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The Impact of Growth Hormone Supplementation on Ovarian Response and IVF Outcomes in Poor Responders: A Prospective Observational Study

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Abstract

Background: Poor ovarian response (POR) is a significant challenge in in-vitro fertilization (IVF) treatment, characterized by a limited number of oocytes retrieved, poor embryo quality, and reduced pregnancy rates. Growth hormone (GH) supplementation has been proposed as a potential adjunct therapy to improve ovarian response and reproductive outcomes in poor responders. This study aimed to evaluate the effectiveness of GH supplementation in enhancing ovarian response and IVF outcomes in poor responders.

Methods: This single-centre prospective observational study was conducted at the Department of Reproductive Medicine, SAIMS, Indore. A total of 40 women diagnosed as poor responders according to the Bologna criteria were enrolled in the study. Participants were divided into two groups: the intervention group (n=10), which received GH supplementation alongside standard ovarian stimulation, and the control group (n=30), which underwent standard IVF treatment without GH. The primary outcome was the number of mature oocytes retrieved, while secondary outcomes included fertilization rate, embryo quality, blastocyst formation, implantation rate, and clinical pregnancy rate. Data were analyzed using Stata 17.0.

Results: The intervention group showed a significant improvement in the number of mature oocytes retrieved (5.0 ± 1.2 vs. 3.4 ± 1.1, $p < 0.05$). The fertilization rate was higher in the GH group ($71.2\% \pm 9.3\%$) compared to the control group ($63.8\% \pm 8.7\%$, $p < 0.05$). Embryo quality on Day 3 and blastocyst formation on Day 5 were significantly improved in the GH group ($p < 0.05$). While the implantation rate was higher in the GH group ($38.0\% \pm 7.5\%$ vs. $29.2\% \pm 6.8\%$, $p < 0.05$), the clinical pregnancy rate showed a trend toward improvement but was not statistically significant (30% vs. 20%, $p = 0.08$). No significant adverse events were reported.

Conclusion: GH supplementation significantly improves ovarian response, oocyte quality, and early reproductive outcomes in poor responders undergoing IVF. Although the clinical pregnancy rate did not reach statistical significance, the overall trend suggests that GH may offer a beneficial adjunctive treatment for improving IVF success rates in this challenging patient population.

Keywords: Poor ovarian response, growth hormone, IVF, oocyte quality, fertilization rate, clinical pregnancy.

INTRODUCTION

Infertility is a significant global health issue affecting approximately 10-15% of couples of reproductive ages[1]. In-vitro fertilization (IVF) being one of the most widely used assisted reproductive technologies (ART) to overcome infertility challenges[2]. Despite advances in ART, a subset of patients known as "poor responders" continues to experience suboptimal outcomes during IVF treatment, characterized by a low number of oocytes retrieved, poor embryo quality, and reduced pregnancy rates[3]. The definition of poor ovarian response (POR) varies, but it is generally identified based on criteria such as advanced maternal age, previous poor response to ovarian stimulation, and abnormal ovarian reserve tests[4]. Managing these patients remains a complex clinical challenge, often requiring innovative strategies to improve their chances of successful conception[5].

One of the emerging therapeutic approaches in managing poor responders involves the use of adjuvants, among which growth hormone (GH) has gained attention[6]. Growth hormone, a peptide hormone secreted by the anterior pituitary gland, plays a critical role in various physiological processes, including growth, metabolism, and cellular differentiation[7]. In the context of ovarian physiology, GH has been shown to

exert direct and indirect effects on follicular development and oocyte maturation[6]. These effects are primarily mediated through the insulin-like growth factor (IGF) system, which enhances granulosa cell proliferation, steroidogenesis, and oocyte competence[6]. However, the role of GH as an adjunct to ovarian stimulation in IVF, particularly among poor responders, remains a topic of ongoing research and debate.

The rationale for incorporating GH in IVF protocols stems from its potential to improve ovarian response and reproductive outcomes in patients with diminished ovarian reserve[8,9]. The underlying mechanisms through which GH exerts its effects on the ovaries include increased sensitivity of follicles to follicle-stimulating hormone (FSH), enhancement of IGF-1 levels, and modulation of intra-ovarian paracrine signalling[8,9]. Studies have suggested that GH can augment the number of mature oocytes, improve embryo quality, and increase the likelihood of implantation and pregnancy in poor responders[10,11]. Despite these promising findings, the clinical efficacy of GH in IVF treatment remains controversial, with some studies reporting significant benefits while others show limited or no improvement in outcomes.

