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Angiogenesis Factors and Uterine Artery Doppler Ultrasound Resistance Index and Pulsatility Index in Pregnancies with High-Risk of Preeclampsia

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Abstract

Background: Endothelial dysfunction in the maternal circulation is an early finding during preeclampsia. Early diagnosis is very important to protect from maternal and neonatal morbidity we aimed to investigate the Vascular Endothelial Growth Factor (VEGF), anti-angiogenic VEGFR-1 (sVEGFR-1) or soluble FMS-like tyrosine kinase-1 (sFlt-1), and angiogenic PlGF using uterine artery Doppler ultrasonography and to evaluate placental vascular and fetomaternal blood flow changes.

Methods: This cross-sectional study included a total of 64 pregnant women aged between 15 and 40 years who were in their 20 to 24 weeks of gestation and who were at a risk of developing preeclampsia. The patients were re-examined after delivery and divided into two groups according to those who developed preeclampsia/IUGR (n=9/7) and those who did not (n=48). We compared the VEGF, sFlt1 and PlGF using uterine artery Doppler ultrasonography changes.

Results: Univariate analysis results of potential factors for preeclampsia were insignificant except age (p=0.047) and body mass index (0.004). In our ROC curve, the pvalue was found to be significant.

Conclusion: Our study results demonstrated that biochemical and radiologic markers did not give any clues for early diagnosis at the 20 to 24 weeks of gestation.

Keywords: Preeclampsia; Angiogenesis factors

Introduction

Preeclampsia is a risky disease both for the health of mother and baby [1]. Diagnosis of the condition before its occurrence during pregnancy would help in preparing treatment plan and future treatment protocols. The risk factors for preeclampsia include nulliparity, cardiovascular diseases, chronic hypertension, obesity and diabetes mellitus, hyperlipidemia, renal disease, and advanced maternal age [2].

Although the pathophysiology of preeclampsia is a controversial condition, disorders in the formation of the vascular bed that provides maternal infant exchange, excessive immune response to paternal antigens, systemic inflammatory reactions, and genetic and environmental factors which affect all these processes play a role. Inadequate trophoblastic invasion and the absence of changes in spiral arteries to provide low-resistance flow lead to insufficient maternal-fetal flow and placental ischemia. Many vasoactive substances are reported to be released by ischemia which develops as a result of disorders in placental vascular remodeling. As a consequence of failure in trophoblastic invasion, the uterine artery pulsation index is reported to be elevated at gestation weeks 12 and 22, may produce a 10% false positive, and detection rate of 40% and 50% [3]. Angiogenic parameters including vascular endothelial growth factor (VEGF), vascular endothelial growth factor receptor-1 (VEGFR-1), and placental growth factor (PIGF) are considered as parameters which can be used in the early diagnosis of preeclampsia. In addition, the fact that preeclampsia is detected in 3% to 5% of all pregnancies, and that they result in maternal and neonatal mortality and morbidity is important in early diagnosis and the formation of a clinical presentation [1,4,5]. Endothelial dysfunction in the maternal circulation is an early finding during preeclampsia. In addition, predisposing factors such as chronic hypertension, diabetes mellitus, and hyperlipidemia may contribute to the development of this disease [6].

The clinical presentation of preeclampsia is characterized by an arterial blood pressure of 140/90 mmHg or an increase of 30 mmHg in systolic pressure or of 15 mmHg in diastolic pressure; and proteinuria (≥ 300 mg/dL in 24-hour urine sample, or 2 urine dipstick tests + or 1 strip measurement ++) and edema. It leads to complications such as renal failure, pulmonary edema, and coagulopathy [7,8]. In normal placental development, fetal syncytiotrophoblast are known to invade maternal spiral arteries and change from low resistance vessels to high resistance vessels, making provision for fetal growth. During vascular invasion, syncytiotrophoblastare differentiated from epithelial phenotype to endothelial phenotype, a process known as pseudovasculogenesis. In preeclampsia, cytotrophoblasts do not adapt to the invasive endothelial phenotype and spiral arteries remain shallow and small in diameter. This leads to uteroplacental circulation defect and placental ischemia [7].

