HJOG An Obstetrics and Gynecology International Journal

Research

HJOG 2021, 20 (3), 143-148 | DOI: 10.33574/HJOG.0205

Relationship of soluble Fms-like tyrosine kinase 1, soluble endoglin, placental growth factor blood levels with the severity of late onset preeclampsia

Ethem Serdar Yalvac[1], Mustafa Kara[2], Emre Baser[1], Taylan Onat[1], Melike Demir Caltekin[1], Müjgan Ercan[3], Demet Aydogan Kirmizi[1]

[1]Yozgat Bozok University, Faculty of Medicine, Department of Obstetrics and Gynecology, Yozgat, Turkey
[2]Ahi Evran University Training and Research Hospital, Department of Obstetrics and Gynecology, Kırşehir, Turkey
[3]Harran University Faculty of Medicine, Department of Medical Biochemistry, Şanlıurfa, Turkey

Corresponding Author

Dr. Emre Başer, Department of Obstetrics and Gynecology, Yozgat Bozok University Faculty of Medicine, Yozgat, Turkey.
Tel.: +90 505 2749203, e-mail: emrebasermd@gmail.com

Abstract

Purpose: Preeclampsia (PE) is a pregnancy-specific syndrome characterized by placentation disorder that increases maternal and fetal morbidity and mortality. Overproduction of anti-angiogenic factors such as soluble fms-like tyrosine kinase receptor 1 (sFlt-1) and soluble endoglin (sEng) and low production of placental growth factor (Pgf) from angiogenic factors contribute to preeclampsia pathogenesis. In this study, factors involved in angiogenesis including sEng, Pgf and sFlt1 were investigated for pre-recognition of preeclampsia.

Methods: A total of 54 pregnant women were included in the study and the patients were divided into normotensive (n = 25) and preeclampsia groups (n = 29). Both groups demographic characteristics, laboratory parameters, sEng, sFlt1 and placental growth factor levels were compared.

Results: While AST, uric acid, LDH mean values were significantly higher in the study group compared to the control group ($p<0.05$), there was no significant difference between the groups in terms of ALT, creatinin, hemoglobin, leucocyte, and platelet values. sEng, sFlt1 values were significantly lover in the preeclampsia group compared to the control group ($p<0.05$).

Conclusion: it is thought that Pgf may have a place in the prediction of preeclampsia in advanced pregnancy weeks, but sFlt-1 and sEng are weak in predicting preeclampsia in advanced pregnancy weeks as well.

Key words: Angiogenesis, preeclampsia, soluble endoglin, soluble fms-like tyrosine kinase 1

Introduction

Since preeclampsia, which is seen at a rate of % 7 during pregnancy, cannot be brought under control, may cause maternal deaths. Early diagnosos parameters have been studied for a long time. In recent

years, an increasing number of studies have been conducted on angiogenic factors in the pathogenesis of preeclampsia. In order the placentation to be healthy, angiogenic and anti-angiogenic factors must work in harmony. Among angiogenic factors, we can count vaso-endothelial growth factor (VEGF), Placental Growth Factor (Pgf), and as anti-angiogenic factors including fms-like Tyrosine kinase 1 (sFlt-1) and soluble Endoglin (sEng)[1,2]. It is thought that the balance in preeclamptic pregnant women is disturbed, in favor of anti-angiogenic factors[3]. It is assumed that, before the clinical picture of preeclampsia appears, maternal Pgf and VEGF levels decrease, whereas maternal sFlt-1 and sEng levels increase. As a result, placentation is impaired, maternal blood pressure is increased by inter-synthetic factors so that the oxygen and nutrients needed by the fetus can be directed to the fetus as a result of insufficient perfusion and the PE table begins its clinical course in this way.

The aim is to recognize the problem early. For this purpose, both clinical diagnosis can be made before symptoms appear, as the levels of angiogenic factors such as s-Flt1, Placental Growth Factor and sEng are detected early in maternal blood. Unwanted results can be prevented as a result of close follow-up of these patients. Although PE has not yet found a definitive treatment, it will be possible to prevent possible adverse events by early detection of the risky group.

Preeclampsia is a picture accompanied by hypertension, proteinuria and end organ damage in pregnant women after 20 weeks of gestation. The trigger mechanism of the etiopathogenesis today is not known during the placentation phase, resulting decrease of the placental perfusion. Reduced placental perfusion can lead release of intrinsic factors that causes blood pressure elevation in order to direct the needed oxygen and nutrients to the fetus while at the same time causing the symptoms of PE.

