Efficacy of Growth Hormone Supplementation with Gonadotrophins in IVF/ICSI for Poor Responders; Randomized Controlled Trial

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Abstract: **Objective**: To compare the ICSI-ET outcomes in poor responders underwent ovarian stimulation by the ultrashort GnRH antagonist protocol with or without adjuvant GH injection. **Methods:** This randomized controlled trial was conducted at Al-Azhar University from November-2016 to January-2019. All patients received the same preparations. After randomization, in the study group, women received GH 4IU/day subcutaneous injection stopped 1 day before ovum pickup. While in the control group, women received subcutaneous saline in the same dosing as in the study group. After intervention, all procedures were the same in both groups. The main outcome measure was the clinical pregnancy rate. **Results**: Both groups were comparable with regard their age, BMI, duration of infertility and the number previous cycles with poor response. Ovulation characteristics were comparable (p 0.618) as well as their AMH (p 0.795). The level of E2 is significantly (p=0.005) higher in the GH group versus the control group. The oocyte retrieved number was significantly (p<0.001) higher in the GH group 4.94 (1.77) than in the control group 3.74 (1.82). The mean number of MII oocytes was significantly (p<0.001) higher in the GH group 3.3(1.36) than in the control group 2.29(1.24). Fertilization characteristics were comparable. The implantation rate, the chemical pregnancy rate and the clinical pregnancy rate were comparable (p-values>0.05) between groups. **Conclusion**: This study showed no significant increase in clinical and chemical pregnancy rates by the addition of GH to the ultrashort antagonist protocol in poor responders. The number of retrieved oocytes was significantly higher in the GH group.

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1. Introduction

In the last three decades, there were numerous advancements in artificial reproductive technology (ART); however, the clinical pregnancy and the live-birth rates remain at approximately 30–40%. [1]

The most well-known methods to improve the outcome of ART are the utilization of maximized controlled ovarian stimulation (COS), the transfer of multiple embryos into the uterine cavity and the cryopreservation of more oocytes/embryos. Nevertheless, the first two of these methods might increase the risk of ovarian hyperstimulation syndrome and multiple pregnancies. [2]

The COS protocols for IVF are continually under revision in an endeavor to reduce hormone (gonadotrophin) requirement, enhance follicular recruitment, and fundamentally to improve the live-birth rates. [3]

Some of these protocols have considered the use of the growth hormone (GH). The growth hormone is a biological peptide hormone, synthesized, stored, and secreted by somatotroph cells located in the anterior pituitary gland. It is synthetically produced using recombinant Deoxyribo Nucleic Acid (DNA) technology and is licensed to be used in the human population. Currently, there is no consensus as to the route, dose, or timing of GH administration in IVF protocols. [4]

Until now, to the best of the available knowledge, no research studied the impact of adding GH to the ultrashort GnRH antagonist protocol in term of ovulation, fertilization, implantation, and pregnancy rate. Thus, the rationale intended for this parallel randomized controlled study was to compare the intra-cytoplasmic sperm injection procedures-Embryo Transfer (ICSI-ET) outcome in term of clinical pregnancy rate in poor responder women underwent controlled ovarian stimulation by the ultrashort GnRH antagonist protocol with or without the addition adjuvant GH injection.

2. Materials and methods

This parallel-randomized controlled double-blinded, single center study was conducted at Al-Azhar University Assisted Reproductive Technology Unit to assess the effectiveness of adjuvant growth hormone injection during controlled ovarian stimulation by ultrashort GnRH antagonist protocol, in poor responder women undergoing ICSI procedures during the period from November 2016 and January 2019.

This study conformed to the principles of the Declaration of Helsinki and following the Medical Research Involving Human Subjects Act (WMO). The local medical ethical review committee approved the study. The purpose of this study was clearly explained in the Arabic language to all subjects before their enrollment, and an informed consent form was signed by and obtained from all of those enrolled.

