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" The Effects of Growth Hormone Administration on ICSI Outcomes in Poor Ovarian Reserve. A Randomized Control Study "

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ABSTRACT:

Objective: Poor ovarian reserve (POR) is one of the major problems that face the society. Different modalities have been tried to overcome this problem. The incidence of poor ovarian reserve is high, its incidence ranges from 9 to 24%. This incidence is unfortunately increasing as the women delay the age of marriage. And despite using different modalities, in cases of poor ovarian reserve both the pregnancy and live birth rates are low. GH is a peptide hormone produced from the anterior pituitary gland; it is produced due to the GHRH and is stopped in response to somatostatin hormone. GHRH and somatostatin are released from the hypothalamus. Growth hormone leads to the formation of IGF-1. IGF-1 and GH are vital in the formation of steroid hormones in the ovary.

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, Hormonal levels of AMH levels and E2 levels, AFC, HMG doses, number of mature follicles and stimulation days, and the number of pregnancy occurrence are collected and statistically analyzed between 2 groups.

Results: The mean age of the GH group (36.11 ± 3.21) is slightly higher than that of the other group (35.81 ± 3.7) . The mean duration of infertility is also the same between the GH (4.81 ± 2.16) and the control groups (4.73 ± 2). The mean AMH level is similar between the GH group (0.6 ± 0.22 ng/ml) and the control group (0.61 ± 0.22 ng/ml. The mean AFC is almost similar between the GH group (5.73 ± 1.88) and the control group (5.73 ± 1.88) and the control group (5.76 ± 1.72), with no significant difference between the two groups. The median AFC is 6 for the two groups, and they ranged from 3 to 9 in the GH and 3 to 8 in the control groups. The mean E2 level is statistically significantly higher in the GH side (1750.84 ± 732.23 pg/ml) than in the control group (1293.78 ± 574.96 pg/ml). There is non statistically significant difference in the mean number of mature follicles between the GH (4.46 ± 1.82) and the control groups (4.32 ± 1.68). The mean number of stimulation days for the GH side (9.84 ± 0.69) is statistically significantly lower than that of the other group (11.11 ± 0.74), with a p-value of less than 0.0001. The median number of stimulation days for the GH group is 10, with a range of 9-11, while the median for the control group is 11, ranging from 9-13. The mean HMG dose for the GH group (4427.03 ± 309.48) is significantly lower than that of the control group (4998.65 ± 331.76), with a p-value of less than 0.0001. The median HMG dose for the GH group is 4500, ranging from 4050-4950, while the median for the control group is 4950, ranging from 4050-5850. Out of the 37 patients in the GH group, 11 (29.73%) achieved pregnancy, while in the control group, 7 (18.92%) achieved pregnancy. However, the p-value for the difference in pregnancy occurrence between the two groups is 0.2848, which is not statistically significant. E2, AMH, AFC and number of Mature follicles were all significantly associated with pregnancy occurrence.

Conclusion: The role of GH as an adjunct in ARTs in POR women is still uncertain, it favors the increase of E2 levels on the HCG day and decreases the duration of stimulation and the gonadotropins dose. However, there was no significant difference in the number of mature follicles between the 2 groups. GH has a limited reported side effects related to its administration as an adjunct therapy.

Keywords: Infertility, GH, Poor ovarian reserve, AMH, AFC, Oocyte

Introduction:

Poor ovarian reserve (POR) is one of the major problems that face the society. Different modalities have been tried to overcome this problem. In vitro fertilization is one of these modalities.Patients with poor ovarian reserve often face major challenges as low number of retrieved oocytes, poor quality embryos, higher rate of cycles cancellation, higher miscarriage rates in comparison to their same age group with better ovarian reserve.(Ferraretti et al., 2011) The incidence of poor ovarian reserve is high, its incidence ranges from 9 to 24%. This incidence is unfortunately increasing as the women delay the age of marriage.(Kolibianakis et al., 2009) And despite using different modalities, Patients with POR still have the lowest rates of pregnancy and live birth rates. (Jeve & Bhandari, 2016) Kyrou et al in their metanalysis suggested that the adjuvant role of growth hormone significantly improved pregnancy outcomes in cases of poor ovarian reserve.(Kyrou et al., 2009) GH is produced from the anterior pituitary gland; it is produced in relation to the GHRH and is stopped in response to somatostatin hormone. GHRH and somatostatin are released from the hypothalamus. Growth hormone leads to the formation of insulin like growth factor 1 (IGF-1). Both GH and IGF-1 important in the formation of steroid hormones in the ovary. (Kurtz et al., 2021; F.-T. Liu et al., 2021) They also play a major role in the intracellular signaling pathway, therefore inhibiting atresia, and promoting the growth of the leading follicle.(Ipsa et al., 2019) Many studies have shown a significant improvement of the ovarian response after adding growth hormone to the induction of ovulation rather than performing the induction without growth hormone.(Alviggi et al., 2009; Hull & Harvey, 2014) Weall et al.(Weall et al., 2015) study revealed that the growth hormone supplementation also augments the receptors expression of growth hormone, and it results in better conception rates in old-aged women. Gonadotropins are medications used to induce and improve ovulation induction in women. In induction of ovulation the follicles reach 18-21 mm, and the treatment dose and duration are tailored according to each case and monitored by the ultrasound scans. (Kurtz et al., 2021; Tülek & Kahraman, 2021) Human chorionic Gonadotropin (HCG) is a similar structure to the natural luteinizing hormone (LH).(Wu et al., 1994) Injection with it leads to the same effect of LH surge and causes the release of ova from the ovaries 34-36 hours after injection.(Lustbader et al., 1998) In this study, both groups will undergo ovarian stimulation and ICSI. The study group will be supplemented with GH 4 IU SC daily at the day of ovarian stimulation till the trigger day by HCG. The ICSI protocol of both groups will be fixed D6 antagonist protocol. Both groups will be compared for the outcomes of induction; the count of mature follicles at HCG day, the gonadotrophin stimulation dose required for ovulation induction , the duration of ovarian stimulation and the Estradiol (E2) level at the day of triggering by injection of HCG to assess the follicles quantity and quality

Methods:

Between 2021 to 2022 at Ganna Fertility Center in Port-said Governorate after the acceptance of the ethical committee. A randomized control study, in which patients were divided into two groups using computer-generated randomization, in which each patient received a sealed envelope with an equal chance to join each group. POR patients seeking pregnancy who were eligible for this study, and willing to join in this study after giving a written consent regarding the nature of the study. *Inclusion criteria* are Previous Poor ovarian response ≤3 oocytes with conventional stimulation, serum Anti-Mullerian hormone (AMH) <1.1 ng/ml, AFC ≤ 4 on second day of cycle and Previous Poor ovarian response after maximum stimulation. *Exclusion criteria* are Patients exposed to radiotherapy and cytotoxic drugs for pelvic malignancies, Cases not to be treated with GH: Diabetes Mellitus, or High blood pressure and Severe male factor (sperm concentration ≤1 million/ml, motility <10%, or abnormal forms ≥99%). Demographic data, Hormonal levels of AMH levels and E2 levels, AFC, HMG doses, number of mature follicles and stimulation days, and the number of pregnancy occurrence are collected.

