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Correlation of serum leptin and ghrelin levels with endocrine and reproductive parameters in women with clomiphene citrate resistant polycystic ovary syndrome

Klomifen sitrat rezistant polikistik over sendromlu hastalarda ghrelin ve leptin düzeylerinin endokrin ve reprodüktif parametrelerle korelasyonu

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Abstract

Objective: To investigate the changes in serum ghrelin and leptin levels in patients with clomiphene-resistant polycystic ovary syndrome (PCOS).

Materials and Methods: Thirty-five patients who could not achieve ovulation or pregnancy despite using 150 mg/day of clomiphene citrate (CC) participated in the study. Thirty-five patients who were compatible with the study group in terms of age and body mass index (BMI) but did not have clinical and laboratory findings of PCOS constituted the control group. On the third day of the cycle, in addition to the basal hormone profile, ghrelin and leptin levels were also measured. Patients in both groups went to IVF/ICSI. Basal hormone values, leptin, ghrelin, metabolic, demographic parameters, and clinical pregnancy rates were correlated.

Results: Patients in both groups were recorded to be similar in terms of age (29.4±0.11 vs 28.5±7.30), BMI (24.3±3.07 vs 23.8±1.55), and infertility time (6.14±4.30 vs 6.03±1.28). Serum ghrelin levels of the PCOS group were significantly lower than the control group (0.48±2.21 vs 1.19±4.02) Serum leptin levels of the PCOS group were significantly higher than the control patients (45.6±304 vs 16.5±0.32). Serum leptin levels and BMI (r=0.65, p<0.01) A positive correlation was found between luteinizing hormone (LH) (r=0.53, p<0.02), and insulin resistance (r=0.74, p<0.03). There was a negative (r=-0.76, p<0.03) correlation between serum ghrelin and LH. A positive and significant correlation was found between serum ghrelin, testosterone, mature oocyte, and implantation rates.

Conclusion: Serum ghrelin correlates with fertility outcomes in women with CC-resistant PCOS undergoing IVF/ICSI.

Keywords: Clomiphene resistance, polycystic ovary syndrome, ghrelin, leptin, HOMA-IR, LH, fertility outcome

Öz

Amaç: Bu çalışmanın amacı klomifen sitrata dirençli polikistik over sendromlu (PKOS) hastalarda serum leptin ve ghrelin düzeylerinin endokrin parametreler ve implantasyon oranları üzerine etkisini göstermektir.

Gereç ve Yöntemler: 150 mg klomifen sitratla yapılan ovulasyon indüksiyonuna cevap vermeyen otuz beş PKOS hastası çalışmaya dahil edilmiştir. Kontrol grubuna da benzer yaş ve vücut kitle indeksine (VKİ) sahip PKOS olmayan otuz beş infertil kadın alınmıştır. Serum ghrelin, leptin ve diğer hormon değerleri siklusun üçüncü gününde ölçülmüştür. Her iki grupta da IVF/ICSI uygulanmıştır.

PRECIS: This study was planned to determine the effect of serum ghrelin and leptin levels on endocrine parameters and implantation rates in patients with clomiphene-resistant polycystic ovary syndrome (PCOS).

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Bulgular: Yaş (29,4±0,11 vs 28,5±7,30), VKİ (24,3±3,07 vs 23,8±1,55), infertilite süresi (6,14±4,30 vs 6,03±1,28) açısından iki grup arasında anlamlı farklılık yoktur. Serum ghrelin düzeyleri PKOS grubunda kontrol grubuna kıyasla anlamlı olarak düşük bulunmuştur (0,48±2,21 vs 1,19±4,02). Serum leptin düzeyleri ise PKOS grubunda kontrol grubuna göre anlamlı yüksek bulunmuştur (45,6±304 vs 16,5±0,32). Serum luteinleştirici hormon (LH), testesteron insülin düzeyleri ve insülin rezistansı PKOS grubunda kontrol grubuna göre anlamlı olarak yüksek bulunmuştur. Serum leptin, VKİ (r=0,65, p<0,01), LH (r=0,53, p<0,02), insülin ve insülin rezistansı (r=0,74, p<0,03) arasında pozitif ve anlamlı korelasyon mevcuttur. Serum ghrelin ve LH düzeyleri (r=-0,76, p<0,03) arasında negatif ve anlamlı korelasyon bulunmuştur. Serum ghrelin, testosterone düzeyleri, toplanan matür oosit sayısı (r=0,70, p<0,02), ve implantasyon oranları (r=0,79, p<0,03) arasında pozitif ve anlamlı korelasyon bulunmuştur.

