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The Impact of Growth Hormone Co-Treatment Duration on Outcomes in IVF/ICSI Cycles Among Poor Ovarian Responders

Zahra Mohammadshirazi [1], Ashraf Alyasin [2], Marzieh Agha Hosseini [2], Vajihe Hazari [3, 4*]

1- Department of Obstetrics and Gynecology, Shariati Hospital, Tehran University of Medical Science, Tehran, Iran
2- Department of Obstetrics and Gynecology, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran
3- Department of Obstetrics and Gynecology, Faculty of Medicine, Birjand University of Medical Sciences, Birjand, Iran
4- Rooyesh Infertility Center, Birjand University of Medical Sciences, Birjand, Iran.

Abstract

Background: The efficiency of in vitro fertilization is improved by growth hormone (GH) during ovarian stimulation. Additionally, patients with diabetes experience impaired insulin resistance and compromised glucose tolerance, which further exacerbate their condition. Due to these side effects, in this study, the duration of GH treatment was compared in IVF/ICSI cycles among poor ovarian responders.

Methods: In this study, POSEIDON criteria were used to choose patients. Subcutaneous administration of gonadotropin-releasing hormone (GnRH) antagonist was done beginning on the sixth day of the cycle and continuing through the day of human chorionic gonadotropin (hCG) injection. In one group, GH was administered 4 units/day from the 2nd day of the cycle until hCG injection, and in another group, the first dose was administered on the 6th day of the cycle. Following the administration of hCG, which lasted from 24 to 36 *hr*, oocytes were retrieved with the support of B-mode sonography.

Results: In our analysis, no significant differences were observed between the two groups in terms of the number of retrieved oocytes, metaphase II oocytes, and quality of grade A and B embryos. The results show that the treatment or conditions did not have a significant impact on the outcomes among the studied groups.

Conclusion: Our findings indicate that a shorter duration of GH administration can yield similar outcomes compared to a longer duration in IVF/ICSI cycles involving poor ovarian responders. This result holds the potential for a more cost-effective and patient-friendly approach in managing assisted reproductive technology procedures. It may lead to reduced side effects and improved adherence to medication regimens in patients.

** Corresponding Author:*
Vajihe Hazar,
Department of Obstetrics and Gynecology, Faculty of Medicine, Rooyesh Infertility Center, Birjand University of Medical Sciences, Birjand, Iran
E-mail:
Hazarivajihe10@gmail.com

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Introduction

In the intricate equilibrium of the origins of life, the pursuit of understanding and resolving infertility reveals a domain where scientific investigation and human ambition intersect. One of the important factors in studying and evaluation of the causes of infertility is delving into the functions of growth hormone (GH), also known as somatotropin, which is a remarkable protein consisting of 191 amino acids. GH shows the potential for regulating cell development, metabolism, and particularly reproductive function (1, 2). The ensuing narrative explores

GH, from its genesis in the hypothalamus to its pivotal role in assisted reproductive technology (ART), embodying a hope that resonates with the aspirations of countless individuals yearning for parenthood.

GH exerts its influence on its receptors through the process of binding. The liver contains a high concentration of GH receptors, while the reproductive system contains a lower concentration (3). GH receptors are found in the granulosa and theca cells of the ovaries, oocytes, cumulus cells, mammary glands, placenta, and uterus. Attachment of GH to its receptors causes modulation of steroid hormone and gamete development, enhancement of the development, reproduction, and maturation of gametes and follicles, regulation of gonadotropin secretion, and improvement of embryo quality and endometrial reception (4-7).

