Content available at: https://www.ipinnovative.com/open-access-journals

International Journal of Clinical Biochemistry and Research

Journal homepage: https://www.ijcbr.in/

Original Research Article

Assessment of serum markers in preeclampsia: A prospective study

Hülya Çiçek[1]*, Abdalrhman Kuba[1], Mete Gürol Uğur[2], Elif Bacak Güllü[3], Neslihan Tepe[2]

[1]*Dept. of Medical Biochemistry, School of Medicine, Gaziantep University, Gaziantep, Turkiye*
[2]*Dept. of Obstetrics and Gynecology, School of Medicine, Gaziantep University, Gaziantep, Turkiye*
[3]*Vocational School of Technical Sciences, Gaziantep University, Gaziantep, Turkiye*

ARTICLE INFO

Article history:
Received 16-10-2023
Accepted 16-11-2023
Available online 10-02-2024

Keywords:
Preeclampsia
Hypoxia- inducible factor 1-α subunit
Nesfatin
Ezrin
Placental protein 13
Neuropilin

ABSTRACT

Preeclampsia is a disease characterized by hypertension, proteinuria, and edema that occurs after the 20th gestational week. It is among the most important reasons for maternal/perinatal morbidity and mortality. Although many studies have been carried out, the pathophysiology of the disease is not fully known. Many methods have been proposed for evaluating risk factors leading to preeclampsia. In the past, the methods used to predict preeclampsia have usually been focused on non-biochemical markers, but nowadays there is a shift towards biochemical markers. Recently, many biochemical agents have been started to be used in the prediction of preeclampsia. In this study, the evaluation of some serum biomarkers in the follow-up preeclampsia was aimed. Serum nesfatin, ezrin, placental protein 13, hypoxia-inducible factor 1-α subunit (HIF1A), and neuropilin 1 levels were examined with the ELISA method. In the study, 90 samples taken from subjects, including pre-treatment preeclampsia (n =35), post-treatment preeclampsia (n = 35), and healthy control (n = 20) groups were evaluated. The data obtained from the study was analyzed with SPSS 22.0. As a result of the statistical analysis, pre-treatment nesfatin-1, and ezrin levels were found significantly lower than post-treatment and the healthy control group and HIF-1A levels were found significantly higher. As a result of these analyses, pre-treatment and post-treatment PP13 levels were found to be significantly higher than the healthy control group.
Considering the results obtained from the study, we can say that nestin, ezrin, HIF1A, PP13, and NRP1 are important biomarkers for predicting preeclampsia.

1. Introduction

Preeclampsia (PE) is one of the major complications encountered during pregnancy. PE is seen in 2 to 8% of pregnancies and is one of the important causes of maternal/fetal mortality.[1,2]

PE manifests clinically with hypertension, edema, and proteinuria after 20 weeks of gestation.[3]

The pathogenesis of PE is still unclear and is probably multifactorial. There is a considerable association between PE and abnormal placentation, endothelial dysfunction, and imbalance of pro-angiogenesis and anti-angiogenesis. Several studies have been conducted to minimize the risks of preeclampsia for mothers and infants and to obtain more detailed information on the early detection and/or prediction of this disease.[4–7] The present study for the first time reveals that nesfatin-1 affects peripheral arterial blood vessels and inhibits the nitric oxide donor-induced smooth muscle relaxations via impairing the cGMP production. The results are the first to demonstrate that nesfatin-1 modulates blood pressure by directly acting

* *Corresponding author*.
E-mail address: drhulyacicek@gmail.com (H. Çiçek).

https://doi.org/10.18231/j.ijcbr.2023.056

on peripheral arterial resistance.[8]

Accumulating evidence demonstrates that nuclear factor kappa-B (NF-_B) signaling contributes to inflammatory responses, and regulates the transcription of genes related to inflammatory responses. These findings suggest that nesfatin-1 may inhibit nuclear factor kappa-B-dependent inflammatory responses.[9] Serum nesfatin-1 levels were significantly decreased in women with preeclampsia.[10]