Sonuç: PKOS hastalarında serum ghrelin düzeyleri ile implantasyon oranları arasında korelasyon bulunmaktadır.

Anahtar Kelimeler: Klomifen sitrat rezistan PKOS, ghrelin, leptin, HOMA-IR, LH, gebelik sonuçları

Introduction

Because of its properties similar to the metabolic syndrome, polycystic ovary syndrome (PCOS) negatively affects the reproductive outcome by causing both endocrine and adipose tissue dysfunction[1,2]. Despite recent advances in assisted reproduction techniques, difficulties in conceiving patients with PCOS persist. We can list the possible causes of subfertility we encounter in patients PCOS as follows. (i) anovulation, (ii) hyperandrogenism, (iii) endocrine dysfunction, (iv) impairment in endometrial responsiveness. In addition to these factors, it is thought that dysfunction detected in the adipose tissues of PCOS cases in the last decade may cause subfertility by affecting the release of peripheral peptides[1-3]. Peptides either cause subfertility by directly affecting the ovary and endometrium or indirectly affect hypothalami-pituitary neurons[1,2,4].

Ghrelin and leptin are peptides that contribute to subfertility in cases of PCOS[1,2,4]. These two peripheral peptides disrupt both gonadotropin secretion and follicle development by having negative or positive energy balance as well as their effects on the release of insulin and other hormones and contribute to the subfertility seen in PCOS[1]. Leptin and ghrelin show their central effects through the GnRH pulse generator[1,2]. The main synthesis site of ghrelin is the gastrointestinal system and shows its effect in the arcuate nucleus[4,5]. Ghrelin increases the feeling of eating but decreases follicle-stimulating hormone (FSH) and luteinizing hormone (LH) secretion[6,7]. The effect of ghrelin on GnRH release is mediated by the GH secretagogue receptor (GHS-R)[8]. Ghrelin inhibits FSH, LH release, and estrogen and progesterone secretion by binding its receptor[4]. Ghrelin also contributes to follicling maturation by preventing apoptosis via GHS-R1a found in follicles[9]. Although the primary synthesis site of leptin is adipose tissue, it is also synthesized in granulosa cells[10]. Since GnRH neurons do not contain a leptin receptor, leptin stimulates GnRH release by acting through kisspeptin neurons[11]. While physiological leptin levels stimulate follicle development and steroidogenesis, cystic development may occur in the ovaries in the presence of high leptin[12]. Relationships between serum leptin and ghrelin levels and other parameters and reproductive outcome in infertile patients with PCOS have been discussed in previous studies[1,2,4,10]. However, the effect of serum levels of these two peptides on implantation, pregnancy rates, and other parameters in clomiphene-resistant PCOS cases were not investigated.

The aim of the study was to determine the relationship between serum ghrelin and leptin levels and reproductive outcome and endocrine parameters in women with CC-resistant PCOS.

Materials and Methods

A total of 70 patients who decided to on IVF/ICSI were included in the study. While 35 of these patients were clomiphene-resistant patients with PCOS, the remaining 35 were non-PCOS control patients. Both groups were matched for age and body mass index (BMI). In this way, adiposity affecting ghrelin and leptin synthesis was disabled. Failure to achieve ovulation or pregnancy despite 150 mg clomiphene citrate (CC) Daily for six months was accepted as CC resistance. The control group was selected from unexplained infertile women. They did not carry the clinical, laboratory, or dermatological findings of PCOS. In the control group, 13 of 35 (37.1%) patients complied with the metabolic syndrome criteria. Letrozole treatment was administered to CC-resistant cases before IVF/ICSI. PCOS cases unresponsive to letrozole were referred to IVF/ICSI. Serum samples were taken on the third day of the cycle of the patients in the PCOS and control groups. Serum LH, FSH, testosterone, insulin, ghrelin, and leptin levels were measured in fasting blood samples. Serum Leptin levels were measured by ELISA kit following the manufacturer's protocol. The sensitivity of the kit was 2 pg/mL and ranged 2-400 pg/mL. Ghrelin levels were measured with an enzyme immunoassay kit following the manufacturer's protocol. The sensitivity of the kit was 0.13 ng/mL and the range was 0.13-1.34 ng/mL. The homeostatic model assessment (HOMA-IR) Formula was used for insulin resistance. The cases who became pregnant with letrozole were excluded. Women with a history of antiandrogens, antidiabetics, and lipid-lowering drugs were excluded. Females with known causes of infertility like uterine fibroids, male factors, and other metabolic disorders were excluded from the study. Local Ethics Committee approval was obtained from Memorial Kayseri Hospital. Both PCOS and non-PCOS participants underwent conventional antagonist protocol. Relationship between serum ghrelin and leptin levels and implantation rates (IR), clinical pregnancy rate (CPR), and other metabolic and demographic parameters.

