Research Article

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High serum angiopoietin-like protein-4 levels are associated with gestational hypertension and preeclampsia: a case-control study

https://doi.org/10.1515/tjb-2023-0087
Received April 13, 2023; accepted February 9, 2024;
published online March 11, 2024

Abstract

Objectives: Investigation of angiopoietin-like protein-4 (ANGPTL-4) and vascular endothelial growth factor A (VEGF-A) levels as a biochemical marker in gestational hypertension (GH) and preeclampsia (PE), which are known to have important roles in the maintenance of angiogenesis and endothelial functions.

Methods: A total of 90 patients included in this case-control study. Group 1 (G1) (n=30)=patients with healthy pregnancy between 37 and 41 weeks, G2 (n=30)=patients diagnosed with gestational hypertension between 20 and 37 weeks, G3 (n=30) =patients diagnosed with preeclampsia between 20 and 37 weeks. The sera obtained from the patients were stored at −80 °C until they were studied. Demographic parameters, systolic, diastolic and mean arterial blood pressure were recorded. VEGF-A and ANGPTL-4 levels were studied with enzyme-linked immunosorbent assay (ELISA) kit.

Results: The mean age was similar in both groups. The number of primigravida pregnant was higher in G2 and G3 than in G1. Gestational week was more advanced in G1 compared to G2 and G3. While ANGPTL-4 and VEGF-A levels were similar between G2 and G3, they were significantly higher in both groups compared to G1.

Conclusions: We showed that ANGPTL-4 and VEGF-A levels were elevated in maternal serum in GH and PE cases. Increased maternal serum ANGPTL-4 levels may be a biomarker that can be used in the early diagnosis of PE.

Keywords: pregnancy; preeclampsia; gestational hypertension; ANGPTL-4; VEGF-A

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Introduction

Preeclampsia (PE), a serious complication of pregnancy, affects 8.5 million women every year in the world, with a prevalence ranging from 3 to 8 %. PE, which is a multisystemic disease, is responsible for 18 % of pregnancy-related maternal deaths and 40 % of fetal deaths. Currently, there is no definitive diagnostic tool and effective treatment method that can be used in the early diagnosis of PE [1]. Hypertension diagnosis criteria were used if a pregnant woman had a systolic blood pressure exceeding 140 mmHg or a diastolic blood pressure exceeding 90 mmHg, which was measured at least twice with a 4 h interval while at rest. On the other hand, if the amount of protein detected in the 24 h total urine is over 300 mg/dL, it was accepted as the diagnostic criterion for preeclampsia [2]. Detection of hypertension after 20 weeks of gestation in a previously normotensive pregnant is defined as gestational hypertension (GH). In these cases, hypertension resolves after delivery [3]. According to the American College of Obstetricians and Gynecologist (ACOG) in 2013, proteinuria is not mandatory for the diagnosis of preeclampsia [4].

Conditions such as inflammation, oxidative stress, some angiogenic and/or antiangiogenic and endothelial damaging agents, enzymes associated with hormone and lipid metabolism, and fetal distress are among the currently used and investigated markers for the early diagnosis of PE [5]. The effectiveness of biomarkers is determined by the ability to diagnose the disease long before the appearance of clinical symptoms, and it would be an advantage if possible changes

could be detected through minimally invasive blood tests performed as part of routine controls [6]. However, when they are used together rather than alone, these markers increase their effectiveness in the early diagnosis of PE [7]. Placental growth factor (PIGF) is angiogenic, fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng) are antiangiogenic proteins. Antiangiogenic factors are increased in PE [8]. Before the clinical feature of preeclampsia appears, maternal PIGF levels decrease, whereas maternal sFlt-1 and sEng levels increase [9]. Serum neutrophil gelatinase-related lipocalin levels were found to be higher in patients with both early- and late-onset preeclampsia than in patients without preeclampsia [10]. It has been reported that fractalkine, a chemokine involved in the inflammatory process, is increased in the serum of patients with premature rupture of membranes and preeclampsia [11, 12]. Angiopoietin-like protein 4 (ANGPTL-4) is involved in the regulation of angiogenesis as well as in energy, lipid, and glucose metabolism [13]. It has been shown that increased ANGPTL-4 levels are associated with hypertension [14], atherosclerosis [15], and coronary artery disease [16]. ANGPTL-4 can act as an antiangiogenic protein as well as showing a proangiogenic effect. Although ANGPTL-4 has been shown to be effective in protecting endothelial cell integrity, it has also been shown to play a role in the development of atherosclerosis by causing endothelial damage [17]. Vascular endothelial growth factor (VEGF) is a major regulator of angiogenesis and lymphangiogenesis [18]. VEGF-A induces endothelial cell proliferation and increased vascular permeability [19]. VEGF-A, which is expressed in the placenta during pregnancy, plays an important role in the regulation of placental angiogenesis and maternal spiral artery remodeling [20].

