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The Relationship Between Serum Growth Differentiation Factor-15 Levels and Clinical Outcomes in Infertile Women Receiving In-vitro Fertilization Treatment

İn-vitro Fertilizasyon Tedavisi Alan İnfertil Kadınlarda Serum Büyüme Farklılaşma Faktörü-15 Düzeyi ile Klinik Sonuçlar Arası İlişki

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The Relationship Between Serum Growth Differentiation Factor-15 Levels and Clinical Outcomes in Infertile Women Receiving In-vitro Fertilization Treatment

Abstract

Objective: It has been reported in many studies that Growth Differentiation Factor-15 (GDF-15) has an important role in physiological or pathological processes. This study was aimed to investigate the role of GDF-15 in infertility and its treatment outcomes.

Material and Method: According to their ovarian reserve characteristics, 88 infertile women were divided into three groups: normal ovarian reserve (NOR) (n= 42), diminished ovarian reserve (DOR) (n= 22), and polycystic ovary syndrome (PCOS) (n= 24). Serum estradiol (E_2), follicle-stimulating hormone (FSH), luteinizing hormone (LH), anti-Mullerian hormone (AMH), and GDF-15 levels were measured in their serum. The antagonist protocol patients' total oocyte, meiosis II (MII) oocytes, embryo count, and clinical pregnancy rates were documented and compared.

Results: In terms of serum GDF-15 concentrations, there was no statistically significant difference among the mean values of the three study groups. The mean FSH level at baseline was substantially higher in the DOR group compared to the PCOS group *(p=0.006*)*. The median serum AMH levels of all three groups were found to be statistically different *(p=<0.001*)*. When the groups were compared in terms of averages of total oocytes, MII oocytes, and embryos, it was observed that the NOR group and the PCOS group both had higher values than the AOR group *(p=0.001*)*.

Conclusion: In our study, a significant and strong relationship was found between serum GDF-15 level and the number of embryos formed as a result of in-vitro fertilization (IVF) treatment. Thereby, serum GDF-15 level may be considered to be a biomarker for predicting IVF clinical outcomes.

Keywords: GDF-15, growth Differentiation Factor- 15, IVF, infertility, ovarian reserve

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Özet

Amaç: Büyüme Farklılaşma Faktörü-15 (GDF-15)'in fizyolojik veya patolojik süreçlerde önemli rolu olduğu birçok çalışmada bildirilmiştir. Bu çalışmada GDF-15'in infertilitedeki rolünün ve tedavi sonuçlarının araştırılması amaçlandı.

Gereç ve Yöntem: Çalışmaya 88 infertil kadın dahil edildi ve over rezerv özelliklerine göre çalışma populasyonu üç gruba ayrıldı. Bunlar; normal over rezervi (NOR) grubu (n= 42), azalmış over rezervi (AOR) grubu (n= 22), polikistik over sendromu (PKOS) grubu (n= 24). Serumlarında östradiol (E2), follikül uyarıcı hormon (FSH) ve luteinize edici hormon (LH), anti-müllerian hormon (AMH) ve GDF-15 düzeyleri ölçülmüştür. Antagonist protokolü ile tedaviye alınan hastaların total oosit, mayoz II (MII) oosit, embriyo sayısı ve klinik gebelik oranları dökümente edilmiştir.

Bulgular: Serum GDF-15 konsantrasyonları dikkate alındığında her üç çalışma grubunun ortalama değerleri arasında istatistiksel yönden anlamlı bir fark bulunmamıştır. Bazal FSH ortalaması AOR grubunda PKOS grubundaki katılımcılara göre anlamlı düzeyde yüksekti *(p=0,006*)*. Her üç grubun serum AMH düzey ortancası istatistiksel anlamlılıkta farklı bulunmuştur*(p=<0,001*)*. Total Oosit, MII oosit ve embriyo ortalama karşılaştırmalarında NOR grubu AOR grubuna göre *(p=<0,001*)* ve PKOS grubu AOR grubuna göre (p=<0,001*) daha yüksek değerlere sahiptir. Gruplar total oosit, MII oosit ve embriyo ortalamaları bakımından karşılaştırıldığında NOR grubu AOR grubuna göre *(p=<0,001*)*, PKOS grubu da AOR grubuna göre (p=<0,001*) daha yüksek değerlere sahip olduğu görüldü.