Statistical Analysis

The Statistical Package for Social Sciences software 21.0 for Windows software software (SPSS, Inc., Chicago, IL, USA)

was used for the analysis of collected data. The normality of disturbance was analyzed with the Kolmogorov-Smirnov test. A t-test was used for data comparisons. Pearson correlation analyses were used to detect possible correlations among the data. A p-value of <0.05 was set as significant. Data were expressed as mean ± SD.

Results

Table 1 shows all endocrine, metabolic, and demographic parameters. The age (29.4±0.11 vs 28.5±7.30), BMI (24.3±3.07 vs 23.8±1.55), and duration of infertility (6.14±4.30 vs 6.03±1.28) were similar. Serum total Ghrelin levels of PCOS cases were found to be significantlylower whencomparedwithnon-PCOS cases in the control group (0.48±2.21 vs 1.19±4.02). Serum levels of leptin in women with PCOS were significantly higher than in the patients in the control group (45.6±304 vs 16.5±0.32). The cases in the PCOS grouparenon-obese and their BMI values and ages are similar to the control cases. Therefore, fluctuations in leptin and ghrelin levels depending on age and BMI values were eliminated. The PCO group had significantly higher LH, testosterone, and insulin levels compared with the control group. Both groups had similar serum FSH and glucose levels. PCOS group had higher HOMA-IR than those in the control group. Ghrelin and leptin levels were not correlated with any group. Serum leptin showed positive correlation with BMI (r=0.65, p<0.01) LH (r=0.53, p<0.02), insulin and HOMA-IR (r=0.74, p<0.03). Serum leptin levels were not correlated with the number of mature oocytes (MII). Any correlation was not detected between CRP and leptin. Serum ghrelin and LH levels were negatively correlated (r=-0.76, p<0.03). Serum ghrelin showed a positive correlation with testosterone, mature oocytes (r=0.70, p<0.02), and implantation rates (r=0.79, p<0.03). No correlation was not detected between ghrelin, insulin, HOMA-IR, age, and BMI. Ghrelin did not show any correlation with CPR (Table 2).

Discussion

The impact of serum ghrelin and leptin on metabolic and demographic findings of infertile women with PCOS has been investigated in previous studies[1,13]. However, the effect of serum ghrelin or leptin on the metabolic parameters of women with clomiphene-resistant PCOS has not been studied to date. This study is the first clinical study investigating the relationship between serum ghrelin and leptin levels and endocrine and reproductive parameters in CC-resistant PCOS cases and is important in this respect. Our study clearly showed that, while a significant increase in serum leptin levels, a significant decrease in ghrelin levels in CC-resistant PCOS. While these changes in leptin and ghrelin levels are consistent with the results of some previous PCOS studies, they are different from the results of some[1,2].

Table 1. Demographic, hormonal and reproductive characteristics of CC resistant PCOS and control groups

	CC resistant PCOS (n=35)	Non-PCOS (n=35)	p
Age (y)	29.4±0.11	28.5±7.30	0.60
BMI (kg/m^2)	24.3±3.07	23.8±1.55	0.33
Infertility duration (y)	6.14±4.30	6.03±1.28	0.07
Testosterone (ng/mL)	0.87±5.03*	0.39±7.60	0.001
Day 3 Estradiol (pg/mL)	39.5±2.11	38.8±3.04	0.65
Day 3 Progesterone (ng/mL)	0.24±0.10	0.25±0.012	0.32
LH (mIU/mL)	11.33±0.11*	5.44±1.43	0.002
FSH (mIU/mL)	6.22±3.44	5.88±1.70	0.65
Insulin (mU/L)	12.2±3.43*	7.01±8.33	0.002
HOMA-IR	3.66±5.12*	1.74±3.02	0.001
Glucose (mg/dL)	91.4±4.05	88.5±644	0.21
MII oocyte	13.4±4.69*	7.40±6.10	0.002
Implantation rate (%)	40.0%	37.1%	0.057
Clinical pregnancy (%)	51.4%	48.7%	0.06
Ghrelin (ng/mL)	0.48±2.21*	1.19±4.02	0.02
Leptin (pg/mL)	45.6±304*	16.5±0.32	0.001