Although many markers have been examined for the possible diagnosis and follow-up of PE, we investigated the maternal serum values of ANGPTL-4 and VEGF-A, which are known to have important roles in the maintenance of angiogenesis and endothelial functions, with the thought that they may have a role in the pathophysiology of PE.

Materials and methods

This case-control study was carried out in the Obstetrics Clinic of Fırat University, Faculty of Medicine, after obtaining the approval of the Ethics Committee (Ethics Committee decision no: 2021/02-10). The study was conducted in accordance with the Helsinki principles. Three groups (G) were formed with a total of 90 patients included in the study.

G1 (n=30)=control group consisting of healthy pregnant women between 37 and 41 weeks.

G2 (n=30)=patients diagnosed with GH between 20 and 37 weeks.

G3 (n=30)=patients diagnosed with PE between 20 and 37 weeks.

Age, number of pregnancies, gestational week, systolic, diastolic and mean arterial blood pressure were recorded.

Diagnosis of preeclampsia

ACOG 2013 criteria were used in the diagnosis of PE. After the 20th week of pregnancy, in two measurements made at least 4 h apart at rest; having a blood pressure of 140 and/or 90 mmHg and above, a protein of 300 mg or more in 24 h urine, or a protein/creatinine ratio of 0.3 and above, or if other tests cannot be performed, at least 1 (+) positive in the dipstick test (persistent in random urine sampling), a diagnosis of PE was made in the presence of 30 mg/dL proteinuria and/or organ dysfunction. Presence of one of the symptoms or findings such as serum creatinine >1.1 mg/dL or two-fold elevation, thrombocytopenia, at least two-fold elevation of liver enzymes, pulmonary edema, cerebral or visual disturbances, without proteinuria with high blood pressure was also considered as PE [4].

Diagnosis of gestational hypertension

GH was defined as the measurement of systolic blood pressure above 140 mmHg and/or diastolic blood pressure above 90 mmHg in two different measurements made 4 h apart after the 20th gestational week in a pregnant woman who had normal blood pressure before the 20th week of pregnancy [3].

Patient exclusion criteria

Chronic hypertensive pregnant women, those with multiple pregnancies, pregnant women with diabetes, eclampsia, HELLP syndrome and those with chronic liver and renal disease were excluded from the study.

Pregnant women who did not have any health problem and who gave birth after 37 weeks were considered as healthy pregnant group. Age, gestational week, and previous pregnancy history, if any, were recorded.

Sampling technique

For the determination of ANGPTL4 and VEGF-A serum levels after the diagnosis of the pregnant women in the GH and PE group was made, 10 cc venous blood was taken into a straight biochemistry tube, centrifuged at 5,000 rpm for 10 min, and the serums were stored at −80 °C until they were studied. When the routine examination cards of healthy pregnant women were examined, it was observed that no high blood pressure was detected, and after blood pressure measurements were made again, the necessary blood samples were taken and stored in the same way, adhering to the criteria specified in the general information section.

Biochemical measurements

ANGPTL-4 level was studied using the Human ANGPTL-4 enzyme-linked immunosorbent assay (ELISA) kit (Shanghai Sunredbio Technology Co. Ltd. Catalog no: 201-12-3155, China) in accordance with the kit user manual. Absorbance was read spectrophotometrically at 450 nm in a Multiskan FC Microplate Photometer (Thermo Scientific, USA).

Test results were presented in ng/mL. Kit sensitivity: 2.178 ng/mL, measurement range: 2.5–700 ng/mL.

Serum VEGF-A level was studied in accordance with the kit instruction manual using the Human VEGF-A ELISA kit (Shanghai Sunredbio Technology Co. Ltd. Catalog no: 201-12-0051, China). Absorbance was read spectrophotometrically at 450 nm in a Multiskan FC Microplate Photometer (Thermo Scientific, USA). Test results were presented as pg/mL. Kit sensitivity: 2.677 pg/mL, measurement range: 3–90 pg/mL.

