Reproductive Biology and Endocrinology

RESEARCH

Open Access

Exploring the potential benefits of growth hormone co-treatment on embryo quality in IVF: a randomized controlled open-label trial

Yi Tang[1,2†], Xiaofeng Li[2†], Change Hu[2], Ruyi Guan[2], Zhimin Wang[2], Shunji Zhang[2], Guoping Tao[2], Jingfei Qu[2] and Fei Gong[1,2*]

Abstract

Research question While growth hormone (GH) is hypothesized to potentially enhance embryo quality, results of current basic and clinical researches remain inconclusive. This study assesses the effect of GH supplementation on embryo quality and explores the relationship between baseline insulin-like growth factor-1 (IGF-1) levels and the efficacy of GH supplementation among Chinese patients undergoing in vitro fertilization (IVF).

Design A randomized controlled Open-label trial was performed with 128 women experiencing poor embryonic development in IVF. Participants were allocated to the GH group (GH + Gonadotropin-Releasing Hormone [GnRH] antagonist protocol) and the Control group (GnRH antagonist protocol). The primary outcome was the number of high-quality embryos on Day 3.

Results Patients in the GH group required significantly lower total doses of gonadotropin (2213 ± 667 IU vs. 2573 ± 630 IU, $p = 0.0058$) and shorter duration of controlled ovarian stimulation (10.1 ± 1.60 days vs. 10.6 ± 1.30 days, $p = 0.0488$). While there was no statistically significant overall increase in the number of high-quality embryos, subgroup analysis indicated that patients with lower baseline IGF-1 levels, especially those below the lowest quartile, might show a higher rate of high-quality embryos with GH supplementation ($p = 0.0488$). Additionally, the fresh embryo transfer clinical pregnancy rate was numerically higher in the GH supplementation group (46.2%) compared to the control group (38.5%), although not statistically significant.

Conclusions This study suggests that GH co-treatment may enhance ovarian responsiveness in IVF patients with poor embryo quality, thereby reducing the dosage and duration of Gonadotropin (Gn) administration. Among individuals with lower IGF-1 levels, adding GH may improve the rate of high-quality embryos, highlighting the potential benefits of personalized treatment strategies in IVF.

Clinical trial registration ClinicalTrials.gov ID: NCT03966339 (Registration time: 2019-05-24).

[†]Yi Tang and Xiaofeng Li are contributed equally to this work.

*Correspondence:
Fei Gong
lj_0305@126.com

Full list of author information is available at the end of the article

© The Author(s) 2025. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

Keywords Growth hormone, IVF, Embryo quality, IGF-1, Personalized treatment, Ovarian responsiveness

Introduction

The success of in vitro fertilization (IVF) depends on various factors, with the quantity and quality of embryos being key determinants of clinical pregnancy and live birth rates. Several factors influence the quality of embryos, including the patient's age, genetic composition, metabolic status [1, 2], elevated levels of reactive oxygen species (ROS) [3, 4], insufficient adenosine triphosphate (ATP) supply during development [5], low levels of insulin-like growth factor-1 (IGF-1) [6, 7], etc.

The role of growth hormone (GH) in enhancing embryo quality is a research hotspot, with studies indicating that GH can increase the expression of gonadotropin (Gn) receptors on the surface of granulosa cells, thereby enhancing ovarian responsiveness to Gns [8]. Additionally, GH has been shown to reduce oxidative stress levels [9], increase the copy number of mitochondrial DNA in oocytes, and boost energy supply [10], which in turn promotes the expression of genes related to oocyte maturation [11], collectively contributing to improved embryo quality. Clinical studies have demonstrated that adding GH can improve the rate of high-quality embryos and pregnancy outcomes in patients with poor embryonic development [10, 12]. However, the definition of poor embryonic development is not yet established, leading to different criteria across studies. In this study, we aimed to understand the relationship between GH supplementation and embryo quality using our center's specific criteria for defining poor embryonic development.

GH exerts its effects in the body through two pathways: one is by directly binding to its receptors on target organs [13–15], and the other is by stimulating the liver to secrete IGF-1, which then exerts its effects indirectly by acting on target organs [16–18].

The role of IGF-1, a key mediator of GH action, has been extensively studied in folliculogenesis and embryonic development [19, 20]. It could play a crucial role in follicular development by promoting granulosa cell proliferation and differentiation, as well as influencing oocyte maturation and early embryonic growth [21, 22]. Studies have indicated that IGF-1 levels in follicular fluid can be used to assess embryo quality, implantation rates, and their correlation with clinical pregnancy rates [6, 23]. Patients with low IGF-1 levels may have lower IVF success rates [15, 24, 25]. The complex interplay between GH and IGF-1 suggests that their combined action may be essential for optimizing the conditions necessary for high-quality embryo production [21, 26].

While the correlation between IGF-1 levels and IVF outcomes has been explored in previous studies, there is limited data on the Chinese population. Hence, the correlation between the baseline IGF-1 levels of the Chinese IVF population and the outcomes following GH supplementation remains unclear. This study assesses the effect of GH supplementation on embryo quality and preliminarily examines the association of different baseline IGF-1 levels with the potential benefits of GH supplementation among Chinese IVF patients.