Data presented as means ± SD. BMI: Body mass index, FSH: Follicle-stimulating hormone, HOMA-IR: Homeosta-sis model assessment of insulin resistance, LH: Luteinizing hormone, PCOS: Polycystic ovary syndrome, MII: Mature oocyte, *p<0.05

Table 2. The resulst of correlation analysis between leptin, ghrelin levels and other measured parameters

	Age	BMI	HOMA-IR	LH	MII oocyte	Testosterone	IR	CPR
Leptin	r=0.34 p=0.43	r=0.65 p<0.01*	r=0.74 p<0.03*	r=0.53 p<0.02*	r=0.32 p=0.22	r=0.50 p=0.65	r=-0.60 p=0.52	r=0.42 p=0.12
Ghrelin	r=0.43 p=0.33	r=0.30 p=0.54	r=0.31 p=0.66	r=-0.76 p<0.03*	r=0.70 p<0.02*	r=0.876 p<0.01*	r=0.79 p<0.03*	r=0.51 p=0.32

BMI: Body mass index, HOMA-IR: homeostasis model assessment of insulin resistance, LH: Luteinizing hormone, IR: Implantation rate, CPR: Clinical pregnancy rate, MII: Mature oocyte, *p<0.05

When we evaluated both peptides separately, the high leptin levels we found were consistent with those in other studies[14-16]. However, there are studies reporting normal serum leptin levels in infertile cases of PCOS[17,18]. However, serum leptin levels showed a positive correlation with BMI, LH, insülin levels, and HOMA-IR in CC-resistant PCOS cases. The correlation findings we obtained are compatible with the literature except for LH[15,16,19]. The relationship between high leptin levels and insülin resistance in infertile patients with PCOS is known fact[14], and we found the same finding in CC-resistant PCOS cases. The positive relationship between BMI and leptin may be evidence that adipose tissue content and function change in CC-resistant PCOS cases. As for the positive relationship between LH and leptin, increased peripheral leptin levels may increase LH by stimulating GnRH release via kisspeptin receptors in arcuate neurons[1,11].

We detected a positive but insignificant correlation between leptin and the number of mature oocytes. Similarly, there was no significant correlation between leptin levels and implantation rates, and clinical pregnancy rates. These data do not mean that there is no relationship between leptin and reproductive outcome. While physiological amounts of leptin induce sex steroid synthesis and oocyte development in the ovaries, supraphysiological concentrations of leptin may lead to an ovarian cyst formation[12]. However, in patients with hypothalamic amenorrhea, leptin treatment regulates the LH pulse frequency[1,20]. However, in the presence of high leptin, there is a decrease in the response of the ovaries to gonadotropins[21,22]. High HOMA-IR levels may also limit the physiological effects of leptin on the ovary. Insulin ensures successful ovulation by regulating both gonadotropic hormone receptors and GnRH pulse frequency in the ovaries[23]. Since all physiological pathways will be dysregulated in the presence of high leptin, it will not be possible for leptin to positively affect reproductive parameters in CC-resistant PCOS cases. However, the presence of central leptin resistance due to chronic inflammation in PCOS cases may also prevent leptin from fully performing its physiological functions in the hypothalamic-pituitary-ovarian axis[24].

The second parameter that we evaluated in CC-resistant PCOS cases and found a significant decrease in their levels is ghrelin. In most of the studies in the literature, decreased serum ghrelin levels have been reported in infertile PCOS cases[15,17]. Our study is the first clinical study to report a decrease in ghrelin levels in CC-resistant PCOS cases. We found a negative correlation between a decrease in ghrelin levels and an increase in LH levels. Under normal conditions, physiological levels of ghrelin block LH release[4]. Ghrelin exerts this inhibitory effect on LH in both animals and humans through GnRH neurons[25,26]. Because of the decreased ghrelin levels, found in our study, the suppressive effect of ghrelin on LH may have been neutralized and increased LH. However, the positive correlation we found between Ghrelin levels and serum testosterone levels may also be a physiological consequence of the LH increase. This is how we can explain the positive correlation between ghrelin and testosterone synthesis, as increasing LH levels stimulate androgen synthesis in the ovary.

