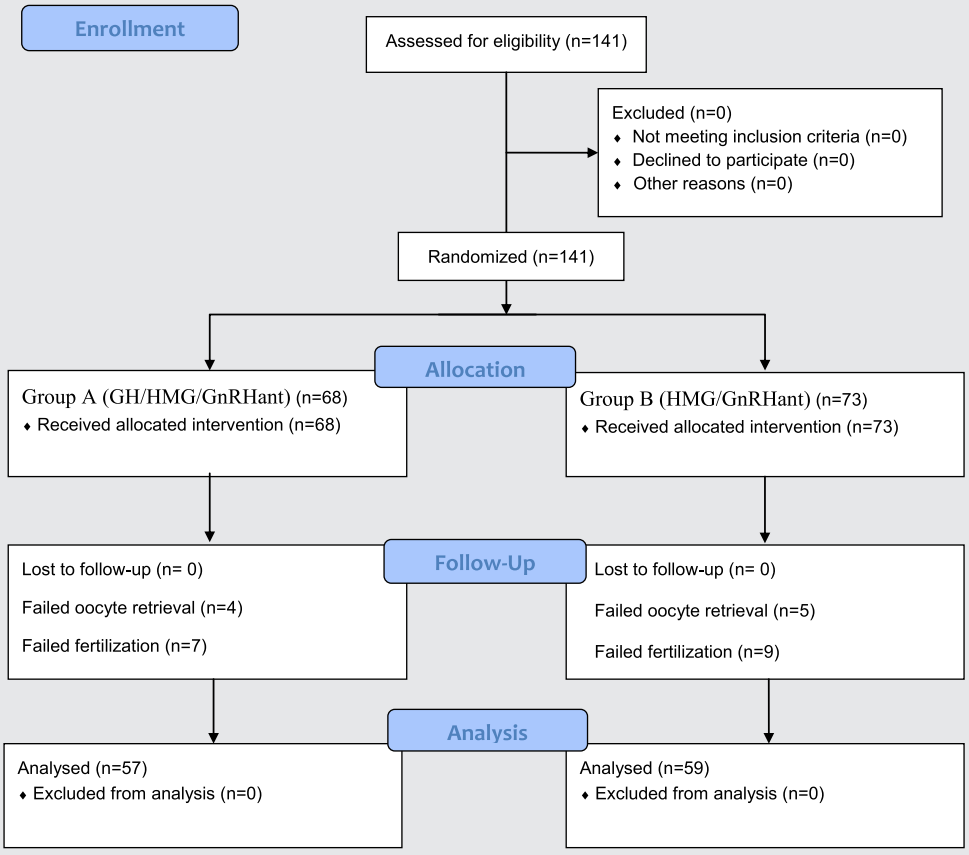
Chemical pregnancy was defined as serum β-hCG level $>$50 IU/L 14 days after ET. Clinical pregnancy was defined as the presence of a positive heart beat by transvaginal ultrasound evaluation in a healthy gestational sac 5 weeks after positive β-hCG. The implantation rate was calculated as the ratio of 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

FIGURE 1



CONSORT 2010 flow diagram.

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randomized into two groups: 68 were assigned to the GH/antagonist group (group A) and 73 to the antagonist group (group B). None of the patients was lost to follow-up. In the two groups, nine cases were canceled because of oocyte retrieval failure, which was due to either the absence of follicular growth after stimulation (in two cases) or the growth of a maximum of two follicles on the day of hCG trigger. These patients were counseled about oocyte retrieval; four cases agreed to cancel their cycles, while three cases opted to go on with the procedure. Unfortunately no oocytes were retrieved. There were 16 failed fertilization cases in the two groups; they were all due to low numbers of retrieved oocytes, which did not achieve fertilization, and those patients were also counseled regarding this outcome.

Baseline characteristics of patients are displayed in Table 1; there was no difference between the two groups in age, body mass index, infertility duration, number of previous cycles with poor response, or basal FSH level, AMH level, or AFC.

The results of ovarian stimulation are shown in Table 2. The duration of hMG treatment, the duration of GnRH antagonist administration, and the doses of gonadotropin used were significantly lower in the GH group. The mean E_2 value on the day of hCG administration, endometrial thickness, number of collected oocytes, number of MII oocytes, number of fertilized oocytes, and number of transferred embryos were significantly higher in the GH group. The number of cycles with frozen embryos and the number of embryos cryopreserved showed no significant difference between the two groups. Overall, 20 patients from the GH group had cycles with frozen embryos, from which a total of 30 embryos were cryopreserved; 10 patients had their cryopreserved embryos transferred, resulting in four chemical pregnancies that continued to three clinical pregnancies and two live births. In the antagonist-only group, 13 patients had cycles with cryopreserved embryos, in which a total of 15 embryos were cryopreserved; seven patients had their cryopreserved embryos transferred, with two chemical pregnancies and two live births.

The cumulative live birth rate from fresh and frozen cycles in our study cannot be assessed because not all patients had their cryopreserved embryo transferred.

