Impact of Growth Hormone Co-Treatment in Patients with Diminished Ovarian Reserve on *In-Vitro* Fertilisation Outcomes

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ABSTRACT

Objective: To assess the efficacy of growth hormone (GH) co-treatment during controlled ovarian stimulation for *in-vitro* fertilisation (IVF).
Study Design: Descriptive analytical.
Place and Duration of the Study: Department of Gynaecology, Etlik Zubeyde Hanim Training and Research Hospital, Ankara, Turkiye, from January 2010 to 2023.
Methodology: A total of 191 women with diminished ovarian reserve (DOR) who underwent IVF cycles were included in the study. Eighty-nine patients with DOR who received GH during the study period were designated as the study group (Group A), and the 102 patients with DOR who did not receive GH were chosen as the control group (Group B). Chi-square and Mann-Whitney U tests were used to compare groups' variables.
Results: The Group B's basal estradiol and FSH levels were higher than those of Group A. No significant correlation was found in regards to number of 2PNs (pro-nuclear), and the count of collected oocytes. The clinical pregnancy rate of the groups was comparable [(n = 13 (27.7%) *vs*. n = 19 (35.2%), p = 0.417)].
Conclusion: This study has shown that the clinical pregnancy rate did not increase significantly in the GH group.

Key Words: *Controlled ovarian hyperstimulation*, *Growth hormone*, *In-vitro fertilisation*, *Clinical pregnancy rate*.

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INTRODUCTION

In-vitro fertilisation (IVF) has emerged as a widely used and practical approach among the various treatment options.[1-4] However, certain patient populations, such as those with diminished ovarian reserve (DOR), face unique challenges in achieving successful IVF outcomes.[5] DOR, a clinical condition characterised by a decline in the number and quality of a woman's remaining eggs, can significantly impact the success of IVF treatment.[6-9]

One potential strategy to improve IVF outcomes in women with decreased ovarian reserve is using growth hormone (GH) co-treatment during the controlled ovarian stimulation phase.[10-14] GH receptors have been identified in human oocytes and cumulus cells, suggesting a direct influence of GH on oocyte maturation and quality. Previous studies have reported conflicting results regarding the efficacy of GH in patients undergoing IVF.[10-14]

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GH is hypothesised to enhance ovarian response to stimulation, potentially leading to a greater oocyte count and improving embryo quality. While some studies suggest a positive correlation between GH administration and increased pregnancy rates, others have reported inconclusive or even detrimental effects.[10]

This study aimed to evaluate the effect of GH co-treatment on IVF outcomes in patients with DOR.

METHODOLOGY

This study was conducted retrospectively at the Department of Gynaecology, Etlik Zubeyde Hanim Training and Research Hospital, IVF Clinic, Ankara, Turkiye. Decreased ovarian reserve, defined as having a basal FSH value of > 10 IU/L, E2 of > 80 pg/mL, and an AFC of < 7 or AMH levels of < 1.1 ng/mL, was included in the analysis. Those aged 23 years and over, who underwent IVF treatment, and had DOR were included in the study. The exclusion criterion was growth hormone deficiency/disorder.

Patients were evaluated in two groups: Those who received GH co-treatment (Group A) and those who underwent standard IVF treatment without GH (Group B, the control group). Controlled ovarian stimulation was performed using gonadotropins, and the administration of GH was initiated on the

first day of stimulation and continued throughout the stimulation period. Since this study is retrospective, no randomisation was performed for the groups. Some of the patients who were planned to have IVF with a diagnosis of DOR between 2010 and 2023 were treated with GH, and some were not. The choice of GH application was not made according to any criteria and was random. Since the study was retrospective, no sample size calculation was made. All patients between 2010 and 2023 were scanned. In the clinic, all IVF cycles were recorded as electronic data. The patient data created for this study were also recorded from this electronic data set.

A total of 191 women were enrolled. Eighty-nine of them received GH (Group A), while the remaining 102 patients underwent standard IVF treatment without GH (Group B). The primary outcome measures were oocyte count and clinical pregnancy rate.

In the descriptive statistics of the study, continuous variables were presented as median (IQR) and categorical data were presented as frequency (%). Mann-Whitney U was used for continuous variable comparisons of two independent groups, and the chi-square test was used for the comparisons of categorical data. A p-value of < 0.05 was considered statistically significant. The SPSS version 25.0 was used for analyses.

RESULTS

The patient groups were similar in terms of median age and BMI. The median basal FSH level was lower in Group A compared to Group B [7.4 (5.3 – 10.8) *vs*. 8.6 (6.8 – 13.0) IU/l, p = 0.003]. The median basal estradiol level was higher in Group B than in Group A [44.5 (30.8 – 65.2) *vs*. 39.0 (20.0 – 51.8) IU/l, p = 0.011]. However, estradiol levels were comparable, and the p-value was 0.514 (Table I).

The median number of oocytes retrieved was comparable between the group that received GH co-treatment and the group that underwent standard IVF treatment without GH [4 (2 – 11) *vs*. 4 (2 – 6), p = 0.181]. No significant difference was observed related to 2PN embryos (p = 0.403). The clinical pregnancy rate was similar between the two groups [n:13 (27.7%) *vs*. n:19 (35.2%), p = 0.417, Table I].