The field of assisted reproductive technology (ART) has made significant advancements over the past ten years (8, 9). Regardless of the fact that the clinical pregnancy rate has been steadily increasing, the results have not been satisfactory. In 2012, the European Society for Human Reproduction and Embryology (ESHRE) proposed that about 33.8 percent of embryo transfers result in successful clinical pregnancies (10). GH plays a crucial role in preserving fertility in both men and women; it has been prescribed for years in the monitoring of fertility problems, especially in individuals who have a poor ovarian response or a poor prognosis. Administering growth hormone to women undergoing IVF during ovarian stimulation can enhance the pregnancy rate. This accomplishment could potentially be attributed to the positive impact of GH on oocyte quality. This is evidenced by the higher fertility rate observed in female patients treated with GH, as well as the increased number of mature oocytes and embryos that successfully progress to the transfer stage. Pretreatment of ovaries with GH has been shown in a number of studies to boost the chances of successful pregnancy, implantation, and subsequent live births (11-13). Patients with poor ovarian response are those in whom the number of collected oocyte is lower than expected despite appropriate ovarian stimulation. This particular group of women represents one of the most significant limiting factors for the success of IVF and intracytoplasmic sperm injection (ICSI) (4). The estimated number of poor responders among women who undergo ART is between 9 and 24 percent. Different protocols and strategies were used for poor responders, but no valid treatment has been found yet (14). Several meta-analyses showed that incorporating GH to the protocol of treatment can significantly enhance the clinical pregnancy outcome, live birth rate, and proportion of patients who undergo embryo transfer, particularly in cases involving poor ovarian responses. Some randomized clinical trials showed no significant increase in live birth rates in poor responders. Despite the fact that these studies showed a significant increase in endometrial thickness, the number of retrieved oocytes, fertilized oocytes, and embryos for both transfer and freezing were all significantly lower (4). In another meta-analysis of 15 clinical trials, the outcomes of GH use in poor ovarian responders were investigated. Results demonstrated that adding GH can make significant changes in live birth rate, clinical pregnancy rate, and number of retrieved oocytes. They also showed a significant decline in cycle cancellation and dose of required gonadotropin (15). Therefore, GH in patients with poor ovarian responses can have positive effects on pregnancy outcomes.

GH can induce significant metabolic alterations. It can increase cholesterol level and interfere with renin-angiotensin system. It also has negative effects on insulin resistance and glucose tolerance in diabetic patients. However, the effects of long-term use of GH on cancers patients metabolic disorders, and other unknown side effects should be investigated more comprehensively (16). Due to these side effects, the treatment duration of GH in IVF/ICSI cycles among poor ovarian responders was compared in this study. If administration of GH over a shorter period has the same effects as administration over a longer period, opting for the shorter duration can help minimize the side effects. Furthermore, adopting this approach would provide cost-effectiveness and potential cost savings. It is important to consider that reducing the use of drugs and injections can improve the quality of other medication use, reduce the likelihood of medication non-adherence, and improve the patients' quality of life.

Methods

Study participants: Currently, two methods are used to define patients' ovarian responses in infertility treatment: BOLOGNA and POSEIDON criteria. Accordingly, the subjects of the current study were classified into four categories:

Group 1 included individuals with normal ova-

rian reserve [anti-Müllerian hormone (AMH) ≥1.2 *ng/ml*, antral follicular count (AFC) ≥5] and age <35 years.
Group 2 included individuals with normal ovarian reserve (AMH ≥1.2 *ng/ml*, AFC ≥5) and ages ≥35 years.
Group 3 included individuals with poor ovarian reserve (AMH <1.2 *ng/ml*, AFC <5) and age <35 years.
Group 4 included individuals with poor ovarian reserve (AMH <1.2 *ng/ml*, AFC <5) and ages ≥35 years (17).

In this study, the patients were classified using the POSEIDON criteria, and specifically, the poor responders were assigned to Groups 3 and 4. The study included women who met the following inclusion criteria:
1) women classified as poor responders based on the POSIEDON criteria, 2) women who had not used synthetic hormones within the past three months, 3) women undergoing an antagonist cycle, and 4) women who received GH during their ovarian stimulation cycle. Participants who met any of the following exclusion criteria were removed from the study: 1) positive test result of anti-nuclear antibodies; 2) having infectious disease, 3) having the history of chromosomal abnormality or thalassemia, in either partner; 4) history of oocyte donation, 5) having cycles treated with aspirin, sildenafil, or vitamin E; 6) having congenital uterine abnormalities, hydrosalpinx, or endometrial disorders such as tuberculosis or hyperplasia; 7) FSH level ≥15; and 8) having systemic diseases including systemic lupus erythematosus, hyperthyroidism, and hyperprolactinemia.

The patients were all recruited from Shariati Hospital (Tehran, Iran) and one infertility clinic in Tehran, as both were referral centers in our country. The patients' information was collected from their medical records, interviews, and clinical measurements.