Sonuç: Çalışmamızda serum GDF-15 düzeyinin in-vitro fertilizasyon (İVF) tedavisi sonucunda oluşan embriyo sayıları arasında anlamlı ve güçlü bir ilişki saptanmıştır. Dolayısı ile serum GDF-15 düzeyi İVF klinik sonuçlarını öngören bir biyobelirteç olabileceği düşünülebilir.

Anahtar Sözcükler: Büyüme farklılaşma faktörü-15, GDF-15, İVF, infertilite, over rezervi

Introduction

The term ovarian reserve generally refers to a woman's reproductive capacity, specifically associated with the quantity and quality of her oocytes. Ovarian reserve is a complex clinical condition that is influenced by age, genetics, and environmental factors (1). Identifying infertile women at risk of diminished ovarian reserve (DOR) is one of the purposes of using ovarian reserve tests in clinical practice. It is also known that patients with DOR respond significantly less effectively to ovulation induction and in-vitro fertilization (IVF) treatments. It is also aimed at determining the probability of the development of ovarian hyperstimulation syndrome before treatment. By assessing ovarian reserve comprehensively and precisely, it aims to reduce the number of unnecessary treatments given to patients who are incorrectly classified as DOR but have normal ovarian reserve (NOR) (2).

Ovarian reserve tests applied to patients in clinical applications are performed with both biochemical tests and ultrasonographic imaging. The measurement of serum anti-Mullerian hormone (AMH) level and the count of total antral follicles count (AFC) in the extant ovaries are the most generally preferred and most reliable ovarian reserve tests. It has been determined in many studies that both tests are of equivalent value (3). Neither AMH nor AFC correlate strongly with qualitative outcomes such as oocyte quality, clinical pregnancy rate, or live birth rate (4). Bootcov et al. achieved the first cloning of Growth Differentiation Factor-15 (GDF-15) from a human monocytic cell line in 1997. GDF-15 is also an autocrine protein that modulates lipopolysaccharide-activated macrophages by inhibiting the production of tumour necrosis factor (TNF).Consequently, its initial name was GDF-15 Macrophage Inhibitory Cytokine-1 (MIC-1) (5). Due to the diversity of biological functions in both physiological and pathological processes, GDF-15 has been referred to by numerous other names in subsequent studies (including Nonsteroidal Anti-Inflammatory Drug Activated Gene-1, Placental Transformation Growth Factor, Prostate-Derived Factor, and Placental Bone Morphogenic Protein (6). GDF-15 Transforming Growth Factor (TGF) is a member of the superfamily that exhibits significant functional distinctions from its other members (7). In general, GDF-15 functions as a hormone, a cytokine induced by stress, or a stress-sensitive blood factor (8). The expression of GDF-15 was mostly detected in the placenta and prostate of healthy individuals (9). GDF-15 is also expressed at low levels in the mammary glands, kidney, liver, lung, colon, pancreas, endometrium, and peripheral and central nervous systems (10).

According to studies in the known literature, GDF-15 cardiovascular diseases (heart failure, acute coronary syndrome), kidney diseases (acute kidney disease, diabetic nephropathy, IgA nephropathy, amyloidosis, idiopathic membranous nephropathy), liver diseases (non-alcoholic fatty liver disease, liver cirrhosis, hepatitis C infection), metabolic syndrome, diabetes mellitus, sepsis, and iron metabolism-related anemia are known to be significantly associated with many medical conditions (11). Despite the fact that the functions of GDF-15 in a variety of physiological or pathological processes have been reported, there is currently no research on infertility and GDF-15 treatments.