Materials and methods

Study design and participants

This randomized open-label controlled trial (RCT) examined the effect of growth hormone (GH) supplementation on embryo quality in women who had experienced poor embryonic development. The study participants were infertile patients planning to undergo IVF or ICSI treatment at the Reproductive and Genetic Hospital of CiticXiangya between December 2019 and June 2023. Eligible participants were women aged 39 years or younger who had undergone at least one IVF/ICSI treatment cycle. The inclusion criteria were women with a history of six or more oocytes retrieved in at least one cycle, achieving a fertilization rate of 50% or higher, and having no embryos of 6-cell grade II or higher on Day 3 or no blastocysts formed after blastocyst culture in their previous cycles. The main exclusion criteria were relevant diseases affecting the outcome of IVF pregnancy, such as untreated hydrosalpinx, uterine fibroids affecting the uterine cavity, adenomyosis, endometrial lesions, and significant uterine malformations; severe acute or chronic liver and kidney diseases, endocrine and metabolic diseases, and adrenal diseases.

Informed consent was obtained from all participants after a thorough explanation of the study protocol, including the potential benefits and risks. The study protocol was approved by the hospital's ethics committee to ensure that all research activities were conducted in accordance with the ethical standards and regulatory requirements (NCT03966339).

Randomization

Eligible and consenting participants were randomly assigned to the GH supplementation group or the control group in a 1:1 ratio. The randomization process was facilitated by a statistician using SAS 9.2 to generate a stratified random sequence based on age groups, ensuring an equal distribution of patients aged 30 years or younger and those aged between 31 and 39 years.

Outcomes assessment

The primary outcome was the number of high-quality embryos on Day 3. The embryos were graded according

to specific criteria, with high-quality embryos classified as either Grade I or II. Secondary outcomes included changes in hormone levels (FSH, LH, P, and E2) on the day of HCG administration and their changes from baseline, endometrial thickness on the day of HCG administration, the total gonadotropin (Gn) dosage and treatment duration, the number of follicles measuring 18 mm or larger on the trigger day, serum IGF-1 levels on the day of oocyte retrieval and their changes from baseline, the count of metaphase II (MII) oocytes, number of 2PN fertilized oocytes, the rate of high-quality embryos on Day 3, implantation rate, clinical pregnancy rate (CPR), and live birth rate of fresh embryo transfer and frozen-thawed embryo transfer.

Controlled ovarian stimulation (COS) protocols

The study utilized a GnRH antagonist protocol for COS, commencing on the second or third day of the menstrual cycle with recombinant follicle-stimulating hormone (rFSH [Gonal - F, Merck Serono, Germany]) at a daily dose of 150–300 IU. Dosages were adjusted according to the ovarian response as monitored by vaginaultrasound folliculometry and serum estrogen (E2) level. The GnRH antagonist (ORGALUTRAN, Organon, America) was introduced when a follicle reached 12 mm or larger. When at least 2–3 follicles reached a diameter of 18 mm or only 1–2 follicles were at least 17 mm, a trigger injection of 250 μg recombinant human chorionic gonadotropin (rhHCG [Ovidrel, Merck Serono, Germany]) plus 200 μg gonadotropin-releasing hormone agonist (GnRHa [Decapeptyl, Ferring Pharmaceuticals, Switzerland]) was administered subcutaneously in the evening. Ovulation was triggered with recombinant hCG and GnRH agonist once the follicles met the criteria, with oocyte retrieval scheduled 35–36 h post-trigger.

Growth hormone (GH) supplementation

Recombinant human GH (rhGH) was administered as an adjunct therapy in the GH group. Participants received rhGH (Jintropin, China, GenSci) treatment during the mid-luteal phase of the two menstrual cycles preceding COS, starting at a daily dose of 2 IU, followed by 4 IU daily from the initiation of ovarian stimulation until hCG day. This supplementation continued for up to 7 weeks. The control group underwent the standard IVF treatment protocol without GH supplementation.

IGF-1 level assessment

IGF-1 levels were measured at key time points throughout the treatment process using an automatic chemiluminescence analyzer (AutoLumo A2000PLUS, Autobio). In the control group, blood samples for IGF-1 measurement were collected on the day of rFSH initiation and repeated on the day of oocyte retrieval. For the GH group, an initial sample was taken before the start of GH supplementation, with subsequent samples aligning with the control group's schedule. These assessments were essential for monitoring the endocrine milieu and evaluating the influence of GH on oocyte development.

Embryo quality assessment

On Day 3 post-retrieval, morphological criteria were used to assess the embryo quality, such as the number of blastomeres, their uniformity, and the proportion of fragmentation [27]. Cleavage-stage embryos were graded as follows: Grade 1 embryos: no fragmentation with equal-sized, homogeneous blastomeres, Grade 2 embryos: less than 20% fragmentation with equal-sized, homogeneous blastomeres, Grade 3 embryos: 20–50% fragmentation with blastomeres of equal or unequal sizes, Grade 4 embryos: greater than 50% fragmentation with blastomeres of equal or unequal sizes. Embryos classified as Grade 2 with six cells or higher were considered high quality. Rate of high-quality embryos (%) = (Number of high-quality embryos / Number of normally fertilized oocytes) × 100%.

Embryo transfer, luteal phase support and pregnancy confirmation

Embryo transfer was carefully scheduled based on the patient's condition. In cases with a risk of ovarian hyperstimulation syndrome (OHSS), elevated progesterone levels, or other conditions deemed unsuitable for fresh embryo transfer by the physician, embryos were cryopreserved for subsequent thaw and transfer in a later cycle. In the absence of such complications, fresh embryo transfer was performed, with a maximum of two embryos transferred per cycle.

