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ARTICLE

Growth Hormone's Impact on Oxidative Stress, Ovarian Response, and *In Vitro* Fertilization in Polycystic Ovary Syndrome Across Different Ages

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Abstract

Aims/Background Growth hormone (GH) supplementation contributes to improved reproductive and pregnancy outcomes in *in vitro* fertilization (IVF)–embryo transfer (ET) in polycystic ovary syndrome (PCOS) women. This study aimed to explore the effects of GH on the oxidative stress, ovarian reactivity, and pregnancy outcomes of IVF-ET in PCOS patients of different ages.

Methods The clinical data of 342 women with PCOS undergoing *in vitro* fertilization/intracytoplasmic sperm injection–embryo transfer (IVF/ICSI-ET) were collected for retrospective analysis. Based on age, patients were divided into three groups: <35 years (n = 118), 35–40 years (n = 120), and >40 years (n = 104). Each age group was further subdivided into a GH subgroup and a control subgroup, according to whether GH was supplemented during ovarian stimulation. Ovarian stimulation parameters and IVF/ICSI-ET outcomes were recorded. Levels of malondialdehyde (MDA) and superoxide dismutase (SOD) in both follicular fluid and serum were measured using commercial assay kits.

Results In the 35–40 years group, the total number of oocytes retrieved, metaphase II (MII) oocytes, and ovarian sensitivity index (OSI) were significantly higher in the GH group compared to the control group (p = 0.012, 0.049, 0.006, respectively). In the >40 years group, the total number of oocytes retrieved and OSI were also significantly increased in the GH group compared to the control group (p = 0.001, 0.002, respectively). In the <35, 35–40, and >40 years groups, the serum SOD level on the trigger day was significantly higher in the GH groups than in the control groups (p = 0.004, 0.001, 0.012, respectively), while the serum MDA level was significantly lower (p = 0.032, 0.015, 0.004, respectively). In the 35–40 and >40 years groups, the fertilization rate was significantly higher in the GH subgroups compared to the control subgroups (p = 0.040, 0.001, respectively). A total of 43 ET cycles were cancelled, and 299 ET cycles were analyzed. In the 35–40 years group, the GH subgroup showed a significantly higher pregnancy rate compared to the control subgroup (p = 0.043); although the live birth rate was slightly higher, the difference was not statistically significant (p = 0.064). In the <35 years and >40 years groups, no significant differences were observed in pregnancy rate, miscarriage rate, or live birth rate between the GH and control subgroups ($p > 0.05$).

Conclusion GH improves serum oxidative stress and ovarian reactivity in women with PCOS, and increases both the number of oocytes retrieved and the fertilization rate in those aged ≥35 years. Additionally, GH increases the pregnancy rate in PCOS patients aged 35–40 years, although it does not show a significant benefit in live birth rate.

Key words: polycystic ovary syndrome; growth hormone; age; oxidative stress; *in vitro* fertilization; ovarian hyperstimulation syndrome

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Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder that affects approximately 8–13% of reproductive-aged women (Tay et al, 2023). It is associated with metabolic disturbances, ovarian dysfunction, hyperandrogenism, obesity, insulin resistance, and infertility (Tay et al, 2023; Di Lorenzo et al, 2023). PCOS is a highly heterogeneous condition and is classified into four phenotypes based on the Rotterdam diagnostic criteria (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). Each phenotype exhibits distinct clinical manifestations, metabolic characteristics, and treatment responses (Elsayed et al, 2023). Assisted reproductive technology is an effective treatment for infertility in patients with PCOS. For those who fail to conceive following ovulation induction therapy, *in vitro* fertilization–embryo transfer (IVF-ET) can improve fertilization rates and help them achieve their reproductive goals (Li et al, 2024). However, due to the endocrine and metabolic abnormalities in PCOS, these patients are more susceptible to ovarian hyperstimulation syndrome (OHSS) and poor oocyte quality during controlled ovarian hyperstimulation (COH) (Yin et al, 2025).

Growth hormone (GH) is a peptide hormone secreted by the anterior pituitary gland. It promotes protein synthesis and lipolysis, and regulates ovarian function via the hypothalamic–pituitary–ovarian axis (HPOA) (Zhou et al, 2023). GH secretion is reduced in women with PCOS (Zhou et al, 2023; Yang and Chen, 2024), and supplementation may offer benefits during IVF-ET. Gong et al (2020a) reported that GH reduced oxidative stress in the follicular fluid of Chinese women with PCOS and increased the number of fertilized oocytes and cleavage-stage embryos during IVF-ET. GH has also been shown to inhibit apoptosis and reactive oxygen species (ROS) accumulation in granulosa cells of PCOS patients by activating the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway (Gong et al, 2020b). However, other studies have reported conflicting results. For example, Dunne et al (2015) found that GH did not improve the number of oocytes retrieved or the pregnancy rate in IVF-ET. These inconsistent findings limit the clinical application of GH in IVF-ET. Therefore, further investigation is needed to clarify the effects of GH on reproductive outcomes in PCOS patients undergoing IVF-ET.

