Comparison of maternal serum NRG-4 levels in healthy and preeclamptic pregnancies

Kadriye Yakut, Filiz Halıcı Öztürk, Doğa Fatma Öcal, Betül Yakıştıran, Fatma Didem Yücel Yetişkin, Turhan Çağlar

Clinic of Perinatology, Ankara City Hospital, Ankara, Turkey

Abstract

Objective: The new adipokine, neuregulin-4 (NRG-4), acts as a signaling protein and plays a role in lipogenesis, inflammatory events and atherosclerosis. The aim was to investigate maternal levels of NRG-4 in preeclampsia (PE) disease.

Material and Methods: Pregnant women with PE, divided into severe and mild PE, and gestational age-matched healthy pregnant women, as a control group, were recruited. NRG-4 levels were measured using an ELISA. NRG-4 levels in the groups and the relation between NRG-4 and clinical and laboratory parameters were analyzed.

Results: There were 41 women in the PE group, 11 (26.8%) in the severe and 30 (73.2%) in the mild subgroups and 41 controls. There were no significant differences between the groups in terms of maternal age, gravidity, parity, abortion, gestational week at the time of blood sampling, levels of hemoglobin, platelet count, alanine and aspartate transaminases ($p=0.067$, $p=0.819$, $p=0.957$, $p=0.503$, $p=0.054$, $p=0.217$, $p=0.306$, and $p=0.270$ respectively). The PE group had higher body mass index, nitrogen urea and creatinine values, and diastolic and systolic blood pressure ($p=0.005$, $p<0.001$, $p<0.001$, $p<0.001$, and $p<0.001$ respectively). In addition, earlier gestational week at delivery, lower birth weight and Apgar scores at 1 and 5 minutes and the occurrence of non-reassuring fetal heart rate tracing were found in the PE group ($p=0.010$, $p=0.004$, $p=0.005$, $p=0.005$, and $p=0.026$ respectively). There were no significant differences between the groups in terms of NRG-4 ($p=0.611$). No correlation was identified between clinical parameters examined and NRG-4 levels ($p=0.722$).

Conclusion: No association was found between NRG-4 concentrations and PE patients, regardless of severity of PE, compared to healthy pregnancies. Future longitudinal studies are needed to confirm this lack of association in PE. (J Turk Ger Gynecol Assoc 2022; 23: 8-13)

Keywords: NRG-4, neuregulin, preeclampsia, perinatal outcome

Received: 28 November, 2020 **Accepted:** 08 September, 2021

Introduction

Preeclampsia (PE) is a serious cardiovascular disorder of pregnancy, which is characterized by hypertension in addition to proteinuria or hypertension and end-organ dysfunction in the absence of proteinuria (1). The course of the disorder is unpredictable, and associated with neonatal and maternal life-threatening complications (1-3). The pathogenesis of PE is multifactorial and involves abnormal development of placenta, endothelial dysfunction, and immunological and genetic factors (4-6). Changes in the balance of angiogenic and antiangiogenic factors, and the presence of insulin resistance and/or obesity contribute to the pathogenesis of the PE and clinical symptoms (7).

Neuregulins are members of the endothelial growth factor-like growth factor family. Four subtypes of neureglins have been identified, one of which is neuregulin-4 (NRG-4) (8). NRG-4 is mainly produced by brown adipose tissue and plays a role as signaling protein during cell-to-cell interaction (9). In vivo studies have suggested that NRG-4 levels change during the process of lipogenesis, inflammatory events and as a result of changes in energy metabolism (10,11). It has been suggested that NRG-4 positively correlates with the development of obesity related disorders, such as type 2

Address for Correspondence: *Kadriye Yakut*
e.mail: yakutkadriye@hotmail.com ORCID: orcid.org/0000-0003-3182-4312

Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.galenos.2021.2020-0224

diabetes mellitus (DM) and non-alcoholic fatty liver disease (NAFLD) and plays a role in the development of coronary artery disease (CAD) by promoting atherosclerosis (12-17).