In the present study, we aimed to investigate the VEGF, anti-angiogenic VEGFR-1 (sVEGFR-1) or soluble FMS-like tyrosine kinase-1 (sFlt-1), and angiogenic PlGF using uterine artery Doppler ultrasonography (USG)and to evaluate placental vascular and fetomaternal blood flow changes. We believe that our study findings will shed light to further studies.

Materials and Methods

The study protocol was approved by the Istanbul Education and Research Hospital Ethics Committee. A written informed consent was obtained from each participant. The study was conducted in accordance with the principles of the Declaration of Helsinki.

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Between January 2012 and December 2013, this cross-sectional study included a total of 64 pregnant women aged between 15 and 40 years who were in their 20 to 24 weeks of gestation and who were at a risk of developing preeclampsia (i.e., diabetes mellitus, systemic lupus erythematosus, thyroid function disorders, those with body mass index (BMI) >30 kg/m^2, previous history of preeclampsia or those with a poor obstetric medical history, diagnosis of pre-gestational polycystic ovary syndrome, <18 years and >35-year-old pregnancy, and nulliparity). The routine obstetric examinations, arterial blood pressure, weight, height, and bilateral umbilical artery Doppler USG Pulsatility Index (PI), Resistance Index (RI), and the presence or absence of uterine artery notch were evaluated at the obstetrics and gynecology outpatient clinic. The patients were re-examined after delivery and divided into two groups according to those who developed preeclampsia and those who did not.

Fasting venous blood samples were obtained between 8.00 and 10.00 AM. For the measurements of VEGF (Human VEGF immunassay, Quantikinine, Minnepolis, USA), SVEGF-R1 (Human SVEGF-R1, eBioscience, North America), PIGF (Human PlGF Immunoassay Quantikinine, Minnepolis, USA), blood samples were centrifuged immediately at 4°C for 10 minand frozen at -80°C. Additional blood samples were also obtained for the analysis of uric acid, calcium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and urine protein. The levels of serum and urine parameters were measured using commercially available kits (Siemens Healthcare Diagnostics Inc., Deerfield, IL, USA) with the Siemens Advia 2400 autoanalyzer.

Statistical Analysis

Statistical analysis was performed using the SPSS version 21 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation. The Student's t-test was used to compare normally distributed continuous variables for independent samples. The Mann-Whitney U test was used to compare abnormally distributed continuous variables. A stepwise logistic regression analysis was performed for multivariate analysis to identify the independent predictors. The Fisher's exact test was used to compare categorical variables. The receiver operating characteristic curve (ROC) was generated to examine the accuracy of estimations and to identify potential cut-off values. The sensitivity and specificity were calculated. A p value of less than 0.05 was considered statistically significant.

Results

Of the patients, the mean age was 28.9 ± 6.0 years (range, 18 to 41 years). At the time of the examination, the mean gestational age, which was assessed using USG, was 22.1 ± 2.0 weeks (range, 16 to 28 weeks). During follow-up, 48 patients (75%) had uncomplicated pregnancy, while nine (14%) and seven pregnancies (11%) resulted in preeclampsia and intrauterine growth retardation (IUGR), respectively.

Table 1 shows univariate analysis of potential factors for preeclampsia. Patients who developed eclampsia had significantly older age (32.7 ± 6.5 vs 28.5 ± 5.8 years, p=0.047) and higher BMI values (31.4 ± 6.1 vs 25.6 ± 4.0 kg/m^2, p=0.004). There was no significant difference in other variables between the patients with or without preeclampsia (p>0.05 for all). Table 2 shows univariate analysis of potential factors for IUGR. None of the parameters significantly differed between pregnancies with or without IUGR (p>0.05 for all).

In addition, multivariate analysis using a stepwise logistic regression model revealed only BMI as a significant independent predictor of preeclampsia (OR: 1.24 [95% CI: 1.01-1.52], p=0.036). Area under the ROC curve for predicting preeclampsia was found to be 0.798 (95% CI, 0.648-0.949, p<0.004) for the BMI. A cut-off value of 25 kg/m^2 for BMI (≥ 25) resulted in 78% sensitivity and 52% specificity. In our ROC curve, the p value was found to be significant (apart from BMI) (Figure 1).

