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Original Article

Maternal serum copeptin concentrations in early- and late-onset pre-eclampsia

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ABSTRACT

Objective: Early-onset pre-eclampsia is primarily associated with placental dysfunction, whereas late-onset pre-eclampsia is defined as a maternal constitutional disorder. As a protein cosynthesized with vasopressin, copeptin is a potential marker of metabolic syndrome and insulin resistance, which shares similar risk factors with pre-eclampsia. The aim of this study was to investigate the copeptin levels in patients with early-onset and late-onset pre-eclampsia.

Materials and methods: A total of 80 pregnant women receiving antenatal and obstetric care were recruited. The patients were subdivided into four groups: Early-onset pre-eclampsia ($n = 20$), late-onset pre-eclampsia ($n = 20$), and two control groups of similar gestational ages for both pre-eclamptic groups ($n = 20$ in each group). The maternal serum copeptin levels were measured using an enzyme-linked immunosorbent assay.

Results: The mean copeptin levels were 0.92 ± 0.57 ng/mL and 1.65 ± 0.95 ng/mL in the early-onset and late-onset pre-eclampsia groups, respectively. These values were higher compared with the control groups (0.54 ± 0.25 ng/mL and 1.15 ± 0.94 ng/mL, respectively). However, the difference was only statistically significant in the early-onset pre-eclampsia group ($p = 0.011$). Copeptin levels were associated only with gestational age and systolic–diastolic blood pressure.

Conclusion: Our results suggest that copeptin levels might be useful in the evaluation of the severity of pre-eclampsia. However, copeptin might be involved in early- rather than late-onset pre-eclampsia.

Introduction

Pre-eclampsia is a multisystem disease of pregnancy, characterized by new-onset hypertension and proteinuria, which develops after 20 weeks of gestation in previously normotensive women, complicating 3–5% of all pregnancies [1]. Although the exact cause of pre-eclampsia remains unknown, this disease is characterized by inadequate placentation, oxidative stress, inflammation, and widespread endothelial dysfunction [2]. Pre-eclampsia can be classified as early onset and late onset, according to the development of symptoms before or after 34 weeks of pregnancy, respectively [3,4]. Early-onset pre-eclampsia associated with placental dysfunction is markedly severe, frequently leading to deliveries of growth-retarded premature babies or poor outcomes for mothers [5].

Women affected with pre-eclampsia have significantly increased risks of metabolic and cardiovascular diseases following pregnancy [6,7]. Pre-eclampsia, metabolic syndrome, and cardiovascular diseases share the same risk factors, including obesity, hypertension, dyslipidemia, hypercoagulability, and insulin resistance, and these conditions are characterized by endothelial dysfunction [8–10]. Recently, the activation of the stress-mediated hypothalamic–pituitary–adrenal (HPA) axis, regulated through copeptin, was implicated in the pathophysiology of metabolic

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syndrome and cardiovascular diseases [11]. Corticotropin-releasing hormone and copeptin-regulated stress-mediated HPA axis activation are involved in the endocrine stress response [12–14]. Copeptin is superior to cortisol in the determination of the stress level, because cortisol has a strong circadian rhythm, and the measurement of cortisol as a free hormone in serum remains challenging [15].

Zulfikaroglu et al [16] reported that increased maternal levels of copeptin might be involved in the pathogenesis of pre-eclampsia, and copeptin might be a clinically useful biomarker for the assessment of disease severity in early-onset pre-eclampsia. Similarly, as an indicator of inadequate placentation in pre-eclampsia, copeptin levels have been associated with abnormal uterine and umbilical artery Doppler velocimetry values. Inadequate placentation is primarily associated with early-onset rather than late-onset pre-eclampsia, whereas late-onset pre-eclampsia results from an underlying maternal constitutional disorder. However, the outcomes of late-onset pre-eclampsia resemble those of normal pregnancies compared with early-onset pre-eclampsia. Therefore, we hypothesized that copeptin might be an important biomarker of early- rather than late-onset pre-eclampsia.

Copeptin, a 39-amino acid glycopeptide, is cosynthesized in the hypothalamus with vasopressin, which is also an antidiuretic hormone. Copeptin can be used as an indicator of serum vasopressin levels, because the levels of this hormone in serum are more stable in plasma and serum compared with vasopressin [17]. In addition to reflecting individual stress levels, vasopressin also has hemodynamic and osmoregulatory effects. Interestingly, copeptin has been shown to act identically with vasopressin during the course of disorders of the osmoregulatory system, and copeptin levels have been directly correlated with the plasma vasopressin levels in both healthy volunteers and critically ill patients [18]. In addition, copeptin levels have been demonstrated as independent predictors of survival in patients suffering from hemorrhagic and septic shock and have shown prognostic implications in diseases other than infections [19].