Following oocyte retrieval, luteal phase support was commenced through daily injections of 60 mg progesterone (Progesterone injection, XianJu, China) or 90 mg vaginal progesterone gel(Crinone, Merck Serono, Germany) and maintained until pregnancy testing. Luteal phase support of frozen embryo transfer was initiated on the day of progesterone conversion with either 60 mg/day intramuscular progesterone injections or 90 mg/day vaginal progesterone gel. Additionally, we have clarified the criteria for freezing remaining embryos: all embryos not used for fresh transfer were cultured to the blastocyst stage and then cryopreserved. If a pregnancy was confirmed, as indicated by a positive serum β-hCG level 14 days post-transfer, luteal support was continued until at least the 10th week of gestation. In the absence of pregnancy, luteal support was discontinued.

A clinical pregnancy was defined as an ultrasound observation of one or more gestational sacs, which was conducted to confirm the pregnancy and assess fetal development.

Statistical analysis

Sample size was calculated based on preliminary data from a self-controlled study design, comparing the number of high-quality embryos produced in cycles with and without GH supplementation. Prior to GH use, the average number of high-quality embryos was 0.4 per cycle, which increased to an average of 1.2 embryos per cycle with GH supplementation. Assuming a significance level of 0.05 and a power of 90% to detect a difference, the estimated minimum sample size required per group was 55 participants.

The recruitment target was set at 64 participants per group to account for an expected dropout rate of 15%. This sample size estimation ensures that the study is adequately powered to detect a significant improvement in the primary outcome measure, which is the rate and number of high-quality embryos on Day 3 post-retrieval.

Data was analyzed using appropriate statistical tests, including chi-square test or Fisher's exact test for categorical variables and t-test or non-parametric test for continuous variables, based on the nature of the data and distribution. All statistical analyses were conducted using SPSS 25.0 software, with a p-value < 0.05 considered as statistically significant.

Results

Patient characteristics and baseline data

A total of 128 patients were enrolled and randomized to the GH group ($n = 64$), which received GH supplementation, and the control group ($n = 64$). Ultimately, 104 patients completed the trial, with 51 in the GH group and 53 in the control group. (Fig. 1)

The study's stringent enrollment process ensured that key baseline characteristics, including age, body mass index (BMI), anti-Müllerian hormone (AMH), FSH, LH, and insulin-like growth factor-1 (IGF-1) levels, Infertility Cause, Infertility duration were well-matched between the two groups. Specifically, the mean baseline levels of FSH were 6.341 mIU/ml for the GH group and 6.314 mIU/ml for the control group ($P = 0.9377$), while LH levels were 4.019 mIU/ml and 3.576 mIU/ml, respectively ($P = 0.9120$). IGF-1 levels at baseline were also comparable, with means of 199.603 ng/ml in the GH group and 200.962 ng/ml in the control group ($P = 0.9323$). (Table 1)

GH supplementation, gonadotropin dosage and the change in hormone levels

Significant hormonal changes were observed with GH supplementation alongside Gn dosage in IVF treatments. The GH group received a total mean rhGH dose of 120.7 IU, and the median duration was 52.4 days. This reduction in FSH on the day of Gn initiation suggests that GH supplementation may enhance ovarian response, thereby requiring less exogenous FSH. The change in FSH levels from the baseline to the initiation day of Gn showed a decrease in the GH group but an increase in the control group (-0.306 vs. 0.324 mIU/ml, $p = 0.0458$). (Table 2) The mean total Gn dosage in the GH group was

