MEDICINE UPDATES JOURNAL
Faculty of Medicine Port Said University
Volum: 16 No:3 PP:23 - 28

" Complications of Growth Hormone administration in Poor Ovarian Reserve undergoing ICSI. A Randomized Control study "

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Submitted: 25/12/2023
Accepted:27/12/2023

DOI:10.21608/MUJ.2023.258185.1159

ISSN : 2682-2741

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ABSTRACT:

Objective: Poor ovarian reserve (POR) is considered a serious condition that affects couples. There are different medical modalities and intervention trying to overcome POR. In vitro fertilization (IVF) is one of these interventions. Patients with poor ovarian reserve always suffer from low retrieved oocytes , low quality developed embryos, higher chances of cycle failures and cancellations, higher rates of abortion. GH as an adjuvant therapy to ART is promising. However, GH complications are understudied.

Methods : Between 2021 to 2022 at Ganna Fertility Center in Port-said, Egypt. A randomized control study, Study group will receive an ICSI cycle with GH supplementation and control group will only receive ICSI cycle. Demographic data and GH reported complications are analyzed.

Results :37 patients per group were included**.** The mean age of the Study group (36.11 ± 3.21) and the control group (35.81 ± 3.7). The mean duration of infertility is also similar between the GH group (4.81 ± 2.16) and the control group (4.73 ± 2) with a non significant difference. The average systolic blood pressure for the study and Control groups were 113 ± 20 (88 -135) and 110 ± 22 (87-130) mmHg respectively with a non-statistical significant difference (p = 0.7412). The average random blood sugar mg/dl for the study and the control groups were 123±20 (90-140) and 119 ±24 (87-138) with no statistical significant different (P= 0.6539). There were no cases with leg edema, added pain or change in overall features.

Conclusion :GH may have a positive role in POR undergoing ovaria stimulation. In addition, no sinister side effects of GH have been reported.

Keywords: GH, Complications, POR, infertility

Introduction:

Poor ovarian reserve (POR) is considered a serious condition that affects couples. There are different medical modalities and intervention trying to overcome POR. In vitro fertilization (IVF) is one of these interventions. Patients with poor ovarian reserve always suffer from low retrieved oocytes , low quality developed embryos, higher chances of cycle failures and cancellations, higher rates of abortion. (Ferraretti et al., 2011) The incidence of poor ovarian reserve ranges from 9 to 24%, and it is higher in women with delayed the age of marriage.(Kolibianakis et al., 2009) Pregnancy and live birth rates are still low in POR despite recent high technological interventions .(Jeve & Bhandari, 2016) Premature ovarian insufficiency (POI) is considered a phenomenon that may occur in females in their mid to late 30s where a rapid decline in the follicular pool occurs, and it even may be discovered in much younger females as well. (Wang et al., 2021) GH is a peptide hormone and non-lipid soluble with 191 amino acids. GH is secreted from the pituitary gland (anterior part of the gland), and metabolized by the liver. The gene of human GH is located in chromosome 17. The maximal amount of GH secretion is around the age of puberty. Growth hormone receptors are expressed on the granulosa cells, theca cells, and testicular cells. It affects the ovarian and testicular functions directly and indirectly. Its direct effect is through the binding of GH to its receptors, while indirectly through the production of Insulin-like growth factor (IGF) locally and from the liver in response to the stimulation of the GH. Both GH and IGF-1 play an essential role in the growth and development of primordial follicles, they regulate the recruitment of non-gonadotropin sensitive primordial follicles into gonadotropin sensitive growing follicles, and this explains the advantageous effects observed with GH as an adjuvant in IVF cycles.(Ipsa et al., 2019) GH/IGF axis is an important growth factor scheme that is related to folliculogenesis, promote steroidogenesis, and can directly regulate the gamete development, in addition to, the quality and the competency for implantation. Moreover, they decrease follicular atresia by (JAK/STAT and PI3/AK) as an intracellular signaling pathways. (Devesa & Caicedo, 2019; Ipsa et al., 2019). This study is to report any complications of GH supplementation in POR undergoing ICSI.

