RESEARCH PAPER

Impact of Growth Hormone Administration on Intracytoplasmic Sperm Injection (ICSI) Outcomes in Patients with Diminished Ovarian Reserve

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ABSTRACT
Background: Poor ovarian reserve (POR) affects IVF/ICSI outcomes, according to the Bologna criteria, factors like older age, a low number of oocytes retrieved, decreased antral follicle count (AFC) and Low levels of anti-Müllerian hormone (AMH) suggest a poor ovarian response (POR). Growth hormone (GH) might enhance follicle development through IGF-1, potentially boosting the ovarian response in individuals with POR. Aim: The objective is to examine how growth hormone adjuvant therapy affects outcomes of ICSI procedures for women with diminished ovarian reserve. Patients and methods: Prospective study focused on patients diagnosed as POR and underwent ICSI, and it was conducted at Beni-Suef University from February 2022 through January 2024. Participants were allocated into 2 groups: (A) a control group without adjuvant therapy and (B) a group that received GH adjuvant therapy. Results: There were no initial differences in age, BMI, hormones, or AFC between the groups. The GH group experienced fewer days of stimulation (11.67±1.5 compared to 12.87±1.2, P<0.001), required a lower dose of gonadotropins (4828±1005 versus 5207±1018 IU, P=0.008), and had more number of metaphase II oocytes (2.99 ± 1.8 compared to 2.2±1.1, P=0.002). No variations in peak E2 levels, endometrial thickness, embryo transfer rates, or rates of chemical/clinical pregnancy (19.4% versus 14.8%, P=0.437), ongoing pregnancy, or miscarriage. Conclusion: Growth hormone (GH) adjuvant therapy is effective in reducing the duration and dosage of stimulation while increasing mature oocytes count in patients of poor ovarian response (POR). However, it does not improve pregnancy rates. To determine the optimal dosing and timing, large-scale randomized controlled trials (RCTs) are required.
Keywords: Growth Hormone, Poor ovarian Reserve, ICSI
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INTRODUCTION

Somatotropin, commonly referred to as growth hormone (GH), produced by pituitary gland. Its production is stimulated by the GH-releasing hormone from the hypothalamus and is suppressed by somatostatin.GH secretion pulsatile The GH is secreted from the anterior pituitary somatotroph cells but changing frequency and amplitude through the day (1). GH acts through second messengers. The liver is the major site for GH action, where it triggers insulin-like growth factor 1 (IGF-1) synthesis by mediating many effects of GH. (2)

The Bologna criteria are widely accepted for identifying poor ovarian reserve. "They require at least two of the following conditions: (i) advanced maternal age (≥40 years) or other risk factors linked to a poor ovarian response, (ii) a history of poor ovarian response (≤3 oocytes with a standard stimulation protocol), and (iii) an abnormal ovarian reserve test result (antral follicle count <5–7 or anti-Müllerian hormone <0.5–1.1 ng/ml)."(3).

For more than 25 years, growth hormone (GH) has played an essential role in folliculogenesis. It has also served additional treatment in ICSI. Insulin-like growth factor 1 (IGF-1) activates AKT and gene expression supported by FSH through (IGF-1R) receptor in granulosa cells. IGF-1 enhances the effects of FSH during folliculogenesis .

Although the FDA has not approved growth hormone (GH) for use in ICSI, except when there is a GH deficiency, It is frequently employed as a supplementary treatment in ovarian stimulation for IVF cycle. Although GH has been utilized for 25 years in treating women subfertility, its role in IVF treatment continues to be a topic of discussion.(6).

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The difficulties linked to the reporting of studies with insufficient power, particularly those involving patients with a low likelihood of successful pregnancy, contribute in part to this problem. Furthermore, identifying the benefit of growth hormone (GH) in addressing women infertility is challenging due to several factors: the drug's high expense, the lack of clarity about the correct dosage, the best timing for starting GH therapy, and the specific patient sub-group that would benefit from its use.(7).

The research objective was to detect how growth hormone, when used as an additional treatment, affects the results of (ICSI) procedures in women with diminished ovarian reserve.