Stimulation protocol

On the 2nd day of ICSI Cycle, all cases started Human menopausal gonadotropins (HMG) 450 IU/D. The study group recieved GH supplementation 4 IU (=1.33mg) SC injection (somatropin® 4 IU Sedico company) daily starting from the day one of HMG until the triggering day by HCG. On Day 6 of induction of ovulation all cases started GnRH antagonist injection cetrotide® (cetrorelix acetate) 0.25mg on daily basis until the triggered by HCG. All cases were monitored by serial transvaginal U/S, and the subsequent HMG doses was measured individually based on the size of recruited follicles. A blood test for E2 level was done on day of HCG trigger, just before the HCG dose to examine the quality of recruited follicles. It is done through collecting 4-5 ml of blood, then centrifuged to fractionate the blood and separate 1.0 ml of plasma. No pretreatment was needed to the specimen. The test was done through Electrochemiluminescence immunoassay (ECLISA). HCG trigger (choriomon® 10,000 IU) intramuscular injection was administered when the follicles reach 17 mm or more, then ovum pickup was done 34-36 hrs later. A double lumen needle was used for ovum pickup in all cases. Luteal phase support using prontogest® (progesterone) 400 mg vaginal suppository twice daily was given to all cases from the day of ovum pick up till the day of pregnancy test.Both groups were assessed for the outcomes of induction, where the gonadotropins stimulation dose needed for induction of ovulation, the count of mature follicles at HCG day, the duration of ovarian stimulation and the E2 level at the day of HCG triggering injection.

Statistical analysis

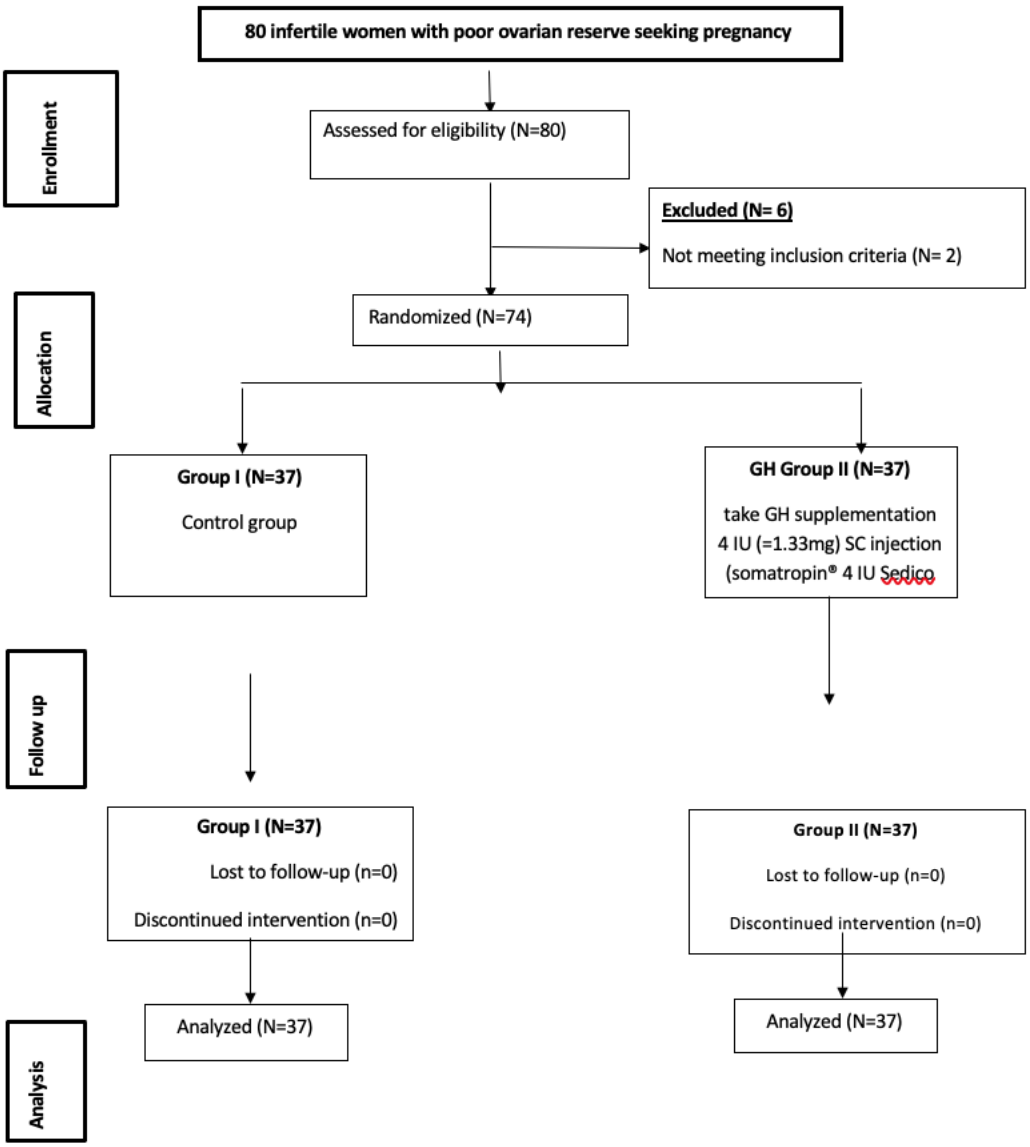
Collected data were processed using SPSS version 25. The data will be, collected, and analyzed using SPSS program version 26.0. Descriptive statistics were done for numerical parametric data as mean±SD and for numerical nonparametric data as median and 1st& 3rd inter-quartile range, while they were done for categorical data as number and percentage. Inferential