We recruited all infertile poor responder women in the reproductive period that met the inclusion and exclusion criteria and were eligible for participation in this study (176 subjects) from November 2016 and January 2019. For inclusion in the study, all of the following criteria were to be fulfilled: age 25 to 38 years, IVF previous poor responders with at least two failed cycles with < five oocytes, abnormal ORT e. g. antimullarian hormone < 1, patients with unexplained infertility, normal hormonal profile (FSH, LH, PRL), normal ovarian ultrasound, normal pelvic ultrasound, women that were willing to do ICSE-ET. Poor responders were identified according to the Bologna Criteria but without advanced maternal age. [5]

Exclusion criteria included: women with known medical disease (e.g. sever hypertension or hepatic disease), history of altered karyotype in one or both partners, history of chronic, autoimmune or metabolic diseases, presence of endocrinopathies, male factor infertility, participation in any other clinical trial during enrollment, women who in the investigator's judgment cannot be expected to comply with the protocol or study procedures, and refusal to participate in the study.

Randomization and blinding

For allocation of the participants, a computer-generated list of random numbers was used. Block randomization with a block size of four was used with a 1:1 ratio of the study group (GH group) and the control. Computer-based tables were used to randomize women; allocation was done using the closed envelope technique. The allocation sequence was concealed from the researcher assessing the implantation and the pregnancy; hence, he did not know the relation between the patients' numbers and the allocation sequence.

The study was a double-blinded study, as the patient did not know which groups she is assigned for, and the assessor was blinded.

Procedures

After randomization, in all patients in both study groups, controlled ovarian stimulation by the ultrashort GnRH antagonist protocol was started day (day 2–3 of the menstrual cycle). Transvaginal ultrasound examination was made; COS was started only if no follicle ≥ 10 mm in diameter was observed and the estradiol level was < 50 pg/mL. Controlled ovarian stimulation was performed using ultrashort GnRH antagonist protocol with injection of 0.1 mg SC GnRH daily, triptorelin acetate (Decapeptyl) or Leuprolide (Lupron) for pituitary flare followed by down regulation and endogenous gonadotropin depletion, which was continued for three consecutive days. HMG (MerionalIpsa) at 450 IU per day started from day 2 of the cycle. [6]

However, in all patients in the study group women received GH 4 IU/day administered subcutaneously from the 2nd day of the cycle and stopped one day before ovum pickup. While in all patients in the control group, women received subcutaneous saline (as a placebo) in the same dosing and timing as in the study group.

After intervention, in all patients in both groups, transvaginal ultrasound was done starting from day 6 of COS for assessment of follicular development and assessment of endometrial thickness. Also, serial E2 measurement was scheduled to start on day 6 of COS repeating every other day. The GnRH antagonist (Cetrorelix, Serono Laboratories, Aubonne, Switzerland) at a dose of 0.25 mg SC per day was started on day 6 of COS. Final follicular maturation was triggered when the leading follicle>18mm in diameter, using recombinant human chorionic gonadotropin (hCG, 10,000 IU, single injection). After 34 to 36 hours. Oocytes retrieval were done. Follicular fluid was aspirated into sterile tubes.

After denudation, the oocytes were assessed for maturity and quality, using an inverted (Olympus 1x71) microscope with Hoffman optics, hot stage and automatic manipulators Narishige. Maturation stages were be recorded as prophase I, metaphase I (M I), metaphase II (M II) and post mature. [7]

Semen were applied to swim-up technique and centrifuged at 1,800 rpm for 10 minutes. The injection procedure was carried out using holding pipettes and injection needle. ICSI was performed on M II oocyte. After 17 hours, assessment for normal fertilization was done. Two pronuclei (PN) are considered as normal fertilization. One, three or more than three PN are considered abnormal fertilization. Attention is paid to: a) pronuclear size and symmetry; b) size, number,

equality and distribution of nucleoli; 3) appearance of cytoplasm. [8]

Embryos that are cleaved were identified and embryos grading were done according to equality of blastomeric size and proportion of nucleate fragments. Then, best embryos were transferred to the uterus in 30µl of Global medium containing 10% HSA using ET catheter 48–72 h after oocyte retrieval. [9]

Luteal phase support was given to the patient for 14 days, using micronized progesterone 600mg/day and then beta hCG titter was done for the detection of pregnancy and then was confirmed by transvaginal ultrasound examination after 10-15 days of gestation. [10]

Statistical Considerations

The primary outcome measure was clinical pregnancy per allocated woman, defined as the presence of at least one fetus with heartbeat. The secondary outcome measures were: E2 levels of hCG day, number of oocytes collected, M II oocyte number, number of G1 embryos, number of G1 Embryos transferred, the implantation rate, the chemical pregnancy rate, multiple pregnancy, endometrial thickness when at least one follicle ≥ 17 mm is observed.