Therefore, the purpose of this study was to investigate the potential relationship between GDF-15 and treatment outcomes in infertile women undergoing IVF treatment based on their ovarian reserve type.

Material and Method

Study population and design

This prospective observational study was conducted at the Hitit University Faculty of Medicine IVF Centre between January 1, 2022, and March 31, 2023. The Hitit University Ethics Committee approved this study, and it complies with the Declaration of Helsinki (Decision No. 493 dated October 13, 2021).

All participants were informed, and consent was obtained prior to the study. All participants' medical characteristics relevant to the study were recorded during the initial interview. The exclusion criteria of the study were the presence of previous pelvic surgery, endometriosis, adnexal mass, chemotherapy, radiotherapy, smoking, systemic diseases that may affect fertility potential, and drug use.

The body mass index (BMI) was calculated as weight (kg/height (m2)) using the height and weight measurements obtained during the initial physical examination. Pelvic evaluation and AFC were performed using an ultrasonography device with a transvaginal 7.5 MHz probe (Toshiba Xario 100, Toshiba Medical System Co., Nasu, Japan) during the early proliferative phases of the participants' menstrual cycles.

"Unexplained infertility" is defined as the absence of an identifiable cause of infertility after at least 12 months of trying to get pregnant in an evaluation (12). The most widely accepted criteria for the diagnosis of "polycystic ovary syndrome (PCOS)" are the Rotterdam Criteria, prepared by the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine (13). According to the Rotterdam Criteria, the diagnosis

of PCOS requires the presence of at least two of the following features:
1- Anovulation or oligoovulation
2- The presence of clinical and/or biochemical indicators of hyperandrogenism
3- Ultrasonography demonstrates polycystic ovary morphology [12 or more follicles 2-9 mm in diameter per ovary and/or increased ovarian volume (over 10 ml)]
The diagnosis of DOR is established using the Bologna criteria (14). According to these requirements, the definition of DOR must include at least two of the following:
1- Maternal age is advanced (>40 years)
2- Obtaining fewer than three oocytes following standard ovarian stimulation
3- Abnormal ovarian reserve tests (AFC < 5-7 and/or AMH level < 1.1 ng/ml)
Consequently, 88 infertile female participants who were scheduled to undergo IVF treatment and who met the inclusion criteria were accepted for participation in the study. The study population was classified into three study groups according to the ovarian reserve characteristics defined above.
(i) NOR group (infertile women diagnosed with unexplained infertility, n= 42)
(ii) DOR group (infertile women diagnosed with DOR, n = 22)
(iii) PCOS group (infertile women diagnosed with PCOS, n = 24)

Sample collection and measurements

Venous blood samples were taken from all participants between 9:00 and 10:00 in the morning after an 8–10 hour fasting night on days 2-4 of the menstrual cycle. Blood samples were centrifuged at 1000 x g for 20 minutes for hormonal analysis. The serum concentrations of estradiol (E2), follicle stimulating hormone (FSH), and luteinizing hormone (LH) were measured daily using an autoanalyzer (Cobas 6000, E601, Roche Diagnostics GmbH, Mannheim, Germany) and the electrochemiluminescence immunoassay (ECLIA) technique. After centrifugation, blood samples were frozen at -80 °C for measurements of AMH and GDF-15. AMH levels were measured using ECLIA on an autoanalyzer (Cobas 6000, E601, Roche Diagnostics GmbH, Mannheim, Germany), whereas GDF-15 levels were measured using ELISA (Bioassay Technology Laboratory, Shanghai, China).