analyses were done for qualitative data by Chi square test for independent groups. (ANOVA or F test): One-way ANOVA test was used for continuous data to examine for significant difference between more than two distributed groups. 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. None of patients were excluded during the follow-up period; hence, 37 patients per group were included in the final analysis as seen in flow chart **(Graph 1).** Their mean age was 29.74± 5.88 years. 37 participants in each group. The mean age of the GH group (36.11 ± 3.21) is little higher than that of the other group (35.81 ± 3.7), but the difference is a non-statistically significant (p = 0.71331). The median age of both groups falls within the range of 27-41 years. **(Table 1 & Graph 2)** 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-statistical significant difference between the groups (p = 0.86721). The median duration of infertility for both groups is 4 years ranges from 1-11 and 1-9 years, respectively. **(Table 1 & Graph3)** The mean AMH level is closely equal between the GH (0.6 ± 0.22 ng/ml) and the control groups (0.61 ± 0.22 ng/ml), and there is no statistical significant difference between the groups (p = 0.87305). The median AMH level for both groups falls within the range of 0.2-1 ng/ml. **(Table 2 & Graph 4)** The mean AFC is almost similar between the GH group (5.73 ± 1.88) and the control group (5.76 ± 1.72), with no statistical significant difference between the two groups (p = 0.94878). The median AFC is 6 for the two groups, ranging from 3 to 9 in the GH group and 3 to 8 in the control group. **(Table 2 & Graph 5)** The mean E2 level is significantly more elevated in the GH group (1750.84 ± 732.23 pg/ml) than in the control group (1293.78 ± 574.96 pg/ml) the p-value of 0.00386. The median E2 level for the GH group (1660 pg/ml) is also more elevated than that of the control group (1246 pg/ml). **(Table 3 & Graph 6)** Similarly, there is no significant difference in the mean number of mature follicles between the GH group (4.46 ± 1.82) and the control group (4.32 ± 1.68) (p = 0.7412). The median of mature follicles for both groups is 4, ranging from 2 to 8 in both groups. **(Table 3 & Graph 7)** The mean number of stimulation days for the GH group (9.84 ± 0.69) is significantly lower than that of the control group (11.11 ± 0.74), with a p-value of less than 0.0001. The median number of stimulation days for the GH group is 10, with a range of 9-11, while the median for the control group is 11, ranging from 9-13. **(Table 4 & Graph 8)** The mean HMG dose for the GH side (4427.03 ± 309.48) is significantly lower than that of the control group (4998.65 ± 331.76), with a p-value of less than 0.0001. The median HMG dose for the GH side is 4500, ranging from 4050-4950, while the median for the control group is 4950, ranging from 4050-5850. **(Table 4 & Graph 9)** Out of the 37 patients in the GH side, 11 (29.73%) achieved pregnancy, while in the control group, 7 (18.92%) achieved pregnancy. However, the p-value for the difference in pregnancy occurrence between the two groups is 0.2848, which is not statistically significant. **(Table 5 & Graph 10)** The mean age of the pregnant group is 34.89 years with a standard deviation of 3.41, while the mean age of the non-pregnant group is 36.3 years with a standard deviation of 3.42. However, the p-value for the difference in age between the two groups is 0.13065, which indicates that the difference is not statistically significant. **(Table 6 & Graph**

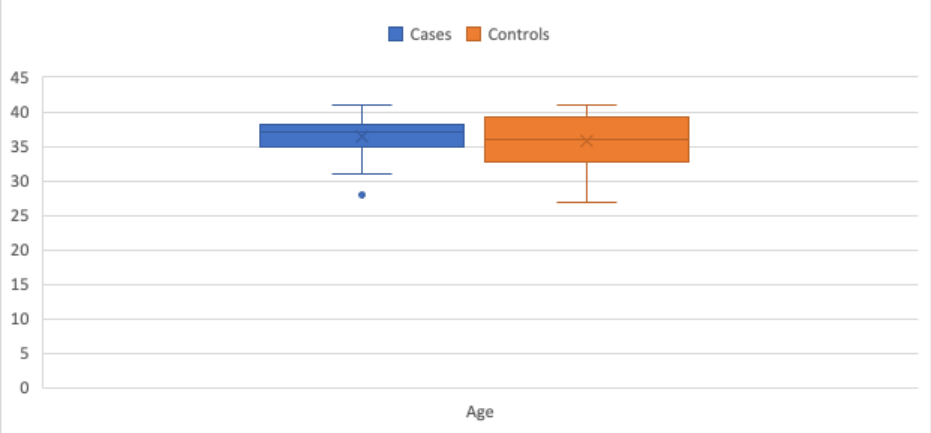
11) The mean infertility duration in the pregnant group is 4.44 years with a standard deviation of 2.28, while the mean infertility duration in the non-pregnant group is 4.88 years with a standard deviation of 2.0. However, the p-value for the difference in infertility duration between the two groups is 0.44524, which indicates that the difference is not statistically significant. **(Table 6 & Graph 12)** The AMH levels were significantly higher in subjects who got pregnant compared to those who did not (mean ± SD: 0.73 ± 0.23 ng/ml vs. 0.57 ± 0.2 ng/ml, p=0.00358). **(Table 7 & Graph 13)** The mean AFC was 6.94 ± 1.43 in subjects who got pregnant, and 5.36 ± 1.73 in subjects who did not get pregnant. This difference was statistically significant (P=0.00076). Similarly, the mean number of mature follicles was higher in subjects who got pregnant (5.5 ± 1.82) than in those who did not (4.04 ± 1.57) (P=0.00148). **(Table 7 & Graph 14)** The mean of the number of mature follicles is 5.5±1.82 in the pregnant group while it was 4.04±1.57 in the non-pregnant group, the difference is statistically significant. **(Table 8 & Graph 15)** Similarly, the E2 levels were significantly higher in the pregnancy group (mean ± SD: 2023.72 ± 755.23 pg/ml) compared to the non-pregnancy group (mean ± SD: 1361.14 ± 593.77 pg/ml, p=0.00026). These findings suggest that higher AMH and E2 levels may be associated with a higher likelihood of pregnancy. **(Table 8 & Graph 16)** The average number of stimulation days (the duration of hMG treatment) was 10.72 ± 1.02 days for subjects who got pregnant and 10.39 ± 0.93 days for subjects who did not get pregnant. The difference in stimulation days was not statistically significant (p = 0.20476), indicating a similar duration of hMG treatment between the two groups. **(Table 9 & Graph 17)** Similarly, the mean hMG doses in IU (international units) were 4825 ± 458.02 for subjects who got pregnant and 4676.79 ± 417.56 for subjects who did not get pregnant. The difference in hMG doses was not statistically significant (p = 0.20476), suggesting a comparable amount of hMG administered in both groups. **(Table 9 & Graph 18)** E2, AMH, AFC and number of Mature follicles were all significantly associated with pregnancy occurrence. **(Table 10).**


80 infertile women with poor ovarian reserve seeking pregnancy
Enrollment
Assessed for eligibility (N=80)
Excluded (N= 6)
Not meeting inclusion criteria (N= 2)
Allocation
Randomized (N=74)
Group I (N=37)
Control group
GH Group II (N=37)
take GH supplementation
4 IU (=1.33mg) SC injection
(somatropin® 4 IU Sedico
Follow up
Group I (N=37)
Lost to follow-up (n=0)
Discontinued intervention (n=0)
Group II (N=37)
Lost to follow-up (n=0)
Discontinued intervention (n=0)
Analysis
Analyzed (N=37)
Analyzed (N=37)

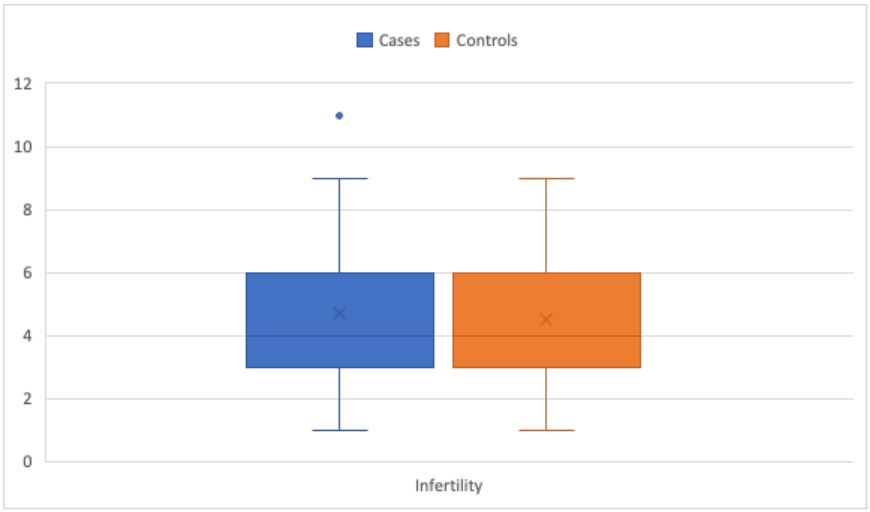
Graph 1: Study Flow chart

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)	