Identifying patients who are most likely to benefit from GH supplementation is crucial for maximizing therapeutic outcomes and minimizing unnecessary interventions.
Aim: The aim of this study is to evaluate the effectiveness of growth hormone (GH) supplementation in improving ovarian response and overall reproductive outcomes among poor responders undergoing in-vitro fertilization (IVF) treatment.

MATERIAL AND METHODS:

- **Study Design:** A single centre, 1:3, comparative, prospective, observational study to evaluate the role of growth hormone (GH) supplementation among poor responders undergoing in-vitro fertilization (IVF) treatment. The study aimed to compare the effects of GH on ovarian response, oocyte quality, embryo development, and M2 rates.
- **Study Settings:** The study was conducted at the Department of Obstetrics and Gynaecology, SAIMS, Indore specializing in assisted reproductive technologies. The setting provided comprehensive IVF services, including ovarian stimulation, oocyte retrieval, embryo transfer, and pregnancy monitoring. The data were collected from patients attending the fertility clinic of the hospital.
- **Study Duration:** The total duration of the present study was 18 months: from September 2022 to February 2024.
- **Primary Outcome:** The primary outcome was the number of mature oocytes retrieved, measured during the oocyte retrieval procedure.
- **Secondary Outcomes:** Fertilization rate, assessed by grading embryos on Day 3 and Day 5 post-fertilization.
- **Confounding Variables:** Factors such as baseline ovarian reserve, previous IVF attempts, and co-existing medical conditions that could influence IVF outcomes.
- **Definition of the Exposure:** The intervention consisted of administering growth hormone supplementation as an adjunct to standard ovarian stimulation protocols during IVF treatment. GH was administered subcutaneously at a dosage defined by the study protocol, starting from the onset of ovarian stimulation until the day of oocyte retrieval.
- **Study Universe:** The study universe comprised all women undergoing in-vitro fertilization (IVF) treatment at the Department. These women were seeking fertility treatment and met the defined criteria for poor ovarian response according to established guidelines.
- **Study Participants:** The participants of the present study were women classified as poor responders undergoing IVF treatment. Eligible participants were those who met the inclusion criteria of being poor responders, defined by the Bologna criteria, with a history of poor ovarian response in previous IVF cycles[12].
- **Inclusion Criteria:**
  i. Women aged > 35 years undergoing IVF treatment.
  ii. First cycle of primary or secondary infertility treatment.
  iii. Serum AMH < 2 ng/ml
  iv. Antral follicle count < 5.
  v. Willingness to comply with the study protocol and provide written informed consent.
- **Exclusion Criteria:**
  i. Donor cycles
  ii. Failed IVF
  iii. Cases of Surgical Sperm Retrieval
  iv. BMI > 35.0

v. Severe male factor infertility that could independently affect IVF outcomes.

Study Groups: The study participants were divided into two groups:

i. Exposure Group: Received standard IVF treatment along with growth hormone supplementation starting from the onset of ovarian stimulation until the day of oocyte retrieval.
ii. Control Group: Received standard IVF treatment without the addition of growth hormone.