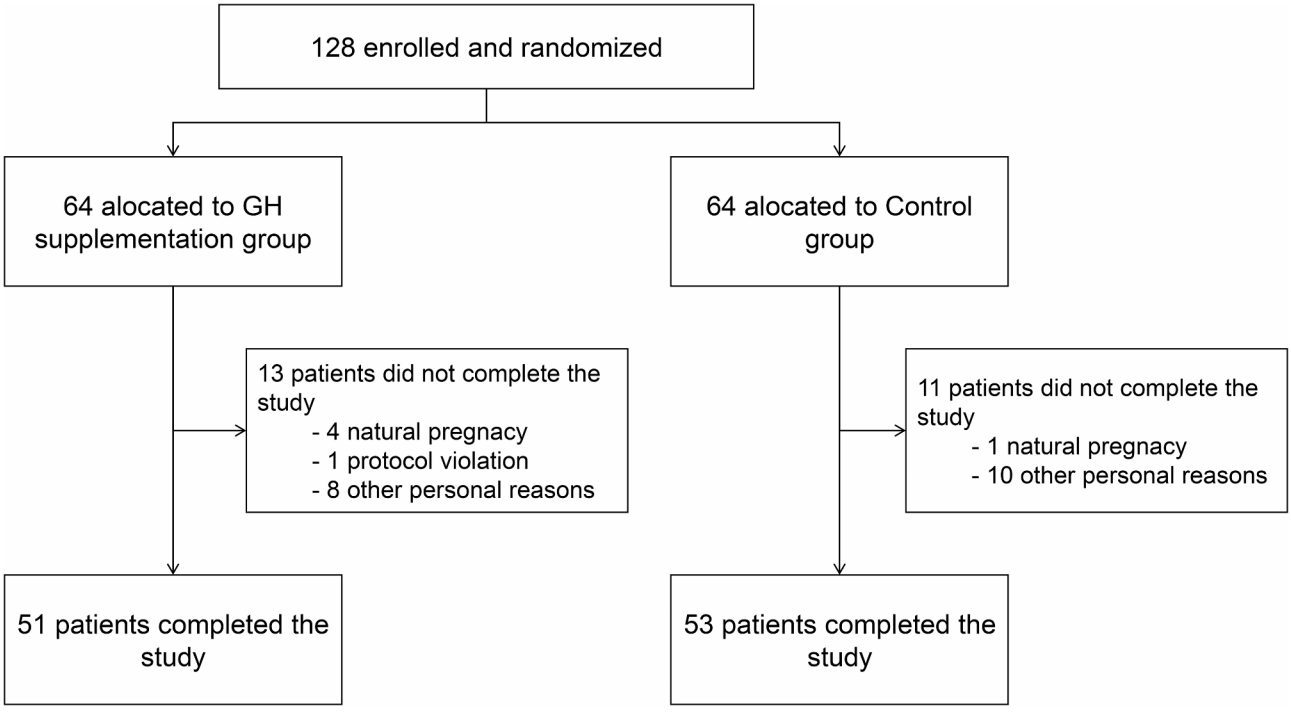

Fig. 1 Flow Diagram of Patient Inclusion Process

Table 1 Patient characteristics and baseline data

Characteristic	GH group (*n* = 51)	Control group (*n* = 53)	*P* value
Age (years)	31.1 ± 3.49	31.7 ± 3.30	0.2188
Infertility duration (years)	3.3 ± 2.12	3.8 ± 2.55	0.2798
Infertility Cause, n(%)			
Tubal factor	42 (82.4)	48 (90.6)	0.2199
Ovulatory disorders	4 (7.8)	2 (3.8)	0.4324
Endometriosis	4 (7.8)	7 (13.2)	0.3739
Male factor	23 (45.1)	28 (52.8)	0.4304
BMI (kg/m2)	21.918 ± 2.6867	21.376 ± 2.5597	0.2944
AMH	3.9504 ± 2.6211	3.8823 ± 3.1059	0.6536
AFC	11.0 ± 5.04	9.9 ± 3.47	0.1798
Basal FSH (mIU/ml)	6.341 ± 1.6645	6.314 ± 1.7719	0.9377
Basal LH (mIU/ml)	4.019 ± 3.4409	3.576 ± 1.3065	0.912
Basal E2 (pg/ml)	31.712 ± 14.1619	35.075 ± 11.8323	0.1911
Basal Progesterone (pg/ml)	0.3791 ± 0.5887	0.3308 ± 0.2860	0.718
Basal IGF-1 (ng/ml)	199.603 ± 74.1931	200.962 ± 54.8212	0.9323

BMI body mass index, AMH anti-Müllerian hormone, AFC antral follicle count, FSH follicle stimulating hormone, E2 estradiol, LH luteinizing hormone

2213.24 ± 667.015 IU, which was significantly lower than 2573.32 ± 630.009 IU in the control group ($p = 0.0058$). The GH supplementation group had a mean COS duration of 10.1 ± 1.60 days, which was significantly shorter than 10.6 ± 1.30 days in the control group ($p = 0.0488$). This suggested that GH supplementation might enhance ovarian response to Gn, thereby reducing the total number of days required for effective ovarian stimulation.

Similarly, LH levels also differed between the groups on the day of Gn initiation, with the GH group demonstrating a lower mean LH level compared to the control group (3.926 vs. 4.704 mIU/ml, $p = 0.0017$). As compared to the baseline levels, LH levels decreased in the GH group but increased in the control group (-0.094 vs. 1.127 mIU/ml, $p = 0.0134$).

Progesterone levels on the day of hCG injection were significantly higher in the control group compared to the GH group ($p = 0.0098$). IGF-1 levels were assessed at critical time points during the treatment process. The GH group showed a higher mean IGF-1 level on the day of oocyte retrieval compared to the control group (208.998 vs. 185.958 ng/ml, $p = 0.027$). Additionally, the change in IGF-1 levels from baseline to the day of oocyte retrieval was significantly greater in the GH group ($p = 0.0006$). (Table 2)

Embryo quality and pregnancy outcomes

In the GH supplementation group, the mean number of high-quality embryos on Day 3 post-retrieval was 3.5, which was slightly higher than the 3.4 embryos in the control group. Although not statistically significant, there was an increasing trend in the rate of high-quality embryos in the GH group compared to the control group, with rates of 52.0% and 46.6%, respectively ($p = 0.622$). (Table 3)

For fresh embryo transfers, the clinical pregnancy rate (CPR) was numerically higher in the GH group (46.2%) compared to the control group (38.5%), although without statistical significance ($p = 1$). (Table 3)

Table 2 GH supplementation, gonadotropin dosage and the change in hormone levels

Characteristic	GH group (*n* = 51)	Control group (*n* = 53)	*P* value
Total dose of rhGH (IU)	120.7 ± 28.90		
Median duration of GH supplementation (Day)	52.4 ± 19.04		
FSH (mIU/ml)			
on the initiation day of Gn	6.035 ± 1.5517	6.638 ± 1.7685	0.053
the change from baseline	-0.306 ± 1.5138	0.324 ± 1.6585	0.0458
LH (mIU/ml)			
on the initiation day of Gn	3.926 ± 1.7738	4.704 ± 1.5462	0.0017
the change from baseline	-0.094 ± 3.4831	1.127 ± 1.5142	0.0134
E2 (pg/ml)			
on HCG day	2844.112 ± 1244.9055	2735.585 ± 1071.3677	0.6773
the change from baseline	2812.400 ± 1245.3048	2700.510 ± 1071.4906	0.6631
Progesterone (pg/ml)			
on HCG day	0.9386 ± 0.5157	1.2362 ± 0.6094	0.0098
the change from baseline	0.5595 ± 0.8020	0.9054 ± 0.6505	0.0219
IGF-1 (ng/ml)			
on the day of oocyte retrieval	208.998 ± 60.7129	185.958 ± 73.7515	0.027
the change from baseline	19.895 ± 54.3752	-16.033 ± 68.0917	0.0006
Total Gn dosage (IU)	2213.24 ± 667.015	2573.32 ± 630.009	0.0058
Duration of Gn (Day)	10.1 ± 1.60	10.6 ± 1.30	0.0488

rhGH recombinant human GH, Gn gonadotropin, FSH follicle stimulating hormone, E2 estradiol, LH luteinizing hormone, IGF-1 insulin-like growth factor-1, COS Controlled Ovarian Stimulation