Statistical analysis and sample size justification

A sample size calculation was done to calculate the number of subjects needed in each group. Sample size was calculated using EpiInfo version 7.0, setting the power at 80% and the two-sided confidence level at 95%. Data from the Cochrane systematic review conducted by Duffy et al. showed that the overall combined pregnancy rates were 31.7% and 12.2% in poor responders who received GH and placebo, respectively. Calculation according to these values produces a minimal sample size of 70 women in each group. To count for the dropouts, 158 women were enrolled. [11]

The statistical analysis was made on the intent-to-treat (ITT) population. All statistical tests were made using a significance level of 95%. A p-value < 0.05 was considered statistically significant. SPSS software (Statistical Package for the Social Sciences, version 20.0, SSPS Inc., Chicago, IL, USA) was used for the statistical analyses. Data were presented as (mean ± SD) or median (range) for continuous variables and as frequency & percent for categorical variables. Comparisons between groups were made using Chi-square test for categorical variable and the independent t-test for the continuous variables.

3. Results:

The current RCT was conducted at Al-Azhar University Center of Assisted Reproduction during the period between November 2016 and January 2019. A total of 176 patients eligible for ICSI-ET defined as poor responders were enrolled in the trial. Eight subjects refused to participate, and 12 subjects were excluded before randomization because they did not meet the inclusion criteria, leaving 156 participants for randomization with 78 assigned to each group. The dispositions of these subjects are shown in Figure1.

Patients' baseline characteristics:

Both the study group and the control group were comparable with regard their baseline characteristics. There was no statistically significant difference (p > 0.05) between the two groups regarding the age, BMI, the duration of infertility and the number previous cycles with poor response as shown in Table 1. There was no significant difference between the two study groups with regard to the age (p-value = 0.185). The mean age was 34.27 (2.41) and 34.74 (1.98) years for the study group & the control group, respectively.

There was no significant difference between the two study groups with regard to the BMI (p-value = 0.120). The mean BMI was 24.39 (1.52) and 25.06 (3.47) kg/m^2 for the study group & the control group, respectively. The durations of infertility in both groups were comparable (p-value 0.417). They were 6.62 (2.13) and 6.35 (2.01) years for the study group & the control group, respectively. In addition, the number previous cycles with poor response was not significantly different between both groups (p-value = 0.113), it was 2.5 (0.18) and 2.56 (0.28) cycles for the study group & the control group, respectively.

Patients' AFC & hormonal profile:

In both groups, the ovulation characteristics in term of AFC is comparable (p 0.782) between groups; it was 5.73 (1.82) & 5.81 (1.78) for the GH group and the control group, respectively. Both the study group and the control group were comparable with regard their AMH. The two groups were comparable (p 0.151) regarding the AMH level. AMH level was 0.72 (0.09) ng/ml and 0.69 (0.16) ng/ml for the study group & the control group, respectively.

Ovarian induction, ICSI parameters, and oocytes' characteristics

The number of ovarian stimulation days was not significantly different between both groups (p-value = 0.520), it was 12.62 (1.05) and 12.52 (1.08) days for the study group & the control group, respectively. The cycle cancellation rate was 7 (8.97%) in the GH group versus 9 (11.54) in the control group, (p-value = 0.774)

Both the study group and the control group were comparable with regard endometrial thickness at the day of HCG injection (p-value 0.236), as shown in Table 2. However, the level of E2 at the same day is significantly (0.003) higher in the GH group 929.94 (306.02) versus the control group 777.97 (319.81) pn/mL. The oocyte retrieved number was significantly (p < 0.001) higher in the GH group 4.94 (1.77) than in

the control group 3.74 (1.82). The oocyte-retrieved number is shown in Table 2.