Informed consent was obtained from all participants in our study, and the doctor personally communicated with the participants, providing verbal explanations. The registered information of participants only included codes, ensuring that their identities cannot be disclosed from the registration sheets.

Protocols: The sample size for each group was determined using a formula specific to survival analysis based on the log-rank test, resulting in a total of thirty three patients participating in each group (18). Every patient went through a process of controlled ovarian stimulation using GnRH antagonists. Gonadotropin in the form of recombinant FSH (GONAL-F) (Merck Serono, Germany) was administered sub-cutaneously by injection in the amount of 300 *IU/day* from the second day of the cycle.

GnRH antagonists in the form of Cetrotide (Merck Serono, Switzerland) 0.25 *mg/day* were administered subcutaneously from the sixth day of the cycle until hCG injection. In one group, GH (Somatropin, Sedico, Egypt) was administered on the second day of the cycle, concurrently with the use of gonadotropins. In another group, GH was used on the sixth day of the cycle, concurrently with the administration of GnRH antagonist.

In both groups, GH was administered at a rate of 4 units per day via subcutaneous injection. The injection of GH in both groups was continued up to the day of hCG injection. Follicles' growth was investigated by transvaginal ultrasound on the 8 th day of the cycle. Next, 10000 units of hCG (two 5000-unit ampoules, Puyesh Pharmaceutical Company) were administered intramuscularly when the follicles' diameters were equal to or greater than 18 *mm* and there were at least 5 follicles. After 24-36 *hr* of hCG injection, oocytes were retrieved under the guidance of B-mode sonography.

In instances where ovarian stimulation via gonadotropins for 10 days did not yield follicles of at least 14 *mm* in size, the cycle was discontinued. Following retrieval, oocytes were immediately denuded using a hyaluronidase solution to remove the cumulus oophorus and corona radiata. Subsequently, these oocytes were incubated for a period of up to two *hr*. After the incubation period, they were transferred in a specialized IVF culture medium and allowed to culture for an additional 2-4 *hr*.

A thorough assessment of oocyte quality was conducted, with particular attention given to identifying mature oocytes that had reached the metaphase II stage. These oocytes were carefully selected for the fertilization process. The embryos were cultivated under optimal conditions, maintained at 37°*C* in an atmosphere comprising 5% CO_2 and 20% O_2. Embryo transfers, conducted 3-5 days following the preparation phase, adhered strictly to the Tesarik et al.'s criteria for evaluation (19). This involved a detailed structural examination on days two and three, scrutinizing the number of blastomeres, degree of fragmentation,

symmetry, mononucleation, and compaction.

For embryos categorized under groups A and B, the decision was made to either proceed with transfer or cryopreservation. Progesterone levels were closely monitored on the day of the hCG injection to ensure uterine receptivity. If the progesterone level was below 1, and the uterine condition was determined to be favorable, the transfer of two three-day-old embryos or blastocysts was performed. The remaining embryos were cryopreserved.

Luteal phase support was initiated from the day of embryo transfer, involving a regimen of vaginal progesterone (400 *mg*, thrice daily) and intramuscular progesterone (50 *mg*, daily) across all patients. To confirm clinical pregnancy, serum beta-hCG levels were measured 14-16 days following the transfer. The progesterone administration was continued until the conclusion of the 12th gestational week, in alignment with the established protocols (4, 20, 21).

Results of puncture: In this section, it is crucial to establish the definition of embryo grading. 'Grade A embryos' are distinguished by their ideal cell number and minimal fragmentation, signifying the highest quality. On the other hand, 'Grade B embryos', while still considered of good quality, may exhibit slight irregularities in cell size or minor fragmentation.

Data analysis: SPSS version 26 (IBM, USA) was used for our statistical analysis. Statistical indicators of mean, median, and standard deviation were applied to describe our results.

Results

The demographic features and treatment regimens of the 66 individuals who participated in our research are provided in table 1. The data includes the age, body mass index (BMI), and administration schedule of growth hormone (GH) for the participants. This table provides a basic understanding of the composition of the cohort.