Ovarian stimulation and oocyte retrieval

Controlled ovarian stimulation (COS) of infertile women undergoing IVF with the antagonist protocol started with subcutaneous injections of recombinant FSH (Gonal-F, Merck Serono, S.p.A., Modugno, Italy) in individualized doses (150-300 IU daily) on days 2 or 3 of the menstrual cycle. During the treatment's follow-up, transvaginal ultrasonography and serum E2 levels were both used to monitor follicle development. When at least one of the responding follicles reached a diameter of 13 mm, daily subcutaneous injections of 250 mcg cetrorelix (Cetrotide, Merck, Pierre Fabre Medicament Production, Idron, France) were given. Ovulation was triggered by a single subcutaneous injection of 250 mcg of recombinant human choriogonadotropin (rhCG) (Ovitrelle, Merck Serono, S.p.A., Modugno, Italy) when at least three follicles measuring 18 mm in diameter were obtained as a result of COS. After 34 to 36 hours of ovulation induction, oocyte retrieval was performed. Following this procedure, a capsule containing 200 mg of natural progesterone (Progestan, Kocak Farma, Istanbul) was applied vaginally three times per day to support the luteal phase.

The number of retrieved oocytes, the number of meiosis II (MII) oocytes, the number of embryos formed, and the clinical pregnancy rates were documented. The presence of pregnancy was determined by measuring the level of hCG in the serum 12 to 14 days after oocyte retrieval. The presence of an intrauterine gestational sac and the detection of a fetal heartbeat by ultrasonography were used to define clinical pregnancy.

Statistical Analysis

The statistical analyses were performed using *Statistical Package for the Social Sciences version 15.0* (SPSS Inc., Chicago, IL). The Shapiro-Wilk test was used to determine the distribution of the data. One-way ANOVA analysis of continuous and normally distributed variables was preferred and expressed as mean ± standard deviation (SD). The Kruskal Wallis test was used for the analysis of continuous variables that did not show normal distribution and was shown as the median (minimum-maximum). Categorical variables are represented as percentages (numbers). Using Chi-square or Fischer-Exact tests, the differences between categorical data were evaluated. In this analysis of correlations between measurements, Pearson or Spearman correlation analyses were utilized as appropriate. P values below 0.05 were regarded as statistically significant.

Results

This study was accomplished with the participation of 88 infertile women who conformed to the inclusion criteria and received IVF treatment. Table I compares the demographic and clinical characteristics of the population subject to study. The comparison of the mean ages of the different study groups found statistically significant differences between the NOR

Table I. Comparison of demographic and clinical characteristics of study groups

	NOR Grubu (Grup 1) (n=42)	DOR Grubu (Grup 2) (n=22)	PKOS Grubu (Grup 3) (n=24)	*p*		
				1 vs 2	1 vs 3	2 vs 3
Age (years)	29.8±5.2	34.6±5.2	29.6±4.4	*0.001**	*0.984*	*0.002**
VKİ (kg/m²)	24.7 (23.1-28.4)	24.9 (21.9-28.2)	23.6 (21.9-27.1)	*0.427*		
BAsal E2 (pg/mL)	42.1 (34.7-55.1)	47.7 (33.1-63.4)	49.2 (32.7-57.8)	*0.620*		
Basal FSH (IU/L)	7.2±1.3	9.4±1.4	5.4±1.2	*0.121*	*0.249*	*0.006**
Basal LH (IU/L)	5.7 (4.3-7.3)	6.3 (3.7-10.5)	7.8 (4.7-10.9)	*0.150*		
AMH (ng/ml)	2.8±1.4	0.6±0.2	7.3±2.1	*<0.001**	*<0.001**	*<0.001**
GDF-15	390.0±125.6	268.4±120.3	331.5±110.0	*0.696*		
Number of oocytes retrieved (n)	9.6±2.6	4.8±1.3	12.0±4.4	*<0.001**	*0.140*	*<0.001**
MII oocyte number (n)	7.1±1.7	3.5±1.9	8.7±2.7	*0.011**	*0.365*	*<0.001**
Number of embryos (n)	4.29±1.4	1.68±0.4	5.88±1.8	*0.016**	*0.183*	*<0.001**
Clinical pregnancy (n,%)	14 (33.3%)	3 (13.6%)	11 (45.8%)	*0.078*	*0.314*	*0.026**

ABBREVIATIONS: NOR: Normal ovarian reserve, DOR: Diminished ovarian reserve, PCOS: Polycystic ovary syndrome, BMI: Body mass index, E2: Estradiol, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, AMH: anti-Mullerian hormone, GDF: Growth diffentiation factor, MII: Meiosis II. *$p<0.05$ value was accepted as statistical significance

and DOR groups, as well as the NOR and PCOS groups ($p=0.001$ and $p=0.002$, respectively).