Age can influence the clinical and biochemical characteristics of PCOS. A longitudinal cohort study found that, as age increases, both metabolic and reproductive parameters change in women with PCOS, and these changes appear to impact female fertility (Jacewicz-Święcka et al, 2021). Baseline luteinizing hormone (LH)/follicle-stimulating hormone (FSH) ratios and androgen levels were significantly higher in PCOS women aged 18–29 years compared to those aged 30–40 years, and these differences were associated with distinct clinical features of PCOS (Guo et al, 2023). Moreover, female age is closely related to IVF-ET outcomes. In Nigeria, the success rate of IVF-ET was significantly lower in women over 34 years of age (Adebayo et al, 2023). In women of advanced maternal age (>35 years), IVF-ET has been associated with increased risks of abnormal placentation, gestational diabetes mellitus, and preterm birth (Li et al, 2025). These findings suggest that age is an important factor affecting IVF-ET outcomes in women with PCOS. On the other hand, the effects of GH treatment may also vary with age.

Chen et al (2025) compared the effects of GH on pregnancy outcomes in women with decreased ovarian reserve across different age groups. GH was shown to improve embryo quality and live birth rate in women aged 35–40 years, but not in those under 35 or over 40 years (Chen et al, 2025). However, it remains unclear whether the effect of GH on pregnancy outcomes in PCOS patients is influenced by age. Therefore, this study aimed to explore the effects of GH on oxidative stress, ovarian reactivity, and pregnancy outcomes in PCOS patients undergoing IVF-ET across different age groups.

Methods

Patients

This retrospective study collected clinical data from female patients with PCOS (n = 342) who underwent *in vitro* fertilization/intracytoplasmic sperm injection–embryo transfer (IVF/ICSI-ET) at the General Hospital of Northern Theater Command. The study was approved by the Ethics Committee of the General Hospital of Northern Theater Command (Approval No. Y(2024)021). All procedures were conducted in accordance with the Declaration of Helsinki, and all participants provided written informed consent.

The inclusion criteria were as follows: (1) Female patients meeting the diagnostic criteria for PCOS (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004); (2) Undergoing IVF/ICSI-ET; (3) Age between 20 and 50 years; (4) Availability of complete clinical data. Patients who meet any of the following criteria were excluded: (1) Male partner with poor sperm quality; (2) Presence of uterine diseases, such as endometriosis, endometritis, or uterine fibroids; (3) History of ovarian or uterine surgery; (4) History of miscarriage or stillbirth; (5) Uncontrolled diabetes, hyperthyroidism, or hypothyroidism; (6) Chromosomal abnormalities in either partner; (7) Use of hormone therapy or antioxidant supplements (e.g., vitamin E, vitamin C, or coenzyme Q10) within the past 3 months; (8) Non-compliance by either partner with IVF-ET requirements, including cessation of smoking and alcohol consumption before and during IVF-ET treatment, abstinence prior to sperm collection, and adherence to medication and monitoring protocols.

All patients were categorized into three age groups: <35 years (n = 118), 35–40 years (n = 120), and >40 years (n = 104). Each age group was further subdivided based on whether GH supplementation was used during the IVF-ET cycle: a GH subgroup and a control subgroup. Specifically: In the <35 years group: GH subgroup (n = 57), control subgroup (n = 61); In the 35–40 years group: GH subgroup (n = 62), control subgroup (n = 58); In the >40 years group: GH subgroup (n = 50), control subgroup (n = 54). Fig. 1 presents the flowchart of patient selection. Additionally, to assess whether baseline characteristics influenced the efficacy of GH treatment, all participants were grouped according to GH use into a GH group (n = 169) and a control group (n = 173).

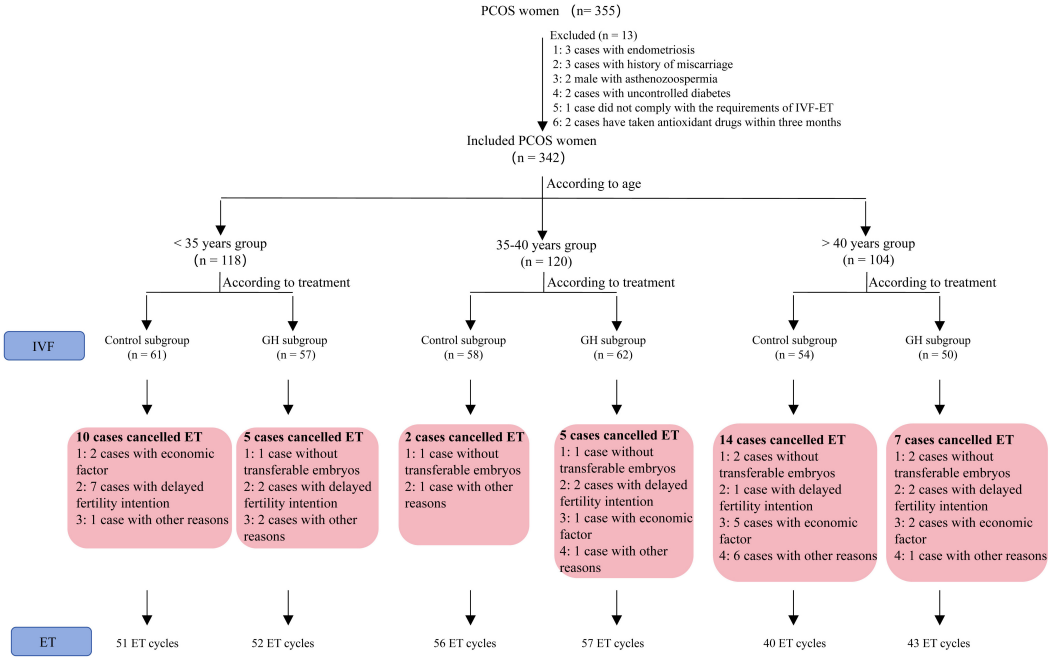

Fig. 1. The flowchart of patient inclusion and grouping. The figure was created using Adobe Photoshop (version 12.0, Adobe, San Jose, CA, USA). PCOS, polycystic ovary syndrome; GH, growth hormone; IVF, *in vitro* fertilization; ET, embryo transfer.

