The Egyptian Journal of Hospital Medicine (April 2025) Vol. 99, Page 2469-2472

Growth Hormone Pretreatment in Poseidon Type IV Undergoing ICSI Using Minimal Induction Protocol: A Randomized Controlled Trial

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ABSTRACT

Background: Poor ovarian reserve (POR) makes it harder for assisted reproductive technology (ART) to succeed, often resulting in lower success rates for in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) treatments. Researchers are constantly looking for new ways to improve how ovaries respond and to increase pregnancy rates for these patients. **Objective:** This clinical trial aimed to investigate whether growth hormone (GH) pre-treatment could improve the success rates of IVF/ICSI for women with poor ovarian reserve.

Patients and methods: This clinical trial included 132 participants who were 35 years or older and had an anti-mullerian hormone (AMH) level under 1.2 ng/mL. These criteria categorize them as POSEIDON group 4, meaning they have poor ovarian reserve. The participants were split evenly into two groups: One receiving growth hormone (GH) as a pre-treatment (GH+ group) and a control group without GH (GH- group), with 66 patients in each. To minimize the influence of other factors, a one-to-one case-control matching was employed. All patients underwent ART using minimal ovarian stimulation protocols. **Results:** Adding GH as an extra treatment didn't significantly improve how ovaries responded (like the number of eggs retrieved) or increase the live birth rate for the overall group of patients with poor ovarian reserve. Even when specifically analyzing patients meeting the POSEIDON group 4 criteria, GH adjuvant therapy still showed no benefit in terms of promoting live births. **Conclusion:** This study concluded that using GH pretreatment as an additional therapy did not significantly improve clinical outcomes, specifically the live birth rate, for patients classified under POSEIDON group 4. These are women aged 35 or older with poor ovarian reserve who underwent ICSI treatment using minimal ovarian stimulation protocols. This suggests that for this specific group of patients, adding GH pretreatment may not be an effective strategy to increase their chances of a live birth.

Keywords: Growth hormone, Poor ovarian reserve, POSEIDON criteria.

INTRODUCTION

Infertility is consistently identified as a significant, serious, and costly health concern globally, with approximately 10-15% of affected couples reporting it as the most challenging experience of their lives [(1)].

For roughly 25% of cases, the reason for a couple's inability to conceive remains unknown, a condition called unexplained infertility. This diagnosis is made when standard fertility tests (like checking ovulation, fallopian tube openness, and sperm quality) show no issues after at least one year of unprotected intercourse [(2)].

POR is a known challenge in IVF and ICSI cycles. It occurs when, despite proper stimulation, fewer eggs than expected are retrieved [(3)]. This impacts about 5–18% of all assisted reproductive technology (ART) cycles, resulting in low pregnancy rates (often 2–4%), making it a significant barrier to successful IVF/ICSI [(4)].

Due to various risk factors, a single definition for POR has been difficult to establish, although researchers have suggested standardized criteria [(3)]. In 2016, the POSEIDON (Patient-Oriented Strategies Encompassing Individualized Oocyte Number) criteria were introduced. These criteria offered a more precise definition for "low prognosis" patients in ART, shifting the focus from "poor ovarian response" to this broader concept [(5)]. The POSEIDON criteria categorize low-prognosis ART patients into four groups. This classification is based on ovarian reserve markers (AMH and/or AFC), woman's age, and the number of eggs previously retrieved from conventional ovarian stimulation [(6)]. During controlled ovarian stimulation (COS) for POR, many "adjuvant therapies" have been explored to improve IVF outcomes. An adjuvant therapy is any treatment given in addition to standard GnRH analogues and gonadotropins, aimed at increasing pregnancy success, especially for women with POR or a history of failed IVF/ICSI cycles [(7)].

While GH has been used in IVF treatment for over 25 years, there's still no agreement on the best way to administer it (route), the ideal amount (dose), or when to give it (timing) within IVF protocols [(8)]. GH is used in IVF treatment for various patient groups, including women with PCOS, those with suboptimal ovarian stimulation response, older women, and individuals facing poor oocyte or embryo quality concerns [(9, 10)].