Variable	No preeclampsia (n=55)	Preeclampsia (n=9)	P value
Age, years	28.3 ± 5.8	32.7 ± 6.5	0.047
BMI, kg/m^2	25.6 ± 4.0	31.4 ± 6.1	0.004
Systolic arterial pressure, mmHg	105.7 ± 11.4	108.9 ± 22.6	0.984
Diastolic arterial pressure, mmHg	64.8 ± 6.4	62.8 ± 4.4	0.468
Mean arterial pressure, mmHg	78.3 ± 7.2	78.1 ± 8.0	0.946
USG assessments			
Umbilical artery S/D ratio	3.7 ± 1.0	3.5 ± 1.3	0.809
Umbilical artery pulsatility index	1.2 ± 0.2	1.1 ± 0.5	0.847
Umbilical artery resistive index	0.7 ± 0.1	0.6 ± 0.3	0.779
Uterine artery S/D ratio	2.6 ± 1.1	2.4 ± 0.6	0.582
Uterine artery pulsatility index	1.0 ± 0.5	0.9 ± 0.2	0.569
Uterine artery resistive index	0.6 ± 0.2	0.5 ± 0.1	0.339
Presence of notch, n (%)	11 (20.3%)	0 (0%)	0.359
Biochemical assessments			
VEGF, pg/ml	38.6 ± 9.2	36.2 ± 9.9	0.735
sFlt1, mg/ml	0.5 ± 0.4	0.5 ± 0.5	0.787
PIGF, pg/ml	167.1 ± 101.0	169.1 ± 89.8	0.623
sFlt1/PIGF ratio	5.2 ± 8.6	3.6 ± 3.6	0.735
Uric acid, mg/dl	2.9 ± 0.6	2.7 ± 0.5	0.403
Calcium, mg/dl	8.3 ± 0.5	8.2 ± 0.7	0.458
ALT, U/L	11.9 ± 4.9	12.5 ± 3.8	0.469
AST, U/L	14.6 ± 3.9	15.0 ± 5.3	0.760
LDH, U/L	149.1 ± 25.6	127.8 ± 17.9	0.053
Unless otherwise stated, data are presented as mean ± standard deviation.			

Table 1: Univariate analysis of potential factors for preeclampsia.

Variable	No IUGR (n=57)	IUGR (n=7)	P value
Age, years	29.3 ± 6.2	26.4 ± 3.5	0.094
Body Mass Index, kg/m^2	26.4 ± 4.6	26.5 ± 6.4	0.873
Systolic arterial pressure, mmHg	106.1 ± 13.6	107.1 ± 12.2	0.784
Diastolic arterial pressure, mmHg	64.5 ± 6.3	64.3 ± 5.3	0.966
Mean arterial pressure, mmHg	78.3 ± 3.4	78.6 ± 6.8	0.900
USG assessments			
Umbilical artery Systolic/Diastolic ratio	3.7 ± 1.1	3.6 ± 0.7	0.993
Umbilical artery pulsatility index	1.2 ± 0.3	1.2 ± 0.2	0.966
Umbilical artery resistive index	0.7 ± 0.1	0.7 ± 0.1	1.000
Uterine artery Systolic/Diastolic ratio	2.5 ± 0.9	3.4 ± 1.8	0.129
Uterine artery pulsatility index	1.0 ± 0.4	1.4 ± 0.8	0.129
Uterine artery resistive index	0.6 ± 0.2	0.7 ± 0.1	0.201
Presence of notch, n (%)	10 (17.9%)	1 (14.3%)	1.000
Biochemical assessments			
VEGF, pg/ml	37.6 ± 9.0	43.5 ± 9.8	0.276
sFlt1, mg/ml	0.5 ± 0.4	0.4 ± 0.2	0.620
PIGF, pg/ml	164.3 ± 93.2	192.2 ± 142.8	0.661
sFlt1/PIGF ratio	5.3 ± 8.6	2.8 ± 2.5	0.685
Uric acid, mg/dl	2.9 ± 0.6	2.7 ± 0.4	0.338
Calcium, mg/dl	8.3 ± 0.5	8.5 ± 0.3	0.216
ALT, U/L	12.1 ± 5.0	11.6 ± 3.2	0.845
AST, U/L	14.5 ± 4.0	15.7 ± 3.8	0.375
LDH, U/L	146.6 ± 25.3	148.9 ± 30.0	0.831
Unless otherwise stated, data are presented as mean ± standard deviation. IUGR: Intrauterine Growth Retardation			

Table 2: Univariate analysis of potential factors for intrauterine growth retardation.