The reproductive outcomes are displayed in Table 3. No statistically significant difference between the two groups was identified in number of cycles reaching ET, fertilization rate, implantation rate, chemical pregnancy rate, clinical pregnancy rate, early miscarriage rate, ongoing pregnancy rate, live birth rate per cycle start or per ET, or multiple

TABLE 1

Basal characteristics of patients.

Variable	Group A, GH/hMG/GnRHant (n = 68)	Group B, hMG/GnRHant (n = 73)	*P* value
Age (y)	35.79 ± 5.56	35.53 ± 5.98	.806
Body mass index (kg/m^2)	23.71 ± 5.06	22.67 ± 3.71	.655
Duration of infertility (y)	6.44 ± 3.62	6.75 ± 3.75	.643
No. of previous cycles with poor response	2.49 ± 1.35	2.63 ± 1.51	.611
Basal FSH (IUI/L)	10.87 ± 2.26	10.67 ± 2.49	.643
AMH (ng/mL)	0.39 ± 0.23	0.41 ± 0.24	.676
AFC	5.77 ± 1.76	5.81 ± 1.71	.898

Note: All values presented as mean ± SD. A *P* value < .05 is considered statistically significant. GnRHant = GnRH antagonist.

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pregnancies. The odds ratio (95% confidence interval) was 1.56 (0.65–3.76) for the clinical pregnancy rate and 1.36 (0.49–3.73) for the live birth rate, indicating a favourable but nonsignificant effect for using GH. No adverse events were associated with the use of GH in this study.

DISCUSSION

In this study we wanted to detect the effect of adding GH to the antagonist stimulation protocol in 141 poor responder women undergoing IVF/ICSI cycles. We found that the number of oocytes collected and fertilized as well as the number of transferred embryos were significantly higher in the GH group. On the other hand, there was no statistically reliable difference between groups when comparing the chemical pregnancy rates, clinical pregnancy rates, miscarriage rates or live birth rates.

To the best of our knowledge this study is the second study to analyze the impact of cotreatment with GH in GnRH antagonist protocol IVF/ICSI cycles. The first one, conducted in 2013 by Eftekhar et al. (11), concluded that GH treatment with the antagonist protocol in patients with a previous history of poor response undergoing IVF/IVSI did not increase the pregnancy rate, although it did increase the number of collected oocytes and obtained embryos (11).

The data from both human and animal studies suggest that GH plays a critical role in the process of ovarian steroidogenesis and in the development of follicles. It is believed to play an important role in ovarian function (12, 13), stimulating follicular development, estrogen production, and oocyte maturation (14). This might explain why the duration of hMG treatment and the duration of GnRH antagonist treatment were significantly shorter in the GH group in this study. Additionally, the total hMG dose was significantly lower, which is consistent with the results of Kucuk et al. (3) and of the European and Australian Multicenter Study (15), in which GH addition led to a reduction in the gonadotropin dose and duration in hypogonadotropic hypogonadism patients.

In this trial, mean serum E_2 levels on hCG day were higher in the GH group. This may be attributed to the increased number of recruited follicles producing E_2 in the GH group. Better chances of pregnancy are achieved with a higher preovulatory level of E_2 in the follicular fluid (16), making GH cotreatment in the recruitment phase a promising technique in poor responders (3).

TABLE 2

Cycle characteristics.

Variable	Group A, GH/hMG/GnRHant (n = 68)	Group B, hMG/GnRHant (n = 73)	*P* value
Duration of hMG treatment (d)	10.77 ± 1.51	12.02 ± 1.46	< .001[a]
Duration of GnRHant treatment (d)	6.86 ± 1.41	7.98 ± 1.47	< .001[a]
Total doses of gonadotropin (IU)	3,900 ± 839	4,906 ± 1,481	< .001[a]
E_2 levels on hCG day (pg/mL)	1,862.47 ± 504.03	854.44 ± 413.96	< .001[a]
P levels on hCG day (ng/mL)	0.70 ± 0.27	0.80 ± 0.38	.099
Endometrial thickness (mm)	12.14 ± 1.25	11.56 ± 1.56	.029[a]
No. of collected oocytes	7.58 ± 1.40	4.90 ± 1.78	< .001[a]
No. of MII oocytes	4.53 ± 1.29	2.53 ± 1.18	< .001[a]
No. of fertilized oocytes	4.04 ± 0.96	2.42 ± 1.03	< .001[a]
No. of transferred embryos	2.89 ± 0.45	2.03 ± 0.81	< .001[a]
No. of frozen embryos	1.50 ± 0.68	1.15 ± 0.37	.054
No. of cycles with frozen embryos per cycle start, n/n (%)	20/68 (29.4)	13/73 (17.8)	.104
No. of cycles with frozen embryos per embryo transfer n/n (%)	20/57 (35.1)	13/59 (22.0)	.119

Note: All values presented as mean ± SD, unless stated otherwise.
[a] *P* value < .05 is considered statistically significant.

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TABLE 3

Reproductive outcomes.