Methods

This is a randomized controlled study between 2021 to 2022 at Ganna Fertility Center in Portsaid Governorate after Ethical committee approval at the faculty of medicine, Portsaid University. Patients with POR undergoing ICSI were assembled into two groups, study and a control groups using computer randomization. A written consent informing the patients with the trial is signed by both partners. *Inclusion criteria* are Previous Poor ovarian response ≤3 oocytes with conventional stimulation, Serum Anti-Mullerian hormone (AMH) <1.1 ng/ml,Previous Poor ovarian response after maximum stimulation and Low antral follicle counts (AFC) ≤ 4 on Day 2 of cycle *Exclusion criteria* are Patients received radiotherapy or cytotoxic for pelvic malignancies, Cases has contraindications to be supplemented with GH: Diabetes Mellitus, or High blood pressure and Severe male factor (sperm concentration ≤1 million/ml, motility <10%, or abnormal forms ≥99%). Data collected are set at regular follow-up visits during ICSI cycle: Blood pressure, Random blood sugar and any limb pain or edema.

Stimulation protocol

In the ICSI cycle 2nd day, all patients are given HMG 450 IU/D. The GH group received 4 IU SC injection (somatropin® 4 IU Sedico company) on daily basis starting from the first fay of HM until triggering with HCG. In the ICSI cycle day 6 of ovarian induction all patients received GnRH antagonist injection cetrorelix acetate, 0.25 mg daily until triggering by HCG. Standard transvaginal US serial folliculometry was done to all patients along with serum E2 on the same day of triggering by HCG.

Statistical analysis

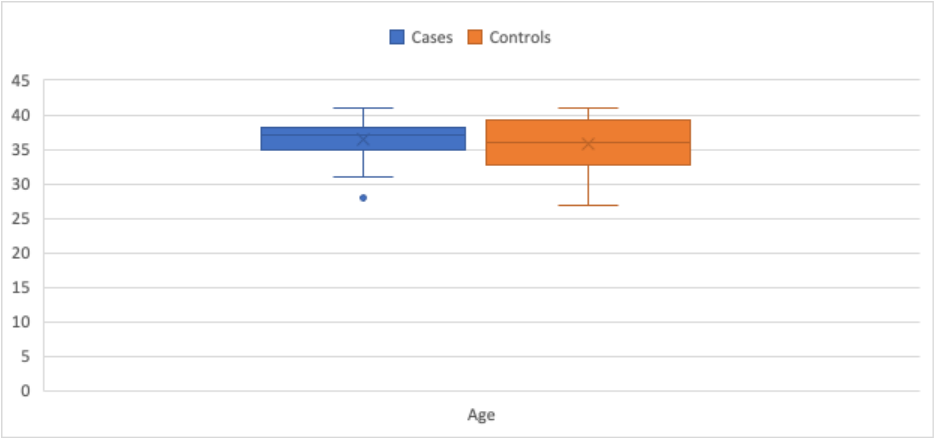
Collected data were processed using SPSS version 25. The data will be, collected, and analyzed using SPSS software (Statistical Package for Social Sciences) software version 26.0, Microsoft Excel 2016 and MedCalC program software version 19.1 Descriptive statistics were done for numerical parametric data as mean±SD, while they were done for categorical data as number and percentage. The level of significance was taken at P value <0.05 is significant, otherwise is non-significant.

Results

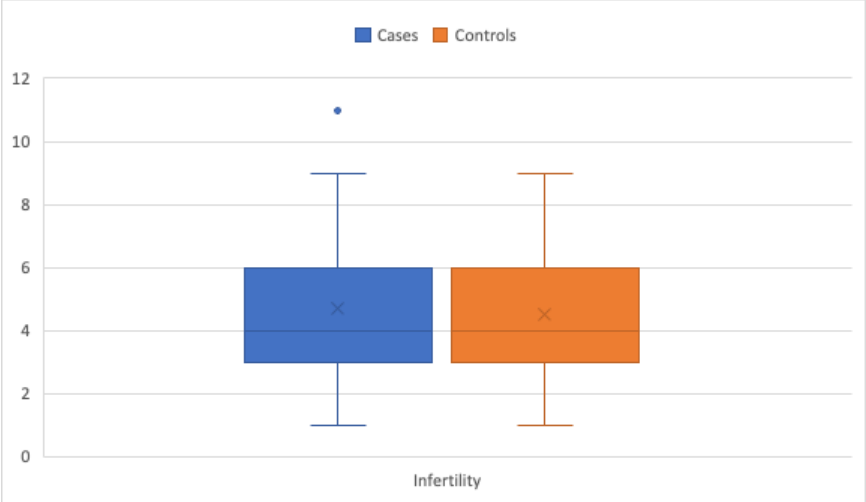
This randomized controlled study was conducted on 74 infertile women with poor ovarian reserve seeking pregnancy who attending at Ganna Fertility Center in Port-said Governorate. No Patient was excluded; So, 37 patients per group were included in the analysis**.** Their mean age was 29.74± 5.88 years. They divided into: **GH group:** 37 participants and **Control group:** 37 participants. The mean age of the GH group (36.11 ± 3.21) is slightly higher than that of the other group (35.81 ± 3.7), but there was a non-significant statistical difference (p = 0.71331). The median age of both groups falls within the range of 27-41 years. **(Table 1 & Graph 1)** The mean duration of infertility is also similar between the GH group (4.81 ± 2.16) and the control group (4.73 ± 2) with no significant difference between the groups (p = 0.86721). The median duration of infertility for both groups is 4 years with a range of 1-11 and 1-9 years, respectively. **(Table 1 & Graph2)** The average systolic blood pressure for the study group and the control group were 113 ± 20 (88 -135) and 110 ± 22 (87-130) mmHg respectively with no statistical significant difference (p = 0.7412). The average random blood sugar mg/dl for the study group and the control group were 123±20 (90-140) and 119 ±24 (87-138) with no statistical significant different (P= 0.6539). (Table **2)** There were no cases with leg edema, added pain or change in overall features.