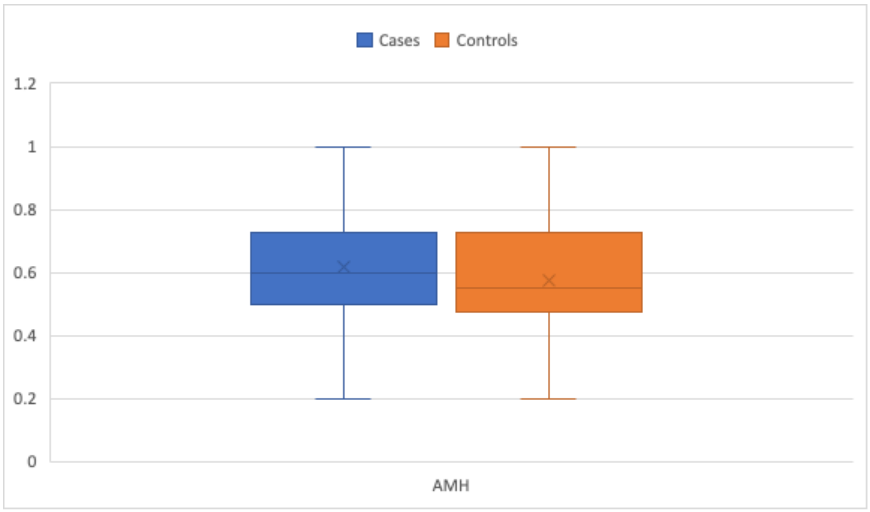
Graph (2): Age distribution among cases and controls



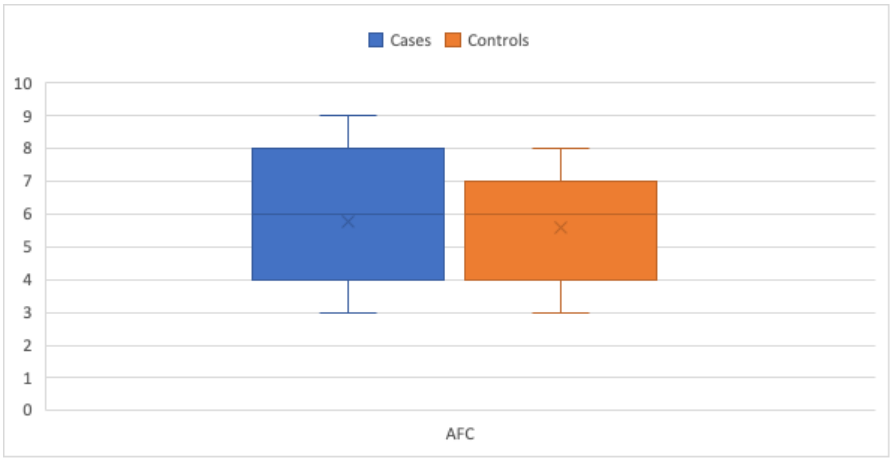
Graph (3): Infertility duration distribution among cases and controls

Table (2): AMH levels and AFC in both GH group and controls

	GH Group (N = 37)	Controls (N = 37)	P. value
AMH (ng/ml)			
• **Mean ± SD**	0.6 ± 0.22	0.61 ± 0.22	0.87305
• **Median** • **Range**	0.6 (0.2-1)	0.6 (0.2-1)	
AFC			
• **Mean ± SD**	5.73 ± 1.88	5.76 ± 1.72	0.94878
• **Median** • **Range**	6 (3-9)	6 (3-8)	



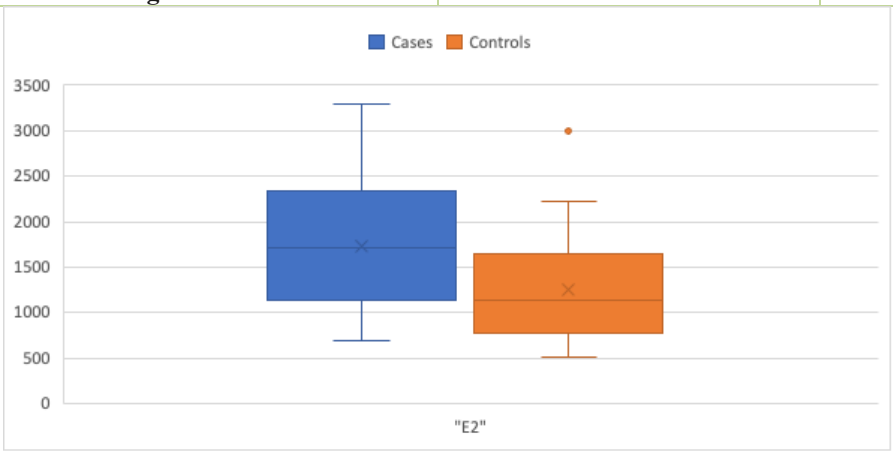
Graph (4): AMH level distribution among cases and controls



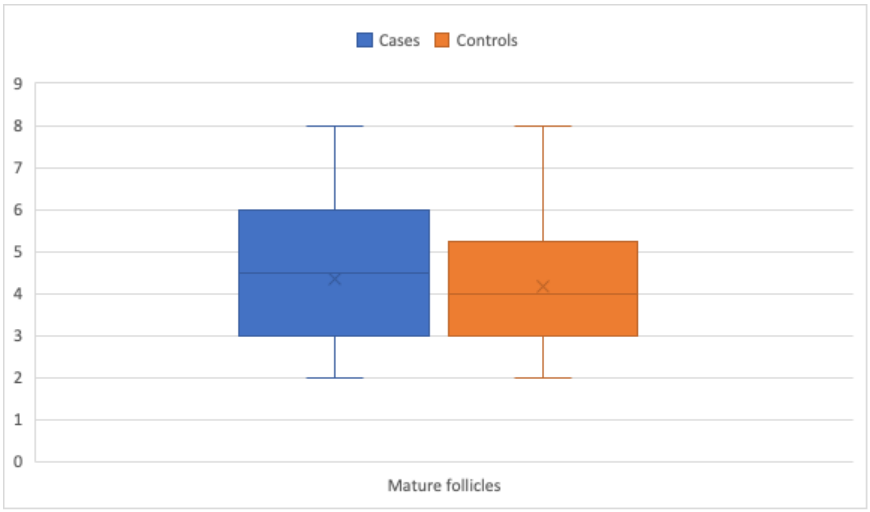
Graph (5): AFC distribution among cases and controls

Table (3): E2 and number of mature follicles in both GH group and controls

	GH Group (N = 37)	Controls (N = 37)	P. value
No. Mature follicles			
• **Mean ± SD**	4.46 ± 1.82	4.32 ± 1.68	0.7412
• **Median** • **Range**	4 (2-8)	4 (2-8)	
E2 (pg/ml)			
• **Mean ± SD**	1750.84 ± 732.23	1293.78 ± 574.96	0.00386*
• **Median** • **Range**	1660 (690-3290)	1246 (503-2997)	