Table 3 Clinical outcomes between the GH group and the control group

Characteristic	GH group ($n=51$)	Control group ($n=53$)	*P* value
Number of oocytes retrieved	12.6 ± 6.25	11.5 ± 5.58	0.2855
Number of MII oocytes	9.8 ± 4.97	9.8 ± 4.77	0.9584
Number of 2PN fertilized oocytes	6.6 ± 3.75	7.0 ± 3.88	0.5696
Endometrial thickness on the day of HCG administration	12.33 ± 2.180	12.22 ± 1.854	0.4162
Number of high-quality embryos*	3.5 ± 3.27	3.4 ± 2.92	0.911
Rate of high-quality embryos, %	52.0	46.6	0.622
CPR of fresh embryo transfer	6/13 (46.2)	5/13 (38.5)	1
CPR of frozen embryo transfer	26/41 (63.4)	25/40 (62.5)	0.9321
Live birth rate of fresh embryo transfer	6/13 (46.2)	5/13 (38.5)	1
Live birth rate of frozen embryo transfer	21/41 (51.2)	20/40 (50.0)	0.9126

CPR, clinical pregnancy rate. * Embryos classified as Grade 2 with six cells or higher were considered high quality. Clinical pregnancy rate of fresh transfer cycles = (Number of fresh transfer cycles with clinical pregnancy / Number of fresh transfer cycles) × 100%. Clinical pregnancy rate of frozen transfer cycles = (Number of frozen transfer cycles with clinical pregnancy / Number of frozen transfer cycles) × 100%. Live birth rate of fresh transfer cycles = (Number of fresh transfer cycles with live birth / Number of fresh transfer cycles) × 100%. Live birth rate of frozen transfer cycles = (Number of frozen transfer cycles with live birth / Total number of frozen transfer cycles) × 100%. Rate of high-quality embryos = (Number of high-quality embryos / Number of normally fertilized oocytes) × 100%

Table 4 Subgroup analysis of different baseline IGF-1 levels

Characteristic	GH group ($n=49$)*	Control group ($n=51$)*	*P* value
IGF-1 levels below Q1 (158.220 ng/ml)			
Patient number	12	13	
Number of high-quality embryos	4.4 ± 3.32	1.3 ± 2.21	0.0318
Rate of high-quality embryos, %	64.0	25.5	0.0488
IGF-1 levels between Q1 (158.220 ng/ml) and the median (205.980 ng/ml)			
Patient number	11	14	
Number of high-quality embryos	3.4 ± 3.23	3.7 ± 3.52	0.8406
Rate of high-quality embryos, %	56.7	50.6	0.7209
IGF-1 levels between the median (205.980 ng/ml) and Q3 (243.070 ng/ml)			
Patient number	15	10	
Number of high-quality embryos	3.9 ± 4.03	3.6 ± 2.66	0.8376
Rate of high-quality embryos, %	45.8	49.3	0.8125
IGF-1 levels above Q3 (243.070 ng/ml)			
Patient number	11	14	
Number of high-quality embryos	2.0 ± 2.09	4.7 ± 2.27	0.0057
Rate of high-quality embryos, %	43.2	57.4	0.3259

* In the GH group and the control group, 2 participants each were missing baseline IGF-1 data

Subgroup analysis of different baseline IGF-1 levels

A detailed subgroup analysis was conducted based on quartile ranges of baseline IGF-1 levels to assess the impact of GH supplementation on the number and rate of high-quality embryos. The most pronounced effects were observed in the subgroup with IGF-1 levels below the lowest quartile (Q1), where the GH group had a higher mean number of high-quality embryos compared to the control group (4.4 vs. 1.3, $p = 0.0318$). Correspondingly, the rate of high-quality embryos of 64.0% in the GH group surpassed the rate of 25.5% in the control group ($p = 0.0488$). In the subgroup with IGF-1 levels between Q1 and the median, the GH group showed an insignificant increase in the number of high-quality embryos (3.4 vs. 3.7) and their rate (56.7% vs. 50.6%) compared to the control group, with *P* values of 0.8406 and 0.7209, respectively. These results underscore the potential importance of baseline IGF-1 levels in determining the efficacy of GH supplementation in IVF treatments, especially for patients with lower IGF-1 levels, who may experience enhanced embryo development and quality. In contrast, in the subgroups with IGF-1 levels above the median or at the third quartile (Q3), no significant differences in the mean number or rate of high-quality embryos were observed between the GH supplementation and control groups. (Table 4)

Discussion

The key finding of this study is that GH supplementation may improve embryo quality in specific patient populations, particularly those with relatively lower baseline IGF-1 levels.

GH supplementation can improve embryo quality and IVF outcomes, especially among patients with poor embryo quality [24, 28]. The enhancement in embryo quality is likely due to GH's role in fostering follicle development and oocyte quality, which in turn boosts embryo quality. By increasing the expression of FSH/LH receptors on granulosa cells, GH supplementation may amplify the sensitivity of ovaries to gonadotropins [15, 24]. Consistent with prior research [29, 30], our findings suggest that GH, when co-administered with gonadotropins, can reduce the required dosage for ovulation induction, similar to the effect of gonadotropins themselves. Although the increase in high-quality embryos on Day 3 with GH supplementation did not achieve statistical significance in this study, there was a notable trend. Additionally, a reduction in FSH levels was observed at the initiation of gonadotropin treatment and a significant decrease in both the total dosage and duration of gonadotropin use in

the GH group, signifying an improved ovarian response with GH supplementation.

