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ARAŞTIRMA / RESEARCH

Relationship between growth hormone levels and ovarian reserves

Büyüme hormonu seviyeleri ile over rezervleri arasındaki ilişki

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Abstract

Purpose: The aim of this study was to investigate the relationship between serum anti mullerian hormone levels and serum growth hormone levels in patients with diminished ovarian reserve and unexplained infertility who are planned for in vitro fertilization.

Materials and Methods: This prospective cohort study includes 154 women and comprises three study groups which include infertile women with diminished ovarian reserve (Group I), women with unexplained infertility (Group II) and healthy women (Group III) as control group. Prospectively recorded patient data comprehended age, body mass index (BMI), antral follicle count (AFC), gravidity and parity, education, occupation, smoking and alcohol use, and laboratory results (Anti-Mullerian hormone (AMH), Growth Hormone (GH), Follicle-Stimulating hormone, Luteinizing Hormone and Estradiol).

Results: The study population consisted of 154 subjects, 52 in Group-I, 52 in Group-II, and 50 in Group-III. The mean women age was higher in DOR group than the other two groups (Respectively with quartiles; 35.5(25-40), 29.5(20-38), 33(19-39)). The other demographic parameters were similar between the groups. Median serum AMH levels was lower in DOR group. Growth hormone levels were similar between the groups..

Conclusion: Our results show that growth hormone has no relationship between ovarian reserve markers. Although lack of relation with ovarian reserve, it's widely known that GH plays major role in granulosa cell function.

Keywords: Growth hormone, diminished ovarian reserve, anti-mullerian hormone, infertility, ovarian function

Öz

Amaç: Bu çalışmanın amacı düşük over rezervi ve açıklanamayan infertilite sebebi ile in-vitro fertilizasyon uygulanacak hastalarda serum Anti-Mulleryen hormon seviyeleri ile büyüme hormonu seviyeleri arasındaki ilişkiyi araştırmaktır.

Gereç ve Yöntem: Bu prospektif kohort çalışması 154 kadını içermektedir. Kadınlar üç ana grup altında incelenmiştir. Grup 1; düşük over rezervi (DOR) nedeni ile, Grup-2 ise açıklanamayan infertilite nedeni ile IVF-ICSI (in vitro fertilizasyon, intrasitoplazmik sperm enjeksiyonu) tedavisi uygulanan kadınlardan, Grup-3 ise sağlıklı kadınlardan oluşmaktadır. Hasta verileri prospektif olarak kaydedilmiş olup, yaş vücut kitle indeksi, antral folikül sayısı, gravida, parite, eğitim, meslek, sigara ve alkol kullanımı ve laboratuvar sonuçları (anti-mullerian hormon (AMH), Büyüme hormonu (GH), folikül sitmulan hormon, luteinizan hormon ve estradiol).

Bulgular: 154 kadından oluşan çalışma popülasyonu; Grup-1 de 52, Grup-2 de 52 ve Grup-3 de 50 kadın olmak üzere gruplandırılmıştır. Ortalama kadın yaşı Grup-1 de diğer iki gruba göre daha yüksek bulunmuştur (Sırasıyla, medyan ve çeyrek değerleri ile, 35.5 (25-40), 29.5 (20-38), 33 (19-39). Diğer demografik veriler her üç grup arasında benzer bulunurken, serum AMH medyan değerleri Grup-1 de daha düşük bulunmuş ancak büyüme hormon seviyeleri üç grup arasında benzer olarak saptanmıştır.

Sonuç: Bu çalışma, serum büyüme hormonu ve over rezerv belirteçleri arasında herhangi bir korelasyon olmadığını göstermiştir. Her ne kadar over rezervi ile GH arasında korelasyon gözlenmese de büyüme hormonunun granuloza hücre fonksiyonlarında önemli rolü olduğu unutulmamalıdır.