One of the most important results of the current study is the presence of a positive correlation between ghrelin levels and the number of mature oocytes collected and implantation rates. In CC-resistant PCOS cases, we can explain the increase in the number of mature oocytes and implantation rates due to the decrease in ghrelin level in two ways. Due to decreased ghrelin levels, the inhibitory effect of Ghrelin on GnRH neurons is removed and FSH and LH release are activated[1,4]. As a result, the number of mature eggs collected in IVF/ICSI casesduetoincreased FSH and LH release also increases, which increases the implantation rates. The most interesting finding of our study was that there was no correlation between clinical pregnancy rates and ghrelin levels. The physiological amount of ghrelin increases follicle maturation and quality due to its anti-apoptotic effect on ovarian follicles[4,9]. The decreased ghrelin levels found in CC-resistant cases may in oocytes and reduce the follicle quality. This may explain the lack of a correlation between clinical pregnancy rates and serum ghrelin.

Conclusion

In this observational study where we compared serum levels of ghrelin or leptin with endocrine, demographic, and reproductive parameters of CC-resistant PCOS and non-PCOS cases. We found a significant decrease in ghrelin levels despite an increase in leptin levels in the PCOS group. Despite the significant correlation between leptin levels and BMI, LH, insülin levels, and HOMA-IR, we did not detect a relationship between implantation and pregnancy rates and leptin levels.

However, in addition to the correlation between ghrelin levels and serum testosterone and LH levels, ghrelin levels correlated significantly with the total number of mature oocytes and implantation rates. Thanks to more comprehensive studies evaluating ghrelin and leptin levels as well as other peptides in CC-resistant PCOS cases, we can reach more definite conclusions about the reproductive outcome in cases with metabolic syndrome.

Ethics

Ethics Committee Approval: Local Ethics Committee approval was obtained from Memorial Kayseri Hospital (approved number: 16481, date: 21.01.2021).
Informed Consent: Written consent from all participants were obtained.
Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: A.Y., N.D.G., K.G., Ş.H., Design: A.Y., N.D.G., K.G., Ş.H., Data Collection or Processing: A.Y., N.D.G., K.G., Ş.H., Analysis or Interpretation: A.Y., N.D.G., K.G., Ş.H., Literature Search: A.Y., N.D.G., K.G., Ş.H., Writing: A.Y., N.D.G., K.G., Ş.H.
Conflict of Interest: No conflict of interest was declared by the authors.
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References