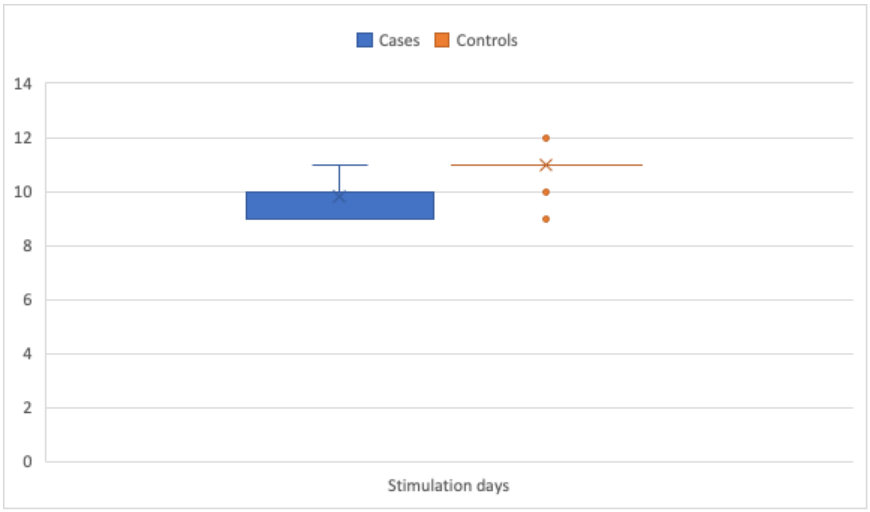
Graph (6): E2 distribution among cases and controls



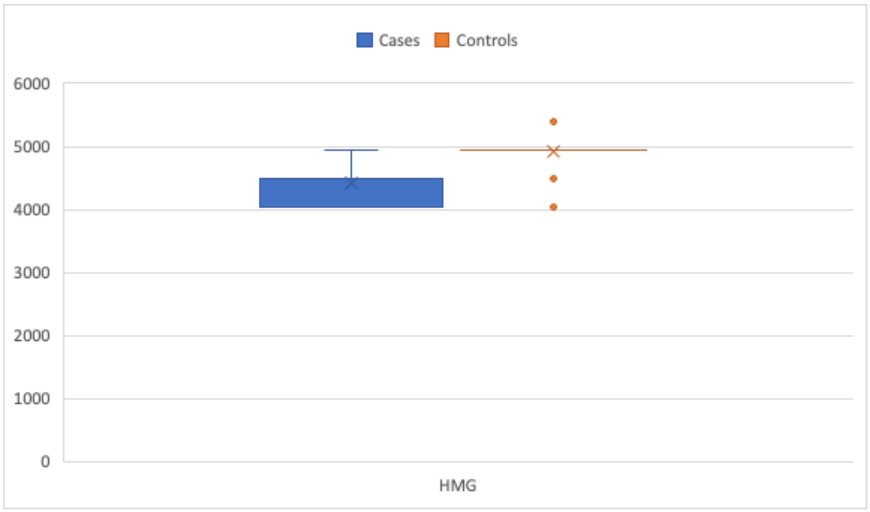
Graph (7): Mature follicles number distribution among cases and controls

Table (4): HMG dose and stimulation days in both GH group and controls

	GH Group (N = 37)	Controls (N = 37)	P. value
Stimulation days			
• **Mean ± SD**	9.84 ± 0.69	11.11 ± 0.74	<0.0001*
• **Median** • **Range**	10 (9-11)	11 (9-13)	
HMG (Dose/ IU)			
• **Mean ± SD**	4427.03 ± 309.48	4998.65 ± 331.76	<0.0001*
• **Median** • **Range**	4500 (4050-4950)	4950 (4050-5850)	



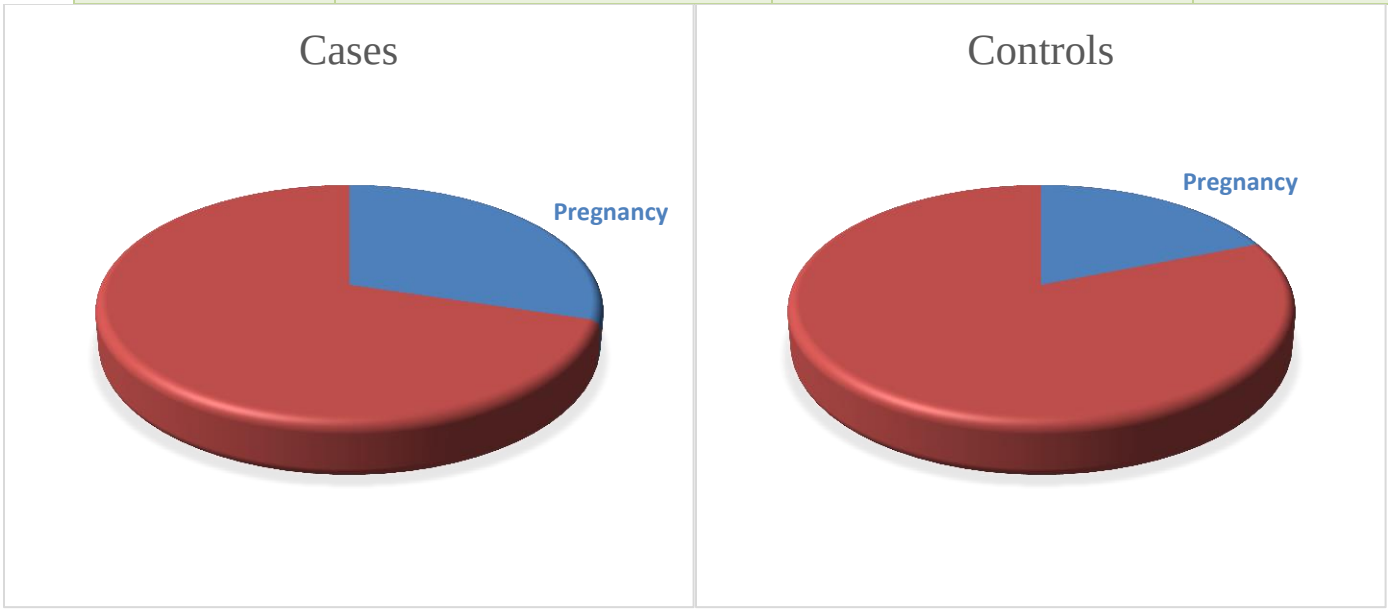
Graph (8): Stimulation days distribution among cases and controls