The relationship between adipokines and metabolic disorders is complex and is not fully understood. In addition to adipose tissue, placental tissue is thought to be a source of adipokines. The relationship between metabolically active proteins, such as leptin, resistin, adiponectin and tumor necrosis factor-α has been investigated in the pathogenesis of PE. However, no clear relationship between adipokine levels and PE has been found (18-21). Therefore, the aim of this study was to investigate if there was an association between PE and NRG-4 levels for the first time. We also aimed to understand whether NRG-4 levels are associated with the severity of PE and neonatal and maternal clinical parameters.

Material and Methods

Study participants

This was a case-control study. Pregnant women with PE, divided into two subgroups as severe PE and mild PE, and gestational age-matched healthy pregnant women as a control group were recruited. All data were collected between September 2018 and March 2019 at the Department of Perinatology of Zekai Tahir Burak Women's Health Training and Research Hospital in Ankara, Turkey. The study design was approved by the institutional research ethics committee (approval number: 28/2019) and written informed consent was obtained from all participants. The study was performed according to the universal principles expressed in the Declaration of Helsinki. All participants were in the third trimester of pregnancy. Exclusion criteria included any patient having: a chronic systemic disease; an autoimmune disease; chronic drug use; or presence of multiple gestation; presence of fetal congenital abnormality; and presence of complication of pregnancy including gestational DM, chorioamnionitis, and premature preterm rupture of pregnancy. Body mass index (BMI) was calculated as body weight (in kilograms) divided by squared height (in metres). According to the ACOG guideline (1), the criteria for the diagnosis of PE and in which cases it is called PE with severe features (the group called severe PE according to the old nomenclature) are given below.

Diagnostic criteria for preeclampsia:

- New onset of hypertension, defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg in at least two measurements over four hours or six hours apart, or systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110 mmHg confirmed within a short interval (minutes).

and

- Proteinuria defined as protein/creatinine ratio ≥0.3 mg/dL, dipstick reading of 2+ or ≥300 mg in a 24-hour urine collection after 20 weeks of gestation,

or

- In the absence of proteinuria - new onset of hypertension with signs of end-organ dysfunction, such as platelet count <100,000/μL, increased liver transaminases on at least two occasions, pulmonary edema, serum creatinine >1.1 mg/dL or two-fold elevation of basal creatinine level or new-onset headache, unresponsive to medication, or visual symptoms

The presence of any of the following criteria was grouped as "severe PE" (according to the old nomenclature, and "severe PE with severe feature" according to the new nomenclature).

PE with severe features as following:

- Systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110 mmHg on two occasions at least 4 hours apart (unless antihypertensive therapy was initiated),
- Platelet count <100,000/μL,
- At least two episodes of increased liver transaminases,
- Pulmonary edema,
- Serum creatinine >1.1 mg/dL or there was a two-fold elevation of basal creatinine level,
- New-onset headache unresponsive to medication,
- Visual symptoms,
- Severe persistent right upper quadrant or epigastric pain unresponsive to medications (Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222 Obstet Gynecol 2020; 135: e237-60. doi: 10.1097/AOG.0000000000003891).

Based on the ACOG guideline (1), patients who met the above-mentioned PE diagnostic criteria but did not have the criteria of PE with severe features; were classified as mild PE group (mild PE with the old nomenclature, PE without severe features with the new nomenclature).