Furthermore, the mean number of M II oocytes was significantly ($p < 0.001$) higher in the GH group 3.3 (1.36) than in the control group 2.29 (1.24).

Fertilization characteristics were comparable between both groups ($p > 0.05$). The mean number of embryos developed per patient was 2.32 (1.01) in the GH group and 2.11 (1.12) in the control group (p 0.221). The mean number of the good embryo grade (G1) was 1.82(0.68) in the GH group and 1.68 (0.71) in the control group (p 0.210). The mean number of embryos transferred per patient was 1.73 (0.72) in the GH group and 1.58 (0.69) in the control group (p-value 0.186).

The number of embryos transferred was comparable between groups ($p = 0.397$). In the GH group a total number of 123 embryos were transferred; Single embryo (SET) in 30, double embryos (DET) in 30 and triple embryos (TET) in 11 patient. On the other hand, in the control group a total number of 109 embryos was transferred; single embryo (SET) in 37, double embryos (DET) in 24 and triple embryos (TET) in 8 patient (Table 2).

Implantation rate and Pregnancy rate

The implantation rate was comparable (p 0.11) between groups. In the GH study group 96 fetuses from 123 transferred embryos versus 74 fetuses from 109 transferred embryos in the control group. The chemical pregnancy rate, was insignificantly (p 0.367) higher in the GH group than in the control group**.** It was 30.77% in the GH and 23.08% in the control group.

The clinical pregnancy rate, as confirmed by US, was insignificantly (p 0.519) higher in the study group than in the control group**.** It was 19.23% in the GH group and 14.10% in the control group. Twin pregnancy was seen in one case (out of 15) in the GH group and one case (out of 11) of the control group.