The aim is to recognize early. For this purpose, the early detection of the levels of angiogenic factors such as s-Flt, Pgf and sEng in maternal blood, allows clinical diagnosis to be made before symptoms appear. Besides, as a close follow-up of these patients, unwanted results will be prevented. Although, a definitive treatment of PE has not found yet, it will be possible to prevent negativities by early detection of the risky group.

Materials and Methods

This study was carried out prospectively between January 2018 and February 2019 in a tertiary center. 54 patients included in the study, were divided into two groups. Preeclamsia group (n=29) with an age range between 18-40 and who have PE between $34^{1/7}$- $36^{6/7}$ gestational weeks with singleton pregnancy were compared with the control group (n=25) formed from healthy singleton pregnancies between $37^{0/7}$-$40^{6/7}$ gestational weeks, without having any pregnancy comlications. The study was approved by the local ethical committee in our hospital and informed consent was obtained from all participants.

Late onset Preeclampsia diagnosis after 34th week of gestation was made by blood pressure measurements taken at least four hours intervals and determined by systolic pressure above 140 mmHg and diastolic pressure above 90 mm Hg and also by measuring proteinuria in 24-hour urine ≥ 0.3 g; proteinuria/creatinine ratio ≥ 0.3 or ≥+1 proteinuria in spot urine sample[4]. Chronic hypertension, liver, kidney and heart diseases, hypercholesterolemia, diabetes mellitus, rheumatological diseases, twin pregnancies, fetal anomalies, having fetal growth retardation (FGR), or small for gestational age (SGA) fetuses, presence of any infection, smoking and alcohol use, and basic proteinuric patients and patients whose blood samples could not be obtained were excluded from the study. Patients' age, gravidity, parity, gestational weeks, systolic/distolic blood pressure levels, protein levels in spot urine, leucocyte,

hemoglobine, platelet counts and creatinine, uric acid, liver function markers (AST, ALT, LDH), angiogenic and antiangiogenic factors sEng, sFlt,and Pgf levels were recorded. Gestational weeks were determined according to the last menstruel period confirmed by ultrasonography.

Fasting blood taken from the patients with PE before the administration of any medication and from normotensive pregnant women was centrifuged within 30 minutes and stored at -80º Celsius until analysis. Blood samples were taken after 34 weeks in both groups. sEng, sFlt1and Pgflevels with commercial Elisa kits (Quantikine; R&D Systems Europe, Abingdon, United Kingdom) and analyed in accordance with standard protocols. The study was conducted at the Gynecology and Obstetric Department and Biochemistry Laboratory of Yozgat Bozok University, Medical Faculty, Turkey.

Statistical package program SPSS 20 (IBM Corp. released 2011. IBM SPSS Statistics for Windows, version 20.0, Armonk, NY: IBM Corp.) was used to evaluate the data. Continuous variables were investigated using analytical methods (Kolmogrov-Simirnov / Shapiro-Wilk's test) to determine whether or not they are normally distributed. For double comprasion, The Mann-Withney U test was utilized for the non parametric numarical data while the Student T test was adopted for the parametric numerical data. Results were evaluated as ± standard deviation value. A "p" value of <0.05 was considered significant.

Results

25 controls and 29 preeclamptic patients were included in the study. The mean age of the control goup was 29.00 (±4.9), and that of the study group was 31.76 (±5.61 (p=0.048). There was no significant difference in gravida and parity between two groups. The mean values of arterial blood pressures of the control group was found as systolic 100.83 (±10.18) mmHg, and diastolic 64.16 (±9.28) mmHg; while the systolic and diastolic values of preeclampsia group was 149.1(±12.19) and100.83 (±10.17) mmHg, respectively. The difference was significant (p=o.000) (Table-1).

While AST, uric acid, LDH mean values were significantly higher in the study group compared to the control group (p<0.05), there was no significant difference between the groups in terms of ALT, creatinin, hemoglobin, leucocyte, and platelet values. sEng, sFlt1 values were significantly lover in the preeclampsia group compared to the control group (p<0.05). Pgf, 1st and 5th minutes APGAR scores and birth weight were significantly lower in the preeclampsia group compared to control group (p<0.05) (Table 2).