It has been reported that ezrin is found extensively in the microvilli of placental syncytiotrophoblasts, and this situation is associated with the cytoskeleton.[11] The role of ERM proteins during embryonic development has also been the subject of many studies[12] and it has been shown that radixin is the main protein that provides the connection between actin and membranes in blastocyst formation.[13]

In recent years, there has been increased interest in predicting PE in asymptomatic pregnancies with the help of clinical parameters and biochemical markers. In this study, we aimed to identify changes in serum levels of nesfatin, ezrin, placental protein-13 (PP-13), hypoxia-inducible factor-1a (HIF-1a), and neuropilin-1 (NRP-1) that affect the development of preeclampsia by separate mechanisms. No study evaluated all of these molecules together.

Determining the level of these biomarkers will probably contribute to the identification of asymptomatic pregnant women before the onset of the clinical symptoms of the disease, thereby providing promising results for fetal and maternal health, as well as enabling substantial savings in health expenses.

2. Materials and Methods

This study included 35 pregnant women with a gestational age of 24-42 weeks, who were admitted to Gaziantep University Faculty of Medicine, Department of Obstetrics and Gynecology with a diagnosis of preeclampsia, according to the criteria of American College of Obstetrics and Gynecology Guidelines,[14] and 20 maternal and gestational age-matched healthy pregnant women. This study was conducted upon the approval of the ethics committee of Gaziantep University Faculty of Medicine (2016/06) and by the Helsinki Declaration Rules. All patients included in the study were informed about the study and signed written consent forms.

Pregnant women with multiple pregnancies, gestational hypertension (HT), chronic HT, diabetes mellitus (DM), nephrotic syndrome, and other metabolic diseases, and pregnant women with anomalous fetuses were excluded from the study. Venous blood samples of 6 cc were taken from 35 patients who were diagnosed with preeclampsia before delivery and within the first 6 hours after delivery. The sera of the samples were obtained by centrifugation 1,500 x g for 10 min and were finally put into the Eppendorf tubes within an hour and stored at -80° C. In addition, we formed a control group consisting of 20 healthy pregnant women matching with those patients in terms of maternal and gestational age and collected serum samples. Serum levels of nesfatin, ezrin, HIF-1a, PP-13, and NRP-1 were determined by the ELISA method. All concentration/absorption curve charts and calculations related to the results were performed with the software of the Biotec® ELx808 absorbance microplate reader (Winooski, Vermont, ABD).

Serum PP13 levels were assessed with a commercially available quantitative sandwich-enzyme-linked immunosorbent assay kit, following the manufacturer's instructions (MyBioSource, Inc. San Diego, USA). The minimum detectable level of human serum PP13 was 9.4 pg/mL and the detection range was 15.625-1000 pg/mL. The intra- and inter-assay coefficients of variations were 6,38% and 5,13% respectively.

Serum HIF-1alpha levels were assessed with a commercially available quantitative sandwich-enzyme-linked immunosorbent assay kit, following the manufacturer's instructions (MyBioSource, Inc. San Diego, USA). The minimum detectable level of human serum HIF-1alpha was 1.0 pg/mL and the detection range was 6.25-200 pg/mL. The intra- and inter-assay coefficients of variations were 4,62% and 6,28% respectively.

Serum neuropilin-1 levels were assessed with a commercially available quantitative sandwich-enzyme-linked immunosorbent assay kit, following the manufacturer's instructions (MyBioSource, Inc. San Diego, USA). The minimum detectable level of human serum neuropilin-1 was 1.56 pg/mL and the detection range was 6.25-400 was 3,9-250 pg/mL. The intra- and inter-assay coefficients of variations were 8, 15% and 7,22% respectively.

Serum ezrin levels were assessed with a commercially available quantitative sandwich-enzyme-linked immunosorbent assay kit, following the manufacturer's instructions (Cusabio, Wuhan Hi-tech Medical Devices, Hubei/China). The minimum detectable level of human serum ezrin was 0.0178 ng/mL and the detection range was 0.312-20 ng/mL. The intra- and inter-assay coefficients of variations were 7, 85% and 8,16% respectively.