Anahtar kelimeler: Anti-mulleryen hormon, büyüme hormonu, yumurtalık rezervi, infertilite

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INTRODUCTION

Infertility is defined as the inability to achieve pregnancy within 12 months of unprotected intercourse in women under 35 years of age and six months in women between 35-40[1]. The rate of infertility is higher among couples with advanced female age[2]. Ovarian reserve (OR) refers to the population of resting primordial follicles in the ovaries and the pool of follicles that can be stimulated by gonadotropins (exogenous or endogenous). Diminished ovarian reserve (DOR) has been associated with poor response to ovarian stimulation, reduced oocyte yield, poor embryo quality, and low pregnancy rates[3]. Anti-Müllerian hormone (AMH) synthesis, first occurring in the granulosa cells of primary ovarian follicles, reaches its peak in preantral and antral follicles with 2-6 mm diameter.[4,5] Therefore, AMH is thought to play a role in regulating ovarian follicle development and is considered a biochemical marker of OR.[6-8] Beyond the AMH, today we also know that Growth Hormone (GH) has positive effects on ovarian reserve via insulin-like growth factor 1 (IGF-1). It was first shown in 1987 by Hsu and Hammond; GH stimulates the proliferation and differentiation of granulosa cells by insulin-like growth IGF-1[9]. While doing that, GH also plays a role in folliculogenesis by preventing apoptosis and follicular atresia in these cells[10]. The prevention of the latter is due to GH regulating the expression of IGF-1, Bcl-2-associated X protein (BAX), and anti-apoptotic Bcl-2 protein[11-13]. GH replacement is currently used as adjuvant therapy in patients with a poor ovarian response to controlled ovarian hyperstimulation protocols as per the Bologna criteria[14-17]. A novel Cochrane meta-analysis, which includes 16 randomized controlled trials about GH role in in vitro fertilization (IVF), concluded that the use of adjuvant GH in IVF treatment protocols slightly increases the number of oocytes retrieved and pregnancy rates in poor responders, while there is an uncertain effect on live birth rates in this group[18]. Although GH has been shown to influence ovarian function, its mechanism of action on OR and relationship with serum GH levels and OR markers of patients with DOR remain ambiguous. While most pre-clinic studies showed that GH impacts ovarian functions via IGF-1 and clinical trials used GH as an adjuvant in IVF treatment protocols, there is still an unknown issue that the relationship between GH and ovarian reserve is still unknown.

We hypothesized that GH activity in the ovary protects the resting follicle pool by reducing the burn-out. If our hypothesis is correct, it may explain the positive effects of GH co-treatment on poor ovarian responder IVF patients.

The present study aims to investigate the relationship between serum AMH levels and serum GH levels in patients with DOR and unexplained infertility who are planned for IVF.

MATERIALS AND METHODS

Study design

This prospective cohort study was conducted at Bursa Uludag University Faculty of Medicine, Department of Obstetrics and Gynecology. Clinical Research Ethics Committee of the Bursa Uludag University Faculty of Medicine approved the investigation with the decision dated 12.02.2019 and numbered 2019-3/15.

Patient enrollment

The study population was prospectively selected from the patients who presented to the Department of Obstetrics and Gynecology, General Gynecology, and Infertility Outpatient Clinic between February 2019 and April 2019. The study protocol was explained to all patients by one of the co-authors (N.D.), and informed consent was obtained from all participants.

The patients were classified into three groups; DOR group (Group-I), unexplained infertility group (Group-II), and healthy control group (Group-III). Group-I consisted of patients, aged 18-40 years, who presented to the infertility outpatient clinic, were planned to undergo IVF, and were diagnosed with DOR as per the Bologna criteria (i.e., abnormal OR test result [AMH <0.5-1.1 ng/mL or antral follicle count (AFC) <5-7], <3 oocyte retrieval with conventional stimulation, age >40, or other risk factors for poor ovarian response]. Group-II included patients, aged 18-40 years, who presented to the infertility outpatient clinic and were planned for IVF due to unexplained infertility. Finally, Group-III comprised healthy controls, aged 18-40, who presented to the general gynecology outpatient clinic for non-infertility reasons, had no history of IVF treatment, subfertility, or infertility but a history of live birth, and possessed AFC >7 in routine ultrasound examination.

Exclusion criteria were <18 or >40 years of age; infertility with a diagnosis of male factor, tubal factor, endometriosis, or anovulation; GH >10 ng/mL; presence of a pituitary tumor, or intracranial extra pituitary tumor; history of chemotherapy or radiotherapy, traumatic brain injury, systemic disease (e.g., sarcoidosis) that may cause pituitary infiltration, or infection (e.g., tuberculosis) that may affect GH levels.