- **Allocation to Groups**: Participants were allocated to the treatment groups based on mutual discussion with each participant about the available treatment options, including the potential benefits and risks of growth hormone supplementation. The allocation was conducted in a transparent manner, allowing participants to make an informed decision about their treatment preference, ensuring ethical standards were maintained.
- **Sample Size:** The minimum required sample size for this study was calculated based on expected differences in oocyte retrieval between the intervention and control groups, with a significance level of 5% and a power of 80%. Assuming an effect size that reflects a clinically meaningful improvement in outcomes, a total sample size of approximately 10 participants in exposure group and 30 participants in the non-exposure control group.
- **Sampling Methodology:** The study utilized non-probability convenience sampling, where participants were recruited based on their availability and willingness to participate during their routine clinical visits. This method allowed for a more flexible recruitment process, accommodating patients' schedules and treatment timelines.
- **Participant's Recruitment:** Participants were recruited from the Department. During clinic visits, eligible women were approached by research staff and were provided with detailed information about the study, including its purpose, procedures, potential risks, and benefits. Following initial discussions, interested participants underwent a screening process to confirm eligibility based on inclusion and exclusion criteria. Upon meeting the criteria, participants were invited to join the study.
- **Obtaining Informed Consent:** Written informed consent was obtained by the Principal Investigator (PI) using a bilingual consent form available in Hindi and English. The PI explained the study details to each participant in a language they understood, addressing any questions or concerns they had.
- **Data Sources:** The data for this study were collected from multiple sources. The primary source of data was the clinical records of women undergoing IVF treatment at the Department. These records provided detailed information on the independent variables, such as age, ovarian reserve (measured by AMH levels), and previous IVF history. The dependent variables included the number of mature oocytes retrieved, fertilization rates, and embryo quality. Confounding variables like baseline ovarian reserve, co-existing medical conditions, and previous IVF attempts were also extracted from the same clinical records to control for their potential influence on the study outcomes.
- **Data Collection Procedure:** Initially, potential participants were identified. Once identified, each participant was approached by the research team and provided with detailed information about the study. Informed consent was obtained using a bilingual consent form (Hindi and English) to ensure that all participants fully understood the purpose, procedures, potential risks, and benefits of the study. The Principal Investigator (PI) and research staff answered any queries raised by the participants before proceeding.
- Following the consent process, the participants were assigned to either the intervention group (IVF treatment with growth hormone supplementation) or the control group (IVF treatment without growth hormone supplementation) based on their treatment preference after a thorough discussion of the possible risks and benefits. Growth hormone (GH) was administered to the intervention group subcutaneously, following the dosage protocol established in the study, starting from the first day of ovarian stimulation and continuing until the day of oocyte retrieval. The data collection process began with the recording of baseline demographic and clinical characteristics, including age, body mass index (BMI), ovarian reserve (measured by AMH levels and antral follicle count), and previous IVF attempts. These data were gathered from the participants' clinical records and interviews conducted during their clinic visits. Information on co-existing medical conditions that could affect IVF outcomes, such as polycystic ovarian syndrome (PCOS) or thyroid disorders, was also documented as potential confounders.
- During the treatment cycle, specific clinical outcomes were measured at various stages:

  1. Ovarian Stimulation: Data related to ovarian response, including the number of follicles observed during ultrasound monitoring, the total dosage of gonadotropins used, and the duration of stimulation, were recorded.

  2. Oocyte Retrieval: On the day of oocyte retrieval, the primary outcome (number of mature oocytes retrieved) was measured. Oocytes were classified based on their stage of maturity, with mature (M2) oocytes being the primary focus.

3. Fertilization and Embryo Development: Fertilization outcomes were assessed by embryologists. Fertilization rate, embryo quality, and grading on Day 3 and Day 5 post-fertilization were recorded as secondary outcomes.

The research team ensured that all data points were consistently recorded in paper-based forms, which were specifically designed for this study. Data entry was cross-checked by the research staff and subsequently transferred to an electronic database for statistical analysis. To maintain consistency in the collection of data, the research team followed standardized operating procedures (SOPs) at each step of the data collection process. This included clear protocols for clinical measurement (such as using the same ultrasound equipment for monitoring ovarian response) and detailed guidelines for embryologists regarding embryo grading to minimize variability in outcome assessment. Finally, the PI and other senior staff regularly supervised the data collection process, ensuring adherence to the protocols, timely collection of data, and prompt resolution of any discrepancies that arose during the study.

- **Data Quality Assurance:** The study employed multiple measures to ensure the quality of the collected data. The data collection forms were regularly reviewed by the study supervisor to identify and correct any potential errors or inconsistencies. Additionally, the ethical committee performed periodic audits of the data to ensure that all procedures were in line with ethical guidelines and that the data were accurate and complete. Any discrepancies found during these audits were addressed promptly to maintain data integrity throughout the study.
- **Statistical Analysis:** The data from paper-based data collection were initially entered into MS Excel and imported into Stata 17.0. All statistical and graphical analyses for this study were undertaken using Stata software version 17.0. Descriptive statistics were used to summarize the demographic and clinical characteristics of the participants, while inferential statistics, including regression analysis, were used to evaluate the association between growth hormone supplementation and reproductive outcomes.
- **Data Handling and Security**: The study data were handled and secured in accordance with institutional guidelines. All paper-based data collection forms were stored in a locked cabinet within the PI's office, accessible only to authorized personnel. Electronic data were password-protected and stored on the institute's secure server to prevent unauthorized access. After the findings of the study are published, the paper-based data collection forms will be shredded, and the electronic version of the data will be deposited in the institute's repository.
- **Funding:** There were no external fundings for this study. All expenses related to the research, including the costs of data collection, were borne by the study institute. The Principal Investigator personally covered any additional expenses. Furthermore, participants in the study were not compensated for their participation.
- **Conflict of Interest:** The authors declare no conflict of interest in the design, implementation, or interpretation of the findings of this study. All aspects of the research were conducted with complete academic integrity, and no external parties influenced the outcomes or conclusions presented in this work.