Statistical analysis

Statistical analysis of the data was evaluated using the IBM SPSS Statistics Version 22.0 package program. In the evaluation of categorical measurements, numbers and percentages were used, and continuous measurements were shown as mean and standard deviation. Kolmogorov-Smirnov test was used to determine the normal distribution of continuous measurements. One-Way Analysis of Variance (ANOVA) was used for overall comparison of continuous measures of more than two groups. $p<0.03$ was considered significant.

Results

Mean age of both groups was similar ($p>0.03$). The number of nulliparous pregnant was higher in G2 and G3 compared to G1 ($p<0.001$). Gestational week was lower in G2 and G3 than G1 ($p<0.001$). Systolic, diastolic and mean arterial pressure (MAP) values were higher in G2 and G3 than in G1 ($p<0.001$) (Table 1).

While ANGPTL-4 and VEGF-A levels were similar in G2 and G3 ($p>0.03$), they were significantly higher than G1 in both groups ($p<0.001$) (Table 1).

Discussion

In this study, we evaluated serum concentrations of ANGPL-4 and VEGF-A in maternal serum. As a result of our study, the mean values of ANGPL-4 and VEGF-A serum levels were found to be significantly higher in the PE and GH group than in normal pregnant women. We think that it can be used as an early marker in the development of PE by establishing the cut-off value for ANGPI-4 and VEGF-A serum levels by studying in larger patient groups.

PE and GH are more common in primigravids [21]. In our study, we found the number of primigravid pregnant women to be high in the GH and PE groups.

PE has been shown to be associated with an imbalance between angiogenic and anti-angiogenic factors, also defined as “angiogenic imbalance”. It includes proangiogenic factors VEGF and PlGF, sEng [22], soluble VEGF receptor 1 (sVEGF-R1), and a soluble form of fms-like tyrosine kinase 1 (sFlt1) known as its generic splice variant [23]. Blocking VEGF and PLGF by sFlt1 inhibits angiogenic effects in the maternal circulation [24]. It has been reported that sFlt-1 levels increase in maternal serum five weeks before the onset of PE [25].

In a preeclamptic placenta, the remodeling of the spiral arteries is impaired, which reduces the oxygenation of the placenta, resulting in ischemia. Placental ischemia contributes to maternal endothelial damage by increasing the production of antiangiogenic factors [26]. Placental hypoxia causes endothelial damage in preeclampsia by activating hypoxia Inducible Factor-1α (HIF-1α). sFlt1 causes endothelial damage in preeclampsia due to its antiangiogenic property. However, ANGPTL-4 regulates inflammation, lipid and glucose metabolism, and increased vascular permeability [27, 28].

Hypoxia-induced expression of ANGPTL-4 in human endothelial cells elicits a potent VEGF-independent proangiogenic response [29]. HIF-1α causes placental disorder by inducing ANGPTL-4 in placental hypoxia and it also blocks trophoblast invasion because it increases TGF-β3, which is another target [30], and thus it is associated with PE [31].

Table 1: Dermographic parameters, angiopoietin-like protein 4 (ANGPTL4) and vascular endothelial growth factor A (VEGF-A) serum levels of control group (G1), gestational hypertension (G2) and preeclampsia group (G3).

Parameters	Control group (G1) (n=30)	Gestational hypertension group (G2) (n=30)	Preeclampsi group (G3) (n=30)	p-Values
Age, years	31.4 ± 5.1	33.6 ± 3.7	30.3 ± 4.8	>0.03
Parity, n	2.7 ± 1.53	1.9 ± 1.24[a]	1.8 ± 0.83[a]	<0.001
Gestational week, week	38.2 ± 1.4	32.7 ± 3.74[a]	30.70 ± 4.21[a,b]	<0.001
Systolic blood pressure, mmHg	101.2 ± 10.33	142.62 ± 7.90[a]	161.23 ± 11.68[a,b]	<0.001
Diastolic blood pressure, mmHg	68.56 ± 6.32	96.72 ± 4.77[a]	119.20 ± 3.26[a,b]	<0.001
Mean arterial blood pressure, mmHg	79.44 ± 7.6	112.02 ± 5.8[a]	133.21 ± 6[a,b]	<0.001
ANGPTL4, ng/mL	53.05 ± 7.25	94.909 ± 7.56[a]	117.806 ± 7.63[a]	<0.001
VEGF-A, pg/mL	57.80 ± 4.02	117.22 ± 4.16[a]	135.81 ± 4.34[a]	<0.001

Data are given as mean ± standard deviation, $p<0.03$ was considered to be statistically significant. [a]G2, G3 were compared with G1, [b]G3 was compared with G2.