In this study, we evaluated the copeptin levels in normal pregnancy and pregnancies complicated by early-onset and late-onset pre-eclampsia. We also investigated the association between maternal serum copeptin levels and umbilical and uterine artery Doppler velocimetry values in pre-eclamptic patients.

Materials and methods

A total of 80 pregnant women, comprising 40 women with normal pregnancies and 40 women diagnosed with pre-eclampsia, receiving antenatal and obstetric care at the Department of Obstetrics and Gynecology, Istanbul University Cerrahpasa Faculty of Medicine Hospital (Istanbul, Turkey), from May 2012 to July 2012, were recruited for this case-control study. Pre-eclampsia was defined according to the criteria of the American College of Obstetrics and Gynecology (ACOG practice bulletin) [20]. Pre-eclampsia was determined through increased blood pressure (>140/90 mmHg) occurring in a pregnant woman after 20 weeks of amenorrhea, accompanied by proteinuria (≥0.3 g/24 h), as defined according to the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy.

The patients with pre-eclampsia were divided into two groups as follows: 20 patients diagnosed before 34 weeks of gestation were defined as having “early-onset pre-eclampsia,” and those diagnosed and delivered at 34 weeks of gestation or later were defined as having “late-onset pre-eclampsia.” For each patient with pre-eclampsia, one control woman was randomly matched according to weeks of gestation among normotensive patients with uncomplicated pregnancies who delivered healthy babies weighing >2500 g at term. This group was divided into two subgroups based on the gestational weeks (early and late control groups). The early control group comprised 20 healthy pregnant women recruited during a routine visit to the antenatal clinic at 24–34 gestational weeks; only those women whose pregnancies continued normally remained in this group. The late control group comprised 20 healthy pregnant women recruited during a routine visit to the antenatal clinic following the completion of 34 gestational weeks. Therefore, the control groups were appropriately structured for statistical evaluation in terms of gestational weeks for both early-onset and late-onset pre-eclamptic patient groups. The mean ages, gestational weeks, and body mass index (BMI) were evaluated. The BMI was calculated using the following formula: weight (kg)/height $(m)^2$.

The following exclusion criteria were used: multiple pregnancies, pregestational or gestational diabetes mellitus, smoking, chronic hypertension, polyhydramnios, prior renal diseases, and evidence of acute or chronic inflammation. The diagnosis of pregnancy was based on a positive serum beta-human chorionic gonadotropin test and the presence of fetal heart beat in the uterine cavity on ultrasonographic evaluation. The gestational ages were evaluated according to the last menstrual period and confirmed through ultrasound performed until 14 gestational weeks, based on the crown rump length values of the embryos.

Blood samples were collected from each participant before administration of any medication and before any medical or surgical intervention. None of the patients was in labor at the time of sampling. The serum was separated by centrifuging the samples at 4000*g* for 10 minutes and freezing at −80°C for later analysis. The serum copeptin concentrations were measured in duplicate using a competitive enzyme immunoassay (Catalog No. EK-065-32 copeptin-human EIA kit: Phoenix Pharmaceuticals, Inc., CA, USA). The assay sensitivity was 0.12 ng/mL, and the interassay and intra-assay calculation values were 5–10% and <15%, respectively.

The umbilical artery and uterine artery blood-flow velocity values were obtained using transabdominal color and pulsed Doppler velocimetry measurements of the uterine and umbilical arteries, performed by the same physician (A.T.) for all study patients. Voluson 730 Pro ultrasound machines (GE Healthcare, UK), equipped with pulsed and color Doppler technologies, were used, and uterine and umbilical artery Doppler velocimetry values were measured. Informed consent was obtained from all women, and the study protocol was approved through the Human Ethics Committee of Istanbul University.

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software version 18.0, SPSS Inc., Chicago, IL, USA. The data are presented as the arithmetical means, and the standard deviations were calculated for each group. Student *t* test was used for comparison of the parametric variables, and chi-square test was used for comparison of the nonparametric variables. The relationship between a particular biochemical parameter and the stage or grade was evaluated using Pearson correlation test. A p value < 0.05 was considered statistically significant.

Results

The clinical characteristics, uterine and umbilical artery Doppler velocimetry findings, and mean maternal serum copeptin levels of the subgroups (early-onset pre-eclampsia, late-onset pre-eclampsia, and 2 control groups) are summarized in Table 1. Pre-eclamptic patients in both early-onset and late-onset groups were compared with their gestational age-matched controls.

No statistical differences were observed between the patients with early-onset pre-eclampsia and their respective controls in terms of mean maternal ages, BMI values, mean gestational ages at