Serum nesfatin levels were assessed with a commercially available quantitative sandwich-enzyme-linked immunosorbent assay kit, following the manufacturer's instructions (Bio Vendor Laboratory Medicine, Brno, Czech Republic). The minimum detectable level of human serum nesfatin was 0.021 ng/mL and the detection range was 0.125–4 ng/ml ng/mL. The intra- and inter-assay coefficients of variations were 6, 21% and 7, 54% respectively.

2.1. Statistical analysis

Data obtained from the study were analyzed using SPSS 22.0 (Statistical Package for Social Sciences) package software. The normal distribution of numerical data was tested by the Shapiro–Wilk test. ANOVA and LSD tests were used to compare the variables with normal distribution between the 3 groups, whereas Kruskal-Wallis and all subset multiple comparison tests were used for the comparison of numerical variables with non-normal distribution between 3 groups. Correlations between categorical variables were tested by the Chi-square test. All results were evaluated at a 95% confidence interval ($p < 0.05$).

3. Results

This study included a total of 55 pregnant women, including 35 with preeclampsia and 20 healthy controls. Eleven of the patients were primigravid, [7 in preeclamptic patients (20%) and 4 in controls (20%) while 44 were multiparous 28 in preeclamptic patients (80%) and 16 (80%) in controls)] (Table 1).

Table 1: Distribution of subjects according to the number of pregnancies

	Preeclamptic	Healthy Pregnant
Primigravid	7(20%)	4(20%)
Multiparous	28(80%)	16(80%)
Total	35	20

The mean age of patients with preeclampsia and controls were 31.54±7.01 and 31.25±7.82; respectively (p=0.906). The mean gestational age of patients with preeclampsia and controls were 34.91±4.00 weeks and 35.50±3.36 weeks; respectively (p=0.783). The BMI of patients with preeclampsia before (group I) and after (group II) delivery, and controls (group III) were 30.7±5.06 kg/m^2, 26.39±4.77 kg/m^2,and 28.48±3.45 kg/m^2; respectively (p=0.001). There was a significant difference in BMI between patients in groups I and II (p=0.001) but there was no difference between group I vs III and group II and III (p=0.084 and p=0.112; respectively) (Table 2).

The biomarker levels of the subjects included in the study are shown in Table 3. Nesfatin-1 and ezrin levels of the patients were found to be significantly lower in group I compared to groups II and III (p=0.001). At the same time, the nesfatin-1 level was significantly lower in patients with preeclampsia after delivery than in the control group (p=0.002).

Neuropilin-1 was significantly lower in patients with preeclampsia before delivery than in the control group (p=0.001). HIF-1A levels were significantly higher in preeclampsia patients compared to patients with preeclampsia after delivery and control groups (p=0.001). Also, HIF-1a levels were significantly higher in patients with preeclampsia after delivery than in the control group (p=0.001). PP-13 levels were significantly higher in patients with preeclampsia before and after delivery than in the control group (p=0.001). But, there was no significant difference in PP-13 levels between the preeclampsia patients before and after delivery (p= 0.106).

4. Discussion

PE is associated with both maternal and fetal mortality and morbidity. Early diagnosis of preeclampsia is therefore crucial for the implementation of the appropriate preventive measures.[15]

Although there are many studies regarding the etiopathogenesis of PE, the process as a whole has not been elucidated yet.

Investigation of the presence of maternal risk factors, hypertension, proteinuria, and edema has been traditionally utilized for the early detection of PE. Recently, for the aim of prediction of preeclampsia, there has been a shift towards the measurable indicators of abnormal placentation and decreased placental perfusion. In parallel with studies on non-biochemical markers, a serious effort has been made in the last few years to find biochemical markers that will allow us to predict the risk of preeclampsia in asymptomatic pregnancies.[16]

Our present study aimed to evaluate changes in probable serum biomarker levels of nesfatin, ezrin, placental protein-13 (PP-13), hypoxia-inducible factor-1a (HIF-1a), and neuropilin-1 (NRP-1) that can be effective in the development of preeclampsia in pregnancies.

