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Yalçın KİMYA[1]
Candan CENGİZ[1]
Hakan OZAN[1]
Levent BÜYÜKUYSAL[2]
Sami AYDIN[2]
Serhat TATLIKAZAN[1]

The Role of Plasma Endothelin-1 in Preeclampsia

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Departments of [1]Obstetrics and Gynecology. [2]Pharmacology, Medical Faculty, Uludağ University, Bursa-Turkey.

Abstract: Endothelin-1 levels in normal and preeclamptic pregnant women were determined serially to investigate the correlation between renal function tests and the severity markers of preeclampsia.

Plasma endothelin-1 levels were determined in 45 serial plasma samples from 15 pregnant women who subsequently developed preeclampsia, and in 43 plasma samples from 25 women with uncomplicated pregnancies retrospectively. Renal function tests, complete blood counts, urinalysis and blood pressure measurements were performed during antenatal follow-ups of these patients.

No correlations were set between plasma endothelin-1 levels and renal function tests, thrombocyte and white blood cell counts, proteinuria, systolic and diastolic blood pressures. There was no significant difference between the mean plasma endothelin-1 concentrations of the preeclamptic and uncomplicated groups at all gestational weeks but at the time of delivery. None of the endothelin-1 values at any gestational week differed significantly from any other in the study group; therefore, the risk of subsequent development of preeclampsia could not be estimated by plasma endothelin-1 measurements.

Key Words: Endothelin-1, pregnancy, preeclampsia.

Introduction

A factor in circulation may lead to endothelial cell damage and contribute to the development of preeclampsia (1, 2). Plasma endothelin–1 (ET–1), which is liberated by the endothelial cells, is the most potent endogenous vasoconstrictor known, and its efficacy has been shown to be potentiated in arteries without endothelium (3, 4). To determine the importance of ET–1 in the pathophysiology of preeclampsia, we studied the levels of ET–1 in normal and preeclamptic pregnant women serially and investigated the correlation between the renal function tests and the severity markers of preeclampsia.

Materials and Methods

This study included 437 pregnant women and was conducted between January 1993 and August 1995. The study was approved by the ethical committee and the participants signed a written consent form.

At the time of joining the study and just before delivery all women had blood samples taken for determination of endothelin, urea, uric acid, creatinine and complete blood counts. Proteinuria was also determined by the ESBACH method. Each patient was physically examined and blood pressure was recorded at the initial visit. During monthly follow–ups, in addition to blood pressure determinations, peripheral blood samples were taken for ET–1 measurements.

Blood samples for ET–1 were collected into prechilled test tubes containing aprotinin at a concentration of 400 kallikrein inhibitor units per milliliter and disodium ethylenediaminetetraacetic acid at a concentration of 1.5 mg/ml for 5 milliliters of blood. All samples were immediately centrifuged at 3000 rpm for 10 minutes and the plasma was then removed and stored in vacutainer tubes at –70°C until assay, for a maximum of 22 months.

Patients were classified as preeclamptic if they fulfilled the standard criteria: absence of a history of hypertension before pregnancy and confirmation by anamnesis with

fundoscopic examination, blood pressure higher than 140/90 mmHg or an increase in diastolic pressure of 15 mmHg or systolic pressure of 30 mmHg compared with blood pressures obtained before 20 gestational weeks and proteinuria ≥0.5 gm/24 hr or ≥30 mg/dl on at least two occasions more than 6 hours apart.

Women who developed any pregnancy–related disorder during follow–ups or had any chronic disorders prior to gestation, multiple gestations or any actue infection were excluded from the study. All assays were performed in a blinded fashion by a physician who was unaware of the diagnosis.

ET–1 concentrations were determined by ^{125}I assay system with Amerlex^{TM}–M magnetic separation (Amersham, Arlington Heights III) in 45 plasma samples from 15 pregnant women who subsequently developed preeclampsia, in 12 plasma samples from 12 preeclamptic pregnant women who were admitted for labor but had not any had antenatal visit and in 43 plasma samples from 25 randomly chosen women with uncomplicated gestations according to the manufacturer's protocol, and evaluated retrospectively.

Results were analyzed by paired student t–test and correlation–regression analysis.

Results

The mean age, gravidity, parity and number of abortions are seen in Table 1. No statistically significant difference was determined between the groups (P>0.05). However, the blood leukocyte count was significantly higher (P<0.01) and the blood platelet count was significantly lower (P<0.05) in the preeclampsia group than in the uncomplicated pregnancy group at term (Tables 2 and 3).

Table 1. Characteristics of the patients (Mean±SD).

	UNCOMPLICATED (n=25)	PREECLAMPTIC (n=15)
Age	27.12±4.29	28.86±8.22
Gravidity	2.08±1.12	2.21±2.39
Parity	0.68±0.80	0.50±0.76
Abortion	0.40±0.76	0.71±2.13
Gestational age (days)	270.48±9.23	231.00±39.79
Birth weight (gr)	3172.00±338.83	2087.14±1099.81
APGAR (5^{th} min)	9.44±0.65	6.00±4.28

The renal function test results the mean systolic and diastolic blood pressures and the mean plasma ET–1 levels for each 5–week interval by the 20^{th} week of gestation are seen in Tables 2 and 3. ET–1 showed no statistically significant correlation with any of the renal functions tests. No correlations were found between ET–1 and the weeks of gestation, proteinuria, leukocyte counts, systolic and diastolic blood pressures (P>0.05). There was no significant difference between the groups in the means of plasma ET–1 levels at all gestational weeks (P>0.05) except just prior to delivery (P<0.05).