RESULTS:

A total of 40 participants were included in the study, with 10 participants in the intervention group (IVF with growth hormone supplementation) and 30 participants in the control group (IVF without growth hormone). The baseline demographic characteristics of the participants were recorded at the time of recruitment and are summarized as follows.

The mean age of participants in the intervention group was 36.5 ± 2.1 years, while in the control group, the mean age was 37.2 ± 3.0 years. Participants in both groups were over 35 years, meeting the inclusion criteria of poor ovarian response as defined by the Bologna criteria[12]. The mean BMI of the intervention group was 28.3 ± 3.2 kg/m², compared to 27.6 ± 3.5 kg/m² in the control group. No significant differences were observed between the two groups in terms of BMI, and both groups had participants within the overweight range (BMI > 25). The duration of infertility was similar between the two groups. In the intervention group, the mean duration of infertility was 6.1 ± 2.5 years, while the control group had a mean duration of 6.7 ± 2.8 years. In terms of prior IVF attempts, 30% of participants in the intervention group and 33% in the control group had undergone one or more failed IVF cycles prior to the current study. This suggests a comparable history of previous poor ovarian response between both groups.

Table 1: Baseline Characteristics of the participants in the two groups

Characteristic	GH Group (Mean ± SD or %)	Control Group (Mean ± SD or %)
Age (years)	36.5 ± 2.1	37.2 ± 3.0
BMI (kg/m²)	28.3 ± 3.2	27.6 ± 3.5
Duration of Infertility (years)	6.1 ± 2.5	6.7 ± 2.8
Previous IVF Attempts (%)	30%	33%

Antral Follicle Count (AFC)	4.3 ± 1.2	4.1 ± 1.4
AMH Levels (ng/mL)	1.5 ± 0.3	1.4 ± 0.4
Co-existing Medical Conditions (%)	10%	10%
Smoking Status (%)	0%	0%

The mean AFC in the intervention group was 4.3 ± 1.2, while the control group had a mean AFC of 4.1 ± 1.4. Both groups had an AFC below the normal threshold, in line with the study's inclusion criteria for poor ovarian responders. AMH levels were similar between the groups, with the intervention group having a mean AMH of 1.5 ± 0.3 ng/mL and the control group having a mean of 1.4 ± 0.4 ng/mL. Both groups had low AMH levels, which is consistent with poor ovarian reserve.

Approximately 10% of participants in both groups had been diagnosed with co-existing medical conditions such as hypothyroidism or polycystic ovarian syndrome (PCOS), which are known to affect fertility outcomes. None of the participants in either group reported current smoking or alcohol consumption, and all participants adhered to lifestyle modifications as recommended by the clinic's reproductive health guidelines.

The average number of mature oocytes (M2) retrieved was significantly higher in the GH group compared to the control group. Participants in the GH group retrieved an average of 5.0 ± 1.2 mature oocytes, whereas participants in the control group retrieved an average of 3.4 ± 1.1 mature oocytes. The difference between the two groups was statistically significant ($p < 0.05$), indicating that GH supplementation enhanced ovarian response in poor responders.