Blood samples

All blood samples were taken from the antecubital vein. Samples for the measurement of NRG-4 levels were taken into tubes containing ethylene diamine tetra-acetic acid blood samples of 5 mL volume were centrifuged for 10 minutes at 1,000×g at 2-8 °C within 30 minutes of collection. Then plasma was stored at -80 °C until analysis. Concentrations of alanine transaminases, aspartate transaminases, creatinine, urea, hemoglobin and platelet count were measured as routine laboratory parameters. NRG-4 levels were measured using an ELISA (Human NRG-4 ELISA Kit, Cloud-Clone Corp., Katy, TX 77494, USA) following manufacturer's instructions. The intra- and inter-assay coefficients of variation were <10% and <12%, respectively. The detection range was 0.156-10 ng/mL. The

minimum detectable dose of NRG-4 is typically less than 0.056 ng/mL.

Statistical analysis

IBM SPSS Statistics, version 21.0 (IBM Corp. Armonk, NY, USA) was used to analyze the collected data. Kolmogorov-Smirnov test was used to evaluate the closeness of data sets to normal distribution. Descriptive statistics were expressed as mean ± standard deviation and median (minimum-maximum). The parametric Sample t-test and non-parametric Mann-Whitney U test were used to determine statistically significance between two independent groups, as appropriate. Comparison of two qualitative variables was done with the chi-square test, according to the expected value levels. Spearman and Pearson correlation tests were used to examine the association between two variables. Statistical significance was assumed when $p<0.05$.

Results

Eighty-two women participated in this case-control study, equally divided between the PE group (n=41) and control group (n=41). Clinical and demographic parameters of study groups are shown in Table 1. There were no significant differences between the PE and control groups in terms of maternal age, gravidity, parity, abortion and gestational week at the time of blood sampling. BMI was significantly higher in the PE group compared to the control group. Similarly, there was no difference between the PE and control groups in terms of hemoglobin concentration, platelet count, and alanine and aspartate transaminases levels. However, renal function tests such as blood nitrogen urea and creatinine were significantly elevated in the PE group in comparison with the control group (Table 1).

Perinatal outcomes of the study groups are shown in Table 2. Gestational week at the time of delivery was earlier in the PE group than in the control group. Babies born to mothers in the control group had significantly elevated birth weight compared to babies born to mothers with PE. Mothers with PE were more likely to deliver by cesarean section when compared with controls. Apgar scores at 1 minute and 5 minutes were much lower in babies from the PE group but there was no difference between the groups in terms of neonatal intensive care unit admission likelihood (Table 2).

The PE group was divided into severe (n=11, 26.8%) and mild (n=30, 73.2%). Statistically, there was no difference in terms of NRG-4 levels between the PE group as a whole and the control group (Table 1). In addition, there was no difference in NRG-4 levels between the severe and mild PE groups (p=0.72). As shown Table 3, no significant correlations were identified between NRG-4 levels and clinical, laboratory and demographic parameters.

Discussion

NRG-4, a new brown adipose tissue-associated adipokine, has been reported to play an important role in the regulation of energy metabolism and in the development of obesity related diseases (12-16). Besides acting in paracrine and autocrine

Table 1. Demographic and laboratory parameters of study groups

	Preeclampsia group (n=41)	Control group (n=41)	p
Maternal age, years	30.0 (18.0-43.0)	29.0 (19.0-39.0)	0.067
Gravidity (number)	2.0 (1.0-6.0)	2.0 (1.0-6.0)	0.82
Parity (number)	1.0 (0.0-3.0)	1.0 (0.0-3.0)	0.96
Abortion (number)	0.0 (0.0-3.0)	0.0 (0.0-3.0)	0.50
BMI (kg/m^2)	31.27±6.55	27.90±3.68	**0.005**
Gestational age at the time blood sampling, weeks	35.0 (25.0-41.0)	36.0 (26.0-41.0)	0.054
SBP (mmHg)	149 (140-189)	109 (85-128)	**<0.001**
DBP (mmHg)	89.83±11.0	61.93±7.79	**<0.001**
Hemoglobin (g)/dL	12.05±1.57	11.70±1.03	0.217
AST (U/L)	16.0 (8.0-62.0)	14.5 (8.0-26.0)	0.306
ALT (U/L)	10.0 (4.0-80.0)	9.0 (6.0-20.0)	0.270
BUN (mg/dL)	21.5 (8.0-50.0)	13.5 (7.0-33.0)	**<0.001**
Creatinine (mg/dL)	0.6 (0.1-1.0)	0.5 (0.4-0.8)	**<0.001**
Platelet (10^3/mL)	232 (30.0-363)	221 (116-540)	0.899
Serum NRG-4 level (ng/mL)	1.5 (1.0-6.6)	1.6 (0.1-3.5)	0.611

BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, BUN: Blood urea nitrogen, NRG-4: Neuregulin-4

Table 2. Perinatal outcomes of preeclampsia and control groups

	Preeclampsia group (n=41)	Control group (n=41)	p
Gestational age at delivery (week)	36 (28-40)	38 (29-41)	**0.010**
Birth weight (gr)	2355 (450-3920)	3000 (1220-3930)	**0.004**
Apgar score at 1 minute	7 (6-8)	8 (7-9)	**0.005**
Apgar score at 5 minutes	9 (7-10)	10 (9-10)	**0.005**
C/S rate	34/41 (82.9%)	9/41 (21.9%)	**<0.001**
Non-reassuring fetal heart rate trace	10/41 (24.3%)	2/41 (4.8%)	**0.026**
NICU admission	12/41 (29.3%)	8/41 (19%)	0.411
NICU: Neonatal intensive care unit, C/S: Cesarean section			

signal transduction, NRG-4 decreases hepatic lipogenesis and increases fatty acid beta-oxidation in an endocrine fashion (9). Thus, NRG-4 contributes to lipid and glucose homeostasis. It has been reported that NRG-4 promotes the development of obesity-related disorders, such as type-2 DM and NAFLD (12-16). In addition to the metabolic roles ascribed to NRG-4, Ma et al. (21) suggested that excessive production of NRG-4 may have anti-atherogenic and anti-inflammatory effects. Similarly, it has been suggested that decreased NRG-4 levels may induce the development of atherosclerosis (20). Sato and Minatsuki (17) reported that NRG-4 levels were lower in patients with CAD than in the control group. However, it has not been clearly established which metabolic pathways NRG-4 interacts with. Activating ERB B4, a member of the epidermal growth factor receptor and plays role in the diseases such as cancers, DM may lead to the progression of atherosclerosis by inhibiting the apoptosis of endothelial cells via NRG-4 (14). It has also been shown that reduced NRG-4 levels were related to increased carotid intima thickness and carotid plaque in a group with obesity when compared to a control group (22). In the light of this evidence, we investigated whether there was an alteration of NRG-4 levels in women with PE. This seemed a reasonable hypothesis, given that PE is known to be associated with obesity, endothelial dysfunction, inflammation and metabolic diseases. Considering the similarities between mechanisms and risk factors, it was expected that there would be a correlation between NRG-4 and PE. However, we did not find any such relationship. As has been previously reported, we found higher BMI in the PE group, but there were no difference in NRG-4 levels between the groups. Furthermore, there was no correlation between NRG-4 level and the severity of PE, nor with clinical and laboratory parameters. It is thought that NRG-4 is a marker of brown adipocytes in human adipose tissue and is also associated with obesity. No such relationship was evident in after analysis of the data from our study populations; we could not find any correlation between NRG-4 levels and BMI.