Epidemiological studies show that obesity is an important risk factor for the development of preeclampsia. In 2005, Bodnar et al.[17] showed that as BMI increases, the risk of preeclampsia increases.

In this present study, there was no significant difference in BMI between patients with PE and controls as seen in Table 2. Nesfatin-1 plays an important role in the regulation of eating habits**.** Nesfatin-1 has been shown to reduce food intake and weight in rats. This suggests that nesfatin-1 can establish a link between obesity and preeclampsia. In our study, nesfatin-1 levels were found to be lower in preeclamptic patients than in postpartum preeclampsia and control groups. In patients included in our study, the BMI of preeclamptic patients was higher than in patients with preeclampsia after delivery (p = 0.001). This supports the finding that nesfatin-1 reduces food intake and weight. However, Anwar et al. showed that serum nesfatin-1 levels were significantly higher in the obese group than in the control group. This discrepancy can be attributed to differences in the ethnicity of the study groups and the kits used.[18]

Therefore, there is a need for further studies to fully elucidate nestin-1's mechanism of action in obesity.

Nesfatin-1 is also an important mediator involved in the anti-inflammation. The administration of nesfatin-1 after

Table 2: Clinical variables of the subjects

	Preeclamptic		Healthy Pregnant	p Value
Maternal Age (years)	31,54±7,01 (18-42)		30.14±7.13 (19-39)	0,906
Gestational Age (months)	34,91±4,00 (27-38)		35,50±3,36 (28-42)	0,783
BMI (kg/m2)	Group I 30,7±5,06	Group II 26,39±4,77	Group III 28,48±3,45	<0,001*, =0.084, =0.112

*p<0.05 considered significant

Table 3: Comparison of serum biomarker levels according to study groups

	Preeclamptic before delivery (n=35) Group I	Preeclamptic after delivery (n=35) Group II	Healthy Pregnant Control(n=20) Group III	p Value
Nesfatin-1 (ng/mL)	0.35±0.19	0.72±0.16	1.09±0.28	0.001*
Ezrin (ng/mL)	0.34±0.17	0.53±0.27	0.82±0.44	0.001*
Neuropilin -1 (pg/mL)	43.52±24.42	50.11±21.86	68.42±27.01	0.004*
HIF-1alpha (pg/mL)	38.85±13.92	29.34±10.14	18.59±5.81	0.001*
PP13 (pg/mL)	391.80±82.29	351.39±93.99	203.20±67.07	0.001*

*p<0.05 considered significant

head trauma was observed to suppress nuclear factor kappa-B gene expression to a significant extent and decrease TNF-alpha, IL-1beta, and IL-6 concentrations in traumatic rat brain tissue.[19] Inflammation has also been associated with the pathogenesis of preeclampsia.[20]

Thus, the reduction in nesfatin-1 levels may be effective in the pathogenesis of preeclampsia by the suppression of anti-inflammatory activity. In our study, low nesfatin-1 levels in the preeclamptic patient group also support this theory as seen in Table 3.

Ezrin is an ezrin-radixin-moesin (ERM) family protein. ERM proteins provide cross-linking between plasma membrane proteins and the actin cytoskeleton. They are found in actin-rich structures within the cell.[21]

It has been reported that ezrin is abundant in the microvilli of placental syncytiotrophoblasts, which is associated with the cellular skeleton.[22]

As there is abnormal trophoblastic invasion in preeclampsia, a reduction in ezrin levels may be expected. However, this needs to be supported by further studies. Ezrin is synthesized in the glomerular and tubular epithelial cells of renal tissue, and a study conducted on renal tissue samples of preeclamptic women showed that ezrin levels were significantly lower in preeclamptic patients compared to patients with and without chronic hypertension.[23]

Similarly, in our study, ezrin levels were lower in preeclamptic patients than in patients with preeclampsia after delivery and control groups as seen in Table 3. There is a need for extensive studies to determine the exact mechanism of action of Ezrin in the pathogenesis of preeclampsia.