Sample collection and analysis

Blood samples were collected on any day of the menstrual cycle by the clinic nurses. Patients were fasting and at complete rest 30 minutes before blood collection. Anti-Mullerian hormone was analyzed by "Beckman Coulter Access II" enzymatic-immunoassay, United States of America. The detection limit of the test was ≤0.02 ng/ml. Growth Hormone was analyzed by Growth Hormone chemiluminescent immunometric assay, "IMMULITE® 2000 XPi Siemens Healthcare Diagnostic Immunoassay System", Siemens®, Germany.

Statistical analysis

We used SPSS 21.0 software package for statistical analysis. The patients were evaluated in 3 groups as DOR, unexplained infertility, and healthy control. Woman age, Body Mass Index (BMI), Smoking, Alcohol Abuse, Duration of Infertility were analyzed as the demographic parameters. Antral Follicle Count (AFC), Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), Anti-Mullerian Hormone were the parameters to assess the ovarian reserve. Descriptive statistics were expressed in numbers, percentages, minimum-maximum, and mean values. Pearson's chi-squared and Fisher's exact tests were used to investigate the differences between categorical variables. According to distribution, continuous data were given as mean (± standard deviation) or median (minimum-maximum) depending on whether a parametric or non-parametric test was used. The t-test was used for parametric data analysis of variance, and the Mann-Whitney U test for non-parametric data. Categorical data were given as number and frequency (%), and Pearson's chi-squared test was used for their analysis. We performed the assessments between three groups by the Kruskal-Wallis test and pairwise subgroup comparisons by the Mann-Whitney U test. The relationship between measurements was investigated by correlation analysis. Besides, Spearman's rank correlation coefficient (rs) was calculated. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 163 subjects were included in the study, but 154 remained after 4 healthy controls with AMH <1.1 ng/mL, and 5 patients with GH >10 ng/mL were excluded. Prospectively recorded patient data comprehended age, body mass index (BMI), antral follicle count (AFC), gravidity and parity, education, occupation, smoking and alcohol use, and laboratory results.

The subjects were divided into three groups as DOR (Group-I), unexplained infertility (Group-II), and healthy control (Group-III). The study population consisted of 154 subjects, 52 in Group-I, 52 in Group-II, and 50 in Group-III.

The median age was 35.5 (25-40) in Group-I, 29.5 (20-38) in Group-II, and 33.0 (19-39) in Group-III, and the difference between the groups was statistically significant (p<0.001). The mean BMI was 23.55 in Group-I, 23.1 in Group-II, and 24.0 in Group-III (p=0.751). Besides, there was no significant difference between the groups by education and occupation. Furthermore, the rate of smokers was 19.2% in Group-I, 11.5% in Group-II, and 16% in Group-III, with no significant difference (p=1.00). Also, there was no statistical significance regarding alcohol use among the subjects (p=1.00). (Table-1)

Table-1. Demographic parameters of the groups

	Group-I (n=52)	Group-II (n=52)	Group-III (n=50)	p
Age (years)*	35.5 (25-40)	29.5 (20-38)	33 (19-39)	**<0.001**
BMI (kg/m²)*	23.55 (17.2-35.3)	23.1(17.2-39)	24(18-30)	0.751
Smoking Rate (%)	10 (19.2%)	6 (11.5%)	8 (16%)	1.00
Alcohol Use (%)	1 (1.9%)	0	1 (2%)	1.00

*Parameters with median (min-max) values. BMI: Body Mass Index.

The mean AMH level was 0.7 ng/mL (0.01-1.1 ng/mL) in Group-I, 2.7 ng/mL (1.45-7.9 ng/mL) in Group-II, and 2.4 ng/mL (1.31-8.8 ng/mL) in Group-III, with a significant difference (p<0.001). In addition, the mean GH level was 0.625 ng/mL (0.005-9.09 ng/mL) in Group-I, 0.32 ng/mL (0.005-6.8 ng/mL) in Group-II, and 0.163 ng/mL (0.005-9.1 ng/mL) in Group-III, with no significant difference (p=0.129). (Table-2).

Table-2. Basal hormone levels of patients with infertility.

	Group-I (n=52)	**Group-II (n=52)**	**p**
FSH (IU/L)*	5.78 (0.98-35.42)	4.8 (1.8-11.36)	0.21
LH (IU/L)*	2.51 (0.62-12.59)	2.77 (0.98-12.71)	0.583
E2 (ng/ml)*	41 (15-267)	45 (24-191)	0.661

*Parameters with median (min-max) values. FSH: Follicle Stimulating Hormone, LH: Luteinizing Hormone, E2: Estradiol.