1. Celik O, Aydin S, Celik N, Ugur K, Yavuzkir S, Hatirnaz S, et al. Molecular role of peptides/proteins in subfertility of polycystic ovarian syndrome. Cell Mol Biol (Noisy-le-grand) 2019;65:32-40.
2. Celik O, Aydin S, Celik N, Yilmaz M. Peptides: Basic determinants of reproductive functions. Peptides 2015;72:34-43.
3. Moffett RC, Naughton V. Emerging role of GIP and related gut hormones in fertility and PCOS. Peptides 2020;125:170233.
4. Celik O, Celik N, Aydin S, Aygun BK, Haberal ET, Kuloglu T, et al. Ghrelinaction on GnRH neurons and pituitary gonadotropes might be mediated by GnIH-GPR147 system. Horm Mol Biol Clin Investig 2016;25:121-8.
5. Hoover SE, Gower BA, Cedillo YE, Chandler-Laney PC, Deemer SE, Goss AM. Changes in Ghrelin and Glucagon following a Low Glycemic Load Diet in Women with PCOS. J Clin Endocrinol Metab 2021;106:e2151-61.
6. Fernández-Fernández R, Tena-Sempere M, Navarro VM, Barreiro ML, Castellano JM, Aguilar E, et al. Effects of ghrelin upon gonadotropin-releasing hormone and gonadotropin secretion in adult female rats: in vivo and in vitro studies. Neuroendocrinology 2005;82:245-55.
7. Wang X, Qu F, Wang C, Wang Y, Wang D, Zhao M, et al. Variationanalysis of Ghrelin gene in Chinese patients with obesity, having polycystic ovarian syndrome. Gynecol Endocrinol 2020;36:594-8.
8. Farkas I, Vastagh C, Sarvari M, Liposits Z. Ghrelindecreasesfiringactivity of gonadotropin-releasing hormone (GnRH) neurons in an estrous cycle and endo cannabinoid signaling dependent manner. PLoS One 2013;8:e78178.
9. Celik N, Aydin S, Ugur K, Yardim M, Acet M, Yavuzkir S, et al. Patatin-like phospholipase domain-containing 3-gene (adiponutrin), preptin, kisspeptin and amylin regulates oocyte developmental capacity in PCOS. Cell Mol Biol (Noisy-le-grand) 2018;64:7-12.
10. Abir R, Ao A, Jin S, Barnett M, Raanani H, Ben-Haroush A, et al. Leptin and its receptors in human fetal and adult ovaries. Fertil Steril 2005;84:1779-82.
11. Burcelin R, Thorens B, Glauser M, Gaillard RC, Pralong FP. Gonadotropin-releasing hormone secretion from hypothalamic neurons: stimulation by insulin and potentiation by leptin. Endocrinology 2003;144:4484-91.
12. Gregoraszczuk EL, Rak-Mardyła A. Supra physiological leptin levels shift the profile of steroidogenesis in porcine ovarian follicles toward progesterone and testosterone secretion through increased expressions of CYP11A1 and 17b-HSD: a tissue culture approach. Reproduction 2013;145:311-7.
13. Houjeghani S, Pourghassem Gargari B, Farzadi L. Serum leptin and ghrelin levels in women with polycystic ovary syndrome: correlation with anthropometric, metabolic, and endocrine parameters. Int J Fertil Steril 2012;6:117-26.
14. Zheng SH, Du DF, Li XL. Leptin levels in women with polycystic ovary syndrome: A systematic review and a meta-analysis. Reprod Sci 2017;24:656-70.
15. Mitkov M, Pehlivanov B, Orbetzova M. Serum ghrelin level in women with polycystic ovary syndrome and its relationship with endocrine and metabolic parameters. Gynecol Endocrinol 2008;24:625-30.
16. Pehlivanov B, Mitkov M. Serum leptin levels correlate with clinical and biochemical indices of insülin resistance in women with polycystic ovary syndrome. Eur J Contracept Reprod Health Care 2009;14:153-9.
17. Glintborg D, Andersen M, Hagen C, Frystyk J, Hulstrøm V, Flyvbjerg A, et al. Evaluation of metabolic risk markers in polycystic ovary syndrome (PCOS). Adiponectin, ghrelin, leptin, and body composition in hirsute PCOS patients and controls. Eur J Endocrinol 2006;155:337-45.
18. Carmina E, Orio F, Palomba S, Cascella T, Longo RA, Colao AM, et al. Evidence for altered adipocyte function in polycystic ovary syndrome. Eur J Endocrinol 2005;152:389-94.
19. Celik O, Hascalik S, Ozerol E, Hascalik M, Yologlu S. Cerebrospinal fluid leptin levels in preeclampsia: relation to maternalserum leptin levels. Acta Obstet Gynecol Scand 2004;83:519-23.
20. Welt CK, Chan JL, Bullen J, Murphy R, Smith P, DePaoli AM, et al. Recombinant human leptin in women with hypothalamic amenorrhea. N Engl J Med 2004;351:987-97.
21. Polak AM, Krentowska A, Łebkowska A, Buczyńska A, Adamski M, Adamska-Patruno E, et al. The Association of Serum Levels of Leptin and Ghrelin with the Dietary Fat Content in Non-ObeseWomen with Polycystic Ovary Syndrome. Nutrients 2020;12:2753.
22. Agarwal SK, Vogel K, Weitsman SR, Magoffin DA. Leptin antagonizes the insulin-like growth factor-I augmentation of steroidogenesis in granulosa and theca cells of the human ovary. J Clin Endocrinol Metab 1999;84:1072-6.
23. Nestler JE, Jakubowicz DJ. Lean women with polycystic ovary syndrome respond to insülin reduction with decreases in ovarian P450c17 alpha activity and serum androgens. J Clin Endocrinol Metab 1997;82:4075-9.
24. Lian Y, Zhao F, Wang W. Central leptin resistance and hypothalamic inflammation are involved in letrozole-induced polycystic ovary syndrome rats. Biochem Biophys Res Commun 2016;476:306-12.

25. Kluge M, Schussler P, Uhr M, Yassouridis A, Steiger A. Ghrelin suppresses secretion of luteinizing hormone in humans. J Clin Endocrinol Metab 2007;92:3202-5.

26. Baldani DP, Skrgatic L, Kasum M, Zlopasa G, Kralik Oguic S, Herman M. Altered leptin, adiponectin, resist in and ghrelin secretion may represent an intrinsic polycystic ovary syndrome abnormality. Gynecol Endocrinol 2019;35:401-5.