NPR-1 is a Type-1 transmembrane receptor in glycoprotein structure[24] and can bind to VEG-F165, VEGF-B, and some VEGF-E isoforms. In the presence of NRP-1, there is a 4-to 6-fold increase in the binding capacity of VEGF-A165 to VEGFR-2.[25,26] NRP-1 is a co-receptor that enhances the angiogenic activity of VEGF.[27] It has been reported that VEGF, an angiogenic factor, decreases in preeclamptic patients while other anti-angiogenic factors increase.[28]

NRP-1 acts as a receptor for VEGF-A and Semaphorin-3A.[29] NRP-1 and Semaphorin-3B have been reported as major factors affecting the VEGF family in PE.[30] Compared with healthy placentas, NRP-1 and VEGF levels were found to decrease in the placenta of preeclamptic patients.[31]

This was found to be consistent with the results of some other studies. In line with our study, it can be concluded that low NRP-1 levels in patients with PE contribute to pathogenesis via anti-angiogenetic activity as seen in Table 3. We believe that NRP-1 may play a role in angiogenic imbalance in preeclamptic pregnancies. In addition, NRP-1 may enhance the Soluble fms like tyrosine kinase-1 (sFlt-1) function by providing the augmentation of its binding to VEGF. sFlt-1 is a soluble form of Flt-1 secreted from the placenta and is effective in anti-angiogenesis.[32]

Jarvenpaa et al. found that VEGF is down-regulated in PE by profiling gene expression. Down-regulated VEGF levels prevent physiological vasodilatation, allowing the disclosure of vascular lesions in the maternal uteroplacental bed in preeclampsia.[33]

There is also some evidence indicating that NRP-1 inhibits apoptosis (colon cancer, breast cancer, etc). This inhibition is thought to be mediated through the regulation of Bcl-2 expression and Bax translocation.[34]

Therefore, we think that low expression of NRP-1 in preeclamptic placenta may also contribute to the apoptotic process.

In case of inadequate oxygenation of the tissues, hypoxia arises. HIF-1 is a nucleoprotein that plays an important role in the oxygen balance of cells. HIF-1 is formed by the combination of an oxygen-regulated HIF-1α subunit and a consistently expressed HIF-1ß subunit. Cells synthesize and eliminate HIF-1α protein on a continuous and regular basis in non-hypoxic conditions for a very rapid response to hypoxia.[35]

Semenza investigated the regulation of placental hypoxia, which occurs when uteroplacental circulation is reduced in preeclampsia. In hypoxic conditions, the increase in HIF and its associated transcription factors in response to decreased intracellular oxygen concentration has a significant effect on the formation of physiological responses.[36]

Similarly, in our study, HIF-1a levels were higher in preeclamptic pregnancies than in postpartum preeclamptic pregnancies and the control group, consistent with its physiology as seen in Table 3.

PP-13 is one of more than 50 proteins known to be synthesized from placenta. It is a member of the galectin family and contributes to the immunological tolerance at the maternal-fetal interface. The function of PP-13 in normal pregnancy and the pathogenesis of preeclampsia is not yet clear. Recently, the concentration of PP-13 is reduced in late-onset preeclamptic patients.[37,38]

In a prospective case-control study involving 423 controls with a gestational age of 11-13 weeks and 10 pregnant women who developed preeclampsia at a later stage and required delivery before 34 weeks, PP-13 has been identified as the first-trimester marker in the prediction of preeclampsia.[39]

Serum PP-13 concentration was low in the preeclamptic patient group. Conversely, PP-13 levels in our study were found to be higher in preeclamptic patients before and after delivery than in the control group as seen in Table 3. Tahan et al. found in their study, that placental PP-13 levels were low while serum PP-13 levels in the third trimester were high.[40]

In this regard, Sekizawa et al. measured maternal serum levels of PP-13 and evaluated the uterine artery pulsatility index for the prediction of preeclamptic cases requiring delivery before the 34th week. They compared preeclampsia-affected pregnancies with the control group and reported that PP-13 levels were higher in the preeclamptic group.[41]

The discrepancies in PP-13 levels between the studies suggest that PP-13 is still a marker for preeclampsia pathophysiology that should still be investigated in further studies.