Ovarian Stimulation and GH Treatment

The gonadotropin-releasing hormone antagonist (GnRH-Ant) protocol was used for ovarian stimulation. Recombinant human follicle-stimulating hormone (rec-FSH; SJ20160040, 150–225 IU; Merck Serono, Darmstadt, Germany) was administered to female patients via subcutaneous injection starting on day 3 of menstruation and continued until the ovulation trigger day. Follicular development was monitored using transvaginal ultrasound, and serum estradiol (E2) levels were measured regularly. The dose of rec-FSH was adjusted according to follicular growth and serum E2 levels. When the diameter of dominant follicles reached 14 mm, cetrorelix (250 μg/day; HJ20140476, FAREVA PAU, Idron, France) was administered daily until the trigger day. Ovulation was triggered when the diameter of 2–3 dominant follicles reached 18 mm, using a subcutaneous injection of recombinant human chorionic gonadotropin (HCG; 10,000 IU; S20210010, Lizhu Pharmaceutical, Zhuhai, China). Transvaginal oocyte retrieval (TVOR) was performed 36 hours after the trigger to obtain oocytes.

In all GH subgroups, GH (4 IU/day; S20050025, Changchun GeneScience Pharmaceuticals, Changchun, China) was administered via subcutaneous injection starting on the same day as rec-FSH initiation and continued until the trigger day (Gong et al, 2020a; Chen et al, 2025; Guo et al, 2025). The control group did not receive GH treatment.

IVF/ICSI-ET

After oocyte retrieval, fertilization was performed using either IVF or intracytoplasmic sperm injection (ICSI). ICSI was chosen when sperm quality fell within

the critical range defined by the World Health Organization criteria (World Health Organization, 2021) or if fertilization had failed in a previous IVF cycle. The fertilized zygotes were cultured in an embryo incubator at 37 °C with 5% carbon dioxide (CO_2) for 3 to 5 days. Embryo quality was evaluated according to the consensus guidelines from the laboratory group of the Reproductive Medicine Branch of the Chinese Medical Association and the Istanbul consensus (Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group of Embryology, 2011). Blastocysts cultured until day 5 or 6 were assessed using the Gardner and Schoolcraft scoring system (Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group of Embryology, 2011), with scores of 3BB or higher considered high-quality blastocysts.

Transferable embryos or blastocysts were either frozen for subsequent frozen embryo transfer (frozen ET) or used immediately for fresh embryo transfer (fresh ET). Vitrification was employed for embryo or blastocyst freezing. One to two embryos or blastocysts were transferred into the uterus using a Wallace® Sure-Pro® catheter (PEB623, Smiths Medical International Limited, Ashford, UK). A total of 43 women canceled ET for reasons including absence of transferable embryos, financial considerations, delayed fertility intentions, or other factors (Fig. 1). This study included both fresh ET cycles and the first frozen ET cycle, totaling 299 ET cycles.

Four weeks after ET, a vaginal ultrasound was performed to assess clinical pregnancy, defined as the presence of a fetal heartbeat and an intrauterine gestational sac. Miscarriage was defined as pregnancy loss before 28 weeks of gestation. Live birth was defined as delivery of a fetus showing any signs of life, including breathing, heartbeat, umbilical cord pulsation, or definite voluntary muscle contraction.

Outcome Indicator

The outcome indicators of IVF/ICSI-ET included fertilization rate, cleavage rate, high-quality embryo rate, high-quality blastocyst rate, pregnancy rate, miscarriage rate, and live birth rate. A metaphase II (MII) oocyte was defined as an oocyte at the metaphase II stage that has extruded the first polar body. Normal fertilization was defined by the presence of two pronuclei (2PN). The fertilization rate was calculated as the ratio of 2PN zygotes to the total number of MII oocytes. Cleavage rate was defined as the ratio of the total number of cleavage-stage embryos to the total number of fertilized oocytes. The high-quality embryo rate was the ratio of high-quality embryos to total cleavage-stage embryos, while the high-quality blastocyst rate was the ratio of high-quality blastocysts to total blastocysts. Pregnancy rate was defined as the ratio of clinical pregnancies to the total number of ET cycles. Miscarriage rate was calculated as the ratio of miscarriages to total ET cycles, and live birth rate was the ratio of live births to total ET cycles.

Ovarian sensitivity index (OSI) was used to evaluate ovarian reactivity (Huber et al, 2013). OSI (oocytes/1000 IU rec-FSH) = The total number of oocytes retrieved / total dose of rec-FSH × 1000. Meanwhile, the OHSS was diagnosed (Navot et al, 2019). In addition, the other side effects were collected, including edema and joint pain.

Table 1. General clinical information of PCOS patients.