The fertilization rate, defined as the percentage of oocytes that successfully fertilized, was higher in the GH group compared to the control group. The mean fertilization rate in the GH group was 71.2% ± 9.3%, while the control group had a fertilization rate of 63.8% ± 8.7% ($p < 0.05$). Embryo quality was assessed based on embryo grading on Day 3 and Day 5 post-fertilization. On Day 3, the percentage of good-quality embryos (Grade 1 and 2) in the GH group was 65.0% ± 10.5%, compared to 53.6% ± 9.8% in the control group ($p < 0.05$). By Day 5, the percentage of embryos that developed into blastocysts was higher in the GH group (48.0% ± 8.7%) than in the control group (37.5% ± 8.4%) ($p < 0.05$). The implantation rate, defined as the percentage of transferred embryos that successfully implanted and resulted in a gestational sac, was higher in the GH group (38.0% ± 7.5%) compared to the control group (29.2% ± 6.8%) ($p < 0.05$). The clinical pregnancy rate, defined by the presence of a fetal heartbeat, was 30% in the GH group and 20% in the control group, though the difference was not statistically significant ($p = 0.08$).

Table 2: Outcome of Growth Hormone Supplementation

Outcome	GH Group (Mean ± SD)	Control Group (Mean ± SD)	p-value
Number of Mature Oocytes Retrieved	5.0 ± 1.2	3.4 ± 1.1	< 0.05
Fertilization Rate (%)	71.2 ± 9.3	63.8 ± 8.7	< 0.05
Good-quality Embryos on Day 3 (%)	65.0 ± 10.5	53.6 ± 9.8	< 0.05
Blastocysts Formed on Day 5 (%)	48.0 ± 8.7	37.5 ± 8.4	< 0.05
Implantation Rate (%)	38.0 ± 7.5	29.2 ± 6.8	< 0.05
Clinical Pregnancy Rate (%)	30%	20%	0.08
Total Gonadotropin Dosage (IU)	3000 ± 400	3200 ± 500	0.09
Duration of Ovarian Stimulation (Days)	10.3 ± 1.4	10.5 ± 1.6	NS

The total gonadotropin dosage required was lower in the GH group (3000 ± 400 IU) compared to the control group (3200 ± 500 IU), though this difference was not statistically significant ($p = 0.09$). The duration of ovarian stimulation was similar between the two groups, with a mean of 10.3 ± 1.4 days in the GH group and 10.5 ± 1.6 days in the control group. There were no significant adverse events reported in either group. Both groups tolerated the treatments well, and no cases of ovarian hyperstimulation syndrome (OHSS) were observed.

DISCUSSION:

In the present study, both groups had similar baseline characteristics in terms of age, BMI, and ovarian reserve markers, ensuring that the two groups were comparable. The mean age of participants in the GH group (36.5 ± 2.1 years) and control group (37.2 ± 3.0 years) was consistent with the inclusion criteria for poor ovarian responders, defined by advanced maternal age and low ovarian reserve according to the Bologna criteria. This similarity aligns with other studies on poor responders, such as the study by Safdarian et al. (2019), where the mean age of participants was comparable across study groups[13]. In terms of body mass index (BMI), both groups were within the overweight range, with the GH group at 28.3 ± 3.2 kg/m² and the control group at 27.6 ±

3.5 kg/m². While some studies, such as Norman et al. (2019), excluded participants with a BMI >33 kg/m² due to potential effects on IVF outcomes, the slight differences in BMI between our study groups were not statistically significant, and both groups had comparable BMI range[14].

Both groups had similar Antral Follicle Counts (AFC), with the GH group averaging 4.3 ± 1.2 and the control group at 4.1 ± 1.4. These AFC values are below the normal threshold, consistent with the classification of poor ovarian responders in other studies, such as Yang et al. (2020), where participants were characterized by low AFC and reduced ovarian reserve[15]. The low AFC and AMH levels in both groups reflect the inclusion of participants with diminished ovarian reserve, as defined by the Bologna criteria. The duration of infertility was also comparable between the two groups, with the GH group having a mean duration of 6.1 ± 2.5 years, and the control group averaging 6.7 ± 2.8 years. This is in line with the findings of Safdarian et al. (2019), where the duration of infertility was similarly long in patients classified as poor responders[13].

Overall, the similarity in baseline characteristics between the GH and control groups demonstrates that the differences observed in outcomes can be attributed to the intervention (GH supplementation) rather than confounding variables. The comparable demographics and ovarian reserve markers strengthen the validity of the study's findings and allow for meaningful comparisons with other studies, such as the randomized trials by Norman et al. (2019)[14] and the meta-analysis by Yang et al. (2020)[15].

Table 2 highlights the significant differences in key IVF outcomes between the GH and control groups. The results indicate that growth hormone (GH) supplementation had a positive effect on ovarian response and embryological outcomes in poor responders.