In previous studies on the use of GH for poor embryonic development in IVF, poor embryo quality was often diagnosed by the absence of high-quality embryos in previous cycles [31, 32]. However, our criteria for defining poor embryonic development are more specific. We require that patients have retrieved more than six oocytes with a fertilization rate greater than 50% in their previous cycles, yet still fail to produce embryos of grade II or higher with at least six cells, or fail to form blastocysts after extended culture. We believe it is essential to ensure a sufficient number of retrieved oocytes, as it is difficult to determine whether a patient truly has poor embryo quality if they only retrieve 1–2 oocytes and subsequently fail to form high-quality embryos. This approach provides a more accurate assessment of poor embryonic development and ensures that our study population is well-defined.

In this study, despite no difference in the number of oocytes retrieved between groups, the GH supplementation group showed lower progesterone levels on the hCG day compared to the control group. The increase in progesterone levels may be related to the duration of Gn administration, as the control group had a longer duration of Gn treatment compared to the GH group, which could lead to higher progesterone levels. In our center, the criterion for canceling fresh embryo transfer due to elevated progesterone is when progesterone levels exceed 1.5 ng/ml on the day of HCG administration. Some patients, although having higher progesterone levels compared to the GH group, did not meet this threshold for canceling the transfer. Overall, the control group had higher progesterone levels on the day of HCG compared to the GH group, and elevated progesterone on the day of HCG may be associated with endometrial receptivity. Increased progesterone levels at this stage are suggested to prematurely activate progesterone receptor expression, leading to earlier endometrial transformation and potentially closing the implantation window [33]. Additionally, higher pre-retrieval progesterone levels have been linked to increased stromal expression of vascular endothelial growth factor A (VEGF-A) and placental growth factor (PlGF), which can alter angiogenic factors and decrease endometrial receptivity, affecting implantation rates [34]. The lower progesterone levels observed in the GH group might have contributed to the improved embryo quality and the insignificant trend toward higher clinical pregnancy rates after fresh embryo transfer, indicating that GH supplementation could influence endometrial receptivity and IVF outcomes. Further investigation is required to understand how GH affects progesterone levels and endometrial receptivity, as well as its impact on IVF success.

The subgroup analysis in this study revealed that GH supplementation may have a more pronounced effect on improving embryo quality in patients with lower IGF-1 levels, particularly those below the first quartile. This finding is supported by previous research suggesting that low IGF-1 levels may be associated with poor embryonic development [23] and reduced IVF success rates [25]. Different studies have shown variable impact of IGF-1 levels on pregnancy outcomes, with a range of cut-off values reported to influence outcomes. This discrepancy underscores the necessity for a standardized approach to evaluate IGF-1 levels in IVF treatments. Prior research has demonstrated that IGF-1 might influence both embryo quality and pregnancy outcomes, yet no consensus exists on the exact level at which IGF-1 becomes detrimental to these outcomes. One study included 48 women undergoing controlled ovarian stimulation for assisted conception and found that the group with poor ovarian response had significantly lower levels of IGF-1 in follicular fluid compared to the normal ovarian response group [35]. There was a positive correlation between the levels of IGF-1 in follicular fluid and the number of oocytes retrieved. Another study included 146 women with normal ovulation and divided them into high and low IGF-1 groups based on their levels of IGF-1 in follicular fluid. The results showed that the high IGF-1 group had significantly higher rates of fertilization, blastocyst formation, high-quality embryo rate, clinical pregnancy rate, and implantation rate compared to the low IGF-1 group [23]. Notably, our study assessed the baseline IGF-1 levels and examined the relationship between these levels and the outcomes of IVF with GH supplementation.

Professor Yovich conducted extensive research on GH and proposed that GH supplementation may improve the IVF outcomes for patients with poor prognosis who may be in a state of "subclinical degree of adult growth hormone deficiency (AGHD)" [15, 25]. Our findings align with this hypothesis, suggesting that patients with IGF-1 levels below the lowest quartile, potentially representing this subclinical deficiency, might benefit from GH supplementation, as evidenced by improved embryo quality and a trend towards higher clinical pregnancy rates. The patients with lower IGF-1 levels in our study may correspond to the group described by Professor Yovich, where IGF-1 levels are below the norm but do not meet the diagnostic criteria for AGHD. In these patients, GH supplementation appears to enhance both embryo quality and pregnancy outcomes. This observation underscores the importance of considering individual IGF-1 levels for deciding GH supplementation, offering valuable insights into the development of tailored treatment plans for personalized IVF care. In the context of the Chinese IVF population, where IGF-1 levels can be significantly affected by age, BMI, and geographical region [36], it is

becoming increasingly important to assess IGF-1 levels before initiating IVF. This assessment could guide the decision to supplement GH in patients with lower levels, potentially improving the production of high-quality embryos and CPR. Future research should continue to investigate the relationship between IGF-1 levels and the efficacy of GH supplementation in IVF to further refine patient selection and treatment strategies.

This study has some limitations. A key constraint is the relatively small sample size, which may have reduced the statistical power to detect significant differences in clinical outcomes such as CPR and live birth rates. The benefits observed in patients with low IGF-1 levels from GH supplementation, as identified in this study, need to be confirmed with a larger sample size. Future studies with larger cohorts will be necessary to establish these cut-off values and confirm the potential benefits of GH supplementation in IVF for patients with specific IGF-1 levels.