PATIENTS AND METHODS

This prospective study was conducted with patients with POR who had ICSI procedures at Beni-Suef University Hospital. This study spanned from February 2022 to January 2024. Participants were allocated into two groups: Group A, Control group -Group B, which received GH adjuvant treatment.

Sample size: carried out using G*Power Version 3.1.9.2 [computer software] (Franz Faul, Kiel, Germany). A power analysis for t-test was executed, focusing on oocytes as the primary outcome. This analysis employed an alpha error rate of 0.05, a statistical power of 0.9, an effect size (w = 0.417) as referenced by Beder et al (8), and considered degree of freedom=1. Based on these assumptions, the sample size is 200 (100 patients per group).

Inclusion criteria: patient who presented for icsi trial with poor ovarian reserve defined by the Bologna criteria (ESHRE, 2011)" at least two should be present: maternal age (over 40years), a previous low ovarian response with 3 oocytes retrieved following conventional stimulation and decreased ovarian reserve tests (ORT) [i.e., (AFC)<7 or (AMH)<1.1ng/ml]".

Exclusion criteria: Any prohibitions on the administration of fertility medications, any restrictions on administering growth hormone, the existence of hydrosalpinx and uterine deformities or an atypical uterine cavity, basal FSH levels surpassing 17 IU, abnormal karyotype, a partner with significant male infertility issues, and unmanaged endocrine disorders such as diabetes, hyperthyroidism, and hypothyroidism.

A comprehensive evaluation was conducted for each patient, including medical history, physicl examination, body mass index (BMI), pelvic physical findings, and antral follicle count (AFC) through transvaginal ultrasound during early menstruation. Routine laboratory tests were conducted excluding any general diseases that might contraindicate induction or pregnancy. Moreover, baseline serum (FSH), (LH), (AMH), (E2) and prolactin (PRL).

The induction protocol employed was the antagonist protocol. In this trial, growth hormone administration consisted of 4 IU of recombinant growth hormone (Somatotropin) administered via subcutaneous injection every other day for four weeks before starting the cycle. The treatment plan was maintained from the beginning of stimulation (day 2) up until the trigger day of (hCG).

Outcomes: Primary outcome: Number of oocytes collected and secondary outcomes: pregnancy rate, quantity and quality of embryos, cycle cancellation rate, total gonadotropin dosage required, endometrial thickness achieved before ovum retrieval, and miscarriage rates.

Ethical consideration

The Research Ethics Committee of the Faculty of Medicine at Beni-Suef University reviewed and approved the study. Prior to participating, all individuals provided informed consent.

Statistical Methods

The data summarized using mean ± standard deviation, with frequencies and percentages provided where applicable. The Kolmogorov-Smirnov test was employed assessing the normality of continuous demographic variables. To compare study groups, an independent-samples t-test was used for data following a normal distribution, while the Mann-Whitney U test was applied to data that did not meet normality assumptions. To compare categorical data, the Chi-square test was utilized, while Fisher's Exact Test was utilized for smaller sample sizes. P value of ≤ 0.05 was considered statistically significant. Statistical analyses were done using SPSS (version 22).

RESULTS

Table (1): The baseline characteristics of the study groups were analyzed

Variable	Group A (Control) Mean ± SD	Group B (GH) Mean ± SD	*P* value
Age (years)	36.7 ± 3.3	36.1 ± 3.2	0.141
BMI (kg/m²)	28.9 ± 2.8	29.4 ± 2.8	0.708
Duration of infertility (years)	6.2 ± 2.9	5.8 ± 4.1	0.065

Table 1 The baseline characteristics of the study groups had no significant .

Table (2): Baseline hormonal profile of the study groups.