It has been reported that hypoxia causes maternal glomeruloendotheliosis, proteinuria, maternal hypertension and fetal growth retardation in the pathophysiology of preeclampsia [32], decreased choroidal blood flow causes low oxygenation, causing the release of hyphae [33], causing the release of angiogenic factors such as VEGF [26] and ANGPTL-4 [34], thus leading to pathological macular neovascularization [35]. They reported that the hypoxic environment increased the production of ANGPTL-4 levels in human periodontal ligament fibroblasts via HIF-1 [36]. In contrast, Kubo H et al. showed that ANGPTL-4 expression in gastric cancer cells under hypoxia is regulated through a pathway independent of HIF-1α [37].

As a result of our study, we showed that ANGPL-4 serum levels in PE and GH cases were significantly higher than in healthy pregnant women. We think that this is the result of placental hypoxia in PE as stated in the literature above. It has been reported that serum ANGPTL-4 levels are greatly increased in patients with end-stage renal disease and nephritic syndrome. It has been shown that ANGPTL-4 can also be used as a kidney function marker due to its association with glomerular capillary wall damage and proteinuria [38]. We also think that high ANGPTL-4 serum levels in the PE group may be related to the proteinuria seen in patients with PE. We also showed that ANGPTL-4 level increased in our GH group, similar to the PE group. This supports the ACOG's view that the presence of proteinuria is not essential for the diagnosis of PE in 2013. This is because we showed that ANGPTL-4 levels were increased in maternal serum before proteinuria in GH cases before the development of PE. This may indicate that maternal serum ANGPTL-4 measurement may be a candidate for a marker that can be used in the diagnosis of PE.

VEGF-A is a mitogen that induces proliferation of endothelial cells and vascular permeability [39]. In our study, we showed that serum VEGF-A values in our GH and PE group were higher than the control group. This may be the reason for the increase in VEGF level which increases angiogenesis in the placenta with the compensatory mechanisms that can be induced by hypoxia as a result of abnormal angiogenesis. It can be thought that VEGF-A may increase in GH cases even before PE develops, contributing to the development of edema and proteinuria in PE.

Some limitations of our study; the limited number of cases, the inability to study more advanced hypoxic biochemical markers, and the fact that ANGPTL-4 in the placenta has not been evaluated immunohistochemically. Another limitation of ours is that it could not be determined from which gestational week the ANGPTL-4 levels in maternal serum started to increase in cases with PE. Our other limitations are that our cases do not have body mass indexes, that the gestational weeks, pregnancy and birth numbers of our control group and case groups do not match, and that the cases receiving multivitamin, antihypertensive and aspirin treatment are not differentiated in our GH and PE groups.

In addition, the fact that ANGPTL-4 and VEGF-A levels were increased in both our PE and GH cases reduces the level of discrimination. We could not follow up the babies after birth. In this context, different studies can be designed by adding some other data such as IUGR development, preterm labor, birth weeks, normal spontaneous vaginal birth, and cesarean section rates.

One of the strengths of our study is that ANGPTL4 levels were evaluated for the first time in GH and PE cases. Another strength of ours is that it has been shown that maternal serum ANGPTL-4 and VEGF-A levels increase in pregnant women with GH even before the development of PE. Therefore, ANGPTL-4 may be a candidate for an easily available, effective biochemical marker that can be used in the early diagnosis of PE.

In conclusion, we showed that ANGPTL-4 and VEGF-A levels were increased in maternal serum in GH and PE cases. Increased maternal serum ANGPTL-4 levels may be a biomarker that can be used in the early diagnosis of PE.

Research ethics: The local Institutional Review Board deemed the study exempt from review.
Informed consent: Informed consent was obtained from all individuals included in this study.
Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Competing interests: Authors state no conflict of interest.
Research funding: This study was funded by Fırat University Scientific Research Projects (FÜBAP), numbered TF. 21. 08.

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