DISCUSSION

This study evaluated the impact of GH used during ovarian stimulation in women undergoing IVF due to decreased ovarian reserve affected IVF results. According to the findings obtained in the study, it was determined that GH had no effect on IVF results.

Conflicting results have been presented in the literature regarding the contribution of adjuvant GH to IVF outcomes. Ho *et al*. evaluated the effect of GH in three different groups (advanced age, those with repeated IVF failures, and poor responders). It was shown that GH applied for ovarian stimulation in the advanced age group did not increase either the oocyte count or the clinical pregnancy rate. However, it was shown that adjuvant GH increased both the oocyte count and the clinical pregnancy rate in poor responders and those with repeated IVF failures.[14] In a meta-analysis investigating the effects of adjuvant GH administration, it was shown that although it increased the number of oocytes, especially in poor responders, it did not affect clinical pregnancy outcomes.[15] A randomised clinical trial investigating adjuvant GH showed that adjuvant GH increased the number of oocytes retrieved but had no effect on clinical pregnancy rates (18% *vs*. 14%).[10] Similarly, in the present study, it was determined that while the number of oocytes collected was on an increasing trend, pregnancy rates were not changed.

Lattes *et al*. conducted a study with a slightly different design than other studies. They applied low-dose adjuvant GH to 64 women who had not previously received GH and had failed IVF in their next cycle and compared their previous results. They stated that low-dose GH application increased clinical pregnancy rates.[12] However, the controversial aspect of this study was comparing the previous cycles of the same patients because those who had failed IVF in the previous cycle were already included in the study.

Table I: Comparison of the groups that received or did not receive GH.

Parameters	Group A (GH group, n = 89) median (IQR)	Group B (control group, n = 102) median (IQR)	p-value
Age, years	33 (30 – 37)	33 (32 – 35)	0.738
BMI, kg/m^2	25.4 (23.1 – 28.5)	24.9 (22.7 – 28.3)	0.614
Basal FSH, IU/l	7.4 (5.3 – 10.8)	8.6 (6.8 – 13.0)	0.003
Basal estradiol, pg/ml	39.0 (20.0 – 51.8)	44.5 (30.8 – 65.2)	0.011
Duration of stimulation, days	10 (9 – 12)	10 (9 – 11)	0.016
Total gonadotropin dose, IU	3200 (2400 – 3825)	2712 (2100 – 3300)	0.001
Progesterone on day of hCG day, pg/ml	0.36 (0.20 – 0.83)	0.40 (0.26 – 0.60)	0.683
Estradiol on day of hCG day, pg/ml	1073 (504 – 2060)	999 (625 – 1454)	0.514
Number of oocytes retrieved	4 (2 – 11)	4 (2 – 6)	0.181
Number of mature (M2) oocyte number	3 (1 – 7)	3 (1 – 5)	0.721
2PN (pronuclear)	1 (0 – 3)	2 (0 – 3)	0.403
Clinical pregnancy rate, n (%)	13 (27.7)*	19 (35.2)**	0.417

*IQR: Interquartile range, IU: International unit, pg/l: Picograms per millilitre, hCG: Human chorionic gonadotropin. *Calculated through 47 patients, **Calculated through 54 patients. Statistical tests for p-value: All p-values were calculated with Mann-Whitney U test except the comparison of clinical pregnancy rate. A p-value of the clinical pregnancy rate was calculated via Chi-square test.*

In studies investigating the effect of adjuvant GH on IVF outcomes, there are many differences in terms of both the patient groups included and the doses and durations of GH administration. Therefore, in a study investigating whether the duration of adjuvant GH administration affects IVF outcomes, no significant difference was found between GH administration on the second and sixth day of the cycle. Thus, it was suggested that the duration of GH administration would not make any difference.[16]

The mechanisms by which growth hormones affect oocyte development have not been established. Both animal and human studies have shown that GH increases the response of granulosa cells to gonadotropins. This improved response is thought to be related to the production of insulin-like growth factor 1 (IGF-1) and its important role in ovarian steroidogenesis.[17,18] The presence of GH receptors on granulosa cells increases the sensitivity of granulosa cells to GH. Increased proliferation and steroidogenesis lead to increased estrogen, affecting follicle development and oocyte quality.[19]

There were many limitations in this study. The retrospective nature of the study may have caused the different baseline characteristics when creating the study and control groups, which may have created bias. The relatively small number of participants included in the study may have made a statistical weakness. Another limitation was that adjuvant GH was not administered at a standard dose and on standard days.

Despite the limitations, it may provide significant contributions, especially since studies have presented confusing results regarding adjuvant GH administration. Better results may be obtained with well-planned control research groups, and standard dose and day adjuvant GH administration studies.

CONCLUSION

This study investigated the role of adjuvant GH in patients with reduced ovarian reserve, and showed that GH had no effect on the clinical pregnancy rate.

ETHICAL APPROVAL:
Approval was obtained from the Ethical Committee of Etlik Zubeyde Hanim Training and Research Hospital, Ankara, Turkiye (Approval Number: 01, Dated: 22.01.2024).

PATIENT'S CONSENT:
Due to the retrospective nature of the study, patient consent was not needed for this study according to the Ethical Committee's decision

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
PK: Formal analysis.
PK, SD: Conception, data curation, investigation, methodology, and writing of the original draft.
RO, EK, DKK, YU: Writing, reviewing, and editing.
All authors approved the final version of the manuscript to be published.

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