The analysis of infertility causes among participants with poor ovarian response (POR) is crucial for comprehending the underlying complexities of their conditions. The various etiologies are described in the following section, presenting an organized categorization based on the data collected. Table 2 details the various causes of infertility in poor ovarian responders, highlighting the frequency and percentage of each cause in the study population. The cumulative percentage column in the table displays the running total of all preceding categories, culminating in 100% when including the 'Other POR-related causes' category. This comprehensive classification emphasizes that the most common cause of infertility in this group was ovulatory dysfunction, accounting for 30.30% of the participants.

Table 1. Demographic characteristics of patients regarding BMI and GH administration

Demographic features	Details
Age range	29 to 44 years
Average age	37.3 years
BMI range	15.62 to 34.29
BMI categories	
- Underweight	2 patients (3%)
- Normal	40 patients (60.6%)
- Overweight	24 patients (36.4%)
GH administration	33 patients on day 2 33 patients on day 6
Total number of patients	66

Table 2. Categorization of infertility etiologies in poor responders

Cause of infertility in POR Patients	Frequency (%)
Uterine factor	5 (7.58)
Tubal factor	8 (12.12)
Ovulatory dysfunction	20 (30.30)
Unexplained infertility (related to POR)	10 (15.15)
Combination of female factors (POR)	13 (19.70)
Other POR-related causes	10 (15.15)

Side effects and cycle cancellation: Out of all the participants, only two cycles were canceled. One cancellation occurred because the patient did not return, and the other was due to a lack of response and oocyte retrieval. Importantly, no cases of ovarian hyperstimulation syndrome (OHSS) was observed as a result of the ovarian stimulation cycles. In our study population, three individuals expressed a desire to freeze their oocytes for fertility preservation, while the remaining oocytes were either cryopreserved or used for immediate transfer. All three individuals who wanted to freeze their oocytes were in the same group that was given GH on the second day of the cycle.

Our oocyte retrieval analysis displayed a range of 0 to 24 oocytes per individual, with both the

Table 3. Comparative analysis of oocytes retrieved and embryo grading outcomes

Variables	Mean	Std. error	t (df)	p-value
Oocytes	0.50758	1.08876	0.466	0.643
Metaphase II oocytes	-0.47917	0.78798	-0.608	0.546
Grade A and B embryos	-0.81466	0.65214	-1.249	0.217

mean and median being 4, and a standard deviation of 4. The highest count of metaphase II oocytes was observed in participants who received GH starting on cycle day 2, while the most favorable outcomes for grade A and B embryos were observed in those who received GH from cycle day 6 onwards.

In this study, oocyte count, metaphase II oocytes, and embryo quality were compared between different treatment groups. The analysis showed no significant differences in the number of oocytes retrieved, the prevalence of metaphase II oocytes, or the quality of embryos between the groups, suggesting similar outcomes across all groups. Ultimately, none of the variables exhibited a significant difference between the tested groups $p>0.05$. This implies that there are no significant differences in the number of oocytes retrieved, the number of metaphase II oocytes, or the quality of embryos between the groups that were compared based on the data and tests performed, as detailed in table 3.

Discussion

Enhancing IVF success with growth hormone therapy: Previous studies showed that GH was applied in ART in order to improve the number and quality of oocytes, increase the implantation, the chemical and clinical pregnancy, and the live birth rates (4, 15, 16). Specifically, in patients with poor responses or a poor prognosis, administration of GH during an IVF/ICSI cycle can increase the success rate. Poor ovarian response is attributed to patients among whom the number of retrieved oocytes is not enough, despite undergoing adequate ovarian stimulation. This group of women is one of the limiting factors in IVF/ICSI success (4). Also, in women classified as normal responders, GH administration can improve implantation and clinical pregnancy rate (16). Inefficient ovarian response, poor-quality embryos, and inadequate endometrial receptivity were all treated clinically with GH adjuvant therapy. Growth hormone can also be useful in in vitro fertilization to prevent repeated implantation failure (RIF). When an embryo of exceptional quality has been implanted at least three times, and potentially even more than ten times, without resulting in a successful pregnancy, this condition is recognized as "repeated implantation failure". It is possible to improve the synthesis of estradiol during early and late follicular development in both animal and human ovaries by stimulating the proliferation and alteration of granulosa cells. This leads to better functioning of the FSH hormone (4).