The mean age of the DOR group was higher than that of the NOR and PCOS groups, as predicted. There was no statistically significant difference ($p>0.05$) between the medians of BMI, basal E2, and basal LH levels between the three study groups. Nevertheless, the mean FSH at baseline was considerably higher in the DOR group compared to the PCOS group ($p=0.006$). Consistent with previous findings, the median serum AMH levels in all three groups exhibited statistically significant differences ($p<0.001$, $p<0.001$, $p<0.001$). The PCOS group has the greatest AMH levels, whereas the DOR group has the lowest AMH levels. Regarding serum GDF-15 concentrations, none of the three study groups exhibited statistically significant mean values ($p>0.05$). The NOR group had higher values for the mean total number of oocytes, MII numbers, and embryos obtained after the *Oocyte pick-up* procedure than the DOR group ($p0.001$, $p=0.011$, and $p=0.016$, respectively). Once more, it has been shown that the PCOS group exhibits significantly higher values compared to the DOR group for the given parameters ($p<0.001$, $p<0.001$, and $p<0.001$). Statistically, only participants in the PCOS group had a significantly higher clinical pregnancy rate than those in the DOR group ($p=0.026$).

The analysis of the connection between serum GDF-15 level and other research parameters is displayed in Table II. Serum GDF-15 levels were not correlated with age, BMI, serum E2, FSH, or AMH levels. It was determined that study parameters such as the number of oocytes retrieved, the number of MII oocytes, and the clinical pregnancy rate were not statistically significantly correlated with serum GDF-15 levels.

However, only in the DOR group were GDF-15 levels significantly and moderately correlated ($r=0.430$, $p=0.046$) with serum LH level and significantly and highly correlated ($r=0.633$, $p=0.001$) with the number of embryos.

Discussion

The objective of this study was to examine the correlation between serum GDF-15 levels and clinical outcomes among women undergoing IVF therapy, categorized by their ovarian reserve types. In terms of serum GDF-15 levels, there was no significant difference between the three ovarian reserve groups. However, statistically significant, and positive correlations were found with serum GDF-15 concentration, serum LH level, and embryo number only in women in the DOR group. Based on our analysis, no other study with regard to this subject matter has been identified in the existing literature.

In some animal studies, an increase in plasma GDF-15 levels has been linked to mitochondrial dysfunction and excessive oxidative activity (15,16). An increase in GDF-15 expression is observed as a result of the increase in reactive oxygen species caused by ageing (17). Therefore, it has been suggested that GDF-15 may serve as a biomarker for biological ageing and mitochondrial dysfunction in healthy

humans (2,17,18). GDF-15 is thought to function as a protective mechanism against tissue damage (19). Multiple research studies have linked ageing to chronic low-grade inflammation (20). Unfortunately, the results of our investigation did not reveal a statistically significant association between blood GDF-15 levels and the study groups.