The mean follicle-stimulating hormone (FSH) level was 5.78 IU/L in Group-I and 4.8 IU/L in Group-II, with no significant difference (p=0.21). Besides, the mean luteinizing hormone (LH) level was 2.51 IU/L in Group-I and 2.77 IU/L in Group-II, again with no statistical significance (p=0.583). Furthermore, the mean level of estradiol (E2) was 41 ng/L in Group-I and 45 ng/L in Group-II, also with no significance (p=0.661). (Table-3).

Table 3. Comparison of serum AMH and GH levels between the groups.

	Group-I (n=52)	**Group-II (n=52)**	**Group-III (n=50)**	**p**
AMH* (ng/dl)	0.7 (0.01-1.1)	2.7 (1.45-7.9)	2.4 (1.31-8.8)	**<0.001**
GH* (ng/ml)	0.625 (0.005-9.09)	0.32 (0.005-6.8)	0.163 (0.005-9.1)	0.129

*Parameters with median (min-max) values. AMH: Anti-Mullerian Hormone, GH: Growth Hormone

Table 4. Correlation analysis of variables between GH levels in all Groups.

	Group – I		**Group – II**		**Group – III**	
	r	p	r	p	r	p
Age	-0.367	**0.008**	-0.038	0.79	-0.050	0.73
AMH	0.081	0.567	-0.092	0.516	-0.189	0.188
FSH	-0.037	0.796	-0.010	0.945	N/A	N/A
LH	0.116	0.413	0.048	0.736	N/A	N/A
E2	0.314	**0.028**	0.311	**0.025**	N/A	N/A
AFC	0.03	0.832	-0.111	0.432	N/A	N/A
Infertility duration	-0.158	0.264	-0.038	0.788	N/A	N/A
BMI	-0.532	**<0.001**	-0.210	0.135	-0.095	0.513

AMH: Anti-Mullerian Hormone, FSH: Follicle-Stimulating Hormone, LH: Luteinizing Hormone, E2: Estradiol, AFC: Antral Follicle Count, BMI: Body Mass Index, N/A: Not Applicable

The primary aim of our study was to investigate the correlation between serum GH and AMH levels in all patients' groups. We observed no significant correlation between GH and AMH levels (r 0.081, p=0.567) in Group-I, and none between GH levels and FSH, LH levels, infertility duration, and AFC (p=0.796, p=0.413, p=0.264, and p=0.832, respectively). (Table-4).

We observed a statistically significant negative correlation between GH levels and age in Group-I (r=–0.367**, p=0.008), as shown in Figure-1a. Our analysis also yielded a significant positive correlation

between GH and E2 levels in Group-1 (r=0.314*, p=0.028), as shown in Figure-1b. In addition, we detected a statistically significant negative correlation between GH levels and BMI values in Group-I (r=–0.532**, p<0.001). (Figure-1c).In Group-II, we observed no significant correlation between GH levels and AMH, FSH, LH levels, age, BMI, and infertility duration. However, our analysis revealed a positive correlation between GH and E2 levels (r=0.311**, p=0.025). (Table-4).

In Group-III, there was no significant correlation between GH levels and age, AMH, and BMI (p=0.73, p=0.188, and p=0.513, respectively). The other ovarian reserve parameters (FSH, LH and E2) did not evaluated in fertile-healthy controls. (Table-4).In the whole study population, we found no statistically significant correlation between GH levels and age. However, a subgroup analysis in Group-I yielded a significant negative correlation between GH levels and age (r=–0.367**, p=0.008). Thereupon, we classified the Group-I subjects into four groups: 18-22 years of age (I), 23-28 (II), 29-34 (III), and 35-40 (IV) and performed further analysis to determine the age group produced a significance. Our pairwise comparison revealed a significant difference between the GH levels in subgroups II and IV (p=0.009).

DISCUSSION

The present study mainly investigated the relationship between the levels of GH and AMH, a marker of OR, in infertile patients diagnosed with DOR but determined no statistical significance in this regard. As far as we can find, there is no study in the literature on the correlation between GH levels and OR. However, various studies report an increased number of oocytes retrieved and improved IVF pregnancy outcomes with the addition of GH adjuvant therapy to controlled ovarian stimulation protocol in patients with poor ovarian response, suggesting that GH could play a role in OR.[19] So, we focused on the correlation between GH and AMH levels in DOR patients.