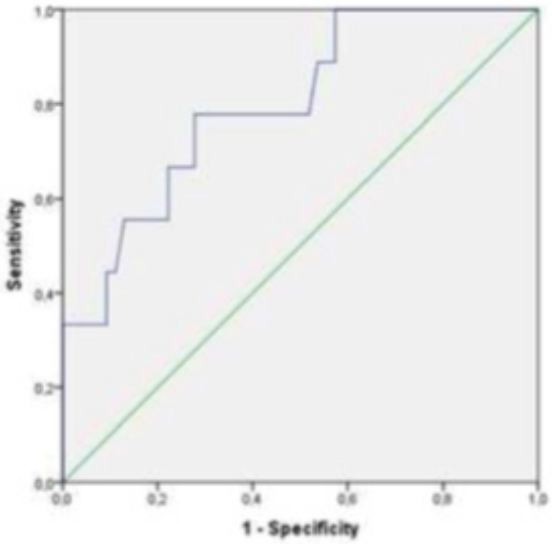

Figure 1: ROC curve, the pvalue was found to be significant (apart from BMI).

Discussion

Early-onset preeclampsia has been reported to be riskier, compared to late-onset preeclampsia in terms of maternal mortality rate, severity of preeclampsia, prevention of fetal development, and placental pathology [4]. Several studies have shown that angiogenic and antiangiogenic factors, fibronectin, plasma thrombomodulin, and endothelin are elevated as early as 20 weeks of gestation and that Doppler USG is valuable diagnostic tool [1-6,8,9]. In the present study, we investigated whether preeclampsia could be detected by Doppler USG and angiogenic parameters in the risky patients who did not develop clinical signs, yet. The reason for choosing the 20th week of gestation was that it was the earliest period of detecting meaningful pathogenesis as demonstrated from previously conducted studies. Mechanisms responsible for preeclampsia include, vascular remodeling in maternal-fetal connection, immunological response to paternal antigens, systemic inflammatory response and dysfunction of placental or endothelial response [9].

The women affected by preeclampsia are also reported to carry a risk of cardiovascular diseases [9]. Various meta-analyses have also demonstrated that initiation of low dose aspirin before the 16th week of gestation reduces the risk of preeclampsia and IUGR by as much as 50% in high-risk women [9]. Therefore, women at risk should be identified to attain the desired perinatal and maternally protection. In 2004, the World Health Organization (WHO) published that there was no clinically useful screening test to predict the development of preeclampsia in the low- and high-risk groups and that there was a need for further, prospective, comprehensive studies [10]. However, there is no systematical study showing the predictive performance of biochemical and USG markers commonly used together. As a result, developing a predictive algorithm for the early detection of women with preeclampsia and taking precautions before the development of a clinical presentation may prevent clinical outcomes. Several studies have shown that there is a 42% prediction rate for preeclampsia in low risk communities [9]. In addition, this rate was suggested to increase to about 89%, when the uterine artery PI (10% false positive rate) was combined with maternal characteristics (race, BMI, parity) [11].