5. Conclusion

Considering the results of our study, it can be suggested that nesfatin, ezrin, NRP-1, HIF-1a, and PP-13 are important biomarkers for diagnosing preeclampsia. The positive aspect of our study is that a large number of serum markers should be considered in the same study. Literature has preeclampsia studies in which these markers are studied but in these studies, the examination contained only 1 or 2 markers.

Early detection of preeclampsia will not only prevent maternal-fetal mortality and morbidity but also reduce the health expenditures for this issue. Therefore, there is a need for more extensive studies to investigate the relationship between these serum markers and preeclampsia from the first trimester.

In conclusion, it has been shown that in preeclamptic patients; serum levels of nesfatin-1, ezrin, and NRP-1 were decreased, whereas HIF-1a and PP-13 serum levels were increased.

6. Limitations

However, our study has some limitations. First, the number of patients is not enough to make a decision. There is a need for studies with large numbers of patients. Although serum biomarkers showed significant differences in preeclamptic patients, they were studied in the second and third trimesters. For early diagnosis of preeclampsia, which is a significant obstetric pathology, it would be more beneficial to study serum markers in the first trimester and to combine serum marker levels with the findings as to whether preeclampsia developed in these pregnancies or not.

7. Author Contribution Statement

All authors have reviewed and approved the manuscript before submission.

8. Conflict of Interest

Conflict of interest declared none.

References

1. Redman CW, Sargent IL. Latest advances in understanding preeclampsia. *Science*. 2005;308(5728):1592–4.
2. Bolte AC, Geijn HPV, Dekker GA. Management and monitoring of severe preeclampsia. *Eur J Obstet Gynecol Reprod Biol*. 2001;96(1):8–20.
3. Gallos ID, Sivakumar K, Kilby MD, Coomarasamy A, Thangaratinam S, Vatish M. Pre-eclampsia is associated with, and preceded by, hypertriglyceridaemia: a meta-analysis. *BJOG*. 2013;120(11):1321–32.
4. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. *Am J Obstet Gynecol*. 2000;183(1):1–22.
5. Sibai BM. Diagnosis and management of gestational hypertension and preeclampsia. *Obstet Gynecol*. 2003;102(1):181–92.
6. Lepage N, Chitayat D, Kingdom J, Huang T. Association between second-trimester isolated high maternal serum maternal serum human chorionic gonadotropin levels and obstetric complications in singleton and twin pregnancies. *Am J Obstet Gynecol*. 2003;188(5):1354–9.