One of the primary outcomes, the number of mature oocytes retrieved, was significantly higher in the GH group (5.0 ± 1.2) compared to the control group (3.4 ± 1.1, $p < 0.05$). This finding aligns with previous studies, such as the trial by Safdarian et al. (2019), which also reported a significant increase in the number of metaphase II oocytes in poor responders receiving GH supplementation[13]. The increase in the number of mature oocytes can be attributed to GH's ability to enhance follicular sensitivity to gonadotropins, promoting better follicular development and oocyte maturation. The fertilization rate was also significantly higher in the GH group (71.2% ± 9.3%) compared to the control group (63.8% ± 8.7%, $p < 0.05$). This is consistent with the meta-analysis by Yang et al. (2020), which found that GH supplementation improves fertilization outcomes in poor responders undergoing IVF. The mechanism by which GH improves fertilization rates may involve its role in the insulin-like growth factor (IGF) pathway, which enhances granulosa cell proliferation and oocyte competence[16].

Embryo quality and blastocyst formation were notably improved in the GH group. On Day 3, the percentage of good-quality embryos was significantly higher in the GH group (65.0% ± 10.5%) compared to the control group (53.6% ± 9.8%, $p < 0.05$). By Day 5, the percentage of embryos that reached the blastocyst stage was also higher in the GH group (48.0% ± 8.7%) compared to the control group (37.5% ± 8.4%, $p < 0.05$). These findings align with those of Safdarian et al. (2019), where GH was shown to improve embryo quality and increase the number of transferable embryos[13]. Improved blastocyst formation in the GH group supports the hypothesis that GH enhances oocyte and embryo quality by improving the intra-ovarian environment and promoting better follicular recruitment[17,18].

The implantation rate was higher in the GH group (38.0% ± 7.5%) compared to the control group (29.2% ± 6.8%, $p < 0.05$). However, the clinical pregnancy rate showed only a trend towards improvement in the GH group (30% vs. 20%), with the difference not reaching statistical significance ($p = 0.08$). These results are consistent with those of Norman et al. (2019), who found that while GH may enhance some IVF outcomes, its effect on live birth rates is less clear. Although the clinical pregnancy rate in the GH group was higher, the lack of statistical significance may be due to the small sample size in the present study.

The total gonadotropin dosage required was lower in the GH group (3000 ± 400 IU) compared to the control group (3200 ± 500 IU), although this difference was not statistically significant ($p = 0.09$). This reduction in gonadotropin use is in line with Yang et al. (2020), who reported a decrease in gonadotropin dosage with GH supplementation in their meta-analysis[15]. The ability of GH to lower gonadotropin requirements while maintaining or improving ovarian response suggests a potential cost-saving benefit, despite the additional cost of GH itself. In terms of safety, both groups tolerated the treatments well, with no significant adverse events reported. The absence of ovarian hyperstimulation syndrome (OHSS) in either group aligns with the findings of Norman et al. (2019), where GH use did not increase the risk of adverse events[14].

In summary, the findings of the present study along with previously published studies provide strong evidence that GH supplementation improves ovarian response, fertilization rate, embryo quality, and implantation rate in poor responders. These findings are consistent with previous studies and suggest that GH may be a valuable adjunctive therapy in IVF for this challenging patient population. However, the lack of a statistically significant improvement in clinical pregnancy rates calls for further studies with larger sample sizes to fully assess the potential of GH in improving live birth rates.

Conclusion

This study demonstrates that growth hormone (GH) supplementation significantly improves key IVF outcomes in poor responders, particularly in terms of ovarian response, fertilization rates, embryo quality, and blastocyst formation. The use of GH led to a higher number of mature oocytes retrieved, improved fertilization rates, and better embryo development compared to the control group. Although the clinical pregnancy rate showed a positive trend, it did not reach statistical significance, indicating the need for further research with larger sample sizes to fully assess GH's impact on live birth rates.

Overall, GH supplementation appears to be a promising adjunct therapy for improving reproductive outcomes in poor responders undergoing IVF. It offers the potential to enhance ovarian response and oocyte quality without increasing the risk of adverse events. Future studies should focus on optimizing GH dosing protocols and identifying the specific patient populations that may benefit the most from this intervention.

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