Pregnancy-associated plasma protein-A (PAPP-A) and PlGF were found to be significantly lower in women with preeclampsia during the first trimester, and slightly decreased in late developing women [12]. Levene et al. [13] demonstrated that there was a significant increase in the sFlt1: PlGF ratio and soluble endothelial level in two- and three-months pregnant woman with preeclampsia before the development of a clinical presentation of the disease. Since these two parameters are associated with endothelial dysfunction by different mechanisms, their use together at the same time was suggested to strengthen diagnosis. In another study, the patients were divided into three groups aspregnancies which ended with small for gestational age (SGA), pregnancies including both SGA and preeclampsia, and normal pregnancies [14]. In this longitudinal study, samples were collected and examined every four weeks until termination of pregnancy, and plasma soluble endoglin, sVEGFR-1 and PlGF were analyzed using the ELISA the method. Soluble endoglin and PlGF values were reported to be significantly different between normal pregnancies and patients with SGA and preeclampsia by the 23rd to 30th week; however, the sVEGFR-1 levels were not different between the SGA and normal pregnancies, but were reported to be significantly high by the 26th and 29th weeks of gestation of preterm and term pregnancies of patients with preeclampsia. However, the authors found no significant difference between the 25th and 40th weeks of gestation in SGA pregnancies (p=0.147; p=0.8285). Changes in the VEGF and sVEGFR-1 balance have been reported to be a major factor in the pathophysiology preeclampsia [15]. Preeclampsia is often described in literature as a vascular event associated with placental ischemia [2,5-7]. However, when these parameters would be effective and whether they are affected by Doppler USG findings are important issues. In a longitudinal case-controlled study conducted by Offer Erez et al. [16], 402 women having their first pregnancy were investigated and separated as normal pregnancies, SGA pregnancies and pregnancies with preeclampsia. The first samples were collected at weeks 6 and 15, while the second samples were collected between weeks 20 and 25 and the angiogenesis related factors (sVEGFR-1 and PlGF) were evaluated. A significant increase in these parameters was reported to be an important risk factor for the development of preeclampsia and SGA.

Although preeclampsia is known as a systemic disease characterized by hypertension during pregnancy, the molecular pathogenesis of phenotypic preeclampsia in not understood [17]. However, the hypothesis that the clinical manifestation of the disease is mediated by placental anti-angiogenetic factors is supported by several publications, suggesting hopes for treatment. During sever preeclampsia there is placental hypoperfusion and ischemia, acute atherosis, intimal thickness, necrosis, atherosclerosis, and endothelial injury, and placental infarction. Abnormal uterine artery Doppler USG is reported to be consistent with decreased uteroplacental perfusion [17]. However, this finding alone is not sufficient to make a definite diagnosis.

The pathology of preeclampsia is known to be complicated. In 2004, the WHO reported that there was no clinically useful screening test to predict the development of preeclampsia in the low and high-risk groups, and re-emphasized that there was a need for further, prospective, comprehensive studies [10]. Due to the heterogeneous nature of preeclampsia and the fact that each of the independent markers indicates different pathophysiological processes, it has been reported that it was necessary for appropriate predictive algorithms to be developed [18].

On the other hand, there is no systematic study evaluating how biochemical and USG markers affect each other's predictive performance when used together [18]. Human chorionic gonadotropin (hCG), inhibin A, soluble fms-like tyrosine kinase 1 (sFlt-1),

α-fetoprotein (AFP), activin A, PAPP-A, PlGFwere used as biochemical markers, whereas the uterine artery Doppler PI was included as an USG marker [18].

However, although emphasis was placed on the fact that a combination instead of single parameters or USG markers alone would help in early diagnosis, Duckworth et al. [19] conducted a study on 286 women evaluating 47 markers. The women who were in the gestational period earlier that the 35th week were included in the study; however, it was concluded that a combination of PlGF, podocalyxin, endoglin, and procalcitonin was not superior to PlGF alone. Similarly, the area under curve values of the combination of PlGF, cystatin, and PAPP-A were not different from PlGF alone [19]. The authors, therefore, concluded that parameters such as PlGF, sFlt-1 or endoglin alone would be useful for the diagnosis. Its large sample size and enrollment of the women who were more than the 35th week of gestation were not compatible with our study. In the study by Forest et al. [20], 7,929 pregnant women were screened, and 338 normotensive women were compared to 69 gestational hypertensive women. At the 20th and 32nd week of gestation, the ratio of sFLT-1/PlGF was assessed using the multiple of the median (MoM) values and the concluded that the ratio of sFLT-1/PlGF was a potential marker in the early diagnosis of asymptomatic women [20].

Conclusion

In conclusion, our study results demonstrated that biochemical and radiologic markers did not give any clues for early diagnosis. On the other hand, preeclampsia is not known to certainly develop in every risk group. As a result, among patients whom we followed after delivery, we placed those who developed preeclampsia in the patient group and those who did not as the control group. We believe that including pregnant women who were after the 14th week of gestation in the study and following them on a regular basis using angiogenic factors and Doppler USG would strengthen the nature of the study.

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