7. Costa SL, Proctor L, Dodd JM, Toal M, Okun N, Johnson JA, et al. Screening for placental insufficiency in high-risk pregnancies: is earlier better? *Placenta*. 2008;29(12):1034–40.
8. Yamawaki H, Takahashi M, Mukohda M, Morita T, Okada M, Hara Y. A novel adipocytokine, nesfatin-1 modulates peripheral arterial contractility and blood pressure in rats. *Biochem Biophys Res Commun*. 2012;418(4):676–81.
9. Tang CH, Fu XJ, Xu XL, Wei XJ, Pan HS. The anti-inflammatory and anti-apoptotic effects of nesfatin-1 in the traumatic rat brain. *Peptides*. 2012;36(1):39–45.
10. Zhang C, Wang Y, Wang Y, Li J, Liu R, Liu H, et al. Decreased levels of serum nesfatin-1 in patients with preeclampsia. *Biomarkers*. 2014;19(5):402–6.
11. Berryman M, Gary R, Bretscher A. Ezrin oligomers are major cytoskeletal components of placental microvilli: a proposal for their involvement in cortical morphogenesis. *J Cell Biol*. 1995;131(5):1231–42.
12. Louvet S, Aghion J, Santa-Maria A, Mangeat P, Maro B. Ezrin becomes restricted to outer cells following asymmetrical division in the preimplantation mouse embryo. *Dev Biol*. 1996;177(2):568–79.
13. Matsumoto H, Daikoku T, Wang H, Sato E, Dey SK. Differential expression of ezrin/radixin/moezin (ERM) and ERM-associated adhesion molecules in the blastocyst and uterus suggests their functions during implantation. *Biol Reprod*. 2004;70(3):729–36.
14. ACOG Practice Bulletin No. 202: Gestational Hypertension and Preeclampsia. *Obstet Gynecol*. 2019;133(1):1–8.
15. Tjoa ML, Oudejans CBM, Vugt JMV, Blankenstein MA, Wijk IJV. Markers for presymptomatic prediction of preeclampsia and intrauterine growth restriction. *Hypertens Pregnancy*. 2004;23(2):171–89.
16. Baumann MU, Bersinger NA, Surbek DV. Serum markers for predicting pre-eclampsia. *Mol Aspects Med*. 2007;28(2):227–44.
17. Bodnar LM, Ness RB, Markovic N, Roberts JM. The risk of preeclampsia rises with increasing prepregnancy body mass index. *Ann Epidemiol*. 2005;15(7):475–82.
18. Anwar GM, Yamamah G, Ibrahim A, El-Lebedy D, Farid TM, Mahmoud R. Nesfatin-1 in childhood and adolescent obesity and its association with food intake, body composition and insulin resistance. *Regul Pept*. 2014;188:21–4.
19. Tang CH, Fu XJ, Xu XL, Wei XJ, Pan HS. The anti-inflammatory and antiapoptotic effects of nesfatin-1 in the traumatic rat brain. *Peptides*. 2012;36:39–45.
20. Vitoratos N, Hassiakos D, Iavazzo C. Molecular mechanisms of preeclampsia. *J Pregnancy*. 2012;doi:10.1155/2012/298343.
21. Amieva MR, Furthmayr H. Subcellular localization of moesin in dynamic filopodia, retraction fibers, and other structures involved in substrate exploration, attachment, and cell-cell contacts. *Exp Cell Res*. 1995;219(1):180–96.
22. Berryman M, Gary R, Bretscher A. Ezrin oligomers are major cytoskeletal components of placental microvilli: a proposal for their involvement in cortical morphogenesis. *J Cell Biol*. 1995;131(5):1231–42.
23. Zhao S, Gu X, Groome LJ, Wang Y. Decreased nephrin and GLEPP-1 but increased VEGF, Flt-1 and nitrotyrosine, expressions in kidney tissue sections from women with preeclampsia. *Reprod Sci*. 2009;16(10):970–9.
24. Peles E, Nativ M, Lustig M, Grumet M, Schilling J, Martinez R, et al. Identification of a novel contactin-associated transmembrane receptor with multiple domains implicated in protein-protein interactions. *EMBO J*. 1997;16(3):978–88.
25. Whitaker GB, Limberg BJ, Rosenbaum JS, Rosenbaum JS. Vascular endothelial growth factor receptor-2 and neuropilin-1 form a receptor complex that is responsible for the differential signaling potency of VEGF(165) and VEGF(121). *J Biol Chem*. 2001;276(27):25520–31.