Table 1. Demographic Characteristics

SPECIFICATIONS	STUDY GROUP (N:29)	CONTROL GROUP (N:25)	P
Age (years)	31.76 (±5.61)	29.00 (±4.90)	0.048**
Gravidity	2.71(±1.56)	3.08 (±1.50)	0.347*
Parity	1.36 (±1.22)	1.58 (±1.14)	0.430*
Gestational age at delivery (weeks)	35.59 (±2.67)	38.12 (±0.97)	<0.001*
Systolic Blood Pressure (mm Hg)	149.10 (±12.19)	100.83 (±10.18)	<0.001*
Diastolic Blood Pressure (mm Hg)	100.83 (±10.17)	64.16 (±9.28)	<0.001*

The results are presented as mean ± SD. *Mann-Withney U test,**Student T test.

Table 2: Laboratory analysis

SPECIFICATIONS	STUDY GROUP (N:29)	CONTROL GROUPOL (N:25)	P
AST (IU/L)	35.29 (±37.41)	16.65 (±4.66)	**0.026**
ALT (IU/L)	31.50 (±48.65)	14.75 (±10.41)	0.275
Uric acid (µmol/L)	8.79 (±3.88)	6.85 (±1.90)	**0.008**
Creatinine (µmol/L)	0.61 (±0.11)	0.57 (±0.05)	0.078
LDH (IU/L)	252.96 (±99.80)	181.74 (±35.51)	**0.003**
Wbc (×1.000/mm3)	10241.43 (±3179.45)	10075.71 (±2404.28)	0.904
Platelet (K/mL)	223095.24 (±44180.20)	223464.29 (±79228.45)	0.606
Hgb (g/dL)	12.33 (±1.15)	12.10 (±1.31)	0.664
sEng (ng/mL)	5.08 (±0.89)	10.83 (±1.22)	**<0.001**
sFlt1 (ng/mL)	757.64 (±67.67)	1325.84 (±186.55)	**<0.001**
Pgf (pg/mL)	99.49 (±21.70)	822.40 (±183.93)	<0.001

*The results are presented as mean ± SD. *Mann-Withney U test, **Student T test.*

AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, WBC: white blood cell, Hgb: haemoglobin, Pgf: placental growth factor, sFlt-1: soluble fms-like Tyrosine kinase 1, sEng: soluble Endoglin.

Discussion

Preeclampsia is a systemic disease that begins after the 20th week of pregnancy and progresses with hypertension and proteinuria. Since preeclampsia, which is seen about %7 of the pregnancy population, cannot be controlled, it causes complications such as eclampsia and HELLP syndrome which might cause maternal deaths. For his reason, early diagnosis parameters are being worked on in order to recognize the picture in advance.

Both maternal and fetal/placental factors play a role in the pathophisiology of preeclampsia. Especially, some intrinsic factors come into play as reactive to insufficient placental vascular development resulting from insufficient placentation, and hypertension occurs in the mother to provide placental perfusion, while fetal groth retardation may ocur due to insufficient placental perfusion in the fetüs despite this high blood pressure 4. A placental disease, preeclampsia progresses in 2 stages: (1) abnormal placentation early in the first trimester followed by (2) a "maternal syndrome in the later second and third trimesters characterized by an excess of antiangiogenic factors. A number of theories have been put forward for the placental dysfunction observed in stage 1, including oxidative stress, abnormal natural killer cells (NKs) at the maternal-fetal interface, and genetic and environmental factors, but none has conclusive evidence. However, substantial evidence strongly supports the idea that the diseased placenta causes the release of soluble toxic factors into the maternal circulation, leading to inflammation, endothelial dysfunction, and maternal systemic disease[5,6].

As mentioned above, angiogenic factors VEGF and Pgf and anti-angiogenic factors sFlt-1 and sEng should work in harmony. It is asusumed that maternal Pgf and VEGF levels decrease, while maternal sFlt-1 and sEng levels increase before preeclampsia clinical picture emerges[7]. The aim of our study is to investigate whether these angiogenic factors can have a place in early diagnosis in cases with late-onset preeclampsia. In our study, Pgf among angiogenic factors was found to be low in accordence with literature, while anti-angiogenic factors sFlt-1 and sEng

were found to be low. The low level of these last two anti-angiogenic factors is not compatible with the literature. Although the result contradicts the literature, the difficulties in detecting late preeclampsia cases have been confirmed by many publications. Our results may have been contradictory in relation to this situation.