Variable	Group A, GH/hMG/GnRHant (n = 68)	Group B, hMG/GnRHant (n = 73)	*P* value
Cycles reaching ET, n/n (%)	57/68 (83.8)	59/73 (80.8)	.641
Fertilization rate (%)	53.95	49.36	.050
Implantation rate (%)	11.98	9.88	.608
Chemical pregnancy rate/cycle start, n/n (%)	28/68 (41.2)	22/73 (30.1)	.171
Chemical pregnancy rate/ET, n/n (%)	28/57 (49.1)	22/59 (37.3)	.198
Clinical pregnancy rate/cycle start, n/n (%)	15/68 (22.1)	11/73 (15.1)	.285
Clinical pregnancy rate/ET, n/n (%)	15/57 (26.3)	11/59 (18.6)	.322
Single intrauterine sac, n/n (%)	11/15 (73.3)	8/11 (72.7)	.972
Double intrauterine sacs, n/n (%)	4/15 (26.7)	3/11 (27.3)	.972
Early miscarriage rate/cycle start, n/n (%)	5/68 (7.4)	3/73 (4.1)	.405
Early miscarriage rate/ET, n/n (%)	5/57 (8.8)	3/59 (5.1)	.433
Ongoing pregnancy rate/cycle start, n/n (%)	10/68 (14.7)	8/73 (10.9)	.505
Ongoing pregnancy rate/ET, n/n (%)	10/57 (17.5)	8/59 (13.6)	.553
Live birth rate/cycle start, n/n (%)	10/68 (14.7)	8/73 (10.9)	.505
Live birth rate/ET, n/n (%)	10/57 (17.5)	8/59 (13.6)	.553

Note: P value < .05 is considered statistically significant.

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Several studies using GH as an adjuvant treatment to improve the results of IVF/ICSI cycles in poor responders reported an increased number of retrieved oocytes (3, 11, 17), as well as an increased number of MII oocytes collected (3). These increases resulted in better fertilization rates and more embryos available for transfer (3, 11). This study confirms these findings and proves that the use of GH improved pregnancy rates by increasing the number and quality of collected oocytes. Sugaya et al. (18) conducted a similar study demonstrating that adjuvant GH therapy significantly increased the number of retrieved oocytes and the number of good-quality embryos in poor responders.

One meta-analysis suggested that GH administration might be associated with an increased proportion of patients who reach the ET stage and are thus exposed to the chance of pregnancy (19). However, this possibility was not supported by the results of this study, because there was no difference in the percentage of cycles that reached ET.

In the same meta-analysis, the pooled effect of the six trials that were analyzed showed that the addition of GH increased the clinical pregnancy and live birth rates, although four of the six trials individually reported no significant difference regarding clinical pregnancy rate, and four of the five reporting live birth rate also found no significant difference (19).

In another systematic review and meta-analysis of different interventions to improve outcome in poor responders undergoing IVF, the only two interventions with a favorable impact and increased pregnancy rates were the use of GH and day-2 transfer (5). A Cochrane meta-analysis showed a statistically significant increase in both the clinical pregnancy rate and the live birth rate, thus encouraging the use of adjuvant GH in IVF protocols in poor responder women without an increase in the adverse events. However, the specific subgroup of patients who would benefit the most from such treatment could not be identified (20). Another study, by Tesarik et al. (10) on women aged >40 years, showed a significant increase in live birth rates by adding GH to the ICSI program. They concluded that this effect was mainly due to an improvement in oocyte development potential.

This study did not find a significant increase in the fertilization rate, implantation rate, chemical pregnancy rate, clinical pregnancy rate, early miscarriage rate, ongoing pregnancy rate, or live birth rate; this might be due to the small sample size. Data in this study are underpowered regarding the ultimate effect of GH on clinical pregnancy rate and live birth rate, because patients with POR are mostly discouraged from performing IVF/ICSI cycles owing to the low pregnancy rates achieved. Other limitations of this study are that we did not assess the cost-effectiveness of using GH in the treatment cycles, nor did we study the long-term safety of GH on the mothers and their children. However, there were no adverse effects reported during the course of the study. Additionally, we only tested a single dose of GH and used a standard high-dose GnRH antagonist protocol. We have no information regarding the potential effect of GH when either other GH doses or other protocols that are typically used for poor responders (e.g., microdose flare protocols and E_2 priming protocols with GnRH antagonist) are used. On the other hand, a major strength of this study is its randomized nature.

In conclusion, this study showed that GH cotreatment with the antagonist protocol in poor responder women undergoing IVF/ICSI cycles significantly improved the number of oocytes collected, the number of MII oocytes retrieved, the number of fertilized oocytes, and the number of embryos transferred. However, although reproductive outcomes, including live birth rates, were higher, these differences did not reach statistical significance. Thus, although these data are encouraging, the use of GH as an adjuvant treatment in IVF/ICSI cycles in poor responders should be treated cautiously pending further larger and more conclusive systemic reviews and meta-analyses.

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