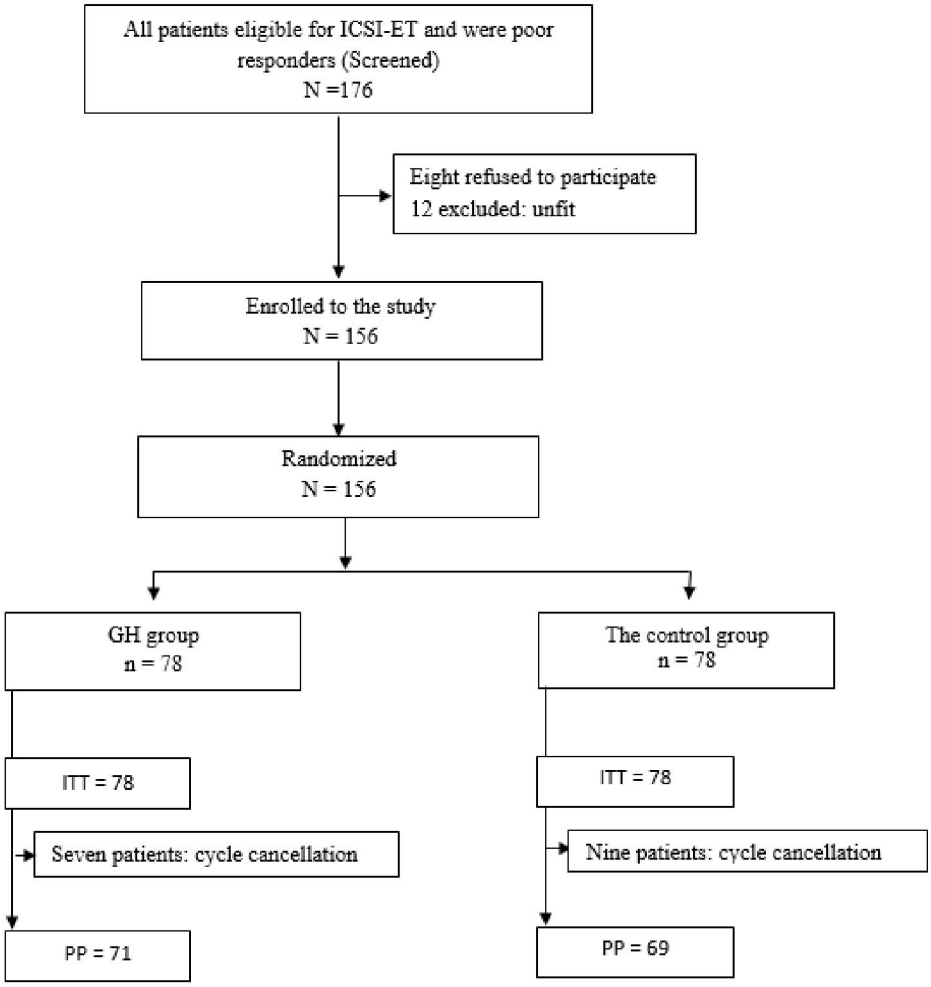

Figure 1: CONSORT diagram

Table 1: Baseline characteristics, AFC and hormonal profile

	GH N = 78	**Control N = 78**	**p value**
Age in years, mean (SD)	34.27 (2.41)	34.74 (1.98)	0.185
BMI (kg/m2), mean (SD)	24.39 (1.52)	25.06 (3.47)	0.120
Duration of infertility in years, mean (SD)	6.62 (2.13)	6.35 (2.01)	0.417
Number previous cycles with poor response, mean (SD)	2.5 (0.18)	2.56 (0.28)	0.113
AFC, mean (SD)	5.73 (1.82)	5.81 (1.78)	0.782
AMH (ng/mL), mean (SD)	0.72 (0.09)	0.69 (0.16)	0.151

Table 2: Ovarian induction, ICSI parameters

	GH N = 78	**Control N = 78**	**p value**
Number of stimulation days, mean (SD)	12.62 (1.05)	12.51 (1.08)	0.520
E2 (pg/mL), mean (SD)	929.94 (306.02)	777.97 (319.81)	**0.003**
Endometrial thickness at day of HCG mm, mean (SD)	10.27 (1.79)	9.99 (1.06)	0.236
Cycle cancellation, n (%)	7 (8.97)	9 (11.54)	0.770
Ovulation characteristics			
Oocyte retrieved number, mean (SD)	4.94 (1.77)	3.74 (1.82)	< 0.001
M II, mean (SD)	3.3 (1.36)	2.29 (1.24)	< 0.001
Fertilization characteristics			
Number of embryos fertilized, mean (SD)	2.32 (1.01)	2.11 (1.12)	0.221
G1 embryos, mean (SD)	1.82 (0.68)	1.68 (0.71)	0.210
Number of transferred embryos, mean (SD)	1.73 (0.72)	1.58 (0.69)	0.186
Total number of embryos transferred: n	123	109	
Single embryo transfer (SET)	30	37	0.397
Double embryo transfer (DET)	30	24	
Triple embryo transfer (TET)	11	8	

Table 3: Implantation rate and pregnancy rate

	GH N = 78	Control N = 78	p value
Total number of embryos transferred	123	109	
Implantation rate/ET, n (%)	96 (78.05)	74 (67.89)	0.110
Chemical pregnancy rate, n (%)	24 (30.77)	18 (23.08)	0.367
Clinical pregnancy rate, n (%)	15 (19.23)	11(14.10)	0.519
Number of fetuses, n	16	12	
Singleton	14	10	0.887
Twins	1	1	

4. Discussion

This parallel randomized controlled trial was conducted at Al-Azhar University Center of Assisted Reproduction during the period between November 2016 and January 2019 upon poor responders patients eligible for ICSI-ET according to Bologna Criteria with the aim to assess the effectiveness of adjuvant growth hormone injection added to the controlled ovarian stimulation (Ultrashort antagonist protocol).

In our study male factor with abnormal sperm parameters are excluded from our study to avoid bias of being a contributing factor in cases of ICSI failure. Patients were randomized into two groups; the study group included women who received ultrashort antagonist protocol in addition to GH 4 IU/day SC injection, and the control group included women who received ultrashort antagonist protocol in addition to subcutaneous saline (as a placebo) in the same dosing as in the study group. In our study, we only used Cook intrauterine ET.