Baseline indicators	<35 years group (n = 118)				35–40 years group (n = 120)				>40 years group (n = 104)			
	Control subgroup (n = 61)	GH subgroup (n = 57)	*t*/Z	*p*	Control subgroup (n = 58)	GH subgroup (n = 62)	*t*/Z	*p*	Control subgroup (n = 54)	GH subgroup (n = 50)	*t*/Z	*p*
Age (year)	29 (28, 31)	29 (26, 31)	0.785	0.432	38 (37, 38)	38 (37, 38)	0.328	0.743	43 (42, 45)	44 (42, 45)	1.031	0.302
Duration of infertility (year)	4 (3, 4)	3 (3, 4)	1.122	0.262	4 (3, 5)	4 (4, 5)	1.123	0.262	4 (4, 5)	4 (4, 5)	0.166	0.868
BMI (kg/m^2)	23.1 (22.1, 24.1)	23.4 (22.4, 25.0)	0.940	0.347	23.50 ± 1.59	23.40 ± 1.67	0.335	0.738	23.83 ± 1.77	23.57 ± 1.54	0.796	0.428
AFC (n)	23.33 ± 3.37	23.46 ± 3.46	0.207	0.837	23.74 ± 3.66	23.63 ± 3.42	0.170	0.865	23.28 ± 2.95	22.46 ± 3.41	1.314	0.192
AMH (ng/mL)	8.05 (6.97, 9.15)	8.54 (6.70, 10.15)	1.217	0.224	8.52 ± 2.12	8.34 ± 1.71	0.513	0.609	8.69 (7.32, 9.97)	8.00 (6.90, 9.39)	1.646	0.100
Basal FSH (mIU/mL)	6.75 ± 2.03	6.92 ± 1.94	0.464	0.643	6.63 ± 1.82	6.75 ± 1.84	0.359	0.720	6.69 ± 1.67	7.11 ± 1.80	1.234	0.220
Basal LH (mIU/mL)	10.46 (7.76, 12.25)	8.83 (6.72, 11.28)	1.871	0.061	9.36 ± 3.37	9.94 ± 2.86	1.019	0.310	9.80 ± 2.65	10.24 ± 2.66	0.844	0.400
Basal E2 (pmol/L)	50.49 ± 11.12	52.42 ± 13.55	0.848	0.398	52.05 ± 14.53	52.09 ± 11.26	0.017	0.987	53.59 ± 12.31	51.26 ± 11.65	0.990	0.325
Basal testosterone (ng/mL)	0.61 ± 0.14	0.65 ± 0.13	1.605	0.111	0.66 ± 0.13	0.67 ± 0.14	0.405	0.686	0.66 ± 0.18	0.70 ± 0.18	1.132	0.260

Note: GH, growth hormone; BMI, body mass index; AFC, antral follicle count; AMH, anti-Müllerian hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; E2, estradiol.

Evaluation of Oxidative Stress

Fasting venous blood samples were collected from the patients' antecubital vein before ovarian stimulation (baseline) and on the trigger day. Blood samples were centrifuged at 4 °C at 3000 rpm for 15 minutes to obtain serum. Follicular fluid was collected during oocyte retrieval. Both serum and follicular fluid samples were stored at –80 °C until analysis. According to the manufacturers' instructions, malondialdehyde (MDA) and superoxide dismutase (SOD) levels in serum and follicular fluid were measured using commercial kits. The MDA kit (A003-1-2, detection limit: 0–113.0 μmol/L) and SOD kit (A001-3-2, detection range: 0.5–122.0 U/mL) were obtained from Nanjing Jiancheng Bioengineering Institute Co., Ltd. (Nanjing, China).

Statistical Analysis

Statistical analysis was performed using SPSS version 27.0 software (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to assess data normality. Normally distributed data were presented as mean ± standard deviation (SD), and differences between groups were compared using the independent *t*-test. Data with a skewed distribution were expressed as median and interquartile range (IQR), and group comparisons were performed using the Mann-Whitney U test. Categorical data were presented as counts and percentages (n [%]) and analyzed using the chi-square test when the expected frequency was greater than 5, the continuity correction test when the expected frequency was between 1 and 5, and Fisher's exact test when the expected frequency was less than 1. A *p*-value less than 0.05 was considered statistically significant.

Table 2. Comparison of general information between GH group and control group.

General information	GH group (n = 169)	Control group (n = 173)	*t*/Z	*p*
Age (year)	38 (31, 42)	37 (31, 42)	0.078	0.938
Duration of infertility (year)	4 (3, 5)	4 (3, 5)	0.158	0.874
BMI (kg/m^2)	23.46 ± 1.76	23.51 ± 1.65	0.271	0.786
AFC (n)	23.22 ± 3.45	23.45 ± 3.34	0.626	0.531
AMH (ng/mL)	8.34 (6.94, 9.66)	8.45 (7.12, 9.53)	0.222	0.824
Basal FSH (mIU/mL)	6.89 (5.50, 8.35)	6.76 (5.35, 8.11)	0.946	0.344
Basal LH (mIU/mL)	9.83 ± 2.79	9.82 ± 2.98	0.032	0.974
Basal E2 (pmol/L)	51.31 (42.51, 61.25)	51.29 (42.82, 59.79)	0.156	0.876
Basal testosterone (ng/mL)	0.67 ± 0.15	0.64 ± 0.15	1.849	0.065

Note: GH, growth hormone; BMI, body mass index; AFC, antral follicle count; AMH, anti-Müllerian hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; E2, estradiol.

Results

General Clinical Information

The general clinical information is presented in Table 1. There was no significant difference in baseline information between GH subgroup and control subgroup in each group ($p > 0.05$). In addition, no significant difference in general information between the GH group and control group ($p > 0.05$, Table 2).

Comparison of Ovarian Stimulation Parameters

Table 3 presents the ovarian stimulation parameters for each group. In the <35 years group, there were no significant differences between the control and GH subgroups in total dose of rec-FSH, duration of rec-FSH stimulation, E2 concentration, endometrial thickness on the trigger day, total number of oocytes retrieved, number of MII oocytes, OSI, or side effects (OHSS, edema, and joint pain) (all $p > 0.05$).