Despite being used in female infertility treatment for 25 years, GH is not currently FDA-approved for general use in IVF cycles, except in cases where a GH deficiency has been confirmed. Its main application is as an adjunct to ovarian stimulation for women who have previously shown a suboptimal response in an IVF cycle. The exact role and benefits of GH within IVF treatment continue to be a subject of considerable debate and research [(9)]. GH is thought to boost the effects of follicle-stimulating hormones (FSH) on granulosa cells. It does this by increasing the local creation of insulin-like growth factor-1 (IGF-1) [(11)].

Interest in GH for IVF treatment stems from animal research suggesting its ability to boost intraovarian IGF-1 synthesis. The connection between GH and IGF-1 is crucial because IGF-1 is a proven

Received: 20/01/2025
Accepted: 20/03/2025

essential factor for healthy ovarian function in both animals and humans [12].

When IGF-1 is added to gonadotropins in granulosa cell cultures, it has been shown to amplify gonadotropin action on the ovary through several mechanisms [11]. These include increased aromatase activity, enhanced production of 17-beta-estradiol and progesterone and formation of luteinizing hormone receptors. In human ovarian cells, IGF-1 works with FSH to stimulate protein synthesis and steroidogenesis. Once LH receptors are present, IGF-1 further boosts LH-induced progesterone synthesis and promotes granulosa-luteal cell proliferation. Additionally, IGF-1 and FSH together significantly increase aromatase activity in preovulatory follicles, contributing to both estradiol and progesterone production [12].

Growth hormone plays a fundamental role in both follicular development and ovarian steroidogenesis. Similarly, IGF-1 is also known to promote follicular development, stimulate estrogen production, and contribute to oocyte maturation [11].

This clinical trial aimed to investigate whether growth hormone (GH) pre-treatment could improve the success rates of IVF/ICSI for women with poor ovarian reserve. The study focused on patients in patient-oriented strategies encompassing individualized oocyte number (POSEIDON) group 4, defined as women aged 35 or older who have a low pre-stimulation ovarian reserve (e.g., antral follicle count (AFC) less than 5 or AMH less than 1.2 ng/mL).

PATIENTS AND METHODS

Patients: This study, conducted at Ain Shams University Maternity Hospital and Queen's Fertility Center, recruited women undergoing infertility treatment who met POSEIDON group 4 criteria (age 35-42, AFC < 5, AMH < 1.2 ng/ml).

Exclusion criteria: Serious systemic diseases, cancer history, endocrine/metabolic disorders affecting oocyte quality, chromosomal abnormalities in either partner, severe male factor infertility, GH contraindications, female infertility not due to poor ovarian reserve, uterine anomalies, or BMI > 35 kg/m^2.

Participants were randomized into 2 groups: Group A received mild stimulation with daily 8 IU recombinant human GH from Day 14 of the previous cycle until HCG trigger, while group B received mild stimulation alone. Both groups underwent an identical mild stimulation protocol. Follicular development was monitored with transvaginal ultrasounds every other day starting from Day 6 of stimulation. Cetrotide® 0.25 mg was administered if luteinizing hormone (LH) exceeded 10 IU/L, a follicle reached an average diameter over 12 mm, or serum estradiol (E2) levels surpassed 150 pg/mL, continuing until HCG trigger. Once the dominant follicle hit 16 mm, daily ultrasounds began until the largest follicle exceeded 18 mm, with rFSH stimulation capped at 16 days.

Oocyte retrieval fertieization and embryo transfer: Ovarian pick-up occurred 36 hours post-HCG injection, with each follicle aspirated and flushed thrice for maximal oocyte retrieval. Mature metaphase II oocytes underwent ICSI via direct penetration. Fertilization was assessed 16-19 hours post-ICSI, confirmed by two pronuclei; degeneration was noted by cytoplasmic collapse and zona separation, and fertilization failure by absent pronuclei. Embryo transfer on day 3 post-ICSI was ultrasound-guided to the mid-uterine cavity. Luteal phase support comprised 400 mg vaginal progesterone suppositories twice daily, initiated on retrieval day and continued until the pregnancy test.

Data collection and outcome measures: Patients' demographics (Age, BMI & infertility duration), ovarian reserve markers (AFC, basal FSH, LH, E2, Prolactin, TSH & AMH), and cycle parameters (Total Gn dosage, endometrium thickness, mature/fertilized oocytes, embryo development) were comprehensively compared, alongside clinical outcomes.