In summary, this study suggests that GH supplementation may improve the quality of embryos and potentially enhance IVF outcomes, particularly in patients with lower baseline IGF-1 levels. The observed decrease in gonadotropin requirements and the trend towards improved embryo quality and clinical pregnancy rates warrant further investigation. Continuing to explore the complex interactions between GH supplementation, IGF-1 levels, and IVF outcomes can facilitate personalized and effective treatment strategies for patients undergoing IVF.

Acknowledgements
The authors thank all the participants who contributed to the success of this study. We also acknowledge the support of the nursing and technical staff at the Reproductive and Genetic Hospital of Citic-Xiangya, whose expertise and dedication were instrumental in the collection and analysis of data. Special thanks go to the biostatistician who assisted with the randomization process and statistical analysis.

Author contributions
Fei Gong, Yi Tang and Xiaofeng Li conceived and coordinated the study, designed, performed and analyzed the experiments, and wrote the paper. Change Hu, Ruyi Guan, Zhimin Wang, Shunji Zhang, Guoping Tao and Jingfei Qu conducted the data collection, data analysis, and revised the paper. All authors reviewed the results and approved the final version of the manuscript.

Funding
This work was supported by the Natural Science Foundation of Hunan Province of China, 2024JJ9091.

Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Reproductive and Genetic Hospital of CITIC-XIANGYA's ethics committee to ensure that all research activities were conducted in accordance with the ethical standards and regulatory requirements (NCT03966339). Informed consent to participate was obtained from all participants after a thorough explanation of the study protocol, including the potential benefits and risks.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]NHC Key Laboratory of Human Stem Cell and Reproductive Engineering, School of Basic Medical Sciences, Central South University, Changsha, Hunan, China
[2]Clinical Research Center for Reproduction and Genetics in Hunan Province, Reproductive and Genetic Hospital of CITIC-XIANGYA, Changsha, Hunan, China

Received: 30 December 2024 / Accepted: 26 February 2025
Published online: 15 March 2025

References

1. McDonald SD, Han Z, Mulla S, Murphy KE, Beyene J, Ohlsson A. Preterm birth and low birth weight among in vitro fertilization singletons: a systematic review and meta-analyses. Eur J Obstet Gynecol Reprod Biol. 2009;146(2):138–48.
2. Wang YA, Sullivan EA, Black D, Dean J, Bryant J, Chapman M. Preterm birth and low birth weight after assisted reproductive technology-related pregnancy in Australia between 1996 and 2000. Fertil Steril. 2005;83(6):1650–8.
3. Askoxylaki M, Siristatidis C, Chrelias C, Vogiatzi P, Creatsa M, Salamalekis G, et al. Reactive oxygen species in the follicular fluid of subfertile women undergoing in vitro fertilization: a short narrative review. J Endocrinol Invest. 2013;36(11):1117–20.
4. Liu J, Zhu K, Xu S, Tu W, Lin X, Su Y, et al. Double-edged sword: effects of human sperm reactive oxygen species on embryo development in IVF cycles. Reprod Biol Endocrinol. 2023;21(1):1.
5. Wang LY, Wang DH, Zou XY, Xu CM. Mitochondrial functions on oocytes and preimplantation embryos. J Zhejiang Univ Sci B. 2009;10(7):483–92.
6. Gleicher N, Darmon SK, Molinari E, Patrizio P, Barad DH. Importance of IGF-I levels in IVF: potential relevance for growth hormone (GH) supplementation. J Assist Reprod Genet. 2022;39(2):409–16.
7. Yu Y, Yan J, Li M, Yan L, Zhao Y, Lian Y, et al. Effects of combined epidermal growth factor, brain-derived neurotrophic factor and insulin-like growth factor-1 on human oocyte maturation and early fertilized and cloned embryo development. Hum Reprod. 2012;27(7):2146–59.
8. Regan SLP, Knight PG, Yovich JL, Arfuso F, Dharmarajan A. Growth hormone during in vitro fertilization in older women modulates the density of receptors in granulosa cells, with improved pregnancy outcomes. Fertil Steril. 2018;110(7):1298–310.
9. Gong Y, Luo S, Fan P, Jin S, Zhu H, Deng T, et al. Growth hormone alleviates oxidative stress and improves oocyte quality in Chinese women with polycystic ovary syndrome: a randomized controlled trial. Sci Rep. 2020;10(1):18769.
10. Li J, Chen Q, Wang J, Huang G, Ye H. Does growth hormone supplementation improve oocyte competence and IVF outcomes in patients with poor embryonic development? A randomized controlled trial. BMC Pregnancy Childbirth. 2020;20(1):310.
11. Li Y, Liu H, Yu Q, Liu H, Huang T, Zhao S, et al. Growth hormone promotes in vitro maturation of human oocytes. Front Endocrinol (Lausanne). 2019;10:485.
12. Liu X, Bai H, Xie J, Shi J. Growth hormone co-treatment on controlled ovarian stimulation in normal ovarian response women can improve embryo quality. Gynecol Endocrinol. 2019;35(9):787–91.
13. Liu C, Li S, Li Y, Tian J, Sun X, Song T, et al. Growth hormone ameliorates the age-associated depletion of ovarian reserve and decline of oocyte quality via inhibiting the activation of Fos and Jun signaling. Aging. 2021;13(5):6765–81.
14. Pan P, Huang X. The clinical application of growth hormone and its biological and molecular mechanisms in assisted reproduction. Int J Mol Sci. 2022;23(18):10768