In the 35–40 years group, the total number of oocytes retrieved, number of MII oocytes, and OSI were significantly higher in the GH subgroup compared to the control subgroup ($p = 0.012$, 0.049, and 0.006, respectively). However, no significant differences were observed between subgroups regarding total rec-FSH dose, duration of stimulation, E2 concentration, endometrial thickness on trigger day, or side effects (OHSS, edema and joint pain) (all $p > 0.05$).

For the >40 years group, the GH subgroup showed a significant increase in total number of oocytes retrieved and OSI compared with the control subgroup ($p = 0.001$ and 0.002, respectively). No significant differences were found in total rec-FSH dose, duration of stimulation, E2 concentration, endometrial thickness on the trigger day, number of MII oocytes, or side effects (OHSS, edema and joint pain) (all $p > 0.05$) between control and GH subgroups.

Comparison of Oxidative Stress

No significant differences were observed in serum SOD and MDA levels at baseline, nor in follicular fluid SOD and MDA levels between the control and GH groups (both $p > 0.05$). In the <35, 35–40, and >40 years groups, serum SOD levels on the trigger day were significantly higher in the GH subgroups compared to the control subgroups ($p = 0.004$, 0.001, and 0.012, respectively), while serum MDA levels on the trigger day were significantly lower in the GH subgroups than in the control subgroups ($p = 0.032$, 0.015, and 0.004, respectively) (Table 4).

Comparison of Outcome Indicator of IVF/ICSI-ET

In the 35–40 and >40 years groups, the fertilization rate in the GH subgroup was significantly higher compared with the control group ($p = 0.040$ and 0.001, respectively). However, across all three age groups, there were no significant differences between the control and GH subgroups in fertilization method, cleavage rate, high-quality embryo rate, or high-quality blastocyst rate (all $p > 0.05$) (Table 5).

A total of 43 PCOS patients canceled ET due to reasons including lack of transferable embryos, economic factors, delayed fertility intention, and others. There were no significant differences between the GH and control groups in the number of canceled ET cycles or reasons for cancellation ($p > 0.05$) (Table 5). Ultimately, 299 ET cycles were analyzed. In the 35–40 years group, GH supplementation significantly increased the pregnancy rate compared to the control subgroup ($p = 0.043$), while the live birth rate showed a non-significant upward trend ($p = 0.064$). In the <35 years and >40 years groups, no significant differences were observed between the control and GH subgroups in pregnancy rate, miscarriage rate, or live birth rate (all $p > 0.05$) (Table 6).

Table 3. Comparison of ovarian stimulation parameters.

Ovarian stimulation parameters	<35 years group (n = 118)				35–40 years group (n = 120)				>40 years group (n = 104)			
	Control subgroup (n = 61)	GH subgroup (n = 57)	$t/Z/\chi^2$	p	Control subgroup (n = 58)	GH subgroup (n = 62)	$t/Z/\chi^2$	p	Control subgroup (n = 54)	GH subgroup (n = 50)	$t/Z/\chi^2$	p
Total dose of rec-FSH (IU)	2202.79 ± 382.96	2192.28 ± 339.61	0.157	0.875	2288 (2095, 2502)	2117 (1958, 2513)	1.187	0.235	2085 (1944, 2263)	2067 (1872, 2286)	0.566	0.571
The duration of rec-FSH stimulation (days)	10 (9, 11)	10 (9, 11)	0.117	0.907	10 (9, 11)	10 (9, 11)	1.147	0.251	10 (9, 11)	10 (9, 11)	1.292	0.196
E2 concentration on the trigger day (pg/mL)	2397.01 (2243.07, 2545.67)	2396.67 (2217.52, 2558.90)	0.089	0.929	2319.10 (2192.67, 2453.73)	2315.87 (2152.11, 2446.90)	0.368	0.713	2108.15 (1892.04, 2250.00)	2120.10 (1987.89, 2322.42)	1.087	0.277
Endometrial thickness on the trigger day (mm)	10 (8, 13)	9 (8, 11)	1.235	0.217	9 (8, 12)	9 (8, 11)	0.090	0.928	9 (8, 11)	10 (8, 12)	1.234	0.217
Total number of oocytes retrieved	13 (10, 15)	14 (12, 16)	1.480	0.139	11.67 ± 3.06	13.03 ± 2.77	2.555	0.012	10.31 ± 2.52	12.10 ± 2.71	3.490	0.001
MII oocyte	10 (7, 13)	10 (9, 13)	1.030	0.303	8 (7, 11)	10 (8, 11)	1.969	0.049	7 (6, 8)	8 (7, 10)	1.628	0.103
OSI (oocytes/1000 IU rec-FSH)	5.96 (4.41, 7.65)	6.00 (5.25, 7.34)	1.123	0.261	5.21 ± 1.58	6.04 ± 1.67	2.792	0.006	4.94 ± 1.37	5.87 ± 1.59	3.202	0.002
OHSS (n, %)	7 (11.47%)	6 (10.53%)	0.027	0.869	6 (10.34%)	6 (9.68%)	0.015	0.903	3 (5.56%)	4 (8.00%)	0.011	0.916
Edema (n, %)	2 (3.28%)	4 (7.02%)	0.255	0.614	1 (1.72%)	3 (4.84%)	0.194	0.659	1 (1.85%)	2 (4.00%)	0.005	0.946
Joint pain (n, %)	0 (0.00%)	1 (1.75%)	/	0.483	1 (1.72%)	2 (3.23%)	0.003	0.953	0 (0.00%)	1 (2.00%)	/	0.481

Note: GH, growth hormone; rec-FSH, recombinant human follicle-stimulating hormone; E2, estradiol; MII, metaphase II; OSI, ovarian sensitivity index; OHSS, ovarian hyperstimulation syndrome.