Table 2. The liver and renal function tests, blood pressures and the plasma ET–1 levels of patients in the uncomplicated pregnancy group (Mean±SD).

	GESTATIONAL AGES (weeks)			
	20–25 (n=13)	26–30 (n=9)	31–35 (n=8)	At the time of delivery (n=13)
Systolic BP (mm Hg)	110.62±5.74	113.33±4.92	111.14±7.86	112.92±4.64
Diastolic BP (mmHg)	70.00±5.16	73.33±4.92	71.14±6.53	71.25±5.37
Proteinuria (dipstick)	0	0	0	0
ESBACH (gr/day)	0	0	0	0
Hemoglobin (gr/dl)	11.85±0.76	12.73±1.22	11.02±0.83	11.74±1.23
Leukocytes (count/cc)	8335.38±2016.29	848374±2183.47	8664.72±1954.28	9537.50±2579.11
Platelets (count/cc)	256545.45±51958.37	264927.74±48663.76	235892.83±47374.38	279153.85±10971.88
Urea (mg/dl)	17.90±6.89	17.27±3.83	16.38±3.44	14.27±4.27
Uric acid (mg/dl)	2.65±0.69	2.84±0.26	3.37±1.43	3.84±2.16
Creatinine (mg/dl)	0.54±0.21	0.57±0.27	0.53±0.19	0.51±0.21
ET–1 (pmol/ml)	20.45±11.92	20.70±5.63	22.21±6.45	19.44±9.29

Table 3. The liver and renal function tests, blood pressures and the plasma ET–1 levels of patients in the preeclampsia group (Mean±SD).

	GESTATIONAL AGES (weeks)			
	20–25 (n=15)	26–30 (n=14)	31–35 (n=11)	At the time of delivery (n=15)
Systolic BP (mm Hg)	112.50±12.58	126.67±15.28	165.00±21.21	156.67±32.15
Diastolic BP (mmHg)	77.50±15.00	73.33±5.77	101.34±5.46	109.62±6.42
Proteinuria (dipstick)	0	+++	++	+++
ESBACH (gr/day)	0	2.95±3.18	2.78±1.83	4.37±3.27
Hemoglobin (gr/dl)	11.50±2.45	11.37±3.25	11.35±0.35	12.43±2.03
Leukocytes (count/cc)	7800.00±1131.37	8900.00±1555.63	9287.50±1283.63	15333.33±4932.88
Platelets (count/cc)	216000.00±82024.39	178000.00±8485.28	194586.20±26743.23	201666.67±52880.37
Urea (mg/dl)	16.00±4.24	34.00±5.66	29.46±3.68	22.67±6.66
Uric acid (mg/dl)	4.45±3.18	6.80±3.82	4.96±2.78	6.25±1.91
Creatinine (mg/dl)	0.66±0.49	0.75±0.49	0.46±0.37	0.80±0.42
ET–1 (pmol/ml)	20.84±8.89	23.25±11.01	23.56±64.68	26.55±7.99

Discussion

Although preeclampsia is a major cause of obstetric and perinatal morbidity, the pathophysiology is still obscure (5). The vascular endothelium is possibly involved in the etiology of the disease (1, 2). The recently discovered endothelium–derived peptide, ET–1, is a very potent vasoconstrictor and plays an important role in the course of essential hypertension (6). Many studies up to now have demonstrated elevated plasma levels of ET–1 in preeclampsia (7), that ET–1 may play an important role in the pathophysiology of preeclampsia, either by acting on vascular smooth muscle directly to induce contraction or by increasing the formation of angiotensin II, to which there is an increased vasopressor response in preeclampsia (8, 9).

In our study we did not find any significant elevation of plasma ET–1 in preeclampsia with respect to uncomplicated gestations at all gestational weeks but at the time of delivery (Tables 2 and 3). However, one should keep in mind that ET–1 elicits a contractile response in arteries with damaged endothelium, and the severity of the damage in preeclampsia may potentiate the effect of ET–1 (3).

In order to estimate the importance of ET–1 levels in pregnancy, its correlation with patient characteristics is of great value. Because it is one of the major vasoconstrictors in the circulation, ET–1 might limit renal blood flow, an effect which is expected to be worse in preeclampsia. ET infusion was shown to increase vascular resistance and decrease renal perfusion and hence the glomerular filtration rate in animal experiments (10–12). However, Schiff et al. and Clark et al. did not find any correlation with blood pressure, proteinuria and gestational age (7, 12). In our study, no relationships were found between plasma ET–1 levels and blood pressure, proteinuria and gestational age as well as renal function parameters, white blood cell and thrombcyte counts in our study. This is similar to the findings of Taylor et al., who observed no correlation of ET–1 with gestational age, maternal age, parity, thrombocyte count, serum creatinine, proteinuria, serum uric acid and mean arterial pressure (13).

Although ET–1 has been suggested to play role to take a part in the pathogenesis of preeclampsia, our findings do not support this hypothesis. Though it increase significantly at the time of delivery, by which time preeclampsia had already developed, there were no correlations between the plasma ET–1 level and the severity of disease and the gestational week in our study. Therefore we believe that ET–1 is not predictive in preeclampsia and probably has a complementary rather than an etiological role in its pathophysiology.

Corresponding author:
Yalçın Kimya,
İhsaniye Mahallesi
Dört Yıldız Sitesi
A2 Blok, No: 4
BURSA

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