Tsiakkas et al. (2016) reported the sensitivity of evaluating Pgf and maternal factors together at 12 weeks of gestation with a false positive rate of %10 and predicting early and late onset preeclampsia as %79 and %40, respectively[8]. Kleinrouweler et al. found the sensitivity of Pgf, sFlt-1 and sEng in the prediction of preeclampsia as %32,%26, and %18, respectively, with a false positive rate of %5[9].

As a result, they claim that these markers alone do not have sufficent efficiency in predicting preeclampsia. Hirodata et al. stated that the sFlt value in the early weeks of pregnancy was higher compared the values obtained in the late weeks, and they claimed that looking at this parameter at 32 weeks and after may be misleading[10].

In our result it turned out as suggested by Hirodata et.al. In this case, it is thought that it may be misleading to look at angiogenic markers during the advanced gestational week. In the light of this information; considering that the low number of our cases may also have an effect, Pgf may have a place in the prediction of preeclampsia in advanced weeks of gestation, however, it can be thougt that sFlt-1 and sEng are weak in predicting preeclampsia in advanced gestational weeks, as they have low sensitivity stated in the literature.

Ethics

Ethics Committee Approval: This study was approved by the Research Ethics Committee of the Bozok University Faculty of Medicine.

Informed Consent: It has been taken.

Peer-review: External and internal peer-reviewed

Authorship Contributions

Surgical and Medical Practices: Concept: D.A.K, M.K., E.S.Y. Design: M.K., E.S.Y., T.O.,M.E., Data Collection or Processing: E.B., M.D.C., Analysis or Interpretation: E.B.,T.O,Writing: E.S.Y, D.A.K., E.B.

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

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

Acknowledgement

This study (Project number = 6602b-TF/17-108) was supported by Yozgat Bozok University Scientific Resarch Commision Fund.

References

1. Brownfoot FC, Tong S, Hannan NJ, Hastie R, Cannon P, Tu'uhevaha J. Effects of simvastatin, rosuvastatin and pravastatin on soluble fms-like tyrosine kinase 1 (sflt-1) and soluble endoglin (seng) secretion from human umbilical vein endothelial cells, primary trophoblast cells and placenta. BMC pregnancy and childbirth. 2016;16:1-8.
2. Cheng M, He P, Fu J. The relationship between circulating tissue transglutaminase, soluble fms-like tyrosine kinase-1, soluble endoglin and vascular endothelial growth factor in pre-eclampsia. J Hum Hypertens. 2016;30:788-93.
3. Cim N, Kurdoglu M, Ege S, Yoruk I, Yaman G, Yildizhan R. An analysis on the roles of angiogenesis-related factors including serum vitamin d, soluble endoglin (seng), soluble fms-like tyrosine kinase 1 (sflt1), and vascular endothelial growth factor (vegf) in the diagnosis and severity of late-onset preeclampsia. J Matern Fetal Neonatal Med. 2017;30:1602-7.
4. Steegers EA, Von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. Lancet. 2010;376:631-44.
5. Redman CW, Sargent IL. Latest advances in understanding preeclampsia. Science.

2005;308(5728):1592-4.
6. Romero R, Chaiworapongsa T. Preeclampsia: a link between trophoblast dysregulation and an antiangiogenic state. J Clin Invest. 2013;123(7):2775-7.
7. Madazlı R. Gebelikte tarama ve öngörü. İstanbul tıp kitabevi, 1. Baskı, 2017,s. 197-217.
8. Tsiakkas A, Cazacu R, Wright A, Wright D, Nicolaides K. Maternal serum placental growth factor at 12, 22, 32 and 36 weeks' gestation in screening for pre-eclampsia. Ultrasound Obstet Gynecol. 2016;47:472-7.
9. Kleinrouweler CE, Wiegerinck MM, Ris-Stalpers C, Bossuyt PM, van der Post JA, von Dadelszen P, et al. Accuracy of circulating placental growth factor, vascular endothelial growth factor, soluble fms-like tyrosine kinase 1 and soluble endoglin in the prediction of pre-eclampsia: A systematic review and meta-analysis. BJOG. 2012;119:778-87.
10. Suzuki H, Hirashima C, Nagayama S, Takahashi K, Yamamoto T, Matsubara S, et al. Increased serum levels of sflt-1/plgf ratio in preeclamptic women with onset at< 32 weeks compared with≥ 32 weeks. Pregnancy Hypertens. 2018;12:96-103.

Received 20-05-21
Revised 25-05-21
Accepted 03-06-21