Table 4. Comparison of oxidative stress.

Oxidative stress indicator	<35 years group (n = 118)				35–40 years group (n = 120)				>40 years group (n = 104)			
	Control subgroup (n = 61)	GH subgroup (n = 57)	*t*	*p*	Control subgroup (n = 58)	GH subgroup (n = 62)	*t*	*p*	Control subgroup (n = 54)	GH subgroup (n = 50)	*t*	*p*
Serum SOD (U/mL)—Baseline	15.32 ± 1.27	15.64 ± 1.35	1.327	0.187	15.33 ± 1.27	15.20 ± 1.30	0.549	0.584	14.01 ± 1.17	14.14 ± 1.09	0.585	0.560
Serum SOD (U/mL)—trigger day	15.71 ± 1.03	16.28 ± 1.10	2.907	0.004	15.57 ± 1.20	16.34 ± 1.34	3.308	0.001	14.11 ± 1.21	14.72 ± 1.23	2.548	0.012
Follicular fluid SOD (U/mL)	14.18 ± 1.21	14.58 ± 1.10	1.875	0.063	14.33 ± 0.89	14.52 ± 0.98	1.109	0.270	14.59 ± 1.12	14.91 ± 1.03	1.513	0.133
Serum MDA (μmol/L)—Baseline	3.12 ± 0.87	3.07 ± 0.94	0.300	0.765	3.35 ± 1.09	3.38 ± 1.10	0.150	0.881	3.42 ± 1.09	3.44 ± 1.08	0.094	0.925
Serum MDA (μmol/L)—trigger day	3.44 ± 0.74	3.10 ± 0.95	2.177	0.032	3.78 ± 0.98	3.33 ± 1.02	2.461	0.015	3.89 ± 0.76	3.40 ± 0.95	2.915	0.004
Follicular fluid MDA (μmol/L)	2.12 ± 0.87	2.11 ± 0.76	0.066	0.947	2.29 ± 0.59	2.19 ± 0.67	0.865	0.389	2.25 ± 0.50	2.11 ± 0.47	1.468	0.145

Note: GH, growth hormone; MDA, malondialdehyde; SOD, superoxide dismutase.

Table 5. Comparison of embryo outcome in IVF/ICSI.

Indicator	<35 years group (n = 118)				35–40 years group (n = 120)				>40 years group (n = 104)			
	Control subgroup (n = 61)	GH subgroup (n = 57)	χ^2/Z	*p*	Control subgroup (n = 58)	GH subgroup (n = 62)	χ^2/Z	*p*	Control subgroup (n = 54)	GH subgroup (n = 50)	χ^2/Z	*p*
Fertilization procedure (n, %)			0.235	0.628			0.008	0.927			0.332	0.564
IVF	47 (77.05%)	46 (80.70%)			49 (84.48%)	52 (83.87%)			43 (79.63%)	42 (84.00%)		
ICSI	14 (22.95%)	11 (19.30%)			9 (15.52%)	10 (16.13%)			11 (20.37%)	8 (16.00%)		
Fertilization rate (%)	60.00 (50.00, 67.95)	66.67 (48.08, 84.52)	1.901	0.057	57.14 (45.98, 72.32)	67.95 (56.75, 76.25)	2.057	0.040	50.00 (37.50, 62.50)	66.67 (50.00, 77.78)	3.177	0.001
Cleavage rate (%)	100.00 (86.61, 100.00)	100.00 (85.71, 100.00)	0.554	0.580	83.33 (79.45, 71.43)	87.30 (71.43, 100.00)	1.239	0.215	80.00 (60.67, 91.67)	80.00 (71.07, 87.50)	0.125	0.901
High quality embryos rate (%)	66.67 (57.14, 81.67)	66.67 (60.00, 83.33)	0.460	0.645	66.67 (50.00, 80.00)	66.67 (57.14, 75.00)	0.161	0.872	60.00 (50.00, 100.00)	75.00 (57.12, 89.28)	1.170	0.242
High-quality blastocyst rate (%)	0.00 (0.00, 50.00)	0.00 (0.00, 50.00)	0.886	0.376	0.00 (0.00, 0.00)	0.00 (0.00, 33.33)	1.394	0.163	0.00 (0.00, 8.33)	0.00 (0.00, 50.00)	0.594	0.552
Cancelled ET cycles (n, %)	10 (16.39%)	5 (8.77%)	1.543	0.214	2 (3.45%)	5 (8.06%)	0.474	0.491	14 (25.93%)	7 (14.00%)	2.291	0.130
No transferable embryos (n, %)	0 (0.00%)	1 (1.75%)	/	0.483	1 (1.72%)	1 (1.61%)	/	>0.999	2 (3.70%)	2 (4.00%)	0.186	0.666
Delayed fertility intention (n, %)	7 (11.48%)	2 (3.51%)	1.644	0.200	0 (0.00%)	2 (3.23%)	/	0.496	1 (1.85%)	2 (4.00%)	0.005	0.946
Economic factor (n, %)	2 (3.28%)	0 (0.00%)	/	0.496	0 (0.00%)	1 (1.61%)	/	>0.999	5 (9.26%)	2 (4.00%)	0.459	0.498
Other reasons (n, %)	1 (1.64%)	2 (3.51%)	0.004	0.953	1 (1.72%)	1 (1.61%)	/	>0.999	6 (11.11%)	1 (2.00%)	2.135	0.144

Note: IVF, *in vitro* fertilization; ICSI, intracytoplasmic sperm injection; GH, growth hormone; ET, embryo transfer.