Table 3. The correlation between NRG-4 and clinical, laboratory and demographic parameters in the participants

	NRG-4 concentration	
Variables	**r***	**p**
Maternal age, years	-0.165	0.136
Gravidity (number)	-0.021	0.848
Parity (number)	-0.019	0.862
Abortion (number)	0.083	0.454
BMI (kg/m^2)	-0.166	0.134
SBP (mmHg)	0.001	1.000
DBP (mmHg)	-0.141	0.380
Hemoglobin (g)/dL	0.004	0.975
AST (U/L)	0.131	0.239
ALT (U/L)	0.093	0.407
BUN (mg/dL)	-0.080	0.477
Creatinine (mg/dL)	-0.066	0.554
Platelet (10*3/microL)	-0.056	0.618
Birth weight (gr)	-0.061	0.582
Gestational age at delivery (week)	-0.082	0.461
Birth weight (gr)	-0.048	0.669
Apgar score at 1 minute	0.010	0.928
Apgar score at 5 minutes	0.023	0.837
BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, BUN: Blood urea nitrogen, NRG-4: Neuregulin-4		

There may be a number of possible reasons why these findings emerged from our study. Firstly, the pathogenesis of PE involves a dynamic process, so there may be temporal changes in concentrations of circulating cytokines and adipokines as the pathogenic process progresses. These cytokine/adipokine concentrations may be normalized again by the time clinical symptoms and overt PE appears. However, it is known that obesity, especially with intensive visceral adiposity, can contribute to the pathogenesis of PE by increasing proinflammatory cytokines and adipokines. There have been contrasting reports of the utility of assessing concentrations of

visceral mass-derived adipokines (such as resistin, visfatin) or adipokines reflecting general adiposity (adiponectin, leptin) for the prediction of the development of PE (18,20,23-25). In the study of Chandrasekaran et al. (19), it was demonstrated that PE was associated with elevated level of visceral fat mass-derived adipokines and leptin, but there was no relation between the groups for adiponectin levels. These analyses bring into question the importance of the effect of placentally derived adipokines in the pathogenesis of PE.

Secondly, although higher BMI is known to contribute to developing PE and there is correlation between BMI and increasing PE severity. BMI, which is especially affected by white adipose tissue, may not fully reflect the increased brown adipose tissue. Therefore, BMI may be an insufficient indicator to reflect body fat tissue distribution. Chandrasekaran et al. (19) showed that normal weight and obese women in the PE and control groups had similar levels of visceral mass-derived adipokines, cytokines and inflammatory markers. Kurek Eken et al. (26) demonstrated that serum NRG-4 levels were higher in patients diagnosed with gestational DM compared to healthy pregnant women. Moreover, they reported that NRG-4 concentration was positively correlated with BMI, and triglyceride and low-density lipoprotein cholesterol. Jiang et al. (22) suggested that low NRG-4 levels were associated with increased subclinical atherosclerosis and increased carotid intima thickness in obese patients. They also showed that among the obese patients, those with high NRG-4 levels had lower BMI and systolic blood pressure levels than those with low NRG-4 levels. In the study conducted by Dai at al. (16) decreased NRG-4 levels were found in NAFLD and yet they did not find any relationship between NRG-4 and BMI. Similarly, Sato and Minatsuki (17) showed that NRG-4 is a predictor of the severity of CAD but they did not find any correlation between NRG-4 and BMI, cholesterol levels or high sensitive C-reactive protein. Similar to these studies, we did not detect any correlation between the demographic, clinical and laboratory parameters and NRG-4 levels and the severity of PE was also not related with NRG-4 levels. Therefore, it may be assumed that NRG-4 levels are independent of general measures of obesity or that BMI does not accurately reflect the presence and activity of brown adipose tissue, the main source of NRG-4. It is also possible that NRG-4 levels may be increased in PE pregnancies earlier than the third trimester, when samples were taken in our study.

It should be noted that brown adipose tissue plays a role in energy metabolism by regulating the production of ATP and thermogenesis (10,11). Similarly, Wang et al. (10) demonstrated that NRG-4 stimulates liver lipogenesis by activating Erb B3/B4 receptors. This evidence suggests that the endocrine role of NRG-4 in metabolic diseases, such as type 2 DM, gestational DM, NAFLD and obesity may be more closely associated with vascular and inflammatory pathways. All of these factors, particularly the low levels of NRG-4 associated with an atherogenic process, which has similarity with the etiopathogenesis of PE and, conversely, elevated levels in gestational diabetes mellitus, which also has some similarities to PE, may be the reason why we could not detect any significant variation in NRG-4 levels among the study and control groups. We therefore suggest that NRG-4 is an unsuitable biomarker for third trimester PE.