Positive pregnancy was determined by a positive pregnancy test performed 2 weeks after embryo transfer.

Clinical pregnancy was defined by the presence of a gestational sac and embryonic pole with a heartbeat using transvaginal ultrasound performed 6 weeks after embryo transfer.

Ongoing pregnancy was pregnancy continuing after the 20th week of gestation.

Ethical approval: This study has been approved by Ain Shams Faculty of Medicine's Ethics Committee. Following receipt of all information, signed consent was provided by each participant. The study adhered to the Helsinki Declaration throughout its execution.

Statistical analysis

Data were analyzed using SPSS version 27.0. Quantitative data were presented as mean ± SD or Median (IQR), while qualitative data were shown as frequencies and percentages. Statistical comparisons used independent-samples t-tests for means, Chi-square for proportions, and Mann Whitney U for non-parametric comparisons. Spearman's correlation coefficient (r) assessed variable relationships, visualized with scatter diagrams. A p-value $\leq$ 0.05 indicated statistical significance, with a 95% confidence interval and 5% margin of error.

RESULTS

The study randomized 132 patients into two equally sized groups (66 each), which were well-matched in demographics (age & BMI), infertility duration, and hormonal profiles, except for a significant difference in LH levels (P < 0.05). Specifically, baseline age, BMI, basal FSH, AMH, and E2 showed no significant differences between the GH+ and GH- groups. LH

levels, however, were significantly different (6.28 ± 1.42 vs. 4.60 ± 1.14, P < 0.05 respectively) (Table 1).

Table (1): Comparison between groups as regard demographic data and hormonal profile

	Control group (n=66)	GH group (n=66)	p-value
Age (Years)	38.83±2.4	38.02±2.7	0.066
BMI (Kg/m^2)	29.51±3.7	28.31±3.7	0.067
Duration of infertility (Years)	5.00±3.7	5.94±3.7	0.148
FSH (IU/mL)	9.27±2.2	8.47±2.10	0.393
LH	6.28±1.42	4.60±1.14	0.003
Prolactin	12.35±2.91	14.61±3.60	0.052
TSH (mIU/L)	1.67±0.41	1.43±0.34	0.068
AMH	0.77±0.18	0.77±0.18	0.931
E2	43.85±10.91	38.57±9.63	0.330

Both groups followed similar standard protocols and had comparable responses in gonadotropin dose, number of oocytes retrieved, oocytes fertilized, and total embryo count (Table 2).

Table (2): Comparison between groups as regard gonadotropin dose and response

	Control group (n=66)	GH group (n=66)	P-Value
Dose of gonadotropin	54.92±17.8	58.76±17.9	0.219
Endometrial thickness	9.70±2.1	10.74±2.5	0.009

Notable differences were observed in endometrial thickness (9.70 ± 2.1 vs. 10.74 ± 2.5, P=0.009) and both right (3 vs. 2, P<0.001) and left antral follicle counts (3 vs. 2, P < 0.001) (Tables 2 & 3).

Table (3): Comparison between groups as regard response to gonadotropin

	Control group (n=66)			GH group (n=66)			P-Value
	Range	Median	IQR	Range	Median	IQR	
RT AFC	0-8	3	2-4	0-4	2	1-2	<0.001
AFC	0-6	3	2-3	0-5	2	1-3	0.001
No of oocyte	0-12	4	2-6	0-9	4	2-7	0.884
No of fertilized oocyte	0-7	2	1-4	0-11	2	1-5	0.541
No of embryos	0-4	2	1-3	0-7	2	1-3	0.564

Pregnancy outcomes, including biochemical, clinical, and ongoing pregnancy rates, showed no significant differences between the two groups. The chance of ongoing pregnancy was identical, with a relative risk and odds ratio of 1 for both the control and growth hormone groups (Table 4).