Table 6. Comparison of the outcome of ET cycle.

Indicator	<35 years group (n = 103)				35–40 years group (n = 113)				>40 years group (n = 83)			
	Control subgroup (n = 51)	GH subgroup (n = 52)	χ^2	*p*	Control subgroup (n = 56)	GH subgroup (n = 57)	χ^2	*p*	Control subgroup (n = 40)	GH subgroup (n = 43)	χ^2	*p*
ET approach (n, %)			0.001	0.976			0.158	0.691			0.007	0.934
Fresh ET cycle	5 (9.80%)	4 (7.69%)			3 (5.36%)	3 (5.26%)			3 (7.50%)	2 (4.65%)		
Frozen ET cycle	46 (90.20%)	48 (92.31%)			53 (94.64%)	54 (94.74%)			37 (92.50%)	41 (95.35%)		
Pregnancy rate	21 (41.18%)	27 (51.92%)	1.195	0.274	18 (32.14%)	29 (50.88%)	4.081	0.043	13 (32.50%)	20 (46.51%)	1.699	0.192
Miscarriage rate	2 (3.92%)	4 (7.69%)	0.157	0.692	1 (1.79%)	2 (3.51%)	0.000	0.988	3 (7.50%%)	2 (4.65%)	0.007	0.934
Live birth rate	19 (37.25%)	23 (44.23%)	0.519	0.471	17 (30.36%)	27 (47.37%)	3.438	0.064	10 (25.00%)	18 (41.86%)	2.635	0.105

Note: GH, growth hormone; ET, embryo transfer.

Discussion

PCOS leads to hormonal imbalances that affect oocyte development and are a major cause of female infertility (Tay et al, 2023; Di Lorenzo et al, 2023). Elevated testosterone levels in PCOS patients promote the formation of early preantral follicles; however, impaired granulosa cell function prevents these follicles from maturing into dominant follicles (Bongrani et al, 2022). This disruption results in anovulation, infertility, high miscarriage rates, and poor pregnancy outcomes in women with PCOS. Exogenous GH has been shown to improve embryo quality and live birth rates in women with decreased ovarian reserve aged 35–40 years undergoing IVF-ET (Chen et al, 2025), and to increase the likelihood of obtaining euploid blastocysts in women aged 38–40 years (Sui et al, 2023). Additionally, GH can alleviate oxidative stress in women with PCOS and improve mitochondrial dysfunction in granulosa cells, thereby enhancing oocyte quality (Gong et al, 2020a). In this study, GH significantly increased the number of oocytes retrieved and OSI in PCOS patients aged ≥35 years, and increased MII oocytes in those aged 35–40 years. Although GH slightly increased the number of oocytes retrieved and OSI in PCOS patients under 35 years old, these differences were not statistically significant. Importantly, GH supplementation did not increase the incidence of OHSS in PCOS patients. No cases of severe OHSS were observed; 32 patients developed mild to moderate OHSS. Mild OHSS cases required no special treatment and resolved with rest. Eight patients experienced moderate OHSS and received symptomatic treatment, including fluid replacement and anticoagulation. Some women also reported mild edema and joint pain during ovarian stimulation, which resolved after rest. While the incidence of edema and joint pain was slightly higher in the GH group than in controls, the difference was not statistically significant.

GH plays multiple roles in reproduction by regulating insulin-like growth factor 1 (IGF-1) signaling, including activation of primordial follicles, folliculogenesis, steroidogenesis, oocyte maturation, and embryo implantation. It also enhances granulosa cell responsiveness to gonadotropins by increasing gonadotropin receptor expression (Chang et al, 2022). Moreover, GH secretion gradually declines with age (Bartke, 2019), which may explain why the benefits of GH supplementation were more pronounced in PCOS patients aged ≥35 years during ovarian stimulation.

For PCOS women aged >40 years, although GH significantly increased the number of oocytes retrieved and fertilization rate, this advantage did not translate into a significant improvement in pregnancy or live birth rates. This may be related to a decline in oocyte quality with age, characterized by morphological abnormalities, meiotic spindle disruption, and reduced mitochondrial function (Moghadam et al, 2022). While GH can improve oocyte quality, it may not fully reverse the age-related damage. Additionally, poor endometrial receptivity in advanced maternal age (Zhao et al, 2023) could contribute to the lack of significant improvement in pregnancy outcomes. Jiang et al (2023) reported that GH administration did not increase cumulative live births in women aged >42 years or <35 years. Despite differences in patient populations, GH dosage, and ovarian stimulation protocols, their findings align with ours, suggesting that the effects of GH may be age-dependent.