15. Yovich JL, Regan SLP, Zaidi S, Keane KN. The concept of growth hormone deficiency affecting clinical prognosis in IVF. Front Endocrinol (Lausanne). 2019;10:650.
16. Pandey V, Perry JK, Mohankumar KM, Kong XJ, Liu SM, Wu ZS, et al. Autocrine human growth hormone stimulates oncogenicity of endometrial carcinoma cells. Endocrinology. 2008;149(8):3909–19.
17. Sbracia M, Scarpellini F, Poverini R, Alò PL, Rossi G, Di Tondo U. Immunohistochemical localization of the growth hormone in human endometrium and decidua. Am J Reprod Immunol. 2004;51(2):112–6.
18. Strowitzki T, Wiedemann R, Hepp H. Influence of growth factors EGF, IGF-1, and human growth hormone on human endometrial stromal cells in vitro. Ann N Y Acad Sci. 1991;626:308–11.
19. Homburg R, Eshel A, Abdalla HI, Jacobs HS. Growth hormone facilitates ovulation induction by gonadotrophins. Clin Endocrinol (Oxf). 1988;29(1):113–7.
20. Adashi E, Thorner MO, editors. Is the intraovarian IGF system a mediator of growth hormone action? The somatotrophic Axis and the reproductive process in health and disease Serono Symposia. USA Baltimore, MD: Springer- 1995;202–11.
21. Chang CW, Sung YW, Hsueh YW, Chen YY, Ho M, Hsu HC, et al. Growth hormone in fertility and infertility: mechanisms of action and clinical applications. Front Endocrinol (Lausanne). 2022;13:1040503.
22. Scheffler F, Vandecandelaere A, Soyez M, Bosquet D, Lefranc E, Copin H, et al. Follicular GH and IGF1 levels are associated with oocyte cohort quality: A pilot study. Front Endocrinol (Lausanne). 2021;12:793621.
23. Mehta BN, Chimote NM, Chimote MN, Chimote NN, Nath NM. Follicular fluid insulin like growth factor-1 (FF IGF-1) is a biochemical marker of embryo quality and implantation rates in in vitro fertilization cycles. J Hum Reprod Sci. 2013;6(2):140–6.
24. Yovich JL, Stanger JD. Growth hormone supplementation improves implantation and pregnancy productivity rates for poor-prognosis patients undertaking IVF. Reprod Biomed Online. 2010;21(1):37–49.
25. Yovich JL, Zaidi S, Nguyen MDK, Hinchliffe PM. Measuring IGF-1 and IGFBP-3 profiles in women seeking assisted reproduction; relationship to clinical parameters (Study 1). J Pers Med. 2020;10(3):122
26. Man L, Chen Y, Li N, L uo Y, Pan X, Zhou S. Level of IGF1 in follicular fluid associated with IVF pregnancy outcome in the application of growth hormone. Ginekol Pol. 2024;95(12):928-34.
27. Balaban B, Urman B, Isiklar A, Alatas C, Aksoy S, Mercan R, et al. The effect of pronuclear morphology on embryo quality parameters and blastocyst transfer outcome. Hum Reprod. 2001;16(11):2357–61.
28. Tesarik J, Hazout A, Mendoza C. Improvement of delivery and live birth rates after ICSI in women aged > 40 years by ovarian co-stimulation with growth hormone. Hum Reprod. 2005;20(9):2536–41.
29. Liu FT, Hu KL, Li R. Effects of growth hormone supplementation on poor ovarian responders in assisted reproductive technology: a systematic review and Meta-analysis. Reprod Sci. 2021;28(4):936–48.
30. Yang P, Wu R, Zhang H. The effect of growth hormone supplementation in poor ovarian responders undergoing IVF or ICSI: a meta-analysis of randomized controlled trials. Reprod Biol Endocrinol. 2020;18(1):76.
31. Liu X, Li N, Wang D, Wen W, Tian L, Zhou H, et al. Does growth hormone supplementation of in vitro fertilization/intracytoplasmic sperm injection improve cumulative live birth rates in women with poor embryonic development in the previous cycle? Reprod Biol Endocrinol. 2024;22(1):53.
32. Chen QL, Shuai J, Chen WH, Zhang XD, Pei L, Huang GN, et al. Impact of growth hormone supplementation on improving oocyte competence in unexplained poor embryonic development patients of various ages. Gynecol Endocrinol. 2022;38(3):231–7.
33. Bourgain C, Devroey P. The endometrium in stimulated cycles for IVF. Hum Reprod Update. 2003;9(6):515–22.
34. Chen X, Jin X, Liu L, Man CW, Huang J, Wang CC, et al. Differential expression of vascular endothelial growth factor angiogenic factors in different endometrial compartments in women who have an elevated progesterone level before oocyte retrieval, during in vitro fertilization-embryo transfer treatment. Fertil Steril. 2015;104(4):1030–6.
35. Bahceci M, Ulug U, Turan E, Akman MA. Comparisons of follicular levels of sex steroids, gonadotropins and insulin like growth factor-1 (IGF-1) and epidermal growth factor (EGF) in poor responder and normoresponder patients undergoing ovarian stimulation with GnRH antagonist. Eur J Obstet Gynecol Reprod Biol. 2007;130(1):93–8.
36. Zhu H, Xu Y, Gong F, Shan G, Yang H, Xu K, et al. Reference ranges for serum insulin-like growth factor I (IGF-I) in healthy Chinese adults. PLoS ONE. 2017;12(10):e0185561.

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.