Study limitations

However, there were limitations of this study that should be noted. One problem lies with sampling time and the lack of data for NRG-4 levels prior to the onset of clinical PE. Samples in our study were taken only in the third trimester and longitudinal sampling throughout preganacy could have provided more enlightening results. These data collected in a longitudinal fashion may provide a greater understanding of the significance of NRG-4 during the development of PE. A further limitation was the relatively small sizes of the PE sub-groups. Future studies should recruit sufficient patients with PE to sub-divide them on the basis of both obesity and severity of disease. These data may add more detailed and reliable information about the pathogenesis of PE and the role of NRG-4, if any, in this.

Conclusion

In conclusion, despite the limitations, to our knowledge, this is the first study to have investigated maternal levels of NRG-4 in PE. Though we could not find any difference in NRG-4 levels in PE pregnancies compared to healthy pregnancies, future investigations of the role of NRG-4 in PE should address the physiological changes of pregnancy, metabolic pathways known to be affected by NRG-4 and the different stages in the development of PE.

Ethics Committee Approval: *The study design was approved by the institutional research ethics committee (approval number: 28/2019).*

Informed Consent: *Written informed consent was obtained from all participants.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Surgical and Medical Practices: K.Y., D.F.Ö.; Concept: K.Y., F.H.Ö.; Design: K.Y.; Data Collection or Processing: F.D.Y.Y., B.Y.; Analysis or Interpretation: T.Ç.; Literature Search: B.Y.; Writing: K.Y.*

Conflict of Interest: *No conflict of interest is declared by the authors.*

Financial Disclosure: *The authors declared that this study received no financial support.*