Table (1): General Characteristics of both GH group and controls

	GH Group (N = 37)	Controls (N = 37)	P. value
Age			
• **Mean ± SD**	36.11 ± 3.21	35.81 ± 3.7	0.71331
• **Median** • **Range**	37 (28-41)	36 (27-41)	
Infertility /years			
• **Mean ± SD**	4.81 ± 2.16	4.73 ± 2	0.86721
• **Median** • **Range**	4 (1-11)	4 (1-9)	



Graph (1): Age distribution among cases and controls



Graph (2): Infertility duration distribution among cases and controls

Table (2): General Characteristics of both GH group and controls

	GH Group (N = 37)	Controls (N = 37)	P. value
Systolic blood pressure mmHg			
• **Mean ± SD**	113±20	110±22	0.7412
• **Range**	(88-135)	(87-130))	
Random blood sugar mg/dl			
• **Mean ± SD**	123±20	119±24	0.6539
• **Range**	(90-140)	(87-138)	

Discussion

Growth hormone receptors are expressed on the granulosa cells, theca cells, and testicular cells. It affects the ovarian and testicular functions directly and indirectly. Its direct effect is through the binding of GH to its receptors, while indirectly through the production of Insulin-like growth factor (IGF) locally and from the liver in response to the stimulation of the GH. Both GH and IGF-1 play an essential role in the growth of primordial follicles, they regulate the recruitment of non-gonadotropin sensitive primordial follicles into gonadotropin sensitive growing follicles, and this explains the essential effects observed with GH supplementation in IVF cycles.(Ipsa et al., 2019)

GH interaction with its receptors on granulosa cells can modulate the action of FSH, as well as increase the growth of LH receptors (LHR) on granulosa cells, and therefore plays a vital role in granulosa cell differentiation to luteal cells. Additionally, the IGF which is stimulated by the GH, augments the granulosa cell expansion through acting in a paracrine manner (Regan et al., 2018). So, that clarifies that GH can modify and enhance the granulosa cells as well as the theca cells sensitivity to the gonadotropin stimulation. Moreover, GH can regulate the ovarian steroidogenesis of sex hormones in the follicles, where LH stimulates the theca cells to produce androgens, which in turn is converted to oestrogens by the effect of the aromatase enzyme.(Ipsa et al., 2019)

In this study there was no significant change in blood pressure, random blood sugar or any joint pain or edema between study group and control group. Kolbianakis et al, in their systematic review and metanalysis which studies the role of growth hormone as an adjuvant to gonadotrophins in poor responders treated by IVF, and it involved analysis of six randomized controlled trials, and it reported that GH supplementation significantly increased significant higher proportion of patients reaching embryo transfer , clinical pregnancy, and live birth rates. No reported complications associated to GH supplementation. (Kolibianakis et al., 2009) Li et al. in 2017, in their systemic review and meta-analysis studying the effect of GH addition in POR undergoing stimulation protocols reported that GH improved the overall collected oocytes, number of M2 embryos, clinical pregnancy rates and birth rates. They did not report any complications reported with GH supplementation. (Li et al., 2017)

Conclusion

GH may have a positive role in POR undergoing ovaria stimulation. In addition, no sinister side effects of GH have been reported.

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