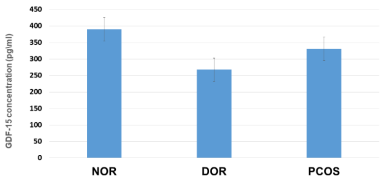
Table II. Correlation analysis of serum GDF-15 level with other study parameteopurs

	NOR Grubu (n=42)		DOR Grubu (n=22)		PKOS Grubu (n=24)	
	r	*p*	*r*	*p*	*r*	*p*
Age (years)	-0.238	*0.129*	-0.035	*0.878*	-0.393	*0.057*
VKİ (kg/m²)	0.150	*0.343*	-0.308	*0.163*	0.113	*0.600*
Basal E2 (pg/mL)	0.037	*0.817*	0.287	*0.195*	0.025	*0.908*
Basal FSH (IU/L)	-0.081	*0.410*	0.183	*0.415*	0.153	*0.477*
Basal LH (IU/L)	-0.024	*0.879*	0.430	*0.046**	0.006	*0.979*
AMH (ng/ml)	0.086	*0.589*	0.415	*0.055*	0.025	*0.908*
Number of oocytes retrieved (n)	0.097	*0.543*	-0.090	*0.691*	-0.032	*0.883*
MII oocyte number (n)	0.038	*0.812*	0.200	*0.373*	0.027	*0.900*
Number of embryos (n)	0.128	*0.420*	0.633	*0.002**	0.124	*0.565*
Clinical pregnancy	-0.216	*0.169*	0.093	*0.680*	0.228	*0.284*

NOR: Normal ovarian reserve, DOR: Diminished ovarian reserve, PCOS: Polycystic ovary syndrome, BMI: Body mass index, E2: Estradiol, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, AMH: anti-Mullerian hormone, GDF: Growth diffentiation factor, MII: Meiosis II. *p<0.05 value was accepted as statistical significance.

It is known that there is an increase in GDF-15 expression in response to different stimuli such as oxygen deprivation (such as oxidative stress, hypoxia, and anoxia) and acute tissue damage (21,22)GDF-15 functions as an autocrine anti-inflammatory and tissue repair factor that is released in proportion to acute and chronic tissue injury, although the exact mechanism is unknown (21–23). In this context, the hypothesis that the DOR status of infertile women and the perception of tissue damage by their bodies may exist. Thus, as a result of this perception, a compensatory mechanism may have been found to correlate with the increase in GDF-15 level and the number of embryos in women with DOR, as in our study.

Figure 1. GDF-15 levels of the groups



NOR: Normal ovarian reserve, DOR: Diminished ovarian reserve, PCOS: Polycystic ovary syndr

Under physiological conditions, the only tissue with a high GDF-15 concentration is the placenta. Both the placenta and fetal membranes contain GDF-15. This indicates that GDF-15 has a role at the maternal-fetal interface (24). In addition, the hypothesis that GDF-15 is effective in the feto-maternal immunotolerance process is accepted (25). Plasma concentrations of GDF-15 reach high levels during pregnancy and are believed to play a crucial role in maintaining pregnancy (26). According to numerous studies, reduced GDF-15 levels in early pregnancy can predict an abortion (27,28)noted to have a confirmed viable fetus, but subsequently miscarry. METHODS We performed a prospective cohort study, recruiting 462 women in the first trimester presenting to EPAU and had fetal viability confirmed by ultrasound. We obtained plasma samples on the same day and measured MIC-1, PAPP-A and human chorionic gonadotrophin (hCG. In this study, we found a significant and strong correlation between serum GDF-15 levels and the number of embryos formed in women in the DOR group.

One notable disadvantage of this study is the only assessment of GDF-15 in the serum of participants, which was mostly due to financial limitations. Ideally, serum and follicular fluid samples should be used to test GDF-15 together. Thus, correlations between serum and follicular fluid levels of GDF-15 will also be observed. One further limitation of this research is the comparatively limited sample size of participants. Nonetheless, this is the first known study to investigate the correlation between serum GDF-15 levels and the clinical outcomes of IVF treatments. This aspect of our investigation makes it significant.

According to the study's findings, there is a significant and strong correlation between serum GDF-15 concentration and the number of embryos formed as a consequence of IVF treatment. The serum GDF-15 level can therefore be considered a biomarker for predicting the clinical outcomes of IVF treatments. It is evident that conducting prospective research with a substantial number of participants is

necessary in order to establish significant associations with clinical pregnancy outcomes.

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