Hormonal profile	Group A Mean ± SD	Group B Mean ± SD	*P* value
Basal FSH (IU/L)	11.29 ± 2.20	11.47 ± 1.70	0.365
Basal LH (IU/L)	8.83 ± 1.46	8.54 ± 1.39	0.083
Basal Estradiol (E2, pg/mL)	51.58 ± 9.00	51.43 ± 10.00	0.178
AMH (ng/mL)	0.53 ± 0.26	0.55 ± 0.26	0.531
AFC (ultrasound)	4.36 ± 1.90	4.43 ± 1.80	0.717

*Mann–Whitney U test

Table 2 The baseline hormonal profiles of the two groups did not exhibit significant differences. Basal FSH levels were similar (11.29 ± 2.20 vs. 11.47 ± 1.70 IU/L; P = 0.365), as were basal LH levels (8.83 ± 1.46 vs. 8.54 ± 1.39 IU/L; P = 0.083). Additionally, no significant differences were noted in basal estradiol concentrations (51.58 ± 9.00 vs. 51.43 ± 10.00 pg/mL; P = 0.178). Likewise, AMH levels (0.53 ± 0.26 vs. 0.55 ± 0.26 ng/mL; P = 0.531) and antral follicle count (4.36 ± 1.90 vs. 4.43 ± 1.80; P = 0.717) were close between the two groups.

Table (3): ICSI Parameters: Days of stimulation, Units of gonadotropins, Peak level of E2 and Endometrial thickness at OPU in both groups.

Variable	Group A (Control group) Mean ± SD	Group B (GH group) Mean ± SD	Test of significance	*P* value
Days of stimulation	12.87 ± 1.20	11.67 ± 1.50	Mann–Whitney U test	≤ 0.001*
Total units of gonadotropins (IU)	5207 ± 1018	4828 ± 1005	Mann–Whitney U test	0.008*
Peak estradiol level (E2, pg/mL)	1288 ± 300	1397 ± 428	Mann–Whitney U test	0.184
Endometrial thickness at trigger (mm)	8.90 ± 1.60	9.10 ± 1.70	Mann–Whitney U test	0.473

Table 3 the duration of stimulation was shorter in the GH group (11.67 ± 1.50 vs. 12.87 ± 1.20 days; P ≤ 0.001). In addition, the total dose of gonadotropins taken was less in the GH group (4828 ± 1005 vs. 5207 ± 1018 IU; P = 0.008). Conversely the table shows no statistically significant differences found regarding peak estradiol levels on trigger day (1397 ± 428 vs. 1288 ± 300 pg/mL; P = 0.184) or endometrial thickness at the time of trigger (9.10 ± 1.70 vs. 8.90 ± 1.60 mm; P = 0.473).

Table (4): Oocyte yield and maturity outcomes in the studied groups.

Variable	Group A (Control group) Mean ± SD	Group B (GH group) Mean ± SD	*P* value
Total number of oocytes	2.60 ± 1.20	3.30 ± 1.90	0.059
Number of MII oocytes	2.20 ± 1.10	2.99 ± 1.80	0.002*

*Mann–Whitney U test

Table the oocyte yield and maturation, the overall count of oocytes retrieved was similar between the two groups, although the GH group had a slightly higher number (3.30 ± 1.90 vs. 2.60 ± 1.20; P = 0.059). Conversely, the GH group had a notably more number of mature (MII) oocytes than the control group (2.99 ± 1.80 vs. 2.20 ± 1.10; P = 0.002).

Table (5): Embryo transfer characteristics in the studied groups

Embryo transfer status	Group A (Control group) n (%)	Group B (GH group) n (%)	*P* value
No transfer	12 (12%)	7 (7%)	0.279
Fresh embryo transfer	75 (75%)	84 (84%)	
thawed embryo transfer	13 (13%)	9 (9%)	

Table 5 showed that the distribution of embryo transfer status was comparable between the two groups. No statistically significant difference was observed in the rates of no transfer, fresh embryo transfer, or thawed embryo transfer between the control and GH groups (P = 0.279).

Table (6): Pregnancy outcomes per embryo transfer for the studied groups.

Outcome	Group A (Control group) n (%)	Group B (GH group) n (%)	*P* value
Chemical pregnancy rate / ET (+ve serum β-hCG)	13 (14.8%)	18 (19.4%)	0.437
Clinical pregnancy rate (CPR) / ET	11 (12.5%)	13 (14.0%)	0.829
Ongoing pregnancy rate ≥ 12 weeks	9 (10.2%)	13 (14.0%)	0.500

Table 6: Pregnancy outcomes were similar in the control and GH groups. The rate of chemical pregnancy was 14.8% (13/88) in the control group and 19.4% (18/93) in the GH group (P = 0.437). Likewise, the rate of clinical pregnancy per embryo transfer was 12.5% (11/88) in the control group and 14.0% (13/93) in the GH group (P = 0.829). Ongoing pregnancy rates (≥12 weeks) were 10.2% in the control group and 14.0% in the GH group, which indicates no significant difference between the groups (P = 0.5).