Table (4): Comparison between groups as regard pregnancy outcome

	Control group (n=66)	GH group (n=66)	X^2	p-value
Biochemical pregnancy	26 (39.4%)	27 (40.9%)	0.03	0.859
Clinical pregnancy	25 (37.9%)	27 (40.9%)	0.13	0.722
Ongoing pregnancy	18 (27.3%)	18 (27.3%)	0.0	1

DISCUSSION

Despite ART advancements, POR remains a major challenge in controlled ovarian stimulation, causing significant stress for infertile couples. Its reported incidence varies from 5.6% to 35.1% (7).

Research interest in POR has surged over the past 37 years, leading to hundreds of publications on its physiology, pathogenesis, molecular mechanisms, clinical features, and management strategies [13]. Growth hormone (GH) has gained considerable interest as an IVF adjuvant, especially since the mid-2000s, driven by promising research [14, 9].

This study assessed GH pretreatment for POSEIDON group IV poor responders undergoing ICSI. We found no significant differences in gonadotropin dose, mature oocyte yield, fertilization, or embryo numbers. Similarly, chemical, clinical, or ongoing pregnancy rates were unaffected. However, significant differences were observed in endometrial thickness and antral follicle counts. These align with **Zhu *et al.*** [15] who also reported no significant differences in embryo availability, transferred embryo count, or various pregnancy rates, and suggested GH may not enhance live birth rates in older anticipated poor ovarian responders (OR, 1.20; 95% CI, 0.82–1.76; p = 0.342). Despite different primary endpoints and **Zhu's** [15] larger sample (1788 vs. 132), both studies' findings are consistent with **Cai *et al.*** [14] regarding retrieved oocytes and good-quality embryos. **Zhu *et al.*** [15] study had strengths in its size and duration, but limitations due to its retrospective design and exclusion of cryopreserved embryo outcomes. **Cai *et al.* study** [14] indicated GH adjuvant therapy significantly reduced total gonadotropin dosage (2351.39 ± 642.95 vs. 2577.80 ± 704.70, P=0.013). Our study differed in design (retrospective vs. prospective) and GH regimen (2 IU for 6 weeks vs. 8 IU from Day 14 of previous cycle).

Mohammad *et al.* [16] found no significant differences in stimulation duration or endometrial thickness, but the GH group had higher E2 levels (P=0.003) and more retrieved oocytes (P<0.001). Embryo development, transfer, and chemical/clinical pregnancy rates were similar. **Mohammad *et al.*** [16] study used a 4 IU/day GH dose and an ultrashort GnRH antagonist protocol. **Norman *et al.*** [17] also found no difference in live birth rates (14.5% GH vs. 13.7% placebo). However, oocyte retrieval was significantly

higher in GH group (95.4% vs. 78.5%; OR 5.67). Embryo transfer rates were comparable. **Norman [17]** study differed in GH regimen (12 IU/day) and lacked POSEIDON inclusion criteria.

The latest Cochrane review by **Sood *et al.* [8],** encompassing 16 RCTs, highlighted the uncertainty of GH's effect on live birth rates for poor responders (OR 1.77, 95% CI 1.17 to 2.70; 8 trials, 737 participants; very low-certainty evidence). It found a slight increase in pregnancy rates (OR 1.85, 95% CI 1.35 to 2.53; 11 trials, 1033 participants; low-certainty evidence) but no significant difference in oocyte count. While GH reduced mean gonadotropin units, study variability limits this finding.

LIMITATIONS

Current literature lacks long-term GH outcomes and cost-effectiveness analyses, raising concerns about affordability and uncertain benefits. Small sample sizes in many studies hinder robust conclusions. Despite increasing oocyte and MII oocyte counts and transferable embryos, GH supplementation did not improve live birth rates [18]. Inconsistent findings due to varying methods and small sample sizes persist, with one RCT showing increased MII oocytes but no improved live birth rate [17]. Consequently, ASRM and ESHRE have not fully endorsed routine GH use for poor responders [19]. Even adequately powered meta-analyses show conflicting clinical outcomes, underscoring the need for further research [4].

CONCLUSION

Despite ongoing efforts to find effective treatments for patients with poor ovarian reserve, this study concluded that GH as an adjuvant therapy did not significantly improve ovarian response (e.g., oocyte yield) or, critically, the live birth rate in POSEIDON group 4 patients undergoing ICSI with minimal induction protocols. Therefore, routine GH pretreatment for these patients is not supported by these findings.

No funding.

No conflict of interest.

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