Both the study group and the control group were comparable concerning their baseline characteristics: age, BMI, the duration of infertility and the number of previous cycles with poor response. In addition, both groups were comparable concerning their AMH level and the AFC. Furthermore, the results of the current study showed that the endometrial thickness at the day of HCG injection was comparable between both groups. In addition, the number of stimulation days as

well as the cycle cancellation rate were comparable between groups.

Despite that the level of E2 at the same day, oocyte retrieved number and number of M2 oocytes were significantly higher in the GH group versus the control group, the fertilization characteristics were comparable between both groups in term of the mean number of embryos developed per patient and the mean number of the excellent embryo grade (G1).

In addition, the number of embryos transferred was insignificantly higher in the GH group than in the control group. Also, the implantation rate was comparable between groups. The chemical pregnancy rate and the clinical pregnancy rate were insignificantly higher in the GH group than in the control group.

To the best of our knowledge, this study is considered the first study to assess the impact of adding growth hormone to the Ultrashort GnRH antagonist protocol in term of ovulation, fertilization, implantation, and pregnancy rate. Therefore, in our discussion, the comparison will be made against the nearest stimulation protocol, which is the antagonist protocol as there are some research studies addressed it.

Bassiouny et al. (2016), in their randomized controlled trial of the impact of the addition of growth hormone to the antagonist protocol in poor responders upon 141 poor responder women found that the number of retrieved oocytes (in accordance with our study) and fertilized as well as the number of transferred embryos (in discordance to our study) were significantly higher in the GH group. On the other hand, and in agreement with the results of our study, there was no statistically reliable difference between groups when comparing the chemical pregnancy rates and clinical pregnancy rates. [12]

However, this study of ***Bassiouny et al. (2016)*** was different from our RCT not only the controlled ovarian stimulation protocol but also in the dosage of GH. They introduced Growth hormone cotreatment on day 6 of HMG stimulation until the day of HCG triggering as 2.5 mg (equivalent to 7.5 IU) SC daily that approached the maximum daily dose (8 IU/d). In our study, 4 IU/day was administered subcutaneously from the 2nd day of the cycle and stopped one day before ovum pickup. [12]

Another study conducted in 2013 by ***Eftekhar et al. (2013)*** upon Eighty-two poor responders, concluded that the addition of GH treatment to the antagonist protocol increased the number of retrieved oocytes (in accordance with our study) and obtained embryos (in discordance with our study). On the other hand, and in agreement with the results of our study, there were no statistically reliable differences between groups when comparing the implantation rate or the chemical pregnancy rates and clinical pregnancy rates. [6]

In addition, in agreement with the results of our study, the number of stimulation days as well as the cycle cancellation rate were comparable between groups in this study. Hence, the usage of GH does not affect the number of stimulation days nor the cycle cancellation rate. [6]

However, this study of **Eftekhar et al. (2013)** was different from ours not only the controlled ovarian stimulation protocol but also in the timing of GH administration. They introduced Growth hormone 4 IU daily injection from day 21 of the previous cycle until the day of HCG injection. [6]

A higher preovulatory level of E2 in the follicular fluid leads to better likelihoods of pregnancy. As one of the physiological actions of GH, it makes the addition of GH a promising method in poor responders. [13]

The results of our study demonstrated that the mean serum level of E2 on HCG day was significantly higher in the study group than in the control group, which can be attributed to the higher number of recruited follicles generating E2. This finding is in agreement with the results showed by ***Bassiouny et al. (2016)***; however, it is in disagreement with ***Eftekhar et al. (2013).*** [6, 12]

The critical roles played by GH in ovarian function, steroidogenesis, follicles' development, and oocyte maturation had been advocated by both animal and human research studies. [12, 14]

The results of our RCT showed that the number of retrieved oocytes was significantly higher in the GH group than in the control group. In accordance with our study, several studies assessed the use of GH as an adjuvant treatment in poor responders to improve the results of IVF/ICSI demonstrated an increased number of the oocytes retrieved. [6, 12]

Also, the results of the current trial showed a significantly higher number of M II oocytes collected in the GH group. That is in agreement with ***Bassiouny et al. (2016)*** [12]. However, ***Eftekhar et al. (2013)*** study showed no significant difference between groups as regards the number of M2 oocytes [6]. Off course, the increased number of M II oocytes collected may result in a higher fertilization rate and more available embryos for transfer.