In PCOS women aged 35–40 years, GH significantly increased the number of oocytes retrieved, MII oocytes, fertilization rate, and pregnancy rate; live birth rate also showed an upward trend, though not statistically significant. Conversely, GH supplementation did not provide significant reproductive benefits for PCOS women under 35 years, including in the number of oocytes retrieved, fertilization rate, pregnancy rate, or live birth rate. This may be because younger PCOS patients have less severe endogenous GH deficiency. Furthermore, the generally good oocyte quality and endometrial receptivity in younger women may result in less noticeable improvement in reproductive outcomes with GH supplementation. Oxidative stress alters the follicular fluid microenvironment, adversely affecting the function of oocytes and granulosa cells. Excessive accumulation of ROS causes the release of large amounts of calcium ions from the endoplasmic reticulum, disrupting cellular calcium homeostasis and triggering apoptosis. This calcium imbalance contributes to follicular stagnation in PCOS patients, resulting in amenorrhea or anovulation (Rudnicka et al, 2022; Gao et al, 2023). In our study, exogenous GH alleviated serum oxidative stress in PCOS patients across all age groups. The GH subgroups exhibited higher serum SOD levels and lower serum MDA levels on the trigger day than those of control subgroup. GH reduced serum oxidative stress levels in PCOS patients of all age groups, and its effect is more significant for patients older than 40 years old. This finding aligns with previous reports demonstrating GH's role in reducing oxidative stress in PCOS patients (Gong et al, 2020a).

Although GH slightly reduced MDA and increased SOD levels in follicular fluid, these differences were not statistically significant. This may be because follicular fluid represents a localized microenvironment, whereas GH exerts more systemic effects, resulting in less pronounced changes in follicular fluid oxidative stress markers compared to serum. Mechanistically, GH activates the PI3K/AKT signaling pathway in granulosa cells, inhibiting the transcription of downstream targets such as Forkhead box O (FOXO), thereby reducing oxidative stress and apoptosis and improving reproductive outcomes (Gong et al, 2020b). Activation of this pathway also promotes the expression of angiogenic factors, enhancing endometrial angiogenesis and uterine receptivity in PCOS rats (Xing et al, 2022). Moreover, *in vitro* studies have shown that GH upregulates sirtuin-3 (Sirt3) expression in ovarian cells; Sirt3 upregulation increases superoxide dismutase 2 (SOD2) levels and decreases ROS, thereby improving oxidative stress. Additionally, Sirt3 upregulation also enhances mitochondrial function and protects granulosa cells from apoptosis (Wang et al, 2021).

Our results showed that exogenous GH increased fertilization rates in PCOS patients aged $\geq$35 years and improved pregnancy rates in those aged 35–40 years. A previous study similarly reported that GH significantly enhances fertilized oocyte numbers, cleavage-stage embryos, and pregnancy rates during IVF-ET cycles (Gong et al, 2020a). However, unlike Jiang et al (2023), who reported increased live birth rates in older women (35–42 years) with GH supplementation, we did not observe a significant benefit in pregnancy outcomes in PCOS patients over 40 years old. This discrepancy may be due to differences in study populations and methodologies.

Our study has several limitations. First, as a small-scale retrospective study, there is potential for bias in the conclusions. Additionally, since all patients were recruited from a single hospital, the generalizability of our findings is limited. Therefore, multi-center prospective studies with larger clinical cohorts are necessary to validate these conclusions in the future. Second, all PCOS patients in this study were treated using the GnRH-Ant protocol. It remains unclear whether the age-related differences in GH efficacy observed here apply to other ovarian stimulation protocols, such as the GnRH-Ant protocol. Third, PCOS is a heterogeneous condition with four recognized phenotypes. Khamaiseh et al (2025) reported that phenotype D has better IVF-ET outcomes compared to phenotype A. Different phenotypes have distinct metabolic and endocrine profiles that may influence the efficacy of GH during IVF-ET. Due to the limited sample size, we did not perform stratified analyses based on PCOS phenotypes. Future studies should explore the impact of GH on different PCOS phenotypes in the context of IVF-ET. Moreover, this study only examined changes in SOD and MDA levels in serum and follicular fluid. Further research is needed to investigate the effects of GH on other oxidative stress markers, such as glutathione, 8-hydroxy-2′-deoxyguanosine (8-OHdG), and ROS. Finally, as an exploratory study, multiple comparison corrections were not applied to avoid missing potentially valuable clinical findings. However, this approach may increase the risk of false-positive results. Our findings require validation in larger clinical cohorts with appropriate statistical corrections, such as Bonferroni or Benjamini-Hochberg adjustments, to confirm the true benefits of GH supplementation in PCOS women across different age groups.

Conclusion

GH supplementation improves serum oxidative stress and ovarian responsiveness in women with PCOS. Additionally, GH increases the number of oocytes retrieved and fertilization rates in PCOS patients aged ≥35 years, as well as the number of MII oocytes in those aged 35–40 years. While GH significantly improves pregnancy rates in PCOS women aged 35–40, it does not show a significant benefit in live birth rates.

Key Points

- Exogenous growth hormone (GH) supplementation improves serum oxidative stress levels and ovarian reactivity in women with polycystic ovary syndrome (PCOS).
- GH increases the number of oocytes retrieved and fertilization rates in PCOS women aged 35 years and older.
- GH supplementation significantly raises the number of metaphase II (MII) oocytes in PCOS women aged 35–40 years.
- GH improves pregnancy rates in PCOS women aged 35–40 years but does not significantly affect live birth rates.

Availability of Data and Materials

All data included in this study are available from the corresponding author upon reasonable request.

Author Contributions

YXY designed the research study. PPZ, XLW, and KXS performed the research. QZ and YLX analyzed the data. YXY wrote the initial draft. All authors contributed to revising the manuscript critically for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of the General Hospital of Northern Theater Command (Approval No. Y(2024)021). All procedures were conducted in accordance with the Declaration of Helsinki, and all participants provided written informed consent.

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Conflict of Interest

The authors declare no conflict of interest.

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