Out of the systematic reviews and meta-analyses available online up to 2019 that examined the effectiveness of GH adjuvant therapy on poor ovarian responders undergoing IVF cycles, only two studies reported an increase in the clinical pregnancy rate or the number of live births (3, 22-25). All of the other studies demonstrated that using GH injections in the IVF process significantly increased the number of successful live births (26-28). Although the results of certain independent randomized controlled trials have not shown notable increases in the live birth rate with GH intake in IVF patients, the collected data from the majority of meta-analyses supported the administration of GH for IVF due to the substantially higher live birth rate (29, 30). To sum up, the application of GH adjuvant therapy throughout in vitro fertilization or intracytoplasmic sperm injection seems to have the potential to improve ovarian reactivity, endometrial receptivity, clinical pregnancy, and live birth rates.

A meta-analysis published in 2020, comprising 12 randomized clinical trials, demonstrated that the addition of GH administration in patients with poor ovarian response resulted in improved outcomes (15, 23, 31). The clinical pregnancy rate, the number of retrieved oocytes, the number of metaphase II oocytes, and the number of embryos are all included in these outcomes. There were no significant changes observed in the number of live births and the number of abortions (23). Another meta-analysis published in 2020 indicated that the

administration of GH can greatly increase the clinical pregnancy rate. It also improved the number of live births, but the difference appeared to be insignificant. According to the findings of this meta-analysis, the use of GH resulted in an increase in endometrial thickness, while concurrently reducing the amount of administered gonadotropins. Both of these showed statistically significant results (14). In fact, multiple studies provide support for the use of GH as an adjuvant treatment in assisted reproductive technology (ART), particularly in patients with poor ovarian responses.

Considerations and future directions for GH use in ART: While acknowledging the positive effects of GH, it is crucial to consider the potential side effects and costs associated with this medication. It is important to be mindful of the metabolic effects of GH. GH has the potential to increase cholesterol levels, impact the renin-angiotensin system, and adversely affect insulin resistance and glucose tolerance, particularly in diabetic patients (16).

There are multiple protocols for co-treatment with GH in ART patients with poor ovarian responses. One such protocol involves administering GH during the preceding luteal phase, typically 4-6 weeks prior to hCG injection (27). In this model, GH should be used for a long period of time. Studies have demonstrated that shorter durations of GH usage can yield positive effects. Adding GH to the ovarian stimulation cycle from the start of gonadotropin administration at a rate of 4.5 units per day can significantly increase the number of retrieved oocytes, metaphase II oocytes, fertilized oocytes, and high-quality oocytes (4). Another clinical trial found that starting gonadotropin at a low dose of GH (4 units/day) increased the number of retrieved oocytes, metaphase II oocytes, and the quality of transferred embryos (32). The effective gonadotropin dose and duration of stimulation were also significantly reduced in this study (32). Two randomized clinical trials demonstrated the bene-fits of GH in antagonist IVF/ICSI cycles (29, 33, 34). In those trials, GH was administered from the 6th day of the cycle at a dose of 7.5 *IU/day* until the day of hCG administration (34). The number of retrieved oocytes, metaphase II oocytes, fertilized oocytes, high-quality oocytes, and endometrial thickness all increased significantly.

There were also some limitations in our study, which future research should address to ensure accurate and optimal use of GH in ART. At this time, there have been no definitive standards established for the indications, methods, and dosages that are involved in the clinical application of GH, and additional research is required to adequately address these concerns. The impact of GH on the quantity of gonadotropin utilized has been examined in quantitative studies, revealing a potential reduction in the required amount. However, further research is needed to explore this issue in greater detail.

Conclusion

Our research indicates that using growth hormone (GH) for a shorter duration is as effective as longer treatment periods for poor ovarian responders undergoing IVF/ICSI. This approach could revolutionize ART by making treatments more affordable and less burdensome for patients. With potentially fewer side effects, this strategy may also lead to better medication adherence and a safer experience for patients.

Shortened GH treatment aligns with the principles of patient-centered care, focusing on minimal effective dosing. However, personalized treatment remains paramount; what our study suggests is not a one-size-fits-all solution but rather a potential option that can be tailored to individual patient needs. Moving forward, these findings prompt re-evaluation of current ART protocols with the aim of integrating more efficient GH regimens that could enhance the quality of care and outcomes for patients facing the challenges of infertility.

Conflict of Interest

Authors declare no conflict of interest.

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