26. Soker S, Miao HQ, Nomi M, Takashima S, Klagsbrun M. VEGF165 mediates the formation of complexes containing VEGFR-2 and neuropilin-1 that enhance VEGF165-receptor binding. *J Cell Biochem*. 2002;85(2):357–68.
27. Gelfand MV, Hagan N, Tata A, Oh WJ, Lacoste B, Kang KT, et al. Neuropilin-1 functions as a VEGFR2 co-receptor to guide developmental angiogenesis independent of ligand binding. *Elife* . 2014;3:e03720.
28. Maynard SE, Karumanchi SA. Angiogenic factors and preeclampsia. *Semin Nephrol*. 2011;31(1):33–46.
29. Battin C, Linhares ADS, Paster W, Isenman DE, Wahrmann M, Leitner J, et al. Neuropilin-1 Acts as a Receptor for Complement Split Products. *Front Immunol*. 2019;10:2209.
30. Gu C, Rodriguez ER, Reimert DV, Shu T, Fritzsch B, Richards LJ, et al. Neuropilin-1 conveys semaphorin and VEGF signaling during neural and cardiovascular development. *Dev Cell*. 2003;5(1):45–57.
31. Xu X, Yang XY, He BW, Yang WJ, Cheng WW. Placental NRP1 and VEGF expression in pre-eclamptic women and in a homocysteine-treated mouse model of pre-eclampsia. *Eur J Obstet Gynecol Reprod Biol*. 2016;196:69–75.
32. Moore KH, Chapman H, George EM. Unfractionated heparin displaces sFlt-1 from the placental extracellular matrix. *Biol Sex Differ*. 2020;11(1):34.
33. Opichka MA, Rappelt MW, Gutterman DD, Grobe JL, Mcintosh JJ. Vascular Dysfunction in Preeclampsia. *Cells*. 2021;10(11):3055.
34. Ochiumi T, Kitadai Y, Tanaka S, Akagi M, Yoshihara M, Chayama K. Neuropilin-1 is involved in regulation of apoptosis and migration of human colon cancer. *Int J Oncol*. 2006;29(1):105–16.
35. Infantino V, Santarsiero A, Convertini P, Todisco S, Iacobazzi V. Cancer Cell Metabolism in Hypoxia: Role of HIF-1 as Key Regulator and Therapeutic Target. *Int J Mol Sci*. 2021;22(11):5703.
36. Semenza GL. Hypoxia-inducible factor 1: control of oxygen homeostasis in health and disease. *Pediatr Res*. 2001;49(5):614–7.
37. Papageorghiou AT, Campbell S. First trimester screening for preeclampsia. *Curr Opin Obstet Gynecol*. 2006;18(6):594–600.
38. Burger O, Pick E, Zwickel J, Klayman M, Meiri H, Slotky R, et al. Placental protein 13 (PP-13): effects on cultured trophoblasts, and its detection in human body fluids in normal and pathological pregnancies. *Placenta*. 2004;25(7):608–22.
39. Nicolaides KH, Bindra R, Turan OM, Chefetz I, Sammar M, Meiri H, et al. A novel approach to first-trimester screening for early pre-eclampsia combining serum PP-13 and Doppler ultrasound. *Ultrasound Obstet Gynecol*. 2006;27(1):13–7.
40. Than NG, Balogh A, Romero R, Kárpáti E, Erez O, Szilágyi A, et al. Placental Protein 13 (PP13) - A Placental Immunoregulatory Galectin Protecting Pregnancy. *Front Immunol*. 2014;5:348. doi:10.3389/fimmu.2014.00348.
41. Sekizawa A, Purwosunu Y, Yoshimura S, Nakamura M, Shimizu H, Okai T, et al. PP13 mRNA expression in trophoblasts from preeclamptic placentas. *Reprod Sci*. 2009;16(4):408–13.

Author biography

Hülya Çiçek, Professor https://orcid.org/0000-0002-1065-1582

Abdalrhman Kuba, Biochemist https://orcid.org/0000-0002-0720-970X

Mete Gürol Uğur, Professor https://orcid.org/0000-0002-0720-970X

Elif Bacak Güllü, Assistant Professor https://orcid.org/0000-0002-2632-0550

Neslihan Tepe, Associate Professor https://orcid.org/0000-0003-0396-5791

Cite this article: Çiçek H, Kuba A, Uğur MG, Güllü EB, Tepe N. Assessment of serum markers in preeclampsia: A prospective study. *Int J Clin Biochem Res* 2023;10(4):314-319.