The results of the current study showed an insignificant higher number of embryos developed per patient, the number of the excellent embryo grade (G1) and the number of embryos transferred in the GH group than in the control group. These higher fertilization rates and more embryos available for transfer were also reported by other research studies. [6, 12]

Several meta-analyses and systematic reviews studied the impact of adding GH for different ovarian stimulation protocol in the improvement of the IVF/ICSI outcomes in poor responders. One of them, ***Kolibianakis et al. (2009)*** advocated that the administration of GH might lead to more patients reaching the stage of embryo transfer and hence have the chance of pregnancy. Conversely, this was not evidenced by the results of the study, as the percentage of cycles reached embryo transfer was not significantly different between groups. [15]

The pooled effect of the six trials included in this meta-analysis showed that 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 found no significant difference. [15]

Added to these notions mentioned above, the sample size of each RCT and the variability between studies concerning the ovarian stimulation protocol can jeopardize the results of the meta-analysis. Likewise, GH doses varied, ranging from 4 IU daily to 24 IU administered on alternate days. [15]

A Cochrane meta-analysis showed a statistically significant improvement in both the clinical pregnancy rate and the live birth rate. However, these research studies used different ovarian stimulation protocols, not just one; thus, it may lead to confounding bias. [11]

A recent meta-analysis and systematic review, ***Li et al. (2017)***, included eleven RCT studies concluded that the addition of GH could significantly improve the clinical pregnancy rate and live birth rate. Furthermore, the GH addition time may affect the pregnancy outcome. [17]

The pooled analysis using fixed-effects model showed that the clinical pregnancy rate was significantly increased in the GH group. GH addition could significantly increase the live birth rate. There was no significant difference between the GH group and the control group in the fertilization rate and the implantation rate. Their results demonstrated that E2 on HCG day was significantly higher in the GH group. [17]

However, the included studies were highly heterogeneous. The sources of heterogeneity may be related to the different timings and doses of GH. Likewise, eligibility criteria were variables; the used COS protocols were not the same; GH dose and time were not consistent. [17]

One strength of this current study is its randomized nature and with enough sample size. Added to the facts as mentioned earlier, the study addressed the impact of GH added to the ultrashort protocol, which to the best of our knowledge is the first in this area.

However, one limitation of this current RCT is that the live birth rate was not included in the results of the study because follow-up of patients was not possible since they were from different, far locations from our hospital. That, of course, added another limitation regarding the assessment of the long-term safety of GH on the mothers and their children.

The third limitation of this RCT is that the study used a low-dose of GH 4 IU that may jeopardize the effect; however, one reason for this dose was to avoid any adverse effects due to the higher doses. In addition, we did not make an economic evaluation in term of cost-effectiveness analysis of using GH in the treatment cycles.

5. Conclusion

This study showed no significant increase in clinical and chemical pregnancy rates by the addition of GH to the ultrashort antagonist protocol in poor responders. The number of retrieved oocytes was significantly higher in the GH group. Moreover, the number of embryos was insignificantly higher in the GH group.

Author contributions

Conceptualization: EHM, AGA, EAM, AHA, MZ, MMS, ERHI; Data curation: EAM, AHA, MZ, MMS; Formal analysis: ERHI, MMS, EAM; Funding acquisition: MMS; Methodology: EHM, AGA, EAM, AHA, MZ, MMS, ERHI; Project administration: EHM, AGA, EAM, AHA, MZ, MMS; Visualization: EHM, AGA, EAM, AHA, MZ, MMS; Writing – original draft: ERHI, EAM, MMS; Writing – review & editing: EHM, AGA, EAM, AHA, MZ, MMS, ERHI.

Clinical Trial Registration:

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Declaration of interest

All authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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