Graph (9): HMG distribution among cases and controls

Table (5): Pregnancy occurrence in both GH group and controls

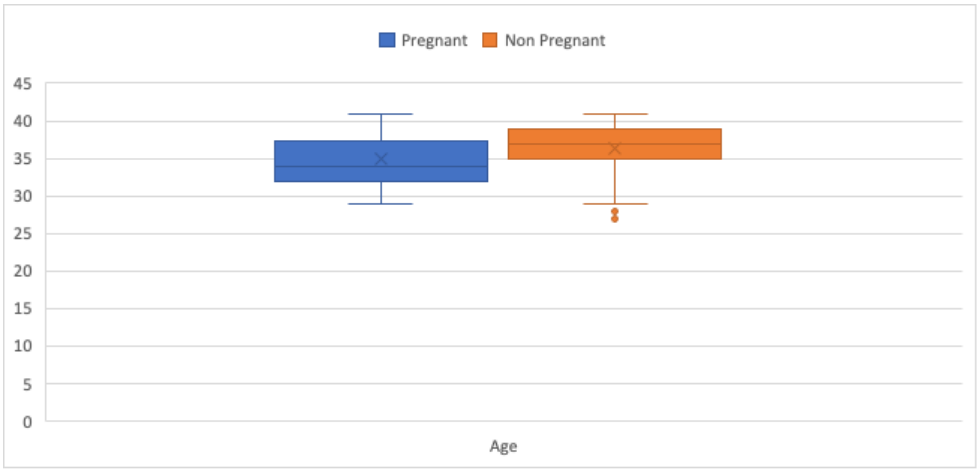
	GH Group (N = 37)	Controls (N = 37)	P. value
Pregnancy	11 (29.73%)	7 (18.92%)	0.2848



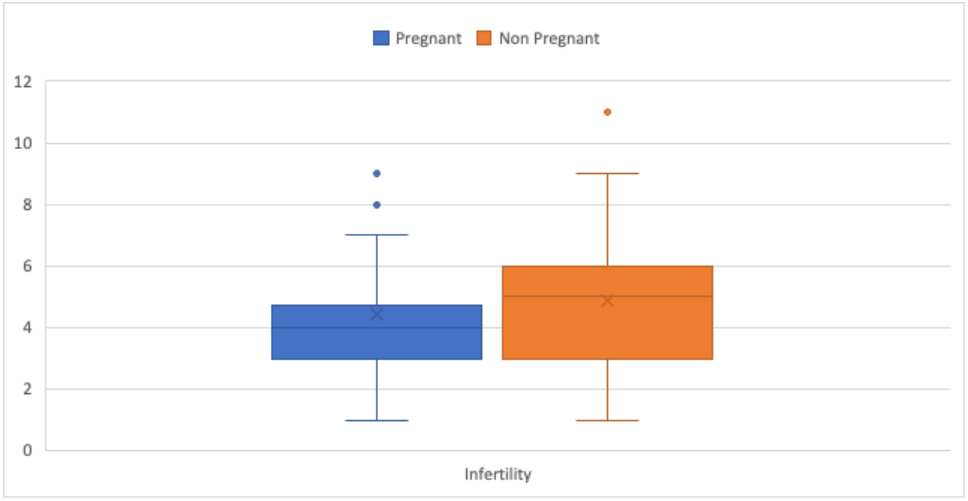
Graph (10): Pregnancy occurrence in both GH group and controls

Table (6): General Characteristics in both pregnant and non-pregnant

	Pregnancy (N = 18)	Non-Pregnancy (N = 56)	P. value
Age (Years)			
• **Mean ± SD**	34.89 ± 3.41	36.3 ± 3.42	0.13065
• **Median** • **Range**	34 (29-41)	37 (27-41)	
Infertility (Years)			
• **Mean ± SD**	4.44 ± 2.28	4.88 ± 2	0.44524
• **Median** • **Range**	4 (1-9)	5 (1-11)	



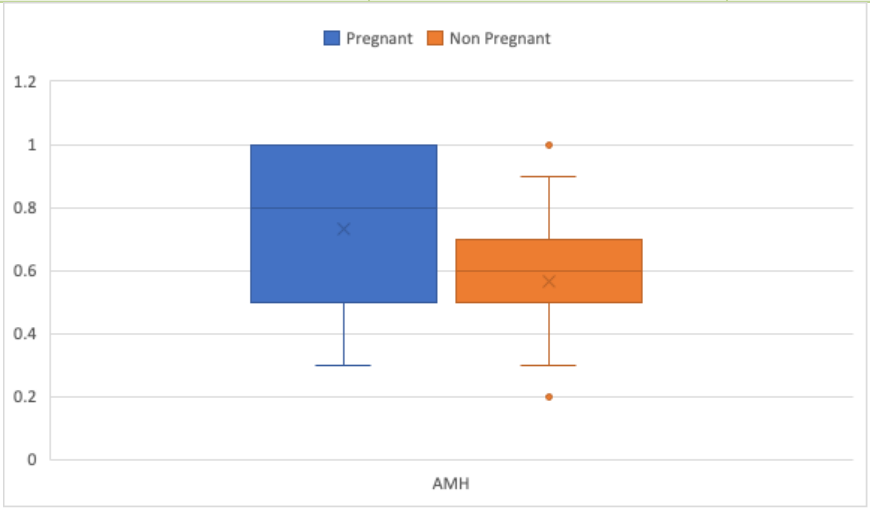
Graph (11): Age distribution among pregnant and non-pregnant women



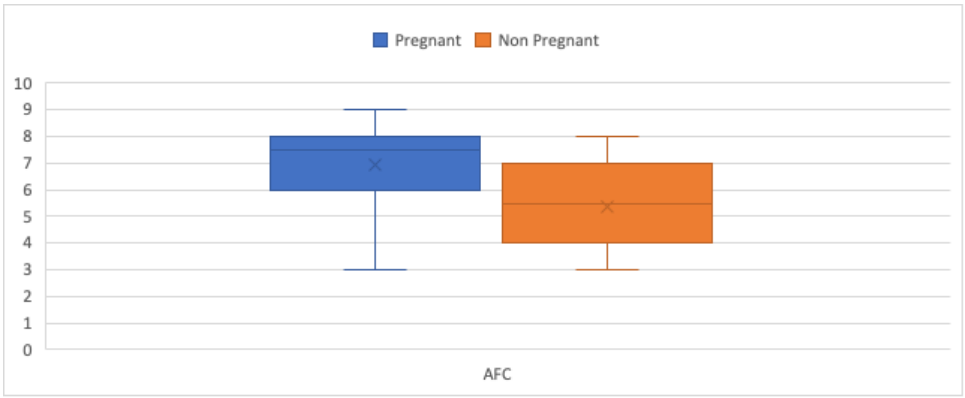
Graph (12): Infertility duration among pregnant and non-pregnant women

Table (7): AMH levels and AFC in in both pregnant and non-pregnant

	Pregnancy (N = 18)	Non Pregnancy (N = 56)	P. value
AMH (ng/ml)			
• **Mean ± SD**	0.73 ± 0.23	0.57 ± 0.2	0.00358*
• **Median** • **Range**	0.8 (0.3-1)	0.6 (0.2-1)	
AFC			
• **Mean ± SD**	6.94 ± 1.43	5.36 ± 1.73	0.00076*
• **Median** • **Range**	7.5 (3-9)	5.5 (3-8)	