Table (7): Pregnancy continuation outcomes in the studied groups.

Outcome	Group A (Control group) n (%)	Group B (GH group) n (%)	Test of significance	*P* value
Miscarriage	4 (30.8%)	5 (27.8%)	χ^2 test	0.856
Continued pregnancy	9 (69.2%)	13 (72.2%)		

Table 7 showed that four women (30.8%) had miscarriage in group A and also 5(27.8%) women of pregnant women group B experienced miscarriage, with P-value=0.86. which statistically; of no significant difference.

No OHSS cases were reported in both groups. The GH adjuvant treatment group reported no serious side effects, with only 4 cases of mild injection site allergy (4%), 3 cases of numbness (3%) and 2 cases of muscle pain (2%).

DISCUSSION

When comparing the two groups, no notable differences were found in age, BMI, subfertility duration, basal levels of FSH, LH, E2, AMH and the antral follicle count as determined by ultrasound. The current study found significant variation comparing two groups concerning the number of stimulation days and the quantity of gonadotropins used for ovarian induction (P ≤ 0.001). Group B (GH Group) required lower doses of gonadotropins and a shorter treatment duration Bassiouny et al. (9) similarly assessing the incorporation of GH into the antagonist protocol. The study involving 141 women, and their findings showed a similar level of significance. In contrast, Eftekhar et al. (10) integrated GH therapy into an antagonist protocol for individuals with poor response and found no differences as regard the gonadotropin dosage and the duration of stimulation.

There wasn't statistically significant difference in peak E2 levels and endometrial thickness on trigger day. Eftekhar et al. (10) and Dunne et al. (11) also found no difference between women treated with growth hormone following IVF. However, Kucuk et al. (12) and Du et al. (13) observed an elevation of E2 the day of HCG treatment and increased momentum for endometrial receptivity. With regard to the reproductive results, a statistical difference was found in the number of metaphase II oocytes extracted from women between Group A (Control group) against those corresponding to Group B (P = 0.002). There was also no significant difference in the embryo transfer rate, 88/100 patients (88%) underwent embryo transfer in Group A vs. 93/100 cycles (93%) in Group B and P = 0.279 (Table III). Research by Hart et al. (6) and Eftekrar et al. (10) presented larger number of retrieved oocytes and embryos in GH group. There was no difference in chemical and clinical pregnancy between the groups, as reported by the study authors. We examined the rates of ongoing pregnancies up to the conclusion of the 12th week and miscarriages, and found no significant differences. In a study by Eftekrar et al. (10) involving 82 patients with poor response, who were administered an antagonist protocol in the GH group, there were no significant differences between the groups in terms of implantation, chemical, and clinical pregnancy rates.

On the other hand, a meta-analysis carried out by Li XL et al. (4) showed that the addition of GH resulted in the enhancement of ovarian response in poor respondersA significant increase in the rate of clinical pregnancy, live births, number of oocytes retrieved, M2 oocytes, and E2 levels on the day HCG was administered was observed in patients who received GH. In addition, the total dose of gonadotropins needed and the number of cycle cancellations were lower in the group treated with GH. The study concluded that patients who received GH had a significantly higher rate of clinical pregnancy and live births. The most important limitation of this study was the lack of stratification of patients based on POSEIDON. (Patient-Oriented Strategies Encompassing Individualized Oocyte Number) criteria.

CONCLUSION AND RECOMMENDATIONS

The findings of the study indicate that administering growth hormone (GH) could improve the retrieval of oocytes in women with diminished ovarian response who are intracytoplasmic sperm injection (ICSI).GH reduced stimulation duration and gonadotropin dosage

requirements, but did not impact pregnancy rates, cycle cancellation, or miscarriage rates. To fully understand GH's potential as adjuvant medication for women with poor ovarian reserve, further randomized controlled trials (RCTs) on a wide scale are needed to establish optimal dosage, timing, and identify patient subgroups that may benefit.

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