In our study population, the difference between the groups by age was statistically significant, as expected, due to the advanced age of the DOR patients. GH levels are known to decrease with age[20,21]. but we observed that the rate of decrease was low in the age range (18-40) of our subjects, thereby not significantly affecting the results.

A comparison of AMH levels in our three groups of subjects revealed a statistical significance, particularly regarding DOR group. This result was in line with studies indicating low AMH levels in patients with DOR[22,23]. However, there was no significant difference between the three groups by GH levels. We think that the factors influencing this outcome require elaboration. First, serum GH levels are typically different in the follicular and luteal phases of the menstrual cycle[24]. Second, GH secretion increases in situations such as stress, physical exercise, trauma, and hunger. Third, a diet high in carbohydrates and fats inhibits GH release[25]. Therefore, to prevent these from affecting our results and standardize procedures, all patients provided test material early in the morning, before breakfast.

Although the AMH levels were significantly different between the groups, we found no significant correlation regarding GH and AMH levels. Studies have shown the effect of GH on ovarian cell functions,[24] but have not demonstrated the direct influence of GH on OR, independent of its IGF-1-mediated effect. Our analysis yielded a significant negative correlation between GH levels and age in DOR patients. The direct effect of advanced age on GH levels and the decrease in OR with age have probably led to this result.

We found a significant positive correlation between GH levels and E2 levels. GH regulates granulosa cell functions through IGF-1, which is responsible for most peripheral effects on these cells. Besides, GH increases E2 and progesterone production in granulosa cells via FSH and stimulates androgen secretion in theca cells via LH. The above result in our study is in line with studies indicating that GH increases E2 production in granulosa cells via IGF-1[26,27]. In Group-I, there was a significant negative correlation between GH levels and BMI values. This result accords with studies citing high BMI as a potent inhibitor reducing spontaneous GH release in obese cases with increased abdominal visceral adiposity[28,29].

While our results indicated that growth hormone has no relationship with ovarian reserve, many studies show the potential benefit of co-treatment of GH on IVF results in patients with poor ovarian response. However, it has no direct relation with OR; the possible positive effect on ovarian response may be related with proliferation and differentiation of granulosa cells by IGF-1. A pilot study published recently investigated the relationship between oocyte

quality and follicular GH and IGF-1 levels[30]. The results show that levels of GH and IGF1 were higher in the normal oocyte cohort than in the abnormal oocyte cohort. Also, the fertilization rate was lower in these abnormal oocytes with low follicular GH and IGF-1 levels. That study was the first to show the correlation between follicular GH and IGF1 levels, and oocyte cohort morphology has not previously been evaluated in IVF. When the results of this study and our study are evaluated together, the question arises whether plasma growth hormone and follicle growth hormone levels are the same? There are limited studies investigated the correlation between follicular and plasma GH levels, and the results were conflicting[31-35]. The main reason for this conflict may be the autocrine role of the IGF-1, which has been well established. It's known that granulosa cells of the developing follicles synthesize IGF-1[36].

A recent study about GH and infertility, investigated the pregnancy results depending on the serum IGF-1 levels (Groups; <25th percentile, 25th-75th percentile, >75th percentile)[37]. The cycle cancellation rates were highest in the IGF-1 <25th percentile group. They concluded that IGF-1 levels affect IVF outcomes. GH treatments, therefore, may be effective only with low IGF-1. The study involved a secondary outcome which is also related to our study. Similar to our results, AMH levels were comparable between the IGF-1 study groups. The ovarian reserve did not change depending on the IGF-1 levels in all patients.

Our study has some strengths and limitations. Firstly, this is a pilot study which is the first to show relationship between GH and OR as a primary outcome with healthy controls. Prospective design, presence of healthy controls strengthen the power of our study. On the other hand, lack of sample size and power analysis limits the results. Lack of follicular fluid GH levels made it difficult to interpret the results.

In conclusion, the present study evaluated serum GH and AMH levels in DOR patients and found no statistically significant correlation. Currently, there are many unresolved questions regarding the effects of GH on OR. In light of available literature and our results, we suggest further investigation on GH levels with multiple measurements due to pulsatile secretion; IGF-1 levels responsible for the peripheral effects of GH; intracycle variability; gonadotropin doses used in IVF treatment; the relationship of GH with embryological parameters; and the effect of GH administration on the follicular fluid during oocyte retrieval.

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