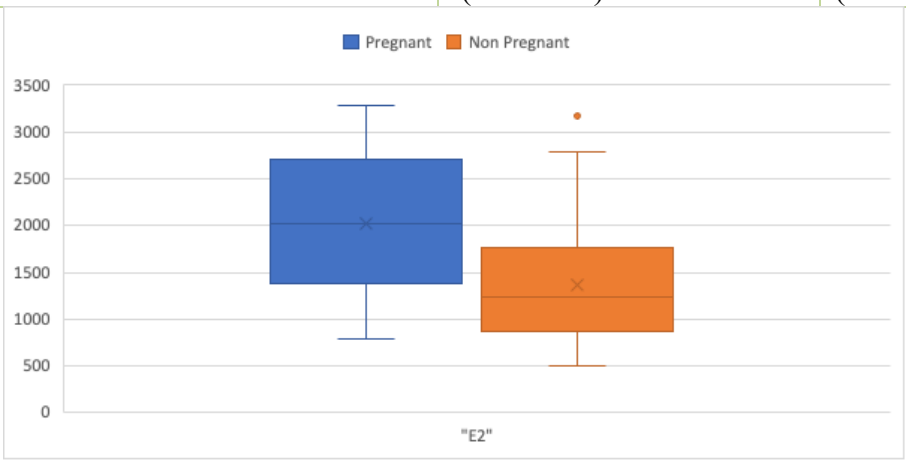
Graph (13): AMH level distribution among pregnant and non-pregnant women



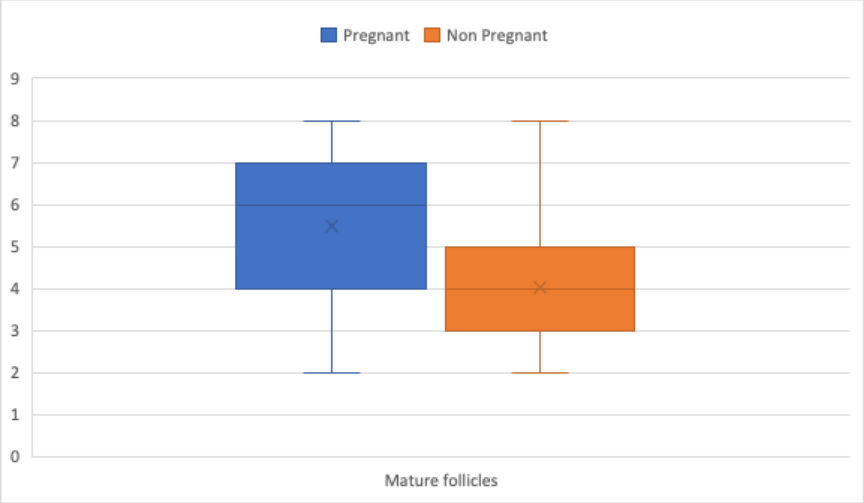
Graph (14): AFC distribution among pregnant and non-pregnant women

Table (8): E2 levels and number of mature follicles in both pregnant and non-pregnant

	Pregnancy (N = 18)	**Non-Pregnancy (N = 56)**	**P. value**
No. Mature follicles			
• **Mean ± SD**	5.5 ± 1.82	4.04 ± 1.57	0.00148*
• **Median** • **Range**	6 (2-8)	4 (2-8)	
E2 (pg/ml)			
• **Mean ± SD**	2023.72 ± 755.23	1361.14 ± 593.77	0.00026*
• **Median** • **Range**	2020 (790-3290)	1230.5 (503-3170)	



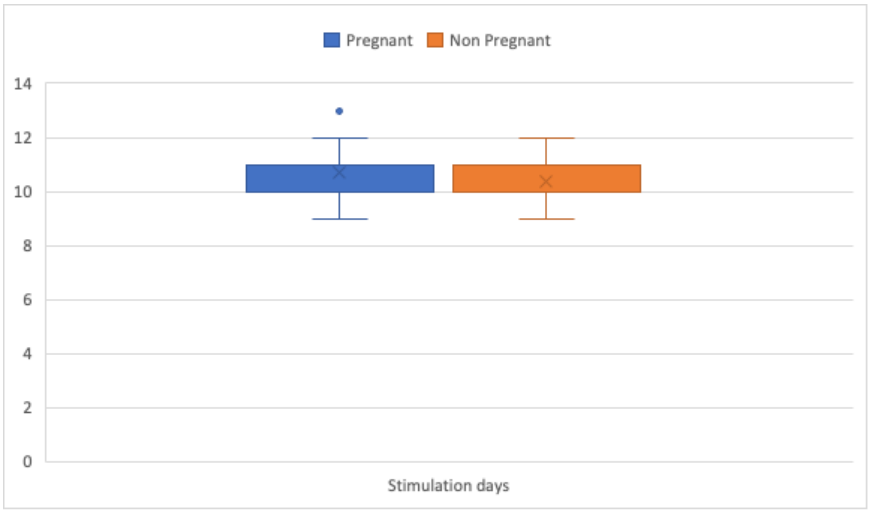
Graph (15): E2 Level among pregnant and non-pregnant women



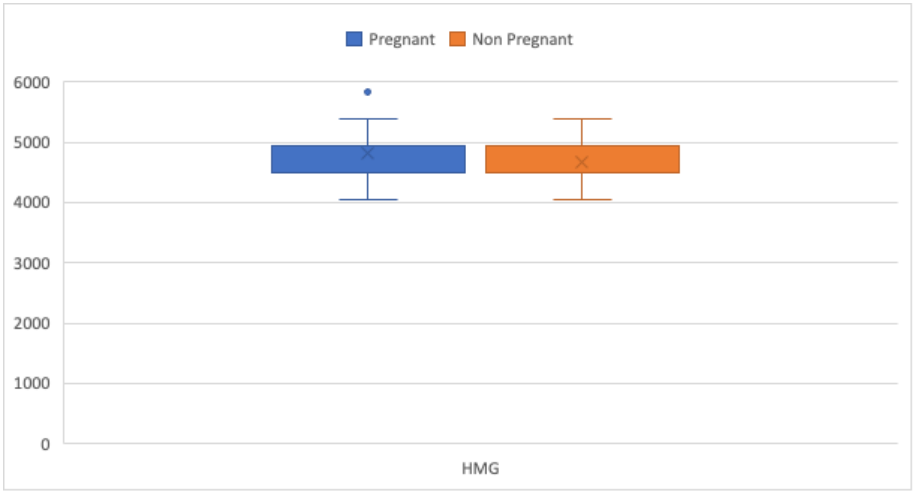
Graph (16): Mature follicles among pregnant and non-pregnant women

Table (9): HMG dose and stimulation days in in both pregnant and non-pregnant.