References

1. ACOG Practice Bulletin No. 202: Gestational hypertension and preeclampsia. Obstet Gynecol 2019; 133: e1-25.
2. Mol BWJ, Roberts CT, Thangaratinam S, Magee LA, de Groot CJM, Hofmeyr GJ. Pre-eclampsia. Lancet 2016; 387: 999-1011.
3. Bokslag A, van Weissenbruch M, Mol BW, de Groot CJ. Preeclampsia; short and long-term consequences for mother and neonate. Early Hum Dev 2016; 102: 47-50.
4. Vennou KE, Kontou PI, Braliou GG, Bagos PG. Meta-analysis of gene expression profiles in preeclampsia. Pregnancy Hypertens 2019; 19: 52-60.
5. Boeldt DS, Bird IM. Vascular adaptation in pregnancy and endothelial dysfunction in preeclampsia. J Endocrinol 2017; 232: R27-44.
6. Oliveira Perucci L, Pereira Santos TA, Campi Santos P, Ribeiro Teixeira LC, Nessralla Alpoim P, Braga Gomes K, et al. Pre-eclampsia is associated with reduced resolvin D1 and maresin 1 to leukotriene B4 ratios in the plasma. Am J Reprod Immunol 2020; 83: e13206.
7. Cerdeira AS, Agrawal S, Staff AC, Redman CW, Vatish M. Angiogenic factors: potential to change clinical practice in pre-eclampsia? BJOG 2018; 125: 1389-95.
8. Falls DL. Neuregulins: functions, forms, and signaling strategies. Exp Cell Res 2003; 284: 14-30.
9. Pfeifer A. NRG4: an endocrine link between brown adipose tissue and liver. Cell Metab 2015; 21: 13-4.
10. Wang GX, Zhao XY, Meng ZX, Kern M, Dietrich A, Chen Z, et al. The brown fat-enriched secreted factor Nrg4 preserves metabolic homeostasis through attenuation of hepatic lipogenesis. Nat Med 2014; 20: 1436-43.
11. Rosell M, Kaforou M, Frontini A, Okolo A, Chan YW, Nikolopoulou E, et al. Brown and white adipose tissues: intrinsic differences in gene expression and response to cold exposure in mice. Am J Physiol Endocrinol Metab 2014; 306: E945-64.
12. Kang YE, Kim JM, Choung S, Joung KH, Lee JH, Kim HJ, et al. Comparison of serum Neuregulin 4 (Nrg4) levels in adults with newly diagnosed type 2 diabetes mellitus and controls without diabetes. Diabetes Res Clin Pract 2016; 117: 1-3.
13. Cai C, Lin M, Xu Y, Li X, Yang S, Zhang H. Association of circulating neuregulin 4 with metabolic syndrome in obese adults: a cross-sectional study. BMC Med 2016; 14: 165.
14. Wurst U, Ebert T, Kralisch S, Stumvoll M, Fasshauer M. Serum levels of the adipokine Pref-1 in gestational diabetes mellitus. Cytokine 2015; 71: 161-4.
15. Zhang L, Fu Y, Zhou N, Cheng X, Chen C. Circulating neuregulin 4 concentrations in patients with newly diagnosed type 2 diabetes: a cross-sectional study. Endocrine 2017; 57: 535-8.
16. Dai YN, Zhu JZ, Fang ZY, Zhao DJ, Wan XY, Zhu HT, et al. A case-control study: Association between serum neuregulin 4 level and non-alcoholic fatty liver disease. Metabolism 2015; 64: 1667-73.
17. Sato T, Minatsuki S. Neuregulin-4 an adipokine, as a Residual risk factor of atherosclerotic coronary artery disease. Int Heart J 2019; 60: 1-3.
18. Haugen F, Ranheim T, Harsem NK, Lips E, Staff AC, Drevon CA. Increased plasma levels of adipokines in preeclampsia: relationship to placenta and adipose tissue gene expression. Am J Physiol Endocrinol Metab 2006; 290: E326-33.
19. Chandrasekaran S, Hunt H, Melhorn S, Gammill HS, Schur EA. Adipokine profiles in preeclampsia. J Matern Fetal Neonatal Med 2020; 33: 2812-7.
20. Hendler I, Blackwell SC, Mehta SH, Whitty JE, Russell E, Sorokin Y, et al. The levels of leptin, adiponectin, and resistin in normal weight, overweight, and obese pregnant women with and without preeclampsia. Am J Obstet Gynecol 2005; 193: 979-83.
21. Ma Y, Gao M, Liu D. Preventing high fat diet-induced obesity and improving insulin sensitivity through neuregulin 4 gene transfer. Sci Rep 2016; 6: 26242.
22. Jiang J, Lin M, Xu Y, Shao J, Li X, Zang H, et al. Circulating neuregulin 4 levels are inversely associated with subclinical cardiovascular disease in obese adults. Sci Rep 2016; 6: 36710.
23. Spradley FT. Metabolic abnormalities and obesity's impact on the risk for developing preeclampsia. Am J Physiol Regul Integr Comp Physiol 2017; 312: R5-12.
24. Huppertz B. Maternal-fetal interactions, predictive markers for preeclampsia, and programming. J Reprod Immunol 2015; 108: 26-32.
25. Daskalakis G, Bellos I, Nikolakea M, Pergialiotis V, Papapanagiotou A, Loutradis D. The role of serum adipokine levels in preeclampsia: A systematic review. Metabolism 2020; 106: 154172.
26. Kurek Eken M, Sahin Ersoy G, Yayla Abide C, Sanverdi İ, Devranoglu B, Kutlu T, et al. Association between circulating neuregulin 4 levels and metabolic, aterogenic, and AMH profile of polycystic ovary syndrome. J Obstet Gynaecol 2019; 39: 975-80.