	Pregnancy (N = 18)	**Non Pregnancy (N = 56)**	**P. value**
Stimulation days			
• **Mean ± SD**	10.72 ± 1.02	10.39 ± 0.93	0.20476
• **Median** • **Range**	11 (9-13)	10 (9-12)	
HMG (Dose/ IU)			
• **Mean ± SD**	4825 ± 458.02	4676.79 ± 417.56	0.20476
• **Median** • **Range**	4950 (4050-5850)	4500 (4050-5400)	



Graph (17): Stimulation days among pregnant and non-pregnant women



Graph (18): HMG level distribution among pregnant and non-pregnant women

Table (10): Correlation between different parameters and pregnancy occurrence

	Pregnancy	
	r	P. Value
Age	-0.17733	0.130654
Infertility	-0.09009	0.445237
AMH	.334**	0.003585
AFC	.383**	0.000761
Stimulation days	0.149127	0.204759
HMG	0.149127	0.204759
Number of Mature follicles	.363**	0.001479
E2	.413**	0.000256

Discussion

In the results of this study was: the GH group showed significant increase in the mean E2 level (1750.84 ± 732.32) versus (1293.78 ± 574.96) in the other group, which is significant statistically. The mean of mature follicles was slightly bigger in the GH group (4.46 ± 1.82) versus (4.32 ± 1.68) in the control group, but it failed to reach statistical significance. The mean of stimulation days was lower in the GH group (9.84 ± 0.69) versus (11.11 ± 0.74) in the other group, which showed significant statistical difference . The mean HMG dose needed for ovarian stimulation in the GH group was less than that of the other group (4427.03 ± 309.48) versus (4998.65 ± 331.76) respectively, and this difference is significant. The GH side had a higher pregnancy rates (29.73 %) than the other group (18.92 %), however it didn't reach statistical significance.

A comparison was done between women who got pregnant women and the non-pregnant women involved in this study to correlate if other parameters can increase the women chances of pregnancy occurrence, and it was found that factors as higher AMH, higher number of mature follicles and a higher basal AFC on day of egg retrieval, as well as higher E2 levels on day of HCG administration, all showed statistically significant elevation in women who got pregnant. While the number of days needed in stimulation, as well as the gonadotropin doses didn't show statistical significance, so weren't correlated with pregnancy occurrence.

Kolbianakis et al, in their systematic review which was about adding of growth hormone to gonadotrophins in ovarian stimulation of POR, and it involved analysis of six randomized controlled trials, and it showed that GH as an adjuvant therapy significantly increased live birth and clinical pregnancy rates. It also showed that GH as an adjuvant therapy was related to a significant bigger proportion of women reach embryo transfer. (Kolibianakis et al., 2009)

Xue-Li Li et al, in their systematic review which was to assess the effect of different growth hormone adjuvant protocols to POR on outcomes in controlled ovarian stimulation therapy. It included 11 studies, and it reported that GH addition can significantly improve the number of MII follicles, the E2 level on day of HCG and the number of collected oocytes, the clinical pregnancy, and live birth rates. It also showed a significant decrease in cycle cancellation rates, and dose of gonadotropins needed for ovarian stimulation in GH group.(Li et al., 2017)

A randomized control trial was reported by Altmae et al to assess the role of GH on the uterine receptivity in cases with implantation recurrent failure, and it showed that GH increased the endometrial thickness and receptivity significantly, as well as the pregnancy rates and the live birth rates. (Altmäe et al., 2018)

A trial by Regan et al, was done on 445 follicles to examine the role of GH as an adjuvant therapy during IVF on the expression of FSH receptors, LH receptors, and granulosa cells GH receptors, and it showed that GH increased the density of these receptors on the granulosa cells, as well as it significantly increased the pregnancy rates.(Regan et al., 2018)

A randomized control trial was done by Cui et al to assess the effect of GH on pregnancy rates of patients with thin endometrium undergoing frozen embryo transfer, and it involved 93 cases, and showed that the GH group had

significantly thicker endometrium, with higher implantation rate (24.4% vs 10.5%), and greater clinical pregnancy rates (42.5% vs 18.9%) compared to the control group. (Cui et al., 2019)

A study was done by Cai et al, it assessed the effect of 6 weeks pretreatment with GH on the IVF outcomes, it was done on 380 POR cases, the study is self-controlled, and concluded that GH pretreatment significantly improved the quality of embryos (1.14 ± 1.50 vs 0.11 ± 0.48), significantly decreased the miscarriage rates (18.8% vs 80.0%), and significantly increased the live birth rate (23.5% vs 3.9%). (Cai et al., 2019)

A meta-analysis of fifteen randomized control trials (RCTs) was done to assess the effect of GH as an adjuvant in poor responders undergoing IVF or ICSI, it was done by Peiwen Yang, and it involved 1448 patients. It concluded that GH as an adjuvant improved the live birth rates, the clinical pregnancy rates, and the retrieved oocytes number. It also concluded that GH as an adjuvant reduced the cycles cancellation rate, and the doses of gonadotropins needed for ovarian stimulation. There was a nonsignificant difference in the miscarriage rate between the two groups.(Yang et al., 2020)

A study was conducted by Gong et al on the effect of GH as an adjuvant on oxidative stress and on the IVF outcomes in poor responders, it showed that GH significantly improved the thickness of endometrium on trigger day, the oocyte quality, the number of embryos, the quality of embryos, the implantation, and the clinical pregnancy rates. Additionally, it showed that GH decreased the oxidative stress which was revealed to be higher in poor ovarian responders.(Gong & Zhang, 2020)

A systemic review was reported by Liu et al to assess the effects of GH as an adjuvant on poor ovarian responders in ART, it included 12 studies from 2010 till 2019, the doses of GH in the studies were divided into: 1 IU/D, 4 IU/D, 12 IU/D, 18 IU/D, 24 IU/ alternate day, 0.1 mg/D, and 2.5 mg/D, and it concluded that GH increased the clinical pregnancy rates with odds ratio 1.51, and it showed that whatever the doses of GH used, a beneficial effect on clinical pregnancy rates was demonstrated. Moreover, an improvement in the endometrial thickness, the number of retrieved oocytes, and decrease in the doses of gonadotropins required. It also showed a higher live birth rate, but it was not statistically significant.(F. T. Liu et al., 2021)

A randomized control trial was reported by Zafardoust et al to examine the effect of GH as an adjuvant in antagonist protocol on poor responders, and it concluded that the count of stimulation days was significantly decreased in the GH group, the count of top-quality day 3 embryos was higher and the clinical pregnancy rates were higher. However, there was a non significant difference in the count of gonadotropin ampoules, number of retrieved oocytes, and in the live birth rates.(Zafardoust et al., 2022)

A systemic review was reported by Shang et al to assess the effect of GH on endometrial function and reproductive results in women having IVF, it included 25 studies involving 2424 women, and concluded that GH increased the endometrial thickness , improved endometrial morphology, as well as improved the clinical pregnancy rates significantly . However, it didn't show improvement in the embryo quality(Shang et al., 2022).

GH supplementation was also shown to decrease the rate of aneuploidy in women younger than 40 years by a study which was done by Guo et al, it involved 208 women who had previous PGT-A showing aneuploidy of more than 50% of blastocysts in a previous cycle, and it concluded that GH co-treatment showed significantly higher euploid blastocysts versus before being supplemented with GH (32% vs 9.14%) with odds ratio 4.7, and their embryo transfers showed higher pregnant women and live birth rates. But there was no difference in the euploid rates in women above 40 years.(Guo et al., 2023)

Conclusion

The role of GH as an adjunct in ARTs in POR women is still uncertain, it favors the increase of E2 levels on the HCG day and decreases the stimulation days and the gonadotropins doses. There was a non statistically difference in the count of mature follicles between the 2 sides. GH has a limited reported side effects related to its administration as an adjunct therapy.

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